Journal of Kyzylorda Scholarly Review

P-ISSN:3006-0265 | E-ISSN:3007-4681. Published by the Open University of Kyzylorda
Copyright © Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC-BY).
https://bulletin.ouk.kz/index.php/bulletin/index



PROTECTIVE EFFECT OF NICOTINAMIDE ON GENTAMICIN-INDUCED NEPHROTOXICITY IN MALE RATS

Watban Abdullah Ahmed[*1]
[1]Department of pharmacology and toxicology /college of pharmacy/ Tikrit University
[*]Correspondance: Watban85@tu.edu.iq

Article History:
Received: 30th Sept 2026; Revised: 20th Oct 2026; Accepted: 10th Nov 2026; Published: 21th Nov 2026

Abstract: Background: Gentamicin is a widely used aminoglycoside antibiotic limited by dose-dependent nephrotoxicity, driven mainly by oxidative stress, inflammation, and mitochondrial dysfunction. Nicotinamide (NAM), a vitamin B3 form and precursor of nicotinamide adenine dinucleotide (NAD^+), may protect renal tubular cells by supporting energy metabolism.
Objectives: To evaluate the prophylactic effect of NAM against gentamicin (GM)-induced nephrotoxicity in rats by measuring serum urea, creatinine, tumor necrosis factor-alpha (TNF-α), and superoxide dismutase (SOD).
Methods: Fifteen adult male Wistar rats were randomly divided into three groups (n = 5): control; GM (100 mg/kg/day, intraperitoneally, for 10 days); and GM + NAM (NAM 200 mg/kg/day, orally, 30 min before GM, for 10 days). Blood and kidneys were collected on day 11. Data were analyzed by one-way ANOVA and Tukey's test.
Results: Compared with control, GM significantly increased serum urea (125.26 ± 29.77 vs 30.20 ± 3.35 mg/dL), creatinine (1.37 ± 0.38 vs 0.51 ± 0.15 mg/dL), and TNF-α (607.20 ± 37.68 vs 292.80 ± 3.70 pg/mL) and decreased SOD (5.15 ± 0.60 vs 9.33 ± 0.40 U/mL) (all $P < 0.001$). Versus GM, NAM reduced urea by 51.0%, creatinine by 58.5%, and TNF-α by 51.0% and increased SOD by 39.5% (all $P < 0.001$). Creatinine, TNF-α, and urea ($P = 0.077$) did not differ significantly from control, whereas SOD remained lower ($P < 0.001$). Histology showed tubular necrosis with GM and nearly normal kidneys with GM + NAM.
Conclusion: Nicotinamide mitigated gentamicin-induced renal dysfunction, inflammation, and oxidative stress in rats, suggesting nephroprotection.

Keywords: Nicotinamide, Gentamicin, Nephrotoxicity, Oxidative stress, Tumor necrosis factor-alpha, Rats

Introduction

Climate Gentamicin, an aminoglycoside antibiotic, remains widely used for the treatment of severe Gram-negative bacterial infections despite its well-established risk of nephrotoxicity. The drug is excreted primarily unchanged by glomerular filtration, and up to 25% of treated patients may develop secondary nephrotoxicity [1]. Drug-induced nephrotoxicity is a common clinical problem and a well-established cause of both acute kidney injury (AKI) and chronic kidney disease [2]. Gentamicin accumulates in the proximal tubular cells, where it impairs lysosomal and mitochondrial function and triggers the production of reactive oxygen species (ROS), ultimately resulting in apoptosis, tubular necrosis, and a reduction in glomerular filtration [1,3Given that oxidative stress plays a significant role in this damage, numerous antioxidant substances have been explored as protective measures. [1,4]; However, a recognized method for prevention has not been developed for practical application. Cells in the proximal tubule are abundant in mitochondria and rely significantly on NAD^+-related metabolism for their energy needs. In research models of acute kidney injury, there is

Journal of Kyzylorda Scholarly Review
P-ISSN:3006-0265 | E-ISSN:3007-4681
https://bulletin.ouk.kz/index.php/bulletin/index

a swift decrease in renal NAD^+ levels; thus, increasing NAD^+ has been demonstrated to reduce damage to the kidneys from lack of blood flow, toxins, and inflammation. [5–8]. Nicotinamide, **which is** a **type** of vitamin B3, **acts** as a **building block** that **helps bring back** NAD^+ levels **by using** the salvage pathway**.** [5,6].

