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The Effect of Treatment with an Herbal Formulation of *Salvia hydrangea*, *Citrus aurantium*, *Lipia citriodora*, and Elm Bark on the Intensity of Tinnitus: A Clinical Trial

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Abstract

Background: Tinnitus is a symptom of an underlying medical condition that is associated with hearing loss in humans. It is a subjective disease where patients hear voices that others cannot hear. Increase in noise pollution, growing development of communication devices, and the long-ranging 8-year war in our country have further accelerated the spread of this disorder. Given that no definitive medical or surgical treatment has been confirmed for this condition, new research to improve treatment options is urgent.

Aim: The purpose of this study was to assess the effect of a formulation prepared from *Salvia hydrangea*, *Citrus aurantium*, *Lipia Citriodora*, and elm bark on the status of tinnitus.

Methods: In this single-blind clinical trial, 144 patients with tinnitus were selected based on pre-defined inclusion criteria and then randomly divided into 3 groups: herbal formulation, cinnarizine, and placebo groups, where the frequency and intensity of tinnitus was measured based on the Tinnitus Handicap Inventory (THI) and Visual Analogue Scale (VAS) criteria before and on 28 and 56 days post treatment. Data were analyzed by the statistical software SPSS version 16, repeated measurement, one-way, and X2 for comparison within and among groups, with the significance level set at $p < 0.05$.

Results: comparably, tinnitus based on THI criteria differed among the 3 groups on 28 and 56 days of intervention, where the difference was statistically significant ($p < 0.05$). This difference was more significant between the cinnarizine and placebo groups. The mean severity of tinnitus, based on the VAS score, differed among the three groups on 28 and 56 days after intervention, although the difference was not statistically significant.

Conclusion: Herbal formulation was effective on tinnitus alleviation, but its effect was not superior to that of conventionally used chemical drug cinnarizine.

Conflicts of Interest: The Authors declare no conflicts of interest.
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Introduction

The function of the auditory system is to convert voice and to detect the environmental signs (1). Tinnitus is a symptom of an underlying medical condition of ear that is associated with hearing loss. (2). James Hall (University of Florida) defines tinnitus as an illusory sense of sound that may not be disturbing because of a person's activities, but may cause discomfort and insomnia to the patient, especially when the patient is alone and at nights (3). The growth of industrial societies, increase in noise pollution, the growing development of electronic communications, and the long-ranging

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8-year war in our country have accelerated the spread of this disease (4). The prevalence of this phenomenon is estimated to be 3–30% (5). In America alone, 40 million people suffer from tinnitus. Of these, 12 million people are severely affected, with association of tinnitus reported in 2 million of them. These problems affect the patients' quality of life through depression and sleep disorders (3). Some ototoxic substances and drugs such as furosemide, acetazolamide, salicylates, alcohol, glycosylated antibiotics, mercury, gold, and lead are also implicated in the incidence of tinnitus. Thyroid diseases, hyperlipidemia, lack of vitamin B_{12}, psychiatric disorders, fibromyalgia, ear diseases such as Meniere, head trauma, and multiple sclerosis may also contribute to tinnitus development (2, 6). As no definitive medical or surgical treatment has been approved for tinnitus and most efforts are focused on the psychological match and normalization of the buzzing sound as important factors of the disease adversely influencing the quality of life of the affected people, new research to improve treatment options and to find a proper solution remains inevitable (7). As a possible remedy, the use of complementary and alternative medicine (CAM) is growing popularity in many parts of the world and in European countries. In addition, most people use different products of this medicine with or without brochures for the treatment of tinnitus (8).

Cinnarizine (25 or 75 mg pills) is an antihistamine drug which can inhibit H1 histamine receptors. It also inhibits calcium channels, vascular smooth muscle contraction, as well as the activity of the vestibular system. The side effects of this drug include drowsiness, concentration loss, gastrointestinal disorders, and anticholinergic complications such as visual disturbances, dry mouth, urinary retention, and headache. A formulation of herbs "*Salvia hydrangea*, *Citrus aurantium*, *Lipia citriodora*, and elm bark" is traditionally used by the citizens of Birjand for tinnitus treatment. The report of pleasant experience of patients when using this formulation has encouraged researchers to conduct further scientific research in this regard.

