Received: 8 September 2021 | Accepted: 3 July 2022

DOI: 10.1111/coa.13989

ORIGINAL ARTICLE

WILEY

Therapeutic effects of *Rosa canina*, *Urtica dioica* and *Tanacetum vulgare* herbal combination in treatment of tinnitus symptoms: A double-blind randomised clinical trial

Mohammad Hossein Khosravi[1] | Amirhomayoun Atefi[2] | Afsaneh Mehri[3] | Fatemeh Sodeifian[4] | Jaleh Yousefi[5] | Ali Bagheri Hagh[5] | Saeed Sohrabpour[6] | Fatemeh Kazemi[7] | Mohammad Ajalloueian[8] | Masoumeh Saeedi[8]

[1]Department of Research, Arka Education and Clinical Research Consultants, Tehran, Iran

[2]Student Research Committee, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[3]Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

[4]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Science, Tehran, Iran

[5]Department of Otorhinolaryngology, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran

[6]Otorhinolaryngology Research Center, Tehran University of Medical Sciences, Tehran, Iran

[7]Student Research Committee, Qazvin University of Medical Sciences, Qazvin, Iran

[8]New Hearing Technologies Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

Correspondence
Masoumeh Saeedi, New Hearing Technologies Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.
Email: m.saeedi67@gmail.com

Funding information
Baqiyatallah University of Medical Sciences, Grant/Award Number: IRCT20170428174113N23

Abstract

Objective: To evaluate the effect of Neurotec® herbal capsule (100 mg twice a day for 3 months) on the tinnitus symptoms in comparison with the placebo.

Design: A double-blind randomised clinical trial.

Setting: Otolaryngology clinic of Baqiyatallah Hospital.

Participants: Patients suffering from subjective tinnitus.

Main Outcome Measures: Pure tone audiometry was measured at .5, 1, 2, 4 and 6 kHz frequencies before and after the third month of intervention. In addition, Tinnitus Handicap Inventory (THI) questionnaire as well as visual analogue scale (VAS) for tinnitus loudness, daily annoyance, daily life or sleep disturbance, daily perception and mood alteration were evaluated.

Results: Finally, 103 (69 males and 34 females) patients with a mean age of 51.33 ± 13.91 years were analysed. In contrast with control group, patients in intervention group showed a remarkable decrease in THI score after 3 months of treatment ($p < .05$). Although both groups had improvements in VAS scores, mood disturbance, daily tinnitus perception and daily life alteration scores were only improved in the intervention group. The mean pure tone air and bone conduction were not significantly different between the control and the intervention group at baseline and 3 months after the intervention at .5, 1, 2 and 4 kHz ($p > .05$).

Conclusion: A 3-month treatment with Neurotec capsules in addition to patient education is of benefit for managing symptoms in patients with chronic tinnitus.

KEYWORDS

Rosa canina, subjective tinnitus, *Tanacetum vulgare*, Tinnitus and Neurotec, Tinnitus Handicap Inventory, *Urtica dioica*

1 | INTRODUCTION

Tinnitus or ringing in the ear is defined as the conscious perception of sound in the ear or head in the absence of an external stimulus which is recognised in about 10%–15% of people.[1,2] About 1% to 2% of world population suffer from highly disabling presence of ear noise and developing comorbid conditions such as depression, demoralisation and social withdrawal.[3]

It has been shown that various social factors including low education level, poor income and some types of occupational activities increasing the noise exposure, lead to development of tinnitus.[1] Furthermore, medical conditions such as trauma, hearing loss, or ototoxic treatments are associated with development of tinnitus. Tinnitus is not considered a disease, but rather it is mainly considered as symptom and presentation of underling medical conditions.[4]

The exact aetiology of tinnitus is not well understood. Traditionally, tinnitus has been considered as ontological disorder. However, advancement in neuroimaging and animal models have demonstrated that it could be associated with neuronal interactions. Enhanced neuronal firing rate, increased neuronal synchrony, altered tonotopic organisation of brain pathway, as well as alteration in non-auditory brain areas are considered as possible mechanisms involved in development of tinnitus.[2]

So far, there is no available medication that could completely resolve the symptoms of tinnitus and most available treatments help patients to cope with tinnitus and increase their quality of life.[5] In addition to pharmacotherapy, other treatments such as cognitive and behavioural therapy, sound therapy, music therapy, acupuncture and hearing aids have been suggested for improvement of tinnitus.[4,6] Herbal medication such as Ginko Biloba and Gushen Pian (Chinese herbal medication) are considered as an alternative treatment for tinnitus.[6] However, there are not enough and well-designed study to recommend these medications for treatment of tinnitus.

