INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Molecular Mechanism, Biomarkers and Prevention Strategies of Drug-Induced Nephrotoxicity

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ARTICLE INFO

Published: 05 May. 2026
Keywords:
Drug-induced nephrotoxicity, Acute kidney injury, Oxidative stress, Mitochondrial dysfunction, Biomarkers
DOI:
10.5281/zenodo.20029249

ABSTRACT

Drug-induced nephrotoxicity is a significant contributor to acute kidney injury (AKI) and chronic kidney disease (CKD), posing a major challenge in clinical therapeutics. The kidneys are particularly vulnerable to toxic insults due to their high blood flow, active transport systems, and role in drug excretion. This review provides a comprehensive analysis of the molecular mechanisms, biomarkers, and prevention strategies associated with drug-induced nephrotoxicity. Key pathogenic mechanisms include oxidative stress, mitochondrial dysfunction, apoptosis, inflammation, endoplasmic reticulum stress, and dysregulated autophagy, all of which contribute to structural and functional damage in renal tissues. The review further highlights the limitations of conventional biomarkers such as serum creatinine and blood urea nitrogen, which often fail to detect early kidney injury. Emerging biomarkers, including kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, interleukin-18 (IL-18), and microRNA-based markers, demonstrate improved sensitivity and specificity for early diagnosis and prognosis. Additionally, experimental models, including in vitro cell cultures and animal studies, are discussed for their role in elucidating mechanisms and evaluating therapeutic interventions. Studies have reported that approximately 10–25% of hospitalised patients experience some degree of drug-related renal impairment. Preventive strategies such as dose optimisation, therapeutic drug monitoring, adequate hydration, pharmacological protective agents, and antioxidant therapies are critically reviewed for their effectiveness in minimising renal damage. Despite advances in understanding and management, challenges remain in translating experimental findings into clinical practice.

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Future research focusing on biomarker validation, precision medicine, and advanced experimental models is essential to improve early detection and develop targeted therapeutic approaches, ultimately reducing the global burden of drug-induced nephrotoxicity.

INTRODUCTION

Overview of Kidney Physiology and Its Susceptibility to Drug Toxicity

The kidneys are highly specialised organs responsible for maintaining systemic homeostasis through regulation of fluid balance, electrolyte composition, acid–base equilibrium, and elimination of metabolic waste products and xenobiotics. Each kidney contains approximately one million nephrons, which function as the structural and functional units responsible for filtration, reabsorption, secretion, and excretion processes. Renal blood flow accounts for nearly 20–25% of total cardiac output, exposing renal tissues to high concentrations of circulating drugs and their metabolites [1]. This extensive exposure is compounded by the presence of specialised transport systems such as organic anion transporters (OATs), organic cation transporters (OCTs), and P-glycoprotein, which actively facilitate drug uptake into tubular epithelial cells. While these transporters are essential for drug clearance, they also contribute to intracellular accumulation of nephrotoxic compounds, thereby increasing susceptibility to cellular injury. The proximal tubule is particularly vulnerable due to its high metabolic activity and abundance of mitochondria, which are required to sustain active transport mechanisms. These cells depend heavily on oxidative phosphorylation, making them highly sensitive to mitochondrial dysfunction and oxidative stress. Furthermore, the renal medulla operates under relatively hypoxic conditions compared to the cortex, rendering it more susceptible to ischemic injury when exposed to nephrotoxic agents. Drugs that alter renal hemodynamics, impair mitochondrial function, or induce oxidative stress can disrupt these finely balanced processes, leading to structural and functional damage. Additionally, the kidney's role in concentrating urine can result in higher intratubular drug concentrations, further exacerbating toxicity. These physiological characteristics collectively explain why the kidney is one of the primary targets of drug-induced toxicity [2].

Importance of Studying Drug-Induced Nephrotoxicity

Drug-induced nephrotoxicity (DIN) is a critical concern in modern clinical practice due to its high prevalence and potential to cause severe and sometimes irreversible renal damage. With the increasing use of complex pharmacotherapy, particularly in elderly and critically ill populations, the risk of nephrotoxicity has risen substantially. Understanding the mechanisms underlying DIN is essential for optimising drug safety, improving therapeutic outcomes, and minimising adverse effects. Early identification of nephrotoxic effects enables clinicians to modify or discontinue offending agents before significant renal damage occurs. Research into DIN also plays a vital role in drug development and regulatory science. Preclinical and clinical studies aimed at identifying nephrotoxic potential can guide safer drug design and reduce the likelihood of adverse renal outcomes. Moreover, advances in molecular biology have provided deeper insights into cellular and subcellular mechanisms of kidney injury, including oxidative stress, apoptosis, and inflammatory pathways. These insights have paved the way for the development of targeted therapies and nephroprotective agents. Additionally, the integration of pharmacogenomics into clinical practice offers the potential to identify individuals at higher risk of nephrotoxicity based on genetic predisposition.

This personalised approach to medicine is expected to significantly reduce adverse drug reactions. Therefore, studying DIN is not only important for patient care but also for advancing the field of precision medicine [3].

Clinical Burden of Kidney Injury Caused by Drugs

Drug-induced kidney injury represents a substantial clinical and economic burden worldwide. It is estimated that approximately 20% of acute kidney injury (AKI) cases in hospitalised patients are attributable to drug exposure [4]. In intensive care units, the incidence may be even higher due to polypharmacy and the use of high-risk medications. The clinical consequences of DIN range from mild, reversible renal impairment to severe kidney failure requiring renal replacement therapy such as dialysis. These outcomes are associated with increased morbidity, mortality, and prolonged hospital stays. The burden of DIN is particularly significant in vulnerable populations, including elderly patients, individuals with pre-existing kidney disease, and those with comorbid conditions such as diabetes and hypertension. In oncology, nephrotoxic chemotherapeutic agents like cisplatin are widely used, further contributing to the prevalence of renal injury. Similarly, in infectious disease management, antibiotics such as aminoglycosides and vancomycin are commonly implicated. The economic impact of DIN includes increased healthcare costs due to extended hospitalisation, additional diagnostic testing, and therapeutic interventions. Furthermore, progression to chronic kidney disease (CKD) can result in long-term healthcare expenses and reduced quality of life. These factors highlight the urgent need for improved prevention, early detection, and management strategies to mitigate the burden of drug-induced nephrotoxicity [5].

2. Epidemiology and Clinical Significance of Drug-Induced Nephrotoxicity

Prevalence of Nephrotoxicity in Hospitalised Patients

The prevalence of drug-induced nephrotoxicity in hospitalised patients varies widely depending on the clinical setting, patient demographics, and types of medications used. Studies have reported that approximately 10–25% of hospitalised patients experience some degree of drug-related renal impairment [6]. In critically ill patients admitted to intensive care units, the incidence is significantly higher due to the combined effects of severe illness, hemodynamic instability, and exposure to multiple nephrotoxic agents. The widespread use of contrast media, antibiotics, and chemotherapeutic drugs further contributes to this high prevalence. Despite its frequency, drug-induced nephrotoxicity is often underdiagnosed or recognised late in its course. This is largely due to the limitations of conventional biomarkers such as serum creatinine, which may not reflect early kidney injury. Additionally, symptoms of nephrotoxicity are often nonspecific, making clinical diagnosis challenging. Epidemiological studies have emphasised the importance of early detection and monitoring strategies to reduce the incidence and severity of renal injury. Improved awareness among healthcare professionals and the implementation of risk assessment protocols can significantly decrease the burden of nephrotoxicity. Furthermore, population-based studies have highlighted disparities in incidence rates across different regions, reflecting variations in healthcare practices and access to diagnostic tools. Understanding these epidemiological patterns is essential for developing effective prevention and management strategies [7].

