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RESEARCH ARTICLE

The Possible Protective Effect of Ferulic Acid Against Cisplatin-Induced Renal Toxicity in Rats

Gamal El-Din A. Shams, El-Sayed R. H. Mahmoud*
Pharmacology Department, Faculty of Veterinary Medicine, Zagazig University, Zagazig, 44511 Egypt
*Corresponding author Email: ramzy_vet79@yahoo.com

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ABSTRACT

Cisplatin (CIS) is a frequently used chemotherapeutic agent with a potential toxic health effect on kidney and liver that make it a public health issue. Ferulic acid (FA) is an anti-inflammatory and antioxidant agent that presents in a wide variety of fruits and vegetables. This study aimed to assess the function of ferulic acid in attenuation of the toxic effects of cisplatin on biochemical parameters and histological alterations in the adult male albino rats' kidney. Forty adult male albino rats were allocated into four groups. group I (Negative control group), group II (ferulic acid group): Each rat received 100 mg/kg body weight ferulic acid for 21 days by gastric gavage daily; group III (CIS treated group): Each rat intraperitoneally injected with 7.5 mg of cisplatin for each kilogram body weight on the 7th and 14th days respectively, and group IV (CIS + FA group). The experiment lasted for 21 days and after 24 hours from the last dose, serum urea and creatinine, renal tissue catalase, glutathione peroxidase (GPx), and malondialdehyde (MDA) were measured. Histopathological examination of the kidney tissue and immunohistochemical staining by inducible nitric oxide synthase (iNOS) were performed. In the CIS treated rats, serum urea and creatinine levels increased. Also, CIS caused an increase in renal tissue MDA and decrease in renal tissue catalase and GPx that all were significantly reversed in CIS+FA group. Histopathology and immunohistochemical staining showed that CIS induced histological damages in the form of marked reno-tubular degenerative and necrotic changes with cystic dilatation of many tubules, and strong immunoreaction decreased by co-treatment of FA. Administration of FA produced significant improvement of kidney function and histology beside significant improvement in oxidative stress caused by CIS.

***Keywords*:** Cisplatin; Ferulic acid; Oxidative stress.

Introduction

Cisplatin is a drug which has broad efficacy in variable types of cancers as brain, breast, ovarian, bladder, lung, head and neck, testicular, cervical and esophageal cancers. Cisplatin is DNA destroying agent. Its chemical name is cis-di-ammine-di-chloro-platinum (II) [1]. Cisplatin molecular structure is a platinum atom in the center, surrounded by two chlorine atoms and two ammonia groups arranged in a cis pattern. DNA bends to fit the drug's structure since the bond angles for the platinum core are predetermined [2].

Previous experiments found that cisplatin clearance was biphasic in nature, with substantial levels of platinum remaining detectable in plasma 12 days after intravenous administration, with a quick phase half-life of 22 minutes and a slow phase half-life of 5 days. Previous researchers found that High plasma platinum levels in people were shown to correlate with nephrotoxicity [3]. In the previous studies, it was reported that All tissues are exposed to cisplatin; however, within the first hour following treatment, it tends to concentrate in the kidney, liver, skin, and muscle, with elevated concentrations in the renal tissue lasting

up to 12 days. It was believed that the presence of cancer may change pharmacokinetics of drugs and its toxicity. It is required to reduce doses when the patient renal functions are reduced, and it is important to know that nephrotoxicity is a dose dependent adverse effect [4].

Shiraishi *et al.* stated that the primary cisplatin toxic effect was thought to be dose-dependent cumulative nephrotoxicity, where nephrotoxicity occurred after a single cisplatin treatment of 50–100 mg/m2 in around one-third of the cases. [5]. This may be explained by the fact that cisplatin has a low molecular weight and is uncharged, which permits the glomerulus to filter free, unbound cisplatin in plasma. This, in turn, leads to cisplatin being trapped in the renal cortex [6]. Moreover, nephrotoxicity resulted from cisplatin accumulation in the proximal tubules, where its concentration rose to around five times the serum levels [7]. This nephrotoxicity could be as severe as it required dose reduction or even treatment discontinuation [8]. According to previous studies, cisplatin-induced nephrotoxicity was therefore thought to be the perfect model for researching the early pathophysiological aspects of acute nephrotoxicity. Consequently, to enhance patient survival, more research into the pathophysiology of cisplatin-induced nephrotoxicity was required. The primary pathophysiological processes via which cisplatin causes nephrotoxicity include oxidative stress, renal vascular damage, proximal tubular injury, and inflammation [9].

Liberation of reactive oxygen species (ROS) and vasoconstriction in the microvasculature is responsible for the cisplatin-induced renal tubular injury. There had been many studies that interestingly stated, reactive nitrogen species (NOS) were encompassed in nephrotoxicity of cisplatin [10].

Researchers have shown a raised concern in getting natural antioxidants from plant origins for treatment or prevention of multiple diseases [11]. It was demonstrated that antioxidant agents; vitamin E and selenium and were effective in diminishing oxidative stress induced toxicity of cisplatin [12].

