JOURNAL OF DIETARY SUPPLEMENTS
https://doi.org/10.1080/19390211.2021.1944947

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Effectiveness of Tinnitan Duo® in Subjective Tinnitus with Emotional Affectation: A Prospective, Interventional Study

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ABSTRACT

To assess the effectiveness of a food supplement (Tinnitan Duo®) containing 5-hydroxytryptophan, *Ginkgo biloba*, magnesium, melatonin, vitamin B5 and B6, and zinc at improving tinnitus response and intensity. Prospective, single-center interventional study including patients with subjective tinnitus and emotional affectation. The primary endpoint was the change in the Tinnitus Handicap Inventory (THI) total score and the emotional subscale after 3 months of treatment. Secondary endpoints were the change from baseline to month 3 in (1) the Tinnitus Distress Rating (TDR) scale, and (2) in hearing status, and the safety profile of patients throughout the study. Sixty-one patients were included, and 29 completed the study. The THI total score was significantly reduced after 3 months of treatment in the per-protocol (PP, all the patients with no major protocol deviations) and intention-to-treat (ITT) populations (−15.7 and −7.5, respectively; $p = 0.001$). The emotional subscale score significantly decreased after 3 months of treatment by −5.6 in the PP ($p = 0.001$) and by −2.6 in the ITT populations ($p = 0.001$). Perceived tinnitus loudness significantly decreased after 3 months of treatment ($p = 0.001$). The audiogram showed no significant changes in hearing status after 3 months of treatment. Of the five adverse events (AEs) reported, all were mild or moderate, and three were related to the study treatment (two headaches and one dizziness). This new food supplement was associated with an improved tinnitus-related emotional affectation and with a good safety profile.

KEYWORDS

emotional affectation; food supplement; tinnitus; tinnitus loudness

Introduction

Tinnitus is a sound perceived by the patient in the absence of an external origin (Bauer 2018). The sound can be intermittent, persistent or pulsatile with variable intensities, and typically manifests as ringing, buzzing, or hissing in one or both ears, or within the head (Tyler and Baker 1983; Baguley et al. 2013). Tinnitus is a heterogeneous condition encompassing different clinical profiles that can be broadly categorized into objective or subjective (Cima et al. 2019). In patients with objective tinnitus, the noise is generated

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/19390211.2021.1944947.

within the body and can be audible by an external observer. In subjective tinnitus, the most common form, the noises have a multifactorial origin, and an external or inner-body source cannot be identified (Langguth et al. 2013). In many cases, tinnitus is caused by initial cochlear damage (such as hearing loss) that impairs the neuronal activity in central auditory pathways and is thereby perceived as auditory stimuli (Noreña and Farley 2013). However, tinnitus can occur with or without hearing loss by different proposed mechanisms (Cima et al. 2019).

Identified risk factors include age, hearing loss, male sex, and persistent or excessive noise exposure (Lockwood et al. 2002; McCormack et al. 2016). The estimated prevalence of tinnitus ranges from 10 to 19% (Axelsson and Ringdahl 1989; Gilles et al. 2013) with higher rates in the elderly (14.3%) (Shargorodsky et al. 2010), although chronic tinnitus is increasingly observed in young adults, probably because of the excessive leisure noise they are exposed to (Gilles et al. 2013; Degeest et al. 2014).

Tinnitus can become bothersome for many patients, deeply affecting their quality of life and sleep (McCormack et al. 2016; Tyler et al. 2020). In fact, an exploratory study found more sleeping trouble in patients with tinnitus than in participants with cochlear implants (Tyler et al. 2020). A systematic review identified that between 3.0% and 30.0% of patients experience bothersome tinnitus, with primary activities impaired being emotions, hearing, sleep and concentration (Tyler et al. 2014; McCormack et al. 2016). These psychiatric and psychosomatic symptoms aggravate the perception of tinnitus, and their level of affectation determines its severity (Langguth et al. 2013).

