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Original Article

The effect of ellagic acid on renal injury associated with acrylamide in experimental rats

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ABSTRACT

Introduction: Acrylamide (ACR) is a toxic substance that has renal toxicity. We aim to investigate the therapeutic activity of ellagic acid (EA) on renal injury induced by ACR in Wistar rats.

Methods: Thirty-five male Wistar rats were assigned into 5 groups: the control group (5ml/kg normal saline), the ACR group (20mg/kg ACR), the ACR+EA10 group (ACR and 10mg/kg EA), the ACR+EA30 group (ACR and 30mg/kg EA) and the EA30 group (30mg/kg EA). ACR and EA were daily administered by gavage for 30 days. Renal function was assessed by measuring the sera levels of creatinine (Cr) and blood urea nitrogen (BUN). Renal oxidative and inflammatory markers including malondialdehyde (MDA), nitric oxide (NO), protein carbonyl (PC), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione (GSH), tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). hematoxylin and eosin staining was employed to assess pathological alternations of the kidney.

Results: EA (more potentially 30mg/kg) administration alleviated the ACR-induced alterations in Cr and BUN levels. Moreover, EA treatment reduced the elevated levels of MDA, NO and PC as well as TNF-α and IL-1β content in renal tissue. Furthermore, reduced activity of SOD and CAT as well as GSH content in the kidney was increased by EA treatment. EA attenuated the ACR-induced pathological alterations in kidney.

Conclusion: These findings suggested that EA could mitigate ACR-induced kidney injury due to its potent antioxidant and anti-inflammatory effects.

Keywords:
Acrylamide
Oxidative stress
Inflammation
Nephrotoxicity
Ellagic acid

Introduction

Acrylamide (ACR, Figure 1A) is a toxic agent and it may be used in many industries, including cosmetics, textile and paper (Friedman, 2003). Consumption of some carbohydrate-rich food including bread and potato chips which are prepared at high temperatures is one of the major cause of ACR exposure (Yaylayan and Stadler, 2005). It is well established that ACR acts via inducing oxidative and inflammatory damages in different organs especially the brain, liver and kidney (Pan

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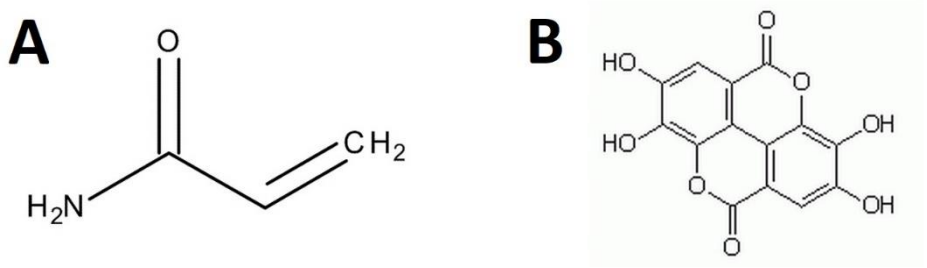

FIGURE 1. Chemical structure of acrylamide (A) and ellagic acid (B).

et al., 2015; Semla et al., 2017). ACR causes oxidative stress due to overproduction of nitric oxide (NO), protein carbonyl (PC) and increasing the lipoperoxidation as well as reduction of the capacity of the antioxidant system (Yousef and El-Demerdash, 2006). In addition, ACR intoxication induced inflammation by increasing the production and/or releasing of inflammatory parameters including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) (Batoryna et al., 2017; Pan et al., 2018).

Ellagic acid (EA, Figure 1B) as a dimeric derivative of gallic acid, is found in numerous nuts and fruits (Karimi et al., 2020; Soong and Barlow, 2006). EA has various pharmacological effects including antivirus, anticancer, antifibrotic and antidiabetic (Garcia-Nino and Zazueta, 2015). Moreover, EA has antioxidant and anti-inflammatory activity through activating and/or inducing antioxidant enzymes and modulates the secretion of proinflammatory cytokines (Goudarzi et al., 2018b; Goudarzi et al., 2019). The nephroprotective effects of EA have been demonstrated in various pathological and toxicological conditions including ischemia-reperfusion injury, diabetic nephropathy, cisplatin and arsenic-induced renal toxicity (Goyal et al., 2019; Liu et al., 2020; Mehrzadi et al., 2018; Zhou et al., 2019).

