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Protective effect of date extract on rat nephrotoxicity induced by gentamicin, clinical, histological and antioxidant evidences

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Abstract: In this study, it was aimed to investigate the effect of the date extract (*Phoenix dactylifera)* on certain biochemical parameters and total antioxidant status (TAS), total oxidant status (TOS) and oxidative stress index in nephrotoxicity induced by gentamicin. The rats used in the study were randomly selected and divided into 4 groups, each consisting of 8 rats: control group, date extract (DE) group, gentamicin (GEN) group, gentamicin+date extract (GEN+DE) group. Blood samples and kidney tissues were taken 24 hours after eight days of trial. Urea, Creatinine, BUN, Na, Cl and K analyzes on the serum samples were carried out in auto analyzer. One of the kidney tissues was examined histopathologically. The supernatant, which was obtained by homogenizing the other kidney tissue was used in TAS and TOS analyzes. OSI was calculated using the formula. Urea, Creatinine, and BUN levels were higher in the GEN group, when compared to the other groups ($p<0.001$), while Na ($p<0.05$), Cl and K levels ($p<0.001$) were lower than those of the other groups. When the control group and the GEN group were compared, it was observed that the level of TAS decreased in the renal tissue and the level of TAS increased in the GEN+DE group. It was determined that TOS ($p<0.01$) and OSI ($p<0.001$) levels increased in the GEN group and renal TOS and OSI levels decreased in the GEN+DE group when compared to the GEN group. In conclusion, when the histopathological changes in kidney tissue with antioxidant and oxidant status in nephrotoxicity with gentamicin are examined, it can be said that date extract with gentamicin attenuates nephrotoxicity caused by gentamicin and date extract protects the kidney.

Key words: Biochemical parameters; Gentamycin; Date extract; Nephrotoxicity; Rat.

Introduction

Gentamicin is an antibiotic from aminoglycoside group that acts as a bactericidal agent in the structure of organic the polycation. Because of its chemical structure and rapid bactericidal effect, it is one of the primarily preferred antibiotics in various clinical situations (1, 2). Gentamicin is used in urinary tract, digestive system, skin-ear-eye infections, metritis and septicemia cases. The use of these antibiotics for more than 7 days is shown to cause renal failure in 30% of patients (1-3). Nephrotoxicity due to gentamicin is characterized by increased concentrations of Blood Urea Nitrogen (BUN) and creatinine, together with severe tubular necrosis (4).

In-vivo methods are being resorted more and more every day with hopes to reach more reliable results in the biomedical investigations. Use of lab animals is one method that is reliable and particularly suitable to model human disease models. Most of the research conducted on laboratory animals is conducted to model human health studies. Rats are especially preferred in research where experimental disease models are created (nephropathies, streptozotocin induced diabetes, metabolic syndromes, obesity etc.) due to their adaptation capabilities and ease of surgical operations on them (5)

Medicinal plants continue to be used as valuable therapeutic agents in both modern and traditional medicine (6-9). Date palm fruit is a good food source with high nutritional value. Because of being a high-carbohydrate source (70-80%), it rapidly gives energy (10). It is rich in dietary fibers, proteins, minerals and B vitamins such as thiamin (B1), riboflavin (B2), niacin (B3), pantothenic (B5), pyridoxine (B6) and folate (B9). The minerals that are found in the date palm fruit are calcium, iron, magnesium, selenium, copper, phosphorus, potassium, zinc, sulphur, cobalt, fluorine, manganese, and boron (11-13). It also has important antioxidant, antibacterial, antifungal and anti-proliferative properties and therapeutic value (11). In addition to antioxidant activity and cholesterol-decreasing properties of the phytochemicals that are found in this fruit, they have the potential to protect against diabetes, cardiovascular diseases and cancer (11, 12). Nephrotoxicity is one of the most common kidney problems and occurs when the body is exposed to a drug or toxin that damages the kidneys (6, 14, 15). The mechanism of action of nephrotoxicity due to gentamicin is not fully illuminated, and many factors, especially the accumulation of reactive oxygen metabolites, are suggested.

