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The Potency of Ginkgo Biloba in Treating Tinnitus: A Review

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ABSTRACT

Extracts of Ginkgo biloba leaves are used for medicinal purposes for at least 5000 years in China. More recently Ginkgo biloba extracts have been used in Western countries. In the USA, Canada and the UK extracts are widely available as nonprescription food supplements. In France and Germany, a standardized dry leaf extract is registered as a drug and is commonly prescribed for. Several studies have been conducted to measure the usefulness and properties of Ginkgo Biloba in connection with the treatment of Tinnitus. This literature review aims to identify the components and the mechanism of action of Ginkgo Biloba in the treatment of tinnitus. The articles selected were all published within the past five years from PubMed. 11 articles were obtained and were included in the review. Based on the articles, The most important active chemical compounds in Ginkgo Biloba are flavonoids (ginkgo-flavone glycosides) and terpenoids (ginkgolides A, B, C, J, and bilobalide). Gingko Biloba has vasoregulatory effect, antagonism of platelet activator factor, antioxidant activity, enhance neuroplasticity and inflammatory. In conclusion, Ginkgo Biloba demonstrated effectiveness in the treatment of tinnitus, through the significant improvement in self-perception of tinnitus loudness and severity.

1. Introduction

Tinnitus has defined a perception of sound that is heard without an external auditory stimulus. It is described as a ringing, hissing, buzzing or wheezing sound due to some pathologic activity that affects the auditory pathway at some point. The brain thus interpreted it as a sound. Tinnitus may be defined variously, as a sound perceived for more than 5 min at a time in absence of any external acoustical or electrical stimulation of the ear. Sound percieved after high intensity noise, and psychological disease are not included. However, tinnitus can be objective and subjective. Objective tinnitus is defined as tinnitus that can be heard by both the examiner and the examinee. Subjective is defined as a tinnitus that only can be heard by the examinee. Both types of tinnitus, objective or subjective, can cause severe mental and physical impairments thus impair the persons quality of life. Symptoms of depression and anxiety are highly prevalent in patients with tinnitus; comorbidity rates between 50 and 90% have been reported from most studies.[1,2,7,11]

The prevalence of tinnitus is about 3-30% in the population and the prevalence is increased with age. Tinnitus is a major health problem, with an estimated prevalence of 9.6% and a 10-year cumulative incidence rate of 12.7% in the United States. In a United Kingdom, tinnitus has an overall burden of approximately 717 GBP per patient. Tinnitus can be acute with recovery between a couple of minutes to weeks. However, if it is experienced for more than three months then it is considered chronic. Despite the advances in technology, the exact

pathophysiology can not be determined. In 90 percent of chronic cases, tinnitus is considered a co- not been established. Some may have hearing loss and tinnitus and some may have normal hearing with tinnitus.[1,2,5]

The theory of tinnitus generation can either involve the function or activity of the peripheral (cochlea and auditory nerve) or the central auditory nervous system. Theories involving the peripheral systems include discordant damage theory. According to this theory, a loss in the outer health cell function, where the inner hair function is left intact, leads to a release from inhibition of inner hair cells and aberrant activity in the auditory nerve. The aberrant nerve activity can be due to excitotoxicity or stress induce enhancement of inner hair cell glutamate release with upregulation of N-Methyl-D Aspartate (NMDA) receptors.[1]

There are several source in the central nervous system that have been thought as a tinnitus generation center which include the dorsal cochlear nucleus, the inferior colliculus, and the auditory and non-auditory cortex. Tinitus was thought to occur as a result of maladaptive neuroplastic response to hearing loss allowing irregular spontaneous hyperactivity within the central neuronal networks morbid with some degree of hearing loss. However, the association between hearing loss and tinnitus has involved in sound processing. Another physiological change thought to be involved in tinnitus generation is a process of functional reorganization, which amounts to a change in the response properties of neurons within the primary auditory cortex to external sounds. This effect is well demonstrated physiologically in animal models of hearing loss. Evidence in humans, however, is limited to behavioral evidence of cortical reorganization after hearing loss.[1]

Some studies suggest that tinnitus is connect to the emoitonal part of the brain. Tinnitus involves many structures of the brain more associated with memory and emotional processing in tinnitus generation. However, further research needs to be done to understand the connection between tinnitus especially which are independent from hearing loss and other etiology. Even so, clinician have a hard time to understand the pathophysiology of tinnitis since not all tinnitus patient have hearing loss, and vise versa, not all patient with hearing loss have tinnitus.[1]

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, on 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 accident.
Pharmacological side effects	Over 10% of subjective tinnitus cases, especially in elderly patients are due to the side effect 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 nay temporomandibular disorder could exacerbate tinnitus. In these cases, the patients feel fulness 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.

