

Original research article

Treating Sensorineural Tinnitus- Oral forms of 5-MTHF (folate), Vitamin B12 and Gingko Biloba Vs oral forms of Caroverine and Gingko Biloba

Suryakant Shukla¹, Saket Gupta^{2*}, Rajeev Kumar Nishad³,
Yogesh Kumar Yadav⁴

¹ Senior Resident, Department of ENT, Rajarshi Dashrath Autonomous State Medical College, Ayodhya, U.P.

^{2*} Assistant Professor, Department of ENT, Rajarshi Dashrath Autonomous State Medical College, Ayodhya, U.P.

³ Associate Professor, Department of ENT, F.H. Medical College & Hospital, Etmadpur, Agra, U.P.

⁴ Associate Professor, Department of Pathology, Rajarshi Dashrath Autonomous State Medical College, Ayodhya, U.P.

Corresponding author: Dr. Saket Gupta

E-mail: saket.gupta58@gmail.com

Abstract

Background: Tinnitus results from the perception of abnormal activity, defined as activity which cannot be induced by any combination of external sounds. Various modalities have been tried with varying results. The aim of our study was to compare efficacy of oral 5-MTHF, Vitamin B12 and Gingko Biloba with oral Caroverine and ginkgo biloba in treatment of Sensorineural tinnitus.

Material and Methods: This prospective study included 60 tinnitus patients both male and female between 18-60 years of age having serum vitamin B12 level <230pg/ml and serum folic acid level < 3ng/ml. Patients with a history of test drug allergy, those on vitamin B12 and folic acid supplementation, pregnancy, psychiatric disorders and those with middle ear/external ear pathology were excluded from the study. After otorhinolaryngological examination, patients were divided into two groups, Group A(32 patients) received a combination of oral 5-methyl tetra hydro folate(5-MTHF) 800 mcg/day as a single daily dose, oral vitamin B12 (methylcobalamin) 1500 mcg/day as a single daily dose and oral Gingko Biloba 120 mg/day in two divided doses and Group B(28 patients) received oral Caroverine 40 mg/day in two divided doses and oral Gingko Biloba 120 mg/day in two divided doses. Patients were followed up and evaluated on 0, 1, 2 and 3 month over a period of 3 months for S.Vitamin B12 level, S.Folic acid level and improvement of clinical symptoms in terms of tinnitus grading and tinnitus matching.

Results: The mean tinnitus matching (in dB) at Pre-Treatment and Post-Treatment (1 month, 2 month and 3 month) was 42.50±11.77, 37.50±12.25, 34.69±11.57 and 32.97±12.30 in group A and 47.86±12.28, 40.89±13.48, 40.36±12.69 and 40.18±12.73 in group B, respectively. The mean tinnitus matching (in dB) was significantly lower in group A as compared to group B at 3rd month. Moreover, the mean tinnitus matching (in dB) was significantly decreased in group A from Pre-Treatment to 3 month.

Conclusion: With 5-MTHF, vitamin B12 and Gingko Biloba, mean serum folate level and mean serum vitamin B12 level shows a significant improvement (p<0.05) after the end of

treatment compared to caroverine and Ginkgo Biloba; similar improvement was also seen for mean tinnitus matching and mean tinnitus grading. Thus, combination of oral 5-MTHF, Vitamin B12 and Ginkgo Biloba is thus found to be more effective treatment modality for Sensorineural tinnitus on long term basis.

Keywords: Sensorineural Tinnitus, 5-MTHF, Ginkgo Biloba, Caroverine, serum vitamin B12, serum Folic acid

Introduction

Tinnitus results from the perception of abnormal activity, defined as activity which cannot be induced by any combination of external sounds. Moreover, it is hypothesized that signal recognition and classification circuits, working on holographic or neuronal network-like representation, are involved in the perception of tinnitus and are subject to plastic modification¹. The prevalence of tinnitus, as per survey carried out in U.S, has been estimated to be as high as 32% in the adult population, with less than one-fifth of them considered it to be severe². In epidemiological study done in UK showed prevalence of about 35 per cent of adults appear to have experienced tinnitus of different type and duration. Even the short duration ones appear to be a nuisance to some of the 'sufferers'. About 15 per cent of adults appear to have or to have had 'spontaneous' tinnitus lasting over five minutes duration. At least 8 per cent experience tinnitus causing interference with their getting to sleep and/or moderate or severe annoyance³.