In this study, it was aimed to investigate the effect of date extract on total antioxidant status, total oxidant status and oxidative stress index together with certain biochemical parameters of nephrotoxicity created by gentamicin.

Materials and Methods

Determination of Total Phenolic Compound Content of Date Extract

Gallic Acid (Merck), Na2CO3 (Sigma Aldrich), Folin–Ciocalteu reagent (Sigma Aldrich) were used in the method. A 1mg/1 mL gallic acid standard solution was prepared and was transferred to measuring cups in different concentrations (10, 20, 30, 40, and 50 µg/µL). 23 mL of distilled water was added to the mixtures. The stock 2N folinic reactive was diluted 10 times, and 0.5 mL of it was transferred to the measuring cups, which were incubated for 10 minutes. Next, 1.5 mL of the 2% Na_2CO_3 solution was introduced to the each of the measuring cups, which were further incubated in the shaker at room temperature (25 °C) for 2 hours. The readings were taken using a Multiskan Go (Thermo Scientific) device at 760 nm wavelength (16, 17). The 0,250 mL of the base 1mg/mL date sample extract was collected, and the procedure was repeated three times.

Drugs and Reagents

100 gr date extract (Deva Trade/Manisa-Turkey) was kept in 1000 ml distillated water for 48 hours and the mixture was centrifuged at 4000 rpm and 4°C for 20 minutes. After sedimentation, the supernatant part was used for gavages (18). Gentamicin (Genta-80 mg/2 ml) was obtained from İ.E. Ulugay Corp.

Animal material and experimental protocol

Ethical approval for this study was obtained from the Siirt University Local Ethics Committee for Animal Experiments (DEHAM). (Approval Number: 2018/02/01).

The animal material of the study consisted of 32 female and 7-8 weeks old Wistar Albino rats obtained from the Saki Yenili Experimental Animals Laboratory. Prior to the experiment, the rats were adapted to the environment for 7 days. Rats were randomly selected and divided into 4 groups:

Physiological saline was given to rats in control group by sending Intraperitoneal (IP) for 8 days.

Rats in the date extract group (DE) were given 1 ml supernatant through intragastric gavage for 8 days.

Rats in the gentamicin group (GEN) were given 80 mg/kg/day IP gentamicin for 8 days.

Rats in the group of Gentamicin+Date Extract (GEN+DE) were given 80 mg/kg/day IP gentamicin and 1 ml supernatant through intragastric gavage for 8 days.

During the 8-day trial, rats were kept in cages in rooms with 12 hours of light/dark ambient and temperature set to 22 ± 2°C. Animals were given ad libitum commercial rat feed (pellet feed) and drinking water.

Drawing the blood samples

After 24 hours following the 8-day trial (9^{th} day), rats in all groups were injected ketamine (90 mg/kg) intraperitoneally and the animals were subjected to anesthesia. Blood samples of the rats were taken into the tubes without anticoagulants, by entering the left ventricle using an injector. The samples were centrifuged for 10 minutes at 3000 rpm at +4°C. Urea, Creatinine, BUN, Na, Cl and K analyses were performed using the ADVIA 1800 Chemistry system auto-analyzer on the serum samples obtained.

Renal tissue removal and preparation of homogenates

As a result of the study, one of the kidney tissues obtained from rats was separated for histopathological analysis and the other was kept at -80 ° C until the analysis was carried out after it was washed using the cold PBS buffer. Renal tissues were homogenized in ice with PH 7.4, 0.1 m, phosphate buffer at 1/10 ratio and centrifuged at 1800xg. The resulting supernatants were used for TAS, TOS analyses.

Measurement of Total Antioxidant Status (TAS)

TAS levels were measured using commercially available kits (Relassay, Turkey). The novel automated method is based on the bleaching of characteristic color of a more stable ABTS (2,2 ′ - Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)) radical cation by antioxidants. The assay has excellent precision values, which are lower than 3%. The results were expressed as mmol Trolox equivalent/L (19).

