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Standardized Ginkgo Biloba Extract in the Treatment of Vertigo and/or Tinnitus: A Review of the Literature

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Abstract

Standardized *Ginkgo biloba* extract (GBE) is an established herbal treatment used for a variety of indications, including vertigo and/or tinnitus. The evidence base in human clinical studies for a clear benefit of GBE in vertigo and/or tinnitus is limited and contradictory due to poor reporting as well as variations in study quality and outcome measures used. The aim of this review is to identify and discuss the rationale for using GBE in the treatment of vertigo and/or tinnitus based on the known pleiotropic actions of GBE and the pathophysiology of vertigo and/or tinnitus. The rationale will be substantiated by a review of the literature in order to identify and evaluate clinical trials investigating the efficacy of GBE in individuals with vertigo and/or tinnitus. The review identified randomized controlled trials (RCTs) investigating the effectiveness of GBE in vertigo and/or tinnitus published in PubMed up to 1st January 2020. In total, 17 RCTs were included 8 of the 9 studies investigating tinnitus and/or vertigo/dizziness found improvements, and 6 of 8 included studies investigating solely tinnitus showed positive effects. Based on the known mechanisms of action of GBE as well as evidence from animal models and human clinical trials identified in this review, GBE is a rational alternative treatment that might provide benefits to individuals with vertigo and/or tinnitus. However, further well-defined RCTs in patients with defined pathological entities are necessary to further substantiate the beneficial effects of GBE for vertigo and/or tinnitus.

Keywords

Ginkgo Biloba, Vertigo, Tinnitus, Dizziness

1. Introduction

Maintaining balance and orientation depend on input from the visual and proprioceptive systems, the inner ear, and integration in the brainstem vestibular nuclei and the cerebellum [1]. Dysfunction of any of these systems can cause disorders of balance and the sense of orientation, often leading to complaints of dizziness and/or vertigo [2].

Vertigo is the illusion of rotation, spinning, or swaying in the objects around or in the patients themselves [3]. Acute vertigo symptoms of the peripheral vestibular system are often associated with nausea, vomiting, sweating and pallor [4]. Many people with vertigo and/or dizziness complaints also experience emotional, memory, and self-perception problems, which are especially common in the elderly [2]. Vertigo and/or dizziness is a common complaint, with an estimated 1-year prevalence between 40% and 50% in adults [5] [6]. Vertigo can be tentatively classified as either vestibular or non-vestibular in origin. Dysfunction of the vestibular system (vestibular vertigo) accounts for about a quarter of dizziness complaints and has a 1-year prevalence of 5% and an annual incidence of 1.4% [7]. Despite the considerable personal and health care burden of dizziness and vertigo symptoms, a large percentage of the underlying disorders remain under diagnosed and, therefore, are probably insufficiently treated [8].

Tinnitus is the perception of sound in the ears or head without any external or internal acoustic stimulation, hence it is considered a symptom rather than a disease per se [9] [10]. If persistent and either intolerable or sufficiently bothersome, tinnitus and/or hearing loss can have a profound impact on quality of life (QoL), causing functional impairment in thought processing, emotions, hearing, sleep, and concentration [11] [12]. Tinnitus is typically classified as either subjective/sensorineural tinnitus, heard only by the affected person, or objective/somatic tinnitus [13]. Another possible distinction is acute versus chronic tinnitus; if persisting longer than a certain amount of time, conventionally between six and twelve months, it is usually regarded as "chronic", reflecting clinical experience that the phantom sound will persist [14]. Moreover, the etiology of tinnitus is often considered idiopathic, as 40% of patients report "no known events" associated with their tinnitus onset [9]. It is therefore a heterogeneous disorder with regard to its etiology, presenting symptoms, and perceptual characteristics [15]. Like vertigo, tinnitus is also a common problem in the general population, with prevalence estimates range from 4.6% to 30% [16]. The prevalence of tinnitus increases with age and the presence of hearing loss [17]. Using the Short Form Health Survey (SF-36), one study assessing QoL in 53 audiology patients reporting tinnitus showed that 43% also had impaired QoL, a high level of distress or both [18]. A U.S. cross-sectional analysis representative 12-month health survey evaluating 21.4 million American adults with tinnitus, reported that 27% experienced symptoms for more than 15 years and 36% had near-constant symptoms [16]. It is estimated that only about 50% of sufferers will discuss their tinnitus with a physician, and medications are recommended in less than half of these

cases [16]. Consequently, tinnitus also remains under diagnosed and insufficiently treated [16].

The ancient herbal extract from the leaves of the Chinese *Ginkgo biloba* tree, which contains about 250 different compounds involved in many different mechanisms, has shown beneficial effects in treatingneurodegenerative diseases like Alzheimer's, cardiovascular diseases, cancer, stress, memory loss, tinnitus, geriatric complaints like vertigo, age-related macular degeneration, and psychiatric disorders like anxiety disorder, adjustment disorder or schizophrenia [19] [20] [21] [22]. Most randomized controlled trials (RCTs) evaluating the effects of *Ginkgo biloba* to date have used the standardized dry leaf extract (GBE) EGb 761 and the similarly manufactured LI 1370. In accordance with regulatory requirements, the active components of both pharmaceutical-grade products contain 24% flavonoids, 6% triterpenes, and both GBEs are purified to contain less than 5 parts per million ginkgolic acids to avoid toxicity [23] [24] [25].

This review consists of two parts. In part one, we discuss the rationale for using GBE for the treatment of vertigo and/or dizziness and tinnitus based on the complex pathophysiology of these disorders as well as the known mechanism of actions of GBE. In part two, we examine the breadth of literature published to reveal the RCTs conducted in relation to the treatment of vertigo and tinnitus with GBE, with the aim of providing insights and guidance for physicians on where to focus their research.

