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**SUPPLEMENTARY MATERIAL**

**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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**Table S1. Detailed search strategy. Run date: October 31, 2024.**

Database	Syntax	Outcome
PubMed	("Tinnitus"[Mesh] OR tinnitus[tiab] OR "phantom sound"[tiab] OR "ringing in ears"[tiab]) AND ("Dietary Supplements"[Mesh] OR "Plant Extracts"[Mesh] OR "Phytotherapy"[Mesh] OR "Complementary Therapies"[Mesh] OR "Medicine, Traditional"[Mesh] OR "Medicine, Kampo"[Mesh] OR "traditional medicine"[tiab] OR "dietary supplement**"[tiab] OR "nutritional supplement**"[tiab] OR "food supplement**"[tiab] OR "herbal medicine**"[tiab] OR "plant extract**"[tiab] OR "herbal capsule**"[tiab] OR "herbal supplement**"[tiab] OR "Neurotec"[tiab] OR "melatonin"[Mesh] OR melatonin[tiab] OR "Zinc"[Mesh] OR zinc[tiab] OR "Vitamins"[Mesh] OR vitamin*[tiab] OR "Thiamine"[Mesh] OR "vitamin B"[tiab] OR "Thioctic Acid"[Mesh] OR "alpha-lipoic acid"[tiab] OR "thioctic acid"[tiab] OR "Caffeine"[Mesh] OR caffeine[tiab] OR "Manganese"[Mesh] OR manganese[tiab] OR "Niacinamide"[Mesh] OR nicotinamide[tiab] OR niacinamide[tiab] OR niacin[tiab] OR "Antioxidants"[Mesh] OR antioxidant*[tiab] OR "Hangekobokuto"[tiab] OR "Hangekoboku-to"[tiab] OR "Banxia houpo"[tiab] OR "Kampo"[tiab] OR "acai"[tiab] OR "Euterpe oleracea"[tiab] OR "complementary medicine"[tiab] OR "alternative medicine"[tiab] OR "dietary therapy"[tiab] OR "nutritional therapy"[tiab] OR "Japanese herbal"[tiab] OR "traditional Japanese"[tiab]) AND ("Clinical Trial"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Random Allocation"[Mesh] OR random*[tiab] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR ((clinical[tiab] OR controlled[tiab]) AND trial[tiab]) OR "therapeutic use"[subheading] OR "therapy"[subheading]) AND ("Treatment Outcome"[Mesh] OR "severity"[tiab] OR "improvement"[tiab] OR "effect"[tiab] OR "effects"[tiab] OR "THI"[tiab] OR "Tinnitus Handicap Inventory"[tiab] OR "TFI"[tiab] OR "Tinnitus Functional Index"[tiab] OR "quality of life"[tiab] OR "QoL"[tiab] OR "VAS"[tiab] OR "visual analog**"[tiab] OR "tinnitus severity"[tiab] OR "tinnitus perception"[tiab] OR "tinnitus questionnaire"[tiab] OR "improvement score"[tiab] OR "symptom score"[tiab] OR "treatment outcome"[tiab] OR "clinical improvement"[tiab] OR "subjective improvement"[tiab] OR "tinnitus improvement"[tiab] OR "tinnitus symptoms"[tiab] OR "tinnitus score"[tiab] OR "audiological assessment"[tiab] OR "hearing test"[tiab] OR "audiometry"[tiab] OR "clinical effect**"[tiab] OR "therapeutic effect**"[tiab] OR "treatment effect**"[tiab])	818

**Table S2. Questionnaires and scales to assess tinnitus outcomes. Aims of measure, characteristics, range, interpretation, and clinically important change.**

