

Ginkgo biloba Administered Singly and Combined With Antioxidants in Tinnitus Patients

Bhushan Chauhan¹, Shantanu Arya¹, and Komal Chauhan²

¹Department of ENT, M. M. Institute of Medical Sciences and Research, MMDU, Mullana, Ambala, Haryana, India

²National Institute of Food Technology Entrepreneurship and Management, Kundli, Sonapat, Haryana, India

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Address for correspondence

Bhushan Chauhan, MS
Department of ENT,
M. M. Institute of Medical Sciences &
Research, MMDU, Mullana,
Ambala, Haryana, India
Tel +91-9357097074
E-mail bhushan.chauhan112@
gmail.com

Background and Objectives: Tinnitus, or ear ringing, involves impulsive and spontaneous activity in the auditory neurons. Its prevalence is high in the elderly, but 10%–15% of adults suffer from tinnitus, affecting their quality of life. Therefore, this study aimed to evaluate the efficacy of *Ginkgo biloba* administered singly and in combination with antioxidants in tinnitus patients. **Subjects and Methods:** Patients were randomly allocated to Placebo (T0, n=22), Treatment 1 (T1, n=24), and Treatment 2 (T2, n=23) groups. The patients were educated on the study's methodology and were instructed to visit at 0, 4, 8, 12, and 14 weeks. The placebo group received starch capsule supplements. Conversely, the treatment groups received *Ginkgo biloba* (60 mg twice a day) singly and in combination with antioxidants. We enrolled 69 patients aged 40–70 years (41 men, 28 women). The Tinnitus Handicap Index (THI), Visual Analogue Score (VAS), and Short Form 36 (SF-36) Health Scores were determined pre- and post-treatment at each visit. **Results:** Supplementation of *Ginkgo biloba*, along with antioxidants, provided marked improvement ($p < 0.05$) in post-treatment THI and VAS scores in the T2 group compared to those in the T1 and T0 groups. The greatest ($p < 0.05$) percent difference was observed in the pre- and post-treatment THI (-36%) and VAS scores (-22.6%) of T2 patients. Likewise, the SF-36 scores improved significantly ($p < 0.05$) in the T2 group in varied parameters. **Conclusions:** *Ginkgo biloba*, along with antioxidants, can be a promising therapy for tinnitus patients, providing marked improvement in THI, VAS, and SF-36 scores.

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Keywords: Tinnitus; *Ginkgo biloba*; Antioxidants; Tinnitus Handicap Index; Visual Analogue Score.

Introduction

Tinnitus or ringing in the ear is defined as perception of sound without an external stimulus [1]. It results with an increase in impulsive and spontaneous activity in auditory neurons. The worldwide prevalence of tinnitus in adults affects 10% to 15% of population, whereby 14.3% in USA showed the peak between 60–69 years [2,3]. Of the total afflicted population 1%–2% have severe impact while 0.5% have a bothersome life with a deep negative impact on sleep and quality of life [3]. The incidence of tinnitus is comparatively higher in geriatric

population with hearing disorders; however general population has also been affected (5%–43%). Moreover, the prevalence is higher in males than females [4]. It is associated with varied audiological symptoms such as hearing loss and hyperacusis, affective disorders namely anxiety, depression along with negative emotional response with symptoms like lack of concentration, insomnia, and irritability [5]. Tinnitus has been classified as subjective and objective tinnitus. The former is the perception of sound in the absence of external acoustic stimulation while the latter is observed when an external source, such as elevated blood flow or muscular cramps inside the middle ear or auditory structures [6,7]. The onset of subjective tinnitus may be acute with or without hearing loss and is described as whistling, crackling, and ringing sound which can be continuous or intermittent affecting the quality of life [7].

