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Full Length Article

Evaluation of cardioprotective activity of *Lepidium sativum* seed powder in albino rats treated with 5-fluorouracil

Eman Taha Mohamed *, *Ghada Mohamed Safwat*

Biochemistry Department, Faculty of Veterinary Medicine, Beni-Suef University, Beni-Suef, Egypt

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ABSTRACT

5-fluorouracil (5-FU) is a chemotherapeutic agent used for treatment of solid tumors. Cardiotoxicity is a major complication of 5-FU therapy. Therefore, the aim of the present study was to evaluate the possible cardioprotective potency of *Lepidium sativum* seed powder (LS) against 5-FU-induced cardiotoxicity and oxidative stress in albino rats. The rats were divided into three groups. Rats in the control group received saline daily for 8 days only. Rats in FU-treated group received saline orally for 8 days, then I.P. injected with 5-FU (150 mg\kg B.W) on the 5th day. Rats in LS-treated group were orally dosed with LS (550 mg\kg B.W\day) for 8 days, and on the 5th day rats were administrated with the same previous dose of 5-FU. 5-FU induced cardiotoxicity was assessed by a significant increase in serum concentrations of cTnI, CK-MB, lipid profile and a moderate elevation of cardiac MDA. 5-FU significantly decreased serum HDL-c and GSH concentration in cardiac homogenate. Its administration also resulted in the release of some inflammatory markers such as myeloperoxidase and Interleukin-1β (IL-1β). All 5-FU altered parameters were markedly ameliorated by LS pre-co-post-treatment. Results of the present study suggest that LS has a significant effect on the protection of the heart against 5-FU-induced cardiotoxicity through maintaining the antioxidant and anti-inflammatory activities.

1. Introduction

5-fluorouracil (5-FU) is an antimetabolite fluoropyrimidine analog of the nucleoside pyrimidine with antitumor activity. 5-FU is widely used systemically for breast, gastrointestinal, pancreatic and skin cancers (Rossi, 2013). The main mechanism of action is interfering with DNA synthesis and mRNA transcription. However, cardiotoxicity is one of the most important associated side effects resulting from its nonspecific cytotoxicity in cancer cells (Álvarez et al., 2012; Carrillo et al., 2015). Clinical cardiac toxicities associated with intravenous infusion of 5-FU covers a wide range of manifestations like angina, myocardial ischemia, congestive heart failure, myocardial infarction, pulmonary edema, and sudden death (Polk et al., 2014; Sorrentino et al., 2012; Tsavaris et al., 2002). Recent

* *Corresponding author.* Biochemistry Department, Faculty of Veterinary Medicine, Beni-Suef University, Beni-Suef, Egypt. Tel.: +20 822327982; fax: +20 822327982.
E-mail address: dr_emantaha@yahoo.com (E.T. Mohamed).

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studies showed that the incidence of 5-FU-induced cardiotoxicity was in the range of 0–20% (Polk et al., 2014), and highlighted an increased risk of toxicity during the administration of higher doses of 5-FU with continuous infusion and not bolus administration. After administration, 5-FU follows different metabolic fates; more than 80% of the dose is inactivated by hepatic biotransformation, about 15–20% is excreted in the urine and only a small fraction remains available to exert its antineoplastic activity (Casale et al., 2004).

Different mechanisms of 5-FU induced cardiotoxicity are proposed, including direct drug or drug metabolite-mediated toxic action on myocytes (Mizuno et al., 1995), coronary vasospasm and thrombogenic effects (Bertolini et al., 2001). 5-FU induces the endothelial damage and extravasation of blood with the drug into cardiac tissue resulting in an inflammatory reaction and myofibril necrosis (Bertolini et al., 2001; Kumar et al., 1995). Another theory has suggested cardiotoxic impurities in the 5-FU formulation (fluoroacetaldehyde, generated in the alkaline solution of fluorouracil during storage, which may be converted to a cardiotoxic agent, fluoroacetate) (Arellano et al., 1998; Becker et al., 1999). Fluoroacetate enters the Krebs' cycle and converts into fluorocitrate, which inhibits the enzyme aconitase (Keller et al., 1996) causing citrate accumulation, disruption of the tricarboxylic acid cycle and severe impairment of energy production within the myocytes (Gradishar and Vokes, 1990). The pathogenesis of 5-FU induced cardiotoxicity may involve cellular damage due to the oxidative stress and the induction of apoptosis (Rashid et al., 2014). Accordingly, therapeutic interventions having antioxidant activity may be effective against oxidative stress associated with cardiovascular diseases.

