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Gentamicin-induced nephrotoxicity: A mechanistic approach

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Abstract: The kidney is more susceptible to poisoning than any other organ in the body because of the number of poisons that are delivered to it. By 2040, it is anticipated that kidney diseases will rank fifth in terms of causes of mortality. Drug-induced nephrotoxicity has been identified as a significant contributor to kidney damage. Gentamicin (GM), the most widely prescribed aminoglycoside (AG) antibiotic, is still utilized in clinical practice despite the fact that it can induce nephrotoxicity due to its strong bactericidal properties, broad antibacterial spectrum, and low bacterial resistance. It has been demonstrated that GM raises the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in the renal cortex, which ultimately results in renal injury. This study aims to discuss the pathogenesis of GM-related nephrotoxicity for clinical trials to uncover promising agents with reno-protective properties that can be used concurrently to counteract the nephrotoxicity of GM.

Keywords: Gentamicin; Nephrotoxicity; Molecular mechanisms; Oxidative stress; Inflammation; Necrosis; Apoptosis.

1. INTRODUCTION

The kidneys are crucial to maintaining fluid homeostasis in the body, controlling blood pressure, managing osmolality, regulating acid-base balance, producing erythrocytes, preserving bone density, and regulating hormonal balance. They also play a part in the metabolism of carbohydrates, protein, lipids, and other nutrients, as well as filtering and eliminating nitrogenous and other waste products [1-3].

The kidney is targeted by several xenobiotic toxicants, including potentially dangerous chemical substances in the environment, because of its special biochemical, anatomical, and physiological characteristics. The kidney's multitude of metabolizing enzymes and transporters, incredibly high renal blood flow, and capacity to collect various solutes during the formation of urine are all characteristics that contribute to the kidney's great sensitivity to xenobiotics [2, 4].

Kidney diseases are being recognized as major global health issues with significant financial costs [5, 6]. Reactive oxygen species (ROS) are a systemic factor in several renal disorders when their generation outpaces cellular antioxidant defenses [6, 7]. The primary pathologies responsible for kidney complications are oxidative stress, apoptosis, fibrosis, and inflammation. Unfortunately, there are currently no available drugs that could be used to treat renal problems. As a result, it's crucial to find a treatment that might treat this condition and has fewer adverse effects [5].

Kidney diseases can be categorized according to the onset time of an illness into acute kidney injury (AKI) and chronic kidney disease (CKD) [8]. AKI, formerly acknowledged as acute renal failure, is the sudden loss of kidney function, which can range from partial kidney failure to total kidney failure. It can happen within a few hours or a few days. On the other hand, a progressive decrease in kidney function lasting longer than three months is referred to as CKD [8, 9]. Production of ROS and reactive nitrogen species (RNS) is associated with both AKI and CKD [9, 10]. AKI is mostly caused by sepsis, ischemia-reperfusion injury, diabetic nephropathy and exposure to nephrotoxic reagents,. [10-12]. AKI patients are more likely to progress to CKD, and whether tubular cells recover sufficiently is a major factor in whether this happens [9, 11].

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Nephrotoxicity is a term used to describe the hazardous impact of some substances on the kidney, including both toxins and medications [2, 6]. Molds and fungus, chemotherapy drugs like cisplatin, antibiotics like aminoglycosides (AGs), non-steroidal anti-inflammatory drugs (NSAIDs), and metals like lead, arsenic, and mercury are some of the different substances that can cause nephrotoxicity [2, 8]. Drug-induced nephrotoxicity represents approximately 19–26% of all hospital cases [12]. Numerous mechanisms donate to drug-induced nephrotoxicity, including renal tubular cytotoxicity, altered glomerular hemodynamics, inflammation, crystal nephropathy, rhabdomyolysis, as well as thrombotic microangiopathy [2, 4, 12, 13]. These consequences can be mostly attributed to increased ROS production by the renal mitochondria, which harm cellular macromolecules like proteins, lipids, and DNA and eventually cause the death of kidney cells [4, 6].

