

Ginkgo biloba in the treatment of tinnitus: An updated literature review

Mohammad Reza Mahmoudian-Sani^{1,2}
Morteza Hashemzadeh-Chaleshtori²
Majid Asadi-Samani³
Qian Yang⁴

Abstract

Introduction: Tinnitus is one of the common diseases of the ear that is associated with numerous physical and mental disorders. One of the known mechanisms in the tinnitus area with unknown reason is oxidative events. Based on the prevalence and economic costs and physical- psychological side effects caused by tinnitus and the importance of finding a suitable solution for its prevention and treatment, the need for further studies becomes more obvious in this context. This review article aimed to review studies on the effectiveness of *Ginkgo biloba* as a medicinal plant on patients with tinnitus. **Evidence Acquisitions:** Google Scholar, Directory of Open Access Journals (DOAJ), PubMed, LISTA (EBSCO) and Web of Science have been searched. **Results:** There are many studies on the therapeutic effect of *Ginkgo biloba* on patients with tinnitus. Most findings are in contrast with each other so that some of studies reported that *Ginkgo biloba* is effective in the treatment of tinnitus and other studies referred to it as ineffective herbal medicine. Generally, according to the previous studies and the present study, it can mention that the *Ginkgo biloba* may somewhat improve tinnitus. **Conclusion:** Since tinnitus is multifactorial, it is recommended to evaluate patients individually based on the cause of tinnitus, treatment formulas, and different doses of *Ginkgo biloba* at the more extensive level in future studies.

Keywords: ear disorders, tinnitus, *Ginkgo biloba*, drug discovery.

¹Research Center for Molecular Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

²Cellular and Molecular Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran

³Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran

⁴Institute of Pharmacy and Molecular Biotechnology, University of Heidelberg, Heidelberg, Germany

Send correspondence to:

Majid Asadi-Samani

Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran, E-mail: biology_2011@yahoo.com

Paper submitted to the ITJ-EM (Editorial Manager System) on April 12, 2017;

and accepted on May 17, 2017.

INTRODUCTION

Tinnitus is described as the perception of sounds created in one or both ears or inside the head without external auditory stimuli¹. Tinnitus is one of the common diseases of the ear, which can cause several mental and physical impairments and can impair the quality of life². The prevalence of this phenomenon is estimated 3-30%³. This disorder strongly affects the patient's life in 25% of cases⁴; 8-10% of patients with tinnitus have normal hearing and there is no reason for tinnitus among them⁵. Despite significant advances in modern medicine, the exact pathophysiology of tinnitus still remains unknown². Various drugs including antihistamines, barbiturates, anesthetics, calcium channel blockers, vasodilators, muscle relaxants, anticonvulsants, and also various methods of psychotherapy and tinnitus masking agents have been used to reduce the tinnitus severity; however, they have little effects and their results are not different from those of placebo⁴.

Previous researches on tinnitus with unknown cause showed that oxidative stress events are one of the proposed mechanisms of tinnitus⁶ in a way that antioxidants are known as one of the effective measures in reducing the severity of tinnitus⁷. Oxidative stress processes often occur in the context of an imbalance in the concentration of rare elements used in the construction of antioxidant enzymes⁸. One of the important mechanisms in the field of creating tinnitus is the increase in the glutamate as the excitatory neurotransmitter. The increase in the glutamate is associated with neurotoxicity impacts. This increase leads to inflammation and necrosis of dendrites of afferent cochlear corti organ cells by stimulating production of free radicals^{9,10}. Different types of causes of tinnitus have been demonstrated in Table 1.

