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The effect of fucoidan on changes of some biochemical parameters in nephrotoxicity induced by gentamicin in rats*

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Summary: Fucoidan is a polysaccharide with high viscosity and mucilage, which contains significant proportion of sulphate ester group and L-fucose. It is present in intercellular spaces of brown algae. This study aimed to investigate the effect of fucoidan on some biochemical parameters and kidney tissues in nephrotoxicity induced by GM in rats. The rats used in the study were randomly divided into 4 groups. Each group had 7 rats as control, fucoidan, GM and GM+fucoidan. Blood samples were taken after 24 hours from the end of experiment which lasted eight days. Creatinine, BUN, uric acid, glucose, triglycerides, total cholesterol, VLDL, HDL, total bilirubin levels and ALT, AST, ALP, LDH, CK, amylase activities were assayed by an autoanalyser. The kidney tissues were examined histopathologically. In GM+fucoidan group, creatinine ($p<0.001$), BUN ($p<0.001$), uric acid ($p<0.05$), triglycerides ($p<0.05$), VLDL ($p<0.05$), AST ($p<0.001$), ALP ($p<0.05$), LDH ($p<0.001$), CK ($p<0.01$) levels statistically decreased, however HDL ($p<0.05$) level increased when compared to GM group. As conclusion, it can be said that administering fucoidan during GM toxicity decreases the nephrotoxicity damage. Considering biochemical parameters and histopathological findings, fucoidan can be suggested as a protective agent for kidneys in nephrotoxicity induced rats.

Keywords: Biochemical parameters, fucoidan, gentamicin, nephrotoxicity.

Ratlarda gentamisin ile oluşturulan nefrotoksisitede bazı biyokimyasal parametreler üzerine fucoidanın etkisi

Özet: Fucoidan, tüm kahverengi alglerin hücreler arası boşluklarında bulunan yüksek vizkoziteye sahip müsilajımsı, önemli oranda sülfat ester grupları ve L-fukoz içeren bir polisakkarittir. Bu çalışmada ratlarda gentamisin (GM) ile oluşturulan nefrotoksisitede fucoidan kullanılmasının bazı biyokimyasal parametreler ile böbrek dokusu üzerine etkisinin araştırılması hedeflenmiştir. Çalışmada kullanılan ratlar rastgele seçilerek her biri 7 rattan oluşan 4 gruba ayrıldı: Kontrol grubu, fucoidan grubu, GM grubu, GM+fucoidan grubu. Sekiz günlük deneme süresinden 24 saat sonra kan örnekleri alındı. Kreatinin, BUN, ürik asit, glukoz, trigliserit, total kolesterol, VLDL, HDL, total bilirubin düzeyleri ile ALT, AST, ALP, LDH, CK, amilaz aktiviteleri otoanalizörde analiz edildi. Böbrek dokuları histopatolojik açıdan incelendi. GM grubuna göre fucoidan+GM grubunda kreatinin ($p<0.001$), BUN ($p<0.001$), ürik asit ($p<0.05$), trigliserit ($p<0.05$), VLDL ($p<0.05$), AST ($p<0.001$), ALP ($p<0.05$), LDH ($p<0.001$), CK ($p<0.01$) düzeylerinin istatistiki olarak önemli ölçüde azaldığı, HDL ($p<0.05$) düzeyinin ise yükseldiği tespit edildi. Sonuç olarak; GM'le oluşturulan nefrotoksisitede incelenen biyokimyasal parametrelere ve böbrek dokusundaki histopatolojik değişimlere bakarak GM'le beraber fucoidan verilmesinin GM'nin oluşturduğu nefrotoksik hasarı zayıflattığı, fucoidanın böbreği koruyucu özelliğinin bulunduğu söylenebilir.

Anahtar sözcükler: Biyokimyasal parametreler, fucoidan, gentamisin, nefrotoksisite.

Introduction

Aminoglycoside antibiotics are widely used to treat serious gram-negative infections. Gentamicin leads to proximal tubular cell dysfunction and necrosis which suggest a relationship between the accumulation of gentamicin within proximal tubular cells and the subsequent development of gentamicin nephrotoxicity (29). Vast amount of in vitro and in vivo evidence indicates that these partially reduced oxygen metabolites are important mediators of gentamicin nephrotoxicity. Gentamicin has been shown to enhance the generation of superoxide anion and hydrogen peroxide by renal cortical mitochondria (40).

