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Protective effect of urolithin a on cisplatin-induced nephrotoxicity in mice via modulation of inflammation and oxidative stress

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ABSTRACT

Limitation of widely used anti-cancer agent cisplatin for a patient is nephrotoxicity. Nephrotoxicity is presentable in mice by injecting cisplatin at 25 mg/kg with 3 days endpoint. We used the same model to understand the protective role of urolithin A. Cisplatin-induced renal damages measured by histological damage in proximal tubular cells and by the increase in serum neutrophil gelatinase-associated lipocalin (NGAL), blood urea nitrogen (BUN), creatinine and urinary Kidney Injury Molecule-1 (KIM-1). Urolithin A pretreatment reduced all the above renal damage parameters in a significant way. Urolithin A attenuated cisplatin-induced pro-inflammatory cytokine/chemokine tumor necrosis factor α (TNFα), interleukin 23 (IL-23), interleukin 18 (IL-18) and macrophage inflammatory protein 2 (MIP2). Cisplatin-induced CD11b positive macrophages in kidneys reduced by urolithin A. Urolithin A also attenuated cisplatin-induced renal oxidative/nitrative stress, which was measured by lipid peroxidation(4-hydroxy-2-nonenal or 4-HNE protein adducts) and protein nitration. Urolithin A cisplatin-induced kidney injury in mice through the down regulation of inflammatory cytokines/chemokine, immune cells, and oxidative/nitrative stress thus improving cisplatin-induced proximal tubular cell death.

1. Introduction

Cisplatin also is known as cisplatinum or cis-diamminedichloroplatinum (II) is widely used as a chemotherapeutic drug alone or in combination with another drug in various cancers such as the bladder, ovarian, lung and testicular. It causes apoptosis by crosslink of purine bases in the DNA followed by DNA damage (Dasari and Tchounwou, 2014). The major limitation of this drug is the side effect such as nephrotoxicity (Florea and Busselberg, 2011; Schanz et al., 2018). Cisplatin is mainly removed from the body by kidneys and cisplatin is specifically accumulated due to basolateral organic cation system (Ciarimboli et al., 2010). Although most studies in cell lines and animal model lead to the hypotheses that cisplatin-induced nephrotoxicity is mediated by the interplay of oxidative stress, cell death, and inflammation (Manohar and Leung, 2018).

Dietary compounds, which have anti-oxidant and/or anti-inflammatory properties, exhibit protective activity in an animal model of cisplatin nephrotoxicity (Gomez-Sierra et al., 2018). Pomegranate contains punicalagin and ellagic acids but their bioavailability is limited (Sreekumar et al., 2014). Urolithin A is a metabolite of polyphenol ellagic acid made by gut bacteria and represents in plasma of animals and human (Espin et al., 2013). Urolithin A promotes lifespan in *C. elegans* and increases muscle function in the mice (Ryu et al., 2016). Urolithin A also shows anti-inflammatory properties *in vitro* and *in vivo* (Boakye et al., 2018; Rodriguez et al., 2017).

Here, we demonstrated that urolithin A is protective against cisplatin-induced nephrotoxicity. The protective effect was through modulation of oxidative stress and inflammatory response.

2. Materials and methods

2.1. Animal study

All animal study proposals were approved by the Committee on the

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Ethics of Animal Experiments of First Affiliated Hospital, College of Medicine, Zhejiang University under the guidance of the Chinese Academy of Sciences. The mouse strain C57BL/6 was used as described before (Wang et al., 2015). Male mice of ~6–8 weeks age with weights of 18–22 g were used in all experiments. Mice were sacrificed under deep anesthesia with 5% isoflurane followed by cervical dislocation on the third day (72 h) after a single injection of cisplatin (cis-diamine platinum (II) dichloride, Sigma) at dose 25 mg/kg i.p. as described earlier. High-Quality Urolithin A (> 98% pure) was also purchased from Sigma. Urolithin A was dissolved in DMSO/saline and administered at 100 mg/kg, i.p, for five days, starting 2 days prior to the cisplatin administration. Urolithin A and vehicle were also administered alone (without cisplatin treatment) as a separate group.

2.2. Kidney function from serum and urine

Serum levels of blood urea nitrogen (BUN), creatinine, NGAL, and urinary KIM-1 were measured as described earlier (Meng et al., 2017).

