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RESEARCH ARTICLE

Protective Effect of Krill Oil Against Gentamicin Induced Oxidative Stress Mediated Nephrotoxicity in Rats

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ABSTRACT

This study aimed to evaluate the protective effect of krill oil against nephrotoxicity caused by gentamicin. Distilled water was given orally to the control and second groups (GI) for seven days while 500 mg/kg krill oil was given to the third (GII), fourth (GIII) groups. In addition, isotonic saline was administered subcutaneously to the control and GIII groups throughout the study, while 80 mg/kg gentamicin was administered to the GI, and GII groups. Alanine aminotransferase (ALT) and gamma glutamyltransferase (GGT) peptidase, total cholesterol, urea, and creatinine levels in plasma and, malondialdehyde (MDA) and total antioxidant status (TAS) levels in both plasma and kidney tissue supernatant were evaluated. Histopathological changes in tubules and glomeruli and vascular changes were evaluated by scoring. Urea level and ALT activity were found to be significantly lower in the GII and GIII groups compared to the GI group ($p<0.001$; $p\leq0.001$). As a result, it was observed that degenerative damage and glomerular changes in the tubule at the histological level mediated by oxidative stress were consistent with the increase in ALT, urea, and MDA levels. In this respect, it is suggested that krill oil can be used as a nephroprotective food supplement to contribute to treatment in cases of toxicity.
Keywords: Gentamicin, Kidney, Krill oil, Nephrotoxicity, Oxidative stress.

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Sıçanlarda Gentamisin ile İndüklenmiş Oksidatif Stres Aracılı Nefrotoksisiteye Karşı Krill Yağının Koruyucu Etkisi

ÖZ

Bu çalışmada, gentamisin'in neden olduğu nefrotoksisiteye karşı kril yağının koruyucu etkisinin değerlendirilmesi amaçlandı. Çalışmada yedi gün boyunca oral yolla kontrol ve ikinci grubuna (GI) distile su verilirken, üçüncü (GII) ve dördüncü (GIII) gruplarına 500mg/kg krill yağı verildi. Ayrıca çalışma boyunca subkutan yolla kontrol ve GIII gruplarına izotonik tuzlu su uygulanırken, GI ve GII gruplarına 80 mg/kg gentamisin uygulandı. Plazma alanin aminotransferaz (ALT) ve gama glutamiltransferaz (GGT), total kolesterol, üre ve kreatinin düzeylerine, hem plazma hem de böbrek doku süpernatından ise malondialdehit (MDA) ve total antioksidan kapasitesi (TAS) düzeylerine değerlendirildi. Histopatolojik olarak tubul ve glomeruluslardaki değişimler ile damarsal değişiklikler skorlanarak değerlendirildi. Üre düzeyi ve ALT aktivitesi GI gruba göre GII ve GIII verilen grupta anlamlı düzeyde düşük bulundu ($p<0.001$; $p\leq0.001$). Sonuç olarak, oksidatif stres aracılı olarak histolojik düzeyde tubulde dejeneratif hasar ve glomerular değişikliklerin özellikle ALT, üre ve MDA düzeyleri artışıyla uyumlu olduğu görüldü. Bu bakımdan, krill yağı nefroprotektif bir gıda takviyesi olarak toksisite durumlarında tedaviye katkı sağlamak için kullanılabileceği önerilmektedir.
Anahtar kelimeler: Böbrek, Gentamisin, Kril yağı, Nefrotoksisite, Oksidatif stres.

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INTRODUCTION

Aminoglycosides have been used for years in the treatment of diseases in veterinary and human medicine. These antibiotics are especially preferred to treat diseases caused by bacteria resistant to other antibiotics and gram-negative bacilli (Papich and Riviere 2018). Gentamicin, which is included in this class of antibiotics and is widely used in the treatment of important diseases, is one of the causes of drug-induced nephrotoxicity (Randjelovic et al. 2017). Oxidative stress has been recognized as an important contributing factor in some pathogenic processes that affect the kidneys. This leads to the possibility of using antioxidants to prevent nephrotoxicity (Sahnoun et al. 1997, Knight 1998, Acharya et al. 2013). It has been shown that gentamicin increases the formation of reactive oxygen species (ROS) such as hydroxyl radicals and hydrogen peroxides in the kidney cortex and reactive nitrogen species, which eventually lead to structural and functional deterioration in the kidney (Balakumar et al. 2010).