Measurement of Total Oxidant Status (TOS)

TOS levels were measured using commercially available kits (Relassay, Turkey. In the new method, oxidants present in the sample oxidized the ferrous ion-o-Dianisidine complex to ferric ion. The oxidation reaction was enhanced by glycerol molecules, which were abundantly present in the reaction medium. The ferric ion produced a colored complex with xylenol orange in an acidic medium. The color intensity, which could be measured spectrophotometrically, was related to the total amount of oxidant molecules present in the sample. The assay was calibrated with hydrogen peroxide and the results were expressed in terms of micromolar hydrogen peroxide equivalent per liter (µol H_2O_2 equivalent/L) (20).

Determination of Oxidative Stress Index

The ratio of TOS level to TAS level was accepted as the oxidative stress index (OSI). For calculation, the resulting unit of TAS was converted to µmol/L, and the OSI value was calculated according to the following Formula (21-23).

$$OSI\ (arbitrary\ unit) = \frac{TOS(\mu ol\ H2O2\ equivalent/L}{TAC\ (\mu ol\ Trolox\ equivalent/L}$$

Histopathologic analysis

Kidney tissues in all groups were fixed in 10% neutral formalin for 48-72 hours. Then, the tissues were trimmed and processed for routine histopathological examination and scoring. Tissues were embedded into paraffin wax and 4-5 micrometer-thick sections were cut. All tissue sections were stained with Hematoxylin and Eosin, and subsequently, they were examined under light microscope (Olympus BX43, Japan).

The kidney damage score was calculated using a previously described semi quantitative index (24). Tissue damages were graded in terms of glomerular atrophy, cellular desquamation, tubular necrosis, epithelial edema of proximal tubules, perivascular edema, vascular congestion and intra-tubular proteinaceous casts. Lesions were graded for each scored histopathological parameter as 0=none, 1=1-20%, 2=21%–40%,

3=41%–60%, 4=61%–80%, and 5=81-100%. Total histopathological score was calculated mean of each parameter scored of each group. At least 7–10 sections were reviewed under 20X magnification for each slide.

Histological and statistical analyses and graphs were prepared using GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA), and $p<0.05$ was statistically significant.

Statistical Analysis

SPSS (SPSS 23.0 Evaluation version) program pack was used for the statistical analysis. One-way ANOVA test was used in comparing the groups. Duncan multiple comparison test was used to determine the difference between groups. $P<0.05$ value was statistically significant.

Results

Total phenolic compound content of Date Extract is given in table-1.

Serum Urea, Creatinine, BUN, Na, Cl and K levels of all groups are given in Table 2. Levels of Urea, Creatinine, and BUN were higher ($p<0.001$), while Na ($p<0.05$), Cl and K levels were lower ($p<0.001$) in Gentamicin group than those of other groups.

The results of total antioxidant (TAS), total oxidant (TOS) and oxidative stress index (OSI) in kidney tissue were given in Table 3. When the control group was compared with the GEN group, it was observed that the level of TAS decreased in the kidney tissue, whereas it was found that the level of TAS increased in the group that date extract and gentamicin were administered together. It was observed that the levels of TOS ($p<0.01$) and OSI ($p<0.001$) increased in gentamicin administered group; and renal TOS and OSI levels were lower in gentamicin and date administered group when compared to GEN group.

Histopathological findings

Kidneys of the control group animals showed a normal histological morphology (Figure 1A). The toxic effect of gentamicin was confirmed by the detection of histological changes in kidney sections (Table 4). The GEN group showed structural damage characterized by tubular necrosis. In addition, vacuolization in endothe-

Table 1. Total phenolic compound content of date extract.

Absorbance Measurement (760 nm)					
Sample	Measurement No.1	Measurement No.2	Measurement No.3	Average Abs	Gallic Acid Calculation
Date Extract	0.0565	0.0568	0.0607	0.0580±0.0019	5.3500 ±1.3783 µg Gallic Acid/µL

Table 2. Changes in biochemical parameters.

