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ROLE OF NATURAL SUBSTANCES AND VITAMIN SUPPLEMENTATION IN TINNITUS PREVENTION AND TREATMENT

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Review

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ABSTRACT

The aim of this review is to refer a possibility of using natural substances for treating or reducing the symptoms of tinnitus. Tinnitus is a sensation of sound without an external source. It often manifests as a ringing in the ears, but it may also sound like a buzzing, hissing, whistling or even roaring in the head. Tinnitus is a symptom of an underlying condition. It can be linked to hearing loss, stress, ear damage, blood pressure, tumours and atherosclerosis. Exposure to loud noise is one major cause of tinnitus, since it wears down the delicate hair cells in inner ear that translate sounds into nerve impulses. Potential therapy of tinnitus is a pharmacological treatments. Fortunately, there are many effective natural alternatives to drugs that can bring considerable relief and help cope. The potential form of treatment is vitamins and natural flavonoids therapy. Low levels of melatonin and vitamin B12 in body have a significant correlation with the development of tinnitus. It was reported that melatonin is useful in the treatment of tinnitus, even in cases associated with sleep disturbance. There are relationship between vitamin B12 deficiency and dysfunction of the auditory pathway. Antioxidants are another substances which have a promising effect in the treatments of tinnitus. The constituents of *G. biloba* are potent scavengers of free radicals and has been prescribed their positive effect on treat of central nervous system disorders and cognitive deficits. Positive antioxidant effects have vitamin C, hesparidin and diosmin also.

Keywords: Tinnitus, vitamins, antioxidants, bioflavonoids, natural substances

INTRODUCTION

Tinnitus

Tinnitus is defined as the perception of sound in the absence of external auditory stimulation **(Hoekstra, 2013)**. Although the experience of short bursts of noise is almost universal, tinnitus is typically defined as noise that lasts at least 5 minutes **(Davis, 1995)**.This is the most common statement among researchers in audiology and related fields, stemming from basic neurosciences **(Kaltenbach, 2011)** to applied psychophysiology **(Kropp *et al.*, 2012)**, audiology **(Caffier *et al.*, 2006)**, and behavioural psychology **(Westin *et al.*, 2008)**. Among severe sufferers, tinnitus causes disability associated with concentration deficits, insomnia, hypersensitivity to sounds, anxiety and depression. Often a combination of several complaints leads to a diminished quality of life **(Erlandsson and Hallberg, 2000; Bauch *et al.*, 2003)**. It poses a significant clinical problem for millions of people and is proportionally problematic in countries where epidemiological data have been reported **(Henry *et al.*, 2005; Erlandsson and Dauman, 2013).**

The overall prevalence of tinnitus in adult populations ranges from 7 % to 19 %. The prevalence of tinnitus increases with age and seems to attain a plateau or even decrease at around 60–80 years **(Henry *et al.*, 2005)**. Within the group of treatment-seeking patients, the male-female ratio is 2:1. In up to 5% of the adult population, tinnitus interferes negatively with the ability to lead a normal daily life, and in 2%, it has a severe effect on daily life **(Nondahl *et al.*, 2002)**. The most common additional complaints are sleep problems, depression and anxiety **(Zoger *et al.*, 2006)**. Patients report limitations in activity and restrictions to participation in work and employment, and in social and civic life **(Tyler and Baker, 1983)**. The distress can become so intense as to drive patients to suicide **(Pridmore *et al.*, 2012)**.

Hearing loss is presumably the most important risk factor for tinnitus, but the association is complex. Tinnitus is reported in individuals with apparently normal hearing, and only some hearing-impaired persons report tinnitus **(Aarhus *et al.*, 2015, Tyler, 2006)**.

For those whose tinnitus has significant clinical impact, a number of therapeutic approaches have been described and employed, from cognitive-behavioral therapies and sound enrichment, to drug approaches. Some studies have shown favorable results, while others did not result in benefits **(Baguley *et al.*, 2013)**.