Ferulic acid (FA) ([E]-3-[4-hydroxy-3-methoxy-phenyl] prop-2-enoic acid) belongs to the phenolic acid group commonly found in plant tissues. It is most commonly present in parsley, rhubarb, grapes, whole grains and cereal seeds. FA has minimal toxicity and variable beneficial physiological functions. One of the most vital roles is their antioxidant impacts. FA was easily absorbed and stayed in the blood much longer than any other phenolic acids [13].

Pre-treatment with FA in methotrexate induced nephrotoxicity in rats resulted in diminished ROS production and enhanced antioxidant defense mechanisms. Pre-treatment with FA inhibited apoptosis of methotrexate through its double antioxidant and anti-inflammatory impacts. In the renal tissues of rats intoxicated with methotrexate, FA upregulated Bcl-2 and downregulated cytochrome c, caspase-3, and Bax, demonstrating a strong anti-apoptotic impact [14].

The current study aimed to assess the function of ferulic acid in attenuation of the toxic effects of cisplatin on biochemical parameters and histological alterations in the adult male albino rats' kidney.

Materials and Methods

Ethical approval

The Institutional Animal Care and Use Committee of Zagazig University (IACUC-ZU) were consulted for developing laboratory animal care guidelines. The approval number was ZU IACUC/2/F/454/2022.

Chemicals

Cisplatin was brought from Mylan company, France and ferulic acid was brought from Sigma–Aldrich, Germany.

Animal model and experimental protocols

Forty adult healthy male albino rats were employed in the study weighing between 150 and 200 g. Rat species were acquired from animal house at Faculty of Veterinary Medicine, Zagazig University. Before the initiation of experiment, 14 days period of passive preliminaries were done for all rats to be adapted for recent conditions, to attain rats' physical wellbeing and to preclude the diseased rats. The rats were fed a well-balanced diet that was full of everything they needed to stay healthy both before and after the drugs were administered. It had milk, bread, and barley. Water was served using distinct, spotless cutlery.

The forty rats were allocated into equal four groups. group I (negative control group): rats were given their usual meal and tap water in order to test the fundamentals for 21 days, group II (ferulic acid group): each rat received 100 mg/kg BW ferulic acid daily [15] for 21 day by gastric gavage, group III (CIS treated group): each rat was intraperitoneally injected with cisplatin (7.5 mg/ kg BW) on the 7th and 14th days [16], group IV (CIS + FA group): rats received ferulic acid (100 mg/kg) everyday via gastric gavage for 21 days and cisplatin (7.5 mg/kg) intraperitoneally at 7th and 14th days, respectively.

At the end of the 21th days, 24 h after the last dose, venous blood samples were taken using light anesthesia from the rats' retro-orbital plexus using capillary glass tubes for estimating kidney function tests including: urea and creatinine. Blood sample (2 ml) in a serum separator tube without anticoagulant were allowed to clot for 30 min before centrifugation then separated by centrifugation of blood at 3000 r.p.m for 10 min. The supernatant sera were pipetted off by fine tipped automatic pipettes and put in deep frozen at -20 ºC for detecting renal function tests. Animals were sacrificed by decapitation; the kidneys were immediately carefully dissected out and cleared of extraneous tissue and grossly inspected to detect any gross abnormalities. Right kidney was transported on dry ice and stored at -80 °C to obtain tissue homogenates analysis of oxidative stress markers (catalase, GPx, and MDA). Immediate fixation with 10% neutral buffered formalin for the left kidney aiming to histopathological examination by light microscopy using H&E stain and immunohistochemical studies by inducible nitric oxide synthase (iNOS).

Biochemical analysis

Urea

Estimation of serum urea was done according to the modified Berthelot reaction [17] as the following: Urea is hydrolyzed in the presence of water and urease to give Ammonia and Carbon dioxide. In a modified Berthelot reaction, the ammonium ions react with hypochlorite and salicylate to form a green dye. The absorbance was detected by colorimeter or spectrophotometer increases at 578 nm equivalent to the concentration of urea in the sample. It was calculated using the following equation:

$\frac{\Delta(A) sample}{\Delta(A) standard}$ x 50 (Standard conc.) = mg/dL urea in the sample

$\Delta(A) = A1_A2$

A1=absorbance after 30 sec.

A2=absorbance after 90 sec.

Creatinine

Estimation of serum creatinine was performed by fully automated COBAS Integra 400+ clinical chemistry analyzer by compensated Jaffe method [18] as the following:

Buffered kinetic Jaffe reaction without deproteinization was compensated for serum/plasma. In alkaline solution creatinine reacts with picrate to form a yellow-red complex.

Creatinine + Picric acid gives Yellow red complex

The rate of the dye formation (color intensity) is directly proportional to the concentration of creatinine in the specimen. It is determined by measuring the increase in absorbance at 512 nm.

- Calculation:

$\frac{\Delta A\ Sample - \Delta A Blank}{\Delta A\ Standard - \Delta A Blank}$x 2 (Standard conc.) = mg/dL of creatinine in the sample.

$\Delta(A) = A2_A1.$

A1=absorbance after 30 sec.

A2=absorbance after 90 sec.

