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# Effects of Plant Extract and Dietary Supplements on Tinnitus Perception in Adults: A Systematic Review and Meta-Analysis

# Efectos de los extractos de plantas y los suplementos dietéticos en la percepción del tinnitus en adultos: Una revisión sistemática y metaanálisis

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## ABSTRACT

**Introduction.** Tinnitus, the perception of sound without an external source, affects millions worldwide and significantly impacts the health-related quality of life (HRQoL). Despite various management strategies, no universally effective treatment exists. While tinnitus sufferers frequently use dietary supplements, their efficacy remains unclear. This systematic review and meta-analysis evaluated the effectiveness of plant extracts and dietary supplements in treating tinnitus symptoms.

**Methods.** We conducted a systematic search in PubMed for randomized controlled trials (RCTs) and crossover trials comparing plant extracts and dietary supplements with placebo or control groups in adults with tinnitus. Selection criteria included patients with subjective tinnitus and studies examining plant extracts or dietary supplements. Using a random-effects model, we estimated standardized mean differences and odds ratios with 95% confidence intervals (95% CIs). Study quality was assessed using the Revised Cochrane risk-of-bias tool for randomized trials. Protocol registered on PROSPERO (CRD42023446824).

**Results.** Twenty-one studies involving 1,759 participants evaluated four plant extracts and six dietary supplements. Five trials investigated plant extracts (*Euterpe oleracea*, traditional herbal medicine Hangekobokuto, Neurotec, and caffeine), while sixteen studies examined dietary supplements (melatonin, zinc, alpha-lipoic acid, manganese, vitamin B complex, and nicotinamide). Meta-analysis revealed no significant efficacy for caffeine in reducing tinnitus impact on HRQoL (SMD=0.07; 95% CI: -0.73 to 0.86; $I^2$=0.0%). However, melatonin showed a modest reduction in tinnitus loudness compared to placebo (OR=2.52; 95% CI: 1.33-4.80; k=2, 168 participants).

**Conclusions.** Among the studied interventions, only melatonin showed modest efficacy in reducing tinnitus loudness, though evidence remains uncertain due to methodological limitations. Further high-quality RCTs with larger samples, standardized outcome measures, and long-term follow-up are necessary to confirm these findings and explore melatonin's potential role in tinnitus management.

**Keywords:** Tinnitus; Dietary Supplements; Melatonin; Plant Extracts; Randomized Controlled Trials

**RESUMEN**

**Introducción.** El tinnitus, la percepción de sonido sin una fuente externa, afecta a millones de personas en todo el mundo y tiene un impacto significativo en la calidad de vida relacionada con la salud (CVRS). A pesar de las diversas estrategias de manejo, no existe un tratamiento universalmente efectivo. Si bien los afectados por tinnitus utilizan frecuentemente suplementos dietéticos, su eficacia sigue siendo incierta. Esta revisión sistemática y metaanálisis evaluó la efectividad de los extractos de plantas y los suplementos dietéticos en el tratamiento de los síntomas del tinnitus.

**Metodología.** Realizamos una búsqueda sistemática de ensayos controlados aleatorios (ECA) o ensayos cruzados que compararan extractos de plantas y suplementos dietéticos con grupos de placebo o control en adultos con tinnitus. Los criterios de selección incluyeron pacientes con tinnitus subjetivo y estudios que examinaran extractos de plantas o suplementos dietéticos. Utilizando un modelo de efectos aleatorios, estimamos las diferencias de medias estandarizadas y las razones de momios con intervalos de confianza del 95% (IC del 95%). La calidad de los estudios se evaluó utilizando la herramienta de riesgo de sesgo revisada de Cochrane para ensayos aleatorios. Protocolo registrado en PROSPERO (CRD42023446824).

**Resultados.** 21 estudios involucraron a 1,759 participantes y evaluaron cuatro extractos de plantas y 6 suplementos dietéticos. 5 ensayos investigaron extractos de plantas (Euterpe oleracea, medicina herbal tradicional Hangekobokuto, Neurotec y cafeína), mientras que 16 examinaron suplementos dietéticos (melatonina, zinc, ácido alfa-lipoico, manganeso, complejo de vitamina B y nicotinamida). El metaanálisis reveló que no hubo una eficacia significativa de la cafeína en la reducción del impacto del tinnitus en la CVRS (DME=0.07; IC del 95%: -0.73 a 0.86; $I^2$=0.0%). La melatonina mostró una reducción modesta en la intensidad del tinnitus vs placebo (OR=2.52; IC del 95%: 1.33-4.80; k=2, 168).

**Conclusiones.** Solo la melatonina mostró una eficacia modesta en la reducción del tinnitus, aunque la evidencia sigue siendo incierta debido a limitaciones metodológicas. Se necesitan más investigaciones de calidad con seguimiento a largo plazo que confirmen estas observaciones.

**Palabras clave.** Tinnitus; Suplementos dietéticos; Melatonina; Extractos de plantas; Ensayos controlados aleatorizados

## HIGHLIGHTS

- Melatonin shows modest potential in reducing tinnitus loudness, but evidence remains uncertain due to small sample sizes (n=46-122), high dropout rates (>20%) and variable study quality.
- Evaluated interventions including Euterpe oleracea extract, traditional herbal medicine (Hangekobokuto), commercial formulation (Neurotec), caffeine, and dietary supplements showed no significant effect on tinnitus symptoms or HRQoL.
- High heterogeneity in outcome measures limits evidence synthesis and impedes clinicians' ability to make informed treatment decisions, highlighting the need for standardized assessment tools to guide treatment selection in clinical practice.
- Clinical trials should define meaningful improvement as ≥20-point reduction in THI/TFI scores, include both subjective (VAS for loudness/annoyance) and objective measures, and report adverse events systematically to enable evidence-based recommendations for dietary supplements or plant-based interventions.

