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Ginkgo biloba for tinnitus (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Ginkgo biloba for tinnitus

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of Ginkgo biloba for tinnitus in adults and children.

BACKGROUND

This is a new protocol for a review that will supersede the Cochrane Review 'Ginkgo biloba for tinnitus', which was first published in the *Cochrane Library* in Issue 3, 2013. The following paragraphs and Description of the condition are based on the Cochrane Review 'Amplification with hearing aids for patients with tinnitus and co-existing hearing loss' and are reproduced with permission (Hoare 2014). Description of the intervention and How the intervention might work are based on the Cochrane Review 'Ginkgo biloba for tinnitus' and are reproduced with permission (Hilton 2013).

Tinnitus is defined as the perception of sound in the absence of an external source (Jastreboff 2004). It is typically described by those who experience it as a ringing, hissing, buzzing or whooshing sound and is thought to result from abnormal neural activity at some point or points in the auditory pathway, which is erroneously interpreted by the brain as sound. Tinnitus can be either objective or subjective. Objective tinnitus refers to the perception of sound that can be also heard by the examiner and is usually due to turbulent blood flow or muscular contraction (Roberts 2010). Most commonly, however, tinnitus is subjective; the sound is only heard by the person experiencing it and no source of the sound is identified (Jastreboff 1988).

Tinnitus affects between 5% and 43% of the general population and prevalence increases with age (McCormack 2016). It can be experienced acutely, recovering spontaneously within minutes to weeks, but is considered chronic and unlikely to resolve spontaneously when experienced for more than three months (Gallus 2015; Hall 2011).

For many people tinnitus is persistent and troublesome, and has disabling effects such as insomnia, difficulty concentrating, difficulties in communication and social interaction, and negative emotional responses such as anxiety and depression (Hall 2018). In approximately 90% of cases, chronic tinnitus is co-morbid with some degree of measurable hearing loss, which may confound these disabling effects (Fowler 1944; Sanchez 2002). Nevertheless, the association between hearing loss and tinnitus is not simple or straightforward; not all people with hearing loss experience tinnitus, and conversely some people with clinically normal hearing have tinnitus (Baguley 2013). It has been reported that 40% of patients are unable to identify what health condition is associated with their tinnitus onset, i.e. the tinnitus is idiopathic (Henry 2005).

An important implication in clinical research is that outcome measures need to distinguish benefits specific to improved hearing from those specific to improvement in the psychological aspects of tinnitus.

Description of the condition

Diagnosis and clinical management of tinnitus

There is no standard procedure for the diagnosis or management of tinnitus. Practice guidelines and the approaches described in studies of usual clinical practice typically reflect differences between the clinical specialisms of the authors or differences in the clinical specialisms charged with meeting tinnitus patients' needs (medical, audiology/hearing therapy, clinical psychology, psychiatry), or the available resources of a particular country or region (access to clinicians or devices, for example) (Biesinger 2010; Cima 2012; Department of Health 2009; Hall 2011; Henry 2008; Hoare 2011). Common across all these documents, however, is the use or recommendation of written questionnaires to assess tinnitus and its impact on patients and their families by measuring tinnitus symptom severity (e.g. impact of tinnitus on quality of life, activities of daily living or sleep), and a judgement about patients who are experiencing a degree of psychological distress (depression or anxiety). Assessment of the perceptual characteristics of tinnitus (pitch, loudness, minimum masking level) and residual inhibition are also recommended (Cima 2019). Although these measures do not correlate well with tinnitus symptom severity (Hiller 2006), they can prove useful in patient counselling (Henry 2004), as a baseline before start of treatment (El Refaie 2004), or by demonstrating stability of the tinnitus percept over time (Department of Health 2009).

Clinical management strategies include education and advice, relaxation therapy, tinnitus retraining therapy (TRT), cognitive behavioural therapy (CBT), sound enrichment using ear-level sound generators or hearing aids, and drug therapies to manage co-morbid symptoms such as insomnia, anxiety or depression (for example, Department of Health 2009; Tunkel 2014). As yet, no drug has been approved for tinnitus by a regulatory body (e.g. the European Medicines Agency or US Food and Drug Administration).