Medicinal plants and tinnitus

Despite recent developments in modern medicine, there are still no definite treatment for hearing losses. These disorders have fueled research to discover new therapeutic approaches and drugs. In this regard, there has been a renewed interest in the approaches of traditional medicine and phytotherapy in medical arena. Medicinal plants and their derivatives have been studied, by the application of scientific approaches, *in vitro*, with animals, and ultimately in clinical trials so that more efficient therapeutic approaches and drugs can be discovered¹⁶⁻²⁶. Apart from drug therapy, other methods are used in tinnitus therapy such as phytotherapy (Table 2). It does not seem that any of the treatments alone or in combination with other treatments are quite effective on tinnitus and that's why FDA has not approved any treatment for tinnitus²⁷. Among the used medicinal plants, *Ginkgo biloba* (Folium Ginkgo) is one of the herbals that frequently used in the treatment of tinnitus and has been studied in various studies^{28,29}. *Ginkgo biloba* belongs to Ginkgoaceae family. Ginkgo leaf has a range of phytochemicals, including alkanes, lipids, sterols, benzoids, carotenoids, phenylpropanoids, carbohydrates, flavonoids and terpenoids^{30,31}. Studies show that *Ginkgo biloba*, which is a monoamine-oxidase inhibitor (MAOI) can effectively improve patients with tinnitus caused by ischemia due to having myricetin and quercetin flavonoids and ginkgolide and bilobalide terpenoids³². *Ginkgo biloba* has antiplatelet and vascular modulator effects. In other words, it improves blood flow and appropriately regulates vascular tone. Vascular problems are one of the suggested causes for tinnitus originating from the area of cochlear nerve cortex. Cardiovascular problems can cause problems in blood supply to labyrinthine artery and this causes hypoxia in the outer hair cells of the

Table 1. Causes of tinnitus^{7,11-15}.

Type	Causes
Ear disorders	More than 90% of tinnitus cases are caused by the ear disorders. Earwax, otitis media, trauma, acoustic trauma, atmospheric pressure changes and direct blows to the ear can also cause tinnitus. Tinnitus is commonly observed in presbycusis and is highly frequent.
Cardiovascular causes	Cardiovascular causes are the second most common causes of tinnitus. Approximately, one third of patients with severe tinnitus are suffering from one or more cardiovascular disorders. 75% of these patients suffer from hypertension and their tinnitus is often treated when their hypertension is treated.
Neurological disorders or head injuries	Neurological disorders or trauma, including skull fractures or injuries of any type of blunt head lead to tinnitus in 5 to 10% of cases. Skull fractures can cause tinnitus and sensory - nerve hearing loss usually towards high frequencies. Also, in the case of the rupture of ear bones, conductive hearing loss will be seen. Tinnitus is caused following the damage caused by the intense back and forth shaking of the head in traffic accidents, usually a few days to a few weeks after the accident.
Pharmacological side effects	Over 10% of subjective tinnitus cases, especially in elderly patients are due to the side effects of drugs, the most important of which is aspirin. Other drugs include non-steroidal, anti-inflammatory drugs, antibiotics, particularly aminoglycosides, antidepressants, and tranquilizers can also cause tinnitus.
Dental diseases	Dental diseases or any temporomandibular disorder could exacerbate tinnitus. In these cases, the patients feel fullness or pressure in the ear and sensitivity in temporomandibular and mandibular joints.
Metabolic disorders	Metabolic disorders are considered as a relatively uncommon cause of tinnitus. Hyperthyroidism causes annoying and problematic tinnitus in 4% of cases. Vitamin A deficiency has also been reported as the cause of tinnitus, but it is very rare.
Psychological causes	Psychological factors may cause or aggravate tinnitus. Also, stress exacerbates the tinnitus severity.
Objective tinnitus	This type of tinnitus is heard with or without the use of the phone by the doctor and has vascular, mechanical, or neoplastic's muscle origin.
Idiopathic tinnitus	Various causes are involved in idiopathic tinnitus. One of them is reactive oxygen species (ROS). High serum values of ROS related to the idiopathic tinnitus has been detected. Evaluated ROS concentrations can lead to cytotoxic effects that affect neurons and ciliated cells in the inner ear. Besides, it can increase the glutamate as the excitatory neurotransmitter and lead to inflammation and necrosis of dendrites of afferent cochlear Corti organ cells by stimulating production of free radicals.

cochlea and lead to subjective tinnitus. Adequate blood supply to the cochlea, which can be justified by *Ginkgo biloba*, can stop this process. Antioxidant and protective effects on nerve cells in the brain, auditory cortex, and

Table 2. Some of the main herbal medicines for treatment tinnitus³⁷⁻⁴⁵.

