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REVIEW

Ginkgo biloba extract in the treatment of tinnitus: a systematic review

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Alexander von Boetticher

Ear, Nose and Throat Surgery, Lueneburg, Germany

Abstract: Tinnitus is a symptom frequently encountered by ear, nose, and throat practitioners. A causal treatment is rarely possible, and drug and nondrug treatment options are limited. One of the frequently prescribed treatments is *Ginkgo biloba* extract. Therefore, randomized, placebo-controlled clinical trials of *Ginkgo biloba* extract preparations were searched for and reviewed systematically. There is evidence of efficacy for the standardized extract, EGb 761® (Dr Willmar Schwabe GmbH & Co KG Pharmaceuticals, Karlsruhe, Germany), in the treatment of tinnitus from three trials in patients in whom tinnitus was the primary complaint. Supportive evidence comes from a further five trials in patients with age-associated cognitive impairment or dementia in whom tinnitus was present as a concomitant symptom. As yet, the efficacy of other ginkgo preparations has not been proven, which does not necessarily indicate ineffectiveness, but may be due to flawed clinical trials. In conclusion, EGb 761®, a standardized *Ginkgo biloba* extract, is an evidence-based treatment option in tinnitus.

Keywords: tinnitus, *Ginkgo biloba*, EGb 761®, systematic review

Introduction

In an ear, nose, and throat office, one is confronted every day with patients suffering from tinnitus. The prevalence of tinnitus in adults is between 10% and 15%.[1] According to the 1999–2004 National Health and Nutrition Examination Surveys, 50 million people in the US suffer from this condition.[1] A British study involving 48,313 subjects reported a 10.1% prevalence of tinnitus in the adult population,[2] which increases with age.[3] Tinnitus has been found to affect more men than women.[4] Approximately 25% of patients with tinnitus report an increase in severity over time.[5] The 2010 Australian Blue Mountains Hearing Study with over 2000 individuals observed over 5 years that nearly one in five older adults suffered from tinnitus.[6]

Classification and characteristics

The patients showing up in the ear, nose, and throat office suffer from various degrees of tinnitus. Subjective tinnitus is the perception of sound in the absence of external acoustic stimulation. In contrast, objective tinnitus is where an external source, such as blood streaming phenomena or muscular cramps inside the middle ear, can be identified. Subjective tinnitus is detectable only by the patient and can often be described as crackling, ringing, or whistling. It can be continuous or intermittent, and the onset may be acute with or without hearing loss.[4] Full or partial spontaneous remission is possible, but tinnitus often becomes a chronic condition.[7] Tinnitus may have a considerable impact on mood, and cause depression, anger, and anxiety, which in turn may enhance

Correspondence: Alexander von Boetticher
Ear, Nose and Throat Surgery, Willy-Brandt-Str 2, 21335 Lueneburg, Germany
Tel +49 4131 47178
Fax +49 4131 404891
Email alexander@boetticher.net

attention to tinnitus.[8] The hearing sensation can be very annoying, so that the patient suffers from a compromised ability to concentrate and relax. This situation is considered a decompensated, pathological chronic tinnitus. A compensated chronic tinnitus is described as a hearing sensation without any disturbing quality.[9]

Etiology

Jastreboff and Hazell suggest a neurophysiological model for tinnitus,[10] ie, an abnormal processing of signals generated in the auditory nervous system, beginning at the sensory level of the cochlear hair cell to cochlear fibers and the nucleus in higher brain structures. In this model, tinnitus could be generated at different levels in the auditory processing system. Hyperactivity or damage to the cochlear hair cells resulting in senseless signals would be translated by the brain into a kind of phantom hearing sensation associated with hearing loss. Depending on the site of damage, the tinnitus is called peripheral, in contrast with central tinnitus originating from higher central nervous damage. Many environmental, iatrogenic, and genetic factors have been described as a potential cause of hearing impairment and tinnitus, the most relevant being acoustic trauma, chronic exposure to occupational or work-related noise, and drug-related impairment caused by loop diuretics, antibiotics, chemotherapeutics, and salicylates.[4] An overview of possible causes is provided in Table 1. However, in 10%–20% of patients no cause for tinnitus can be found, and this is commonly referred to as "idiopathic tinnitus".[11]

