Evaluation of the Effect of Telmisartan on Gentamicin-Induced Nephrotoxicity in Rats

Reem Haj Darwish* and Shadi Homsi

Laboratory of Pharmacology, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Damascus University, Syria

Abstract: Gentamicin (Gen) is widely used against serious infections, but its therapeutic use is limited due to its nephrotoxicity which causes acute renal failure.

We aimed to evaluate the potential protective effect of highly selective angiotensin II (Ang II) type 1 (AT1) receptor blocker Telmisartan (Tel) on the renal damage generated by Gentamicin in rats.

36 Male Wistar rats were divided into six groups (6 rats each): Naive, Tel group (10 mg/kg/day orally for 7 days), control (1 ml/day 0.9% NaCl intraperitoneally i.p. for 7 days), Gen group (100 mg/kg/day i.p for 7 days), Gen + Tel 5 mg/kg/day concurrently for 7 days, Gen + Tel 10 mg/kg/day concurrently for 7 days.

Concentrations of serum urea, serum creatinine, and renal reduced glutathione (GSH) levels were evaluated after treatment.

Gen was observed to cause a severe nephrotoxicity, which was evidenced by an elevation of serum urea and creatinine levels which weren't altered by simultaneous treatment with Tel. The oxidative stress caused by Gen demonstrated by a decrease in renal GSH level was significantly attenuated by Telmisartan (the higher dose).

Conclusion: This study proves the nephrotoxicity caused by Gentamicin, and suggests that concurrent treatment with Telmisartan ameliorate oxidative stress induced by gentamicin without changes to serum urea and creatinine.

Keywords: Nephrotoxicity, Gentamicin, Telmisartan, Oxidative Stress, Rat.

INTRODUCTION

Aminoglycoside antibiotics are widely used in the treatment of a variety of infections (for example, ocular, pulmonary, and intestinal infections) produced by Gram-negative bacteria and bacterial endocarditis [1].

Despite the toxic effects of aminoglycosides (AGs), the emergence of bacterial resistance to commonly used antibiotics has necessitated retention of the aminoglycosides as a viable treatment option. Aminoglycosides are an attractive treatment alternative in these situations due to their chemical stability, fast bactericidal effect, synergy with beta-lactam antibiotics, low incidence of resistance, and relative lower cost [2]. Gentamicin is probably the most commonly used and studied of all the aminoglycosides [3]. The cationic structure seems to have an important role in its toxicity, mostly affecting renal (nephrotoxicity) and hearing (ototoxicity) tissues in which it accumulates [1]. The incidence of aminoglycoside nephrotoxicity has progressively increased until reaching 10–25% of the treatments [1].

The typical clinical manifestation of Gentamicin toxicity is non-oliguric or even polyuric renal excretion dysfunction, accompanied by an increase in plasma creatinine, urea and other metabolic products of the organism, proteinuria, enzymuria, aminoaciduria, glycosuria, and electrolyte alterations (hypercalciuria, hypermagnesuria, hypocalcemia, and hypomagnesemia) [1].

Gentamicin appear to exert its nephrotoxic effects via 3 general mechanisms: renal tubular toxicity, reduced glomerular filtration rate (GFR), and reduction in renal blood flow (RBF) [2].

The gentamicin –induced nephrotoxicity occurs by selective accumulation of the drug in renal proximal convoluted tubules that leads to loss of its brush border integrity [4].

In the proximal tubule of the nephron, Gentamicin undergoes endocytosis and concentrate in lysosomes, the Golgi body, and endoplasmic reticulum. Once a threshold is reached, the Gentamicin empties into the cytosol and act on the mitochondria to induce apoptosis and necrosis [2]. Gentamicin has been demonstrated to increase the generation of reactive oxygen species (ROS) like superoxide anions, hydroxyl radicals and hydrogen peroxides, and reactive nitrogen species (RNS) in the renal cortex which are able of damaging many cellular molecules including proteins,

*Address correspondence to this author at the Laboratory of Pharmacology, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Damascus University, Syria; Tel: 00963-933278680; E-mail: reemd1979@gmail.com

ISSN: 2223-3806 / E-ISSN: 1927-5951/18

lipids, and nucleic acids, thus impairing cell function and leading to cell death [1, 4, 5].