The present investigation was designed to evaluate the nephroprotective efficiency of EA on renal damages induced by ACR.

Material and methods

Chemicals

ACR and EA were purchased from Sigma–Aldrich Chemical Company (St. Louis, MO, USA).

Animals

The experiments were performed on 35 male Wistar rats (190±10g). The animals were kept under standard laboratory conditions (12h light: 12h dark cycle; 20±2°C temperature) with food and water ad libitum (Al-Hasan, 2017). All animal experiments were conducted in accordance with the standard ethical guidelines (NIH, publication no. 85-23, revised 1985; European Communities Directive 86/609/EEC) and were approved by the Ahvaz Jundishapur University Animal Experiment Committee (Registration number: IR.AJUMS.REC.1396.283).

Experimental groups

After 2 weeks of adaptation in the animal house, animals were randomly assigned to 5 groups (n=7) as follows: Control group: oral normal saline (5ml/kg) administration for 30 days; ACR group: oral ACR (20mg/kg) administration for 30 days (Abdel-Daim et al., 2020; Karimi et al., 2020); ACR+EA10 and ACR+EA30 groups: oral ACR and EA (10 and 30mg/kg) administration for 30 days; EA 30 group: oral EA (30mg/kg) administration for 30 days (Goudarzi et al., 2018a; Rahangadale et al., 2012). EA and ACR have been solved in normal saline.

Collection of blood and kidneys

The animals were mildly anesthetized with diethyl ether and after collecting the blood samples, the samples were centrifugated (3000rpm, 10min). Thereafter, sera samples were stored at -80°C for biochemical analyses. Then, kidneys were obtained. The right kidneys were placed in 10% buffered formalin solution for pathological analyses. The left kidneys were homogenized in buffered Tris-HCl (1/10 w/v) for oxidative and inflammatory analyzes (Bazmandegan et al., 2019).

Biochemical analyses

The levels of blood urea nitrogen (BUN) and creatinine (Cr) were assessed by a biochemical autoanalyzer (RA-XT Technicon) using appropriate test kits (ParsAz-

TABLE 1: Effect of ellagic acid on sera parameters in acrylamide-induced nephrotoxicity in rats.

Groups	Sera parameters	
	BUN (mg/dl)	Cr (mg/dl)
Control	16.40±3.84	0.43±0.09
ACR	28.24±5.35***	0.65±0.12***
ACR+EA10	24.58±4.51*	0.61±0.08**
ACR+EA30	20.10±4.12##	0.50±0.06#
EA30	15.30±3.19###	0.38±0.09###

Values are mean±SD (n=7). *Significant change with respect to control group (*P<0.05; **P<0.01; *** P<0.001). #Significant change with respect to ACR group (#P<0.05; ##P<0.01; ###P<0.001).

moon Co., Tehran, Iran) (Bazmandegan et al., 2021).

Oxidative analyses

The glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities as well as the level of glutathione (GSH) in the kidney tissue were determined following the methods as described in our previous study (Goudarzi et al., 2018a). Teb Pazhouhan Razi kits (Tehran, Iran) were used to measure the level of malondialdehyde (MDA) as well as evaluate the activity of catalase (CAT) (Fatemi et al., 2021). For evaluating the level of NO and PC, we used the Griess diazotization reaction (Tracey et al., 1990) and Levine method (Levine et al., 1994), respectively.

Inflammatory analyses

The renal levels of TNF-α and IL-1β were evaluated with appropriate ELISA kits (IBL Company, MN, USA).

Histopathological evaluation

The formalin-fixed paraffin-embedded renal tissues were prepared into 5µm sections and stained hematoxylin and eosin (H&E). The histological lesions including congestion of red blood cells (RBCs), inflammatory cells infiltration, glomerulus diameter and proximal tubule damage were evaluated by a blinded expert pathologist (Dehnamaki et al., 2019; Hosseinzadeh et al., 2020). For each animal 6 microscopy slides and in each slide the mean of 6 fields was calculated.

