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Protective effect of ferulic acid on cisplatin induced nephrotoxicity in rats

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ABSTRACT

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:AGCTCAATGTT GAGCAGG). 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, $p > 0.05$).

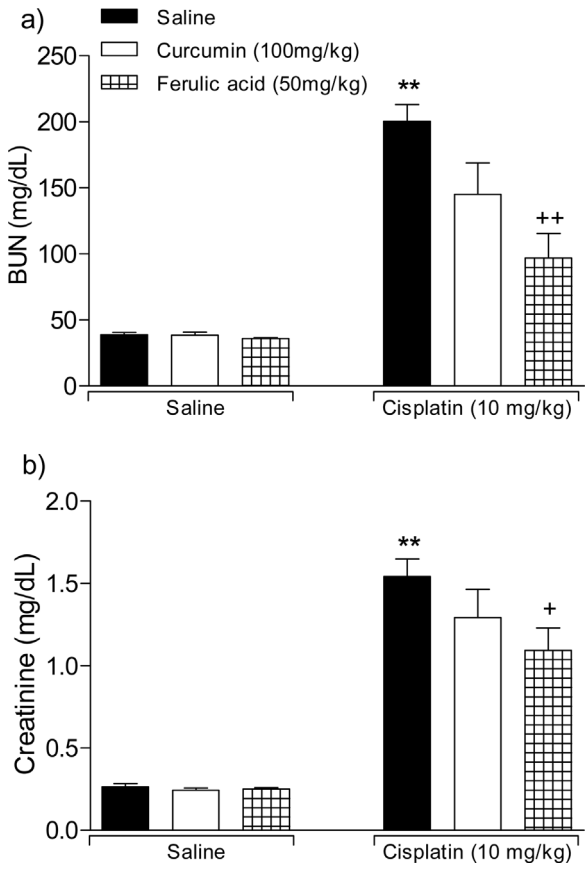

Fig. 1. A) Blood urea nitrogen (BUN) and B) Creatinine levels in rat serum samples. **: $p < 0.01$, in comparison with control saline group, +: $p < 0.05$; ++: $p < 0.01$, in comparison with cisplatin toxicity group.

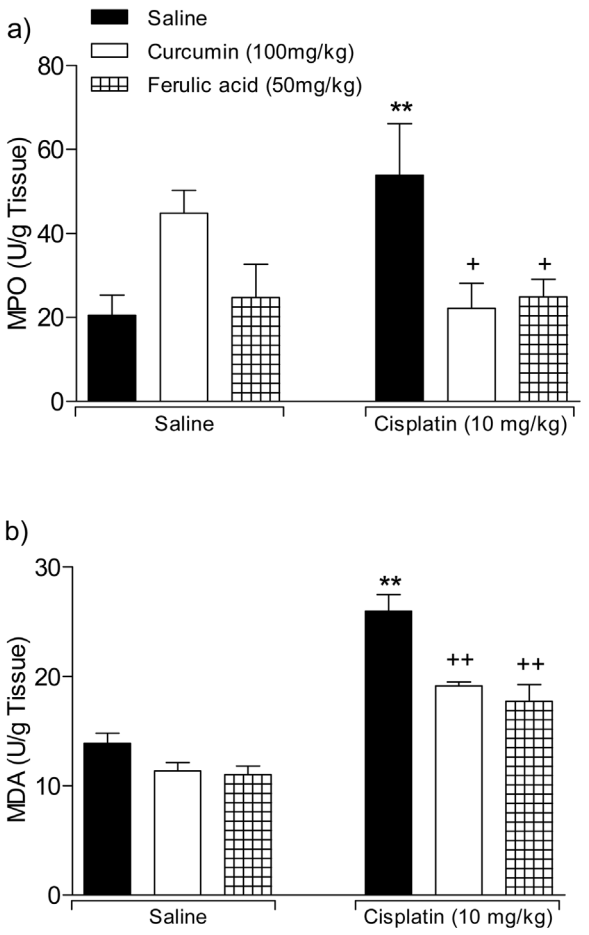

Fig. 2. A) Myeloperoxidase (MPO) activities and B) Malondialdehyde (MDA) levels in rat kidney tissues. **: $p < 0.01$, in comparison with saline control group, +: $p < 0.05$; ++: $p < 0.0$, in comparison with cisplatin toxicity group.

