International Journal of Pathology and Biomarkers
https://ijpb.org/
IJPB
SPBH

Review Article

Role of Antibiotics and Heavy Metals on Kidney Failure

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DOI: https://doi.org/10.71428/IJPB.2026.0104

ABSTRACT

Kidney failure is one of the biggest concerns in terms of worldwide healthcare problems, caused by a wide range of clinical and environmental factors. Among the most important factors involving major contributors to renal damage are nephrotoxic antibiotics and exposure to heavy metals. The kidneys are very sensitive to causing toxic damage due to their rich blood supply, aggressive transport systems, and the ability to concentrate xenobiotics in renal tubular cells. Several commonly used antibiotics, like aminoglycosides and vancomycin, have been documented to cause renal impairment by mechanisms involving oxidative stress, mitochondrial dysfunction, inflammation, and tubular cells undergo apoptosis. Like antibiotics, heavy metals, including cadmium and lead, accumulate in renal tissue and impair antioxidant mechanisms, lipid peroxidation, enzyme inhibition, and loss of kidney function. This study aims to examine the biochemical mechanisms of kidney failure caused by both antibiotics & heavy metals individually and combined. Great emphasis is placed upon analyzing the important biomarkers for renal function, including Serum Creatinine, Urea, and Blood Urea Nitrogen (BUN), and markers of oxidative stress, which include malondialdehyde, glutathione, superoxide dismutase, and catalase. Moreover, the potential protective effects of antioxidant drugs are investigated as a way to lower nephrotoxicity. Understanding the biochemical pathways involved in drug and metal-induced kidney failure may contribute to improving clinical management, using antibiotics in safer ways, and the development of preventive strategies against environmental nephrotoxins.

Keywords: nephrotoxic antibiotics, oxidative stress, cadmium, lead.

INTRODUCTION

Kidney (renal) function plays a critical role in maintaining the body's biochemical homeostasis by filtering blood, reabsorbing essential molecules, and excreting metabolic wastes. The nephron, " the functional unit of the kidney," is particularly vulnerable to toxic insults because of its high blood flow, energy demand, and the accumulation of xenobiotics in renal tubular epithelial cells. Disruption of kidney function can lead to acute or chronic renal failure, which remains a major global health concern [1, 2].

Antibiotic " induced nephrotoxicity" is a well - documented cause of renal injury. Among antibiotics, "gentamicin: an aminoglycoside," commonly used to treat serious Gram-negative bacterial infections, is particularly notorious for its nephrotoxic effects. gentamicin accumulates in the renal cortex, especially in proximal tubular cells, and induces the overproduction of reactive oxygen

Received: December 15, 2025. Accepted: February 15, 2026. Published: March 20, 2026

species (ROS) and reactive nitrogen species (RNS). These reactive species trigger mitochondrial damage, lipid peroxidation, and apoptosis, ultimately impairing renal structure and function. In animal and in vitro models, gentamicin has been shown to disrupt mitochondrial bioenergetics, promote the release of iron from mitochondria, and amplify free radical generation, which collectively contribute to acute kidney injury [4, 5].

On the other hand, heavy metal exposure represents a significant environmental risk factor for nephrotoxicity. Metals such as cadmium (Cd), lead (Pb), and arsenic (As) can accumulate in renal tissues via filtration and reabsorption, especially in the proximal tubular cells. Chronic exposure to these metals is associated with a progressive decline in renal function, including proteinuria and reduced glomerular filtration rate (GFR) in both human epidemiological and animal studies. At the molecular level, heavy metals induce nephrotoxicity largely through oxidative stress pathways. Cadmium, for example, although not redox-active itself, can deplete intracellular glutathione (GSH) and displace other redox- active metals like iron or copper, which participate in "Fenton-type" reactions to generate free radicals. This oxidative overload causes lipid peroxidation, DNA damage, mitochondrial dysfunction, and apoptotic cell death in renal tissue. Recent research has also shown that cadmium and lead impair mitochondrial structural integrity, reduce mitochondrial membrane potential, and inhibit electron transport chain complexes, leading to bioenergetic failure in kidney cell, furthermore, the combined effect of antibiotics and heavy metals on the kidney remains underexplored. Co-exposure is likely in many real - world scenarios, for instance, patients taking antibiotics may simultaneously be exposed to environmental heavy metals. Evidence suggests that such combined exposures may exacerbate renal injury, but the molecular mechanisms are not yet fully understood. Dissecting these mechanisms is essential for developing interventions and minimizing renal risk [6,7].

Given the central role of oxidative stress and mitochondrial damage in both "antibiotic and metal" induced nephrotoxicity, investigating the "Biochemical interplay" between these two classes of nephrotoxicants is a valuable research direction [8, 9]. Moreover, understanding whether antioxidant therapies can mitigate their combined toxicity could offer practical strategies for renal protection. Therefore, this review aims to elucidate the biochemical mechanisms of kidney damage induced by an antibiotic (gentamicin) and a heavy metal (cadmium or lead), both individually and in combination, and to evaluate the potential protective effects of antioxidant agents [10-12].

A- Kidney Structure and Function Overview:

1- Structure of the Kidney:

The kidney is composed of an outer cortex and an inner medulla, each containing the functional units known as nephrons. Each nephron consists of:

a- Glomerulus:

A tuft of capillaries is responsible for the initial filtration of blood. It is surrounded by bowman’s capsule, forming the renal corpuscle. The glomerular filtration barrier includes [13,14]:

- Fenestrated endothelial cells.
- Podocyte foot processes.

This selective barrier ensures that water and small solutes pass through while proteins and blood cells are retained [13,14].

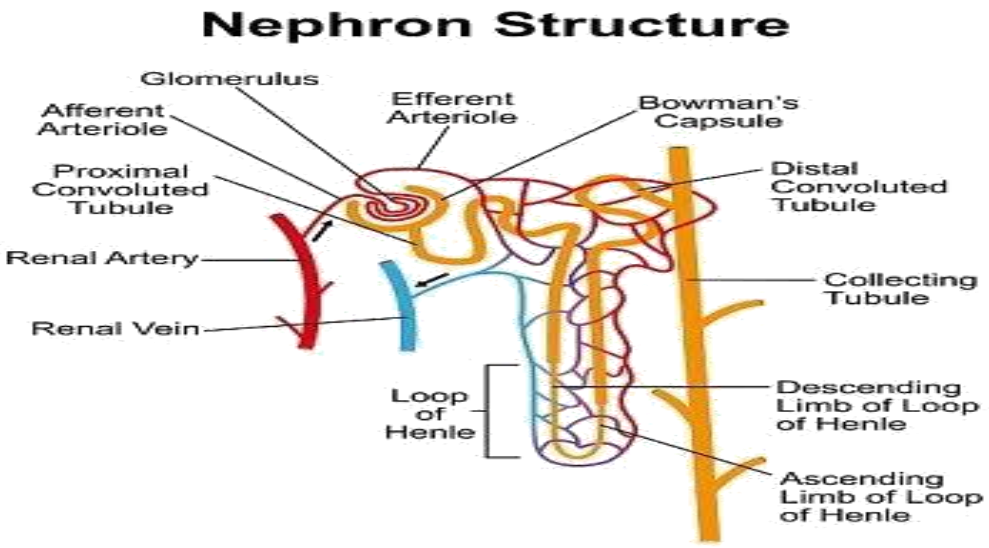

Fig 1: Normal nephron structure [3].