2. Rationale for the Use of GBE in Vertigo and/or Dizziness and Tinnitus

2.1. Pathophysiology of Vertigo and/or Dizziness and Tinnitus

The major vestibular structures located in the inner ear include three semicircular ducts (lateral, anterior and posterior), and two otolith organs (saccule and utricle) [26]. The neuroepithelium of these peripheral vestibular organs are lined with hair cells that relay sensory impulses to the brainstem and the cerebellum [26]. Specific processingareas in the brainstem, cerebellum, and cerebral cortex integrate the sensory information from the peripheral vestibular organs, visual system, and proprioceptive system to allow for proper balance and orientation of the body in its environment [26]. Clear vision during head movements is maintained via an automated function called the vestibular ocular reflex (VOR) [1]. At the same time, the vestibular system controls posture via the vestibular spinal reflex (VSR) [1]. Vestibular dysfunction, arising from peripheral or central components of the vestibular system, may cause disorders of balance and the sense of orientation, often leading to vertigo and/or dizziness. Vestibular vertigo covers a broad range of specific vestibular disorders. The supraregional specialized outpatient clinic of the German Center for Vertigo and Balance Disorders at the Department of Neurology of München University, Germany diagnosed incidences of vertigo-related complaints in 34,860 patients (1998-2019) in the following percentiles: functional dizziness 17.3%, benign peripheral paroxysmal

positional vertigo (BPPV) 14.3%, central vestibular vertigo/dizziness 13.4%, vestibular migraine 12.3%, Menière's disease 10.1%, unilateral vestibulopathy 9.1%, bilateral vestibulopathy 6.7%, vestibular neuritis 8.2%, vestibular paroxysmia 3.2%, psychogenetic dizziness 2.9%, third mobile window syndromes 0.5%, other 8.6%, and vertigo syndromes of unclear origin 4.5% [27]. Due to vestibular compensation, symptoms of many peripheral vestibular disorders may resolve after approximately 6 to 12 weeks. This compensation process involves a number of different complex mechanisms of the brain stem and cerebellum, as well as cortical and spinal functions [4] [28]. However, symptomatic improvement is not analogous with recovery of vestibular function, and the vestibular functional loss is often irreversible [4].

Tinnitus is a symptom that may be associated with dizziness and/or vertigo [29]. In some cases, it is associated with sensorineural hearing loss as a result of damage to the auditory system (24% of tinnitus cases occur due to abnormalities within the inner ear and vestibulocochlear nerve, 35% originate due to abnormalities in the acoustic pathway), although it can also be associated with other factors, such as some head injuries, exposure to certain drugs, nerve damage or blood-flow problems (41% of cases originate within the supratentorial structures of the brain) [30]. The current consensus is that tinnitus is a disorder involving a distributed network of peripheral and central pathways in the nervous system. Though most cases are idiopathic, some tinnitus patients suffer with sensorineural tinnitus that might be caused by pathophysiological changes in either function or activity of the peripheral (*i.e.*, changes in auditory input at the level of the cochlea and auditory nerve) or central auditory nervous systems [13]. Mazurek *et al.* (2007) showed that intensive noise exposure or ototoxic drugs can be a factor in the development of tinnitus [31]. Indeed, pathologic changes in cochlear neurotransmission, e.g. destruction of the hair cells in the inner ear by noise-induced hearing loss (NIHL) has been identified as one of the most frequent causes of sensorineural tinnitus [13]. While damage to the inner and outer hair cells in the inner ear often recovers after acute noise exposure, auditory nerve fibers to the inner hair cells appear more vulnerable [32]. Newer research also suggests that synapses between hair cells and cochlear neurons may be affected, which could lead to "hidden hearing loss" that is not detectable with standard audiometric methods (e.g. Liberman, M.C.) [33]. Detectable damage to the auditory periphery by itself seems neither sufficient nor required to give rise to chronic tinnitus, indicating extra-auditory modulation of the auditory sensation [15]. In addition, several observations suggest that tinnitus has neural correlates in the brain, regardless of peripheral damage that might trigger it [15] [34]. For example, in many cases, tinnitus persists after the transection of auditory nerve VIII, which destroys cochlear input to the brain [15] [35]. A proposed neurophysiological model hypothesizes that peripheral changes in input (deafferentation) causes plastic changes to occur, resulting in altered patterns of brain activity due to anatomic changes in the connectivity of central nervous system

(CNS) neurons [36] [37]. Although the precise mechanism is unclear, several models are under discussion. The neurophysiological model postulates that tinnitus is associated with functional changes not only in the auditory cortex but also in non-auditory regions such as the limbic, frontal, and parietal areas [38]. The most recent model by Sedley *et al*. [39] is based on predictive coding, in which spontaneous activity in the subcortical auditory pathway constitutes a "tinnitus precursor" which is normally ignored as imprecise evidence against the prevailing percept of "silence". Extant models feature as contributory mechanisms acting to increase either the intensity of the precursor or its precision. If precision (*i.e.*, postsynaptic gain) rises sufficiently then tinnitus is perceived. Perpetuation arises through focused attention, which further increases the precision of the precursor, and resetting of the default prediction to expect tinnitus [39].

2.2. GBE Mechanism of Action

GBE has been shown to have neuroprotective effects, including improved energy supply by the mitochondria, antioxidative or radical capturing properties, and to improve cerebral perfusion (through reduction in blood viscosity) and glucose utilization [40]. Which mechanisms play the decisive role in the action of GBE in vertigo and vestibular compensation cannot be stated definitively. Depending on the pathogenetic background, both antioxidative properties and activation of cerebral metabolism may be possible as well as vigilance-enhancing and cognitive activation effects [41].

An influence of GBE on the vestibular system and vestibular compensation could be demonstrated in animal experiment models [42]-[47]. Vestibular compensation could be demonstrated morphologically by an increased new formation of synapses in the vestibular nuclei region of treated cats [44] and biochemically as an increase in protein synthesis in the region of the vestibular nuclei [47].

GBE has demonstrated several effects within the CNS that may enhance neuronal plasticity and neurotransmitter levels. For example, GBE effects have been reported, including, among others, protection of neuronal mitochondrial ATP synthesis in the presence of oxidative stress [48] [49], protection against oxidative damage in erythrocyte membranes [50], which consequently lowers blood viscosity and improves blood flow [51] [52] and neuroprotection through anti-apoptotic activity [53] [54] [55] [56] [57].