The heterogeneous and multifactorial nature of tinnitus challenges its management (McCormack et al. 2016; Cima et al. 2019). No specific treatment is currently recommended for chronic tinnitus, and many interventions to cope with the disease and manage associated comorbidities are educational and behavioral (Zenner et al. 2017). Other interventions suggested for the management of hearing loss and tinnitus include cochlear implantation (Tyler et al. 2008) and hearing aids, although with scarce evidence (Hoare et al. 2014; Ramakers et al. 2015; Cima et al. 2019). Food supplements are broadly employed for the management of tinnitus, but the strength of evidence was insufficient in different studies (Coelho et al. 2013, 2016; Paiva 2017). Specific recommendations on treatments, interventions, dietary or alternative therapies are mainly limited by the lack of high-quality studies showing benefit over harm (Cima et al. 2019). Therefore, higher efforts are required to improve the management of tinnitus, given the high burden that this condition represents for patients and healthcare systems (Maes et al. 2013).

Tinnitan Duo® is a food supplement comprising 2 pills (morning and night) indicated for the management of tinnitus with emotional affectation. This food supplement contains 5-hydroxytryptophan (5-HTP), *Ginkgo biloba* extract, magnesium, melatonin, vitamin B5 and B6 and zinc. The aim of this study was to assess the effectiveness of this food supplement at improving the perception of tinnitus and emotional-related responses, and its safety profile.

Methods

Study design

This prospective, non-controlled, single-center, interventional study was conducted at Centro Médico Teknon (Quirón Salud, Barcelona, Spain). The study adhered to the

tenets of the Declaration of Helsinki and was carried out following the Good Clinical Practice guidelines of the International Council for Harmonization. The study was approved by the Ethics Committee of Centro Médico Teknon with informed consent provided by all participants before inclusion in the study.

The study treatment was Tinnitan Duo® (Laboratorios Salvat, S.A.), a commercialized food supplement containing 5-HTP, *Ginkgo biloba* extract, magnesium, melatonin, vitamin B5 and B6, and zinc. Patients received the supplement orally twice daily for 3 months: one pill in the morning at breakfast and one pill at night 30 min before bedtime. We used a dry extract from leaves of *Ginkgo biloba* (50:1) containing >24.0% of flavonoid glycosides, >6% of ginkgolides A, B, C, J and bilobalide, >55% of quercetin content in total flavone, and <5 ppm of ginkgolic acid content.

The study was scheduled across three visits: Visit 1 (month 0, baseline), Visit 2 (month 1), and Visit 3 (month 3, end of study). At Visit 1, we explained the aims and main procedures of the study and collected demographic, clinical, and concomitant treatment information. Eligible patients who provided written informed consent underwent audiometry and completed the Tinnitus Handicap Inventory (THI) and the Tinnitus Distress Rating (TDR) scale. At Visit 2, we evaluated potential changes in the characteristics of tinnitus, and recorded adverse events (AEs), concomitant medications and treatment adherence. At Visit 3, patients completed the THI and TDR scale, and audiometry was performed. AEs were registered, and data on concomitant medications and treatment adherence were collected. Patients did not receive any instruction regarding diet, dietary supplement use or exercise during the study.

Study population

We included adult patients diagnosed with subjective tinnitus that lasted $\geq$ 6 months, with a THI score $\geq$ 20 and at least four out seven positive items in the emotional subscale of the THI, and who provided written informed consent.

Patients were excluded according to the following criteria: (1) current or previous treatment with antidepressants or anxiolytics, (2) concomitant tinnitus pharmacological treatment within the previous 3 months, (3) anticoagulant treatment, (4) history (within the previous 6 months) of or current alcohol or drug abuse, (5) significant audio-otologic diseases such as Menière's syndrome, otosclerosis, tympanic membrane perforation, or otitis media, (6) diagnosis of psychiatric disorders such as depression or psychosis, (7) disease whose exacerbation, according to investigator's criteria, could alter the interpretation of results, (8) presence of acoustic neuroma, otologic lesions/surgery or pulsatile tinnitus, (9) hypersensitivity or allergy to any component of the study treatment, (10) severe kidney insufficiency, (11) planned surgery, (12) pregnant or lactating women, and (13) treatment with any investigational product within the previous month or previous inclusion in this study.