2. Gentamicin-induced nephrotoxicity

Gentamicin (GM), a key member of the AGs class of bactericidal antibiotics, was first identified in 1963 and is frequently prescribed to treat serious Gram-negative bacterial infections. These infections induce endocarditis, sepsis, pneumonia, pelvic inflammatory disease, meningitis, urinary tract infections, and bone infections [1, 4, 14-16]. Nephrotoxicity and ototoxicity, including vestibular and/or cochlear damage, are among the major side effects of GM [1, 4, 17]. GM's primary dose-limiting adverse effect is nephrotoxicity, in reality [4, 18]. The exact mechanisms by which GM might cause nephrotoxicity are still unknown [19].10% to 25% of patients exposed to GM experience AKI [6, 20]. Because of its effectiveness and inexpensive cost, GM is still used despite its negative effects [17].

2.1 The earliest known mechanism of GM-induced nephrotoxicity

A key mechanism for GM-induced AKI involves the drug building up in the lysosomes of the proximal tubule cells and then inhibiting the activity of certain enzymes. Additionally, the medication can accumulate in lysosomes, where it might damage cells' structural integrity and result in the formation of myeloid bodies as well as in the Golgi and endoplasmic reticulum [4, 16, 20]. Endoplasmic reticulum stress is caused by GM's inhibition of protein synthesis, impairment of translational precision, and potential interference with proper posttranslational protein folding [21]. The medication enters the cytoplasm after destabilizing intracellular membranes and induces mitochondrial damage with the onset of cell apoptosis/necrosis [4, 16, 20].

2.2 The recent mechanism of GM-induced nephrotoxicity

The main pathophysiology of GM-induced nephrotoxicity includes the production of ROS in the tubular, glomerular, and vascular tissues. These ROS include superoxide anions, hydroxyl radicals, and hydrogen peroxide, as well as RNS in the kidney, which induce a significant decrease in antioxidant defense mechanisms. Acid hydrolases are also released as a result of GM, which impairs mitochondrial respiration. Induction of acute tubular necrosis, apoptosis, overexpression of transforming growth factor β (TGF-β), intracellular edema, the elevation of endothelin I, increment of monocyte/ macrophages infiltration, basal membrane disruption, and glomerular congestion have all been linked to GM-induced nephrotoxicity, which leads to a decrease in glomerular filtration rate (GFR) and renal dysfunction [4, 6, 14-16, 18, 22].

3. The GM effect on the kidney

3.1 GM's tubular effects

The nephrotoxicity induced by GM occurs mainly in the proximal tubules, where GM accumulates in the epithelial cells. A higher expression of a transporter called the giant endocytic complex, which is formed by megalin and cubilin, results from a higher accumulation of GM in the epithelial cells of the proximal tubules. This transporter complex is responsible for the transport of GM inside the cells by endocytosis. At that instant, GM moves through the endosomal compartment, accumulates largely in the endoplasmic reticulum, lysosomes, and the Golgi, and since it charges cationically, it is attracted to and bound to anionic membrane phospholipids, modifying their turnover and metabolism, causing a condition known as phospholipidosis, which is firmly linked with the level of toxicity of AGs. A higher accumulation of GM in the endosomal structures leads to disruption of their membrane and moving out of GM along with their content into the cytoplasm. Cytosolic GM has a direct and indirect action on the mitochondria. The direct action is mediated by producing oxidative stress conditions and activating the intrinsic pathway of apoptosis, while the indirect action is mediated by increasing Bax levels via inhibiting its proteosomal degradation, which further contributes to cell death [21, 23].

3.2 GM's glomerular effects

The glomerulus is the first portion of the nephron to be exposed to chemical substances. Filtration is altered by GM's glomerular actions. GFR decreases and mesangial cells contraction occur as a result of GM. Additionally, mesangial cells proliferative activity is stimulated by GM, and this is accompanied by a rise in mesangial cells apoptosis, which essentially balances out one another. Diffuse swelling of the filtration barrier connected to neutrophil infiltration has been observed in high-dose treatments, along with a small increase in size, modification of their round shape, and density [21].

3.3 GM's vascular effects

As a result of higher resistance in the renal vascular bed rather than reduced perfusion pressure, GM causes a decrease in renal blood flow. GFR drops as a result of decreased renal blood flow. Reduced oxygen and ATP availability make tubule cells more susceptible to cell death. Reduced renal blood flow results primarily from TGF activation caused by impaired tubular reabsorption, which is intended to prevent severe fluid and electrolyte loss. In addition, overriding TGF adaptation, the renal vascular tree, and mesangial compartment produce vasoconstrictors such as endothelin-1, platelet-activating factor, and arachidonic acid metabolites, primarily prostaglandins and thromboxane A2, as well as GM's direct actions on vascular cells. GM stimulates the synthesis of vasoconstrictors while inhibiting the synthesis of vasodilator prostaglandins [21].