Parameters	Control	Date Extract	Gentamicin	Gentamicin+ Date Extract	P-Value
Urea (mg/dl)	53.70±3.20^{c}	50.28±4.26^{c}	309.23±92.24^{a}	138.10±25.17^{b}	0.000***
Creatinine (mg/dl)	0.60±0.03^{c}	0.66±0.02^{c}	2.79±0.58^{a}	1.43±0.22^{b}	0.000***
BUN (mg/dl)	25.25±1.58^{c}	23.25±1.83^{c}	144.50±43.13^{a}	64.50±11.84^{b}	0.000***
Na (mmol/L)	143.13±0.83^{b}	144.13±0.99^{a}	142.63±0.92^{b}	143.50±0.76^{ab}	0.015*
Cl (mmol/L)	94.00±0.93^{a}	95.38±1.06^{a}	87.63±0.52^{b}	89.38±3.20^{b}	0.000***
K (mmol/L)	5.55±0.38^{a}	6.01±0.67^{a}	4.74±0.29^{b}	6.06±0.60^{a}	0.000***

^{a,b,c}: The difference between group averages with different letters on the same row is statistically significant, *: $p<0.05$, **: $p<0.01$, ***: $p<0.001$.

Table 3. TAS, TOS, OSI levels of all groups.

Parameters	Control	DE	GEN	GEN+DE	P-Value
TAS (µmol Trolox Eq/mg pr)	1.19 ± 0.11	1.30 ± 0.50	0.83 ± 0.21	1.22 ± 0.43	0.060^{NS}
TOS (µmol H2O2 Eq/mg pr)	8.84 ± 1.31^{b}	9.88 ± 3.15^{b}	15.36 ± 5.66^{a}	11.05 ± 3.28^{b}	0.008**
OSI (AU)	0.76 ± 0.16^{b}	0.80 ± 0.21^{c}	1.88 ± 0.63^{a}	0.94 ± 0.13^{b}	0.000***

^{a,b,c}: The difference between group averages with different letters on the same row is statistically significant, DE: Date extract, GEN: Gentamicin, GEN+DE: Gentamicin + Date extract, ^{NS}: Non-significant, **: $p<0.01$, ***: $p<0.001$.

Table 4. Effects of Date Extract administration on renal histopathological scores induced by gentamicin.

Parameters for Histopathological assessment	Experimental groups			
	Control	DE	GEN	GEN+DE
Glomerular atrophy	0.125±0.125	0.125±0.125	3.870±0.226$^{*\#}$	2.870±0.226$^{*\#}$
Cellular desquamation	0.125±0.125	0.250±0.163	4.120±0.226$^{*\#}$	2.870±0.295$^{*\#}$
Tubular necrosis	0.125±0.125	0.125±0.125	4.000±0.267$^{*\#}$	3.120±0.227$^{*\#}$
Epithelial edema of proximal tubules	0.125±0.125	0.125±0.125	4.000±0.267$^{*\#}$	2.875±0.350$^{*\#}$
Perivascular edema	0.125±0.125	0.125±0.125	3.500±0.189$^{*\#}$	2.750±0.250$^{*\#}$
Vascular congestion	0.125±0.125	0.125±0.125	4.000±0.267$^{*\#}$	2.875±0.125$^{*\#}$
Intra-tubular proteinaceous casts	0.125±0.125	0.125±0.125	4.125±0.226$^{*\#}$	2.625±0.263$^{*\#}$
Total histopathological score	0.125±0.000	0.143±0.017	3.945±0.081$^{*\#}$	2.855±0.056$^{*\#}$

DE: Date extract, GEN: Gentamicin, GEN+DE: Gentamicin + Date extract, *: $p<0.05$, as compared to control group, $^{\#}$: $p<0.05$, as compared to Date extract group.