The main purpose of treating a patient with tinnitus is to alleviate patient of his symptoms and to improve quality of life. Various modalities have been tried with varying results.

The various pharmacological agents that have been tried for tinnitus include antidepressants, GABA analogues like benzodiazepine, gabapentin, baclofen, calcium channel antagonists, antiepileptics, prostaglandin analogues, lignocaine, Ginkgo Biloba extracts and selective glutamate receptor antagonist (Caroverine). Folic acid (vitamin B9) is a member of the B-complex family of vitamins⁴. Low levels of vitamin B12 and 5-Methyltetrahydrofolate(5-MTHF) are associated with the destruction of the microvasculature of the stria vascularis, which might result in decreased endocochlear potential and in hearing loss and tinnitus⁵. Homocysteine is elevated during deficiencies of vitamin B-12, folate, or both⁶, and homocysteine is believed to be a vascular toxin⁷ and a neurotoxin^{8,9}.

Recently, there has been an increased general interest in drug targeting glutamate receptors (Caroverine) and study by Prof Klaus Ehrenberger on Caroverine shows promising result in treatment of sensorineural tinnitus. The quinoxaline-dione, caroverine, exhibit a potent but reversible glutamate antagonism on the excitatory afferent synapses of the cochlear inner hair cells. Caroverine selectively prevent the glutamate induced depolarisation, whereas the acetylcholine induced depolarisation of the same postsynaptic dendritic membrane remained unaffected¹⁰. Quinoxaline derivatives are potent competitive non-NMDA(N-methyl-D-aspartate) receptor antagonists¹¹ and also, at larger doses, antagonists of the NMDA associated glycine site¹². 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 terpenoids. Ginkgo biloba has antiplatelet and vascular modulator effects. In other words, it improves blood flow and appropriately regulates vascular tone¹³. The aim of our study was to compare efficacy of oral 5-MTHF, Vitamin B12 and Ginkgo Biloba with oral Caroverine and ginkgo biloba in treatment of Sensorineural tinnitus.

MATERIAL AND METHODS:

This prospective study was conducted in the Department of ENT, Motilal Nehru, Medical College and Swaroop Rani Nehru Hospital, Prayagraj from 01 August 2020 to 31 July 2021.

This study was conducted after taking ethical clearance from the Institutional Ethics Committee. Patients were properly informed about the nature of disease, its potential outcome and procedure to be done for obtaining sample. Written informed consent was obtained from the patients once they agreed to participate in the study.

- **DIAGNOSIS OF SENSORINEURAL TINNITUS:**

Patients having high frequency loss & sensorineural hearing loss is consistent with the diagnosis of sensorineural tinnitus.

- **SELECTION OF CASES:**

Inclusion Criteria:

- Patient included in it are of age between 18 and 60 years.
- Diagnosis of tinnitus whether unilateral or bilateral
- Patients should be checked for cochlear hearing defect by reflex audiometry done for confirming cochlear-synaptic tinnitus and excluding middle ear tinnitus
- Patients serum vitamin B12 and serum folic acid levels should be < 230pg/ml and < 3ng/ml respectively.

Exclusion Criteria:

- History of supplemental vitamin B12 and folic acid intake.
- Any contra-indication of test drug.
- Pregnancy or plan for having children
- Hydrops cochlea or Meniere's disease
- Retrocochlear hearing defect
- Baro trauma
- Status post psychiatrist therapy
- Pulse-synchronous tinnitus
- Excessive consumption of alcohol, drug or nicotine
- All patients with middle ear/external ear pathology

The cases were registered and given one number for each case. The age, sex, religion, socio-economic status, occupation and address of the patients were recorded. The symptoms of the patients were recorded chronologically.

The history of present episode or any such previous episodes were recorded. The past history of systemic disorders and ototoxic drug use were also taken into account. The familial and personal history including the occupational status, drug abuse (including tobacco), use of headphones and life style were also enquired. Thorough clinical examination was carried out which included a general examination and complete otorhinolaryngological examination.