Pathophysiology

Most people with chronic tinnitus have some degree of measurable hearing loss (Ratnayake 2009), and the prevalence of tinnitus increases with greater hearing loss (Han 2009; Martines 2010). The varying theories of tinnitus generation involve changes in either function or activity of the peripheral (cochlea and auditory nerve) or central auditory nervous systems (Henry 2005). Theories involving the peripheral systems include the discordant damage theory, which predicts that the loss of outer hair cell function, where inner hair cell function is left intact, leads to a release from inhibition of inner hair cells and aberrant activity (typically hyperactivity) in the auditory nerve (Jastreboff 1990). Such aberrant auditory nerve activity can also have a biochemical basis, resulting from excitotoxicity or stress-induced enhancement of inner hair cell glutamate release with upregulation of N-methyl-D-aspartate (NMDA) receptors (Guitton 2003; Sahley 2001).

In the central auditory system, structures implicated as possible sites of tinnitus generation include the dorsal cochlear nucleus (Middleton 2011; Pilati 2012), the inferior colliculus (Dong 2010; Mulders 2010), and the auditory and non-auditory cortex (discussed further below). There is a strong rationale that tinnitus is a direct consequence of maladaptive neuroplastic responses to hearing loss (Moller 2000; Muhlnickel 1998). This process is triggered by sensory deafferentation and a release from lateral inhibition in the central auditory system allowing irregular spontaneous hyperactivity within the central neuronal networks involved in sound processing (Eggermont 2004; Rauschecker 1999; Seki 2003). As a consequence of this hyperactivity, a further physiological change noted in tinnitus patients is increased spontaneous synchronous activity occurring at the subcortical and cortical level, measurable using electroencephalography (EEG) or magnetoencephalography (MEG) (Dietrich 2001; Tass 2012; Weisz 2005). Another physiological change thought to be involved in tinnitus generation is a process of functional reorganisation, which amounts to a change in the response properties of neurons within the primary auditory cortex to external sounds. This effect is well demonstrated physiologically in animal models of hearing loss

(Engineer 2011; Norena 2005). Evidence in humans, however, is limited to behavioural evidence of cortical reorganisation after hearing loss, demonstrating improved frequency discrimination ability at the audiometric edge (Kluk 2006; McDermott 1998; Moore 2009; Thai-Van 2002; Thai-Van 2003), although Buss 1998 did not find this effect. For comprehensive reviews of these physiological models, see Adjamian 2009 and Norena 2011.

It is also proposed that spontaneous hyperactivity could cause an increase in sensitivity or 'gain' at the level of the cortex, whereby neural sensitivity adapts to the reduced sensory inputs, in effect stabilising mean firing and neural coding efficiency (Norena 2011; Schaette 2006; Schaette 2011). Such adaptive changes would be achieved at the cost of amplifying 'neural noise' due to the overall increase in sensitivity, ultimately resulting in the generation of tinnitus.

Increasingly, non-auditory areas of the brain, particularly areas associated with emotional processing, are also implicated in bothersome tinnitus (Rauschecker 2010; Vanneste 2012). Vanneste 2012 describes tinnitus as "an emergent property of multiple parallel dynamically changing and partially overlapping sub-networks", implicating the involvement of many structures of the brain more associated with memory and emotional processing in tinnitus generation. However, identification of the structural components of individual neural networks responsible for either tinnitus generation or tinnitus intrusiveness, which are independent of those for hearing loss, remains open to future research (Melcher 2013). One further complication in understanding the pathophysiology of tinnitus is that not all people with hearing loss have tinnitus and not all people with tinnitus have a clinically significant and measurable hearing loss. Other variables, such as the profile of a person's hearing loss, may account for differences in their tinnitus report. For example, König 2006 found that the maximum slope within audiograms was higher in people with tinnitus than in people with hearing loss who do not have tinnitus, despite the 'non-tinnitus' group having the greater mean hearing loss. This suggests that a contrast in sensory inputs between regions of normal and elevated threshold may be more likely to result in tinnitus. However, this finding is not consistent across the literature (Sereda 2011; Sereda 2015).