Major Classes of Nephrotoxic Drugs

A wide range of therapeutic agents have been implicated in drug-induced nephrotoxicity, each with distinct mechanisms of action and patterns of renal injury. Aminoglycoside antibiotics, such as gentamicin, are well-known for their nephrotoxic potential. These drugs accumulate in proximal tubular cells through receptor-mediated endocytosis, leading to lysosomal dysfunction, oxidative stress, and eventual cell death [8]. Vancomycin, another commonly used antibiotic, has been associated with dose-dependent nephrotoxicity, particularly when used in combination with other nephrotoxic agents such as piperacillin–tazobactam. Cisplatin, a widely used chemotherapeutic agent, is one of the most potent nephrotoxins in clinical practice. It induces renal injury through multiple mechanisms, including oxidative stress, inflammation, and DNA damage. Non-steroidal anti-inflammatory drugs (NSAIDs) exert their nephrotoxic effects by inhibiting cyclooxygenase enzymes, leading to reduced prostaglandin synthesis and decreased renal blood flow [11]. Radiographic contrast agents are another major cause of nephrotoxicity, particularly in patients with pre-existing kidney disease. These agents cause vasoconstriction, oxidative stress, and direct tubular toxicity, resulting in contrast-induced nephropathy [12]. Calcineurin inhibitors such as cyclosporine and tacrolimus are widely used in transplant medicine but are associated with chronic nephrotoxicity characterized by vasoconstriction, fibrosis, and progressive decline in renal function. Other anticancer agents, including methotrexate and ifosfamide, also contribute to renal injury through crystal formation and tubular toxicity. The diversity of these drug classes underscores the complexity of nephrotoxicity and highlights the need for individualized risk assessment and management strategies [13,14].

Risk Factors and Susceptible Populations

The development of drug-induced nephrotoxicity is influenced by a complex interplay of patient-related and drug-related factors. Patient-related factors include advanced age, pre-existing kidney disease, diabetes mellitus, hypertension, and dehydration [15]. Elderly patients are particularly vulnerable due to age-related decline in renal function and increased likelihood of polypharmacy. Drug-related factors such as high dosage, prolonged duration of therapy, and concurrent use of multiple nephrotoxic agents significantly increase the risk of renal injury.

High-risk populations include critically ill patients, transplant recipients, and individuals undergoing chemotherapy. Genetic predisposition also plays a role, with certain polymorphisms affecting drug metabolism and transport. Environmental factors such as inadequate hydration and exposure to nephrotoxic substances further contribute to susceptibility. Understanding these risk factors is essential for identifying at-risk individuals and implementing preventive strategies. Risk stratification models and clinical decision support systems can aid in minimizing the incidence of nephrotoxicity in clinical practice [16].

Clinical Consequences and Outcomes

Drug-induced nephrotoxicity can lead to a broad spectrum of clinical outcomes ranging from mild, transient renal impairment to severe and irreversible kidney damage. One of the most common manifestations is acute kidney injury (AKI), characterized by a rapid decline in glomerular filtration rate (GFR), leading to accumulation of nitrogenous waste products such as creatinine and urea in the blood. AKI can develop within hours to days following exposure to nephrotoxic agents and may progress to life-threatening complications if not managed promptly [17]. In many cases, repeated or severe episodes of AKI can evolve into chronic kidney

disease (CKD), which is associated with progressive loss of renal function and increased risk of cardiovascular morbidity and mortality. Electrolyte imbalances are another important consequence of nephrotoxicity. Disruption of tubular function can lead to abnormalities such as hyperkalemia, hyponatremia, hypocalcaemia, and metabolic acidosis. These disturbances can have significant clinical implications, including cardiac arrhythmias and neuromuscular dysfunction. Fluid overload is also commonly observed due to impaired renal excretion of sodium and water, leading to edema, pulmonary congestion, and hypertension. In severe cases, patients may require renal replacement therapy such as hemodialysis or peritoneal dialysis to maintain homeostasis. The long-term outcomes of drug-induced nephrotoxicity depend on the severity and duration of injury, as well as the patient's baseline renal function and comorbid conditions. Early detection and intervention can significantly improve prognosis, while delayed recognition often results in irreversible damage. Additionally, nephrotoxicity may necessitate discontinuation or modification of essential medications, potentially compromising treatment efficacy in conditions such as cancer and severe infections. Therefore, understanding the clinical consequences of nephrotoxicity is essential for optimising patient management and improving outcomes [18].

Economic and Healthcare Burden

Drug-induced nephrotoxicity imposes a substantial economic burden on healthcare systems worldwide. The direct costs associated with nephrotoxicity include prolonged hospitalisation, diagnostic investigations, pharmacological interventions, and renal replacement therapies. Patients who develop AKI often require intensive monitoring and supportive care, significantly increasing healthcare expenditures. Furthermore, the need for dialysis in severe cases adds considerable financial strain onboth patients and healthcare systems [19]. Indirect costs also contribute significantly to the overall burden. These include loss of productivity due to prolonged illness, long-term disability, and reduced quality of life. Patients who progress to chronic kidney disease require ongoing medical care, including regular monitoring, medication, and potential kidney transplantation. The economic impact is particularly pronounced in low- and middle-income countries, where access to healthcare resources may be limited. In addition to financial costs, nephrotoxicity also affects healthcare resource utilisation. Increased demand for hospital beds, dialysis units, and specialised care services places significant pressure on healthcare infrastructure. Preventive strategies, including early detection and risk management, can help reduce these burdens. Cost-effective approaches such as therapeutic drug monitoring and patient education have been shown to improve outcomes and reduce healthcare expenditures. Therefore, addressing drug-induced nephrotoxicity is not only a clinical priority but also an economic necessity [20].

Clinical Significance and Need for Early Detection

The clinical significance of drug-induced nephrotoxicity lies in its potential to cause irreversible kidney damage if not detected early. Traditional diagnostic methods rely heavily on serum creatinine levels, which are often insensitive and may not reflect early renal injury. By the time creatinine levels rise, significant nephron damage may have already occurred [21]. This delay in detection limits the effectiveness of therapeutic interventions and increases the risk of adverse outcomes. Early detection of nephrotoxicity allows for timely modification or discontinuation of the offending drug, thereby preventing further damage. Advances in

biomarker research have led to the identification of novel indicators such as KIM-1, NGAL, and cystatin C, which can detect kidney injury at an earlier stage. Incorporating these biomarkers into clinical practice can significantly improve diagnostic accuracy and patient outcomes. Moreover, early detection is particularly important in high-risk populations, including critically ill patients and those receiving nephrotoxic chemotherapy. Regular monitoring and risk assessment can help identify early signs of renal impairment and guide appropriate interventions. The integration of electronic health records and clinical decision support systems has further enhanced the ability to detect and manage nephrotoxicity. Therefore, improving early detection strategies is essential for reducing the burden of drug-induced kidney injury [21].