Statistical analyses

Data are expressed as mean±SD and statistical analyses were performed via GraphPad Prism version 8 (GraphPad Software, USA). Statistical comparison was made using one-way ANOVA followed by Tukey's post hoc test. A P<0.05 was considered statistically significant.

Results

EA ameliorates ACR-induced renal dysfunction

The levels of Cr and BUN were elevated after ACR administration which suggesting severe nephrotoxicity (all P<0.001, Table 1). EA treatment (30mg/kg) alongside ACR decreased the sera levels of BUN and Cr in comparison with ACR-treated rats (P<0.01 and P<0.05, respectively). Moreover, EA administration (30mg/kg) to normal rats did not make any changes in these renal function parameters.

EA attenuates ACR-induced renal oxidative stress

The renal MDA, NO and PC levels were increased after ACR administration (all P<0.001, Table 2). EA treatment (10mg/kg) alongside ACR only decreased the kidney levels of NO in comparison with ACR-treated rats (P<0.05). Furthermore, EA treatment (30mg/kg) alongside ACR decreased the kidney levels of MDA, NO and PC when compared with ACR-treated animals (all P<0.01).

The SOD, CAT and GPx activities as well as levels of GSH in renal tissue were decreased after ACR administration (all P<0.001, Table 3). EA treatment (10mg/kg) alongside ACR only elevated the kidney levels of GSH in comparison with ACR-treated rats (P<0.05). Furthermore, EA treatment (30mg/kg) alongside ACR increased the activities of CAT and SOD as well as GSH content in comparison with ACR-treated animals (P<0.05, P<0.05 and P<0.01, respectively). Moreover, EA administration (30mg/kg) to normal rats did not make any changes in

TABLE 2: Effect of ellagic acid on oxidative stress parameters in acrylamide-induced nephrotoxicity in rats.

Groups	Oxidative stress parameters		
	MDA (nmol/mg protein)	NO (nmol/mg protein)	PC (nmol carbonyl/mg protein)
Control	1.37±0.26	28.25±4.35	8.14±1.41
ACR	3.12±0.58****	64.32±7.25***	24.18±4.32***
ACR+EA10	2.71±0.43***	53.69±6.20***#	21.41±3.28***
ACR+EA30	2.34±0.30***##	50.93±5.80***##	17.35±3.25***##
EA30	1.30±0.28###	27.19±4.20###	8.75±1.30###

Values are mean±SD (n=7). *Significant change with respect to control group (***P<0.001). #Significant change with respect to ACR group (#P<0.05; ##P<0.01; ###P<0.001).

TABLE 3: Effect of ellagic acid on antioxidant enzymes activities in acrylamide-induced nephrotoxicity in rats.

Groups	Antioxidant enzymes			
	SOD (U/mg protein)	CAT (U/mg protein)	GPx (U/mg protein)	GSH (nmol/mg protein)
Control	3.35±0.52	45.48±7.47	3.45±0.53	27.35±4.10
ACR	1.56±0.38****	22.50±4.67***	2.16±0.31***	10.14±2.32***
ACR+EA10	2.07±0.35***	27.51±4.96***	2.46±0.42**	15.86±2.80***#
ACR+EA30	2.33±0.45**#	33.50±5.25*#	2.78±0.60	17.54±3.45***##
EA30	3.70±0.46###	51.00±8.50###	3.70±0.62###	28.10±4.14###

Values are mean±SD (n=7). *Significant change with respect to control group (*P<0.05; **P<0.01; ***P<0.001). #Significant change with respect to ACR group (#P<0.05; ##P<0.01; ###P<0.001).

TABLE 4: Effect of ellagic acid on inflammatory parameters in acrylamide-induced nephrotoxicity in rats.

Groups	Inflammatory parameters	
	TNF-α (pg/mg protein)	IL-1β (pg/mg protein)
Control	5.74±0.65	9.36±3.50
ACR	8.94±0.90***	24.25±4.88***
ACR+EA10	7.76±0.71***#	18.20±3.89***#
ACR+EA30	6.86±0.63**###	16.35±3.40*##
EA30	5.42±0.56###	8.20±2.50###

Values are mean±SD (n=7). *Significant change with respect to control group (*P<0.05; **P<0.01; ***P<0.001). #Significant change with respect to ACR group (#P<0.05; ##P<0.01; ###P<0.001).

the renal capacity of these antioxidative and oxidative parameters (Tables 2 and 3).