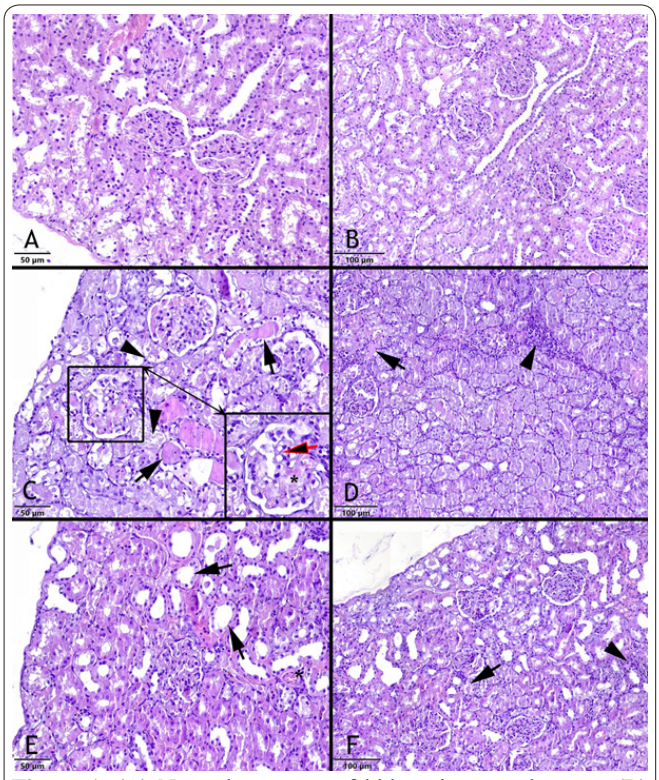

Figure 1. (A) Normal structure of kidney in control group. (B) Hematoxylin and eosin Stained sections of kidney DE group. Histology of kidney was similar to the control group. (C) Stained sections of GEN group. Severe tubular degeneration and necrosis (arrow heads) and hyaline casts (arrows). The lower right figure demonstrates high magnification of selected glomerulus with vacuolization (arrow with red stroke) and glomerular capillary congestion (asterisk). Hematoxylin and eosin. (D) Stained sections of GEN group. Interstitial infiltration (arrow head) and hyaline cast (arrow). Hematoxylin and eosin. (E) Stained sections of GEN+DE group. Mild tubular dilatations were seen (arrows). Congestion was seen (asterisk). Hematoxylin and eosin. (F) Stained sections of GEN+DE group. Mild interstitial infiltration (arrow head) and hyaline casts (arrow) were seen. Hematoxylin and eosin.

lial cells in the glomerulus, glomerular capillary congestion, and tubular dilation was detected. Hyaline casts were seen in tubules throughout cortex (Figure 1C-1D). The semi-quantitative kidney damage score was significantly higher in GEN group than that of the control group. Kidney total damage scores were calculated as 0.125 ± 0.000 in Control group; 0.143 ± 0.017 in DE group; 3.945 ± 0.081 in GEN group and 2.855 ± 0.056 in DE+GEN group. DE group had no effect on renal histology alone, however, it diminished the kidney damage score in GEN group. Congested blood vessels were also encountered in the renal cortex and some sections contained hyaline casts and mild interstitial infiltration in DE+GEN group (Figure 1E-1F). Sections DE+GEN group maintained a better histological structure with a prominent degradation of proximal tubular necrosis.

Discussion

Gentamicin is one of the medicines with the highest spectrum and antibacterial effect among aminoglycosides (1). It is known that it is excreted from the kidneys without being subjected to biotransformation and its most important side effect is nephrotoxicity (25). Reduction in glomerular filtration rate and increase in serum creatinine and BUN levels are interpreted as nephrotoxicity. Nephrotoxicity is known to be characterized by the accumulation of the drug in renal cortex and decrease in renal concentration ability, acute tubular necrosis, and renal insufficiency (26). Serum urea and creatinine levels increase as an indication of renal damage after gentamicin administration (27-29) and it was suggested that this increase was due to the decrease in glomerular filtration (30). In the early stage of renal damage, serum creatinine level was reported to be more important than that of urea (31).