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Psychotherapy and several allopathic drugs such as anesthetics, anti-inflammatory, antidepressants, muscle relaxants, calcium channel blockers, anticonvulsants, and the drugs that enhances blood circulation around cochlear region and brain have been used for clinical management of tinnitus [8]. These drugs besides increasing economic burden attributes to several side effects. Nevertheless, there is no effective single pharmacological treatment owing to unknown pathophysiology and multiple etiologies. Hence the focus of research is towards finding a treatment that prevents the progression and provides relief from annoying discomfort associated with tinnitus.

Ginkgo biloba extracts have been used in Chinese medicine for varied treatments since times immemorial [7,8]. The phytoconstituents present in *Ginkgo biloba* namely flavonoids (ginkgo-flavone glycosides) and terpenoids (ginkgolides A, B, C, J and bilobalide) and ginkgolides are responsible for its therapeutic potential [8]. Some studies have reported mild to severe side effects (gastrointestinal disturbances, headache, bleeding, skin allergies, and seizures) with *Ginkgo biloba* in some clinical trials; however, no chronic impact has been observed upon its supplementation [9,10]. Studies have pointed out oxidative stress as one of the prime causal factor for tinnitus [8,11-13]. An imbalance between oxidants and antioxidants in favor of the former weakens one's antioxidant defense system thereby resulting in increased production and accumulation of free radicals. Henderson, et al. [13] demonstrated that increased noise promotes oxidative stress which triggers the synthesis of glutamate, an excitatory neurotransmitter. The upsurge in the glutamate levels have neurotoxic impact which in turn causes inflammation, necrosis of postsynaptic dendrites of auditory

afferent nerve fibers thereby leading to cell death and increased severity of tinnitus [13]. Hence dietary intake of antioxidants as well as supplements have proven their efficacy in reducing the tinnitus symptoms.

Studies have been conducted to evaluate the effect of *Ginkgo biloba* in tinnitus [11,14]. Likewise, effect of supplementation of antioxidants in tinnitus patients have been conducted; however, limited data is available wherein combinatorial approach for synergistic effect of *Ginkgo biloba* and antioxidants for treatment of tinnitus have been studied. In the present study, the efficacy of *Ginkgo biloba* alone and *Ginkgo biloba* along with antioxidants have been evaluated to determine its effectiveness in tinnitus.

Subjects and Methods

Study design

The prospective, open label randomized controlled, placebo study was conducted in outpatient department of Ear, Nose, and Throat (ENT) and Head and Neck Surgery at Tertiary Care Hospital. The approval to undertake the study was sought from Institutional Ethical Committee (5/A/NECHR/2020). The study consisted of a 2-week screening period followed by a 12-week treatment period followed by 2-week follow up. The ENT physician counseled the patients about the aim of the study, methodology adopted, the probable benefits and potential hazards associated with the study. The information leaflet about the study was given to each of the selected patient along with the informed consent. The visits were scheduled periodically (0, 4, 8, 12 weeks) followed by follow up for 2 weeks