Cisplatin toxicity group BUN has had a significant increase in accordance with saline control group (Fig. 1A, $p < 0.01$). Although FA treated toxicity group has shown statistically improvement in comparison with the cisplatin toxicity group (Fig. 1A, $p < 0.01$), while curcumin treated toxicity group has not been appeared a significant decrease (Fig. 1A, $p > 0.05$).

In cisplatin toxicity group, creatinine levels have appeared obviously higher when compared to saline treated control group (Fig. 1B, $p < 0.01$). According to cisplatin toxicity group, FA treated toxicity group has recorded significant lower creatinine levels (Fig. 1B, $p < 0.05$), while curcumin treated toxicity group has shown a slight but not statistically significant decrease on creatinine (Fig. 1B, $p > 0.05$).

In addition, curcumin treated toxicity group has recorded higher BUN and creatinine levels in comparison with FA treated toxicity group; but the differences between these groups have not been significant when compared to each other (Fig. 1A and B, $p > 0.05$).

3.2. MPO levels

Cisplatin toxicity group has experienced increase in MPO levels in accordance with control saline group levels (Fig. 2A, $p < 0.01$). Thus, FA significantly reduced MPO levels increased after administration of cisplatin (Fig. 2A, $p < 0.05$). Curcumin treated toxicity group has also resulted in significantly lower MPO levels (Fig. 2A, $p < 0.05$).

3.3. MDA levels

Saline treated control group, cisplatin toxicity group has experienced highly increase in MDA levels (Fig. 2B, $p < 0.01$). Both of curcumin and FA treated toxicity groups significantly reduced MDA levels in kidney tissues of rats (Fig. 2B, $p < 0.01$).

3.4. TOS and TAS levels

Cisplatin toxicity group TOS has revealed to be significantly high (Fig. 3A, $p < 0.05$). In addition, FA and curcumin treated toxicity groups have revealed significant decrease in level of TOS when compared with cisplatin toxicity group (Fig. 3A, $p < 0.05$).

TAS level in cisplatin toxicity group has shown to be significantly lower when compared with the saline treated control group (Fig. 3B, $p < 0.05$). TAS level in FA treated toxicity group has appeared significantly higher when compared with cisplatin toxicity group (Fig. 3B, $p < 0.05$). Similarly, curcumin treated toxicity group has revealed significant TAS increase when compared with cisplatin toxicity group (Fig. 3B, $p < 0.05$).

3.5. PtNT levels

Cisplatin toxicity group exhibited significantly high nitrotyrosine levels when compared with the control saline group (Fig. 4, $p < 0.01$). However nitrotyrosine levels in toxic groups treated with either FA or curcumin were significantly decreased when compared with alone cisplatin treated toxicity group (Fig. 4, $p < 0.01$).

3.6. Heme oxygenase – 1 (HO-1) assessment

Administration of cisplatin resulted in significantly high levels of HO-1 versus control FA and control curcumin groups (Fig. 5, $p < 0.001$). However a significant decrease in HO-1 level was obtained after administration of FA compared to cisplatin toxicity group (Fig. 5,

