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Protective effect of *Apium Graveolens* seeds (Celery Seeds) extract against Gentamicin-induced Hepato-renal toxicity in rats

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The current study was conducted to evaluate the protective effect of *Apium graveolens* seeds (celery seeds) extract against gentamicin (G)-induced renal and hepatic toxicity. Fifty four albino rats were randomly assigned into 6 groups. Group I, control group (C); Group II: was intraperitoneally injected with 100 mg/kg BW of 80% gentamicin (G);Group III: was orally administered with250 mg/kg BW of hexanic extract (HE) of celery (in liquid paraffin);Group IV: was orally administered with ethanolic extract (EE) of celery(250 mg/kg BW in 0.9 % NaCl solution); Group V:was pre-treated with HE as in group III for 2 weeks, then they were cotreated with HE along with gentamicin treatment as in group II for additional 2 weeks; Group VI: was pre-treated with EE as in group III for 2 weeks, then co-treated with EE along with gentamicin treatment as in group II for additional- 2 weeks (G+EE). Treatment was continued for 4 weeks day after day. Gentamicin increased ALT, total protein, urea, creatinine, sodium and MDA, while decreased potassium and GSH with no effect on AST, albumin or glucose compared to control group. Moreover, gentamicin increased tumor necrosis factor (TNF)-α while decreased transforming growth factor (TGF)-β expressions in renal tissue. Gentamicin induced renal and hepatic tissue alterations including atrophy of glomerular tuft with increased Bowman's space, necrosis of glomerular cells with pyknotic nuclei, cloudy swelling of renal tubules with inflammatory cell infiltration, congestion of hepatic central vein with necrosis of the lining intimal cells, coagulative necrosis around central vein, fatty degeneration of hepatocytes. Treatment with HE or EE of celery seeds significantly reversed all of these biochemical and histological alterations. In Conclusion: The present study reveals the protective role of *A. graveolens* extract against gentamicin-induced nephrotoxicity.

Keywords: Gentamicin, Nephrotoxicity, *Apiumgraveolens*, Rats

INTRODUCTION

As kidney has a relatively high blood supply and is able to sieve and concentrate the water-soluble toxic molecules, it is susceptible to drug induced damage (Randjelovic et al., 2017). In this context, there are various environmental pollutants and drugs, can injure the kidneys and adversely affect the renal functions (Dursun et al., 2018). Among these drugs, is gentamicin which is an aminoglycoside (AG_s) antibiotics synthesized by Micro monospora. Gentamicin is widely used for the treating Gram-negative bacterial infections, and also Gram-positive bacteria (Gilbert et al., 2000; Balakumar et al., 2010). Nephrotoxicity is a well-known potential adverse effect of aminoglycosides. Depending on the clinical

scenario, in 7-58% of therapeutic courses, it leads to nephrotoxicity, which limits their frequent and prolonged clinical use (Oliveira et al., 2009). Nephrotoxicity of AGs is known to affect both glomerular and tubular structure and function via immune and non-immune processes (Quiros et al., 2011). Aminoglycosides are mostly excreted in in urine; approximately 5–10 % of the dose accumulates and stores in the renal cortex for a long time after cessation of the drug administration (Nagai and Takano, 2004). Previous studies reported that gentamicin can induce nephrotoxicity in 30 % of patients treated for a period of more than 7 days by a direct dose dependent manner (Rougier et al., 2004; Dursun et al., 2018). Although many more recent, less toxic antibiotics have been introduced, gentamicin is still widely used due to its broad-spectrum antibacterial activity, rapid action, high rate of efficacies, synergistic effect with beta-lactam and economic cost (Edson and Terrell, 1999).

Herbal medicine is now an accepted medicine as complementary and alternative therapy in combination with the main line therapies (Smith et al., 2014 and Izzo et al., 2016). Celery is one of the most well-known plants used in the history of mankind as a medicament or spice (Al-Sa'aidi et al., 2013). Celery *(Apium graveolens)* has been cultivated for the last 3000 years, notably in pharaonic Egypt, and was known in China in the fifth century BC (Chevallier, 1998).*Apiumgraveolens Linn. (Apiaceae*) has a long history of use in Ayurveda and Unani system of medicine (Sorour et al., 2015). Nowadays, all parts of celery are used for both nutrition and medicine purposes (Simderu et al., 2016). Celery used in traditional medicine for the treatment of urinary tract disease, celery is excellent diuretic that promotes the flow of urine through the kidney and increase uric acid excretion, helping to clean toxins from the system (Mill, 1988). This is especially good for gout, where excess uric acid crystals collect in the joint. Its diuretic action may also relieve bladder disorders, cystitis and other kidney problem including stones and gravel (Aboud et al., 2014).Extracts from the fruits of *Apium graveolens* used in Ayurvedic medicine for treatment of urinary calculi, kidney stones, gut diseases and visceral spasms (Zhou et al., 2009), especially a wide traditional use is documented in traditional Persian medicine (Bahmani et al., 2016) for treatment of uncomplicated urinary tract infections (UTI). The herbal material is also used in traditional European phytotherapy due to its diuretic activity and anti-inflammatory activity against UTI (Apiifructus – Sellerieffüchte, 2016).