Treatments proffered for tinnitus can be grouped into four main classes: pharmacological, acoustic–physical, psychological, and some combination of elements from at least two of these three. Pharmacological and physical treatments principally aim to affect the tinnitus itself, ideally to eliminate it or reduce its prominence to the point that it is no longer troublesome **(Noble, 2008)**.Various substances have been used and tested as drug treatments. Among them, antioxidants have appeared promising **(Polanski *et al.*, 2016)**. Oxidative stress is a consequence of the inefficient utilization of molecular oxygen (O_2) by cells **(Reiter *et al.*, 2004)**. ROS including the superoxide anion radical (O_2•−) and hydroxyl radical (•OH), hydrogen peroxide (H_2O_2), and singlet oxygen (IO_2) are generated as by-products of cellular respiration and other metabolic processes. They damage cellular macromolecules including DNA, proteins, and lipids **(Kozina *et al.*, 2007)**. Additionally, however, there are also highly devastating agents which are nitrogen based e.g. nitric oxide (NO•) and especially the peroxynitrite anion (ONOO−) **(Tengattini *et al.*, 2008)**. Oxidative stress is thought to play an important role in atherosclerotic vascular disease. Thus, dietary antioxidants such as ascorbate (vitamin C) can protect against the development and progression of atherosclerosis in experimental models. Numerous observational studies have shown an inverse association between antioxidant intake of body status and the risk of cardiovascular diseases **(Cares *et al.*, 2000)**. Antioxidant vitamins may reduce risks of cardiovascular disease has been the subject of considerable research attention in recent years. Basic research studies have provided evidence of possible mechanisms for an effect of antioxidants on atherosclerosis, and several observational epidemiologic studies have suggested that risk of coronary heart disease (CHD) may be 20 – 40 % lower among those with high dietary intake or serum levels of antioxidant

vitamins. CHD remains the leading cause of death in the United States, as well as most developed countries, accounting for approximately one of every four deaths. For this reason, even the modest reductions in CHD risk suggested by studies to date, if real, could yield substantial public health benefits. Due to the changing environment including a lot of noise pollution is very important **(Ayepola *et al.*, 2014)**. Hearing protection is very important as the hearing right after eyesight is one of the most important senses. Numerous neurological, vascular and other somatic disorders have been linked to the development of the tinnitus. Therefore no single treatment will be effective for treating all tinnitus patients **(Loockwood *et al.*, 2002)**. It was reported that the several natural substances have a potential benefit effect on the cause of this disorders.

Effects of selected natural substances at the cell level

Melatonin

Melatonin is an evolutionally phylogenic old molecule, which can be traced back to the ancient photosynthetic prokaryotes. It is a tryptophan derivative that was first isolated from bovine pineal glands **(Lerner *et al.*, 1958)**. Melatonin was later found to be also present or synthesized in extrapineal tissues such as retina, Harderian gland, gastrointestinal tract, testes and lymphocytes **(Reiter *et al.*, 2013)**. Melatonin is a functionally diverse molecule **(Reiter *et al.*, 2010)**, its originally described mission was the regulation of circadian and circannual cycles **(Marczynski *et al.*, 1964; Reiter, 1991, 1993; Zhang and Zhang, 2014)**. This molecule, acting through the melatonin receptor, seems to affect sleep, mood, sexual maturation and reproduction, immune function, aging and the antioxidative defense system. Clinical research has explored several influences that melatonin could exert on a wide range of disorders, symptoms and pathologies **(Altun *et al.*, 2007, Lanfumey *et al.*, 2013)**. A clinical study conducted on healthy volunteers revealed that low plasma melatonin concentrations may significantly correlate with the development of subjective idiopathic tinnitus **(Lasisi *et al.*, 2012).** Melatonin is thought to produce therapeutic effects through different mechanisms such as antioxidant and free radical scavenger activities. Furthermore, melatonin appears to interfere with the peripheral and central autonomic systems, with a subsequent decrease in tone of the adrenergic system and increase in cholinergic activity **(Simko *et al.*, 2010)**. Melatonin exerts advantageous vascular changes that improve labyrinth perfusion, thus protecting the inner ear from hypoxia. Melatonin can reduce muscular tone, and it may relieve tensor tympani muscle spasms, thus improving symptoms. In addition to relieving tinnitus, melatonin improves sleep quality **(Hurtuk et at., 2011; Miroddi *et al.*, 2015; Pinpdda *et al.*, 2010).**

Melatonin, dubbed the hormone of darkness, is known to regulate a wide variety of physiological processes in mammals. **Dubocovich and Markowska (2005)** describes well-defined functional responses mediated through activation of high-affinity MT_1 and MT_2 protein coupled receptors viewed as potential targets for drug discovery. MT_1 melatonin receptors modulate neuronal firing, arterial vasoconstriction, cell proliferation in cancer cells, and reproductive and metabolic functions. Activation of MT_2 melatonin receptors phase shift circadian rhythms of neuronal firing in the suprachiasmatic nucleus (SCN), inhibit dopamine release in retina, induce vasodilation and inhibition of leukocyte rolling in arterial beds, and enhance immune responses. The melatonin-mediated responses elicited by activation of MT_1 and MT_2 native melatonin receptors are dependent on circadian time, duration and mode of exposure to endogenous or exogenous melatonin, and functional receptor sensitivity. Together, these studies underscore the importance of carefully linking each melatonin receptor type to specific functional responses in target tissues to facilitate the design and development of novel therapeutic agent **(Dubocovich and Markowska, 2005)**.