Apparently, ROS and oxidative stress have been shown to play a key role in the toxicity of Gentamicin resulting in acute kidney injury [6].

Other factors induced by Gentamicin increase intracellular calcium concentration and cause mesangial cell contraction and results in *K*f (ultrafiltration coefficient) and GFR reduction: (i) platelet-activating factor (PAF) secretion and autocrine action; (ii) activation of the renal renin–angiotensin system (RAS); (iii) production and action of vasoconstrictors such as endothelin-1 and thromboxane A2 arising from endothelial dysfunction or imbalance; (iv) and extracellular calcium-sensing receptor (CaSR) stimulation [1].

Contracting factors produced by mesangial, vascular, and tubular cells, including ROS, PAF, angiotensin-II (Ang II), and endothelin-1 act in an autocrine and paracrine manner to induce contraction of glomerular vessels and mesangial cells, which reduce RBF and *K*f, respectively, and lower GFR [1].

As mentioned earlier, oxidative stress has been suggested to have a key role in Gentamicin nephrotoxicity. Cotreatment with a variety of antioxidants protects from Gentamicin-induced renal damage [1, 3].

This effect of antioxidants might be related to a combined action at different levels, including the following: (i) softening of Gentamicin's direct cytotoxicity; (ii) inhibiting vasoconstriction and mesangial contraction; and (iii) an antiinflammatory action [1].

The peptide hormone (Ang II) is a primary effector of the renin-angiotensin system (RAS) [7]. There are 4 types of angiotensin receptors (AT1, AT2, AT3, AT4) [8]. Ang II is thought to mediate its pathophysiological effects through AT1 receptors, which are primarily found in blood vessels, the liver, kidneys, heart and brain [9]. AT1 is the receptor that enables most of the hemodynamic changes in the body that are related to angiotensin II, these include vasoconstriction and stimulation of aldosterone release. In response to Ang II, there is an increase in glomerular pressure and glomerular permselectivity as well as activation of fibrosis and cellular growth in the kidney [8].

Angiotensin converting enzyme (ACE) inhibitors block the RAS by inhibiting conversion of angiotensin I to Ang II, whereas Ang II receptor blockers (ARBs), have the potential to block the system more completely through antagonism of Ang II binding to the (AT1) receptor, thereby inhibiting the vasoconstrictor and aldosterone-secreting effects of Ang II [10].

Telmisartan is a well established angiotensin receptor blocker that can be administered orally once daily. It has the longest half-life t½ among ARBs [9]. The drug had the strongest binding affinity to the AT1 receptor among commercially available ARBs evaluated in an *in vitro* study [9]. The highly selective and potent antagonism of the AT1 receptor by the nonpeptide antagonist Telmisartan in many tissues, including vascular smooth muscle and the adrenal gland, results in inhibition of the vasopressor and aldosterone secreting effects of Ang II [10]. The high affinity of Telmisartan for AT1-receptors is associated with negligible or marginal affinity for other known receptors (such as adenosine, adrenergic, dopaminergic, endothelin receptors and others) [11].

Also Telmisartan acted as a partial agonist of Peroxisome proliferator-activated receptor (PPARγ), a nuclear transcription factor that is expressed mainly in adipose tissue, but also in muscle and liver, it plays a role in the regulation of carbohydrate and lipid metabolism as it causes differentiation of adipocytes, increases lipogenesis and enhances uptake of fatty acids and glucose [10, 12].

The selective block of AT1-receptors is expected to block the deleterious action of Ang II, as well as selective activation of PPAR-γ can induce a suppression of inflammatory molecules, oxidative stress and preservation of endothelial function [11].

The antioxidant property of Telmisartan was proved in many studies. Telmisartan significantly restored renal reduced glutathione level in rats have acute ischemia/reperfusion renal injury [13], and attenuated the depletion of antioxidant defense system GSH in rats with Cisplatin-induced nephrotoxicity [14].

In this study we aimed to assess whether the nephrotoxic effects caused by acute administration of Gentamicin could be prevented or reduced by treatment with Telmisartan using biochemical tests of serum urea and creatinine as markers of renal function and renal GSH level as a marker of oxidative stress.