The pathological changes at the level of the inner ear hair cells include damage to the mitochondrial DNA or endothelial damage with dysfunction of microcirculation.[12,13] The underlying mechanism of ototoxicity varies with different drugs. According to Schacht, for example, aminoglycoside antibiotics can cause loss of cochlear outer hair cells secondary to damage from free radicals and accumulation of calcium and potassium ions.[14,15]

Treatment

Tinnitus is complex and multifactorial, and involves many etiological loci.[3] Until now, there has been no specific therapy for all the different kinds of tinnitus. Current schemes include the use of hearing aids, counseling, supportive therapy including tinnitus retraining therapy, and different medications such as vasodilators, corticosteroids, anticonvulsants, spasmolytic drugs, lidocaine, benzodiazepines, and *Gingko biloba* preparations.[4]

EGb 761® (Dr Willmar Schwabe GmbH & Co KG Pharmaceuticals, Karlsruhe, Germany) is a dry extract from *Ginkgo biloba* leaves (35-67:1), extraction solvent: acetone 60% (w/w). The extract is adjusted to 22.0–27.0% ginkgo flavonoids calculated as ginkgo flavone glycosides and 5.0–7.0% terpene lactones consisting of 2.8–3.4% ginkgolides A, B, C and 2.6–3.2% bilobalide and contains less than 5 ppm ginkgolic acids. It is known to enhance microperfusion by increasing red blood cell deformability and decreasing whole blood viscosity.[16,17] In a cat model, it specifically increased the blood flow in the cochlea.[18] Moreover, EGb 761® protects

Table 1 Causes of tinnitus (according to Lockwood)[4]

TYPE	CAUSES
Subjective tinnitus	
Otologic	Noise-induced hearing loss, presbycusis, otosclerosis, otitis, impacted cerumen, sudden deafness, Ménière's disease, and other causes of hearing loss
Neurologic	Head injury, whiplash, multiple sclerosis, vestibular schwannoma (commonly called an acoustic neuroma) or other cerebellar-pontine-angle tumors
Infectious	Otitis media and sequelae of Lyme disease, meningitis, syphilis, and other infectious or inflammatory processes that affect hearing
Drug-related	Common side effect of many drugs, such as salicylates, nonsteroidal antiinflammatory drugs, aminoglycoside antibiotics, loop diuretics, and chemotherapy agents (eg. platins and vincristine)
Other	Temporomandibular-joint dysfunction and other dental disorders
Objective Tinnitus	
Pulsatile	Carotid stenosis, arteriovenous malformations, other vascular anomalies, vascular tumors (eg., of the glomus jugulare), valvular heart disease (usually aortic stenosis), states of high cardiac output (anemia and drug-induced high output), and other conditions causing turbulent blood flow
Muscular or anatomical	Palatal myoclonus, spasm of stapedius or tensor tympani muscle, patulous eustachian tube
Spontaneous	Spontaneous otoacoustic emissions

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the mitochondria from oxidative stress and improves energy metabolism,[19,20] thus attenuating damage to cochlear cells subject to increased energy demand or decreased perfusion. In a rat model of salicylate-induced tinnitus, Jastreboff et al demonstrated that EGb 761® treatment resulted in a significant decrease in the behavioral manifestations of tinnitus.[21] Cisplatin-induced hair cell loss in rats, as well as subsequent alterations of endocochlear potentials and auditory brain stem responses, could be prevented by EGb 761®.[22]

Randomized controlled trials of a variety of *Ginkgo biloba* extracts in the treatment of tinnitus have shown different results, and reviews published during recent years have arrived at different conclusions. The objective of this review was to assess the methodological quality of available randomized controlled trials of *Ginkgo biloba* extract in tinnitus, and to provide a synopsis of the evidence of efficacy for each specific extract. The results will be discussed in the context of former reviews, the scientific soundness of which will be evaluated.

Methods

Randomized, placebo-controlled, double-blind trials that met the following criteria were eligible for inclusion in this review:

- Use of an identifiable, standardized *Ginkgo biloba* extract, the composition of which is described adequately
- Dosing and duration of treatment appropriate for type of tinnitus
- Enrollment of inpatients or outpatients suffering from tinnitus as the primary or concomitant complaint
- No major methodological shortcomings or bias
- Publication in English, French, German, Spanish, or Italian language.