MATERIALS AND METHODS

Chemicals:

EPIGENT^{R} Ampoules, the commercial form of Gentamicin, each ampoule contains 80 mg Gentamicin (as sulphate) was purchased from the local drug stores.
nhexane (CAS number 110-54-3) and ethanol (CAS Number: 64-17-5) were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Preparation of plant extracts:

Five hundred grams of celery seeds (*Apium graveolens*) were bought from a local market at Menoufia, Egypt and used for plant extract preparation according to Moghadam et al., (2013) Briefly, celery seeds were ground and powdered and the dry powder (50 g) was suspended in 250 mL of solvent (n hexane, or aqueous-ethanol [20/80, v/v] at room temperature and shaken for 48 h in the darkness. Then, the suspension was centrifuged (2594 g for 10 min) and the supernatant was separated. The solution was allowed to dry up in darkness at room temperature. The hexane extract was dissolved in liquid paraffin and the ethanolic extract was dissolved in normal saline (0.9%) before oral administration.

Animals:

A total of 54 male albino rats of body weights ranged from 120 to 160 g were purchased from Al-Zyade experimental animal production center, Giza, Egypt and used for this study. Animals were housed in polypropylene cages at the animal facility of the Faculty of Veterinary Medicine, University of Sadat City, Egypt at 22 °C and 55% humidity with 12h light/12h dark cycle. They were supplied with balanced diet and clean water *ad libitum*. Before the onset of the experiment, animals were kept under observation one-week acclimatization. All procedures were approved by the Animal Care Committee of University of Sadat City

The diet:

The rats offered a commercial ration pellets (Ayad Company, Egypt). Pellets ingredient was performed according to A. O. A. C. (1980); National research council (1995). The pellets ingredients and chemical composition are shown in table 1.

Table 1: Ingredients and chemical composition of basal diet

Ingredient composition	g%
Berseem hay	30
Yellow maize	25.0
Wheat bran	26.2
Soybean meal	44.0
Molasses	3.0
Cacl	1.0
Nacl	0.4
Mixture of minerals & vitamins (8477)	0.3
Methionine	0.1
Chemical Composition	**g %**
Total protein	21
Fiber	3.41
Ether extract	2.2
Ash	5.52
Minerals &vitamins	0.3

Experimental design:

Fifty- four albino rats were assigned into 6 groups of 9 rats each and designated as follows:

Group I, rats were orally co-administered with 0.5 mL liquid paraffin (vehicle of celery hexanic extract) along with 0.5 mL 0.9 % NaCl solution (vehicle of celery ethanolic extract) in addition, they were injected with 0.25 mL sterile injectable water (vehicle of gentamicin) every other day for 4 weeks and served as control group (C).

Group II: rats were given intraperitoneal injection of 80% gentamicin (G) at dose of 100 mg/kg BW (Farag et al., 1996) for a period of 4weeks every other day

Group III: rats were administered hexanic extract (HE) of celery at dose of 250 mg/kg BW (dissolved in liquid paraffin) by oral intubation every other day for a period of 4weeks.

Group IV: rats were orally administered ethanolic extract (EE) of celery at dose of 250 mg/kg BW (dissolved in 0.9 % NaCl solution) every other day.

Group V: rats were pre-treated with hexanic extract as in group III for 2 weeks, then they were co-treated with hexanic extract along with gentamicin treatment as in group II (G+HE) for additional 2weeks

Group VI rats were pre-treated with ethanolic extract as in group III for 2 weeks, and then they were co-treated with ethanolic extract along with gentamicin treatment as in group II for additional 2 weeks (G+EE). All animal groups were allowed to gain free access to feed and water throughout the experimental period.

Sampling:

At the end of the experimental period (4 weeks), animals were subjected to 12 h fasting. Then, anaesthetized using diethyl ether (≥99.0%; Sigma-Aldrich), blood samples were withdrawn from medial canthus of the eyes. Blood samples were left to clot, centrifuged for 10 min at 3000 *xg*. The collected serum samples were kept at - 80 °C until used for biochemical assays. Rats were then sacrificed by head dislocation and both liver and kidney were immediately excised, washed with 0.9% NaCl. Samples from kidney were preserved in - 80 °C until used for assaying lipid peroxidation (MDA) and antioxidant (GSH) markers. Liver and another portion from kidney tissues were collected in 10% neutral buffered formalin for histopathological examination using H and E stain and for immuno histochemical studies.

Biochemical analysis

Specific commercial diagnostic kits from Human diagnostic (GmbH 56205 wiesbaden Germany) were used for determination of serum level of Urea (REF10505), ALT (REF12012) and AST (REF12011) following the manufacturer's instructions. Specific commercial diagnostic kits for determination of serum levels of albumin (Item# BK-467858D), total protein (Item# BK-465986D), and creatinine (Item# BK-472525D) were purchased from Diamond Diagnostics Inc (Diamond Diagnostics Inc., Holliston, MA, USA) and used according to instructions of the manufacturer. Serum glucose was assayed using specific commercial kit (Glucose-HK 1001200) from Spinreact, Ctra. Santa Coloma, SPAIN) according to instructions of the manufacturer. To determine lipid peroxidation (MDA) and antioxidant defense system (GSH) biomarkers, specific commercial diagnostic kits for assay of MDA (Cat. No. MD 25 29) and GSH (Cat. No. GR 25 11), in the homogenate of renal tissue were from Biodiagnostic company (Biodiagnostic Giza, Egypt) and tissue homogenate was prepared according toShawky et al. (2014). Serum levels of Na^+, K^+ were determined using the Diamond Diagnostics SmartLyte PLUS Electrolyte Analyzer (Diamond Diagnostics Inc., Holliston, MA, USA) utilizing Ion Selective Electrode technology.