Krill are zooplankton-shaped crustaceans that are especially abundant in the North and South polar seas. Krill is a sustainable source of omega-3 polyunsaturated fatty acids, particularly docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) (Burri and Johnsen 2015). It also contains very effective antioxidants such as krill oil, vitamins (A and E), and astaxanthin (Cicero and Collett 2015). Krill oil causes an anti-inflammatory response due to omega-3 polyunsaturated fatty acids (EPA and DHA) that are found in its structure (Kwantes and Grundmann 2015). The consumption of these fatty acids has been reported to contribute to the treatment and prevention of diseases such as hypertension, diabetes, asthma, depression (Celebi et al. 2017).

Supplementary foods widely used in recent years; have been known to have a protective and preventive effect against most diseases (Halsted 2003, Özden et al. 2021). It is important to find the mechanism or substances that will reduce the nephrotoxicity caused by gentamicin. In this study; nephroprotective effects of krill oil against gentamicin-induced nephrotoxicity have been investigated by evaluating the damages caused by gentamicin after being metabolized and the protective effects of krill oil on the kidney damage were also determined.

MATERIAL AND METHOD

Animals

Twenty-four Sprague-Dawley (8 - 12 weeks old) male rats with an average weight of 180 - 220 grams were used in the study.

Animal Experimental Protocol

The animals used in this study were randomly selected and divided into 4 groups with 6 rats in each. The first group was the control group and was administered sterile distilled water orally and physiological isotonic saline subcutaneously for seven days. In the GI group, sterile distilled water was given orally and 80 mg/kg gentamicin (Gentavet %10®, Vetaş, Turkey) was administered subcutaneously for seven days (Matsushita et al. 2011, Dungca 2016).

The GII and GIII groups were given oral 500 mg/kg krill oil (Krilom® ultra krill oil, Tabilaç, Turkey) for seven days (Yeral et al. 2019). While 80 mg/kg gentamicin was administered subcutaneously to the GII for 7 days, physiological isotonic saline was administered subcutaneously to the GIII. 24 hours after the seventh-day applications; rats were anesthetized [10 mg/kg xylazine (Xylazinbio 2%®, Bioveta, Czech Republic), 90 mg/kg ketamine (Vetaketam®, Vetagro, Poland), intraperitoneal] blood was drawn from Vena cava caudalis. After blood collection, animals were sacrificed and kidney tissue was taken.

Sample Collection and Biochemical Analysis

Blood samples taken from rats were centrifuged at 3000 rpm for 10 minutes at 4 °C, and their plasma was separated. ALT and GGT activities, total cholesterol, urea, and creatinine (Abs, Turkey) levels in plasma were determined with commercial test kits in a spectrophotometer device (Shimadzu UV 1700, Japan).

Distilled water was used to remove the blood and similar residues from the kidney tissue and then washed with cold 0.9% NaCl and dried with gauze for the analysis of oxidative stress parameters. Dried tissues were wrapped in aluminum foils and stored at -80 °C. During preparation for the analysis, the kidney tissue was weighed approximately 0.5 g on a precision balance and 1/10 phosphate buffer (pH 7.4) was added. Firstly kidney tissues were divided into small pieces with a glass teflon homogenizer. Afterward, it was homogenized for 10 seconds on the ice, kept for 30 seconds, and homogenized using an ultrasonic homogenizer 5 times for a total of 50 seconds. Tubes containing homogenate were centrifuged at 13000 rpm for 10 minutes and the supernatants were obtained. MDA levels in plasma and tissue supernatant were determined by the method of Buege and Aust (1978) by measuring in a spectrophotometer device (Shimadzu UV 1700, Japan) at a wavelength of 536 nm. TAS levels in plasma and kidney tissue supernatant were determined with commercial test kits (Rel Assay Diagnostics, Turkey) with a microplate reader (Thermo Scientific™ Multiskan, UK) (Erel, 2005).

