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Effects of tadalafil on vancomycin-induced nephrotoxicity in rats

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ABSTRACT

Tadalafil (TAD) is a member of the Phosphodiesterase 5 (PDE 5) inhibitors used to treat erectile dysfunction. However, recent evidence suggests that it has beneficial nephroprotective effects via a variety of mechanisms. The aim of the present study was to investigate the protective effect of TAD against vancomycin (VAN) - induced nephrotoxicity in rats (n=24), which divided into three groups; model control group that received intraperitoneal VAN, TAD group that received oral TAD and intraperitoneal VAN and normal healthy group. TAD group demonstrated a significant decrease in serum levels of renal function biomarkers and a significant increase in creatinine clearance level compared to the model control group. Furthermore, it showed a significant reduction in the renal levels of malondialdehyde (MDA), neutrophil gelatinase-associated lipocalin (NGAL), and TNF-α with a significant elevation in the renal level of glutathione (GSH) compared to the model control group. Histologically, TAD group showed a significant reduction in renal tissue injury that prove its nephroprotective effect due to its antioxidant and anti-inflammatory properties.

Keywords: oxidative stress, nephrotoxicity, tadalafil, vancomycin

INTRODUCTION

The kidney performs many vital functions, including eliminating medications in their initial state or metabolites. Many drugs undergo filtration, secretion,

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reabsorption, and elimination by the kidney, making it a common site of toxicity[1]. As well as, the kidneys take about 25% of the cardiac output, which expose them to more circulating drug than other organs[2]. Several medications like amphotericin B, vancomycin, aminoglycosides, and platin-containing chemotherapeutics are highly nephrotoxic[3]. Vancomycin (VAN) is a glycopeptide used as a first-line antibacterial drug for treating infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA)[4]. Subsequently, numerous randomized clinical trials demonstrated that VAN poses a higher risk of nephrotoxicity than most other antibiotics[5]. The reported incidence of VAN-induced nephrotoxicity was 14.3%[6]. The recommended criteria for VAN-induced nephrotoxicity were a rise in serum creatinine level of at least 0.5 mg/dL or a 50% increase over baseline in consecutive daily tests[7]. The accurate pathophysiological mechanisms of VAN-induced nephrotoxicity are not yet completely known. However, the existing consensus states that vancomycin's nephrotoxic effect is primarily due to its intracellular accumulation in the proximal convoluted tubules[5].

Tadalafil (TAD) is a member of phosphodiesterase enzyme type-5 inhibitors approved in the management of erectile dysfunction, lower urinary tract symptoms (LUTS) secondary to benign prostatic hypertrophy (BPH)[8], and pulmonary arterial hypertension[9]. TAD inhibits the PDE5 enzyme with a greater selectivity (in comparison with sildenafil and vardenafil), thus improving intracellular levels of cGMP[10]. Experimental studies have confirmed that PDE-5 inhibitors improve endothelial function[11,12] and reduce infarct size in animal models of myocardial infarction[13]. PDE-5 inhibitors exert beneficial renal effects in the I/R rat model[14,15]. Several previous studies have shown that tadalafil can significantly improve renal injury due to several nephrotoxic agents[16–18], but the effect of TAD on VAN-induced nephrotoxicity has not been investigated. Therefore, the present study was conducted to determine the in vivo influence of orally administered TAD on VAN-induced renal injury in rats.

METHODOLOGY

Drugs

Vancomycin (vial) was obtained from Gulf pharmaceutical industries, United Arab Emirates and dissolved in distilled water according to the manufacturer's instructions. TAD powder was obtained from Hangzhou hyper chemical market, China and suspended in 0.5% carboxymethyl cellulose (CMC)[19,20].

Animals

Adult male Wistar albino rats weighing 175–285g were housed for two weeks for acclimatization under controlled conditions, including 12 h light/dark cy-

cles and controlled temperature (25 ºC), with free access to standard food and water.