Fucoidans are a class of sulfated polysaccharides that are mainly found in marine organisms, including brown algae species such as *Fucus vesiculosis, Cladosiphon okamuranus*, *Laminaria japonica* and *Undaria pinnatifida* (12, 14, 15). These algal derived marine carbohydrate polymers present numerous valuable bioactivities (15). These sulfated polysaccharides were reported to have

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blood anticoagulant, anti-tumor, anti-mutagenic, anti-inflammatory, antiviral, antioxidant and anti-complementary activities (18, 30, 39, 42, 48).

Brown seaweeds are one of the popular seafood in Far East. People use them as a traditional medicine for curing edema, a symptom of kidney diseases, for more than thousand years (44, 47). There have been many studies performed in recent years related with fucoidan which is indicated for protective effect in kidney diseases (9, 44, 48).

In a study conducted as a review reported that a lot of methods have been used to induce renal failure in rats that include IP administration of gentamicin sulfate at a dose of 100 mg/kg/day for 5–8 days (34). A number of drugs or chemicals have been used to prevent aminoglycoside-induced renal injury (6, 21, 33). To date, none of any studies were performed related with the protective effect of fucoidan on gentamicin induced nephrotoxicity. Therefore, we aim to evaluate the effect of fucoidan on some biochemical parameters and kidney tissues in nephrotoxicity induced by GM in rats.

Materials and Methods

Materials and experimental conditions

Female Wistar Albino rats (aged 7-8 weeks) weighing 150-240 g were housed in a temperature - controlled (22 ± 2 ^{0}C) room in which a 12 h:12 h light: dark cycle was maintained. The animals were fed with standard diet and *ad libitum* water. All rats were adapted to laboratory conditions for 7 days prior to the experiment. All experiments were performed in accordance with protocols approved by the Yüzüncü Yıl University Animal Researches Local Ethic Committee (07/07/2014, 2014/08).

Experimental procedure

Twenty-eight rats were randomly divided into four groups and each group consisted of 7 rats:

Rats in control group were injected intraperitoneally (IP) with physiological saline for 8 days.

Rats in fucoidan group were administered with fucoidan (F5631, Sigma, USA) (100 mg/kg/day) by intragastric gavage for 8 days.

Rats in GM group were injected IP with gentamicin (80 mg/kg/day) for 8 days.

GM+fucoidan group was injected IP with gentamicin (80 mg/kg/day) and fucoidan (100 mg/kg/day) was given by intragastric gavage for 8 days.

Biochemical analysis

Following 24 hours from the end of eight-day experimental period, blood samples were taken and sera was obtained. Biochemical parameters (BUN, creatinine, uric acid, glucose, triglycerides, total cholesterol, VLDL, HDL, total bilirubin levels and ALT, AST, ALP, LDH, CK, amylase activities) were assessed with an automatic analyzer (Roche Modular P800).

Histopathological examinations

Rats in all groups were sacrificed and the kidneys were quickly removed and placed into formaldehyde solution for routine histopathological examination by light microscopy. The tissues were fixed in 10 % formalin, embedded in paraffin, sectioned at 5 μm and stained with hematoxylin-eosin.

Data statistical analysis

All data were expressed in the means ± S.D. Kruskal-Wallis Test was used to check differences among the groups. Dunnett's test were used to determine different groups. $p < 0.05$ was considered statistically significant. Statistical analyses were performed by using SPSS v.13.0 software.

Results

The results of biochemical analyses were presented in Table 1 and 2.

Table 1. Changes in biochemical parameters.
Tablo 1. Biyokimyasal parametrelerdeki değişiklikler.

Parameters	Control		Fucoidan		GM		GM+Fucoidan		
	n	X ± S$\bar{x}$	n	X ± S$\bar{x}$	n	X ± S$\bar{x}$	n	X ± S$\bar{x}$	p
Creatinin (mg/dl)	7	0.51±0.05^b	7	0.41±0.09^b	7	2.08±1.39^a	7	0.90±0.43^b	0.001
BUN (mg/dl)	7	14.29±1.50^b	7	15.71±1.25^b	7	67.14±39.10^a	7	31.71±14.96^b	0.001
Uric Acid (mg/dl)	7	0.93±0.25^b	7	1.09±0.41^b	7	4.26±1.35^a	7	1.29±0.64^b	0.047
Glucose (mg/dl)	7	153.00±10.42^a	7	137.57±53.97^a	7	185.57±84.77^a	5	142.40±43.74^a	0.407
Triglycerides (mg/dl)	7	83.27±5.68^{ab}	7	78.89±7.39^b	7	98.66±13.77^a	7	76.71±16.66^b	0.030
Total cholesterol	7	66.00±8.94^a	7	58.00±8.56^a	7	76.43±11.57^a	7	66.29±7.87^a	0.053
VLDL (mg/dl)	7	22.57±3.82^b	7	18.71±4.42^b	7	27.71±2.63^a	7	22.86±4.78^b	0.012
HDL (mg/dl)	7	54.00±8.94^{ab}	7	56.86±6.89^a	7	46.57±5.00^b	7	60.43±5.88^a	0.009
Total Bilirubin (mg/dl)	7	0.10±0.01^{ab}	7	0.08±0.02^b	7	0.21±0.16^a	7	0.12±0.04^{ab}	0.022