These effects of GBE have been well documented in both animal and human studies, and may treat tinnitus by preventing free-radical damage to the cochlea, or increasing blood flow and ultimately improving the health of the inner ear [58] [59] [60]. GBE provided a statistically significant decrease in behavioral manifestation of tinnitus induced by sodium salicylate toxicity in a rat model [61]. In 9 Mongolian gerbils (*Meriones unguiculatus*) that displayed behavioral signs of subjective tinnitus, three weeks of daily oral GBE led to improvement in all 9 animals, with 7 of them showing complete relief of tinnitus [62]. After dis-

continuation of GBE treatment, tinnitus related behavior reappeared in all but one animal while auditory thresholds remained restored [62]. The authors suggested that a global inhibitory mechanism was involved to counteract tinnitus. Tian *et al.* (2013) showed that GBE prevents cisplatin-induced hearing loss in rats and enhanced the antiatherogenic effects of cisplatin by inhibiting the generation of reactive oxygen species [63]. Tziridis *et al.* (2014) investigated the effectiveness of prophylactic treatment with GBE for NIHL and development of tinnitus after noise trauma in an animal model. Results suggested that significant neuroplastic effects of GBE had an effect on auditory processing at the peripheral and central level of the auditory pathway as measured with behavioral and electrophysiological approaches [64]. The authors of this study proposed two main effects of GBE: 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 [60] [64].

3. Methods

3.1. Identification of Relevant Studies

Relevant studies were identified by a systematic search in PubMed of the literature up to 1 January 2020. Studies were eligible for inclusion if they met predefined inclusion criteria: 1) employed a study design with no major methodological shortcomings or bias, e.g. RCT; 2) evaluated an identifiable, standardized GBE, the composition of which is adequately described; 3) treatment dosing and duration (≥12 weeks) were appropriate for the indication (tinnitus/vertigo); 4) enrollment of patients (inpatients or outpatients) suffering from vertigo of unknown etiology or not otherwise specified, or tinnitus as the primary or concomitant complaint; and 5) publication in English, French, German, Russian, Spanish, or Italian language. We excluded non-RCT designs (including cross-over designs), combination treatments, and non-human studies.

3.2. Search Strategy

RCTs of interest were identified by searching the PubMed database (up to 1 January 2020) using the search terms "Ginkgo" and "vertigo" or "tinnitus" in the title/abstract, and by requesting information on randomized controlled trials of any EGb 761 or LI 1370 GBE product on tinnitus or vertigo from a manufacturer. Reference lists of retrieved studies were searched by hand to ensure all potential RCTs were included. Initial screening was based on title and abstract reading. When there was uncertainty whether or not a record was relevant, the full text record was screened.

4. Results

4.1. Characteristics of Included Studies

Of the 67 citations retrieved, 17 research reports (4 for vertigo only, 5 for vertigo/dizziness and tinnitus, and 8 for tinnitus only) were found eligible and are

included in this review (Figure 1). The two GBEs, EGb 761 and LI 1370, are deemed analogous products, and equivalence can be assumed based on ESCOP-Monographs and the same amounts of the active ingredients flavonglycosides and terpenlactones [24] [65].

Characteristics of the included vertigo and/or tinnitus studies are shown in Table 1. The majority of included tinnitus and/or vertigo (6/9) and tinnitus only studies (5/8) have been published in the past two decades (*i.e.*, since 2000). The 17 articles range by year between 1986 and 2019. The mean age of patients included in all studies is approximately 60 years.

For included vertigo only studies, all 4 studies used subjective visual analogue scales (VAS) orvertigo symptom scale (VSS), and 2 used the Romberg test and other neuro-otologic and balance tests as the main outcome measures. For the 5 included vertigo/dizziness and tinnitus studies, change in 11-point box scales for the rating of presence and severity of dizziness and tinnitus from baseline was used as a secondary outcomes measure.

4.2. Efficacy of GBE in Vertigo

A RCT by Sokolova *et al.* (2014) showed that there was no statistically significant difference in vertigo treatment outcomes between GBE versus betahistine group, though GBE had a better tolerance profile [66].

Cesarani *et al.* (1998) reported that in the first month of therapy, vertigo and dizziness improved in patients treated with betahistinedihydrochloride and GBE to a similar extent [67]. Differences in side effects reported in a few patients

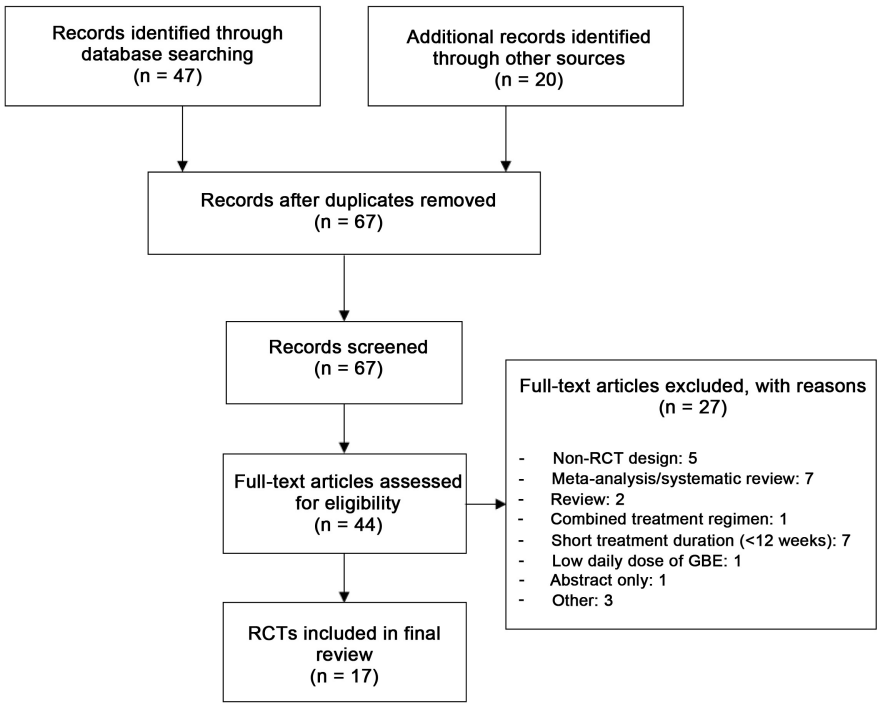

Figure 1. PRISMA flowchart of articles screened for inclusion [114]. RCT: randomized controlled trial; GBE: *Ginkgo biloba* special extract.