Herbal medicines	Their components and effects	Ref
Ming Fang (EMF01)	It is a herbal formula including <i>Rehmannia glutinosa</i> , <i>Cornus officinalis</i> , <i>Salvia miltiorrhiza</i> , <i>Pueraria</i> , <i>Schisandra chinensis</i> , <i>Poria cocos</i> , and <i>Platycodon grandiflorum</i> plants.	37
EIZCW	Er-long-zuo-ci-wan is a compound of Chinese Traditional Medicine.	38
Garlic	This effect is only theoretical, and no scientific studies have been conducted to investigate the possible effects of garlic on tinnitus.	39
Banxia and Tianma	Banxia and Tianma used in combination for the treatment of tinnitus.	40
<i>Cornus (Cornus officinalis)</i>	It does not seem to relieve the symptoms of tinnitus alone, but when it used in combination with Chinese foxglove root and Chinese yam proves to be effective in the treatment of tinnitus.	41
Black cohosh	It has traditionally been used to calm the nervous system by nourishing blood vessels, and it is theorized that it may improve cerebral blood flow, providing relief from tinnitus in some patients.	42,43
Bojungkigtang and Banhabaekchulchonmatang	They are among the most strongly preferred and widely used herbal medicines as herbal medications for tinnitus in Korea, as they cause very few serious adverse effects.	44
<i>Rhodiola rosea</i> , <i>Hydrastis canadensis</i> , <i>Sesamum indicum</i> , <i>Heliantus annus</i>	These herbs were effective and safe for the treatment of tinnitus.	45

Table 3. The main studies of the effects of *Ginkgo biloba* on tinnitus.

Number of participants or samples	Duration of treatment	Drug dose	Main results	Ref
94 patients	Four months	58 patients had been treated with simvastatin (40 mg) and 36 patients with <i>Ginkgo biloba</i> (120 mg).	After administration of simvastatin over 4 months, this retrospective study has shown no significant efficacy in treatment of subacute tinnitus. Then after treatment with simvastatin or <i>Ginkgo biloba</i> , tinnitus score decreased; However, independently of the treatment regimen, differences of tinnitus scores were considered not significant.	28
1243 patients	12 weeks	150 mg per day.	50 mg <i>Ginkgo biloba</i> extract that is given 3 times daily for 12 weeks is no more effective than placebo in treating tinnitus.	55
38 patients	Clonazepam or <i>Ginkgo biloba</i> for the first three weeks. For the next two weeks of washout no medication was taken. For the final three weeks, subjects were given the other drug.	Clonazepam 0.5 mg; <i>Ginkgo biloba</i> 40 mg.	Clonazepam was effective and <i>Ginkgo biloba</i> was ineffective in treating tinnitus.	56
80 patients	Two weeks. Responders (20 patients) were then treated for two weeks each.	29.2 mg per day.	Statistical group analysis gives no support to the hypothesis that <i>Ginkgo biloba</i> extract has any effects on tinnitus; although it is possible that <i>Ginkgo biloba</i> extract has an effect on some patients due to several reasons, e.g. the diverse etiology of tinnitus.	54
84- Rat model of salicylate-induced tinnitus.	Began two weeks before behavioral procedures and continued until the end of the experiment.	10 to 100 mg/ kg/day EGb 761	Administration of EGb 761 resulted in a statistically significant decrease of the behavioral manifestation of tinnitus for doses of 25, 50 and 100 mg/kg/day.	48
20 Mongolian gerbils (<i>Meriones unguiculatus</i>)	Three weeks of daily oral EGb 761	100 mg/kg body weight	All 9 animals that displayed behavioral signs of subjective tinnitus showed improvement, with 7 of them showing complete relief of tinnitus symptoms during the time of EGb 761 treatment. After discontinuation of EGb 761 treatment tinnitus related behavior reappeared in all but one of these animals while auditory thresholds remained restored.	49
100 patients	Three months	160 mg/day	The results were conclusive as regards the effectiveness of <i>Ginkgo biloba</i> extract and made it possible to determine the prognostic value of different parameters. Of special importance among these parameters were site and periodicity of the disease. However, the <i>Ginkgo biloba</i> extract treatment improved the condition of all the tinnitus patients, irrespective of the prognostic factor.	50
90 patients	Three months	-	Results suggest that trimetazidine, betahistin and <i>Ginkgo biloba</i> extract reduce tinnitus symptoms. However, symptomatic relief can be mostly achieved with trimetazidine treatment.	51
66 patients	12 weeks	120 mg per day	<i>Ginkgo biloba</i> does not benefit patients with tinnitus.	57
30 patients	Three months	A dose of one vial a day	Treated patients has been reported an improvement in symptoms and quality of life.	52
36-Mongolian gerbil	Prophylactic treatment over two weeks before starting the experiments.	EGb 761 (100 mg extract/kg body weight).	Animals were fed daily with the extract in agar development upon EGb761 application, compared to vehicle treated animals.	53