a, b: Different letters in the same row are statistically significant.

Table 2. Changes in some enzyme activities.
Tablo 2. Bazı enzim aktivitelerindeki değişiklikler.

Parameters	Control		Fucoidan		GM		GM+ Fucoidan		
	n	X ± Sx̄	n	X ± Sx̄	n	X ± Sx̄	n	X ± Sx̄	p
ALT (U/L)	7	49.43±7.61^{b}	7	39.86±3.72^{b}	7	63.14±14.72^{a}	7	51.14±13.96^{ab}	0.004
AST (U/L)	7	154.57±23.55^{bc}	7	139.86±6.77^{c}	7	238.29±32.00^{a}	7	171.71±18.63^{b}	0.001
ALP (U/L)	7	235.43±23.89^{b}	7	212.29±35.81^{b}	7	279.43±33.34^{a}	7	223.86±39.52^{b}	0.019
LDH (U/L)	7	1912.57±385.28^{b}	7	1390.71±226.99^{c}	7	2501.71±255.21^{a}	7	1993.86±451.34^{b}	0.001
CK (U/L)	7	1285.29±284.55^{b}	7	1354.43±383.59^{b}	7	2402.43±722.27^{a}	7	1705.86±314.70^{b}	0.002
Amilase (U/L)	7	1494.86±186.06^{a}	7	1437.71±300.83^{a}	7	1545.00±268.98^{a}	7	1504.14±126.88^{a}	0.749

a, b, c: Different letters in the same row are statistically significant.

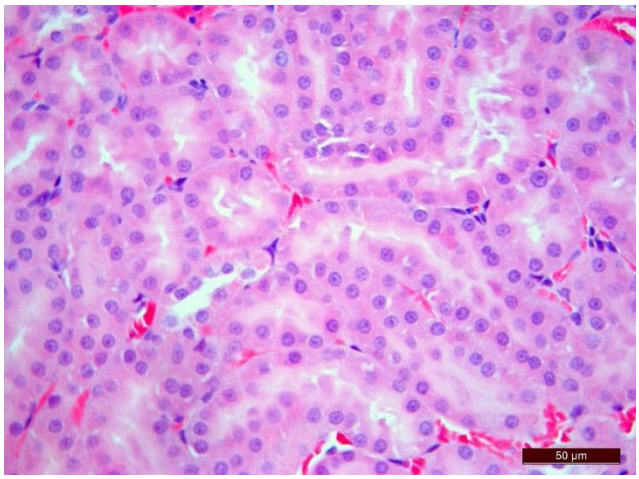

Figure 1. Histopathological studies on renal tissues in control group (HxE), Bar=50µm.
Şekil 1. Kontrol grubundaki ratlara ait böbreklerin histolojik yapısı (HxE), Bar=50µm.

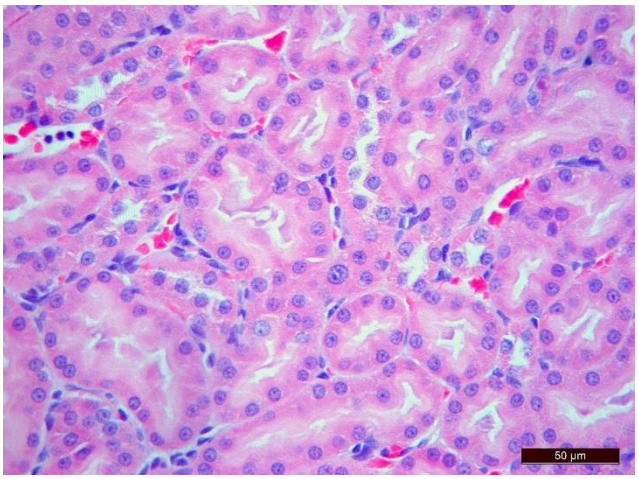

Figure 2. Histopathological studies on renal tissues in fucoidan group (HxE), Bar=50µm.
Şekil 2. Fucoidan grubundaki ratlara ait böbreklerin histolojik yapısı (HxE), Bar=50µm.

