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A Multi-Compound Nutraceutical Formulation for Tinnitus Management: A Retrospective Observational Study

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Abstract: Tinnitus is a multifactorial condition with limited effective treatment options. Natural compounds have been proposed to modulate molecular pathways potentially involved in its pathophysiology, although clinical evidence remains preliminary. This retrospective observational study, conducted without a control group, evaluated 92 patients receiving a multi-compound nutraceutical (4 capsules/day) containing *Auricularia auricula-judae*, *Curcuma longa*, *Hericium erinaceus*, *Ganoderma lucidum*, *Berberis aristata*, and *Rosa canina*. Tinnitus severity was assessed using the Tinnitus Handicap Inventory (THI) at baseline (T0), 1.5 months (T1), and 3 months (T2). Concurrently, hearing thresholds were evaluated at T0 and T2. Patients were stratified into secondary (Group A; N = 48) and primary (Group B; N = 44) tinnitus. THI scores decreased significantly in both groups over time ($p < 0.001$), with more than 90% of patients showing improvement. A shift toward lower severity grades was observed, with a reduction in moderate-to-catastrophic tinnitus. A decline in tinnitus grade occurred in 29% of patients, with no cases of worsening. At T2, approximately 30% of patients achieved a clinically relevant improvement (>7-point THI reduction). Hearing thresholds remained stable in both groups. A modest correlation between THI and dB variation was observed in Group A at T2 ($r = 0.346$; $p < 0.05$), although this exploratory finding should be interpreted with caution. These preliminary, hypothesis-generating findings suggest that the nutraceutical may represent a supportive option for tinnitus management, particularly in mild-to-moderate cases, with potential benefits for quality of life. However, given the retrospective, uncontrolled design of this study, randomized controlled trials are warranted to confirm these preliminary findings.

Keywords: Tinnitus; Food Supplement; Herbal Extracts; Medicinal Fungi

1. Introduction

Tinnitus is defined as the perception of auditory sensations in the absence of external sound stimuli and is commonly referred to as a “phantom sound”. People with tinnitus—affecting over 70 million people in Europe – often describe it as a ringing, hissing, buzzing, or roaring sound localized in the ear canal or perceived within the cranial cavity. This phenomenon is attributed to aberrant neural activity along the auditory pathway, which is misinterpreted by the brain as genuine auditory signals [1].

Tinnitus can be classified as (i) primary or idiopathic, characterized by unknown etiology with or without concomitant sensorineural hearing loss (SNHL), and (ii) secondary, arising from identifiable organic causes other than SNHL [2].

Etiological factors include ageing, environmental stressors such as loud noise, trauma, and ototoxicity [3, 4]. Traditionally, chronic primary tinnitus was considered a disorder of the peripheral auditory system, including the cochlea and auditory nerve, or of the central auditory pathways [5]. It is now well recognized that tinnitus often reflects complex interactions between peripheral and central mechanisms [6].

The impact of tinnitus on quality of life is highly variable, ranging from mild annoyance to severe anxiety, depression, and impaired daily functioning [2, 7]. To date, no pharmacological treatment has consistently alleviated tinnitus symptoms, although cognitive-behavioral therapy, as well as sound and music therapies, are gaining interest for their potential to improve this condition [8].

There is also a growing interest in dietary supplements, including melatonin, B vitamins, minerals, and *Ginkgo biloba* extracts, although evidence supporting their efficacy remains limited [9–11]. Other natural compounds may have potential in modulating mechanisms implicated in cochlear hair cell (HC) degeneration. Vijayakumar et al. [3] suggested that several mechanisms, including mitochondrial dysfunction, oxidative stress, excitotoxicity and inflammation, contribute to sensory neural HC loss.

Preclinical studies indicate that plant-derived compounds, such as curcumin and berberine, can protect against HC degeneration and hearing loss (HL), likely due to their antioxidant and anti-inflammatory properties [12, 13]. Curcumin, a yellow pigment extracted from *Curcuma longa*, modulates multiple molecular targets, including transcription factors, cytokines, growth factors, and apoptotic pathways. Curcumin effectively reduces ototoxicity and significantly protects cochlear morphology and function in rats with induced ototoxicity [14]. Berberine, an isoquinoline alkaloid from *Berberis* species, alleviates cisplatin-induced ototoxicity in murine cochlear explants, preserving HC survival and stereocilia morphology [15].

Fungal extracts may also counteract mechanisms relevant to tinnitus. *Ganoderma lucidum* contains bioactive compounds with antioxidant, anti-inflammatory, and vascular modulatory properties. Experimental studies have shown that *G. lucidum* administration can modulate vascular function and blood flow, suggesting that these properties may be relevant to disorders involving inner ear homeostasis [16, 17]. This effect may be complemented by *Auricularia auricula-judae*, whose polysaccharides exhibit antioxidant [18], anticoagulant, and antithrombotic activities [19]. *Hericium erinaceus* is recognized for its neuroprotective properties; preliminary clinical studies suggest that oral supplementation with its sporophore has nootropic effects, while erinacine A, a bioactive compound, stimulates nerve growth factor synthesis and may improve a wide range of neurological conditions [20].