2.3. Kidney histology

Periodic acid–Schiff (PAS) staining for histological examination was performed as described earlier (Pan et al., 2014). Tubular damage was typically represented by the loss of the proximal tubular brush border, blebbing of apical membranes, tubular epithelial cell detachment from the basement membrane.

2.4. Scoring of tubular damage

Tubular damage in PAS-stained sections was examined under the microscope and scored based on the percentage of cortical tubules showing epithelial damage: 0-normal; 1 < 10%; 2-10–25%; 3-26–75%; 4 > 75%. In details, scoring was carried out based on tubular dilatation, cast formation, granulovacuolar degeneration, and tubular cell necrosis. The morphometric examinations were performed in a blinded manner.

2.5. Fluorescence microscopy

Kidneys were sectioned with a microtome, deparaffinized and stained as provided below with fluorescence microscope. CD11b conjugated Alexa Fluor 647 (BD Biosciences, USA) for neutrophil/monocytes (leukocytes) and nuclear stain by Hoechst 33342 (Solarbio, China) was stained in kidney sections.

2.6. Renal HNE protein adducts and protein nitration

Nitrotyrosine content was evaluated by ELISA as described (Wang et al., 2015) HNE adducts were determined using OxiSelect™ HNE Adduct ELISA Kit (Cell Biolabs, GENETIMES TECHNOLOGY, INC, Shanghai, China) as described earlier (Wang et al., 2015).

2.7. Quantitative determination of SOD activity

SOD activity was determined from tissue lysates using SOD activity kit (Enzo Life Sciences International, Inc., Plymouth Meeting, PA, USA) as described before (Wang et al., 2015).

2.8. Renal glutathione peroxidase assay

Glutathione peroxidase in kidney lysate was determined using Glutathione Peroxidase (GPX) Assay Kit (Abcam Trading Company Ltd. Shanghai, China) according to the manufacturer's instruction.

2.9. Renal glutathione content

Glutathione (GSH and GSSG) content in the kidney was measured by using a colorimetric kit (Jiancheng Bioengineering Institute, China) according to the manufacturer's instructions.

2.10. Measurement of renal apoptotic cell death marker in mice

Caspase-3/7 activities of the kidney extracts were measured using Apo- One Homogenous caspase-3/7 Assay Kit (Promega Corp., Madison, WI, USA) as described earlier (Pan et al., 2014).

Measurement of renal DNA fragmentation in mice.

The DNA fragmentation assay was carried out from kidney extracts using a commercially available kit (Cell Death Detection ELISA Kit, Roche China Ltd., Shanghai) according to manufacturer's instructions (Pan et al., 2014).

2.11. Real-time PCR

Isolation of RNA and Real-time PCR were carried out as described earlier (Pan et al., 2014; Wang et al., 2015). The primer sets for TNFα (PPM03113G), IL-18 (PPM03112B), MIP2 or CXCL2 (PPM02969F), IL23 (PPM03763F), NOX2 (PPM32951A), and β-actin (PPM02945B) were purchased from Qiagen (Pudong, Shanghai, China).

2.12. Renal western blot

Western blot was performed as described previously (Pan et al., 2009). All antibodies were purchased from Abcam (USA).

2.13. Statistical analysis

All data were presented as means ± SEMs. Multiple comparisons (Tukey) were performed using one way ANOVA. The analyses were performed with Graph Pad Prism software (GraphPad Software, Inc, CA, USA). A p-value < 0.05 was considered statistically significant.

3. Results and discussion

3.1. Effect of urolithin a in cisplatin-induced tubular damage and kidney injury

The mice were treated with urolithin A two days and 1 h prior to cisplatin administration (Fig. 1A). The reason for pretreatment is to acclimatize the mice to the dietary compound. This is relevant to the clinical setting where cisplatin treatment for cancer patients are always determined in advance.

Cisplatin cause kidney dysfunction in mice and all parameters such as NGAL, BUN, creatinine and urinary KIM-1 were increased significantly (Fig. 1B). Pretreatment with urolithin A attenuated all four parameters significantly. Histological analyses of kidney section also demonstrated that significant tubular damage by cisplatin was attenuated by pretreatment with urolithin A at 100 mg/kg (Fig. 2). Quantification of histological score demonstrated that urolithin A did attenuate the damage significantly.

