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The Protective Efficacy of Curcumin and *Nigella sativa* Herbals on Hepato-renal Toxicities Induced by Amikacin

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Abstract

ALTHOUGH AMINOGLYCOSIDES like amikacin have strong antibacterial properties, they also cause nephrotoxicity and hepatotoxicity. The point of this study was to find out how well curcumin (CR) and Nigella sativa (NS) herbal extracts protected rats from the liver and kidney damage that amikacin (AK) caused. The study involved 35 adult male albino rats, which were randomly and equally divided into 7 groups. Group 1 (G1) rats were injected intraperitoneally (IP) with normal saline and served as the negative control. In Group 2, rats were intraperitoneally injected with a dosage of 25 mg/kg body weight of AK for a duration of 7 days. In Group 3, rats were orally administered a dosage of 2 ml/kg body weight of NS daily for a duration of 14 days. Besides, in group 4, rats were orally administered a dosage of 200 mg/kg body weight of CR daily for a duration of 14 days. In group 5, rats were given NS one hour prior to AK treatment, but in group 6, rats were given CR one hour prior to AK administration. In group 7, rats were given both NS and CR one hour before AK treatment. The obtained results demonstrated elevated serum levels of ALT, AST, urea, creatinine, and malonaldehyde (MDA) in the AK groups. However, the levels of these markers significantly decreased when the rats were administered NS, CR, or a combination of both. The histological characteristics of the liver and kidney were enhanced following the administration of NS, CR, or a combination of both. Ultimately, the use of both CR and NS plays a defensive function in safeguarding the liver and kidney from the detrimental consequences of AK.

Keywords: Amikacin, curcumin, Nigella sativa, nephrotoxicity, hepatotoxicity

Introduction

Aminoglycosides are highly effective antibiotics against bacteria, particularly those that require oxygen and are gram-negative. They also work together with other antibiotics to control certain gram-positive bacteria [1, 2]. Amikacin is a semisynthetic derivative of kanamycin among aminoglycosides [3]. Amikacin has a significant advantage over other aminoglycosides in that it is resistant to aminoglycoside inactivating enzymes. As a result, it is employed in circumstances where gentamicin resistance is present [4]. Amikacin has several positive effects, including strong antibacterial properties, fast action, a low likelihood of resistance, and the ability to work well with β-lactam antibiotics. Additionally, it is a cost-effective option.

It is important to note, however, that amikacin also produces free oxygen radicals, which can cause tissue damage such as nephrotoxicity and hepatotoxicity. Furthermore, aminoglycosides have the potential to exhibit toxicity when their levels exceed the therapeutic limit by a small margin [5]. It was also discovered that aminoglycosides, specifically amikacin and tobramycin, had effects on the kidneys, the ears, the liver, and the muscles [6]. Renal damage from aminoglycosides happens when the kidneys are exposed to the drug for a long time. The tubules and glomeruli get damaged [7]. Aminoglycosides bind to negatively charged phospholipids and build up in the lysosomes of tubular cells. This accumulation inhibits lysosome phospholipases, leading to phospholipidosis. This process may cause necrosis [8]. It is known that

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aminoglycosides can damage the liver by increasing the activity of liver enzymes like AST [9]. Aminoglycosides can induce hepatotoxicity by elevating oxidative stress levels. Tissue damage may be caused by aminoglycosides making free radicals and changes in the activity of antioxidant enzymes, according to the hypothesis. Because aminoglycosides change the way liver glycogen phosphorylase works, they lower the amount of glycogen in the liver [10].

Antioxidants are compounds that, in small quantities, prevent or slow down the process of oxidation in a substance [11]. Antioxidant systems either stop the production of reactive oxygen species (ROS), which are linked to the harmful effects of aminoglycosides, or get rid of them before they damage important parts of cells [12]. Therefore, it may be asserted that antioxidants are administered in order to mitigate the adverse effects of antibiotics. Presently, as a result of several detrimental impacts of chemical pharmaceuticals, herbal remedies are commonly employed in the medical field. In recent years, there has been significant interest in the pharmacological actions of plant-derived natural products, such as flavonoids, carotenoids, and steroids. These compounds have gained attention for their antioxidant and hepatoprotective activities [13].