Table 1. Summary of RCTs for vertigo/dizziness and tinnitus.

RCT (author, year, reference)	Main complaint	Study Design	No. of patients randomized	Age of patients	Treatment strategy	Outcome measures	Key results
Cesarani, 1998, [67]	Vertigo caused by vascular vestibular disorders	Open, controlled	44	47 to 73 years of age	2 × 80 mg = 160 mg EGb 761/day (vs. 2 × 16 mg betahistine) for 12 weeks, no information on follow-up	Change in subjective symptomatology (VSS), Romberg test, Babinsky-Weil test and other neuro-otologic and balance tests.	In the first month of therapy, vertigo and dizziness improved in 64.7% of patients treated with betahistine and in 65% of those who received GBE. Considerable improvement was found in oculomotor and visuovestibular function, although no change was noted in the overall balance score.
Claussen, 1985 [article in German], [69] [97]	Vertigo and ataxia symptoms	Randomized, placebo-controlled, double-blind	33	Mean: 59 years	120 mg EGb 761/ day (vs. placebo) for 12 weeks, no information on follow-up	Change in subjective symptomatology (VSS), cranio-corpography.	Body sway amplitudes decreased significantly more in the GBE treatment group than in the placebo group. There was a corresponding improvement in the vertigo symptomatology by 20% in the placebo group and by 50% in the GBE treatment group.
Haguenauer, 1986 [article in French], [68] [97]	Vertigo (undetermined origin)	Randomized, placebo-controlled, double-blind, multicenter	67 (34 in the GBE treatment group and 33 in the placebo group)	Mean: 52 ± 2.5 years for GBE group vs. 46.4 ± 2.4 years for the placebo group	160 mg EGb 761/ day (vs. placebo) for 12 weeks, no information on follow-up	VAS scale of severity, Romberg test, Babinsky-Weil test and other neuro-otologic and balance tests including electronystagmography.	Statistically significant improvement in the intensity, frequency and duration of vertigo in the GBE treatment group. At the end of the trial, 47% of patients treated with GBE were cured of their vertigo compared to 18% for those treated with placebo.
Sokolova, 2014, [66]	Vertigo (undetermined origin)	Randomized, placebo-controlled, double-blind, multicenterl	160 (80 in the GBE treatment group and 80 in the betahistine group)	Mean: 58 years	240 mg EGb 761/ day (vs. 32 mg betahistine) for 12 weeks, 2 days follow-up to monitor adverse events	NAS, VSS-SF, SDS and CGI	Both treatment groups improved in all outcome measures—there was no significant intergroup difference with regard to changes in any outcome measure. Numerically, improvements of patients receiving GBE were slightly more pronounced on all scales.

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Herrschaft, 2012, [21] [95]	Mild to moderate dementia associated with neuropsychiatric symptoms	Multicenter, double-blind, randomized, placebo-controlled	402 (200 in the treatment group and 202 in the placebo group)	>50 years (no upper limit; mean 65 ± 9)	240 mg EGb 761/ day (vs. placebo) for 24 weeks, no follow-up	Secondary outcome variable: change in 11-point box scales for the rating of presence and severity of dizziness and tinnitus from baseline.	**Dizziness**: Change from baseline at week 24 for the dizziness 11-point box scale was significant between groups (−0.6 for GBE vs. −0.2 for placebo; $p < 0.001$); mean reduction difference in dizziness severity in favor of GBE treated patients compared to placebo was statistically meaningful (−0.58 [95% CI: −0.90, −0.26]) **Tinnitus**: Change from baseline at week 24 for the tinnitus 11-point box scale was not significantly different between groups (−0.4 for GBE vs. −0.3 for placebo; $p = 0.31$); mean reduction difference in tinnitus severity in favor of GBE treated patients compared to placebo was statistically meaningful (−0.14 [95% CI: −0.50, −0.22]).
Ihl, 2011, [21] [93]	Mild to moderate dementia with neuropsychiatric symptoms	Multicenter, randomized, placebo-controlled	404 (202 in the treatment group and 202 in the placebo group); i.d.	>50 years (no upper limit)	240 mg EGb 761/ day (vs. placebo) for 24 weeks, no information on follow-up	Secondary outcome variable: change in 11-point box scales for the rating of presence and severity of dizziness and tinnitus from baseline.	**Dizziness**: Change from baseline at week 24 for the dizziness 11-point box scale was −0.8 for the GBE group and −0.3 for the placebo group; $p < 0.001$; mean reduction difference in dizziness severity in favor of GBE treated patients compared to placebo was statistically meaningful (−0.74 [95% CI: −1.02, −0.46]) **Tinnitus**: Change from baseline at week 24 for the tinnitus 11-point box scale was −0.5 for the GBE group and −0.1 for the placebo group; $p < 0.001$; mean reduction difference in tinnitus severity in favor of GBE treated patients compared to placebo was statistically meaningful (−0.97 [95% CI: −1.27, −0.67]).

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Napryeyenko, 2007, [21] [91]	Mild to moderate dementia with neuropsychiatric features	Multicenter, randomized, placebo-controlled	395 (198 GBE treatment group and 197 placebo group); i.d.	≥50 years (no upper limit); mean age = 65 ± 8 years for GBE treatment group and 63 ± 8 years for placebo group	2 × 120 mg = 240 mg EGb 761/day (vs. placebo) for 22 weeks, no information on follow-up	Secondary outcome variable: change in patient self-ratings of presence and severity of dizziness and tinnitus using 11-point box scales.	**Dizziness**: Change from baseline at week 22 for the dizziness 11-point box scale was −1.7 for the GBE group and −0.3 for the placebo group; $p < 0.001$; mean reduction difference in dizziness severity in favor of GBE treated patients compared to placebo was statistically meaningful (−1.93 [95% CI: −2.24, −1.62]) **Tinnitus**: Change from baseline at week 22 for the tinnitus 11-point box scale was −1.1 for the GBE group and −0.0 for the placebo group; $p < 0.001$; mean reduction difference in tinnitus severity in favor of GBE treated patients compared to placebo was statistically meaningful (−1.96 [95% CI: −2.35, −1.57]).
Nikolova, 2013, [21] [92] [article in Russian]	Mild to moderate dementia	Randomized, placebo-controlled, double-blind	408 (203 received GBE treatment and 205 received placebo); i.d.	Not specified	240 mg EGb 761/day (vs. placebo) for 22 weeks, no information on follow-up	Secondary outcomes variable: change in 11-point box scales for the rating of presence and severity of dizziness and tinnitus from baseline.	**Dizziness**: Mean reduction difference in tinnitus severity in favor of GBE treated patients compared to placebo was statistically meaningful (−0.29 [95% CI: −0.88, −0.30]) **Tinnitus**: Mean reduction difference in tinnitus severity in favor of GBE treated patients compared to placebo was statistically meaningful (−0.66 [95% CI: −1.23, −0.09]).