Study outcomes

We aimed to assess the effectiveness of this food supplement in reducing the impact of tinnitus on patient's life and emotional aspects, and in improving the perception of

tinnitus loudness. The primary objective of the study was to assess the change from baseline to month 3 in the THI total score and the THI emotional subscale. Secondary objectives included (1) the change from baseline to month 3 in tinnitus loudness measured by the TDR scale, (2) the change in hearing status from baseline to month 3 assessed with audiometry, and (3) the safety profile of patients throughout the study.

The THI is used to quantify the impact of tinnitus on daily life. The questionnaire consists of 25 questions divided into three subgroups: functional ($n = 13$), emotional ($n = 7$) and catastrophic ($n = 5$) (Newman et al. 1996). Each question can be answered as 'Yes' (4 points), 'Sometimes' (2 points) or 'No' (0 points). THI scores can range from 0 to 100, being 100 the greatest tinnitus affectation (Newman et al. 1996). In this study, we used the Spanish validated version of the questionnaire (Martínez 2006). The treatment was deemed effective when the reduction in the THI total score after 3 months was $\geq$ 20% higher than the baseline value.

Tinnitus loudness was self-rated by the patients using the TDR scale that can range from 0 (no tinnitus) to 10 (worst possible tinnitus). The change in hearing status after 3 months of treatment was evaluated with pure tone audiometry at four frequencies (500, 1000, 2000, and 4000 Hz).

Treatment adherence was assessed by recording the number of returned pills. The number of doses received was divided by the number of doses prescribed throughout the study. Treatment adherence was considered achieved with a proportion of doses $\geq$ 80%.

Statistical analyses

Sixty-two patients were required for this study, considering a population size of 90,000 patients with 20% heterogeneity, 10% error and 95% confidence interval. Assuming an estimated dropout rate of 15%, the resulting sample size was 73 patients.

Since the dropout rate was higher than expected, a *post-hoc* sensitivity analysis was performed by imputing missing data (baseline observation carried forward [BOCF]) for those patients who did not attend Visit 3.

Effectiveness outcomes were analyzed in the intention-to-treat (ITT) and per-protocol (PP) populations and safety data in the safety population. The ITT population comprised all the patients included in the study. The PP population comprised all the patients included in the study with no major protocol deviations. The safety population comprised all the patients included in the study who received at least one treatment dose.

Effectiveness data were described as mean ± SD and compared between visits with the paired Student's *t*-test. Safety data were analyzed descriptively. Statistical analyses were two-sided, with a level of statistical significance set at $p < 0.05$. The Minitab 18 Statistical Software was used for statistical analyses.

Results

Study population

A total of 61 patients were included, of whom 29 (47.5%) completed the study. Among the 32 patients who withdrew prematurely, 29 were lost to follow-up, two presented AEs and one withdrew the consent to participate. The ITT and safety populations

Table 1. Baseline characteristics of patients with tinnitus.

	$N = 61$
Age (years), mean	48
Median (min; max)	48 (24; 78)
Sex (men), N (%)	42 (68.9 %)
Tinnitus, N (%)	
Central	40 (65.6 %)
Left	12 (19.7 %)
Right	9 (14.8 %)
Hyperacusis, N (%)	42 (69.0 %)
High-frequency hearing loss, N (%)	41 (67.0 %)
Tinnitus triggering factors	
Stress	59 (96.7 %)
Noises	44 (72.0 %)
Sleepiness	36 (59.0 %)
Tiredness	32 (52.0 %)
Employed, N (%)	54 (88.5 %)

Data are expressed as mean, median (min; max) or N (%).

Table 2. Change in the THI total score and emotional subscale after 3 months of treatment.

	PP population ($N = 29$)	ITT population ($N = 61$)
THI total score		
Baseline, mean ± SD	47.03 ± 16.45	47.18 ± 15.75
Month 3, mean ± SD	31.31 ± 20.33	39.70 ± 19.49
ΔTotal score	−15.72 ± 21.31	−7.48 ± 16.57
% of reduction	33.4 %	15.9 %
***P*-value**	0.001	0.001
Emotional subscale		
Baseline, mean ± SD	12.21 ± 7.15	12.98 ± 6.60
Month 3, mean ± SD	6.57 ± 6.37	10.39 ± 7.14
ΔEmotional score	−5.64 ± 7.83	−2.59 ± 5.97
% of reduction	46.2 %	20.0 %
***P*-value**	0.001	0.001

Data are expressed as mean ± SD or change from baseline to month 3.
Statistical significance was calculated with the Student's *t*-test.
THI, Tinnitus Handicap Inventory; PP, per-protocol; ITT, intention-to-treat; SD, standard deviation.

comprised 61 patients and the PP population 29 patients (Supplementary Figure 1). All the patients who completed the study reported adherence rates ≥ 80%.