4. The molecular mechanism of GM-induced nephrotoxicity

4.1 GM-induced alterations in kidney function

In experimental studies, serum creatinine (SCr), blood urea nitrogen (BUN), and kidney weight/body index are the most accurate indicators of renal disease. Studies have shown that elevated levels of BUN and SCr are regarded as key indicators of renal failure (glomerular damage marker) [18, 24]. The functional characteristics of GM-induced nephrotoxicity include an increase in SCr and BUN, as well as kidney/body weight, occurrences of albuminuria and urinary losses of carnitine, a decrease in GFR, and renal failure [4, 14, 18, 24]. Additionally, GM-induced nephrotoxicity increases the renal tubular biomarker kidney injury molecule-1 (KIM-1), revealing that GM damages the proximal tubules [13].

4.2 GM-induced oxidative stress

Oxidative stress, widely recognized as the imbalance between oxidation and anti-oxidation in the body, is brought on by an imbalance between the body's excessive production of ROS and insufficient antioxidant defense. This condition causes the body's overall state to tend toward oxidation, which then triggers neutrophil infiltration during inflammation, an increase in protease secretion, and the production of numerous oxidation intermediates, which ultimately results in tissue degeneration and apoptosis. It frequently occurs in kidney diseases [5, 6, 25]. Oxidative stress is the primary mechanism via which GM mediates kidney damage [24].

4.2.1 Antioxidant enzymes

The accumulation of GM, intracellularly or in the cell membrane, results in increased ROS production in both the renal cortex and medulla [10, 16, 18]. The activity of antioxidant enzymes like catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), glutathione reductase (GR) and glutathione peroxidase (GPx) is decreased as a result of increased ROS generation by GM[10, 14, 16, 18, 24]. Furthermore, these ROS cause proteinuria, inflammation, fibrotic alterations, and altered renal blood flow [10].

4.2.2 MDA

The GM-produced ROS interact with cellular macromolecules (lipids, protein, DNA). Protein denaturation and DNA damage are accelerated by these ROS. Additionally, these ROS induce polyunsaturated fatty acid peroxidation (PUFAs) and the production of malondialdehyde (MDA), which is a hallmark of lipid peroxidation of the lipids in the cell membrane. The cellular damage and necrosis cascades result from these occurrences [4, 14, 16, 18, 24].

4.2.3 LDH

The lactate dehydrogenase (LDH) enzyme, which is present in the proximal renal tubules, is a sensitive biomarker of tubular damage. GM-induced nephrotoxicity results in significant increases in LDH activity. The reason for this rise is that GM treatment alters the redox status, as shown by a drop in GSH levels and an increase in lipid peroxidation [24].

4.2.4 Nrf2/HO-1

Nuclear factor erythroid-2 related factor 2 (Nrf2), a master regulatory element in adjusting oxidative stress responses of cells, contributes to the maintenance of cellular redox homeostasis, minimizes the cell damage brought on by redox imbalance, and maintains the dynamic balance of the

systematic oxidation/reduction consequences by inducing and controlling the expression of numerous antioxidant enzymes [1, 4, 7, 26, 27]. Partaker proteins like Nicotinamide adenine dinucleotide phosphate (NADPH), NAD(P)H:quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), glutathione-S-transferases (GSTs) and glutamate-cysteine ligase catalytic (GCLC) are examples of common downstream gene products [26, 27]. Additionally, Nrf2 is essential for controlling the oxidation/reduction approach of L-γ-glutamyl-cysteinyl-glycine (GSH). By controlling the expression of the rate-limiting enzyme γ-glutamyl cysteine synthetase, Nrf2 controls GSH production [27].

Heme oxygenase-1 plays a significant role in the regulation of oxidative stress and inflammation and is hypothesized to be involved in the protection of non-specific damage after AKI or as a result of CKD through these processes [28]. The ability of HO-1 to catalyze the breakdown of heme (Fe-protoporphyrin IX) into free iron, carbon monoxide (CO), and biliverdin, which is quickly transformed into bilirubin, is one of its key functions[25, 28].