EA mitigates ACR-induced renal inflammation

The renal levels of TNF-α and IL-1β were elevated after ACR administration (all P<0.001, Table 4). EA treatment (10mg/kg) alongside ACR reduced the kidney levels of IL-1β and TNF-α in comparison with ACR-treated rats (all P<0.05). Furthermore, EA treatment (30mg/kg) alongside ACR attenuated the levels of TNF-α and IL-1β in comparison with ACR-treated animals (P<0.001 and P<0.01, respectively). Moreover, EA administration (30mg/kg) to normal rats did not make any changes in the renal levels of these inflammatory parameters.

EA attenuates ACR-induced renal pathological alternations

Control rats and rats treated with EA showed the morphology of normal kidneys (Figure 2A and Table 5). The sections from the ACR-treated rats displayed renal injury induced by ACR including inflammatory cells infiltration, RBCs congestion, proximal tubule damage and glomerulus collapse (all P<0.001, Figure 2B and Table 5). EA treatment (10mg/kg) alongside ACR attenuated the inflammatory cells infiltration and proximal tubular damage (P<0.05 and P<0.01, respective-

TABLE 5: Histology assessments in control and experimental groups.

Groups	Histological Criteria			
	Glomerulus diameter (µm)	Proximal tubule damage (%)	Infiltration of inflammatory cells	Congestion of RBCs
Control	185.35±28.50	0.92±0.15	0.13±0.07	0.09±0.02
ACR	95.10±15.35***	19.35±4.50***	2.80±0.45***	2.25 ± 0.52***
ACR+EA10	113.46±21.10***	12.83±3.60$^{***\,\#\#}$	2.30±0.38$^{***\,\#}$	2.02 ± 0.46***
ACR+EA30	138.40±25.40$^{*\#}$	7.70±2.55$^{***\,\#\#\#}$	0.80±0.13$^{***\,\#\#\#}$	1.70 ± 0.43***
EA30	205.67±32.30$^{\#\#\#}$	0.95±0.2$^{\#\#\#}$	0.15±0.03$^{\#\#\#}$	0.08±0.03$^{\#\#\#}$

Values are mean±SD (n=7). *Significant change with respect to control group ($^{*}P$<0.05; $^{***}P$<0.001). $^{\#}$Significant change with respect to ACR group ($^{\#}P$<0.05; $^{\#\#}P$<0.01; $^{\#\#\#}P$<0.001).