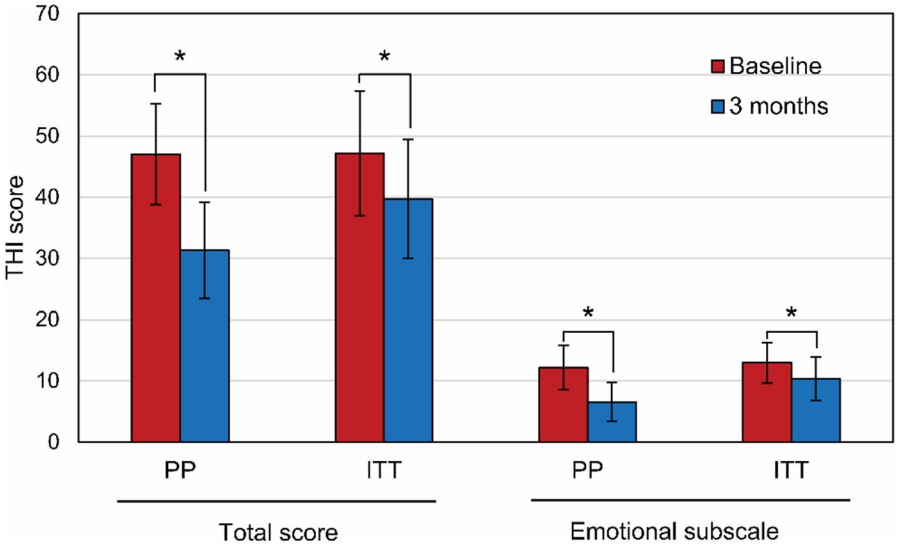
Mean age was 48 years and 68.9% of patients were men. Forty patients (65.6%) reported central tinnitus, 12 (19.7%) in the left ear and 9 (14.8%) in the right ear. The sound was mostly perceived as high-pitched (93.0%), and as low-pitched in 15% of patients. The proportion of patients with hyperacusis was 69.0%, and 67.0% showed high-frequency hearing loss (Table 1).

Stress was the predominant factor affecting tinnitus characteristics (96.7%), followed by noises (72.0%), sleepiness (59.0%) and tiredness (52.0%). Of note, 80.0% of patients showed night rest problems. At baseline, 88.5% of patients were employed.

Effectiveness assessments

THI total score

The THI total score decreased from 47.0 ± 16.5 at baseline to 31.3 ± 20.3 after 3 months of treatment (−15.7 ± 21.3 points decrease; $p = 0.001$) in the PP population. In the ITT population, the change after 3 months of treatment was −7.5 ± 16.6 points ($p = 0.001$), which was higher than the 20% prespecified cutoff (Table 2, Figure 1).



Data are expressed as mean ± standard deviation. * indicates p ≤ 0.001 (Student's t-test). THI, Tinnitus Handicap Inventory; PP, per-protocol; ITT, intention-to-treat.

Figure 1. Change in the THI total score and emotional subscale after 3 months of treatment.

Table 3. Change in the Tinnitus Distress Rating Scale after 3 months of treatment.

	PP population ($N = 29$)	ITT population ($N = 61$)
Baseline, mean ± SD	6.59 ± 1.59	6.61 ± 1.56
Month 3, mean ± SD	5.04 ± 1.81	5.99 ± 1.83
ΔTotal score	−1.55 ± 1.87	−0.62 ± 1.40
% of reduction	23.5 %	9.4 %
***P*-value**	0.001	0.001

Data are expressed as mean ± SD or difference from baseline to month 3.
Statistical significance was calculated with the Student's *t*-test.
PP, per-protocol; ITT, intention-to-treat; SD, standard deviation.