The present study investigated the potential of a multi-compound natural formulation to improve quality of life in subjects with tinnitus, in the context of a real-world, retrospective, observational study. The formulation contained extracts of *Auricularia auricula-judae*, *Curcuma longa* L., *Hericium erinaceus*, *Ganoderma lucidum*, *Berberis aristata* DC., and *Rosa canina*.

2. Materials and Methods

2.1. Study Design and Setting

A retrospective analysis of data collected during routine clinical practice at the Departments of Otolaryngology of Siena and Pisa (Italy) between March 2022 and April 2023 was conducted. All consecutive adult patients meeting the eligibility criteria during this period were included, with no additional selection criteria applied. Data were extracted from fully anonymized records, with patient identifiers removed prior to analyses and data processed exclusively in aggregated form. The study was designed, conducted, and written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for retrospective cohort studies, national data protection regulations (EU Regulation 2016/679, GDPR), and the ethical principles of the Declaration of Helsinki.

2.2. Study Groups

Patients were retrospectively stratified into two groups (Group A and Group B) based on predefined clinical and audiometric criteria. Group A included patients with secondary tinnitus associated with an audiometric profile

consistent with presbycusis. Group B comprised patients with primary tinnitus, in which tinnitus was not clinically associated with hearing loss, although mild audiometric alterations could be present.

2.3. Inclusion/Exclusion Criteria

Patients with tinnitus and complete THI data were included in the analysis. Eligible participants were adults (≥18 years) of both sexes, presenting with unilateral or bilateral tinnitus and treated with the nutraceutical at a dose of 4 capsules/day for three months. All patients underwent pure-tone audiometry.

To minimize potential confounding factors, patients were excluded if they presented with asymmetric hearing thresholds on audiometry, confirmed occupational or environmental noise exposure, or suspected specific inner ear or auditory nerve diseases (e.g., Ménière's disease, neurinoma of the VIII cranial nerve, or labyrinthine ischemia). Additional exclusion criteria included diabetes, thyroid disorders, uncontrolled hypertension or hypotension, and psychiatric diseases. Patients receiving concomitant pharmacological or different nutraceutical treatments potentially affecting tinnitus outcomes were also excluded. Furthermore, patients with poor adherence to the nutraceutical regimen or without informed consent were not included in the analysis.

2.4. Treatment, Timing, and Outcomes

Nutraceutical composition: a multi-compound natural formulation (Laboratori Aliveda srl, Crespina Lorenzana, Pisa, Italy). Each daily dose (4 capsules) contained the following active ingredients: *Auricularia auricula-judae* (Auricularia, 800 mg powder, of which 16 mg polysaccharides), *Curcuma longa* L. (Curcuma, 400 mg dry extract titrated to 95%, of which 380 mg curcuminoids), *Hericium erinaceus* (*Hericium*, 200 mg dry extract titrated to 10%, of which 20 mg polysaccharides), *Ganoderma lucidum* (Reishi, 200 mg dry extract titrated to 10%, of which 20 mg polysaccharides), *Berberis aristata* DC. (Berberis, 200 mg dry extract titrated to 97%, of which 194 mg berberine), and *Rosa canina* (80 mg dry extract titrated to 70%, of which 56 mg vitamin C). This product is classified as a food supplement and is registered with the Italian Ministry of Health's Food Supplements Register, in accordance with current Italian regulations.

Primary outcome: variation in tinnitus severity assessed using the Italian version [21] of the THI questionnaire [22]. Data were collected at baseline (T0), after 1.5 months (T1), and after 3 months (T2) of nutraceutical supplementation (**Figure 1**). According to the literature, THI outcomes were classified into five severity grades: Grade 1 (negligible tinnitus), Grade 2 (mild tinnitus), Grade 3 (moderate tinnitus), Grade 4 (severe tinnitus), and Grade 5 (catastrophic tinnitus) [23].

Secondary outcome: variation in hearing thresholds evaluated using pure-tone audiometry at T0 and T2 (**Figure 1**). All audiometric tests were performed in a 5.2 m × 3.5 m sound-isolated room using an Otometrics MADSEN Astera2 audiometer with TDH39 headphones and Indiana Line Loudspeakers. Hearing loss was defined as follows: normal or subnormal (<20 dB), mild (21–40 dB), moderate (41–70 dB), severe (71–90 dB), very severe (91–119 dB), and profound (>120 dB) [24].

Exploratory outcome: correlation between tinnitus severity and audiometric thresholds.

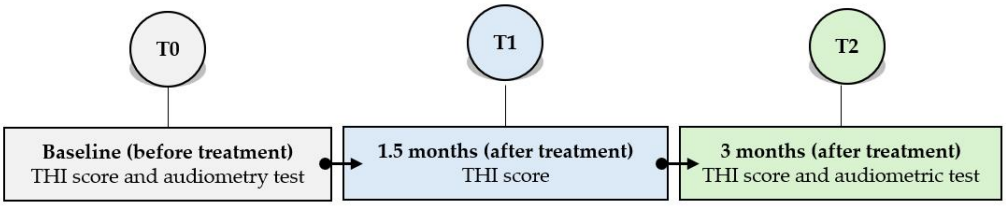


Figure 1. Schematic representation of time point analysis.