Pathological Examinations

Kidneys were examined according to macroscopic evaluation criteria dimension, shape, lesional

distribution, color, texture, and all tissue samples were fixed in 10% buffered formalin for 48 hours. After the fixation, the tissues were treated with graded ethanol and xylol series (Leica, TP1020, Germany) and blocked in paraffin (Leica 1150H, Germany). Five μm thickness sections were cut at rotary microtome (Shandon, AS320, UK). From paraffin blocks, sections were stained according to the hematoxylin-eosin (H&E) staining procedure (Luna 1968) and evaluated under a digital optical light microscope, and images were taken with a camera attachment (Olympus BX51digital microscope, DP25 camera attachment, Japan). For scoring histopathological findings, a number will be obtained by counting 10 fields at 400x magnification (10 HPFs). Counted fields were getting proportioned and stated as a percentage (%). According to density of findings, scores were semiquantitatively performed as (-): no finding 0-10%, (+): mild 10-30%, (++): moderate: 30-50%, (+++) strong: >50%.

Statistical Analysis

Statistical analyzes of the data were performed with the SPSS 25.0 package program (SPSS Inc., Chicago, USA). First of all, to determine the appropriate type of analysis, it was determined whether the data showed a normal distribution (Shapiro-Wilk test). Parametrically distributed parameters (parametric) were analyzed with a one-way ANOVA test, and Duncan's test was performed when F values were significant. In the statistical evaluation, the $p \leq 0.05$ level was accepted as an indicator of significant difference. Data were given as mean+standard error (X+SE).

RESULTS

Biochemical Parameters

Plasma biochemical parameters of the groups were given in Table 1. Plasma GGT activity was numerically decreased in the GII and GIII groups compared to the GI group, but there was no statistical difference ($p>0.05$). ALT activity was found to be significantly lower in the GII and GIII groups compared to the GI group ($p \leq 0.001$). Total cholesterol levels were found to be significantly higher in the GI and GII administered group compared to the control group ($p \leq 0.001$). Plasma urea levels were significantly decreased in the GII and GIII groups compared to the GI and control groups ($p<0.001$). Plasma creatinine levels were found to be increased in the GI and GII groups compared to the control group ($p<0.01$).

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Table 1. Some plasma biochemical parameter levels in rats applied with gentamicin and krill oil (n=6)

Parameters	Control group (C)	Gentamicin group (GI)	Gentamicin + Krill oil group (GII)	Krill oil group (GIII)	p
ALT (U/L)	62.37±4.97^{ab}	71.14±6.76^{a}	56.27±2.80^{b}	39.92±2.47^{c}	≤0.001
GGT (U/L)	6.87±1.35	8.22±0.70	7.65±0.67	7.43±0.58	>0.05
Total Cholesterol (mg/dl)	150.49±12.32^{b}	222.12±20.00^{a}	211.16±9.69^{a}	159.39±4.59^{b}	≤0.001
Urea (mg/dl)	41.29±0.54^{a}	42.01±0.43^{a}	38.94±0.57^{b}	36.62±0.65^{c}	<0.001
Creatinine (mg/dl)	0.51±0.12^{b}	1.03±0.11^{a}	0.99±0.021^{a}	0.76±0.05^{ab}	<0.01

^{a,b,c}: The difference between values with different letters on the same line is statistically significant ($p<0.01$; $p \leq 0.001$; $p<0.001$).

Oxidative Stress Parameters

It was determined that plasma MDA levels increased numerically in the GI group compared to the control group, but there was no statistically significant difference, while it decreased significantly in the GIII group ($p<0.05$). Plasma TAS levels decreased numerically in the GI group compared to the control group, but there was no statistically significant difference ($p>0.05$). Plasma MDA and TAS parameters of the groups are given in Table 2.

Table 2. Plasma MDA and TAS levels in rats applied with gentamicin and krill oil (n=6)

Parameters	Control group (C)	Gentamicin group (GI)	Gentamicin + Krill oil group (GII)	Krill oil group (GIII)	p
MDA (µmol/L)	1.20 ± 0.04[a]	1.27 ± 0.071[a]	1.13± 0.05[ab]	1.03 ±0.017[b]	<0.05
TAS (mmol/L)	0.74±0.08	0.45±0.11	0.61±0.07	0.69±0.07	>0.05

[a,b]: The difference between values with different letters on the same line is statistically significant (p<0.05).