Histopathological examination:

Liver and kidney tissue samples intended for histopathological investigation were fixed in 10 % neutral formalin. Samples were prepared according to Bancroft et al. (1996) and stained by Hematoxylin and Eosin (Harris 1900).

Immunohistochemical investigation:

The serial sections were de waxed , hydrated and immersed in an antigen retrieval (EDTA solution,PH8) then, The slides were treated with hydrogen peroxide 0.3% and protein block, followed by incubation with poly clonal antibody of TNF-α(Invitrogen, USA, catalog # P300A) and TGF-β (Invitrogen, USA, catalog # PA1-9574) . The slides were rinsed three times with PBS, incubated with anti- rabbit IgG secondary antibodies (Envision + system HRP; Dako)for 30minutes at room temperature, visualized with di-aminobenzidine commercial kits (liquid DAB+ substrate chromogen system; Dako) and finally counter stained with May's hematoxylin. As a negative control procedure, the primary antibody was replaced by normal mouse serum antibody of TNF-α and TGF-β. The reaction of both biomarkers was expressed as the percentage of Positive cells per total 1000 counted cells in a total of ten random high-power fields

Statistical analysis

Statistical analysis of the obtained results was performed using analysis of variance (ANOVA) by SPSS software (SPSS version 13.0, IBM, Chicago, IL, USA) with $P< 0.05$ regarded as statistically significant. The results were expressed as means ± standard errors of means (SEM).

RESULTS

Effect of gentamicin and celery seed extracts on serum chemistry:

Biochemical analysis of the serum revealed that, administration of gentamicin (groupII; G) increased ALT, urea, creatinine, sodium, and MDA levels while significantly decreased potassium and GSH level with no effect on AST, total protein, albumin and glucose compared to control group (C). Administration of either ethanolic or hexanic celery extract (EE or HE respectively) to the gentamicin-treated animals (group V and group VI), counteract gentamicin-induced alterations in ALT, creatinine and potassium and GSH levels (Table 2). Interestingly, there was no significant difference in the kidney (urea, creatinine) and liver (ALT, AST) function markers between control group and groups received celery seed extracts alone.

Immunohistochemistry findings:

Immunohistochemical study of renal tissues for TNF-α expression revealed that, gentamicin (**G**) treatment results in a significant increase in TNF –α protein expression within renal tubules compared to control group (Fig. 1 A, B). Kidneys of either group III or group IV that were treated with either HE or EE alone showed scanty TNF-α expression within renal tubules (Fig. 1C and D respectively) where there was no statistical difference in the expression level between animals of group III, group IV and those of group 1 (control group). There was a significant reduction in the TNF-α expression level on administration of HE or EE to gentamicin-treated rats as shown in Fig.1E where Kidney of G5 showed a mild TNF-α expression within interstitial inflammatory cells and Fig. 1 F where Kidney showed focal TNF-α expression within renal tubules.

Parallel to these results for TNF-α expression, Gentamicin (**G**) treatment (group II) significantly suppressed TGF-β expression within the renal tubular epithelium compared to control (**C**) group (Fig 2A, B). Neither HE nor EE alone showed a significant difference in TGF-β expression compared to control group where only diffuse cytoplasmic TGF-β expression within the renal tubular epithelium was detected in group III and group IV (Fig. 2 C, D).

Table 2: Effect of gentamicin and celery seed extracts on serum chemistry.

	C	G	HE	EE	HE+G	EE+G
AST	130.7 ± 5.1^{ab}	131.6 ± 5.9^{ab}	135.6 ± 7.4^{a}	125.0 ± 4.5^{ab}	123.9 ± 5.8^{ab}	113.9 ± 2.2^{b}
ALT	43.2 ± 5.1^{b}	55.1 ± 4.2^{a}	42.2 ± 2.9^{b}	42.4 ± 1.7^{b}	47.4 ± 1.4^{ab}	39.7 ± 2.9^{b}
Albumin	3.98 ± 0.1^{ab}	4.22 ± 0.1^{ab}	4.27 ± 0.2^{bc}	4.45 ± 0.1^{c}	4.24 ± 0.1^{bc}	4.7 ± 0.2^{bc}
Total protein	5.3 ± 0.2^{a}	5.4 ± 0.05^{a}	5.7 ± 0.29^{a}	$5.1\pm0.17^{a,b}$	5.3 ± 0.1^{a}	$4.8\pm0.18^{a,b}$
Urea	40.0 ± 1.5^{bd}	44.7 ± 1.9^{ac}	42.2 ± 0.7^{acd}	37.2 ± 0.8^{b}	45.8 ± 1.9^{a}	40.6 ± 0.9^{bc}
Creatinine	0.55 ± 0.03^{a}	0.83 ± 0.04^{b}	0.60 ± 0.003^{a}	0.58 ± 0.04^{a}	0.66 ± 0.26^{c}	0.7 ± 0.29^{c}
Na^{+}	137.0 ± 0.0^{b}	142.0 ± 0.6^{a}	139.25 ± 0.8^{bc}	138.8 ± 0.6^{bc}	139.5 ± 0.8^{c}	140.7 ± 1.1^{ac}
K^{+}	4.9 ± 0.3^{a}	4.44 ± 0.1^{b}	4.5 ± 0.3^{ab}	4.6 ± 0.2^{ab}	4.4 ± 0.1^{b}	4.8 ± 0.3^{ab}
Glucose	145.3 ± 6.7^{ab}	150.5 ± 5.6^{a}	129.2 ± 6.1^{b}	129.7 ± 10.2^{b}	144.8 ± 4.4^{ab}	132.4 ± 3.2^{ab}
MDA	72.32 ± 3.9^{b}	118.2 ± 5.8^{a}	75.4 ± 7.9^{bc}	181.95 ± 5.8^{b}	91.6 ± 3.7^{c}	89.5 ± 5.4^{c}
GSH	176.4 ± 7.6^{b}	97.7 ± 15.6^{a}	240.2 ± 2.5^{b}	236.08 ± 2^{b}	216.1 ± 5.7^{b}	226.7 ± 3.3^{b}