## INTRODUCTION

Tinnitus, the perception of sound without an external source, is a global burden affecting between 4.1% and 37.2% of adults[1,2]. It manifest as ringing or hissing in the ears or head, resulting from the brain's misinterpretation of abnormal auditory activity[1]. While both objective (sound heard by patient and examiner) and subjective (sound heard only by patient) forms exist, subjective tinnitus is more common and occurs without organic or pathological lesions[3,4]. Its prevalence increases with age, affects both sexes equally, and persistently bothers 3-31% of sufferers[3]. The condition significantly impacts quality of life, causing difficulties with concentration, sleep, and communication, often triggering anxiety and depression [5]. Its disabling effects can parallel those of deafness, particularly as approximately 90% of patients also have hearing loss[5].

Despite its significant prevalence and impact, tinnitus lacks standardized treatment approaches, largely due to complex and multifactorial pathophysiology involving maladaptive neuroplasticity, central auditory system dysfunction, and oxidative stress[1,3]. These mechanisms provide a foundation for exploring therapeutic interventions targeting oxidative stress, neuroinflammation, and neuronal hyperactivity[1]. However, no drug has received

approval from international regulatory bodies for tinnitus treatment[4,5]. Current diagnosis relies on self-administered questionnaires, psychological evaluations, and assessments of perceptual characteristics[3,6]. Management strategies primarily focus on symptom control through education, psychology-based approaches, sound therapy, hearing aids, and alternative and traditional therapies[3,7], while drug therapies primarily address comorbid symptoms like insomnia or anxiety[3,8].

In this context, many patients turn to alternative treatments, particularly plant extracts and dietary supplements, seeking relief from their symptoms[9,10]. These interventions are chosen for their natural origin, accessibility, and lower cost compared to traditional treatments, though their safety and effectiveness are not always guaranteed[3,9]. Plant extracts, whether derived from the entire plant or specific parts, are widely used; despite limited scientific evidence supporting their efficacy[9,10]. Similarly, while approximately fifty-two dietary supplements have been reported for tinnitus treatment, including vitamin B12, zinc, and melatonin[9], scientific evidence supporting their efficacy remains limited [9,10,11], despite their popularity among older adults[8].

While previous reviews have examined specific supplements like zinc and melatonin[12,13], no comprehensive systematic review has synthesized the evidence for both dietary supplements and plant extracts in tinnitus treatment. This gap is particularly notable given the variety of interventions being studied, including Açaí, traditional herbal medicines (e.g., Hangekobokuto), caffeine, and various dietary supplements (melatonin, alpha-lipoic acid, manganese, zinc, and vitamin B complex). Although previous research on vitamin B complex showed no superiority over placebo[14], and a 2015 review suggested potential benefits of melatonin for tinnitus-related sleep disorders[12], the overall evidence landscape remains fragmented and unclear.

Therefore, this systematic review aims to comprehensively evaluate the efficacy of plant extracts and dietary supplements for tinnitus treatment, addressing a critical gap in current literature and providing evidence-based guidance for clinicians and patients.

## METHODS

*Study design and protocol registration*

This systematic review and meta-analysis followed PRISMA guidelines[15], with the protocol registered in PROSPERO (CRD42023446824).

*Research question framework*

The review question followed the PICO framework. The study population consisted of adults with acute or chronic tinnitus. Interventions encompassed herbal substances (e.g., Açaí extract, caffeine) and dietary supplements (e.g., melatonin, alpha-lipoic acid, manganese, zinc sulfate, and vitamin B complex). Comparisons included placebo or concomitant interventions. Outcomes focused on tinnitus severity reduction, assessed through subjective measures including visual analogue scales (VAS), tinnitus loudness or pitch matching, and standardized self-reported questionnaires assessing the impact on health-related quality of life (HRQoL).

*Search strategy*

A systematic search was conducted in PubMed from inception through October 31, 2024. The search strategy, developed with a medical librarian, combined three conceptual blocks: tinnitus-related terms, dietary supplements and plant extracts interventions, and clinical trial methodology and outcomes assessment. Both Medical Subject Headings (MeSH) and free-text terms ([tiab]) were utilized, including specific terms for supplements (e.g., "melatonin", "zinc", "vitamins"), plant-based interventions (e.g., "herbal medicine", "plant extracts"), and validated outcome measures (e.g., "Tinnitus Handicap Inventory", "visual analog scale"). The complete search strategy is available in Supplementary Table S1 (https://www.renhyd.org/renhyd/article/view/2308/1305). Reference lists of eligible trials, systematic reviews, and meta-analyses were manually screened. The search was limited to English-language publications, with no date restrictions.

*Inclusion criteria*

Studies were included if they met four criteria: 1) design: randomized controlled trials (RCTs) or crossover trials (CO); 2) participants: adult patients with subjective tinnitus (either acute or chronic), or tinnitus due to sudden sensorineural hearing loss; 3) interventions: plant extracts (therapeutic plant-based substance or their derivatives, such as Açaí, caffeine), or dietary supplements (including melatonin, alpha-lipoic acid, manganese, zinc, vitamin B

complex); and 4) comparators: no intervention, placebo, or concomitant intervention control groups.