Experimental design

Twenty-four male Wistar albino rats (*Rattus norvegicus*) were randomly assigned to three groups of 8 rats each as follows: (1) Normal control group: Maintained on standard food and water for 14 days. (2) Model control (VAN) group: Treated with intraperitoneal VAN (200mg/kg/ twice daily) for 14 days. (3) TAD group: Treated with oral TAD (5mg/kg/ once daily) and intraperitoneal VAN (200mg/kg/twice daily) for 14 days.

The induction of significant nephrotoxicity in the rat model depended on a pilot study and a previous study by Uhuo and his colleagues[21]. The dose of TAD was selected according to previous studies[18,22].

Samples collection

On the 15th day, the rats were anaesthetized by a mixture of ketamine 90mg/kg (Alfasan, Holland) and xylazine 10mg/kg (Bimeda, Canada) given intramuscularly. After that, Rats were sacrificed by decapitation. The blood samples were taken from the trunk and allowed to clot at room temperature. Thereafter centrifuged for 15-20 minutes at 3000 rpm. The isolated serum was kept at -80 ºC to be available afterwards for biochemical examination. Both kidneys of each rat were excised and washed with phosphate buffer saline (pH 7.4). One of the kidneys was rapidly frozen with dry ice and stored at -80 ºC to be available afterwards for homogenization. At the same time, the other kidney was kept in a neutral buffered formalin of 10% for histopathological analysis.

Renal tissue homogenization

Kidney tissues were homogenized in phosphate buffer saline in a proportion of 10% (w/v), using tissue homogenizer (IKA, Germany) for 1 minute at 4 ºC. After that, centrifuged at 3000 rpm for 20 minutes.

Biochemical analyses

Urea and creatinine serum levels were measured according to the urease-modified Berthelot method[23] and Jaffe method[24] respectively, using reagent kits (Linear Chemicals, Spain) with UV/Visible spectrophotometer (Cecil, England). Creatinine clearance was calculated using a neural network-based calculator of rat creatinine clearance from serum creatinine and body weight[25]. Renal levels of glutathione (GSH), malondialdehyde (MDA), neutrophil gelatinase-associated lipocalin (NGAL), and tumor necrosis factor- alpha (TNF-α) as well as serum cystatin C level, were measured according to the sandwich

ELISA technique[26], using rat ELISA kits (MyBioSource, USA) with ELISA plate reader (HUMAN Diagnostic Worldwide, Germany).

Histopathological analysis

Kidney tissue processing was done using the paraffin section technique[27]. The slides were examined under a light microscope (Olympus, Japan) at 20X magnification. Kidney tissue damage was graded according to the affected area in the tubulointerstitial area of the cortex, including tubular epithelial cell swelling, cast deposition, necrosis, desquamation, and interstitial inflammation as follows: 0 for normal tissues, 1 (mild) for < 25%, 2 (moderate) for > 25% but < 50%, 3 (severe) for ≥ 50% but < 75%, 4 (very severe) for ≥ 75%.

Statistical analysis

SPSS software version 26 was applied for data analysis. Numerical data are expressed as Mean ± SEM and one-way ANOVA with least significant differences (LSD) post hoc test for comparison among groups. For histopathological scores, Kruskal-Wallis and Mann-Whitney U tests were used. The difference was considered significant when p value was < 0.05.

RESULTS and DISCUSSION

Effects of tadalafil on renal function biomarkers

Serum levels of cystatin C, urea, and creatinine were significantly higher ($p < 0.05$) in the VAN group as compared to their corresponding levels in the normal healthy group. Furthermore, the level of creatinine clearance (Cr Cl) was significantly lower ($p < 0.05$) in the VAN group compared to that of the normal group. On the other hand, the TAD group showed significantly lower ($p < 0.05$) serum levels of renal function biomarkers and a significant ($p < 0.05$) higher level of Cr Cl as compared with their corresponding levels in the VAN group (Table 1).

Table 1. Effects of tadalafil on renal function biomarkers (mean + SEM)

Groups	Serum cystatin C (ng/ml)	Serum urea (mg/dl)	Serum Cr (mg/dl)	Cr Cl (ml/min)
Normal	269.62±10.43	28.68±1.29	0.49±0.03	0.79±0.07
VAN	553.15±27.82[a]	42.28±1.69[a]	1.30±0.21[a]	0.35±0.08[a]
TAD	324.11±11.03[ab]	34.39±2.08[ab]	0.55±0.03[b]	0.74±0.05[b]

Cr: creatinine; Cr Cl: creatinine clearance; a: $p < 0.05$ compared to normal group; b: $p < 0.05$ compared to VAN group.

