Original Article

# Repeated Administration of Fluvoxamine Worsens Gentamicin-induced Nephrotoxicity in Rats

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## Abstract

**Background:** Depression is one of the most prevalent and life-threatening forms of mental disorders in chronic kidney disease. Antidepressant agents such as fluvoxamine are broadly prescribed in this situation. This study investigated the effects of fluvoxamine on gentamicin (GEN)-induced nephrotoxicity in rats. **Materials and Methods:** Twenty-four male Wistar rats were randomly divided into four groups ($n = 6$) including (1) control group, (2) GEN group, (3) GEN + fluvoxamine (25 mg/kg) group, and (4) GEN + fluvoxamine (50 mg/kg) group. Fluvoxamine was orally given to animals 45 min before GEN was injected (100 mg/kg, intraperitoneally [i.p.]). Blood urea nitrogen (BUN), creatinine (Cr), sodium ($Na^+$), potassium ($K^+$), and malondialdehyde (MDA) levels in serum were measured. Moreover, the glucose (Glu) and protein (Pro) levels in urine and the ratio of kidney to body weight (g/100 g body weight) were determined. Histopathological alterations in kidney were evaluated. **Results:** GEN significantly increased the Cr and BUN serum levels as well as urine Glu and Pro concentrations ($P \leq 0.001$). Fluvoxamine exacerbated the elevation in the indicated parameters. GEN also significantly increased the serum MDA levels. Fluvoxamine had no effect on the elevated serum levels of MDA. GEN did not show any effect on the $K^+$ and $Na^+$ serum concentrations. Increased kidney-to-body weight ratio due to GEN nephrotoxicity was further exacerbated by 25 mg/kg of fluvoxamine ($P \leq 0.001$). Pathologic findings also confirm the biochemical results. **Conclusion:** The data suggest that fluvoxamine worsens the nephrotoxicity of GEN. However, further clinical and animal investigations are required to elucidate the mechanism of this interaction.

**Keywords:** *Fluvoxamine, gentamicin, nephrotoxicity, rat*

## Introduction

Aminoglycoside antibiotics, such as gentamicin (GEN), have been widely used in the treatment of gram-negative and mixed infections. These antibiotics also induce dose-dependent nephrotoxicity in 10%–20% of therapeutic courses.[1-3] Therefore, the clinical value of these drugs is limited by the development of renal toxicity. The precise mechanism of the aminoglycoside-induced nephrotoxicity has not been clear very well. Some of the published studies have suggested that oxidative stress and mitochondrial dysfunction have an important role in the pathogenesis of GEN-induced nephrotoxicity.[4,5]

Reactive oxygen species, through vasoconstriction, reduction in glomerular filtration rate, lipid peroxidation, and protein (Pro) modifications, cause cellular damage and necrosis.[6,7] It has been also reported that superoxide anion and hydroxyl radicals inhibit the regular function of mitochondria in the GEN-induced kidney toxicity.[8,9] In line with the indicated works, several studies have shown that the use of compounds with antioxidant properties could decrease aminoglycoside-induced nephrotoxicity.[10,11]

On the other hand, depression is one of the most common diseases in patients with chronic renal failure and antidepressants are broadly prescribed for these people.[12,13] Some studies have suggested that oxidative stress parameters rise in depressed patients.[14] Furthermore, antioxidant and anti-inflammatory properties of antidepressant medicines were reported both in *vivo* and *in vitro* conditions.[15,16] It is reported that treatment with a 12-week regimen of antidepressant agents increases antioxidant capacity and decreases circulating free radicals in patients with major depressive disorder.[17]

Fluvoxamine is an effective and specific selective serotonin reuptake inhibitor (SSRI), which is widely used for the treatment of



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depression and obsessive-compulsive disorder.[18] It has been shown that the administration of fluvoxamine in rats decreased indomethacin-induced peptic ulcers via the antioxidant pathways.[19] It was also reported that fluvoxamine showed strong anti-inflammatory effects in various animal models of inflammation.[20] On the other hand, several studies have found that antidepressant drugs are associated with inhibition of cellular respiration and oxidative stress.[21,22] Considering the role of mitochondrial dysfunction and oxidative stress in the GEN-induced nephrotoxicity,[8,9] as well as contradictory reports on antioxidant activities and effects of antidepressants on cell mitochondrial function, this study was designed to investigate the effects of fluvoxamine on GEN-induced nephrotoxicity in male rats.