2.5. Statistical Analysis

Categorical data are presented as percentages (%) and continuous variables as mean ± standard deviation (SD). For continuous variables, deviations from normality were tested using the Shapiro-Wilk test. As indicated in each figure and table legend, one-way ANOVA for repeated measures with Bonferroni test at 95% confidence interval

(CI) was used to analyze data for within-group/between-time (T2 vs. T1 vs. T0) comparisons for data with normal distribution. If the normality assumption was not met, the Friedman test was used for repeated-measures comparisons, followed by Dunn's post-test to assess differences between time points. Analysis between two variables was performed using a paired or unpaired t-test, with Welch's correction where appropriate, at a two-sided significance level with 95% CI. Correlation analyses between clinical scores were performed using Spearman's correlation (for non-parametric data), with a two-tailed significance level. For qualitative variables, Fisher's exact test (two-tailed) or chi-square test (χ^2) was used to assess differences in patient distribution.

For subgroup analysis, data were pooled when the number of observations was insufficient to allow statistical testing. All analyses were performed using GraphPad Prism 5.0 and Microsoft Excel. The level of significance was set at $p < 0.05$ (*), $p < 0.01$ (**), and $p < 0.001$ (***). The specific statistical test applied is indicated in the legend of each figure.

3. Results

A total of 92 patients with tinnitus were included in the analysis. The flow chart of patient selection is shown in **Figure 2**.

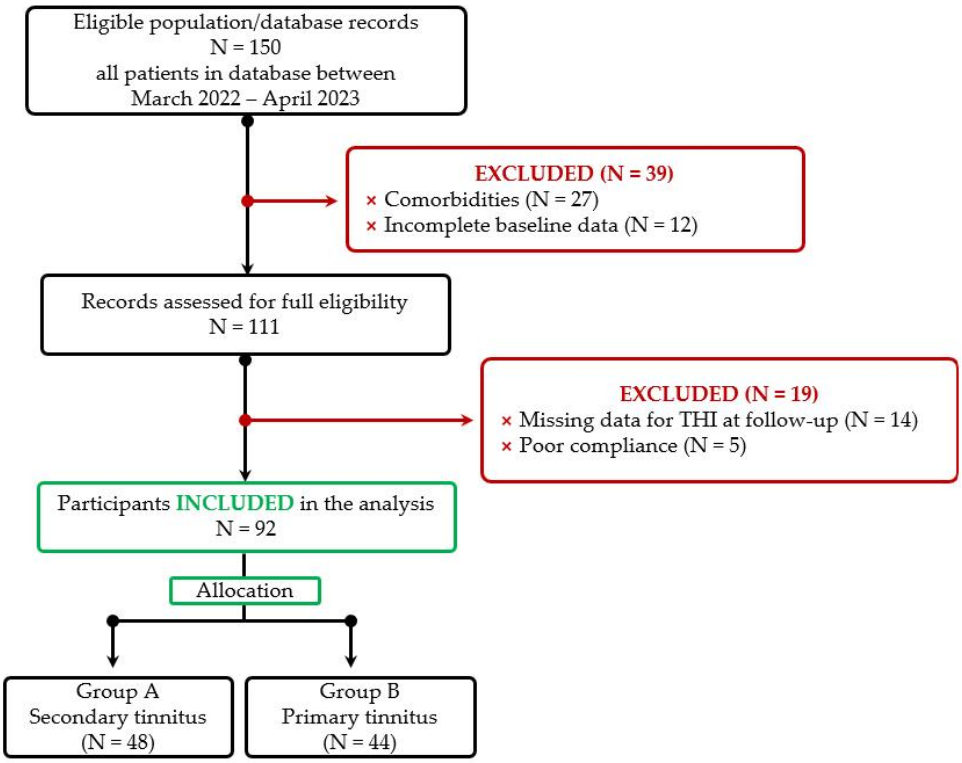


Figure 2. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flow chart illustrating the selection of eligible patients, including reasons for exclusion at each stage.

Baseline characteristics of patients are summarized in **Table 1**. Patients with secondary tinnitus (Group A) showed significantly higher values at baseline (T0) compared to those with primary tinnitus (Group B) across several parameters, including age ($p < 0.001$), THI scores ($p < 0.001$), and pure-tone audiometric thresholds ($p < 0.001$).

Table 1. Baseline general characteristics of patients.

Patients' Characteristics	Group A	Group B	*p*-Value	95% CI
Number (M/F)	48 (24/24)	44 (19/25)	-	-
Age (mean ± SD)	74.3 ± 5	47.5 ± 13.3	< 0.001	22.3–30.9