4. Classification of Drug-Induced Nephrotoxicity

Drug-induced nephrotoxicity can be classified based on the site and mechanism of injury, which provides a useful framework for diagnosis and management. Acute kidney injury (AKI) is the most common form and is characterized by a sudden decline in renal function, often associated with reduced urine output and elevated serum creatinine levels. AKI may result from direct tubular toxicity, hemodynamic alterations, or obstruction within the renal tubules [22]. Tubular toxicity primarily affects the proximal tubular epithelial cells, which are highly susceptible to drug-induced damage due to their active role in reabsorption and secretion. This type of injury is commonly observed with aminoglycosides and cisplatin. Glomerular injury, on the other hand, involves damage to the glomerular filtration barrier, leading to proteinuria and impaired filtration. Drugs such as non-steroidal anti-inflammatory agents and certain biologics have been implicated in glomerular injury.

Interstitial nephritis is an immune-mediated form of nephrotoxicity characterized by inflammation of the renal interstitium. It is often associated with hypersensitivity reactions to drugs such as antibiotics and proton pump inhibitors. Chronic kidney disease related to drugs develops following prolonged or repeated exposure to nephrotoxic agents and is characterized by progressive fibrosis and loss of renal function. Understanding these classifications helps clinicians identify the underlying mechanism of injury and tailor appropriate treatment strategies [23].

5. Pathophysiology of Drug-Induced Kidney Injury

The pathophysiology of drug-induced nephrotoxicity involves complex interactions between pharmacokinetic properties of drugs and renal physiology. One of the key mechanisms is renal drug accumulation, which occurs due to high renal blood flow and active transport processes. Drugs are filtered through the glomerulus and subsequently taken up by tubular cells via transporters such as OATs and OCTs. This leads to intracellular accumulation and potential toxicity [24]. Another important mechanism is alteration of renal hemodynamics. Certain drugs, such as NSAIDs and ACE inhibitors, affect the balance of vasodilatory and vasoconstrictive factors within the kidney, leading to reduced renal perfusion and glomerular filtration rate. This hemodynamic imbalance can result in ischemic injury and exacerbate the effects of other nephrotoxic mechanisms. In addition to these mechanisms, drugs may induce oxidative stress, inflammation, and apoptosis, contributing to cellular injury and dysfunction. The interplay between these pathways determines the severity and progression of nephrotoxicity. Understanding the pathophysiology of drug-induced kidney injury is essential for developing targeted therapeutic interventions and preventive strategies [25].

6. Molecular Mechanisms of Drug-Induced Nephrotoxicity

Drug-induced nephrotoxicity is mediated through a complex network of molecular and cellular mechanisms that ultimately result in structural and functional damage to renal tissues. These mechanisms are often interconnected and may act synergistically to amplify kidney injury. The proximal tubular epithelial cells are particularly vulnerable due to their high metabolic activity, abundance of mitochondria, and exposure to high concentrations of drugs and their metabolites. At the molecular level, nephrotoxicity is primarily driven by oxidative stress, mitochondrial dysfunction, activation of apoptotic and necrotic pathways, inflammatory signaling cascades, endoplasmic reticulum (ER) stress, and dysregulation of autophagy. These processes disrupt cellular homeostasis, impair energy metabolism, and lead to cell death. Understanding these molecular mechanisms is crucial for identifying therapeutic targets and developing effective prevention strategies. Furthermore, the interplay between genetic susceptibility and environmental factors can modulate these pathways, influencing the severity and progression of renal injury. Advances in molecular biology have provided significant insights into these mechanisms, paving the way for novel interventions aimed at mitigating drug-induced kidney damage [24,25].

Oxidative Stress and Reactive Oxygen Species (ROS)

Oxidative stress is one of the most critical and widely recognised mechanisms underlying drug-induced nephrotoxicity. It occurs when there is an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defence systems of the cell. Nephrotoxic drugs such as cisplatin, aminoglycosides, and radiocontrast agents significantly increase ROS production within renal tubular cells. These reactive species, including superoxide anions, hydrogen peroxide, and hydroxyl radicals, can cause extensive damage to cellular components such as lipids, proteins, and DNA [26]. Lipid peroxidation of cell membranes leads to loss of membrane integrity and increased permeability, while protein oxidation affects enzyme activity and structural proteins. DNA damage can result in mutations and activation of cell death pathways. In addition to direct damage, ROS also act as signalling molecules that activate various intracellular pathways, including nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), which promote inflammation and apoptosis. The depletion of endogenous antioxidants such as glutathione, superoxide dismutase, and catalase further exacerbates oxidative stress. In the kidney, the proximal tubular cells are particularly susceptible due to their high metabolic rate and reliance on oxidative phosphorylation. Persistent oxidative stress can lead to mitochondrial dysfunction, further increasing ROS production in a vicious cycle. Moreover, oxidative stress has been shown to impair renal blood flow by affecting endothelial function, thereby contributing to ischemic injury. Therapeutic strategies aimed at enhancing antioxidant defences have shown promise in reducing nephrotoxicity, highlighting the central role of oxidative stress in the pathogenesis of drug-induced kidney injury [26].

Mitochondrial Dysfunction

Mitochondrial dysfunction plays a pivotal role in the development of drug-induced nephrotoxicity due to the high energy demands of renal tubular cells. Mitochondria are responsible for ATP production through oxidative phosphorylation, which is essential for maintaining cellular functions such as active transport and ion balance. Nephrotoxic drugs can disrupt mitochondrial

integrity and function by damaging the electron transport chain, leading to decreased ATP production and increased generation of ROS [27]. Structural alterations in mitochondria, such as swelling, loss of cristae, and membrane depolarization, are commonly observed in nephrotoxic conditions. These changes compromise mitochondrial permeability and lead to the release of pro-apoptotic factors such as cytochrome c into the cytosol. The release of these factors triggers the intrinsic apoptotic pathway, resulting in programmed cell death. Additionally, mitochondrial DNA is highly susceptible to oxidative damage due to its proximity to the electron transport chain and lack of protective histones. Damage to mitochondrial DNA further impairs energy production and exacerbates cellular injury. Mitochondrial dysfunction also disrupts calcium homeostasis, leading to intracellular calcium overload, which can activate various degradative enzymes and contribute to cell death. The interplay between oxidative stress and mitochondrial dysfunction creates a feedback loop that amplifies renal injury. Therapeutic approaches targeting mitochondrial protection, such as the use of mitochondrial antioxidants and agents that stabilize mitochondrial membranes, have shown potential in reducing nephrotoxicity. Therefore, preserving mitochondrial function is a key strategy in preventing drug-induced kidney injury [27].