Description of the intervention

Extracts of Ginkgo biloba leaves have been used for medicinal purposes for at least 5000 years in China, where they form an important component of the traditional Chinese pharmacopoeia (a book which lists drugs and instructions for their use). More recently Ginkgo biloba extracts have been used in Western countries. In the USA, Canada and the UK extracts are widely available as non-prescription food supplements (Diamond 2013; Mei 2017; Ude 2013). In France and Germany a standardised dry leaf extract is registered as a drug and is commonly prescribed for tinnitus (Hall 2011; Ude 2013). However, there are several components in the available Gingko biloba preparations. A purified and enriched liquid extract is prepared from dried leaves of the maidenhair plant. The liquid extract is dried to give one part extract from 50 raw leaves. The most important active chemical compounds are flavonoids (ginkgo-flavone glycosides) and terpenoids (ginkgolides A, B, C, J and bilobalide). Ginkgolides appear to be unique to Ginkgo biloba and have not been isolated from any other plant species. Standardised Ginkgo leaf extracts have been used in clinical trials for tinnitus, and cognitive and cardiovascular disorders, at daily doses of 60 mg to 450 mg (Mei 2017; Yang 2011). These preparations contain standardised amounts of the above compounds. EGb761 (Tebonin, Tanakan, Rökan) contains 24% ginkgo-flavone glycosides and 6% terpenoids, and LI 1370 (Kaveri) contains 25% ginkgo flavone glycosides and 6% terpenoids (Blumenthal 1998; Mei 2017). Although the quantities are standardised, the manufacturing process is different and the ratio of active ingredients within each sub-class may be different. There is no standardisation for food supplement preparations (Mei 2017).

The most commonly reported side effect of Ginkgo biloba is mild gastrointestinal disturbance (e.g. stomach pain, change in bowel habit). Serious side effects are rare, but include bleeding problems, interaction with anticoagulant medication and seizures (Ernst 2002; Mei 2017; Rajarajan 2018).

How the intervention might work

Several mechanisms of action of Ginkgo biloba have been proposed in the light of its many active ingredients. Human, animal and in vitro studies indicate the following effects:

- A vasoregulatory effect (altering the tone of blood vessels) promoting increased blood flow (Diamond 2013; Lichota 2019; Nuhu 2014; Shu 2019; Xia 2007; Zhou 2004). Animal and human studies have shown that Ginkgo biloba can increase skin (Boelsma 2004; Jung 1990; Koltinger 1989), cardiac (Xiao 2019) and cerebral blood flow (Li 2018; Mashayekh 2011).
- Antagonism of platelet activating factor (PAF) (Diamond 2013; Nash 2015; Xia 2007; Zhou 2004). This effect is specific to the ginkgolides (predominantly B). PAF causes platelet (a blood constituent involved in blood clot formation) aggregation, neutrophil degranulation (activation of immune cells within the blood stream) and oxygen radical production. Ginkgolides appear to protect against the effects of hypoxic brain injury from cerebral ischaemia (permanent brain damage caused by insufficient blood and oxygen supply) in laboratory animals (Braquet 1991; DeFeudis 1991; Li 2018; Smith 1996) and humans (Oskouei 2013).
- Antioxidant activity including scavenging of free radicals, indirectly inhibiting formation of free radicals, regulation of oxidative stress and anti-lipid peroxidation (Lichota 2019; Mahadevan 2008; Singh 2019; Zhou 2004; Zuo 2017).
- Changes in the metabolism of neurons (Blecharz-Klin 2009; DeFeudis 2000; Eckert 2005) and restoration of age-related deficiencies in central neurotransmitter systems (Blecharz-Klin 2009; DeFeudis 2000; Fehske 2009).
- Enhancement of neuronal plasticity including increased long-term potentiation, spine density, neuritogenesis and neurogenesis, as shown in pre-clinical reports (Müller 2012).
- Anti-inflammatory effects and protective actions against brain damage, possibly through its terpenoids and ginkgolides (Cheng 2003; Lichota 2019; Nuhu 2014; Shu 2019; Xia 2007; Zhang 2016). The Ginkgo biloba leaf extract has been shown to reduce the level of cytokines and inflammatory factors such as tumour necrosis factor alpha (TNF-α), interleukin 6 (Il-6), interleukin 1 beta (Il 1-β) and matrix metalloproteinase 9 (Omidkhoda 2019; Zhang 2016).