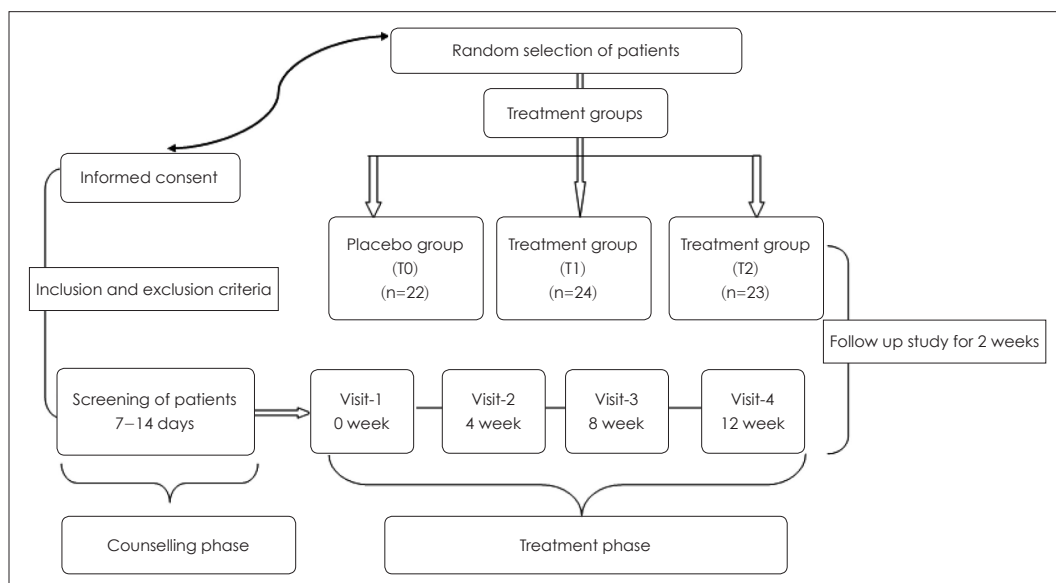


Fig. 1. Schematic representation of study. T0, placebo; T1 (Treatment 1), receiving *Ginkgo biloba* 60 mg BD; T2 (Treatment 2), receiving *Ginkgo biloba* 60 mg BD along with antioxidants).

for any discomfort. The schematic representation of the study is depicted in Fig. 1. The sample size was calculated using power analysis software (G*Power ver. 3.1.9.7; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) with margin of error at 5%, power 0.8 and effect sized at 0.8

Inclusion and exclusion criteria

Subjects between 40 and 70 years of age with a clinical history of hearing loss with tinnitus for more than one month duration and audiometrically proved sensory neural hearing loss (SNHL) were included in the study. Patients with noise induced hearing loss or sudden SNHL, pregnant, lactating women, and patients with clinical history of cardiovascular diseases, taking anticoagulants, antihypertensives, antidepressants, ototoxic drugs, undergoing other tinnitus treatments namely acupuncture, homeopathy, hypnotherapy in last six months were excluded.

Patients selection

Subjects fulfilling the inclusion criteria and who willingly volunteered to participate in study were subjected to screening for a minimum of 7 days and maximum of 14 days. The selected patients were assessed periodically at each visit using questionnaires.

Therapeutic protocol

The subjects were randomly allocated into three groups: T0 (Placebo), received starch capsules; T1 (Treatment 1), receiving *Ginkgo biloba* capsules 60 mg twice a day; and T2 (Treatment 2), receiving *Ginkgo biloba* capsules 60 mg twice a day along with antioxidant preparation (β -carotene [provitamin A] 20 mg, vitamin C [ascorbic acid] 200 mg, vitamin E 200 mg, and selenium 50 μ g). Antioxidant preparation was used from our earlier study [15].

Clinical measurements

The tinnitus handicap was evaluated with 25-item Tinnitus Handicap Index (THI) questionnaire. It is a widely used, unbiased (age, gender, and hearing loss) and reliable questionnaire to assess the severity and intensity of tinnitus. The THI was adopted from Korean adaptation consisting of 25 items [11]. Of the total items, further categorization was made into functional (11 items), emotional (9 items), and catastrophic (5 items). The patients were counseled and briefed about the questionnaire. Three response alternatives (0=none, 2=sometimes, 4=always) were given for each item, and the total THI score was calculated by adding up all the responses. The possible score of THI ranges between 0 to 100, and the higher THI score represents greater handicap from tinnitus. Furthermore, patients themselves as-

sessed tinnitus intensity using Visual Analogue Score (VAS). VAS score values ranged between 0 to 10 and higher values indicated higher intensity. Short Form 36 (SF-36) aggregate scores for each domain range between 0 to 100, expressed as percentage. Higher the score, better the health index [11].