For otorhinolaryngological examination, examination of ear with head mirror and otoscope was done. Tuning fork tests were also performed. Examination of eustachian tube function was checked by Valsalva maneuver. Examination of facial nerve was also done. Examination of oral cavity was done by using head mirror and bull's eye lamp. The nasal cavities were examined by anterior rhinoscopy and posterior rhinoscopy. Indirect laryngoscopy was performed to look for any laryngeal pathology.

The subjects were then given / explained a tinnitus handicap inventory questionnaire and tinnitus grading was done accordingly. The educated patients were asked to write down

answers whereas in case of uneducated patients the questions were asked and their answers marked accordingly. After the completion of the questionnaire the patients were given appointment for pure tone audiometry. During the examination other audiological tests including ART, clinching reflex, tympanometry, SISI, ABLB and TDT were also performed. By using computer generated randomization method participants were randomized into two groups:

- **GROUP A- 5-METHYL TETRA HYDRO FOLATE, VITAMIN B12 AND GINKGO BILOBA SUPPLEMENTATION-** patient treated with oral 5-methyl tetra hydro folate 800 mcg/day as a single daily dose, oral vitamin B12 (methylcobalamin) 1500 mcg/day as a single daily dose and oral Ginkgo Biloba 120 mg/day in two divided doses.
- **GROUP B- CAROVERINE AND GINKGO BILOBA-** patients treated with oral Caroverine 40 mg/day in two divided doses and oral Ginkgo Biloba 120 mg/day in two divided doses.
- **FOLLOW UP-** Patients were followed up and evaluated on 0, 1, 2 and 3 month over a period of 3 months for S.Vitamin B12 level and S.Folic acid level and improvement of clinical symptoms in terms of tinnitus grading and tinnitus matching.

RESULTS:

Distribution of study population into oral 5-MTHF (Group A) and oral Caroverine (Group B) groups in the treatment of Sensorineural Tinnitus group are shown in Table 1 and Figure 1. Total 60 patients were included in the study, in which total 32 (53.33%) patients were in oral 5-MTHF group and 28 (46.67%) were in oral Caroverine group

Table 1: Distribution of study population into oral 5-MTHF and oral Caroverine group

Groups	Details	Numbers	Percentage
Group A	Oral 5- MTHF group	32	53.33
Group B	Oral Caroverine group	28	46.67
Total		60	100.00%

Distributions of study population according to the age are shown in Table 2. The distribution of study population according to the different age group was not statistically significant different in between groups. The mean age was also not statistically significantly different between groups.

Table 2: Distribution of study population according to different age in between groups

Age group	Group A (n=32)		Group B (n=28)		Total		Chi Sq.	¹ p value
	N	%	N	%	n	%		
≤20 years	3	9.38	2	7.14	5	8.33	3.78	0.437
21-30 years	9	28.13	9	32.14	18	30.00		
31-40 years	5	15.63	9	32.14	14	23.33		
41-50 years	5	15.63	4	14.29	9	15.00		

51-60 years	10	31.25	4	14.29	14	23.33		
Mean \pm SD	40.31 \pm 15.30		34.71 \pm 11.00		60	100	² p=0.114	

*Significant (p<0.05), ¹ Chi-square, ²t-test

Table 3 shows the comparison of mean tinnitus matching (in dB) in between group A and group B at Pre-Treatment and Post-Treatment (1 month, 2 month and 3 month) which was 42.50 \pm 11.77, 37.50 \pm 12.25, 34.69 \pm 11.57 and 32.97 \pm 12.30 in group A, respectively and 47.86 \pm 12.28, 40.89 \pm 13.48, 40.36 \pm 12.69 and 40.18 \pm 12.73 in group B, respectively. The mean tinnitus matching (in dB) was significantly lower in group A as compared to group B at 3rd month. Moreover, the mean tinnitus matching (in dB) was significantly decreased in group A from Pre-Treatment to 3 months.