Chemotherapy drug related to acute kidney injury in the hospital is significant (Peres and da Cunha, 2013; Schanz et al., 2018). Many dietary compounds are tested successfully against cisplatin-induced kidney injury (Guerrero-Beltran et al., 2012b). Urolithin A, a metabolite derived from plant-derived ellagitannins and ellagic acid are examined for safety (Heilman et al., 2017). The stability of urolithin A in human plasma last up to two days (Seeram et al., 2006). Thus, we hypothesized if urolithin is also a good candidate for protection in cisplatin-induced nephrotoxicity. In mice model we observed significant protect by urolithin-A in all kidney injury markers and also protected against tubular damages.

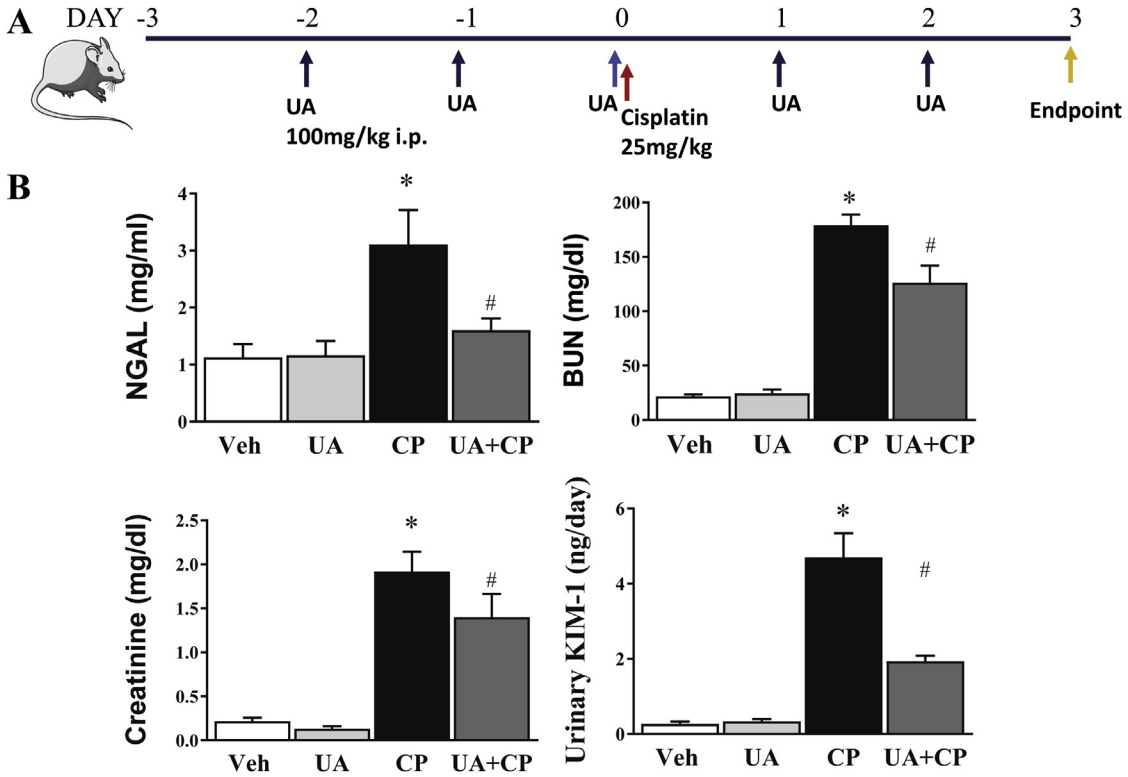

Fig. 1. Protective effect of urolithin A on cisplatin-induced renal dysfunction in mice. A. Schematic diagram of the experimental design. B. Cisplatin caused significant renal dysfunction as determined by the levels of NGAL, BUN, creatinine and urinary KIM-1 at 72 h. Cisplatin-induced renal dysfunction parameters were attenuated by urolithin A treatment. Results are mean ± S.E.M. n = 4/group. *p < 0.05 versus vehicle; and #p < 0.05 versus cisplatin.

3.2. Effect of urolithin a on cisplatin-induced pro-inflammatory cytokine/chemokine followed by leukocyte infiltration in the kidney

Pro-inflammatory cytokine/chemokine production followed by leukocyte infiltration in cisplatin-induced kidney injury has been reported earlier (Meng et al., 2017; Pan et al., 2014; Sahu et al., 2014). Renal damages by cisplatin-induced several cytokine/chemokine such as TNFα, IL-23, IL-18, and MIP2 in kidney injury (Faubel et al., 2007; Fouad and Al-Melhim, 2018; Ramesh and Reeves, 2002; Tadagavadi and Reeves, 2010). Cisplatin-induced TNFα, IL-23, IL-18, and MIP2 mRNA level significantly (Fig. 3A). Urolithin A pre-treatment attenuated TNFα, IL-23, IL-18, and MIP2 mRNA expression respectively. The mRNA levels of MIP2 and TNFα were further verified by protein level (Fig. 3B). In agreement with earlier finding, we also observed CD11b positive cells in cisplatin-induced kidney injury and urolithin A significantly reduced CD11b positive cells (Fig. 4).