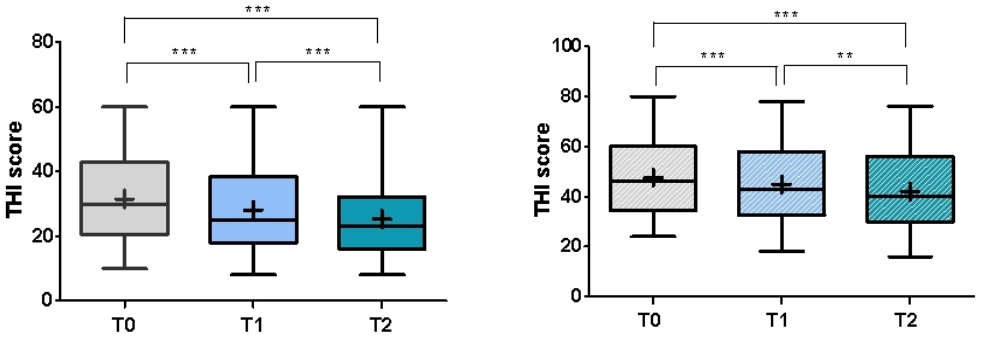
Table 1. *Cont.*

Patients' Characteristics	Group A	Group B	*p*-Value	95% CI
THI (mean ± SD)	49.9 ± 15.1	31.4 ± 14.1	< 0.001	10.0–22.1
Audiometric test (mean ± SD)	53.6 ± 6.9	18.3 ± 10.5	< 0.001	31.5–39.2

Note: M, males; F, females; SD, standard deviation; Group A: patients with secondary tinnitus; Group B: patients with primary tinnitus.

3.1. Tinnitus Severity

In both groups, THI scores were significantly reduced at 1.5 months (T1) and 3 months (T2) compared to T0 following nutraceutical supplementation ($p < 0.001$ for both time points; **Figure 3**).

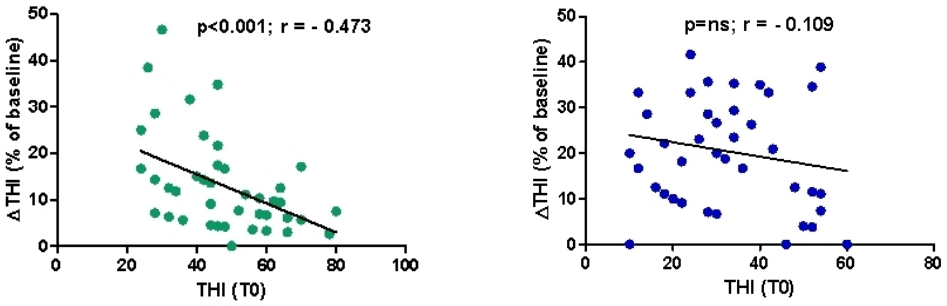


(**a**) (**b**)

Figure 3. THI score variation at different time points (T0, T1, and T2) in (**a**) Group A patients; (**b**) Group B patients.
Note: *p*-values were calculated using repeated-measures ANOVA, with Bonferroni test (95% CI).

This trend was consistently observed when patients were stratified by disease severity. In Group A, patients classified as Grade 2 (**Appendix Figure A1a**), Grade 3 (**Appendix Figure A1b**) and Grade 4–5 (**Appendix Figure A1c**) demonstrated a progressive decrease in THI score proportional to treatment duration (*p*-value ranging from <0.05 to <0.001). In Group B, Grade 1 patients showed a statistically significant reduction in THI score at T2 compared to T0 ($p < 0.05$; **Appendix Figure A2a**). Similarly, significant inter-time differences were observed in Grade 2 patients ($p < 0.001$; **Appendix Figure A2b**) and Grade 3 and 4 patients (**Appendix Figure A2c**) at each time point (*p*-value ranging from <0.05 to <0.001).

The magnitude of THI score variation (ΔTHI) following nutraceutical supplementation was inversely related to baseline tinnitus severity. In Group A, ΔTHI showed a significant negative correlation with the THI score recorded at T0 ($r = -0.473$, $p < 0.001$; **Figure 4a**), while no significant correlation was observed in Group B (**Figure 4b**).



(**a**) (**b**)

Figure 4. Correlation analysis between THI score at baseline (T0) and treatment response (ΔTHI, expressed as a percentage of baseline) in (**a**) Group A patients and (**b**) Group B patients.
Note: *p*-values were calculated using Spearman's r correlation (two-tailed); ns, not significant.

Analysis revealed that 97.9% of patients in Group A and 93.2% in Group B demonstrated improvement in THI scores. Only 2.1% and 6.8% of patients in Groups A and B, respectively, showed no significant change, and no patients experienced worsening, with no significant differences between groups. Overall, approximately 29% of patients exhibited a decrease in tinnitus grade, while more than 70% remained stable, and no patients progressed to a higher grade (**Table 2**).

Table 2. Changes in tinnitus severity after treatment.

Outcome	THI Score	Group A (N = 48)	Group B (N = 44)	*p*-Value
THI change	Improved	47 (97.9%)	41 (93.2%)	-
	Unchanged	1 (2.1%)	3 (6.8%)	-
	Worsened	0 (0%)	0 (0%)	0.347 [1]
Tinnitus grade variation	Decreased	14 (29.2%)	13 (29.5%)	-
	Unchanged	34 (70.8%)	31 (70.5%)	-
	Increased	0 (0%)	0 (0%)	1.000 [2]

Note: Values are expressed as n (%). *p*-values were calculated using Fisher's exact test. [1] Odds ratio: 3.439; 95% CI: 0.344–34.38. [2] Odds ratio: 0.981; 95% CI: 0.399–2.411.

Furthermore, a minimal clinically important difference in THI score—defined as a change exceeding 7 points—was recorded in 25% of Group A patients, 36.4% of Group B patients, and overall in 30.4% of the total study population, with no statistically significant difference in the distribution between the two groups (**Table 3**).

