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Drug-Induced Nephrotoxicity: Mechanistic Insights and Emerging Therapeutic Strategies

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***Abstract*—*Drug-induced nephrotoxicity is a significant contributor to acute and chronic kidney injury in clinical and preclinical settings. This review provides an integrative overview of the diverse pathophysiological mechanisms underlying DIN, including hemodynamic alterations, direct tubular toxicity, crystal nephropathy, thrombotic microangiopathy, rhabdomyolysis, interstitial nephritis, and glomerulonephritis. Evidence from human studies and animal models (primarily rodents) is synthesized, highlighting how various drugs disrupt renal structure and function. A comprehensive table categorizes nephrotoxic agents, their mechanisms, pathological changes, and clinical manifestations. Both herbal and synthetic treatments are reviewed in rat and human models. Furthermore, this review explores novel therapeutic strategies, including mitochondria-targeted therapy, regenerative medicine with stem cell approaches, RNA-based interventions, artificial intelligence, and machine learning for predictive modeling, and the development of kidney-on-a-chip systems. The new technologies would provide successful approaches to detect nephrotoxicity early and understand pharmaceutical mechanisms while delivering individualized care, which minimizes traditional animal testing needs and boosts drug development translation.*

***Keywords*—** *Artificial intelligence; Drug-induced nephrotoxicity; Herbal therapy; Kidney-on-a-chip; Mechanism; Mitochondria-targeted therapy; RNA-based therapy; Nephrotoxic agents; Synthetic therapy; Regenerative medicine.*

I. INTRODUCTION

The kidney maintains endocrine function while regulating acid-base balance, controls blood pressure, and facilitates erythropoiesis. The essential kidney functions involve the creation of urine, together with the regulation of water-electrolyte conditions and endocrine activities. The kidneys remain highly prone to harm because of exposure to life choices and dangerous chemicals, along with harmful drugs, which frequently cause tissue damage [1,2].

When toxic substances attack the kidneys through exposure, the kidneys' detoxification functions with excretory mechanisms become damaged. Many essential drugs that cause nephrotoxicity represent a major clinical practice concern for drug-induced nephrotoxicity (DIN) [3]. Different nephrotoxic agents damage kidneys through intraglomerular hemodynamic changes, tubular toxicity, inflammatory actions, crystal deposition, and muscle breakdown (Iftikhar, 2015). The incidence of acute kidney injury (AKI) is attributed to DIN when 20% of hospital admissions are due to AKI, and 8–60% of patients with in-hospital AKI develop the condition, leading to fatal outcomes [4]. The increasing recognition of DIN as a significant factor in AKI and chronic kidney disease highlights the immediate need for new intervention strategies [5].

Treatment options for AKI remain undefined, so prevention stands as the main strategy to fight the condition. The promising agents being tested for chemical and biological interventions exist only in preclinical development stages. The development of AKI doubles the chances of developing chronic kidney disease during subsequent years [6].

The need for immediate preventive and therapeutic options remains essential because there are no definitive AKI treatments, and there is a continuing increase in CKD cases worldwide. This review explores the pathophysiological mechanisms of DIN and evaluates potential interventions, including herbal and synthetic drug treatments. Additionally, it highlights novel therapeutic approaches, offering promising advancements in nephroprotection.

II. MECHANISM

Compared to 30 years ago, the average patient today is older, has more comorbidities, and undergoes more diagnostic and therapeutic procedures that can potentially impair kidney function. Drugs that are recognized to induce nephrotoxicity achieve their harmful effects through one or several shared pathogenic mechanisms. These mechanisms may vary among different drugs or drug classes, which are typically categorized according to the particular histological element of the impacted kidney. This categorization aids in understanding the underlying mechanisms that contribute to kidney damage. Several distinct mechanisms have been identified for the development of nephrotoxicity caused by pharmacological agents. These include: hemodynamic changes, direct tubular toxicity, crystal nephropathy, rhabdomyolysis, glomerulonephritis, interstitial nephritis, and thrombotic microangiopathy [4,7].

A. Hemodynamic changes

Ensuring hemodynamic stability is critical for renal perfusion and glomerular filtration. The kidneys autoregulate blood flow through interactions between vasodilators (prostaglandins, nitric oxide) and vasoconstrictors (angiotensin II, endothelin). Disruptions—often caused by pharmacologic agents—can impair renal perfusion, reduce glomerular filtration rate (GFR), and predispose patients to AKI [7,8].