Statistical analysis

Statistical analysis was performed using Student's t-test to compare differences between pre- and post-treatment THI and VAS scores and inter groups. Pre- and post-treatment changes in SF-36 scores were analyzed using one-way analysis of variance, Student's t-test and Wilcoxon signed-rank test. Values of $p < 0.05$ were considered significant. All analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Study population

A total of 89 patients suffering from tinnitus were subjected to screening for the study. A total number of 77 patients following the inclusion criteria and willingly volunteered for the study were selected. Patients were briefed about the study protocol, risks, potential benefits, medications, and the periodical visits to the hospitals (0, 4, 8, 12, 14 weeks). The selected ones were subjected to screening for audiological and tinnitus evaluation through THI, VAS, and SF-36 questionnaire at each visit. The patients were randomly allocated to the placebo (T0) and treatment groups (T1 and T2). Of the total, 69 patients received the treatment and completed the study wherein 22 served as placebo with 12% dropout (T0); 24 patients received *Ginkgo biloba* with 11% dropout (T1); and 23 received *Ginkgo biloba* along with antioxidants with 8% dropout (T2). They were also weekly communicated telephonically for compliance with the study and any discomfort associated with medication. A total of 8 patients (10%) dropped the study in between (3 from T0; 3 from T1; and 2 from T2 groups) (Table 1). The patients, who discontinued the study, did not give any specific reason for discontinuity.

Physical characteristics

The demographic profile mainly the physical parameters such as gender, age and duration of tinnitus of placebo (T0) and treated (T1 and T2) patients are shown in Table 1. There was no statistically significant ($p > 0.05$) difference between the placebo and treatment groups regarding age, sex, and duration of tinnitus.

THI score

Treatment with *Ginkgo biloba* singly and *Ginkgo biloba* along

Table 1. Demographic profile of patients

Variables	Number of patients			
	T0 (n=22)	T1 (n=24)	T2 (n=23)	Total (n=69)
Gender wise distribution of patients in treatment groups				
Male:female	14:8 (63.6:36.4)	13:11 (54.2:45.8)	14:9 (60.9:39.1)	41:28 (59.4:40.6)
Age-wise distribution of patients (yr)				
40–50	5 (22.7)	6 (25)	8 (34.8)	19 (27.5)
50–60	8 (36.4)	10 (41.7)	8 (34.8)	26 (37.7)
60–70	9 (40.9)	8 (33.3)	7 (30.4)	24 (34.8)
Duration of finnitus in patients (mo)				
< 6	7	9	8	24
6–12	6	8	7	21
> 12	9	7	8	24

Numbers in parentheses are percentages. $p > 0.05$. Non significant. T0, placebo; T1 (Treatment 1), receiving *Ginkgo biloba* 60 mg BD; T2 (Treatment 2), receiving *Ginkgo biloba* 60 mg BD along with antioxidant preparation