These mechanisms may treat tinnitus by preventing free-radical damage to the cochlea, or increasing blood flow, improving the health of the inner ear (Didier 1996; Smith 2013). Tziridis 2014

tested the effectiveness of prophylactic treatment with EGb 761 for noise-induced hearing loss and development of tinnitus after noise trauma in an animal model. Based on the results they suggested significant neuroplastic effects of EGb 761 on auditory processing at the peripheral and central level of the auditory pathway as measured with behavioural and electrophysiological approaches. They proposed a model of the effects of EGb 761 on auditory processing with two main effects: 1) an increase in auditory brainstem activity leading to an increased thalamic input to the primary auditory cortex; and 2) an asymmetric effect on lateral inhibition in the primary auditory cortex.

A study by Krauss 2016 examined the therapeutic effects of EGb 761 after the formation of permanent noise-induced hearing loss and tinnitus in an animal model. They found that treatment with EGb 761 led to recovery of auditory thresholds and reduced behavioural signs of tinnitus. Interestingly, while the auditory thresholds were maintained, behavioural signs of tinnitus reappeared after discontinuation of treatment. An analysis of the auditory brainstem responses (ABRs) showed changes in ABR wave amplitude and latency at different levels of the auditory pathway (increase of response to low stimulus intensities and decrease at high intensities) rather than restoration of the auditory processing back to pre-trauma conditions. Based on that result, the authors suggested a global inhibitory mechanism that counteracts tinnitus. The EGb 761 extract was also shown to protect against noise-induced hearing loss by inhibiting the expression of proinflammatory cytokines and cyclooxygenase 2 (COX-2), and increasing values of heat shock proteins in the rat cochlea (Dogan 2018). It was also shown to protect against cisplatin- and gentamicin-induced hair cell loss, and subsequent changes in brain activity in animal models (Huang 2007; Yang 2011).

Why it is important to do this review

In England alone there are an estimated ¾ million general practice consultations every year where the primary complaint is tinnitus (El Shunnar 2011), equating to a major burden on healthcare services. Use of Gingko biloba for tinnitus is currently recommended against in the European tinnitus guideline (Cima 2019) and the American Academy of Otolaryngology Clinical Practice Guideline (Tunkel 2014). Both guidelines conclude that there is no proven efficacy of Gingko biloba and that there is potential for harm. There is evidence that Ginkgo biloba interacts with antithrombotic drugs to cause serious bleeding and increases bleeding risk in clotting disorders (Posadzki 2013). A worldwide survey of dietary supplements used to treat tinnitus reported that Ginkgo biloba was the most cited supplement resulting in adverse effects (diarrhoea, nausea, hearing, dizziness, headache, bleeding, blood pressure changes, chest pain, palpitation and increased urination) (Coelho 2016). Despite this, Ginkgo biloba is the most commonly used herbal supplement for tinnitus (Hall 2011). A survey of treatment options for subjective tinnitus showed that Ginkgo biloba was a popular first-line treatment prescribed by general practitioners (GPs) and ENT physicians across Europe, with a proportion of patients prescribed Ginkgo biloba as high as 71% in some countries (Hall 2011). Ginkgo biloba is freely available for purchase in health food stores across Europe and America (Chan 2007). A recent survey showed that 1 in 10 people with tinnitus in the UK use alternative therapies, including Gingko biloba (McFerran 2018).

The previous Cochrane Review on this question concluded that there was no evidence that Gingko biloba was effective in patients with a primary complaint of tinnitus (Hilton 2013). However, the methods and searches used in that review now require updating.

OBJECTIVES

To assess the effects of Ginkgo biloba for tinnitus in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

We will include studies with following design characteristics:

- randomised controlled trials, including cluster-randomised (cross-over trials will be eligible if data from before the cross-over can be extracted, to avoid the potential for a carry-over phenomenon).

We will exclude studies with the following design characteristics:

- quasi-randomised controlled studies.

We will apply no restrictions on language, year of publication or publication status.

Types of participants

Adults and children with acute (≤ 3 months) or chronic (> 3 months) subjective idiopathic tinnitus.