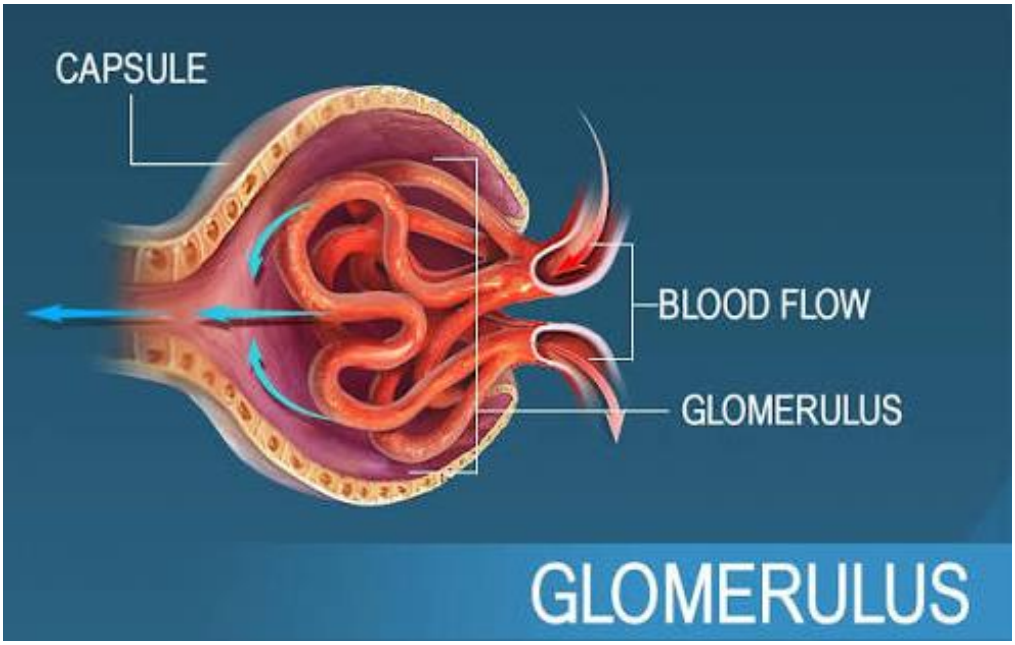

Fig 2: Normal glomerulus structure [15].

b- Renal Tubules:

- Proximal convoluted tubule (PCT): reabsorbs ~65% of sodium and water, all glucose, amino acids, and bicarbonate.
- Loop of Henle: establishes osmotic gradients for urine concentration.
- Distal convoluted tubule (DCT): adjusts electrolyte composition.
- Collecting duct: regulates water balance under the control of ADH and aldosterone. These structures work together to maintain fluid and electrolyte homeostasis [13, 14].

2- Basic Biochemical Roles of the Kidney:

a- Filtration

The glomerulus filters approximately 180 liters of plasma per day. This process removes metabolic wastes while retaining essential molecules. The efficiency of filtration is commonly expressed as the glomerular filtration rate (GFR) [16, 17].

b- Reabsorption:

- Recovery of water, sodium, glucose, and amino acids
- Regulation of acid-base balance by reabsorbing bicarbonate
- Maintenance of plasma osmolarity

This reabsorption prevents loss of important Nutrients [16, 17].

c- Secretion:

The tubules actively secrete additional substances such as: (Hydrogen ions - Ammonia - Drug metabolites - Heavy metals - Xenobiotics "foreign chemicals"). This makes the kidneys essential for detoxification and maintaining biochemical homeostasis [16, 17].

3- Key Biochemical Markers of Kidney Function:

a- Creatinine:

Creatinine, a product of muscle metabolism, is filtered freely but not significantly reabsorbed. Elevated serum creatinine indicates decreased GFR and renal impairment [18].

b- Urea:

Urea results from protein catabolism. High levels suggest impaired filtration or dehydration. It is less specific than creatinine [18].

c- Blood Urea Nitrogen (BUN):

BUN measures nitrogen from urea in the blood. Elevated BUN may indicate kidney dysfunction, hypovolemia, or increased protein breakdown. Other markers often used in research include: (Cystatin C, Urinary biomarkers "NGAL, KIM-1, NAG"), but creatinine and BUN remain the primary clinical indicators [18].

4-Why the Kidney Is Highly Sensitive to Toxins:

The kidney is one of the most vulnerable organs to toxic injury due to several biochemical and structural reasons [19]:

a- High Blood Flow:

The kidneys receive 20-25% of cardiac output, exposing them to circulating toxins more than most organs [19].

b- Concentration of Toxins:

During filtration and reabsorption, toxic Substances (including antibiotics and heavy metals) may become highly concentrated in tubular cells [19].

c- Active Transport Systems:

Proximal tubule cells contain organic anion and cation transporters that actively uptake: (Drugs - Metals - Xenobiotics), which increases intracellular accumulation and toxicity [19].

d- High Mitochondrial Activity:

Tubular cells require high ATP levels, making them vulnerable to: (oxidative stress, mitochondrial dysfunction - ROS production caused by antibiotics and Metals) [19].

e- Limited Regenerative Ability:

Though some tubular regeneration occurs, severe toxic injury often leads to permanent structural damage [19].

