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Preparation of hydrophilic $C_{60}(OH)_{10}$/2-hydroxypropyl-β-cyclodextrin nanoparticles for the treatment of a liver injury induced by an overdose of acetaminophen

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Acetaminophen (paracetamol, *N*-acetyl-*p*-aminophenol) is a widely used analgesic and antipyretic drug. While there are generally few side effects when the recommended dose is used, an overdose causes hepatic injury and is the most frequent cause of the acute liver failure in the United State, the United Kingdom and other countries. The development and progression of liver injury induced by acetaminophen (APAP) is related to the production of ROS, such as superoxide anions and peroxynitrite. *N*-acetylcysteine is used to treat patients with an APAP overdose. However, the efficacy is limited and a novel approach for addressing this issue is required.

$C_{60}(OH)_{10}$ is a C_{60} derivative that 10 hydroxyl groups are introduced into a C_{60} molecule. It has been reported that polyhydroxylated C_{60} has a powerful antioxidant activity compared to unmodified C_{60}. Although $C_{60}(OH)_{10}$ is more soluble than unmodified C_{60}, further enhancement in their solubility is necessary for a precise evaluation of their biological activities and for extensive biomedical applications. In this study, we prepared the stable hydrophilic $C_{60}(OH)_{10}$ nanoparticles using HP-β-CyD, and investigated the therapeutic effect of $C_{60}(OH)_{10}$ nanoparticles as an antioxidant on the APAP overdose induced liver injury.

$C_{60}(OH)_{10}$/HP-β-CyD nanoparticles were prepared by grinding the mixture of $C_{60}(OH)_{10}$ and HP-β-CyD (mainly 1:3 molar ratio) for 3h at 4ºC under reduced pressure. The resulting nanoparticles were characterized by means of a dynamic light scattering machine (DLS) and a

ζ-potential analyzer. The antioxidant ability of $C_{60}(OH)_{10}$/HP-β-CyD nanoparticles was evaluated by the scavenging ability to DPPH, ABTS and hydroxyl radicals. $C_{60}(OH)_{10}$/HP-β-CyD nanoparticles were applied to the treatment of an APAP overdose induced liver injury. Serum ALT and AST levels were monitored in order to measure the level of the liver injury.

$C_{60}(OH)_{10}$/HP-β-CyD nanoparticles showed a small particle size, ca. 50 nm, and maintained this size over 28 days in water at 25˚C. $C_{60}(OH)_{10}$/HP-β-CyD nanoparticles scavenged DPPH, ABTS and hydroxyl radicals in a dose dependent manner. When $C_{60}(OH)_{10}$/HP-β-CyD nanoparticles were intravenously administered to mice with a liver injury induced by an overdose of APAP, the ALT and AST levels were markedly reduced to almost the same level as that of normal mice. These results clearly indicate that $C_{60}(OH)_{10}$/HP-β-CD nanoparticles have a protective effect against the progression of liver injury induced by an overdose of APAP. To reveal the mechanism responsible for liver protection by $C_{60}(OH)_{10}$/HP-β-CyD nanoparticles, GSH level, CYP2E1 expression and peroxynitrite formation in the liver were assessed. $C_{60}(OH)_{10}$/HP-β-CyD nanoparticles had no effect on CYP2E1 expression and GSH depletion, but suppressed the generation of peroxynitrite in the liver. The findings indicated that the protective effect of $C_{60}(OH)_{10}$/HP-β-CyD nanoparticles was due to the suppression of oxidative stress in mitochondria, as the result of scavenging ROS such as $O_2^{\bullet-}$, NO and peroxynitrite, which act as critical mediators in the liver injuries.

Keywords: $C_{60}(OH)_{10}$/HP-β-CyD nanoparticles; Liver injury; Overdose of acetaminophen

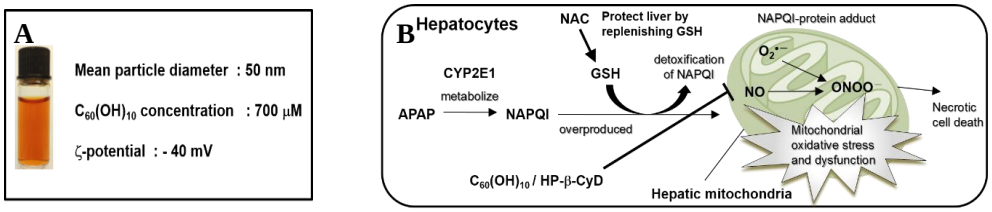

Fig 1. Appearance and characterization of $C_{60}(OH)_{10}$/HP-β-CyD nanoparticles (A) and protective mechanism of $C_{60}(OH)_{10}$/HP-β-CyD nanoparticles against APAP induces hepatotoxicity (B)

Reference

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