In **experiments with rodents**, **taking** nicotinamide **beforehand lowered kidney swelling**, **scarring**, and the **increase** in urea nitrogen and creatinine **levels in the blood.** [9,10], **Clinical studies** have **linked** niacinamide **to better results** in **cases of AKI related to** COVID-19**.** [11]. **Nonetheless**, **information regarding** its **influence on** nephrotoxicity **caused** by **aminoglycosides** (**gentamicin**) **is limited**. **Consequently**, **this research** was **aimed at assessing** the **preventive role** of nicotinamide against gentamicin-induced nephrotoxicity in rats **through the analysis of** serum urea, creatinine, tumor necrosis factor-alpha (TNF-α), and superoxide dismutase (SOD), **along with** histopathological **evaluation**.**2.**

Materials and Methods

1. Drugs and chemicals

Gentamicin injection (Pioneer Co., Iraq) and nicotinamide (Macklin, China; purity 99%) were dissolved in distilled water immediately before use. Serum urea and creatinine were determined using commercial colorimetric kits (Biolab, China), and serum TNF-α and SOD were measured using commercial kits (Sunlong Biotech, China).

2. Animals and ethical approval

Fifteen adult male Wistar albino rats (8–10 weeks old, 200–250 g) were housed in polypropylene cages at 22 ± 2 °C under a 12-h light/dark cycle with free access to standard chow and water, and were acclimatized for one week before the experiment. The study protocol was approved by the Institutional Animal Ethics Committee of the College of Pharmacy, Tikrit University (approval No. SERC31, dated 31/08/2026), and was conducted in accordance with international guidelines for the care and use of laboratory animals and the ARRIVE 2.0 reporting recommendations [12].

3. Experimental design

The rats were randomly divided into three groups (n = 5 per group) (Figure 1): **Group 1 (Control)**, healthy animals that received no treatment; **Group 2 (GM)**, received gentamicin 100 mg/kg intraperitoneally once daily for 10 days; and **Group 3 (GM + NAM)**, received nicotinamide 200 mg/kg orally 30 min before gentamicin 100 mg/kg intraperitoneally, once daily for 10 days.

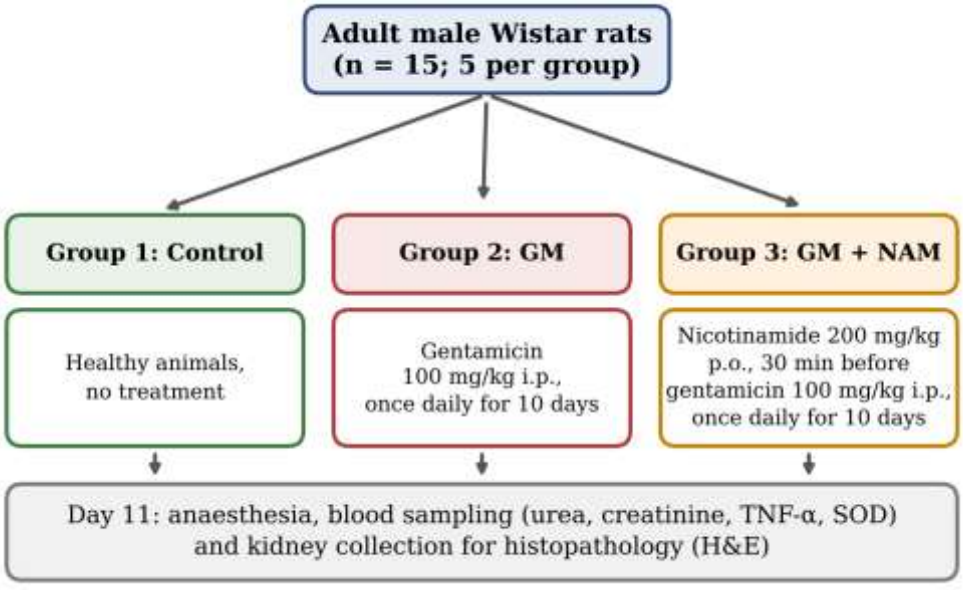


Figure 1. Schematic representation of the experimental design. GM, gentamicin; NAM,

nicotinamide; i.p., intraperitoneal; p.o., oral.

4. Sample collection and biochemical analysis

Twenty-four hours after the final dose (day 11), the animals were anaesthetized with ketamine and xylazine, and blood samples were obtained by cardiac puncture. Serum was separated by centrifugation at 3000 rpm for 10 min and stored at −20 °C until analysis. Serum urea and creatinine (mg/dL), TNF-α (pg/mL), and SOD (U/mL) were quantified spectrophotometrically with commercial kits, following the manufacturers' protocols. The animals were then sacrificed.