Pro-inflammatory cytokine/chemokine plays a critical role in cisplatin-induced nephrotoxicity (Guerrero-Beltran et al., 2012a; Meng et al., 2017; Wang et al., 2018). The role of TNFα in tubular cells by cisplatin is well known by multiple studies (Ramesh and Brian Reeves, 2006; Ramesh and Reeves, 2002). We also observed increased TNFα in cisplatin and urolithin A pretreatment is able to mitigate those effect. Another cytokine IL23 has been implicated in acute kidney injury (Bajwa et al., 2009). Urolithin A pretreatment also ameliorated

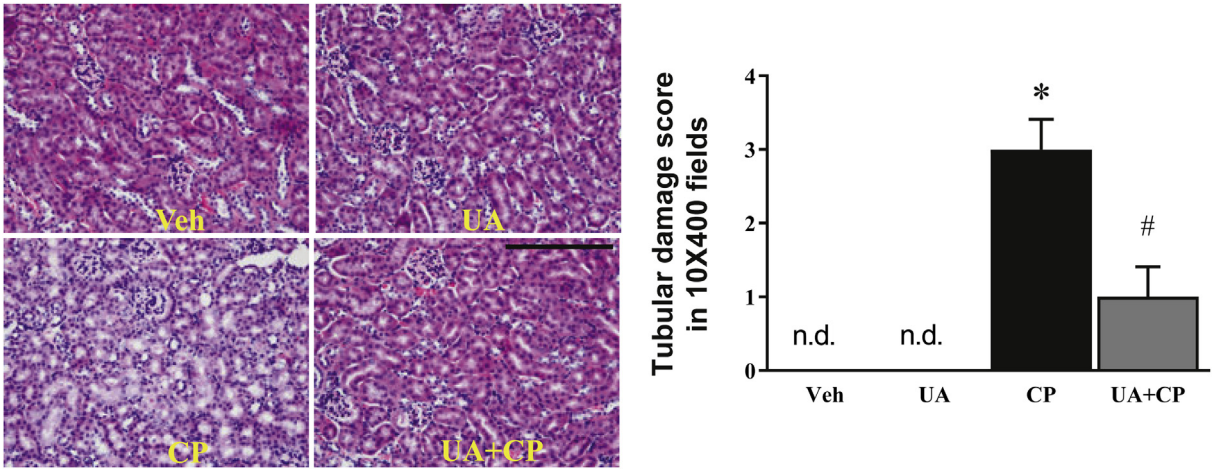

Fig. 2. Protective effect of urolithin A on cisplatin-induced kidney tubular damage in mice. A. Cisplatin-induced tubular damage as shown by PAS staining. The damage was attenuated by urolithin A treatment at dose 100 mg/kg. Scale bar 100 μM. B. Quantification of damage score from PAS staining. Results are mean ± S.E.M. n = 4 mice/group. *p < 0.05 versus vehicle; and #p < 0.05 versus cisplatin.