In humans, expression of the MT1-receptor subtype in the SCN was first shown by Weaver and Reppert 1996. Transcripts for the MT2-receptor were not detected in humans but in mice (**Dubocovich *et al.*, 1998)**. The role of melatonin in the SCN has been described in several rodent studies and may be also valid for humans. The general opinion is that melatonin is an endogenous synchronizer **(Cajochen *et al.*, 2003)**. It provides the SCN with the information about the night and timed secretion of melatonin adjusts to the light/dark cycle. In rats it is able to stabilize circadian rhythms, reinforce them and maintain their mutual phase relationship. Furthermore, melatonin entrains free running activities in rodents **(Korf *et al.*, 2003)**. The mechanisms behind these effects are an inhibiting of neuronal firing, which might be important for defining SCN sensitivity to entraining stimuli. In humans this might contribute to the regulation of sleep. **Ekmekcioglu *et al.* (2003)** identified MT1 and MT2 receptors in human coronary arteries from pathological samples and also from healthy controls. Furthermore, **Ekmekcioglu *et al.* (2001a)** presented preliminary evidence for a circadian variation of the MT1-receptor in coronary arteries. The role of melatonin in human coronary arteries needs to be evaluated. **Ekmekcioglu *et al.* (2003)** and **Ekmekcioglu *et al.* (2001b)** showed that both types of MT-receptors are present in the human aorta. **Monroe and Watts, (1998)** assume that melatonin has vasodilatory effects, since studies in aortic rings from rat and rabbits showed that melatonin induces vasodilatation.

Melatonin, the main hormone produced by the pineal gland, displays a circadian rhythm peaking at night **(Arendt, 1995)**. Pinealocytes uses tryptophan as substrate for melatonin synthesis, and melatonin levels change as a function of tryptophan availability **(Yaga *et al.*, 1993)**. Pyridoxine is converted to its active coenzyme form, pyridoxal phosphate (PLP). More than 60 PLP-dependent enzymes are known, including enzymes that participate in decarboxylation reactions such as the decarboxylation of DOPA to dopamine and 5-hydroxytryptophan to serotonin **(Abou-Saif and Lipman, 2001, Salzmann *et al.*, 2000)**. The activity of pyridoxine as a coenzyme in the tryptophan metabolism was described in the kinurenine and methoxyindole pathways. Pyridoxine acts as a coenzyme of 5-hydroxytryptophan decarboxylase. The enzyme carboxylates 5-hydroxytryptophan to serotonin, the immediate precursor of melatonin. The effect of pyridoxine on aromatic amino acid decarboxylase activity supports a regulatory role of pyridoxine on the synthesis of neurotransmitters **(Dolina *et al.*,1993, Geng *et al.*, 1995)**. Melatonin was shown to increase brain pyridoxal phosphokinase activity, inhibition of glutaminergic neurotransmission, resulting in inhibitory effects on central nervous system activity **(Acuna-Castroviejo *et al.*, 1986 Luboshitzky *et al.*, 2002)**.

In study **Lasisi *et al.* (2012)**, the main finding is that low plasma melatonin and vitamin B12 have significant correlation with the development of tinnitus among the elderly. Melatonin is a neurohormone produced centrally by the pineal gland; it regulates the sleep-wake cycle by inducing sleepiness and reducing body temperature through its effects on the circadian clock **(Megwalu *et al.*, 2006; Saunders, 2007)**. Several researchers have reported that melatonin is useful in the treatment of tinnitus, even in cases associated with sleep disturbance **(Megwalu *et al.*, 2006; Simko and Paulis, 2007)**.