Effects of tadalafil on oxidative stress biomarkers

The VAN group showed a significant increment ($p < 0.05$) in the level of renal tissue malondialdehyde (MDA) and a significant decline ($p < 0.05$) in the level of renal tissue glutathione (GSH) as compared to their corresponding levels in the normal group. On the other hand, the TAD group showed significantly lower ($p < 0.05$) level of renal tissue MDA and significantly higher ($p < 0.05$) level of GSH in renal tissue as compared to the VAN group (Table 2).

Table 2. Effects of tadalafil on renal tissue oxidative stress biomarkers (mean + SEM)

Groups	MDA (nmol/ml)	GSH (µg/ml)
Normal	1.17±0.04	38.14±1.08
VAN	4.04±0.10 [a]	10.83±0.23 [a]
TAD	1.83±0.03 [ab]	28.69±0.40 [ab]

MDA: malondialdehyde; GSH; glutathione; a: $p < 0.05$ compared to normal group; b: significant difference $p < 0.05$ compared to VAN group.

Effects of tadalafil on inflammatory biomarkers

Table 3 showed that the levels of neutrophil gelatinase-associated lipocalin (NGAL) and tumor necrosis factor-alpha (TNF-α) in renal tissue were significantly higher ($p < 0.05$) in the VAN group than in the normal group. More interestingly, the TAD group showed significantly lower ($p < 0.05$) renal tissue levels of NGAL and TNF-α compared with the VAN group.

Table 3. Effects of tadalafil on renal tissue inflammatory biomarkers (mean + SEM)

Groups	NGAL (pg/ml)	TNF-α (pg/ml)
Normal	254.02±12.41	870.43 ± 50.93
VAN	1269.73±62.24 [a]	1761.96±46.4 [a]
TAD	351.30±11.37 [ab]	872.2±84.7 [b]

NGAL: neutrophil gelatinase-associated lipocalin; TNF-α: tumor necrosis factor- alpha; a: $p < 0.05$ compared to normal group; b: $p < 0.05$ compared to VAN group.

Histopathological examination

VAN group showed significant kidney tissue damage ($p < 0.05$) as compared to the normal group, with the development of tubular epithelial cell swelling, desquamation, necrosis, cast deposition and interstitial inflammation (Figure 1-B). VAN group had 87.5% highly severe (score 4) and 12.5% severe (score 3) histopathological changes compared to healthy kidney tissue. More interestingly, The TAD group showed a significant decline ($p < 0.05$) in kidney tissue injury compared to the VAN group (Figure 1-C). In comparison to those of normal kidney tissue, the TAD group showed 12.5% mild (score 1), 75% moderate (score 2), and 12.5% severe (score 3) histopathological changes.