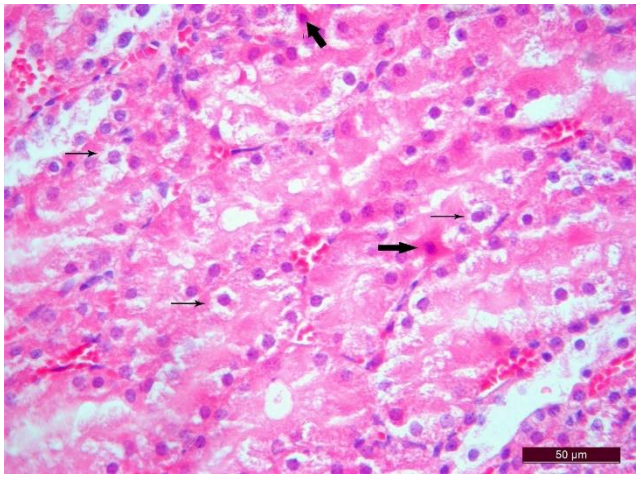

Figure 3. Histopathological studies on renal tissues in GM group (HxE), Bar=50µm.
GM group indicated severe hydropic degeneration (thin arrows) and a few necrotic cells (thick arrows) in tubular epithelium of kidney.
Şekil 3. Gentamisin grubundaki ratlara ait böbreklerin histolojik yapısı (HxE), Bar=50µm. Tubulus epitellerinde şiddetli hidropik dejenerasyon (ince oklar) ve az sayıda nekrotik hücre (kalın oklar).

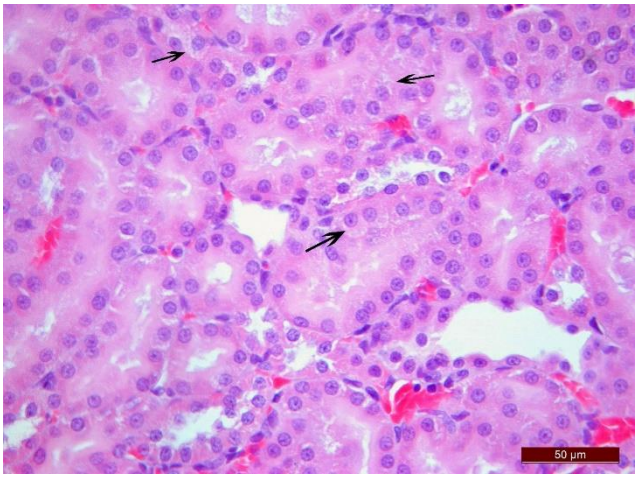

Figure 4. Histopathological studies on renal tissues in GM+fucoidan group (HxE), Bar=50µm. GM+fucoidan group indicated a slight degeneration in tubular epithelium of kidney (arrows).
Şekil 4. GM+fucoidan grubundaki ratlara ait böbreklerin histolojik yapısı (HxE), Bar=50µm. Böbrek tubuluslerinde hafif dejenerasyon (oklar).

In the group of GM+fucoidan it was determined that the levels of creatinine ($p<0.001$), BUN ($p<0.001$), uric acid ($p<0.05$), triglycerides ($p<0.05$), VLDL ($p<0.05$), AST ($p<0.001$), ALP ($p<0.05$), LDH ($p<0.001$), CK ($p<0.01$) statistically decreased, but the HDL ($p<0.05$) increased compared to GM group.

The histopathological results were cited in Figure 1-4. Kidneys of the control and fucoidan group were shown normal histologic features (Figure 1 and 2). GM treated group were indicated severe hydropic degeneration and necrotic cells were observed in this group (Figure 3). On the other hand, the tubules from rats of GM+ fucoidan group were shown a slight degeneration and necrotic cells were not observed (Figure 4).

Discussion and Conclusion

Sulfated polysaccharides protect kidney by independent mechanisms of glomerular haemodynamic changes that have been shown in many experiments (10, 44). It could be probably due to its inhibition of mesangial cell proliferation. Modulation of synthesis and composition of the extracellular matrix may play a role as well (10, 44). Besides, sulfated polysaccharides were mediated by replacing the electronegative content of the glomerular cells (9, 16, 44, 48). Wang et al. (44) reported that the benzoylate group substituted in fucoidan could enhance the electronegativity of fucoidan, and they could replace the electronegative content of glomerular cells more easily.