Table 3: Comparisons of mean tinnitus matching (in dB) in between group A and group B at Pre-Treatment and Post-Treatment (1 month, 2 month and 3 month)

Mean tinnitus matching (in dB)	Group A (n=32)		Group B (n=28)		t-Test value	¹ p-value
	Mean	\pm SD	Mean	\pm SD		
Pre-Treatment	42.50	11.77	47.86	12.28	-1.72	0.09
1 month	37.50	12.25	40.89	13.48	-1.02	0.311
2 months	34.69	11.57	40.36	12.69	-1.81	0.075
3 months	32.97	12.30	40.18	12.73	-2.23	0.030*
p-Value	<0.011*		0.062			

*Significant (p<0.05), ¹t- test

Table 4 shows the changes of tinnitus grading from Pre-Treatment to 3 month in group A. At Pre-Treatment, 65.64% patients were having \geq Grade 3 tinnitus and 34.38% patients were having grade 2 tinnitus. After 1 month of treatment, 25% patients were having Grade 1 tinnitus i.e., patients having Grade 2 and Grade 3 tinnitus had become Grade 1 (from 0% to 25%) which increased to 28.13% and 37.50% after 2 month and 3 month of treatment respectively. Percentage of patients having \geq grade 3 decreased from 65.64% at Pre-Treatment to 40.64%, 25.01% and 25.01% after 1 month, 2 month and 3 month of treatment, respectively.

Table 4: Changes of Tinnitus Grading from Pre-Treatment to Post-Treatment(1 month, 2 month and 3 month) in group A

Group A (n=32)	Tinnitus Grading										p-Value
	1		2		3		4		5		
	N	%	N	%	N	%	N	%	N	%	
At Pre-Treatment	0	0.00	11	34.38	15	46.88	5	15.63	1	3.13	Ref.
At 1 month	8	25.00	11	34.38	9	28.13	3	9.38	1	3.13	0.040*
At 2 month	9	28.13	15	46.88	6	18.75	1	3.13	1	3.13	0.003*
At 3 month	12	37.50	12	37.50	6	18.75	1	3.13	1	3.13	0.001*

*Significant (p<0.05)

Table 5 shows the changes of tinnitus grading from Pre-Treatment to 3 months in group B. At Pre-Treatment, 64.29% of all patients were having \geq grade 3, after 1 month of treatment 57.14% of all patients belong to grade 2. After 2 month of treatment 53.57% of all patients belong to \geq grade 3 with only 39.29% belong to grade 2 and remaining same after 3 month of treatment.

Table 5: Changes of Tinnitus Grading from Pre-Treatment to Post-Treatment(1 month, 2 month and 3 month) in group B

Group B (n=28)	Tinnitus Grading										p-Value
	1		2		3		4		5		
	N	%	N	%	N	%	n	%	n	%	
At Pre-Treatment	0	0.00	5	17.86	18	64.29	4	14.29	1	3.57	Ref.
At 1 month	0	0.00	16	57.14	9	32.14	3	10.71	0	0.00	0.019*
At 2 month	0	0.00	11	39.29	15	53.57	2	7.14	0	0.00	0.242
At 3 month	0	0.00	11	39.29	15	53.57	2	7.14	0	0.00	0.242

*Significant (p<0.05)

DISCUSSION:

Tinnitus, or "ringing in the ears, " is one of the most frequent otolaryngology issues. The recognition that tinnitus is a phantom auditory perception and the importance of numerous brain structures and systems has resulted in significant progress in the study and treatment of tinnitus.

There is minimal evidence that surgical treatment for tinnitus is effective. Tinnitus retraining therapy has become one of the most popular tinnitus treatment options in many audiology offices. Noise generators and tinnitus maskers are behind-the-ear or in-the-ear devices that are worn to provide sound in a regulated manner to minimize or eliminate tinnitus perception. Cognitive re-structuring, or the disconnection of unpleasant emotions from tinnitus perception, and the adjustment of avoidance behavior caused by tinnitus are both part of psychotherapy. Pharmacotherapy, on the other hand, has remained the basis of tinnitus treatment.

In our present study, 60 selected patients suffering from Sensorineural Tinnitus were registered of which 32 patients were in Group A receiving oral 5-MTHF, Vitamin B12 and Gingko Biloba and 28 patients in Group B receiving oral Caroverine and Gingko Biloba. Most of the patients were in third decade of life (30.00%) followed by fourth (23.33%) and sixth decade of life (23.33%) and the age range of patients was from 18 years to 60 years. The relatively lower percentage of elderly people in this study i.e., 15.00% in the fifth decade and 23.33% in sixth decade of life as compared to 30% in third decade of life is not due to the lower prevalence of tinnitus in elderly, but due to lower turnover of elderly patients to health-care facilities to seek medical care due to the prevailing underlying socioeconomic conditions in the developing nations.