Neurotec® is a medication of herbal origin which contains extracts of dog-rose (*Rosa canina*), common nettle (*Urtica dioica*) and tansy (*Tanacetum vulgare*). Neurotec® is an IFDA approved medication for treatment of peripheral neuropathies in diabetic patients and exerts its action through improving neural message conduction. According to previous studies, combination of herbal extracts including *Rosa canina*, *Urtica dioica* and *Tanacetum vulgare*, can significantly improve motor function of cerebral ischemic rats and has a protective effect against ischemic brain injury.[7] In addition, since Neurotec® ingredients have improved spatial learning and memory in rat models of Alzheimer disease, its anti-oxidant and anti-inflammatory effects can be used as a neuroprotective herbal combination.[8]

Considering all the above-mentioned points and according to neuroprotective role of Neurotec ingredients, we hypothesised that it can improve auditory nerve function resulting in better environmental sound perception and consequent reduced tinnitus symptoms. In this study, we used a standardised dose of Neurotec in a double-blinded randomised clinical trial to determine whether it can be effective for management of tinnitus symptoms.

Key Points

1. Treatment with Neurotec beside baseline conservative treatments, could decrease tinnitus loudness, Tinnitus Handicap Inventory (THI) score, annoyance severity, daily life alteration, sleep disturbance, daily tinnitus perception and mood disturbance in patients with Tinnitus.
2. A 3-month treatment with Neurotec capsules accompanied by educational counselling is of benefit for managing symptoms in patients with chronic tinnitus.
3. Treatment with Neurotec beside baseline conservative treatments, could decrease THI score in patients with tinnitus.
4. Treatment with Neurotec beside baseline conservative treatments, could decrease tinnitus loudness in patients with Tinnitus.
5. A 3-month treatment with Neurotec capsules accompanied by educational counselling is of benefit for managing symptoms in patients with chronic tinnitus.

2 | MATERIALS AND METHODS

2.1 | Ethical consideration

Th Following registration at ethics committee of Baqiyatallah University of Medical Sciences (Ref. No: IR.BMSU.REC.1395.176) and Iranian Registry of Clinical Trials (Ref. No: IRCT2017042817413N23), this double-blind randomised clinical trial was conducted on patients with tinnitus, who attended otolaryngology clinic of Baqiyatallah Hospital between 2015 and 2016. All participants provided written informed consent—this study adhered to the principles of the Declaration of Helsinki. Figure 1 shows a flowchart of the trial.

2.2 | Trial design

This double-blind randomised clinical trial was conducted on patients with subjective tinnitus, who attended otolaryngology clinic of 'blinded for review' between 2015 and 2016.

2.3 | Patients

Patients were assessed for eligibility by an otolaryngologist. One hundred eighty Patients with chief complaint of subjective tinnitus were included in the study. Exclusion criteria were as follows: Patients over 75 or below 19 years of age, pregnant women, those with chronic or acute neurological diseases, concomitant psychiatric illnesses, pulsatile tinnitus and underlying conditions such as epilepsy, multiple sclerosis, and history of severe head and neck trauma or ear surgery. Also, patients who did not meet inclusion criteria and declined to participate in study, were excluded. In addition, patients should not have taken any medication for treatment of tinnitus within at least 1 month prior to intervention. Finally, the remaining 150 patients were randomly allocated in two groups of intervention ($n = 80$) and placebo ($n = 70$). An additional 27 patients were also excluded (17 patients in intervention group and 10 patients in placebo group) due