Emotional subscale

The emotional subscale score significantly decreased by −5.6 ± 7.8 points in the PP population ($p = 0.001$) and by −2.6 ± 6.0 points in the ITT population ($p = 0.001$) after 3 months of treatment (Table 2, Figure 1).

Tinnitus Distress Rating Scale

The TDR scale showed a significant reduction in the perception of tinnitus both in the PP and ITT populations (−1.6 ± 1.9 and −0.6 ± 1.4 points, respectively; $p = 0.001$ in both comparisons) (Table 3).

Safety assessment

A total of five AEs were reported, all of them of mild (40%) or moderate (60%) intensity. Among them, three were related to the study treatment (two headaches and one dizziness). The two patients with headache discontinued the study (Table 4).

Audiograms showed no significant changes in hearing status after 3 months of treatment in any of the frequencies assessed (500, 1000, 2000, and 4000 Hz) in both ears ($p > 0.05$) (Table 5).

Table 4. Adverse events throughout the study.

	PP population ($N = 29$)
Adverse events	5
Severity	
Mild	2 (40 %)
Moderate	3 (60 %)
Severe	0
System Organ Class Preferred Term	
Ear and labyrinth disorders	
Tinnitus	1 (1.6 %)
Musculoskeletal and connective tissue disorders	
Muscle tightness	1 (1.6 %)
Nervous system disorders	
Headache	2 (3.3 %)
Dizziness	1 (1.6 %)

Data are expressed as N (%).
PP; per-protocol.

Table 5. Change in hearing status after 3 months of treatment.

Hz	Right Ear (ΔdB)	p-value	Left Ear (ΔdB)	p-value
500	−0.96 ± 4.00	0.232	−0.19 ± 2.64	0.713
1000	−0.96 ± 4.90	0.327	−1.15 ± 4.08	0.161
2000	−1.73 ± 4.68	0.071	−1.35 ± 3.89	0.090
4000	−0.19 ± 13.23	0.941	3.46 ± 11.29	0.131

Statistical significance was calculated with the Student's *t*-test.
Hz, hertz; dB, decibels.

Discussion

In this study, we observed a significant reduction in tinnitus-related emotional distress and an improvement in the perception of tinnitus loudness, with no impairment of hearing status and good safety profile after 3 months of treatment with Tinnitan Duo®.

Tinnitus is difficult to manage with few interventions currently recommended in the guidelines and scarce well-designed studies available (Tunkel et al. 2014). The management of tinnitus is also challenged by the heterogeneous underlying conditions and associated comorbidities, among which emotional responses are particularly relevant. Associated symptoms become bothersome and impair the quality of life in 3.0% to 30.0% of patients and may aggravate the perception and tolerance to tinnitus, generating a vicious cycle of tinnitus-stress (McCormack et al. 2016). Indeed, the extent of psychological affectation determines the severity of tinnitus, highlighting the importance of managing emotional symptoms. Different mechanisms have been proposed to explain tinnitus-related distress and awareness, involving the activation of limbic and autonomic nervous systems, the co-activation of self-awareness and salience brain networks or impaired inhibitory gating mechanisms (Cima et al. 2019). The Psychological Model proposed by Tyler *et al.* in 1992 suggested that tinnitus annoyance is the result of (1) the tinnitus loudness and (2) the psychological makeup of the patient (Tyler et al. 1992). Therefore, the authors suggested that treatments should address both the tinnitus and the reactions to tinnitus. To this end, the authors developed the Tinnitus Activities Treatment, which combines cognitive-behavioral and sound therapy and focuses on the primary functions affected by tinnitus: (1) thoughts and emotions, (2) hearing, (3) sleep and (4) concentration (Tyler et al. 1989, 2007).

Tinnitan Duo® is composed of vitamins, minerals and a herbal extract targeting both tinnitus perception and related emotional symptoms. Although different studies assessed the effectiveness of some agents such as *Gingko Biloba*, zinc or melatonin; this is, to our knowledge, the first study with a food supplement incorporating all these substances.