Apoptosis and Necrosis Pathways

Apoptosis and necrosis are two important forms of cell death involved in drug-induced nephrotoxicity, and their relative contribution depends on the severity and duration of injury. Apoptosis is a regulated, energy-dependent process characterised by cell shrinkage, chromatin condensation, and DNA fragmentation.It is primarily mediated through intrinsic (mitochondrial) and extrinsic (death receptor) pathways. In nephrotoxicity, mitochondrial damage leads to the release of cytochrome c, which activates caspase enzymes and initiates the apoptotic cascade [28]. Necrosis, on the other hand, is an uncontrolled form of cell death resulting from severe cellular injury. It is characterised by cell swelling, membrane rupture, and release of intracellular contents, which can trigger inflammation. In the context of drug-induced nephrotoxicity, high concentrations of toxic agents or prolonged exposure can overwhelm cellular repair mechanisms, leading to necrosis. The coexistence of apoptosis and necrosis in renal tissues contributes to both structural damage and inflammatory responses. Recent studies have also identified other forms of regulated cell death, such as necroptosis and ferroptosis, which play a role in nephrotoxicity. Ferroptosis, in particular, is characterised by iron-dependent lipid peroxidation and has been implicated in cisplatin-induced kidney injury. The balance between cell survival and death pathways is critical in determining the outcome of nephrotoxic injury. Targeting these pathways through pharmacological interventions may provide new therapeutic opportunities for preventing renal damage [28].

Inflammation and Cytokine Signalling

Inflammation is a key contributor to the progression of drug-induced nephrotoxicity and is closely linked to oxidative stress and cell death mechanisms. Nephrotoxic drugs can activate immune responses within the kidney, leading to the release of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β). These cytokines promote the recruitment and activation of immune cells, including neutrophils and macrophages, which further exacerbate tissue injury [29]. Activation of transcription factors such as NF-κB plays a central role in regulating inflammatory gene expression. Once activated, NF-κB translocases to the nucleus and induces the

expression of various pro-inflammatory mediators, chemokines, and adhesion molecules. This leads to sustained inflammation and tissue damage. Additionally, inflammation can disrupt endothelial function, leading to reduced renal blood flow and increased vascular permeability. Chronic inflammation contributes to fibrosis and long-term kidney dysfunction. The deposition of extracellular matrix proteins and activation of fibroblasts result in structural remodelling of renal tissues. Anti-inflammatory therapies targeting cytokine signaling pathways have shown potential in reducing nephrotoxicity. Therefore, controlling inflammation is essential for preventing the progression of drug-induced kidney injury [29].

Endoplasmic Reticulum (ER) Stress

Endoplasmic reticulum stress is an important mechanism in drug-induced nephrotoxicity, particularly in conditions where protein folding and processing are disrupted. The ER is responsible for the synthesis and folding of proteins, and any disturbance in its function can lead to accumulation of misfolded proteins, triggering the unfolded protein response (UPR). Nephrotoxic drugs can induce ER stress by disrupting calcium homeostasis and protein folding mechanisms [30]. The UPR initially acts as a protective mechanism to restore normal ER function; however, prolonged or severe stress can lead to activation of apoptotic pathways. Key signaling pathways involved in ER stress include PERK, ATF6, and IRE1, which regulate gene expression and cellular responses. Persistent ER stress results in activation of pro-apoptotic factors such as CHOP (C/EBP homologous protein), leading to cell death. ER stress is closely linked to oxidative stress and inflammation, forming a network of interconnected pathways that contribute to renal injury. Therapeutic strategies aimed at reducing ER stress, such as chemical chaperones and modulators of UPR signaling, have shown promise in experimental models. Therefore, targeting ER stress represents a potential approach for mitigating drug-induced nephrotoxicity [30].

Autophagy and Cell Death Mechanisms

Autophagy is a cellular process that involves the degradation and recycling of damaged organelles and proteins, playing a crucial role in maintaining cellular homeostasis. In the context of drug-induced nephrotoxicity, autophagy can have both protective and detrimental effects depending on the extent and duration of activation. Under mild stress conditions, autophagy helps remove damaged mitochondria and proteins, thereby promoting cell survival [31]. However, excessive or dysregulated autophagy can lead to autophagic cell death, contributing to renal injury. Nephrotoxic drugs such as cisplatin have been shown to modulate autophagy pathways, leading to either protective or harmful outcomes. The balance between autophagy and apoptosis is critical in determining cell fate. Autophagy is regulated by various signaling pathways, including the mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK). Disruption of these pathways can impair autophagic function and exacerbate kidney injury. Recent studies suggest that modulation of autophagy may provide therapeutic benefits in preventing nephrotoxicity. Therefore, understanding the role of autophagy in kidney injury is essential for developing targeted interventions [31].

7. Conventional Biomarkers for Nephrotoxicity

The assessment of renal function in clinical practice has traditionally relied on a limited set of biochemical markers, primarily serum creatinine and blood urea nitrogen (BUN). These conventional biomarkers have been widely used

due to their simplicity, accessibility, and cost-effectiveness. However, despite their routine clinical use, these markers have significant limitations, particularly in the early detection of drug-induced nephrotoxicity. Renal injury often begins at the cellular and molecular levels long before measurable changes in these biomarkers become evident. As a result, reliance on traditional indicators can delay diagnosis and intervention, potentially leading to irreversible kidney damage.

The need for accurate and timely detection of nephrotoxicity has prompted extensive research into alternative biomarkers that can provide earlier and more specific indications of renal injury. Nevertheless, understanding the role, advantages, and limitations of conventional biomarkers remains essential, as they continue to serve as the foundation of clinical assessment. These biomarkers are particularly useful for monitoring disease progression and guiding treatment decisions in established kidney injury. However, their inability to detect subtle or early changes in renal function underscores the importance of integrating them with more sensitive diagnostic tools. In this section, the characteristics and clinical relevance of serum creatinine, blood urea nitrogen, and the limitations of traditional biomarkers [32].

Serum Creatinine

Serum creatinine is the most commonly used biomarker for evaluating renal function and is widely regarded as a standard indicator of glomerular filtration rate (GFR). Creatinine is a metabolic byproduct of creatine phosphate in muscle tissue and is produced at a relatively constant rate under normal physiological conditions. It is freely filtered by the glomerulus and is not significantly reabsorbed, making it a useful marker for assessing kidney function. In clinical practice, increases in serum creatinine levels are indicative of reduced GFR and impaired renal function. Despite its widespread use, serum creatinine has several important limitations that reduce its effectiveness as an early marker of nephrotoxicity. One of the major drawbacks is its delayed response to kidney injury. Significant nephron damage, often exceeding 50%, may occur before a detectable rise in serum creatinine is observed [32]. This delay limits its utility in early diagnosis and timely intervention. Additionally, serum creatinine levels can be influenced by various non-renal factors, including age, gender, muscle mass, diet, and hydration status. For example, individuals with low muscle mass may have deceptively low creatinine levels despite impaired kidney function, while those with high muscle mass may have elevated levels without actual renal dysfunction. Furthermore, serum creatinine does not provide information about the location or mechanism of kidney injury. It is primarily a functional marker and does not reflect structural damage at the cellular level. In the context of drug-induced nephrotoxicity, this limitation is particularly significant, as early injury often occurs at the tubular level before affecting glomerular filtration. Despite these limitations, serum creatinine remains an essential tool for monitoring renal function due to its availability and ease of measurement. It is often used in combination with estimated GFR (eGFR) calculations to provide a more comprehensive assessment of kidney function. However, reliance solely on serum creatinine may result in underestimation of early nephrotoxic effects, highlighting the need for more sensitive biomarkers [32].