The Nrf2/HO-1 cascade reaction significantly inhibits oxidative stress in the pathophysiological processes of the kidney [25]. GM depresses Nrf2/HO-1 signaling in the kidney, inhibits renal Nrf2 activation, and prevents Nrf2 gene expression, exacerbating renal oxidative stress and kidney inflammation [29, 30].

4.3 GM-induced inflammation

At the time that the inflammatory cascade turn out to be more active, pro-inflammatory mediators including cytokines and chemokines are generated, which leads to inflammatory signals, and with the help of these signals, the body is able to identify, annihilate, and get rid of foreign things, producing an effective acute inflammatory response [24]. Inflammation is the major pathophysiology of kidney disease [5]. An increase in inflammatory pathways has been triggered by GM [24].

4.3.1 P38-MAPK

P38 mitogen-activated protein kinase (P38-MAPK) is one of the chief signaling trajectories of the mitogen-activated protein kinases (MAPKs) family and is considered a pro-apoptotic and pro-inflammatory pathway [24, 25]. Numerous immunological and inflammatory genes are regulated by p38-MAPK [24]. GM-induced nephrotoxicity is connected to renal p38-MAPK overexpression [14, 18].

4.3.2 NF-κB

Nuclear factor-kappa beta (NF-κB), a class of eukaryotic transcription factors, have a key role in the inflammatory response and the production of pro-inflammatory molecules, including cytokines and enzymes like cyclooxygenase-2 (COX-2), inducible nitric oxide synthases (iNOS), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6). NF-κB also controls the expression of genes related to cell division, differentiation, and apoptosis [4, 24-26, 31]. NF-κB pathway overexpression in the kidneys is linked to GM-induced nephrotoxicity [14, 18, 30].

Gentamicin increases the expression of iNOS and results in the formation of peroxynitrite. Due to this, the glomerulus is injured and becomes inflamed. iNOS generates a lot of nitric oxide (NO) in pathological circumstances, which causes lipopolysaccharide (LPS) and interferon (IFN) to elevate endothelial nitric oxide synthase (eNOS) levels 10 times, which has a dual role in inflammation. NO overproduction has also been linked to GM-induced nephrotoxicity [24].

In response to GM, glomerular and tubular cells as well as extrinsic inflammatory cells generate the pro-inflammatory cytokine TNF-α [4, 24]. TNF-α has been linked to GM-induced nephrotoxicity by causing tubular cell death [14]. TNF-α functions by way of the NF-κB and MAPK signaling pathways [24].

4.3.3 ICAM-1 and MCP-1

Gentamicin-induced tubular necrosis causes renal injury that triggers inflammatory reactions by attracting intercellular adhesion molecule (ICAM-1) and monocyte chemoattractant protein (MCP-1) to the site of tissue damage, which enhances the migration of monocytes and macrophages to the site of tissue damage and ultimately results in renal pathogenesis [14].

4.3.4 TGF-β

Transforming growth factor-beta (TGF-β), which is produced and secreted by inflammatory cells and effector cells, is an efficient activator of extracellular matrix protein synthesis in the majority of fibroblasts. The TGF-β is crucial for controlling fibrosis [25]. GM causes the advancement of tubulointerstitial nephritis by promoting macrophage infiltration and raising TGF-β levels [14].

4.4 GM-induced apoptosis

Apoptosis, a type of programmed cell death, is a natural means of eliminating senescent cells in vivo. Apoptosis also serves as a mechanism to maintain the equilibrium of cell numbers in tissues [5,

[25]. Two pathways primarily mediated apoptosis: the endogenous pathway, which is handled by mitochondria, and the exogenous pathway, which is mediated by death receptors. Numerous illnesses, including neurological disorders, ischemia injury, autoimmune diseases, and various cancers, are brought on by inappropriate apoptosis, which can be either too much or too little [25].

B-cell lymphoma-2 (Bcl-2) family proteins trigger mitochondrial apoptosis through controlling mitochondrial outer membrane permeability (MOMP) and subsequently activate the caspase cascade. These comprise pro-apoptotic effectors, Bcl-2 homologous antagonist/killer (Bak) and Bcl-2 associated x protein (Bax), as well as the anti-apoptotic proteins like Bcl-2 and B-cell lymphoma-extra large (Bcl-XL), which interact with one another and are crucial for both health and sickness in humans [25]. Bcl-2 suppresses apoptosis by stopping the release of cytochrome C and the activation of caspase [5].

