RESEARCH ARTICLE

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The Effectiveness of Ginkgo Biloba Extract EGB 761 in Tinnitus: A Randomized-controlled Trial

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ABSTRACT

Aim: To evaluate the effectiveness of Ginkgo biloba extract EGb 761 in the treatment of subjective tinnitus.

Background: Subjective tinnitus significantly impairs quality of life and is frequently associated with anxiety, depression, and sleep disturbances. Currently, no curative treatment exists, and management primarily focuses on symptom relief. Although Ginkgo biloba has been used for tinnitus treatment, evidence supporting its efficacy remains limited.

Materials and Methods: A randomized, double-blind, placebo-controlled trial was conducted at a tertiary referral center. Forty-six adults aged ≥18 years with unilateral or bilateral subjective tinnitus of 4 weeks to 1 year duration were enrolled. Participants were randomly assigned to receive either EGb 761 (120 mg twice daily; total 240 mg/day) or matching placebo for 12 weeks. Outcomes were assessed using the Tinnitus Handicap Inventory (THI), Visual Analog Scale (VAS) for tinnitus loudness, and Hospital Anxiety and Depression Scale (HADS) at baseline, 6 weeks, and 12 weeks.

Statistical Analysis: Between-group differences in changes in THI, VAS, and HADS scores from baseline to 12 weeks were analyzed using independent t-tests or Mann–Whitney U tests, as appropriate. Within-group changes over time were assessed using repeated-measures ANOVA or the Friedman test for non-normally distributed data. Clinically significant changes in THI scores within groups were evaluated using McNemar's test.

Results: THI scores decreased significantly in both the EGb 761 group (34.2 ± 19.2 to 25.0 ± 18.5) and the placebo group (34.4 ± 23.0 to 22.2 ± 15.9), with no significant between-group difference ($p = 0.51$; 95% CI: −6.2 to 12.3). VAS scores also declined in both groups (EGb 761: 4.1 ± 2.4 to 3.7 ± 2.6; placebo: 4.5 ± 2.5 to 3.9 ± 2.3), without a significant intergroup difference ($p = 0.78$; 95% CI: −1.2 to 1.5). HADS anxiety and depression scores improved significantly within groups; however, no statistically significant differences were observed between groups (HADS-Anxiety: $p = 0.64$, 95% CI: −1.1 to 1.8; HADS-Depression: $p = 0.70$, 95% CI: −1.4 to 1.0).

Keywords: Tinnitus; Ginkgo biloba; EGb 761; Tinnitus Handicap Inventory; Hospital Anxiety and Depression Scale

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INTRODUCTION

Subjective tinnitus, the perception of sound without an external source, affects approximately 10–15% of adults and is commonly linked to sensorineural hearing loss. When persistent for more than six months, it is classified as chronic. Tinnitus can significantly impair quality of life, often accompanied by anxiety, depression, sleep disturbances, and concentration difficulties, with symptom severity correlating with psychological distress[1-3]. Currently, no curative treatment exists; management focuses on symptom relief through approaches such as hearing aids, sound therapy, cognitive-behavioral therapy, pharmacological agents, and dietary supplements[1].

Ginkgo biloba is a traditional Chinese herbal remedy. Its main active compounds, ginkgolides and bilobalide, contribute to its pharmacological effects. Standardized extracts like EGb 761 contain 22–27% flavone glycosides and 5–7% terpene lactones, including 2.8–3.4% ginkgolides A, B, and C and 2.6–3.2% bilobalide. For safety, ginkgolic acids are kept below 5 mg/kg (5 ppm), and harmful alkylphenol and alkylbenzoic acid derivatives are completely removed[4-6].

Preclinical studies suggest neuroprotective effects, including antioxidant and antiapoptotic activity, improved cochlear blood flow, and modulation of neurotransmitters related to tinnitus such as dopamine, norepinephrine, and acetylcholine[7-13]. These findings also link Ginkgo biloba to reduced tinnitus-like behavior and psychological symptoms in animal models.