MATERIALS AND METHODS

Chemicals

Gentamicin sulphate was purchased from (YANTAI JUSTWARE Pharmaceutical-China), Telmisartan purchased from MYLAN API Laboratories.

Animals

In this study, 36 healthy adult male Wistar rats, weighing 230–290 g, were used. The animals were kept under controlled temperature (22 ± 2°C), humidity (60%), and regular light cycle (12h light/ 12h dark) conditions. They were fed with standard rat chow and allowed free access to food and water during the experiments. All experimental procedures were conducted in accordance with the principles for the care and use of laboratory animals for scientific purposes.

Experimental Protocol

The animals were randomly divided into 6 groups (six rats each): (A) Naive group, (B) Telmisartan group treated orally with Telmisartan by gavage at a dose of 10 mg/kg for 7 consecutive days, (C) Control group received 1 ml/day 0.9% NaCl intraperitoneally (i.p.) for 7 consecutive days; (D) Gentamicin group received Gen (i.p.) at a daily dose of 100 mg/kg for 7 consecutive days which is known to cause nephrotoxicity in rats; [15-17], (E) group treated orally with Telmisartan by gavage at a dose of 5 mg/kg, [18-20] for 7 consecutive days concomitantly with the same dose of GEN applied in the D-group, (F) group treated orally with Telmisartan using gavage at a dose of 10 mg/kg, [20, 21] for 7 consecutive days concomitantly with the same dose of Gen applied in the D-group. The animals were anesthetized 24h after the last application (8 days after the beginning of the experiment) using ether, blood samples for biochemical analysis were taken through heart puncture, then the animals were sacrificed, and the right kidneys were subsequently removed.

Assessment of Serum Urea and Creatinine Levels

Serum urea was determined using commercial kit (Diasys) according to Urease-GLDH method using 902 Roche / Hitachi Automatic Analyzer. Serum creatinine was determined using Commercial kit (Human) according to Jaffe reaction using HumaLyzer 3500 HUMAN.

Determination of Kidney Oxidative Stress Parameter

The right kidneys were isolated from each animal, kept at -80°C. Subsequently the tissue was homogenized in cold potassium phosphate buffer. The renal homogenates were centrifuged at 10000 g for 15 min at 4°C. The resulting supernatant was used for determination of GSH level using a commercial kit from Abnova (reduced glutathione assay kit KA1649) according to improved 5,5'-dithiobis(2-nitrobenzoic acid DTNB) method which combines deproteination and detection into one reagent. DTNB reacts with reduced glutathione to form a yellow product. The optical density was measured following 96-well plate procedure using microplate reader (Elisys Uno Human) at wave length 405.

Statistical Analysis

Results were expressed as mean ± SEM. Statistical significant difference was determined by one-way analysis of variance (ANOVA) followed by Tukey's post test for multiple comparison using (Graphpad Prism version 5). *P* values < 0.05 were considered to be statistically significant.

RESULTS

Effects of Gen and Tel Treatments on Serum Urea and Creatinine Levels

Serum urea levels were significantly higher in Gentamicin group in comparison to control (P<0.01) but there was no significant difference between Gen and Gen+Tel groups (Tel 5mg/kg and Tel 10mg/kg) (Figure **1**, Table **1**).

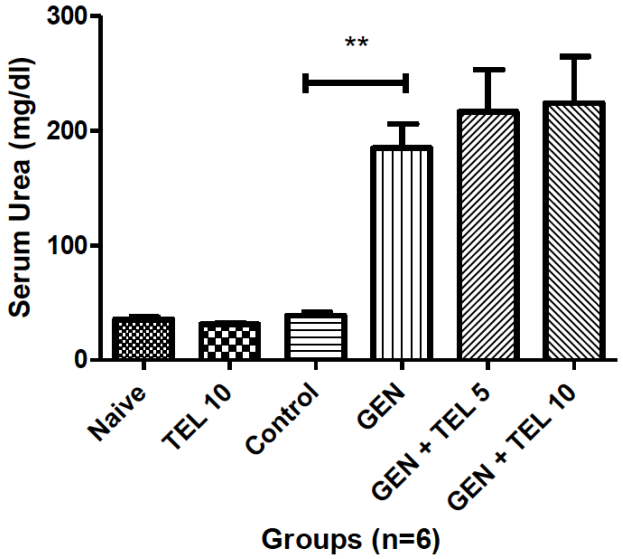

Figure 1: Effect of Gen and its combination with Tel on serum urea level. Results represent the mean ± SEM (n= 6 rats). ** P< 0.01 *vs* control group.