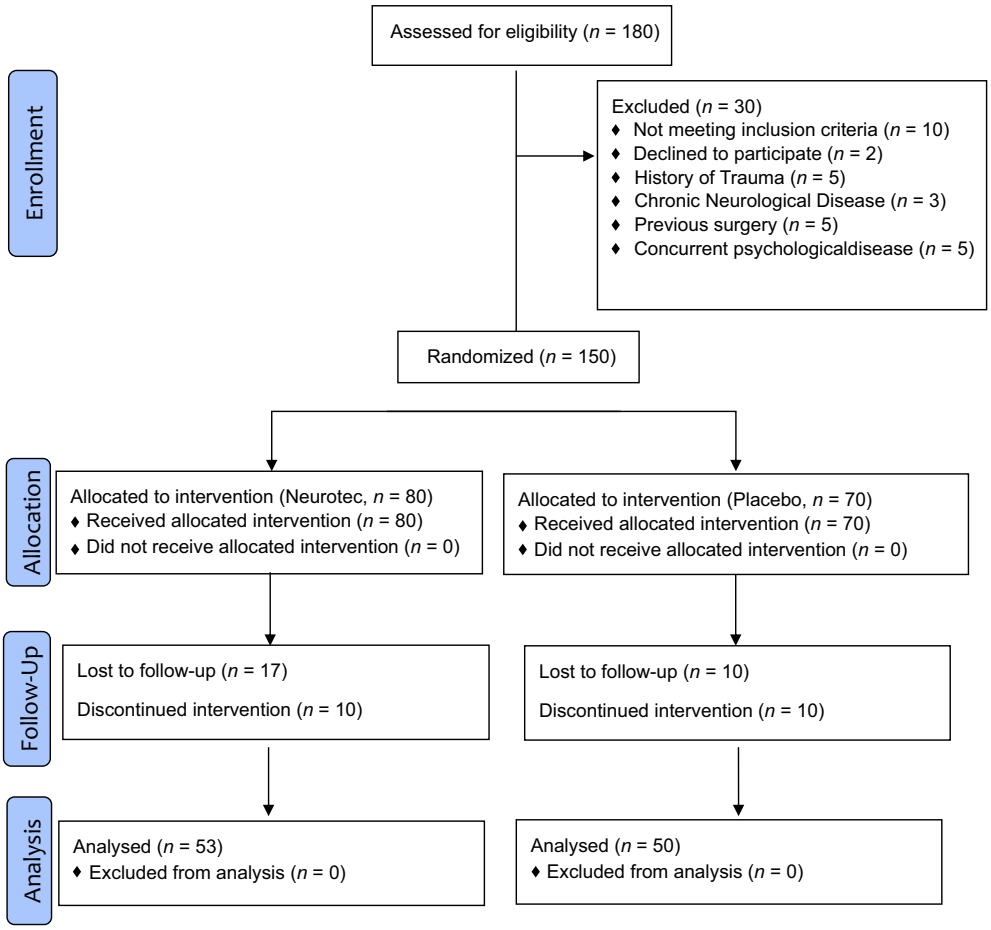

FIGURE 1 Study flowchart (CONSORT trial flow diagram)

to inadequate follow-up. A total of 103 cases were analysed (53 patients in intervention group and 50 patients in placebo group). Figure 1 shows a flowchart of the trial.

2.4 | Intervention and randomisation

Patients were randomly allocated to intervention and control groups using random number table. Patients in intervention group were treated with Neurotec® 100 mg capsules, every 12 h for 3 months. Patients in control group received placebo capsules, which had exactly the same shape and packaging with Neurotec® 100 mg capsules, in the same manner for the same duration. Patients in both groups received primary tinnitus treatments including reassurance and necessary trainings. Neurotec® and Placebo capsules were provided by Rose Pharmed®, the Neurotec® manufacturer in Iran. The company had no contribution neither in design or conduction of the trial, nor interpretation or dissemination of the results.

2.5 | Primary outcome measures

Patients in both groups underwent pure tone audiometry (PTA) at baseline and 3 months after intervention. Auditory threshold of patients was measured at .5, 1, 2, 4 and 6 kHz frequencies.