***Ginkgo biloba* L.**

Ginkgo biloba L., also popularly known as living fossil, possesses a variety of biological and pharmacological activities **(Singh *et al.*, 2008)**. The 2 main pharmacologically active groups of compounds present in the *Ginkgo* leaf extract are the flavonoids and the terpenoids **(Smith and Luo, 2004)**. Flavonoids, also called phenylbenzopyrones or phenylchromones, are a group of low molecular weight substances that are widely spread in the plant kingdom. Flavonoids present in the *Ginkgo* leaf extract are flavones, flavonols, tannins, biflavones (amentoflavone, bilobetol, 5-methoxybilobetol, ginkgetin, isoginkgetin and sciadopitysin), and associated glycosides of quercitin and kaempferol attached to 3-rhamnosides, 3-rutinosides, or p-coumaric esters **(McKenna *et al.*, 2000)**. These compounds are known to act mainly as antioxidants/free radical scavengers, enzyme inhibitors, and cation chelators **(DeFeudis and Drieu, 2000)**. Two types of terpenoids are present in *Ginkgo* as lactones (nonsaponifiable lipids present as cyclic esters): ginkgolides and the bilobalide **(Mahadevan and Park, 2008; Smith and Luo, 2004)**.

The extracts of the leaves of *Ginkgo biloba* have been found to possess cardioprotective, antiasthmatic, antidiabetic, hepatoprotective and potent CNS activities **(Liebgott *et al.*, 2000; Naik and Panda, 2007)**.

The constituents of *G. biloba* are potent scavengers of free radicals **(Naik *et al.*, 2006; Pietri *et al.*, 1997)**. By scavenging free radicals and ROS, *G. biloba* inhibits lipid peroxidation and augments levels of endogenous antioxidants. Literature reports extensive work on the cardioprotective activity of *Ginkgo biloba* extracts (EGb). Most studies have shown EGb to improve the recovery of post ischemic cardiac function (coronary flow, aortic flow, LVdP and its first derivative) in the ischemic reperfused myocardium **(Bao *et al.*, 2008; Clostre, 2001)**.

It has been demonstrated that EGb protects the heart by its antioxidant properties and its ability to adjust fibrinolytic activity **(Panda and Naik, 2014)** In study **Haramaki *et al.* (1994)**. EGb diminished the decrease of myocardial ascorbate content after 40 minutes of ischemia and 20 minutes of reperfusion and also suppressed the increase of dehydroascorbat.

Clinically, it has been prescribed to treat CNS disorders such as Alzheimer's disease and cognitive deficits. It exerts allergy and changes in bleeding time. While its mutagenicity or carcinogenic activity has not been reported, its components, quercetin, kaempferol and rutin have been shown to be genotoxic. There are no standards or guidelines regulating the constituent components of *Ginkgo biloba* leave extract nor are exposure limits imposed **(Chan *et al.*, 2007)**.

The standardized *Ginkgo biloba* extract (EGb 761) is recommended for the treatment of geriatric memory disorders including vascular and neurodegenerative dementia. Its use is steadily increasing around the world **(Alber Kader *et al.*, 2007)**. Clinical efficacy in cognitive decline and dementia has been confirmed by a series of randomized, double-blind, placebo-controlled clinical trials **(Beck *et al.*, 2016; Gauthier and Schlaefke, 2014; Janssen *et al.*, 2010; Weinmann *et al.*, 2010; Tan *et al.*, 2015)**. Improved microcirculation, enhanced neuroplasticity and support of mitochondrial energy production have been discussed as underlying mechanisms of action **(Spieß *et al.*, 2014)**. However, these suggested modes of action are mainly based on animal and in-vitro-data and have not been verified in human **(Beck *et al.*, 2016)**.

Hesperidin

Fortunately, organisms are endowed with a series of agents that can either directly detoxify radicals or their associated reactants (free radical scavengers) or

they metabolize them to innocuous molecules (antioxidative enzymes) **(Kozina *et al.*, 2007; Tengattini *et al.*, 2008)**.

Hesperidin is a naturally occurring flavonoide that exists in citrus and other plants and can be isolated in large amounts from the peels of *Citrus aurantium* (bitter orange), *Citrus sinensis* (sweet orange), and *Citrus unshiu* (satsuma mandarin) **(Crozier *et al.*, 2009)**. Hesperidin is reported to exert a wide range of pharmacological effects such as antioxidant, anti-inflammatory, anti hypercholesterolemic and anticarcinogenic properties **(Chen *et al.*, 2010)**. It has also been demonstrated that hesperidin can protect neurons against various types of insults associated with many neurodegenerative diseases **(Cho, 2006)**. In study **Tamilselvam *et al.* (2013)** investigated the neuroprotective effect of hesperidin on rotenone-induced cellular model for Parkinson disease by analysing its effect on rotenonemediated oxidative stress generation, mitochondrial dysfunction and apoptosis in human neuroblastoma SK-N-SH cells. Their data suggests that hesperidin exerts neuroprotective effect against rotenone due to its antioxidant effect, maintenance of mitochondrial function, and antiapoptotic properties in a neuroblastoma cell line.