Table 3. Clinically meaningful improvement in THI score.

Group	ΔTHI > 7	ΔTHI < 7	*p*-Value
Group A	12 (25%)	36 (75%)	-
Group B	16 (36.4%)	28 (63.6%)	0.263

Note: Values are expressed as n (%). *p*-values were calculated using Fisher's exact test. Odds ratio: 0.583; 95% CI: 0.471–1.230.

3.2. Audiometric Test

Analysis of baseline audiometric thresholds revealed that, in Group A, 98% of patients presented with moderate HL and 2% with mild HL. In contrast, in Group B, 3% had mild HL, 27% had moderate HL, and approximately 71% exhibited normal hearing ($p < 0.001$). This significant intergroup difference in audiometric distribution persisted following treatment at T2 ($p < 0.001$) (**Table 4**). Within Group A, a significant shift was observed at T2 compared to T0, with a reduction in the proportion of patients with moderate HL and a corresponding increase in those with mild HL ($p < 0.05$). A similar, albeit non-significant, trend was observed in Group B, where the proportion of patients with mild and moderate hearing loss decreased, while the proportion of patients with normal hearing increased at T2 compared to T0 (**Table 4**).

Table 4. Distribution of hearing loss in Group A and Group B at T0 and T2.

Hearing Loss	Group A – T0 N (%)	Group B – T0 N (%)*	Group A – T2 N (%)	Group B – T2 N (%)
None (normoacusis)	0 (0%)	29 (71%)	0 (0%)	34 (83%)
Mild	1 (2%)	11 (27%)	6 (12.5%)	7 (17.1)
Moderate	47 (98%)	1 (2.5%)	42 (87.5%)	0 (0%)
Severe-Profound	0 (%)	0 (%)	0 (0%)	0 (0%)

Note: Chi-square test for trend comparing T2 vs. T0 within groups: Group A, $p < 0.05$ (χ^2: 3.852; df: 1); Group B, $p = 0.147$ (χ^2: 2.103; df: 1). Fisher's exact test comparing Group A and Group B: T0, $p < 0.001$; T2, $p < 0.001$. *Data were available for 41 patients.

In Group A, mean audiometric thresholds decreased by 3% (**Figure 5a**), and a significant positive correlation was observed between ΔTHI score and ΔdB (r = 0.346, $p < 0.05$; **Figure 5b**). In Group B, a greater, although not clinically meaningful, decrease in audiometric thresholds (8.9%) was observed at T2 compared with T0 (**Figure 5c**); however, no significant correlation was found between ΔTHI score and ΔdB (**Figure 5d**).

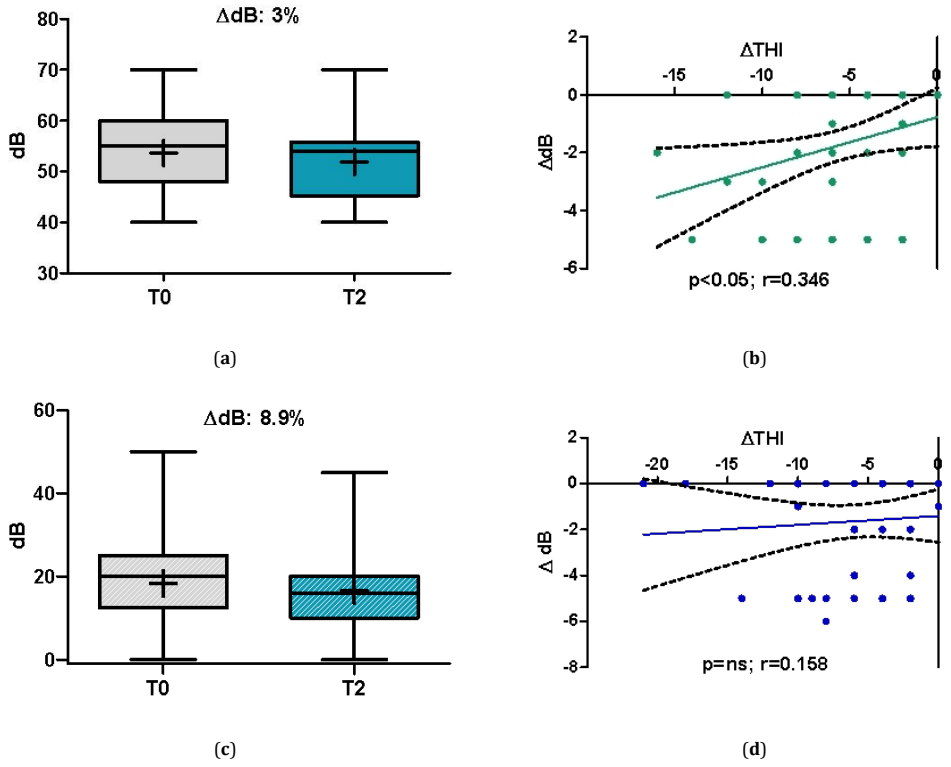


Figure 5. Audiometric outcomes and correlation analyses in Group A and Group B. (**a**) Audiometric thresholds at T0 and T2 in Group A; (**b**) Correlation between changes in THI score and audiometric threshold in Group A; (**c**) Audiometric thresholds at T0 and T2 in Group B; (**d**) Correlation between changes in THI score and audiometric threshold in Group B.