B- Antibiotics and Nephrotoxicity:

Antibiotic-induced nephrotoxicity is a major cause of drug-related kidney injury and represents a serious limitation in antimicrobial therapy. The kidneys play a central role in drug elimination through glomerular filtration, tubular secretion, and reabsorption. As a

result, renal tissues, particularly the proximal tubular epithelial cells, are exposed to high concentrations of antibiotics and their metabolites. This exposure, combined with the kidney's high metabolic activity and oxygen demand, makes it highly susceptible to toxic damage. Nephrotoxicity may manifest as acute kidney injury (AKI) or progress to chronic kidney disease (CKD) if exposure is prolonged or recurrent. The risk of antibiotic-induced kidney injury is influenced by dose, duration of therapy, patient Age, dehydration, pre-existing renal disease, and concurrent exposure to other nephrotoxic substances, including heavy metals [20-22]

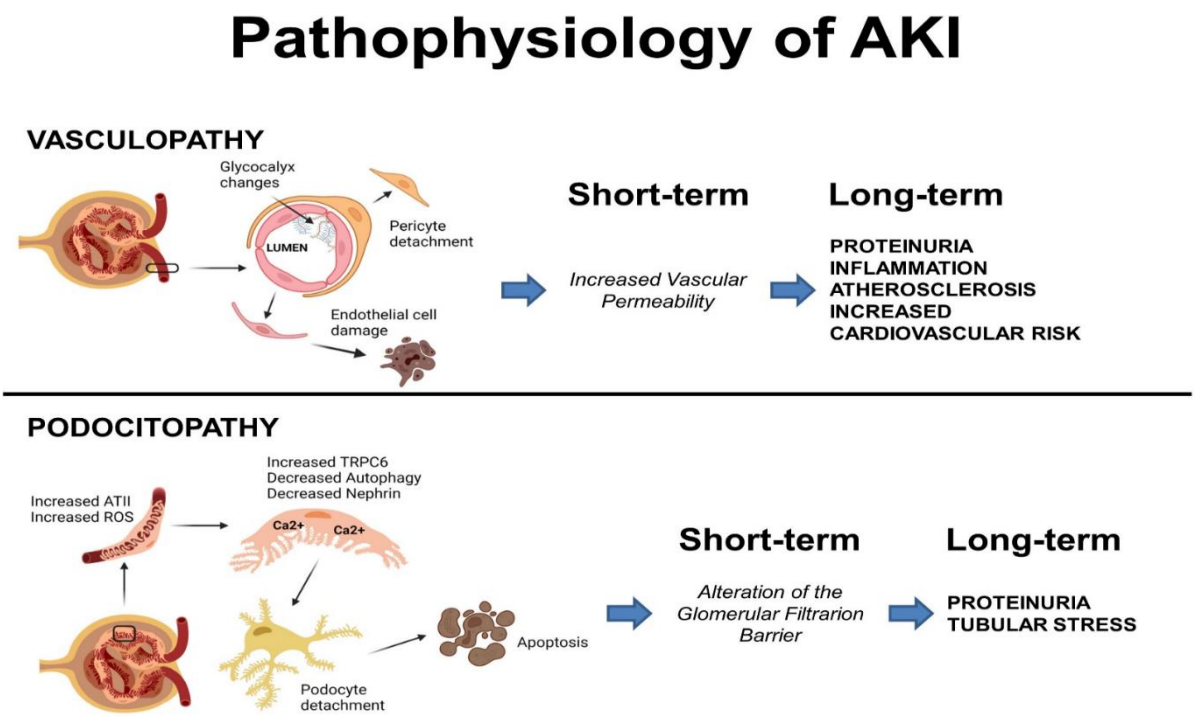

Fig (3): Mechanism of "AKI" [23].

1.1 Aminoglycosides (Gentamicin):

Gentamicin is one of the most extensively studied nephrotoxic antibiotics and remains widely used for the treatment of severe Gram- negative infections [24,25].

Mechanism of Renal Accumulation:

- Gentamicin is freely filtered at the glomerulus.
- It binds to negatively charged phospholipids on the brush border membrane of proximal tubular cells.
- Once internalized, gentamicin accumulates in lysosomes, mitochondria, and the endoplasmic reticulum [24,25].

Cellular Effects:

- Mitochondrial damage results in impaired oxidative phosphorylation and ATP depletion.
- Severe exposure causes acute tubular necrosis, particularly in the S1 and S2 segments of the proximal tubule.

Gentamicin nephrotoxicity is typically dose-dependent and may be reversible if detected early, and therapy is discontinued [24,25].

1.2 Glycopeptides (Vancomycin):

Vancomycin is essential for treating serious Gram-positive infections, particularly MRSA, but its nephrotoxic potential has gained increasing Attention [26].

Pathophysiology:

The risk of nephrotoxicity increases significantly at high trough concentrations and when Vancomycin is co-administered with other nephrotoxic drugs, such as aminoglycosides [26].

2. Sulfonamides and Acyclovir: Mechanisms of Kidney Injury:

2.1 Oxidative Stress and ROS Formation:

A central mechanism of antibiotic-induced nephrotoxicity is excessive generation of reactive oxygen species (ROS), including superoxide anions, hydrogen peroxide, and hydroxyl radicals [27].

2.1 Lipid Peroxidation:

ROS attack polyunsaturated fatty acids in cellular and mitochondrial membranes, initiating lipid Peroxidation. Lipid peroxidation is a major contributor to Tubular cell dysfunction [27].

2.3 Mitochondrial Dysfunction:

Mitochondria are primary targets of nephrotoxic antibiotics. Energy depletion ultimately leads to tubular cell death [25].

- Reduced ATP synthesis compromises energy-dependent transport processes.
- Loss of mitochondrial membrane potential disrupts calcium homeostasis.
- Release of pro-apoptotic proteins activates caspase cascades [25].

2.4 Tubular Necrosis:

Prolonged oxidative and mitochondrial damage results in necrosis of proximal tubular cells [25, 26].

- Necrotic cells obstruct tubular lumens.
- Back-leak of filtrate reduces effective urine formation.
- Results in acute kidney injury characterized by reduced GFR [25,26].

2.5 Inflammation:

Antibiotic-induced injury activates inflammatory responses. Increased expression of cytokines (TNF-α, IL-1β, IL-6) [26, 27].

- Sustained inflammation promotes fibrosis and chronic kidney damage.
- Poor solubility leads to crystallization within renal tubules.
- Causes tubular obstruction, inflammation, and reduced urine flow [26, 27].

3. Clinical Biochemical Markers of antibiotic-induced nephrotoxicity

3.1 Serum Creatinine:

Creatinine is the most commonly used marker of renal function [27-29].

- Elevated levels indicate reduced glomerular filtration rate.
- A rise in creatinine is often the earliest clinical sign of nephrotoxicity.

3.2 Blood Urea Nitrogen (BUN):

BUN reflects renal excretory capacity and protein metabolism [27-29].

- Elevated BUN occurs due to impaired urea clearance.
- Used in combination with creatinine to assess renal injury severity.