Oxidative stress biomarkers

1 - *Catalase*

CAT activity was estimated following the method described by Fossati *et al.* [19] and Aebi [20]. Catalase reacts with a known quantity of H2O2. The reaction ends after precisely one minute with catalase inhibitor. In the presence of peroxidase (HRP), remaining H2O2 reacts with 3,5-Dichloro -2-hydroxybenzene sulfonic acid (DHBS) and 4-aminophenazone (AAP) to produce a chromophore that a color intensity inversely proportional with the am0unt of catalase in the original sample.

2- Glutathione peroxidase (GPx)

GPx activity was detected according to the method of Paglia and Valentine [21].

It is an indirect measure of the activity of cGPx. Oxidized glutathione produced upon decrease of an organic peroxide by c-GPx, is reconverted to its reduced form by the enzyme glutathione reductase (GR). The oxidation of NADPH to NADP+ is accompanied by a reduction in absorbance at 340 nm (A340) providing a spectrophotometric means for detecting GPx enzyme activity. The molar extinction coefficient for NADPH is 6220 M-1 cm-1 at 340 nm. To measure c-GPx, a tissue or cell homogenate is added to a solution containing glutathione, glutathione reductase, and NADPH. The enzyme reaction is started by addition of the substrate, hydrogen peroxide and the A340 is recorded. The rate of reduction in the A340 is directly proportional to the GPx activity in the sample [21].

3- Malondialdehyde (MDA)

MDA in kidney tissues was done with the guide of Satoh [22] and Ohkawa *et al.* [23].

At temperature of 95°C for 30 min; thiobarbituric acid (TBA) reacts with MDA in acidic medium to form thiobarbituric acid reactive product. The absorbance of the resultant pink product can be detected at 534 nm [22,23].

Histopathological preparations

The samples were immediately fixed in a solution consisting of 10% neutral buffered formalin. They were then dehydrated using a series of increasing concentrations of ethanol, cleaned using xylene, and finally embedded in paraffin. Sections with a thickness of 5 micrometers were prepared and stained with hematoxylin and eosin stain. They were then examined under the light microscope [24].

Immunohistochemical study

Paraffin sections were deparaffinized with xylene and rehydrated with alcohol in ascending grades and used to evaluate the expression of iNOS using anti-inducible nitric oxide synthase antibody, mouse monoclonal reacts specifically with iNOS (Sigma Aldrich Co.-USA) as described by Kolasa *et al.* [25].

Statistical Analysis:

One way analysis of variance (ANOVA or F-test) and least significant Difference (LSD) were used. The stastical analysis was done by Epi-info stastical package pr0gram version 6.O4d, january 2OO5 [26].

Results

Regarding urea and creatinine, the results of the present study reflected a highly significant elevation in the mean value of urea and creatinine in CIS treated rats opposite to that in control and ferulic acid groups. A highly significant diminution in the mean value of urea and creatinine were observed in CIS+FA group when compared to CIS group (Tables 1 and 2 and Figure 1).

Table (1): Statistical comparison among control, ferulic, cisplatin and ferulic + cisplatin treated groups as regard mean values of serum level of urea, creatinine

Parameter	Control	Ferulic	Cisplatin	Ferulic and Cisplatin	F	*P*-value
Urea (mg/dl)	37.00±2.10	35.60±1.71	74.50±4.81	42.30±3.43	190.8953	<0.001**
Creatinine (mg/dl)	1.40±0.10	1.31±0.08	5.95±0.13	2.09±0.59	305.3188	<0.001**

All values are expressed as mean ±SD. (SD: standard deviation)

Number of rats in each group=6 rats. F: ANOVA test

**: highly significant (P<0.001).

Table (2): Least significance difference (LSD) for comparison between mean values of serum level of urea, creatinine of control, ferulic, cisplatin and ferulic + cisplatin treated groups.

Parameters	Group	Ferulic	Cisplatin	Ferulic + Cisplatin
	Control	0.8772 NS	<0.001**	0.023*
Urea	**Ferulic**		<0.001**	0.012*
	Cisplatin			<0.001**
	Control	0.183NS	<0.001**	0.033*
Creatinine	**Ferulic**		<0.001**	0.015*
	Cisplatin			<0.001**

NS: statistically non-significant ($p>0.05$), *: statistically significant ($p<0.05$), **: statistically highly significant ($p<0.001$). Number of rats in each group = 6 rats.

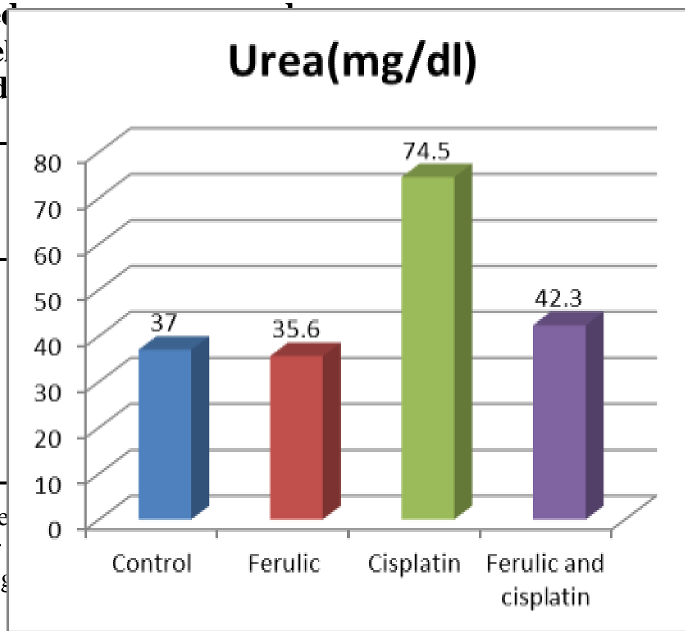
Regarding renal tissue oxidative markers MDA (Malondialdehyde), a highly significant elevation in MDA mean values was found in CIS treated rats compared to that in control and ferulic acid groups. Also, a highly significant diminution in the mean value of catalase and GPx were determined in CIS treated rats opposite to that in control and ferulic acid groups. The results also showed a highly significant decrease in the mean value of MDA levels and showed a highly significant elevation in the mean value 0f catalase and GPx in CIS + FA treated rats opposite to that in CIS treated rats (Tables 3 and 4 and Figure 2).

