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Activation of Sirtuin 1 by Ellagic Acid Ameliorates Cisplatin-Induced Apoptosis, Oxidative Stress and Nephrotoxicity

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Authors' contributions

This study was performed by collaboration between all authors. Authors TN, BGE and NAE did the literature review, designed and conducted the experimental work, computed the statistical study and wrote the manuscript draft. Authors AMB and MZN helped in performing the experiments-animal research and review the written manuscript. Authors SSA and ZMM performed the histological study. All authors approved the final manuscript.

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ABSTRACT

Background: Cisplatin (Cis) is a chemotherapeutic agent commonly applied in treating different cancers. However, acute renal injury remains a major side effect of Cis that limits its clinical use. Oxidative stress in renal tissues play a key role in Cis-induced toxicity. This research aimed to investigate the impact of ellagic acid (Ella) on Cis-induced apoptotic renal injury and the possible

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involvement of sirtuin 1 (SIRT1) and oxidative stress as a possible protective mechanism.
Methods: Twenty-four Sprague Dawley rats were divided into four groups (n=6) and treated as follows. The control (Cont) group (0.9% saline), Ella group (10 mg/kg), Cis group (7.5 mg/kg), Ella + Cis group (10 mg/kg + 7.5 mg/kg). Ella was administered 7 days prior to Cis injection. Seventy-two hours later, the rats were sacrificed, and blood and kidney samples were collected. Biochemical analyses were performed on serum and kidney homogenate. The histopathological and immunohistochemical analyses were performed on the formalin preserved kidneys.
Results: Ella significantly decreased serum creatinine and urea levels compared to the Cis group. Furthermore, Ella protects the kidney cortex and medulla against most Cis-induced histopathological changes. Ella significantly decreased kidney contents of malondialdehyde (MDA). Moreover, Ella reversed the Cis-induced reduction of kidney antioxidants, including glutathione peroxidase, superoxide dismutase, and catalase. Ella decreased kidney protein expression of both cyclooxygenase-2 (COX-2) and Bax proteins while increased SIRT1 and Bcl2 expression.
Conclusion: The results revealed a reduction in SIRT1 protein expression in rat renal medullary and cortical tissues following Cis treatment. However, Ella significantly enhanced SIRT1 expression, antioxidants levels, and reduced Cis-induced apoptosis, inflammation, and oxidative stress by increasing the ratio of Bax/Bcl-2 and reducing the expression of COX-2 and MDA, respectively. These findings provide additional evidence of the antioxidant and antiapoptotic effect of Ella in Cis-induced renal toxicity.

Keywords: Cisplatin; ellagic acid; apoptosis; inflammation; oxidative stress; SIRT1.

1. INTRODUCTION

Cisplatin (Cis) is a chemotherapeutic agent commonly applied in treating different cancers such as lung, ovarian, and bladder cancer. However, acute kidney injury (AKI), which occurs in 30% of patients receiving Cis, remains a major side effect limiting its clinical use [1,2]. Inflammation and oxidative stress in renal tissues play a key role in Cis toxicity. In addition, DNA damage, activation of tumor suppressor p53, and apoptotic pathways are important mechanisms of Cis cytotoxicity. We and others have reported the protective role of antioxidants and/or anti-inflammatory polyphenols such as ellagic acid, resveratrol, and quercetin to modulate these mechanisms in Cis-induced nephrotoxic rat models [3–6].

Sirtuin 1 (SIRT1) is a nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylase that regulates several physiological processes, including energy metabolism and apoptosis [7–9]. In the kidneys, SIRT1 has been shown to be abundantly expressed in medullary tubular cells, while lower levels have been reported in the cortical proximal tubular cells. SIRT1 protects the kidney functions, inhibiting renal inflammation, apoptosis, and oxidative stress accelerated by nephrotoxic toxic compounds [9]. Apart from histone deacetylation, SIRT1 can deacetylate p53 protein and p65 subunit of the nuclear factor kappa-B (NF-κB). SIRT1-dependent deacetylation of p53 transcription factor inhibits cell apoptosis provoked by oxidative stress while inhibiting p65 attenuates the inflammatory responses [10-11]. A reduction in mouse renal medullary cells' resistance to oxidative stress was observed following knocking down the SIRT1 gene [12]. Cis specifically has been reported to reduce the expression of SIRT1 protein in mouse proximal tubular cells. The use of polyphenol, resveratrol attenuated Cis-induced apoptosis and improved the glomerular filtration rate [6]. Moreover, SIRT1 overexpression in transgenic mice's proximal tubules ameliorated Cis-induced AKI by inhibiting oxidative stress and apoptosis [13].