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Schneider, 2005, [21] [94]	Tinnitus associated with AD	Randomized, placebo-controlled, double-blind, parallel-group, multicenter	513 with tinnitus and AD (169 received GBE 120mg, 170 received GBE 240 mg, and 174 received placebo).	Mean age 78 years	120 mg EGb 761/ day or 240 mg EGb 761/day (vs. placebo) for 26 weeks, no follow-up	Secondary outcome variable: change in 11-point box scales for the rating of presence and severity of dizziness and tinnitus from baseline.	**Dizziness**: Mean reduction difference in dizziness severity in favor of placebo treated patients compared to GBE treated patients (+0.47 [95% CI: −1.18, +2.12]) **Tinnitus**: Mean reduction difference in tinnitus severity in favor of GBE treated patients compared to placebo was statistically meaningful (−1.84 [95% CI: −3.00, −0.68]).
Drew and Davies, 2001, [77]	Tinnitus	Double-blind, placebo-controlled	1,121 (559 to active treatment and 562 to placebo)	Mean: 53 years	3 × 50 mg = 150 mg LI 1370/day (vs. placebo) for 12 weeks, 2 weeks follow-up	Participants' assessment of tinnitus before, during, and after treatment recorded in a questionnaire (changes in loudness were rated on a 6-point scale and changes in how troublesome were rated on a 5-point scale).	No significant differences between the groups.
Halama, 1988, [71] [article in German]	Light to moderate cerebrovascular insufficiency	Randomized, double-blind, placebo-controlled	40; i.d.	>55 years (no upper limit)	3 × 40 mg = 120 mg EGb 761/day (vs. placebo) for 12 weeks, no information on follow-up	Change in SCAG from baseline.	In the treatment group, SCAG score decreased by an average of 9 points, but remained unchanged in the placebo group ($p < 0.005$); superior effects of GBE were demonstrated for headache and tinnitus.
Meyer, 1986, [76] [article in French]	Tinnitus	Multicenter, randomized, double-blind, placebo-controlled	103 with tinnitus	Mean age treatment group 50.97 years vs. placebo group 49.76 years	4 ml containing 160 mg EGb 761/day (vs. placebo) for 12 weeks, no follow-up	Overall effects were assessed using a 6-point ordinal scale and the symptoms a 4-point ordinal scale.	Better efficacy for GBE vs. placebo irrespective of initial description or prognostic factors; $p = 0.05$: a statistically significant difference in favor of the group treated with GBE, the evolution of which was much faster (unilateral test $p = 0.03$); duration until disappearance or significant improvement in 50% of patients was 70 days in the GBE group and 119 days in the placebo group; change in intensity appeared to be statistically better in the GBE group (unilateral test $p = 0.03$); and change in nuisance (unilateral test $p = 0.08$).

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Morgenstern, 1997, [75] [article in German]	Non-auditory tinnitus	Prospective, double-blind, randomized, placebo-controlled	99 with tinnitus (49 in the treatment group and 50 in the placebo group)	>18 years (no upper limit)	3 × 40 mg = 120 mg EGb 761/day (vs. placebo) for 12 weeks, no follow-up	Audiometrically detectable change in tinnitus sound intensity on the ear that is initially severely affected. Accompanying variables: tinnitus-volume in the contralateral ear, reproducibility click-evoked OAE and their response, tinnitus intensity, hearing loss and subjective patient impression.	From the eighth week of treatment onwards, there was a significant decrease in the average noise level in the GBE treatment group. The observed improvements were within a range of 5 to 10 decibels (dB), which is considered clinically relevant; the values in the placebo group remained unchanged.
Morgenstern and Biermann, 2002, [72]	Non-auditory tinnitus	Double-blind, randomized, placebo-controlled, monocentric	52 with tinnitus	median age: 45 years in the GBE treatment group and 47 years in the placebo group	2 x 80 mg = 160 mg EGb 761/ day (vs. placebo) for 12 weeks, no information on follow-up	Primary outcome: difference in tinnitus volume between day 10 of an in-patient phase and months 3, 2 and 1 of an out-patient phase, *i.e.*, change in tinnitus volume in the more severely affected ear; Secondary outcomes: click-evoked OTE, tone threshold audiometry, speech audiometry, 6-point rating scale of subjective tinnitus intensity.	Statistically significant superiority of GBE over placebo in the reduction of the loudness of subjective ear sounds (tinnitus) already evident after 4 weeks and persisted until the end of the study at 12 weeks ($p = 0.039$).
Polanski, 2016, [78]	Tinnitus associated with SSHL	Prospective, randomized, double-blinded, placebo-controlled	53 with tinnitus (12 GBE treatment group, 13 placebo, 13 *α*-lipoic acid plus vitamin C, 15 papaverine hydrochloride plus vitamin E	Mean age 72.6 years	120 mg EGb 761/ day (vs. *α*-lipoic acid [60 mg/day] plus vitamin C [600 mg/day], papaverine hydrochloride [100 mg/day] plus vitamin E [400 mg/day], and placebo [starch capsules] for 24 weeks, no information on follow-up	Change from baseline in THI.	No statistically significant difference between THI by degree ($p = 0.441$) and by score ($p = 0.848$) before and after treatment for any of the treatment arms.
Procházková, 2018, [73]	Unilateral or bilateral chronic or subchronic tinnitus	Randomized, double-blind, reference-controlled single-center	200 with tinnitus (100 received GBE treatment and 100 received pentoxifylline)	Mean age = 55.4 ± 10.5 years for GBE treatment group and 53.1 ± 10.9 years for pentoxifylline	120 mg EGb 761/ day (vs. 600 mg pentoxifylline/ day) for 12 weeks, no follow-up	Change in two 11-Point Box Scales for tinnitus loudness and annoyance by tinnitus from baseline.	Significant improvements were observed in the 11-Point Box Scales for tinnitus loudness and annoyance, but there was no relevant difference between the two treatment groups ($p = 0.93$ and 0.94, respectively).