Validated Persian version of Tinnitus Handicap Inventory (THI) questionnaire was administered to patients in both groups prior to, 1 month and 3 months after intervention.[9]

A 0-to-10 visual analogue scale (VAS) was used to evaluate tinnitus loudness, daily annoyance, disturbance in daily life, daily tinnitus perception, sleep disturbance and mood alteration.

2.6 | Secondary outcome measures

Possible complications of Neurotec®, including diarrhoea, itchy skin or rashes were recorded based on patients report in a pre-designed checklist.

2.7 | Statistical analysis

Data were analysed using Statistical Package for Social Sciences (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp). Descriptive analysis was performed using mean and standard deviation as well as percentages and frequencies. Kolmogorov–Smirnov test was used to check the normal distribution of data. Comparison of the main outcomes between baseline and after intervention within the groups was performed using paired *t*-test. In addition, *t*-test and Mann–Whitney *U* test

were performed for comparison between groups. A p-value of less than .05 was considered as statistically significant.

3 | RESULTS

Finally, a total of 103 patients (53 cases in intervention and 50 in control group) with a mean age of 51.33 ± 13.91 years underwent analysis. Among the patients, 69 (67%) were male with a mean age of 49.39 ± 15.02 and 34 (33%) were female with a mean age of 55.26 ± 10.47 ($p = .024$).

There were no statistically significant differences between the mean age of patients in intervention (52.96 ± 14.64) and control (49.60 ± 13.02) groups ($p = .222$).

The intervention group included 35 (66%) and the control group included 34 (68%) male patients. The gender distribution was not significantly different between the two groups ($p = .834$). Twenty-five (24.3%) patients had right side, 40 (38.8%) had left side and 38 (36.9%) patients had bilateral tinnitus.

Among the patients, 36 patients (35%) had tinnitus symptoms for less than a year; 28 patients (27.2%) had symptoms for 1 to 3 years; 16 patients (15.5%) had symptoms for 3 to 11 years and 23 patients (22.3%) had symptoms for more than 11 years. Duration of tinnitus symptoms was not significantly different between the two groups ($p = .417$).

3.1 | Patients' symptoms

About all patients' symptoms, such as tinnitus loudness, annoyance severity, daily life alteration, daily tinnitus perception, sleep alteration, mood disturbance and quality of life, there was no significant difference between the intervention group and the control group, before the intervention and 1 month after the intervention. While there was a significant difference between the intervention group and the control group, 3 months after the intervention, as shown in Table 1.

3.2 | Audiometric test

PTA thresholds were analysed in two frequency groups: low frequency (.5 and 1 kHz) and high frequency (2, 4 and 6 kHz).

TABLE 1 Mean THI and VAS scores before, 1 month and 3 months after intervention

Patients' symptoms		Intervention group ($N = 53$)	Control group ($N = 50$)	p Value
Tinnitus loudness score	At baseline	7.19 ± 2.17	6.68 ± 2.63	.282
	1 month after intervention	6.37 ± 2.14	6.29 ± 2.59	.866
	3 months after intervention	4.92 ± 2.22	5.96 ± 2.85	.043
	p Value	.00	.034	
Annoyance severity score	At baseline	7.25 ± 2.46	7.05 ± 2.57	.691
	1 month after intervention	6.36 ± 2.13	6.36 ± 2.13	.997
	3 months after intervention	4.79 ± 2.15	6.26 ± 2.46	.002
	p Value	.00	.001	
Daily life alteration score	At baseline	6.08 ± 2.84	5.57 ± 2.99	.376
	1 month after intervention	5.37 ± 2.48	5.48 ± 2.97	.849
	3 months after intervention	4.14 ± 2.21	5.38 ± 2.87	.012
	p Value	.00	.880	
Daily tinnitus perception score	At baseline	7.36 ± 2.68	6.36 ± 3.02	.079
	1 month after intervention	2.42 ± 6.23	5.96 ± 3.10	.625
	3 months after intervention	4.5 ± 2.33	5.82 ± 2.87	.012
	p Value	.00	.138	
Sleep disturbance score	At baseline	5.76 ± 3.52	5.67 ± 3.48	.890
	1 month after intervention	4.95 ± 2.98	4.56 ± 2.87	.498
	3 months after intervention	3.38 ± 2.60	4.84 ± 2.99	.010
	p Value	.00	.002	
Mood disturbance score	At baseline	5.86 ± 3.30	5.26 ± 3.10	.348
	1 month after intervention	5.37 ± 2.75	4.80 ± 2.98	.315
	3 months after intervention	3.97 ± 2.30	5 ± 2.83	.045
	p Value	.00	.621	
Quality of life score (THI score)	At baseline	58.22 ± 25.13	52.92 ± 28	.313
	1 month after intervention	49.09 ± 22.22	48.36 ± 27.46	.882
	3 months after intervention	37.52 ± 20.69	49.72 ± 29.23	.017
	P value	.00	.370	