Name (abbreviation) / authors, (publication year)	Objective	Characteristics	Score range	Interpretation	Clinically important change
Tinnitus Handicap Inventory (THI) Newman et al. (1996)	Measures the impact of tinnitus on quality of life, sleep, depression, and mood	25-item self-administered questionnaire with three subscales (functional, emotional, and catastrophic). Patients rate symptom frequency/intensity on a three-point Likert Scale (0-4)	0-100	Slight tinnitus: Grade 1 (0-16) Mild tinnitus: Grade 2 (18-36) Moderate tinnitus: Grade 3 (38-56) Severe tinnitus: Grade 4 (58-76) Catastrophic tinnitus: Grade 5 (78-100):	Seven points considered minimal clinically significant change
Tinnitus Handicap Questionnaire (THQ) Kuk et al. (1990)	Assesses patients' perceived tinnitus-related handicap	27-item self-administered questionnaire measuring tinnitus impact through three subscales: physical health, emotional status, and social consequences (including hearing difficulties and tinnitus perception)	0-100	Higher scores indicate greater handicap (no standardized grading system available)	21 points proposed, though reliability may be limited due to inconsistencies in the third factor subscale
Tinnitus questionnaire (TQ) 1 <sup>st</sup> version: Hallam et al. (1996) 2 <sup>nd</sup> version: Hallam et al. (2008)	Evaluates tinnitus severity and associated psychological distress	52-item self-administered questionnaire assessing five domains: emotional/cognitive distress, intrusiveness, auditory perceptual difficulties, sleep disturbances, and somatic complaints	0-84	Higher scores indicate greater tinnitus distress	Not reported
Tinnitus Questionary SF (TQ-SF) Hiller and Goebel (2004)	Measures tinnitus-related distress	12-item self-administered questionnaire using a three-point Likert Scale (0-2)	0-24	Higher scores indicate greater tinnitus distress	Not reported
Tinnitus severity index (TSI) Meikle et al. (1995)	Evaluates tinnitus impact on quality of life	12-item self-administered questionnaire using a 5-point Likert Scale (0-5)	12-60	Very mild tinnitus: 1-12 Mild tinnitus: 13-24 Moderate tinnitus: 25-36 Severe tinnitus: 37-48 Catastrophic tinnitus: 49-60	Not reported
Visual Analogue Scales (VAS)	Provides subjective assessment of tinnitus severity	10-cm linear scale with endpoints labeled "minimally" (left) and "maximally" (right)	0-10	Not reported	Not reported

**Table S3. Participants demographics, clinical symptoms characterizations and inclusion criteria.**

Reference	Population Age T:C (mean) M:F (T/C)	Clinical diagnosis	Tinnitus duration T/C(mean)*	Eligibility criteria	Additional Inclusion Parameters
Abtahi et al, 2017	Tinnitus patients Age (71.92:71.52) M:F 35:35/35:35	Chronic idiopathic tinnitus (uni or bilateral)	NE	Adult patients with tinnitus for at least 6 months. Males and females	Not stated
Albu et al, 2014	Tinnitus patients Age (48.4:50.2) M:F NE	Unilateral acute idiopathic tinnitus developed within 3 months	T (5,2 weeks)/ C (4,5 weeks)	Adult patients with idiopathic unilateral acute tinnitus. Males and females	Not stated
Arda et al, 2003	Tinnitus patients Age (51.2:55) M:F 12:16/4:8	Unspecified	T (3,28 yrs) / C (2,17 yrs)	Adult patients with no know pathologic conditions of the ear, nose, and throat. Males and females	Not stated
Balatsouras et al, 2024	Tinnitus patients Age (57.7:56.3) M:F 54:50/51:49	Recent-onset idiopathic tinnitus (uni or bilateral)	≤12 months	Adult patients (18-70 years) with idiopathic tinnitus of recent onset ≤12 months. Males and females	Normal otoscopy, no history of ear disease, normal tympanometry, and no conductive hearing loss. Patients with sensorineural hearing loss, including presbycusis and noise-related hearing loss were included.
Claire et al, 2010	Tinnitus patients Age (59.7:58.6) M:F 16:10/15:12	Unspecified	NE	Adult males and females were eligible if they were annoyed by their tinnitus, consumed more than 150 mg of caffeine each day	Not stated
Coelho et al, 2013	Tinnitus patients ≥ 60 years Age (67.5:67.7) M:F 34:24/34:24	Chronic tinnitus	T (17.9 yrs) / C (15.6 yrs)	60 years or older, tinnitus duration for 6 months or more	Not stated
Dadgarnia et al, 2024	Tinnitus patients Age (58.8:59.1) M:F 37:33/38:32	Idiopathic tinnitus	NE	Adult patients with idiopathic tinnitus. Males and females	Patients without anatomic or organic ear diseases, pulsatile tinnitus, traumatic head and neck injury, and previous ear surgery. Normal, mild, and moderate hearing loss patients were included (87.14% had normal or mild hearing loss)
Hulshof et al, 1987	Tinnitus patients Age (55) M:F NE	Annoying idiopathic tinnitus	NE	Adults aged 18 to 74 years who had idiopathic bothersome tinnitus	Not stated
Hurtuk et al, 2011	Tinnitus patients Age (57.8) M:F 42:19	Chronic tinnitus	AP Mean (10.5 yrs)	Males and females older than 18 years with chronic tinnitus of more than 6 months duration as their chief complaint	Not stated
Ino et al, 2013	Tinnitus patients Age (60:58.7)	Chronic tinnitus, subjective mild to severe	AP Mean (8.8 yrs) T (9.6 yrs) / C (8 yrs)	20 years or more	THI score ≥ 18