The plant "*Salvia hydrangea*" is a mint plant, with anti-inflammatory, analgesic, antispasmodic, and anti-bloating properties (9).

Citrus aurantium is the blossom of orange tree that is used as a drug. The most important medicinal properties of Citrus aurantium include its impact on the nervous system as a sedative and anti-anxiety compound.

The pharmacological effect of elm bark is greater than that of its leaves. The leaves and bark of elm have sweating and diuretic properties, and their medicinal properties help relieve ear pain (9, 10)

This study aimed to assess the impact of four drugs including *Salvia hydrangea*, *Citrus aurantium*, *Lipia citriodora*, and elm bark on the frequency and intensity of tinnitus.

Methods

In this single-blind clinical trial, 144 patients were selected from among patients referring for ear, nose, and throat disorders, in the clinic of Imam Reza Hospital (Birjand, Iran) who were diagnosed with tinnitus and the associated criteria.

Before participation in this study, written informed consent obtained from each participant and/or their legal representative.

Inclusion criteria of study subjects were willingness to participate in the study, age of 17–70 years, and suffering from tinnitus for more than 4 months. Exclusion criteria of the study subjects: Presence of otitis media, ear tumor, deformity within the ear, use of ototoxic drugs such as gentamicin, ear surgery, pregnancy, breastfeeding or being on birth control pills, history of extensive surgery or blood transfusion in the previous month, kidney failure, history of stroke or thyroid disease, otosclerosis, addiction to drugs or alcohol, and occupational exposure to noise.

The included patients were divided into 3 groups based on random blocking: (a) receiving cinnarizine, (b) receiving herbal formulation (*Salvia hydrangea*, *Citrus aurantium*, *Lipia citriodora*, and elm bark), and (c) placebo. Cinnarizine tablet (25 mg; Osveh Co., Tehran,

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Iran), formulated in sealed packages (4 g of each herb and 12 g of elm bark) with a cup and recipe of herbal tea (5 g of the mixed herb powder in a cup of boiled water three times a day before each meal), and placebo in the form of gelatin capsules containing starch were prescribed for 28 days. The intervention was discontinued with the control of patients' tinnitus, but, in patients who failed to respond effectively, (Tinnitus Handicap Inventory, THI>30), the intervention was extended for another 28 days. Data collection was based on THI and Visual Analogue Scale (VAS) criteria before and on 28 and 56 days post intervention. THI criteria, based on the ear audiology registry center (11), consisted of 25 questions with three levels of responses: Yes (score 4), Sometimes (score 2), and No (zero), by which the degree of tinnitus was measured. Thus, the minimum and maximum of THI questionnaire ranged from 0 to 100. In the qualitative classification, the scores 0–16 were considered as "absence of defect", the scores 18–36 as "minor defect", the scores 38–56 as "moderate defect", the scores 58–76 as "severe defect", and the scores 78–100 as "catastrophic failure". The validity and reliability of the aforementioned criteria had been confirmed in numerous national (12) and foreign studies (13).

VAS criterion measures the severity of tinnitus and includes the agreed features expressible from 0 to 10 according to the patient's imagination. The zero score indicated the minimum severity of tinnitus, while score 10 revealed the maximum severity of tinnitus. This criterion has been used in national and foreign studies to measure the severity of tinnitus (12, 13).

The patients were required to avoid OTC drugs, except for unavoidable cases, such as colds, headaches, or heartburn. They were also requested to avoid using drugs and dietary supplements such as Ginkgo, zinc, and vitamin B_{12}, which directly affected the treatment of tinnitus. The data were analyzed by statistical software SPSS version 16, specifically through one-way, repeated measurement, and X^2 test at the significant level of $p<0.05$.