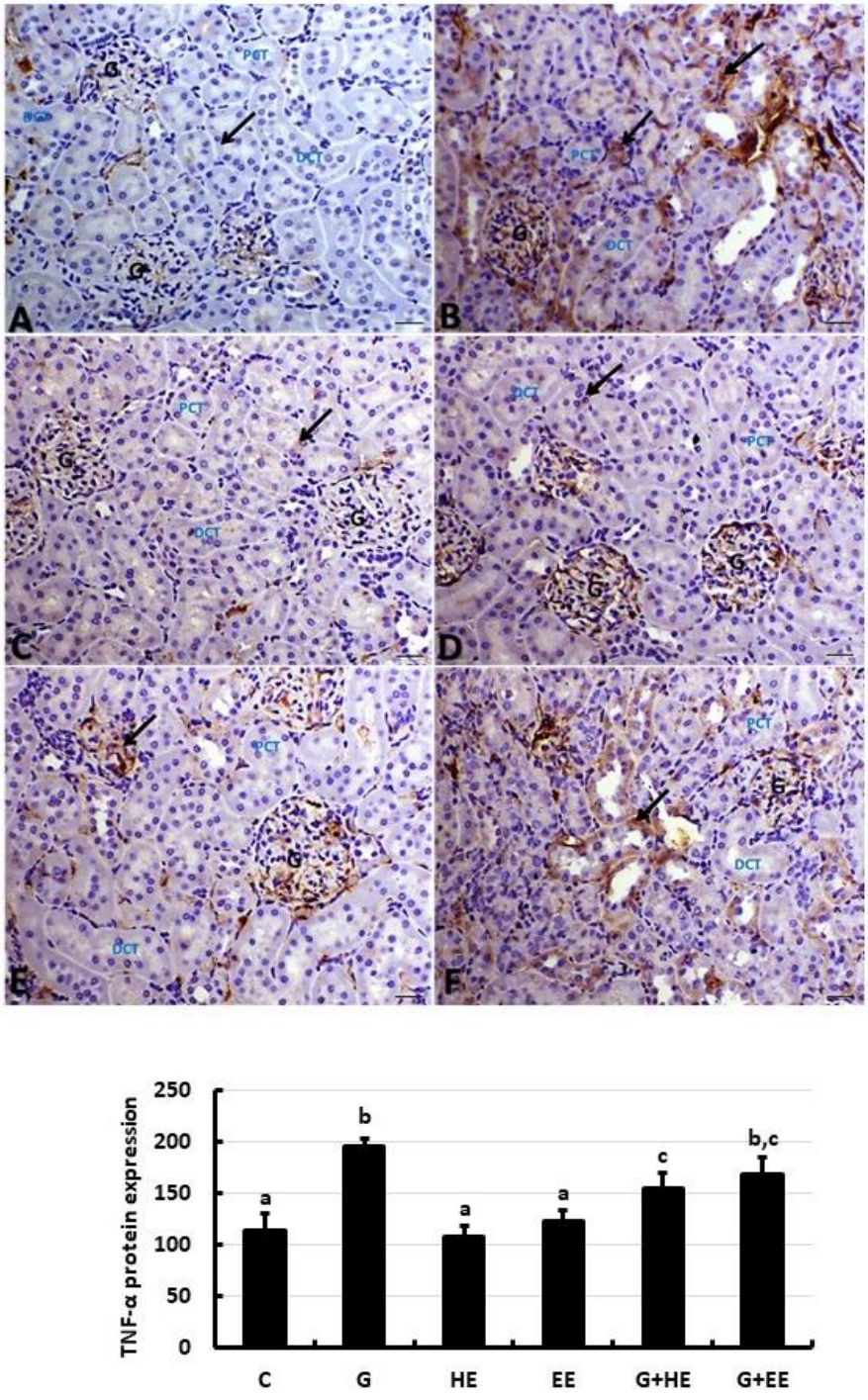