	M:F 13:25/22:16				
Khosravi et al, 2022	Tinnitus patients Age (52.96:49.9) M:F 69:34	Subjective tinnitus	NE	Adult patients having tinnitus as the main complain	Not stated
Ledesma et al, 2021	Tinnitus patients Age (51.09:51.11) M:F 20:20/18:22	Chronic tinnitus	T (12.3 yrs) / C (12.0 yrs)	Adult patients having tinnitus as the main complain	Not stated
Lopez-Gonzalez et al, 2007	Tinnitus patients Age (65:63:62:65) M:F 16:14/18:12/ 17:13/15:15	Subjective tinnitus	AP (Range: 1-11 yrs)	Patients over 18 years of age with subjective tinnitus. Males and females	Not stated
Markou el al, 2004	Military male personnel Age (22) M:F 108:0	Tinnitus due to acute acoustic trauma following firearm use	NE	Military males aged 18 to 31 years with tinnitus due to acute acoustic trauma	Not stated
Neri et al, 2009	Tinnitus patients Age (41.1:46.3:44.2) M:F 45:57	Chronic tinnitus	NE	Males and females older than 18 years, with tinnitus for at least 1 year, absence of psychiatric or neurological diseases, noise-induced hearing loss, cochlear and retro-cochlear damage	Not stated
Oppitz et al, 2022	Tinnitus patients Age (50.5) M:F 14:16	Chronic tinnitus	NE	Males and females older than 18 years, with normal hearing thresholds or sensorineural hearing loss up to mild degree	Annoyance score of at least four on the VAS, considered a moderate annoyance
Paaske et al, 1991	Tinnitus patients Age (60:48) M:F NE	Unspecified	AP Median: 5 years (Range: 3 months-34 yrs)	Males and females, aged between 29 to 77 years old suffered from tinnitus	Not stated
Petridou ht al, 2019	Tinnitus patients Age (56.5:59.2) M:F NE	Chronic tinnitus (uni or bilateral)	NE	Males and females, aged between 25 and 75 years old, with chronic unilateral or bilateral persistent tinnitus of at least 6 months' duration, with normal hearing or up to moderate sensorineural hearing loss	Tinnitus maskable with noise of at least 5 decibel and a score of minimum 4 in THI
Rojas-Roncancio et al, 2016	Tinnitus patients Age (56:58) M:F 11:9/13:7	Chronic tinnitus	T (20.5 yrs) / C (17.9 yrs)	Adults with tinnitus longer than 6 months	Tinnitus loudness and annoyance rated more than 50% in a scale from 0% to 100%
Rosenberg et al, 1998	Tinnitus patients Age (64.4) M:F 15:8	Subjective chronic tinnitus	NE	Males and females, aged between 28 to 81 years old suffered from tinnitus as their primary complaint	Not stated
Singh et al, 2016	Tinnitus patients Age (38.37) M:F 16:24 (total)	Subjective chronic tinnitus	≥6 months	Adult patients (18-60 years) with chronic subjective tinnitus with/without sensorineural hearing loss. Males and females	Not stated

