Enhanced efficacy of curcumin with phosphatidylserine-decorated nanoparticles in the treatment of hepatic fibrosis

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ABSTRACT: Hepatic macrophages have been considered as a therapeutic target for liver fibrosis treatment, and phosphatidylserine (PS)-containing nanoparticles are commonly used to mimic apoptotic cells that can specifically regulate macrophage functions, resulting in anti-inflammatory effects. This study was designed to test the efficacy of PS-modified nanostructured lipid carriers (mNLCs) containing curcumin (Cur) (Cur-mNLCs) in the treatment of liver fibrosis in a rat model. Carbon tetrachloride-induced liver fibrosis in rats was used as an experimental model, and the severity of the disease was examined by both biochemical and histological methods. Here, we showed that mNLCs were spherical nanoparticles with decreased negative zeta potentials due to PS decoration, and significantly increased both mean residence time and area under the curve of Cur. In the rats with liver fibrosis, PS-modification of NLCs enhanced the nanoparticles targeting to the diseased liver, which was evidenced by their highest accumulation in the liver. As compared to all the controls, Cur-mNLCs were significantly more effective at reducing the liver damage and fibrosis, which were indicated by in Cur-mNLCs-treated rats the least increase in liver enzymes and pro-inflammatory cytokines in the circulation, along with the least increase in collagen fibers and alpha smooth muscle actin and the most increased hepatocyte growth factors (HGF) and matrix metalloprotease (MMP) two in the livers. In conclusion, PS-modified NLCs nanoparticles prolonged the retention time of Cur, and enhanced its bioavailability and delivery efficiency to the livers, resulting in reduced liver fibrosis and up-regulating hepatic expression of HGF and MMP-2.

KEYWORDS: Phosphatidylserine; curcumin; nanostructured lipid carriers; liver fibrosis; macrophages

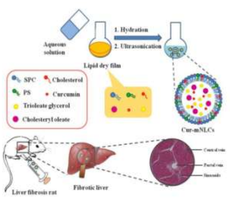

Figure 1. A schematic diagram of preparation procedures and liver targeting properties of Cur-mNLCs.

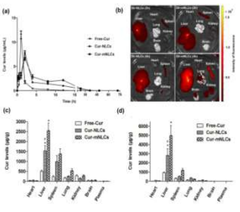

Figure 3. PS enhanced the retention times of Cur encapsulated in NLCs in sera as well as Cur delivery by NLCs to the liver in vivo. (a) The changes of plasma concentration of Cur after i.p. injection. (b) Ex vivo imaging of organs in rats with liver fibrosis. (c–d) Tissue distribution of Cur after i.p. injection at 2 h (c) and 4 h (d).

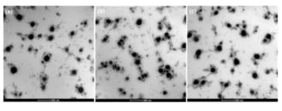

Figure 2. Typical TEM images of NLCs. (a) Cur-NLCs; (b) Cur-mNLCs; (c) B-mNLCs.

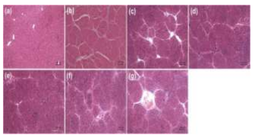

Figure 4. Effects of different drug formulations on the histological changes in the liver of CCl_4-treated rats as shown by H&E staining.

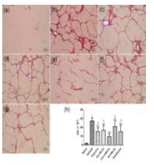

Figure 5. Fibrosis assessed by using Sirus Red staining.

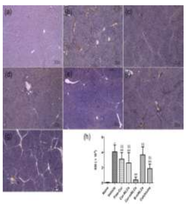

Figure 6. Representative images of liver sections processed for immunohistochemistry staining for Collagen-I.

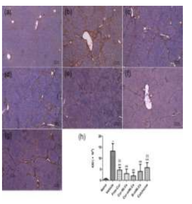

Figure 7. Representative images of liver sections processed for immunohistochemistry staining for α-SMA.

Figure 4-7, (a) Naive group, (b) Vehicle group (positive control), (c) Free-Cur group, (d) Cur-NLCs group, (e) Cur-mNLCs group, (f) B-mNLCs group, (g) Colchicine group.

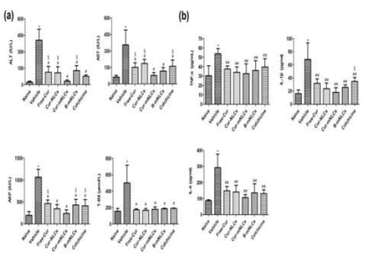

Figure 8. Treatment with Cur-mNLCs significantly more reduced CCl_4-induced elevation of liver disorder markers and pro-inflammatory cytokines in sera. (a) Serum levels of ALT, AST, AKP and T-Bil. (b) Serum levels of inflammatory cytokines TNF-α, IL-1 β and IL-6.

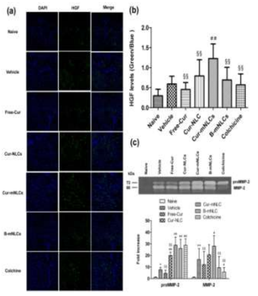

Figure 9. Treatment with Cur-mNLCs significantly up-regulated HGF expression and activated MMP-2 secretion in the liver. (a) Immunofluorescent staining of liver slices for HGF. (b) HGF fluorescence intensity. (c) Gelatin zymography assay of proMMP-2 and MMP-2 activity.