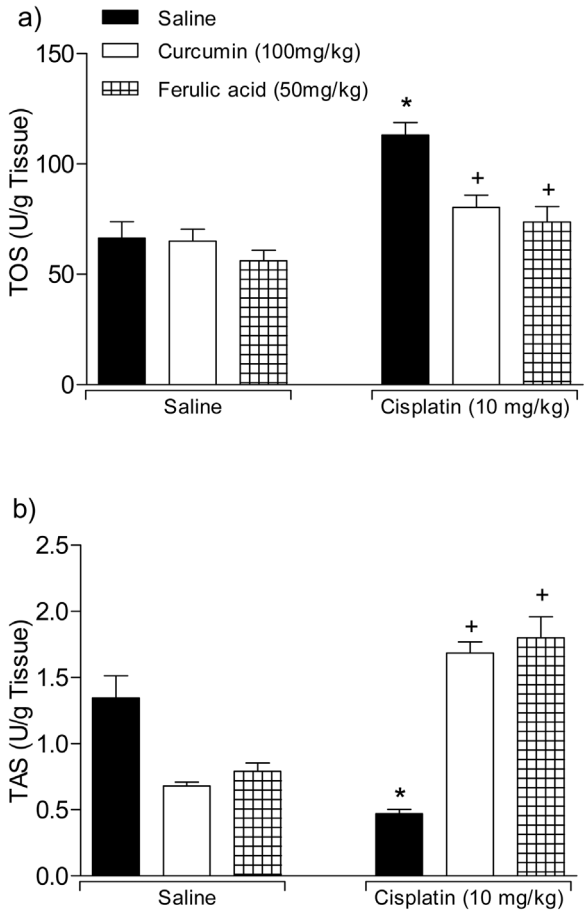

Fig. 3. A) Total Oxidant Status (TOS) and B) Total Antioxidant Status (TAS) in rat kidney tissues. *: $p < 0.0$, in comparison with saline control group, +: $p < 0.05$, in comparison with cisplatin toxicity group.

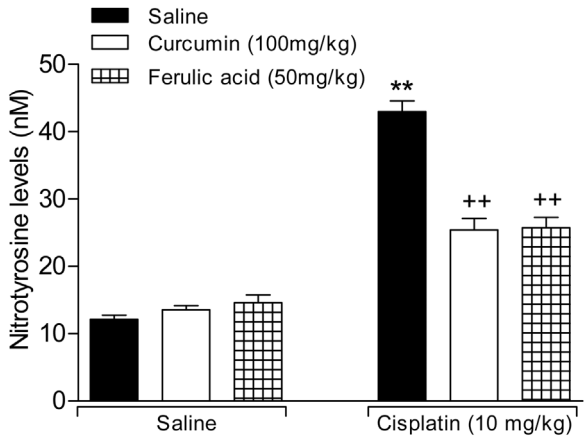

Fig. 4. Protein Nitrotyrosine (PtNT) levels in rat kidney tissues. **: $p < 0.01$, in comparison with saline control group, ++: $p < 0.01$, in comparison with cisplatin toxicity group.

$p < 0.01$). Similarly, in the cisplatin toxic group treated with curcumin exhibited a significant decrease in HO-1 levels when compared to cisplatin toxicity group (Fig. 5, $p < 0.05$).

3.7. Histological evaluations

In the saline (Fig. 6A), curcumin (Fig. 6B) and FA (Fig. 6C) applied control groups, regular morphology of kidney with renal corpuscles and tubuli were observed. In the cisplatin applied toxicity group severe

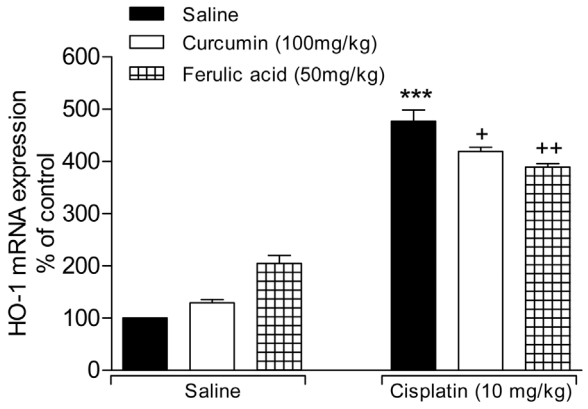

Fig. 5. Heme Oxygenase- 1 (HO-1) mRNA expression% of control. ***: $p < 0.001$, in comparison with saline control group, +: $p < 0.05$; ++: $p < 0.01$, in comparison with cisplatin toxicity group.

degeneration of the tubular epithelium, dilatation of Bowman's space and glomerular congestion and inflammatory cell infiltration in kidney were observed (Fig. 6D). Curcumin + cisplatin treatment group showed mild degeneration in renal corpuscles and tubules in kidney (Fig. 6E). FA plus cisplatin applied treatment group showed quite regular renal corpuscles and tubules, with mild vascular congestion in kidney (Fig. 6F). Histological analysis was performed on rat kidneys of each group and results obtained are displayed on Fig. 6.

