Life Sciences 160 (2016) 2–11

Contents lists available at ScienceDirect

Life Sciences

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

Ellagic and ferulic acids alleviate gamma radiation and aluminium chloride-induced oxidative damage

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ARTICLE INFO

Article history:
Received 27 May 2016
Received in revised form 12 July 2016
Accepted 15 July 2016
Available online 17 July 2016

Keywords:
Ellagic acid
Ferulic acid
Gamma radiation
Aluminium chloride
Oxidative stress

ABSTRACT

Aim: Ionizing radiation interacts with biological systems through the generation of free radicals, which induce oxidative stress. Aluminium (Al) can negatively impact human health by direct interaction with antioxidant enzymes. Ellagic acid (EA) and Ferulic acid (FA) are plant polyphenolic compounds, have gained attention due to their multiple biological activities. To date, no studies investigating the antioxidant effect of EA/FA in a model involving both γ radiation and aluminium chloride ($AlCl_3$) have been reported. Herein, we investigated the protective effect of EA and FA against oxidative stress induced by γ radiation and $AlCl_3$ in rats.

Methods: Rats were divided into thirteen groups: a negative control group, 3 positive control groups (γ-irradiated, $AlCl_3$ – treated and γ-irradiated + $AlCl_3$ – treated) and 9 groups (3 γ-irradiated, 3 $AlCl_3$ – treated and 3 γ-irradiated + $AlCl_3$ – treated) treated with EA and/or FA. Liver function and lipid profile were assessed. Levels of lipid peroxidation, protein oxidation and endogenous antioxidants as well as the concentrations of copper, iron and zinc were estimated in liver tissue homogenate. Furthermore, liver tissue sections were histologically examined.

Results: Oral administration of EA and/or FA resulted in 1) amelioration of $AlCl_3$ and/or γ-radiation-induced hepatic function impairment, dyslipidemia and hepatic histological alterations; 2) reduction in liver MDA and PCC levels; 3) elevation of liver CAT, GPx and SOD activity as well as GSH level; 4) elevation in liver Cu concentrations which was accompanied by a reduction in Fe and Zn concentrations.

Conclusions: Oral administration of EA and/or FA may be useful for ameliorating γ radiation and/or $AlCl_3$-induced oxidative damage.

1. Introduction

Oxidative stress refers to the enhanced generation of reactive oxygen species (ROS) and/or depletion in the antioxidant defense system. Uncontrolled increases in oxidant concentrations can cause reactions in chain, mediated by free radicals, affecting normal biological functions. Many pathological conditions are associated with either high levels of free radicals or with the reduction in free radical scavenging capacity [1].

The steadily increasing applications of radiation in clinical practice, industrial and agricultural activities, on top of residual radio-activity resulting from nuclear test explosions, have a measurable impact contributing to possible radiation hazards in humans. The deleterious effects of ionizing radiation in biological systems are mainly mediated through the generation of ROS, which may contribute to radiation-induced oxidative stress, leading to cellular damage and organ dysfunction [2].

Aluminium (Al) is the third most abundant element and the most common metal in the earth's crust. The primary food sources of Al are corn, yellow cheese, salt, herbs, spices and tea. In addition, Al is a constituent of food additives, toothpaste, cooking utensils, cosmetics and medicines such as antacids. Furthermore, Al salts are widely used as flocculants in the treatment of drinking water for purification purposes. Exposure to Al occurs via various routes, including inhalation, ingestion and dermal absorption. Due to the abundance of Al in numerous food products, its ingestion has been the predominant route of how this metal gains entry into human biological systems [3]. Al has been implicated in the generation of an oxidative milieu by aiding in the production of ROS [4]. It has been suggested that there is a relationship between excessive/prolonged Al exposure and increased risk of numerous acute and chronic health disorders [5].

There is a growing interest in the use of naturally occurring antioxidants. In particular, phenolic acids are naturally occurring compounds that are widely distributed in vegetables, fruits, whole grains and beverages such as red wine and tea [6]. Phenolic acids have been described to

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http://dx.doi.org/10.1016/j.lfs.2016.07.006
0024-3205/

exert a variety of biological actions such as free radicals scavenging, metal chelation, modulation of enzymatic activity, alteration of signal transduction pathways, activation of transcription factors and gene expression. They received particular attention because of their therapeutic potential for a variety of diseases such as inflammatory diseases, diabetes, cardiovascular diseases, neurodegenerative disorders and cancer [7].

Ellagic acid (EA) is a polyphenol found in a wide variety of vegetables and fruits such as blackberries, cranberries, pecans, pomegranates, raspberries, strawberries, walnuts, wolfberry, grapes and peach [8]. EA has been found to have antioxidant [9], antidiabetic [10], antiproliferative [11] and anticarcinogenic activities [12].

Ferulic acid (FA), a ubiquitous natural phenolic phytochemical, is commonly found in vegetables and fruits such as tomatoes, sweet corn, and rice bran. Moreover, FA is found in the seeds of coffee, apple, artichoke, peanut and orange as well as in both seeds and cell walls of rice, wheat and oats plants [13]. FA exhibits a wide range of biological activities [14] such as antioxidant [15], anti-inflammatory [16], hepatoprotective [17], anticarcinogenic [18] activities.

To the best of our knowledge, despite numerous groups attempting to demonstrate the antioxidant effect of EA and FA, no studies exploring the antioxidant activity of EA and FA in an experimental model involving both γ radiation and $AlCl_3$ have been reported to date. In view of the importance of protecting mankind from the deleterious effects of γ radiation and/or $AlCl_3$ and in an attempt to understand the role and mechanism of the naturally occurring plant polyphenols as inhibitors of oxidative stress, the present study was designed to evaluate the potential protective effect of EA and/or FA against γ radiation and/or $AlCl_3$-induced oxidative stress.