Ellagic acid (Ella) is a polyphenolic compound with antioxidant and anti-inflammatory properties found in numerous medical plants [14-15]. In a recent study, we have demonstrated a renoprotective effect of EA nanoformulation in the Cis-induced nephrotoxic rat model by inhibiting NF-κβ and amelioration oxidative stress [5]. Since Cis decreases SIRT1 activity and induces oxidative stress-dependent apoptosis; hence, the present research aimed to investigate the impact of Ella on SIRT1 activation and Cis-induced apoptotic renal injury.

2. METHODOLOGY

2.1 Chemicals

Cis (1 mg/mL; Mylan Institutional LLC, Rockford, IL, USA), and Ella ≥95% (HPLC) (Sigma, USA) were used in the present study.

2.2 Experimental Design

Twenty-four adult male Sprague Dawley rats (12 weeks old and 160 ± 20g body weight) were used. The experiment was conducted in the animal house and biological lab of the Faculty of Pharmacy, King Abdulaziz University, Saudi Arabia, under controlled laboratory conditions. The rats were let eat and drink freely (standard pellet diet and water were provided ad libitum).

The rats were randomly classified into 4 research groups (n=6 per group) and treated as follows: the control (Cont) group (0.9% saline), Ella group (10 mg/kg) [16], Cis group (7.5 mg/kg) [5], Ella + Cis group (10 mg/kg + 7.5 mg/kg). Ella was injected intraperitoneally (i.p.) every day for 7 days before Cis injection. Then rats were sacrificed 72 h after Cis administration.

2.3 Sampling

At the end of the experiment, animals were anesthetized with ether, and blood samples were withdrawn by cardiac puncture technique. The serum was separated by centrifugation at 3000 rpm and stored at -80 °C. Rats were then decapitated, and kidneys were removed and reserved either at -80°C or in buffered formalin solution pH 7.4.

2.4 Measurement of Serum Kidney Function Markers

The levels of creatinine and urea in the serum were measured using the Crescent Diagnostics kits, Jeddah, Saudi Arabia adhering to the manufacturer's guidelines.

2.5 Kidney Histopathology (Hematoxylin and Eosin (H & E) Staining)

After formalin fixation and the tissues were embedded in paraffin, kidneys were sliced into 5 µm-thick sections. The slices were mounted on microscope slides where the wax was dissolved away with xylene and passed through several changes of alcohol to remove the xylene. The slides were thoroughly rinsed in water and stained with hematoxylin and eosin (H&E) stains. The slides were then examined for any histopathological change and photographed using an Olympus type light microscope connected to a digital camera.

2.6 Measurement of Kidney Oxidative Stress / Antioxidants Markers

Kidney levels of several oxidative stress and antioxidants Markers, including malondialdehyde (MDA), reduced glutathione (GSH), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) were quantified utilizing the kits of Biodiagnostic, Egypt adhering to the manufacturer's guidelines.

2.7 Immunohistochemical Staining

The peroxidase-anti peroxidase (PAP) approach was utilized to stain the kidney sections (5 µm-thick) for the proximal tubule and glomeruli expression of COX-2, SIRT1, Bax, and Bcl2. The slides were then examined for histopathological changes and photographed using an Olympus type light microscope connected to a digital camera.

2.8 Statistical Analysis

The data is provided as mean ± standard error (n=6). The significant difference between the experimental groups was discussed using an ANOVA test followed by a Tukey honestly significant difference post-hoc test. Statistical significance was described as a *P* value of less than 0.05.

3. RESULTS

3.1 Impact of Ella and Cis on Serum Kidney Function Markers

Rats injected with 10 mg/kg Ella showed no change in serum creatinine and urea levels compared to the Cont group. Injecting 7.5 mg/kg Cis significantly alleviates serum creatinine and urea levels relative to the Cont group ($P < 0.001$). In contrast to the Cis group, pretreatment of Cis-treated rats with Ella significantly decreased serum creatinine and urea levels ($P < 0.001$) (Fig. 1).

3.2 Impact of Ella and Cis on Kidney Histopathology

Rats pre-treated with 10 mg/kg Ella prior to Cis administration showed normal renal tissue parenchymatous architecture (renal corpuscle and glomeruli), cortical and medullary tubules. Rats injected with 7.5 mg/kg Cis showed enlarged renal corpuscles (hypertrophy) with mesangial substance deposition, dilated

glomerular capillaries, and less cellular density. Cis-treated rats also showed a low height, atrophied lining epithelium, and dilated lumen of both proximal and distal tubules besides cell debris in the lumen. Pretreatment of Cis-treated rats with Ella preserved both the renal corpuscle morphology, tubular epithelium integrity, and height; however, most tubules were found to be dilated (Figs. 2 and 3).