Trials of interest were identified by searching the PubMed database (from the beginning up to October 2010) using the search terms "Ginkgo" and "tinnitus", by hand searching references listed in such identified reviews and trial reports, and by requesting information on randomized controlled trials of any *Ginkgo* product on tinnitus from a manufacturer.

Characteristics of included and excluded studies are described in tabular format and reasons for exclusion of studies are provided. An overview of details and results of included studies is depicted in tabular format and summarized in a descriptive manner.

Results

The PubMed search yielded 57 hits, of which 46 could be ruled out as irrelevant by title and abstract. The search identified seven review articles dealing to a substantial degree with *Ginkgo* and tinnitus and four randomized controlled trials of *Ginkgo* extract and tinnitus. Another randomized, placebo-controlled trial of the special extract, EGb 761®, in tinnitus was identified from the references given in one of the review articles and five randomized, placebo-controlled trials of EGb 761® in dementia or age-related cognitive impairment (including one for which publication was pending) were identified by the manufacturer contacted.

Three studies of patients with tinnitus as a primary complaint fulfilled the inclusion criteria and were included in the review. Five studies on patients suffering from dementia or age-associated cognitive decline with tinnitus as a concomitant complaint met the inclusion criteria and were included in the review. Details are provided in Table 2. The standardized extract, EGb 761®, was used in all studies that fulfilled

Table 2 Characteristics of included trials

Reference	Patients	Diagnoses
Tinnitus as primary complaint		
Morgenstern and Biermann[23]	57 patients, median age approximately 46 years, 57% male	Chronic tinnitus, mean duration approximately 3 years
Morgenstern and Biermann[24]	99 patients, mean age 45.5 years	Chronic tinnitus, mean duration 4.5 years
Meyer[25]	100 patients, mean age 50.4 years, 52% male	Acute or subchronic tinnitus, mean duration 134 days
Tinnitus as concomitant complaint in dementia or aging-related cognitive impairment		
Ihl et al[26]	404 patients, mean age 65 years, 33% male	Mild to moderate dementia (Alzheimer's disease, vascular dementia or mixed form) associated with neuropsychiatric symptoms
Napryeyenko et al[27]	395 patients, mean age 64 years, 28% male	Mild to moderate dementia (Alzheimer's disease, vascular dementia or mixed form) associated with neuropsychiatric symptoms
Schneider et al*	72 patients, mean age 78 years, 47% male	Tinnitus associated with Alzheimer's disease
Halama et al[28]	40 patients, mean age 66 years	Mild to moderate cerebrovascular insufficiency
Eckmann and Schlag[29]	32 patients, aged 45–74 years, 60% male	Tinnitus associated with cerebrovascular insufficiency

Note: *Schneider LS, DeKosky ST, Farlow MR, Tariot PN, Hoerr R, Kieser M. Ginkgo biloba (EGb 761®) effects on mood and neurosensory symptoms (dizziness, tinnitus) in elderly, demented patients: secondary results of a randomized, placebo-controlled, double-blind trial [unpublished data].

all quality criteria set to determine eligibility for this review. Three randomized controlled trials were excluded from the review due to major shortcomings in study conduct and/or reporting.

In the open-label part of the trial reported by Holgers et al,[30] 80 patients with chronic tinnitus were treated with 29.2 mg per day of a Ginkgo product for two weeks. Treatment responders (20 patients) were then treated for two weeks each with 29.2 mg per day of the *Ginkgo* product and placebo in randomized order. The *Ginkgo* product was identifiable, but not described adequately. The daily dose of 29.2 mg seems rather low compared with the daily doses of 120–240 mg of the standardized extract EGb 761®. A treatment period of 2 weeks is too short for chronic tinnitus, which is associated with cortical reorganization. Hence, patients reporting subjective improvement after 2 week's treatment were most likely to be those experiencing the largest placebo effect. Selection of such patients for the placebo-controlled part of the trial does not seem appropriate from a methodological point of view. A crossover design is not state of the art for proof of efficacy because of the possibility of carryover effects.

In a randomized, double-blind, placebo-controlled trial reported by Drew and Davies,[31] 1243 patients with chronic tinnitus were enrolled and treated with LI 1370 150 mg per day or placebo for 12 weeks. This study did not meet minimal standards of Good Clinical Practice. No personal contact between physicians and patients was required; as a consequence, the actual existence and identity of the patients could not be verified, nor was any medical or audiological examination performed. Of 1426 patients who were not excluded from the study, 183 were not selected and 122 were withdrawn without reasons being given. Although patients were paired and then allocated treatment codes, 155 patients who received study medication were unpaired at the end of the study, and only 363 pairs (726 patients) were accounted for in the primary analysis.