Table 1: Different etiology of tinnitus

Currently, counseling and cognitive behavioral therapy is considered the recommend treatment. However, new studies have used a few drugs with promising results in the treatment of tinnitus. Various kinds of drugs such as antihistamines, barbiturates, anesthetics, calcium channel blockers, vasodilators, muscle relaxants, anticonvulsants, various types of psychotherapy, and tinnitus masking agent had been employed as a treatment for tinnitus. However, these treatments are only meant to reduce the severity of tinnitus. Their effects are also considered a little in comparison with placebo. Thus new researches including modern and traditional medicine is needed to cure and effectively managed tinnitus. Ginkgo Biloba is one of the medicinal plants being studied.[2,7]

2. Methods

PubMed were used as the searching engine in this study. The searching was conducted up to Aug 8, 2021 using the keywords "Ginkgo Biloba" and "Tinnius." Articles selected were all published within the past five years. Duplicate articles were excluded. From PubMed 10 results were obtained and were included in the review.

3. Result and Discussion

Based on the result from the review studies, we have found several pertinent information about Gingko Biloba in regards to the treatment tinnitus.

Tinnitus and Ginkgo Biloba

There has been an increase of interest approach tinnitus through medicinal plants. Medicinal plants and derivatives have been studied, by scientific approaches, in vitro, with animals, so that new therapeutic management may be discovered. Ginkgo Biloba is one of the medicinal plants being studied. Several studies have been conducted to measure the usefulness and properties of Ginkgo Biloba in connection with the treatment of Tinnitus. Ginkgo belongs to the Ginkgoaceae family. Ginkgo leaf consists of phytochemicals, including alkanes, lipids, sterols, benzoid, carotenoids, phenylpropanoids, carbohydrate, flavonoid, and terpenoids. The presence of this substances, especially terpenoids, are responsible to decrease the symptoms of tinnitus cause by decrease perfusion. It has also antiplatelet and vascular modulator effects that improve blood flow and regulate vascular tone which is suggested pathophysiology of tinnitus. Ginkgo Biloba has also antioxidant properties and protective effects on the nerve cell of the brain, auditory cortex, and subcortical area that acts as a scavenger for primary and secondary radicals. These properties made Ginkgo Biloba a possible treatment In Tinnitus.[2]

Ginkgo biloba leaves are use for medicinal purposes for at least 5000 years in China, where they form an important component of the traditional Chinese drug book. Currently, Ginkgo biloba is becoming popular in Western countries. In the USA, Canada and the UK extracts are widely available as nonprescription food supplements. In France and Germany, a standardized dry leaf extract is registered as a drug and is commonly prescribed for. A liquid extract is obtained from maidenhair plant approximately about 50 leaves. The most important active chemical compounds are flavonoids (ginkgo-flavone glycosides) and terpenoids (ginkgolides A, B, C, J, and bilobalide). Ginkgolides are only found spesifically in Gingko Biloba. These preparations contain standardized amounts of the above compounds. standardization for food supplement preparations. A common side effect of Ginkgo biloba is a mild gastrointestinal disturbance (e.g. stomach pain, change in bowel habit). Headache may be induced by-products containing ginkgo biloba. The dreaded side effects is increase in bleeding tendencies. High-dose ginkgo biloba reduces the efficacy of omeprazole and echinacea that of corticosteroids. [1,8,11]

A form of Gingko Biloba being used nowadays is Egb 761. It consists of about 250 compounds and has a potential to treast tinnitus with several different

mechanism. Well documented in animal and also human studies are the protection of neuronal mitochondrial ATP synthesis in the presence of oxidative stress, the protection of erythrocyte membranes against oxidative damage, which results in reduced blood viscosity and improved blood flow, and neuroprotection through antiapoptotic properties. The extract is considered beneficial in treating tinnitus because it provides several mechanism in increasing neurotransmitter level and the plasticity of neurons. One of which, is the increase of dopamine. The increase level of dopamin may reduce depressive behavior by partial inhibition of the norepinephrine transporter, or neuroneogenesis of hippocampal neurons which could both lead to cognition increasing effects. Several studies concluded that Egb 761 is safe and tolerated for human consumption. Therefore, EGb 761 has been considered as a therapeutic agent for the treatment of tinnitus.[3]