In rats, which were given gentamicin IP as 80 mg/kg/day, the amount of urea and creatinine in the blood showed a significant increase (28). In the study of Yilmaz et al. (32), in which the effects of fucoidan on rats that nephrotoxicity was induced by gentamicin was examined, creatine and BUN levels were reported to increase in rats in gentamicin group compared to control group. It was found that urea and creatine levels were increased in rats where nephrotoxicity was induced by paracetamol, when compared to control group ($p<0.05$), and as the date fruit extract was given, the urea and creatine levels were found to be decreasing ($p<0.05$) (6). In this study, urea, creatinine and BUN levels were significantly higher in the gentamicin group than in the control group ($p<0.001$), which may indicate the successful occurrence of nephrotoxicity. In addition, a significant decrease in urea, creatine and BUN levels with date extract application may be indicative of the protective effect of date extract in nephrotoxicity.

One of the symptoms of renal damage following gentamicin administration is that some ions increase in the urine output. This is due to the change in the activity of the Na, K-ATPase enzyme, which is responsible for regulating intracellular electrolytes transport (1)**.** Ataman (33) investigated the possible protective or therapeutic effects of fucoid given together with gentamicin in nephrotoxicity generated by gentamicin, and it was found that serum Na levels ($p<0.05$) and serum Cl levels ($p<0.05$) were highest in fucoid group. In this study, the highest serum Na and Cl values were determined in the date extract group. Since the sodium and chlorine levels change in the same direction in certain conditions it can be said that there is an increase in Cl levels in the date extract given rats, in parallel with the increase in Na levels**.**

Aminoglycoside nephrotoxicity in experimental animals has been reported to cause decreased serum potassium levels (34). The effect of resveratrol on gentamicin nephrotoxicity in rats was found to be significantly lower in gentamicin group than in other groups (35). In this study, it was determined that K levels were lower in rats in gentamicin group than in other groups, which is similar to the findings of Silan et al. (35) ($p<0.001$).

Date palm fruits possess high nutritional and therapeutic value with significant antioxidant, antibacterial, antifungal, and anti-proliferative properties (11). Saafi et al. (36) showed that palm fruit extract (Deglet Noor type) protects against oxidative damage and also repairs liver damage. Date fruit has been reported to have a very powerful in vitro antioxidant effect (37). Antioxidants such as melatonin, vitamin E and ascorbic acid in dates have been suggested to play an important role in preventing kidney damage caused by gentamicin (3).

In the other study, the effect of dexmedetomidine on the nephrotoxicity of cholistin in rats was found to be low in the group of cholistin compared to the control group and the TOS was found to be high in the group of cholistin (38). In another study in which the protective effect of naringenin on cisplatin-induced nephrotoxicity was investigated, it was found that renal TOS, OSI levels increased in cisplatin group compared to control group ($p<0.05$) and renal TAS ($p<0.05$) levels decreased significantly (39). In this study, in line with the findings of the Koyuncu (39), TAS level was lowest and TOS level was highest in gentamicin group. In rats treated with gentamicin, increase in TAS level and decrease in TOS level were detected due to antioxidant properties of date extract.

This study evaluated the biochemical parameters of nephrotoxicity created with gentamicin in rats as well as renal histopathology. Histopathological examination revealed structural damage characterized by tubular necrosis in rats in gentamicin group while a better histological structure was detected in GEN+DE group.

As the result, when the histopathological changes in renal tissue with antioxidant and oxidant status in nephrotoxicity created with gentamicin were examined; it can be concluded that giving date extract with gentamicin weakens nephrotoxicity caused by gentamicin and the date extract protects the kidney.

Interest conflict

The authors have not declared any conflict of interests

Author's contribution

OYC designed the research plan and organized the study. OYC and KI collected samples and executed the experimental work. OYC and KI contributed to do data analysis and wrote the manuscript.

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