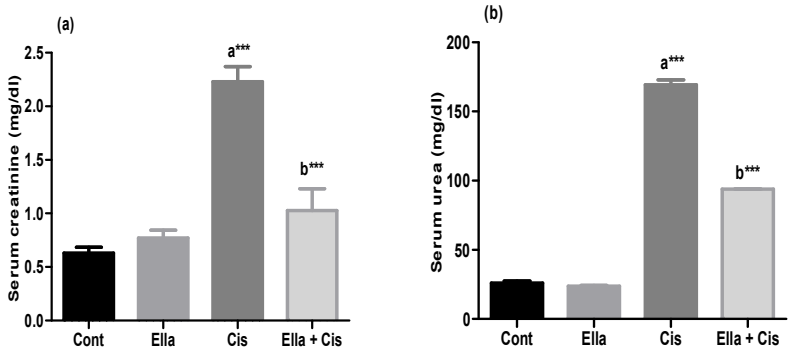

Fig. 1. Impact of ellagic acid (Ella) on serum concentrations of (a) creatinine and (b) urea determined after cisplatin (Cis) injection in rats

Data are presented as mean ± SE (n = 6). [a] significant difference from Cont rats. [b] significant difference than Cis rats. [***] P < 0.001

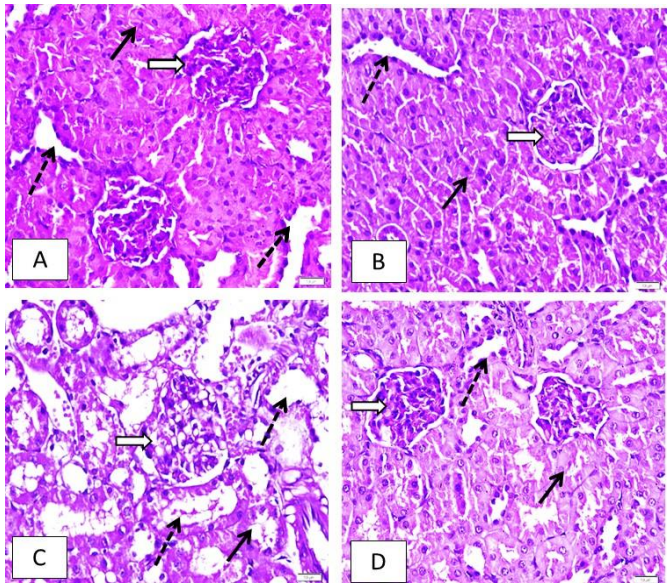

Fig. 2. Sections in rat kidney cortex stained with H & E (Bar 10µm)

Photo A: Cont renal corpuscles with a normal density of glomerular capillaries (white arrow). Proximal tubules possessed narrow lumina and intact high cuboidal epithelial lining (black arrow). Distal tubules showed wider lumina and low cuboidal epithelium (dotted arrows). Photo B: Ella showed normal renal tissue parenchymatous architecture (renal corpuscle and glomeruli) (white arrow) and renal tubules (black and dotted arrows). Photo C: Cis renal corpuscles looked enlarged (hypertrophy) with mesangial substance deposition, dilated glomerular capillaries, and less cellular density (white arrow). Both proximal and distal tubules showed low height atrophied lining epithelium with luminal dilation (black arrow) and the presence of cell debris (dotted arrows). Photo D: Ella + Cis showed potential preservation of normal renal corpuscle morphology (white arrow). Tubular epithelium integrity and height were preserved (black and dotted arrows)