Types of interventions

The review will include all courses of Ginkgo biloba, regardless of dose regimens or formulations and for any duration of treatment**.**

The main comparison will be:

- Ginkgo biloba *versus* placebo.

Other possible comparison pairs include:

- Ginkgo biloba *versus* no intervention;
- Ginkgo biloba *versus* education and information only.

Concurrent use of other medication or other treatment will be acceptable if used equally in each group. For example, Ginkgo biloba with an additional intervention versus placebo with an identical intervention. Where an additional intervention was used equally in both groups, we will analyse this as a separate comparison.

Types of outcome measures

We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies.

Primary outcomes

- Tinnitus symptom severity (such as the impact of tinnitus on quality of life, activities of daily living and sleep), as measured by the global score on a multi-item tinnitus questionnaire (Table 1). These include:
  - Tinnitus Questionnaire (Hallam 1996; Hiller 1992);
  - Tinnitus Functional Index (Meikle 2012);

- Tinnitus Handicap Inventory (Newman 1996);
- Tinnitus Handicap Questionnaire (Kuk 1990);
- Tinnitus Reaction Questionnaire (Wilson 1991);
- Tinnitus Severity Scale (Sweetow 1990).

We will update this list on an ongoing basis whenever other questionnaires are introduced.

- Significant adverse effect: bleeding, seizures.

Secondary outcomes

- Tinnitus loudness (a change in subjective perception) measured using either patient-reported instruments (including visual analogue scales or numerical rating scales) or performance-based procedures (including tinnitus loudness matching or minimum masking level).
- Tinnitus intrusiveness measured using a self-report multi-item questionnaire or validated subscale (Hall 2018a).
- Generalised depression as measured by validated questionnaires, such as the Beck Depression Inventory II (Beck 1996), the depression scale of the Hospital Anxiety and Depression Scale (HADS; Zigmond 1983), and the Hamilton Rating Scale for Depression (Hamilton 1960).
- Generalised anxiety as measured by a validated scale, for example the anxiety scale of the HADS or Beck Anxiety Inventory (Beck 1988) or the Anxiety Sensitivity Index (Reiss 1986).
- Health-related quality of life as measured by a validated scale, for example, the Short-Form 36 (Hays 1993), WHOQoLBREF (Skevington 2004), and other WHOQoL versions, and the Health Utilities Index (Furlong 2001).
- Other adverse effects: gastrointestinal upset, headache, allergic reaction.

We will assess outcomes as short-term (less than three months) and long-term (three to six months). We will also consider whether these outcomes are sustained beyond six months.

Search methods for identification of studies

The Cochrane ENT Information Specialist will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:

- the Cochrane ENT Register (search via the Cochrane Register of Studies to date);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (search via the Cochrane Register of Studies to date);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to date);
- Ovid EMBASE (1974 to date);
- Ovid AMED (1985 to date);
- Web of Science, Web of Science (1945 to date);
- EBSCO CINAHL (1982 to date);
- LILACS (Latin American and Caribbean Health Science Information database), lilacs.bvsalud.org (search to date);
- CNKI, www.cnki.com.cn (searched via Google Scholar 1999 to date);
- ClinicalTrials.gov, (search via the Cochrane Register of Studies and clinicaltrials.gov to date);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search via the Cochrane Register of Studies and www.who.int/ictrp to date).

The subject strategies for databases will be modelled on the search strategies designed for CENTRAL, MEDLINE and Embase (Appendix 1). There are likely to be low numbers of search results therefore an RCT filter will not be applied.

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search Ovid MEDLINE to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. The Information Specialist will also run non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

We will not perform a separate search for adverse effects. We will consider adverse effects described in included studies only.

Data collection and analysis

Selection of studies

Two authors (MS, MH, AER, DJH) will independently review all records retrieved to determine their eligibility for inclusion in the review. The authors will then review the full-text articles of the retrieved studies and independently apply the inclusion criteria. Any disagreements will be discussed, involving a third author if necessary until a consensus is reached.

Data extraction and management

Two authors (MS, MH, AER, JX, DJH) will independently extract data using a purposely designed data extraction form. We will pilot the data extraction form on a subset of articles and revise it if indicated before formal data extraction begins. Where necessary, or where insufficient data are provided for the study, we will contact the study authors for further information.