Continued

Radunz, 2019, [74]	Tinnitus	Randomized-controlled, parallel, double-blind, three-arm	33 with tinnitus (11 received GBE treatment, 11 received hearing aids, and 11 received both GBE and hearing aids)	Mean age = 56.3 ± 16.8 (all participants)	240 mg EGb 761/ day (vs. hearing aids) for 24 weeks, no follow-up	VAS and THI	GBE treatment alone or in combination with hearing aids was effective regardless of patient's tinnitus duration (mean % THI before and after treatment in relation to tinnitus time in months was 54.3% and 53.0% vs. 74.5% and 68.1%, respectively).

All articles are published in English language unless otherwise stated. GBE: standardized *Ginkgo biloba* extract LI 1370 orEGb 761; i.d.: incomplete data on the number of tinnitus patients at baseline; VAS: Visual Analogue Scales; THI: Tinnitus Handicap Inventory; ADL: activities-of-daily-living; ADL-IS: ADL international scale; GBS: Gottfries-Bråne-Steen; OAE: otoacoustic emissions; SCAG: Sandoz Clinical Assessment Geriatric; SKT: Short Cognitive Performance Test or Syndrom Kurztest; NPI: Neuropsychiatric Inventory; ADCS-GIC: ADCS Clinical Global Impression of Change; ADCS-CGIS: Alzheimer's Disease Cooperative Study Clinical Global Impression of Change; DEMQOL: health-related quality of life (HRQoL) for people with dementia; AD: Alzheimer's Disease; Db: decibels; NAS: numeric analogue scale (NAS) with 0 indicating the absence of vertigo and 10 representing extremely severe vertigo; VSS-SF: short form of the Vertigo Symptom Scale; SDS: Sheehan Disability Scale; CGI: Clinical Global Impressions scale; SSHL: sudden sensorineural hearing loss.

suggest that betahistinedihydrochloride and GBE exert their effects at different equilibrium receptor sites. Moreover, GBE treatment consistently improved VOR [67]. It is however important to note that this is difficult to assess; also the improvement of this symptom does not necessarily mean that vestibular functions are restored.

In a much earlier study, Haguenauer *et al*. (1986) using EGb 761, showed that GBE treatment for 12 weeks was significantly superior compared to placebo with regard to the improvement in subjective vertigo symptoms, expressed as a reduction in intensity, frequency and duration of vertigo symptoms, and the associated impairments in daily life [68]. Overall, the difference in improvement between the 2 groups reached 85% at the end of the study ($p < 0.001$) [68]. No results were reported for the Romberg or Babinski-Weil tests, and other neuro-otological findings, e.g., spontaneous nystagmus. However in the caloric test, electronystagmographic findings showed normalization in 80% of those patients having pathological values on enrolment into the study under treatment with GBE vs. 57% of those who received placebo [68].

Usingcraniocorpographyto evaluate vestibular function, Claussen and Kirtane (1985) found GBE to have a positive effect on subjective dizziness symptoms and lateral body sway vs. placebo [69].

4.3. Efficacy of GBE in Vertigo/Dizziness and/or Tinnitus

In the five included RCTs, although the patients treated with GBE had mild to moderate dementia as their primary complaint, 92% reported associated neurosensory symptoms such as dizziness and/or tinnitus at baseline. An 11-point box scale was used to assess the presence and severity of tinnitus and dizziness as a secondary outcome measure in all trials. In all 5 trials, there was a mean reduction in tinnitus severity for the GBE treated patients compared to placebo. The

difference in favor of GBE was statistically meaningful in 4 trials, but not in the trial by Herrschaft *et al.* (2012). In 4 trials (*i.e.*, Nikolova *et al.* [2013], Napryeyenko *et al.* [2007], Herrschaft *et al.* [2012] and Ihl *et al.* [2011] but not Schneider *et al.* [2005]), there was a greater reduction in dizziness for the GBE treated patients. All 5 trials show that 22 to 26 weeks of GBE treatment significantly improves concomitant neurosensory symptoms of tinnitus and dizziness (secondary outcome measures) in patients with dementia.

4.4. Efficacy of GBE in Tinnitus

Of the 8 tinnitus studies included in our review, six studies reported positive benefits with GBE. Halama *et al.* (1988) showed that in the GBE group, a superior effect was shown in the symptom of tinnitus ($p = 0.035$) [70] [71]. A combination of infusion therapy followed by oral administration of GBE appears to be effective and safe in alleviating the symptoms associated with tinnitus aurium (also known as subjective or non-auditory tinnitus) [70] [72]. For the primary outcome measure, Morgenstern and Biermann (2002) reported significant superiority of GBE over placebo in the intent-to-treat (ITT) analysis data set after 4, 8 and 12 weeks of out-patient treatment ($p < 0.05$, 1-tailed), although the absolute treatment group difference was moderate [72]. The results were supported by the secondary outcome measures for efficacy (e.g., decreased hearing loss, improved self-assessment of subjective impairment) [72]. During out-patient treatment, there were no adverse events related to GBE treatment [70] [72].

Procházková *et al.* (2018) showed both GBE and pentoxifylline groups improved over the three months but there was no difference between the two groups [73]. Subgroup analyses were performed based on Hospital Anxiety and Depression Scale (HADS), and for participants with a baseline HADS depression score ≥ 8 (indicating subclinical or clinical depression), there was a statistically significant improvement in Mini-TQ, loudness, and annoyance after 12 weeks in the GBE treatment group that was not seen in the pentoxifylline group [73]. Of the people in the GBE group who had abnormal HADS scores at baseline (34 in the Ginkgo group, 29 in the pentoxifylline group) fewer remained with clinical anxiety than in the pentoxifylline group after 12 weeks ($n = 22$, $P = 0.005$ vs. $n = 26$, $P = 0.105$) [73].