Abbreviations: THI, Tinnitus Handicap Inventory; VAS, visual analogue scale.

TABLE 2 Pure tone audiometry results before and after the 3rd month of intervention

Frequency			Intervention group ($N = 53$)	Control group ($N = 50$)	p Value
.5 kHz	Pure tone air conduction	At baseline	24.56 ± 18.61	22.76 ± 14.91	.589
		3 months after the intervention	24.52 ± 18.31	21.64 ± 13.67	.369
		p Value	.796	.317	
	Pure tone bone conduction	At baseline	15.22 ± 15.28	13.08 ± 8.08	.372
		3 months after the intervention	14.88 ± 13.79	12.82 ± 8.23	.362
		p Value	.513	.617	
1 kHz	Pure tone air conduction	At baseline	26.11 ± 20.48	27.04 ± 14.40	.792
		3 months after the intervention	25.47 ± 19.06	22.78 ± 13.81	.416
		p Value	.131	.00	
	Pure tone bone conduction	At baseline	17.26 ± 16.34	16.96 ± 10.18	.911
		3 months after the intervention	16.73 ± 15.27	15.84 ± 10.21	.729
		p Value	.088	.257	
2 kHz	Pure tone air conduction	At baseline	29.43 ± 19.42	30 ± 14.85	.869
		3 months after the intervention	27.66 ± 18.70	29.18 ± 16.73	.665
		p Value	.00	.034	
	Pure tone bone conduction	At baseline	20.75 ± 14.64	20.08 ± 12.32	.801
		3 months after the intervention	19.66 ± 13.62	18.78 ± 12.49	.734
		p Value	.002	.144	
4 kHz	Pure tone air conduction	At baseline	46.18 ± 26.15	46.72 ± 22.07	.912
		3 months after the intervention	42.60 ± 24.76	43.58 ± 20.69	.829
		p Value	.00	.00	
	Pure tone bone conduction	At baseline	35.75 ± 21.98	35.70 ± 18.69	.989
		3 months after the intervention	33.07 ± 20.43	34.12 ± 18.34	.786
		p Value	.00	.034	
6 kHz	Pure tone air conduction	At baseline	53.79 ± 29.42	50.04 ± 24.02	.482
		3 months after the intervention	50.88 ± 29.75	48.06 ± 23.35	.592
		p Value	.000	.009	

The pure tone air conduction average was not significantly different between the control group and the intervention group before the intervention and 3 months after the intervention at .5, 1, 2 and 4 kHz. The pure tone bone conduction average was not significantly different between the control group and the intervention group before the intervention and 3 months after the intervention at .5, 1, 2 and 4 kHz. The pure tone air conduction average was not significantly different between the control group and the intervention group before the intervention and 3 months after the intervention at 6 kHz as shown in Table 2.

4 | DISCUSSION

4.1 | Synopsis of key findings

We found that a 3-month treatment with Neurotec beside baseline conservative treatments, significantly decreased scores of tinnitus loudness, annoyance severity, daily life alteration, sleep disturbance, daily tinnitus perception and mood disturbance in intervention group. On the other hand, control group which was treated only by baseline educational counselling and placebo, showed the same results except for mood disturbance, daily tinnitus perception and daily life alteration scores.

