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Original Article

Protective effect of some plants against the toxicity of kidneys caused by gentamicin

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Abstract

Objective

The kidneys are a major organ for the removal of waste materials from the body. Plants play an essential role in human health. This work aimed to study the protective effect of some plants vs gentamicin toxicity of the kidneys.

Materials and methods

Thirty adult male albino rats (Sprague Dawley Strain) of weight 100±10 g were investigated. Rats were divided into two mean groups. Group 1 (six rats) was fed on a balanced diet and was present as a negative control for 4 weeks. Group 2 (24 rats) was injected with gentamicin 100 mg/kg BW/day for 8 days to induce kidney damage and then were divided into four subgroups. Subgroup 1 was fed a standard diet as a positive control. Subgroups 2, 3, and 4 were fed a standard diet with an orally administered aqueous extract of Artemisia absinthium, parsley, and fennel at a dose of 5 g/kg body weight, respectively. At the end of the period, blood samples were collected, then urea, uric acid, creatinine, lactate dehydrogenase activity, liver enzymes, and triglycerides were assayed in serum. Organs (liver and kidney) were removed for histopathological examination. Finally, statistical comparisons were made with a one-way analysis of variance test.

Results

The results indicated that renal function, liver function tests, and triglycerides were reduced significantly in treatment groups as compared with the positive control. The best treatment effect of lactate dehydrogenase activity has appeared in rats treated with the extract of fennel.

Conclusion

The present study suggests that Parsley, Artemisia absinthium, and fennel extract have protective effects against gentamicin toxicity.

Keywords: Artemisia absinthium, fennel, gentamicin, parsley

Introduction

The kidneys are an important organ within the human body. They guard blood volumes, filter the blood to form urine, regulate water, electrolytes, acid/base balance, produce some hormones, and participate in the metabolism of others [1].

Acute kidney injury is generally defined as a decline in kidney function resulting in the accumulation of waste products in the bloodstream. The leading causes of acute kidney injury are nephrotoxins, aminoglycosides, oxytetracycline, and nonsteroidal anti-inflammatory drugs [2].

Gentamicin used against most of the Gram-negative microorganisms. It has been the most powerful therapeutic drug inimical to bacterial strains that are resistant to other antibiotics in many conditions; however, its use is limited due to its side effects such as nephrotoxicity and hepatotoxicity [3].

Medicinal plants and herbs play an essential role in the prevention and treatment of kidney diseases [4]. Fennel is a significant chemical components such as 'flavonoids, polyphenols, carotenoids, minerals, and vitamins' [5]. Therapeutically, fennel has been shown to have 'anti-inflammatory, antidiabetic, antibacterial, antifungal, antioxidant, analgesic, estrogenic, hepatoprotective, and antitumor activities [6].

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Parsley (*Petroselinum crispum*, Apiaceae) is an annual herb and can provide sufficient dietary sources of vitamins and essential minerals [7]. Parsley has been used for the treatment of an inflammatory condition, liver diseases, constipation, flatulence, jaundice, colic pain, and rheumatism' [8].

Artemisia absinthium is known as wormwood. The name 'Artemisia' is derived from the Goddess Artemis, who was said to have discovered the plant's effects, while 'absinthium' means undrinkable because of the very bitter taste of the plant [9]. It belongs to the family Asteraceae, subfamily Asteroidea. Artemisia absinthium is presented with high phenolic acids and flavonoids, so it has antioxidant activity and a cytoprotective effect with oxidative damage [10].

Materials and methods

Materials

Ethics committee approval was taken. The plants (parsley, fennel, and Artemisia absinthium) were obtained from a local market. These plants were crushed and collected as a dried powder.

Diet composition: Casein, vitamins, minerals, methionine, and choline chloride were purchased from El-Gomhouria Company. Oil and starch were obtained from a local market in Cairo, Egypt.

Gentamicin (aminoglycosides antibiotics) obtained by Memphis Co. for Pharm. Chem. Ind (Cairo, Egypt).

