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Research Report

Carboxy alkyl esters of *Uncaria tomentosa* augment recovery of sensorineural functions following noise injury

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ABSTRACT

This study tested the hypothesis that hydrophilic chemotypes of the medicinal vine *Uncaria tomentosa* (*UT*) would facilitate recovery of sensorineural functions following exposure to a damaging level of noise. The particular chemotypes investigated were carboxy alkyl esters (CAE) which are known to exhibit multifunctional cytoprotective properties that include: enhanced cellular DNA repair, antioxidation and anti-inflammation. Long–Evans rats were divided into four treatment groups: vehicle-control, noise-only, CAE-only and CAE+noise. The noise exposure was an 8 kHz octave band of noise at 105 dB SPL for 4 h. Outer hair cell (OHC) function was measured with the cubic $2f_1$–f_2 distortion product otoacoustic emissions (DPOAE) at the start of the study (baseline) and at time-points that corresponded to 1 day, 1 week and 4 weeks post-noise exposure to determine within-group effects. Compound action potentials to puretone stimuli were recorded from the VIIIth craniofacial nerve at 4 weeks post-noise exposure to determine between-group effects. Additionally, cytocochleograms were constructed for each row of OHCs from each group. Noise exposure produced significant sensorineural impairments. However, CAE treatment facilitated almost complete recovery of OHC function and limited the magnitude of cell loss. The loss of neural sensitivity to puretone stimuli was inhibited with CAE treatment. Therefore, it appears that the multifunctional cytoprotective capacity of CAE from *UT* may generalize to otoprotection from acoustic over-exposure.

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1. Introduction

Uncaria tomentosa (*UT*) also known as uña de gato or cat's claw is a multifunctional medicinal vine that has been used for over 2000 years by ancient civilizations including that of the Tahuantinsuyo (Inca) empire (Pilarski et al., 2005). The bioactive components of *UT* can be divided into hydrophobic and hydrophilic chemotypes (Desmarchelier et al., 1997; Pilarski et al., 2005). The hydrophobic chemotypes include uncarine F, speciophylline, mitraphylline, isomitraphylline, pteropodine and isopteropodine (Bacher et al., 2006; Laus, 2004; Pilarski et al., 2005; Wagner et al., 1985). These hydrophobic chemotypes are derived from tincture preparations and have received considerable attention for their role in immunomodulation, antimicrobial defense, anti-inflammation and antimutagenicity (Keplinger et al., 1999). However, these hydrophobic chemotypes are not representative of medicinal decoctions consumed by ancient and indigenous peoples. For instance, the Asháninka Indians of the Amazon basin typically boiled *UT* in water and consumed the resulting

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hydrophilic chemotypes (Keplinger et al., 1999; Mammone et al., 2006). Recent experiments have demonstrated that carboxy alkyl esters (CAEs; see Fig. 1) are the bioactive components of these hydrophilic chemotypes (Akesson et al., 2005; Sheng et al., 2005). The documented health benefits of CAEs include: antioxidant protection, augmentation of DNA repair, anti-inflammation and immunomodulation (Akesson et al., 2003a, 2003b; Sandoval et al., 2002). These and other health benefits are based on the potency of CAEs to potentiate several biochemical cascades in order to increase the overall capacity of cells to survive and maintain functional integrity (Pero, 2010; Pero et al., 2009; Pero and Lund, 2010). Furthermore current human, animal and in vitro research has supported a role for CAEs in augmenting cellular repair from various physical or chemical exposures (Akesson et al., 2003a, 2003b; Belkaid et al., 2006; Gurrola-Díaz et al., 2010; Lemaire et al., 1999; Mammone et al., 2006; Pero et al., 2002). However, a role for CAEs in preserving auditory function following noise injury has not been studied.