Blood Urea Nitrogen (BUN)

Blood urea nitrogen (BUN) is another commonly used biomarker for assessing renal function and is often measured alongside serum creatinine. Urea is a nitrogenous waste product formed in the liver as a result of protein metabolism and is excreted

by the kidneys. BUN levels reflect the balance between urea production and excretion, making it an indirect indicator of renal function. Elevated BUN levels are typically associated with reduced kidney function and impaired excretion of urea. However, similar to serum creatinine, BUN has several limitations that restrict its usefulness as a reliable marker of nephrotoxicity. One of the primary limitations is its lack of specificity. BUN levels can be influenced by a variety of non-renal factors, including dietary protein intake, liver function, gastrointestinal bleeding, and hydration status. For instance, high protein intake or increased protein catabolism can lead to elevated BUN levels even in the absence of renal impairment. Conversely, liver disease can result in reduced urea production, leading to lower BUN levels despite kidney dysfunction. In addition, BUN is reabsorbed in the renal tubules, and its levels can be affected by changes in renal blood flow and tubular function. Conditions such as dehydration can increase BUN reabsorption, resulting in elevated levels that may not accurately reflect true renal function. In the context of drug-induced nephrotoxicity, these confounding factors make it difficult to interpret BUN levels accurately. Moreover, BUN is less sensitive than serum creatinine in detecting changes in GFR, particularly in the early stages of kidney injury. It does not provide information about the specific site or mechanism of injury and is therefore limited in its diagnostic utility. Despite these limitations, BUN remains a useful adjunct marker when interpreted in conjunction with serum creatinine and clinical findings. The BUN-to-creatinine ratio is often used to differentiate between prerenal and intrinsic renal causes of kidney dysfunction. However, the overall limitations of BUN highlight the need for more specific and sensitive biomarkers in the diagnosis of drug-induced nephrotoxicity [32].

Limitations of Traditional Biomarkers

Traditional biomarkers such as serum creatinine and BUN, while widely used, have significant limitations that reduce their effectiveness in the early detection and accurate diagnosis of drug-induced nephrotoxicity. One of the most critical limitations is their lack of sensitivity in detecting early renal injury. Both markers typically show significant changes only after substantial loss of kidney function has occurred, which may delay diagnosis and treatment. This delay is particularly problematic in the context of nephrotoxicity, where early intervention is crucial for preventing irreversible damage. Another important limitation is the lack of specificity. Serum creatinine and BUN are influenced by a wide range of non-renal factors, including age, gender, muscle mass, diet, hydration status, and liver function. These variables can lead to misinterpretation of results and reduce the reliability of these markers in clinical practice. Additionally, these biomarkers do not provide information about the underlying cause or location of kidney injury. They are functional markers that reflect changes in GFR but do not indicate structural damage or cellular injury. Furthermore, traditional biomarkers are not capable of distinguishing between different types of kidney injury, such as tubular toxicity, glomerular injury, or interstitial nephritis. This limitation makes it difficult to identify the specific mechanism of nephrotoxicity and tailor appropriate treatment strategies. In addition, these markers are not predictive of long-term outcomes and may not accurately reflect the severity of injury. The growing recognition of these limitations has led to increased interest in the development of novel biomarkers that can provide earlier, more specific, and mechanistically informative insights into kidney injury. Biomarkers such as KIM-1, NGAL, and cystatin C have shown promise in addressing these gaps.

However, despite their limitations, traditional biomarkers continue to play an important role in clinical practice due to their accessibility and established use. Integrating these markers with newer diagnostic tools represents a promising approach for improving the detection and management of drug-induced nephrotoxicity [32].

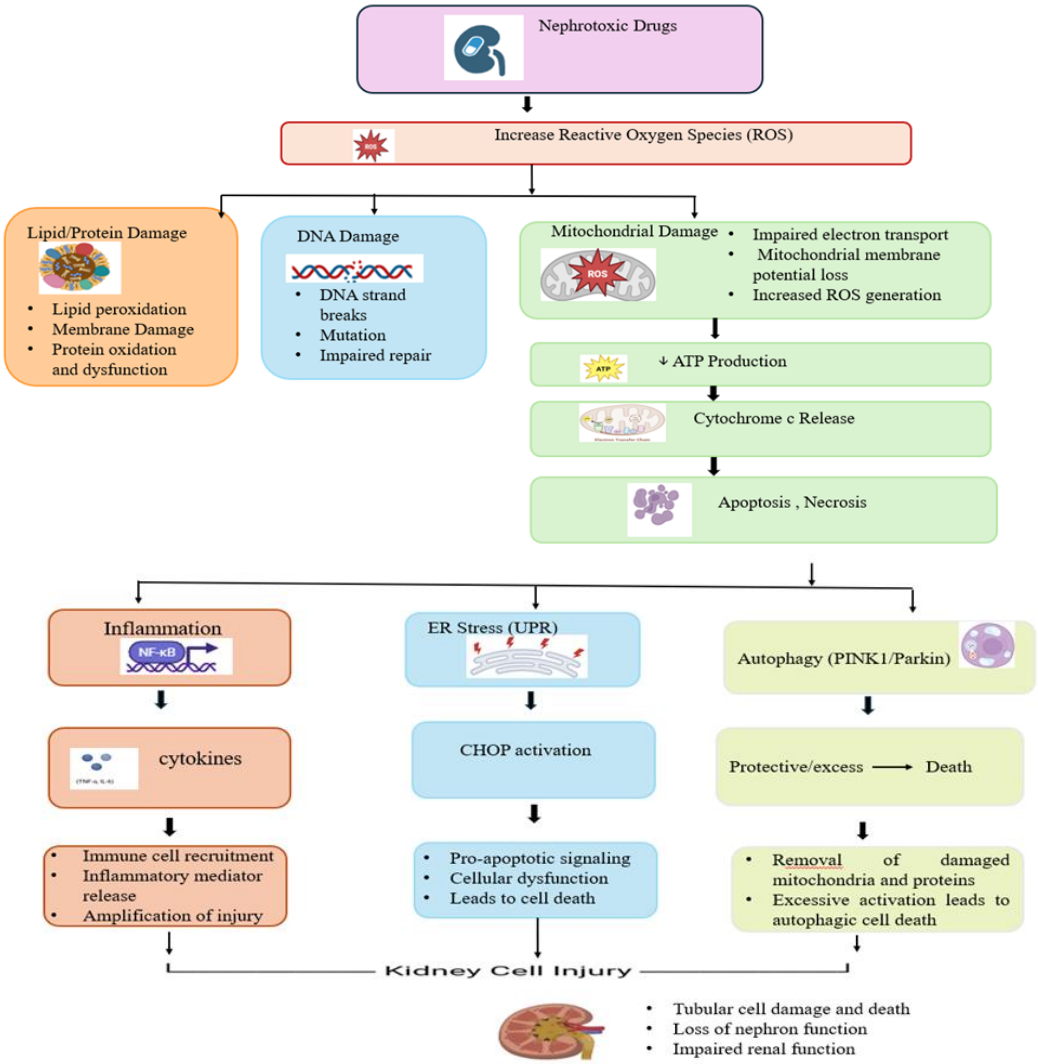

Figure: Molecular Mechanisms of Drug-Induced Nephrotoxicity

8. Emerging Biomarkers of Drug-Induced Nephrotoxicity

The limitations of conventional biomarkers such as serum creatinine and blood urea nitrogen have driven the search for more sensitive and specific indicators of kidney injury. Emerging biomarkers have significantly improved the ability to detect renal damage at an early stage, often before significant loss of kidney function occurs. These biomarkers are typically released in response to specific cellular injury processes and provide mechanistic insights into nephrotoxicity. Unlike traditional markers, which reflect changes in glomerular filtration rate, emerging biomarkers can detect tubular injury, inflammation, and oxidative stress at the molecular level. Advances in molecular biology and omics technologies have facilitated the identification of a wide range of novel biomarkers, including proteins, enzymes,

cytokines, and nucleic acids. These biomarkers are often measurable in urine or blood, making them minimally invasive and clinically practical. Furthermore, many of these markers demonstrate high sensitivity and specificity, allowing for early diagnosis and improved risk stratification. The use of biomarker panels combining multiple indicators has also been proposed to enhance diagnostic accuracy. Despite these advantages, challenges remain in terms of standardisation, validation, and integration into routine clinical practice. In this section, key emerging biomarkers such as KIM-1, NGAL, cystatin C, interleukin-18, and microRNAs are discussed in detail [33].