## Materials and Methods

### Animals

In this study, 24 healthy adult male Wistar rats were obtained from the animal house of Yasuj University of Medical Sciences. All the animals were kept under standard laboratory conditions (12-h light and 12-h dark). The animals had free access to laboratory chow diet and tap water. All experiments were conducted according to the guide to the care and use of laboratory animals.

### Experimental design

Twenty-four healthy adult male Wistar rats with an average weight of 180–220 g were randomly divided into four groups with six animals in each group:

(1) Control (saline) group: Animals received a daily intraperitoneal (i.p.) injection of 0.5 mL isotonic saline for 8 consecutive days.
(2) GEN group: Animals received GEN (100 mg/kg in 0.5 mL of isotonic saline, i.p.) for 8 consecutive days.
(3) Fluvoxamine + GEN group: Animals received fluvoxamine (25 mg/kg, orally) 45 min before injection of GEN.
(4) Fluvoxamine+ GEN group: Rats received fluvoxamine (50 mg/kg, orally) 45 min before injection of GEN.

It should be noted that the doses of fluvoxamine[19,20] and GEN were selected on the basis of the previous studies.[23,24]

All animals were kept in metabolic cages 24 h before sacrifice and urine samples were collected. After collecting the blood specimens, the animals were sacrificed by diethyl ether and both kidneys were removed and weighed. The right kidneys were used for pathologic examinations. Blood samples were centrifuged for 15 min at 2500 rpm and the serum was removed and frozen at −20°C for further investigations.[2] Serum blood urea nitrogen (BUN) and creatinine (Cr) levels were measured according to commercial kits instructions (Ziest Chem Diagnostics Co., Tehran, Iran), and sodium ($Na^+$) and potassium ($K^+$) concentrations were measured by using auto analyzer (Olympus AU 600, Tokyo, Japan). The serum level of malondialdehyde (MDA) was measured by the colorimetric method and the reaction of thiobarbituric acid and MDA.[25]

Glucose (Glu) and total Pro levels of urine were measured by a colorimetric method with local diagnostic kits (Pars Azmoon, Tehran, Iran).

### Histopathological examinations

The right kidney was excised after sacrifice, halved, and fixed by immersion in a 10% formaldehyde solution for several days. After that, the fixed tissues were embedded in paraffin and cut into 4–5 µm slices. The slices were mounted on the glass slides and stained with hematoxylin and eosin (H&E) for light microscopy analysis.[26] The assessment was conducted by a pathologist in a blinded way.

### Statistical analysis

All results are expressed as mean ± standard deviation (SD). The differences group means were estimated by one-way analyses of variance (ANOVA) followed by the Tukey *post hoc* test, using the SPSS 12 for windows. *P*-values less than 0.05 were considered to show significant differences for all comparisons made.

## Results

### Effect of fluvoxamine on gentamicin-induced changes in body and kidney weight

As shown in Table 1, the weight of the control group increased during the course of experiment compared to their initial weight (14.43%). Intraperitoneal injection of GEN decreased the bodyweight of the GEN group compared with their initial

**Table 1: Effect of fluvoxamine on gentamicin-induced changes in body and kidney weight**

| Treatment groups | Primary body weight (g) | Secondary body weight (g) | kidney weight/100 g body weight | Changes in body weight (%) |
|---|---|---|---|---|
| Control | 194 ± 18 | 222 ± 15 | 0.34 ± 0.3 | 14.43 |
| GEN | 220 ± 20.9 | 216.6 ± 23.8 | 0.54 ± 0.06*** | −1.5 |
| GEN + fluvoxamine (25 mg/kg) | 185 ± 5.7 | 160 ± 14.7 | 0.68 ± 0.05***,### | −13.5 |
| GEN + fluvoxamine (50 mg/kg) | 180 ± 2 | 159 ± 10.8 | 0.60 ± 0.02*** | −11 |

GEN = gentamicin
Data are presented as mean ± SD of six rats for each group. GEN was injected at the dose of 100 mg/kg i.p. in 0.5 mL in isotonic saline for 8 consecutive days. Fluvoxamine was orally given at the doses of 25 and 50 mg/ kg 45 min before gentamicin injection
***$P < 0.0001$ compared to control group
###$P < 0.0001$ compared to gentamicin group

weight (−1.5%). The decline in body weight of animals due to GEN nephrotoxicity was noticeably exacerbated by fluvoxamine at 25 and 50 mg/kg doses (−13.5% and −11%, respectively).

