ENVIRONMENTAL TOXICOLOGY AND PHARMACOLOGY 37 (2014) 729–737

Available online at www.sciencedirect.com

ScienceDirect

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

Zn(II)–curcumin protects against hemorheological alterations, oxidative stress and liver injury in a rat model of acute alcoholism

Chuan Yu, Xue-Ting Mei, Yan-Ping Zheng, Dong-Hui Xu *

Laboratory of Traditional Chinese Medicine and Marine Drugs, Department of Biochemistry, School of Life Sciences, Sun Yat-sen University, Guangzhou 510275, China

ARTICLE INFO

Article history:
Received 14 November 2013
Received in revised form
9 February 2014
Accepted 12 February 2014
Available online 20 February 2014

Keywords:
Zn(II)–curcumin
Alcohol
Oxidative stress
Hemorheology
Liver injury

ABSTRACT

Curcumin can chelate metal ions, forming metallocomplexes. We compared the effects of Zn(II)–curcumin with curcumin against hemorheological alterations, oxidative stress and liver injury in a rat model of acute alcoholism. Oral administration of Zn(II)–curcumin dose-dependently prevented the ethanol-induced elevation of serum malondialdehyde (MDA) content and reductions in glutathione level and superoxide dismutase (SOD) activity. Zn(II)–curcumin also inhibited ethanol-induced liver injury. Additionally, Zn(II)–curcumin dose-dependently inhibited hemorheological abnormalities, including the ethanol-induced elevation of whole blood viscosity, plasma viscosity, blood viscosity at corrected hematocrit (45%), erythrocyte aggregation index, erythrocyte rigidity index and hematocrit. Compared to curcumin at the same dose, Zn(II)–curcumin more effectively elevated SOD activity, ameliorated liver injury and improved hemorheological variables. These results suggest that Zn(II)–curcumin protected the rats from ethanol-induced liver injury and hemorheological abnormalities via the synergistic effect of curcumin and zinc.

1. Introduction

Alcohol abuse has become a global social, economic and health issue. Alcohol abuse results in oxidative stress, leading to the modification of all biological structures and serious malfunction of the cells and tissues (Kaphalia and Calhoun, 2013). Ethanol ingestion elevates the level of malondialdehyde (MDA) and perturbs the plasma enzymatic antioxidant system, including enzymes such as superoxide dismutase (SOD). Furthermore, alcohol abuse contributes to the depletion of glutathione (GSH) by reducing its synthesis and metabolism (Liang et al., 2013). GSH is a major cellular antioxidant and redox regulator, and plays an important role in preventing the oxidation of cellular constituents (Brocardo et al., 2011). Depletion of hepatic GSH makes hepatocytes more vulnerable to the oxidative stress induced by alcohol, and contributes to alcoholic liver disease. The pathogenesis of alcoholic liver disease is closely related to alcohol-induced oxidative stress (Radosavljevic et al., 2009).

Moreover, chronic alcohol consumption can lead to an abnormal erythrocyte morphology and increased erythrocyte fragility as a result of the oxidation and cross-linking of erythrocyte ghost proteins (Tyulina et al., 2006). Increased

* *Corresponding author*. Tel.: +86 20 84113651; fax: +86 20 84113651.
E-mail address: Donghuixu007@163.com (D.-H. Xu).

http://dx.doi.org/10.1016/j.etap.2014.02.011
1382-6689/

blood viscosity, erythrocyte rigidity and impaired erythrocyte flexibility have also been reported to be induced by the administration of alcohol (Guillet et al., 1991). In patients with ischemic cerebrovascular disease, ingestion of ethanol at a dose of 0.5 or 1 g/kg body weight increased whole blood viscosity and blood viscosity corrected for hematocrit, and impaired red blood cell deformability (Nagai et al., 2001). These effects of alcohol consumption can largely be ascribed to the oxidative stress induced by alcohol. Since erythrocytes have a limited biosynthetic capacity and poor repair mechanism, constant exposure to alcohol-induced oxidative stress may lead to the accumulation of physical or molecular modifications in erythrocytes. Such modifications can result in abnormal erythrocyte function and blood rheology, which directly affects the ability of the blood to deliver oxygen to the tissues and remove toxic metabolites.

Notably, approximately 30–50% of individuals with alcohol dependency have a low zinc status, as alcohol consumption decreases intestinal absorption of zinc and increases urinary zinc excretion (Osredkar and Sustar, 2011). Zinc deficiency may also give rise to oxidative stress. Increased oxidative stress and oxidative stress-induced damage have been observed in humans with a sub-optimal zinc intake (Zhao et al., 2011). A significant increase in the MDA levels and decrease in the GSH content and SOD activity are observed in the liver of rats fed on a zinc-deficient diet, and zinc supplementation resulted in a decrease in the MDA levels and increases in GSH content and SOD activity (Tupe et al., 2010). Additionally, zinc deficiency is linked to alcohol-induced intestinal barrier dysfunction, as well as alveolar epithelial cell and macrophage dysfunction (Zhong et al., 2010; Joshi et al., 2009).