Experimental animals: a total of 20 normal male albino rats weighing 100 ± 10 g were obtained from the Research Institute of Ophthalmology.

Methods

Preparation of water extracts

The water extracts of test plants were prepared according to the Mansour method (1995) where taken 10 g of the dry powder of the studied plants is taken and is placed in a 500 ml flask containing distilled water and mix with an electric mixer for 15 min and then mix the mixture at 50° with filter leaves and take the leachate and save in dark bottles in the fridge until use.

Biological evaluation

Twenty male albino rats of Sprague Dawley strain weighing (100 ± 10 g) were housed individually in wire cages in a hygienic condition and fed on a basal diet for 1 week for adaptation. The basal diets were prepared according to the methods of Reeves *et al.* [11].

Induction renal and hepatotoxicity

After feeding on a basal diet for 1 week for adaptation, the rats were divided into two groups. The first group (four rats) was fed on a basal diet; the second group (24 rats) was injected intraperitoneally with gentamicin (100 mg/kg/day for 8 days) to induce renal and hepatotoxicity according to Farombi and Ekor [12].

After injection, the rats (24 rats) were randomly divided into four subgroups each containing six rats:

(1) Subgroup 1 (group 2): a positive control (positive C group) fed on a balanced diet.
(2) Subgroup 2 (group 3): the rats were fed on a standard diet with an orally aqueous extract of Artemisia absinthium at a dose of 5 g/kg body weight.
(3) Subgroup 3 (group 4): the rats were fed on a basal diet plus an orally aqueous extract of the parsley at a dose of 5 g/kg body weight.
(4) Subgroup 4 (group 5): the rats were fed on a balanced diet plus an orally aqueous extract of fennel at a dose of 5 g/kg body weight.

At the end of the experiment, the rats were starved for 12 h and then killed under ether anesthesia. Blood samples were collected from the portal vein by means of fine capillary glass tubes according to the method described by Schermer [13]. Blood samples were received into a clean, dry centrifuge tube, and were left to clot at room temperature, then centrifuged for 10 min at 3000 rpm to separate the serum. Serum was carefully separated into dry clean Wasserman tubes by using a Pasteur pipette and kept frozen at (−20°C) till Biochemical analysis.

Biochemical analysis and structure determination

Serum samples in all groups were analyzed for the following biochemical parameters, that is, creatinine was according to the method described by Bohmer [14]. Uric acid was according to the technique described by Fossati *et al.* [15]. Urea in the plasma was analyzed according to the enzymatic method of Patton and Crouch [16]. Serum triglyceride (TG) in the plasma was evaluated according to the Fossati and Principle [17]. Lactate dehydrogenase (LDH) activity was determined according to the method described by Bais and Philcox [18]. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were measured according to Reitman and Frankel [19]. Alkaline phosphatase (ALP) was determined according to the method described by Kind and King [20].

Histopathological examination

After decapitation and dissection, the liver and kidneys from each rat were rapidly excised and then perfused in saline solution. Liver and kidney samples from four groups were fixed in 10% neutral buffered formalin. The fixed liver and kidney samples were transferred to the National Cancer Institute, Cairo University (Egypt), for further processing. These formalin-fixed tissues were embedded in paraffin, sectioned (5 μm), stained with hematoxylin and eosin, and examined under a light microscope for histopathological assessment [21].

Statistical analysis

The statistical analysis was carried out by SPSS, PC statistical software (version 10.0; SPSS Inc., Chicago, Illinois, USA). The results were expressed as mean SD. Data were analyzed by one-way analysis of variance. The difference between means was tested for significance using the least significant difference test ($P < 0.05$) [22].

Results

Table 1 illustrated that the results of AST, ALT, and ALP enzymes, which recorded a significant increase in the (positive) control group as compared with the (negative) control group. Data in this table showed that there was a decrease in serum liver enzymes in all treated groups with an aqueous extract of all tested plants as compared with the (positive) control group. The highest decreased in serum AST was recorded in the group treated with the extract of fennel, while the highest decrease in serum ALT was recorded in those treated with the extract of parsley. Also, it was clear from Table 1 that there were no significant differences between rats treated with aqueous extract of all tested plants for serum ALP.