The ratio of an average weight of left and right kidneys to 100 g body weight also significantly increased in the GEN-treated animals compared with the control group ($P \leq 0.001$). Pretreatment with fluvoxamine augmented the elevated ratio of kidney weight in 100 g bodyweight compared with the GEN group. These changes at 25 mg were statistically significant ($P \leq 0.001$).

### Effect of fluvoxamine treatment on gentamicin-induced changes in serum blood urea nitrogen and creatinine concentrations

As shown in Figure 1, i.p. injection of GEN (100 mg/kg) significantly increased serum BUN and Cr concentrations compared with the saline group ($P < 0.001$ and $P < 0.01$). Treatment with 25 and 50 mg/kg of fluvoxamine, 45 min before the injection of GEN (100 mg/kg), augmented the increase in serum BUN concentration which was statistically significant at the dose of 25 mg/kg ($P < 0.001$).

### Effect of fluvoxamine on gentamicin-induced changes in urine glucose and protein levels

As shown in Figure 2, GEN (100 mg/kg, i.p.) significantly increased the concentration of urine Glu and Pro compared with the saline group ($P < 0.001$). Concurrent administration of fluvoxamine (25 and 50 mg/kg) with GEN intensified the elevation in urine Glu levels which was statistically significant at the dose of 25 mg/kg ($P < 0.001$). However, it had no significant effect on urine Pro level.

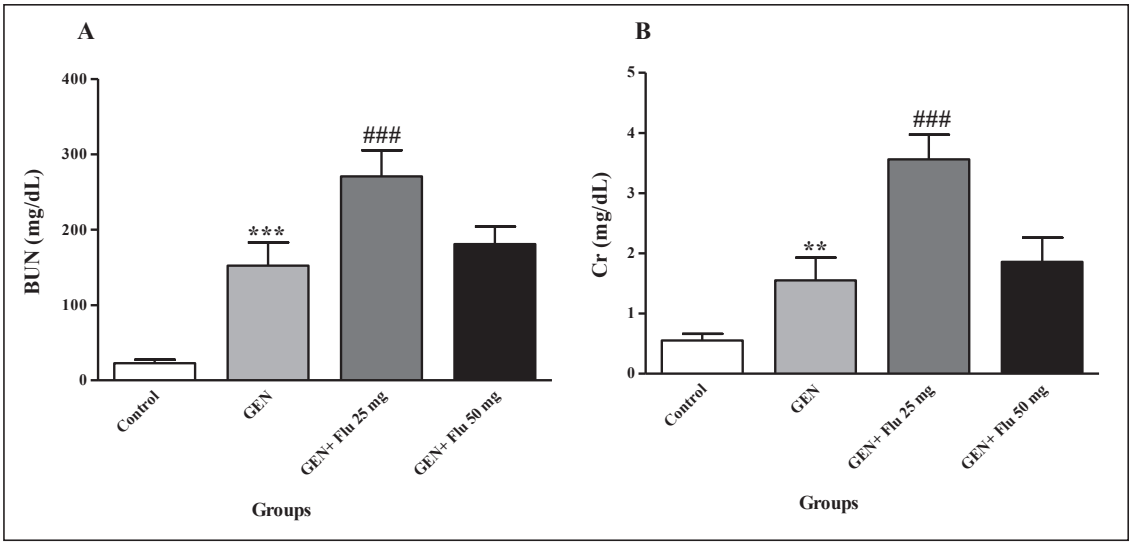


**Figure 1: Effect of fluvoxamine on GEN-induced changes in serum BUN (A) and Cr (B) concentrations. Data are presented as mean ± SD of six rats for each group. **Compared to the control group ($P \leq 0.01$). ***Compared to the control group ($P \leq 0.001$). ###Compared to GEN group ($P \leq 0.001$). BUN = blood urea nitrogen; GEN = gentamicin; Flu = fluvoxamine**

