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Review

A review on medicinal plants used for treating ototoxicity and acoustic trauma induced hearing loss

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Hearing loss induced by chemotherapy and acoustic trauma is mainly associated with two factors, free radical formation and apoptosis pathway activation. Despite numerous efforts on reducing the effects of these factors, no definite strategy is still determined to interfere with and control these processes. In recent studies, various protective agents, including antioxidants have been used on animal models, to inhibit the formation of free radicals thus improving hearing loss.In this review article we will discuss the role of traditional herbal medicine in treatment of noise/drug induced hearing loss, focusing on medicinal plants' active substances,as well as their mechanisms of action in reducing or preventing the formation of free radicals thus increasing the rate of survival of cochlea cells. Data have been gathered since year 2000, from scientific publications including the following keywords: deafness, drug toxicity, acute trauma, medicinal herbs and oxidative stress. The study includes all herbs and medicinal plants that have been experimentally used in studies on animal models and clinical trials. The results from these studies indicate the effectiveness of most of these herbs and their active substances through their antioxidative properties. Medicinal plants reported in this review can thus be considered as effective remedies intreating noise/drug induced hearing loss,yet further studies need to be done.

Keyword: Hearing Loss/ prevention & control. Ototoxicity. Acoustic Trauma/ physiopathology. Herbal Medicine/ instrumentation. Oxidative stress/ drug effects. Antioxidants/ therapeutic use. Hearing Loss, Noise-Induced/ therapy. Plants, Medicinal/ drug effects.

INTRODUCTION

Hearing loss is the most common neuro-sensory disorder (Asgharzade *et al.*, 2017). Several factors are associated with the cause and exacerbation of hearing loss such as genetic mutations (Asgharzade *et al.*, 2017), alterations in the vascular function of the auditory system, reduced oxygenation and increased reactive oxygen and nitrogen species (Melgar-Rojas *et al*., 2015). Formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is the main factor involved in the pathophysiological mechanisms of cochlear damage inducedby ischemia, ototoxicity, and noise (Huang *et al*., 2000). The presence of highly reactive oxygen and nitrogenspecies is essential for survival of the cells. However, increased amounts of these reactive species can damage various cell organelles. Studies have shown that mitochondria are the main source of active reactive oxygenspecies in response to hypoxia-ischemia. Superoxide radicals (super O_2) react with nitric oxide (NO) and create toxic peroxynitrateanions (Huang *et al*., 2000; Asgharzade *et al*., 2015). Superoxide also convertsto inactive form of H_2O_2 through superoxide dismutase (SOD), and the resulting H_2O_2further converts to OH reactive radicals by iron-catalyzed Fenton's reaction. These toxic compounds can damage cell biomolecules such as lipids, proteins and DNA (Kurabi *et al*., 2017). Chemotherapy drugsand glycosylated antibiotics administration and exposure to noise can damage the auditory system by increasing the production of ROS and

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RNS and activating the apoptotic pathway in cochlea cells. Antioxidant properties of Medicinal plants can inhibit ROS and RNS as well as the apoptosis pathway therefore medicinal plants would make an effective complimentary drug option to reduce adverse effects of common ototoxic medications (Rabiei *et al*., 2015; Mahmoudian-Sani *et al*., 2017a). Various studies have examined the simultaneous use of ototoxic drugs and various medicinal plants. This review article intends to focus on different medicinal plants used to treat hearing loss (induced by ototoxic drugs and noise) as well as their protective mechanism in the auditory system.

OTOTOXICITY

Ototoxicity is a chemical/drug induced tissue degeneration of the inner ear, caused by several therapeutic medicines. Such damage can lead to vestibular function impairment and temporary or permanent hearing loss or ototoxic substances that are commonly used in clinics include aminoglycoside and macrolide antibiotics, chemotherapy drugs such as cisplatin and carboplatin, antimalarial drugs and loop diuretics (Kalinec *et al*., 2017).