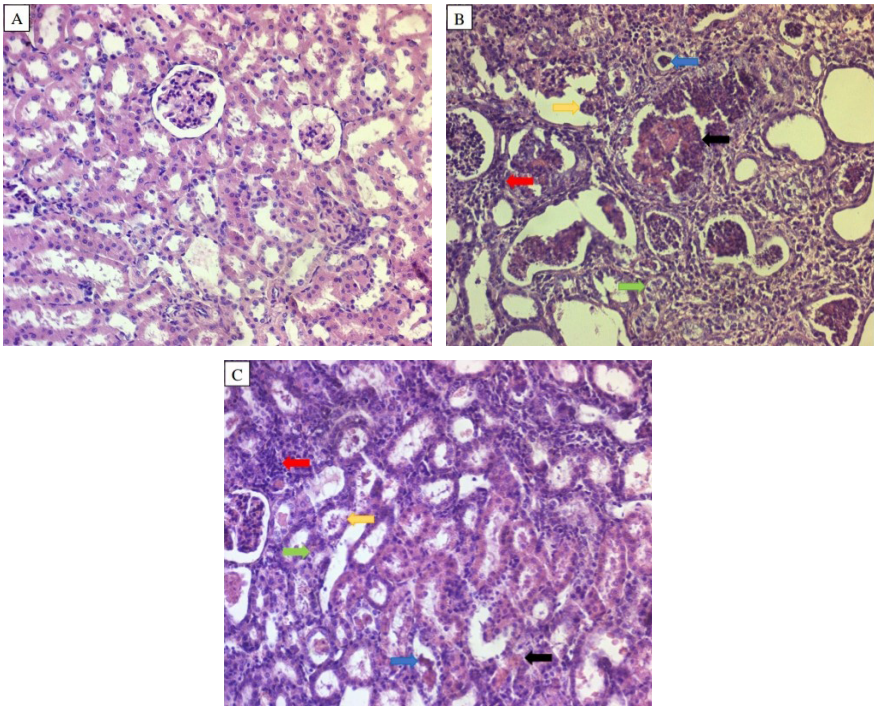

Figure 1. Kidney tissue sections of the experimental groups

(A): Normal healthy group, (B): VAN group, (C): TAD group, green arrow: tubular epithelial cell swelling, yellow arrow: desquamation, black arrow: necrosis, blue arrow: cast deposition, red arrow: interstitial inflammation [H&E, 20X]

Oxidative stress is one of the primary mechanisms of intracellular renal damage induced by VAN, which may result in acute tubular necrosis (ATN). VAN increases oxygen consumption by inducing mitochondrial oxidative phosphorylation. High oxygen consumption promotes reactive oxygen species (ROS)

generation. ROS cause depolarization of the mitochondrial membrane and liberation of cytochrome C, which activates the apoptotic caspases chain. Subsequently, necrosis will develop after ATP depletion[28].

The current study demonstrated that intraperitoneal VAN administration in a total dose of 400mg/kg for fourteen days deteriorates renal function in accordance with a previous study[21] and could be related to oxidative stress, which could enhance the formation of a set of vasoactive mediators that can deteriorate renal functions directly by causing renal vasoconstriction and thus reduce GFR[29]. Likewise, oxidative stress can enhance the action of adenosine[30]. In the VAN group, the renal tissue level of MDA was significantly increased, while the renal tissue level of GSH was significantly reduced, in agreement with previous studies[21,31,32]. The highly sensitive compound to ROS is lipid. MDA is produced as a byproduct of lipid peroxidation by ROS[31]. GSH is a significant tissue antioxidant that directly overcomes reactive hydroxyl free radicals and other oxygen free radicals. It functions as a substrate of glutathione peroxidase, permitting the reduction of peroxides. So, the exhaustion of GSH is considered an indicator of oxidative stress[33]. NGAL and TNF-α renal tissue levels were significantly increased in the VAN group in agreement with previous studies[34,35], which could be attributed to NF-κB pathway activation by high ROS, resulting in the release of many cytokines that cause inflammation and necrosis[36]. Histologically, VAN causes significant kidney tissue damage with the development of tubular epithelial cell swelling, desquamation, necrosis, cast deposition and interstitial inflammation in line with previous study[32]. ROS subsequently cause cellular energetics depletion[5]. Cell necrosis is historically regarded as a passive process due to the loss of cellular energetics. ATP depletion results in a loss of a cytoskeletal element, cell polarity, and membrane integrity with increased back leak of tubular filtrate. As well as ATP depletion causes a high increase in intracellular ca^{+2} level which can participate in cell death[30].