3.3 Electrolyte Imbalance:

Tubular dysfunction leads to disturbances such as:

- Hyperkalemia (impaired potassium secretion).
- Hyponatremia (defective sodium reabsorption).
- Metabolic acidosis (reduced hydrogen ion secretion).

These abnormalities reflect impaired tubular transport mechanisms

C- Heavy Metals and Nephrotoxicity:

Heavy metals are among the most potent environmental nephrotoxins due to their chemical stability, long biological half-lives, and strong affinity for cellular macromolecules. exposure may occur acutely or chronically through contaminated water, food chains, occupational hazards, pharmaceuticals, and tobacco smoke. Unlike organic toxins, heavy metals cannot be metabolized into non-toxic forms, leading to bioaccumulation and progressive renal damage. The kidney is a primary target organ because it receives approximately 20-25% of cardiac output and possesses specialized transporters that actively uptake metal ions.

Proximal tubular epithelial cells are particularly vulnerable due to their high mitochondrial density, intense reabsorptive activity, and abundant metal transport systems [30-32].

1. Major Nephrotoxic Heavy Metals:

1.1 Cadmium (Cd):

Cadmium is considered one of the most dangerous environmental nephrotoxins [33, 34].

Renal Transport and Accumulation:

- Cadmium binds to metallothionein (MT) in the liver.
- The Cd-MT complex is freely filtered through the glomerulus.
- Proximal tubular cells reabsorb the complex via endocytosis.
- Lysosomal degradation releases Cd2+ ions, which accumulate intracellularly.
- Cadmium has an extremely long half-life (10-30 years) in renal tissue [33, 34].

Clinical Consequences:

- Tubular proteinuria.
- Fanconi syndrome.
- Osteomalacia secondary to calcium loss.
- Progressive renal fibrosis [33,34].

1.2 Lead (Pb):

Lead causes chronic tubulointerstitial nephropathy and is often underdiagnosed [35].

Renal Handling:

- Filtered at the glomerulus.
- Reabsorbed by proximal tubules via divalent metal transporters (DMT1).
- Accumulates primarily in renal cortex [35].

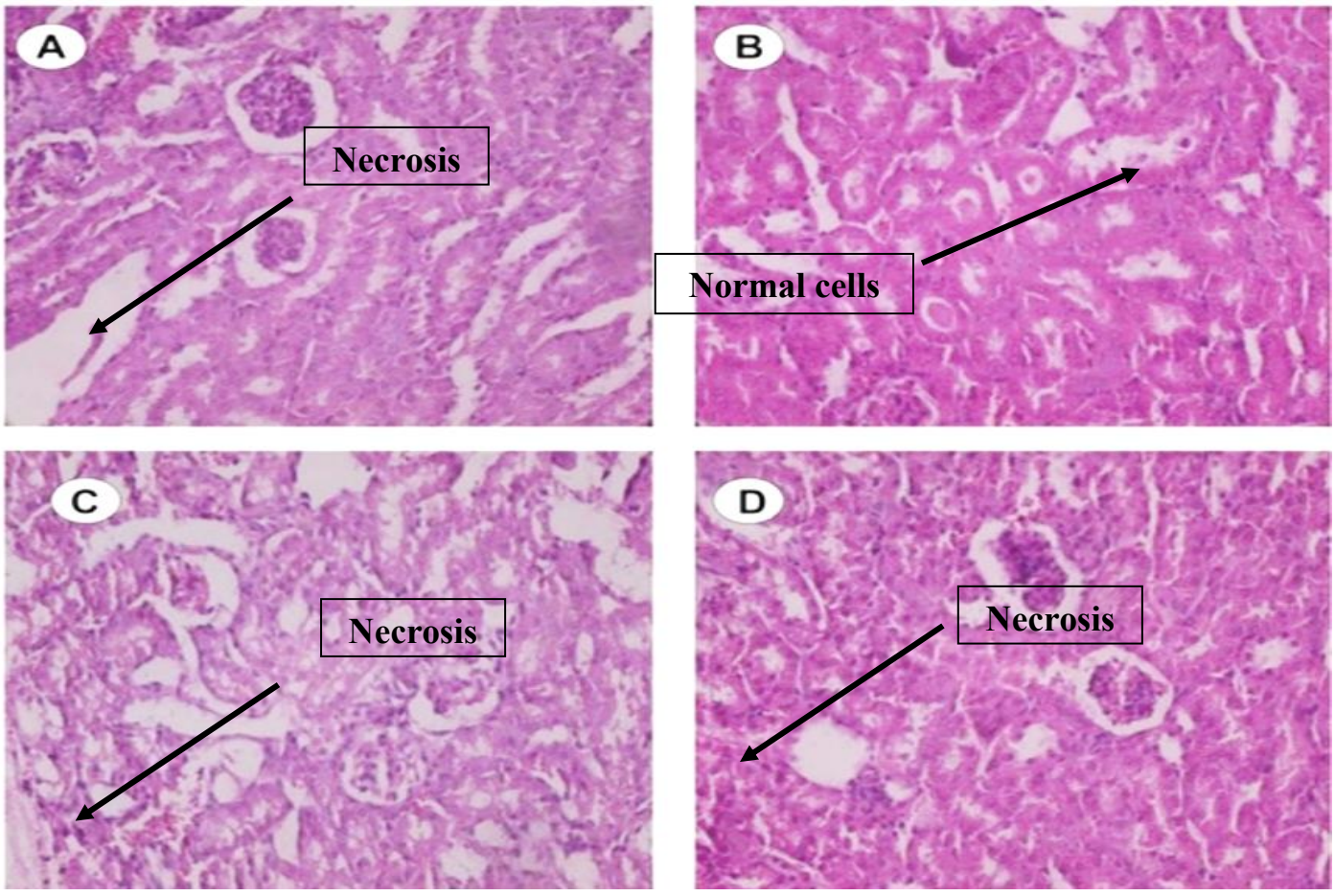

Fig 4: Necrotic cells and normal cells [23].