Results

Of the 144 patients with tinnitus who enrolled in this study, data of 138 patients were analyzed. Six patients were excluded from the study as their tinnitus was controlled after 28 days of intervention. The mean age of the participants was 48.73±14.77; 64 (46.4%) of the patients were male and 74 (53.6%) were female; and the mean duration of patients' tinnitus was 3 ± 1.35 years. No significant difference was noted in these items between the three groups (Table 1).

Based on the THI criteria, the comparison of the mean severity revealed no significant difference before the intervention, though significant difference was noted after 28 and 58 days of intervention. Tukey's test showed that the difference was significant at 28 days of intervention between the cinnarizine and placebo groups and after 56 days of intervention between the cinnarizine and placebo groups along with the formulation and placebo groups. However, no significant difference was noted between the results of the formulation and cinnarizine groups. Significant difference was observed within the groups at different times (Table 2). Based on the VAS criteria, the mean severity of tinnitus showed no significant difference among the three groups before the intervention, with differences after 28 and 56 days after the intervention, although the difference between the groups was not significant. However, the difference in the intensity of tinnitus was statistically significant within the groups at 28 and 56 days after treatment (Table 3). Based on the qualitative categorization, 6 patients (0.13) suffered from severe tinnitus and 3 (6.5%) from catastrophic failure in the cinnarizine group before intervention, but no patient reported severe or catastrophic defect after 28 days. In the herbal formulation group, 10 patients (21.7%) suffered from severe tinnitus, 2 (4.3%) from catastrophic failure before the intervention, and 3 (6.5%) had severe defect, but no patient experienced catastrophic failure after 28 days, while 1 patient (2.2%) showed severe defects after 56 days. In the placebo group, 11 patients (23.9%) suffered from

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severe tinnitus, 1 patient (2.2) experienced catastrophic failure before the intervention, and 2 patients (4.3%) showed severe tinnitus, but no patient showed catastrophic failure after 28 days although 1 patient (2.2%) reported severe tinnitus 56 days after the study (Table 4).

Table 1. Mean and SD deviation characteristics in study groups

Characteristics		Herbal formulation (Mean±SD)	Cinnarizine (Mean±SD)	Placebo (Mean±SD)	p-value
Age (year)		51.13±14.25	48.8±14.02	47±15.97	0.7
Duration of tinnitus (year)		2.73±1.35	2.39±1.14	2.89±1.47	0.4
Gender	Male	21 (%45.7)	21 (%45.7)	22 (%47.8)	0.9
	Female	25 (%54.3)	25 (%54.3)	24 (%52.2)	

Table 2. Comparison of THI score (Mean±SD) of cinnarizine, herbal formulations, and placebo, in different study times

Group \ Time	Before intervention (Mean±SD)	28 days after intervention (Mean±SD)	56 days after intervention (Mean±SD)	Repeated measurement
Cinnarizine	51.30±12..43	36.26±6.08	31.23±9.64	p= 0.01
Herbal formulation	50.95±13.04	39.65±11.53	32.02±10.66	p= 0.01
Placebo	49.08±12.59	41.84±8.15	38.52±8.90	p= 0.01
One way	p= 0.6	p= 0.01	p= 0.001	

Table 3. comparison of VAS score (mean and SD) of Cinnarizine, herbal formulations, and placebo, in different times of study

Group \ Time	Before intervention (Mean±SD)	28 days after intervention (Mean±SD)	56 days after intervention (Mean±SD)	Repeated measurement
Cinnarizine	5.06±2.33	4±1.46	3.34±1.30	p= 0.001
Herbal formulation	5.21±2.14	4.36±1.81	3.78±1.63	p= 0.001
Placebo	4.80±2.56	4.26±1.67	3.80±1.98	p= 0.001
One way	p= 0.6	p= 0.5	p= 0.3	