Note: Paired t-test for T0 vs. T2 comparisons (**a**,**c**); Spearman's rank correlation (two-tailed) for association analyses (**b**,**d**); ns, not significant.

3.3. Safety

The nutraceutical was generally well tolerated. No treatment discontinuations, serious adverse events, or clinically relevant gastrointestinal adverse effects were reported during the observed supplementation period. Five patients were excluded from the final analysis due to poor adherence to the nutraceutical regimen, as reported in the study flow chart (**Figure 2**).

4. Discussion

Tinnitus is a prevalent condition for which no definitive pharmacological treatment has been established to date [25]. Current approaches, including sedatives, anticonvulsants, antidepressants, and antipsychotics, demonstrate inconsistent efficacy [11, 26]. Naturally occurring dietary compounds, such as red ginseng, *Ginkgo biloba*, alpha-lipoic acid, and vitamins A, B, C, D, and E, have been investigated for their capacity to protect against HC death and HL through antioxidant, anti-inflammatory, and pro-autophagic mechanisms [27, 28]. These compounds have shown reported benefits on cochlear microcirculation and neuroinflammation, although clinical evidence remains inconsistent [28–30]. These findings provide broader context for the auditory protective effects of the phytochemical components evaluated in the present study, as discussed below.

Data from patients with secondary (Group A) and primary (Group B) tinnitus were retrospectively analyzed. As expected, significant baseline differences were observed between groups, reflecting their distinct clinical profiles. Group A comprised older patients with mild-to-severe tinnitus and moderate HL, whereas Group B consisted of younger patients with negligible-to-moderate tinnitus and normal or slight hearing impairment, consistent with the differing etiology underlying each condition.

Following nutraceutical supplementation, both groups showed a decrease in THI score, with improvement

in over 90% of patients and no cases of worsening. A reduction in tinnitus severity grade was recorded in 29% of patients, while 71% remained stable, with no progression observed. Improvement was distributed across all severity grades (1–5) in both groups. Collectively, these findings suggest that the nutraceutical supplement may alleviate tinnitus severity irrespective of baseline clinical characteristics, with a potentially sustained effect.

Longitudinal evaluation revealed a modest increase in the proportion of patients transitioning to a less severe tinnitus category after 3 months, more pronounced in Group B than in Group A. These findings suggest a potentially different pattern of response between groups. This is further supported by the negative correlation between ΔTHI and baseline THI score observed exclusively in Group A, where patients with severe-to-catastrophic tinnitus showed smaller improvements than those with mild-to-moderate tinnitus. However, given the marked differences in age, baseline THI scores, and hearing thresholds between groups, these comparisons should be interpreted with caution and do not allow conclusions regarding differences in treatment efficacy between primary and secondary tinnitus. A clinically meaningful reduction in THI score, exceeding the minimal clinically important difference of 7 points [31,32], was recorded in approximately 30% of patients, with no statistically significant difference between groups. Importantly, this indicates that nearly 70% of the study population did not achieve a clinically meaningful improvement. Therefore, although a statistically significant reduction in THI scores was observed in both groups, the clinical relevance appears limited at the individual patient level. Despite considerable heterogeneity in sample size, patient characteristics, and intervention composition limiting direct cross-study comparisons, these results are partially consistent with previous evidence showing that a combination of *Ginkgo biloba*, vitamin B12, and melatonin improved THI scores and reduced discomfort after 3 months in patients with tinnitus and comorbid headache [30]. Overall, these results underscore that statistically significant improvements in THI scores at the group level do not necessarily translate into clinically meaningful benefits for most patients, highlighting the need for responder-based analyses in future studies.

Regarding audiometric outcomes, hearing threshold reductions of 3% and 8.9% were observed in Groups A and B, respectively; however, given that a minimum of 10% reduction is generally required to exceed measurement error, these changes do not constitute clinically meaningful improvements.

The relationship between tinnitus severity and degree of hearing impairment remains debated, with some studies reporting a positive correlation [33–35] and others failing to confirm it [36]. In this context, the positive correlation between THI score and hearing threshold observed in Group A—but not in Group B—may reflect the distinct pathophysiology of secondary tinnitus, in which auditory dysfunction and tinnitus burden are more likely to share a common peripheral origin. Accordingly, Group A patients, who presented with more pronounced baseline hearing impairment, also showed greater improvement in tinnitus-related symptoms following supplementation, suggesting that tinnitus relief may be indirectly associated with improved auditory function in this subgroup. This interpretation is further supported by evidence that interventions concurrently targeting both auditory function and tinnitus — such as vitamin D as an add-on to methylprednisolone and *Ginkgo biloba* — have been reported to improve both audiometric thresholds and tinnitus symptoms at short- and long-term follow-up in patients with sudden SNHL and vitamin D deficiency [29].

A shift in the distribution of hearing loss severity was observed only in Group A following supplementation, which was characterized by a decrease in the proportion of patients with moderate HL and a concomitant increase in those with mild HL. These intergroup differences may reflect the greater baseline hearing impairment and the likely peripheral origin of tinnitus in Group A.