There are numerous herbal formulations with hepato-renal protective activities that can be found worldwide [14]. Curcumin is the predominant and biologically active compound found in turmeric, constituting approximately 2–5% of the spice [15]. It possesses numerous pharmacological and physiological properties, such as reducing inflammation, preventing oxidative damage, inhibiting cancer growth, preventing genetic mutations, preventing blood clotting, reducing fertility, controlling diabetes, combating fungal infections, fighting against protozoal infections, inhibiting viral replication, preventing fibrosis, neutralizing venom, protecting against ulcers, lowering blood pressure, and reducing high cholesterol levels [16].

Nigella sativa enhances the function of antioxidant enzymes such as catalase, glutathione peroxidase, and glutathione-S-transferase. It also works as a scavenger for free radicals [17].

The aim of this study was to find out if curcumin and *Nigella sativa* could protect male albino rats from the adverse effects of amikacin on kidneys and liver.

Material and Methods

Drugs and Chemicals

Amikacin was supplied by SmithKline Beecham an affiliated Co. to GlaxoSmithKline. Each vial contains 500 mg Amikacin sulphate. Amikacin was injected IP once daily at a dose of 25 mg /kg body weight for 7 consecutive days. *Curcuma longa* (Curcumin) powder was purchased from Sigma Chemicals Co. (USA), stored at 2-4° C and protected from sunlight. Curcumin powder was dissolved in 0.5 ml 2% Tween 80 then completed to 10 ml of distilled water. Curcumin at a dose rate of 200 mg/kg body weight was supplied daily via oral route. *Nigella sativa* oil was obtained from El shatby ASH Company and was taken daily at a dose of 2 ml/Kg body weight via oral route.

Experimental design

For this investigation, a total of 35 adult male albino rats weighing 200±10 g were utilized. The animals were obtained from the breeding colony, which is housed at the Animal Facility of the National Organization for Drug Control and Research (NODCAR) in Cairo, Egypt. The animals were divided into seven equal groups and placed in cages. The cages were maintained at a controlled temperature of 23–25 ºC with a humidity level of 60%. The animals were exposed to cycles of 12 hours of light and 12 hours of darkness. They were given two weeks to acclimate to these conditions. The animals were provided with a conventional rat meal and unlimited access to water. Their weights were determined at the start of the experiment. The experiment was carried out following the ethical rules for laboratory animal research set by the Faculty of Veterinary Medicine at Zagazig University, Egypt, under the reference number (ZU-IACUC/2/F/211/2023).

Following the acclimatization period, the animals were randomly assigned to seven groups based on group allocation. Group 1 (negative control): the animals received an intraperitoneal injection of a standard saline solution. Group 2 (AK): The animals received intraperitoneal injections of AK at 25 mg/kg body weight for 7 consecutive days. Group 3 (NS): The animals were administered a daily dose of NS at 2 ml/kg body weight via the oral route for a period of 14 consecutive days. Group 4 (CR): The animals were administered curcumin at a dosage of 200 mg/kg body weight per day for 14 consecutive days via the oral method. Group 5 (AK+NS): The animals were administered Nigella sativa one hour prior to amikacin for a period of 14 consecutive days. Group 6 (AK+CR): The animals were administered curcumin one hour prior to amikacin for duration of 14 consecutive days. Group 7 (AK+NS+CR): The animals were administered *Nigella sativa* and curcumin one hour before receiving amikacin for duration of 14 consecutive days. After the study was completed, samples of serum and tissue were collected for biochemical and histological analysis.

Biochemical tests

Sera were obtained by collecting blood samples from the medial canthus of the eye at the end of the study period. Following euthanasia, liver and kidney

samples were promptly taken from all animals. Sera samples were used to estimate the serum content of urea and creatinine. The levels of serum aspartate and alanine aminotransferase (AST and ALT) enzymes were evaluated using the method described by Reitman and Frankel [18]. The concentration of malondialdehyde (MDA) was also determined following the protocol established by Schattmann [19]. We also looked at the amounts of superoxide dismutase (SOD) and total antioxidant capacity (TAC) in liver and kidney tissues using the methods established before [20-23].

