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Original Article

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Hypericum perforatum Extract Increased Necrosis in Amikacin-Induced Kidney Injury

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ABSTRACT

Objective: The present study aimed to investigate the effect of *Hypericum perforatum* extract on amikacin-induced kidney disease in rats.

Methods: About 28 female Spraque-Dawley rats were separated into groups. The control, amikacin, amikacin+ *H. perforatum* extract, and *H. perforatum* extract groups were given intraperitoneally 1 mL of serum physiologic, amikacin (1.2 g/kg), *H. perforatum* extract (50 mg/kg) + amikacin (1.2 g/kg), and *H. perforatum* extract (50 mg/kg), respectively. On the third day, serum blood urea nitrogen, creatinine, malondialdehyde, superoxide dismutase, catalase, glutathione peroxidase, histopathology, and apoptosis were explored in kidney tissue.

Results: The serum blood urea nitrogen and creatinine levels were higher in *H. perforatum* extract-pretreated amikacin group than in the other groups. Kidney malondialdehyde levels which showed oxidative injury were lowest in the serum physiologic group and highest in amikacin and amikacin+*H. perforatum* extract groups. Anti-oxidative enzyme (superoxide dismutase, catalase, glutathione peroxidase) levels decreased more in amikacin and amikacin+*H. perforatum* extract groups than serum physiologic (control) and *H. perforatum* extract groups. Histopathological damage scores of the amikacin+*H. perforatum* extract group were higher than the other groups. Proximal tubular tissue necrosis was observed in all of the rats in amikacin and amikacin+*H. perforatum* extract groups. Amikacin and amikacin+*H. perforatum* extract groups demonstrated the highest apoptotic index percentage.

Conclusion: We found that *H. perforatum* extract increased kidney injury mostly through oxidative damage and induction of apoptosis.

Keywords: Amikacin, Hypericum perforatum, rat, acute kidney injury

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INTRODUCTION

Aminoglycosides are a family of antibiotics which are used in case of severe infections as they provide bactericidal activity against many gram-negative bacteria. Amikacin (AK) is one of the most commonly used parenteral form of aminoglycosides which are administered to patients with serious multi-drug resistant gram-negative bacterial infections or allergy to beta lactams.[1,2] After the uptake of these drugs in the kidneys through interaction with megalin-cubilin receptors and endocytosis by proximal tubular cells, they are transferred to lysosomes. Lysosomal injury and rupture and mitochondrial injury are the mechanisms leading to tubular injury which occurs in nearly 25% of these patients and limit the effectiveness and usage of these group of drugs. Drug-induced toxicity might result in acute loss of kidney functions which might lead to patients' morbidity (progression to chronic kidney disease) and mortality.[3,4]

Hypericum perforatum (HP), previously recognized as St. John's Wort (SJW), is a herbal drug practiced for many

diseases such as dermatological lesions, mood disorders, liver injury, and convulsions because of its anti-inflammatory, antioxidative, and anti-apoptotic effects.[5] The extract of *Hypericum perforatum* (HPE) was useful in tubular injury models like ischemia-reperfusion injury and cisplatin toxicity in kidneys performed in rats.[6,7]

The present study was designed to investigate whether HPE facilitates or prevents AK-induced kidney injury in rats. To the best of our knowledge, there has been no report showing the effects of HPE on AK-induced kidney disease.

METHODS

Female Sprague-Dawley rats (taken from Surgery Research Center of our University) with an average weight of ≅250 g were fed with standard diet and water *ad libitum* and kept in a controlled room in which 12 : 12 hours light/dark cycle was maintained. The study protocol was accepted and performed according to the guidelines of the University Animal Ethics Committee (approval number: 53488718-686, protocol number: 2017/41).