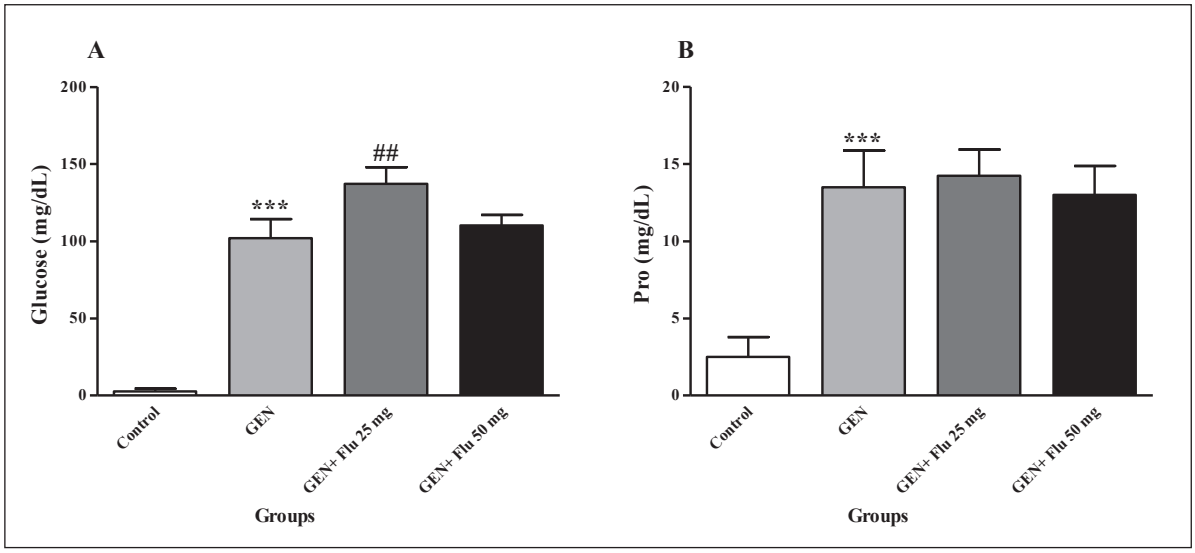


**Figure 2: Effect of fluvoxamine on GEN-induced changes in urine Glu (A) and Pro (B) levels. Data are presented as mean ± SD of six rats for each group. ***Compared to the control group ($P \leq 0.001$). ##Compared to GEN group ($P \leq 0.01$). Flu = fluvoxamine; GEN = gentamicin; Glu = glucose; Pro = protein**

### Effect of fluvoxamine on gentamicin-induced changes in serum $Na^+$ and $K^+$ concentrations

Injection of GEN (100 mg/kg) slightly raised the serum $Na^+$ and $K^+$ concentrations compared with the control group [Figure 3]. Oral administration of fluvoxamine (25 and 50 mg/kg) slightly augmented the serum $Na^+$ and $K^+$ concentrations as compared with the GEN group.

### Effect of fluvoxamine on gentamicin-induced changes in serum malondialdehyde levels

Administration of GEN (100 mg/kg, i.p.) resulted in a considerable rise in the serum concentration of MDA compared with the saline group ($P < 0.001$). Fluvoxamine (25 and 50 mg/kg) was not able to modify the elevated serum levels of MDA compared with GEN-treated group [Figure 4].