Despite promising mechanisms, clinical evidence remains inconsistent. Guidelines do not recommend Ginkgo biloba due to insufficient and conflicting data[1]. A Cochrane review (2004) found limited support for its efficacy, citing poor trial quality and lack of tinnitus-specific outcomes[14]. Therefore, this study aimed to evaluate the effectiveness of standardized Ginkgo biloba extract EGb761 in treating tinnitus.

MATERIALS AND METHODS

The randomized, double-blind, placebo-controlled trial evaluated the efficacy of Ginkgo biloba extract (EGb761) in patients with tinnitus. The study was conducted at the Otolaryngology Clinic, in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the institutional review board, and all participants provided written informed consent.

Eligible participants were adults aged 18 years or older with unilateral or bilateral subjective tinnitus lasting between 4 weeks and 1 year. Exclusion criteria included active otitis media, ongoing tinnitus treatments (e.g., hearing aids, sound therapy), or the use of tinnitus-related medications within one month prior to enrollment. Individuals were also excluded if they had severe cardiovascular, renal, or hepatic conditions; major psychiatric disorders (e.g., schizophrenia, anxiety, or depression); neurodegenerative diseases such as dementia or Alzheimer's disease; were illiterate; pregnant; of childbearing potential without contraception; or had known allergies to EGb761.

Participants were randomly assigned in a 1:1 ratio to either the EGb761 or placebo group using block randomization with blocks of four to ensure balanced allocation. Randomization codes were sealed in opaque envelopes and opened only after written informed consent. To maintain blinding, EGb761 and placebo tablets were identical in appearance and packaged in matching amber bottles. Both participants and investigators remained blinded throughout the study.

The intervention group received 120 mg EGb761 tablets twice daily (240 mg/day) for 12 weeks, while the control group took matching placebo tablets on the same schedule. Participants could continue their regular medications and use sleeping pills if needed, but no additional tinnitus-specific treatments were allowed during the study.

At the pre-treatment visit, all participants underwent audiometric evaluation. Follow-up assessments were conducted at 6 and 12 weeks after initiating treatment. Outcome measures included the Thai version of the Tinnitus Handicap Inventory (THI-Thai), the Visual Analog Scale (VAS) for tinnitus loudness, and the Thai version of the Hospital Anxiety and Depression Scale (HADS-Thai), all administered at baseline, 6 weeks, and 12 weeks. Any adverse effects related to the study medication were monitored and recorded throughout the trial.

The primary outcome was the change in tinnitus severity from baseline to 12 weeks, measured by the Thai version of the Tinnitus Handicap Inventory (THI). The THI is a validated instrument used to assess the impact of tinnitus on daily life[15]. It consists of 25 items divided into three subscales: functional, emotional, and catastrophic. Each item is scored on a scale of 0 (never), 2 (sometimes), or 4 (always). Based on the total score, tinnitus severity is categorized as follows: 0–16 (no handicap), 18–36 (mild), 38–56 (moderate), 58–76 (severe), and 78–100 (catastrophic). The Thai version of the THI has been validated, demonstrating good internal consistency with a Cronbach's alpha of 0.902[16].

The Visual Analog Scale (VAS) was used as a self-rated tool to measure perceived tinnitus loudness. It consists of a 10-centimeter horizontal line anchored at 0 (no tinnitus) and 10 (extremely loud tinnitus). Participants marked a point along the line that best represented their tinnitus loudness. The distance from the 0 point was measured in centimeters, providing a simple, subjective, and trackable quantification of symptom severity.

The Hospital Anxiety and Depression Scale (HADS) was used to assess levels of anxiety and depression, specifically in the context of tinnitus[17]. The scale consists of 14 items: 7 for anxiety (HADS-A) and 7 for depression (HADS-D). Each item is scored from 0 to 3, with higher scores indicating greater severity. Total subscale scores are categorized as follows: 0–7 (normal), 8–10

(borderline abnormal), and 11–21 (abnormal). HADS has been demonstrated to be a reliable and valid screening instrument for evaluating psychological distress in tinnitus patients.2 The Thai version has been validated, showing good internal consistency (Cronbach's alpha: 0.855 for anxiety, 0.826 for depression)[18].