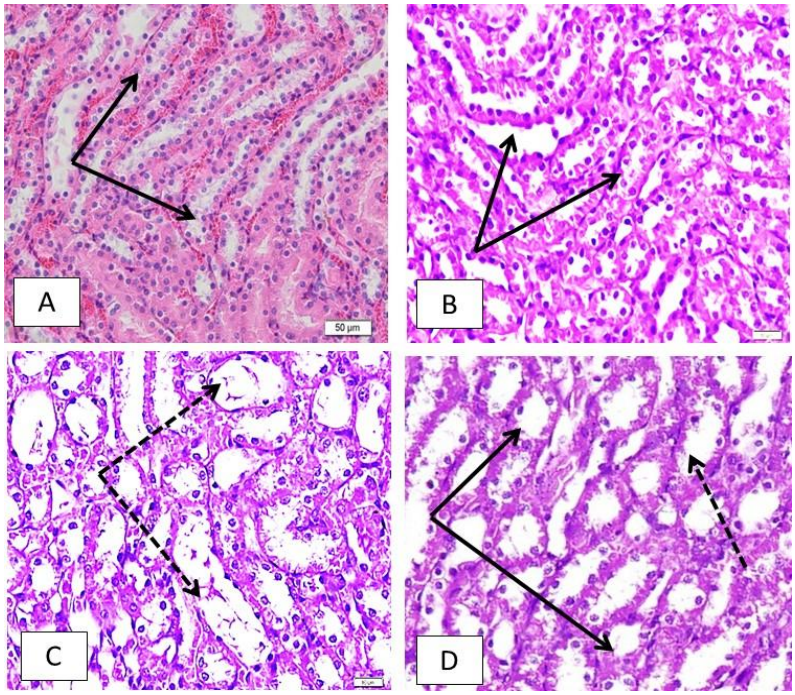

Fig. 3. Sections in rat kidney medulla stained with H & E (Bar 10µm)

Photo A: Cont showed normal kidney distal and collecting tubules possessing narrow lumina and intact cuboidal epithelial lining (black arrows). Photo B: Ella showed a normal structure of medullary tubules (black arrows). Photo C: Cis showed a marked decrease in cell height with pyknosis of their nuclei. The lumina of most tubules are dilated with the presence of cell debris (dotted arrows). Photo D: Ella + Cis showed potential preservation of tubular epithelium integrity (black arrows); however, most looked dilated (dotted arrows)

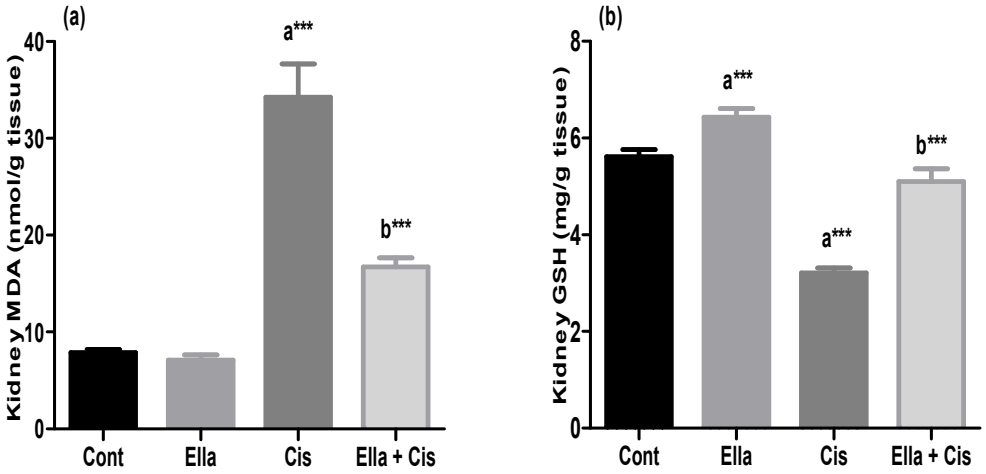

Fig. 4. Impact of ellagic acid (Ella) on kidney concentrations of (a) MDA and (b) GSH determined after cisplatin (Cis) injection in rats

Data are presented as mean ± SE (n = 6). [a] significant difference from Cont rats. [b] significant difference than Cis rats [***] P < 0.001

3.3 Impact of Ella and Cis on Kidney Oxidative Stress / Antioxidants Markers

Rats injected with 10 mg/kg Ella showed no increase in kidney MDA content than the Cont group. Injecting 7.5 mg/kg Cis drastically alleviates the kidney MDA level in comparison to the Cont group ($P < 0.001$). The pretreatment of Cis-treated rats with Ella drastically reduced kidney MDA content in contrast with the Cis group ($P < 0.001$) (Fig. 4 a).

A significant elevation in kidney GSH content was found in rats injected with 10 mg/kg Ella than the Cont group ($P < 0.001$). Injecting 7.5 mg/kg, Cis significantly decreased kidney GSH content than the Cont group ($P < 0.001$). The pretreatment of rats with Ella prior to Cis administration produced a significant elevation in the kidney GSH level in relation to the Cis-treated group ($P < 0.001$) (Fig. 4 b).