### Effect of fluvoxamine on gentamicin-induced changes in renal histopathology

As shown in Figure 5A, the histology of kidney tissues of control groups showed a normal appearance. In the GEN-treated group, however, the kidney tissue showed degenerative changes [Figure 5B], such as tubular necrosis/degeneration and tubular dilation. The GEN-induced histopathological lesions were intensified by concurrent treatment with fluvoxamine,

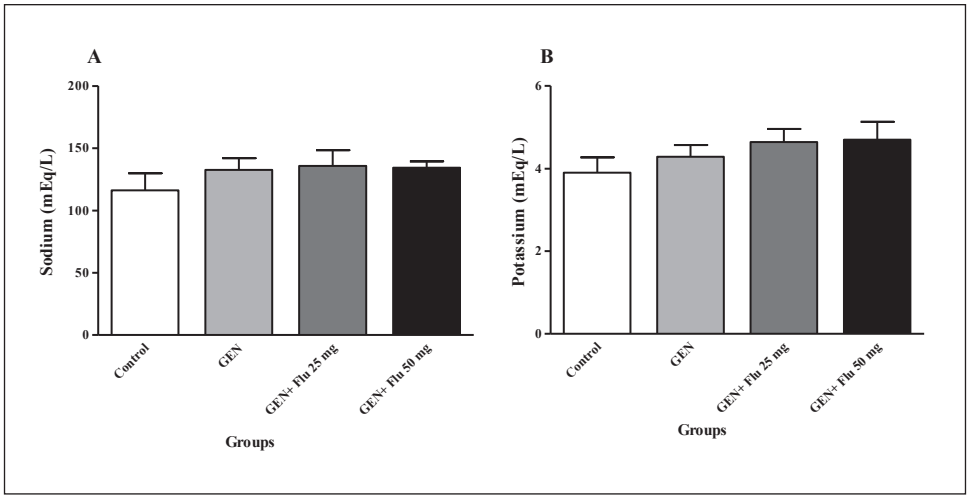


**Figure 3: Effect of fluvoxamine on GEN-induced changes in serum sodium (A) and potassium (B) concentrations. Data are presented as mean ± SD of six rats for each group. Flu = fluvoxamine; GEN = gentamicin**

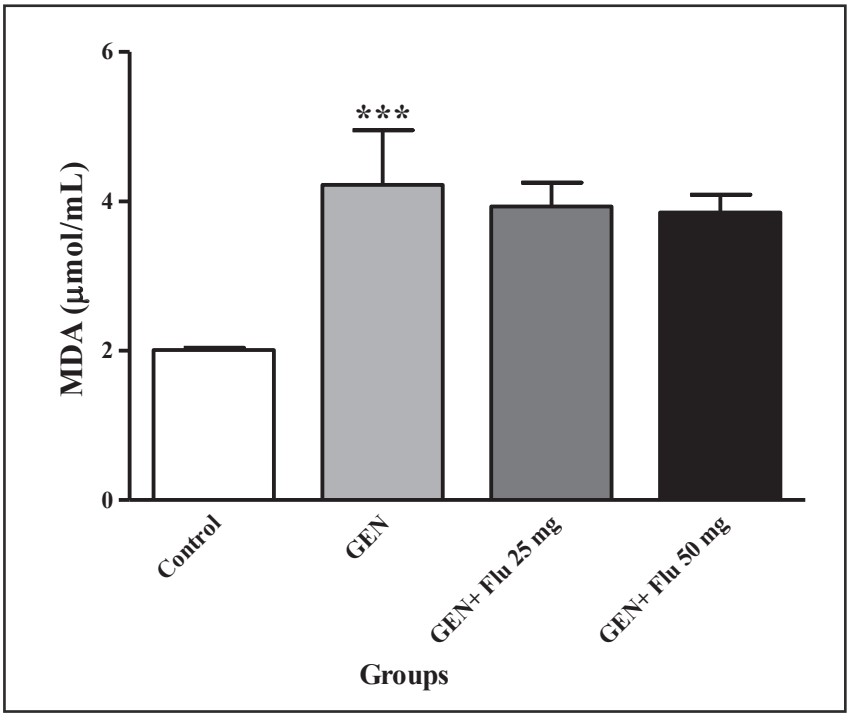


**Figure 4: Effect of fluvoxamine on GEN-induced changes in serum MDA levels. Data are presented as mean ± SD of six rats for each group. ***Compared to the control group ($P \leq 0.001$). Flu = fluvoxamine; GEN = gentamicin; MDA = malondialdehyde**

in comparison with those observed in the GEM-treated group [Figure 5C and D].