Information to be extracted will include: study design, setting, methods or randomisation and blinding, power, inclusion and exclusion criteria, type of intervention and control, treatment duration, treatment fidelity, type and duration of follow-up, outcome measures used and statistical tests performed.

Data to be extracted will include: baseline characteristics of participants (age, sex, duration of tinnitus, tinnitus symptom severity, tinnitus loudness estimates, details of co-morbid hearing loss, anxiety or depression), details of any attrition or exclusion, group mean and standard deviation for outcome measures at pre- and post-intervention and follow-up, and results of any statistical between-group comparisons.

We will contact authors where further information is required that is not contained within the study publication or in an accessible database. If not reported or provided by the authors, we will estimate standard deviations in RevMan 5.3 (RevMan 2014) using the available data, such as standard errors, confidence intervals, P values and t values. Where data are only available in graph form, we will make and agree numeric estimates.

After independent data extraction by two authors, we will review the extracted data for disagreements, and revisit and discuss the relevant studies as required to reach a final consensus.

Assessment of risk of bias in included studies

Two authors (MS, MH, AER, JX, DJH) will undertake assessment of the risk of bias of the included trials independently, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5) (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane 'Risk of bias' tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias. We will resolve differences of opinion by discussion. If no consensus is reached, we will consult a third author to adjudicate.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs). We will summarise continuous outcomes as mean differences (MD) with 95% CI. We will use standardised mean differences (SMD) (Cohen's d effect size (ES)) when different scales of measurement have been used to measure the same outcome. A positive ES indicates that the treatment group achieved better outcomes than the control group.

Unit of analysis issues

For parallel-group RCTs the unit of analysis will be the group mean. However, some studies included in the review may involve clustering or compare more than two intervention groups. To avoid unit of analysis errors we will consider alternative analyses for cluster-randomised trials and for studies with more than two intervention groups. For cluster-randomised trials we will adopt approximate analyses - effective sample sizes (Donner 2002). For studies with more than two intervention groups, we will either combine groups to create a single pair-wise comparison or, if this is not appropriate, select the most relevant pair of interventions for comparison.

Dealing with missing data

Where necessary and where sufficient data from the study are not provided, we will contact the authors of the study requesting further details about missing data and reasons for the incompleteness of the data. If no response is obtained, we will impute data if we judge the data to be 'missing at random'. If we judge data to be 'missing not at random', the missing data may affect the overall results; we will therefore not impute data. In the latter case, we will conduct sensitivity analyses with different assumptions. We will be alert to potential mislabelling or non-identification of standard errors and standard deviations. Our methods for imputation will be according to Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2019). If data are missing, we will use an available case analysis using all data (as reported) for all randomised patients available at the end of the study/time point of interest, regardless of the actual treatment received. We will consider the quality of outcome assessment as a study limitation (GRADE) and not as a stratifying factor.

Assessment of heterogeneity

We will assess studies for clinical, statistical and methodological heterogeneity. We will assess and quantify statistical heterogeneity through visual inspection of the forest plots and by looking at the I^2 statistic and the Chi^2 test. An approximate guide to interpretation of the I^2 statistic is provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2019). An I^2 value of 50% or higher may represent substantial or considerable heterogeneity. Where Chi^2 is greater than the degrees of freedom (K-1 degrees of freedom, where K is the number of studies), then heterogeneity is likely to be present. We will consider heterogeneity to be statistically significant if the P value is less than 0.10. We will perform the meta-analysis using fixed-effect (in the absence of heterogeneity) and random-effects modelling (in the presence of heterogeneity). If there is considerable statistical heterogeneity, we will use subgroup analyses to explore the sources.

Assessment of reporting biases

We will investigate potential publication bias and the influence of individual studies on the overall outcome identified in this review. We will search for and request study protocols for the included studies and, where available, we will evaluate whether there is evidence of selective reporting. If a meta-analysis contains at least 10 studies, we will assess publication bias using a funnel plot and Egger's test.

Data synthesis

If more than one study is identified for a given option, and if combining studies is appropriate, we will use RevMan 5.3 to perform meta-analyses (RevMan 2014). We will pool data from RCTs using a fixed-effect model, except when heterogeneity is found. We will pool dichotomous data using the RR measure. We will pool continuous data using the SMD measure, if more than one instrument is used to measure the same outcome.