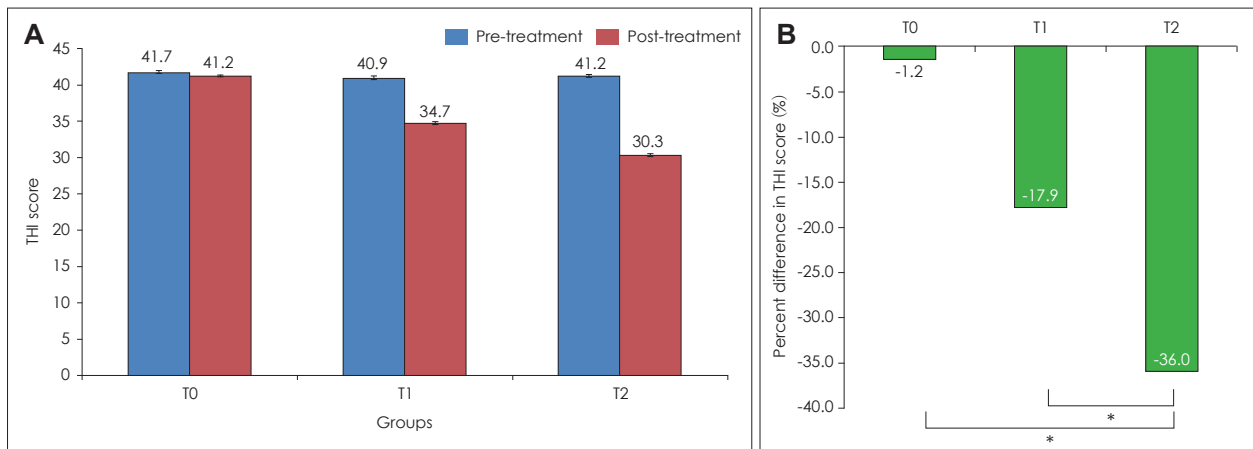


Fig. 2. Pre- and post-treatment THI scores (A) and percent difference (B) of the patients supplemented with *Ginkgo biloba* singly and *Ginkgo biloba* with antioxidants. Values are presented as mean±standard deviation unless otherwise indicated. THI, tinnitus handicap index; T0, placebo; T1 (Treatment 1), receiving *Ginkgo biloba* 60 mg BD; T2 (Treatment 2), receiving *Ginkgo biloba* 60 mg BD along with antioxidant preparation. * $p < 0.05$ between T2 and T1, T2 and T0.

with antioxidants to T1 and T2 respectively resulted in marked improvement ($p < 0.05$) from pre- to post-THI scores (Fig. 2A). However, patients serving as placebo (T0) did not show any significant ($p > 0.05$) percent variation (-1.2%). Maximal ($p < 0.05$) percent difference was observed in pre- and post-treatment THI scores of T2 patients (-36%) followed by T1 patients (-17.9%) (Fig. 2B). The study revealed significant difference ($p < 0.05$) in THI scores of T2 in comparison to T1 and T0.

VAS score

Treatment with *Ginkgo biloba* singly and blend of *Ginkgo biloba* and antioxidants showed marked improvement ($p < 0.05$) in post-VAS scores; however, the improvement was not statistically significant ($p > 0.05$) in T0 group (Fig. 3A).

The percent difference in pre- and post-treatment in VAS scores showed similar trend as THI scores with maximal difference exhibited by T2 group (-22.6%) while T0 showed the least (-1.5%) indicating that T1 and T2 showed marked im-

provement in VAS scores after treatment regime period (Fig. 3B). Furthermore, significant difference ($p < 0.05$) was observed in T2 in comparison to T1 and T0.

SF-36 scores

SF-36 questionnaire was evaluated to assess the overall health of the patients treated with *Ginkgo biloba* singly and *Ginkgo biloba* along with antioxidants. There were no intergroup differences in SF-36 pre-treatment scores of all the treated groups (Table 2). A significant difference ($p < 0.05$) was observed between pre- and post-treatment in SF-36 scores for patients treated with *Ginkgo biloba* along with antioxidants in comparison to its counterparts. The SF-36 parameters scores significantly ($p < 0.05$) improved upon in patients treated with *Ginkgo biloba* along with antioxidants. None of the patients reported any serious adverse effects during the study.