*Outcome measures*

The study included three outcome categories to evaluate the efficacy of plant extracts and dietary supplements on tinnitus: 1) subjective severity, measured through VAS for self-reported frequency or annoyance[7]; 2) psychoacoustic parameters, assessed through tinnitus loudness or pitch matching in decibels[7]; and 3) health-related quality of life (HRQoL), evaluated using standardized self-reported questionnaires including Tinnitus Handicap Inventory (THI), Tinnitus Functional Index (TFI), Tinnitus Handicap Questionnaire (THQ), or the Tinnitus Questionnaire (TQ)[7]. Detailed characteristics of assessment tools are provided in Table S2 (supplementary material, https://www.renhyd.org/renhyd/article/view/2308/1305).

*Exclusion criteria*

Studies were excluded if they met any of the following criteria: 1) non-RCT trials, or studies lacking a control group; 2) trial using Ginkgo biloba extracts, due to insufficient evidence for efficacy based on recent reviews, including an updated Cochrane review [11]; 3) animal studies; 4) studies where tinnitus was a secondary outcome in populations with other primary conditions (e.g., dementia, Alzheimer's disease); and 5) non-English publications.

*Study selection process*

The reviewers (YEC, GD) independently screened the titles and abstracts against predefined inclusion and exclusion criteria. Full texts of potentially eligible studies were then retrieved and evaluated in detail. Disagreements were resolved through discussion, with a third author (RP) consulted when consensus could not be reached.

*Data extraction*

Two reviewers (YEC, LM) independently extracted data using standardized Excel forms. Extracted information included: first authors, publication year, recruitment country, study design, participant number, tinnitus type, treatment characteristics (dosage and administration methods), co-interventions, follow-up time, dropouts, adverse events, and outcome measurement. Disagreements were resolved through discussion.

*Risk of bias assessment*

Two reviewers (YE, RP) independently assessed risk of bias using the Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB2)[16]. Assessment covered six domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, selection of reported results, and other bias sources. Studies were classified as 'low risk' (all domains rated low), 'some concerns' (one or more domains with issues but none at high risk), or 'high risk' (significant methodological flaws). This classification system determined the overall quality of each study. Disagreements were resolved through consultation with a third author (LM).

*Certainty of evidence assessment*

We evaluated evidence certainty for each meta-analysis outcome using the modified GRADE (Grading, Development and Evaluation of Recommendations) approach. This framework assessed five domains that could reduce evidence certainty: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Assessment method included: 1) inconsistency: $I^2$ statistic [$I^2 = ((Q - df)/Q) \times 100\%$], where Q is Cochran's heterogeneity statistic and df is the degrees of freedom [17]; 2) publication bias: Egger's test [$bias = \beta_0 + \beta_1 \times (1/SE)$], where SE is the standard error of the effect estimate [18]; 3) imprecision: optimal information size (OIS) calculation [$n = 2 \times (Z\alpha + Z\beta)^2 \times \sigma^2/\delta^2$], where $Z\alpha$ is the standard normal deviate for $\alpha$, $Z\beta$ is the standard normal deviate for $\beta$, $\sigma$ is the population standard deviation, and $\delta$ is the minimum clinically important difference[19,20]. Evidence was ultimately rated as high, moderate, low, or very low certainty.

*Statistical analysis*

Analyses were conducted using RStudio (version 2022.07.02, RStudio PBC, Boston, MA, US) with the 'metafor' package. Random-effect models with restricted-maximum likelihood (REML) estimation were employed for all analyses. For continuous outcomes, we calculated standardized mean differences (SMDs)[18] with 95% confidence intervals (95% CIs) using bias-corrected Hedges' g[18]. For binary outcomes, odds ratios (OR) and their 95% Cis were computed. Forest plots were generated to visualize treatment effects.

Statistical heterogeneity was assessed using $I^2$ statistics for between-study variance ($I^2$), $tau^2$ for absolute heterogeneity, and Q statistic (Q) for heterogeneity significance[18]. Subgroup analyses were conducted where possible. We performed sensitivity analyses using the leave-

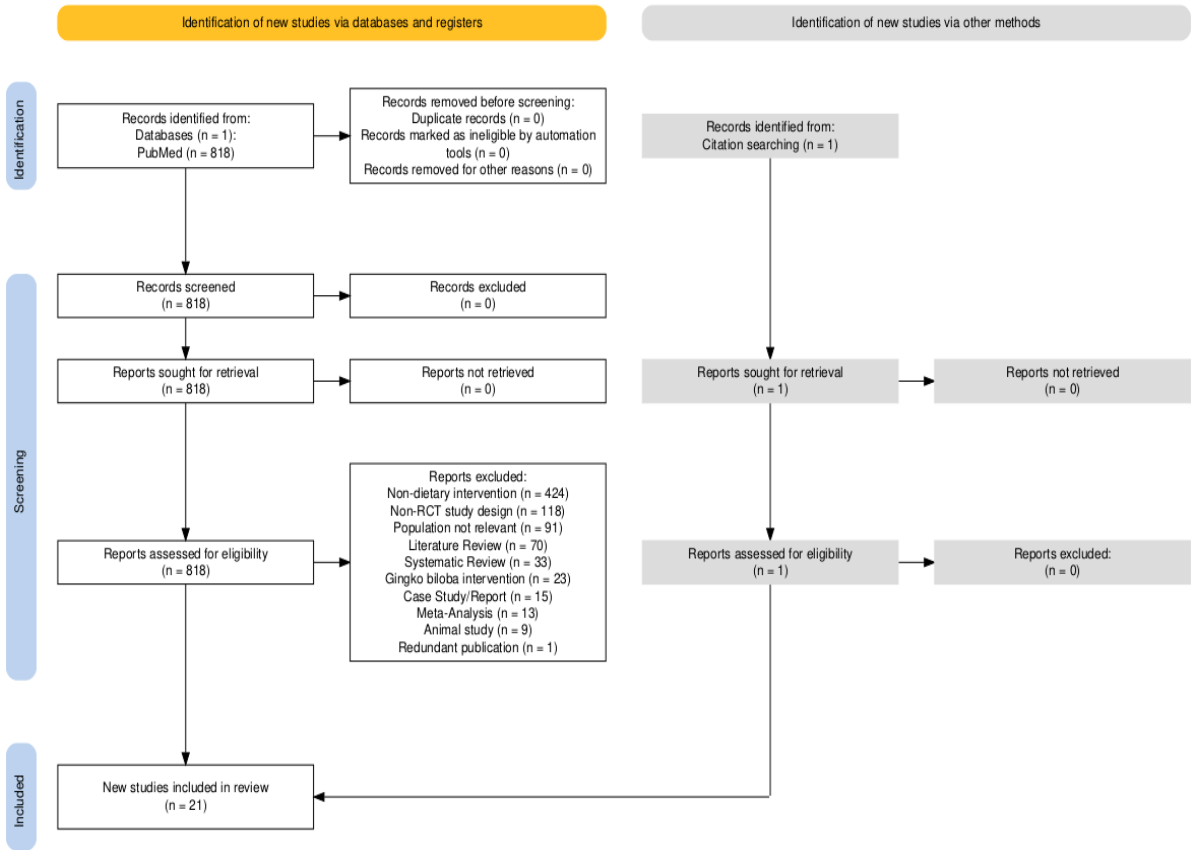
one-out method. Publication bias was evaluated through funnel plot inspection and the trim-and-fill method.