GM was injected intraperitoneally at the dose of 80 mg kg^{-1}, for eight consecutive days, which is well known to cause significant nephrotoxicity in rats (24, 32). Several studies reported that nephrotoxicity can be induced by GM treatment which results in reduced renal functions (3, 37). The renal function is characterized by an increase in serum creatinine and BUN level accompanied by impairment in glomerular functions. Serum creatinine concentration is a more significant indicator than the BUN level in the earlier phases of kidney disease (19). On the other hand, BUN rises only after a marked renal parenchymal injury occurs. In the present study, serum levels of creatinine and BUN were significantly higher in the GM group, when compared with the control group. The administration of fucoidan by intragastric gavage ensured significant decreases in serum creatinine and BUN levels when compared with GM group ($p<0.001$). Besides, serum uric acid was found to be significantly increased ($p<0.05$) in rats treated with only gentamicin; whereas treatment with fucoidan was found to protect the rats from such effects of gentamicin. Similar results were also observed by Wang et al. (44) and Zhang et al. (48).

Fucoidan exhibits a considerable hypoglycemic effect, possibly by stimulating the pancreatic release of insulin and/or by reducing insulin metabolism (41). Fucoidan also has a protective effect in rats with diabetic nephropathy. The most likely mechanism of renal protection is the modulating activity of fucoidan in metabolic disturbances and effect on reducing blood glucose levels (43). It was reported that high doses of Fucoidan (2500 mg/kg) caused to decrease in glucose levels of female rats (25). In the present study, the serum glucose level was higher in the GM group, when compared with the other groups and the difference was not significant. When the low dose of fucoidan (100 mg/kg for 8 day) was administered to rats, the serum glucose level decreased. The results suggest that fucoidan can be considered as a potential candidate for reducing the blood glucose level.

Secondary hyperlipidemia was observed in rats with gentamicin induced nephrotoxicity which has been suggested for the progression of renal injury induced by the drug (2). Observed secondary dyslipidemia was attributed to increased hepatic cholesterol biosynthesis as a result of increased availability of mevalonate due to its reduced catabolism by the injured kidney (17). It was suggested that the hypertriglyceridemia can be associated with nephrosis to the delayed removal of the circulating triglyceride-rich lipoproteins caused by a reduction in the activity of the lipoprotein lipase which is responsible for the degradation of the triglyceride in the VLDL (11). Ahmadvand et al. (4) reported that serum levels of triglyceride, cholesterol, LDL, VLDL and cardiac risk ratio were higher in gentamicin induced nephrotoxicity rats when compared with the coenzyme Q10 group. In the present study, the hypercholesterolemia and hypertriglyceridemia were observed in the gentamicin-treated animals. Obtained results were in agreement with their findings in the rat (3, 4, 11, 17).

Huang et al. (20) reported that fucoidan polysaccharide sulfuric acid ester from *Laminaria japonica* Aresch (Laminariaceae) notably reduced the concentration of serum total cholesterol, triglyceride, and low-density lipoprotein cholesterol of hyperlipidemic rats and increased the concentration of high-density lipoprotein cholesterol and the activities of lipoprotein lipase, hepatic lipoprotein, and lecithin cholesterol acyltransferase (LCAT). Park et al. (28) also found that fucoidan can be useful for the prevention or treatment of obesity due to its stimulatory lipolysis. In this study, in the GM group, it was determined that the levels of triglyceride ($p<0.05$), VLDL ($p<0.05$) were statistically increased, but the HDL ($p<0.05$) was decreased compared to GM+fucoidan group. The serum cholesterol level was higher in the GM group when compared with GM+fucoidan group and the difference was not significant ($p= 0.053$). Elevated levels of serum HDL and decreased level of triglyceride, cholesterol, VLDL after treatment with fucoidan were observed. The results suggest that fucoidan can be considered as a potential anti-atherogenic agent.

Generation of oxygen free radicals is the major factor responsible for the hepatotoxicity because the pathophysiology of gentamicin-induced hepatotoxicity is

multi-factorial (5, 35). Fucoidan has been reported to interact with transforming growth factor-β and to scavenge reactive oxygen species (8, 27, 46). Hayashi et al. (18) reported that fucoidan prevents hepatocyte cell death and induces the death of hepatic stellate cells in an animal model of hepatic fibrosis. This anti-fibrogenic activity of fucoidan is due, at least in part, to attenuation of hepatic stellate cell activation by inhibition of transforming growth factor-β and/or by scavenging of reactive oxygen species, which can suppress the cascade of events that leads to hepatic stellate cell activation.