Lepidium sativum (LS) is locally known as 'hub arachad' belonging to family *Brassiaceae*. Chemically, the plant seeds and leaves contain flavonoids and isothiocynates glycosides, essential oils, carbohydrates, proteins, fatty acids, β-carotene and vitamins like riboflavin, niacin and ascorbic acid (Yadav et al., 2010). The seeds are consumed in salad and as a spice (Maier et al., 1998). The plant leaves and seeds have been used in traditional medicine. The plant is reported to have hypoglycemic, antihypertensive, diuretic (Jouad et al., 2001; Patel et al., 2009) hemagglutinating, fracture healing (Eddouks et al., 2005; Yadav et al., 2011), anti-inflammatory (Raval et al., 2013), hepatoprotective (Abuelgasim et al., 2008; Al-Asmari et al., 2015), antioxidant (Agarwal and Verma, 2011; Zia-Ul-Haq et al., 2012) and anti-carcinogenic activities (Maghrani et al., 2005).

The present study was designed to investigate the cardioprotective effect of LS against 5-FU-induced cardiotoxicity in rats by studying some biochemical cardiac injury markers, antioxidant defense system, serum lipid profile and inflammatory markers.

2. Materials and methods

2.1. Chemicals

5-fluorouracil was obtained from ACDIMA International (AiT) Shanghai Xudong Haipu Pharmaceutical Co., Ltd. Reduced glutathione (GSH), malondialdehyde (MDA) and nitric oxide (NO) commercial kits were purchased from Bio-diagnostic Company for research kits, Egypt. Triacylglycerol (TAG), total cholesterol (TC) and HDL-cholesterol commercial diagnostic kits were purchased from Spinreact Company, Spain. Rat Troponin I (cTnI) (Catalog number KT-639), rat Creatinine kinase-MB isoenzyme (CK-MB) (Catalog number KT-12247) and rat myeloperoxidase (Catalog number KT-60345) immunoassay kits were purchased from Kamiya Biomedical Company, USA. Rat Interleukin-1β (IL-1β) (Catalog number K 0331212) ELISA kit was purchased from Komabiotech Company, Korea.

2.2. Plant material

Lepidium sativum L. seeds (known as garden cress) (LS) were obtained from Agricultural Research Center, Egypt. Garden cress seeds were dried and ground to powder. The suspension of Lepidium seed powder was made with a sufficient quantity of distilled water by a dose of 550 mg/kg B.W (Raval and Ravishankar, 2010). It was administered through the oral route with the help of a gastric gavage. Other non-mentioned chemicals used in the present study were of the highest analytic grade and purchased from Sigma-Aldrich Company, USA.

2.3. Animals and experimental design

Thirty adult male albino Sprague–Dawley rats (120–150g) were provided by the Helwan farm of laboratory animals Cairo, Egypt. Rats were kept in standard cages at room temperature (25 ± 2 °C) with a 12: 12 h dark-light cycle and humidity (70%). All animals were allowed free access to water and fed with uniformly basal diet. All experimental procedures were conducted in accordance with the guide for the care and use of laboratory animals and in accordance with the local Animal Care and Use Committee. After acclimatization, rats were randomly divided into 3 groups (n = 10). Animals in the control group received only saline daily for 8 days by oral gavage. Animals in FU-treated group received saline orally for 8 days, then were given a single dose of 5-FU (150 mg\kg B.W\I.P injection on the 5th day) (Blijham, 1991). Animals in LS-treated group received a suspension of LS seed powder (550 mg\kg\day) (Raval and Ravishankar, 2010) orally for 8 days and were injected with a single dose of 5-FU (150 mg\kg B.W\I.P) on the 5th day.

2.4. Blood sampling and tissue preparation

Blood samples were collected 24 hours after the last dose, and all rats were sacrificed by cervical decapitation. The obtained sera were monitored for lipid profile, cTnl and CK-MB activity. Heart tissues were excised after dissection of the animals and designated for biochemical analysis. The excised heart tissue (0.5 g) was homogenized in ten volumes of ice cold phosphate buffer (pH:7) until a uniform suspension was obtained. The homogenate was then centrifuged at 20,000 × g for 10 min at 4 °C using high speed cooling centrifuge. The clear supernatant was used for the assay of GSH, MDA, NO, MPO and IL-1β.

2.5. Biochemical assays

2.5.1. Serum analysis

Serum cardiac markers (CK-MB and cTnI) were measured according to instruction of diagnostic kits. Serum lipid profile (TAG,