## RESULTS

### *Study selection*

The bibliographic search in PubMed identified 818 records. One additional record was identified through citation searching. After checking for duplicates, no duplicate records were found, and 818 articles underwent title and abstract screening. Following this process, 21 studies fulfilled all inclusion criteria and were selected for the final review (Figure 1 and supplementary material, https://www.renhyd.org/renhyd/article/view/2308/1305).

**Figure 1.** Flowchart of the search and selection of papers on efficacy of plant extracts and dietary supplements for tinnitus (published before 31 October 2024) according to PRISMA guidelines.



*Study characteristics*

The characteristics of the 21 articles are summarized in Table 1. The trials, published between 1987 and 2024, showed uneven geographic distribution: 28.6% (6 studies) from the USA (4)[21–24] and Brazil (2)[25,26]; 42.8% (9 studies) in Europe (including the United Kingdom (1)[27], Greece (3)[28–30], Spain (1)[31], Denmark (1)[32], the Netherlands (1)[13], Italy (1)[33], and Romania (1)[34]); 19.0% (4 studies) in the Middle East region (Turkey (1)[35] and Iran (3)[36–38]); and 9.6% (2 studies) in Asia (India (1)[39], Japan (1)[40]). No studies were identified from Africa or Oceania. All studies were RCTs, with four being CO (RCTs)[20,21,23,26]. The trials included 1,759 participants (mean 83.8 ±50.3 per study; range 30 to 240), with mean age of 53.8 years (±9.9; IQR 7.7; range: 22-67.5). While gender distribution details are available in Table S3, comorbidity reporting was inconsistent across studies.

In tinnitus assessment, THI was the predominant tool for HRQoL measurement (47.6%, 10 studies), with additional use of THQ and TSI. For subjective perception, the VAS for loudness (19%, 4 studies) and for annoyance in one study. Psychoacoustic outcomes using pitch-match procedures in 14.3% (3) of trials.

Interventions fell into two categories: plant extracts and dietary supplements. Plant extracts were investigated in 5 trials: *Euterpe oleracea* (Açaí) extract[24], Hangekobokuto[36], Neurotec [35], and caffeine[25,26]. Dietary supplements were examined in 16 studies, including: melatonin [21,23,29,31,32,34], zinc [20,30,33], alpha-lipoic acid [28], manganese with Lipoflavonoid Plus [22], vitamin B (B1, B6, and B12)[27,38,39], and vitamin B3 (nicotinamide)[13], and MemoVigor 2[30]. Treatment durations ranged from 0.1 to 24 weeks (median 8 weeks, IQR 8.0).

Clinical improvement parameters were defined in 50% of studies, typically as a 20-point THI reduction. No serious adverse events were reported (see supplementary Table S4).

*Risk of bias assessment with RoB2*

Overall, 57.1% (12/21) of studies showed 'some concerns' (7/12) or 'high risk' (5/12) of bias (Figure S1). The randomization process was the most affected domain due to poor reporting of randomization and allocation concealment, followed by missing outcome data due to high dropout rates. As shown in the summary graph, at the bottom of Figure S1, while some studies demonstrated low risk across multiple domains, the quality of methodological reporting varied considerably, with better control in outcome measurement and result selection domains.