Rejali et al[32] reported a randomized, placebo-controlled, double-blind trial involving 66 outpatients with tinnitus who were treated with 120 mg per day of a *Ginkgo* preparation or placebo for 12 weeks. Neither the type of *Ginkgo* preparation used is described nor is any information provided about composition or standardization. After 12 weeks' treatment, 51% of patients treated with placebo and 21% of those treated with *Ginkgo* were unable to attend the final visit. Concomitant illness was the reason for this in 27% and 12% of placebo-treated and *Ginkgo*-treated patients, respectively. There is reason to assume that concomitant illness, which was severe enough to prevent patients from clinic visits, interfered with the subjective self-assessment of tinnitus handicap and health status.

All eight randomized, placebo-controlled trials of the standardized *Ginkgo biloba* extract EGb 761® showed statistically significant superiority of the active treatment over placebo. This holds for change in tinnitus volume/intensity (assessed and significant in three studies) as well as for overall severity (assessed in six, significant in five studies). Hence, there is evidence of efficacy for this specific preparation in patients with tinnitus as a single or major complaint, as well as in subjects suffering from tinnitus associated with dementia or aging-related cognitive impairment. Details of individual studies and outcomes are provided in Table 3.

Discussion

In all identified and retrieved studies using the standardized *Ginkgo biloba* extract, EGb 761®, this specific preparation was found to be superior to placebo in the treatment of tinnitus. None of the identified studies using other *Ginkgo* products found a difference from placebo. However, considering the methodological flaws of these studies, it would be imprudent to conclude that all these products are ineffective.

Several reviews addressing the efficacy of *Ginkgo biloba* have been published in recent years. Smith et al uncritically lumped together studies of different *Ginkgo biloba* preparations irrespective of their quality and dosage.[33] They did not address the serious problems of the study by Drew and Davies,[31] and concluded that there is no proven support for the efficacy of *Ginkgo biloba* treatment. They may have relied on publication in a peer-reviewed journal as proof of quality rather than going into the detection of flaws in the different publications. In a meta-analysis of trials of *Ginkgo biloba* in the treatment of tinnitus, Rejali et al also pooled studies using various *Ginkgo* products of different and partly unknown quality.[32] Their conclusion was that *Ginkgo biloba* does not benefit patients with tinnitus. Similarly, Hilton and Stewart included three clinical trials with three different products in their Cochrane Review.[34] Although they contend that they applied rigorous methodological criteria for study selection, they accepted two seriously flawed trials. They concluded that there was no statistical proof of an effective tinnitus treatment with *Gingko*. On the contrary, Holstein, who only included studies with *Gingko biloba* extract EGb 761® in his review, found evidence of efficacy for this standardized extract