- Article in Turkish; EGb 761: It is a standardized extract of *Ginkgo biloba* leaves.

sub-cortical area can also justify the anti-tinnitus effects of *Ginkgo biloba*³³. *Ginkgo biloba* was reported to scavenge primary (O₂⁻, OH.) and secondary (ROO.) free radicals^{34,35}. These beneficial properties seem in part to come from the activity of *Ginkgo biloba* constituents such as flavonoids and terpenes. *Ginkgo biloba* that can be described as an herbal medicine whose active pharmacological groups are flavonoids with antioxidant and vasodilator action; and terpene lactones, which act as antiplatelet agents³⁶.

RESULTS

Simultaneous use of soft-laser for exposure to the cochlea and administration of *Ginkgo biloba* extract for 4 weeks on a 20-50% of patients has been reported to be useful. Soft-laser mechanism of action is unknown, but it has been proved that light leads to athermic stimulation of biochemical processes. Actually, the combination of Ginkgo-soft-laser was very effective in the treatment of chronic tinnitus. Ginkgo provided better oxygen and laser directly operated on flavoproteins to activate repair mechanisms⁴⁶. Besides, Plath and Olivier demonstrated that Ginkgo-soft-laser reduced the severity of tinnitus in some cases and concluded that the combination of soft-laser and Ginkgo can be useful in some patients with severe tinnitus⁴⁷. Moreover, *Ginkgo biloba* is clinically used for the treatment of inner ear disorders such as hearing loss, dizziness, and tinnitus. This herb is widely used to treat tinnitus in European countries and elsewhere. However, in some studies and clinical trials it has been stated that this herb has no beneficial effect in comparison with placebo in the treatment of tinnitus (Table 2). There are many studies on the effects of *Ginkgo biloba* in the treatment of patients with tinnitus that most of the findings of these studies are in contrast with each other; on the one hand, some of the studies reported that *Ginkgo biloba* is effective in the treatment of tinnitus effective⁴⁸⁻⁵³ and on the other hand other studies referred to it as ineffective herbal medicine^{28,54-57}. The results of a systematic review showed that *Ginkgo biloba* is little/less effective in the treatment of tinnitus. This study reported that choosing those treatments are beneficial for patients that not only reduce costs for patients, but also prevent patients from choosing and searching for other ineffective treatments⁵⁸ (Table 3).

CONCLUSION

According to the previous studies and the present study, *Ginkgo biloba* can be considered as a promising option to improve tinnitus along with further studies. Since tinnitus is multifactorial, it is recommended to evaluate patients individually according to the cause of tinnitus, treatment formulas, and different doses of *Ginkgo biloba* at more extensive level in future studies. Categorizing tinnitus based on its comorbid conditions such as mental disorders, presbycusis, acoustic trauma damage (noise), and medical underlying conditions and also investigating the effect of drugs in these subgroups can be considered as a more accurate solution to evaluate a therapy ranging

from drug or non-drug methods. In addition, it seems that finding new ways to control tinnitus in the future will require neurophysiologic and neuroscience research; also promoting effective drug treatments certainly depends on understanding the changes in neurotransmitters and their receptors. Therefore, unless the mechanisms of tinnitus are not well understood, designing a detailed treatment will fail.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Acknowledgement

This work financially was supported by Research deputy of Hamadan University of Medical Sciences and was a part of Ph.D Thesis of Mr. Mahmoudian Sani.