Histopathological analysis

The kidney and liver tissue samples were kept in a 10% neutral buffered formalin solution. They were then dried out using a range of alcohol concentrations, from 70% to 100%. Next, they were cleaned using xylene and then embedded in paraffin. Paraffin slices with a thickness of five microns were made and stained using hematoxylin and eosin (HE) dyes. The stained sections were then viewed under a microscope [24].

Statistical analysis

The data were analyzed using GraphPad Prism 8.0.2 (GraphPad Software, Inc). The findings were presented as the Mean ± Standard Error (SE). The Shapiro-Wilk test was employed to assess the assumption of normality, whereas Bartlett's test was utilized to examine the assumption of homogeneity of variance. The data exhibited a normal distribution and showed homogeneity of variance. A one-way analysis of variance (ANOVA) was conducted to assess the variations among groups in relation to specific parameters under different treatments. The Turkey's honest pairwise comparison test was employed as a post hoc test. A significance level of $P < 0.05$ was used to determine statistical significance.

Results

The levels of ALT, AST, Albumin, Cr, Urea, SOD, TAC and MDA in serum showed highly significant differences between groups ($p < 0.001$) as shown in Tables 1-3. The results revealed that ALT (87.33±4.09), AST (96.67±5.24), and Urea (80.00 ±2.10) levels were the highest in AK-treated groups compared to control and other groups. Moreover, their levels showed a decrease with the addition of NS (AK+NS) or CR (AK+CR) to AK and a marked reduction with the addition of both NS and CR (AK+NS+CR) to AK. On the other hand, ALT, AST and Urea levels where the lowest in NS and CR-treated groups and showed non-significant difference to the control group. Albumin level of NS, CR, AK+NS+CR, and control groups was the highest compared to other groups, while AK and AK+NS are the groups with the lowest albumin level. Cr level was the highest in AK and AK+CR treated groups, while MDA was in its high level in AK and AK+NS groups. Cr and MDA lowest levels were recorded in the control, NS, CR, AK+NS+CR groups. The pattern of SOD and TAC levels in the groups was similar. Their levels were high and did not show a significant difference in the control, NS, and CR groups, while the other treatments make a significant decrease in their levels.

Histologically, in the control group, the liver showed normal histological structure consisting of central vein and hepatocytes attached with other in form of radiation and portal area contain portal vein, hepatic artery and bile duct (Fig. 1 a).

In amikacin-treated group, the liver showed fatty change of hepatocytes with nucleus in the peripheral give signet ring appearance with presence of Kupffer cells (Fig. 1b) and the portal area showed congestion of portal vein with periportal aggregation of mononuclear cell (Fig. 1 b, c and d). In animals received nigella, the liver showed congestion of central vein and hepatic sinusoids and infiltration of few mononuclear cells (Fig. 1 e). In animals received curcumin, the liver showed dilated of central vein and infiltration of few mononuclear cells (Fig. 1f). In animals received amikacin and nigella, the portal area showed congestion and hyalinization in the wall of the portal vein with periportal aggregation of few mononuclear cells (Fig. 1 g). In animals received amikacin and curcumin, the liver showed dilation of central vein and focal aggregation of few mononuclear cells (Fig. 1h). In animals received amikacin and curcumin and nigella, the liver restored its normal histological structure with dilation of central vein (Fig. 1i).

Regarding the kidney tissue, in the control group, it showed normal histological structure consisting of renal tubules and glomeruli (Fig. 2 a). In animals received amikacin, the kidney showed congestion of peritubular capillaries and glomeruli tufts with breakdown of bowman's capsules and hemorrhage between renal tubules with infiltration of mononuclear cells. Focal aggregation of mononuclear cells replaced necrotic renal tubules. Thickening of interstitial tissue by fibrous tissue proliferation and aggregation of mononuclear cells was observed. Few renal tubules showed pyknotic nuclei (Fig. 2b, c and d). In animals received nigella, the kidney showed congestion of renal blood vessel and glomeruli tufts (Fig. 2 e). In animals received curcumin, the kidney showed congestion and hyalinization in the wall of renal blood vessels with perivascular edema (Fig. 2f). In animals received amikacin and nigella, the kidney showed focal aggregation of few mononuclear cells replaced few necrotic renal tubules with congestion of peritubular capillary (Fig. 2 g). In animals received amikacin and curcumin, the kidney showed congestion of renal blood vessel and perivascular aggregation of few mononuclear cells (Fig. 2h). In animals received amikacin and curcumin and nigella, the kidney

restores of its normal histological structure with congestion of peritubular capillary (Fig. 2i).

