様式 7

論　文　内　容　要　旨

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学位論文題目	Effects of liposomes encapsulating ferulic acid on CCl_4-induced oxidative liver damage in a rat model （四塩化炭素誘導酸化的肝障害モデルラットに対するフェルラ酸含有リポソームの影響）		

Oxidative stress is well known as one of the causative agents of liver diseases. Antioxidants are helpful for the treatment of oxidative stress-mediated liver damage. A naturally occurring antioxidant, γ- oryzanol, is rapidly hydrolyzed to its active hydrophobic metabolite, ferulic acid, inside the body. As a hydrophobic drug, ferulic acid has several limitations, such as poor solubility and low bioavailability associated with minimal drug delivery in the body. Limitations related to the hydrophobicity of ferulic acid can be overcome by encapsulating it in a liposomal formulation. As intravenously administered nanoparticles (including liposomes) can effectively reach the liver, such systems may be suitable drug delivery carriers to treat liver injury. Therefore, in this study, I prepared a liposomal formulation of ferulic acid (ferulic-lipo) and examined its effects on liver damage induced by CCl_4. Ferulic-lipo was prepared by lipid hydration method, size was ~100nm, and drug encapsulation efficiency was about 92%. At first, I measured the hydroxy radical scavenging capability of ferulic-lipo and compared it with a known antioxidant α-tocopherol. I found that ferulic-lipo showed higher radical scavenging than α-tocopherol liposomes. As ferulic-lipo showed a significant antioxidative effect, I examined whether ferulic-lipo exhibited protective effects against CCl_4-mediated cytotoxicity in human hepatocarcinoma (HepG2) cells. Ferulic-lipo showed significant improvement in the viability of HepG2 cells (~30%) against CCl_4-induced toxicity. Based on this finding, next, I applied ferulic-lipo for *in vivo* study by preparing a liver-injured rat model to assess its potentiality against CCl_4-induced oxidative liver damage. Then, I examined the serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, which indicate the severity of liver damage in the rat model of liver injury. I found a marked elevation in serum ALT and AST levels in the CCl_4-treated group, demonstrating the development of a liver-injured rat model. With the intravenous administration of ferulic-lipo, serum ALT & AST levels significantly reduced (30% & 35%) dose-dependently indicating hepatoprotective effects of ferulic-lipo. Next, I studied the impact of ferulic-lipo on ROS production in the liver. Administration of CCl_4 results in a high level of ROS generation in the liver. Contrary, the liver's ROS was markedly reduced (~50%) by intravenous administration of ferulic-lipo. To further confirm ferulic-lipo's hepatoprotective effects, I performed histopathological observation of liver tissues and found that ferulic-lipo significantly reduced CCl_4-mediated hepatocyte damage in the treatment group. Next, I found that the stability of ferulic acid was not so high in ferulic-lipo, so I focused on improving the stability of ferulic acid. I hypothesized that γ- oryzanol would be a prodrug of ferulic acid because it tends to metabolize into ferulic acid inside the body rapidly. Then, I prepared a liposomal formulation of γ- oryzanol (γ-ory-lipo) and checked its chemical stability. Regarding the stability of γ-oryzanol in the liposome, I found γ-ory-lipo showed high stability. Additionally, I measured the antioxidant activity of γ-ory-lipo, but the activity was lower than ferulic-lipo. Next, I checked the conversion of ferulic acid to γ- oryzanol and found that γ- oryzanol was successfully and immediately converted into the ferulic acid in the cultured cells (HepG2 cells) analyzed by HPLC. Based on these findings, it was suggested that γ-ory-lipo would be a good prodrug formulation of ferulic acid. The overall results of this study indicate that ferulic-lipo exhibited potent antioxidative capacity and was suggested to be an effective formulation for preventing oxidative damage of liver tissue.