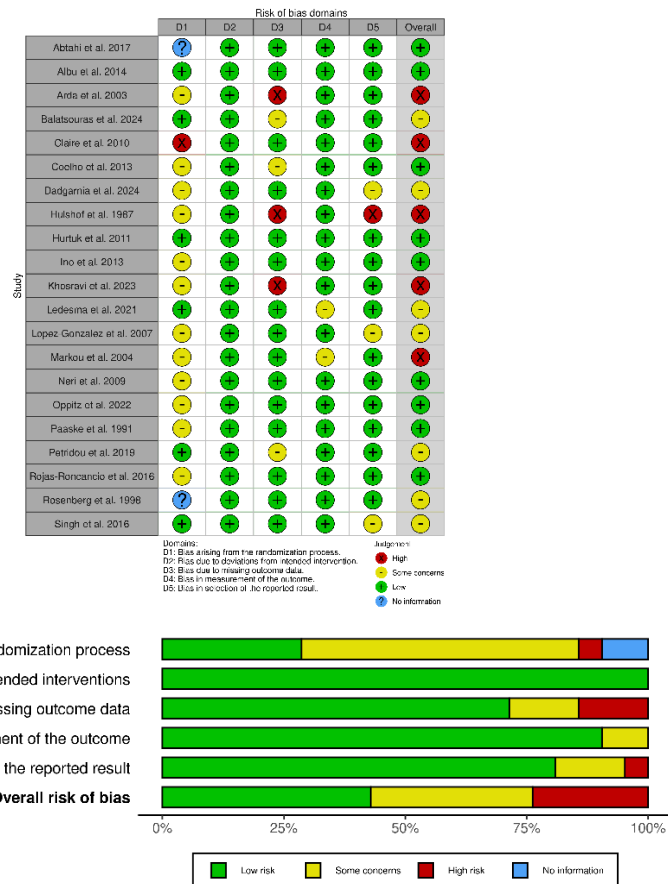
**Abbreviations:** AP Mean: all population mean; NE: No extractable data; T/C: treatment group/control group; M/F: Gender distribution (male/female); THI: Tinnitus Handicap Inventory; THQ: Tinnitus Handicap Questionnaire; TQ: Tinnitus questionnaire; TQ-SF: Tinnitus questionnaire short form; TSI: Tinnitus severity index; VAS: visual analogue scale; yr(s): year(s).

**Table S4. Parameters of clinical improvements and adverse events reported in the included trials.**

Reference	Parameters of clinical improvement	Reported adverse events (T/C)
Abtahi et al, 2017	Not stated	No adverse events observed
Albu et al, 2014	A >10% reduction of tinnitus awareness score, >2-point reduction of tinnitus loudness score, and >20-points reduction in THI. Cure was defined as a reduction in tinnitus awareness score to 0%	No adverse events observed
Arda et al, 2003	Not stated	No adverse events observed
Balatsouras et al, 2024	Improvement defined by THI score reduction and PGIC scale. Complete remission was defined as complete disappearance of tinnitus.	No adverse events observed
Claire et al, 2010	A change of 10 points on the total score of the Tinnitus Questionnaire	No serious adverse events observed. Reported: headache and nausea increased during phased caffeine withdrawal
Coelho et al, 2013	A group difference score of at least 10% after this treatment	No adverse events observed
Dadgarnia et al, 2024	Improvement measured by THI score reduction and VAS scale changes	No adverse events observed
Holgers et al, 1994	Not stated	No information about adverse events
Hulshof et al, 1987	A subjective judgement of the patient about the annoyance of tinnitus	No serious adverse events observed. Reported: dizziness or nausea (2/0)
Hurtuk et al, 2011	Decrease, on at least 2 of the 3 tinnitus assessment parameters: tinnitus matching, TSI, or VAS	No adverse events observed
Ino et al, 2013	A change of 20 points on THI for the treatment group and 10 points for placebo	No adverse events observed
Khosravi et al, 2022	Not stated	No adverse events observed
Ledesma et al, 2021	A 3-point reduction in THI	No serious adverse events observed. Reported: palpitation, headache
Lopez-Gonzalez et al, 2007	Not stated	No serious adverse events observed. Reported: morning drowsiness
Markou et al, 2004	(i) complete remission in the form of complete disappearance of tinnitus; (ii) significant improvement with a decrease in the total score by at least 50%; (iii) mild improvement with a decrease in the total score by 20% to 50%; (iv) no change with a decrease or increase in the total score by 20%	No information about adverse events
Neri et al, 2009	Not stated	No adverse events observed
Oppitz et al, 2022	A >20-point reduction in THI	No adverse events observed
Paaske et al, 1991	Not stated	No adverse events observed
Petridou et al, 2019	Not stated	No adverse events observed
Rojas-Roncancio et al, 2016	Not stated	No serious adverse events observed. Reported: nausea, vomiting and shaking (8/0)
Rosenberg et al, 1998	Not stated	No serious adverse events observed. Reported: nightmares (4/4)
Singh et al, 2016	Improvement measured by tinnitus severity index score, VAS, and subjective improvement. Subjective improvement was seen in 30% of treatment group and 20% of control group	No adverse events observed