Phytochemicals, particularly antioxidants from natural sources such as fruits, vegetables and herbs have gained popularity due to their protective properties against several chronic diseases such as cancer and cardiovascular diseases **(Temple, 2000)**. Among the natural compounds extracted from plants, polyphenols have received much attention due to their powerful antioxidant,antimicrobial and antiviral activities as well as their capacity to inhibit the proliferation of cancer cells, protect neuron against oxidative stress, stimulate vasodilation, reduce vascularization and improve insulin secretion **(Del Rio *et al.*, 2010)**. Polyphenols are adiverse class of chemical compounds that share the ability to act as chain breaking antioxidants, which are proposed to protect against the damage caused by free radicals to DNA cell membrane and cell components **(Dziri *et al.*, 2012)**. Moreover, they exhibit antibacterial, antiinflammatory, antiallergenic, antiarthrogenic and antithrombotic effects **(Ajila *et al.*, 2010)**. Recent research on the nutritional aspects have shown that polyphenols are able to modulate nutrient availability through the inhibition of digestive enzymes involved in lipid and starch break down, which could lead to beneficial effects on calorie intake, obesity, and bloodglucose **(McDougall *et al.*, 2009, Nagella *et al.*, 2014)**.

Hesperidin exerts protective action in cardiac tissue by its antihypertensive and antioxidant properties **(Wilmsen *et al.*, 2005)**. Some reports evidenced that hesperidin targets peroxisome proliferator-activated receptor-gamma (PPAR-γ) to exert biological actions **(Salam *et al.*, 2008)**. PPAR-γ being a member of the ligand-dependent nuclear receptor category regulates glucose, lipid and energy homeostasis **(Hihi *et al.*, 2002; VandenHeuvel, 1999)**. In addition, PPAR-γ regulates cellular proliferation and differentiation inducing apoptosis in a wide spectrum of human tumor cell lines **(Ondrey, 2009; VandenHeuvel, 1999)**. Flavonoids like hesperidin are reported to possess satisfactory capability to neutralize free radicals. This antioxidant property may be related to their pharmacological actions and they may be used as protective agents in a number of cardiac diseases **(Agrawal *et al.*, 2014)**.

Diosmin

The second natural bioflavonoids is diosmin (3′,5,7-trihydroxy-4′-methoxyflavone) which is is the aglycone of the flavonoid glycoside diosmin (3′,5,7-trihydroxy-4′-methoxyflavone-7-ramnoglucoside). Diosmin is hydrolyzed by enzymes of intestinal microflora before absorption of its aglycone diosmetin. Diosmin is abundant in the pericarp of various citrus **(Campanero *et al.*, 2010; Del Bano *et al.*, 2004; Nogata *et al.*, 2006)** and is considered a vascular-protecting agent in the treatment of hemorrhoids, lymphedema, varicose veins and different types of cancer **(Camarda *et al.*, 2007; Cesarone *et al.*, 2006; Le Marchand *et al.*, 2000)**. As a flavonoid, it also possesses a multitude of biological activities including anti-inflammatory and antioxidant properties **(Jean and Bodinier, 1994; Guillot *et al.*, 1998)**. However, its anti-inflammatory and protective mechanisms on PC12 cells, a model of phenotypic neuronal cells, have not been studied to date **(Milano *et al.*, 2014)**.

Diosmin is a natural flavone glycoside which can be obtained by dehydrogenation of the corresponding flavanone glycoside, hesperidin that is abundant in the pericarp of various citrus fruits **(Campanero *et al.*, 2010)**. Diosmin treatment of streptozotocin-nicotinamide induced diabetic rats, ameliorated oxidative stress in plasma and tissues as evidenced by improved glycemic and antioxidant status along with decreased lipid peroxidation **(Srinivasan and Pari, 2012)**. Experimental evidence showed the potential of rutin, a flavonol to delay glomerulosclerosis of diabetic nephropathy (DN) due to its ability to inhibit cell hypertrophy and the accumulation of ECM mediated by TGF- β1/Smads and ROS signals in mesangial cells cultured by high glucose **(Tang *et al.*, 2011)**.