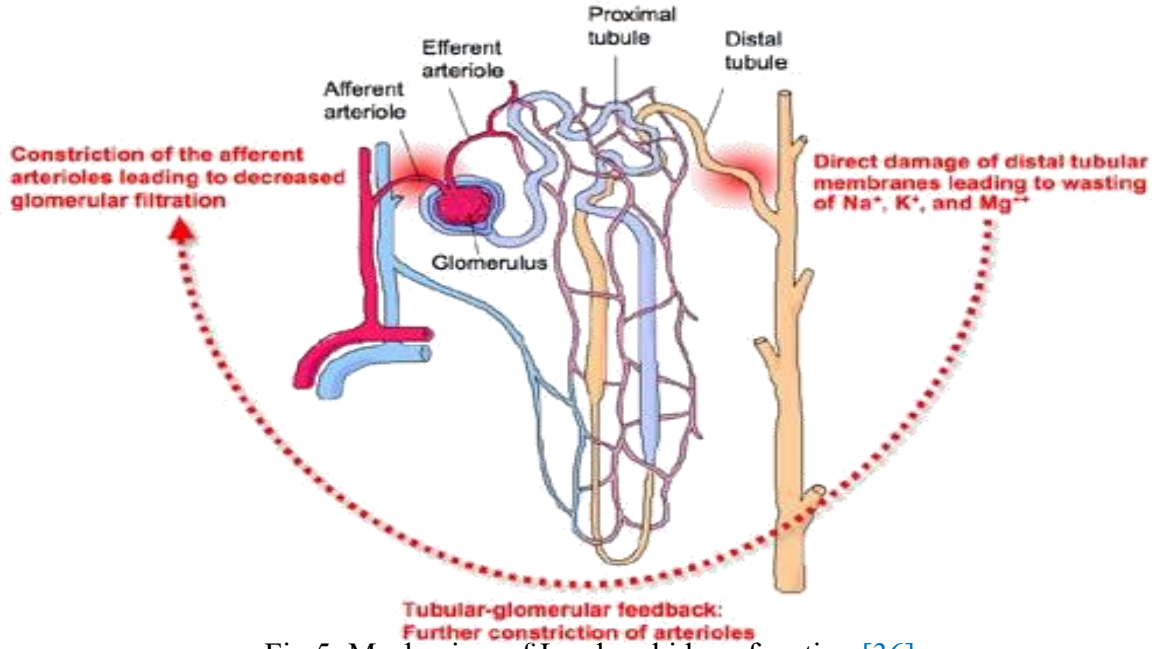

Fig 5: Mechanism of Lead on kidney function [36].

Biochemical Mechanisms:

- Inhibits Na^+/K^+ - ATPase.
- Disrupts calcium-dependent signaling Pathways.
- Induces oxidative stress and nitric oxide imbalance.
- Interferes with vitamin D metabolism [35].

Long-Term Effects:

- Reduced GFR.
- Hypertension (secondary effect).
- Chronic kidney disease [35].

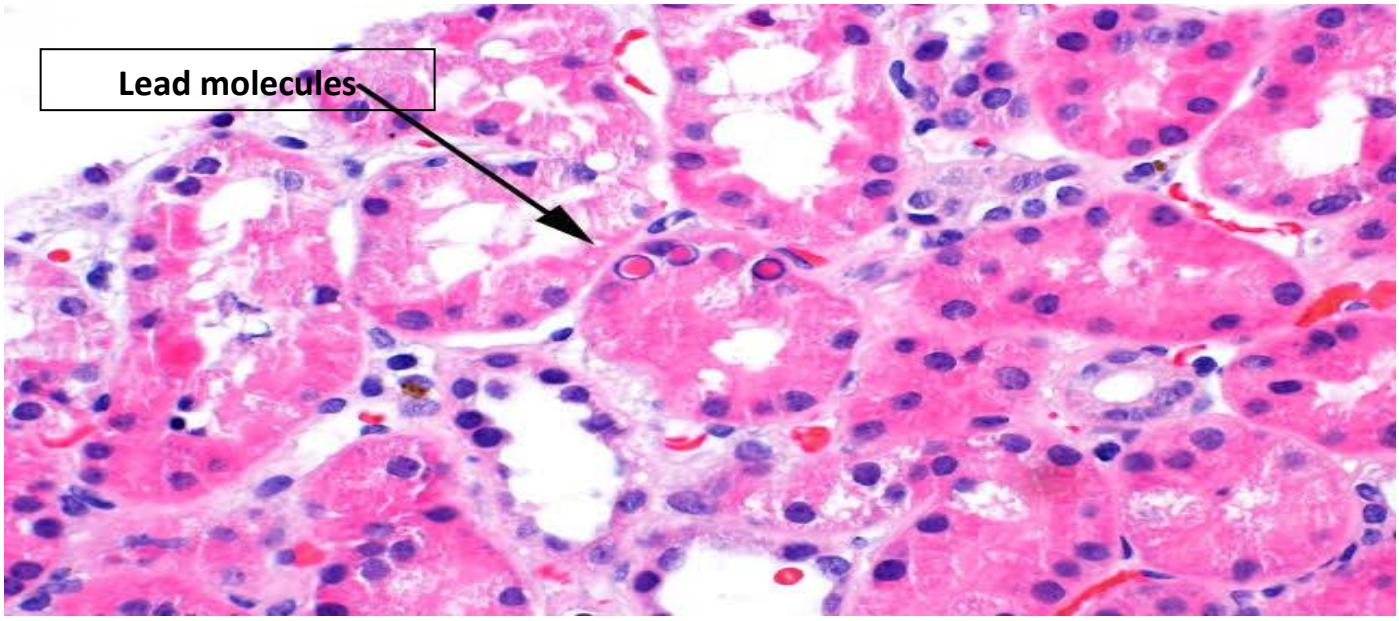

Fig 6: Renal tissue affected by lead [37].

1.3 Mercury (Hg):

Mercury exhibits extreme affinity for thiol (-SH) groups [38].

Forms and Toxicity:

- Inorganic mercury: most nephrotoxic.
- Organic mercury: systemic toxicity with renal involvement [38].

Renal Pathology:

- Acute tubular necrosis.
- Proteinuria.
- Immune complex deposition in glomeruli [38].

1.4 Arsenic (As):

Arsenic toxicity is widespread due to contaminated groundwater [39, 40].

Renal Outcomes:

- Tubular dysfunction.
- Oxidative DNA damage.
- Increased renal cancer risk [39, 40].

2. Advanced Biochemical Mechanisms of Renal Injury:

2.1 Excessive ROS Generation:

Heavy metals promote ROS production via [41]:

- Mitochondrial electron leakage.
- Fenton-like reactions.
- Inhibition of antioxidant enzymes [41].

Resulting ROS includes:

- Superoxide anion ($O_2^{\cdot -}$).
- Hydrogen peroxide (H_2O_2).
- Hydroxyl radical ($^{\cdot}OH$) [41].