Discussion

Aminoglycoside has been widely employed for antibacterial treatment. Although aminoglycosides have therapeutic advantages, they have detrimental effects on the kidneys and liver [25]. In the AK group of our study, higher levels of serum urea and creatinine were seen, along with higher levels of MDA in the kidneys and lower levels of GSH, SOD, and TAC. This shows that the kidneys aren't working as well as they should. The same outcomes were documented [26]. The sharp rise in serum aminotransferase (ALT and AST) levels, along with higher oxidative stress (MDA) and lower antioxidant capacity are clear signs that AK is damaging the liver, which is in line with what other studies have found [27, 28]. Amikacin can generate free radicals that have the ability to damage biological proteins, lipid membranes, and DNA. This can lead to many harmful effects, such as hepato-renal damage [29]. Damage to the liver and kidneys by AK is due to lower levels of glutathione inside cells, damage to the mitochondria, and oxidative stress from free radicals [27, 30].

Aminoglycosides, such as amikacin, can have several negative effects. Patients may experience acute renal failure, which is characterized by elevated levels of blood creatinine and urea, as well as decreased urine output and urine creatinine clearance [31]. Doğan et al. [26] and Kara et al. [32] both found that AK can damage the kidney tissue, causing glomerular damage, tubular necrosis, interstitial inflammation, and an increase in leucocyte infiltration. Possible mechanisms for the development of nephropathy caused by AK include mitochondrial impairment, which leads to an increase in reactive oxygen species (ROS) production as well as a decrease in renal antioxidant molecules such as GSH, SOD, GPx1, and CAT. This imbalance promotes the formation of free radicals, lipid peroxides, and protein adducts, which in turn cause damage to renal cells. These mechanisms have been suggested by Kara et al. [32], Selim et al. [33], and Bulut et al. [34]. It is also thought that oxidative stress in the kidneys causes inflammation by increasing the production of cytokines that cause inflammation (like IL-1β, IL-6, TNF-α, HSP25, and TLR4) while decreasing the production of IL-10, a powerful molecule that fights inflammation [35-37]. These results are similar to those of many other studies that have shown that oxidative stress and inflammation play a big role in how AK damages the kidneys [32-35].

Some signs of kidney and liver damage went down after NS therapy was given. This was because the therapy decreased lipid peroxidation in the tissues. In a previous study conducted by Bayoumi et al. [38], it was found that NS therapy resulted in an elevation in active glutathione levels and hepatorenal antioxidant enzymes. *Nigella sativa* includes thymoquinone, which is an active antioxidant, along with various other volatile oils and thymol. Earlier studies have shown that NS can protect against and fight free radicals caused by chemicals, medications, and foreign substances [38, 39].

Curcumin has many unique properties, such as the ability to fight tumors, reduce inflammation, prevent blood clots, lower cholesterol, protect nerves and the heart, change lipid levels, relieve pain, and fight rheumatism [40].

Preclinical investigations have demonstrated the beneficial effects of curcumin on renal disorders [41]. Furthermore, clinical trials have evaluated the impact of these medicinal herbs on renal illnesses [42, 43].

According to the report, curcumin decreased MDA levels and enhanced CAT activity. Furthermore, the study conducted by Pakfetrat et al. [44] revealed an elevation in serum albumin levels. The study conducted by Vanaie et al. [45] found that administering curcumin supplements to diabetic individuals with overt albuminuria for 16 weeks led to a significant decrease in albuminuria compared to the placebo group.