The administration of 10 mg/kg Ella did not alter the kidney GPx, SOD, and CAT contents than the Cont group. However, injecting 7.5 mg/kg Cis significantly decreased the kidney GPx, SOD, and CAT contents than the Cont group ($P < 0.001$). The pre-administration of Ella to the Cis-treated rats produced a significant increase in kidney GPx, SOD, and CAT contents in relation to the Cis group ($P < 0.05$) (Fig. 5).

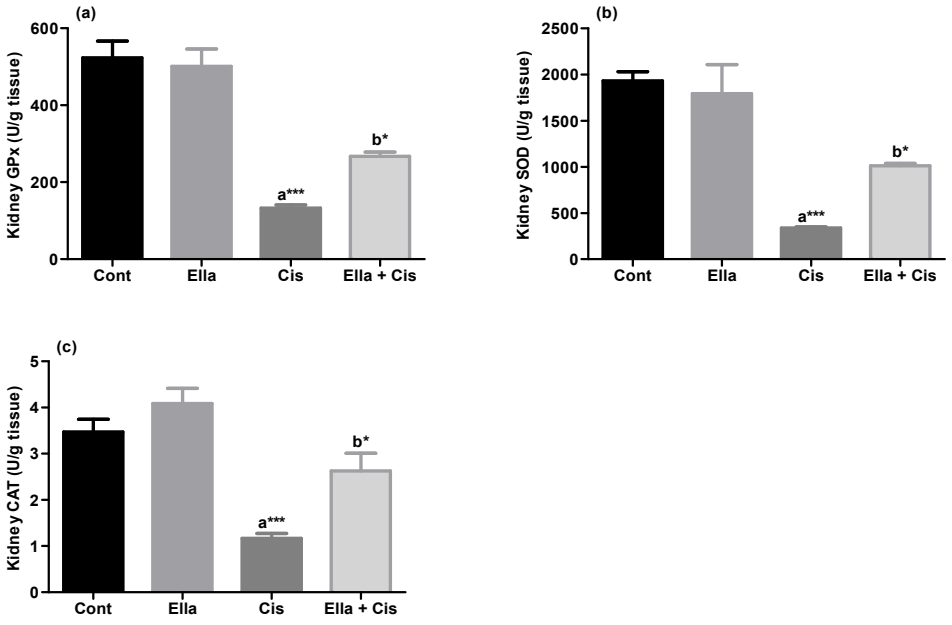

Fig. 5. Impact of ellagic acid (Ella) on kidney concentrations of (a) GPx, (b) SOD, and (c) CAT determined after cisplatin (Cis) injection in rats

Data are presented as mean ± SE (n = 6). [a] significant difference than Cont rats. [b] significant difference from Cis rats. [*] P = 0.05, [***] P < 0.001

3.4 Impact of Ella and Cis on Kidney COX-2 Protein Expression

Rats injected with 10 mg/kg Ella showed a mild increase in the kidney COX-2 protein expression than the Cont group. Injecting 7.5 mg/kg Cis produced a marked induction of COX-2 protein expression in the kidney tubules compared to the Cont group. However, the pre-administration of Ella to the Cis-treated rats showed lower kidney COX-2 protein level relative to the Cis group (Fig. 6).

3.5 Impact of Ella and Cis on Kidney SIRT1 Protein Expression

Rats injected with 10mg/kg Ella showed a marked increase in kidney SIRT1 protein

expression in the glomeruli and tubules than the Cont group. Injecting 7.5mg/kg, Cis produced no expression of SIRT1 protein in the kidney tissue compared to the Cont group. A moderate increase in kidney glomeruli and tubules SIRT1 protein expression was induced by pretreatment of Cis-treated rats with Ella compared to the Cis group (Fig. 7).

3.6 Impact of Ella and Cis on Kidney Bax Protein Expression

Rats injected with 10mg/kg Ella showed a mild kidney tubule Bax protein expression than the Cont group. Injecting 7.5mg/kg, Cis produced a marked expression of Bax protein in the kidney tubules relative to the Cont group. Compared to the Cis group, pretreatment of Cis-treated rats with Ella produced a marked decrease in kidney Bax protein expression (Fig. 8).

3.7 Impact of Ella and Cis on Kidney Bcl2 Protein Expression

Rats injected with 10mg/kg Ella showed a marked increase in kidney Bcl2 protein expression in tubules than the Cont group. Injecting 7.5mg/kg, Cis produced no expression of Bcl2 protein in the kidney tubules compared to the Cont group. In contrast to the Cis group, pretreatment of Cis-treated rats with Ella resulted in a substantial increase in kidney Bcl2 protein expression in tubules (Fig. 9).