Kidney Injury Molecule-1 (KIM-1)

Kidney injury molecule-1 (KIM-1) is a type I transmembrane glycoprotein that is highly upregulated in proximal tubular epithelial cells following renal injury. Under normal physiological conditions, KIM-1 expression is minimal; however, its expression increases dramatically in response to ischemic or toxic injury, making it a highly sensitive marker for tubular damage [33]. KIM-1 is shed into the urine, where it can be easily measured, providing a non-invasive method for detecting kidney injury.

One of the key advantages of KIM-1 is its ability to detect early tubular injury before significant changes in serum creatinine occur. This makes it particularly valuable in the context of drug-induced nephrotoxicity, where early detection is critical for preventing progression to severe kidney damage. KIM-1 has been shown to be elevated in patients exposed to nephrotoxic drugs such as cisplatin, aminoglycosides, and contrast agents. Its levels correlate with the severity of tubular injury, making it useful for both diagnosis and prognosis.

In addition to its role as a biomarker, KIM-1 is involved in the phagocytosis of apoptotic cells and debris, suggesting a role in tissue repair and regeneration. However, persistent elevation of KIM-1 may indicate ongoing injury and impaired recovery. Despite its promising clinical utility, further studies are needed to establish standardized thresholds and validate its use across different patient populations. Nevertheless, KIM-1 represents one of the most promising biomarkers for early detection of drug-induced nephrotoxicity [33].

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL) is a small, iron-binding protein that is rapidly released in response to kidney injury. It is produced by various cell types, including renal tubular epithelial cells, and can be detected in both blood and urine. NGAL levels increase within a few hours of renal injury, making it one of the earliest biomarkers of acute kidney injury [34]. NGAL is particularly useful in detecting nephrotoxicity associated with drugs such as cisplatin, vancomycin, and radiographic contrast agents. Its rapid response allows for early intervention, potentially preventing progression to more severe stages of kidney injury. Studies have shown that NGAL levels correlate with the severity and duration of renal damage, making it a valuable tool for monitoring disease progression.

In addition to its diagnostic value, NGAL plays a role in iron transport and regulation, which may contribute to its involvement in oxidative stress and inflammation. Elevated NGAL levels have also been associated with increased risk of adverse outcomes, including the need for dialysis and mortality. However, NGAL levels can be influenced by factors such as infection and inflammation, which may limit its specificity. Despite these limitations, NGAL remains one of the most extensively studied and clinically relevant biomarkers for early detection of nephrotoxicity [34].

Cystatin C

Cystatin C is a low-molecular-weight protein that is produced by all nucleated cells and is freely filtered by the glomerulus. Unlike serum creatinine, cystatin C is not significantly affected by muscle mass, age, or diet, making it a more reliable indicator of glomerular filtration rate [35]. After filtration, cystatin C is almost completely reabsorbed and degraded by proximal tubular cells, with minimal excretion in urine. One of the major advantages of cystatin C is its ability to detect changes in renal function earlier than serum creatinine. This makes it particularly useful in identifying early stages of drug-induced nephrotoxicity. Studies have shown that cystatin C levels rise before creatinine in patients exposed to nephrotoxic agents, allowing for earlier diagnosis and intervention. In addition to its role as a marker of glomerular function, cystatin C has been associated with inflammation and cardiovascular risk, suggesting broader clinical implications. However, factors such as thyroid dysfunction and corticosteroid use may influence cystatin C levels, which should be considered when interpreting results. Despite these limitations, cystatin C is increasingly being used in clinical practice as a more sensitive and reliable biomarker for kidney function assessment [35].

Interleukin-18 (IL-18)

Interleukin-18 (IL-18) is a pro-inflammatory cytokine that plays a significant role in the pathogenesis of kidney injury. It is produced by renal tubular epithelial cells and immune cells in response to inflammatory stimuli. IL-18 is released into the urine following kidney injury, making it a useful biomarker for detecting renal inflammation [36]. IL-18 is particularly associated with ischemic and toxic forms of acute kidney injury, including those induced by nephrotoxic drugs. Elevated urinary IL-18 levels have been observed in patients with cisplatin-induced nephrotoxicity and contrast-induced nephropathy. Its levels correlate with the severity of injury and can predict clinical outcomes. One of the advantages of IL-18 is its specificity for inflammatory kidney injury, which distinguishes it from other biomarkers that primarily reflect functional changes. However, IL-18 levels may also be elevated in systemic inflammatory conditions, which can limit its specificity in certain clinical settings. Despite this limitation, IL-18 remains a valuable biomarker for assessing inflammatory components of nephrotoxicity and provides important insights into disease mechanisms [36].

MicroRNAs and Omics-Based Biomarkers

MicroRNAs (miRNAs) are small, non-coding RNA molecules that regulate gene expression at the post-transcriptional level. They play a crucial role in various biological processes, including cell proliferation, differentiation, and apoptosis. In the context of drug-induced nephrotoxicity, specific miRNAs have been identified as potential biomarkers due to their altered expression in response to kidney injury [37]. MiRNAs can be detected in blood and urine, making them accessible and minimally invasive biomarkers. Certain miRNAs, such as miR-21 and miR-155, have been associated with renal fibrosis and inflammation. Their expression patterns can provide insights into the underlying mechanisms of nephrotoxicity and may serve as early indicators of kidney injury. In addition to miRNAs, omics-based approaches such as proteomics, metabolomics, and genomics have significantly advanced biomarker discovery. These technologies enable comprehensive analysis of molecular changes associated with nephrotoxicity, allowing for identification of novel biomarkers and therapeutic targets. Omics approaches also support the development of personalized medicine

by identifying patient-specific risk factors and responses to treatment. Despite their potential, challenges remain in terms of standardization, validation, and clinical implementation of miRNA and omics-based biomarkers. Large-scale studies are needed to establish their reliability and reproducibility. Nevertheless, these emerging technologies represent a promising frontier in the diagnosis and management of drug-induced nephrotoxicity [37].

Experimental Models for Studying Nephrotoxicity

The study of drug-induced nephrotoxicity relies heavily on experimental models that help elucidate underlying mechanisms, identify potential biomarkers, and evaluate therapeutic interventions. These models provide essential insights into the pathogenesis of renal injury and allow for controlled investigation of drug effects at cellular, tissue, and organismal levels. Experimental approaches broadly include in vitro cell culture systems and in vivo animal models, each with distinct advantages and limitations. While in vitro models offer simplicity and mechanistic clarity, animal models provide a more comprehensive understanding of systemic interactions and physiological responses.