**Table 1.** Characteristics of the included studies.

| Author (year) Study location [reference] | Design and setting | Sample size T:C (n) | Intervention protocol | Control/comparisons | Treatment duration in weeks | Outcome's measurement | Dropout rate (%) | Risk of bias assessment |
|---|---|---|---|---|---|---|---|---|
| Abtahi et al., (2017) Iran [34] | RCT, parallel arms, DB Hospital center | (n=70) 35:35 | Melatonin (3 mg/evening) | Sertraline (50 mg/evening) | 12 | THI* | 4.29 | Some concerns |
| Albu et al., (2014) Romania [32] | RCT, parallel arms, DB University hospital | (n=60) 30:30 | Melatonin 3 mg + four intratympanic (IT) dexamethasone injections | Melatonin (3 mg) + IT placebo | 12 | THI*, (VAS) loudness; (VAS) awareness | 8.33 | Low |
| Arda et al., (2003) Turkey [33] | RCT, parallel arms, DB Hospital center | (n=41) 28:13 | Zinc (50 mg/day) | Placebo | 8 | (VAS) loudness*, Tinnitus matching | 0.00 | Some concerns |
| Balatsouras et al., (2024) Greece [30] | RCT. Parallel arms, DB Hospital center | (n=240) 120:120 | 900 mg of MemoVigor 2 (Ginkgo biloba 3%, Bilberry 1%, phospholipids, vitamins B1/B6/B12/C/E, selenium, magnesium, potassium, L-acetylcarnitine) once daily | Placebo | 12 | THI* | 15.0 | Low |
| Claire et al., (2010) United Kingdom [26] | RCT [a], CO, DB University center studies | (n=66) 33:33 | Days 1-15, caffeine-containing tea and/or coffee supplied (maintaining usual caffeine consumption) Days 16-18, phased withdrawal (1/2, 1/4 then 1/8th normal caffeine consumption) | Days 19-30, decaffeinated supplies | 4 | TQ*, (VAS) annoyance, (VAS) frequency | 19.70 | High |
| Coelho et al., (2013) USA [20] | RCT, CO, DB Tinnitus clinic | (n=116) 58:58 | Zinc (50 mg/day) followed by a washout period of 30 days | Placebo | 16 | THQ*, (VAS) loudness, (VAS) annoyance | 23.28 | Low |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dadgarnia et al, (2024) Iran [38] | RCT, parallel arms, DB Hospital center | (n=140) 70:70 | Vitamin B12 (500 microgram/day) | Placebo | 4 | THI*, VAS | 0.00 | Some concerns |
| Hulshof et al., (1987) Netherland [13] | RCT, parallel arms, DB University hospital | (n=48) 24:24 | Nicotinamide (B3 vitamin) capsules (70 mg/day) | Placebo | 4 | (VAS) annoyance*, Tinnitus matching | 0.00 | Some concerns |
| Hurtuk et al., (2011) USA [21] | RCT, CO, DB University center | (n=84) 42:42 | Melatonin (3 mg/evening) washout period of 30 days | Placebo | 4 | TSI*, PSQI, BDI | 27.38 | Low |
| Ino et al., (2013) Japan [36] | RCT, parallel arms, DB University hospital | (n=76) 38:38 | 12 tablets twice a day (*Pinellia* tuber 6.0g/day; *Poria sclerotium*, 5.0g/day; Magnolia bark, 3.0g/day; *Pirellia* herb, 2.0g/day; Zingiber rhizome 1.3g/day) | Placebo | 12 | THI*, (VAS) loudness, (VAS) annoyance, SF-36 | 0.00 | Some concerns |
| Khosravi et al., (2023) Iran [35] | RCT, parallel arms, DB Hospital center | (n=150) 80:70 | 100 mg of Neurotec (*Rosa canina*, *Urtica dioica*, *Tanacetum vulgare*) twice a day | Placebo | 12 | PTAs*, THI, (VAS) loudness, (VAS) annoyance | 31.33 | Low |
| Ledesma et al., (2021) Brazil [25] | RCT, parallel arms, TB University hospital | (n=80) 40:40 | Caffeine (300 mg) | Placebo | Same day: evaluation one hour later | THI*, (VAS) loudness, Tinnitus matching | 0.00 | Low |
| Lopez-Gonzalez et al., (2007) Spain [29] | RCT, parallel arms, DB University hospital | (n=120) 30:30:30:30 | Sulpiride (150 mg/day) or Melatonin (3 mg/evening) or sulpiride (150 mg/day) + melatonin (3 mg/evening) | Placebo | 4 | (VAS) loudness*, (VAS) perception: increase to disappearance | 17.50 | Some concerns |
| Markou el al., (2004) Greece [27] | RCT, parallel arms, DB University hospital | (n=108) 24:24:24:36 | Trimetazidine (60 mg) +Piracetam (12 g prednisolone (15 mg) +within the first 30 vitamin B complex (B1, B6 andminutes followed by B12) or trimetazidine 60 mg) | another 12 g during | 6 | Tinnitus questionnaire | 0.00 | Some concerns |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | or prednisolone + vitamin complex (60mg) | B24/h drip infusions + prednisolone (75 mg) | | modified*, acoustic gain | |
| Neri et al., (2009) Italy [31] | RCT, parallel arms, DB University hospital | (n=102) 34:34:34 | Sulodexide (250 mg/day) + Melatonin (3 mg/evening) or melatonin (3 mg/evening) | Placebo | 12 | THI*, Tinnitus matching | 0.00 Some concerns |
| Oppitz et al., (2022) Brazil [24] | RCT, parallel arms, DB University hospital | (n=30) 15:15 | Açaí extract (100 mg/day) | Placebo | 12 | THI*, BDI | 0.00 Some concerns |
| Paaske et al., (1991) Denmark [30] | RCT, parallel arms, DB University hospital | (n=48) 23:25 | Zinc (100 mg/day) | Placebo | 8 | (VAS) loudness*, Tinnitus matching | 0.00 Some concerns |
| Petridou et al., (2019) Greece [28] | RCT, parallel arms, DB NDA | (n=70) 35:35 | 1 multivitamin/multimineral tablet/day + alpha-lipoic acid (600 mg/day) | Placebo | 12 | Tinnitus matching*, THI, TFI, (VAS) annoyance | 10.00 Low |
| Rojas-Roncancio et al., (2016) USA [22] | RCT, parallel arms, DB University center | (n=40) 20:20 | Manganese (8 mg/day) + Lipoflavonoid Plus pills three times a day | Lipoflavonoid Plus | 24 | Tinnitus matching*, THQ, (VAS) loudness | 30.00 Some concerns |
| Rosenberg et al., (1998) USA [23] | RCT, CO, DB Hospital | (n=30) 15:15 | Melatonin (3 mg/evening) washout period of 7 days | Placebo | 4 | THI*, tinnitus matching | 23.33 Some concerns |
| Singh et al., (2016) India [39] | RCT, parallel arms, DB Medical College | (n=40) 20:20 | Vitamin B12 (2500 mcg/week IM) | Placebo (isotonic saline 1ml IM) | 6 | THI*, VAS | 0 Some concerns |