Creatinine levels were significantly higher in Gen group in comparison to control (*P*<0.05), but there was no significant difference between Gen and Gen+Tel groups (Tel 5mg/kg and Tel 10mg/kg) (Figure **2**, Table **1**).

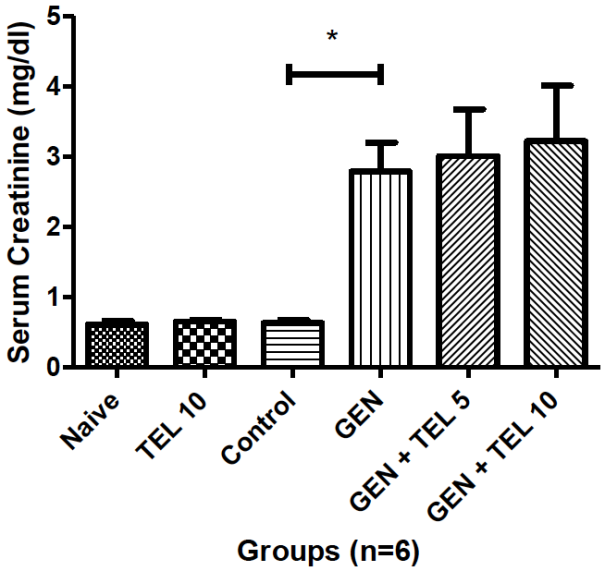

Figure 2: Effect of Gen and its combination with Tel on serum creatinine level. Results represent the mean ± SEM (n= 6 rats). * P< 0.05 *vs* control group.

Table 1: Gentamicin and Telmisartan Effects on Serum Urea and Creatinine Concentrations in Rats Model, Results Expressed as (Mean ± SEM)

Groups	Serum Urea (mg/dl)	Serum Creatinine (mg/dl)
Group A: Naive	35.67 ± 1.647	0.615 ± 0.05143
Group B: Tel 10	31.00 ± 1.390	0.6583 ± 0.02587
Group C: Control	38.83 ± 3.146	0.6350 ± 0.04209
Group D: Gentamicin	184.8 ± 20.98	2.790 ± 0.4100
Group E: Gen + Tel 5	216.7 ± 36.69	3.010 ± 0.6675
Group F: Gen + Tel 10	224.0 ± 40.94	3.225 ± 0.7903

Effects of Gen and Tel Treatments on Renal Reduced Glutathione Level

Rats from Gentamicin group presented significant decrease in GSH content, (P<0.001), whereas GSH levels were higher in the combination treatment group than GEN group with significant difference between Gen group and Gen+Tel 10mg/kg group (P<0.01), which became close to normal value (Figure **3**, Table **2**).

DISCUSSION

The gentamicin-nephrotoxicity involves renal free radical generation, reduction in antioxidant defense mechanisms, and glomerular congestion, resulting in diminished glomerular filtration rate and renal dysfunction [4].