3.8. Apoptosis

Brown- colored TUNEL- positive cells were observed in all groups. In the saline (Fig. 7A), curcumin (Fig. 7B) and FA (Fig. 7C) applied control groups showed a few number of TUNEL positive cells in tubules. In the cisplatin applied toxicity group (Fig. 7D) showed severe increase in TUNEL positive cells in tubules. Both curcumin plus cisplatin applied (Fig. 7E) and FA plus cisplatin applied (Fig. 7F) treatment groups showed moderate increase in TUNEL positive cells in tubules.

4. Discussion

Referring results of the present study, it is presented for the first time presented that pretreatment with FA attenuated acute renal injury induced by cisplatin administration. FA revealed this effect by balancing oxidant/antioxidant system, inhibiting neutrophil infiltration and decreasing apoptosis in renal tissue. As concordance with the other studies (Kuhad et al., 2007; Ueki et al., 2013; Ugur et al., 2015; Waly et al., 2011), it was also shown that curcumin would have a protective effect on cisplatin induced nephrotoxicity via almost the same mechanism.

Cisplatin has presented its toxic effect on kidney by changing renal tubular structure as a result of induced lipid peroxidation and free radical production (An et al., 2011; Hassan et al., 2010). In previous studies, FA reduced lipid peroxidation by interacting with the inflammation pathways and by scavenging free radicals (Alam et al., 2013; Trombino et al., 2013). Curcumin, which was organized as a positive control group in the present study, has been demonstrated dual antioxidant functions by scavenging reactive oxygen species (ROS) due to its phenolic structure, and inducing the upregulation of several endogenous cytoprotective and antioxidant proteins (Dinkova-Kostova and Talalay, 2008).

In this study, MDA levels, as an indicator of lipid peroxidation, obtained in rat kidney tissues. As adherence to previous studies, it was found that increase in MDA level was achieved after administration of cisplatin (Al-Kahtani et al., 2014; Amirshahrokhi and Khalili, 2015; An et al., 2011; Helmy et al., 2014; Motamedi et al., 2014). This elevated MDA level reversed by FA treatment and when compared with the