The kidney tissue MDA and TAS parameters of the groups are given in Table 3. It was determined that kidney tissue MDA levels increased numerically in the GI and GII groups compared to the control group, but decreased numerically in the GIII group, but there was no statistically significant difference (p>0.05). There were numerical increases in renal tissue TAS levels in the other groups compared to the control group (p>0.05).

Macroscopical Findings

In GI group, kidneys were congested and swollen. In GII group, kidneys were mottled (integration of both partly hyperemic and pale areas) in appearance. In GIII group and control group, kidneys were normal in appearance at all animals.

Table 3. Renal tissue MDA and TAS levels in rats applied with gentamicin and krill oil (n=6)

Parameters	Control group (C)	Gentamicin group (GI)	Gentamicin + Krill oil group (GII)	Krill oil group (GIII)	p
MDA (µmol/g-wet tissue)	**6.02 ± 0.66**	**9.77 ± 3.45**	**7.06± 0.88**	**5.32 ±0.55**	**>0.05**
TAS (mmol/g wet tissue)	**1.11±0.21**	**1.25±0.09**	**1.36±0.07**	**1.44±0.18**	**>0.05**

Histopathological Findings

In the control (C) group, the only vasculature changes including hyperemic vessels were observed in a few areas in all cases. In GI group, degenerative and necrotic tubules were encountered in many fields. Tubule cells included cytoplasmic vacuolation, which was not stained. Some of the cells were karyopyknotic and/or karyolytic in appearance. Glomerular podocytes were hyperplastic and active. Bowmann capsules were filled and the glomerular bodies were enlarged in many fields in all cases of this group. There were a few macrophage and lymphocyte infiltration in a case. While there was no infiltration in other cases. Hyperemic vessels and vasculature changes including, the fullness of erythrocyte, vessel enlargement, and perivascular edema were common in every field in all cases. There were neither fibrotic changes nor inflammation apart from one case. The case was commented irrelatively from gentamicin toxicities.

In GII group, tubular degeneration was milder than GI group. There was no necrosis in tubule epitheliums apart from one case. The cases included necrosis in a few tubules in a restricted microscopical field. Glomerular reactions including podocyte activation, filling of Bowman capsule, etc. were milder. However, hyperemic vessels were common in every field as being in the previous GI group. Inflammation and fibrosis were not developed in any cases.

In GIII group, tubular degeneration was milder than being in the previous group. There were no necrotic changes in tubule epitheliums. Inflammation and fibrosis were not encountered in all cases. Glomerular reactions were almost the same as being GII group. Hyperemic vessels were common in five cases of this group. The vasculature reaction was milder when compared with previous groups. Semiquantitative scores in kidney histopathology according to experimental groups were illustrated in Table 4. Histopathological findings of experimental groups were illustrated in Figure 1.

Table 4. Semiquantitative scores in kidney histopathology according to experimental groups (n=6)

	Control group (C)	Gentamicin group (GI)	Gentamicin + Krill oil group (GII)	Krill oil group (GIII)
Glomerular reaction Podocytes	-(6/6)	+/++(1/6) ++(6/6)	-(2/6) -/+(2/6) +(2/6)	-(3/6) + (2/6) +/++(2/6)
Glomerular atrophic	-(6/6)	+(2/6) ++(4/6)	-(1/6) -/+(2/6) +(2/6) +/++(1/6)	-(3/6) -/+(3/6)
Glomerular Bowmann filling	-(6/6)	-(2/6) -/+(4/6)	-(4/6) -/+(1/6)	-(6/6)
Tubular degeneration	-(6/6)	+(1/6) ++(5/6)	-(1/6) -/+ (4/6) +/++(1/6)	-/+(6/6)
Tubulus necrosis	-(6/6)	-/+(1/6) +/++(1/6) ++(4/6)	-(5/6) -/+(1/6)	-(6/6)
Inflammatory cell infiltration	-(6/6)	-(5/6) -/+(1/6)	-(6/6)	-(6/6)
Hyperemia / Edema	+(6/6)	++(2/6) +++(4/6)	+/++(2/6) +++(4/6)	-(1/6) +(5/6)
Fibrosis	-(6/6)	-(6/6)	-(6/6)	-(6/6)

Mean for degeneration-necrosis and Podocyte activation. (-): no findings, (+): mild: in a few microscopic fields, (++): in many microscopic field, (+++): all microscopic fields for other findings including tubular and glomerular changes, hyperemia, inflammation, edema, fibrosis.