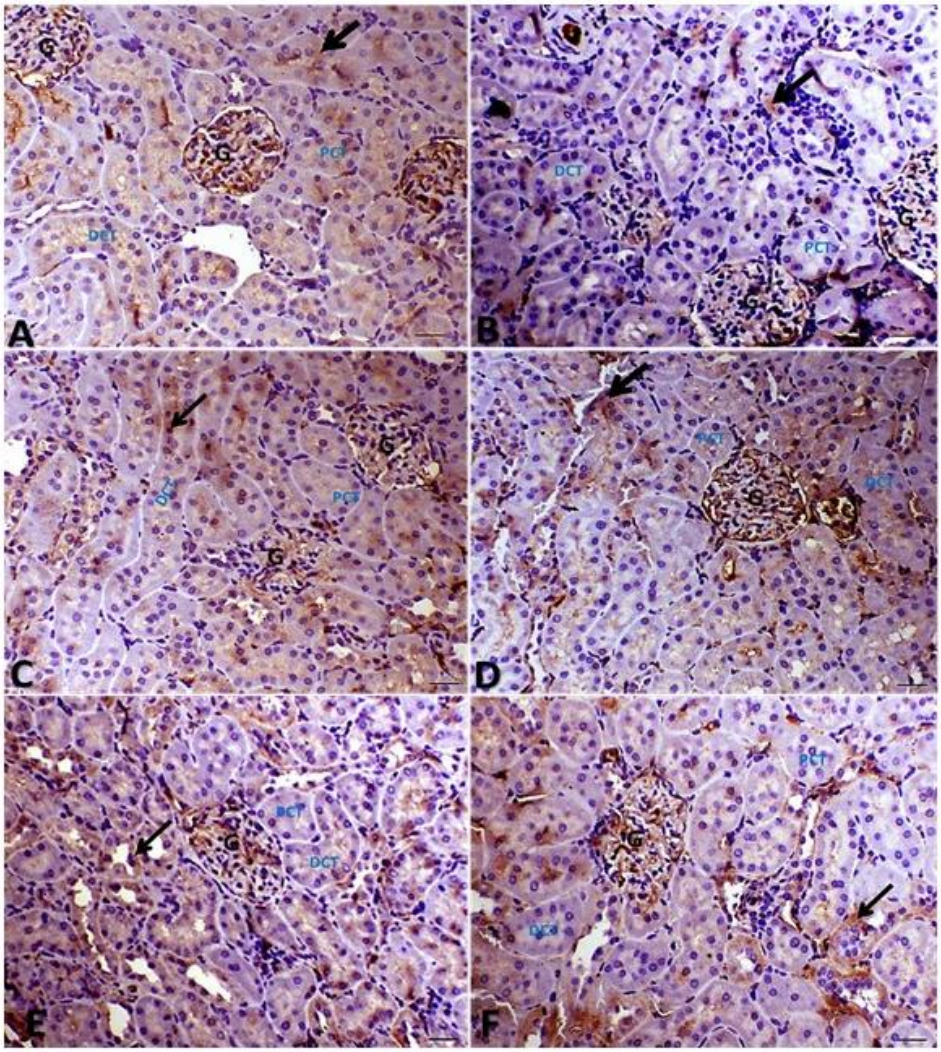