REFERENCES

1. Kalcioğlu MT, Bayındır T, Erdem T, Özturan O. Objective evaluation of the effects of intravenous lidocaine on tinnitus. *Hear Res.* 2005;199(1):81-8.
2. Yetiser S, Tosun F, Satar B, Arslanhan M, Akcam T, Ozkaptan Y. The role of zinc in management of tinnitus. *Auris Nasus Larynx.* 2002;29(4):329-33.
3. Heller AJ. Classification and epidemiology of tinnitus. *Otolaryngol Clin North Am.* 2003;36(2):239-48.
4. Baskill J, Coles R, editors. Relationship between tinnitus loudness and severity. Sixth International Tinnitus Seminar; 1999: The Tinnitus and Hyperacusis Centre Cambridge, United Kingdom.
5. Barnea G, Attias J, Gold S, Shahar A. Tinnitus with normal hearing sensitivity: Extended high-frequency audiometry and auditory-nerve brain-stem-evoked responses. *Audiology.* 1990;29(1):36-45.
6. Neri S, Mauceri B, Cilio D, Bordonaro F, Messina A, Malaguarnera M, et al. Tinnitus and oxidative stress in a selected series of elderly patients. *Arch Gerontol Geriatr.* 2002;35:219-23.
7. Savastano M, Brescia G, Marioni G. Antioxidant therapy in idiopathic tinnitus: preliminary outcomes. *Arch med res.* 2007;38(4):456-9.
8. Ghatreh-Samani M, Esmaeili N, Soleimani M, Asadi-Samani M, Ghatreh-Samani K, Shirzad H. Oxidative stress and age-related changes in T cells: Is thalassemia a model of accelerated immune system aging? *Cent Eur J Immunol.* 2016;41(1):116-24.
9. Le Prell CG, Dolan DF, Bennett DC, Boxer PA. Nutrient plasma levels achieved during treatment that reduces noise-induced hearing loss. *Transl Res.* 2011;158(1):54-70.
10. Henderson D, Bielefeld EC, Harris KC, Hu BH. The role of oxidative stress in noise-induced hearing loss. *Ear Hear.* 2006;27(1):1-19.
11. Han BI, Lee HW, Kim TY, Lim JS, Shin KS. Tinnitus: Characteristics, causes, mechanisms, and treatments. *J Clin Neurol.* 2009;5(1):11-9.
12. Roberts LE, Eggermont JJ, Caspary DM, Shore SE, Melcher JR, Kaltenbach JA. Ringing ears: The neuroscience of tinnitus. *J Neurosci.* 2010;30(45):14972-9.
13. Chan Y. Tinnitus: etiology, classification, characteristics, and treatment. *Discov Med.* 2009;8(42):133-6.
14. Egilmez OK, Kalcioğlu MT. Antioxidant Therapy in Tinnitus. *Br J Med Med Res.* 2015;10(7).
15. Ciorba A, Bianchini C, Pastore A, Mazzoli M. Pathogenesis of Tinnitus: Any Role for Oxidative Stress? *Int Adv Otol.* 2013;9(2):249-54.
16. Gholamian-Dehkordi N, Luther T, Asadi-Samani M, Mahmoudian-Sani MR. An overview on natural antioxidants for oxidative stress reduction in cancers; A systematic review. *Immunopathol Persa.* 2017;3(2).