OTOTOXICITY OF AMINOGLYCOSIDES

Aminoglycoside antibiotics are commonly used to treat infections such as tuberculosis, bacterial endocarditis and pneumonia. Application of these antibiotics causes hearing loss (> 33%) and vestibular toxicity (> 15%) in patients (O'Sullivan *et al*., 2017). Yet, these drugs are still used in developing countries due to the low price (Mahmoudian-Sani *et al*., 2017b). Aminoglycosides rapidly penetrate into the cochlear tissue after systemic administration (Jiang, Karasawa, Steyger, 2017). Although the drug concentration is similarin blood plasma and in inner ear, it remains in the inner ear for longer period of up to 6 months (Huth*et al*., 2015). Therefore, a previous aminoglycoside therapy increases the chance of ototoxicity in patients Long-term exposure of cochlear cells to aminoglycosides induces outer sensory hair celldeath of vestibular organ thus auditory nerve damage. The degree of damage is directly related to the dosage and duration of application of this drug. Increased hair cell damage subsequently leads to hearing loss. Aminoglycosides form a complex with iron after entering the cell and catalyze unsaturated fatty acids to produce ROS. The ROS initiates the apoptosis pathway and necrotic cell death (Figure 1) (Ciorba *et al*., 2013). One of the pathways activated by aminoglycoside via ROS is the c-Jun N-terminal kinase (JNK) pathway which is alsoinvolved in cell apoptosis (Davis, 2000). By controlling the JNK pathway, cochlear cells can be protected against neomycin-induced ototoxicity (Chang-Chien *et al*., 2017). One of the downstream targets of JNK is activating protein-1 transcription factor. Gentamicin applies its ototoxicity effect to the outer hair cells via increasing the activity of this transcription factor (Steyger *et al*., 2018).

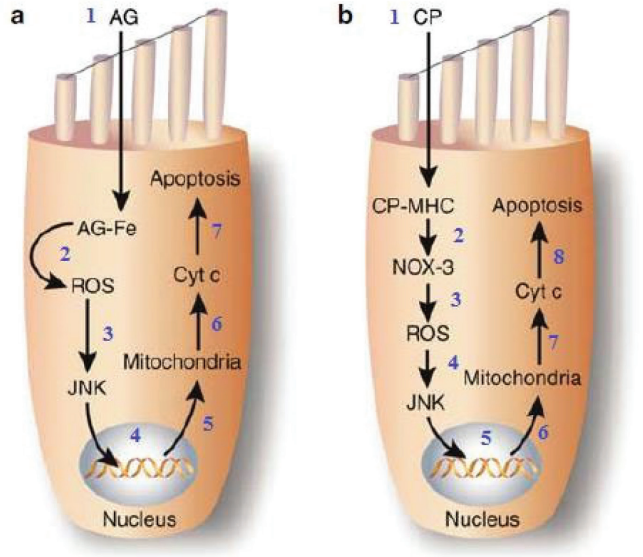

FIGURE 1 - The mechanism of induction of external hair follicles by cisplatin and aminoglycosides. a) Aminoglycoside (AG): 1) Aminoglycoside entry through Mechanotransducer canals; 2) The reaction of the iron-aminoglycoside complex with arachidonic acid and the formation of ROS; 3) activating the JNK pathway by ROS; 4) Transcription of active genes in the cellular death pathway; 5) starting mitochondrial pathway apoptosis; 6) Cytokram release, targeting capepase pathway via caspase; 7) Cell death. b) Cisplatin (CP): 1) Cysplatin entry through Mechano transducer canals CP within cells can beequated to form the monohydrate complex (MHC), which is more; 2) Highly reactive; 3) Activating NOX-3 with CP or MHC and producing ROS; 4) Activating JNK pathway by ROS; 5) Transcribing active genes in the cellular death pathway; 6) staring of mitochondrial-dependent apoptosis; 7) Cytokram release, targeting the pathway of apoptosis through caspase; 8) Cell death.