Supplementation of curcumin or turmeric did not have any notable impact on the lipid profile, as observed in studies conducted before [42, 44, 45]. However, one study by Ortiz et al. [46] found that a 12-week treatment with curcumin and resveratrol resulted in reduced levels of triglycerides, very low-density lipoprotein (VLDL), and cholesterol compared to a placebo. The levels of fasting blood sugar (FBS) and hemoglobin A1C (HbA1c) did not show any changes following the administration of curcumin/turmeric treatment, as reported before for FBS [43, 45], and for HbA1c [42, 45]. Also, the liver function tests, which measured ALT and AST, didn't change in the research groups after they took curcumin and turmeric supplements, as reported before [47].

In this investigation, the administration of both NS and CR might decrease AK-induced oxidative stress. This can occur either directly by lowering lipid peroxidation and scavenging free radicals, or indirectly by increasing the enzymatic activities of the antioxidants SOD and TAC.

Conclusion

The hepatoprotective effect of AK was significantly reduced by the antioxidant effect of NS or CR. When the two antioxidants work together, they make the synergistic antioxidant and hepato-renal toxicity-relieving effects stronger.

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Conflicts of interest

The authors declared no competing interests.

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Authors' contribution:

All authors contributed equally to the present study.

TABLE 1. Effects of AK, NS, and CR on some kidney parameters in different groups.

	Cr	Urea
Control	0.97±0.12^{cd}	33.00±1.73^{d}
AK	2.87±0.12^{a}	80.00±2.10^{a}
NS	0.76±0.12^{d}	35±0.58^{d}
CR	0.93±0.14^{cd}	35.67±3.18^{d}
AK+NS	2.00±0.06^{b}	64.67±3.29^{b}
AK+CR	2.37±0.31^{ab}	63.00±3.52^{b}
AK+NS+CR	1.7±0.12^{bc}	50.67±0.67^{c}
P-Value	< 0.0001	< 0.0001

^{abcde} Means within same column with different superscript are statistically different at P<0.05 according to Tukey's Honesty significant test.

TABLE 2. Effects of AK, NS, and CR on some liver parameters in different groups.

Groups	ALT	AST	Albumin
Control	18.33±2.03^{d}	26.00±3.61^{de}	3.80±0.16^{a}
AK	87.33±4.09^{a}	96.67±5.24^{a}	2.8±0.06^{c}
NS	22.33±1.45^{d}	21±2.31^{e}	3.87±0.12^{a}
CR	21.33±1.86^{d}	26.33±3.18^{de}	3.8±0.06^{a}
AK+NS	68.00±2.65^{b}	70.33±5.78^{b}	3.13±0.09^{c}
AK+CR	56.67±3.38^{b}	63.00±4.36^{bc}	3.2±0.12^{bc}
AK+NS+CR	40.67±1.21^{c}	46.33±6.89^{cd}	3.67±0.07^{ab}
P-Value	< 0.0001	< 0.0001	< 0.0001

^{abcde} Means within same column with different superscript are statistically different at P<0.05 according to Tukey's Honesty significant test.

TABLE 3. Effects of AK, NS, and CR on oxidant and antioxidant parameters in different groups.

Groups	MDA	SOD	TAC
Control	2.89±0.12^{c}	107±4.36^{a}	23.67±2.72^{ab}
AK	8.39±0.61^{a}	50.33±3.84^{c}	10.33±0.88^{c}
NS	2.77±0.11^{c}	110.67±3.48^{a}	23.67±2.028^{ab}
CR	2.84±0.08^{c}	113±3.51^{a}	26.33±2.19^{a}
AK+NS	7.58±0.48^{a}	61.67±1.45^{bc}	15.33±1.45^{bc}
AK+CR	5.71±0.25^{b}	69±3.79^{bc}	16.33±1.76^{bc}
AK+NS+CR	4.1±0.11^{c}	80.67±6.39^{b}	17.33±0.88^{bc}
P-Value	< 0.0001	< 0.0001	< 0.0001

^{abcde} Means within same column with different superscript are statistically different at P<0.05 according to Tukey's Honesty significant test.