2. Materials and methods

2.1. Experimental animals

A total of 104 male albino rats of Sprague Dawley strain with body weight ranging from 100 to 110 g were obtained from the holding company for biological products and vaccines (VACSERA), Giza, Egypt. Animals were housed in polypropylene cages (47 × 34 × 18 cm) in an air-conditioned room with 55% of humidity, controlled temperature (25 ± 2 °C), and automatic lighting (alternating 12 h periods of light and dark) throughout the duration of the study. The animals were fed on a commercial standard pellet diet (PMI Nutrition, Shoreview, MN, USA) and fresh drinking water. The animals were allowed to acclimatize to the environmental conditions for one week before experiments. All animal handling procedures were approved by the ethics committee of the national center for radiation research and technology (NCRRT), Atomic Energy authority, Cairo, Egypt and in accordance with the recommendations for the proper care and use of laboratory animals (National Institutes of Health [NIH] publication No.85-23, revised 1996).

2.2. Chemicals

$AlCl_3$ was purchased from Merck KGaA (Darmstadt, Germany), while EA and FA were purchased from Sigma-Aldrich (St. Louis, MO, USA).

2.3. Irradiation procedure

Irradiation of animals was carried out at the NCRRT using a gamma cell-40 Cesium-137 irradiator (Best Theratronics Ltd., Ottawa, Ontario, Canada). Rats of irradiated groups were exposed to a single dose of gamma radiation (6 Gy; dose rate = 0.5 Gy/min).

2.4. Animal treatments

$AlCl_3$ (20 mg/kg bw) [19], EA (60 mg/kg bw) [20] and FA (20 mg/kg bw) [21] dissolved in 0.2% dimethyl sulfoxide (DMSO) were administered once daily via intragastric tube for 8 weeks. Rats of irradiated groups were exposed to gamma radiation on the day prior to overnight fasting at the end of the experimental period.

2.5. Animal groups

The experimental animals were randomly divided into 13 groups, categorized as a negative control group, 3 positive control groups, 3 γ-irradiated groups, 3 $AlCl_3$-treated groups and 3 $AlCl_3$-treated + γ-irradiated groups. Each group containing eight rats (n = 8). The groups were treated as follows:

Group name	Group designation	Treatment
I. Negative control group		
Control	C	0.5 mL of 0.2% DMSO
II. Positive control groups		
1) γ-irradiated	γ	A single dose of 6 Gy γ radiation
2) $AlCl_3$	$AlCl_3$	0.5 mL of 20 mg/kg bw $AlCl_3$
3) $AlCl_3$ + γ-irradiated	$AlCl_3$ + γ	0.5 mL of 20 mg/kg bw $AlCl_3$ + a single dose of 6 Gy γ radiation
III. γ-irradiated groups		
1) Ellagic acid + γ-irradiated	EA + γ	0.5 mL of 60 mg/kg bw EA + a single dose of 6 Gy γ radiation
2) Ferulic acid + γ-irradiated	FA + γ	0.5 mL of 20 mg/kg bw FA + a single dose of 6 Gy γ radiation
3) Ellagic acid + Ferulic acid + γ-irradiated	EA + FA + γ	0.5 mL of 60 mg/kg bw EA + 0.5 mL of 20 mg/kg bw FA + a single dose of 6 Gy γ radiation
IV. $AlCl_3$-treated groups		
1) Ellagic acid + $AlCl_3$	EA + $AlCl_3$	0.5 mL of 60 mg/kg bw EA + 0.5 mL of 20 mg/kg bw $AlCl_3$
2) Ferulic acid + $AlCl_3$	FA + $AlCl_3$	0.5 mL of 20 mg/kg bw FA + 0.5 mL of 20 mg/kg bw $AlCl_3$
3) Ellagic acid + Ferulic acid + $AlCl_3$	EA + FA + $AlCl_3$	0.5 mL of 60 mg/kg bw EA + 0.5 mL of 20 mg/kg bw FA + 0.5 mL of 20 mg/kg bw $AlCl_3$
V. $AlCl_3$-treated + γ-irradiated groups		
1) Ellagic acid + $AlCl_3$ + γ-irradiated	EA + $AlCl_3$ + γ	0.5 mL of 60 mg/kg bw EA + 0.5 mL of 20 mg/kg bw $AlCl_3$ + a single dose of 6 Gy γ radiation
2) Ferulic acid + $AlCl_3$ + + γ-irradiated	FA + $AlCl_3$ + γ	0.5 mL of 20 mg/kg bw FA + 0.5 mL of 20 mg/kg bw $AlCl_3$ + a single dose of 6 Gy γ radiation
3) Ellagic acid + Ferulic acid + AlCl3 + γ-irradiated	EA + FA + $AlCl_3$ + γ	0.5 mL of 60 mg/kg bw EA + 0.5 mL of 20 mg/kg bw FA + 0.5 mL of 20 mg/kg bw $AlCl_3$ + a single dose of 6 Gy γ radiation

2.6. Blood samples collection

At the end of the experimental period of 56 days, rats were kept fasting overnight and then anaesthetized by inhalation of diethyl ether. Blood samples were collected by cardiac puncture. The sera were separated by centrifugation at 3000*g* for 15 min and stored at −80 °C until analysis.

2.7. Preparation of liver tissue homogenate

The liver from dissected rats was immediately excised, blood was cleared off by several washings with ice cold phosphate buffered saline (PBS) and the tissues were weighed and immediately transferred to −80° freezer for storage till analysis. On the day of the analysis, the liver tissue samples were homogenized in 0.1 M Tris-HCl buffer, pH 7.4 (2 mL/100 mg tissue). The homogenate was centrifuged at