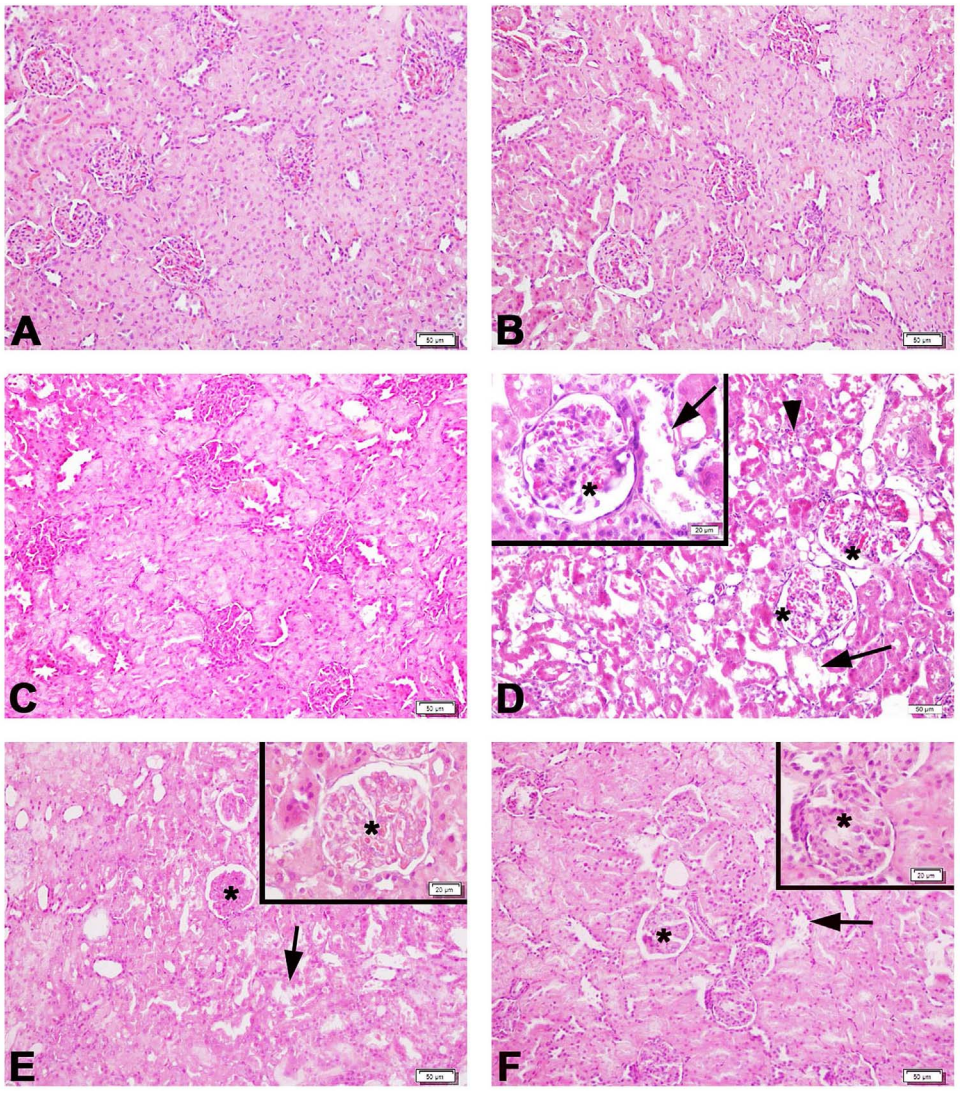

Fig. 6. Representative photomicrographs of kidney in experimental rat groups. Regular parenchyma morphology of kidney in the saline (A), curcumin (B) and ferulic acid (C) applied control groups; glomerular congestion (*), degenerated tubules (arrow) and vascular congestion (arrowhead) in cisplatin applied toxicity group (D); quite regular renal corpuscles with decreased glomerular congestion (*), a few degenerated tubules (arrow) in curcumin plus cisplatin applied (E) and ferulic acid plus cisplatin applied (F) treatment groups. H & E staining scale bars: 50 μm, and inset: 20 μm.

positive control group curcumin, this reduction was not found statistically different. In agreement with the study of Amirshahrokhi and Khalili (2015), toxicity induced by cisplatin exhibited elevation in MPO activity. After administration of FA, reduction in neutrophil infiltration to the kidney tissue was observed. Moreover, in the present study, curcumin could also decrease neutrophil infiltration in kidney tissue verifying the anti-inflammatory effect of curcumin observed in previous studies (Kuhad et al., 2007; Ueki et al., 2013). These observations support our hypothesis that the beneficial therapeutic effects of FA in nephrotoxicity are consequent to its anti-inflammatory effects.

While TOS and TAS levels were evaluated in previous studies, cisplatin appeared to increase TOS while decreasing TAS in kidney tissues (Toplu et al., 2014). Pabla et al. (Pabla and Dong, 2008) concluded that cisplatin-induced nephrotoxicity leads to changes in oxidative status by increasing oxidative stress. Our findings expand on these considerations by assessing the TOS and TAS response to the nephrotoxicity and it was determined that treatment with FA and curcumin could improve both TOS levels as a result of administration of cisplatin. Despite that the current study resulted in altered TAS levels due to cisplatin administration, and improvements of these measurements were obtained due to curcumin and FA treatments. TAS levels were shown to be reduced due to depletion of antioxidant protein deposits (Chandran et al., 2014). FA and curcumin were able to increase TAS level in rat kidney tissues.