Sample size was calculated using the Epitools program. Based on previous studies, the mean THI score was 36 with a variance of 441. To detect a clinically significant difference of 16 points with 80% power at a 0.05 significance level, 18 participants per group were required. Accounting for a 20% dropout rate, the target sample size was increased to 23 participants per group.

Continuous variables were summarized as mean ± standard deviation for normally distributed data, or median with interquartile range for non-normal data. Categorical variables were presented as frequencies and percentages.

Between-group differences in changes in THI, VAS, and HADS scores from baseline to 12 weeks were analyzed using independent t-tests or Mann–Whitney U tests, depending on data distribution. Within-group changes over time (baseline, 6 weeks, and 12 weeks) were assessed using repeated measures ANOVA or the Friedman test for non-normally distributed data. McNemar's test was used to evaluate clinically significant changes in THI scores within each group.

All analyses followed an intention-to-treat approach. Missing data were handled using multiple imputation in SPSS, and sensitivity analyses were conducted to confirm result robustness.

RESULTS

Between September 2023 and January 2025, 58 participants were screened, of whom 46 were enrolled. Five were excluded for not meeting the inclusion criteria, and seven declined to participate. Using block randomization (blocks of four), 23 participants were assigned to the EGb761 group and 23 to the placebo group. All participants completed the follow-up evaluations (**Figure 1**).

The EGb761 group had 7 males (30.4%) and 16 females (69.6%), while the placebo group included 9 males (39.1%) and 14 females (60.9%). Both groups were similar in age, tinnitus duration, comorbidities, pure-tone average, and speech discrimination scores. Tinnitus duration was slightly longer in the EGb761 group (5.7 ± 3.0 months) than placebo (4.2 ± 3.0 months), and unilateral tinnitus was more common in the placebo group (69.6% vs. 39.1%). Baseline characteristics are shown in **Table 1**.

At 12 weeks, both the EGb761 and placebo groups showed significant within-group improvements in THI scores. The EGb761 group's mean THI score decreased from 34.2 ± 19.2 to 25.0 ± 18.5, while the placebo group's score declined from 34.4 ± 23.0 to 22.2 ± 15.9. However, the difference in THI score improvement between groups was not statistically significant ($p = 0.51$; 95% CI: –6.2, 12.3) (**Table 2**).

In both groups, THI scores significantly decreased over time, with the greatest improvement occurring within the first 6 weeks (EGb761: $p = 0.01$; placebo: $p < 0.01$). No significant changes were observed between weeks 6 and