4.2 | Strengths of the study

A variety of herbal extracts have been so far proposed for management of tinnitus; from Ginkgo biloba (Jinko) to garlic and *Yoku-kan-san*.[10] To the best of our knowledge this is the very first study which has assessed the therapeutic effect of Neurotec (herbal combination of *Rosa canina*, *Urtica dioica* and *Tanacetum vulgare*) on symptoms of patients with tinnitus.

4.3 | Comparisons with other studies

A variety of herbal extracts have been so far proposed for management of tinnitus; from Ginkgo biloba (Jinko) to garlic and *Yoku-kan-san*.[10] We found that a 3-month treatment with Neurotec beside baseline

conservative treatments, significantly decreased scores of tinnitus loudness, annoyance severity, daily life alteration, sleep disturbance, daily tinnitus perception and mood disturbance in intervention group. On the other hand, control group which was treated only by baseline educational counselling and placebo-showed the same results except for mood disturbance, daily tinnitus perception and daily life alteration scores. This is in line with results of a recently published meta-analysis in which Xiang et al. concluded that educational counselling alone is as effective as other psychological therapies for improving tinnitus and related problems.[11] In addition, we realised that these improvements were significantly higher for the intervention group. Although patients in intervention group showed a remarkable decrease in THI score (quality of life) after 3 months of treatment, but those in control group experienced no significant decrease in this score.

For intervention group, pure tone air and bone conduction were significantly improved at 2, 4 and 6 kHz frequencies, after 3 months of treatment with Neurotec. Pure tone bone conduction did not show any significant improvement in control group at all the frequencies. However, air conduction was significantly improved in all the frequencies except .5 kHz.

Ghasemi et al. in an animal study concluded that *Urtica dioica* extract has positive effects on learning abilities and memory impairments in wistar rats. They explained this as protective characteristic of *Urtica dioica* against oxidative damage of brain tissues and acetyl choline esterase activity.[12] In another animal study, Patel et al. reported that *Urtica dioica* can remarkably reverse diabetes chronic complications such as central and peripheral neuropathies in adult Swiss albino mice.[13] A recently conducted animal study, has reported that *Urtica dioica* extracts can effectively improve neuro-inflammation and Alzheimer-like phenotypes in rats.[14]

Neuroprotective effects of *Rosa canina* has been evaluated in various settings as in Erfani et al. study which resulted in cognitive and memory improvements in heat stress-exposed rats.[15] Assessing diabetic albino mice, Farajpour et al. showed that hydro-alcoholic extract of *Rosa canina* improves memory impairment through modulation of oxidative stress.[16] In 2016, Daneshmand et al. proved the neuroprotective effects of Neurotec ingredients on rat model of sporadic Alzheimer's disease.[8] Setarud (IMOD™) is an immunomodulatory drug consisted from herbal extracts of *Rosa canina*, *Tancetum vulgare* and *Urtica dioica*. In an animal study, Vafaee et al. showed that setarud has a neuroprotective effect against brain ischemia in rat models.[7] As mentioned before, Neurotec is a safe and IFDA-approved medication for neuropathic pains, especially in diabetic patients.

Pathologies from the ear canal to the auditory cortex, may be responsible for tinnitus perception.[17] Auditory neural plasticity is one of the considered mechanisms, which knows cochlear deafferentation as trigger, and subsequent changes in central nervous system as the cause for maintenance of tinnitus perception.[18] We hypothesised that these neuroprotective features of Neurotec, improve cochlear nerve function and neural conduction; thus, this improvement results in better perception of environmental sounds and consequently decreases tinnitus perception. This is also the rational behind sound therapy by which, low- to moderate-level sound stimulation reverse the role of auditory depriviation in inducing tinnitus and hyperacusis.[19]

Apart from herbal and chemical medications, a wide range of medical and non-medical treatment modalities have been evaluated for management of tinnitus; from non-invasive interventions such as yoga and meditation, sound therapy and smartphone applications to minimally and invasive interventions like acupuncture and surgical neuromodulation.[19–23] Despite all these efforts, no curative treatment has been so far developed for Tinnitus. It seems that patients may take benefits from an intellectual combination of these treatments.[6] On the other hand, herbal medications and extracts are an appropriate alternative therapy as they are both more tolerated by patients and have less side effects.[6]

4.4 | Limitation of the study

The present study has some limitations. We had loss to follow ups in both intervention and placebo groups which may be attributable to nonsensible effects of treatment for patients, especially in initial weeks and month.