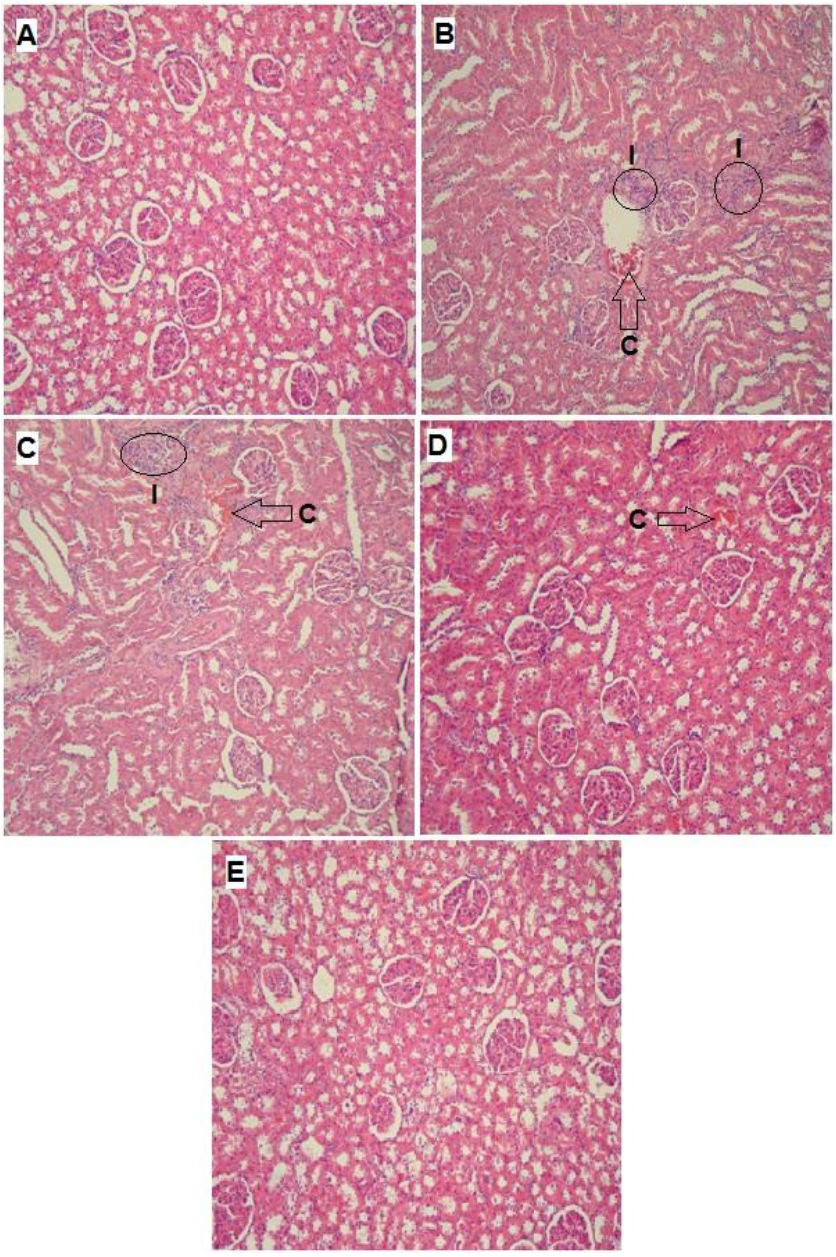

FIGURE 2. Histological changes (stained with Hematoxylin & Eosin, magnification X 40) in the kidney tissue of rats in different experimental. (A) Control group; (B) ACR group; (C) ACR+EA10 group; (D) ACR+EA30 group; (E) EA30 group. I: Infiltration of inflammatory cells, C: Congestion of RBCs.

ly; Figure 2C and Table 5). Furthermore, EA treatment (30mg/kg) alongside ACR decreased the inflammatory cells infiltration and proximal tubular damage as well as increased the glomerulus diameter in comparison with ACR-treated animals ($P<0.001$, $P<0.001$ and $P<0.05$, respectively; Figure 2D and Table 5). Moreover, EA administration (30mg/kg) to normal rats did not make any changes in these renal pathological lesions (Figure 2E and Table 5).

Discussion

In this study, we demonstrated that renal function biochemical parameters, sera levels of Cr and BUN, were markedly elevated in ACR-treated animals (20mg/kg for 30 days). Moreover, oxidative and inflammatory parameters including MDA, PC, NO, TNF-α and IL-1β concentrations were elevated in the renal tissue of ACR intoxicated animals. We also found that ACR decreases the level of GSH as well as GPx, SOD and CAT activities. Furthermore, ACR resulted in histological evidence of renal injury. Oral administration of EA (more potentially at the dose 30mg/kg) significantly attenuated ACR-induced renal injury. Treatment with EA attenuated the renal sera functional parameters. Additionally, EA reduced ACR-induced nephrotoxicity via reducing reduced oxidative stress and inflammation. All these findings have been confirmed with pathological studies which showed EA reduced the renal pathological lesions in ACR-treated animals.

It has been reported that chronic exposure to ACR-induced nephrotoxicity is characterized by increased levels of BUN and Cr (Abdel-Daim et al., 2014; Ghorbel et al., 2017). In parallel with the previous studies, we found that ACR increases the mentioned indices in the sera samples. We also demonstrated that EA treatment reduces the level of Cr and BUN in the ACR-treated animals. Previous reports have shown that antioxidant agents could attenuate these alternations induced by ACR (Abdel-Daim et al., 2014; Atef et al., 2017; Dortaj et al., 2017; Ghorbel et al., 2017). Moreover, it is currently well established that EA can increase the capacity of antioxidant enzymes (Pari and Sivasankari 2008). From the results of our study and the previous studies, one can conclude that EA might cause renoprotection through its antioxidant properties.