***Ruscus aculeatus* L.**

Ruscus aculeatus L. (butcher's broom), belonging to the family of Liliaceae, appears in a great number of dietary supplement patents **(Engl, 2006; Rizza *et al.*, 2011)** present in literature, referring *R. aculeatus* rhizomes extract as an active ingredient to enhance microcirculation. Indeed, *R. aculeatus* preparations are widely distributed in Europe, and have been hardly used for more than 40 years to treat chronic venous insufficiency and vasculitis **(Bouskela *et al.*, 1994; Capra, 1972; Huang *et al.*, 2008)**. Therefore, oral supplementation with *R. aculeatus* extracts may prevent time-consuming, painful, and expensive complications of varicose veins and other venous insufficiency, representing an alternative to traditional treatments which require a high degree of patient compliance to be effective **(MacKay, 2001)**. While anthocyanins are the main compounds of *R. aculeatus* skin berries **(Longo and Vasapollo, 2005)**, steroidal saponins represent the main class of chemical compounds isolated from rhizomes and roots of *R. aculeatus* and are considered to be the active compounds of *R. aculeatus* commercial products **(de Combarieu *et al.*, 2002; Mimaki *et al.*, 1998a)**. *R. aculeatus* saponins are characterized by spirostanol or furostanol aglycones, bearing a sugar chain at C-1 or at C-3 **(de Combarieu *et al.*, 2002; Kite *et al.*, 2007; Mimaki *et al.*, 1999)**. In particular, a mixture of two spirostane aglycons, neoruscogenin and its (25*R*)-Δ25,27 dihydro derivate ruscogenin, is considered the active ingredient of some *R. aculeatus* commercial drugs **(de Combarieu *et al.*, 2002)**.

L- ascorbic acid - Vitamin C

Vitamin C or ascorbic acid is a water-soluble vitamin, critical for collagen and L-carnitine biosynthesis, for the conversion of dopamine to norepinephrine; it also improves iron absorption. Under physiological conditions,this vitamin also acts as a potent antioxidant **(Li and Schellhorn, 2007)**. Papaverine hydrochloride is a synthetic alkaloid that exerts a tissue protective effect correlated to antioxidants, because this substance promotes non-specific smooth muscle relaxation,leading to vasodilation **(Mathis *et al.*, 1997)**. Antioxidants act synergistically with other agents or in isolation, functioning in different ways, protecting cell membranes and also eliminating oxygen free radicals **(Polanski *et al.*, 2015; Seidman, 2000)**.

The beneficial effects of vitamin C supplementation in humans are controversial. A study reported that vitamin C may improve glycemic control, lowering both fasting blood glucose and glycated haemoglobin (HbA1c) **(Eriksson and Kohvakk, 1995)**. Chronic oral administration of vitamin C to patients with type 2 diabetes causes a decline in plasma free radicals that is associated with improved whole body glucose disposal **(Mullan et a., 2002; Paolisso *et al.*, 1995)** and improved endothelial function **(Regensteiner *et al.*, 2003)**. Recently, another study reported a reduction in the malondialdehyde (MDA) level, a major product of oxidative damage in both fasting and postprandial states of type 2 diabetic patients after vitamin C (1000 mg day-1) supplementation for 6 weeks although no effect was observed on lipid profiles **(Mazloom *et al.*, 2011)**. Some studies have indicated that the intra-arterial infusion of vitamin C restores endothelium-dependent vasodilation in patients with type 1 or type 2 diabetes **(Timimi *et al.*, 1998; Ting *et al.*, 1996)** suggesting that hyperglycemia-induced oxidative stress mediates endothelial dysfunction in diabetic patients **(Ayepola *et al.*, 2014)**.

B Vitamins

Except the typical antioxidants for the proper functioning of the nervous and vascular system in the body are also important B-group vitamins. Maintaining the proper functioning of the nervous system is very important because it affects the function of other systems. The nervous system, is responsible for sensing the internal and external environmental stimulus and as well as coordinating muscles and organs activities. Thiamine (Vitamin B1) is a coenzyme in the pentose phosphate pathway, which is a necessary step in the synthesis of fatty acids, steroids, nucleic acids and the aromatic amino acid precursors to a range of neurotransmitters and other bioactive compounds essential for brain function **(Kerns *et al.*, 2015)**. Thiamine playsa neuromodulatory role in the acetylcholine neurotransmitter system, distinct from its actions as a cofactor during metabolic processes **(Hirsch and Parrott, 2012)** and contributes to the structure and function of cellular membranes, including neurons and neuroglia **(Ba, 2008)**.