Exposure to high levels of sound may induce a multiplicative array of biochemical cascades that perpetuate cell death and/or loss of auditory function (Le Prell et al. 2007; Ohlemiller, 2008). These biochemical cascades may propagate within minutes following exposure and are driven by processes such as ionic dyshomeostasis, mitochondriopathy, energy catastrophe and the proliferation of free radicals. For instance, loud-sound exposure may alter cochlear homeostasis of Ca^{2+}, K^{+}, and Na^{+} particularly through glutamate excitotoxicity (Hakuba et al., 2000; Le Prell et al. 2007). Mitochondriopathy is evidenced by sound induced increase in mitochondrial permeability and the independent release of at least two mitochondrial nucleases, endonuclease-G and apoptosis-inducing-factor (Han et al., 2006; Yamashita et al., 2004b). Furthermore, it is known that loud-sound exposure activates the mitochondria-mediated caspase-dependent cell death pathway (Nicotera et al., 2003; Wang et al., 2007). Energy catastrophe relates to depleted stores of high energy phosphates (e.g., ATP) following loud-sound exposure (Minami et al., 2007). The proliferation of free radicals is exemplified by increased production of reactive lipid, oxygen and nitrogen species (Ohlemiller et al., 1999; Yamashita et al., 2004a). These combined processes (ionic dyshomeostasis, mitochondriopathy, energy catastrophe and free radical production) complement each other to elicit acute and chronic inflammation that ultimately results in cell death and/or loss of auditory function (Masuda et al., 2006; Ohlemiller, 2008). The clinical manifestation of this combinatorial process includes permanent sensorineural hearing loss, tinnitus, loudness recruitment, hyperacusis, dyploacusis and speech intelligibility deficits (Basta et al., 2005; Pienkowski and Eggermont, 2010). These auditory impairments reduce an individual's quality of life and work productivity such that the economic burden to society may average $297,000 over an individual's life span (Mohr et al., 2000).

A major goal in audiologic rehabilitation and neuro-otologic medicine is the development of biomedical strategies that preserve auditory sensory and/or neural function following loud-sound exposure. To this end an impressive mosaic of pharmaceuticals that target individual pathophysiologic cascades has been employed (Le Prell et al. 2007; Ohlemiller, 2008). For instance, Ca^{2+} blockers have been used to regulate ionic homeostasis, creatine supplementation has been employed to restore energy and several types of free radical scavengers have been tested (Minami et al., 2007; Shen et al., 2007). Unfortunately, none of these single-target approaches has gained wide-spread clinical acceptance due in part to inconsistent outcomes. Since loud-sound exposure induces multiple pathologic cascades, then, an alternative approach might be to employ a multifunctional agent that simultaneously targets several pathophysiologic mechanisms. Given that CAEs of *UT* have demonstrated efficacy as a multifunctional cytoprotective agent in both human and animal studies, we speculated that CAEs might be otoprotective. Therefore, in the current experiment we tested the hypothesis that CAEs of *UT* will augment recovery of sensory and neuronal functions following noise injury.

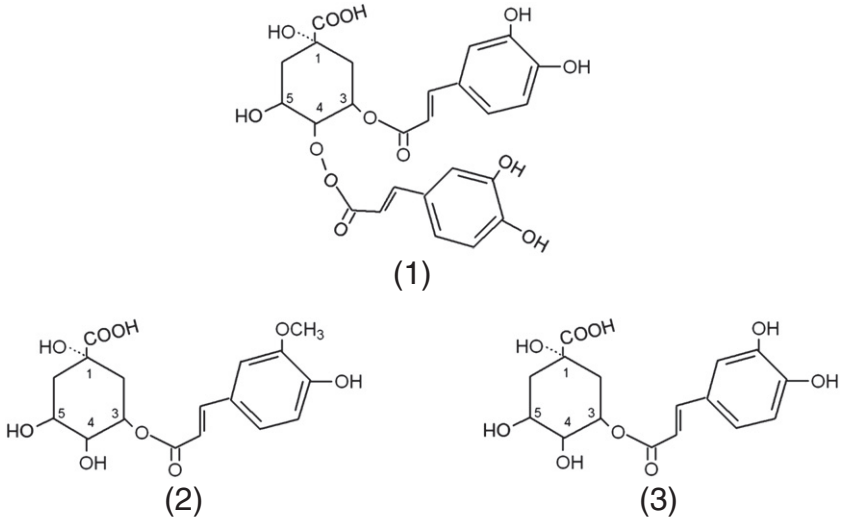

Fig. 1 – Chemical structure. The structure of three representative carboxy alkyl esters are shown: (1) 3,4-O-dicaffeoylquinic acid; (2) 3-O-feruloylquinic acid; and (3) 3-O-caffeoylquinic acid.