Serum bilirubin is one of the most sensitive tests which is commonly used for the diagnosis of hepatic diseases. Bilirubin, is a chemical breakdown product of hemoglobin, is conjugated with glucuronic acid in hepatocytes to increase its water solubility (19). Several studies reported that gentamicin administered rats showed a highly significant increase in plasma total bilirubin when compared to the control group (19, 23). In the present study, the highest total bilirubin levels were found in the GM group. An increase in total bilirubin level was recorded in this study which is concomitant to findings of Hozayen et al. (19) and Khan et al. (23). The treatment of gentamicin intoxicated rats with fucoidan presented a non-significant decrease in serum total bilirubin level (0.12±0.04 mg/dl), when compared to the gentamicin group (0.21±0.16 mg/dl). The increase in plasma total bilirubin levels by gentamicin may suggest that gentamicin can be a toxic agent for the liver.

ALT is an enzyme which is widely used as an indicator of GM hepatic damage in rat hepatocytes (13). AST presents two isozymes, one located in the cytoplasm and the other in the mitochondria. The leakage of these enzymes outside the cell represents damage to the hepatic cells. Alkaline phosphatase is an ectoenzyme of the hepatocyte plasma membrane; an increase in serum alkaline phosphatase activity has been related to damage to the liver cell membrane (22). Increased level of LDH in serum in the present investigation apparently indicated the toxic effects of gentamicin in rats (23). In the present study, the serum ALT, AST, ALP and LDH activities in gentamicin intoxicated rats showed a highly significant increase ($p<0.01$, $p<0.001$, $p<0.05$, $p<0.001$ respectively) compared to the control rats. These results are in agreement with Abbas et al. (1) and Khan et al. (23). The treatment with fucoidan exerted a highly significant decrease in serum AST, ALP and LDH activities ($p<0.001$, $p<0.05$, $p<0.001$ respectively) when compared to gentamicin group. Administration of fucoidan enabled to restore the normal functional status of the intoxicated liver.

Creatine phosphokinase (CK) is an enzyme, released into the blood stream upon muscle cell disintegration. It exists in three isomeric forms: CK-MM present in muscles, CK-MB present in heart, and CK-BB present in kidneys and brain (36). CPK-BB isoenzyme in the sera of patients with chronic renal insufficiency was observed. The source of the enzyme may be nerve tissue and may represent neuronal cell damage in uremics over a period of time (45). In this study the serum CK activities in GM group showed significant increase ($p<0.01$) compared to the GM+fucoidan group. Elevated activity of CK found to be decreased upon treatment with fucoidan.

Amylase is one of the enzymes that is produced by exocrine pancreas and salivary gland which hydrolyses starch. It is rapidly cleared by kidney. Twenty percent of pancreatic enzymes is excreted by the kidney thus patients with end stage renal disease have elevated levels of serum pancreatic enzymes (7). The serum amylase and lipase are elevated in patients with end stage renal disease in the absence of pancreatitis (26, 31, 38). In this study, the serum amylase activity was higher in the GM group, when compared with the other three groups and the difference was not significant. However, elevated activity of amylase decreased after treatment with fucoidan.

In conclusion, it can be said that administering fucoidan during GM treatment decreases the nephrotoxicity caused by GM. When considering some biochemical parameters and histopathological findings, fucoidan demonstrated kidney protective features in rats which nephrotoxicity was induced by GM administration.