5. Histopathological Examination.

The kidneys were extracted and preserved in a solution of 10% formalin, transformed into tissue slices, and dyed with hematoxylin and eosin (H&E). These slices were analyzed using a light microscope at a magnification of ×400.

6. Statistical Analysis.

Data were **examined** and **showcased through** the Statistical Package for the Social Sciences (SPSS, version 23) and Microsoft Office Excel 365. **The findings** are **reported** as mean ± standard deviation (SD) **with** n **equal to** 5 **for each** group. **The distinctions between** the three groups (control, GM, and GM + NAM) were **evaluated using** one-way analysis of variance (ANOVA), **succeeded** by Tukey's post hoc test for **various** comparisons. A P value **beneath** 0.05 was **deemed** statistically significant.

Results

1. Serum biochemical parameters

One-way ANOVA showed highly significant differences among the three groups for all measured parameters ($P < 0.001$; Table 1, Figure 2). Compared with the control group, gentamicin significantly increased serum urea (about four-fold), creatinine (about 2.7-fold), and TNF-α (about 2.1-fold) and significantly decreased SOD (all $P < 0.001$).

Compared with the GM group, nicotinamide significantly reduced serum urea, creatinine, and TNF-α and significantly increased SOD (all $P < 0.001$). In the GM + NAM group, creatinine ($P = 0.921$) and TNF-α ($P = 0.943$) did not differ significantly from control values, and the difference in urea was also not significant ($P = 0.077$). In contrast, SOD remained significantly lower than in the control group ($P < 0.001$), indicating partial recovery.

Table 1. Serum urea, creatinine, TNF-α, and SOD in the experimental groups.

Parameter	Control	GM	GM + NAM	*F(2,12)*	*P*
Urea (mg/dL)	30.20 ± 3.35[a]	125.26 ± 29.77[b]	61.42 ± 18.63[a]	28.29	< 0.001
Creatinine (mg/dL)	0.51 ± 0.15[a]	1.37 ± 0.38[b]	0.57 ± 0.15[a]	18.26	< 0.001
TNF-α (pg/mL)	292.80 ± 3.70[a]	607.20 ± 37.68[b]	297.34 ± 2.92[a]	337.88	< 0.001
SOD (U/mL)	9.33 ± 0.40[a]	5.15 ± 0.60[b]	7.18 ± 0.58[c]	76.59	< 0.001

Values are mean ± SD (n = 5 per group). **In every** row, **items that have** the same letter **above them** are not **meaningfully** different (Tukey's post hoc test, P > 0.05). **The** P values **come** from **a** one-way ANOVA. GM **stands for** gentamicin; NAM **refers to** nicotinamide; TNF-α **means** tumor necrosis factor-alpha; **and** SOD **represents** superoxide dismutase**.**.

Journal of Kyzylorda Scholarly Review
P-ISSN:3006-0265 | E-ISSN:3007-4681
https://bulletin.ouk.kz/index.php/bulletin/index