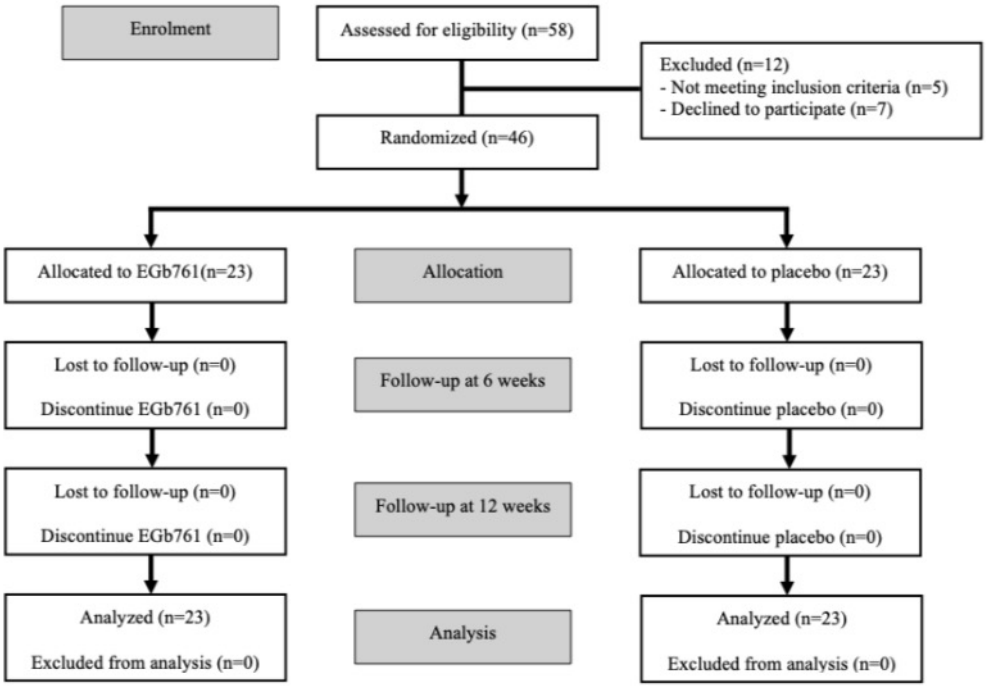

Figure 1: CONSORT flow diagram of participant progression through the trial. A total of 58 patients were assessed for eligibility; 12 were excluded (5 did not meet inclusion criteria, 7 declined participation). Forty-six participants were randomized equally into the EGb761 and placebo groups. All participants completed the 6-week and 12-week follow-ups, with no dropouts or discontinuations. All randomized participants were included in the final analysis.

Table 1. Patient's baseline demographic and characteristics.

	EGb716 (N= 23)	Placebo (N= 23)
Gender Male, n (%)	7 (30.4)	9 (39.1)
Female, n (%)	16 (69.6)	14 (60.9)
Age (yr), Mean±SD	55.6 ± 10.6	55.7 ± 13.9
Duration (month), Mean±SD	5.7 ± 3.0	4.2 ± 3.0
Unilateral, n (%)	9 (39.1)	16 (69.6)
Persistent tinnitus, n (%)	16 (69.6)	16 (69.6)
Underlying	10 (43.5)	8 (34.8)
Hypertension, n (%)	7 (30.4)	4 (17.4)
Diabetic mellitus, n (%)	3 (13.0)	3 (13.0)
Dyslipidemia, n (%)	8 (34.8)	5 (21.7)
Air-PTA $_{\text{poorer ear}}$ (dB), Median (Q1, Q3)	17 (12, 27)	22 (17, 35)
SDS $_{\text{poorer ear}}$ (%), Median (Q1, Q3)	96 (92, 100)	96 (88, 100)

dB, decibel; EGb761, Ginkgo biloba; PTA, pure-tone average; Q, interquartile range; SD, standard deviation; SDS, speech discrimination score; yr, year.

Table 2. Comparison of mean changes between EGb761 and placebo groups at pre-treatment and 12 weeks.

Parameter	EGb761			Placebo			Mean difference between group (95%CI)	p-value
	Pre-treatment	12-week	Mean difference	Pre-treatment	12-week	Mean difference		
THI (mean±SD)	34.2±19.2	25.0±18.5	9.1±15.9	34.4±23.0	22.2±15.9	12.2±15.2	3.0±4.6 (-6.2, 12.3)	0.51
Tinnitus loudness (mean±SD)	4.1±2.4	3.7±2.6	0.4±1.9	4.5±2.5	3.9±2.3	0.6±2.6	0.2±0.7 (-1.2, 1.5)	0.78
HADS $_{\text{anxiety}}$ (mean±SD)	4.7±3.2	3.3±2.2	1.4±2.7	5.2±3.1	3.4±2.5	1.7±2.2	0.3±0.7 (-1.1, 1.8)	0.64
HADS $_{\text{depression}}$ (mean±SD)	3.9±3.0	2.2±2.4	1.7±1.8	3.7±3.2	2.3±2.9	1.4±2.2	0.2±0.6 (-1.4, 1.0)	0.70

CI, confidence interval; EGb761, Ginkgo biloba; HADS, Hospital Anxiety and Depression Scale; SD, standard deviation; THI, Tinnitus Handicap Inventory; VAS, Visual Analog Scale.