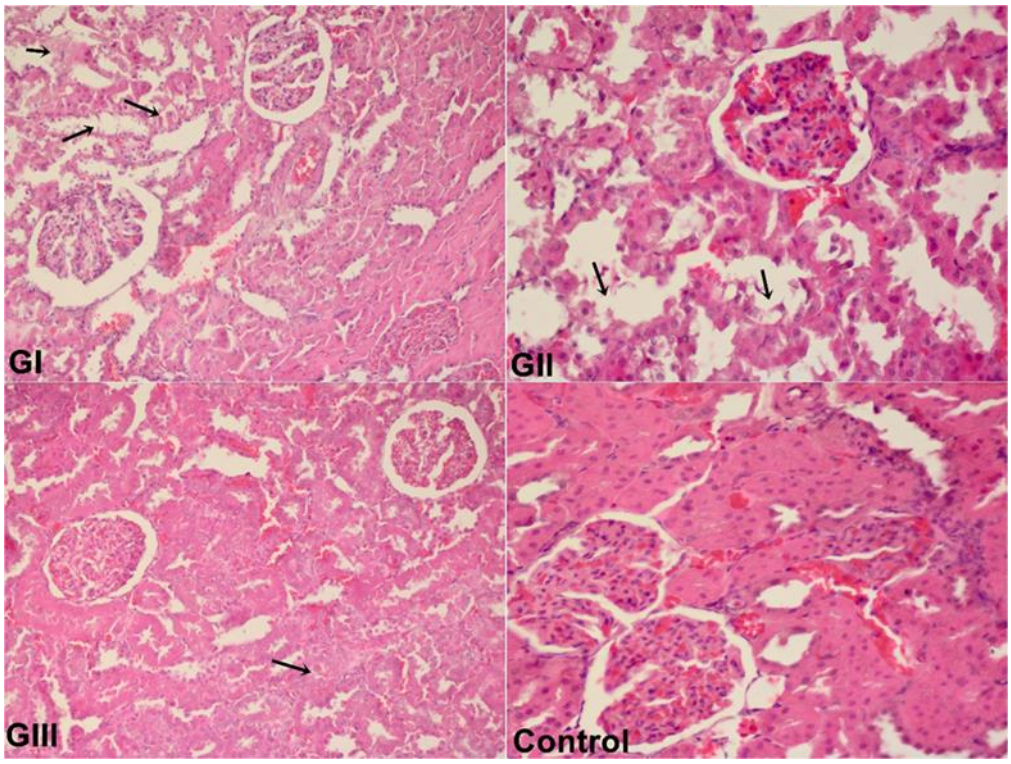

Figure 1: Histopathological findings of the experimental group. Degeneration in tubule epithelium (arrows). GI: Gentamicin group, GII: Gentamicin and krill oil group, GIII: Krill oil group, C: Control group, H&E, x400 magnification.

DISCUSSION

Gentamicin, an aminoglycoside antibiotic, is one of the most important antibiotics used to treat serious infections caused by gram-negative bacteria (Jiang et al. 217, Hayward et al. 2018). Especially due to the increase in the clinical use of these antibiotics, toxic conditions such as nephrotoxicity occur (Vargo and Edwards 2014). To significantly reduce this toxic effect of gentamicin, the use of various substances or agents is required (Cuzzocrea 2002, Khan et al. 2009, Quiros et al. 2011). Therefore the effect of krill oil, a food supplement, against kidney damage caused by gentamicin was investigated.

Many animal studies have been conducted with Krill oil in terms of these beneficial properties. Studies with krill oil have indicated therapeutic beneficial effects in cardiac infarction, obesity, depression, chronic low-grade, and ulcerative inflammation. It has been reported that LC n3 PUFA in krill oil regulates inflammatory C-reactive protein and cytokines levels, and decreases plasma triglycerides with phospholipids (Hung et al. 2001, Buang et al. 2005, Winther et al. 2011, Schneider et al. 2010, Leslie et al. 2015). It also contains astaxanthin, which is an antioxidant and a fat-soluble carotenoid (Kwantes and Grundmann 2015). In this study, it was observed that gentamicin regressed the damage in the kidney tissue, thus these results support the hypothesis of the presented study.