CISPLATINIC OTOTOXICITY

Cisplatin is a chemotherapeutic agentto treat a variety of cancers including ovarian, testicular, bladder, cervical and lung cancers The platinum atom of cisplatin forms a covalent bond with the N7 position of purines in DNA, and the damage activates MAPK/ JNK/ ERK signaling pathways (Davis, 2000). Cisplatin induces

cell death in cancerous cells through two mechanisms, namely apoptosis and necrosis. The occurrence of either mechanism is dose dependent, high doses of drug leads to cell death through necrosis while lower doses induce apoptosis pathway.

Cisplatin administration has been restricted due to renal toxicity, neurotoxicity and ototoxicity (Wang, Lippard, 2005) and severe hearing loss may occur in approximately 75-100% of patients after high-dose chemotherapy (Rybak and Ramkumar, 2007). The early stages of drug administration, hearing loss is usually bilateral at high frequencies but it progresses to lower frequencies as treatment continues. Cisplatin affects three areas of the cochlear including cortical limb cells, spiral ganglion cells and lateral wall tissue (spiral ligament and StriaVascularis). It then enters hair cells to produce ROS (Rybak, Ramkumar, 2007).ROS increases the calcium influx in the cochlear cells and induces apoptosis. The increase in NADPH Oxidase 3 (NOX3) expression was observed when treating rats with Cisplatin. NOX3 boosts the production of superoxide (O_2^-) and hydrogen peroxide (H_2O_2) compounds which react with unsaturated fatty acids in thecell membrane to produce highly toxic aldehydes. Superoxides also react with nitric oxide (NO) to form proxy nitrite which in turn reacts with proteins to produce nitrotyrosine (Mukherjea *et al*., 2006). Finally, through activating the downstream pathways, these radicals activate the apoptosis pathway in the hair cells and spiral ganglion cells (Figure 1) (Steyger *et al*., 2018).

NOISE-INDUCED HEARING LOSS

Up until a decade ago, the main cause of hearing loss was believed to be the mechanical destruction of the subtle hair cell membrane and the supportive structure of the cortex as well as an alteration in blood flow into the inner ear as a result of severe noise (Fetoni *et al*., 2015). Studies show that exposure to noise leads to increased production

TABLE I -The list of medicinal plants used to treat ototoxicity induced by gentamicin, cisplatine and noise in the warld

Latin Name	Part used	Medicinal uses	Geographical Regions	Deafness Experimental	Functional Pathway	Refrence
Radix astragali	Root	Chronic fatigue syndrome Candidiasis Herpes simplex virus Hypoglycemia	Chinese	Acoustic trauma	inhibiting the down−regulation of connexin 26and KCNQ1 Antioxidant against free radicals	(Xiong *et al*., 2012a; Xiong*et al*., 2015)
Gushen pian	-	Splenonephric Hypofunction phlegm Accumulation stasis	Chinese	Clinical trial II Sensorineural deafness Tinnitus	-	(Zhai, Fang *et al*., 2013)
Korean red ginseng	Root	Diabetes immune enhancement	Korean	3-Nitropropionic acid Gentamicin Cisplatine Loud noise	Antioxidants against free radicals	(Tian *et al*., 2013)
Astragalus membranaceus	Root	Allergic rhinitis Diabetes	Chinese	Impulse noise Cisplatine	Antioxidants inhibiting the apoptosis of cochlear cells through the suppression of ROS	(Xiong *et al*., 2012b)
Maytenus ilicifolia	Leaves	Inhibits tumors Detoxifies Gastric ulcers	Brazil	Cisplatin	Antioxidants against free radicals	(Kasse *et al*., 2008)
Salvia miltiorrhiza	Root rhizome	Cerebrovascular Disorders, angina Pectoris Hypertension Diabetes	Chinese	Aminoglycoside Gentamicin	Antioxidants against free radicals	(Wang *et al*., 2003)