Gentamicin-induced ROS generation in the mitochondria stimulates the opening of the mitochondrial permeability transition (MPT) pore. As a result, the MPT pore opening initiates the release of cytochrome C into the cytosol, which causes the mitochondria to expand, the caspase cascade to be activated, and ultimately, the cell to undergo apoptosis. A crucial element in regulating apoptosis, the Bcl-2/ Bax ratio is also reduced in the kidney as a result of GM-induced nephrotoxicity [10]. The significant increases in caspase-3 expression in renal cortical tissue as a result of GM-induced nephrotoxicity show that GM causes endoplasmic reticulum (ER) stress and activates ER-mediated cell death markers [24]

4.5 GM-induced structural changes in the kidney

Histopathologically, GM has an impact on the kidney's tubular and glomerular structure [16]. Multiple histopathological kidney damage ranging from mild to severe is brought on by GM [4]. The glomerular changes are manifested as mesangial cell hypercellularity, glomerular atrophy, glomerular hypertrophy, glomerular congestion, and glomerular endothelial cell proliferation with a resultant decrease in Bowman's space [14, 16, 18]. Necrosis, degeneration, and vacuolization are the earliest signs of GM-induced renal tubular changes, and with time, the degeneration progresses to severe necrosis. Most of the proximal convoluted tubules, and to a lesser extent, the distal tubules, are affected by degeneration up to severe necrosis. Swelling, cytolysis, and tubular irregularity can be seen in the degenerated tubules. GM induces tubular necrosis to extend to the proximal tubules' distal portion, epithelial cell dissociation with cast formation, loss of brush border in significant portions of proximal tubules, tubular obstruction, and leukocyte infiltration into the interstitium [4, 14, 16, 18, 24].

5. GM-induced nephrotoxicity mitigation techniques

Nephrotoxicity prevention is an essential therapeutic goal that will considerably enhance the pharmacotoxicological profile and clinical value of numerous medications, including AGs. There are no therapeutic techniques available to prevent or treat medication nephrotoxicity other than proper monitoring, maintaining the patient's hydration, and applying dialysis when necessary [21]. Different new preventative methods for GM nephrotoxicity are currently being developed, primarily at the preclinical stage [14, 21].

5.1 Tubular accumulation avoidance

One suggested technique is to find medications that interfere with transport systems to prevent the accumulation of AGs. The megalin-related endocytic system responsible for the transport and accumulation of AGs in tubular and auditory cells is an apparent target. Using specific inhibitors of this endocytic pathway or competitors for the receptor that prevent AGs from attaching to it, one can prevent the transport of AGs. Statins have been demonstrated to lessen gentamicin buildup in tubule cells and renal injury [21].

5.2 Use of renoprotective medications in combination

Another approach uses nephroprotective medications as a cotreatment with AGs. Numerous compounds have been demonstrated to have protective effects against nephrotoxicity, and more especially, nephrotoxicity caused by AGs, at the preclinical level [21].

5.2.1 Antioxidants

The ability of antioxidants to reduce AG's nephrotoxicity has by far been the subject of the majority of studies [21]. To stop GM nephrotoxicity, medications with direct or indirect antioxidant capabilities have been found [14]. It is possible to hypothesize that the effect of antioxidants is related to a coordinated action at various levels, including the following: softening of GM's direct cytotoxicity; suppressing vasoconstriction and mesangial cells contraction; and anti-inflammatory action [21].

5.2.2 Renal blood flow enhancement

An increase in renal blood flow has the potential to reduce the nephrotoxicity of AGs. Preglomerular or general vasodilatation can boost GFR and lessen the tubular damage brought on or exacerbated by the lower flow. Verapamil and nifedipine, calcium channel blockers, have been shown to reduce GM-induced nephrotoxicity [14, 21].

6. Conclusion

Even though the benefits of GM in treating a variety of bacterial infections, predominantly gram-negative bacteria, GM-induced nephrotoxicity is a significant clinical obstacle to its widespread therapeutic application. High renal oxidative stress, renal inflammatory cascades, necrosis, apoptosis, and associated pathological signaling processes are the pathological mechanisms relating to GM-induced nephrotoxicity. In order to reduce GM-induced nephrotoxicity, reno-protective medicines including ROS scavengers, potent direct or indirect antioxidants, and cellular anti-inflammatory agents should be used concurrently.