The results in Table 2 showed that there was a significant increase in serum levels of uric acid, urea, and creatinine in rats' injection by gentamicin as compared with normal rats. It could be noticed that rats injected with gentamicin and then fed on an aqueous extract of all tested plants showed the highest decrease of uric acid, urea, and creatinine enzyme levels in the serum. Also, it was clear from the same (Table 2) that the best value for uric acid was rats treated with extract of the fennel. Data in the same table shows that there were nonsignificant differences between treatment groups for urea and creatinine.

The obtained results from Table 3) indicated that the level of TG and LDH in the gentamicin group (untreated) was significantly higher than that of the normal control group. However, there was a decrease in serum TG and LDH in all treated groups with an aqueous extract of all tested plants as compared with the positive (positive) control group. Besides, it was clear from the Table 3 that the best value for TG was in rats treated with the extract of parsley. Data in the same table show that the best value for LDH was rats treated with the extract of fennel.

Histopathological examination

Histological profile of the liver

Microscopically liver examination of rats from the negative (negative control) normal group showed the normal histological structure of the hepatic lobule (Fig. 1). On the contrary, the liver of rats without the treatment (positive C) group showed congestion of central vein and fatty degeneration of hepatocytes (Fig. 2) and congestion of hepatoportal blood vessel and portal infiltration with inflammatory cells (Fig. 3).

The liver tissue treatment with extract of Artemisia absinthium, group C, showed cytoplasmic vacuolation of centrilobular hepatocytes, necrosis of sporadic hepatocytes (Fig. 4), and other sections from this group showed no histopathological alterations (Fig. 5). Moreover, the liver of rats from groups 4 and 5 showed marked improvement as the examined sections revealed no histopathological alterations. This study shows that parsley is rich with an antioxidant arsenal that includes luteolin, a flavonoid that searches out and eradicates free radicals in the body that cause oxidative damage in the cell.

Table 1: Effect of feeding with an aqueous extract of all tested plants on serum liver enzymes

Groups	Parameters		
	AST (U/l)	ALT (U/l)	ALP (U/l)
Negative control (group 1)	75.0±5.7^{d}	44.7±3.3^{d}	3.6±0.18^{b}
Positive control (group 2)	187.0±3.4^{a}	107.5±6.4^{a}	5.3±0.64^{a}
Group 3: extract of Artemisia absinthium	169.0±5.2^{b}	69.2±3.2^{b}	3.8±0.26^{b}
Group 4: extract of parsley	124.2±3.3^{c}	55.0±2.1^{c}	3.9±0.014^{b}
Group 5: extract of fennel	123.5±3.4^{c}	66.2±1.7^{b}	4.0±0.17^{b}

Values denote arithmetic means±SD of the mean. ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase. Means with different letters (a, b, c, d) in the same column differ significantly at $P<0.05$ using one-way analysis of variance test, while those with similar letters are nonsignificantly different.

Table 2: Effect of feeding with an aqueous extract of all tested plants on serum kidney function

Groups	Parameters (mg/dl)		
	Uric acid	Urea	Creatinine
Negative control (group 1)	0.52±0.06^{d}	24.2±3.8^{c}	0.55±0.05^{c}
Positive control (group 2)	1.31±0.04^{a}	52.2±3.7^{a}	1.95±0.2^{a}
Group 3: extract of Artemisia absinthium	0.84±0.04^{b}	35.5±2.6^{b}	1.45±0.05^{b}
Group 4: extract of parsley	0.88±0.09^{b}	39.2±0.9^{b}	1.47±0.09^{b}
Groups 5: extract of fennel	0.63±0.02^{c}	39.5±0.5^{b}	1.57±0.05^{b}

Values denote arithmetic means±SD of the mean. Means with different letters (a, b, c, d) in the same column differ significantly at $P<0.05$ using one-way analysis of variance test, while those with similar letters are nonsignificantly different.