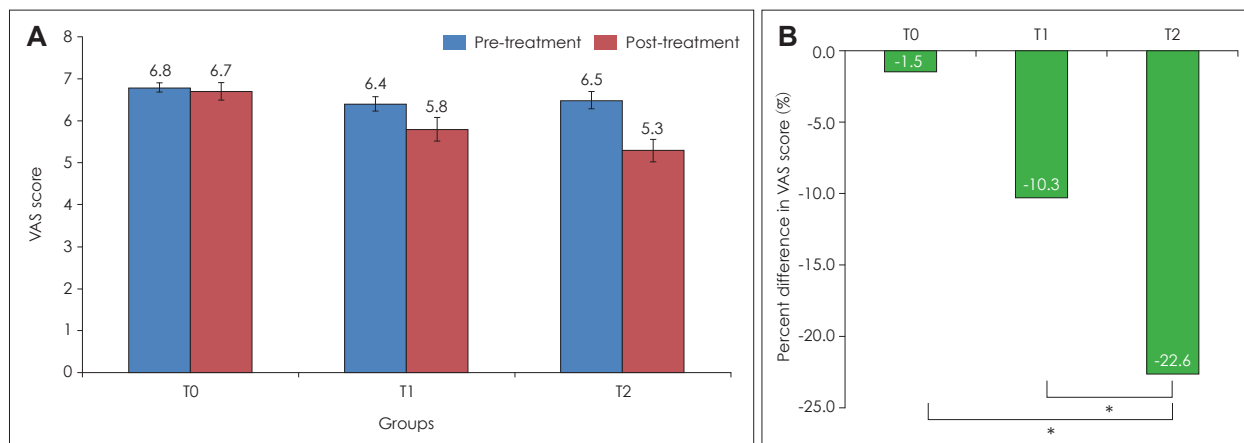


Fig. 3. Pre- and post-treatment VAS scores (A) and percent difference (B) of the patients supplemented with *Ginkgo biloba* singly and *Ginkgo biloba* with antioxidants. Values are presented as mean±standard deviation unless otherwise indicated. THI, tinnitus handicap index; T0, placebo; T1 (Treatment 1), receiving *Ginkgo biloba* 60 mg BD; T2 (Treatment 2), receiving *Ginkgo biloba* 60 mg BD along with antioxidant preparation. * $p < 0.05$ between T2 and T1, T2 and T0.

Discussion

Tinnitus is one of the common complaints associated with ear leading to huge burden on healthcare services [16]. Despite recent developments in modern medicine, there is still no definite treatment for tinnitus. Notably, this has led to renewal in approaches in medical arena and fueled interest in phyto-therapeutic research to discover new herbal alternatives to commonly used pharmaceutical drugs. Several in vitro, in vivo and clinical trials have been conducted on medicinal plants and its phytoconstituents to evaluate their efficacy to devise novel therapies with lesser side effects [16]. Nevertheless, the effectiveness of amalgamation of pharmacological drugs and phytotherapeutic treatments on tinnitus needs to be evaluated in detail.

Among the plethora of medicinal plants, *Ginkgo biloba* belonging to Ginkgoaceae family has shown positive results in the treatment of tinnitus. The leaves of *Ginkgo biloba* has an array of phytochemicals namely alkanes, benzoids, carotenoids, phenylpropanoids, flavonoids and terpenoids besides containing carbohydrates, lipids and sterols [17-19]. Terpenoids and ginkgolides renders protective effects against inflammation to reduce the level of cytokines and inflammatory factors such as tumour necrosis factor alpha, interleukin 6, interleukin 1 beta, and matrix metalloproteinase 9 [20]. The myricetin and quercetin flavonoids and ginkgolide and bilobalide terpenoids are effective in treating tinnitus caused by ischemia [18]. Furthermore, *Ginkgo biloba* has been reported to have restorative effects in neuron metabolism and neurotransmitter system [21]. It has antiplatelet, antioxidant and vascular modulating potential [8]. Of the various etiological factors known, vascular problems in the area of cochlear nerve cortex is one of the prime factors for tinnitus [8]. The modulations in vascular system

affect the blood supply to labyrinthine artery which in turn causes hypoxia in the outer hair cells of the cochlea and leads to tinnitus [18]. Supplementation of *Ginkgo biloba* has reported adequate blood supply to the cochlea. Henceforth, it can be used as a phyto-therapeutic approach in delaying the onset, preventing the progression or treatment of tinnitus plausibly due to vasodilation and antiplatelet action around cochlear region [22]. Moreover, anti-tinnitus and protective effects on nerve cells, auditory cortex, and sub-cortical area have been reported for *Ginkgo biloba* owing to its antioxidative potential [23]. Likewise another study demonstrated *Ginkgo biloba* and its phytoconstituents such as flavonoids and terpenes, terpenolactones to scavenge free radicals thereby rendering protective effects against oxidative insults [24].