References

1. **Abbas MT, Hashim Zayni MM, Al-Kadhi NA** (2013): *Effect of garlic oil on gentamicin induced hepatorenal toxicity in rats.* JKU, **11,** 109-117.
2. **Abdel-Gayoum AA, Ali BH, Ghawarsha K, et al.** (1993): *Plasma lipid profile in rats with gentamicin-induced nephrotoxicity.* Hum Exp Toxicol, **12,** 371-375.
3. **Abdel-Raheem IT, Abdel-Ghany AA, Mohamed GA** (2009): *Protective effect of quercetin against gentamicin-induced nephrotoxicity in rats.* Biol Pharm Bull, **32,** 61-67.
4. **Ahmadvand H, Ghasemi Dehnoo M, Dehghani A, et al.** (2014): *Serum paraoxonase 1 status and its association with atherogenic indexes in gentamicin-induced nephrotoxicity in rats treated with coenzyme Q10.* Ren Fail, **36,** 413-418.
5. **Ali BH** (1995): *Gentamicin nephrotoxicity in humans and animals some recent research.* Gen Pharmacol, **26,** 1477-1487.
6. **Başhan İ, Başhan P, Seçilmiş MA, et al.** (2014): *Protective effect of L-arginine on gentamicin-induced nephrotoxicity in rats.* Indian J Pharmacol, **46,** 608-612.
7. **Bindu CM, Vidya Shankar P, Shetty HV, et al.** (2013): *Serum amylase in patients with chronic kidney disease.* IJCRR, **5,** 10-5.
8. **Boisson-Vidal C, Haroun F, Ellouali M, et al.** (1995): *Biological activities of polysaccharides from marine algae.* Drugs Future, **20,** 1237-1249.
9. **Bojakowski K, Abramczyk P, Bojakowska M, et al.** (2001): *Fucoidan improves the renal blood flow in the early stage of renal ischemia/reperfusion injury in the rat.* J Physiol Pharmacol, **52,** 137-143.
10. **Ceol M, Gambaro G, Sauer U, et al.** (2000): *Glycosaminoglycan therapy prevents TGF-beta 1 overexpression and pathologic changes in renal tissue of long-term diabetic rats*. J Am Soc Nephrol, **11,** 2324-2336.