Table 3. Effect of feeding with an aqueous extract of all tested plants on serum triglyceride and LDH

Groups	Parameters	
	Triglyceride (mg/dl)	LDH
Negative control (group 1)	145.8±3.8^{e}	972.0±16.8^{e}
Positive control (group 2)	192.4±3.2^{a}	2004.7±1.7^{a}
Group 3: extract of Artemisia absinthium	179.1±6.5^{b}	1518.7±43.06^{b}
Group 4: extract of parsley	160.1±4.7^{d}	1269.0±5.7^{c}
Groups 5: extract of fennel	167.7±4.0^{c}	1237.2±4.2^{d}

Values denote arithmetic means±SD of the mean. LDH, lactate dehydrogenase. Means with different letters (a, b, c, d) in the same column differ significantly at $P<0.05$ using one-way analysis of variance test, while those with similar letters are nonsignificantly different.

Histological changes of the kidney

Microscopically, kidneys of rats from group A showed the normal histological structure of renal parenchyma (Fig. 6). Meanwhile, kidneys of rats from group B showed vacuolated epithelial lining renal tubules (Figs. 7, 8), and endothelial lining glomerular tuft (Fig. 8), as well as protein, casts in the lumen of renal tubules (Fig. 9).

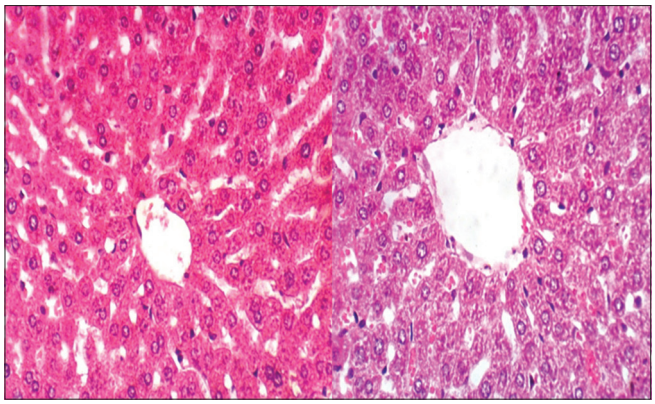

Figure 1: Liver of rat from group A showing the normal histological structure of the hepatic lobule (hematoxylin and eosin, ×400).

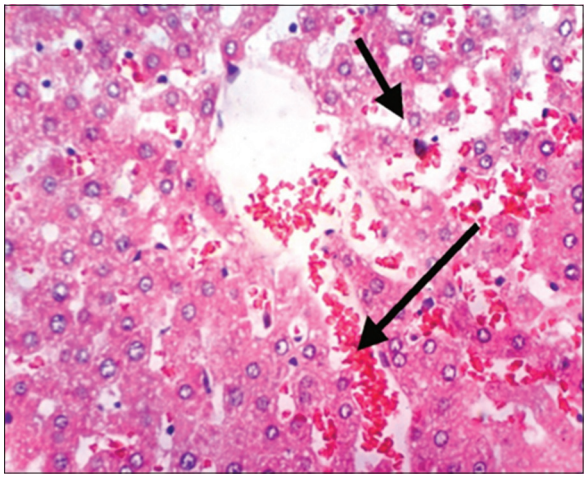

Figure 3: Liver of rat from group B showing cytoplasmic vacuolation of hepatocytes and marked dilatation with congestion of hepatic sinusoids.