Table 3. Comparison of treatment outcome of EGb761 and placebo groups at pre-treatment, 6 weeks, and 12weeks.

Parameter	EGb761				Placebo			
	Pre-treatment	6-week	12-week	p-value	Pre-treatment	6-week	12-week	p-value
THI (mean±SD)	34.2±19.2	26.9±17.8	25.0±18.5	< 0.01 *	34.4±23.0	24.2±15.9	22.2±15.9	< 0.001*
Tinnitus loudness (mean±SD)	4.1±2.4	4.5±2.8	3.7±2.6	0.12	4.5±2.5	4.5±2.2	3.9±2.3	0.25
HADS $_{\text{anxiety}}$ (mean±SD)	4.7±3.2	3.7±2.9	3.3±2.2	0.04 *	5.2±3.1	3.4±2.2	3.4±2.5	< 0.001*
HADS $_{\text{depression}}$ (mean±SD)	3.9±3.0	2.7±2.8	2.2±2.4	< 0.001*	3.7±3.2	2.7±3.1	2.3±2.9	< 0.01 *

EGb761, Ginkgo biloba; HADS, Hospital Anxiety and Depression Scale; SD, standard deviation; THI, Tinnitus Handicap Inventory; VAS, Visual Analog Scale.

Table 4. THI changes in the EGb761 group.

EGb761 THI at baseline	THI at 12-week		Total
	No handicap and Mild handicap	Moderate to Catastrophic handicap	
No handicap to mild handicap	12	1	13
Moderate to catastrophic handicap	4	6	10
Total	16	7	23

EGb761, Ginkgo biloba; THI, Tinnitus Handicap Inventory.

12 (EGb761: p = 0.32; placebo: p = 0.15), suggesting a plateau in treatment response. These findings indicate early improvement followed by stabilization in both groups (**Table 3**).

When THI scores were stratified into two categories—no to mild handicap vs. moderate to catastrophic—the EGb761 group showed improvement in 4 cases and worsening in 1 (p = 0.38; **Table 4**). In the placebo group, 5 cases improved, with no worsening (p = 0.06; **Table 5**). Despite statistically significant mean THI score reductions, no clinically significant changes were observed in either group.

In the EGb761 group, mean VAS scores decreased from 4.1 ± 2.4 to 3.7 ± 2.6 at 12 weeks (p = 0.12), while

Table 5. THI changes in the placebo group.

Placebo THI at baseline	THI at 12-week		Total
	No handicap and Mild handicap	Moderate to Catastrophic handicap	
No handicap to mild handicap	14	0	14
Moderate to catastrophic handicap	5	4	9
Total	19	4	23

THI, Tinnitus Handicap Inventory.

the placebo group showed a reduction from 4.5 ± 2.5 to 3.9 ± 2.3 ($p = 0.25$). Between-group comparison revealed no significant difference in VAS score changes ($p = 0.78$; 95% CI: −1.2, 1.5) (**Tables 2** and **3**).

The mean anxiety scores significantly declined in both groups: from 4.7 ± 3.2 to 3.3 ± 2.2 in the EGb761 group ($p = 0.04$), and from 5.2 ± 3.1 to 3.4 ± 2.5 in the placebo group ($p < 0.001$). However, the between-group difference was not significant ($p = 0.64$; 95% CI: −1.1, 1.8).

Similarly, depression scores improved significantly in both groups: EGb761 from 3.9 ± 3.0 to 2.2 ± 2.4 ($p < 0.001$), and placebo from 3.7 ± 3.2 to 2.3 ± 2.9 ($p < 0.01$), with no significant difference between groups ($p = 0.70$; 95% CI: −1.4, 1.0) (**Tables 2** and **3**).

