In vivo monitoring of treatment effect of cryptotanshinone for non-alcoholic fatty liver disease in mice

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Introduction: Non-alcohic fatty liver disease cause insulin resistance, and may develop into steatohepatitis, type II diabetes, and several other metabolic diseases. AMP-activated protein kinase (AMPK) has become as a novel therapeutic target for the treatment of metabolic syndromes. We have isolated a novel AMPK pathway activator cryptotanshinone (Cryp) from *Salvia militorrhiza*. Here we tested the effect of Cryp on non-alcoholic fatty liver in *Lep*$^{ob/ob}$(*ob*/*ob*) and diet-induced obese (DIO) mouse models.

Materials and methods: MRI was performed by using a 4.7 T MRI system (BioSpec 47/40; Bruker, Ettlingen,Germany). T1-weighted images were obtained to study the distribution of fat stores in mice, using the following parameters: TR/TE = 665/14 ms; slice thickness = 1 mm; FOV = 3.5 × 3.5 cm2; matrix = 256 × 256. ^{1}H localized MR spectra were acquired from the left and right lateral lobes of the liver (Figure 1) using a stimulated echo sequence with TR = 2500 ms, TE = 144 ms, voxel size = 3×3× 3 mm^3, and NEX = 64.

Results and discussion: Cryp treatment significantly reduced hepatic and serum triglyceride in a dose-dependent manner. There was a good correlation in the hepatic lipid content analyses between magnetic resonance imaging (MRI), MR spectroscopy (MRS), and oil red O staining. Also Cryp treatment reduced body weight without visible influence in food intake. This reduction was not due to any toxicity of Cryp, since the levels of serum GPT, LDH, and BUN were all rather reduced significantly by Cryp treatment in a dose-dependent manner. Administration of Cryp to these mice also lowered significantly the circulating levels of glutamate pyruvate transaminase, lactate dehydrogenase, and blood urea nitrogen. Quantitative RT-PCR data showed a decrease in lipogenesis-related gene expressions and an increase in fatty acid oxidation-related gene expressions in the liver. MRS data from male DIO mice (C57BL6/J) also demonstrated that the administration of Cryp well prevented an increase in hepatic lipid content in a dose-dependent manner. Their blood levels of glycosylated hemoglobin (Hb_{A1c}) were dropped significantly as well. Pioglitazone, known to reduce fatty acid production, was also effective in reducing hepatic lipid content, but failed to lower Hb_{A1c}. We conclude that Cryp is safe and highly effective in treating non-alcoholic fatty liver.

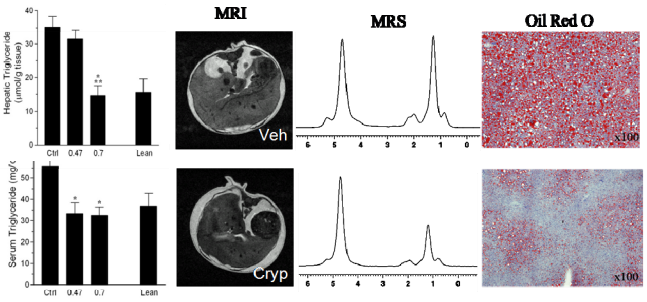

Figure 1. Cryptotanshinone (Cryp) effectively reduced hepatic and circulating triglyceride (TG) as well as hepatic lipid contents in *ob*/*ob* mice.

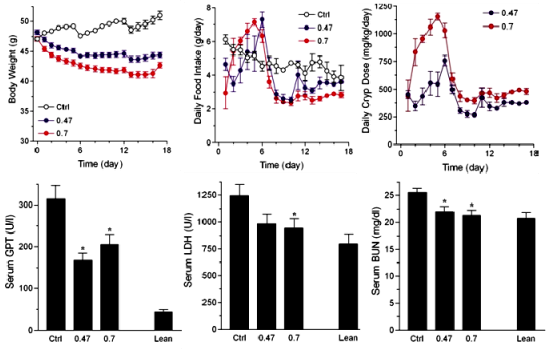

Figure 2. Cryp lowered body weight and was safe in *ob*/*ob* mice. Cryp treatment reduced body weight with limited influence in food intake (4.7±0.1 for control, 4.0±0.3 for Cryp 0.47%, and 3.8±0.4 g/day for Cryp 0.7% in average).