European and American guidelines on otolaryngology and clinical practice recommends *Ginkgo biloba* for reducing the degree of annoyance occurring from tinnitus [25]. In India, the scientific data on *Ginkgo biloba* singly and *Ginkgo biloba* along with antioxidants supplementation to tinnitus patients is limited. Henceforth, the study was planned to evaluate its efficacy in patients suffering from tinnitus.

THI and VAS scores

THI score was calculated on the basis of three subscales categorized as functional, emotional and catastrophic. Further, as per the grading system, determined by the British Association of Otolaryngologists, Head and Neck Surgeons, THI total score was interpreted and graded into varied levels: very mild (0–16), mild (18–36), moderate (38–56), severe (58–76), and catastrophic (78–100) [26]. The present study concluded *Ginkgo biloba* along with antioxidants was more effective in improving THI and VAS scores in patients as compared to *Ginkgo*

Table 2. Effect of supplementation of *Ginkgo biloba* singly and with antioxidants on quality of life assessed by Short Form 36 Health Survey (SF-36) scores

SF-36 parameters	T0 (n=22)			T1 (n=24)			T2 (n=23)		
	Pre	Post	p-value	Pre	Post	p-value	Pre	Post	p-value
Physical functions	78.5±11.50	79.4±12.21		79.1±11.26	78.7±15.21		77.5±13.45	81.7±14.34	
Physical well being	74.0±13.12	73.3±13.17		75.3±12.35	68.6±16.21		68.2±12.67	67.1±15.23	
General body ache	67.6±11.21	61.7±16.33		67.2±12.86	64.2±13.45		66.7±12.48	72.9±13.41	
Overall health status	53.1±14.21	51.3±12.27	p>0.05	55.4±13.41	58.8±12.41	p>0.05	53.0±11.79	58.2±16.63	*p<0.05
Vitality	52.2±16.41	54.6±12.56	NS	48.7±15.45	54.6±11.76	NS	51.2±12.23	55.2±14.84	Significant
Social well being	51.3±13.32	53.4±11.34		46.7±12.49	51.7±13.81		46.1±15.61	53.4±16.38	
Emotional well being	73.4±12.14	67.7±12.24		74.3±14.43	77.6±13.24		73.6±12.11	84.2±14.56	
Mental well being	71.2±11.37	69.9±13.28		72.3±14.87	74.9±14.23		72.6±15.23	83.3±12.23	

Values are presented as mean ± standard deviation. *p<0.05 Significant; Wilcoxon signed ranks test; ANOVA-one way, Student's t-test. T0, placebo; T1 (Treatment 1), receiving *Ginkgo biloba* 60 mg BD; T2 (Treatment 2), receiving *Ginkgo biloba* 60 mg BD along with antioxidant preparation; NS, non significant

