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Turmeric can Prevent Cochlear Damage Due to Ototoxic Drugs

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***Abstract*— The high use of ototoxic drugs, especially antibiotics such as aminoglycosides and anticancer drugs such as cisplatin still can not be avoided as a therapeutic option. The use of ototoxic drugs can cause damage to the cochlea, vestibule, and semicircular canals leading to hearing loss and balance disorders.**

Our previous study has found that curcumin extracted from turmeric (*Curcuma longa* L.) is capable of preventing damage to cochlea of rats exposed to noise at the level of molecular biology (protein level) through the decreased apoptotic index, oxidant status, and increased antioxidant status. Cochlear damage due to ototoxic drugs can occur through the similar pathways, thus we have a strong hypothesis that the cochlear damage due to ototoxic drugs may also be prevented by curcumin.

If it is proven in animal studies, the study could be tested on humans (clinical trials) so that curcumin can be used as a herbal medicine to prevent hearing loss.

***Keywords*— curcumin, ototoxic, cochlea, hearing loss.**

I. INTRODUCTION

Hearing plays a pivotal role in social relationships and one of the causes of hearing impairment is ototoxic drugs. One type of drug inflicting hearing impairment is gentamicin, an aminoglycoside antibiotic [1]. The incidence of cochlear damage caused by aminoglycoside is equal to 7-90%, its rate varies greatly due to differences in study designs and methodologies [2].

Aminoglycosides are ototoxic drugs, widely prescribed due to their effective antimicrobial action and affordable prices [3]. Aminoglycosides are classified as the basic drugs used to treat gram-negative bacterial infections, but gentamicin can cause permanent damage to the sensory hair cells in humans and mammals [4].

Aminoglycosides have the ability to produce an active metabolite that can catalyze the formation of ROS (reactive oxygen species), a highly reactive compound. The human body has a defense system against ROS in the form of antioxidant agents, namely superoxide dismutase, glutathione and catalase [5].

Aminoglycosides-induced ototoxicity develops from low to high frequency, related to oxidative stress. Aminoglycosides, eg. Gentamicin, may react with iron to produce ROS in the inner ear, resulting permanent damage to hair cells and neurons. Excessive ROS levels trigger the apoptotic pathway, which then produces cell death due to aminoglycoside-induced ototoxicity. Eventhough aminoglycoside-induced ototoxicity is well-documented, its molecular mechanisms still have not been precisely determined [6].

Noise is defined as an unwanted, unpleasant and disturbing sound since it can potentially cause disruption or damage to the inner ear organs [7]. Continuous noise exposure over an extended period of time causes damage to various structures gradually in the cochlea, initially affects higher frequencies, then spreads to lower frequency [7], [8].

Reference [9] found the increased expressions of HSP-70, TNF-α, IL-6, NFkB, TLR-2, TLR-4 and MMP-9 as well as the decreased expressions of Type II and IV Collagen in cochlear fibroblasts of *Rattus norvegicus* due to noise exposure with frequency of 1-10 kHz in the dose variation of noise intensity of 100 dB SPL for 15 minutes, 91 - 100 - 110 - 120 dB SPL for 2 hours.

Curcumin is a yellow pigment belonging to a group of phenolic compounds extracted from the rhizome of *Zingiberaceae* plant family, including: *Curcuma longa* Linnaeus (synonymous with *Curcuma domestica* Valeton or turmeric) and *Curcuma xanthorrhiza* Roxburgh or Java turmeric, often used as a seasoning and coloring agent [10] .Curcumin is known to have a broad spectrum of biological activities as an antioxidant; anti-inflammatory; inhibit initiation, promotion and metastasis of tumor; prevent and treat cancer;

antiviral; antibacterial; antifungal; antiamyloid; immunomodulator that activates T cells, B cells, macrophages, neutrophils, NK cells and dendritic cells; has the potential to treat allergies, arthritis, Alzheimer's disease and other chronic diseases mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases and other enzymes [11]-[13].

According to a number of studies that have been conducted, curcumin has been shown to reduce the expressions of cytokines such as IL-1, IL-2, IL-6, IL-8 and chemokines, plays a role in the suppression of NFkB activation [14], inhibits inflammatory processes due to TLR-4 and MyD88 [15], decreases the expressions of MMP-2 and MMP-9 [16], increases the expressions of Type III and IV Collagen [17], inhibits the binding of AP-1 via MEKK1-JNK pathway, blocks the phosphorylation of JNK and c-Jun; cell cycle (cyclin D1 and cyclin E); apoptosis (caspase activation and "down-regulation" of anti-apoptosis gene products); proliferation (HER-2, EGFR, AP-1); P13K/AKT survival pathway; invasion (MMP-9 and adhesion molecules); angiogenesis (VEGF); metastasis (CXCR-4); inflammation (NFkB, TNF, COX-2, 5-LOX) [10], [18], [19].

II. PUBLICATION OF RESULTS

In previously published studies, the authors have proved that curcumin is able to prevent damage to the cochlear fibroblasts via several pathways, namely inflammatory, oxidative metabolic and apoptotic pathways. The studies were divided into 4 groups using 24 male *Wistar* rats (*Rattus norvegicus*), which consisted of group 1 (control), group 2 (exposed to noise of 100 dB 2 hours per day for 14 days), group 3 (exposed to noise of 100 dB 2 hours per day followed by the administration of 50 mg curcumin for 14 days) and group 4 (exposed to noise of 100 dB 2 hours per day followed by the administration of 100 mg curcumin for 14 days). Results of the study has found that curcumin is able to increase the expressions of SOD and CAT concentration [20]; decrease the expressions of MDA and H_2O_2 concentration [21]; decrease the expressions of calcineurin, NFATc1, apoptotic index [22]; and decrease the expressions of AP-1 [23] on cochlear fibroblasts of *Rattus norvegicus*.

III. ADVANCED STUDY

Histopathologically, similar findings are detected between cochlear damage due to noise exposure and cochlear damage due to ototoxicity. Cochlear histopathological damage caused by aminoglycosides, macrolides, cisplatin and loop diuretics may demonstrate damage to the hair cells, stria vascularis, degeneration of VIII nerve fibers and spiral ganglion cells [24]-[26].

Those findings make the authors believe that damage to cochlear fibroblasts caused by ototoxicity can also be prevented with curcumin.

IV. HYPOTHESIS

Curcumin can prevent damage to cochlear fibroblasts caused by ototoxicity.

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