Plant Material and Preparation of Extract

Hypericum perforatum was collected from Ordu (1300 m), which is a province in Turkey. The voucher specimen was put in the Herbarium of the Ankara University Faculty of Pharmacy (AEF 26820). The aerial parts of the plant were dried in the shade and thoroughly pulverized. Fifty grams of dried plant powder were weighed and blended with 500 mL methanol (3 times). Then, this mixture was stirred for 24 hours at room temperature. The filtrate of the mixture was evaporated by a rotary evaporator (Heidolph Instruments, Nuremberg, Germany) and 4 g of the crude residue was obtained. This extract was maintained at 4°C until used for assays.[8]

Grouping and Experimental Protocol

28 rats were divided into groups as follows: rats in SP group (control group, n = 7) were injected with 1 mL of serum physiologic (SP) intraperitoneally (i.p.); rats in AK group (n = 7) were given daily i.p. injections of AK (1.2 g/kg; Amikozit® 500 mg/2 mL flacon; Zentiva Sanofi Pharma Corp, İstanbul, Turkey) in a single dose; rats in AK+HPE group (n = 7) were injected i.p. with 50 mg/kg HPE plus 20 minutes later with AK (1.2 g/kg) in a single i.p. dose, while rats in HPE group (n = 7) were given i.p. with 50 mg/kg HPE. Three days after all injections were given, rats were anesthetized with i.p. injection of ketamine hydrochloride (Ketalar®, 90 mg/kg; 500 mg/10 mL, Pfizer; Turkey).[6,9-11] A midline incision of the abdominal cavity made the aorta visible where blood was taken for serum biochemistry. The left kidneys were observed and dissected. The left kidneys were cut in half, transversely. One-half of the left kidneys were fixed in 10% formalin for histological evaluation, the other half of the left kidneys were taken to −20°C refrigeration for tissue biochemistry. The rats died under deep anesthesia after researchers gathered blood and kidney tissue.

Blood Biochemistry

Blood was obtained from the abdominal aorta for serum creatinine and serum blood urea nitrogen (BUN) levels measurement. After serum was collected by centrifugation of blood samples at 2000 rpm for 10 minutes, it was kept at −20°C for the measurements which were performed by Beckman AU 5800 autoanalyzer using Beckman's own commercial kits.

Tissue Biochemistry

Malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) levels were evaluated in the kidney tissue.

Preparation of Tissue Homogenate for Assay

Kidney tissue was weighed and homogenized in ice-cold 1.15% KCl (2% and 10% w/v, respectively). The centrifugation of the homogenate at 2000 g for 10 minutes was performed.[12] All kit studies were performed on kidney homogenate.

Malondialdehyde Assay

Malondialdehyde level of the kidney was evaluated using the method described by Mihara and Uchiyama[13] by determining the appearance of thiobarbituric acid-reactive substances (TBARS). Tetramethoxypropane was utilized as the standard. Levels of MDA were presented as nanomole per milligram protein.

Protein Assay

The method described by Lowry et al[14] was used for protein concentration determinations. Bovine serum albumin was utilized as the standard.

Superoxide Dismutase Assay

A SOD activity assay kit (Cayman Chemical, Ann Arbor, Mich, USA) was used considering the manufacturer's orders to measure superoxide activity. One unit of SOD is identified as the amount of enzyme needed to exhibit 50% dismutation of the superoxide radical.[15] Spectrophotometrical measurement of SOD activity at 460 nm was performed and the results were expressed as units per milligram protein.

Catalase Assay

Catalase activity measurements were performed with a commercial assay kit (Cayman Chemical Company). The reaction of the enzyme with methanol in the presence of H_2O_2 constitutes the base of the method.[15] The decomposition of H_2O_2 was followed directly by a decrease in absorbance at 540 nm. The results were expressed as units per milligram protein.

Glutathione Peroxidase Assay

Glutathione peroxidase activity measurements were done with a commercial assay kit (Cayman Chemical Company,). Glutathione peroxidase activity is coupled with the oxidation of NADPH by glutathione reductase.[15] Oxidation of NADPH was monitorized spectrophotometrically at 340 nm at 25°C. The results were expressed as units per milligram protein.