On the other hand, oral daily TAD during parenteral VAN administration improved renal function in consistency with a recent study done by Mohammed et al. showing that the antioxidant, anti-inflammatory, and anti-apoptotic effects of TAD reduce gentamicin-induced renal injury in rats[17]. Moreover, TAD group showed significantly lower renal MDA and higher renal GSH levels. This finding is in accordance with a previous study[18], which can be attributed to the activation of the Nrf2/HO-1 mediated antioxidant pathway[37]. The TAD group showed significantly lower renal levels of inflammatory biomarkers NGAL and TNF-α in agreement with previous studies[16,22]. This anti-inflammatory effect of tadalafil can probably be attributed to inhibiting NF-κB activation through

increased intracellular levels of cGMP and cGMP-dependent protein kinase (PKG)[38]. Histologically, TAD group showed a significant reduction in renal tissue injury as compared to the VAN group. TAD treatment markedly reduced the development of tubular cell swelling, desquamation, cast, necrosis, and interstitial inflammation. These outcomes appear in accordance with a previous study done by Gasanove et al. showed tadalafil administration before renal ischemia/reperfusion injury attenuated necrosis, leukocyte infiltration, brush border abnormality, and glomerular sclerosis in rat kidney compared to that of the induced group[39]. In conclusion, according to this research's findings, the protective effect of TAD against VAN-induced nephrotoxicity could be attributed to the antioxidant and anti-inflammatory properties of TAD.

STATEMENT OF ETHICS

The protocol of the current study was approved by the Institutional Review Board (IRB) of the College of Medicine / Al-Nahrain University, with an ethical clearance number of 178 on August 23, 2022.

CONFLICT OF INTEREST STATEMENT

The authors declare to have no conflict of interest.

AUTHOR CONTRIBUTIONS

Hassanen A. ABDULAMEER conducted experiments, interpreted the results, wrote the draft of the manuscript and formatted the manuscript to Journal specifications. Adeeb A. AL-ZUBAIDY designed the research concept, supervised the conduct of all experiments, and reviewed the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Sri Laasya TP, Thakur S, Poduri R, Joshi G. Current insights toward kidney injury: decrypting the dual role and mechanism involved of herbal drugs in inducing kidney injury and its treatment. Curr Res -Biotechnol, 2020;2:161-175. Doi: 10.1016/j.crbiot.2020.11.002

2. Griffin BR, Faubel S, Edelstein CL. Biomarkers of drug-induced kidney toxicity. Ther Drug Monit, 2019;41(2):213-226. Doi: 10.1097%2FFTD.0000000000000589

3. Gray MP, Barreto EF, Schreier DJ, Kellum JA, Suh K, Kashani KB, et al. Consensus obtained for the nephrotoxic potential of 167 drugs in adult critically ill patients using a modified Delphi method. Drug Saf, 2022;45(4):389-398. Doi: 10.1007/s40264-022-01173-4

4. Brown NM, Goodman AL, Horner C, Jenkins A, Brown EM. Treatment of methicillin-resistant Staphylococcus aureus (MRSA): updated guidelines from the UK. JAC Antimicrob Resist, 2021;3(1). Doi: 10.1093/jacamr/dlaa114

5. Kan W-C, Chen Y-C, Wu V-C, Shiao C-C. Vancomycin-associated acute kidney injury: a narrative review from pathophysiology to clinical application. Int J Mol Sci, 2022;23(4):2052. Doi: 10.3390/ijms23042052

6. Kunming P, Can C, Zhangzhang C, Wei W, Qing X, Xiaoqiang D, et al. Vancomycin associated acute kidney injury: a longitudinal study in China. Front Pharmacol, 2021;12:632107. Doi: 10.3389/fphar.2021.632107

7. Rybak M, Lomaestro B, Rotschafer JC, Moellering Jr. R, Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. AJHP, 2009;1;66(1):82-98. Doi: 10.2146/ajhp080434

8. Carson CC, Rosenberg M, Kissel J, Wong DG. Tadalafil – a therapeutic option in the management of BPH-LUTS. Int J Clin Pract, 2014;68(1):94-103. Doi: 10.1111/ijcp.12305

9. Henrie AM, Nawarskas JJ, Anderson JR. Clinical utility of tadalafil in the treatment of pulmonary arterial hypertension: an evidence-based review. Core Evid, 2015;10:99-109. Doi: 10.2147/ce.s58457

10. Mónica FZ, De Nucci G. Tadalafil for the treatment of benign prostatic hyperplasia. Expert Opin Pharmacother, 2019;20(8):929-937. Doi: 10.1080/14656566.2019.1589452

