Accepted Manuscript

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PII: S0168-3659(18)30492-9
DOI: doi:10.1016/j.jconrel.2018.08.026
Reference: COREL 9435

To appear in: *Journal of Controlled Release*

Received date: 21 April 2018
Revised date: 22 July 2018
Accepted date: 16 August 2018

Please cite this article as: Mona A. Abdelmoneem, Mazen Mahmoud, Amira Zaky, Maged W. Helmy, Marwa Sallam, Jia-You Fang, Kadria A. Elkhodairy, Ahmed O. Elzoghby , Dual-targeted casein micelles as green nanomedicine for synergistic phytotherapy of hepatocellular carcinoma. Corel (2018), doi:10.1016/j.jconrel.2018.08.026

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ACCEPTED MANUSCRIPT

Dual-Targeted Casein Micelles as Green Nanomedicine for Synergistic Phytotherapy of Hepatocellular Carcinoma

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Abstract

In recent years, green nanomedicines have made transformative difference in cancer therapy researches. Herein, we propose dual-functionalized spray-dried casein micelles for combined delivery of two phytochemicals; berberine (BRB) and diosmin (DSN) as targeted therapy of hepatocellular carcinoma (HCC). The nanomicelles enabled parenteral delivery of the poorly soluble DSN via its encapsulation within their hydrophobic core. Moreover, sustained release of the water soluble BRB was attained by hydrophobic ion pairing with sodium deoxycholate followed by genipin crosslinking of casein micelles (CAS-MCs). Dual-active targeting of MCs, via conjugating both lactobionic acid (LA) and folic acid (FA), resulted in superior cytotoxicity and higher cellular uptake against HepG2 cells compared to single-targeted and non-targeted CAS-MCs. The dual-targeted DSN/BRB-loaded CAS-MCs demonstrated superior in vivo anti-tumor efficacy in HCC bearing mice as revealed by down regulation of cell necrosis markers (NF-κB and TNF-α), inflammatory marker COX2, inhibition of angiogenesis and induction of apoptosis. Histopathological analysis and immunohistochemical Ki67 staining confirmed the superiority of the dual-targeted micelles. Ex-vivo imaging showed preferential liver-specific accumulation of dual-targeted CAS-MCs. Overall, this approach combined the benefits of traditional herbal medicine with nanotechnology via LA/FA-CAS-MCs loaded with BRB and DSN as a promising nanoplatform for targeted HCC therapy.

Key words: Green nanomedicine; hepatocellular carcinoma; casein micelles; dual-targeting; lactobionic acid; folic acid.

Introduction

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