**Abbreviations:** T/C: treatment group/control group; THI: Tinnitus Handicap Inventory

### Risk of bias assessment



**Figure S1.** Risk of bias assessment for included studies with RoB2 assessment tool. The upper panel shows individual risk of bias assessments for each included study across six domains using a traffic light system (green = low risk, yellow = some concerns, red = high risk, blue = no information). The lower panel presents the overall risk of bias across studies as percentages for five key categories. The overall risk of bias assessment indicates varying levels of potential bias across studies, with concerns noted in the selection of reported results and overall risk assessment.

Forest plot of dropout rates of all included trials.

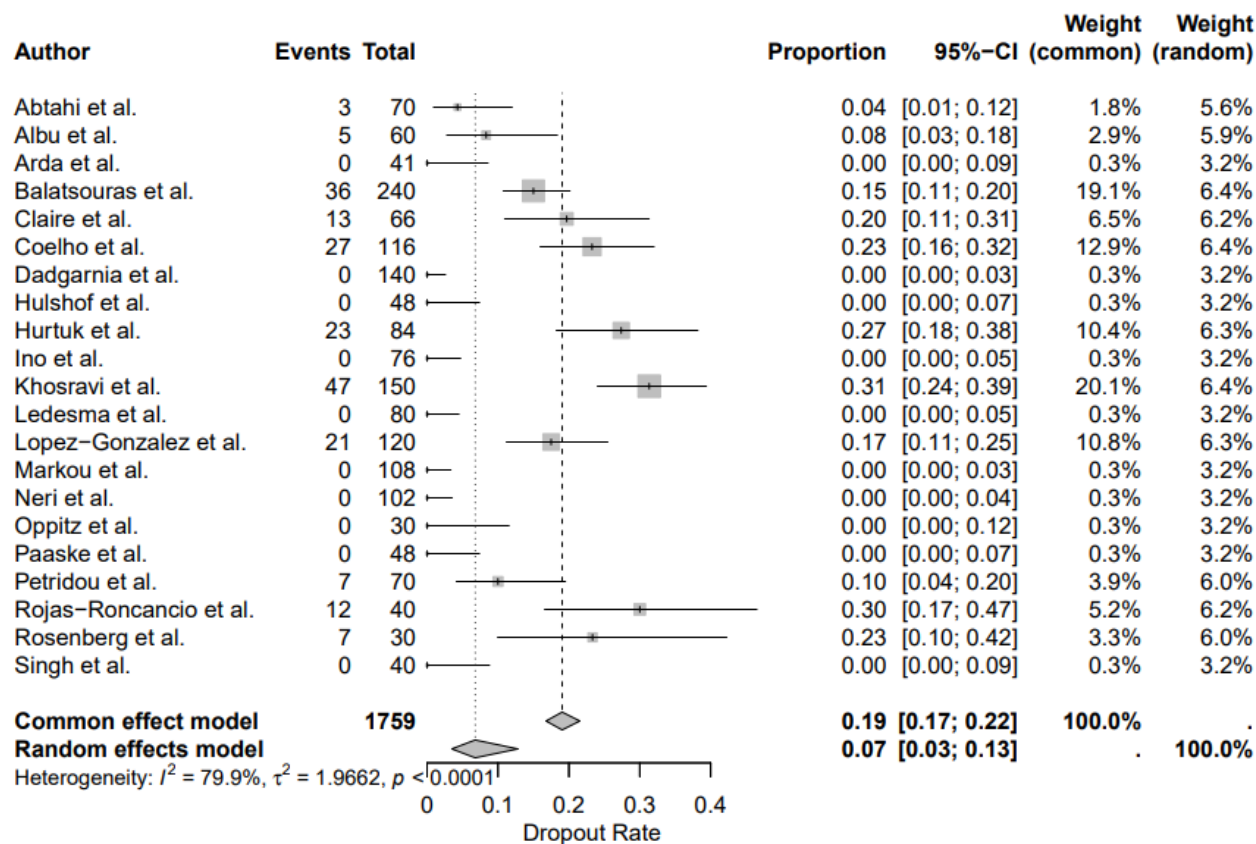
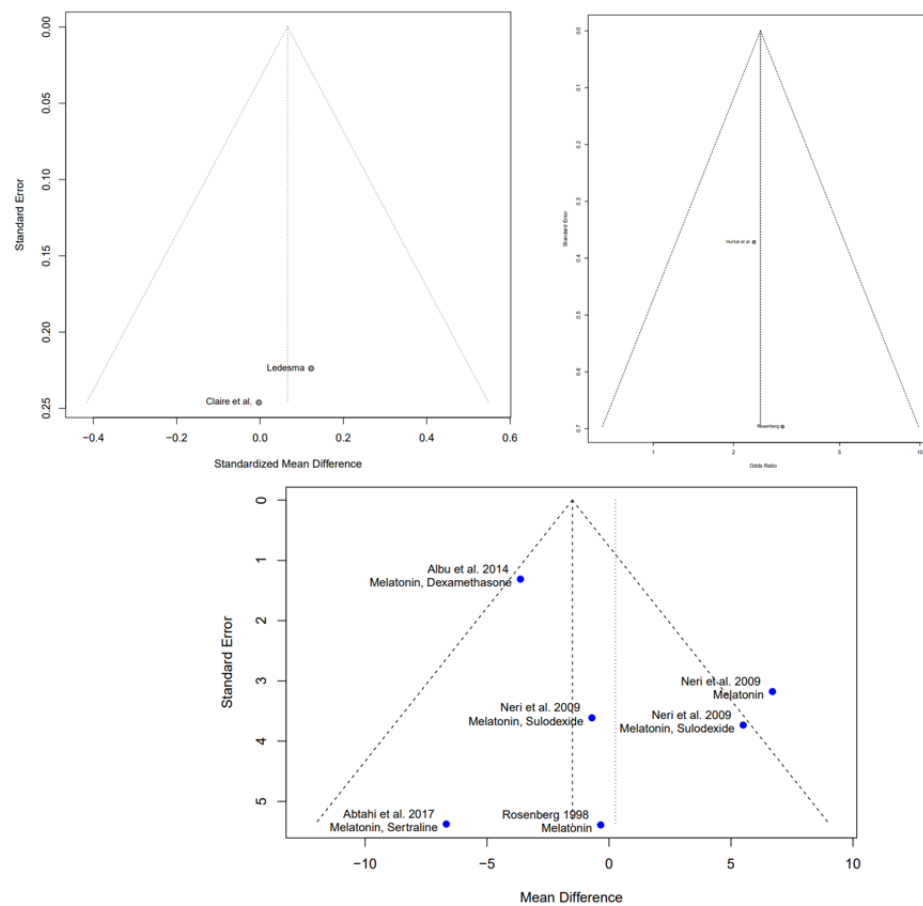


Figure S2. Forest plot of rates of loss to follow-up of the included studies. Squares and horizontal lines represent the proportion and 95% confidence interval (95% CI) for each study. The diamond is the average dropout rate across studies and its 95% CI.