## Discussion

The findings of the current study showed that fluvoxamine could exacerbate the renal toxicity of GEN in rats. Despite the introduction of new drugs in the pharmaceutical market, GEN still plays an important role in the treatment of gram-negative infections. GEN-induced nephrotoxicity is related to its selective accumulation in the kidney cortex.[3,6]

In the present study, i.p. injection of GEN (100 mg/kg) significantly increased the concentrations of parameters related to renal toxicity such as Cr and BUN. GEN also inhibited the weight gain in rats and increased the index of kidney weight to body weight. These changes in biochemical parameters were well correlated with the pathological findings. In agreement with our results, there is much evidence that GEN induces nephrotoxicity in the experimental animals, which is characterized by a rise in serum Cr and BUN concentrations.[2,27]

Concurrent administration of fluvoxamine with GEN exacerbated the renal injury, which is evident by the increase in serum levels of Cr and BUN. Fluvoxamine also decreased the ratio of an average weight of kidneys to 100 g body weight. Our results showed that GEN also induced the excretion of Pro and Glu in the urine. Simultaneous administration of fluvoxamine with GEN augmented the urine Glu secretion compared with the GEN-treated rats.

The injection of GEN did not affect the serum concentrations of $Na^+$ and $K^+$. These results have been confirmed by the previous studies.[28,29] Taken together, our finding proposed that the nephrotoxicity of GEN was intensified by concurrent administration of fluvoxamine. Histological evaluation of the kidney tissues revealed that fluvoxamine along with GEN