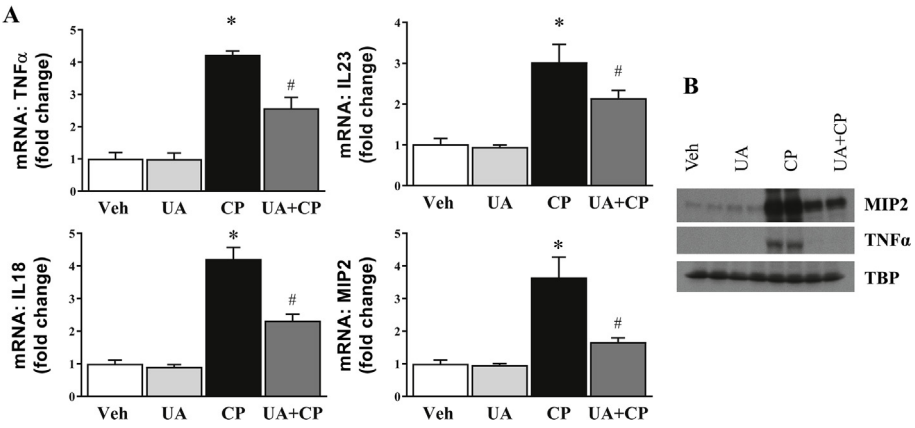

Fig. 3. Protective effect of urolithin A on cisplatin-induced pro-inflammatory cytokines/chemokine in mice. A. Real-time PCR based analyses of pro-inflammatory cytokines TNFα, IL23, IL18, and MIP2 indicated an increase in cisplatin-treated mice. Urolithin A treatment attenuated cisplatin-induced all cytokine and chemokine mRNA expression. Results are mean ± S.E.M. n = 4/group.*p < 0.05 versus vehicle; and #p < 0.05 versus cisplatin. B. Western blot analyses of MIP2 and TNFα from the same sample group. Tata binding protein was used as loading control.

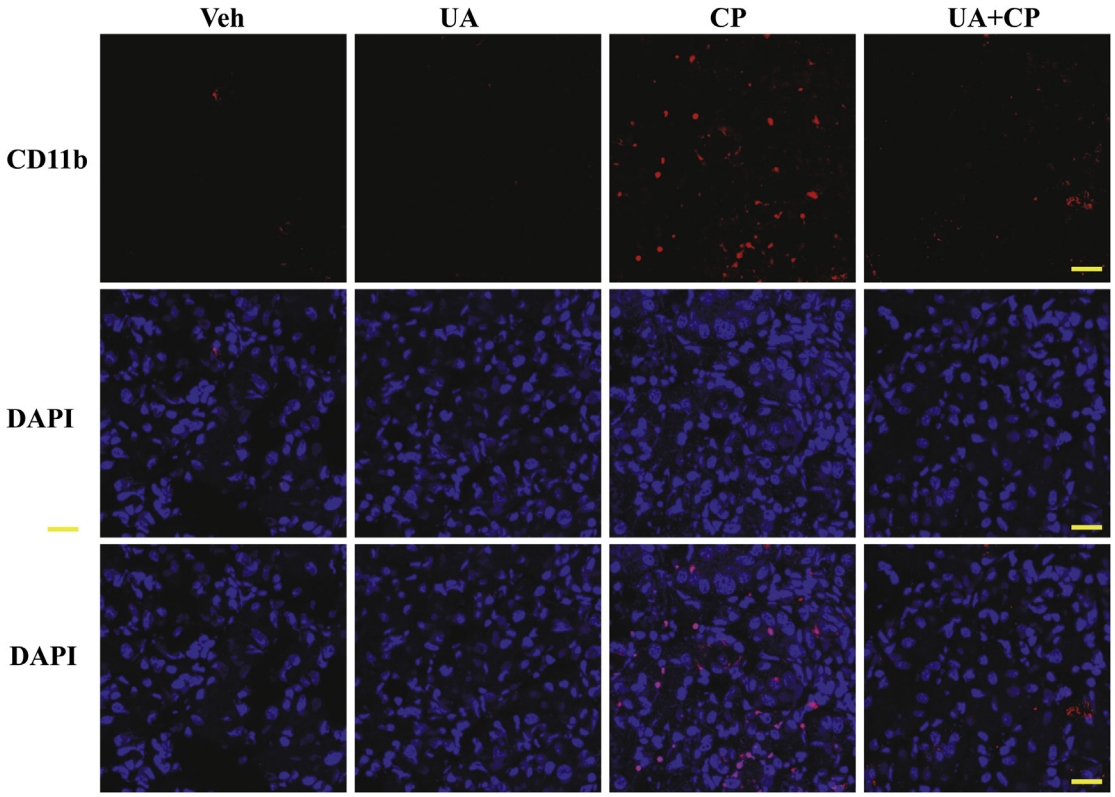

Fig. 4. Effect of urolithin A on cisplatin-induced CD11b positive monocyte/macrophage in mice. Immuno-fluorescence examination revealed significant CD11b positive cells (red) of the cisplatin-treated group. Nuclear stain (blue) was carried out by Hoechst 33342. Urolithin A treatment reduced the number of CD11b positive cells. Either vehicle (Veh) or urolithin A (UA) control group had few CD11b positive cells. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

cisplatin-induced level of IL23. In the rodent model of cisplatin, IL18 is also induced in response to cisplatin in kidneys (Fouad and Al-Melhim, 2018; Meng et al., 2017). We also observed a similar pattern with IL18 and urolithin A ameliorated such effect. MIP2, a chemokine, is also implicated in cisplatin-induced renal epithelial cell damage (Ramesh et al., 2007). Our findings are consistent with those findings and urolithin A was effective in mitigating those pro-inflammatory effects. To find cause and effect relationship, we further looked infiltrating leukocytes by CD11b staining. In agreement to earlier findings (Lu et al., 2008), we also observed increased immune cell infiltration and urolithin A reduced those cell number significantly.