In primary tinnitus, the condition may originate within the central nervous system (CNS), whereas secondary tinnitus is thought to arise peripherally before undergoing central processing. Central tinnitus refers to abnormal neuronal activity in the central auditory pathways while peripheral tinnitus stems from dysfunction at the cochlear level, primarily due to the outer hair cells (OHC) degeneration [37,38]. OHC damage – including stereocilia alterations – increases spontaneous cochlear activity, which may secondarily contribute to inner ear cells (IHC) degeneration. Elevated intracellular calcium levels and structural changes in HC proteins have been proposed as triggers of this pathological cascade [3,37].

Although IHCs are less numerous and less vulnerable than OHCs, they are responsible for transmitting virtually all acoustic information to the brain via type I auditory nerve fibers (90–95%) [39]. Cumulative damage to OHC, IHC, and cochlear neurons raises the hearing threshold, potentially explaining the association between presbycusis and tinnitus observed in Group A patients, as well as the improvement in audiometric thresholds following

supplementation.

The observed reduction in tinnitus severity, as indicated by THI scores, suggests a potential beneficial effect of the nutraceutical on perceptual outcomes. Although modest shifts toward lower HL grades were noted in Group A, these changes did not reach clinical significance. While causality cannot be inferred from this observational study, the findings may be supported by the complementary molecular actions of the formulation components. Preclinical evidence provides a plausible mechanistic basis for these effects, particularly for berberine and curcumin, which exert targeted molecular actions beyond their antioxidant activity, potentially preserving cochlear HC integrity and function [37]. Berberine has been shown to attenuate HC loss induced by ototoxic insults through multiple mechanisms, including reduction of reactive oxygen species, restoration of mitochondrial membrane potential, and modulation of mitophagy via the PINK1–Parkin pathway. It also promotes autophagy through upregulation of Atg5 and Atg7, pathways implicated in auditory protection [13,37].

Curcumin shares several of these mechanisms while additionally targeting inflammatory signaling. It has demonstrated protective effects against drug- and noise-induced ototoxicity by inhibiting lipid peroxidation, suppressing NF-κB activation, and activating the Nrf2 pathway, thereby enhancing cytoprotective responses and limiting inflammation [40].

Other components may further contribute through complementary mechanisms. *Rosa canina* is rich in polyphenols and vitamin C, supporting antioxidant defenses and potentially reducing oxidative damage [41]. Herbal formulations containing *Rosa canina* have also shown beneficial effects in patients with tinnitus, although the specific contribution of each component remains unclear [42]. *Hericium erinaceus* has been associated with neuroprotective effects, partly through stimulation of nerve growth factor synthesis. *Ganoderma lucidum* (Reishi) may improve microcirculation and exert anti-inflammatory and antiplatelet effects, while *Auricularia auricula-judae* provides antioxidant and antithrombotic polysaccharides [18–20,43].

While the present findings suggest a potential association between the nutraceutical supplementation and changes in tinnitus-related outcomes, the absence of a randomized, placebo-controlled design and the relatively small sample size per group (less than 50 participants) limit the strength and generalizability of the results. Therefore, a definitive causal relationship between the observed changes and the nutraceutical intervention cannot be established. To partially address these limitations, a large-scale statistical analysis was conducted, and data were stratified according to disease severity. This approach allowed for the description of outcome variations across different subgroups and provided preliminary insights into heterogeneous response patterns under different clinical conditions. Furthermore, the between-group comparisons were exploratory and should not be interpreted as evidence of differential response between primary and secondary tinnitus, given the substantial differences between groups.

For this reason, the study should be considered a pilot investigation, and the findings should be interpreted with caution. In the absence of a placebo or control group, it is not possible to determine whether the observed changes in tinnitus-related outcomes are attributable to the nutraceutical intervention, natural symptom variability over time, or placebo-related effects.

Nevertheless, the observed changes were statistically significant, suggesting a consistent trend in tinnitus-related outcomes over time. These preliminary results support further investigation of this nutraceutical formulation in tinnitus management through prospective, randomized, placebo-controlled trials aimed at confirming these observations and clarifying the underlying mechanisms.

5. Conclusions

The multi-compound nutraceutical evaluated was well tolerated during the treatment period and was associated with a reduction in THI scores. Modest changes in audiometric thresholds were observed, likely reflecting improved cochlear function, though clinical relevance remains uncertain. The observed changes may be consistent with the known antioxidant, anti-inflammatory, and neuroprotective properties of some formulation components, including curcumin, berberine, *Hericium*, and *Rosa canina*. Outcome variations appeared to differ according to disease severity, and it would be of interest to assess whether longer treatment durations could further improve tinnitus-related quality of life and auditory function. The findings also underscore the importance of patient adherence to maximize potential outcomes. However, due to the observational design and the absence of a placebo-controlled group, the present findings are preliminary and hypothesis-generating and do not allow any causal in-

ference regarding the relationship between the nutraceutical and the observed changes.

Future prospective, randomized, placebo-controlled studies are warranted to further investigate the role of this nutraceutical combination in tinnitus management and to clarify the molecular mechanisms potentially associated with the observed changes. Additionally, identifying predictors of treatment response could help optimize patient selection and improve outcomes in both primary and secondary tinnitus.