Table (3): Statistical comparison among control, ferulic, cisplatin and ferulic + cisplatin treate[d] ... values of leve[l] ... perioxidase and ... tissue

[Param]eter	Control	Ferulic
	7.15±0.05	7.18±0.13
/g)	8.08±0.12	8.24±0.18
g)	1.30±0.10	1.31±0.08

All values are expre[ssed] ... deviation). Number ... ANOVA test **: hig[hly] ...

NS: statistically non-significant (*p* >0.05), *: statistically significant (*p*<0.05), **: statistically highly significant (*p* <0.001).



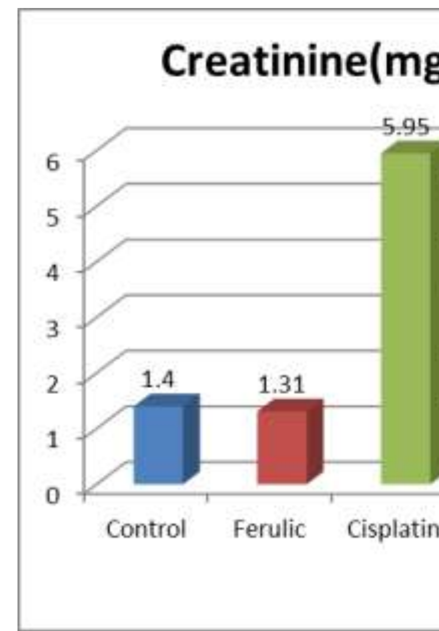
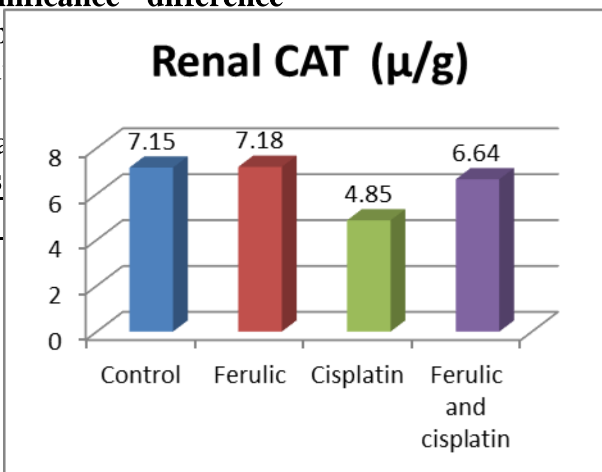
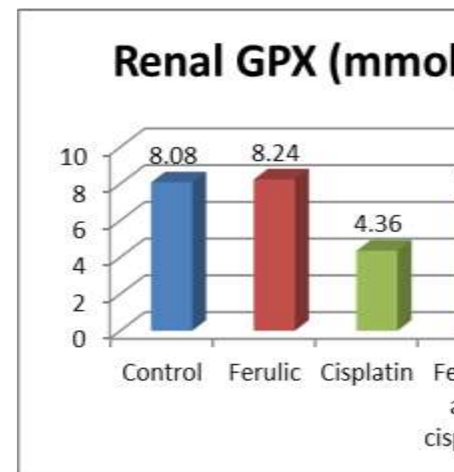


Figure 1: Bar chart showing comparison of mean values of urea and creatinine among negative control group, ferulic, Cisplatin group and Cisplatin+ ferulic acid group.

Table (4): Least significance difference (LSD) for comparison b... of level of catalase, glu... and Malondialdehyde ... control, ferulic, cispla... cisplatin treated groups

[Pa]rameters	Group	Ferulic		
[CA]T	Control	**0.**968 NS		
	Ferulic			
	Cisplatin			
[GP]X	Control	0.773NS		
	Ferulic			
	Cisplatin			
[M]DA	Control	**0.**999 NS	<0.001**	0.019*
	Ferulic		<0.001**	0.020*
	Cisplatin			<0.001**





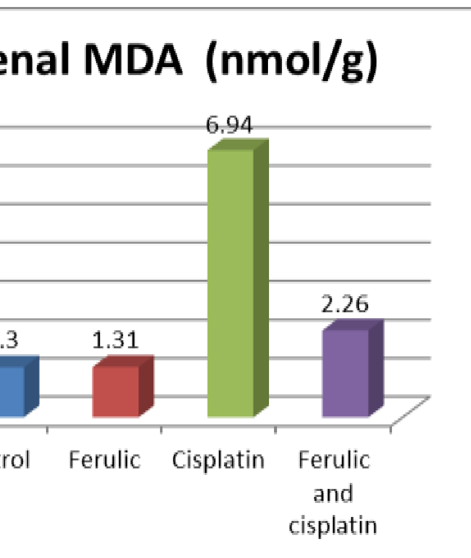


Figure 2: Bar charts showing comparison of mean values of renal tissue oxidative stress markers among negative control groups, ferulic, Cisplatin group and Cisplatin+ ferulic acid group.