Cytokine and chemokines play a role in cisplatin-induced nephrotoxicity (Pabla and Dong, 2008; Volarevic et al., 2019). IL18 plays a critical role in acute kidney injury(Wu et al., 2008). CD11b positive leukocytes are known to produce IL18 cytokine and modulate the activities of macrophages in acute kidney injury (Neighbors et al., 2001). Thus, leukocytes modulate both inflammatory cytokine production and activation of immune cells. Urolithin A was able to play a role in this process by reducing the inflammatory response.

Urolithin A is shown to have increased autophagy in macrophage and thus increase anti-inflammatory potential (Boakye et al., 2018). Autophagy induction by urolithin A also reported in microglia and human neural progenitor cells (Velagapudi et al., 2019). Based on that literature, we can not exclude the involvement of autophagy in the modulation of inflammation by urolithin-A in cisplatin-induced nephrotoxicity.

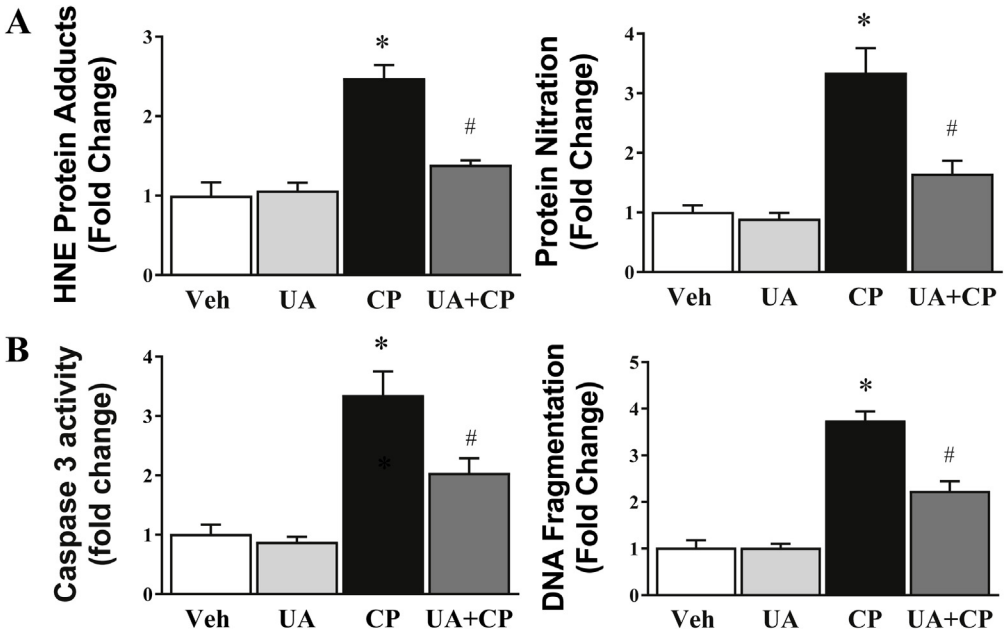

Fig. 5. Effect of urolithin A on cisplatin-induced oxidative/nitrative stress and cell death. A. Quantitative measurement of HNE protein adducts and protein nitration by ELISA demonstrated cisplatin-induced lipid peroxidation and protein nitration. Urolithin A (UA) attenuated both cisplatin-induced oxidative/nitrative stress markers. B. Quantitative determination of cell death markers caspase 3 activity and DNA fragmentation. Urolithin A (UA) attenuated both cisplatin-induced apoptotic cell death markers. Results are mean ± S.E.M. n = 4/group.*p < 0.05 versus vehicle; and #p < 0.05 versus cisplatin.