In our study, 61.66% of patients were less than 40 years of age whilst 38.34% were above 40 years but it does not correlate with that of **Coles et al (1984)³** who found tinnitus to be a

positive function of age in which 38% of patients were less than 40 years and the remaining 62% more than 40 years of age.

In our study, Serum Folate(ng/ml) and Serum Vitamin B12(pg/ml) levels was checked in all patients complaining of tinnitus and 60 patients were selected having Serum Folate <3 ng/ml and Serum Vitamin B12 <230 pg/ml. Before starting treatment serum level of Folate and Vitamin B12 was not statistically different between the two groups but after starting treatment significant improvement was seen in level of Serum Folate and Serum Vitamin B12 levels in patients receiving oral 5-MTHF, Vitamin B12 and Gingko Biloba in comparison to patients receiving oral Caroverine and Gingko Biloba. On comparing for monthly improvement between the two groups, statistically significant improvement($p<0.001$) was seen at the end of Serum Folate levels at 1 month, 2 month and 3 month of treatment of Group A. This result is in accordance with the study conducted by **Durga J et al (2007)**¹⁴ where folic acid supplementation increased Serum Folate concentrations by 573% in comparison to placebo group after 3 years of folic acid supplementation. While in case of Serum Vitamin B12 levels statistically significant improvement was seen at the end of 2 month($p<0.002$) and 3 months($p<0.001$) of treatment of Group A patients in comparison to Group B patients. As in Indian population majority of peoples are vegetarian and of lower socio-economic status, they are not able to receive adequate nutritional diet hence suffer from deficiency of essential vitamins and minerals. Due to this nutritional deficiency, peoples suffer from wide variety of diseases, most of patients coming to hospital for tinnitus large number of them had lower level of Serum Folate and Serum Vitamin B12. Poor auditory function was consistently associated with low concentrations of serum vitamin B-12 and red cell folate as in **Houston D et al (1999)**⁵ study while **Shemesh et al**¹⁵ suggested that inadequate vitamin B-12 may be associated with myelin damage in persons with repeated noise exposure.

Results from **Raquel Mart´mez-Vega et al (2014)**¹⁶ study confirm that insufficient folic acid intake induces severe impairment of cochlear homocystiene metabolism, along with a profound oxidative imbalance, ultimately leading to hearing loss. The positive correlation between hyperhomocysteinemia and hearing loss in folate deficiency also suggests the potential of the former as a prognostic value. In addition, targeting Homocystiene metabolism by nutritional intervention could be a novel pathway to achieve therapeutic protection against hearing loss and tinnitus.

No significant improvement was seen in level of Serum Folate and Serum Vitamin B12 in Group B patients receiving Caroverine.

In our study, patients were evaluated on basis of improvement of subjective symptoms (Tinnitus Grading) and psycho-acoustic measure (Tinnitus Matching). At pre-treatment level, 55% patients were having grade 3 tinnitus while 26.67% patients were having grade 2 tinnitus, 15% patients were having grade 4 tinnitus and no patient was having grade 1 tinnitus. After 1 month of treatment, in group A patients, percentage of patients having \leq grade 2 tinnitus increased to 59.38% from 34.38% at pre-treatment levels which was statistically significant($p<0.04$), similar result was seen for group B patients where 57.14% patients were having \leq grade 2 tinnitus from just having 17.86% patients at pre-treatment level which was statistically significant($p<0.019$). This result for Group B was quite similar to study conducted by **Prof. Klaus Ehrenberger et al**¹⁷, where single dose infusion of Caroverine in patients suffering from cochlear synaptic tinnitus, 63.3% responded to therapy immediately after the infusion and the value sustained at 1, 3 and 6 months. However, after

2nd and 3rd months of treatment, responses was obtained for group A patients, with percentage of patients having \leq grade 2 tinnitus increasing to 64.99% which was statistically significant ($p < 0.05$), however in case of Group B patients, tinnitus grading was not sustained in many patients with just 39.29% patients having grade 2 tinnitus which was not statistically significant ($p > 0.05$), this results is in contrast of **Prof. Klaus Ehrenberger et al**¹⁷ study where effects sustained on long term basis.