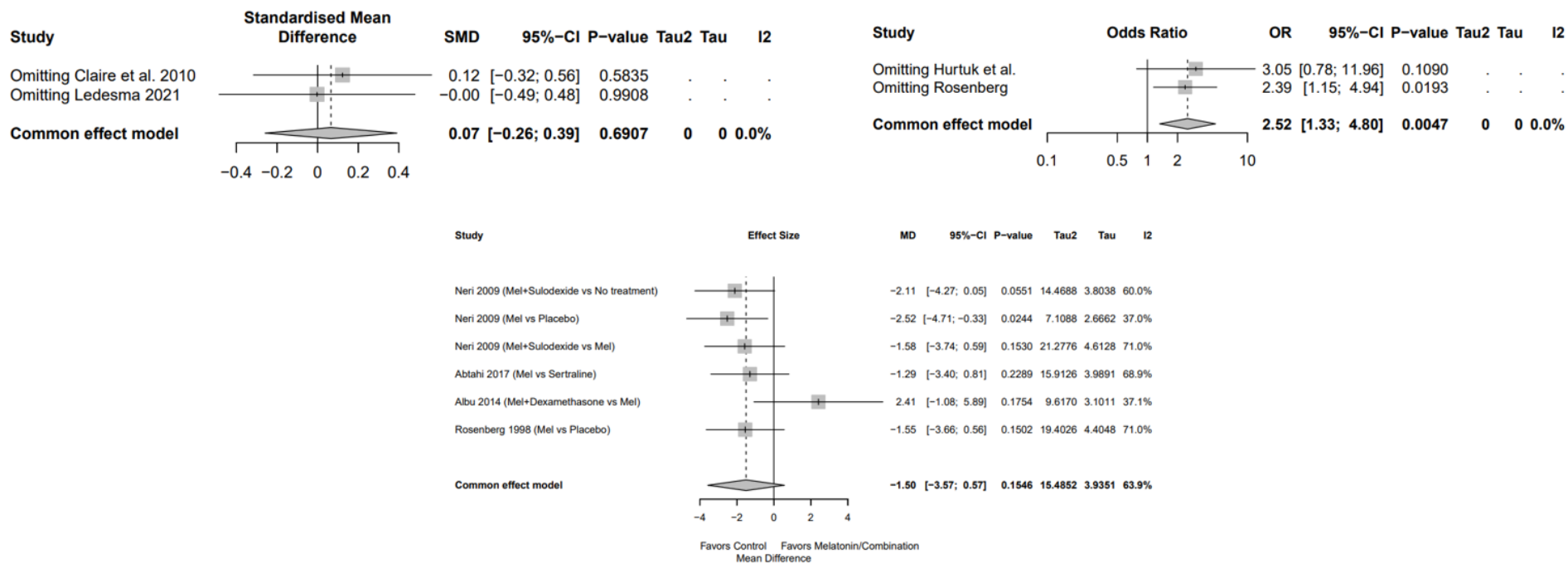


### Publication bias analysis: funnel plots



**Figure S3.** Funnel plots with the included studies in meta-analysis to assess publication bias. The plot shows three sections for different comparisons: (a) Caffeine vs placebo (SMD), (b) Melatonin vs placebo (OR), (c) Melatonin vs controls groups (MD). The dots represent the included trials, the triangular area, marked by lines, shows the 95% pseudo confidence limits.

### Influence analysis



**Figure S4.** Leave-one-out influence analysis. The plot shows three sections for different comparisons: (a) Caffeine vs placebo (SMD), (b) Melatonin vs placebo (OR), (c) Melatonin vs controls groups (MD). Each section displays the size effect on the vertical axis against the Study ID on the horizontal axis. This analysis helps to understand the influence of each individual study on the overall meta-analysis result.

# Excluded Studies Report

## Effects of plant extract and dietary supplements on tinnitus perception in adults: A systematic review and meta-analysis

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### Summary of Excluded Studies

A total of **797** studies were excluded from the systematic review. Below is the breakdown by exclusion categories and the complete reference list.

### Distribution of Excluded Studies

Table 1: Distribution of Excluded Studies by Category

Exclusion Category	Number of Studies
Non-dietary intervention	424
Non-RCT study design	118
Population not relevant	91
Literature Review	70
Systematic Review	33
Gingko biloba intervention	23
Case Study/Report	15

Exclusion Category	Number of Studies
Meta-Analysis	13
Animal study	9
Redundant publication	1

## Complete Reference List by Category

### Systematic Review

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## **Ginkgo biloba intervention**

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