Histopathological Evaluation

The fixation of half of the left kidney specimens was performed using 10% formalin and Bouin solution. Afterward, specimens were embedded in paraffin for histopathological examination. For light microscopy, the paraffin-embedded tissue blocks were cut into 5 µm thick layers by a rotary microtome (RM 2255; Leica Instruments, Nussloch, Germany) and stained with hematoxylin and eosin (H&E). The slides were examined using a light microscope (Olympus BX51, Olympus, Tokyo, Japon) and with Olympus DP 71 microscope camera. All histopathological analysis was performed by 2 different specialists blinded to the study groups. The scoring method described by Houghton et al[16] was performed for the histopathological examination of proximal tubules under light microscopy:

Grade 0 = No desquamated or necrotic tubule,
Grade 1 = less than 1% of the tubuli desquamated,
Grade 2 = 1%-50% of tubuli desquamated or necrotic,
Grade 3 = necrosis in more than 50% of tubuli but intact tubuli are also present,
Grade 4 = necrosis present in 100% of tubuli.

At least 100 proximal tubules of left kidneys in each rat were evaluated for scoring.[16]

Terminal deoxynucleotidyl Transferase deoxyuridine Triphosphate Nick End Labeling Staining

Sections were stained using In situ Cell Death Detection kit POD (11 684 817 910, Roche Diagnostics, Mannheim, Germany). The number of triphosphate nick-end labeling (TUNEL)-positive tubular cells were counted in 20 nonoverlapping random cortical fields under 400× magnifications.[17] The apoptotic index (AI) was calculated using the formula AI = number of TUNEL positive tubular cells/total number of cells × 100.[10]

Statistical Analysis

We performed nonparametric analysis (because most of the variables were not normally distributed). Results were presented as median (min-max). A Kruskal–Wallis test and Mann–Whitney *U*-test were used in order to compare continuous data (serum creatinine, BUN levels and tissue SOD, CAT, GPx, MDA levels) of the groups using a computer-assisted program by Statistical Package for Social Sciences (SPSS) software version 23 licensed to our University. (SPSS Inc., Chicago, Ill, USA). The categorical data (histopathological score percentages) of the groups were compared by using the chi-square test. $P < .05$ was considered to be statistically significant.

RESULTS

Serum AK levels were not determined. During the 3-day experiment period, 1 rat in AK group, 6 rats in the AK+HPE group, and 1 rat in the HPE group were found dead. Etiologies of deaths were not identified as autopsies could not be performed. So the experiment was reperformed with new rats (n = 7 for the SP group, n = 8 for the AK group, n = 9 for the AK+HPE group, n = 6 for the HPE group).