**Abbreviations:** BDI: Beck Depression Inventory; CO: Crossover trial; DB: Double-blind; mcg: Micrograms; n: Number of participants for each group; NDA: No data available; PSQI: Pittsburgh Sleep Quality Index; PTAs: Pure-tone audiograms; RCT: Randomized controlled trial; SF-36: Short Form Health Survey 36; T:C (n): Number of participants in treatment and control groups; TB: Triple-blind; THI: Tinnitus Handicap Inventory; THQ: Tinnitus Handicap Questionnaire; TQ: Tinnitus Questionnaire; TSI: Tinnitus Severity Index; VAS: Visual analogue scale.
**Note:** [a] pseudo-randomized trial; * primary outcome.

**Findings from the meta-analysis**

*Effects of caffeine and melatonin on HRQoL and tinnitus loudness*

For HRQoL, caffeine showed no significant effect compared to placebo in both common and random effects models (SMD=0.07; 95% CI: -0.73 to 0.86; p=0.706) with low heterogeneity ($I^2$=0.0%; Q=0.14; p=0.706) across two studies [25,26] (n=73 per group) (Figure 2,A). For melatonin interventions (Figure 2,B), three subgroup analyses were performed: combined therapy (n=95 intervention, n=96 control) showed a non-significant effect (MD=-2.43; 95% CI: -4.72 to -0.14; $I^2$=64.1%); melatonin versus placebo (n=57 intervention, n=57 control) demonstrated no significant difference (MD=4.53; 95% CI: -1.85 to 10.90; $I^2$=21%); and melatonin versus other drugs (n=35 intervention, n=35 control) showed no significant effect (MD=-6.67; 95% CI: -17.21 to 3.87) [24,33,34,36]. For tinnitus loudness as a binary outcome (Figure 2, C), melatonin showed a significant reduction compared to placebo (OR of 2.52; 95% CI: 1.33-4.79; p=0.005), and low heterogeneity ($I^2$=0.00; Q=0.10; p=0.755) for the two trials [21,23].

*Dropout rate and publication bias*

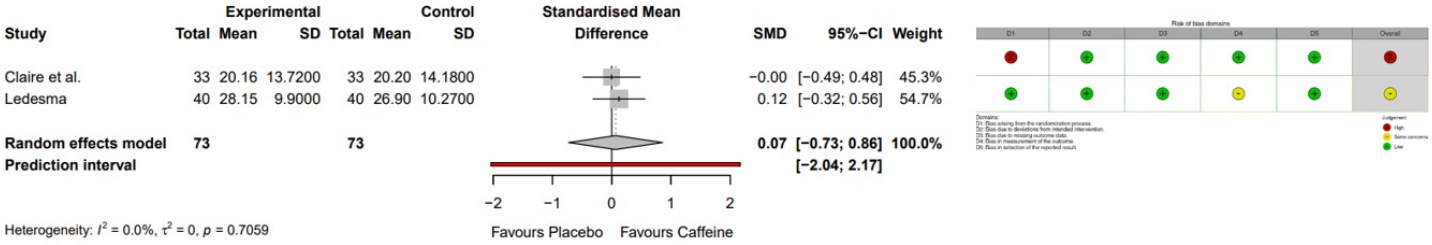
The pooled dropout rate across 21 studies (n=1,759) was 19% (95% CI: 17%-22%) using a random effect model, with substantial heterogeneity ($I^2$=79.9%; $\tau^2$=1.9662; p<0.0001). Individual rates ranged from 0% to 31% (Khosravi et al.) and 30% (Rojas-Roncancio et al.), as detailed in Figure S2. Funnel plots (Figure S3) showed asymmetric distribution patterns across all comparisons, although trim-and-fill analysis did not impute any studies for caffeine and melatonin effects. Formal publication bias assessment via Egger's test was not feasible due to limited studies per comparison (<10). Leave-one-out sensitivity analysis (Figure S4) confirmed stability of effect estimates when removing individual studies.