TABLE II - The list of Active Components ofmedicinal plants used to treat ototoxicity induced by gentamicin, cisplatine and noise in the world

Active Components	Materials Constructive	Medicinal uses	Geographical regions	Experimental use	Functional Pathway	Reference
Wu-Ling-San (blackish-brown pill)	Poria Rhizoma Alismatis Polyporus Cortex Cinnamomi Rhizoma Atractylodis Macrocephalae	Vomiting, Diarrhea Edema, Abdominal Distension	Chinese	Clinical trialII Acute low-tone Sensorineural hearing loss	-	(Okada, *et al*., 2012)
Astragaloside IV ($C_{41}H_{68}O_{14}$)	Astragalus membranaceus	Anti-inflammatory Antibacterial Cardioprotective Neuroprotective	Chinese	Impulse noise	Decreased the expression of ROS iNOS and Cas-3	(Xiong *et al*., 2012 b)
Purple Bamboo salt	sea salt and bamboo	Anti-allergic Antiinflammatory	Korean	Cisplatin	Inhibited expression IL-6 Suppressed cytochrome c, caspase-3	(Myung*et al*., 2011)
Carboxy Alkyl Esters	Uncariato mentosa Cat's claw	Arthritis, Allergies Asthma, Diabetes	America	Noise	Antioxidant protection DNA repair Anti-inflammation	(O'Neil *et al*., 2011)
Bojungikgitang, Banhabaek chulchonmatang	Astragali Radix White Ginseng Atractylodes rhizome Glycyrrhizae Resina Fraxini Cortex Cimicifugae Rhizoma Bupleuri Radix	Tinnitus Allergic Rhinitis	Korean	Clinical trial II Tinnitus	Antioxidants against free radicals	(Kim *et al*., 2010)

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of free radicals in mitochondria, reduced cochlear blood flow, excitotoxicity, and eventually apoptosis and necrosis of the cortex (Fetoni *et al*., 2015). Exposure to noise for 1 to 2 hours leads to a fourfold increase of hydroxyl radicals, which causes severe DNA damage. Noise induces production of free radicals in StriaVascularis (marginal cells) and outer hair cells, and these free radicals are the main cause of reduced blood flow to the cochlea, which may in turn induce ischemia, which in turn stimulates production of free radicals (Fetoni *et al*., 2015). Lipids are the main biological compounds of the cell membrane, the peroxidation of which is easily initiated by OH free radicals. This initial reaction can trigger multiple oxidative stress chain reactions, ultimately leading to hair cell damage and death (Le Prell *et al*., 2007).

Loud sound exposure increases the number and spread of phagocytes–special resident macrophages in the spiral ligaments, StriaVascularis, and optic capsules; activates the transcription factor of NF-KB; and regulates the expression of the proinflammatorygenes such as tumor necrosis factor (TNFα) and interleukin 1 beta (IL-1 β) in the cochlea (Watson *et al*., 2017).

EFFECTIVE HERBS IN HEARING LOSS

Radix astragali

Radix astragali (RA) is a traditional Chinese herbal medicine. The foliage of Rahas antioxidant properties and is widely used to treat organ damages caused by ROS. Studies have shown that RA reduces symptoms of ROS-induced ischemia in myocardial ischemia reperfusion in rats. Also, simultaneous administration of RA with cisplatin reduces ototoxicity through inhibition of apoptosis in hair cells (Xiong *et al*., 2015). Experiments modeling acoustic trauma induced hearing loss in guinea pigs showed that RA improves auditory function by inhibiting ROS and nitric oxide in cochlear cells.

Gap junction proteins such as connexin 26 (Cx26) and potassium voltage-gated channel subfamily Q member1 (KCNQ1) play important roles in the intracellular signaling and potassium metabolism in StriaVascularis (SV) cells. ROS reducing intercellular coupling in cochlea by inhibiting Cx26 gene expression. RA has a protective role by reducing inhibition of CX26 and KCNQ1expression in SV cells, therefore reducing brainstem hearing impairment and SV cell damage. (Xiong *et al*., 2012a; Xiong *et al*., 2015).