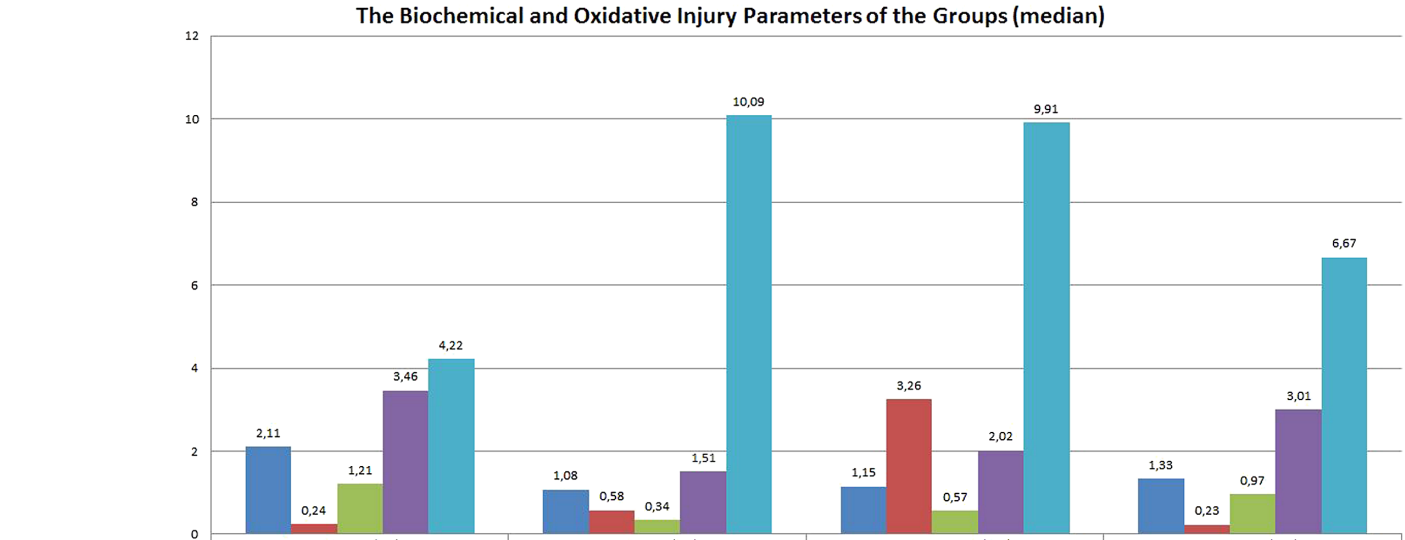
Kidney Functions

Serum BUN and creatinine levels were significantly higher in the AK+HPE group than in other groups (presented in Table 1). Serum BUN and creatinine levels of the AK group were higher than SP and HPE groups. There was no statistical difference between the SP and HPE groups regarding BUN and creatinine levels.

Table 1. The Biochemical and Oxidative Injury Parameters of the Groups (Median; Min-Max)

Variables	SP Group (n = 7)	AK Group (n = 8)	AK+HPE Group (n = 9)	HPE Group (n = 6)
Serum BUN (mg/dL)	17 (15-18)^{z,q}	42.5 (26-92)^{x}	161 (19-325)^{y}	16.5 (13-27)
Serum creatinine (mg/dL)	0.24 (0.19-0.27) ^{a}	0.58 (0.37-1.23)^{b}	3.26 (0.37-7.33)	0.23 (0.17-0.33)^{c}
Tissue GSH-P_x (units/mg protein)	1.21 (1.04-1.74)^{d,e}	0.34 (0.26-0.52)^{f}	0.57 (0.01-0.74)^{g}	0.97 (0.83-1.21)
Tissue MDA (nmol/mg protein)	4.22 (3.42-5.11)^{h,i,j}	10.09 (8.66-11.82)^{k}	9.91 (9.53-10.76)^{l}	6.67 (6.45-6.96)
Tissue CAT (units/mg protein)	3.46 (2.97-3.63)^{m,n}	1.51 (1.31-1.64)^{0}	2.02 (1.12-2.17)^{p}	3.01 (2.61-3.16)
Tissue SOD (units/mg protein)	2.11 (2.06-2.31)^{r,s}	1.08 (0.87-1.21)^{t}	1.15 (0.80-1.28)	1.33 (1.29-1.56)