Table 4. The tinnitus frequency and percent in 3 groups during 3 times of study

Group	Time	Before intervention		28 days after intervention		56 days after intervention	
		frequency	percent	frequency	percent	frequency	percent
Cinnarizine	No handicap	-	-	-	-	4	8.7
	Mild handicap	5	10.9	27	58.7	29	63
	Moderate handicap	32	61.6	19	41.3	13	28.3
	Sever handicap	6	13	0	0	0	0
	Catastrophic handicap	3	6.5	0	0	0	0
Herbal formulation	No handicap	-	-	-	-	4	8.7
	Mild handicap	7	15.2	21	45.7	29	6.3
	Moderate handicap	27	58.7	22	47.8	12	26.1
	Sever handicap	10	21.7	3	6.5	1	2.2
	Catastrophic handicap	2	4.3	0	0	0	0
Placebo	No handicap	-	-	-	-	0	0
	Mild handicap	6	13	21.7	10	21	45.7

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Moderate handicap	28	60.9	34	73.9	24	52.2
Sever handicap	11	23.9	2	4.3	1	2.2
Catastrophic handicap	1	2.2	0	0	0	0

Discussion

Several studies have suggested diverse drugs, such as carbamazepine, gabapentin, cinnarizine, and herbal compounds, such as Ginkgo biloba, for reducing the severity of tinnitus. However, the recent systemic and meta-analysis studies do not report any significant effect of these drugs or herbs on tinnitus, especially on the complications and possible risks. The findings on the efficacy of various medicinal herbs on tinnitus are diverse and sometimes contradictory. For example, numerous studies have reported the effectiveness of Ginkgo biloba in treatment of tinnitus (14). According to the results of the current study, the mean intensity of tinnitus (THI criteria) showed significant difference after 28 and 56 days of intervention, with the cinnarizine and herbal formulation groups showing better control over tinnitus as compared to the placebo group. The clinical trial of Choi et al. (7) on the impact of tympanic dexamethasone and placebo (saline) revealed that the extent of tinnitus improved in both groups, based on the THI criteria, but these changes were not statistically significant ($p < 0.05$), which is dissimilar to our result. Coelho et al. (5) study on the impact of dietary supplement and placebo showed that tinnitus was negligible in both groups, based on the THI criteria where these changes were statistically significant ($p = 0.16$ in the zinc group and $p = 0.06$ in the placebo group), which remains inconsistent with our study. Majd examined the mean scores of THI criteria between the gabapentin and placebo group and demonstrated better medical effect of gabapentin on tinnitus, which is in accordance with our results (12). According to ENTs' and neurologists' opinion, who consider tinnitus a multidisciplinary issue, the similar efficacy of cinnarizine and herbal formulation can be attributed to the nature of the disease, which is a subjective symptom where patients' experience of the intensity and the frequency of the disturbance is different. The tolerance of patients is also different under psychological disturbances.

Our results revealed that the severity of tinnitus was similar across the three groups before the intervention, according to the VAS scale and that it reduced similarly at 28 and 56 days of the intervention, though the difference was not statistically significant. In the formulation group, 10 patients (21.7%) suffered from severe defects and only 1 patient (2.2%) had severe defect at the end of the study, suggesting 19.5% reduction in the severity of tinnitus. Our research is consistent with that of Berj et al. (15) on the effect of transcutaneous electrical nerve stimulation, which indicated 15% reduction in tinnitus on a numerical rating scale.

Conclusion

Our results indicated that herbal formulation in comparison with chemical drug and cinnarizine had the same effect on controlling tinnitus and it can replace them without any side effects. It is therefore recommended that the THI questionnaire be completed several times and its mean be analyzed before prescription, considering that tinnitus is a mental symptom and the emotional-mental state of patients varies at different occasions, which may affect the diagnosis.

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Conflicts of Interest

The Authors declare no conflicts of interest.

Ethics

This study was approved by the "Ethics Committee of Birjand University of Medical Sciences (Birjand, Iran)"; Registration Code: IR.BUMS.REC.394.460

This clinical trial study has been registered in "Iranian Registry of Clinical Trials" (URL: https://en.irct.ir); Trial Registration Code (IRCTID): IRCT2013082814505N1

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