No serious adverse effects, such as bleeding, drug allergy, or anaphylaxis, were reported in either group. Mild symptoms such as dizziness and palpitations occurred sporadically in both the EGb761 (n=5) and placebo (n=3) groups, with no clear difference between them.

DISCUSSION

This randomized, controlled trial evaluated the efficacy of standardized Ginkgo biloba extract (EGb761) in alleviating tinnitus symptoms over a 12-week period. The primary outcome was the change in Tinnitus Handicap Inventory (THI) scores, with secondary outcomes including tinnitus loudness (VAS) and psychological distress (HADS). Previous studies on EGb761 for tinnitus have reported mixed results, largely due to variations in study design, treatment duration, and outcome measures. By employing a randomized, controlled design and focusing specifically on tinnitus-related outcomes over a 12-week period, this study aimed to address existing gaps in the literature.

For the primary outcome, both the EGb761 and placebo groups showed significant improvements in THI scores at 12 weeks compared to baseline. THI scores decreased from 34.2 ± 19.2 to 25.0 ± 18.5 in the EGb761 group and from 34.4 ± 23.0 to 22.2 ± 15.9 in the placebo group. However, the between-group difference in score reduction was not statistically significant ($p = 0.51$; 95% CI: −6.2, 12.3). Moreover, when THI scores were stratified into two categories—no to mild handicap and moderate to catastrophic handicap—McNemar's test showed no clinically significant changes in either group (EGb761: $p = 0.38$; placebo: $p = 0.06$). These findings suggest that while both groups improved over time, the changes were likely due to placebo effects, natural adaptation, or non-specific intervention effects rather than a specific benefit of EGb761.

The results of this study align with those reported by Rejali et al., who found a negligible difference in THI score changes between the Ginkgo and placebo groups (mean difference = 2.51; $p = 0.51$; 95% CI: −10.1, 5.1). In their meta-analysis, 21.6% of patients treated with EGb761 reported improvement, compared to 18.4% in the placebo group, resulting in a non-significant odds ratio of 1.24 (95% CI: 0.89, 1.71). These findings suggest no significant therapeutic benefit of Ginkgo biloba in tinnitus management[19].

Han SS et al. conducted an open-label, randomized, crossover trial in 65 patients comparing EGb761 and clonazepam. Clonazepam significantly improved THI scores and visual analogue scales for tinnitus loudness, duration, and annoyance, while EGb761 showed no significant effect on any of these parameters. However, the findings were limited by a high dropout rate, with 40% of participants not completing the study[20]. Polanski et al. also found no significant improvement in THI scores with EGb761 or other antioxidants in elderly patients with sensorineural hearing loss[21].

Drew and Davies, in a large double-blind, placebo-controlled trial (n = 978), reported no difference in tinnitus improvement between Ginkgo biloba and placebo groups. The study used Ginkgo IL 1370 rather than EGb761. Both extracts are standardized Ginkgo biloba leaf preparations containing similar amounts of flavonoids (~24%) and terpene trilactones (~6%) and are considered pharmaceutically equivalent. However, they differ in composition: EGb761 contains a specific profile of ginkgolides and bilobalide, while Ginkgo IL 1370 lacks biflavones. Despite the large sample size, the study's reliance on remote assessments may have impacted data quality[22].

In contrast, Radunz et al. observed THI score improvements in all treatment arms—EGb761, hearing aids, and the combination—though only the hearing aid group showed a significant reduction in tinnitus loudness and discomfort on the VAS. However, this study did not report exact mean changes, limiting the interpretability of its results[23].

Morgenstern and Biermann reported a significant reduction in mean tinnitus volume with EGb761 treatment, decreasing from 42.2 dB to 39.0 dB, whereas the control group showed no improvement (44.3 dB to 45.1 dB). The observed reduction in tinnitus volume ranged from 5 to 10 dB[24]. Several studies have assessed

the effectiveness of EGb761 using the 11-point box scale. Spiegel et al. conducted a meta-analysis of randomized, placebo-controlled trials in dementia patients and found a significant reduction in tinnitus severity with EGb761 (weighted mean difference: −1.06; p = 0.003; 95% CI: −1.77, −0.36). However, as the study population had mild to moderate dementia, rating inaccuracies due to cognitive impairment may have affected the results[25].