17. Sani MRM, Asadi-Samani M, Saeedi-Boroujeni A, Banitalebi-Dehkordi M, Bahmani M. Suppressive effects of medicinal plants and their derivatives on inflammasome complex: A systematic review. *Int J PharmTech Res.* 2016;9(6):325-33.
18. Mahmoudian Sani M, Asadi-Samani M, Rouhi-Boroujeni H, Banitalebi-Dehkordi MP. phytotherapy of regulatory T cells: A new approach to treat multiple sclerosis. *Der Pharm Lett.* 2016;8:215-20.
19. Afkhami-Ardakani M, Hassanzadeh S, Shahrooz R, Asadi-Samani M, Latifi M, Luther T. Phytotherapy and phytopharmacology for reduction of cyclophosphamide-induced toxicity in the male urinary system. *J Renal Inj Prev.* 2017;6(3):164-70.
20. Asadi-Samani M, Kooti W, Aslani E, Shirzad H. A systematic review of Iran's medicinal plants with anticancer effects. *J Evid Based Complementary Altern Med.* 2016;21(2):143-53.
21. Asadi-Samani M, Moradi M, Mahmoodnia L, Alaei S, Asadi-Samani F, Luther T. Traditional uses of medicinal plants to prevent and treat diabetes; An updated review of ethnobotanical studies in Iran. *J Nephropathol.* 2017;6(3):118-25.
22. Baharvand-Ahmadi B, Asadi-Samani M. A mini-review on the most important effective medicinal plants to treat hypertension in ethnobotanical evidence of Iran. *J Nephroarmacol.* 2017;6(1):3-8.
23. Kooti W, Hasanzadeh-Noohi Z, Sharafi-Ahvazi N, Asadi-Samani M, Ashtary-Larky D. Phytochemistry, pharmacology, and therapeutic uses of black seed (*Nigella sativa*). *Chin J Nat Med.* 2016;14(10):732-45.
24. Mansouri E, Asadi-Samani M, Kooti W, Ghasemiboroon M, Ashtary-Larky D, Alamiri F, et al. Anti-fertility effect of hydro-alcoholic extract of fennel (*Foeniculum vulgare* Mill) seed in male Wistar rats. *J Vet Res.* 2016;60(3):357-63.
25. Mirhoseini M, Moradi MT, Asadi-Samani M. Traditionally used medicinal plants in the treatment of kidney stone: A review on ethnobotanical studies in Iran. *Ambient Science.* 2016;3(2):16-21.
26. Mahmoudian-Sani M, Luther T, Asadi-Samani M, Saeedi-Boroujeni A, Gholamian N. A new approach for treatment of type 1 diabetes: Phytotherapy and phytopharmacology of regulatory T cells. *J Renal Inj Prev.* 2017;6(3):158-63. DOI: 10.15171/jrip.2017.31.
27. Dobie RA. A review of randomized clinical trials in tinnitus. *Laryngoscope.* 1999;109(8):1202-11.
28. Canis M, Olzowy B, Welz C, Suckfüll M, Stelter K. Simvastatin and Ginkgo biloba in the treatment of subacute tinnitus: A retrospective study of 94 patients. *Am J Otolaryng.* 2011;32(1):19-23.
29. Ernst E, Stevinson C. Ginkgo biloba for tinnitus: A review. *Clin Otolaryngol Allied Sci.* 1999;24(3):164-7.
30. Van Beek T, Scheeren H, Rantio T, Melger WC, Lelyveld G. Determination of ginkgolides and bilobalide in Ginkgo biloba leaves and phytopharmaceuticals. *J Chrom A.* 1991;543:375-87.
31. Hasler A, Gross G-A, Meier B, Sticher O. Complex flavonol glycosides from the leaves of Ginkgo biloba. *Phytochemistry.* 1992;31(4):1391-4.
32. Kleijnen J, Knipschild P. Ginkgo biloba. *Lancet.* 1992;340(8828):1136-9.
33. Diamond BJ, Shiflett SC, Feiwei N, Matheis RJ, Noskin O, Richards JA, et al. Ginkgo biloba extract: mechanisms and clinical indications. *Arch Phys Med Rehabil.* 2000;81(5):668-78.
34. Louajri A, Harraga S, Godot V, TOUBIN G, KANTELEP JP, MAGNIN P. The effect of ginkgo biloba extract on free radical production in hypoxic rats. *Biological and Pharmaceutical Bulletin.* 2001;24(6):710-2.
35. Droy-Lefaix M, Cluzel J, Menerath J, Bonhomme B, Doly M. Antioxidant effect of a Ginkgo biloba extract (EGb 761) on the retina. *Int J Tissue React.* 1994;17(3):93-100.
36. Ude C, Schubert-Zsilavecz M, Wurglics M. Ginkgo biloba extracts: A review of the pharmacokinetics of the active ingredients. *Clin Pharmacokinet.* 2013;52(9):727-49.
37. Zheng Y, Vagal S, Zhu XX, de Waele C, Smith PF, Wang G, et al. The effects of the Chinese herbal medicine EMF01 on salicylate-induced tinnitus in rats. *J Ethnopharmacol.* 2010;128(2):545-8.
