Biomedicine & Pharmacotherapy 97 (2018) 481–488

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Original article

Protective effect of dioscin against thioacetamide-induced acute liver injury via FXR/AMPK signaling pathway *in vivo*

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ARTICLE INFO

Keywords:
Dioscin
Thioacetamide
Acute liver injury
Oxidative stress
FXR/AMPK signal pathway

ABSTRACT

Our previous works showed that dioscin, a natural product, could protect liver from acute liver damages induced by dimethylnitrosamine, ethanol, carbon tetrachloride and acetaminophen. However, the effect of dioscin on thioacetamide (TAA)-induced acute liver injury still remained unknown. The purpose of this study was to investigate whether dioscin confers a protective effect against TAA-induced acute liver injury in rats and mice. The results showed that dioscin decreased the serum levels of ALT, AST, and rehabilitated histopathological changes compared with the model groups. In addition, dioscin obviously increased the levels of GSH, GSH-Px, SOD, and significantly reduced MDA levels compared with the model groups. Mechanistic study showed that dioscin significantly up-regulated the expression levels of FXR, *p*-AMPKα, and then increased the expression levels of Nrf2, HO-1, NQO-1, GCLM and GST. Furthermore, dioscin obviously down-regulated the expression levels of NF-κB (p65), ICAM-1, HMGB1, COX-2, TNF-α, IL-1β and IL-6. Taken together, dioscin showed protective effect against TAA-induced acute liver injuries in rats and mice and the effects might be obtained through inhibiting oxidative stress and inflammation via FXR/AMPK signal pathway. These findings provided a new insight on the role of doscin in the treatment of acute liver injury.

1. Introduction

Liver has the functions to remove toxins, fight infections, and control cholesterol levels [1–3]. Some liver diseases including acute liver injury, fibrosis, cirrhosis, and hepatocellular carcinoma, can be triggered by various risk factors. Some animal models have been developed for pharmacological investigation and mechanistic study of drugs or chemicals against liver diseases [4]. Thioacetamide (TAA), a classic liver toxic compound, can induce oxidative stress and inflammation to cause organ damage [5,6], which has been used to establish experimental models of liver injury [7,8].

Many signals are related to oxidative stress and inflammation regulation [9]. Farnesoid X receptor (FXR), a highly expressed hepatic nuclear bile acid receptor, plays crucial roles in cholesterol/bile acid metabolism, glucose/lipid metabolism, oxidative stress and inflammation [10,11]. Some studies have suggested that FXR is a potential therapeutic target for liver diseases [12,13]. FXR agonist can inhibit bile acid-induced oxidative stress [14] and FXR ligands may be the potential therapeutic implication for the treatment of liver inflammatory diseases [15]. Furthermore, FXR can regulate AMP-activated protein kinase (AMPK) to protect hepatic damage [16,17], which also plays the regulatory roles in oxidative stress, inflammation and mitochondrial dysfunction [18,19]. Many agents used for cellular protection can inhibit free radicals and induce antioxidant enzymes through AMPK activation [20,21]. In addition, AMPK activation can protect carbon tetrachloride-induced acute liver damage [22], and adjust the expression of nuclear erythroid factor 2-related factor 2 (Nrf2) [23,24], which plays important roles in regulating antioxidant process [25,26]. Furthermore, AMPKα can suppress the production of tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) [27] and inhibit the activation of nuclear factor-κB (NF-κB) [28]. In D-GalN (D-Galactosamine)/LPS (lipopolysaccharide)- induced acute liver failure in mice, AMPK activation ameliorated liver damage via inhibiting inflammation through decreasing the levels of TNF-α, IL-1β and IL-6 [29]. Thus, FXR/AMPK signal may exert a positive regulating effect on Nrf2 and NF-κB signals to adjust oxidative stress and inflammation.