The two flavoprotein coenzymes derived from riboflavin, FMN and FAD are crucial rate limiting factors in most cellular enzymatic processes. As an example, they are crucial for the synthesis, conversion and recycling of niacin, folate and vitamin B6, and for the synthesis of all hemo proteins, including hemeglobin, nitric oxide synthases, P450 enzymes, and proteins involved in electron transfer and oxygen transport and storage **(Rivlin, 2007)**. The flavoproteins are also co-factors in the metabolism of essential fatty acids in brain lipids **(Sinigaglia-Coimbra, 2011)** the absorption and utilisation of iron **(Mushtaq, 2011)** and the regulation of thyroid hormones **(Rivlin, 2007)**. Dysregulation of any of these processes by riboflavin deficiency would be associated with its own broad negative consequences for brain function. Riboflavin derivatives also have direct antioxidant properties and increase endogenous antioxidant status as essential cofactors in the glutathione redox cycle **(Ashoori and Saedisomeolia, 2014)**.

Vitamin B6 sufficiency is required for optimal health. This is due to the participation in many different biochemical reactions. Vitamin B6 and its derivatives are needed, especially for coenzyme functions in main metabolic pathways in the human body. For that reason, it is clear that a vitamin B6 deficiency, even in mild forms, has effects on the human metabolism. Several

diseases and impairments of health are connected to the wide variety of B6 functions in suboptimal status. This can also be worsened through ageing **(Spinneker *et al.*, 2007)**.Vitamin B6 has an important role in the process of melatonin biosynthesis. Journal of Gergion Med News reported the study on the 30 laboratory white rats which were divided into two groups - experimental and control groups. The animals in the first group were treated with vitamin B6 injection. Every other day at 22 00, melatonin concentration was defined by means of ELISA. The experiment has lasted for two months. At the end of the experiment, the plasma level of melatonin increased by 35,95% in the first group of animals in comparison with the second control group. It is found that, B6 vitamin injections strengthens melatonin biosynthesis; consequently strengthening of melatonin biosynthesis influences positive therapeutic effects. One of the reasons for pathological processes, developed in organism on the background of B6 vitamin deficiency, is reduction of endogen melatonin production **(No authors listed, 2007)**.

Vitamin B12 is a largest known biomolecule and the only nutrient with a stable carbon-metal bond. One molecule of cobalt lies at the centre of each B12 molecule. Isolated B12 is a crystalline compound with a bright red colour, due to the presence of cobalt. Vitamin B12 works with folic acid in many body processes including synthesis of DNA, red blood cells and the insulation sheath (myelin sheath) that surrounds nerve cells and facilitates the conduction of signals in the nervous system. Severe depletion manifests as pernicious anaemia which was invariably fatal until the discovery of B12 in liver. But long before anaemia sets in, other conditions may manifest, most often neurological problems (numbness, pins and needles sensations a burning feeling in the feet, sharing muscle fatigue, sleep disorders, memory loss, irrational anger, impaired mental function and Alzheimers or psychological conditions (dementia, depression, psychosis and obsessive-compulsive behaviour) **(Fallon, 1987; Singh and Sachan, 2011)**. There are many reasons for reviewing the neurology of vitamin-B12 and folic-acid deficiencies together, including the intimate relation between the metabolism of these two vitamins, their morphologically indistinguishable megaloblastic anaemias, and their overlapping neuropsychiatric syndromes and neuropathology, including their related inborn errors of metabolism. Folates and vitamin B12 have fundamental roles in CNS function at all ages, especially the methionine-synthase mediated conversion of homocysteine to methionine, which is essential for nucleotide synthesis and genomic and non-genomic methylation. Folic acid and vitamin B12 may have roles in the prevention of disorders of CNS development, mood disorders, and dementias, including Alzheimer's disease and vascular dementia in elderly people. Vitamin-B12 and folic-acid deficiency and related inborn errors of metabolism may result in similar megaloblastic anaemias and overlapping neuropsychiatric complications. In the early stages there is often dissociation between the neuropsychiatric and haematological manifestations, as occurs in other general metabolic disorders that affect the CNS. The occurrence of CNS complications is influenced by the duration as well as the severity of either deficiency, by predisposing genetic factors, including polymorphisms of folate or vitamin-B12 dependent enzymes, and by any associated metabolic disorders. The administration of folic acid in the presence of vitamin-B12 deficiency may be harmful to the nervous system, after brief temporary improvement, and ultimately harmful to the blood, after more striking but suboptimal temporary improvement. In the CNS, as in the blood, failure or blocking of the supply of methyl folate will result in impaired purine, thymidine, nucleotide, and DNA synthesis, as well as disruption of DNA transcription, methylation, gene expression, and other epigenetic mechanisms affecting tissue growth, differentiation, and repair. There is now substantial interest in the role of folic acid, vitamin B12, and related pathways in nervous-system function and disease at all ages and the potential use of the vitamins, especially folic acid, in the prophylaxis of disorders of CNS development, mood, and cognitive decline, including some dementias **(Reynolds, 2006)**.