Nitrotyrosine formation is based on the modification of tyrosine residues to 3-nitrotyrosine by potential nitrating agents (ex: peroxynitrite), and has been reported in many human, animal or cellular models of disease (Gow et al., 2004). Domitrović et al. (Domitrovic et al., 2013b) have shown increased levels of nitrotyrosine in rat kidneys after cisplatin administration. Kidney nitrotyrosine levels in the current study resulted high in cisplatin administered toxicity group. Both FA and curcumin treatment groups were significantly reduced protein nitrotyrosine levels by decreasing nitrotyrosine production due to cisplatin induced toxicity.

It is hypothesized that HO-1 protects the kidney from further injury due to its antioxidant and anti-inflammatory properties (Elmarakby et al., 2012). HO-1 is a protein inducible by stress presence, upregulated as a response to current chemical and physical stress (Gozzelino et al., 2010). It is well known that HO-1 level could be increased due to oxidative stress (Vile et al., 1994). HO-1 level modifications due to various compound administrations such as berberine, curcumin, metalloporphyrines, melatonin, has been targeted in several previous studies, resulting in high HO-1 levels of the toxicity group and decreased ones in treatment groups (Domitrovic et al., 2013a; Fetoni et al., 2014; Kilic et al., 2013; Pan et al., 2014). In agreement with previous studies (Domitrovic et al., 2013a; Fetoni et al., 2014; Kilic et al., 2013; Pan et al., 2014), in the current study it was observed high levels of HO-1 in cisplatin treated toxicity group. Thus, the current study indicated that HO-1 significantly increased due to cisplatin induced oxidative stress in order to scavenge free radicals and protect renal tissue from toxicity. Meanwhile antioxidants such as FA and