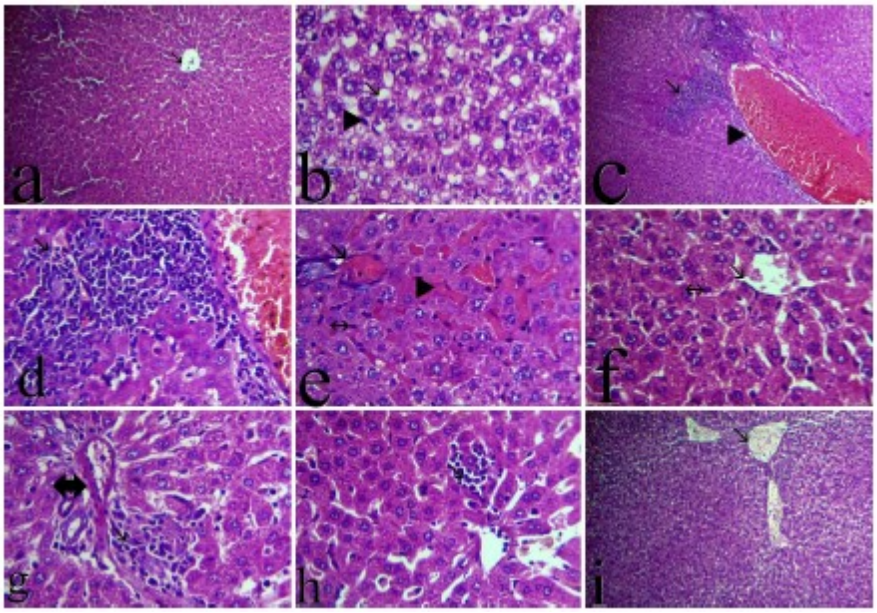

Fig.1. Photomicrograph of liver stained with HE, G1 a: central vein (arrow) x300. G2 (b-d): b: fatty change (arrow) kupffer cells (arrow head) x1200. c: congestion of portal vein (arrow head) focal aggregation of leukocytes(arrow)x300. d: high power of previous figure (c) to show mononuclear cells (arrow)x1200. G3 e: congestion of central vein (arrow) congestion of hepatic sinsoidues (arrow head) mononuclear cells (arrow with 2 head) x1200. G4 f: dilation of central vein (arrow) mononuclear cells (arrow with 2 head) x1200. G5 g: congestion and hyalinization in the wall of the portal vein (arrow with 2head) aggregation of few mononuclear cells (arrow) x1200. G6 h: aggregation of few mononuclear cells (arrow) x1200. G7 i: dilation of central vein (arrow) x300.