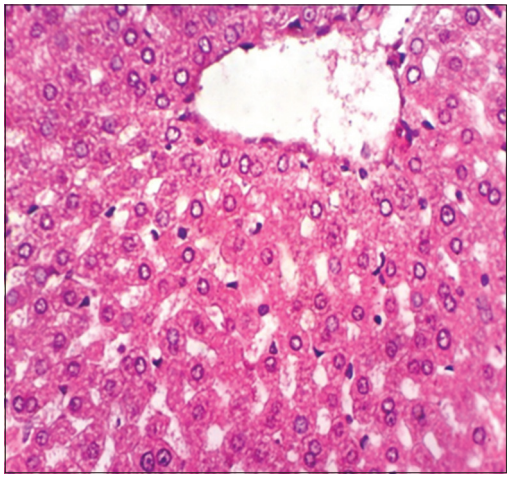

Figure 5: Liver of rat from group C showing no histopathological alterations.

However, some kidneys from group C showed vacuolations of the epithelial lining renal tubules and endothelial lining glomerular tuft (Fig. 10), whereas other sections from (group C)

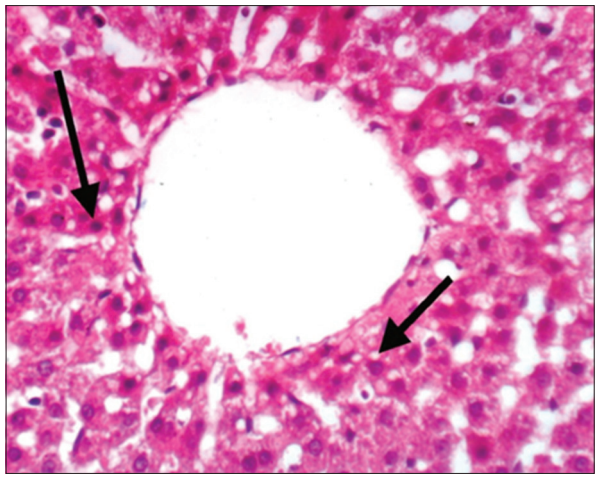

Figure 2: Liver of rat from group B showing cytoplasmic vacuolation of centrilobular hepatocytes and necrosis of sporadic hepatocytes.

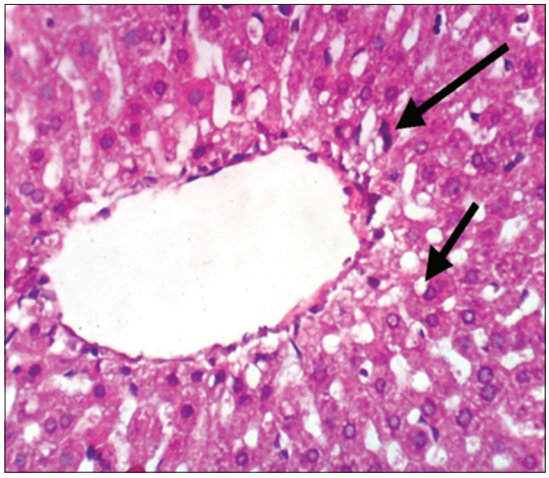

Figure 4: Liver of rat from group C showing cytoplasmic vacuolation of centrilobular hepatocytes and necrosis of sporadic hepatocytes (hematoxylin and eosin, ×400).

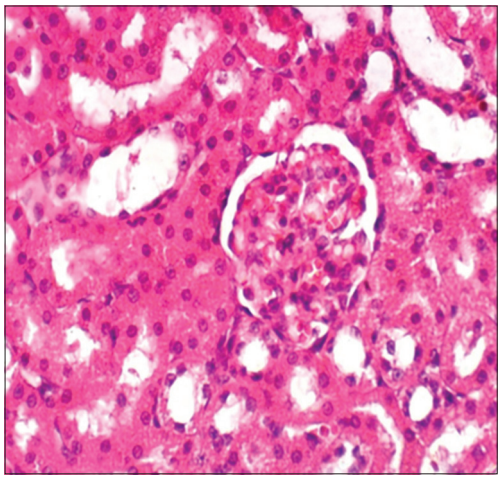

Figure 6: Kidney of rat from group A showing the normal histological structure of renal parenchyma (hematoxylin and eosin, ×400).

showed only slight vacuolations of the epithelial lining of some renal tubules (Figs. 11–13).