Author Contributions

A.P.C. and L.C. contributed equally to the work. Conceptualization, D.N. and L.B.; methodology, A.P.C. and M.M.; investigation, A.P.C. and M.M.; data curation, L.C., L.B., and G.D.S.; writing—original draft preparation, L.C.; writing—review and editing, D.N., L.C., L.B., G.D.S. and A.P.C.; supervision, D.N. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and applicable data protection regulations (EU Regulation 2016/679, GDPR), as well as institutional policies for retrospective observational studies using fully anonymized data. The study had a retrospective, observational design and evaluated a food supplement administered during routine clinical practice; no intervention in clinical practice or modification of patient management was performed for research purposes. The analysis was based exclusively on fully anonymized medical records, from which no subject is directly or indirectly identifiable. All patient identifiers were removed prior to analyses, and data were processed exclusively in aggregated form. Given these characteristics, formal review and approval by a Local Ethics Committee were not sought.

Informed Consent Statement

The authors declare that patient informed consent for this study was waived due to the retrospective, observational, and fully anonymized nature of the study. No individual patient data capable of directly or indirectly identifying study participants were collected, retained or processed at any stage of the research.

Data Availability Statement

All data supporting the findings of this study are included within the article; additional information may be obtained from the corresponding author upon reasonable request.

Conflicts of Interest

The authors L.C., L.B., and G.D.S. are affiliated with Laboratori Aliveda srl. The other authors declare that the research was carried out in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

AI Use Statement

During the preparation of this manuscript, the authors used Claude Sonnet 4.6 solely for the purposes of language refinement. No AI tools were used for data analysis, interpretation, or generation of scientific content. All outputs were critically reviewed and edited by the authors. The authors take full responsibility for the integrity and accuracy of the work.

Appendix A

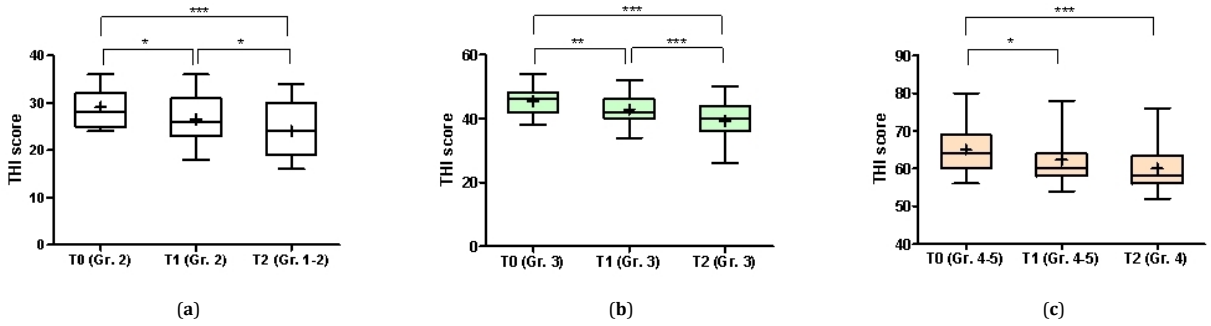

Figure A1. THI score in Group A patients stratified by disease severity at baseline. (**a**) patients of Grade 2; (**b**) patients of Grade 3; (**c**) patients of Grade 4 and Grade 5 (consistent with the paucity of patients with catastrophic tinnitus).

Note: ANOVA with Dunn's multiple comparisons. Gr., Grade. *$p < 0.05$; **$p < 0.01$; $p < 0.001$.

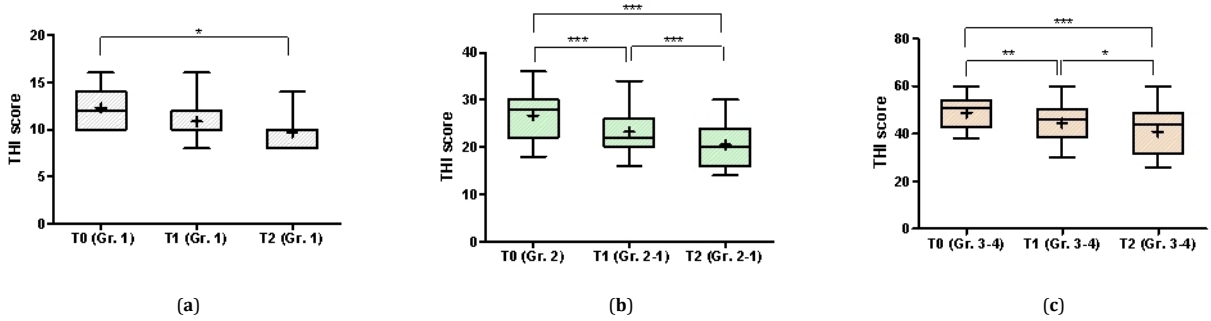

Figure A2. THI score in Group B patients stratified by disease severity at baseline. (**a**) Patients of Grade 1 (ANOVA with Dunn's Multiple comparison test); (**b**) Patients of Grade 2 (ANOVA with Bonferroni's multiple comparison test); (**c**) Patients of Grade 3 and Grade 4 (consistent with the paucity of patients with severe tinnitus).

Note: ANOVA with Bonferroni's multiple comparison test. Gr., Grade. *$p < 0.05$; **$p < 0.01$; $p < 0.001$.

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