Figure: 1. Effect of celery seeds extract on gentamycin-induced TNF-α expression in kidney.



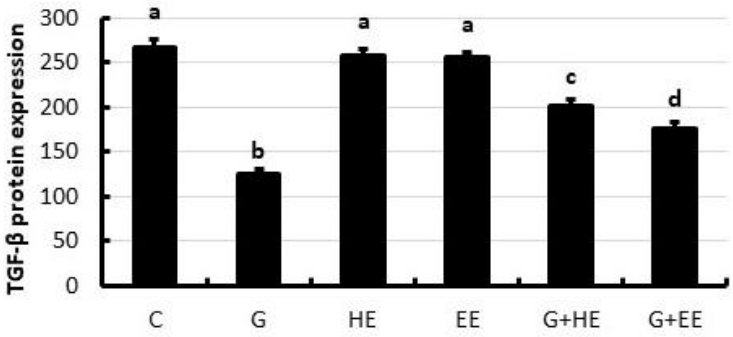


Figure 2: effect of celery seed extracts on gentamycin-induced TGF-β expression in kidney

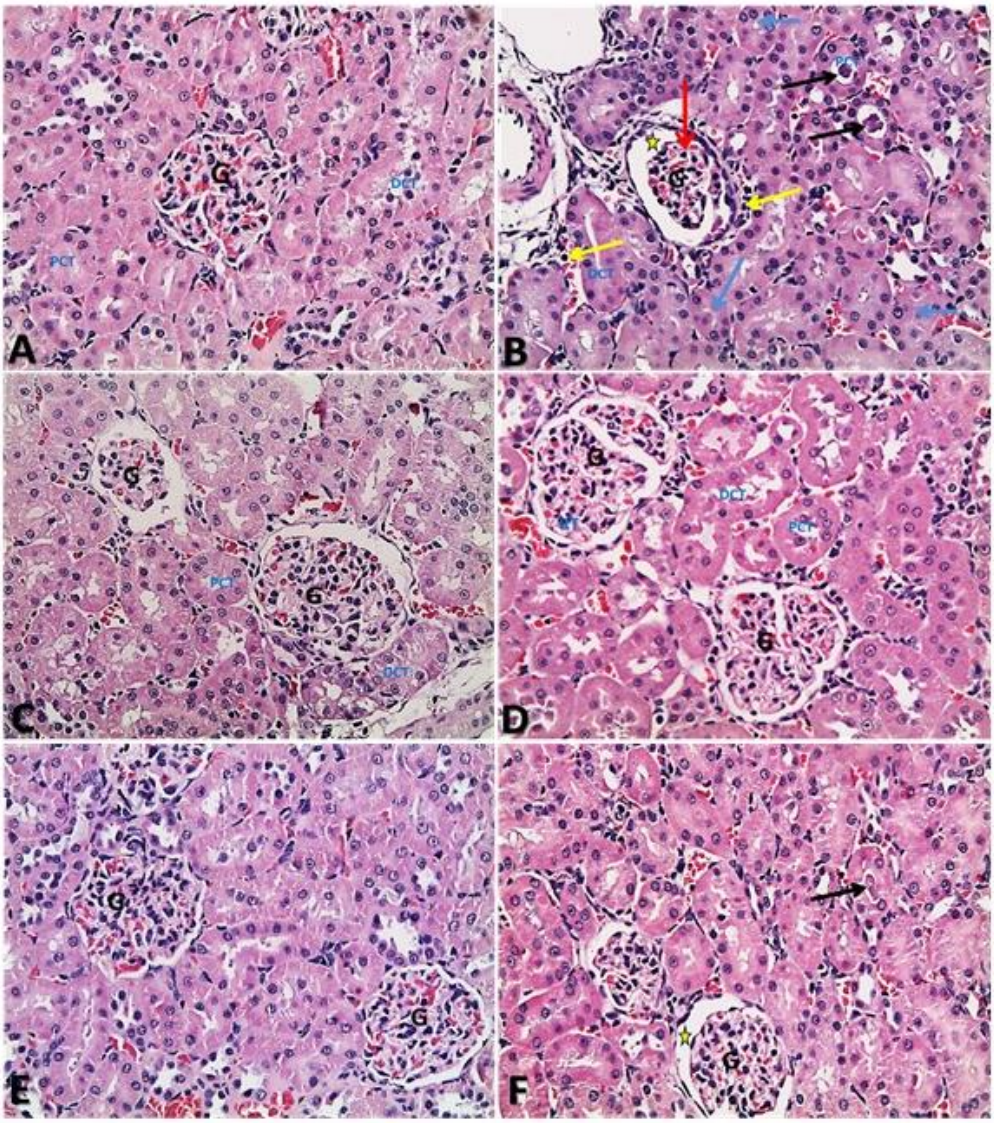


Figure: 3 Effect of celery seed extract on gentamicin-induced histopathological alterations of rat kidney.