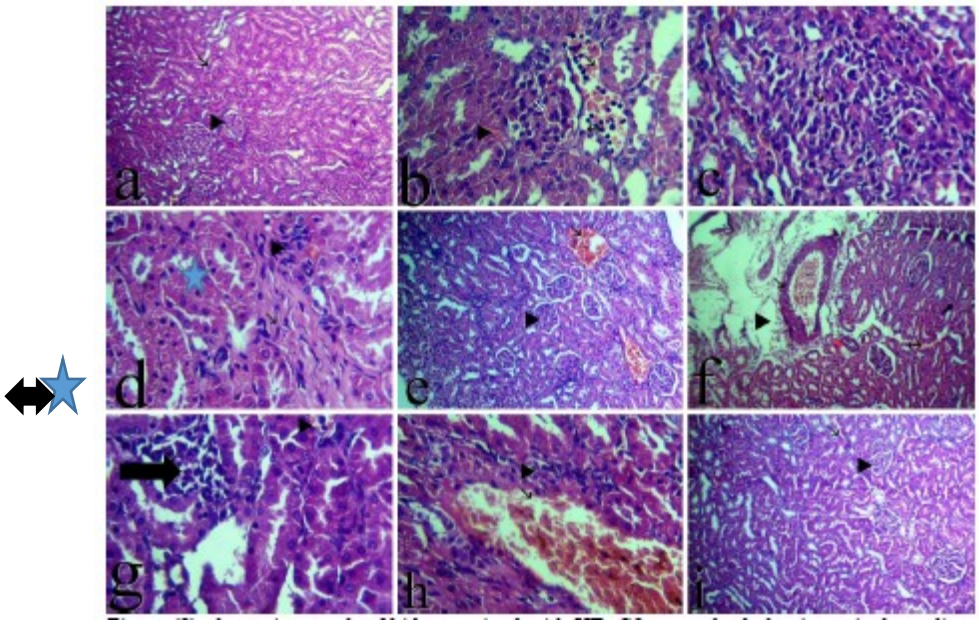

Fig.2. Photomicrograph of kidney stained with HE. G2 a: renal tubules (arrow) glomurli (arrow head)x300. G2 (b-d): b: hemorrhage (black arrow) congestion of peritubular capillary (arrow head) congestion of glomurli tuft (white arrow) mononuclear cells (arrow with 2head) x1200. c: Focal aggregation of mononuclear cells (arrow)x1200. d: fibrous tissue proliferation (arrow) aggregation of mononuclear cells (arrow head) pyknotic nuclei (blue star)x1200. G3 e: congestion of renal blood vessel (arrow) congestion of glomruli tuft s (arrow head) x300. G4 f: congestion and hyalinization in the wall of renal blood vessels (arrow) perivascular edema (arrow head) x300. G5 g: congestion of peritubular capillary (arrow head) focal aggregation of few mononuclear cells (arrow)x1200. G6 h: congestion of renal blood vessel (arrow) aggregation of few mononuclear cell (arrow head)x1200. G7 i:normal glomurli (arrow head) congestion of peritubular capillary (arrow) x300.

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الفعالية الوقائية للكركمين والأعشاب السوداء (حبة البركة) ضد السمية الكبدية والكلوية الناتجة عن الأميكاسين

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الملخص

على الرغم من أن الأمينوغليكوزيدات مثل الأميكاسين تتمتع بخصائص مضادة للبكتيريا قوية، إلا أنها تسبب أيضًا سمية كلوية و كبدية. كان الهدف من هذه الدراسة هو معرفة مدى فعالية مستخلصات الكركمين وحبة البركة في حماية الفئران من الأضرار التي تسببها الأمينوجليكوزيد أميكاسين على الكبد والكلى. شملت الدراسة 35 من ذكور الفئران البيضاء البالغة، التي تم تقسيمها عشوائيًا وبشكل متساوٍ إلى 7 مجموعات. تم حقن الفئران من المجموعة 1 داخل الصفاق بمحلول ملحي عادي واستخدمت كعينة تحكم سلبية. في المجموعة الثانية، تم حقن الفئران داخل الصفاق بجرعة قدرها 25 ملغ/كغ من وزن الجسم من الأميكاسين لمدة 7 أيام. في المجموعة 3، تم إعطاء الجرذان عن طريق الفم جرعة مقدارها 2 مل/كغ من وزن الجسم من حبة البركة يوميًا لمدة 14 يومًا. بالإضافة إلى ذلك، في المجموعة الرابعة، تم إعطاء الجرذان عن طريق الفم جرعة مقدارها 200 ملغ/كغ من وزن الجسم من الكركمين يوميًا لمدة 14 يومًا. في المجموعة 5، تم إعطاء الجرذان محلول حبة البركة قبل ساعة من علاج الأميكاسين ، بينما في المجموعة 6، تم إعطاء الجرذان محلول الكركمين قبل ساعة من إعطاء الأميكاسين في المجموعة 7، تم إعطاء الفئران كل من حبة البركة و الكركمين قبل ساعة من العلاج بالأميكاسين أظهرت النتائج المستخلصة ارتفاع مستويات السيروم لانزيمات الكبد واليوريا والكرياتينين والمالونالديهايد في مجموعات الأميكاسين ومع ذلك، انخفضت مستويات هذه المؤشرات بشكل ملحوظ عندما تم إعطاء الجرذان محلول حبة البركة أو الكركمين ، أو مزيج من كلاهما. تم تعزيز الخصائص النسيجية للكبد والكلى بعد إعطاء محلول حبة البركة أو الكركمين أو مزيج من كلاهما. في النهاية، يلعب استخدام كل من الكركمين وحبة البركة وظيفة دفاعية في حماية الكبد والكلى من العواقب الضارة للأميكاسين

الكلمات الدالة: الاميكاسين ، الكركمين ، حبة البركة ، السمية الكبدية والكلوية.