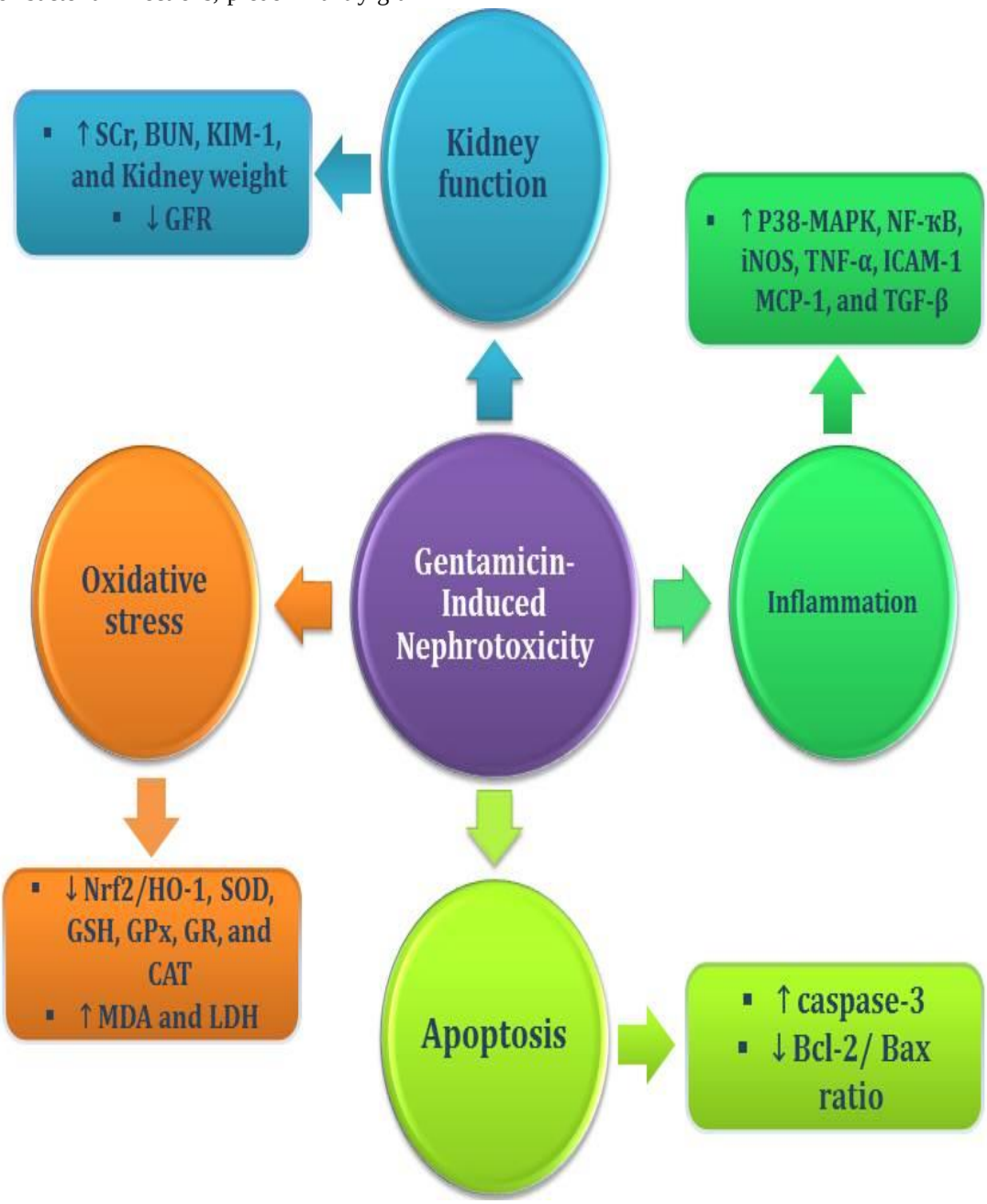

Figure 1. Schematic diagram showing the molecular mechanism of gentamicin-induced nephrotoxicity