Concerning vitamin B12, finding **Lasisi *et al.* (2012)** is supported by the report of **Shemesh *et al.* (1996)**. They reported that the incidence of vitamin B12 deficiency is significantly higher among patients with tinnitus and noise-induced hearing loss (47 %) compared with those with noise induced hearing loss alone and normal subjects who exhibited vitamin B12 deficiency in 27 % and 19 %, respectively. In addition they reported some improvement in tinnitus and associated complaints in 12 patients following vitamin B12 replacement therapy. These suggest a relationship between vitamin B12 deficiency and dysfunction of the auditory pathway; hence authors recommended that routine vitamin B12 serum levels be determined when evaluating patients for chronic tinnitus.

The presence of tinnitus as the only features in these subjects with low plasma vitamin B12 suggest that perhaps tinnitus may be one of the early features of the various neurological abnormalities associated with B12 deficiencies **(Lasisi *et al.*, 2012)**.

The B vitamins folate, vitamin B_6 (pyridoxine), and vitamin B_{12} (cobalamin) are important regulators of homocysteine metabolism in the body, and randomized controlled trials have demonstrated that supplementation with folate (natural dietary folate or the synthetic folic acid) alone or in combination with vitamins B_6 and B_{12} significantly reduces blood homocysteine concentrations **(Bønaa *et al.*, 2006, Lonn *et al.*, 2006)**. Although increased intakes of these B vitamins could plausibly reduce the risk of stroke, findings from observational studies on folate **(Van Guelpen *et al.*, 2005)**, vitamin B_6 **(He *et al.*, 2004)**, and vitamin B_{12} **(Virtanen *et al.*, 2005)** in relation to stroke risk have been inconsistent. Likewise, randomized clinical trials examining the effects of supplemental folic acid and other B vitamins on stroke incidence among individuals with preexisting cardiovascular or renal disease have produced conflicting results **(Bazzano *et al.*, 2006, Wang *et al.*, 2007, Larsson *et al.*, 2008)**.

Globally 24 million people have some form of dementia, with 4.6 million new cases diagnosed each year. It is estimated that the number of people affected will double every 20 years and reach 81 million by 2040. Pharmacotherapy of Alzheimer disease and other dementias can provide only modest cognitive or disease-modifying benefits. However, even modest benefits may have significant effects on quality of life, caregiver burden, and societal economic costs. Increased homocysteine levels in conjunction with low levels of folate, vitamin B6, and vitamin B12, which interact to control homocysteine, have been reported to correlate with decreased performance on cognitive tests. For these reasons, B vitamin supplementation has been proposed to prevent or reverse cognitive decline. Several studies examined whether supplementation with pyridoxine hydrochloride (hereinafter “vitamin B6”), cyanocobalamin or hydroxycobalamin (hereinafter “vitamin B12”), and folic acid can prevent, decrease the progression rate of, or reverse the neurologic changes associated with age-related neurodegenerative retinal blood flow via the diacylglycerol-protein kinase C pathway **(Agarwal, 2011)**.

CONCLUSION

Due to multifactorial mechanisms behind formation of tinnitus it is difficult to determine the most appropriate treatment. Pharmacological treatments is one of several potential method of therapy. This review described positive effects of natural substances on various types of underlying condition that cause tinnitus or can alleviating symptoms. It was determined that low plasma melatonin and vitamin B12 have significant correlation with the development of tinnitus among the elderly. Melatonin exerts advantageous vascular changes that improve labyrinth perfusion, thus protecting the inner ear from hypoxia. Melatonin can reduce muscular tone, and it may relieve tensor tympani muscle spasms, thus improving symptoms. In addition to relieving tinnitus, melatonin improves sleep quality. The large group of substances with potential positive effect on tinnitus or for alleviating the symptoms are substances with antioxidant action. Hesperidin exerts protective action in cardiac tissue by its antihypertensive and antioxidant properties. The compounds of *Ginkgo Biloba* L. are known to act mainly as antioxidants/free radical scavengers, enzyme inhibitors, and cation chelators. Diosmin as a flavonoid, also possesses a multitude of biological activities including anti-inflammatory and antioxidant properties. In the pharmacologic therapy is important not only directly effect of some substances but also their synergistic action. Synergistic effect can bring different results. Therefore is necessary evaluating their effect with the combinations with another substances.

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