Radunz *et al.* (2019) demonstrated that the use of GBE alone or in combination with a hearing aid was effective regardless of patient's tinnitus duration [74]. The authors concluded that this result may be associated with GBE's mode of action, *i.e.*, free radical scavenger activity, anti-inflammatory activity and enhanced neuronal plasticity that can reduce tissue and neurological damage [74].

Although Morgenstern and Biermann (1997) reported a larger regression of tinnitus loudness in the GBE vs. placebo group, the subjective impression change for the patients was not positively impacted [75].

In the earliest study, Meyer (1986) reported that GBE improved the condition of all the tinnitus patients, irrespective of the prognostic factor [76].

Two studies were negative with regard to GBE efficacy in tinnitus. Drew and Davies (2001) concluded that GBE is no more effective than placebo in treating tinnitus [77]. In 12 tinnitus patients treated with GBE, Polanski, *et al.* (2016) reported that there was no benefit from the use of GBE and other antioxidant agents for tinnitus in their study [78].

5. Discussion

In contrast to other *Ginkgo biloba* leaf preparations, the standardized EGb 761 and LI 1370 are considered pharmaceutically equivalent, are well-defined, and have documented efficacy in improving neurologic functions for a wide array of disorders, including cerebrovascular insufficiency [79], memory impairment in the elderly [80], Alzheimer's disease [81], multi-infarct dementia [82], depression [83], peripheral artery insufficiency/improved microcirculation [84] [85], venous insufficiency [86], and asthma [87] [88]. Other studies suggest GBE has potential efficacy in conditions such as tinnitus [76] and vertigo of undetermined etiology [68]. Standardized GBE as a herbal treatment in vertigo and/or tinnitus therefore deserves careful consideration by physicians because of evidence of the promising aforementioned benefits and well-documented tolerability, as well as the limited or complete lack of efficacy with conventional pharmacological agents for these conditions and the increasing patient demand for CAMs [89]. Moreover, given the high patient burden caused by tinnitus and/or vertigo, any therapy that can even moderately improve symptoms can have a considerable impact on QoL for many sufferers [90].

The aim of this review was to identify RCT evidence pertaining to the use of GBE for individuals with symptoms of vertigo of undetermined etiology and/or tinnitus. Except for the two standardized GBE products EGb 761 and LI 1370, our literature search did not identify any RCT of any other Ginkgo preparations in which the effects on tinnitus or dizziness were evaluated. Due to the underlying pathophysiology of these two symptomatic disorders, clinical trials with GBE are based on a rational treatment approach. Of the 4 studies evaluating GBE in vestibular vertigo [66] [67] [68] [69], all showed positive benefits vs. placebo and/or effects similar to betahistine, however we acknowledge there still remains a lack of strength of the evidence, since the observed improvements are subjective (patients' perception) rather than based on objective tests, and more studies are necessary to establish the efficacy of *Ginkgo biloba* in this indication. Similarly, in most of the 5 studies evaluating GBE in neurosensory symptoms in patients with dementia, GBE was superior to placebo in alleviating symptoms of tinnitus and vertigo/dizziness [91] [92] [93] [94] [95]. Notably, the exact 5 studies evaluated in this review for tinnitus and/or dizziness were previously identified and included in a meta-analysis reported by Spiegel *et al.* (2018). Based on the Jarad scale assessment of methodological quality, the authors judged that the 5 studies included in their meta-analyses had a low bias risk [21]. Overall, they showed that GBE was superior to placebo, with weighted mean differences for

change from baseline, calculated using random effects models, of −1.06 (95% CI: −1.77, −0.36) for tinnitus (p = 0.003) and −0.77 (95% CI: −1.44, −0.09) for dizziness (p = 0.03) [21]. Interestingly, our review of the literature with regard to the effects of GBE in this indication (up to 1 January 2020) also failed to identify any additional RCTs that had been published in the last six years, *i.e.*, since the RCT was published by Nikolova *et al.* in 2013 [92]. Importantly, the included studies on vertigo/dizziness do not follow a pathophysiologically defined definition of the underlying disorder. The fact that different underlying vestibular pathologies can cause different types of vertigo means that treatment should be differentiated based on etiology, and this warrants further study [92].

Although our review includes 9 RCTs which suggest that GBE has clinical efficacy in vestibular and non-vestibular vertigo, we acknowledge that no definitive conclusions can be drawn based on this small evidence-base due to a lack of standardized research methodology between the trials. Although the results from the included studies support findings from animal studies, namely that GBE improves vestibular compensation [96], no human RCT for vertigo was identified with GBE for inclusion in this review in the past 5 years. However, in this context, the general difficulties of transferring results from animal models to humans should be considered, especially in symptoms with an arguably large subjective component. A 2006 systematic review of the literature by Hamann *et al.* (2006) included 2 of the 4 included vestibular vertigo studies in our review. Hamann *et al.* reported that GBE as an additional treatment may lead to further improvement in the capacity for compensation with habituation training [97]. They also concluded that central nervous action of GBE has been demonstrated for non-vestibular vertigo (dizziness), *i.e.*, the correlate of a central nervous dysfunction [97].

As evidenced by evaluating the studies identified in our review, results from 13 RCTs of GBE for treating tinnitus, as either the main or concomitant complaint, have yielded conflicting results. A study of 103 patients with tinnitus reported by Meyer in 1986 [76] was positive with regard to GBE vs. placebo efficacy in tinnitus whereas in a more recent study by Polanski, *et al.* (2016) [78], albeit using different outcome measures and evaluating only 12 tinnitus patients with GBE, reported no benefit with GBE. We consider the group size of only 12 patients in the Polanski study as far too low for a statistically relevant conclusion. The largest trial evaluating GBE in tinnitus to date (n = 1121) also failed to show any benefit of GBE in tinnitus, however this study was criticized in a recent systematic review for not meeting minimal standards of Good Clinical Practice [90]. Also, immediately after publication in 2001, Prof. Ernst criticized in his letter to BMJ's editor that this study was only conducted by post and telephone and that therefore the quality and reliability of the rough data was questionable [98]. A meta-analysis of pooled RCTs by Rejali *et al.* in 2004 concluded that *Ginkgo biloba* does not benefit patients with tinnitus, but studies included in this meta-analysis used different Ginkgo products of unknown quality [90] [99].