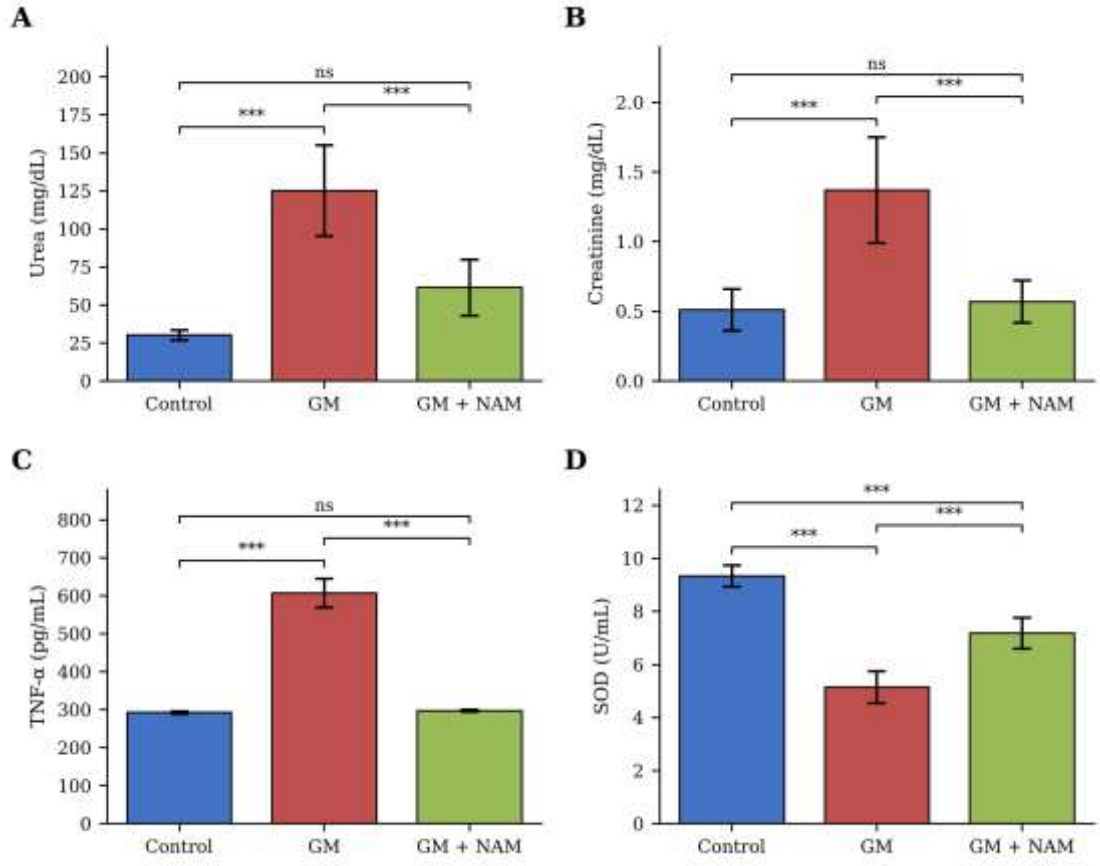


Figure 2. Serum levels of (A) urea, (B) creatinine, (C) TNF-α, and (D) SOD in the experimental groups (mean ± SD, n = 5). ** P* < 0.001; ns, not significant (Tukey's post hoc test). GM, gentamicin; NAM, nicotinamide; TNF-α, tumor necrosis factor-alpha; SOD, superoxide dismutase.

2. Histopathological findings

Kidney sections from the control group showed normal renal architecture, with an intact renal corpuscle (glomerulus and Bowman's capsule), proximal and distal convoluted tubules, and a normal periglomerular space (Figure 3A, B). In contrast, kidneys from the GM group showed inflammatory cell infiltration, hemorrhage within the renal tissue, desquamation and swelling of the tubular epithelial cells, tubular cell necrosis with desquamated cells in the tubular lumen, vacuolated cytoplasm, and tubular casts (Figure 3C, D). Kidneys from the GM + NAM group appeared nearly normal, with a well-preserved glomerulus, proximal and distal convoluted tubules, and periglomerular space (Figure 3E) and normal-appearing collecting tubules (Figure 3F).

Journal of Kyzylorda Scholarly Review
P-ISSN:3006-0265 | E-ISSN:3007-4681
https://bulletin.ouk.kz/index.php/bulletin/index