Histopathological results

1- Examination of H&E-stained renal tissues

Histopathological findings of renal tissues in rats in control groups and FA treated groups showed preserved nephron structures including the Bowman's capsule, glomeruli, proximal and distal convoluted tubules. beside normal structures of the collecting ducts, renal papillae, and renal pelvis. No pathologic changes could be detected (Figures 3 a and 3 a*) while in CIS group, findings revealed marked reno-tubular degenerative and necrotic changes with cystic dilatation of many tubules were characteristic observation. Many of the affected tubules were seen involving the cortex and the medulla Some of the renal tubules showed hyaline casts. Some of the renal blood vessels showed degenerated walls associated with perivascular edema. Most of the renal glomeruli showed glomerulosclerosis (Figure 3 b). Current research reflected that rats which received CIS + FA showed preserved kidney structure with decreased pathological findings. Moderate number of the renal tubules were cystically dilated with atrophy of the intervening tubules. A moderate number of the renal glomeruli were lobulated (Figure 3c).

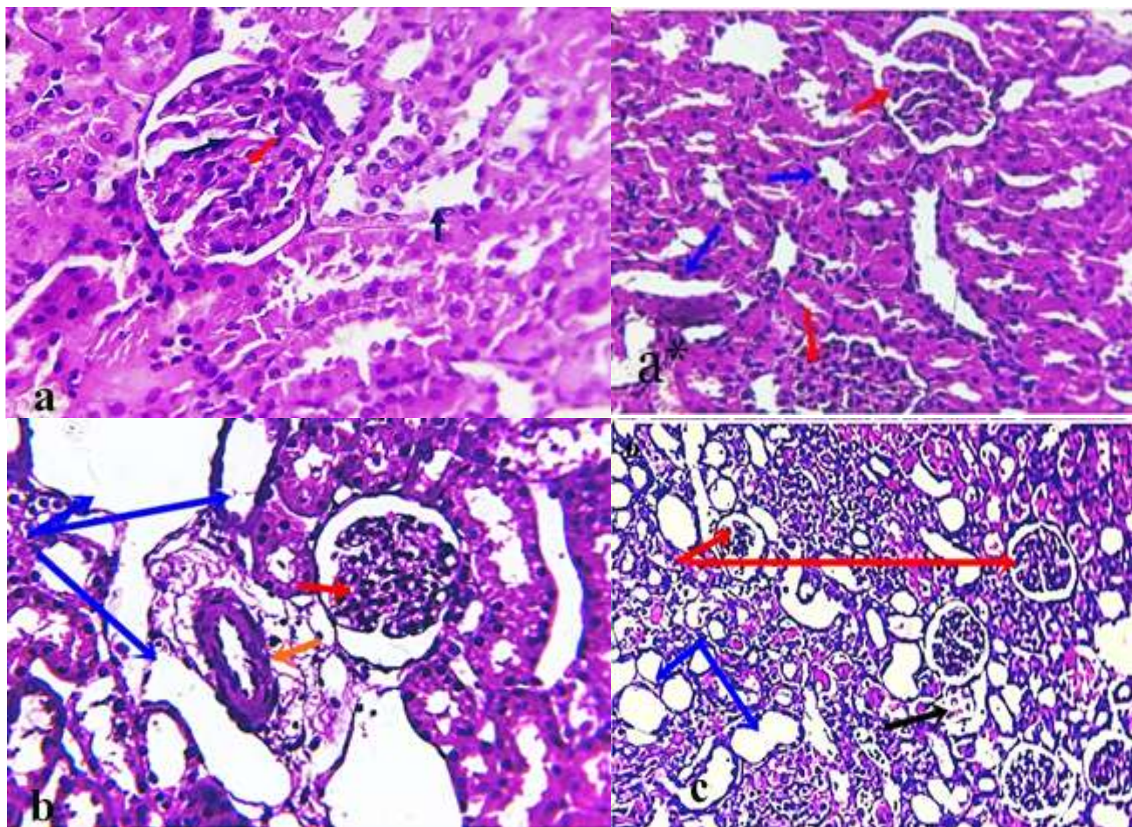


Figure (3): Photomicrographs from rat's kidney tissues (a) control group showing preserved nephron structures including the Bowman's capsule, glomeruli (red arrows), proximal and distal convoluted tubules beside normal structures of the collecting ducts (dark arrows) H&E X 400, (a*) ferulic acid group showing normal kidney structural configuration comparable to the control group with preserved nephron units and collecting tubules (red and dark blue arrows) H&E X 400, (b) Cisplatin treated group showing marked reno-tubular degenerative and necrotic changes with cystic dilatation of many tubules (blue arrows). Some of the renal blood vessels shows degenerated walls associated with perivascular edema (orange arrow) Most of the renal glomeruli showing glomerulosclerosis (red arrows) H&E X 400, (c) Cisplatin-ferulic acid treated group showing moderate number of the renal tubules are cystically dilated with atrophy of the intervening tubules (dark blue arrows). A moderate number of the renal glomeruli appears lobulated (red arrows) H&E X 400