Ramasamy et al. (2017) investigated the protective effect of soybean oil against gentamicin (80 mg/kg) induced nephrotoxicity in a study on rats. In their study, they reported that urea and creatine levels increased in the gentamicin applied group, whereas urea and creatine levels decreased in the soybean oil and gentamicin given groups. They stated that the decrease in urea and creatine levels was due to the antioxidant effect of soybean oil. Similarly, in this study, it was found that krill oil reduced the increase in urea and creatine levels caused by gentamicin. The increase in urea and creatinine levels in the group given gentamicin is probably due to the decrease in glomerular filtration due to degenerations in the kidney (Hur et al. 2013).

Ataman et al. (2018) investigated the effect of fucoidan against gentamicin-induced nephrotoxicity on rats and reported that total cholesterol and ALT levels increased in the gentamicin given group, whereas total cholesterol and ALT levels decreased in the fucoidan and gentamicin given groups. Consistent with the aforementioned study, the presented study found that krill oil reduced the elevation in total cholesterol and ALT levels caused by gentamicin.

It is known that gentamicin plays a significant role in kidney damage by increasing ROS production (Said 2011, Tavafi and Ahmadvand 2011). Sandhya and Varalaxmi (1997) found a significant reduction in kidney GPx, GSH, SOD, and catalase activities in rats administered 100 mg/kg gentamicin. In addition, they also observed an increase in the production of MDA, the end product of lipid peroxidation, in the kidney. In the presented study, MDA levels increased in the kidney, but it was not found to be statistically significant.

In this study, the plasma TAS level was decreased consistently with the study of Acharya et al. (2013) who showed that serum TAS levels decreased in rats administered 70 mg/kg (i.m) gentamicin. TAS provides a guideline for an individual's ability to resist oxidative stress.

Although the mechanism of gentamicin-induced nephrotoxicity cannot be explained, several researchers have reported that damage directly caused by Gentamicin is a class of drugs that can cause the formation of ROS. MDA causes a decrease in the polyunsaturated fatty acids, which act as a substrate for free radicals.

Many studies have confirmed a link between oxidative stress and nephrotoxicity. It has been reported that deterioration in renal function is accompanied by either an increase in creatinine and urea levels or an increase in renal tissue MDA levels, which indicates lipid peroxidation (Cuzzocrea et al. 2002, Atessahin et al. 2003). Many mechanisms have been proposed to explain gentamicin toxicity, it has been suggested that nephrotoxicity causes oxidative stress and therefore antioxidant therapy is required to prevent it (Cuzzocrea et al. 2002, Atessahin et al. 2003, Du and Yang 1994, Walker et al. 1999). Ulutaş et al. (2006) investigated the effect of allopurinol on gentamicin-induced nephrotoxicity in rats. They found that gentamicin increased MDA levels in plasma. In this study, it was found that krill oil numerically reduced the increase in plasma MDA level caused by gentamicin.

Karakoyun et al. (2009) reported that gentamicin (80 mg/kg) increased the MDA level in rat kidney tissue and halofuginone reduced this increase. The presented study is consistent with the aforementioned study, and it was found that krill oil numerically reduced the increase in MDA level in kidney tissue. A study on rats investigated the antioxidant effect of date fruit extract against gentamicin-induced nephrotoxicity. In this study, they reported that the TAS level that gentamicin decreased in the kidney tissue, increased the date extract (Celik and Irak 2018).

Krill oil contains a very powerful natural antioxidant called astaxanthin, which gives it its red color. Studies on astaxanthin in previous years have been examined and it has been proven that astaxanthin has many

beneficial biological effects, including suppression of carcinogenesis in some cancer types such as bladder and colon cancer, prevention of cardiovascular diseases, protection against free radicals, strengthening and modulation of the immunological system (Pashkow et al. 2008, Higuera-Ciapara et al. 2006, Tripathi and Jena 2010).