In contrast, our study found no significant change in tinnitus loudness measured by VAS within either the EGb761 group (p = 0.12) or placebo group (p = 0.25), and no significant difference between groups (p = 0.78). Procházková et al. similarly observed statistically significant but clinically minimal reductions in tinnitus loudness with EGb761 (–0.41, p = 0.0021) and pentoxifylline (–0.43, p = 0.0015)[26].

A more recent randomized controlled trial by Teeravanittrakul et al. also demonstrated no significant difference in tinnitus loudness on the 11-point box scale between EGb761 and placebo. However, THI scores were significantly lower in the EGb761 group at 2, 6, and 12 weeks (p = 0.039, p = 0.008, and p = 0.002, respectively). Importantly, participants in that study had a longer tinnitus duration (<6 months in our study) and also presented with higher baseline THI scores (41.78 ± 19.89 in the EGb761 group and 50.17 ± 20.64 in the placebo group), compared with our study (34.2 ± 19.2 and 34.4 ± 23.0, respectively). Additionally, their study used a lower daily dose of EGb761 (120 mg/day)[27]. These differences highlight methodological and clinical heterogeneity across studies and suggest that the effectiveness of EGb761 may depend on baseline tinnitus severity and symptom chronicity. Further well-designed trials are needed to clarify its therapeutic role in tinnitus.

EGb761 may alleviate tinnitus both directly and indirectly. Brüggemann et al. reported greater improvements in tinnitus severity, depression and anxiety, and cognition with EGb761 than with placebo. Direct effects accounted for 58.5% of the benefit, while indirect effects via reduced depression, anxiety, and improved cognition explained the remaining 41.5%[28].

The efficacy of EGb761 in reducing anxiety and depression was assessed using HADS. Both EGb761 and placebo groups showed significant reductions in anxiety (EGb761: 4.7 ± 3.2 to 3.3 ± 2.2; placebo: 5.2 ± 3.1 to 3.4 ± 2.5) and depression scores (EGb761: 3.9 ± 3.0 to 2.2 ± 2.4; placebo: 3.7 ± 3.2 to 2.3 ± 2.9), but no significant differences were found between groups. These findings are consistent with Procházková et al., who observed modest improvements in anxiety and depression following EGb761 treatment, though between-group differences were similarly non-significant. While within-group changes suggest possible psychological benefits, the clinical relevance remains uncertain[26].

No serious adverse effects were reported in this study, consistent with previous findings. Overall, EGb761 was well tolerated and demonstrated a favorable safety profile.

Although our study found no significant effects of EGb761 compared to placebo, previous trials—particularly those with longer durations or specific populations like chronic tinnitus or dementia—have shown potential benefits, suggesting context-dependent efficacy. Limitations such as short treatment duration and small sample size may affect generalizability. Future research should include longer follow-up and more targeted populations to better evaluate EGb761's effectiveness in tinnitus management.

CONCLUSION

EGb761 may provide modest improvements in tinnitus-related symptoms, as reflected in THI and HADS scores. However, its efficacy was not significantly different from placebo in the general tinnitus population. Further research is needed to confirm these findings across diverse patient groups and to better define the therapeutic role of EGb761 in tinnitus management. Future studies with larger sample sizes and extended follow-up periods are recommended to more comprehensively evaluate its potential benefits.

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AUTHOR CONTRIBUTIONS

All authors were involved in the study conception and design. Material preparation, data collection and analysis were performed by Suppasa Tangchirakhaphan and Paninee Charusripan. The first draft of the manuscript was written by Suppasa Tangchirakhaphan and Paninee Charusripan commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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DATA AVAILABILITY

The datasets analyzed for the present study can be obtained from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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