Curcumin is the major yellow pigment extracted from the rhizome of *Curcuma longa*, commonly known as turmeric. Curcumin has demonstrated great potential for the prevention and treatment of a wide variety of human diseases due to its pharmacological safety and efficacy (Aggarwal and Harikumar, 2009). However, the low bioavailability of curcumin has become an obstacle to its application in clinical treatment. Phase I clinical trials suggested that curcumin is safe, even at high doses (12 g/day); however, the bioavailability of curcumin is relatively low (Anand et al., 2007). One strategy to improve its bioavailability and biological efficacy is to chelate curcumin with metal ions. Chelates of curcumin with manganese exhibit a greater capacity to protect brain lipids against peroxidation than native curcumin (Sumanont et al., 2006). Zn(II)–curcumin, a mononuclear (1:1) zinc complex of curcumin has been synthesized and processed into solid dispersions (SDs) in our laboratory. SDs of Zn(II)–curcumin have been proven to exert potent antioxidant and gastroprotective effects in rat models of gastric ulceration induced by pylorus-ligature and ethanol, respectively (Mei et al., 2009a, 2012).

As Zn(II)–curcumin is a potent antioxidant and could potentially help to reverse the zinc deficiency observed in individuals with alcohol dependency, we aimed to explore whether Zn(II)–curcumin could effectively alleviate the detrimental alterations induced by ethanol in rats, such as an imbalance between oxidation and antioxidants, liver injury and abnormal hemorheology.

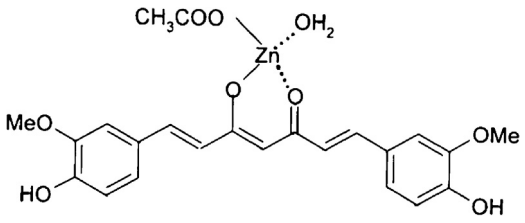

Fig. 1 – Molecular structure of the Zn(II)–curcumin complex.

2. Materials and methods

2.1. Materials

Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione]; 99% pure, was manufactured by Guangdong Zhongda Greenfield Bio-tech. Co. (Guangzhou, China). Polyvinylpyrrolidone K30 (PVP) was purchased from BASF Chemical Ltd. (New Jersey, USA). All other chemicals were of reagent grade. Solid dispersions (SDs) of Zn(II)–curcumin and curcumin were prepared according to the procedures described in our previous report (Mei et al., 2009b). The molecular formula of the Zn(II)–curcumin complex is shown in Fig. 1.

2.2. Animals

Female Sprague-Dawley rats (6–7 weeks-old; body weight, 250–300 g) were housed under a 12 h/12 h light/dark cycle at controlled temperature and humidity with free access to food and water. All procedures were carried out in accordance with guidelines approved by the Animal Ethics Committee of Sun Yat-sen University (Guangzhou, China).

2.3. Experimental design

The rats were randomly divided into six groups ($n = 8$/group) and treated as follows: Group 1, control group, 800 mg/kg PVP + saline; Group 2: model group, 800 mg/kg PVP + ethanol; Group 3: 225 mg/kg Zn(II)–curcumin SDs orally (*p.o.*; equivalent to 25 mg/kg Zn(II)–curcumin) + ethanol; Group 4: 450 mg/kg Zn(II)–curcumin SDs *p.o.* (equivalent to 50 mg/kg Zn(II)–curcumin) + ethanol; Group 5: 900 mg/kg Zn(II)–curcumin SDs *p.o.* (equivalent to 100 mg/kg Zn(II)–curcumin) + ethanol; and Group 6: 700 mg/kg curcumin SDs *p.o.* (equivalent to 100 mg/kg curcumin) + ethanol.

Rats were pretreated with the vehicle PVP or the drugs at the indicated doses by gavage every 12 h for a period of 7 days. From the eighth day, in addition to receiving PVP or the drugs, the rats in Groups 2–6 were administered ethanol (2.5 g/kg, 25%, *w/v* in saline) by intraperitoneal injection, while the rats in Group 1 received an equal volume of saline (0.9% NaCl, *w/v*) once per day for consecutive 4 days.

2.4. Blood and liver collection

Before the last injection of saline or ethanol, the animals were fasted overnight with free access to water. On the day of