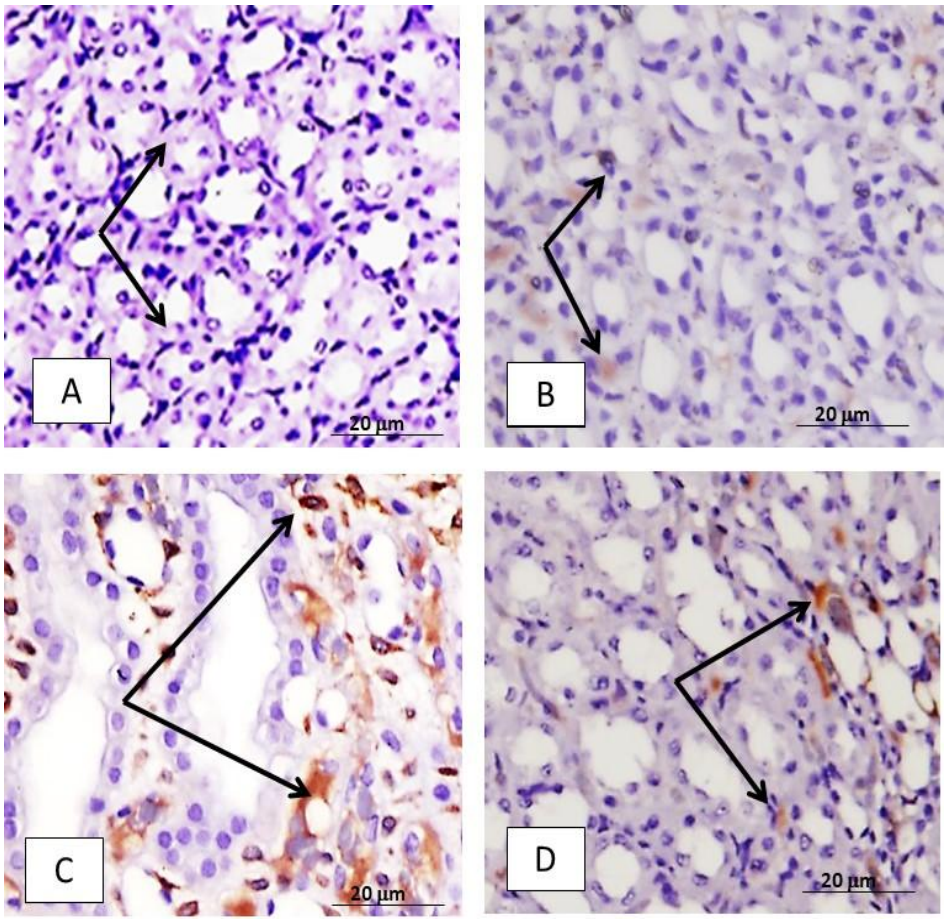

Fig. 6. Impact of ellagic acid (Ella) on kidney COX-2 protein expression determined after cisplatin (Cis) injection in rats. (Bar 20µm)

(A) Control; (B) Ella; (C) Cis and (D) Ella + Cis.

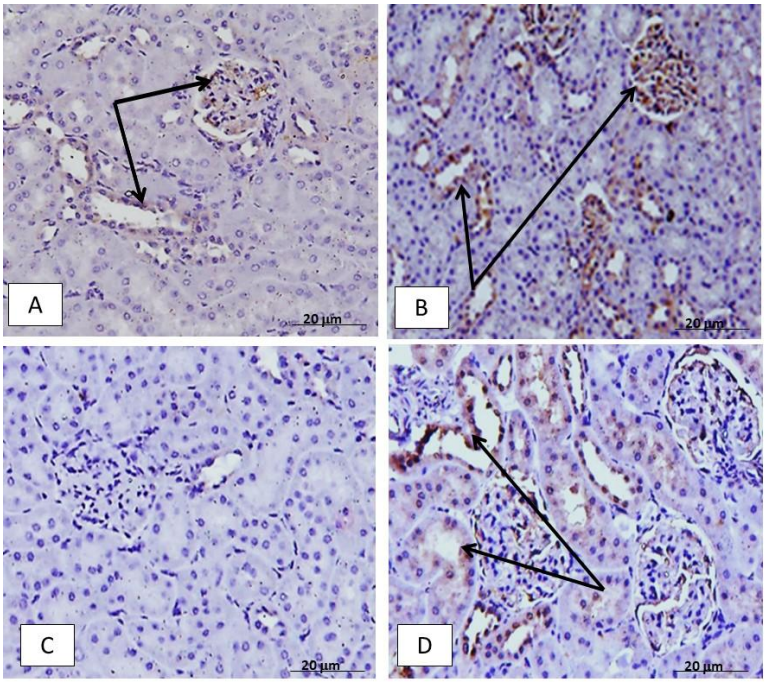

Fig. 7. Impact of ellagic acid (Ella) on kidney SIRT1 protein expression determined after cisplatin (Cis) injection in rats. (Bar 20µm)