5 | CONCLUSION

In conclusion, we found that a 3-month treatment with Neurotec capsules accompanied by educational counselling is of benefit for managing symptoms in patients with chronic tinnitus. Further studies with a larger sample size and also longer duration of follow up are recommended.

AUTHOR CONTRIBUTIONS

Mohammad Hossein Khosravi, Jaleh Yousefi, Ali Bagheri Hagh and Masoumeh Saeedi contributed in design of study and data collection. Mohammad Hossein Khosravi, Amirhomayoun Atefi, Fatemeh Sodeifian and Afsaneh Mehri contributed in drafting the manuscript and data analysis. Fatemeh Kazemi and Mohammad Ajalloueian contributed in data analysis and data collection.

ACKNOWLEDGEMENTS

We would like to thank the Baqiyatallah otolaryngology clinic secretary, Mr. Abbaspour, for his nice cooperation upon the management of visit sessions. In addition, we appreciate the efforts of the audiology team at Baqiyatallah otolaryngology clinic for this project.

CONFLICT OF INTEREST

Authors declare that there are no conflicts of interest in terms of the present article.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/coa.13989.

DATA AVAILABILITY STATEMENT

The data for this article will be available upon request.

ETHICS STATEMENT

We adhered to the provisions of Declaration of Helsinki throughout the study. All the personal infomation were kept anonymously by the main researcher. Patients had the choice to leave the study at any desired stages.

ORCID

Mohammad Hossein Khosravi https://orcid.org/0000-0003-0426-5092
Amirhomayoun Atefi https://orcid.org/0000-0002-0556-5372
Afsaneh Mehri https://orcid.org/0000-0002-3993-9053
Fatemeh Sodeifian https://orcid.org/0000-0001-5824-3396
Jaleh Yousefi https://orcid.org/0000-0001-7668-0813
Ali Bagheri Hagh https://orcid.org/0000-0002-2079-6662
Saeed Sohrabpour https://orcid.org/0000-0002-3204-7116
Fatemeh Kazemi https://orcid.org/0000-0001-6116-738X
Mohammad Ajalloueian https://orcid.org/0000-0001-5501-9516
Masoumeh Saeedi https://orcid.org/0000-0002-6940-4447