11. Radovits T, Arif R, Bömicke T, Korkmaz S, Barnucz E, Karck M, et al. Vascular dysfunction induced by hypochlorite is improved by the selective phosphodiesterase-5-inhibitor vardenafil. Eur J Pharmacol, 2013;710(1-3):110-119. Doi: 10.1016/j.ejphar.2013.04.012

12. Yaguas K, Bautista R, Quiroz Y, Ferrebuz A, Pons H, Franco M, et al. Chronic sildenafil treatment corrects endothelial dysfunction and improves hypertension. Am J Nephrol, 2010;31(4):283-291. Doi: 10.1159/000279307

13. Hutchings DC, Anderson SG, Caldwell JL, Trafford AW. Phosphodiesterase-5 inhibitors and the heart: compound cardioprotection?. Heart, 2018;104(15):1244-1250. Doi: 10.1136/heartjnl-2017-312865

14. Lahoud Y, Hussein O, Shalabi A, Nativ O, Awad H, Khamaisi M, et al. Effects of phosphodiesterase-5 inhibitor on ischemic kidney injury during nephron sparing surgery: quantitative assessment by NGAL and KIM-1. World J Urol, 2015;33(12):2053-2062. Doi: 10.1007/s00345-015-1579-3

15. Amasyali AS, Akkurt A, Kazan E, Yilmaz M, Erol B, Yildiz Y, et al. The protective effect of tadalafil on IMA (ischemia modified albumin) levels in experimental renal ischemia-reperfusion injury. Int J Clin Exp Med, 2015;8(9):15766.

16. Salama AAA, Mostafa RE, Omara EA. Ameliorative effects of phosphodiesterase (PDE) inhibitors in potassium dichromate-induced acute renal failure in rats. Int J Pharm Sci Rev Res, 2016;36(2):40-46.

17. Mohammed EM, Elberry AA, Sayed MM, Abdelfatah SF. Evaluation of the effect of administration of tadalafil on gentamicin-induced nephrotoxicity in rats. Egypt J Med Hum Genet, 2022;3(4):114-139. Doi: 10.21608/ejmr.2022.267691

18. Adeneye AA, Benebo AS. Chemopreventive effect of tadalafil in cisplatin-induced nephrotoxicity in rats. Niger J Physiol Sci, 2016;31(1):1-10.

19. Bhatia P, Singh N. Ameliorative effect of phosphodiesterase-5 inhibitor in rat model of vascular dementia. Curr Neurovasc Res, 2019;16(1):27-39. Doi: 10.2174/1567202616666190130153954

20. Rashid M, Kotwani A, Fahim M. Long-acting phosphodiesterase 5 inhibitor, tadalafil, and superoxide dismutase mimetic, tempol, protect against acute hypoxia-induced pulmonary hypertension in rats. Hum Exp Toxicol, 2012;31(6):626-636. Doi: 10.1177/0960327111429138

21. Uhuo EN, Egba SI, Nwuke PN, Odinamadu H. Renoprotective effects of Adansonia digitata leaf extract on renal function and histopathological changes in vancomycin-induced nephrotoxicity in Wistar rats. Comp Clin Path, 2022;31(2):229-242. Doi: 10.1007/s00580-022-03325-5

22. Hamdy MM, Abdel-Rahman MS, Badary DM, Sabra MS. Effects of furosemide and tadalafil in both conventional and nanoforms against adenine-induced chronic renal failure in rats. Eur J Med Res, 2022;27(1):1-17. Doi: 10.1186/s40001-022-00747-3

23. Fawcett J, Scott J. A rapid and precise method for the determination of urea. J Clin Pathol, 1960;13(2):156-159. Doi: 10.1136/jcp.13.2.156

24. Heinegård D, Tiderström G. Determination of serum creatinine by a direct colorimetric method. Clin. Chim. Acta, 1973;43(3):305-310. Doi: 10.1016/0009-8981(73)90466-X

25. Pellicer-Valero ÓJ, Massaro GA, Casanova AG, Paniagua-Sancho M, Fuentes-Calvo I, Harvat M, et al. Neural network-based calculator for rat glomerular filtration rate. Biomedicines, 2022;10(3):610. Doi: 10.3390/biomedicines10030610

26. Aydin S. A short history, principles, and types of ELISA, and our laboratory experience with peptide/protein analyses using ELISA. Peptides (NY), 2015;72:4-15. Doi: 10.1016/j.peptides.2015.04.012

27. Mescher A. L. Histology & Its Methods of Study. In: Junqueira's Basic Histology Text and Atlas. 14th edition. New York: McGraw-Hill Education; 2016. pp. 1-15.