3.3. Effect of urolithin a in cisplatin-induced oxidative stress, impaired antioxidant defense, and cell death

Inflammation is caused by oxidative damage and it also generates new oxidative stress to the renal cells. We evaluated the effect of urolithin A in cisplatin-induced oxidative damage by determining 4-HNE and nitration modification of renal protein using quantitative ELISA. Both oxidative stress markers were increased in cisplatin-treated mice (Fig. 5A). Urolithin A pretreatment almost completely reduced those oxidative stress levels to control vehicle groups. We also quantified the cell death by two apoptotic marker caspase 3 activity and DNA fragmentation. Cisplatin-induced both of them and UA attenuated significantly (Fig. 5B).

Glutathione(GSH) always work as protective by and it depleted in cisplatin-induced kidney damage (Appenroth and Winnefeld, 1993) whereas oxidized glutathione indicates the level of redox state inside the cells. We also observed such a decrease in reduced glutathione and increase in oxidized glutathione from our study and urolithin A reversed cisplatin-mediated depletion of reduced glutathione and increase of oxidized glutathione in mice kidney (Fig. 6A). Thus UA improved cisplatin mediated decrease in GSH/GSSG ratio significantly. One of the major effects of infiltrating leukocyte is to increase reactive oxygen species generating enzyme gp91phox or NOX2 (Sedeek et al., 2013). We observed a significant increase in NOX2 mRNA level in the cisplatin-treated group and urolithin A pretreatment reduced its level (Fig. 6B). This might be due to reduced infiltrating leukocytes. In addition to that urolithin, A restored cisplatin-mediated loss in glutathione peroxidase activity and total SOD activity (Fig. 6C).

The primary target of cisplatin in the kidney are damages to tubular cells and vessels. Most proteins in those specific zones were modified by two mechanisms such as lipid peroxidation and peroxynitrite modification (Domitrovic et al., 2014; Meng et al., 2017; Pan et al., 2015; Wang et al., 2018). Here we demonstrated that urolithin A pretreatment significantly prevented both cisplatin-induced protein nitration and lipid peroxidation. NOX2 is the major source for oxidative stress in cisplatin-induced oxidative stress (Sahu et al., 2014). Urolithin A attenuated cisplatin-induced NOX2 expression.

Increases of reactive oxygen species generating enzymes result in an increase of oxidative stress but a decrease of anti-oxidant defense in cells also result in an increase of oxidative stress. In cisplatin-induced nephrotoxicity model, three major anti-oxidant defense mechanisms are compromised namely reduced glutathione content, SOD activity and glutathione peroxidase (Hassan et al., 2017; He et al., 2016; Meng et al., 2017). We also observed cisplatin impaired reduced glutathione reserve and decreased glutathione peroxidase activity and SOD activity. Urolithin A improved all three anti-oxidant defense mechanism in the kidney.

In addition to the direct effect on oxidative damage and cell death, reactive oxygen species also contribute to the immune cell effector function (Lee and Lee, 2018). Little is known about their role in acute kidney injury. The interplay of innate immunity and inflammasome to reactive oxygen species has been shown in acute kidney injury (Hutton et al., 2016; Jang and Rabb, 2009).

Protective effect of dietary compounds in cisplatin-induced nephrotoxicity will not be effective if those compounds are proliferative of cancer cells and it will be devastating in chemotherapy. Numerous published articles demonstrate that urolithin A also kills various cancer cells (Norden and Heiss, 2019; Stanislawska et al., 2018; Zhang et al., 2016). Thus, the scope of urolithin A in cisplatin-induced nephrotoxicity is synergistic with chemotherapy. Microenvironment also plays a role in cancer development and endogenous small metabolites play a critical role in cancer development (Mukhopadhyay et al., 2015). Similarly, urolithin A can be targeted in such microenvironment to control cancer development.

In brief, urolithin A protected against cisplatin-induced kidney injury by multi-steps (Fig. 7). First, urolithin A reduced pro-inflammatory cytokine/chemokine and thus limiting infiltrating leukocytes. Secondly, urolithin A reduces reactive oxygen species generating enzymes and also reduced oxidative stress by reducing inflammation. At last, it improved anti-oxidant defense mechanisms in response to cisplatin injury. Thus, all of the above effects led to cell death and all are interconnected. Pomegranate has been wisely using as traditional medicine particularly in the middle east and our finding on urolithin may lead to developing the new scope of therapeutic possibilities.

