[PE1-14] [ 04/18/2003 (Fri) 09:30 - 12:30 / Hall P ]

## Protective Effects of Acanthoic acid on Tertiary-Butyl Hydroperoxide or Carbon tetrachloride-Induced Liver Injury

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The aim of this study was to investigate the protective effect of acanthoic acid on liver injury induced by either tertiary-butyl hydroperoxide (tBH) or carbon tetrachloride *in vitro* and *in vivo*. Acanthoic acid , (-)-pimara-9(11),15-diene-19-oic acid, is a diterpene isolated from the root bark of *Acanthopanax koreanum*. In in vitro study, the cellular leakage of lactate dehydrogenase (LDH) with 1.5 mM tBH for 1 h, were significantly inhibited by treatment with acanthoic acid (25 and 5 mg/mL). Treatment with acanthoic acid significantly inhibited the generation of intracellular reactive oxygen species (ROIs) and intracellular glutathione (GSH) depletion induced by tBH. The cellular leakage of LDH by 1-hour treatment with 2.5 mM carbon tetrachloride was significantly inhibited by treatment with acanthoic acid (25 mg/mL). Treatment with acanthoic acid (25 mg/mL) significantly inhibited the generation of intracellular reactive oxygen species (ROIs) and the intracellular GSH depletion induced by carbon tetrachloride. In acute liver injury models induced by either tBH or carbon tetrachloride, levels of aspartate transaminase and alanine transaminase were significantly reduced by acanthoic acid treatment (100 mg/kg/day for 4 consecutive days, p.o.). Histologicals observations revealed that fatty acid changes, hepatocyte necrosis and inflammatory cell infiltration in injured liver was improved in mice treated with acanthoic acid (100 mg/kg/day). From the results above, acanthoic acid had a protective effect against tBH or carbon tetrachloride induced hepatotoxicity *in vitro* and *in vivo*.

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## Enhanced in vitro/in vivo Characteristics of Glucagon-like Peptide-1 by PEGylation

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The insulinotropic hormone, glucagons-like peptide-1 (GLP-1), which has been proposed as a new potential therapeutics for type-II diabetes, but this is metabolized extremely rapidly by the ubiquitous enzyme, dipeptidyl peptidase IV (DPP IV), forming a metabolite, which acts as an antagonist at the GLP-1 receptor. To surmount this problem, GLP-1 was conjuagted with polyethylene glycol (mPEG-SPA, M.W. 2000) and the metabolic stability and biological activity of PEGylated GLP-1 were evaluated in vitro and in vivo, respectively. Mono-PEG-GLP-1 was separated by size-exclusion chromatography (SEC) and characterized by matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry. In stability test, incubation of GLP-1 with DPP IV resulted in degradation of native GLP-1 (7-36) forming GLP-1 (9-36), whereas mono-PEG-GLP-1 was resistant to DPP IV, consequently, exhibited a 17 folds-increased half-life. The in vivo biological activity was assessed by IVGTT in rats, in this study,mono-PEG-GLP-1 showed ten fold-increased glucose lowering effect compared with native GLP-1. The results of these in vitro/ in vivo experiments demonstrate that modification of GLP-1 with PEG increased the stability against DPP IV and improved the biological activity. This may indicate that PEGylation can improve the therapeutic potential of GLP-1 in type-II diabetes.