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Protective effect of ferulic acid on cisplatin induced nephrotoxicity in rats

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A R T I C L E I N F O

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A B S T R A C T

This study aims to determine the potential protective effects of ferulic acid against cisplatin-induced nephrotoxicity and to compare its effect with curcumin, a well-known protective agent against cisplatin- induced toxicity in rats. Administration of cisplatin resulted in high BUN (Blood Urea Nitrogen), creatinine, MDA (Malondialdehyde), MPO (Myeloperoxidase), TOS (Total Oxidative Status), PtNT (Protein Nitrotyrosine) levels ($p < 0.05$). Histological observations showed abnormal morphology of kidney; in addition with appearance of TUNEL positive cells indicating apoptosis in cisplatin administered group. HO-1 (Heme Oxygenase-1) levels measured by RT-PCR (Real Time Polymerase Chain Reaction), and TAS (Total Antioxidative Status) revealed antioxidant depletion due to cisplatin toxicity in animals ($p < 0.05$). All parameters showed improvement in groups treated with ferulic acid ($p < 0.05$). Ferulic acid treatment was found significant in preventing oxidative stress, increasing antioxidative status and regaining histological parameters to normal, indicating nephroprotective and antioxidant effects of this phenolic compound.

1. Introduction

Cisplatin is an effective anti-neoplastic agent, that could be used against many types of cancers (Delord et al., 2009). Even high dosages of cisplatin are more effective, there is a concern due to their toxic side effects especially on renal tissue (Arany and Safirstein, 2003; Sanchez-Gonzalez et al., 2011; Sohn et al., 2011). The harmful effects of cisplatin were resulted in oxidative stress, apoptosis and also DNA damage (Sohn et al., 2011).

Ferulic acid (FA), is a plant phenolic acid that turns out to be a potential antioxidant phenoxy radical (Maistro et al., 2011). Phenolic compounds are known for their roles on neurodegenerative diseases, cancer, diabetes, coronary heart diseases, inflammation states and idleness as potential therapeutic agents (Ferguson et al., 2001). It has been already reported that FA with its antioxidant properties is able to neutralize nitric oxide and hidroxy-radical groups that lead to DNA damage (Alam et al., 2013; Kanski et al., 2002; Manikandan et al., 2014; Roy et al., 2014).

Furthermore, curcumin (1, 7-bis(4-hydroxy-3-methoxypentyl)-1,6-hepadiene-3,5-dione, *Curcuma longa*) is another polyphenolic compound that exerts antioxidant, anti-inflammatory and anti-cancer effects (Sahin et al., 2014), and possesses nephro-protective effects by scavenging free radicals and increasing the antioxidant mechanisms in kidney mitochondria (Waly et al., 2011; Waseem et al., 2013). Especially on cisplatin-induced nephrotoxicity, it has been pointed out that curcumin displayed protective effects on renal tissue via its own anti-inflammatory and antioxidant effects (Kuhad et al., 2007; Ueki et al., 2013). Curcumin has demonstrated effectiveness against reactive oxygen and nitrogen species. Curcumin antioxidant activity is enhanced by increasing glutathione synthesis and by inhibiting inflammatory enzymes (Sreejayan and Rao, 1997).

The effect of FA on cisplatin-induced nephrotoxicity has not been studied previously. Our study aims to examine the effects of FA on cisplatin induced nephrotoxicity, and compare its nephro-protective effect with the other poly-phenolic compound curcumin which has been concluded in several studies (Kuhad et al., 2007; Ueki et al., 2013; Waly et al., 2011).

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2. Materials and methods

2.1. Animals, chemicals and drug

Animal experiments for this study were supplied from "Marmara University Experimental Animal Center (DEHAMER)" being previously approved by Marmara University Animal Experiments Ethical Committee. The study was performed on male Wistar Albino rats weighing approximately 250–350 g. All the animals were fed with standard laboratory pellets and tap water *ad libitum*. Each group was kept in metal cages, each one containing 3 animals, in an environment with suitable humidity and temperature. Compounds such as Ferulic acid (Lot. 128708) and curcumin (Lot. C1386) were purchased from Sigma-Aldrich Chemical Co. Cisplatin was supplied by Ebewe Pharma (Austria).

2.2. Experimental protocol

The experimental protocol was conducted in six groups as described below:

- *saline- control group (single dose of 1 ml saline i.p, 1 ml distilled water, oral gavage for 5 days, n = 6),*
- *FA- control group (50 mg/kg, oral gavage for 5 days, n = 6),*
- *curcumin- control group (100 mg/kg, oral gavage for 5 days, n = 6),*
- *saline- cisplatin toxicity group (single dose of cisplatin [10 mg/kg, i.p], 1 ml distilled water, oral gavage for 5 days, n = 6),*
- *FA- cisplatin toxicity group (single dose of cisplatin [10 mg/kg, i.p], 50 mg/kg FA, oral gavage for 5 days, n = 6),*
- *curcumin- cisplatin toxicity group (single dose of cisplatin [10 mg/kg, i.p], 100 mg/kg curcumin, oral gavage for 5 days, n = 6).*

The dosage of FA (Gim et al., 2013) and curcumin (Palipoch et al., 2014) were selected according to previous studies estimating no toxicity or negative effects even in higher dosages. Cisplatin treatments were only administered on the second day of the experiment. The dose of cisplatin was selected according to previous studies that demonstrated significant nephrotoxicity in rats (Al-Kahtani et al., 2014; Kusumoto et al., 2011; Palipoch and Punsawad, 2013).