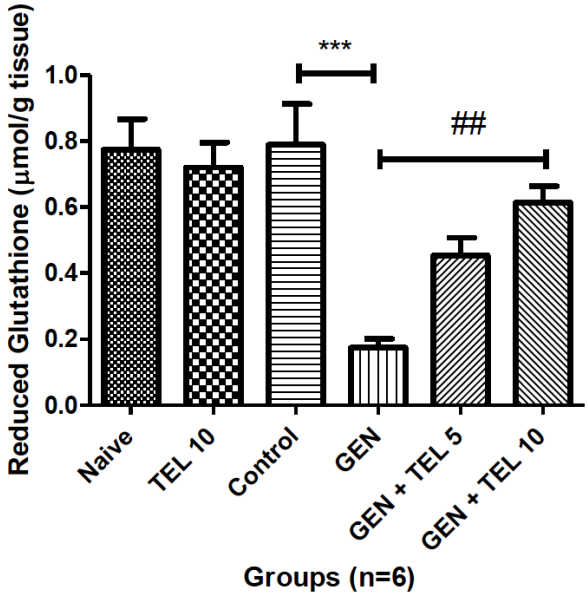

Figure 3: Effect of Gen and its combination with Tel on renal GSH level. Results represent the mean ± SEM (n= 6 rats). *** P < 0.001 *vs* control group, ## P < 0.01 *vs* Gentamicin group.

Table 2: Gentamicin and Telmisartan Effects on Renal GSH Levels in Rats Model, Results Expressed as (Mean ± SEM)

Groups	Renal Reduced Glutathione (µmol/g tissue)
Group A: Naive	0.7745 ± 0.09219
Group B: Tel 10	0.7204 ± 0.07597
Group C: Control	0.7898 ± 0.1230
Group D: Gentamicin	0.1748 ± 0.02676
Group E: Gen + Tel 5	0.4537 ± 0.05408
Group F: Gen + Tel 10	0.6146 ± 0.04884

Gentamicin-induced nephrotoxicity is functionally characterized by an increase in serum creatinine and blood urea nitrogen, incidences of albuminuria, decrease in glomerular filtration rate, and renal dysfunction [4].

These changes are preceded and accompanied by signs of tubular dysfunction (release of brush-border and lysosomal enzymes, renal wasting of K^+, Mg^{2+}, Ca^{2+} and glucose) [22].

Ang II is one of the most potent endogenous vasoconstrictors, and its known pressor effects are all mediated by AT1 receptors [23, 24].

Experimental studies provide ample evidence that Ang II stimulates intracellular formation of $\cdot O^{2-}$ by upregulating subunits of the membrane-bound NAD(P)H oxidase and by facilitating assembly of

subunits. Studies also suggest that mitochondrial ROS generation is stimulated by Ang II [25].

Ang II-induced ROS may play a pivotal role in several pathophysiologic diseases of the kidney and vasculature (*e.g.*, glomerulonephritis, diabetic nephropathy, hypertension, acute renal failure, progression of renal disease) [25]. Additionally, several studies showed that angiotensin-converting enzyme inhibitor or AT1 receptor antagonist treatment reduces oxidative stress in patients with renal diseases [25].

There are many experimental data suggesting that Gentamicin increases levels of serum creatinine, and urea [26-29]. Results of our study confirmed that Gen, at a dose of 100 mg/kg/day for 7 consecutive days, produces typical nephrotoxicity, as Gen-induced increase in serum creatinine subsequently a reduction in glomerular filtration rate (GFR). This impairment in glomerular function was also accompanied by an increase in serum urea level, refer to (Figures **1**, **2**; Table **1**).

In vivo, ROS have been identified as mediators of proximal tubular necrosis, mesangial cell contraction, and acute renal failure caused by Gentamicin. ROS scavengers have proved to be beneficial at reducing the development of renal damage induced by the administration of Gen [30].

In our study, Gen-induced increase in serum creatinine and urea levels weren't significantly changed by concurrent administration of Telmisartan.

Our study results regarding Telmisartan effect on serum urea and creatinine levels in rats suffers from kidney disease are in conflict with some animal model studies reported that administration of Telmisartan alleviated the increase in the levels of serum creatinine in several induced renal failure models as seen in rats with renal failure induced by 5/6 nephrectomy, [19, 31] in rats with nephrotoxicity induced by contrast media, [18] and also in rats with ischemia/reperfusion renal injury [13].

A specific transport mechanism (megalin) has been identified in proximal tubule epithelial cells, which accumulate aminoglycosides at higher levels than those detected in plasma [30].

Megalin belongs to the supergene family of the low-density lipoprotein receptor (LDLR) and therefore it is also referred as LDL-receptor-related protein-2, LRP-2 [32].