We will consider the psychometric properties of outcome instruments with regard to their suitability for pooling. For meta-analyses on the primary outcome (tinnitus symptom severity), whenever studies report outcomes measured using more than one instrument, we will include data only when those instruments are known to measure the same underlying construct of tinnitus symptom severity (high convergent validity) and show a similar direction of treatment-related effect. We will take the same approach for the secondary outcomes.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, we will carry out subgroup analyses to explore potential effect modifiers. This will be restricted to a very small number of subgroups. If considerable heterogeneity is identified then we will also use these subgroup analyses to explore sources of statistical heterogeneity. The planned subgroups are defined by:

- age (children < 18 years and adults ≥ 18 years);
- duration of tinnitus (acute ≤ 3 months and chronic > 3 months);
- dose of Ginkgo biloba administered;
- additional interventions (Ginkgo biloba with and without an additional intervention);
- standardised Ginkgo biloba extracts (i.e. EGb 761) versus non-standardised food supplement.

Sensitivity analysis

We will conduct a sensitivity analysis by excluding those studies with a high risk of bias, thereby checking the robustness of the conclusion from the studies included in the meta-analysis. In addition, we will use sensitivity analyses for studies in which data were imputed.

Summary of findings and assessment of the certainty of the evidence

Three independent authors (MS, PS and JX) will use the GRADE approach to rate the overall quality of evidence using GRADEpro GDT (https://gradepro.org/). The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We will include a 'Summary of findings' table, constructed according to the recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2019), for the following comparison(s):

- Ginkgo biloba *versus* placebo;
- Ginkgo biloba *versus* no intervention;
- Ginkgo biloba *versus* education and information only.

We will include the following outcomes in the 'Summary of findings' table:

- tinnitus symptom severity;
- significant adverse effects (bleeding disorders, seizures);
- tinnitus loudness;
- tinnitus intrusiveness;
- depression;
- anxiety;
- health-related quality of life;
- other adverse effects (gastrointestinal upset, headache, allergic reaction).

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ADDITIONAL TABLES

Table 1. Examples of questionnaires measuring tinnitus symptom severity

Measurement instrument (author, year)	Number of items and subscales	Internal consistency (Cronbach's alpha for global score)
Tinnitus Functional Index (Meikle 2012)	25 items, 8 subscales	a = 0.97
Tinnitus Handicap Inventory (Newman 1996)	25 items, 3 subscales	a = 0.93
Tinnitus Handicap Questionnaire (Kuk 1990)	27 items, 3 subscales	a = 0.94

Table 1. Examples of questionnaires measuring tinnitus symptom severity *(Continued)*

Tinnitus Questionnaire (Hallam 1996)	52 items, 5 subscales	a = 0.94
Tinnitus Reaction Questionnaire (Wilson 1991)	26 items, 4 subscales	a = 0.96
Tinnitus Severity Scale (Sweetow 1990)	15 items	Not reported