When mean tinnitus matching for Group A and Group B patients was compared after end of 1st month of treatment, mean tinnitus matching decreased in both group but this reduction in both groups was statistically insignificant. On further continuation of treatment, Group A patients mean tinnitus matching further reduced which was statistically significant ($p < 0.05$), however for Group B patients, the mean tinnitus matching didn't change much and changes were statistically insignificant ($p > 0.05$). Hence results from our study suggest that oral 5-MTHF, Vitamin B12 and Ginkgo Biloba showed improvement in reducing the tinnitus grading and mean tinnitus matching over pre-treatment values and the effects were sustained over time with continuation of therapy. Although Caroverine was found to be effective in reducing the tinnitus grading and mean tinnitus matching from the pre-treatment value but the effects didn't improve after the 2nd and 3rd month of therapy.

A comparison of reduction of tinnitus grading and mean tinnitus matching at the end of 12 weeks of treatment reveals that, 5-MTHF, Vitamin B12 and Ginkgo Biloba is more effective ($p < 0.05$) than Caroverine and Ginkgo Biloba in reducing the tinnitus grading and mean tinnitus matching.

Though studies conducted by **Durga J et al (2007)**¹⁴, **Berkiten G et al (2013)**¹⁸ and **Singh C et al (2016)**¹⁹ showed no significant improvement in tinnitus matching and subjective symptoms but association of 5-MTHF and Vitamin B12 with tinnitus was seen.

From the present study we conclude that 5-MTHF, Vitamin B12 and Ginkgo Biloba is effective in controlling the symptoms of tinnitus along with improvement in mean Serum Folate and mean Serum Vitamin B12 level and the response increases with continuation of therapy for three consecutive months.

The unique feature of the present study is that it strives to compare the efficacy of combination of oral formulation of 5-MTHF, Vitamin B12 and Ginkgo Biloba and combination of oral formulation of Caroverine and Ginkgo Biloba to cure Sensorineural tinnitus. An extensive internet search yielded no results regarding a comparative study of the efficacy of combination of oral formulations of these drugs.

However, it is prudent to continue the same study and observe patients for symptom free period after cessation of treatment to ascertain whether the symptoms of Sensorineural tinnitus are completely abolished or not.

CONCLUSION:

- With Caroverine and Ginkgo Biloba, subjective symptoms and mean tinnitus matching showed improvement from Pre-Treatment level of 47.86 ± 12.28 dB to 40.89 ± 13.48 dB after 1st month of therapy but remain constant over time (40.36 ± 12.69 dB and 40.18 ± 12.73 dB at the end of 2nd and 3rd month of treatment) whereas with 5-MTHF, Vitamin B12 and Ginkgo Biloba, subjective symptoms and mean tinnitus matching showed improvement from Pre-Treatment level of 42.41 ± 11.77 dB to 37.50 ± 12.25 dB after 1st month of therapy and kept improving over time(34.69 ± 11.57 dB and

- 32.97±12.30 dB at the end of 2nd and 3rd month of treatment).
- With 5-MTHF, vitamin B12 and Gingko Biloba, mean serum folate level shows a significant improvement ($p < 0.05$) after the end of treatment compared to caroverine and Gingko Biloba.
 - With 5-MTHF, vitamin b12 and Gingko Biloba, mean serum vitamin b 12 level shows an insignificant improvement ($p > 0.05$) during the 1st month of treatment but shows significant improvement ($p < 0.05$) during 2nd and 3rd month of treatment compared to caroverine and Gingko Biloba.
 - At the end of 1st month of therapy, caroverine and Gingko Biloba was found to be more effective than 5-MTHF, vitamin b12 and Gingko Biloba in improving mean tinnitus matching but was found to be statistically insignificant ($p > 0.05$) however at the end of 2nd and 3rd month of therapy, oral formulation of 5-MTHF, vitamin b12 and Gingko Biloba was found to be statistically significant ($p < 0.05$) in improving mean tinnitus matching.
 - However the patients could not be followed over a further period of time to observe the long term benefit of the drugs after cessation of therapy and is accepted as a limitation of the present study.