Some active nature products of Traditional Chinese medicines (TCMs) including curcumin, resveratrol and berberine show protective effects against liver injury [30,31]. Dioscin (Dio, Fig. 1A), a nature product from the famous vegetable *Dioscoreae rhizoma* (Shanyao in

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http://dx.doi.org/10.1016/j.biopha.2017.10.153
Received 2 October 2017; Received in revised form 25 October 2017; Accepted 25 October 2017

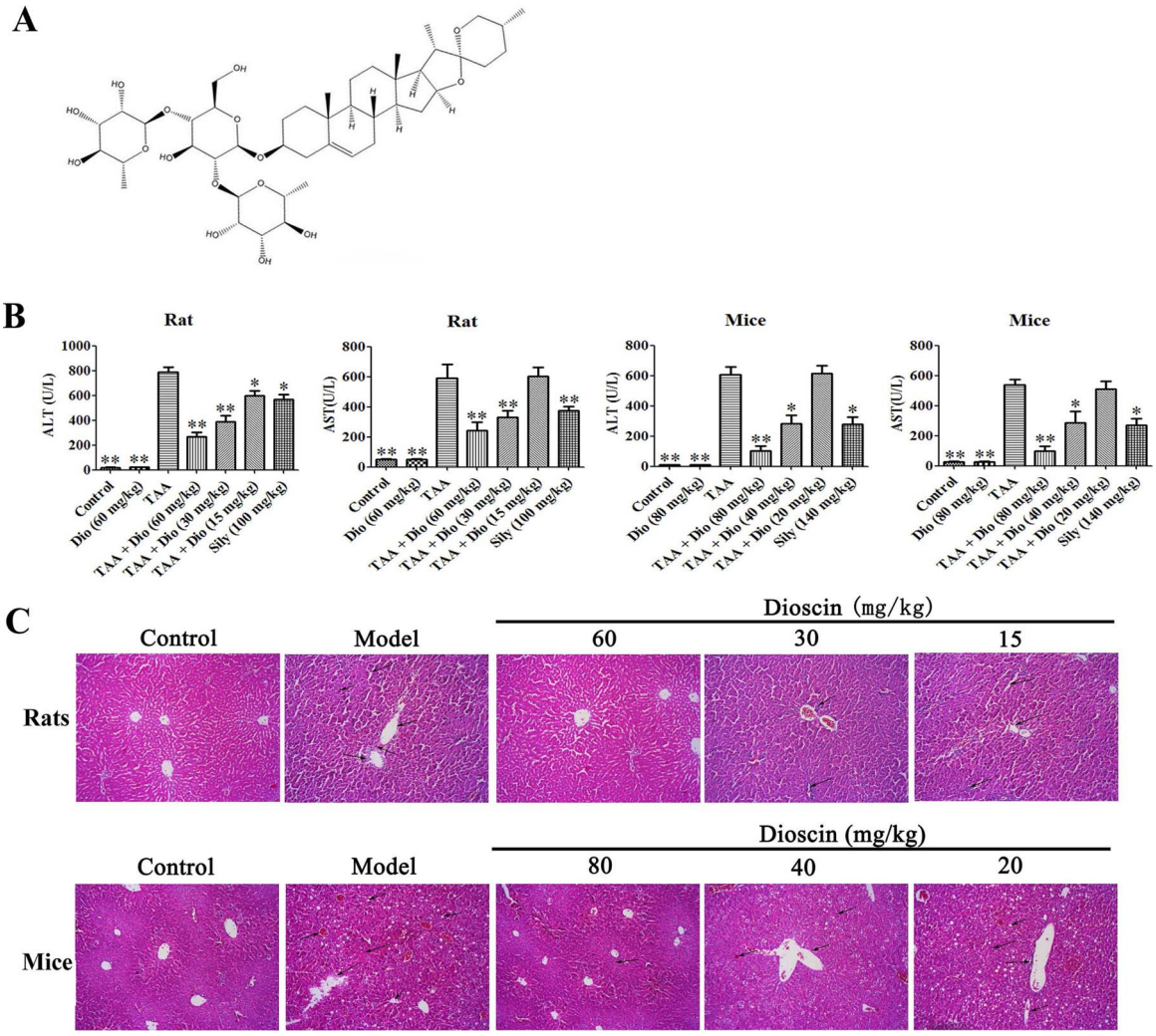

Fig. 1. Effects of dioscin against TAA-induced liver injuries in rats and mice. (A) The chemical structure of dioscin. (B) Effects of dioscin on serum levels of ALT and AST in rats and mice. (C) H & E staining of livers in rats and mice (200 × original magnification). Data are expressed as the mean ± SD (n = 10). *p < 0.05 and **p < 0.01 compared with model groups.