11. **Chan MK, Persaud JW, Varghese Z, et al.** (1984): *Post-heparin hepatic and lipoprotein lipase activities in nephrotic syndrome.* Aust New Zeal J Med, **14,** 841-847.
12. **Chevolot L, Foucault A, Chaubet F, et al.** (1999): *Further data on the structure of brown seaweed fucans: relationships with anticoagulant activity*. Carbohydr Res, **319,** 154-165.
13. **El-Tawil OS, Abdel-Rahman MS** (2001): *The role of enzyme induction and inhibition on cypermethrin hepatotoxicity.* Pharmacol Res, **44,** 33-40.
14. **Feldman SC, Reynaldi S, Stortz CA, et al.** (1999): *Antiviral properties of fucoidan fractions from Leathesia difformis*. Phytomedicine, **6,** 335-340.
15. **Fitton JH** (2011): *Therapies from fucoidan; multifunctional marine polymers*. Mar Drugs, **9,** 1731-1760.
16. **Gambaro G, D'Angelo A, Del Prete D, et al.** (1999): *Mesangial cell proliferation in long-term streptozotocin-induced diabetes mellitus in the rat and the renoprotective activity of heparin.* Am J Nephrol, **19,** 530-534.
17. **Golper TA, Feingold KR, Fulford MH, et al.** (1986): *The role of circulating mevalonate in nephrotic hypercholesterolemia in the rat*. J Lipid Res, **27,** 1044-1051.
18. **Hayashi S, Itoh A, Isoda K, et al.** (2008): *Fucoidan partly prevents CCl4-induced liver fibrosis*. Eur J Pharmacol, **580,** 380-384.
19. **Hozayen W, Bastawy M, Elshafeey H** (2011): *Effects of aqueous purslane (Portulaca Oleracea) extract and fish oil on gentamicin nephrotoxicity in albino rats.* Nature and Science, **9,** 47-62.
20. **Huang L, Wen K, Gao X, et al.** (2010): *Hypolipidemic effect of fucoidan from Laminaria japonica in hyperlipidemic rats.* Pharm Biol, **48,** 422-426.
21. **Janjua A, Waheed A, Bakhtiar S** (2014): *Protective effect of metformin against gentamicin induced nephrotoxicity in rabbits.* Pak J Pharm Sci, **27,** 1863-1872.
22. **Kaplan MM** (1986): *Serum alkaline phosphatase-Another piece is added to the puzzle*. Hepatology, **6,** 226-228.
23. **Khan MR, Badar I, Siddiquah A** (2011): *Prevention of hepatorenal toxicity with Sonchusasper in gentamicin treated rats. BMC Complement Altern Med*, **11**, 111-113**.**
24. **Kopple JD, Ding H, Letoha A, et al.** (2002): *L-carnitine ameliorates gentamicin-induced renal injury in rats*. Nephrol Dial Transplant, **17,** 2122-2131.
25. **Li N, Zhang Q, Song J** (2005): *Toxicological evaluation of fucoidan extracted from Laminaria japonica in Wistar rats.* Food Chem Toxicol, **43,** 421-426.
26. **Lin XZ, Chen TW, Wang SS, et al.** (1988): *Pancreatic enzymes in uremic patients with or without dialysis.* Clin Biochem, **21,** 189-192.
27. **McCaffrey TA, Falcone DJ, Vicente D, et al.** (1994): *Protection of transforming growth factor-beta 1 activity by heparin and fucoidan*. J Cell Physiol, **159,** 51-59.
28. **Park MK, Jung U, Roh C** (2011): *Fucoidan from marine brown algae inhibits lipid accumulation.* Mar Drugs, **9,** 1359-1367.
29. **Pastoriza-Munoz E, Bowman RL, Kaloyanides GJ** (1979): *Renal tubular transport of gentamicin in the rat.* Kidney Int, **16,** 40-450.
30. **Rocha de Souza MC, Marques CT, Guerra Dore CM, et al.** (2007): *Antioxidant activities of sulfated polysaccharides from brown and red seaweeds*. J Appl Phycol, **19,** 153-160.
31. **Royes VL, Jensen DM, Corwin HL (**1987): *Pancreatic enzymes in chronic renal failure.* Arch Intern Med, **147,** 537-539.
32. **Shifow AA, Kumar KV, Naidu MU, et al.** (2000): *Melatonin, a pineal hormone with antioxidant property, protects against gentamicin-induced nephrotoxicity in rats.* Nephron, **85,** 167-174.
33. **Shin HS, Yu M, Kim M, et al.** (2014): *Renoprotective effect of red ginseng in gentamicin-induced acute kidney injury.* Lab Invest, **94,** 1147-1160.
34. **Singh AP, Muthuraman A, Jaggi AS, et al.** (2012): *Animal models of acute renal failure.* Pharmacol Rep, **64,** 31-44.
35. **Sivachandran M, Hariharan P** (2013). *Gentamicin induced hepatic oxidative stress and its amelioration using Andrographis paniculata extract in rats*. Inter J Vet Sci, **2,** 50-54.
36. **Subramanian A, Sukheeja D, Trikha V, et al.** (2013): *Evaluation of serum creatine kinase and urinary myoglobin as markers in detecting development of acute renal failure in severely injured trauma patients.* ISRN Emergency Medicine, **44**, 1-8.
37. **Ullah N, Azam Khan M, Khan T, et al.** (2014): *Protective potential of Tamarindus indica against gentamicin-induced nephrotoxicity.* Pharm Biol, **52,** 428-434.
38. **Vaziri ND, Chang D, Malekpour A, et al.** (1988): *Pancreatic enzymes in patients with end stage renal disease maintained on hemodialysis.* Am J Gastroentrerol, **83,** 410-412.
39. **Veena CK, Josephine A, Preetha SP, et al.** (2007): *Beneficial role of sulfated polysaccharides from edible seaweed Fucus vesiculosus in experimental hyperoxaluria*. Food Chemistry, **100,** 1552-1559.
40. **Walker PD, Barri Y, Shah SV** (1999): *Oxidant mechanisms in gentamicin nephrotoxicity*. Ren Fail, **21,** 433-442.
41. **Wang J, Jin W, Zhang W, et al.** (2013): *Hypoglycemic property of acidic polysaccharide extracted from Saccharina japonica and its potential mechanism.* Carbohydr Polym, **95,** 143-147.
42. **Wang J, Zhang Q, Jin W, et al.** (2011): *Effects and mechanism of low molecular weight fucoidan in mitigating the peroxidative and renal damage induced by adenine*. Carbohydr Polym, **84,** 417-423.
43. **Wang J, Liu H, Li N, et al.** (2014): *The protective effect of fucoidan in rats with streptozotocin-induced diabetic nephropathy.* Mar Drugs, **12,** 3292-3306.
44. **Wang J, Wang F, Yun H, et al.** (2012): *Effect and mechanism of fucoidan derivatives from Laminaria japonica in experimental adenine-induced chronic kidney disease.* J Ethnopharmacol, **139,** 807-813.
45. **Weseley SA, Byrnes A, Alter S, et al.** (1977): *Presence of creatine phosphokinase brain band in the serum of chronic renal disease patients.* Clin Nephrol, **8,** 345-348.
46. **Xue CH, Fang Y, Lin H, et al.** (2001): *Chemical characters and antioxidative properties of sulfated polysaccharides from Laminaria japonica*. J Appl Phycol, **13**, 67-70.
47. **Yen HJ** (1996): *Laminaria japonica Aresch Chinese Pharmaceutics of Maine Lakes and Marshes.* Xueyuan Press, Beijing.
48. **Zhang Q, Li Z, Xu Z, et al.** (2003): *Effects of fucoidan on chronic renal failure in rats.* Planta Med, **69,** 537-541.

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