In recent years, advances in biotechnology have led to the development of more sophisticated models, including three-dimensional cell cultures, organoids, and microfluidic "kidney-on-a-chip" systems. These innovative approaches aim to bridge the gap between traditional experimental models and human physiology. Despite these advancements, challenges remain in translating findings from experimental models to clinical practice. Differences in species-specific responses, drug metabolism, and environmental factors can limit the predictive value of preclinical studies. Therefore, careful selection and interpretation of experimental models are essential for advancing our understanding of nephrotoxicity and improving translational outcomes [38].

In Vitro Cell Culture Models

In vitro cell culture models are widely used for studying the cellular and molecular mechanisms of drug-induced nephrotoxicity. These models typically involve the use of renal epithelial cell lines, such as human proximal tubular cells, which are exposed to nephrotoxic agents under controlled laboratory conditions. One of the primary advantages of in vitro systems is their ability to provide detailed insights into specific cellular processes, including oxidative stress, apoptosis, mitochondrial dysfunction, and inflammatory signaling pathways. Cell culture models allow researchers to manipulate experimental conditions precisely, including drug concentration, exposure duration, and environmental factors. This level of control enables the identification of dose-dependent effects and mechanistic pathways involved in nephrotoxicity. Additionally, in vitro models are cost-effective, reproducible, and suitable for high-throughput screening of potential nephrotoxic compounds and protective agents.

Recent advancements have led to the development of more physiologically relevant systems, such as three-dimensional (3D) cultures and renal organoids derived from stem cells. These models better mimic the structural and functional complexity of the kidney compared to traditional two-dimensional cultures. Microfluidic systems, commonly referred to as "kidney-on-a-chip," further enhance physiological relevance by simulating fluid flow and mechanical forces present in vivo. Despite these advantages, in vitro models have limitations. They lack the complexity of whole-organ systems and do not fully replicate interactions between different cell types, immune responses, and systemic factors. Additionally, differences in gene expression and metabolic activity between cell lines and human tissues may

affect the accuracy of results. Nevertheless, in vitro models remain indispensable tools for initial screening and mechanistic studies in nephrotoxicity research [38].

Animal Models of Nephrotoxicity

Animal models play a crucial role in understanding the systemic and physiological aspects of drug-induced nephrotoxicity. These models involve the administration of nephrotoxic agents to experimental animals, such as rodents, to study the resulting renal injury. Commonly used models include cisplatin-induced nephrotoxicity, gentamicin-induced tubular damage, and contrast-induced kidney injury. These models closely mimic clinical conditions and provide valuable insights into the pathophysiology of nephrotoxicity. One of the key advantages of animal models is their ability to replicate complex interactions between different organ systems, including the immune system, cardiovascular system, and endocrine pathways. This allows for a comprehensive evaluation of drug effects and identification of systemic factors that contribute to kidney injury. Animal models also enable the study of long-term outcomes, such as progression to chronic kidney disease and fibrosis.

In addition, animal studies are essential for evaluating the efficacy and safety of potential therapeutic interventions before clinical trials. They provide important information on pharmacokinetics, pharmacodynamics, and toxicity profiles of drugs. Histopathological analysis of renal tissues in animal models offers detailed insights into structural changes associated with nephrotoxicity. However, animal models also have limitations. Species differences in drug metabolism and renal physiology can affect the extrapolation of results to humans. Ethical considerations and regulatory requirements also pose challenges in the use of animal models. Despite these limitations, animal studies remain a cornerstone of nephrotoxicity research and play a vital role in bridging the gap between in vitro findings and clinical applications [38].

Translational Relevance

The ultimate goal of experimental nephrotoxicity research is to translate preclinical findings into clinical practice to improve patient outcomes. Translational relevance refers to the extent to which results obtained from experimental models can be applied to human conditions. Achieving effective translation requires careful consideration of model selection, study design, and validation of findings in human populations. One of the major challenges in translational research is the discrepancy between preclinical and clinical outcomes. Many therapeutic interventions that show promise in experimental models fail to demonstrate efficacy in human trials. This may be due to differences in drug metabolism, genetic variability, and environmental factors. To address these challenges, researchers are increasingly adopting integrated approaches that combine data from in vitro studies, animal models, and clinical observations. Advances in personalized medicine and omics technologies have further enhanced translational research by enabling the identification of patient-specific risk factors and biomarkers. The use of human-derived cell models and organoids also improves the relevance of experimental findings. Additionally, computational modeling and artificial intelligence are being used to predict nephrotoxicity and optimise drug development. Collaborative efforts between researchers, clinicians, and regulatory agencies are essential for improving translational outcomes. Standardisation of experimental protocols and validation of biomarkers across different populations are also critical steps. Ultimately, enhancing the translational relevance of experimental models will lead to more effective

prevention and treatment strategies for drug-induced nephrotoxicity [38].

9. Prevention Strategies for Drug-Induced Nephrotoxicity

Preventing drug-induced nephrotoxicity is a critical component of clinical practice, particularly in high-risk populations such as critically ill patients, elderly individuals, and those with pre-existing renal impairment. Given that many nephrotoxic drugs are essential for treating serious conditions, complete avoidance is often not feasible. Therefore, the focus shifts toward minimising risk through a combination of pharmacological, clinical, and supportive strategies. Prevention requires a comprehensive understanding of drug pharmacokinetics, patient-specific risk factors, and early indicators of renal dysfunction. A multidisciplinary approach involving clinicians, pharmacists, and laboratory specialists is essential for effective prevention. Strategies include dose optimisation, therapeutic drug monitoring, adequate hydration, use of nephroprotective agents, and incorporation of antioxidant therapies. Advances in biomarker research and personalised medicine have further improved the ability to identify high-risk patients and tailor interventions accordingly. Additionally, patient education and regular monitoring play an important role in reducing the incidence of nephrotoxicity. The integration of these strategies into routine clinical practice can significantly reduce the burden of kidney injury and improve patient outcomes [39].

Dose Optimisation and Therapeutic Drug Monitoring

Dose optimisation is one of the most effective strategies for preventing drug-induced nephrotoxicity. Many nephrotoxic drugs exhibit dose-dependent toxicity, meaning that higher concentrations increase the risk of renal injury. Adjusting drug dosage based on individual patient characteristics, particularly renal function, is essential for minimising toxicity while maintaining therapeutic efficacy. Renal function is commonly assessed using estimated glomerular filtration rate (eGFR), which guides dose adjustments for drugs that are primarily eliminated by the kidneys. Therapeutic drug monitoring (TDM) plays a crucial role in ensuring that drug concentrations remain within the therapeutic range. This is particularly important for drugs with a narrow therapeutic index, such as aminoglycosides and vancomycin. Monitoring plasma drug levels allows clinicians to adjust dosing regimens in real time, reducing the risk of accumulation and toxicity. TDM is especially valuable in patients with fluctuating renal function, such as those in intensive care units. In addition to dose adjustment, avoiding the concurrent use of multiple nephrotoxic drugs can significantly reduce the risk of kidney injury. Drug interactions may potentiate nephrotoxic effects and should be carefully evaluated. Clinical decision support systems integrated into electronic health records can assist healthcare providers in identifying potential risks and optimising drug therapy. Overall, individualised dosing and careful monitoring are essential components of nephrotoxicity prevention [39].