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List of Abbreviations: AGs;Aminoglycsides**,** AKI; Acute kidney injury, Bak; Bcl-2 homologous antagonist/killer, Bax; Bcl-2 associated x protein, Bcl-2; B-cell lymphoma-2, Bcl-XL; B-cell lymphoma-extra large, BUN; Blood urea nitrogen, CAT; Catalase, CKD; Chronic kidney disease, GCLC; Glutamate-cysteine ligase catalytic, GFR; Glomerular filtration rate, GM; Gentamicin, GPx; Glutathione peroxidase, GR; Glutathione reductase, GSH; Glutathione, GSTs; Glutathione-S-transferases, HO-1; Heme oxygenase-1, ICAM-1; Intercellular adhesion molecule, KIM-1; Kidney injury molecule-1, LDH; Lactate dehydrogenase, MCP-1; Monocyte chemoattractant protein, MDA; Malondialdehyde, MOMP; Mitochondrial outer membrane permeability, MPT; Mitochondrial permeability transition, NADPH; Nicotinamide adenine dinucleotide phosphate, NF-κB; Nuclear factor-kappa beta, NO; Nitric oxide, NQO1; NAD(P)H: quinone oxidoreductase 1, Nrf2; Nuclear factor erythroid-2 related factor 2, P38-MAPK; P38 mitogen-activated protein kinase, PUFAs; Polyunsaturated fatty acid peroxidation, RNS; Reactive nitrogen species, ROS; Reactive oxygen species, SCr; Serum creatinine, SOD; Superoxide dismutase, TGF-β; Transforming growth factor-beta.

REFERENCES

1. Molaei E, Molaei A, Abedi F, Hayes AW, Karimi G. Nephroprotective activity of natural products against chemical toxicants: The role of Nrf2/ARE signaling pathway. Food Sci Nutr. 2021;9(6):3362-84.

2. Pathan N. A Systematic Review on Nephroprotective Plants. Int J Res Publ Rev. 2021;2(6):174-84.

3. Tienda-Vázquez MA, Morreeuw ZP, Sosa-Hernández JE, Cardador-Martínez A, Sabath E, Melchor-Martínez EM, et al. Nephroprotective Plants: A Review on the Use in Pre-Renal and Post-Renal Diseases. Plants. 2022;11(6):818.

4. Zarei B, Elyasi S. Saffron nephroprotective effects against medications and toxins: A review of preclinical data. Iran J Basic Med Sci. 2022;25(4):419-34.

5. Akter T, Rahman MA, Moni A, Apu MAI, Fariha A, Hannan MA, et al. Prospects for Protective Potential of Moringa oleifera against Kidney Diseases. Plants. 2021;10(12):2818.

6. Hoseinynejad K, Mard SA, Dianat M. An Overview on Antioxidant and Anti-inflammatory Properties of Ellagic Acid in Renal Dysfunction. Jundishapur j physiol. 2021;2(1):16-21.

7. Hejazian SM, Khatibi SMH, Barzegari A, Pavon-Djavid G, Soofiyani SR, Hassannejhad S, et al. Nrf-2 as a therapeutic target in acute kidney injury. Life Sci. 2021;264:118581.

8. Song A, Zhang C, Meng X. Mechanism and application of metformin in kidney diseases: An update. Biomed Pharmacol. 2021;138:111454.

9. Zhang X, Agborbesong E, Li X. The Role of mitochondria in acute kidney injury and chronic kidney disease and its therapeutic potential. Int J Mol Sci. 2021;22(20):11253.

10. Ashkar F, Bhullar KS, Wu J. The Effect of Polyphenols on Kidney Disease: Targeting Mitochondria. Nutrients. 2022;14(15):3115.

11. Chen X-c, Li Z-h, Yang C, Tang J-x, Lan H-y, Liu H-f. Lysosome depletion-triggered autophagy impairment in progressive kidney injury. Kidney Dis. 2021;7(4):254-67.

12. 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.

13. Yu P, Duan Z, Liu S, Pachon I, Ma J, Hemstreet GP, et al. Drug-Induced Nephrotoxicity Assessment in 3D Cellular Models. Micromachines. 2021;13(1):3.

14. Balakumar P, Rohilla A, Thangathirupathi A. Gentamicin-induced nephrotoxicity: Do we have a promising therapeutic approach to blunt it? Pharmacol Res. 2010;62:179-86.