Gushen pian

Gushen pian is a traditional Chinese medicine obtained from four different herbs: Drynariafortunei, Danshen, CalcinedCi Shi and Glycyrrhiza. This herbal medicineis akidney and spleen enhancer, moister andstasis eliminator, blood circulation promoter and obstructions remover. Early studies showed that Gegen, Danshen and Drynaria fortune can prevent otoxic effects of drugs by increasing blood circulation in the cochlear (Zhai *et al*., 2013). Gushen Pian is effective in treating sensor neuronal hearing loss, tinnitus and pressure in the ear caused by decreased activity of splenonephric and mucus accumulation. Clinical trials confirmed the non-toxicity of this herbal medicine (Zhai *et al*., 2013).

Korean Red Ginseng

Ginseng isaherbal remedy used for over 5,000 years. The main ingredient of this drug is Ginsenoside or Ginseng Saponins. Based on the structural difference, there are three main groups of Ginseng, Panaxadiol, Panaxatriol, and Oleanolic acid (Tachikawa *et al*., 1999). Korean Red Ginseng (KRG) is a biological drug produced by a Korean company from Ginseng. This product is mainly composed of Panaxadiol Saponins extracted from roots (70%) and root hairs (30%) of 6 year mature Ginseng plant (Jee *et al*., 2014). KRG is known as a non-toxic drug with anti-cancer, anti-inflammatory, antioxidant gastric ulcer protective, and anti-Alzheimer properties. It also has protective effects against the ototoxic damage caused by cisplatin, gentamicin and acoustic trauma (Hong, Lyu, 2011).Ginseng extract reduces apoptosis in internal and external hair follicles in the cortex, saccharum, and etricol by stimulating the production of superoxide dismutase and inhibiting the production of free radicals and lipid peroxidase due to cisplatin, as well as inhibition of caspase 3 and poly adenosine diphosphate polymerase ribosomes (Tian *et al*., 2013). KRG also showed to have protective effect in acute cochlear injuryin mouse models (induced by intra-tympanic injection of 3-nitropropionic acid) by restoring the function of fibrocytes. Spiral ligament fibrocyteplay a significant role in maintaining the cochlear's function through cortical limb cells and spiral ganglion cells. As a result, protection and regeneration of fibrocytes in spiral ligament can be protective measure against 3-NP induced hearing loss (Tian *et al*., 2013).

Astragalus membranaceous

Astragalus membranaceous (AM) is another typical Chinese antioxidant herb commonly used in treating ROS induced damages in various organs. Astragaloside IV is one of the major active compounds isolated from AM. (Xiong *et al*., 2012b). Due to its antioxidant properties, this compound prevents the formation of ROS and initiates apoptotic pathways in cochlea cells. Studies have shown that this combination also inhibits iNOS and forms reactive nitrogen species which reduce NO production and preventhair cell damage in Indian guinea pigmodels of noise-induced hearing loss (Xiong *et al*., 2011).

Uncaria tormentosa

Uncaria tormentosa (UT) or cat's clawis a multi-purpose herbal remedy cultivated in South America and used for more than 2000 years by ancient civilizations such as Amazonian Indians Tian *et al*., 2013).Carboxy Alkyl Esters (CAE) are the bioactive compounds found in UT. Many studies have been conducted on the otoprotection property of CAE. In rat modes of noise induced hearing loss, CAE protects cochlea from inflammation by inhibiting TNF-α and IL-1β production via alteration in NF-kB expression pattern.it also prevents apoptosis pathway and ROS and RNS formationin hair cells via its antioxidant property (O'Neil *et al*., 2011). CAE supplementation has been shown to repair noise induced DNA damaged in less than 3 hours. Its dose dependent properties have also been confirmed in experiments (Sheng, Pero, Wagner, 2000). As a result, CAE with its antioxidant, anti-inflammatory and DNA repair properties mayimprove the damaged sensory nerve cells function.