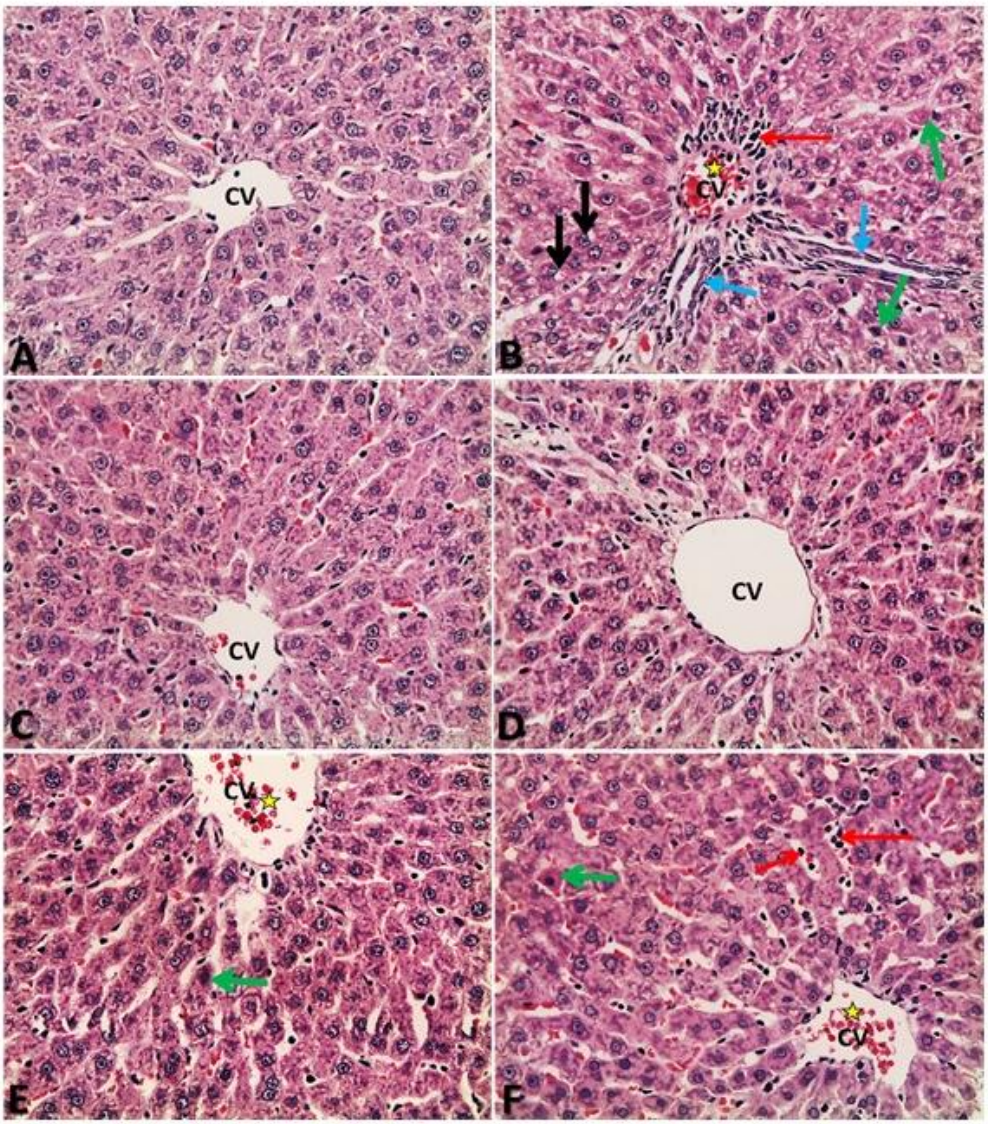


Figure 4: Effect of celery seed extracts on gentamicin-induced histopathological alterations of rat liver.

Administration of either HE (group V) or EE (group VI) of celery seeds significantly abrogated gentamicin-induced suppression of TGF-β although, this effect was more potent in ethanolic extract than hexanic extract where Kidney of group V and showed a marked cytoplasmic TGF-β expression within the renal tubular epithelium (Fig. 2 C, D).

Histopathological findings:

Histopathological examination of kidney tissue demonstrated that, Kidney of rats from group I has normal architecture of glomeruli (Glo), proximal renal tubules (PCT) and distal convoluted tubules (DCT), (Fig3 A). Group II animals which were

treated with gentamicin showed atrophy of glomerular tuft with increased Bowman's space (star), necrosis of glomerular cells with pyknotic nuclei (red arrow), PCT with hyaline casts (black arrows), marked cloudy swelling in most renal tubules and inflammatory cell infiltration periglomerular and in between renal tubules (yellow arrows) as shown in Fig.3 B. Group III and group IV showed normal renal glomeruli (Glo) and normal renal tubules (Fig.3 C). Administration of either HE (group V) or EE (group VI) improved the gentamicin-induced alteration in renal tissue architecture (Fig. 3 E, F).

Similarly, histopathological examination of liver samples from group I, showed normal architecture of central vein (CV) and normal hepatocytes arranged in trabecular manner (Fig 4 A). However, gentamicin treatment in group II induced congestion of central vein (star) with necrosis of the lining intimal cells, formation of newly formed bile ducts around central vein (blue arrows), focal area of coagulative necrosis infiltrated with leucocytes around central vein (red arrow) and the hepatic parenchyma showed fatty degeneration of hepatocytes with signet ring appearance (black arrows) and coagulative necrosis of some hepatocytes with pyknotic nuclei (green arrows) (Fig 4B). Group III and group IV showed normal architecture of hepatic tissue (Fig.4 C, D). Treatment with either HE (group V) or EE (group VI) improved the gentamicin-induced alteration in renal tissue architecture where they showed somewhat normal architecture except for mild congestion of central vein (star), mild congestion and some leucocytic infiltration in hepatic sinusoids plus single cell necrosis (green arrow). (Fig. 4 E, F).

DISCUSSION

Aminoglycoside antibiotics including gentamicin are widely used in the treatment of gram-negative infections. One of its main side-effects is nephrotoxicity, manifested by non-oliguric renal failure with a progressive increase of serum creatinine levels. The specificity of gentamicin for renal toxicity is apparently related to its preferential accumulation in the renal proximal convoluted tubules (Parlakpinar et al., 2003 and Alexandridis et al., 2003) The animal models of aminoglycoside nephrotoxicity show acute tubular necrosis, interstitial fibrosis in the renal cortex as well as glomerulosclerosis (Geleilete et al., 2002). Agents with free radical scavenging property can either inhibit or attenuate the renal damage induced by drugs (Abdelmeguid et al., 2010). Several chemicals and phyto derived compounds (because of their antioxidant properties) have been experimentally used to reduce the gentamicin nephrotoxicity (Ali, 2003).*A. graveolens* is rich in phenolic compounds which serve as a good source of antioxidants (Jung et al., 2011). Extracts from the fruits of *Apium graveolens* have been used in Ayurvedic medicine for treatment of urinary calculi, kidney stones, gut diseases and visceral spasms (Zhou et al., 2009).