It has been reported that megalin, a giant endocytic receptor abundantly expressed at the apical membrane of renal proximal tubules, plays an important role in binding and endocytosis of aminoglycosides in proximal tubule cells. Megalin antagonists (molecules which bind megalin and block megalin-mediated endocytosis) have been developed (e.g. cytochrome c and derived peptides), which hold promise as prospective therapeutic agents for preventing or minimizing the iatrogenic tubular damage induced by Gen [30].

This slight elevation of creatinine and urea concentrations in our study can be attributed to Telmisartan property as a partial agonist of PPARγ, [33] as both PPARα and PPARγ nuclear receptors are involved in the activation of megalin gene transcription, [34] and treatment with Telmisartan, resulted in the induction of megalin at protein level in kidney of rats [34].

We expect that this induction of megalin might be the cause that Telmisartan didn't attenuate Gentamicin induced increase of serum urea and creatinine levels.

On the other hand, our study confirmed that Gentamicin can induce oxidative stress reported in several *in vivo* studies as Gen caused depletion in kidney GSH level which is commonly used to monitor the development and extent of renal tubular damage caused by oxidative stress [17, 35, 36].

In this study, Concurrent treatment with Telmisartan reduced oxidative stress caused by Gentamicin only at the higher dose (10mg/kg) which significantly restored renal GSH level to almost the normal value (Figure **3**; Table **2**). This came in consistent with several studies which reported that the higher dose of Tel is more beneficial for renal function.

Battershill 2006 reported that at the higher dosage of 80mg twice daily, Telmisartan exhibits renoprotective effects, reducing proteinuria from baseline, and slowing the progression to end stage renal disease (ESRD) in hypertensive patients with chronic nephropathy [10].

Also Malik and coworkers (2015) indicated that Telmisartan attenuated the depletion of antioxidant defense system (GSH) level caused by Cisplatin-induced nephrotoxicity and the effect was significant at 10mg/kg dose of telmisartan (but not with the dose of 5mg/kg) [14].

CONCLUSION

This study confirms the nephrotoxicity caused by Gentamicin administration and suggests that concurrent treatment with Telmisartan ameliorate oxidative stress induced by Gentamicin, but without significant changes to the elevation of serum urea and creatinine levels caused by Gentamicin.

REFERENCES

[1] Lopez-Novoa JM, Quiros Y, Vicente L, Morales AI, Lopez-Hernandez FJ. New insights into the mechanism of aminoglycoside nephrotoxicity: an integrative point of view. Kidney International 2011; 79(1): 33-45. https://doi.org/10.1038/ki.2010.337

[2] Wargo KA, Edwards JD. Aminoglycoside-induced nephrotoxicity. Journal of Pharmacy Practice 2014; 27(6): 573-7. https://doi.org/10.1177/0897190014546836

[3] Ali BH, Al Za'abi M, Blunden G, Nemmar A. Experimental gentamicin nephrotoxicity and agents that modify it: a mini-review of recent research. Basic & Clinical Pharmacology & Toxicology 2011; 109(4): 225-32. https://doi.org/10.1111/j.1742-7843.2011.00728.x

[4] Balakumar P, Rohilla A, Thangathirupathi A. Gentamicin-induced nephrotoxicity: Do we have a promising therapeutic approach to blunt it? Pharmacological Research 2010; 62(3): 179-86. https://doi.org/10.1016/j.phrs.2010.04.004

[5] Koyner JL, Sher Ali R, Murray PT. Antioxidants. Do they have a place in the prevention or therapy of acute kidney injury? Nephron Experimental Nephrology 2008; 109(4): e109-17. https://doi.org/10.1159/000142935

[6] Zorov DB. Amelioration of aminoglycoside nephrotoxicity requires protection of renal mitochondria. Kidney International 2010; 77(10): 841-3. https://doi.org/10.1038/ki.2010.20

[7] McClellan KJ, Markham A. Telmisartan. Drugs 1998; 56(6): 1039-44; discussion 45-6. https://doi.org/10.2165/00003495-199856060-00007

[8] Ladino M, Hernandez Schulman I. Renovascular and renoprotective properties of telmisartan: clinical utility. International Journal of Nephrology and Renovascular Disease 2010; 3: 33-8.