Significant differences between the groups:
$^{z}P < .05$ between groups SP and AK; $^{q}P < .01$ between group SP and group AK+HPE; $^{x}P < .05$ between groups AK and HPE; $^{y}P < .01$ between groups AK and AK+HPE; $^{a}P < .01$ between group SP and group AK+HPE; $^{b}P < .01$ between groups AK and AK+HPE; $^{c}P < .01$ between groups HPE and AK+HPE; $^{d}P < .0001$ between groups SP and AK; $^{e}P < .0001$ between groups SP and AK+HPE; $^{f}P < .0001$ between groups AK and HPE; $^{g}P < .01$ between group AK + HPE and HPE; $^{h,i,j}P < .0001$ between groups SP and AK; AK+HPE and HPE respectively; $^{k}P < .0001$ between groups AK and HPE; $^{l}P < .0001$ between groups AK+HPE and HPE; $^{m,n}P < .0001$ between groups SP and AK and AK+HPE respectively; $^{o}P < .0001$ between groups AK and HPE; $^{p}P < .0001$ between groups AK+HPE and HPE; $^{r}P < .0001$ between groups SP and AK; $^{s}P < .01$ between groups SP and AK+HPE; $^{t}P < .05$ between groups AK and HPE. SP, serum physiologic; AK, amikacin; HPE, *H. perforatum* extract.



	SP group (n:7)	AK group (n:8)	AK+HPE group (n: 9)	HPE group (n: 6)
Tissue SOD (units/mg protein)	2,11	1,08	1,15	1,33
Serum creatinine (mg/dL)	0,24	0,58	3,26	0,23
Tissue GSH-PX (units/mg protein)	1,21	0,34	0,57	0,97
Tissue CAT (units/mg protein)	3,46	1,51	2,02	3,01
Tissue MDA (nmol/mg protein)	4,22	10,09	9,91	6,67

Figure 1. The biochemical and oxidative injury parameters of the groups (median).

Oxidative Parameters

Kidney MDA levels were lowest in the SP group and highest in AK and AK+HPE groups compared to the others (Table 1 and Figure 1). Malondialdehyde levels of the HPE group were significantly higher than the SP group and lower than AK and AK+HPE groups. No significant difference was found between SP and HPE groups with regard to kidney CAT levels. The CAT levels were lower in the AK group than the others, the AK+HPE group had CAT levels higher than the AK group and lower than SP and HPE groups. The GPX levels of AK and AK+HPE groups were significantly lower than SP and HPE groups. The AK group had significantly lower SOD levels than SP and HPE groups and the SP

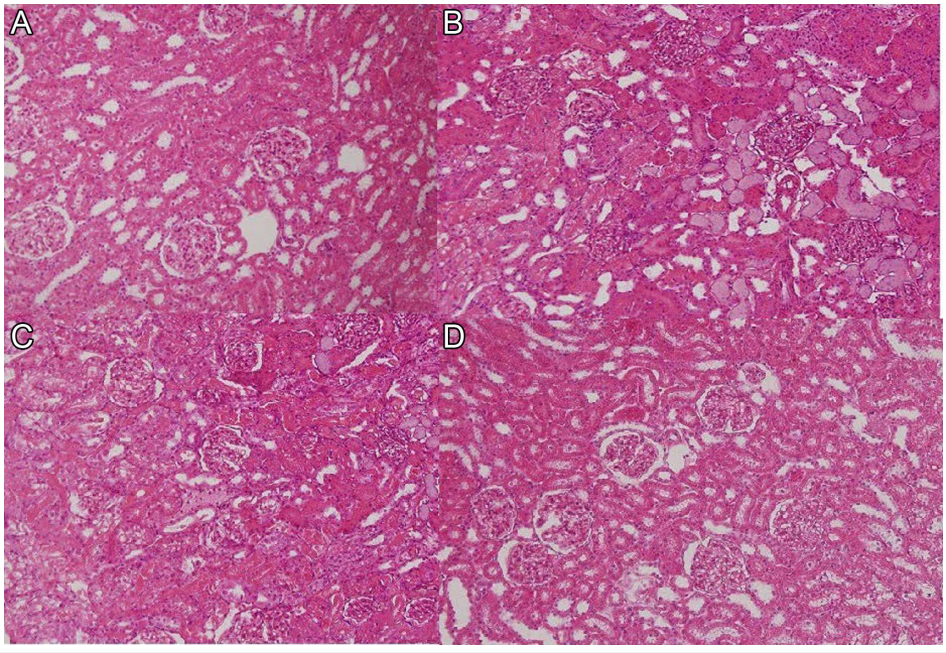


Figure 2. (a). The SP group: Normal corticotubular structure. H&E, ×200. (b). AK group: Kidney sections showing tubular granulovacuolar degeneration and necrosis. H&E, ×200. (c). AK+HPE group: Grade 3 tubular granulovacuolar degeneration and necrosis. H&E, ×200. (d). The HPE group: Minimal focal tubular granulovacuolar epithelial degeneration. H&E, ×200. SP, serum physiologic; AK, amikacin; HPE, *H. perforatum* extract.