2.2 Antioxidant Enzyme Inhibition:

Heavy metals disrupt antioxidant defenses at multiple levels [41]:

Antioxidant	Effect
SOD	Metal displacement from active
CAT	Inhibited breakdown of H_2O_2
GSH	Direct binding to -SH groups
GP_X	Reduced enzymatic activity
This imbalance causes oxidative stress amplification [41].	

2.3 Mitochondrial Dysfunction:

Heavy metals:

- Collapse mitochondrial membrane potential.
- Inhibit ATP synthesis.
- Disrupt calcium homeostasis.
- Trigger mitochondrial permeability transition Pore (mPTP) opening.

Energy failure is a critical step toward cell death [41].

2.4 Apoptosis and Necrosis:

Apoptotic Pathway:

- Cytochrome-c release.
- Caspase-9 ▶ caspase-3 activation.
- DNA fragmentation [41].

Necrotic Injury:

- Severe ATP depletion.
- Membrane rupture.
- Tubular obstruction [41].

2.5 Chronic Inflammation and Fibrogenesis:

Persistent metal exposure activates:

- NF - kB signaling.
- TGF-β/Smad pathway.

- Myofibroblast differentiation [41].

Results in:

- Collagen I & III deposition.
- Tubulointerstitial fibrosis.
- Irreversible nephron loss [41].

3. Biochemical & Clinical Biomarkers:

Classical Markers:

- Serum creatinine.
- BUN [41].

Early Tubular Injury Markers:

- β2-microglobulin.
- NAG.
- KIM-1.
- NGAL [41].

Oxidative Stress Markers:

- MDA.
- GSH.
- SOD, CAT [41].

D. Combined Toxicity: Interactions Between Antibiotics and Heavy Metals in Kidney Injury

Combined exposure to nephrotoxic antibiotics and heavy metals represents a biologically significant and clinically relevant challenge [42, 43]. In real-world scenarios, individuals are rarely exposed to isolated toxicants – they are exposed to complex mixtures that can interact at molecular, cellular, and systemic levels. antibiotics and heavy metals frequently occur due to environmental contamination, pharmaceutical use, and lifestyle factors. Their interactions can lead to synergistic nephrotoxicity that surpasses the additive effects of each agent alone. Understanding these interactions requires an integrated view of renal physiology, toxicokinetics, and cellular biochemistry [44, 45].

1. Mechanistic Basis of Synergistic Nephrotoxicity

1.1 Enhanced Oxidative Stress Beyond Additivity:

Both antibiotics and heavy metals stimulate the generation of reactive oxygen species (ROS) through distinct pathways [46, 47]:

Antibiotic-Induced ROS Production:

- Aminoglycosides (gentamicin) disrupt mitochondrial electron transport, increasing leakage of electrons and formation of superoxide anions ($O_2^{\bullet -}$).
- Glycopeptides (vancomycin) impair mitochondrial respiratory complexes, increasing ROS and peroxynitrite production [46, 47].

Heavy Metal-Induced ROS:

- Cadmium indirectly increases ROS via depletion of antioxidant defenses and substitution of redox-active metals in enzymes.
- Lead catalyzes Fenton-like reactions and disrupts heme biosynthesis, amplifying oxidative damage [48, 49].

Synergistic Mechanisms:

When combined, their effects on oxidative metabolism overlap and reinforce each other [44, 45]. Crosstalk between ROS pathways results in disruption of thiol redox status, mitochondrial DNA damage, and activation of cell death pathways [44, 45].

1.2 Mitochondrial Dysfunction and Energetic Collapse:

The kidney, especially the proximal tubule, relies heavily on oxidative phosphorylation. both antibiotics and heavy metals [48,49]. The combined impact leads to ATP depletion, disrupting sodium-potassium ATPase and organic cation transporters (OCTs), impairing tubular reabsorption and promoting cell swelling and necrosis [48,49].

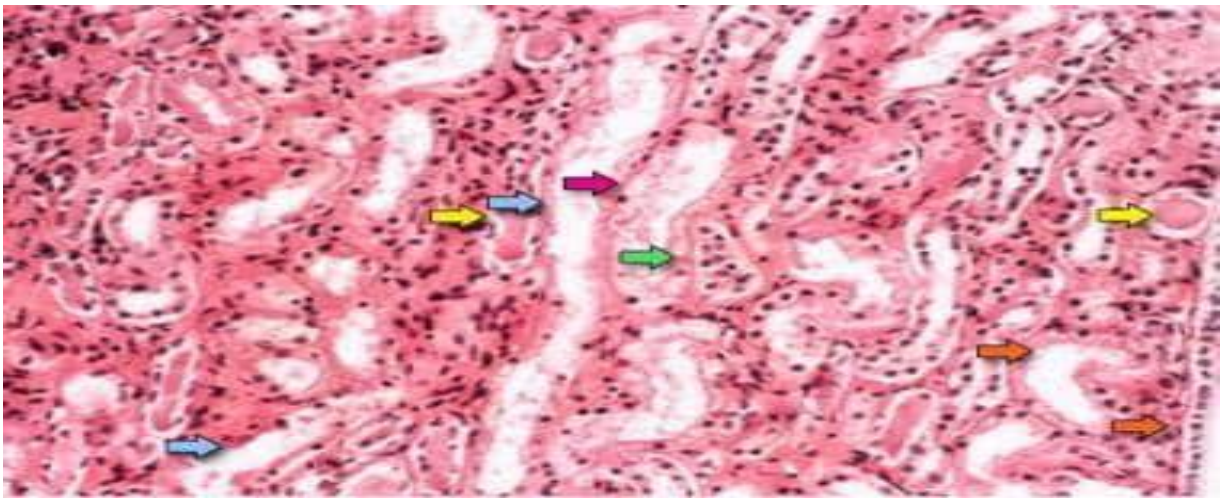

Fig 7: Normal tubular necrosis [50].

1.3 Amplified Inflammatory Signaling:

Inflammation is a central driver of chronic kidney injury. combined exposures potentiate pro-inflammatory signaling through [43, 44]:

Inflammasome Activation:

- NLRP3 inflammasome is activated by oxidative stress and mitochondrial damage.
- Caspase-1 activation increases IL-1β and IL- 18 production [43, 44].

Toll-Like Receptor (TLR) Modulation:

The resulting microenvironment recruits macrophages and neutrophils, exacerbating Tissue injury and fibrogenic signaling [43, 44].

2. Pathophysiological Consequences:

2.1 Glomerular-Tubular Dysfunction:

Synergistic injury affects both glomerular and tubular compartments:

Together, these lead to glomerulosclerosis and tubular atrophy, reducing filtration surface area and functional nephron numbers [51].