biloba supplemented singly and T0 group. The THI grades in T1 and T2 groups improved from moderate (38–56) to mild (18–36) however, no improvement was observed in T0 group. It is noteworthy that a marked reduction in THI score was exhibited in T2 group (10.9) as compared to T1 (6.2) and T0 (0.5). The results conferred the previous findings of the study conducted by Zeman, et al. [27] demonstrating that change of THI score of at least seven points show reliable clinically significant improvement. Similar trend was observed with VAS in treated groups with maximal difference in T2 group (1.2). Nevertheless, it has been illustrated by Figueiredo, et al. [28] that there is a significant correlation between THI and VAS indicative of direct relation between the two. The results are in accordance with earlier study conducted by Radunz, et al. [29] whereby significant correlation was reported between pre- and post-treatment (90 days) in THI and VAS score of tinnitus patients treated with *Ginkgo biloba* extract EGb 761 and/or hearing aids. Another study compared the efficacy of *Ginkgo biloba* (EGb 761, 120 mg twice a day) and caroverine (1-[2-(diethylamino)ethyl]-3-[(4-methoxyphenyl)methyl]quinoxalin-2-one) injection (10 mL in 100 mL saline) followed by oral intake of capsules (twice a day) in the management of idiopathic tinnitus. A marked reduction was observed in tinnitus (63.3% and 60%) with concomitant improvement in hearing thresholds and consequently on the quality of life of the patients was reported [30]. Similarly randomized, double-blind clinical trial was conducted with *Ginkgo biloba* extract EGb 761 (120 mg) versus pentoxifylline (600 mg) in patients suffering from sub-chronic or chronic tinnitus. It was reported that both the drugs were equally effective in reducing the noise and irritation due to tinnitus and resulted in overall improvement of the health of the patients. Furthermore, the side effects of pentoxifylline were more pronounced in comparison to *Ginkgo biloba* extract [31]. Similar results have been reported in another study, demonstrating marked decrease in THI, VAS score as well as in tinnitus functional index-relaxation and emotional scores along with tinnitus loudness, minimum masking level in patients supplemented with antioxidants as compared to the placebo counter parts [32]. Likewise, the findings are in accordance with earlier study wherein supplementation of blend of multivitamins and phospholipids for 1.5 years resulted in significant reduction in VAS score and tinnitus loudness [33]. Notably it is a well proven fact that excess generation of reactive oxygen species (ROS) in hair cells has been observed on recurrent exposure to several insults namely cisplatin, aminoglycosides, or noise [34]. Thus antioxidant supplements have shown to reduce intracellular damages mediated by ROS [33].

SF-36 score

The SF-36 Health Survey elucidated marked improvement in varied SF-36 parameters scores in T2 group supplemented with *Ginkgo biloba* and antioxidants as compared to T1 group supplemented with *Ginkgo biloba* alone. In concurrence, the study conducted by Kim, et al. [11] depicted no significant change in SF-36 scores of patients treated with 160 mg of *Ginkgo biloba*. Likewise, Knäpper, et al. [35] studied the effect of supplementation of Tinnitan Duo (food supplement, containing 5-hydroxy tryptophan, *Ginkgo biloba*, magnesium, zinc melatonin, vitamin B5 and B6) in patients with subjective tinnitus and emotional affectation for 3 months. The study resulted in improved emotional affectation and safety profile with no adverse effects. To sum up, synergistic effect of *Ginkgo biloba* and antioxidants have beneficial effects beyond those of *Ginkgo biloba* alone. The antioxidants and bioactives of *Ginkgo biloba* together counteract the excess free radical production and oxidative damage in auditory structures thereby improving tinnitus. The subjective evaluation of clinical outcome was major limitation. Furthermore, a double-blind study with larger sample size and increased duration would have been ideal.

To conclude, *Ginkgo biloba* along with antioxidants resulted in marked improvement in THI, VAS and SF-36 scores. Thus a combinatorial approach can be a promising therapy to improve tinnitus. Studies evaluating the mechanism of the duo at molecular level should be undertaken.

Acknowledgments

None

Conflicts of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Bhushan Chauhan. Data curation: Bhushan Chauhan, Shantanu Arya, Komal Chauhan. Formal analysis: Bhushan Chauhan, Shantanu Arya. Investigation: Bhushan Chauhan, Shantanu Arya, Komal Chauhan. Methodology: Bhushan Chauhan, Shantanu Arya, Komal Chauhan. Project administration: Bhushan Chauhan. Supervision: Bhushan Chauhan. Validation: Bhushan Chauhan. Visualization: Bhushan Chauhan, Shantanu Arya. Writing—original draft: Bhushan Chauhan, Komal Chauhan. Writing—review & editing: Bhushan Chauhan, Komal Chauhan. Approval of final manuscript: all authors.

ORCID iDs

Bhushan Chauhan <https://orcid.org/0000-0002-9070-628X>
 Shantanu Arya <https://orcid.org/0000-0003-4135-0480>
 Komal Chauhan <https://orcid.org/0000-0002-6216-6626>

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