28. Kwiatkowska E, Domański L, Dziedziejko V, Kajdy A, Stefańska K, Kwiatkowski S. The mechanism of drug nephrotoxicity and the methods for preventing kidney damage. Int J Mol Sci, 2021;22(11):6109. Doi: 10.3390/ijms22116109

29. Choi YK, Elaine D, Kwon Y-G, Kim Y-M. Regulation of ROS production and vascular function by carbon monoxide. Oxid Med Cell Longev, 2012;2012. Doi: 10.1155/2012/794237

30. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. Compr Physiol, 2012;2(2):1303. Doi: 10.1002%2Fcphy.c110041

31. Sadeghi H, Karimizadeh E, Sadeghi H, Mansourian M, Abbaszadeh-Goudarzi K, Shokripour M, et al. Protective effects of hydroalcoholic extract of rosa canina fruit on vancomycin-induced nephrotoxicity in rats. J Toxicol, 2021;2021:5525714. Doi: 10.1155/2021/5525714

32. Uckun Z, Guzel S, Canacankatan N, Yalaza C, Kibar D, Coskun Yilmaz B. Potential protective effects of naringenin against vancomycin-induced nephrotoxicity via reduction on apoptotic and oxidative stress markers in rats. Drug Chem Toxicol, 2020;43(1):104-111. Doi: 10.1080/01480545.2018.1512612

33. Gaucher C, Boudier A, Bonetti J, Clarot I, Leroy P, Parent M. Glutathione: antioxidant properties dedicated to nanotechnologies. Antioxidants, 2018;7(5):62. Doi: 10.3390/antiox7050062

34. Kandemir FM, Yildirim S, Kucukler S, Caglayan C, Mahamadu A, Dortbudak MB. Therapeutic efficacy of zingerone against vancomycin-induced oxidative stress, inflammation, apoptosis and aquaporin 1 permeability in rat kidney. Biomed Pharmacother, 2018;105:981-991. Doi: 10.1016/j.biopha.2018.06.048

35. Yu P, Luo J, Song H, Qian T, He X, Fang J, et al. N-acetylcysteine ameliorates vancomycin-induced nephrotoxicity by inhibiting oxidative stress and apoptosis in the in vivo and in vitro models. Int J Med Sci, 2022;19(4):740-752. Doi: 10.7150%2Fijms.69807

36. Alsawaf S, Alnuaimi F, Afzal S, Thomas RM, Chelakkot AL, Ramadan WS, et al. Plant flavonoids on oxidative stress-mediated kidney inflammation. Biology (Basel), 2022;11(12):1717. Doi: 10.3390/biology11121717

37. Abdel-Wahab BA, Alkahtani SA, Elagab EAM. Tadalafil alleviates cisplatin-induced reproductive toxicity through the activation of the Nrf2/HO-1 pathway and the inhibition of oxidative stress and apoptosis in male rats. Reprod Toxicol, 2020;96:165-174. Doi: 10.1016/j.reprotox.2020.06.015

38. He Y, Huang Y, Mai C, Pan H, Luo H-B, Liu L, et al. The immunomodulatory role of PDEs inhibitors in immune cells: Therapeutic implication in rheumatoid arthritis. Pharmacol Res, 2020;161:105134. Doi: 10.1016/j.phrs.2020.105134

39. Gasanov F, Aytac B, Vuruskan H. The effects of tadalafil on renal ischemia reperfusion injury: an experimental study. Bosn J Basic Med Sci, 2011;11(3):158-162. Doi: 10.17305/bjbms.2011.2567