2.2 Accelerated Decline in Glomerular Filtration Rate (GFR)

Combined toxicity can cause abrupt or progressive declines in GFR via:

- Tubular obstruction due to necrotic cell debris.
- Interstitial edema compressing nephrons.
- Vasoconstriction of afferent arterioles.
- Increased intraglomerular pressure and filtration barrier disruption

These changes result in elevated serum creatinine and BUN beyond what is seen with single exposures [51].

2.3 Extracellular Matrix (ECM) Remodeling and Fibrosis

Persistent inflammatory and oxidative signaling triggers profibrotic pathways:

- TGF-B/Smad activation increases collagen (types I, III) and fibronectin deposition.
- Matrix metalloproteinase (MMP) imbalance reduces ECM degradation.
- Persistent fibroblast activation leads to interstitial fibrosis.

This represents the final common pathway to chronic kidney disease (CKD) and eventual organ failure [51].

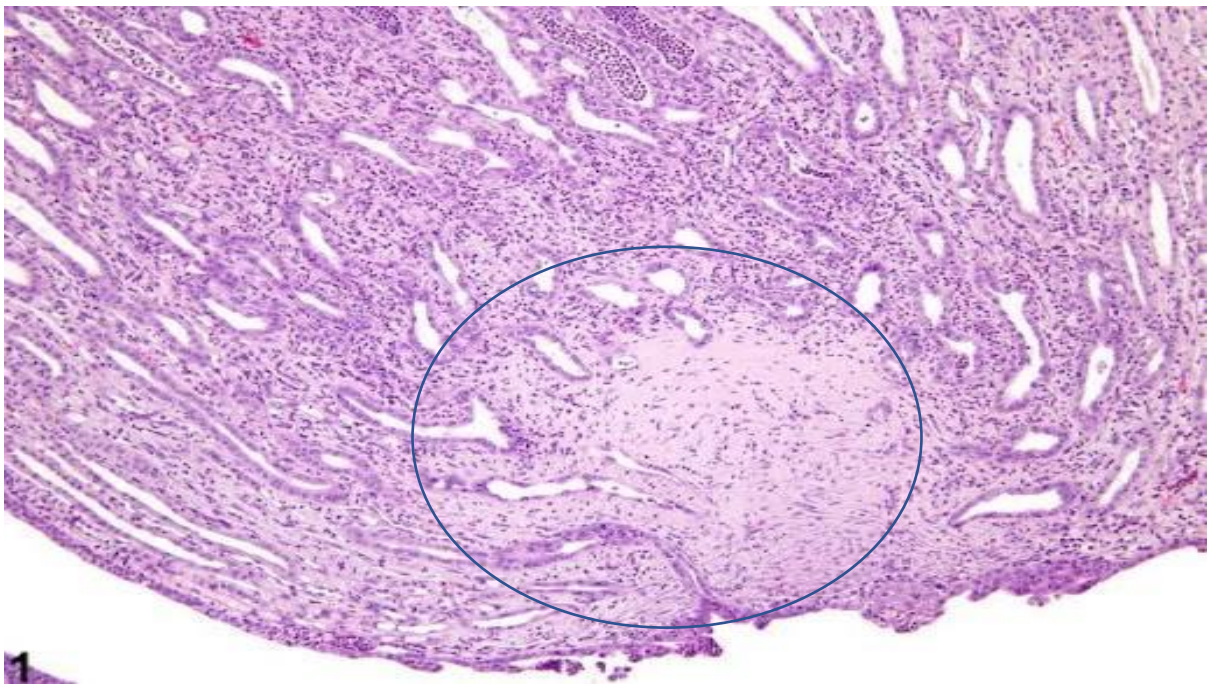

Fig 8: Tissue fibrosis region [52].

3. Mechanisms of Interaction at the Molecular Level

3.1 Metal-Drug Complex Formation:

Heavy metals can bind directly to antibiotics:

- Chelation alters drug pharmacokinetics.
- Complexes may increase renal tubular uptake.
- Some complexes are more reactive and toxic than parent compounds [53].

3.2 Transporter Interference

Common transporters affected include:

- Organic Anion Transporters (OAT1, OAT3).
- Organic Cation Transporters (OCT2).
- Multidrug and Toxin Extrusion (MATE) proteins.

Heavy metals and antibiotics compete for transporter binding, leading to accumulation within tubular cells [53].

4. Why Combined Exposures Are Common

4.1 Clinical and Lifestyle Factors:

- Antibiotic prescriptions are common, especially in hospitalized patients.
- Smoking and diet contribute to cadmium and lead accumulation.
- Chronic disease patients are often on polypharmacy regimens.
- Some traditional medicines contain heavy metals.

Thus, background metal exposure and antibiotic therapy often coincide, especially in vulnerable populations [54].

5. Biomarkers Specific to Combined Toxicity

In addition to classical markers (creatinine, BUN), **Combined toxicity shows**:

- ↑ Kidney Injury Molecule-1 (KIM-1).
- ↑ Neutrophil Gelatinase-Associated Lipocalin (NGAL).
- ↑β2-Microglobulin.
- ↑ Urinary N-acetyl-B-D-glycosaminidase NAG).
- Altered metabolomic profiles (uremic toxins, amino acid dysregulation).

These markers increase earlier than creatinine, making them valuable for the detection of synergistic Injury [55].

E. Methods and Biochemical Tests for the Assessment of Nephrotoxicity:

Evaluation of nephrotoxicity caused by antibiotics and heavy metals relies on a multidimensional methodological approach combining functional

renal biomarkers, oxidative stress indices, antioxidant defense measurements, and histopathological examination. Together, these methods provide both quantitative biochemical data and qualitative structural evidence of kidney injury [56,57].

1. Functional Kidney Biomarkers:

Functional biomarkers reflect the overall ability of the kidney to filter and excrete metabolic waste. They are essential first-line indicators of renal damage [56,57].

1.1 Serum Creatinine:

Biochemical Background:

Creatinine originates from the non-enzymatic conversion of creatine and phosphocreatine in skeletal muscle. Under normal conditions, creatinine is [56,57]:

- Freely filtered by the glomerulus
- Not reabsorbed
- Minimally secreted by renal tubules

Thus, serum creatinine concentration is inversely related to glomerular filtration rate (GFR) [56,57].

Analytical Methods:

- Jaffé Method: reaction with alkaline picrate; simple but susceptible to interference.

- Enzymatic Assays: higher specificity and accuracy [58,59].

1.2 Serum Urea and Blood Urea Nitrogen (BUN)

Biochemical Background:

Urea is synthesized in the liver via the urea cycle and excreted mainly by the kidneys. Unlike creatinine, urea undergoes partial tubular reabsorption [58, 59].