Oxidative stress plays an important role in the pathogenesis of nephrotoxicity induced by ACR (Pan et al., 2018). We measured MDA, NO and PC as the hallmarks of cellular oxidative stress (Jamshidi and Zahedi, 2015). Increased level of these oxidative stress mediators including in the renal tissue of ACR-treated animals, in the present investigation, agrees with previous reports (Atef et al., 2017; Ghorbel et al., 2017). We also found that EA treatment attenuated the ACR-induced oxidative stress in the renal tissue, which was accompanied by decreasing in level of these oxidative stress mediators. Previous studies showed that natural extract and antioxidants including olive oil, *Trigonella foenum-graecum* extract, vitamin E and C markedly attenuated these oxidative parameters in the kidneys after ACR administration (Abdel-Daim et al., 2014; Atef et al., 2017; Dortaj et al., 2017; Ghorbel et al., 2017). As a powerful antioxidant EA inhibits the production of free radicals and scavenging the free radical (Yüce et al., 2008). Moreover, it has been revealed that EA suppresses the lipid peroxidation and NO in nicotine-induced nephrotoxicity (Vijaya Padma et al., 2014). These findings indicate that EA nephroprotective effect may be due to the reduction of oxidative stress in renal tissue.

Antioxidant systems have a maintenance role in maintaining the integrity of cells against exogenous and endogenous free radicals (Kalantar et al., 2016; Yousef and El-Demerdash, 2006). Previous studies exhibited that exposure to ACR is associated with reduction of the activities and/or levels of antioxidant mediators including SOD, CAT, GPx and GSH (Atef et al., 2017; Batoryna et al., 2017). Our investigations clearly demonstrated that ACR markedly decreased the activities of SOD, CAT and GPx as well as GSH content in kidney tissue. Also, we revealed that EA administration to ACR-treated animals increases the activities of SOD and CAT as well as GSH content. Previous reports demonstrated that EA elevates the activities and levels of these mentioned antioxidant parameters in different conditions including diabetic nephropathy, cyclosporine A and cisplatin-induced oxidative damage (Ahad et al., 2014; Pari and Sivasankari, 2008; Yüce et al., 2007). Accordingly, it seems that EA shows its protective effects, to some extent, through increasing the antioxidant capacity.

Over-production of free radicals leads to up-regulate inflammatory responses in kidneys via the production of inflammatory parameters (Goudarzi et al., 2017; Jin et al., 2016). Moreover, it is well established that toxicity with ACR induced the production of inflammatory cy-

tokines including TNF-α and IL-1β in different organs through overgeneration of free radicals (Jamshidi and Zahedi, 2015; Pan et al., 2018). Our results also indicated that ACR administration for 30 consecutive days increased the level of these cytokines in the kidneys. Moreover, we demonstrated that EA administration to ACR-treat animals attenuated the levels of TNF-α and IL-1β. EA has anti-inflammatory effects is accompanied by reducing the levels of inflammatory mediators in different pathological conditions including nephrotoxicity induced by sodium arsenite and doxorubicin-induced neurotoxicity (Rizk et al., 2017).

In parallel with the results of biochemical and molecular evaluations, the results of pathological observations also indicated structural lesions in kidney tissue of the ACR group. Pathological lesions like inflammatory cells infiltration, RBCs congestion, proximal tubule damage and glomerulus collapse were found in kidney samples. We also demonstrated that EA treatment mitigated these pathological changes in renal tissues of ACR-treated animals. These nephroprotective effects of EA against these pathological alternations have been demonstrated in a previous report which shows the beneficial effects of EA against cyclosporine A-induced renal injury (Yüce et al., 2008).

Conclusion

To conclude, this is the first investigation to reveal the nephroprotective effect of EA against kidney damage induced by ACR. Our results revealed that administration of EA to ACR-treated animals markedly reduces the levels of BUN and Cr in sera as well as MDA, PC, NO, TNF-α and IL-1β concentrations in the renal tissue. It was also found that EA increases the levels of GSH, SOD and CAT in kidneys of the ACR-treat rats. All these results were confirmed with pathological evaluations. Therefore, the results of the present investigation open new horizons to the protective effects of EA in attenuating ACR-induced nephrotoxicity in humans.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest related to this work.

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