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File: ■ Ginkgo (*Ginkgo biloba*)
■ Tinnitus
■ Ringing in the Ear

HC 051352-480

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RE: Ginkgo Extracts Show Mixed Results for the Treatment of Primary Tinnitus and Show Promise for the Treatment of Tinnitus from Cerebral Insufficiency and Especially in Vascular Dementia

Hilton MP, Zimmermann EF, Hunt WT. *Ginkgo biloba* for tinnitus. *Cochrane Database Syst Rev.* March 2013;3:CD003852. doi: 10.1002/14651858.CD003852.pub3.

Tinnitus, also called ringing in the ears, is the perception of sound when there is no external sound. Ringing, humming, hissing, crackling, and other sounds can occur continuously or only intermittently. Some people describe their tinnitus as mildly annoying, but others describe their tinnitus as severe and debilitating. Tinnitus can be caused by many disorders of the ear or auditory nerve, but it also occurs with no known cause. Tinnitus treatment includes drugs, cognitive behavior therapy, masking (use of white noise generators), and complementary medicine therapies, but treatment is not effective for everyone. Ginkgo (*Ginkgo biloba*) has been used medicinally for several thousand years. Ginkgo leaf extracts are most commonly used to increase blood flow in circulatory disorders, such as peripheral vascular disease and cerebral insufficiency, and to improve memory and cognitive function in dementia. Some research suggests ginkgo may be helpful in reducing tinnitus. The authors conducted this systematic review of randomized, controlled trials to assess the effect of ginkgo in people with tinnitus.

The following databases were searched through March 2012: the Cochrane Ear, Nose, and Throat Disorder Group Trials Register; the Cochrane Central Register of Controlled Trials; PubMed; EMBASE; AMED; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; ISRCTN; ClinicalTrials.gov; ICTRP; and Google Scholar. Reference lists from published studies and abstracts from conference proceedings were also searched to identify additional trials. Randomized, controlled trials were included if patients were ≥ 18 years of age and if the primary complaint was either tinnitus or another condition in which tinnitus was measured. Trials were excluded if patients had tinnitus associated with conductive hearing loss or blood vessel abnormalities in the brain.

Only four trials that enrolled 1,543 patients met the criteria and were included in the analysis. Three trials enrolled patients (n = 1,143) with a primary complaint of tinnitus,

and one trial enrolled patients (n = 400) with a primary complaint of dementia, some of whom had tinnitus. In all four trials, the methodological quality was rated as high and the risk of bias was rated as low by the authors.

One trial was a double-blind, randomized, placebo-controlled trial of patients with stable tinnitus (n = 978). Patients were given either placebo or 150 mg of the ginkgo extract LI 1370 (Lichtwer Pharma; Berlin, Germany) daily for 12 weeks. No significant differences were found between the ginkgo and placebo groups for loudness, awareness, or impact of tinnitus. Several shortcomings of this study were not discussed by the reviewers. The patients were interviewed by mailed questionnaires; they did not see a physician nor did they undergo otological examinations; some patients were not included in the analysis for unclear reasons; and the sample size was too small for the type of matched-pair analysis to have sufficient statistical power.

Another trial was a double-blind, randomized, placebo-controlled trial of patients with tinnitus (n = 99). Patients were given either placebo or 120 mg of the ginkgo extract EGb 761® (Dr. Willmar Schwabe GmbH & Co. KG; Karlsruhe, Germany) daily for 12 weeks. According to the original paper, there was a statistically significant improvement in the loudness of tinnitus in the ginkgo group compared to the placebo group. It remains unclear why the reviewers refer to this as nonsignificant. No significant differences were found for the patients' rating of tinnitus intensity or effectiveness of treatment between the ginkgo and placebo groups.

The third trial was a double-blind, randomized, placebo-controlled trial of patients with tinnitus (n = 66). Patients were given either placebo or 120 mg of ginkgo extract (source not identified) daily for 12 weeks. No significant differences were found in the ratings of tinnitus status or its improvement between the ginkgo and placebo groups. The purportedly high quality of this study may be questioned, because a considerable proportion of patients did not show up for the follow-up visit, mostly due to other illnesses, which may well have had an influence on subjective ratings of tinnitus.

The fourth trial was a double-blind, randomized, placebo-controlled trial of patients with mild-to-moderate Alzheimer's dementia (n = 218) or vascular dementia (n = 182). Patients were given either placebo or 240 mg of ginkgo extract (source not identified) daily for 22 weeks. Patients self-rated the presence and severity of tinnitus. After 22 weeks, dementia patients reported significantly greater improvement with ginkgo than with placebo ($P < 0.01$). The improvement in those with vascular dementia was twice that of those with Alzheimer's dementia.

In all four trials, the reporting of adverse side effects was similar for the ginkgo and placebo groups. The most common adverse side effects reported by both groups were gastrointestinal upset, diarrhea, and headache.

The authors conclude that, "The limited evidence from the included studies does not demonstrate that *Ginkgo biloba* is effective for tinnitus when tinnitus is the primary complaint." However, they did not take into account that different ginkgo extracts are composed differently and are therefore different active substances that are not necessarily comparable with respect to efficacy and safety. Therefore, a meta-analysis across different ginkgo extracts cannot unequivocally ascertain efficacy. Efficacy and safety should be demonstrated for each single extract separately. Patients with dementia reported a small improvement in tinnitus after taking ginkgo; the daily dose and duration

were both almost twice as great in that trial. The authors express the opinion that although this improvement was statistically significant, it is unlikely to be clinically significant, but do not give reasons for this. They noted that improvement in tinnitus in those with cerebral insufficiency was supported by results from a majority of studies that examined this condition but were excluded from the review due to inadequate methodological quality. They suggest the following two possible explanations for the improvement in people with cerebral insufficiency and lack of improvement in people with primary tinnitus: (1) the etiology of tinnitus is fundamentally different in people with cognitive insufficiency, possibly from central vascular insufficiency or neural metabolic disorders, and (2) ginkgo improves cognitive function in patients with dementia, which in turn improves habituation to tinnitus. They suggest that subsequent studies should carefully define patient populations and utilize validated questionnaires before, during, and after treatment.

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to reprint the original article.