Table 3 Results of included trials

Reference	Treatment (orally unless stated otherwise)	Type of analysis, results (means ± SD or 95% CI unless stated otherwise)
Morgenstern and Biermann[23]	Part I: EGb 761®: 57 patients, 200 mg/d IV 10 days Part II: EGb 761®: 30 patients, 160 mg/day; placebo: 27 patients; 12 weeks	ITT-LOCF Part I: Tinnitus volume decreased by approximately 8 dB on average Part II: (changes after end of part I) **Change in tinnitus volume week 12: EGb 761® –3.5 ± 17.8 dB,** **Plc –1.9 ± 17.3 dB, $P < 0.05$** **Change in tinnitus volume week 8: EGb 761® –3.0 ± 17.6 dB,** **Plc –1.3 ± 16.2 dB, $P < 0.05$** **Change in tinnitus volume week 4: EGb 761® –5.8 ± 13.0 dB,** **Plc 0.0 ± 17.7 dB, $P < 0.05$** Hearing loss at 3.0 kHz: EGb 761® –0.5 ± 7.1 dB, Plc +3.7 ± 7.7 dB, $P < 0.05$ Hearing loss at 4.0 kHz: EGb 761® –4.8 ± 11.4 dB, Plc +4.3 ± 9.8 dB, $P < 0.01$ Hearing loss at 6.0 kHz: EGb 761® –1.8 ± 13.8 dB, Plc +1.7 ± 6.4 dB, ns Hearing loss at 8.0 kHz: EGb 761® –2.2 ± 12.0 dB, Plc +1.7 ± 3.9 dB, ns (negative change in hearing loss means improvement) Rates of patients with self-assessed intensity of permanent tinnitus as annoying or very annoying: EGb 761® 59% at baseline, 37.9% at week 12; Plc 43.4% at baseline, 47.8% at week 12
Morgenstern and Biermann[24]	EGb 761®: 49 patients, 120 mg/day; placebo: 50 patients; 12 weeks	ITT-LOCF **Change in tinnitus volume in the more severely affected ear (baseline/week 12):** **EGb 761® from 42.2 (36.6, 48.1) to 39.0 (31.9, 46.1),** **Plc from 44.3 (39.2, 49.4) to 45.1 (39.1, 51.2),** **$P = 0.015$** Patients' global impression of change: EGb 761® 31% improved, Plc 14% improved No significant differences between treatment groups regarding tinnitus volume in the less severely affected ear, subjective rating of tinnitus intensity and hearing loss.
Meyer[25]	EGb 761®: 55 patients, 160 mg/day; placebo: 45 patients 3 months	Type of analysis not specified Global rating of change: EGb 761® 40% much improved, Plc 24% much improved, $P = 0.05$ Duration until disappearance or significant improvement in 50% of patients: EGb 761® 70 days, Plc 119 days (medians), $P = 0.03$ Change in tinnitus intensity (scale 0–3): EGb 761® –1.0, Plc –0.67, $P = 0.03$ Change in nuisance (scale 0–3): EGb 761® –0.84, Plc –0.59, $P = 0.08$
Ihl et al[26]	EGb 761®: 202 patients, 240 mg/day; placebo: 202 patients; 24 weeks	ITT-LOCF 11-point box scale* for tinnitus: EGb 761®: –0.5 (–0.6, –0.3), Plc: –0.1 (–0.2, 0.0), $P < 0.001$
Napryeyenko et al[27]	EGb 761®: 198 patients, 240 mg/day; placebo: 197 patients; 22 weeks	ITT-LOCF 11-point box scale for tinnitus: EGb 761®: –1.1 ± 1.6 Plc: –0.0 ± 0.9 $P = 0.003$
Schneider et al**	EGb 761® high dose: 19 patients, 240 mg/day; EGb 761® low dose: 29 patients, 120 mg/day; placebo: 24 patients; 26 weeks	ITT-LOCF 11-point box scale for tinnitus: EGb 761® high dose: –2.1 ± 2.1, $P = 0.003$ vs Plc EGb 761® low dose: –1.1 ± 2.1, $P = 0.09$ vs Plc Plc: –0.2 ± 1.7

(*Continued*)

Table 3 (Continued)

Reference	Treatment (orally unless stated otherwise)	Type of analysis, results (means ± SD or 95% CI unless stated otherwise)
Halama et al[28]	EGb 761®: 20 patients, 120 mg/day; placebo: 20 patients; 12 weeks	Type of analysis not specified Severity rating tinnitus (scale 0–3): EGb 761® from 1.05 ± 1.05 to 0.45 ± 0.83, Plc from 1.25 ± 0.91 to 1.10 ± 0.97, $P = 0.035$
Eckmann and Schlag[29]	EGb 761®: 12 patients, 120 mg/day; placebo: 20 patients; 30 days	Type of analysis not specified Tinnitus disappeared: EGb 761® 100%, Plc 50%, $P < 0.005$

Notes: *Consisting of 11 boxes numbered 0 to 10, with 0 representing no tinnitus and 10 representing extremely severe tinnitus. **Schneider LS, DeKosky ST, Farlow MR, Tariot PN, Hoerr R, Kieser M. Ginkgo biloba (EGb 761®) effects on mood and neurosensory symptoms (dizziness, tinnitus) in elderly, demented patients: secondary results of a randomized, placebo-controlled, double-blind trial [unpublished data]. Bold print = primary outcome measure, if defined.
Abbreviations: CI, confidence interval; SD, standard deviation; IV, intravenous; ITT-LOCF, intention-to-treat, last value carried forward; Plc, placebo; ns, not significant.

from randomized, placebo-controlled trials, supported by findings from reference-controlled and uncontrolled trials in a more true-to-life setting.[35]

The efficacy of a plant extract depends on its composition, which is determined by the extraction process, the bioavailability of its active compounds, which depends on the composition and the galenical formulation, and its dosage. Products made from the same plant species by different production processes cannot be assumed to be bioequivalent. Therefore, it is not possible to generalize findings from studies of one specific extract to other products. Hence, lumping together studies of different Ginkgo products and trying to draw an overall conclusion about the efficacy of all of these products is not reasonable and is also contradictory to the principles of evidence-based medicine ("… the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients").[36] The question is not whether any treatment may benefit the individual patient but which treatment is most appropriate.