Table 2. Histopathological Grades of the Groups (Percentages of Proximal Tubules)

Groups	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
SP	85.7	14.3	0	0
AK	0	12.5	87.5	0
AK+HPE	0	0	44.4	55.6
HPE	16.7	83.3	0	0

SP, serum physiologic; AK, amikacin; HPE, *H. perforatum* extract.

group had significantly higher SOD levels than AK and AK+HPE groups.

Kidney Histopathology

No damage was seen in 85.7% proximal tubules belonging to the SP group and 16.7% of the HPE group (Figure 2a). There was grade 1 damage in 14.3% of the SP group's tubules, 12.5% of the AK group's, and 83.3% of the HPE group's (Figure 2d). Grade 2 damage was found in 87.5% of AK group's and 44.4% of AK+HPE group's (Figure 2b). There was grade 3 damage in 55.6% of AK+HPE group's (Figure 2c). Grade 3 damage was not observed in the rest of the groups. Proximal tubular tissue damage was observed in all of the rats in AK and AK+HPE groups (Table 2). However, no statistical analysis could have been performed as the distribution of scores in groups was inappropriate for analysis.

Triphosphate Nick-End Labeling Staining

We found significantly fewer TUNEL-positive-stained cells in tubular epithelial cells in the SP group (19 ± 4.5) than the other groups (77 ± 5.4, 44 ± 6.3, 28 ± 2.9 for AK, AK+HPE, and HPE groups, respectively). All the groups were statistically different from each other with respect to apoptotic index (AI) ($P < .0001$). Apoptotic index of the AK group was found in the highest level of the groups. Representative TUNEL stained sections were illustrated in Figure 3a-d.

DISCUSSION

Amikacin is one of the most commonly used antibiotics which are given to patients with serious multi-drug resistant gram-negative bacterial infections or allergy to beta-lactams.[1,2] Tubular toxicity, which is the main mechanism of kidney toxicity, occurs nearly 25% of patients and limits the effectiveness and usage of these groups of drugs. Drug-induced kidney toxicity might result in acute loss of kidney functions leading to patients' morbidity (progression to chronic kidney disease) and mortality.[3,4] We demonstrated AK-related toxicity in the kidneys of the AK group both biochemically and histologically which was mostly due to oxidative injury and induction of apoptosis (Tables 1 and 2). Apoptotic index was increased in this group (77 ± 5.4) which was the highest among the groups. Malondialdehyde levels of the AK group were significantly higher in addition to a destructive appearance in histopathology showing AK-induced tissue injury caused by oxidative reactions, too.[7,18,19]

Hypericum perforatum extract with potent anti-oxidant, anti-inflammatory, anti-cancerogenic, and antidepressant, anti-anxiete, antiviral, tissue-healing, and anti-inflammatory properties may be useful in therapy of illnesses.[20,21] *Hypericum perforatum* extract may be used alone or with