Oxidative Stress and Lipid Peroxidation

Oxidative stress is a central mechanism of kidney injury induced by antibiotics and heavy metals [60, 61].

2.1 Malondialdehyde (MDA)

Biochemical Basis:

MDA is generated from the peroxidation of polyunsaturated fatty acids in cell membranes. It forms adducts with proteins and DNA, impairing cellular function

Significance in Renal Toxicity [60,61]**:**

- High MDA indicates membrane damage in proximal tubules.
- Strongly associated with tubular necrosis and inflammation.
- Elevated in gentamicin, cadmium, mercury, and lead toxicity models.

Methodology:

- TBARS assay using thiobarbituric acid.
- Spectrophotometric detection at 532 nm [60,61].

Interpretation:

- Increased MDA = increased oxidative membrane damage [62].

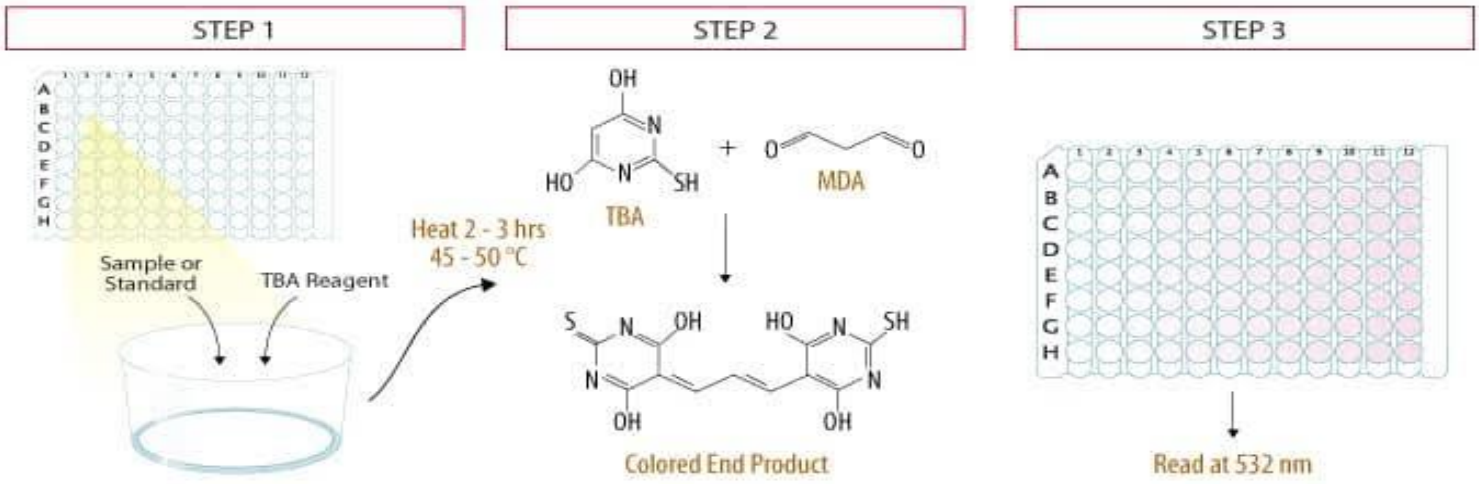

Fig 9: TBARS assay steps [63].

3. Antioxidant Enzyme Activity Measurements

3.1Superoxide Dismutase (SOD) Physiological Role

SOD converts superoxide radicals into hydrogen peroxide, preventing the formation of highly reactive hydroxyl radicals [64,65].

Nephrotoxic Significance:

- Antibiotics and heavy metals inhibit SOD by oxidative modification of active sites.
- Reduced SOD leads to ROS accumulation and mitochondrial damage [64,65].

Assay Methods:

- Nitroblue tetrazolium (NBT) inhibition.
- Pyrogallol autoxidation method.
- Commercial enzyme activity kits [64,65].

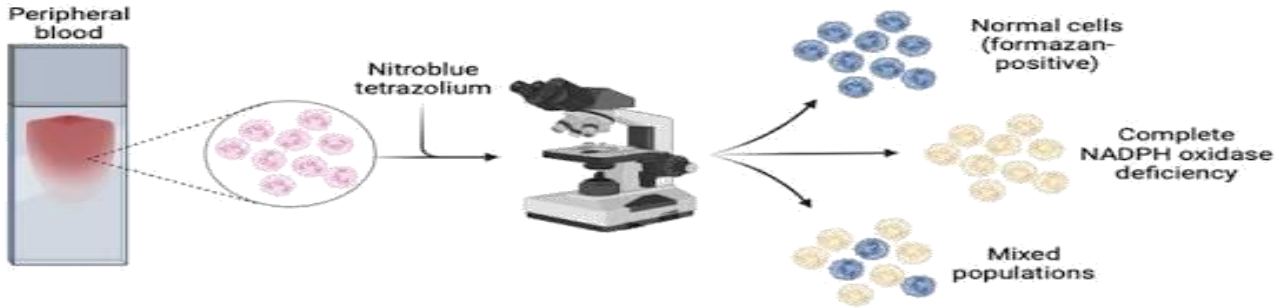

Fig 10: Nitroblue tetrazolium assay results [66].

4. Reduced Glutathione (GSH)

Biochemical Role:

GSH is the most abundant intracellular thiol antioxidant and is essential for the detoxification of xenobiotics [67,68]:

- Maintenance of redox homeostasis
- Prevention of apoptosis

Nephrotoxic Relevance:

- Heavy metals (especially cadmium and Mercury) bind sulfhydryl groups and deplete GSH.
- Antibiotics induce ROS that consume GSH reserves.
- GSH depletion sensitizes renal cells to injury [67,68].

Measurement:

- Ellman's reagent (DTNB) method.
- Fluorometric assays [67,68].

5. Histopathological Evaluation of Kidney Tissue

Histopathology provides direct morphological confirmation of biochemical alterations [69].

5.1 Tissue Processing:

- Fixation in buffered formalin.
- Paraffin embedding.
- Sectioning (4-5 µm) [69].

5.2 Staining Techniques and Interpretation [69]:

stain	Purpose
H&E	General morphology
PAS	Basement membrane integrity
Masson's Trichrome	Fibrosis and collagen deposition

Observed Lesions:

- Proximal tubular necrosis.
- Glomerular atrophy.
- Tubular dilation.
- Interstitial inflammation.
- Fibrosis in chronic exposure [69].

Conflict of interest: **NIL**

Funding: **NIL**

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