CONFLICT OF INTEREST: Nil

REFERENCES

1. Jasterboff PJ. Phantom auditory perception (tinnitus): Mechanism of generation and perception. *Neuroscience Research*. Aug 1990; 8: 221-54.
2. Roberts J. Hearing status and ear examination. Findings among adults. United States-1960-1962. *Vital Health Stat 11*. Nov 1968;(32):1-28.
3. Coles RR. Epidemiology of tinnitus: (1) Prevalence. *Journal of Laryngology and Otology Supplement*. Jan 1984; 9: 7-15.
4. Kelly GS. Folates: supplemental forms and therapeutic applications. *Alternative medicine review : a journal of clinical therapeutic*. Jun 1998;3(3):208- 220.
5. Houston DK, Johnson MA, Nozza RJ, Gunter EW, Shea KJ, Cutler GM, Edmonds JT. Age-related hearing loss, vitamin B-12, and folate in elderly women. *The American journal of clinical nutrition*. Mar 1999;69(3):564-571.
6. Selhub J, Jacques PF, Wilson PWF, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *The Journal of American Medical Association* Dec 1993;270:2693-8.
7. Wall RT, Harlan JM, Harker LA, Striker GE. Homocysteine-induced endothelial cell injury in vitro: a model for the study of vascular injury. *Thrombosis research*. Apr 1980;18(1-2):113-121.
8. Bottiglieri T. Folate, vitamin B12, and neuropsychiatric disorders. *Nutrition reviews*. Dec 1996;54(12):382-390.
9. Schatz RA, Wilens TE, Sellinger OZ. Decreased in vivo protein and phospholipid methylation after in vivo elevation of brain S-adenosyl-homocysteine. *Biochemical and biophysical research communications*. Feb 1981;98(4):1097-107.
10. Ehrenberger K, Felix D. Caroverine depresses the activity of cochlear glutamate receptors in guinea pigs: in vivo model for drug-induced neuroprotection?. *Neuropharmacology*. Dec 1992;31(12):1259-1263.
11. Honoré T, Davies SN, Drejer J, et al. Quinoxalinediones: potent competitive non-NMDA glutamate receptor antagonists. *Science*. Aug 1988;241(4866):701-703.

12. Harris KM, Miller RJ. CNQX (6-cyano-7-nitroquinoxaline-2, 3-dione) antagonizes NMDA-evoked [3H]GABA release from cultured cortical neurons via an inhibitory action at the strychnine-insensitive glycine site. *Brain Research*. Jun 1989;489(1):185-189.
13. Sani MRM, Chaleshtori MH, Asadi-Samani M, Yang Q. Ginkgo biloba in the treatment of tinnitus: An updated literature review. *International Tinnitus Journal*. Jun 2017; 21(1): 58-62.
14. Durga, J., Verhoef, P., Anteunis, L. J., Schouten, E., and Kok, F. J. (2007) Effects of folic acid supplementation on hearing in older adults: a randomized, controlled trial. *Ann. Intern. Med.* 146, 1–9.
15. Shemesh Z, Attias J, Ornan M, Shapira N, Shahar A. Vitamin B12 deficiency in patients with chronic-tinnitus and noise-induced hearing loss. *American Journal of Otolaryngology*. March-April 1993;14(2): 94-99.
16. Martínez-Vega R, Garrido F, Partearroyo T, et al. Folic acid deficiency induces premature hearing loss through mechanisms involving cochlear oxidative stress and impairment of homocysteine metabolism. *The Federation of American Societies for Experimental Biology*. Feb 2015;29: 418-32.
17. Denk DM, Heinzl H, Franz P, Ehrenberger K. Caroverine in tinnitus treatment. A placebo-controlled blind study. *Acta Oto-laryngologica*. Jan 1997;117:825-30.
18. Berkiten G, Yildirim G, Topaloglu I, Ugras H. Vitamin B12 levels in patients with tinnitus and effectiveness of vitamin B12 treatment on hearing threshold and tinnitus. *B-ENT*. Jan 2013;9(2):111-116.
19. Singh C, Kawatra R, Gupta J, Awasthi V, Dungana H. Therapeutic role of Vitamin B12 in patients of chronic tinnitus: A pilot study. *Noise Health*. Mar2016;18(81):93-97.