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Protective effects of caffeic acid phenethyl ester against acute radiation-induced hepatic injury in rats

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ABSTRACT

Caffeic acid phenyl ester (CAPE) is a potent anti-inflammatory agent and it can eliminate the free radicals. The current study was intended to evaluate the protective effect of CAPE against the acute radiation-induced liver damage in rats. Male Sprague–Dawley rats were intraperitoneally administered with CAPE (30 mg/kg) for 3 consecutive days before exposing them to a single dose of 30 Gy of β-ray irradiation to upper abdomen. We found that pretreatment with CAPE significantly decreased the serum levels of alanine aminotransferase and aspartate aminotransferase and increased the activity of superoxide dismutase and glutathione. Histological evaluation further confirmed the protection of CAPE against radiation-induced hepatotoxicity. TUNEL assay showed that CAPE pretreatment inhibited hepatocyte apoptosis. Moreover, CAPE inhibited the nuclear transport of NF-κB p65 subunit, decreased the level of tumor necrosis factor-α, nitric oxide and inducible nitric oxide synthase. Taken together, these results suggest that pretreatment with CAPE offers protection against radiation-induced hepatic injury.

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1. Introduction

Radiation therapy (RT) is commonly applied to the cancerous tumor because of its ability to control cell growth. Almost 50% of patients with pelvic malignancies are candidates for radiation therapy (Timmerman et al., 2014). However, therapeutic radiation affects not only malignant tumors, but also surrounding normal tissues. RT for abdominal tumors often leads to radiation-induced liver disease (RILD), which is characterized by a pathologic change of venous occlusive disease (VOD) (Cheng et al., 2005). RILD is irreversible once the onset of radiation liver fibrosis and is life-threatening complication (Khozouz et al., 2008). Considering that RT can produce severe side effects, it is important to find new radioprotective substance to attenuate RILD. It is now widely accepted that oxidative stress induced by reactive oxygen species (ROS) is involved in the pathogenesis of RILD (Coleman et al., 2014). The interaction of ionizing radiation with water results in the generation of radical species. ROS are highly reactive and could diffuse to vital cellular targets like DNA, proteins and membrane, ultimately leading to cell death.

Since free radicals play a major role in the initiation and progression of radiation-induced toxicity, antioxidants

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might offer protection against radiation-induced damage. Recently, several researches have been focused on the potential use of propolis as free radical scavengers to prevent oxidative damage (Aghel et al., 2014; Noronha et al., 2014). Propolis has properties of anti-virus, anti-inflammation and anti-oxidation. One of the major biologically active components of propolis is the caffeic acid phenethyl ester (CAPE). CAPE prevented the formation of ROS and lipid peroxidation against carbon tetrachloride or cisplatin-induced hepatic oxidative damage (Colakoglu et al., 2011; Kus et al., 2004; Kart et al., 2010). However, no studies have evaluated the role of CAPE in radiation-induced hepatic injury. This study aimed to investigate the potential protective effects of CAPE on radiation-induced hepatotoxicity in rats.

2. Material and methods

2.1. Chemicals

The following reagents were purchased from the indicated sources: CAPE (Sigma-Aldrich, St. Louis, USA); TUNEL in situ detecting kit (KG Nanjing Ltd., China); TNF-α ELISIA KIT (Duosets, R&D Systems, Minneapolis, MN); NF-κB p65 primary antibody and HRP-conjugated secondary antibody (Santa Cruz Biotechnology); GSH and SOD assay kit (Nanjing Jiancheng Bioengineering, China). All other reagents were of analytical grade and obtained commercially.

2.2. Animals

Male Sprague–Dawley (5–6-week-old) rats were provided by the experiment animal center of Jiangsu Institute of Schistosomiasis, Key Laboratory of Jiangsu province (Certificate No. Su BKS 2007-003). Rats were housed under barrier conditions and kept at 22–25 °Cwith a 12 h light–dark cycle. Rats were allowed free access to food and water throughout the experimental period. All animal experiments were started after 1 week of acclimation and were performed in accordance with institutional guidelines.

2.3. Study design

Thirty-two rats were randomly divided into four groups of eight each and intraperitoneally administered with the different treatments for 4 days after radiation: (1) Control group, rats were given daily intraperitoneal (i.p.) injections of normal saline for 3 successive days; (2) CAPE group, rats were given CAPE (30 mg/kg per day, i.p.) for 3 successive days (Yiş et al., 2013); (3) RT group, rats administrated a single 30 Gy fraction to upper abdomen (Du et al., 2010); (4) CAPE and RT group, rats were given CAPE (30 mg/kg per day, i.p.) for 3 successive days; 3 h after the final administration, rats were treated a single 30 Gy fraction to upper abdomen.

2.4. Irradiation

Rats were anesthetized with an intraperitoneal injection of pentobarbital sodium and subjected to a single dose irradiation of 30 Gy fraction ionizing radiation to the upper abdomen, including the whole liver, through an accelerator (Varians, 2300CD23EX, American) producing 6-MV X-rays after simulation, absorbed dose rate being 200 cGy/min, the source–skin distance being 100 cm. After irradiation, the rats were placed in cages and had free access to water.

Four days after radiation, all rats were sacrificed by cervical dislocation, and blood collected from the heart into plain centrifuge tube. The left hepatic lobe of each group from the same position was excised for light microscope and TUNEL assay, while the right hepatic lobe was douched thoroughly with saline for the determination of the activity of GSH and SOD.

2.5. Analyses of serum markers

The blood specimens were centrifuged at 3000 rpm for 5 min. The suctions of upper layer serum were obtained and the content of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined by using automatic biochemical analyzer.

2.6. Determination of glutathione (GSH) activity, superoxide dismutase (SOD) activity in liver tissue

The activities of GSH and SOD were measured using a commercially available kit (Jiancheng Biotech Ltd, Nanjing, China). GSH and SOD activities measurement were based on the instructions of the colorimetric method by the Beckman Coulter DU80.

2.7. Measurement of nitric oxide (NO), inducible nitric oxide synthase (iNOS) levels in liver tissue

The concentration of and the activity in liver tissue were determined by using an NO and NOS Kit (Jiancheng Biotech Ltd, Nanjing, China) according to the manufacture' instructions.

2.8. Assay the level of serum tumor necrosis factor-α (TNF-α)

The concentrations of TNF-α in serum were quantified by ELISA using the manufacturer's suggested protocol (Duosets, R&D systems, Minneapolis, MN).

2.9. Histological assessment

Formalin-fixed and paraffin-embedded tissue sections were cut at 5 μm and stained with hematoxylin and eosin for histological examination. Tissues were examined under light microscopy by a blinded observer and were scored using a system described by Serafin et al. (2002).

2.10. Transmission electron microscopy microscope

Hepatic specimens were fixed in 4% glutaraldehyde buffer and 1% osmium tetroxide in turn. They were then dehydrated through an ethanol series. Thin (0.2–1.0 μm) and ultrathin (pale gold, 40–50 nm) sections were cut with an LKB4801 A ultramicrotome using a diamond knife. The thin sections were stained with uranyl acetate and lead citrate. They were

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