The sample size (61 patients) is in the range of that observed in previous studies on tinnitus (Morgenstern and Biermann 2002; Lopez-Gonzalez et al. 2007; Tziridis et al. 2014; Abtahi et al. 2017) and higher than in several of them (Rosenberg et al. 1998; Arda et al. 2003; Cevette et al. 2010; Radunz et al. 2019). The high dropout rate (52.5%) noted in our study is worth mentioning, resulting in only 29 patients with complete data at the end of follow-up. This notable proportion of withdrawals was previously observed (Rejali et al. 2004; Cevette et al. 2010; Cima et al. 2012), and could be related, at least in part, to the time needed to achieve noticeable differences in a chronic and bothersome condition such as tinnitus. This would support the importance of encouraging patients to remain compliant to achieve perceptible improvements. Patients were slightly younger than in most previously published studies (Cevette et al. 2010; An and Whitney 2015; Radunz et al. 2019) and 88.5% were actively working, with the implications that this bothersome condition can have in productivity. Stress and noises were the most common factors worsening tinnitus, followed by sleepiness and tiredness, and 80% of patients reported problems with night rest. These high rates of complications denote a high degree of emotional affectation, highlighting the suitability of interventions targeting the emotional component of tinnitus.

In assessing the effectiveness of this food supplement, we compared the tinnitus perception at baseline and after 3 months of treatment *via* the THI, an internationally validated and one of the most popular tinnitus instruments recommended in current guidelines (Cima et al. 2019). Mean THI total score at baseline was 47.03, representing a moderate handicap (Zeng et al. 2016), and being higher than that observed in earlier studies (Rosenberg et al. 1998; An and Whitney 2015; Abtahi et al. 2017). The 33.4% reduction in the total score was associated with a mild handicap at the end of follow-up (Zeng et al. 2016). The reduction of 15.7 points in the THI total score is higher than the seven points established for considering a minimal clinically relevant change (Zeman et al. 2011) and than the 20% change (9.4 points with regards to study baseline) prespecified in the protocol. These results, although showing a promising trend, should be analyzed cautiously given the lack of comparator, and warrant further investigation in randomized controlled studies.

We assessed the specific effect of this food supplement on the emotional subscale, given the high prevalence and negative consequences of these symptoms for patients. The 46.2% improvement in the emotional response is greater than the 33.4% observed in the total score, which could indicate greater improvements in the emotional response than in the functional or catastrophic ones. Again, we cannot draw firm conclusions as the emotional response is highly subjective, and our study lacks a control group. The emotional response improvement could be attributed to ingredients such as zinc, melatonin, or 5-HTP with reported effects on emotional symptoms. 5-HTP is the most immediate precursor of serotonin, a neurotransmitter modulating anxiety and stress. This amino acid is used as a dietary supplement for the treatment of depression or insomnia (Jangid et al. 2013), but its role in tinnitus is controversial (Simpson and Davies 2000). To our knowledge, no previous study assessed the effect of 5-HTP in the

management of tinnitus. Zinc, an essential mineral expressed in the central nervous system including the auditory pathway and the cochlea (Coelho et al. 2007), showed lower levels in people with tinnitus compared with control groups (Arda et al. 2003). The potential effect of zinc on tinnitus has been linked to functions such as cochlear protection against free radical damage, maintenance of cochlear integrity, modulation of neurotransmission and antidepressant activity (Coelho et al. 2007). However, a systematic review found, with low quality evidence, that oral zinc supplementation was not associated with improved symptoms in adults with tinnitus (Person et al. 2016), contrasting with a randomized placebo-controlled study showing a significant improvement in subjective tinnitus severity. The potential role of melatonin in tinnitus management is associated with its involvement in the sleep-wake cycle and antioxidant activity (Pirodda et al. 2010). Melatonin promoted a significant decrease in the THI score and sleep quality (Megwalu et al. 2006; Cima et al. 2019), and an improvement in tinnitus loudness and matching (Hurtuk et al. 2011). The effectiveness of melatonin was more pronounced in certain subsets of patients such as those with severe sleeping problems (Megwalu et al. 2006) or high THI scores (Rosenberg et al. 1998; Cima et al. 2019).