The histopathological results of this study support the biochemical findings. Podocyte reactions and glomerular atrophy in the glomerulus against toxicity were evident in almost all areas in the gentamicin administered group alone, even if they were moderately severe. In some cases, it was observed that the glomerulus filled Bowman's space, albeit slightly. Another reflection of kidney damage is moderate degenerative and necrotic damage to the tubular epithelium in the cortical region in almost every case. It is thought that these develop after the severe vascular damage observed in each case in the study. Catabolic products and free radicals may cause stress as a result of the lack of oxygenation in the region. Because gentamicin causes cytotoxicity in the cells of the tissues where it is metabolized (Hung et al 2001, Schneider et al 2010).

Gentamicin is taken into the cytosol by endosomes and when it reaches a certain level, the structure of the cell membrane is deformed and gentamicin disperses into the cytoplasm and then goes to the mitochondria (Regec et al. 1989, Morales et al. 2010). It prevents energy production by disrupting oxidative respiration in mitochondria. Thus, free radicals gradually accumulate in the environment and initiate apoptotic mechanisms, leading the cell to degeneration and then to necrosis (Cuzzocrea et al. 2002, Peyrou et al. 2007).

High doses of gentamicin injection induce the reaction of the Bowman's capsule of the glomerulus (enlargement, necrosis of the epithelium lining the capsule, and lysis of the capsule) and cause a change in the level of glomerular filtration. Alterations are characterized by cell death, especially in the proximal tubular epithelium. As a result of these, absorption and secretion disorders begin in the filtration of urine (Regec et al. 1989, Peyrou et al. 2007, Li et al. 2009, Fauzi et al. 2020).

Fauzi et al. (2020) mentioned that inflammatory changes increase with the increase in the dose (20-50 mg/kg/CA), especially around the proximal tubules, in the kidneys of animals to which gentamicin is administered. In this study, glomerular reactions were noted, but no further changes such as lysis or necrosis in the glomeruli were encountered. The information that the proximal tubule epithelium in the cortex is affected by the tubules is overlapping with our study. However, inflammatory changes reported by Fauzi et al. (2020) were noted in a few foci in only one case. In our study, 80mg/kg dose of gentamicin was applied. In this regard, the effects of the reported doses and the gentamicin dose of our study on the inflammatory response seem to be independent of each other. According to the literature review, since the inhibitory effects of nephrotoxicity with Krill oil were not examined, it was concluded that this study was the first evaluation. In this study, it was observed that krill oil reduced the negative effects of glomerulus and tubules induced by gentamicin and it remained at a low level in scoring because the lesions were not seen in all areas. However, there is no literature on the subject that glomerular podocyte activation and mild atrophic changes may occur in half of the cases when krill oil is applied alone.

In our study, vascular changes related to hyperemia were noted in all three experimental groups except for the control group. In this context, it is seen that when krill oil is applied alone, it has a slightly hyperemic effect on the glomerular capillaries and interstitial capillaries. These hyperemic changes were observed to be more severe in combined applications with gentamicin, on the other hand, it was observed that in some cases it was milder than when gentamicin was administered alone. It is thought that krill oil reduces oxidative stress and increases a load of erythrocytes, possibly by triggering vascular mediators in the vessels to provide oxygenation to the region. This may be due to the possibility of stopping the damage in the oxidative respiration cascade formed in the mitochondria and protecting the tissue integrity in this way. It was concluded that more detailed research should be done specifically on the subject.

CONCLUSION

As a result, it was observed that damage and glomerular reactions in the tubule at the histological level mediated by oxidative stress were especially consistent with the increase in plasma MDA, ALT, creatinine, and urea levels. In this respect, krill oil is an effective biological product to prevent damage to kidney tissue and protect kidney tissue. In this, krill oil can be a nephroprotective food supplement that may contribute to the treatment of toxicities.

Conflict of interest: The authors declare that there is no conflict of interest.

Ethical Approval: The study was carried out after the animal experiment approval of Kırıkkale University Local Ethics Committee (Decision number: 2020/06 - 43).

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Authors Contribution Rate: YŞ:30%, MEA:20%, AŞ:10%, HÖ:10%, HE: 10%, EY: 10%, MÇ: 10%,

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