APPENDICES

Appendix 1. Draft CENTRAL, MEDLINE and Embase search strategies

CENTRAL (CRS)	MEDLINE (Ovid)	Embase (Ovid)
1 MESH DESCRIPTOR Tinnitus EXPLODE ALL AND CENTRAL:TARGET 602 2 (zumbido or tinnit*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 2283 3 MESH DESCRIPTOR Ginkgo biloba EXPLODE ALL AND CENTRAL:TARGET 278 4 (Ginkgo* or Gingko* or Ginko* or Maidenhair):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET1127 5(Egb 761 or Egb761 or EGb-761 or GBE 761 or GBE761 or GBE-761):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 226 6 (GBE50 or EGB50):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 0 7 (rokan or tanakan or tebofortran or tebokan or tebonin or Kavari):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 51 8 (LI 1370 or LI1370 or LI-1370):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 19 9 (flavanoid* or terpenoid* or bioflavanoid*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 50 10 (gingkco* or gingho* or ginosan* or bilobalid* or tanakene or supergin*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET12 11 (biloba):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 965 12 (Eun-haeng* OR Fossil Tree* OR Ginkyo* OR Icho* OR Ityo* OR Japanese Apricot* OR Kew Tree* OR Salisburia* OR Silver Apricot* OR Pterophyllus salisburiensis OR Yinxingye* OR Prunus Ume OR Prunus mume):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 54 13 #1 OR #2 AND CENTRAL:TARGET 2283 14 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 AND CENTRAL:TARGET 1251 15 #13 AND #14 AND CENTRAL:TARGET 86	1 exp Tinnitus/ 7718 2 (tinnit* or zumbido).ti,ab. 10914 3 1 or 2 12584 4 exp Ginkgo biloba/ 2762 5 (Ginkgo* or Gingko* or Ginko* or Maidenhair).ab,ti. 4727 6 (Egb 761 or Egb761 or EGb-761 or GBE 761 or GBE761 or GBE-761).ab,ti. 809 7 (GBE50 or EGB50).ab,ti. 23 8 (rokan or tanakan or tebofortran or tebokan or tebonin or Kavari).ab,ti. 121 9 (LI 1370 or LI1370 or LI-1370).ab,ti. 16 10 (flavanoid* or terpenoid* or bioflavanoid*).ab,ti. 6066 11 (gingkco* or gingho* or ginosan* or bilobalid* or tanakene or supergin*).ab,ti. 281 12 (ginkgo* or "LI 1370").nm. 2044 13 biloba.ab,ti. 3680 14 (Eun-haeng* or Fossil Tree* or Ginkyo* or Icho* or Ityo* or Japanese Apricot* or Kew Tree* or Salisburia* or Silver Apricot* or Pterophyllus salisburiensis or Yinxingye* or Prunus Ume or Prunus mume).ab,ti. 391 15 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 12030	1 exp tinnitus/ 19134 2 (tinnit* or zumbido).ab,ti. 13886 3 1 or 2 21495 4 exp Ginkgo biloba/ 4410 5 (Ginkgo* or Gingko* or Ginko* or Maidenhair).ab,ti. 6468 6 (Egb 761 or Egb761 or EGb-761 or GBE 761 or GBE761 or GBE-761).ab,ti. 1073 7 (GBE50 or EGB50).ab,ti. 36 8 (rokan or tanakan or tebofortran or tebokan or tebonin or Kavari).ab,ti. 132 9 (LI 1370 or LI1370 or LI-1370).ab,ti. 21 10 (flavanoid* or terpenoid* or bioflavanoid*).ab,ti. 9393 11 (gingkco* or gingho* or ginosan* or bilobalid* or tanakene or supergin*).ab,ti. 376 12 biloba.ab,ti. 4941 13 (Eun-haeng* or Fossil Tree* or Ginkyo* or Icho* or Ityo* or Japanese Apricot* or Kew Tree* or Salisburia* or Silver Apricot* or Pterophyllus salisburiensis or Yinxingye* or Prunus Ume or Prunus mume).ab,ti. 509 14 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 18313 15 3 and 14 231

(Continued)

16 3 and 15 108

CONTRIBUTIONS OF AUTHORS

MS and DJH conceived and all authors contributed to the design of the study. MS drafted the protocol. All authors critically revised the protocol for important intellectual content.

Planned author contributions to the full review:

- The Cochrane ENT Information Specialist will develop and run the search strategy.
- MS will obtain copies of studies with the assistance of the University of Nottingham library.
- MS, MH, AER, DJH will be responsible for selection of studies.
- MS, MH, AER, DJH, JX will be responsible for data extraction.
- MS, MH, AER, DJH, JX will be responsible for assessing risk of bias.
- MS will enter data into RevMan.
- MS, PS, JX will conduct the analysis.
- MS, PS, JX will interpret the analysis.
- MS, PS, JX will draft the final review.
- MS and DJH will be responsible for updating the review.

DECLARATIONS OF INTEREST

Magdalena Sereda: MS is funded through the British Tinnitus Association Senior Research Fellow/Head of Research Fellowship. MS is a member of the Steering Committee for the British Society of Audiology Tinnitus and Hyperacusis Special Interest Group. She has received tinnitus research funding from the British Society of Audiology and the NIHR.

Jun Xia: none known.

Polly Scutt: none known.

Malcolm Hilton: none known.

Amr El Refaie: none known.

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