There are studies of various *Gingko* preparations which have shown no effect but these were of poor methodological quality. However, the currently available literature shows that there is evidence for the successful treatment of tinnitus with the *Ginkgo biloba* extract, EGb 761®. Of note, all trials using this extract consistently demonstrate its superiority over placebo. The average treatment effects may be limited in magnitude and not all patients seem to respond to the drug, yet, given the annoying and often disabling nature of tinnitus, even moderate improvements may have a considerable impact on patient quality of life. It is the ear, nose, and throat specialist's responsibility to offer patients counseling, supportive care, and the best alternatives in treatments available for each individual patient. Considering the limited data from methodologically sound, well controlled trials of other therapeutic options, the robust and consistent data available for tinnitus treatment with EGb 761® should be appreciated.

Disclosure

The author reports no conflicts of interest in this work.

References

1. Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among U S adults. *Am J Med*. 2010;123(8):711–718.
2. Davis A, Rafaie EA. Epidemiology of tinnitus. In: Tyler RS, editor. *Tinnitus Handbook*. San Diego, CA: Singular; 2000.
3. Ahmad N, Seidman M. Tinnitus in the older adult: epidemiology, pathophysiology and treatment options. *Drugs Aging*. 2004;21(5): 297–305.
4. Lockwood AH, Salvi RJ, Burkard RF. Tinnitus. *N Engl J Med*. 2002; 347(12):904–910.
5. Stouffer JL, Tyler RS. Characterization of tinnitus by tinnitus patients. *J Speech Hear Disord*. 1990;55(3):439–453.
6. Gopinath B, McMahon CM, Rochtchina E, Karpa MJ, Mitchell P. Incidence, persistence, and progression of tinnitus symptoms in older adults: the blue mountains hearing study. *Ear Hear*. 2010;31(3): 407–412.
7. Eggermont JJ, Roberts LE. The neuroscience of tinnitus. *Trends Neurosci*. 2004;27(11):676–682.
8. Hallam RS, Jakes SC, Hinchcliffe R. Cognitive variables in tinnitus annoyance. *Br J Clin Psychol*. 1988;27(Pt 3):213–222.
9. Mazurek B, Olze H, Haupt H, Szczepek AJ. The more the worse: the grade of noise-induced hearing loss associates with the severity of tinnitus. *Int J Environ Res Public Health*. 2010;7(8):3071–3079.
10. Jastreboff PJ, Hazell JW. A neurophysiological approach to tinnitus: clinical implications. *Br J Audiol*. 1993;27(1):7–17.
11. Goebel G, Buettner U. Basics of tinnitus: diagnostics and therapy. *Psychoneuro*. 2004;30(6):322–329. [German].
12. Yamasoba T, Someya S, Yamada C, Weindruch R, Prolla TA, Tanokura M. Role of mitochondrial dysfunction and mitochondrial DNA mutations in age-related hearing loss. *Hear Res*. 2007;226(1–2):185–193.
13. Neri S, Signorelli S, Pulvirenti D, et al. Oxidative stress, nitric oxide, endothelial dysfunction and tinnitus. *Free Radic Res*. 2006;40(6): 615–618.