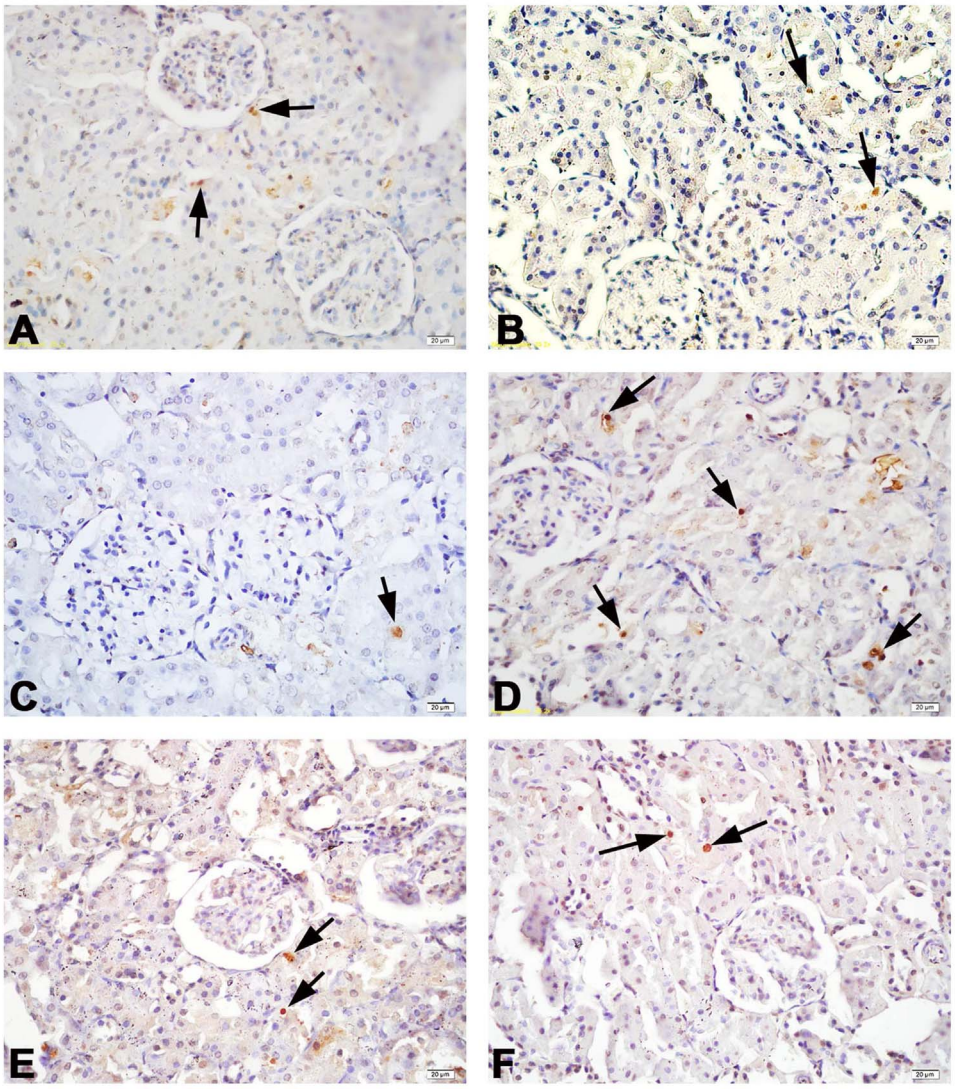

Fig. 7. Representative photomicrographs of TUNEL stained sections of kidney in experimental groups. Brown colored TUNEL positive cells (arrow) in the saline (A), curcumin (B) and ferulic acid (C) applied control groups, cisplatin (D) applied toxicity group, curcumin plus cisplatin (E) and ferulic acid plus cisplatin (F) applied treatment groups.

curcumin were able to decrease HO-1 levels in rat kidney tissues, attributing lower needs for free radical scavenging and protection by HO-1 as a result of oxidative stress and free radical reduction due to antioxidants presence.

Several studies have shown that cisplatin administration has caused an increase in serum BUN and creatinine levels in rats due to glomerular and tubular damage (Domitrovic et al., 2014; Helmy et al., 2014). The current study showed obvious renal dysfunction with increased serum BUN and creatinine levels in cisplatin administered toxicity group. FA significantly improved renal dysfunction, while curcumin could only corrected renal dysfunction slightly. Kim et al. (Kim et al., 2005) found that curcumin (200 mg) poorly attenuated the renal dysfunction after at a single cisplatin administration (45 mg/kg; i.p.). Vlahović et al. (Vlahović et al., 2007) concluded that renal dysfunction could not improve by curcumin administration and only carbonyl content in kidney was improved by curcumin administration in experimental model of myoglobinuric acute renal failure. Antunes et al. (Antunes et al., 2001) found that curcumin had no protective influence on cisplatin induced nephrotoxicity by neither improving renal dysfunction nor attenuating lipid peroxidation.

As a result of cisplatin induced nephrotoxicity, glomerular and tubular modifications have been noted in several studies (McDuffie et al., 2013; Paula Bulacio and Monica Torres, 2013; Sahu et al., 2013). Present histological analysis resulted in severe degeneration of the tubules, congestion and inflammatory cell infiltration in kidneys of cisplatin toxicity group. Moreover, the positive effects of FA and curcumin were demonstrated on renal corpuscles and tubules during histopathological examination.

Apoptosis evaluations in this study in agreement with other studies demonstrated cisplatin has the ability to enhance apoptosis in kidney tissues (Choi et al., 2014; Yang et al., 2015). Oxidation and inflammation, which mainly results in apoptosis of tubular epithelial cells, plays a main role on renal function and tubular structure damage (Lopez-Novoa et al., 2011). Terada et al. (Terada et al., 2013) showed cisplatin induced acute renal failure resulting in increased tubular apoptosis. The present study revealed that FA was able to prevent apoptosis significantly in kidney tissues as well as curcumin, which was also able to reveal anti-apoptotic activity.

5. Conclusion

It has been concluded that cisplatin administration leaded to renal damage by inducing oxidative stress and inflammatory reactions, depleting natural antioxidative status, damaging renal morphology and enhancing apoptosis. On contrary, treatment with antioxidants such as FA and curcumin resulted in renal damage prevention and improved renal morphology, indicating renoprotective effects for FA, and for curcumin.

Conflict of interest

None.

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