[9] Frampton JE. Telmisartan: a review of its use in cardiovascular disease prevention. Drugs 2011; 71(6): 651-77. https://doi.org/10.2165/11206710-000000000-00000

[10] Battershill AJ, Scott LJ. Telmisartan: a review of its use in the management of hypertension. Drugs 2006; 66(1): 51-83. https://doi.org/10.2165/00003495-200666010-00004

[11] Remuzzi A, Remuzzi G. Potential protective effects of telmisartan on renal function deterioration. Journal of the Renin-Angiotensin-Aldosterone System: JRAAS 2006; 7(4): 185-91. https://doi.org/10.3317/jraas.2006.036

[12] Rang H. Rang and Dale's Pharmacology, Churchill Livingstone. Elsevier; 2007.

[13] Fouad AA, Qureshi HA, Al-Sultan AI, Yacoubi MT, Al-Melhim WN. Nephroprotective effect of telmisartan in rats with ischemia/reperfusion renal injury. Pharmacology 2010; 85(3): 158-67. https://doi.org/10.1159/000269779

[14] Malik S, Suchal K, Gamad N, Dinda AK, Arya DS, Bhatia J. Telmisartan ameliorates cisplatin-induced nephrotoxicity by inhibiting MAPK mediated inflammation and apoptosis. European Journal of Pharmacology 2015; 748: 54-60. https://doi.org/10.1016/j.ejphar.2014.12.008

[15] Heeba GH. Angiotensin II receptor blocker, losartan, ameliorates gentamicin-induced oxidative stress and nephrotoxicity in rats. Pharmacology 2011; 87(3-4): 232-40. https://doi.org/10.1159/000325457

[16] El-Kashef DH, El-Kenawi AE, Suddek GM, Salem HA. Flavocoxid attenuates gentamicin-induced nephrotoxicity in rats. Naunyn-Schmiedeberg's Archives of Pharmacology 2015; 388(12): 1305-15. https://doi.org/10.1007/s00210-015-1164-8

[17] Rodrigues FA, Prata MM, Oliveira IC, Alves NT, Freitas RE, Monteiro HS, *et al*. Gingerol fraction from Zingiber officinale protects against gentamicin-induced nephrotoxicity. Anti-microbial Agents and Chemotherapy 2014; 58(4): 1872-8. https://doi.org/10.1128/AAC.02431-13

[18] Duan SB, Wang YH, Liu FY, Xu XQ, Wang P, Zou Q, *et al*. The protective role of telmisartan against nephrotoxicity induced by X-ray contrast media in rat model. Acta Radiologica 2009; 50(7): 754-9. https://doi.org/10.1080/02841850902995544

[19] Zou R, He Y, Li YQ, Han M, Ma ZF, Liu XC, *et al*. Telmisartan protects 5/6 Nx rats against renal injury by enhancing nNOS-derived NO generation via regulation of PPARgamma signaling. American Journal of Translational Research 2014; 6(5): 517-27.

[20] Zhang Q, Xiao X, Li M, Li W, Yu M, Zhang H, *et al*. Telmisartan improves kidney function through inhibition of the oxidative phosphorylation pathway in diabetic rats. Journal of Molecular Endocrinology 2012; 49(1): 35-46. https://doi.org/10.1530/JME-12-0020

[21] Tsunenari I, Ohmura T, Seidler R, Chachin M, Hayashi T, Konomi A, *et al*. Renoprotective effects of telmisartan in the 5/6 nephrectomised rats. Journal of the Renin-Angiotensin-Aldosterone System: JRAAS 2007; 8(2): 93-100. https://doi.org/10.3317/jraas.2007.017

[22] Servais H, Ortiz A, Devuyst O, Denamur S, Tulkens PM, Mingeot-Leclercq MP. Renal cell apoptosis induced by nephrotoxic drugs: cellular and molecular mechanisms and potential approaches to modulation. Apoptosis: an International Journal on Programmed Cell Death 2008; 13(1): 11-32. https://doi.org/10.1007/s10495-007-0151-z

[23] Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. The New England Journal of Medicine 1996; 334(25): 1649-54. https://doi.org/10.1056/NEJM199606203342507