Acknowledgment

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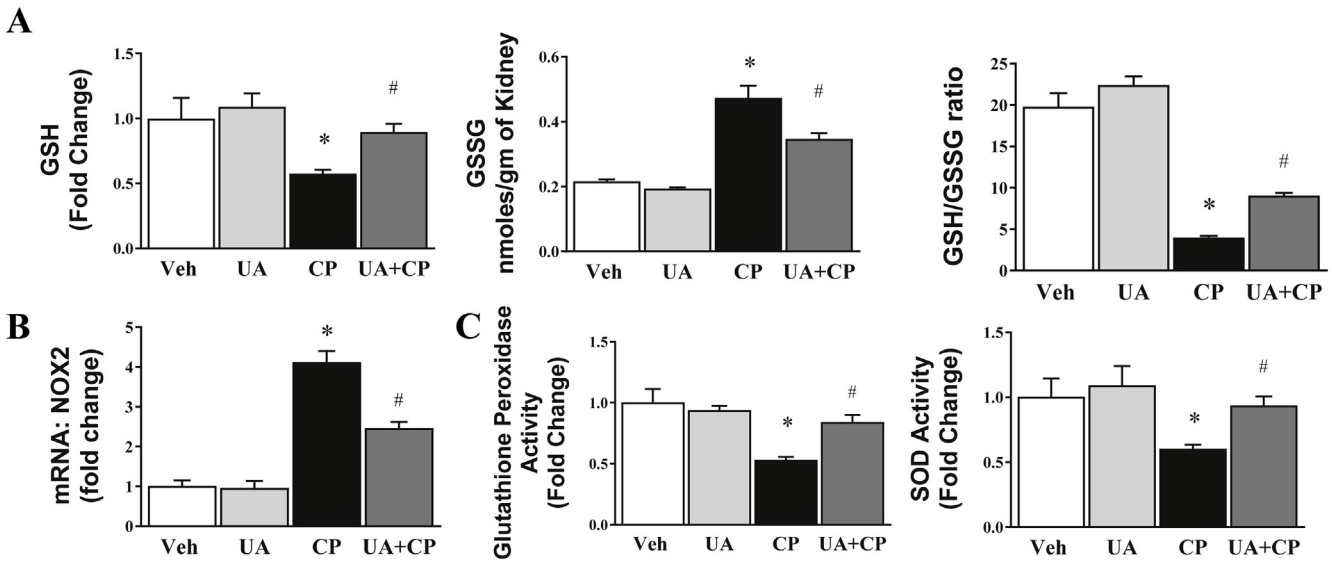

Fig. 6. Effect of urolithin A on cisplatin-induced changes in ROS generating enzyme and antioxidant defense in mice. A. Urolithin A(UA) reversed cisplatin modulated reduced(GSH) and oxidized (GSSG) levels. The ration of GSH/GSSG significantly altered by cisplatin in kidney and attenuated by UA. B. Cisplatin-induced ROS generating enzyme NOX2 mRNA as determined by real-time PCR was attenuated by UA treatment. C. Urolithin A improved cisplatin-mediated antioxidant defenses glutathione peroxidase activity, and SOD activity. Results are mean ± S.E.M. n = 4/group.*p < 0.05 versus vehicle; and #p < 0.05 versus cisplatin.

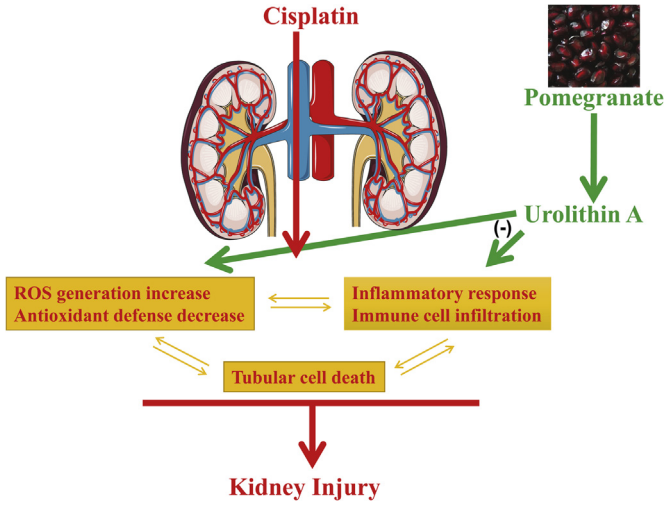

Fig. 7. Schematic diagram of urolithin A mediated protection in cisplatin-induced nephrotoxicity. Cisplatin-induced oxidative damage, inflammation and cell death, which are also interconnected with each other. Urolithin A modulated those and thus attenuated kidney injury.

conclusion.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2019.04.031.

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