(A) Control; (B) Ella; (C) Cis and (D) Ella + Cis

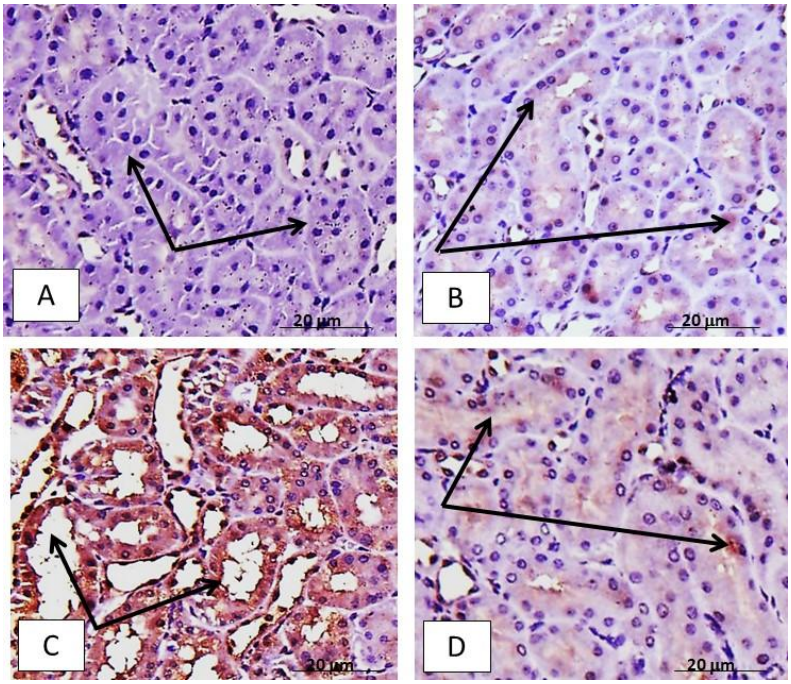

Fig. 8. Impact of ellagic acid (Ella) on kidney Bax protein expression determined after cisplatin (Cis) injection in rats. (Bar 20µm)

(A) Control; (B) Ella; (C) Cis and (D) Ella + Cis

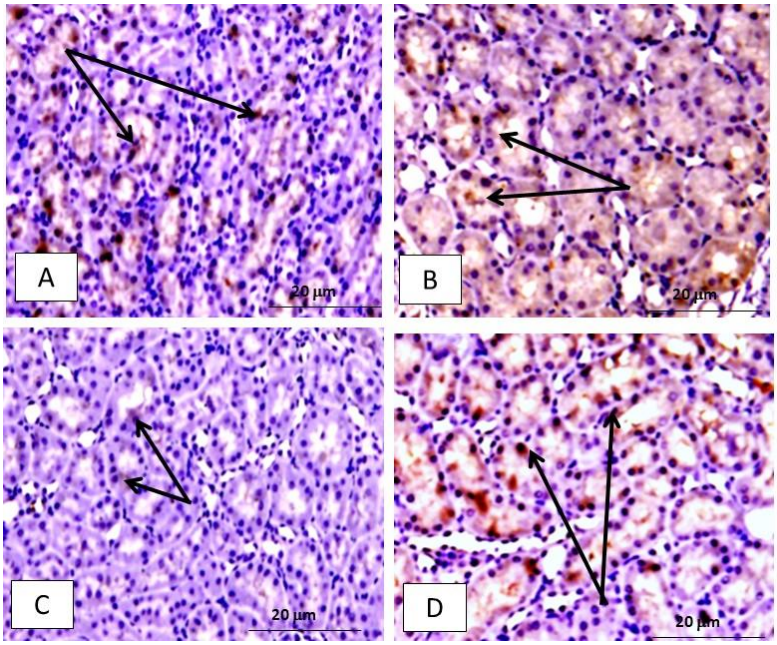

Fig. 9. Impact of ellagic acid (Ella) on kidney Bcl2 protein expression determined after cisplatin (Cis) injection in rats. (Bar 20µm)

(A) Control; (B) Ella; (C) Cis and (D) Ella + Cis

4. DISCUSSION

The current study demonstrates that SIRT1 expression by Ella ameliorated Cis-induced AKI and promoted the resistance of renal tissues to apoptosis and inflammation through increasing the ratio of Bax/Bcl-2 and reducing the expression of COX-2 consequently. These effects were also authenticated by reserving Cis-induced oxidative stress, histopathological alterations of the kidneys, as well as elevation of urea and creatinine.