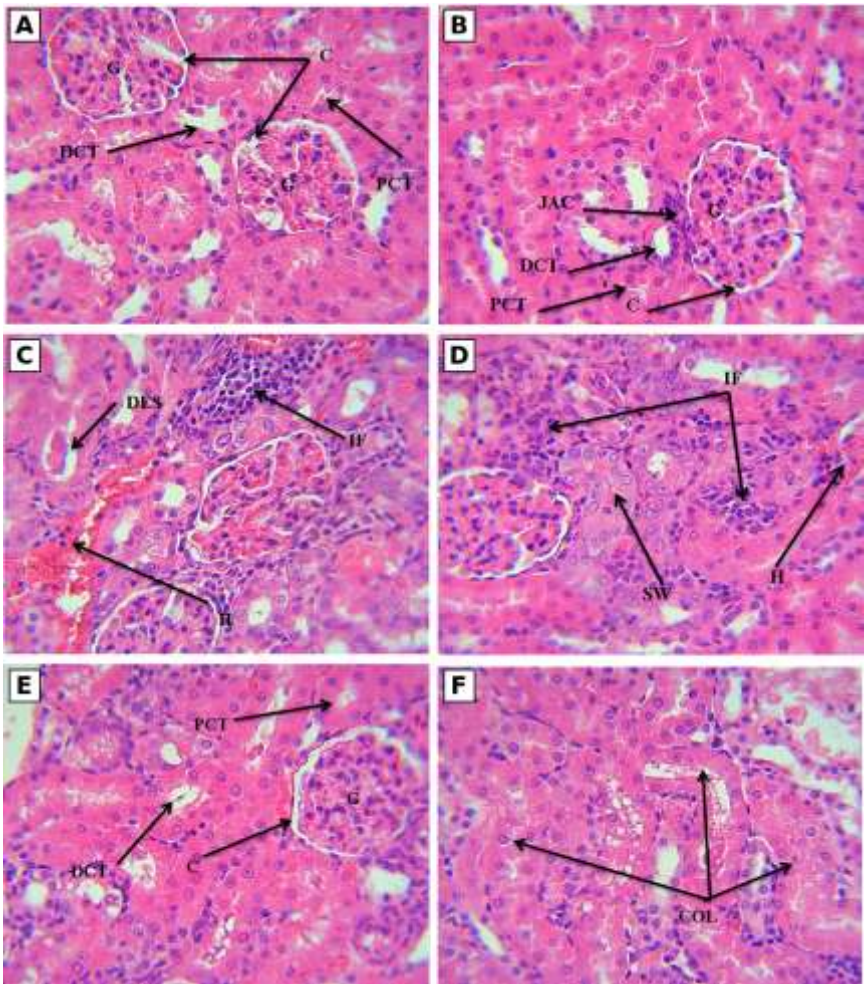


Figure 3. Representative kidney sections stained with H&E (×400). (A) Control group: renal corpuscle (G), proximal convoluted tubule (PCT), distal convoluted tubule (DCT), and periglomerular space (C). (B) Control group: G, PCT, DCT, C, and juxtaglomerular apparatus (JAC). (C) GM group: inflammatory cell infiltration (IF), hemorrhage (H), and desquamation of the tubular epithelium (DES). (D) GM group: IF, H, and swelling of the tubular epithelial cells (SW). (E) GM + NAM group: nearly normal G, PCT, DCT, and C. (F) GM + NAM group: nearly normal collecting tubules (COL). GM, gentamicin; NAM, nicotinamide.

Discussion

This **research demonstrated** that gentamicin **led to considerable damage to kidney** function, **indicated** by a four **times escalation** in serum urea and a 2.7 **times increase** in serum creatinine, **alongside elevated** TNF-α and **reduced** SOD levels. Prophylactic nicotinamide markedly mitigated these effects, reducing serum urea and creatinine by approximately 51% and 59%, respectively. Creatinine and TNF-α **levels went back** to **what is normal**, urea **levels were found to be similar to** the control (**even though they were** still **slightly** higher), and SOD **levels showed some improvement**, **highlighting** the **possible** protective **effects** of nicotinamide in this **study** model**.**. The **increase** in **kidney indicators caused** by gentamicin **aligns** with the **recognized trend** of nephrotoxicity **associated with aminoglycosides. This condition** is **marked** by **the build-up** in the proximal tubules, oxidative **damage**, and **harm to mitochondria**, **which eventually disrupts** glomerular filtration and **leads to the** retention of nitrogenous waste **substances.** [1,3]. Other rat studies have reported similar increases in urea and creatinine that were mitigated by antioxidants such as vitamin C and curcumin [1,4].

The increase in TNF-α and decrease in SOD indicate that inflammation and impaired antioxidant defense accompany gentamicin injury, in line with the central role of oxidative

stress in this experimental model [1,3,4]. The normalization of TNF-α and the increased SOD activity in the nicotinamide-treated group suggest that nicotinamide may act, at least in part, by limiting inflammatory and oxidative injury. Because SOD remained below control values, however, the antioxidant protection was incomplete. The histopathological findings, in which the tubular necrosis, inflammatory infiltration, and hemorrhage seen in the GM group were largely absent in the GM + NAM group, are consistent with the biochemical results. Although the specific mechanisms were not evaluated in this study, several plausible explanations can be proposed. The levels of NAD^+, which decrease during acute kidney injury, might be replenished through the salvage pathway, helping to preserve mitochondrial performance and energy availability within renal tubules [5–8]. Furthermore NAD^+ is a substrate for sirtuins which help adjusting inflammatory responses and oxidative stress [5,6]. Validate this function, nicotinamide has been shown to attenuate the tubular damage, pro-inflammatory signaling, and fibrosis across multiple kidney models [9,10]. Moreover , supplementation of niacinamide correlated with a better outcomes in acute kidney injury [11]. Ramification NAD^+ deficiency demonstrate putative variation between acute and chronic kidney disease [13], which ensure the value of early, prophylactic administration as used in this study.