Tanshinone (*Salviae militiorrhizae*)

Salviae militiorrhizae (SM) known as Chinese sage is a traditional Chinese medicine. It is used in treating angina and cerebrovascular abnormalities. This plant has a high antioxidant property. Studies have shown that SM has a protective role against lipid peroxidation *in vitro* and ototoxicity*in vivo.* In fact, SM is the potential

antidote against free radical-induced disorders. It has shown to have otoprotective properties in mouse models of aminoglycoside-induced deafness. SM inhibits peroxidation of gentamicin-based lipid, superoxide, and radical hydroxyl by increasing the activity of intrathoracic enzymes such as superoxide dismutase, glutathione peroxidase, and catalase (Lee, Cho, 2015).

DISCUSSION AND CONCLUSION

Both cisplatin and aminoglycoside drugs cause neural-sensory hearing loss at high frequencies, which is accompanied by the loss of outer hair cells in the basal turn of the cochlea (Rybak, Ramkumar 2007; Xiong *et al*., 2015). Both drug groups play a role as an early stimulus for cell damage and cell death through increased oxidative stress in the ear. The main mechanism of neural-sensory cell damage by cisplatin is through the apoptosis pathway, while for aminoglycosides, it appears to be via the induction of both apoptosis and necrotic pathways. Experimental studies on animals have shown that different types of antioxidants can reduce the ototoxicity caused by aminoglycosides or cisplatin without any interference with drug effectiveness and thus appear as promising therapeutic agents.(Kim *et al*., 2010; Okada *et al*., 2012) In this regard, reported in several studies the positive effects of the medicinal herbs such as Korean Red Ginseng (Tian *et al.*, 2013), *Astragalus membranaceus* (Xiong *et al*., 2011), *Maytenus ilicifolia* (Kasse *et al*., 2008), and Astragaloside IV (Xiong *et al*., 2011) on the reduction of cisplatin induced ototoxicity by, and others such as *Salvia miltiorrhiza* (Wang *et al*., 2003) and Korean Red Ginseng (Tian *et al*., 2013) on the reduction of aminoglycosides induced ototoxicity. Most plants inhibit the formation of free radicals of ROS and RNS due to their antioxidant properties and prevent the activation of the apoptosis pathway in the cochlea hair cells by inhibiting Caspase3. Anumber of herbal remedies use other mechanisms to improve hearing loss. *Radix astragali* prevents hearing loss caused by acoustic trauma through inhibiting the reduction of Connexin 26 and KCNQ1 gene expression in StriaVascularis (Xiong *et al*., 2015). CAE prevents noise-induced hearing loss through its antioxidant, anti-inflammatory, and DNA repair mechanisms (O'Neil *et al*., 2011). Purple Bamboo Salt is used to treat tinnitus and cisplatin induced hearing loss from (Hong, Lyu, 2011). This compound has an anti-inflammatory property and prevents inner and outer hair cell death, preventing the release of cytochrome C and caspase-3 and inhibiting inflammatory factors. The main focus of this article was to review the important role of medicinal herbs in treating ototoxicity induced by chemotherapy drugs and aminoglycosylated antibiotics, as well as noise induced hearing loss. Many studies have been conducted so far on animal experimental models that confirm the positive effects of these herbal extracts and derivatives on hearing loss, thus it is suggested to investigate in future the use of these herbs more extensively in clinical trialswith regard to drug-related adverse effects and antioxidant properties of medicinal plants, these herbal remedies should be embraced as natural medicine for human use.

COMPLIANCE WITH ETHICAL STANDARD

Disclosure of potential conflicts of interest: Authorsdeclare no conflict of interest for manuscript entitled:

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