The kidney is a key player in maintaining the balance of body water and salt. Renal dysfunction is responsible for the disturbed water and salt balance (Hala, 2012). In this study we observed that gentamicin-administrated group significantly increased serum urea, creatinine and Sodium while decrease serum Potassium compared to with control group which indicate renal dysfunction. This deleterious effect of gentamicin in the current study can be explained at least in part by oxidative stress resulted from gentamicin treatment as indicated by increase renal level of malonaldehyde and decreased level of renal GSH and agree with results obtained by Sabzevar et al., (2016). On treatment with celery seeds extract, there was significant improvement in kidney function biomarkers which can be explained by the antioxidant activity of *A. graveolens*(Jung et al., 2011). Going in a harmony with biochemical findings, histopathological examination revealed that gentamicin treatment induced various alterations with varying degrees of renal tissue damage which was greatly improved in response to A. graveolent extract treatment. This improving effect of *A. graveolens* extract could be attributed to its antioxidant effect and also anti-inflammatory effect. This anti-inflammatory effect of A. graveolent extract was confirmed by its ability to counteract the stimulatory and inhibitory effects of gentamicin on TNF-α and TGF-β expressions respectively. In the present study gentamicin increased renal TNF-α expression in comparison of control group. These results are in agreement with result ofMestry et al. (2018) and Zager et al., (2007) who proven that increase in TNF-α due to gentamicin accumulates in renal tube, administration of *Apiumgraveolenes* protected kidney against nephrotoxic effects of gentamicin. Transforming growth factor-β (TGF-β) is a multifunctional cytokine regulating a wide range of cellular functions including growth, differentiation, apoptosis, wound repair, and the pathogenesis of fibrosis. TGF-β plays important and diverse roles in chronic kidney disease (CKD)

(Patel and Dressler, 2005). It is generally considered a potent profibrotic factor in CKD (Ding and Choi 2014, Lee et al., 2015). Transforming growth factor (TGF)-β is categorized as either anti-inflammatory or proinflammatory cytokines, under various circumstances (Zhang and An, 2007). Other studies confirmed its anti-inflammatory effect (Uçeyler et al., 2006; Elweza et al., 2018). Recently, it was proven that TGF- β1 has both profibrotic and tissue protective effects. It can induce this tissue protective effect through induction of autophagy and inhibiting inflammation (Huang et al., 2008; Chung et al., 2009; Chen et al., 2011 and Sureshbabu et al., 2016). Similar results (Ding et al., 2010) showed that TGF-β protects against mesangial cell apoptosis via induction of autophagy. The results of the present study showed that, TGF-β expression was significantly decreased in response to gentamicin treatment compared with control group showing congestion of glomerular, atrophy of glomerular tuft with necrosis of glomerular cells, proximal convoluted tubule with hyaline cast and congestion. Thus the deteriorative tissue effect of gentamicin on renal tissue can be attributed at least in part to the inhibitory effect of gentamicin on the TGF-β expression which was accompanied with overexpression of TNF-α, the well-recognized potent inflammatory cytokine the results that goes in a harmony with the previous studies reported the protective effects in renal tissues through induction of autophagy and inhibiting inflammation (Huang et al., 2008; Chung al., 2009; Chen et al., 2011 and Sureshbabu et al., 2016). On contrast to, administration of *Apium graveolens*hexanic extract (groups V) significantly counteracted this inhibitory effect of gentamicin on TGF-B expression which interestingly was accompanied with suppression of the gentamicin-induced TNF-a expression. These results go in line with the previous report (Huang et al., 2008; Chung al., 2009; Chen et al., 2011 and Sureshbabu et al., 2016). Treatment with *Apiumgraveolens*ethanolic extract (groups VI) has similar obvious results to that of hexanic extract although it did not reach the significance limits. This effect of *Apiumgraveolens* extracts on TGF-B expression goes parallel to the histopathological findings that showed clear improvement of the tissues indicated by normal renal tissue architectures (glomeruli and renal tubules) some renal tubular show hyaline cast in ethanolic celery extract so hexanic extract is more potent in response to extracts treatment. These results of gentamicin-induced renal injury are in agreement with result of Padmini (2012), Virani et al., (2015). The present results concerning the renal function improving effect of *Apiumgraveolenes* go in line with that of Sabzevar et al. (2016).

In similar manner, gentamicin-induced hepatic dysfunction indicated by increased in ALT activity compared to control group. These results are in agreement with result of Almohawes (2017) and Khan et al. (2011) who attributed that to altering the permeability of hepatocyte membranes. Celery extracts showed hepatoprotective action which was indicated by normalizing ALT activity in animals treated with both gentamicin and celery extracts. This hepatoprotective effect of celery could be due to its antioxidant and anti-inflammatory effects. The efficacy of *A. graveolens* may be attributed to the presence flavonoid apigenin as active constituent, as can be seen by HPLC profile. Apigenin is an antioxidant and inhibitor of cell proliferation and angiogenesis (Fotsis et al., 1997). These results are parallel to the hisopathological findings in hepatic tissue which demonstrated the ability of celery to reverse the gentamicin-induced hepatic tissue alterations as hepatic tissues showed more or less normal architectures on celery treatment. These results are in agreement with result of Sultana et al., (2005).

CONCLUSION

In conclusion, the current study clearly showed the nephrotoxic and hepatotoxic effects of gentamicin indicated by increased serum kidney and liver function biomarkers and histopathological alterations in renal and hepatic tissues. This toxic effect of gentamicin can be abrogated by celery seed extract which execute its protective effect through its antioxidant and anti-inflammatory effect.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

MMA, SHO, HKK designed and performed the experiments and also wrote the manuscript. BAH, MMA, SHO, HKK performed animal treatments,

tissue collection, and data analysis. MMA and SHO designed experiments and reviewed the manuscript. All authors read and approved the final version.

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