2- Immunohistochemical staining using iNOS

Immunohistochemical stained kidney sections for detection of iNOS from control and FA groups showed negative immunoreaction (Figures 3 d and 3 d*). Immunohistochemical stained kidney sections for detection of iNOS from CIS group showed strong positive immunoreaction (Figure 3E). Immunohistochemical stained kidney sections for detection of iNOS from CIS + FA group showed mild positive expression for the renal vascular and glomerular endothelium (Figure 3 F).

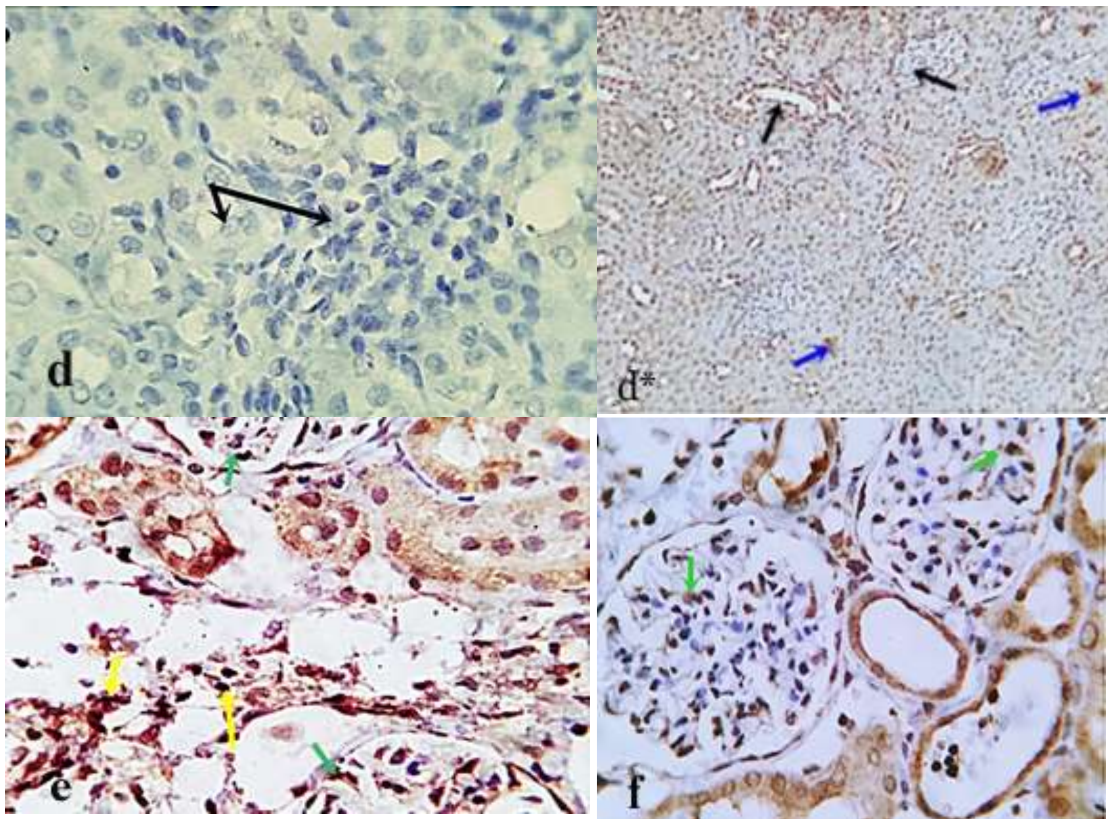


Figure (3): Photomicrographs from rat's kidney tissues (d) control group immune-stained by INOS showing negative labelling of cells (black arrows) X 400, (d*) ferulic acid group showing very few expression of renal epithelium and glomerular endothelium (blue arrows) X 200, (e) cisplatin treated group , immune-stained by iNOS showing strong positive expression for iNOS in the renal vascular and glomerular endothelium(green arrows)with infiltrated mononuclear inflammatory cells(yellow arrows) X 400, (f) cisplatin-ferulic acid treated group, immune-stained by iNOS showing mild +ve expression of renal vascular and glomerular endothelium (green arrows) X 400.

Discussion

As regards kidney function tests (urea and creatinine), the current research reflected a significantly high elevation in urea and creatinine mean values in cisplatin treated rats compared to that in control and ferulic acid groups. The results also showed significant diminution of urea and creatinine mean values in cisplatin-ferulic acid treated rats compared to cisplatin group.

Renal dysfunction and damage attributed to cisplatin treatment are regarded as one of the main drawbacks for cancer patients, with a global incidence varying greatly [27].The results of the current study coincide with Saleh and El-Demerdash [28], Shimeda *et al.* [29], and Palipoch *et al.* [30], who all reported increases in blood urea nitrogen and serum creatinine.