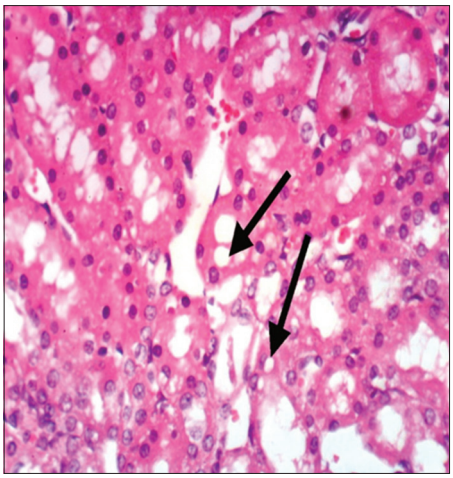

Figure 7: Kidney of rat from group B showing vacuolations of epithelial lining renal tubules (hematoxylin and eosin, ×400).

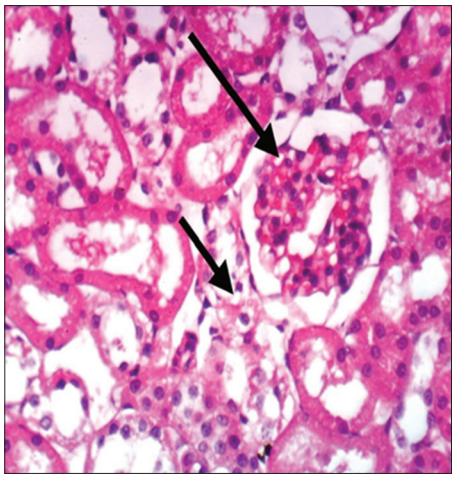

Figure 8: Kidney of rat from group B showing vacuolations of epithelial lining renal tubules and endothelial lining glomerular tuft (hematoxylin and eosin, ×400).

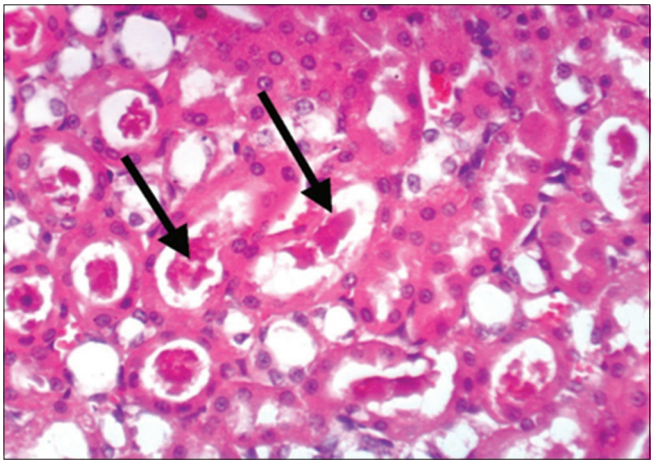

Figure 9: Kidney of rat from group B showing protein casts in the lumen of renal tubules (hematoxylin and eosin, ×400).

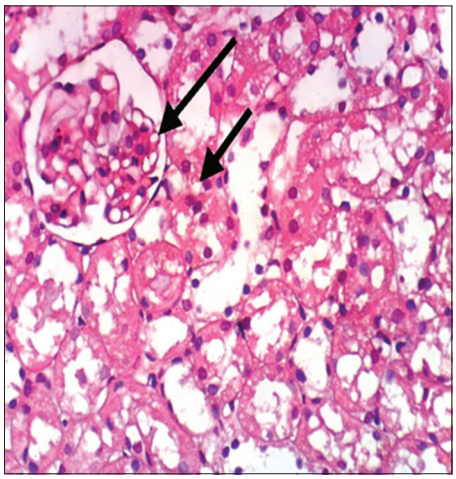

Figure 10: Kidney of rat from group C showing vacuolations of epithelial lining renal tubules and endothelial lining glomerular tuft (hematoxylin and eosin, ×400).