The substantially greater attenuation of creatinine compared with urea merits discussion. Urea is affected by urine flow and protein breakdown , whereas creatinine typically increases after substantial glomerular filtration dysfunction, therefore the two markers may did not change in parallel [1]. Serum urea and creatinine are late and non-specific indicators, and newer biomarkers are recommended for earlier and more accurate assessment of kidney injury [14]. Dosage optimization and timing should be considered, in mice model, nicotinamide was effective when given prophylactically, but it was ineffective at advanced stages, even very high doses were poorly tolerated [9].

Conclusion

Nicotinamide supplementation (200 mg/kg/day orally) demonstrated a significant protective effect against gentamicin-induced nephrotoxicity in rats. The treatment decreased serum urea, creatinine, and TNF-α levels in contrast enhanced SOD activity. These results suggested that nicotinamide may serve as a potential nephroprotective agent. Nonetheless, further histological, biochemical, and mechanistic investigations are required before its clinical relevance can be assessed.

Acknowledgement

The author gratefully acknowledges the College of Pharmacy, Tikrit University, for providing the facilities required to complete this study.

Funding

No funding was received for conducting for this study.

Conflict of interest

The author declares no conflict of interest.

References:

[1] Tomşa AM, Răchişan AL, Pandrea SL, et al. Curcumin and vitamin C attenuate gentamicin-induced nephrotoxicity by modulating distinctive reactive species. *Metabolites.* 2023;13(1):49.

[2] Dobrek L. A synopsis of current theories on drug-induced nephrotoxicity. *Life (Basel).* 2023;13(2):325.

[3] Tomsa AM, Alexa AL, Junie ML, Rachisan AL, Ciumarnean L. Oxidative stress as a potential target in acute kidney injury. *PeerJ.* 2019;7:e8046.

[4] Laorodphun P, Cherngwelling R, Panya A, Arjinajarn P. Curcumin protects rats against gentamicin-induced nephrotoxicity by amelioration of oxidative stress, endoplasmic reticulum stress and apoptosis. *Pharm Biol.* 2022;60(1):491-500.

[5] Ralto KM, Rhee EP, Parikh SM. NAD^+ homeostasis in renal health and disease. *Nat Rev*



Nephrol. 2020;16(2):99-111.
[6] Katsyuba E, Romani M, Hofer D, Auwerx J. NAD⁺ homeostasis in health and disease. *Nat Metab.* 2020;2(1):9-31.
[7] Morevati M, Fang EF, Mace ML, et al. Roles of NAD⁺ in acute and chronic kidney diseases. *Int J Mol Sci.* 2023;24(1):137.
[8] Manrique-Caballero CL, Kellum JA, Gómez H, De Franco F, Giacchè N, Pellicciari R. Innovations and emerging therapies to combat renal cell damage: NAD⁺ as a drug target. *Antioxid Redox Signal.* 2021;35(17):1449-66.
[9] Kumakura S, Sato E, Sekimoto A, et al. Nicotinamide attenuates the progression of renal failure in a mouse model of adenine-induced chronic kidney disease. *Toxins (Basel).* 2021;13(1):50.
[10] Zheng M, Cai J, Liu Z, et al. Nicotinamide reduces renal interstitial fibrosis by suppressing tubular injury and inflammation. *J Cell Mol Med.* 2019;23(6):3995-4004.
[11] Raines NH, Ganatra S, Nissaisorakarn P, et al. Niacinamide may be associated with improved outcomes in COVID-19-related acute kidney injury: an observational study. *Kidney360.* 2021;2(1):33-41.
[12] Percie du Sert N, Hurst V, Ahluwalia A, et al. The ARRIVE guidelines 2.0: updated guidelines for reporting animal research. *PLoS Biol.* 2020;18(7):e3000410.
[13] Faivre A, Katsyuba E, Verissimo T, et al. Differential role of nicotinamide adenine dinucleotide deficiency in acute and chronic kidney disease. *Nephrol Dial Transplant.* 2021;36(1):60-8.
[14] Ostermann M, Zarbock A, Goldstein S, et al. Recommendations on acute kidney injury biomarkers from the Acute Disease Quality Initiative consensus conference: a consensus statement. *JAMA Netw Open.* 2020;3(10):e2019209.