*Certainty of evidence*

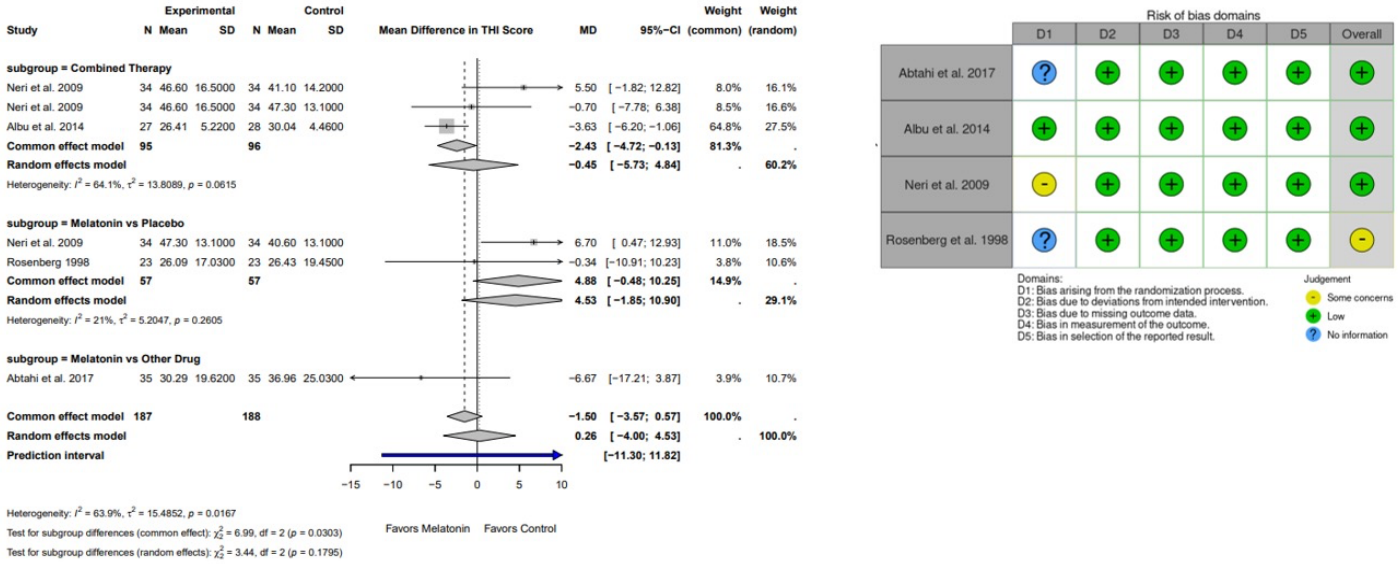
All outcomes were rated as low-certainty evidence (●●○○) using the GRADE system (Table 2). For HRQoL, neither caffeine (SMD: 0.07, 95% CI: -0.73 to 0.86) nor melatonin showed significant effects compared to placebo. Melatonin demonstrated a significant improvement on tinnitus loudness (OR: 2.52, 95% CI: 1.33 to 4.79). Evidence was downgraded due to serious risk of bias (as shown in the risk of bias panels of Figures 2-4) and imprecision from small sample size

**Figure 2.** Metanalysis of the effect of caffeine on HRQoL (A), melatonin on HRQoL (B), and melatonin on tinnitus loudness (C). Forest plot showing odd ratios (OR) and 95% CI. The risk of bias was assessed using RoB2 tool across six domains using traffic light system.

**A**




**B**




**C**

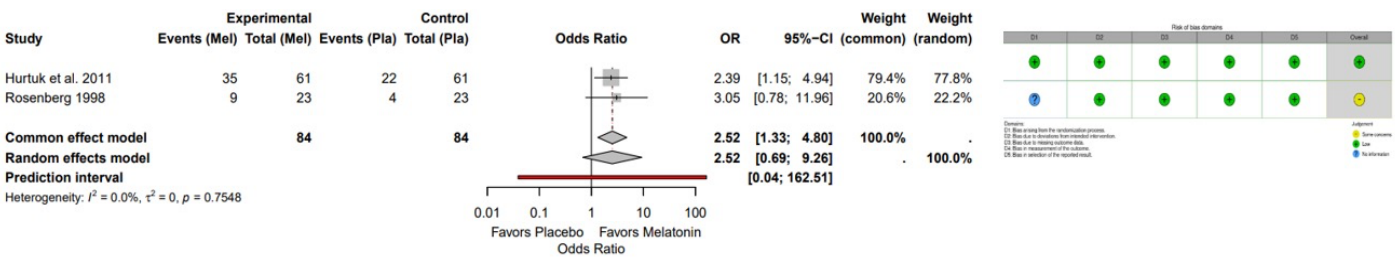


**Table 2.** GRADE summary of findings.

| Outcome | Intervention | Comparator | Pooled effect (95% CI) | Studies (n) | Study design | Certainty of evidence | Downgrade reasons |
|---|---|---|---|---|---|---|---|
| **HRQoL** | Caffeine | Placebo | SMD: 0.07 (-0.73; 0.86) | 2 (146) | RCT | ●●○○ Low | • Risk of bias [1]<br>• Imprecision [2] |
| **HRQoL** | Melatonin | Placebo | MD: 4.53 (-1.85; 10.90) | 2 (114) | RCT | ●●○○ Low | • Risk of bias [1]<br>• Imprecision [2] |
| **Tinnitus Loudness** | Melatonin | Placebo | OR: 2.52 (1.33; 4.80) | 2 (168) | RCT | ●●○○ Low | • Risk of bias [1]<br>• Imprecision [2] |

Certainty of Evidence Legend: ● ● ● ● High; ● ● ● ○ Moderate; ● ● ○ ○ Low; ● ○ ○ ○ Very Low
Abbreviations: HRQoL: health-related quality of life; SMD: Standardized Mean Difference; MD: Mean Difference; OR: Odds Ratio; N: number of participants; RCT: Randomized Controlled Trial; 95% CI: 95% Confidence Interval.
Footnotes: [1] Downgraded one level due to serious risk of bias (multiple domains showing some concerns or high risk); [2] Downgraded one levels due to imprecision (number of studies < 3; Wide confidence intervals).