The kidney accumulates cisplatin to a greater degree than in other organs, and it serves as the primary exit for it. In the proximal and distal nephrons, peritubular absorption is the mechanism by which cisplatin accumulates. The proximal tubular epithelial cells have approximately five times the concentration of cisplatin in them compared to the serum levels. Nephrotoxicity caused by cisplatin is partly caused by the inappropriate build-up of cisplatin in renal tissue. Cisplatin is mostly excreted by glomerular filtration, with some excretion occurring via secretion. Tubular reabsorption does not appear to be present [31].

After 10 days of drug intravenous cisplatin administration, there were 20% to 40% diminution in glomerular filtration and followed by reduced glomerular filtration rates with increased levels of creatinine [32].As regard renal tissue oxidative markers GPx and CAT; The findings of the current research reflected a highly significant diminution in the mean values of cisplatin treated rats opposite to the control and ferulic acid groups. The results of the current research reported a highly significant elevation in the mean value of MDA in cisplatin treated rats opposite to the control and ferulic acid rats. The findings also reflected a high significant elevation in the mean value of GPx and CAT levels while showed a significant diminution in the mean value of MDA in cisplatin-ferulic acid treated rats opposite to cisplatin treated rats in renal tissues.

According to studies by Palipoch *et al.*[30] the production of reactive oxygen species such superoxide anion and hydroxyl radicals caused an increase in lipid peroxidation and cell damage. Excess ROS promoted apoptosis and cell death in both cancer normal tissues which in turn led to cisplatin toxicity .GPx; CAT and SOD are key enzymes which are responsible for neutralization of oxidative stress. Optimum levels of them are essential for cellular signaling processes. Their disturbance has direct and indirect involvement in many diseases and infections. Their activities are reduced in tissues injured by cisplatin and can also indicate oxidative stress [33-35].

Malondialdehyde is an indicator of oxidative stress, it is the lipoperoxidation process's end result. MDA–DNA complexes are created when MDA and DNA interact. It has been demonstrated that MDA–DNA complexes exhibit pro-mutagenic qualities and cause oncogene/tumor suppressor gene alterations in human malignancies [36].

The increased generation of R0S in CIS-treated rats generates an imbalance between oxidant-antioxidant levels, which in turn diminishes the scavenging capability toward R0S and induces oxidative stress. The findings underscore this point, as seen by the increased level

of MDA in the kidney and the decreased levels of enzymatic antioxidants such as hepatic SOD and CAT. Furthermore, the renal tissue of rats given CIS is more vulnerable to oxidative stress due to the reduction in GSH levels [37-40].

Reactive oxygen species are specifically engaged in oxidative damage to cellular macromolecules. ROS enzymes inactivate free radicals and increase the production of endogenous antioxidant enzymes, which reduces their effects. Thus, ferulic acid's antioxidant properties can help with several diseases and serious renal cleansing [41-42].

our results are comparable to the findings of former researchers who stated that cisplatin induced nephrotoxicity through increased inflammatory and oxidative response. They also reported the beneficial role of the antioxidant; gallic acid in protecting rats' kidneys from cisplatin-induced oxidative and inflammatory damage [43]. Studies have also been conducted on reactive nitrogen species and cisplatin-induced nephrotoxicity. Rats treated with cisplatin had higher renal contents of nitric oxide and peroxynitrite [44-45].CIS-induced renal damage has also been linked to nitrosative stress in addition to ROS [46]. It has been shown that the administration of CIS causes an increase in nitric oxide synthase (iNOS) synthesis, which in turn causes an increase in nitic oxide production. This, in turn, leads to the formation of peroxynitrites, which are primarily responsible for the renal damage that CIS mediates through its reaction with superoxide anions [47].

Regarding histopathological changes in the kidney, cisplatin administration pr0duced tubule necrosis, epithelial damage and a rise in cast formation. On the other hand, kidneys removed from Cisplatin with ferulic acid-treated rats displayed reduced tubular necrosis and almost normal epithelial tubular cell shape. The same findings were reported by Mostafa *et al.*, who discovered histological alterations such as tubular degeneration, dilation of the blood vessels, and swelling and vacuolation of the glomerulus' lining endothelium with localized minute bleeding in the cortical region. Additionally visible severe tubular edema, necrosis, and degeneration in the proximal and distal tubules and glomeruli and that findings were reversed through the antioxidant and anti-apoptotic mechanisms of simvastatin and rosuvastatin [48].

Immunohistochemical examination of specimens from kidney tissues of CIS treated rats in the present study, showed strong positive reaction to iNOS while few positive reaction was noticed in the group received ferulic acid with CIS. CIS treatment caused iNOS immunoreactivity to accumulate in hepatic and renal cells and Chirino et al. stated that Selective inhibition of iNOS reduced kidney injury made by cisplatin [46].An increase in iNOS expression prevents too much nitric oxide from being produced. By nitrating cellular macromolecules and increasing the susceptibility to oxidative stress by reducing intracellular glutathione, excess nitric oxide combines with superoxide anion to form a powerful oxidant called peroxynitrite, which is responsible for cell damage [49].Based on the above biochemical, histopathological and immunohistochemical findings; we noticed that ferulic acid had improved the outcome of cisplatin effects. Our results coincide with that of Hasanvand *et al.* [50] who found that Tissue malondialdehyde, serum creatinine and urea, urine albumin/creatinine ratio, and neutrophil gelatinase-associated lipocalin were all reduced by ferulic acid administration, whereas glutathione peroxidase, superoxide dismutase, and catalase were all increased. In gentamycin-induced tubular necrosis and eosinophilic casts, ferulic acid decreased nephrotoxicity.