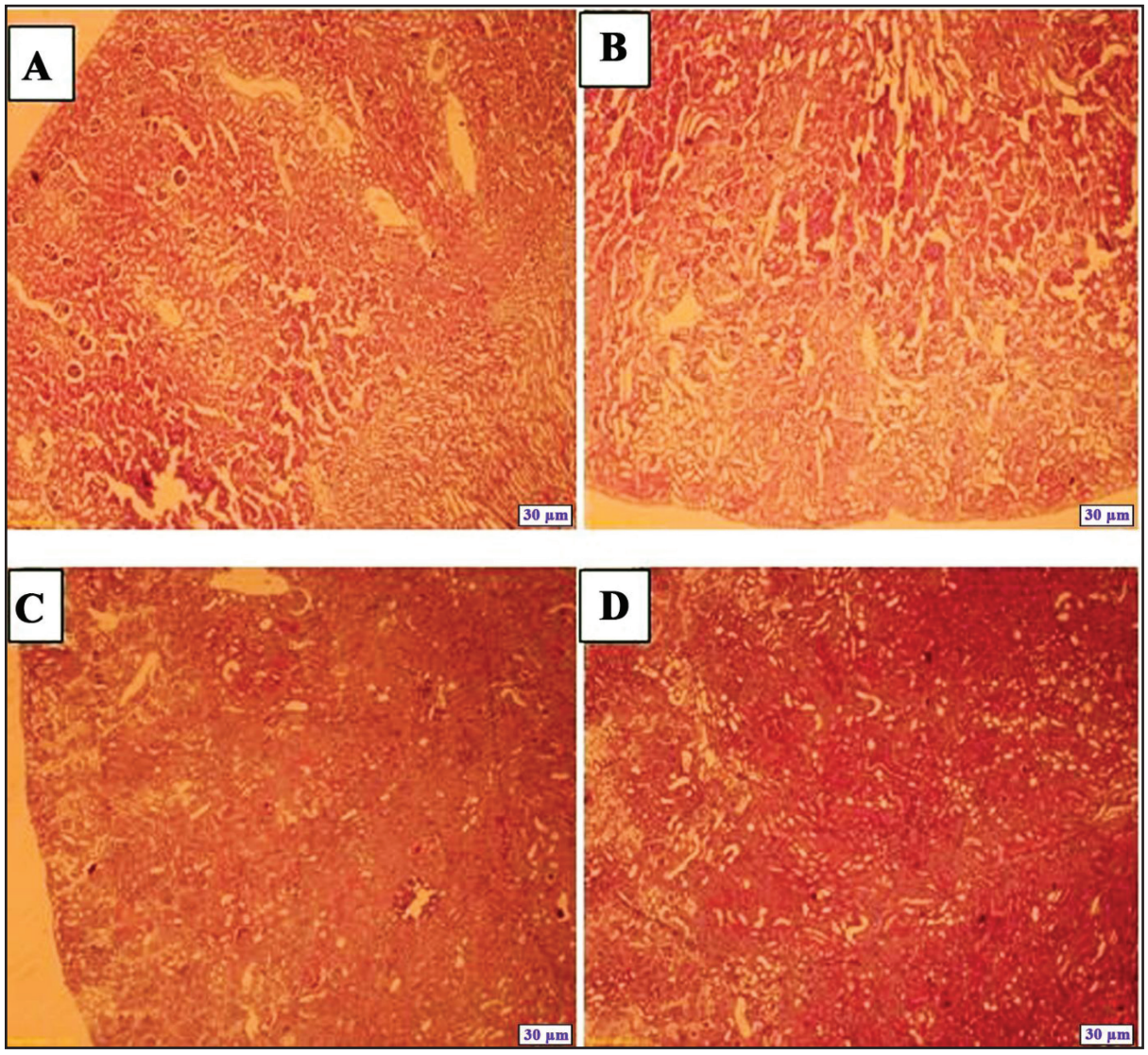


**Figure 5: Pathological examination renal tissue from rats. (A) Control (renal tubules are normal). (B) Gentamicin alone (tubules show degenerative changes and dilation). (C) Simultaneous treatment with fluvoxamine (25 mg/kg) and gentamicin (marked tubular necrosis). (D) Simultaneous treatment with fluvoxamine (50 mg/kg) and gentamicin (marked tubular necrosis). Sections were stained with hematoxylin and eosin, magnification ×20**

exacerbated changes in the kidneys, such as disturbing the structure of the glomeruli and tubules as well as leucocytes infiltration.

The precise mechanism of GEN-induced nephrotoxicity is not clear very well.[3,29] Reactive oxygen species is introduced as an important factor controlling the incidence of GEN-evoked nephrotoxicity.[3] Some studies have suggested that lipid peroxidation plays an essential role in this process.[30] Free radicals react with phospholipids and break the polyunsaturated fatty acids chains that result in lipid peroxidation and destruction of the cell membranes. MDA is an end product of lipid peroxidation process.[31,32]

In this study, GEN noticeably increased the serum MDA levels in the GEN-treated group compared with the control group. Similar results have been found in the other works. Yaman and Balikci[33] observed that renal toxicity of GEN is accompanied by an increase in the serum concentration of MDA. Oral administration of fluvoxamine had no effect on the increased concentration of serum MDA due to GEN. This finding implied that fluvoxamine had no effect on the GEN-induced lipid peroxidation process. This result was in good agreement with Kadkhodaee *et al*.[10] who found that fluvoxamine was not able to inhibit the lipid peroxidation in stomach tissues. On the contrary, Dursun *et al*.[19] showed that fluvoxamine was able to inhibit the indomethacin-induced ulcers in rats by activation of antioxidant mechanisms and inhibition of toxic oxidant mechanisms. This conflict in our finding of MDA with the Dursun *et al*., work may be related to the difference in the model of toxicity and the condition of experiment with the indicated study.

The precise mechanism of how fluvoxamine worsens the nephrotoxicity of GEN requires further investigation, but one possible mechanism is that fluvoxamine could stimulate the mitochondrial dysfunction due to GEN toxicity. In this context, it has been reported that some SSRIs antidepressants were able to stimulate the mitochondrial dysfunction. Li *et al*.[22] found that mitochondrial dysfunction induced by sertraline, an SSRIs, leads to liver toxicity. In addition, some antidepressants may trigger Parkinson's diseases due to mitochondrial dysfunction.[34] Furthermore, mitochondrial dysfunction has been observed in aminoglycosides-induced nephrotoxicity.[8,9]

In conclusion, the present data showed that concurrent administration of fluvoxamine with GEN could exacerbate the nephrotoxicity of GEN. However, further investigations are necessary to explain precise mechanism of this interaction.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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