Biomedicine & Pharmacotherapy 105 (2018) 274–281

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Curcumin regulates endogenous and exogenous metabolism via Nrf2-FXR-LXR pathway in NAFLD mice

Caixia Yan[a,1], Yirui Zhang[a,1], Xiaoxu Zhang[b], Jiye Aa[a], Guangji Wang[a,*], Yuan Xie[a,*]

[a] Key Laboratory of Drug Metabolism and Pharmacokinetics, State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, China
[b] Jiangsu Key Laboratory of TCM Evaluation and Translational Research, Department of Pharmacology of Chinese Materia Medica, China Pharmaceutical University, Nanjing 211198, China

ARTICLE INFO

Keywords:
Curcumin
CYP3A
CYP7A
Metabolic regulation
Endogenous metabolism
Exogenous metabolism

ABSTRACT

Background: Curcumin is a natural polyphenol with beneficial effects on NAFLD patients and NAFLD is accompanied by metabolism decompensation.
Methods: This study was focused on the effect of curcumin on the relationship between endogenous bile acids metabolism pathway and exogenous xenobiotics metabolism pathway in C57BL/6 mice of non-alcoholic fatty liver disease induced by high-fat and high-fructose diet (HFHFr) and in cultured mice hepatocytes.
Results: Our results showed curcumin treatment apparently attenuated the hepatic steatosis and reversed the abnormalities of serum biochemical parameters in HFHFr-fed mice. Curcumin effectively reversed the expression of CYP3A and CYP7A in fatty liver status to restore metabolism capability. In the meantime, lipid synthesis has been controlled by curcumin, evidenced by the expression of CD36, SREBP-1c and FAS. Further, FXR, SHP and Nrf2 expressions were remarkably dropped in HFHFr-fed mice and LXRα expression was significantly enhanced, while curcumin treatment was quite effective to restore this pathway. In addition, LXRα antagonist GGPP pretreatment weakened the curcumin effects on CYP3A, CYP7A and SREBP-1c.
Conclusions: These findings indicate that the Nrf2/FXR/LXRα pathway might synergistically regulate both endogenous and exogenous metabolism in NAFLD mice and LXRα may be a novel therapeutic target of curcumin for the prevention and treatment of NAFLD.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD), due to the high fat and/or high glucose diet, has become one of the most common liver diseases worldwide. The main pathological character of NAFLD is lipid accumulation in liver along with hepatic steatosis. Fatty acid biosynthesis is transcriptionally regulated by liver X receptor-α (LXRα) and its gene target, sterol regulatory element binding protein-1c (SREBP-1c) [1]. LXRα forms heterodimers with retinoid X receptor (RXR) and involves in regulating lipid and cholesterol homeostasis. SREBP-1c is also activated by the nuclear receptor heterodimer which regulates genes such as acetyl-coenzyme (Co) A carboxylase (ACC) and fatty acid synthase (FAS) [2–4].

The superfamily Cytochromes P450s (P450s) are responsible for the metabolism of both a large number of xenobiotics and endogenous molecules. Inhibition or induction of drug metabolism enzymes could cause severe clinical consequences such as drug-drug interactions (DDIs). CYP3A is one of the most crucial P450s which is regulated by Pregnane X receptor (PXR) and androstane receptor (CAR) [5,6]. Both nuclear receptors recognize and bind to the respective DNA recognition elements to induce the expression of CYP3A [7]. Some P450s such as CYP7A1 participate in the biosynthesis and metabolism of endogenous molecules [8]. The nuclear receptors liver X receptor (LXR) and the farnesoid X receptor (FXR) regulate the expression of CYP7A1 [9,10]. However, the metabolism of drugs or xenobiotics and lipids are not independent. [11–13]. There are intricate networks between these nuclear receptors [14].

Curcumin was found to have multiple effects as anti-inflammatory, anti-oxidative and anti-tumor effects, as well as affecting lipid metabolism in NAFLD mouse models [15–18]. Curcumin was proved to

Abbreviations: ACC, acetyl-coenzyme (Co) A carboxylase; BA, bile acid; CAR, androstane receptor; DDI, drug-drug interaction; FAS, fatty acid synthase; GGPP, geranylgeranyl pyrophosphate; HFD, high-fat diet; HNF-4, hepatocyte nuclear factor-4; LXR, liver X receptor; NAFLD, non-alcoholic fatty liver disease; Nrf2, nuclear factor erythroid-2-related factor 2; P450s, cytochromes P450; PA, palmitate; PPAR, peroxisome proliferator-activated receptor; PXR, pregnane X receptor; SHP, small heterodimer partner; SREBP-1c, sterol regulatory element binding protein-1c; CYP3A, cytochrome P450 3A; CYP7A1, cytochrome P450 7A1; CD36, cluster of differentiation 36