Hydration and Supportive Care

Adequate hydration is a fundamental strategy for preventing drug-induced nephrotoxicity, particularly in patients receiving nephrotoxic agents such as cisplatin and radiographic contrast media. Hydration helps maintain renal perfusion, dilutes nephrotoxic substances, and promotes their excretion, thereby reducing the concentration of toxic compounds in the renal tubules. Intravenous fluid administration is commonly used in clinical settings to ensure optimal hydration status before,

during, and after drug administration. In addition to hydration, supportive care measures play a vital role in preserving renal function. These measures include maintaining electrolyte balance, monitoring urine output, and avoiding conditions that may compromise renal perfusion, such as hypotension. Early recognition and management of electrolyte disturbances are essential to prevent complications associated with nephrotoxicity. For patients undergoing contrast imaging procedures, prophylactic hydration combined with the use of low-osmolar or iso-osmolar contrast agents has been shown to reduce the incidence of contrast-induced nephropathy. Similarly, in patients receiving chemotherapy, hydration protocols are routinely implemented to minimise renal damage. Supportive care also involves patient education regarding adequate fluid intake and avoidance of over-the-counter medications that may exacerbate nephrotoxicity, such as NSAIDs. Regular monitoring of renal function during therapy is essential for early detection and intervention. Overall, hydration and supportive care are simple yet highly effective strategies for reducing the risk of drug-induced kidney injury [40].

Pharmacological Protective Agents

Pharmacological interventions aimed at protecting the kidneys from drug-induced injury have gained significant attention in recent years. These agents work through various mechanisms, including reducing oxidative stress, inhibiting inflammation, and preserving mitochondrial function. One of the most widely studied nephroprotective agents is N-acetylcysteine (NAC), which acts as an antioxidant and scavenges reactive oxygen species. NAC has been used in the prevention of contrast-induced nephropathy and has shown varying degrees of efficacy in clinical studies [41]. Another important class of protective agents includes drugs that modulate renal hemodynamics. For example, calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors may help maintain renal blood flow and reduce ischemic injury under certain conditions. Additionally, agents such as amifostine have been used to protect against cisplatin-induced nephrotoxicity by scavenging free radicals and reducing DNA damage. Anti-inflammatory drugs targeting cytokine signaling pathways are also being explored as potential nephroprotective agents. These therapies aim to reduce the inflammatory response associated with nephrotoxicity and prevent progression to chronic kidney disease. Furthermore, novel compounds targeting specific molecular pathways, such as apoptosis and ER stress, are currently under investigation. Despite promising results in experimental studies, the clinical application of many pharmacological protective agents remains limited due to variability in efficacy and potential side effects. Continued research and clinical trials are needed to establish their safety and effectiveness. Nevertheless, pharmacological interventions represent an important component of comprehensive prevention strategies [41].

Antioxidants and Natural Compounds

Antioxidants and natural compounds have emerged as promising therapeutic options for preventing drug-induced nephrotoxicity due to their ability to neutralise reactive oxygen species and reduce oxidative stress. Oxidative stress is a key mechanism underlying nephrotoxicity, and targeting this pathway can significantly mitigate renal injury. Natural antioxidants such as curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG) have demonstrated nephroprotective effects in various experimental models [42]. These compounds exert their protective effects through multiple mechanisms, including enhancement of endogenous antioxidant defences, inhibition of lipid peroxidation, and suppression of

inflammatory pathways. For example, curcumin has been shown to inhibit NF-κB activation and reduce the production of pro-inflammatory cytokines. Resveratrol enhances mitochondrial function and activates antioxidant enzymes such as superoxide dismutase and catalase. In addition to plant-derived compounds, vitamins such as vitamin C and vitamin E have also been studied for their antioxidant properties. These vitamins can reduce oxidative damage and improve renal function in patients exposed to nephrotoxic drugs. However, the clinical efficacy of these compounds varies, and optimal dosing regimens have not been fully established. One of the advantages of natural compounds is their relatively low toxicity and wide availability. However, challenges such as poor bioavailability and variability in formulation may limit their clinical use. Further research is needed to standardise these therapies and evaluate their effectiveness in large-scale clinical trials. Nonetheless, antioxidants and natural compounds represent a promising adjunct approach in the prevention of drug-induced nephrotoxicity [42].

10. Future Perspectives and Research Gaps

The field of drug-induced nephrotoxicity has advanced significantly in recent years; however, several challenges and research gaps remain. One of the most critical areas requiring further investigation is the validation and standardisation of emerging biomarkers. While biomarkers such as KIM-1, NGAL, and microRNAs have shown great promise, their routine clinical use is limited by a lack of standardised assays, variability across populations, and insufficient large-scale validation studies. Future research should focus on establishing reliable thresholds and integrating these biomarkers into clinical guidelines [43]. Another important area is the development of personalised medicine approaches for predicting and preventing nephrotoxicity. Genetic variability plays a significant role in individual susceptibility to drug-induced kidney injury. Pharmacogenomic studies can help identify genetic markers associated with increased risk, enabling tailored therapeutic strategies. Integration of genomic data with clinical and biomarker information has the potential to revolutionise nephrotoxicity management. Advances in artificial intelligence and machine learning also offer new opportunities for improving diagnosis and risk prediction. These technologies can analyse large datasets to identify patterns and predict nephrotoxicity before clinical symptoms appear. Incorporating AI-driven decision support systems into healthcare settings can enhance early detection and optimise treatment strategies. Despite these advancements, there is a need for better translational models that accurately reflect human kidney physiology. Current experimental models often fail to replicate the complexity of human disease, leading to discrepancies between preclinical and clinical outcomes. The development of organ-on-chip technologies and human-derived organoids represents a promising direction for future research.

Finally, the development of safer drugs with reduced nephrotoxic potential remains a key priority. Drug discovery efforts should incorporate nephrotoxicity screening at early stages to minimise adverse effects. Collaborative efforts between researchers, clinicians, and regulatory agencies are essential for addressing these challenges. By bridging existing gaps and leveraging emerging technologies, future research can significantly improve the prevention, diagnosis, and management of drug-induced nephrotoxicity [43].

CONCLUSION

Drug-induced nephrotoxicity remains a major challenge in clinical medicine due to the widespread use of nephrotoxic medications. Multiple molecular mechanisms including

oxidative stress, mitochondrial dysfunction, apoptosis, inflammation, and ER stress contribute to renal injury. Traditional biomarkers such as serum creatinine have limited sensitivity, prompting the development of novel biomarkers, including KIM-1, NGAL, cystatin C, and microRNAs. Preventive strategies such as dose optimisation, hydration therapy, and antioxidant treatment may reduce nephrotoxicity risk. Continued research into molecular mechanisms and early diagnostic markers will improve patient outcomes and guide safer pharmacotherapy.

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44. Figure created by Biorender.com.

HOW TO CITE: Fathima Rasha. N.*, Mohammad Mansoor, Sadiyath Mol V. P., Anson S. Maroky, G. Babu, Molecular Mechanism, Biomarkers and Prevention Strategies of Drug-Induced Nephrotoxicity, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 5, 660-681. https://doi.org/10.5281/zenodo.20029249