Discussion

The kidney is the primary organ for clearance and excretion of drugs from the body. Moreover, electrolyte and water balance are regulated via the kidney. Also, the kidneys excrete urea and creatinine as waste products of protein metabolism. The increase in urea and creatinine is a sign of kidney damage, even though urea concentration increases due to dehydration, drugs, and diet [23]. In this study, we investigated the protective effects of some plants against the toxicity of kidneys caused by gentamicin.

Gentamicin injection caused hepatotoxicity, as indicated by the significant increase in serum levels of ALT, AST, ALP, and LDH. The serum level of transaminases and ALP is generally considered as sensitive markers of the liver function, and their concentrations are increased in the serum because of their cytoplasmic nature and are released in the blood by changing in the permeability of hepatocyte membranes. Increased level of LDH in serum in the present investigation indicated the toxic effects of gentamicin in the rat. The results obtained in this study are consistent with other reports [24], who reported that there were increases in serum AST, ALT, and LDH activities in rats injected with gentamicin intraperitoneally at a dose of 100 mg (every other day) for 21 days.

The present study demonstrated that gentamicin treatment caused significant increases in serum TGs that may be due to inhibition of 7a-hydroxylase activity [25]. This is in agreement with Rashid and Khan[26] and Maha and Haneen [27], who reported that injecting rats with gentamicin (80 mg/kg) increased the levels of total cholesterol and TGs as compared with control animals.

The gentamicin-induced neurotoxicity was confirmed by an increase in serum creatinine, uric acid, and urea, and blood urea nitrogen levels were in agreement with a previous study by Fouzia *et al*. [28], who reported that there were increases in serum creatinine, urea, AST, and ALT in rats injected with gentamicin intraperitoneally at a dose of 80 mg/kg/day for 3,

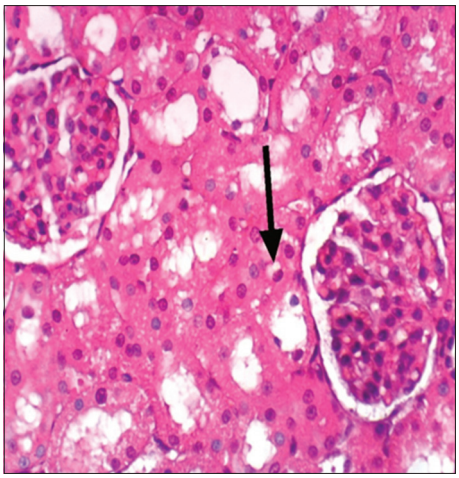

Figure 11: Kidney of rat from group C showing slight vacuolations of epithelial lining some renal tubules (hematoxylin and eosin, ×400).

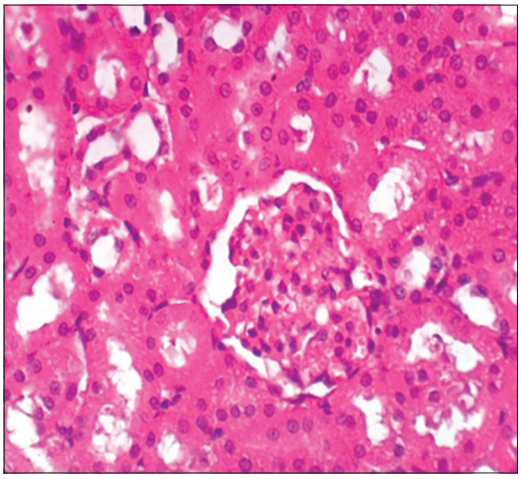

Figure 12: Another section of rat from group D showing no histopathological alterations (hematoxylin and eosin, ×400).