In contrast, a more recent systematic review reported by von Boetticher (2011) described that there is a sufficient evidence-base to recommend GBE as a treatment option in tinnitus [90].

There is no Food and Drug Administration (FDA)-approved indication for tinnitus. Antihistamines (e.g., meclizine and dimenhydinate) are currently approved as prescribed vestibular suppressants for vertigo symptoms by the FDA [100]. The European Medicines Agency (EMA) have recently approved three drugs for the treatment of sudden sensorineural hearing loss (SSHL) symptoms, including tinnitus and/or vertigo: 6-fluoro-9-methyl-9H-pyrido[3,4-b]-indole (2018; AudioCure), pioglitazone hydrochloride (2017) and R-azasetronbesylate (2016). Approval for the metabolic drug trimetazidine was withdrawn by the EMA for these indications in 2012 [101]. Although no GBE is currently endorsed for use in tinnitus and vertigo and/or dizziness by the EMA per se, the EMA recognizes that for many European countries (e.g., Austria, Czech Republic, Denmark, Germany, Poland, Romania, Spain, Slovakiaand Switzerland), GBE for tinnitus and vertigo, among other indications, is a well-established treatment [24].

Although vertigo and/or dizziness and tinnitus are common symptoms, there remain few effective therapeutic options available due to the complex and multifaceted neural mechanisms involved in their underlying etiology, and many pharmacotherapies that are available are aimed at ameliorating the QoL impact rather curing the physiological dysfunction [102] [103]. As stated above, no medications have to date been validated or approved for the treatment of tinnitus, and any medical needs are essentially unmet [24]. Typical treatment options for tinnitus include noise masking, pharmaceuticals (tricyclic antidepressants, selective serotonin reuptake inhibitors, pentoxifylline, steroids, etc.), acupuncture, and cognitive behavioral therapy (CBT) [24] [104] [105]. Newer approaches include acoustic stimulation [106] [107] and neuromodulation, such asvagus nerve stimulation [108], transcranic magnetic stimulation, or neurofeedback [109]. Complementary and alternative medicine (CAM) such as herbal supplements, have also stepped into the void created by the lack of consistently effective therapies [89].

Vertigo and tinnitus follow a complex pattern of pathophysiological effects involving an ambiguous interplay between auditory and somatosensory systems, neuro-cognitive, and neuronal-emotional networks [110] [111]. These underlying processes remain poorly understood and require continued investigation. It should be noted in the context of vestibular vertigo that the underlying pathology is not homogenous, and treatment depends on the underlying disease. Betahistidine e.g. is indicated in Menière's disease. Especially in early studies, the underlying pathology of the vestibular vertigo was unknown. This lack of clearly defined underlying pathological entities, especially for studies published before 2000 when diagnostic tools where limited to the lateral semicircular canal function, is a limitation of this review. The two main bioactive constituents of GBE preparations EGb 761 and LI 1370 are flavonoid glycosides (24%) and terpene

lactones (6%); these standardized products also contain less than 5 ppm of the allergenic component, ginkgolic acid [20] [112]. Details of the exact role of neuroplasticity and how exactly the active constituents of GBE act on CNS and cerebral recovery mechanisms considered as key processes in vestibular compensation is as yet not well understood and requires further investigation. Also, tinnitus has recently been shown to be a highly heterogeneous phenomenon that differs greatly between affected individuals. Origin of the percept, subjective manifestation (e.g., intensity, pitch, location), as well as related distress and other comorbid symptoms of tinnitus have thus been found to show considerable variability within the tinnitus group [113], making it highly likely that distinct subtypes of tinnitus may be identified in the future. As the underlying processes of many different tinnitus subtypes are not yet fully understood, the exact mode of action of GBE remains unknown. One of the key advantages of using a herbal medicine such as GBE for treating complex pathophysiological disorders is that it has a pleiotropic mechanism of action and is able to up- or down-regulate different signaling pathways [112].

6. Conclusion

GBE is the best-studied phytotherapy medicine to date with excellent tolerability in humans. Based on its known mechanisms of action as well as evidence from animal models and/or human clinical trials, EGb 761 and LI 1370 enable a rational alternative treatment that might provide benefit to individuals with vertigo and/or dizziness and tinnitus. The current consensus is that tinnitus and vertigo disorders involve a distributed network of peripheral and central pathways in the nervous system. Among its many functions, GBE has been shown to reduce vascular resistance, improve peripheral blood circulation and promote neuroprotection, which may positively benefit the pathophysiological changes that occur in patients with tinnitus. Further research into the etiology of vertigo and tinnitus is however important in order to improve our understanding of the pathophysiological mechanisms underlying these symptoms. The heterogeneous nature of tinnitus, in particular, requires more research to determine whether GBE can be of benefit to all patients. Additional trials with standardized research methodologies are also required to further assist physicians in their decision-making for patients with vertigo and/or dizziness and tinnitus symptoms.

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Conflicts of Interest

The authors state no conflicts of interest.

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Abbreviations

BPPV: Benign Paroxysmal Positional Vertigo;
CAM: Complementary Alternative Medicine;
CBT: Cognitive Behavioral Therapy;
EMA: European Medicines Agency;
ESCOP: European Scientific Cooperative on Phytotherapy;
FDA: Food and Drug Administration;
GBE: *Ginkgo Biloba* extract;
HADS: Hospital Anxiety and Depression Scale;
Mini-TQ: Mini-Tinnitus Questionnaire;
NIHL: Noise-Induced Hearing Loss;
QoL: Quality of Life;
RCT: Randomized Controlled Trial;
SSHL: Sudden Sensorineural Hearing Loss;
VAS: Visual Analogue Scale;
VOR: Vestibular Ocular Reflex;
VSR: Vestibular Spinal Reflex;
VSS: Vertigo Symptom Scale.