Tinnitus loudness measured with the TDR scale was significantly reduced (23.5% reduction) after 3 months of treatment with Tinnitan Duo. This reduction could indicate that the food supplement not only helps reduce the impact of tinnitus on daily life, but could also improve the perception of tinnitus loudness. However, comparative studies are required to corroborate this finding. In this context, substances such as *Gingko Biloba* or magnesium could be responsible for such effects. *Ginkgo biloba* extracts possess antioxidant and anti-angiogenic properties and are commonly used for the treatment of tinnitus (DeFeudis et al. 2003). Whereas a systematic review found no evidence of the effectiveness of *Gingko biloba* in patients with a primary complaint of tinnitus (Hilton et al. 2013), the extract EGb 761® was proven superior to placebo in another systematic review (von Boetticher 2011). The potential use of magnesium in tinnitus derives from its protective effect against auditory threshold shifts (Attias et al. 2004; Abaamrane et al. 2009) and acoustic trauma (Sendowski 2006), and by the decreased endogenous levels observed in people with tinnitus (Uluyol 2016). However, evidence on its effectiveness is scarce, with only one single-arm, open-label study showing a significant reduction in the THI score after 3 months of treatment (Cevette et al. 2010). Moreover, the antioxidant effects of zinc and melatonin could have also contributed to improving tinnitus perception.

Although previously reported results with the active ingredients contained in this food supplement have provided insufficient evidence, two premises may be considered. First, the lack of recommendation in current guidelines (Tunkel et al. 2014; Cima et al. 2019) is mainly based on the scarce number of well-designed studies supporting their use and; second, earlier studies assessed their effect individually and not the possible additional impact of combining active substances targeting different mechanisms of tinnitus response. In this context, our results are in line with those observed with a combination of magnesium, *Ginkgo biloba* and melatonin, with a reduction of 13.8 points and of 2 points in the THI and TDR, respectively (An and Whitney 2015).

Tinnitan Duo was well tolerated, with none of the five AEs reported being severe. The good safety profile of this food supplement is in accordance with safety data reported for some of its components. For example, previous studies reported no major

side effects with *Ginkgo Biloba*, the most common AEs being mild gastrointestinal symptoms. Most frequently reported AEs associated with melatonin included nightmares and fatigue, but we did not identify any episode in our study (Rosenberg et al. 1998). Previous studies revealed a good safety profile of zinc and 5-HTP, being gastrointestinal symptoms the most common AEs. Likewise, no significant differences were found in the audiogram after 3 months of treatment, in agreement with a previous study showing no change in the audiogram of patients receiving *Ginkgo Biloba* (Rejali et al. 2004).

This study presents some limitations that are worth considering. First, and most important, the lack of comparator did not allow to account for potential placebo effects. This is particularly important given the psychological and subjective component of the disorder and also because of the strong placebo effect previously reported (Pinto et al. 2014). Thus, the conclusions of this study are to be considered preliminary and should be confirmed in further studies. Second, only 29 patients completed the study, representing a high dropout rate. Although the chronic and multifactorial nature of the condition could help explain this high dropout rate, further studies are needed to assess potential causes. Despite this, significant differences were consistent across both the ITT and PP populations. Last, the lack of tinnitus biomarker assessments or the evaluation of the effect of patient's baseline nutritional status are also limitations of the study.

One of the strengths of the study is that it captured self-reported outcomes such as the THI and TDR scale, audiometry assessments, and safety data. The THI is a validated questionnaire widely employed in tinnitus with good internal consistency (Baguley et al. 2000). One of the main limitations of previous studies is that they did not consistently report variables such as the change in psychoacoustic parameters or safety data, limiting the comparison between studies. In contrast, our study collected main outcome measures included in systematic reviews such as the change in THI, audiometry and safety data (Hilton et al. 2013; Person et al. 2016).

Conclusion

Tinnitan Duo was associated with a reduction in tinnitus-related psychological impact and disability and in the perception of tinnitus loudness with a good safety profile. Further randomized, controlled studies are needed to confirm these preliminary results.

Acknowledgements

Doris Álvarez and Marga Nevado from the Medical Department at Laboratorios Salvat, S.A. contributed to the study design, analysis of the data, and revision of the manuscript. Carla Granados from Trialance SCCL provided medical writing assistance.

Disclosure statement

The authors report no conflicts of interest.

Funding

The study was supported by Laboratorios Salvat, S.A.

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