REFERENCES

1. Haider HF, Hoare DJ, Costa RFP, Potgieter I, Kikidis D, Lapira A, et al. Pathophysiology, diagnosis and treatment of somatosensory tinnitus: a scoping review. Front Neurosci. 2017;11:207.
2. Langguth B, Kreuzer PM, Kleinjung T, De Ridder D. Tinnitus: causes and clinical management. Lancet Neurol. 2013;12(9):920–30.
3. Rief W, Weise C, Kley N, Martin A. Psychophysiologic treatment of chronic tinnitus: a randomized clinical trial. Psychosom Med. 2005;67(5):833–8.
4. Han BI, Lee HW, Kim TY, Lim JS, Shin KS. Tinnitus: characteristics, causes, mechanisms, and treatments. J Clin Neurol. 2009;5(1):11–9.
5. Atik A. Pathophysiology and treatment of tinnitus: an elusive disease. Indian J Otolaryngol Head Neck Surg. 2014;66(Suppl 1):1–5.
6. Luetzenberg FS, Babu S, Seidman MD. Alternative treatments of tinnitus: alternative medicine. Otolaryngol Clin North Am. 2020;53(4):637–50.
7. Vafaee F, Zangiabadi N, Pour FM, Dehghanian F, Asadi-Shekaari M, Afshar HK. Neuroprotective effects of the immunomodulatory drug Setarud on cerebral ischemia in male rats. Neural Regen Res. 2012;7(27):2085–91.
8. Daneshmand P, Saliminejad K, Dehghan Shasaltaneh M, Kamali K, Riazi GH, Nazari R, et al. Neuroprotective effects of herbal extract (*Rosa canina*, *Tanacetum vulgare* and *Urtica dioica*) on rat model of sporadic Alzheimer's disease. Avicenna J Med Biotechnol. 2016;8(3):120–5.
9. Mahmoudian S, Shahmiri E, Rouzbahani M, Jafari Z, Keyhani MR, Rahimi F, et al. Persian language version of the "Tinnitus Handicap Inventory": translation, standardization, validity and reliability. Int Tinnitus J. 2011;16(2):93–103.
10. Khosravi MH, Saeedi M, Yousefi J, Bagherihagh A, Ahmadzadeh E. Herbal medicine in the management of tinnitus. Management of tinnitus: the enriching views of treatment options. London: IntechOpen; 2018.
11. Xiang T, Zhong J, Lu T, Pu J-m, Liu L, Xiao Y, et al. Effect of educational counseling alone on people with tinnitus: meta-analysis of randomized controlled trials. Patient Educ Couns. 2020;103(1):44–54.
12. Ghasemi S, Moradzadeh M, Hosseini M, Beheshti F, Sadeghnia HR. Beneficial effects of *Urtica dioica* on scopolamine-induced memory impairment in rats: protection against acetylcholinesterase activity and neuronal oxidative damage. Drug Chem Toxicol. 2019;42(2):167–75.
13. Patel SS, Udayabanu M. Effect of *Urtica dioica* on memory dysfunction and hypoalgesia in an experimental model of diabetic neuropathy. Neurosci Lett. 2013;552:114–9.
14. Abu Almaaty AH, Mosaad R, Hassan M, Ali E, Mahmoud G, Ahmed H, et al. *Urtica dioica* extracts abolish scopolamine-induced neuropathies in rats. Environ Sci Pollut Res Int. 2021;28(14):18134–45.
15. Erfani M, Ghazi Tabatabaei Z, Sadigh-Eteghad S, Farokhi-Sisakht F, Farajdokht F, Mahmoudi J, et al. *Rosa canina* L. methanolic extract prevents heat stress-induced memory dysfunction in rats. Exp Physiol. 2019;104(10):1544–54.
16. Farajpour R, Sadigh-Eteghad S, Ahmadian N, Farzipour M, Mahmoudi J, Majdi A. Chronic administration of *Rosa canina* hydroalcoholic extract attenuates depressive-like behavior and recognition memory impairment in diabetic mice: a possible role of oxidative stress. Med Princ Pract. 2017;26(3):245–50.
17. Wang K, Tang D, Ma J, Sun S. Auditory neural plasticity in tinnitus mechanisms and management. Neural Plast. 2020;2020:1–17.
18. Noreña AJ. Revisiting the cochlear and central mechanisms of tinnitus and therapeutic approaches. Audiol Neurotol. 2015;20(Suppl. 1):53–9.
19. Pienkowski M. Rationale and efficacy of sound therapies for tinnitus and hyperacusis. Neuroscience. 2019;407:120–34.
20. Gunjawate D, Ravi R. Effect of yoga and meditation on tinnitus: a systematic review. J Laryngol Otol. 2021;135:284–7.
21. Mehdi M, Dode A, Pryss R, Schlee W, Reichert M, Hauck FJ. Contemporary review of smartphone apps for tinnitus management and treatment. Brain Sci. 2020;10(11):867.
22. Huang K, Liang S, Chen L, Grellet A. Acupuncture for tinnitus: a systematic review and meta-analysis of randomized controlled trials. Acupunct Med. 2021;39(4):264–71.
23. Deklerck AN, Marechal C, Pérez Fernández AM, Keppler H, Van Roost D, Dhooge IJ. Invasive neuromodulation as a treatment for tinnitus: a systematic review. Neuromodulation. 2020;23(4):451–62.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Khosravi MH, Atefi A, Mehri A, Sodeifian F, Yousefi J, Bagheri Hagh A, et al. Therapeutic effects of *Rosa canina*, *Urtica dioica* and *Tanacetum vulgare* herbal combination in treatment of tinnitus symptoms: A double-blind randomised clinical trial. Clinical Otolaryngology. 2023;48(2):151–7. https://doi.org/10.1111/coa.13989