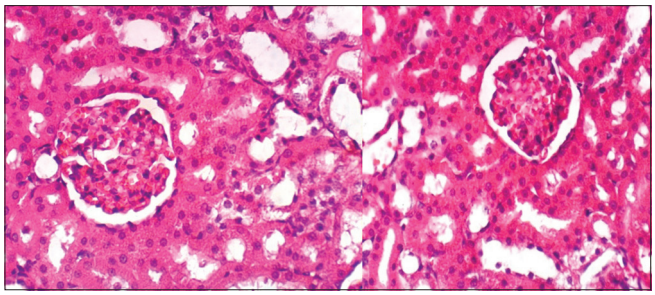

Figure 13: Kidney of rat from group D showing no histopathological alterations (hematoxylin and eosin, ×400).

5,7,10, and 12 consecutive days. High value levels of blood urea and serum creatinine indicated that renal damage might be correlated with the significant progressive body weight loss and kidney weight gain in the administered GM group.

The oral administration of 5% aqueous extract of parsley significantly improved the mean values of TGs, LDH, liver enzymes, and kidney functions as compared with the positive control group. These results agreed with the results of other studies, that is Madeha *et al*. [29], who showed that the methanolic extract of parsley decreased lipid peroxidation and kidney functions and increased antioxidants and also with Haddad and colleagues who reported that there was a decrease in the mean values of liver function in parsley methanol extract. Other studies were observed by Ayman *et al.*[30] who showed that the effect of peppermint and parsley oil at 0.5 ml might be attributed to its antioxidant content and free radical scavenger effects. Mohamed *et al*.[31] illustrated that parsley extract (150 mg/kg BW/day for 6 weeks) resulted in a significant decrease in TG, AST, and ALT. Nabila *et al.*[32] indicated that TG/liver functions were decreased due to receiving parsley leaves extract (E) and parsley seeds oil (O) as compared with the positive control group. The activity of parsley may be due to the antioxidant compounds including flavonoids, carotenoids, and other phenolic compounds [33]. Also, Haidari *et al.*[34] demonstrated that phytochemicals of parsley improve total antioxidant capacity, and suppress the destructive oxygen-free radicals and prevent oxidative stress damage.

The results in this study illustrated that fennel administration resulted in decreased levels of TG, LDH, liver, and kidney functions as compared with the rats' group fed with GM. The results were in agreement with those of other investigators who studied the protective effect of fennel. Nawal, *et al.*[35] who revealed that the administration of fennel significantly decrease the activities of TG, ALT, AST, ALP, and kidney function as compared with the obesity group (the positive control group). Agarwal *et al*.[36] found that methanol and hexane extracts of fennel (400 mg/kg/BW) caused reduction levels of ALT, AST, ALP, and bilirubin. Wael[37] confirmed that fennel oil has positive effects on the histological structure of the liver and kidneys and the biochemical levels of AST, ALT, ALP, creatinine, and urea. Shimaa *et al*.[38] observed that treating rats with fennel seed extracts exerted a significant improvement in most of the biochemical parameters compared with the positive control. Fennel extract contains different polyphenolic compounds. These polyphenolic compounds are known to have tremendous antioxidant activity, and the activity of fennel extracts could likely be due to these active compounds [6]. GM-treated group with 5% aqueous extract of Artemisia significantly improved the mean values of TGs, LDH, liver enzymes, and kidney functions as compared with the positive control group. These results were in agreement with Ali *et al.* [39], who suggested that alcoholic extract of Artemisia can ameliorate liver toxicity in rats. In other studies, the levels of creatinine, urea, and uric acid were increased in diabetic rats, whereas Artemisia extract (50, 100, and 200 mg/kg) lowered these factors [40]. Jayasimha *et al*.[41] who reported that Artemisia absinthium leaves' methanolic extract in different concentrations (100, 250, and 500 mg/kg) produced significant hypoglycemic activity and reduced the levels of urea and creatinine in diabetic rats. It can be probably due to the hypoglycemic activity of this plant. A. absinthium extracts, rich in flavonoids and phenolic acids, showed good antioxidant

activity and cytoprotective effect against oxidative damage [10]. Artemisia absinthium administration was shown to put off the decrease in TG, and improve liver function in rats [42].

Conclusion

The present study suggests that parsley, Artemisia absinthium, and fennel extracts have protective effects against gentamicin toxicity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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