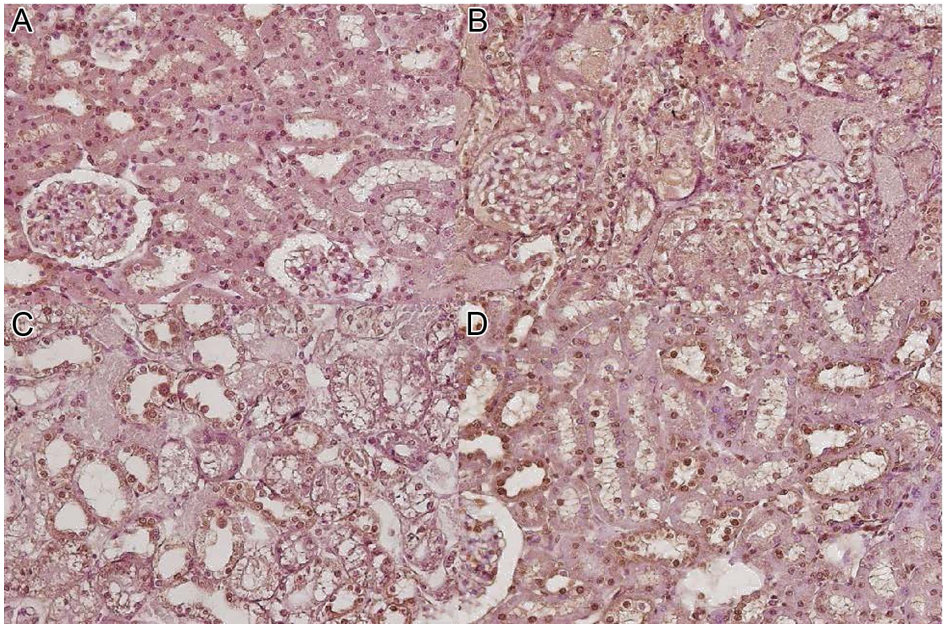


Figure 3. (a). SP group: Very few TUNEL-positive apoptotic cells, ×400. (b). AK group: TUNEL positive apoptotic cells, ×400. (c). AK+HPE group: TUNEL positive apoptotic cells with brown nuclei, ×400. (d). HPE group: TUNEL positive apoptotic cells, ×400. SP, serum physiologic; AK, amikacin; HPE, *H. perforatum* extract; TUNEL, triphosphate nick-end labeling.

other supplements for this purpose.[22] *Hypericum perforatum* extract contains naphthodianthrones (hypericin, pseudohypericin, protohypericin, cyclopseudohypericin), flavonoids (quercetin, luteolin), hyperforin, tannins, xanthone derivatives, and biapigenin.[6,20] Antioxidant efficiency by scavenging of free radicals, reduction of lipid peroxidation, stimulation of signal transducers may be the result of these compounds.[23,24] Zou et al[25] conducted a study reporting the reduction in the hydroxyl (OH) radical production by HPE. In another study, amyloid β-induced neurotoxicity and oxidative damage were reported to be reduced by hyperphorinin.[26] It was also shown that HPE lowered free radical production and lipid peroxidation.[27] Likewise, HPE was demonstrated to decrease ischemia-reperfusion injury and cisplatin toxicity in kidneys.[6,7] In our study, only HPE-given rats had significantly higher MDA levels showing oxidative injury, histopathologically higher injury scores and significantly more apoptotic cells than SP group ($P < .0001$). We found that HPE had more oxidative and apoptotic effects on rat kidneys than SP. Our findings do not support the study of Abd El Motteleb DM and Abd El Aleem DI.[20] Even, our results refute these researchers' claims. However, these researchers gave *Hypericum perforatum* by gavage. In their study, HPE was given by gavage. This substance may have been selectively absorbed from the intestines when applied via the gavage method and had an antioxidant effect. In our study, this substance may be thought to cause oxidative damage since it is administered intraperitoneally. We prepared the extract as Cakir et al[6] and administered the rats intraperitoneally at a dose of 50 mg/kg. Cakir et al[6] reported increased levels of BUN, Cre, and kidney tissue MDA and decreased levels of SOD, CAT, and GSH-P_X enzymes in the ischemia/reperfusion (I/R) group, compared to the control group (*P*/R.05). Also, they reported that in the I/R+HPE group, the levels of MDA reduced significantly, while the SOD, CAT, and GSH-P_X activity increased compared to the I/R group (*P* ac.05).[6] Another study showed that the level of the MDA increased, while decreased levels were observed in SOD, CAT, and GSH-PX enzyme in the I/R group than in the control group.[28] Likewise, in the present study, while the SOD, CAT, and GSH-P_X enzyme levels were lower in the AK group, the MDA levels were increased compared to the control group. But, in the AK+HPE group, the CAT, SOD, and GSH-PX enzyme levels and MDA levels were all higher than those in the AK group. These findings show that HPE increases oxidative and anti-oxidative enzyme levels caused by AK-induced kidney disease.