* Corresponding authors.
E-mail addresses: gjwang@cpu.edu.cn (G. Wang), yuanxie@cpu.edu.cn (Y. Xie).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.biopha.2018.05.135
Received 26 March 2018; Received in revised form 28 May 2018; Accepted 28 May 2018

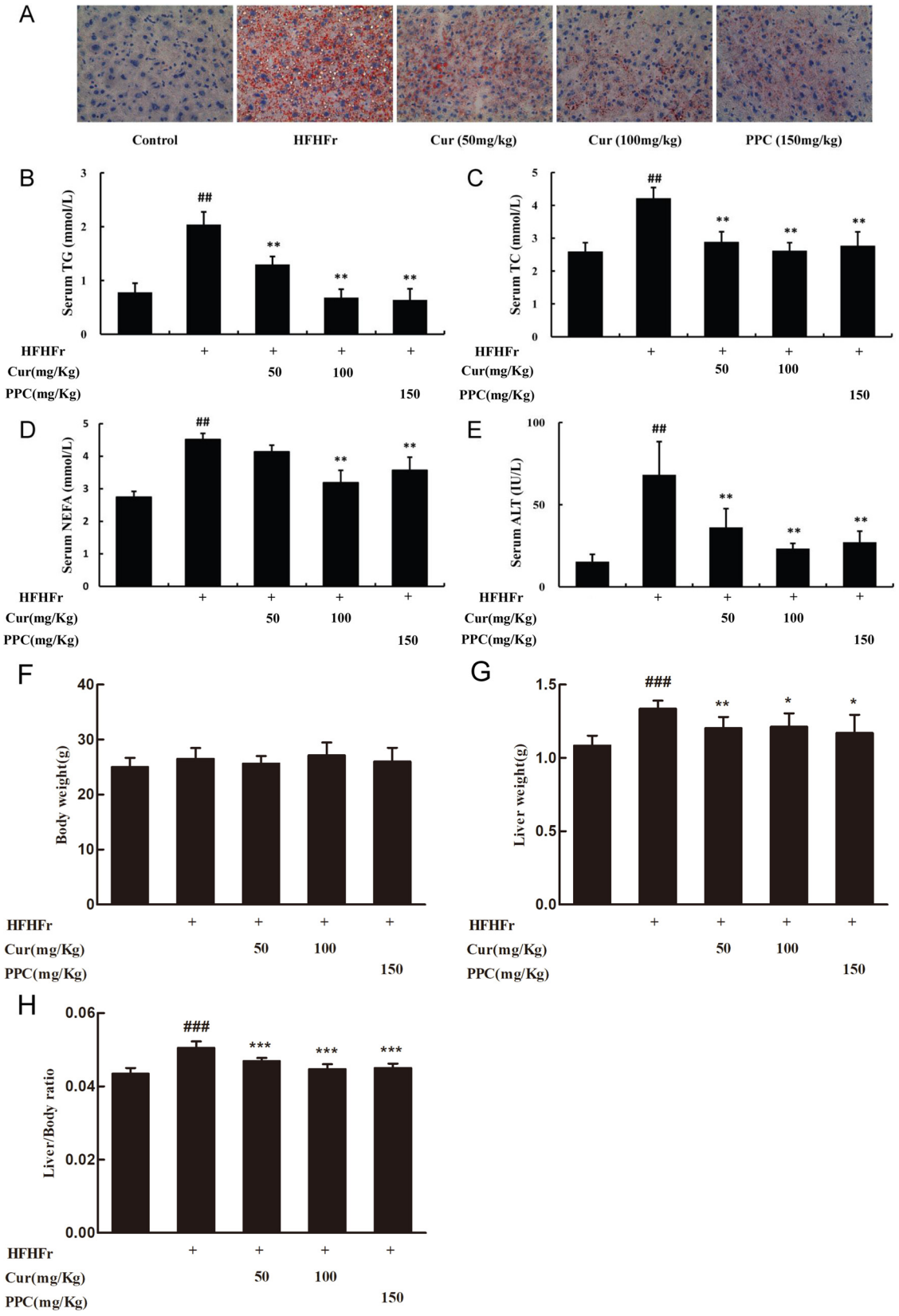

Fig. 1. Effects of Curcumin (Cur) and Polyene Phosphatidyl Choline (PPC) on hepatic lipid accumulation and serum biochemical parameters in high fat and high fructose fed mice. (A) Representative photomicrographs of Oil Red O staining (200×) of livers. Serum levels of (B) TG, (C) TC, (D) NEFA, (E) ALT were measured using kits according to manufacturer's instruction. The effect of high-fat and high-fructose diet on (F) body weight, (G) liver weight and (H) liver/body ratio. Data were shown as mean ± S.D. of six mice per group. $^{\#\#}$ $P < 0.01$, $^{\#\#\#}$ $P < 0.001$, vs. control group; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, vs. HFHFr group.