14. Schacht J. Amino glycoside ototoxicity: prevention in sight? *Otolaryngol Head Neck Surg*. 1998;118(5):674–677.
15. Yamashita D, Jiang HY, Schacht J, Miller JM. Delayed production of free radicals following noise exposure. *Brain Res*. 2004;1019(1–2): 201–209.
16. Költringer P, Langsteger W, Eber O. Dose-dependent hemorheological effects and microcirculatory modifications following intravenous administration of *Ginkgo biloba* special extract EGb 761®. *Clin Hemorheol*. 1995;15(4):649–656.
17. Erdinçler DS, Karakoç Y, Toplan S, et al. The effect of *Ginkgo biloba* glycoside on the blood viscosity and erythrocyte deformability. *Clin Hemorheol*. 1996;16(3):271–276.
18. Maass B, Silberzahn J, Simon R. On the effect of *Ginkgo biloba* extract (Tebonin) on the hydrogen clearance at the cochlea basis under hypotensive ischemia *Extracta Otorhinolanryngol*. 1987;9(5):169–172. [German].
19. Sastre J, Millán A, García J, et al. A *Ginkgo biloba* extract (EGb 761®) prevents mitochondrial aging by protecting against oxidative stress. *Free Radic Biol Med*. 1998;24(2):298–304.
20. Eckert A, Keil U, Scherping I, Hauptmann S, Müller WE. Stabilization of mitochondrial membrane potential and improvement of neuronal energy metabolism by *Ginkgo biloba* extract EGb 761®. *Ann N Y Acad Sci*. 2005;1056:474–485.
21. Jastreboff PJ, Zhou S, Jastreboff MM, Kwapisz U, Gryczynska U. Attenutation of salicylate-induced tinnitus by *Ginkgo biloba* extract in rats. *Audiol Neurootol*. 1997;2(4):197–212.
22. Huang X, Whitworth CA, Rybak LP. *Ginkgo biloba* extract (EGb 761) protects against cisplatin-induced ototoxicity in rats. *Otol Neurotol*. 2007;28(6):828–833.
23. Morgenstern C, Biermann E. The efficacy of Ginkgo special extract EGb 761® in patients with tinnitus. *Int J Clin Pharmacol Ther*. 2002;40(5):188–197.
24. Morgenstern C, Biermann E. Long term therapy of tinnitus with *Ginkgo biloba* extract EGb 761®. *Fortschr Med Orig*. 1997;115(4):57–58. German.
25. Meyer B. A multicentre, randomized, double-blind drug versus placebo study of *Ginkgo biloba* extract in the tratment of tinnitus. *Presse Med*. 1986;15(31):1562–1564. French.
26. Ihl R, Bachinskaya N, Korczyn AD, et al. Efficacy and safety of a once-daily formulation of *Ginkgo biloba* extract EGb 761® in dementia with neuropsychiatric features. A randomized controlled trial. *Int J Geriatr Psychiatry*. 2010 Dec 7.
27. Napryeyenko O, Borzenko I; for the GINDEM-NP Study Group. *Ginkgo biloba* special extract in dementia with neuropsychiatric features. A randomized, placebo-controlled, double-blind clinical trial. *Arzneimittelforschung*. 2007;57(1):4–11.
28. Halama P, Bartsch G, Meng G. Cerebrovascular insufficiency. A placebo-controlled randomized double-blind trial on the effect of *Ginkgo biloba* extract. *Fortschr Med*. 1988;106(19):408–412. German.
29. Eckmann F, Schlag H. Double-blind controlled study on the effectiveness of Tebonin® forte in patients with cerebrovascular insufficiency. *Fortschr Med*. 1982;100(31/32):1474–1478. German.
30. Holgers KM, Axelsson A, Pringle I. *Ginkgo biloba* extract for the treatment of tinnitus. *Audiology*. 1994;33(2):85–92.
31. Drew S, Davies E. Effectiveness of *Ginkgo biloba* in treating tinnitus: double blind, placebo controlled trial. *BMJ*. 2001;322(7278):1–6.
32. Rejali D, Sivakumar A, Balaji N. *Ginkgo biloba* does not benefit patients with tinnitus: a randomized placebo-controlled double-blind trial and meta-analysis of randomized trials. *Clin Otolaryngol Allied Sci*. 2004;39(3):226–231.
33. Smith PF, Zheng Y, Darlington CL. *Ginkgo biloba* extracts for tinnitus: more hype than hope? *J Ethnopharmacol*. 2005;100(1–2):95–99.
34. Hilton MP, Stuart EL. *Ginkgo biloba* for tinnitus. *Cochrane Database Syst Rev*. 2004;2:CD003852.
35. Holstein N. *Ginkgo biloba* special extract EGb 761® in the treatment of tinnitus. An overview of the results of clinical trials. *Fortschr Med Orig*. 2000;118(4):157–164. German.
36. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996; 312(7023):71–72.