There are studies in which HPE was reported to attenuate tubular toxicity in cisplatin and ischemia-reperfusion-induced kidney injury and diabetic kidney disease models in rats.[6,20,29] We discovered that HPE-pretreated AK-given rats had significantly higher serum BUN (156 ± 117 mg/dL) ($P = .044$) and creatinine levels (3.17 ± 2.47 mg/dL) ($P = .006$) than only AK-given group (50.50 ± 22.9; 0.69 ± 0.28 mg/dL, respectively). Histopathologically injury scores were also higher in HPE-pretreated AK group. These histological and biochemical results were obtained even though fewer apoptotic cells were counted in HPE-pretreated AK-given group than in only AK-injected rats. So we can make inferences that HPE decreased apoptosis induction but increased necrosis caused by AK. As far as we know, there is 1 study reporting different effects (both protective at a low dose and damaging at a high dose) of HPE on unilateral ureteral obstruction.[30] As a result, this increased tubular toxicity of AK with HPE might have been due to the effects of dose differences and route of administration.

Extracts of *Hypericum perforatum* (St John's Wort) may result in alterations in serum drug levels such as cyclosporine, antidepressants, theophylline, digoxin, indinavir, phenprocoumon, and irinotecan due to induction of cytochrome P450 enzyme system and transport protein P-glycoprotein.[31] The interaction of HPE with AK is not known so far. That is why we researched the usage of HPE together with AK. It would have been better if serum AK levels were searched in our study.

Limitations of the present study are as follows: AK levels of the groups were not searched, and comparisons of the effects for intraperitoneal versus gavage route HPE applications were not made.

CONCLUSION

In the present study, HPE did not protect but on the contrary increased the AK-induced necrosis. The possible mechanism might be alteration of the AK levels by HPE. Kidney toxicity of HPE-pretreated AK group might have occurred because of toxic levels of AK due to interaction with HPE. Further research will enlighten the interaction of AK levels with HPE usage. Since then, we do not recommend the usage of *Hypericum perforatum,* especially via i.p. route together with AK.

Ethics Committee Approval: This research was supported by the Karadeniz Technical University Scientific Research Fund. Study protocol was accepted and performed according to the guidelines of the University Animal Ethics Committee (Date: December 14, 2017, Decision No: 2017/41).

Informed Consent: No human participants were included. Animals used in our study were taken from the University Research Center where our experiments were performed. The research center manager was completely informed about our protocol.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.K.K., R.A., E.Y.; Design – R.K.K., R.A., E.Y.; Supervision –R.K.K., R.A., E.Y., N.D., O.K., Ş.A., S.Ö.Ş., U.Ö., S.A.; Resources – R.A., N.D., Ş.A., U.Ö., S.A.; Materials – N.D., O.K., Ş.A., S.Ö.Ş., U.Ö., S.A.; Data Collection and/or Processing – R.A., E.Y., U.Ö.; Analysis and/or Interpretation – G.Ç.; Literature Search – R.K.K., R.A., E.Y.; Writing Manuscript – R.K.K., R.A., E.Y., U.Ö.; Critical Review – R.K.K., R.A., E.Y., U.Ö.

Declaration of Interests: The authors have no conflicts of interest to declare.

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