[24] Michel MC, Brunner HR, Foster C, Huo Y. Angiotensin II type 1 receptor antagonists in animal models of vascular, cardiac, metabolic and renal disease. Pharmacology & Therapeutics 2016; 164: 1-81. https://doi.org/10.1016/j.pharmthera.2016.03.019

[25] Sachse A, Wolf G. Angiotensin II-induced reactive oxygen species and the kidney. Journal of the American Society of Nephrology: JASN 2007; 18(9): 2439-46. https://doi.org/10.1681/ASN.2007020149

[26] Kasap B, Turkmen M, Kiray M, Kuralay F, Soylu A, Tugyan K, *et al*. Effects of pentoxifylline on gentamicin-induced nephrotoxicity. Renal Failure 2013; 35(10): 1376-81. https://doi.org/10.3109/0886022X.2013.828359

[27] Randjelovic P, Veljkovic S, Stojiljkovic N, Velickovic L, Sokolovic D, Stoiljkovic M, *et al*. Protective effect of selenium on gentamicin-induced oxidative stress and nephrotoxicity in rats. Drug and Chemical Toxicology 2012; 35(2): 141-8. https://doi.org/10.3109/01480545.2011.589446

[28] Randjelovic P, Veljkovic S, Stojiljkovic N, Jankovic-Velickovic L, Sokolovic D, Stoiljkovic M, *et al*. Salicylic acid attenuates gentamicin-induced nephrotoxicity in rats. The Scientific World Journal 2012; 2012: 390613. https://doi.org/10.1100/2012/390613

[29] Stojiljkovic N, Stoiljkovic M, Mihailovic D, Randjelovic P, Ilic S, Gocmanac-Ignjatovic M, *et al*. Beneficial effects of calcium oral coadministration in gentamicin-induced nephrotoxicity in rats. Renal Failure 2012; 34(5): 622-7. https://doi.org/10.3109/0886022X.2012.664809

[30] Martinez-Salgado C, Lopez-Hernandez FJ, Lopez-Novoa JM. Glomerular nephrotoxicity of aminoglycosides. Toxicology and Applied Pharmacology 2007; 223(1): 86-98. https://doi.org/10.1016/j.taap.2007.05.004

[31] Wang ZK, Liu ZY, Yu HB. Protective effect of telmisartan on rats with renal failure and its mechanism. Asian Pacific Journal of Tropical Medicine 2015; 8(6): 498-501. https://doi.org/10.1016/j.apjtm.2015.05.007

[32] Nagai J, Takano M. Molecular aspects of renal handling of aminoglycosides and strategies for preventing the nephrotoxicity. Drug Metabolism and Pharmacokinetics 2004; 19(3): 159-70. https://doi.org/10.2133/dmpk.19.159

[33] Benson SC, Pershadsingh HA, Ho CI, Chittiboyina A, Desai P, Pravenec M, *et al*. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARgamma-modulating activity. Hypertension 2004; 43(5): 993-1002. https://doi.org/10.1161/01.HYP.0000123072.34629.57

[34] Cabezas F, Lagos J, Cespedes C, Vio CP, Bronfman M, Marzolo MP. Megalin/LRP2 expression is induced by peroxisome proliferator-activated receptor -alpha and -gamma: implications for PPARs' roles in renal function. PloS One 2011; 6(2): e16794. https://doi.org/10.1371/journal.pone.0016794

[35] Otunctemur A, Ozbek E, Cekmen M, Cakir SS, Dursun M, Polat EC, *et al*. Protective effect of montelukast which is cysteinyl-leukotriene receptor antagonist on gentamicin-induced nephrotoxicity and oxidative damage in rat kidney. Renal Failure 2013; 35(3): 403-10. https://doi.org/10.3109/0886022X.2012.761040

[36] Patel Manali B, Deshpande S, Shah G. Evaluation of efficacy of vitamin E and N-acetyl cysteine in gentamicin-induced nephrotoxicity in rats. Renal Failure 2011; 33(3): 341-7. https://doi.org/10.3109/0886022X.2011.560987

Received on 10-02-2017 Accepted on 22-03-2018 Published on 27-04-2018

DOI: https://doi.org/10.6000/1927-5951.2018.08.02.7