38. Wang Y, Song H, Tong Z, Qian S, Guo R, Jing Z, et al. Effects of er-long-zuo-ci-wan on the spontaneous activities of auditory central nucleus in rat model of tinnitus induced by salicylate acid. *Zhongguo Ying Yong Sheng Li Xue Za Zhi.* 2009;25(3):397-401.
39. Linde K, ter Riet G, Hondras M, Vickers A, Saller R, Melchart D. Systematic reviews of complementary therapies—an annotated bibliography. Part 2: Herbal medicine. *BMC Complement Altern Med.* 2001;1(1):5.
40. Shen S, Wang Y, Zheng G, He X, Tan Y, Zhou K, et al., editors. Applying bioinformatic technique to discovery molecular mechanisms of Banxia and Tianma combination treating tinnitus. *Bioinformatics and Biomedicine (BIBM), 2014 IEEE International Conference on;* 2014: IEEE.
41. Newall CA, Anderson LA, Phillipson JD. Herbal medicines. A guide for health-care professionals: The Pharmaceutical Press; 1996.
42. Okamoto H, Okami T, Ikeda M, Takeuchi T. Effects of Yoku-kan-san on undifferentiated somatoform disorder with tinnitus. *Eur Psychiatr.* 2005;20(1):74-5.
43. Seidman MD, Babu S. Alternative medications and other treatments for tinnitus: facts from fiction. *Otolaryngol Clin N Am.* 2003;36(2):359-81.
44. Kim NK, Lee DH, Lee JH, Oh YL, Yoon IH, Seo ES, et al. Bojungikgitang and banhabaekchulchonmatang in adult patients with tinnitus, a randomized, double-blind, three-arm, placebo-controlled trial-study protocol. *Trials.* 2010;11(1):34.
45. Langguth B, Hajak G, Kleinjung T, Cacace A, Moller A. Tinnitus: Pathophysiology and treatment: Elsevier Amsterdam; 2007.
46. Olivier J, Plath P. Combined low power laser therapy and extracts of Ginkgo biloba in a blind trial of treatment for tinnitus. *Laser Ther.* 1993;5(3):137-9.
47. Plath P, Olivier J. Results of combined low-power laser therapy and extracts of Ginkgo biloba in cases of sensorineural hearing loss and tinnitus. *Adv Oto-Rhino-Laryng: Karger Publishers;* 1995. p. 101-4.
48. Jastreboff P, Zhou S, Jastreboff M, Kwapisz U, Gryczynska U. Attenuation of Salicylate-Induced Tinnitus by Ginkgo biloba Extract in Rats. *Audiol Neurootol.* 1997;2(4):197-212.
49. Krauss P, Tziridis K, Buerbank S, Schilling A, Schulze H. Therapeutic Value of Ginkgo biloba Extract EGb 761® in an Animal Model (*Meriones unguiculatus*) for noise trauma induced hearing loss and tinnitus. *PLoS one.* 2016;11(6):e0157574.
50. Meyer B. Multicenter randomized double-blind drug vs. placebo study of the treatment of tinnitus with Ginkgo biloba extract. *Presse Med.* 1986;15(31):1562-4.
51. Orhan I, Aydin S, Altin G, Yilmaz F. An efficacy comparison of betahistin, trimetazidine and ginkgo biloba extract in patients with tinnitus. *Kulak Burun Bogaz Ihtis Derg.* 2013;23(3):143-7.
52. Tasca I, Di Lieto C, Compadretti GC, Gabrielli S. Effectiveness of ginkgo biloba (Brenstar (c)) in the treatment of tinnitus and vertigo. *Prog Nutr.* 2012;14(4):277-83.
53. Tziridis K, Korn S, Ahlf S, Schulze H. Protective effects of Ginkgo biloba extract EGb 761 against noise trauma-induced hearing loss and tinnitus development. *Neural plasticity.* 2014;2014(2):27.
54. Holgers KM, Axelsson A, Pringle I. Ginkgo biloba extract for the treatment of tinnitus: Original Paper. *Audiology.* 1994;33(2):85-92.
55. Drew S, Davies E. Effectiveness of Ginkgo biloba in treating tinnitus: Double blind, placebo controlled trial. *Br Med J.* 2001;322(7278):73.
56. Han S-S, Nam E-C, Won JY, Lee KU, Chun W, Choi HK, et al. Clonazepam quiets tinnitus: A randomised crossover study with Ginkgo biloba. *J Neurol Neurosurg Psychiatry.* 2012;83(8):821-7.
57. Rejali D, Sivakumar A, Balaji N. Ginkgo biloba does not benefit patients with tinnitus: A randomized placebo-controlled double-blind trial and meta-analysis of randomized trials. *Clin Otolaryngol Allied Sci.* 2004;29(3):226-31.
58. von Boetticher A. Ginkgo biloba extract in the treatment of tinnitus: A systematic review. *Neuropsychiatr Dis Treat.* 2011;7(1):441-7.