## DISCUSSION

This systematic review and meta-analysis evaluated the efficacy of plant extracts and dietary supplements on tinnitus, analyzing 21 studies (1,759 adults) across three key outcomes: subjective perception, HRQoL, and perceived loudness. The GRADE assessment rated all meta-analyzed outcomes as low-certainty evidence (●●○○), primarily due to serious risk of bias and imprecision from small sample sizes. Despite low statistical heterogeneity ($I^2$=0%), the limited number of trials (<3 per intervention) and small sample sizes prevented robust assessment of publication bias and reduced confidence in effect estimates. Results varied across studies due to diverse outcome measures and differences in participants' chronic tinnitus conditions. The evidence synthesis focused on nine interventions: four plant extracts and five dietary supplements, with only melatonin and caffeine providing sufficient data for meta-analysis.

Meta-analysis of two crossover trials (164 participants) demonstrated that melatonin modestly reduces tinnitus loudness (OR: 2.52, 95% CI: 1.33 to 4.79)[21,23]. Both trials used similar protocols (30-day treatment, 3mg melatonin dosage), with adequate washout periods given melatonin's short half-life (10-60 minutes post-oral administration)[41]. Although melatonin may improve sleep quality in chronic subjective tinnitus patients[36,42], its long-term clinical remains uncertain. Regarding caffeine, our quantitative synthesis showed no efficacy in reducing the impact of tinnitus on HRQoL (SMD: 0.07, 95% CI: -0.26 to 0.39). This aligns with previous reviews[43], showing mixed results, where some individuals reported temporary

relief[8,44], but larger studies failed to establish a clear benefit[8]. The relationship between caffeine and tinnitus remains complex, warranting more rigorous investigation.

Additionally, evidence for other interventions remains limited. Single studies of plant extracts (Açaí extract[24], Hangekobokuto compound[36], and Neurotec compound[35], alpha-lipoic acid[28], manganese[22] and MemoVigor 2[30]) preclude definitive conclusions about their efficacy. Furthermore, trials using a vitamin B complex in combination with drugs[27] showed no evidence of effect on subjective discomfort or HRQoL. Studies of B12[38,39] and vitamin B3[13] similarly demonstrated no significant benefits, although methodological heterogeneities prevented meta-analysis.

These findings align with current evidence and clinical guidelines. While various supplements have been explored for tinnitus management, including zinc, manganese, and B vitamins, results remain inconsistent[3,44]. Recent recommendations[8,45] and the European multidisciplinary guideline for tinnitus management specifically caution against using dietary supplements and herbal medicines as primary treatments, citing lack of proven efficacy and potential risks[3]. Although certain supplements may benefit specific conditions (e.g., zinc deficiency, sleep disturbances), they should not be recommended as standalone treatments [44,46].

Methodological heterogeneity across studies posed significant challenges for evidence synthesis. Outcome measures varied considerably, with two Visual Analog Scales (VAS-loudness and VAS-annoyance) assessing subjective tinnitus perception and five questionnaires evaluating HRQoL impact (THI, TSI, THQ, TQ, TQ-SF), each with distinct sensitivities to tinnitus domains[6,47]. While tinnitus matching could provide sensitive endpoint measures[4], only 14% of studies reported these outcomes. Additionally, despite focusing on subjective chronic tinnitus[7], only six established minimum tinnitus scores as inclusion criteria. The geographical concentration of trials in Europe and North America, with limited representation from Asia, Africa, and Oceania, further constrains the generalizability of findings, as populations from underrepresented regions might differ in terms of healthcare access, dietary patterns, and genetic factors affecting treatment responses[2,4].

*Future directions, strengths and limitations*

Future studies should adhere to CONSORT guidelines, particularly regarding randomization, allocation concealment, and blinding. Studies should establish minimum threshold for

tinnitus loudness using validated measurement tools. The Unification of Treatments and Interventions for Tinnitus Patients Trial[48] offers standardized methodologies that could enhance study comparability, emphasizing longer follow-up periods and the consideration of common comorbidities like insomnia, anxiety, and depression.

Understanding tinnitus mechanisms remains crucial, given limited evidence on tinnitus risk factors[49]. Novel approaches, such as machine learning and random forest regression[50], show promise for predicting optimal interventions but requires validation in larger, diverse populations. Recent findings on problematic tinnitus predictors[51] emphasize the importance of identifying subgroups for tailored interventions.

Despite our comprehensive search strategy, this review has several limitations. The exclusion of non-English publications, varying methodological quality across studies, and geographical concentration in Europe and North America limit global applicability. Inconsistent reporting of comorbidities and the limited number of studies prevented us from performing robust subgroup analyses and publication bias assessment, though the trim-and-fill method and funnel plots were performed.

## CONCLUSIONS

The systematic review and meta-analysis found low-certainty evidence that melatonin may slightly reduce tinnitus loudness, while caffeine showed no effect on tinnitus symptoms or HRQoL. Evidence for other plants extracts and dietary supplements remains insufficient due to limited studies and methodological limitations. The GRADE assessment revealed serious risk of bias and imprecision across studies, primarily due to small sample sizes. These findings support current clinical practice guidelines that advise against dietary supplements and herbal medicines as primary treatments for tinnitus. While specific supplements might offer targeted benefits (e.g., melatonin for sleep disturbances), their routine use in tinnitus management cannot be recommended based on current evidence.

## COMPETING INTERESTS

The authors declare that there were no conflicts of interest.

## AUTHORS' CONTRIBUTIONS

YE, GD, LM, and RP contributed to the study's conceptualization, design, data collection, analysis, and interpretation. All authors were involved in the methodology and initial article drafting. RP, LM and GD revised the draft. YE completed the final editing. All authors reviewed and approved the final version of the manuscript.

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## DATA AVAILABILITY

Data supporting this study's findings are available from the corresponding author upon reasonable request.

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