Table 1
The primers of real-time PCR assay in the present work.

Gene	GenBank accession	Primer (5′-3′)
Rat-GAPDH	NM_017008.3	Forward: GGCACAGTCAAGGCTGAGAATG Reverse: ATGGTGGTGAAGACGCCAGTA
Rat-TNF-α	NM_012675.3	Forward: TCAGTTCCATGGCCCAGAC Reversed: GTTGTCTTTGAGATCCATGCCATT
Rat-IL-1β	NM_031512.2	Forward: TCAGTTCCATGGCCCAGAC Reverse: GTTGTCTTTGAGATCCATGCCATT
Rat-IL-6	NM_012589.1	Forward: CCCTGAACTCAACTGTGAAATAGCA Reverse: CCCAAGTCAAGGGCTTGGAA
Mouse-GAPDH	NM_008084.2	Forward: TGTGTCCGTCGTGGATCTGA Reverse: TTGCTGTTGAAGTCGCAGGAG
Mouse-TNF-α	NM_013693.2	Forward: TATGGCCCAGACCCTCACA Reverse: GGAGTAGACAAGGTACAACCCATC
Mouse-IL-1β	NM_008361.3	Forward: TCCAGGATGAGGACATGAGCAC Reverse: GAACGTCACACACCAGCAGGTTA
Mouse-IL-6	NM_031168.1	Forward: CCACTTCACAAGTCGGAGGCTTA Reverse: CCAGTTTGGTAGCATCCATCATTTC

Table 2
Antibody information used in the present study.

Antibody	Source	Dilutions	Company
GAPDH	Rabbit	1: 2000	Proteintech Group, Chicago, USA
FXR	Rabbit	1: 1000	Proteintech Group, Chicago, USA
Nrf2	Rabbit	1: 1000	Proteintech Group, Chicago, USA
HO-1	Rabbit	1: 1000	Proteintech Group, Chicago, USA
NQO1	Rabbit	1: 1000	Proteintech Group, Chicago, USA
GCLM	Rabbit	1: 1000	Proteintech Group, Chicago, USA
GST	Rabbit	1: 1000	Proteintech Group, Chicago, USA
AMPKα	Rabbit	1: 1000	Proteintech Group, Chicago, USA
p-AMPKα	Rabbit	1: 1000	Proteintech Group, Chicago, USA
NF-κB	Rabbit	1: 1000	Proteintech Group, Chicago, USA
ICAM-1	Rabbit	1: 1000	Proteintech Group, Chicago, USA
HMGB-1	Rabbit	1: 1000	Proteintech Group, Chicago, USA
COX-2	Rabbit	1: 500	Proteintech Group, Chicago, USA

Chinese) and some other medicinal plants, has anti- inflammatory, antioxidant and anti-tumor activities [32–35]. Our previous works showed that dioscin had protective activities against carbon tetrachloride-, dimethylnitrosamine- and acetaminophen-induced acute liver damages, non- alcoholic fatty liver disease, and hepatic ischemia/reperfusion injury [34–41]. Importantly, we also found that dioscin had protective effects against TAA-induced liver fibrosis [42] via inhibiting the activation of hepatic stellate cells (HSCs). However, there have no papers to report the actions of dioscin on TAA-induced acute liver damage to our best knowledge.

The aim of the current study was to investigate the protective effects and the possible underlying mechanisms of dioscin against TAA-induced acute liver injury in rats and mice.