The usefullness of Egb 761 in treating tinnitus must take in acount the patomechanism of tinnitus itself. Nervous cells of the central vestibular and auditory systems, cochlear hair cells, and vestibular sensory cells need a great amount of energy in order to maintain it's efficiency. Decrease blood flow and decrease in mitochondrial function decreases the function of cochlea and sensory cells. Egb 761 increases blood flow in the ear and brain thus improving tinnitus complains.

The extract also improve inner ear and brain function by increasing the function mitochondria thus helping patient with dementia. Its anti-apoptotic and neuroprotective properties improves the function of cochlea and sensory cell, thus improving the symptoms of vertigo and tinnitus. EGb 761 enhances neuroplasticity, improves learning, and accelerates vestibular compensation. Due to anti-anxiety effect and by decreasing the activation of the stress axis, EGb 761 may decrease the distress. It may improve of gait and unsteadiness by increasing the speed of processed information. [9]

Mechanism of action of Gingko Biloba

The mechanism of action of Gingko biloba in decreasing the symptom of tinnitus are as follow.[1]

Vasoregulatory effect

A vasoregulatory effect is one of the most important action for Gingko Biloba. It increases blood flow by regulation the tone of blood vessel. Animal and human studies have shown that Ginkgo biloba can increase skin, cardiac and cerebral blood. [1]

Antagonism of platelet activating factor (PAF)

This is primarily caused by the presence of ginkgolides. PAF causes platelet (a blood constituent involved in blood clot formation) aggregation, neutrophil degranulation (activation of immune cells within the bloodstream) and oxygen radical production. Ginkgolides appear to protect against the effects of hypoxic brain injury from cerebral ischemia (permanent brain damage caused by insufficient blood and oxygen supply) in laboratory animals. [1]

Antioxidant activity

Antioxidant activity including scavenging of free radicals, indirectly inhibiting the formation of free radicals, regulation of oxidative stress and anti-lipid peroxidation. The use of Gingko Biloba has been proven to treat tinnitus in a systematic review comparing with placebo. [1,2,4]

Changes in the metabolism in neurons

Changes in the metabolism of neurons and restoration of age-related deficiencies in central neurotransmitter systems. [1]

Enhancement of neuronal plasticity

Enhancement of neuronal plasticity including increased long-term potentiation, spine density, neuritogenesis and neurogenesis, as shown in pre-clinical reports. [1]

Anti-inflammatory effect

Anti-inflammatory effects and protective actions against brain damage, possibly through its terpenoids and ginkgolides. The Ginkgo biloba leaf extract has been shown to reduce the level of cytokines and inflammatory factors such as tumor necrosis factor-alpha (TNF-R), interleukin 6 (Il-6), interleukin 1 beta (Il 1-S), and matrix metalloproteinase. [1]

In a study with gerbils by Krauss et al., the dosage of Gingko Biloba extract (Egb 7611) given was 100mg/kg taking note that the metabolic rate is 10 times higher in comparison with humans. The actual dosage was 700 mg, which is 3 times higher of recommended dosage in humans. The recommed dosage in humans was 240 mg/dl. However, 480 mg/dl was said to be wll tolerated. This was also supported by a cochrane systematic review by Sereda et al that describes the usual recommended dosage for tinnitus is 60 to 450 mg/d.[1,3]

4. Conclusion

Ginkgo Biloba demonstrated effectiveness in the treatment of tinnitus, through the significant improvement in self-perception of tinnitus loudness and severity. Since tinnitus is caused by several factor, patient needs to be treated by case to case basis regarding the cause, treatment and doses of Gingko Biloba. Thus studies that categorize tinnitus based on their cause, comorbids (such as mental diorder, acoustic trauma, etc) and the effect of Gingko Biloba in all this disorders are a more appropriate and efficient way in evaluating the potenvy and dose of Gingko Biloba.[1,6]

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