15. Alavi MS, Fanoudi S, Ghasemzadeh Rahbardar M, Mehri S, Hosseinzadeh H. An updated review of protective effects of rosemary and its active constituents against natural and chemical toxicities. Phytother Res. 2021;35(3):1313-28.

16. Alsharidah M, Abdel-Moneim A-MH, Alsharidah AS, Mobark MA, Rahmani AH, Shata A, et al. Thymoquinone, but Not Metformin, Protects against Gentamicin-Induced Nephrotoxicity and Renal Dysfunction in Rats. Appl Sci. 2021;11(9):3981.

17. Natha CM, Vemulapalli V, Fiori MC, Chang C-WT, Altenberg GA. Connexin hemichannel inhibitors with a focus on aminoglycosides. Biochim Biophys Acta - Mol Basis Dis. 2021;1867(6):166115.

18. Elsisi AEE, Sokar SS, Shalaby MF, Abu-Risha SE-S. Nephroprotective effects of febuxostat and/or mirtazapine against gentamicin-induced nephrotoxicity through modulation of ERK 1/2, NF-κB and MCP1. Expert Rev Clin Pharmacol. 2021;14(8):1039-50.

19. Huang H, Jin WW, Huang M, Ji H, Capen DE, Xia Y, et al. Gentamicin-induced acute kidney injury in an animal model involves programmed necrosis of the collecting duct. J Am Soc Nephrol. 2020;31(9):2097-115.

20. Perazella MA, Rosner MH. Drug-induced acute kidney injury. Clin J Am Soc Nephrol. 2022;17:1220–33.

21. 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 Int. 2011;79(1):33-45.

22. Yahyazadeh R, Baradaran Rahimi V, Yahyazadeh A, Mohajeri SA, Askari VR. Promising effects of gingerol against toxins: a review article. Biofactors. 2021;47(6):885-913.

23. Pletz J, Enoch SJ, Jais DM, Mellor CL, Pawar G, Firman JW, et al. A critical review of adverse effects to the kidney: mechanisms, data sources, and in silico tools to assist prediction. Expert Opin Drug Metab Toxicol. 2018;14(12):1225-53.

24. Antar S, Al-Karmalawy AA, Mourad A, Mourad M, Elbadry M, Saber S, et al. Protective effects of mirazid on gentamicin-induced nephrotoxicity in rats through antioxidant, anti-inflammatory, JNK1/iNOS, and apoptotic pathways; novel mechanistic insights. Pharm Sci. 2022;28(4):525-40.

25. Li D, Rui Y-x, Guo S-d, Luan F, Liu R, Zeng N. Ferulic acid: A review of its pharmacology, pharmacokinetics and derivatives. Life Sci. 2021;284:119921.

26. Krajka-Kuźniak V, Baer-Dubowska W. Modulation of Nrf2 and NF-κB Signaling Pathways by Naturally Occurring Compounds in Relation to Cancer Prevention and Therapy. Are Combinations Better Than Single Compounds? Int J Mol Sci. 2021;22(15):8223.

27. Li D, Zhao H, Cui Z-K, Tian G. The role of Nrf2 in hearing loss. Front Pharmacol. 2021;12:620921.

28. Grunenwald A, Roumenina LT, Frimat M. Heme Oxygenase 1: A Defensive Mediator in Kidney Diseases. Int J Mol Sci. 2021;22(4):2009.

29. Ali FEM, Sayed AM, El-Bahrawy AH, Omar ZMM, Hassanein EHM. Targeting KEAP1/Nrf2, AKT, and PPAR-γ signals as a potential protective mechanism of diosmin against gentamicin-induced nephrotoxicity. Life Sci. 2021;275:119349.

30. Althunibat OY, Abukhalil MH, Aladaileh SH, Qaralleh H, Al-Amarat W, Alfwuaires MA, et al. Formononetin Ameliorates Renal Dysfunction, Oxidative Stress, Inflammation, and Apoptosis and Upregulates Nrf2/HO-1 Signaling in a Rat Model of Gentamicin-Induced Nephrotoxicity. Front Pharmacol. 2022;13:916732.

31. Setiawan PYB, Kertia N, Nurrochmad A, Wahyuono S. Curcumin in combination: Review of synergistic effects and

mechanisms in the treatment of inflammation. J Appl Pharm Sci. 2021;11(2):001-11.