Seventy-two hours after cisplatin injection, blood samples were obtained from animals under ether anesthesia by cardiac puncture for further biochemical analysis. After this procedure animals were sacrificed by cervical dislocation. Kidneys were removed for further biochemical and histological observations.

2.3. Measurement of serum blood urea nitrogen (BUN) and creatinine

Serum samples were processed with a special autoanalyser (Beckman Coulter AU 5800) for BUN and creatinine level estimations.

2.4 Myeloperoxidase (MPO) analysis

MPO activity was determined within kidney tissues according to the o-dianisidine method (Bradley et al., 1982). One unit MPO activity has been defined as the reduction of 1 μmol H_2O_2 under 25 °C during 1 min and was represented as Unit/gram.

2.5 Malondialdehyde (MDA) analysis

MDA levels were assessed in kidney tissues in order to evaluate lipid peroxidation levels in this organ. The measure of lipid peroxidation was analyzed through thiobarbituric acid-reactive substances (Ohkawa et al., 1979). Results were represented as nmol/mL (nanomoles of MDA per milligram of protein).

2. 6 Total oxidant status (TOS) and total antioxidant status (TAS)

TOS (Lot. AT140500) and TAS (Lot. MT13033) were evaluated in rat renal tissues supernatants, with an available commercial TOS Assay Kit (Rel Assay Diagnostics®, Turkey).

2.7 Protein nitrotyrosine (PtNT)

Nitrotyrosine levels were measured on rat kidneys with an available competitive ELISA nitrotyrosine quantitation kit (Oxiselect™ Nitrotyrosine ELISA Kit, STA-305, USA).

2.8 Heme oxygenase – 1 (HO-1)

Real-Time Polymerase Chain Reaction (RT-PCR) Analysis for the assessment of HO-1 levels in rat kidney tissues were carried out on an Applied Biosystems 7500/7500 Fast Real-Time PCR System. Total RNA was isolated from renal tissues by using the commercially available kit (PureLink® RNA Mini Kit-ambion® by life technologies™). Complementary DNA was reverse-transcribed from total RNA samples using a High-Capacity cDNA Reverse Transcription Kit (RT Step). PCR products were quantitatively synthesized from cDNA samples using the TaqMan® Gene Expression Master Mix (PCR Step). Primer sets used: HO-1 (forward:AGATCACATTCACGGTGCTG; reverse:AGCTCAATGTTGAGCAGG). The resulting DNA amount was normalized to the beta actin signal (forward: 5′ TGGCGCTTTTGACTCAGGAT −3′; reverse: 5′ GGGATGTTTGCTCCAACCAA 3′) amplified in a reaction. HO-1 mRNA expression was assessed in rat kidney tissues and HO-1 mRNA expressions in groups according to% of control.

2.9 Histological evaluation

For light microscopic evaluation, kidney samples were fixed in 10% buffered formalin for 48 h and processed for routine paraffin embedding. For general morphological evaluation, approximately 4-μm thick sections were stained with hemathoxylin and eosin (H & E). In both of the staining technique at least 5 similar microscopic areas were observed. All of the stained sections were observed and photographed with a digital camera (Olympus C-5060, Tokyo, Japan) attached to a photomicroscope (Olympus BX51, Tokyo, Japan).

2.10 Determination of apoptosis

The TUNEL (terminal deoxynucleotidyl transferase (TdT)-mediated dUTP nick end labeling) method was used in accordance with the user's manual of the manufacturer (Apoptag Plus Peroxidase in situ Apoptosis Kit, Chemicon International, S7101, Temecula, CA, USA). In each section, TUNEL positive cells as brown color were evaluated at x400 magnification.

2.11 Statistical analysis

Statistical analysis was carried out using GraphPad Prism 5.0 (GraphPad Software, Inc.La Jolla, CA, USA). All data are expressed as means ± SEM. Relationship within groups is measured with Mann Whitney U or Kruskal Wallis H one-way analysis of variance (ANOVA) followed by Tukey's post hoc test; where appropriate. Group differences of $p < 0.05$ were considered statistically significant.

3. Results

3.1. Serum blood urea nitrogen (BUN) and creatinine

Control groups including curcumin and FA alone have not shown any changes in BUN and creatinine levels according to saline control group (Fig. 1A and B, $p > 0.05$).

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