Previous studies reported that SIRT1 exerts a reno-protective effect in several kidney diseases. This protective role is mediated through the deacetylation of p53 and p65 NF-κB transcription factors [9,11,12,17–19]. The overexpression of SIRT1 or the use of SIRT1 agonists such as isoorientin or resveratrol has been shown to diminish kidney injury in several animal models [6,17,19,20]. For example, SIRT1-overexpression attenuated Cis-mediated AKI and tubular apoptosis in mice [19]. Herein, we found that the administration of Ella protected against AKI in Cis-treated rats supported by the upregulation of SIRT1 protein in kidney tissues. Cisplatin treatment significantly reduced SIRT1 protein expression while pretreating the rats with Ella markedly augmented SIRT1 protein level. Because cellular apoptosis is an essential process in Cis renal toxicity, we assessed the activity of Bcl2 family members, the central regulators of the intrinsic apoptotic pathway. We showed that in consequence of SIRT1 upregulation, Ella significantly suppressed Bax while increased Bcl-2 protein levels. In agreement with our results, SRT1720, a potent SIRT1 activator, significantly decreased Bax protein level in kidneys after Cis injection [17]. Another study also showed that resveratrol inhibited Cis-induced decrease of Bcl-xL [6]. Furthermore, Matsushita et al. have found that SIRT1 deficient cells were more prone to cell death than wild-type counterparts [21]. These studies suggested that Srit1 activation by Ella mitigates Cis-induced apoptosis by modifying antiapoptotic Bcl-2 family proteins Bcl-2 and Bax.

Oxidative stress plays a critical role in Cis-induced AKI in rats [2,22]. The levels of GSH, GPx, SOD, CAT, and GSH levels were decreased, while the MDA level was significantly increased in nephrotoxic rats' kidney tissues. In the present study, oxidative stress status was successfully reversed by Ella as it markedly elevated the antioxidants level while reduced MDA content in kidney tissues. We and several other studies previously reported these protective

effects of Ella. However, our finding supports the possibility that Ella- dependent- SIRT1 enhancement attenuated the oxidative stress induced by Cis. It has been reported that overexpression of SIRT1 in renal tubules suppressed Cis-induced oxidative stress through the upregulation of catalase expression, which degrades excessive free radicals. In addition, SIRT1 increases purine degradation and promotes ATP synthesis for lipid metabolism and cell apoptosis [9,23]. Both mechanisms significantly inhibit oxidative stress and maintain normal renal cell functions.

Inflammation significantly contributes to the development of Cis-induced AKI. Inflammatory mediators such as COX-2 are highly induced in renal tubular cells *in vivo* and *in vitro* [24,25]. In particular, Cis-induced cell apoptosis was associated with the upregulation of COX-2 in mesangial cells [8]. Here, we showed that Cis-induced renal injury through the induction of COX-2 and prior administration of Ella strikingly decreased COX-2 protein expression in renal tissues. We previously reported that Ella ameliorated Cis-induced inflammatory response in rats by inhibiting p65 NF-κB in renal tissues [5]. This indicates that Ella hinders the induction of COX-2 through the inhibition of p65 NF-κB [4,26]. It is well established that p65 NF-κB is a known candidate of acetylation by SIRT1, which suggests that SIRT1 inhibits the NF-κB pathway and subsequently COX and explains the mechanism by which Ella effectively ameliorated Cis- induced inflammatory responses.

5. CONCLUSION

Overall, the current research contributes to the body of evidence for Ella's therapeutic potential in Cis-induced nephrotoxicity, as well as the mechanism by which it functions. According to our findings Ella's stimulation of SIRT1 protein expression decreased Cis-induced AKI by inhibiting oxidative stress, inflammation and apoptosis. The concept that SIRT1 is a promising target for preventing kidney injury is also supported by this study.

6. STUDY LIMITATION

The study relay mainly on the protein expression investigated by the immunohistochemical staining. Future studies are recommended to confirm further the role of SIRT1 in Cis-induced kidney damage utilizing many molecular techniques such as real time qPCR.

CONSENT

Not applicable.

ETHICAL APPROVAL

The Scientific Research Ethics Committee approved the Faculty of Pharmacy's experimental design, King Abdulaziz University, Saudi Arabia (Ref. No. 1438-108).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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