Ferulic acid had been reported to alleviate acetaminophen induced hepatotoxicity, gentamicin nephrotoxicity. Fascinatingly, serum creatinine and urea levels, kidney Kim-1, and histological investigation all showed that FA protected methotrexate (MTX)-induced kidney injury in mice. It has been observed that FA improves the histological structure of gentamicin and biochemical indicators of renal function-, cisplatin-, and glycerol-intoxicated rodents. Mahmoud et al. also evidenced that FA could also prevent MTX nephrotoxicity in rats [51-53].In the kidney of rats intoxicated with MTX, FA upregulated Bcl-2 and downregulated Bax, cytocyte c, and caspase-3, exhibiting a strong anti-apoptotic impact. According to Ren et al., FA inhibited oxidative stress, Bax, and caspase 3 gene expression, which is consistent with our findings and reduced apoptotic cell death [54].By upregulating cellular defense systems like homoxygenase and lowering the expression of cytotoxic enzymes like inducible nitric oxide synthase (iN0S), FA can lower oxidative stress and has a potent antioxidant activity in scavenging free radicals [55-56].

Conclusion

Cisplatin administration resulted in toxic effects on the kidney manifested by significant elevation in renal functions tests. Cisplatin induced histological and immunohistochemical changes in renal tissues. Cisplatin induced toxicity by inducing oxidative stress that was evident through significant increase in oxidants, significant decrease in antioxidants. Administration of ferulic acid produced partial and incomplete improvement of kidney function and histology beside moderate improvement in oxidative stress caused by cisplatin.

Conflict of interest:

All authors have reviewed and approved the paper for publication, and they all state that they have no conflicting financial or scientific interests.

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الملخص العربى

التأثير الوقائي المحتمل لحمض الفريولك ضد التسمم الكلوى للسيسبلاتين في الجرذان

جمال الدين أمين شمس ، السيد رمزى حسينى محمود
قسم الفارماكولوجى - كلية الطب البيطرى - جامعة الزقازيق - مصر

السيسبلاتين هو عامل علاج كيميائي يستخدم بشكل متكرر وله تأثير صحي سام محتمل على الكلى مما يجعله مشكلة صحية عامة. حمض الفيروليك (FA) هو عامل مضاد للالتهابات ومضاد للأكسدة ويوجد في مجموعة واسعة من الفواكه والخضروات. يهدف هذا البحث إلى تقييم وظيفة حمض الفيروليك في تخفيف التأثيرات السامة للسيسبلاتين على المعايير البيوكيميائية والتغيرات النسيجية في كلية ذكور الجرذان البيضاء البالغة. تم تقسيم أربعين من الفئران البيضاء البالغة إلى أربع مجموعات. المجموعة الأولى (مجموعة المراقبة السلبية)، المجموعة الثانية (مجموعة حمض الفيروليك): تلقى كل فأر 100 ملغم/كغم من وزن الجسم حمض الفيروليك لمدة 21 يومًا عن طريق أنبوب التغذية المعدي يوميًا؛ المجموعة الثالثة (المجموعة المعالجة بالسيسبلاتين): تم حقن كل فأر بريتونيا بـ 7.5 ملغ من سيسبلاتين لكل كيلوغرام من وزن الجسم في اليومين السابع والرابع عشر على التوالي، والمجموعة الرابعة (مجموعة السيسبلاتين + FA). استمرت التجربة لمدة 21 يومًا وبعد 24 ساعة من آخر جرعة، تم قياس اليوريا والكرياتينين في الدم، وكاتالاز الأنسجة الكلوية، والجلوتاثيون بيروكسيديز (GPx)، والمالونديالدهيد (MDA). تم إجراء الفحص النسيجي المرضي لأنسجة الكلى واختبارها الكيميائي المناعي بواسطة سينسيز أكسيد النيتريك المحفز (iNOS). في الفئران المعالجة بالسيسبلاتين، زادت مستويات اليوريا والكرياتينين في الدم. أيضًا، تسبب CIS في زيادة في MDA للأنسجة الكلوية وانخفاض في كاتالاز الأنسجة الكلوية وGPx والتي انعكست جميعها بشكل ملحوظ في مجموعة CIS + FA. أظهر التشريح المرضي والتلوين الكيميائي المناعي أن CIS تسبب في حدوث أضرار نسيجية في شكل تغيرات تنكسية ونخرية أنبوبية كلوية ملحوظة مع توسع كيسي للعديد من الأنابيب، وانخفض التفاعل المناعي القوي عن طريق العلاج المشترك لـ FA. أظهر FA تحسنا كبيرا في وظائف الكلى والأنسجة إلى جانب تحسن كبير في الإجهاد التأكسدي الناجم عن السيسبلاتين.