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Several drug classes contribute to hemodynamic nephrotoxicity: NSAIDs inhibit cyclooxygenase (COX), reducing prostaglandin synthesis, which plays a crucial role in renal vasodilation. COX-derived prostaglandins—especially PGE2 and PGI2—help maintain renal blood flow, particularly in patients with low circulating volume. NSAIDs like naproxen, rofecoxib, and indomethacin lower GFR, especially in salt-restricted individuals or those with compromised renal function [9]. NSAID use can also elevate blood pressure (BP) by 3–5 mmHg, particularly in hypertensive or elderly patients. For instance, ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) reduce efferent arteriole constriction, lowering glomerular filtration pressure. While beneficial in hypertension, they can impair renal perfusion in CKD, heart failure, or sepsis, increasing AKI risk. Studies indicate that AKI patients on ACEi/ARB had lower systolic BP despite a higher prevalence of hypertension, reflecting hemodynamic instability. Intensive BP control with diuretics and ACEi/ARB further raises AKI risk [10,11].

Conversely, calcineurin inhibitors (cyclosporine, tacrolimus) cause afferent arteriole vasoconstriction, reducing renal perfusion via endothelin elevation and nitric oxide depletion [12]. Prolonged Cyclosporin A (CsA) administration in nephrectomized rats increased afferent and efferent arteriole resistance, leading to a 53% reduction in single-nephron GFR [13]. Similar to calcineurin inhibitors, cisplatin-induced nephrotoxicity is associated with renal vasoconstriction and decreased renal blood flow. One proposed mechanism involves increased renovascular resistance due to altered α1-adrenoceptor responsiveness, contributing to impaired renal perfusion and hypoperfusion injury [14].

B. Direct tubular toxicity

DIN is a major contributor to AKI and CKD, primarily through direct tubular toxicity [8]. The proximal tubules are particularly vulnerable due to their active role in drug transport and reabsorption. Nephrotoxic drugs—including aminoglycosides, cisplatin, tenofovir, amphotericin B, radiocontrast agents, and methotrexate—cause cellular injury through oxidative stress, mitochondrial dysfunction, and apoptosis [15]. A crucial factor in tubular toxicity is the accumulation of drugs within tubular cells via organic anion (OAT) and organic cation (OCT) transporters [16]. This leads to mitochondrial homeostasis disruption, excessive generation of reactive oxygen species (ROS), and ATP depletion, ultimately culminating in cell death [17].

Aminoglycosides, such as gentamicin, uptake the proximal tubular cells through endocytosis, which occurs because the kidney filters this aminoglycoside and directs it to megalin- and cubilin-mediated endocytosis. Lysosomal conditions trigger these drugs to cause phospholipidosis and mitochondrial dysfunction, which results in lysosomal rupture and necrosis, together with apoptosis [18]. The toxic impact of gentamicin on mitochondria results from both elevated ROS production and mitochondrial permeability transition (MPT), which creates energy breakdown and organ dysfunction [19]. The damage from ROS triggers additional lipid peroxidation while modifying proteins and damaging DNA, which activates the signaling pathway of NF-κB. The inflammatory cytokine TNF-α, together with others, drives apoptosis and inflammation while causing fibrosis, which intensifies nephrotoxic effects [20]. Nephrotoxicity from cisplatin emerges through OCT2-mediated cellular entry of the drug, resulting in DNA-mitochondria binding and oxidative phosphorylation, thus magnifying ROS production. Tubular injury becomes worse due to both cellular death caused by oxidative stress and inflammation triggered by cytokine release [21]. The pharmacological actions of tenofovir harm mitochondria, resulting in mitochondrial swelling and depletion of ATP, which causes acute tubular necrosis (ATN). The administration of tenofovir through OAT1 and OAT3 transport pathways leads to increased toxic effects that elevate the risk of developing Fanconi syndrome [22,23].

Other nephrotoxic agents also cause tubular injury through oxidative and mitochondrial damage. Zoledronate causes acute tubular necrosis (ATN), which is characterized by the degeneration of tubular cells, the loss of brush borders, and the dysfunction of Na^+/K^+- ATPase, leading to electrolyte disturbances and kidney impairment [24]. Methotrexate (MTX) triggers oxidative stress, mitochondrial depolarization, and ATP depletion, impairing electrolyte reabsorption and further compromising proximal tubular integrity [25].

C. Crystal nephropathy

Crystal nephropathy firmly arises when mineral secretion and urine concentration create conditions for supersaturation, leading to crystal formation within the kidneys. These crystals result in injury through several significant mechanisms.

Firstly, they are directly toxic to kidney cells. Secondly, they activate inflammation, particularly via the NLRP3 inflammasome. Lastly, the deposits can physically obstruct various regions of the kidney, and the specific type of injury is contingent upon where these crystals accumulate, impacting the renal vasculature, nephron tubules, or the draining urinary tract [26]. Numerous medications are known to contribute to crystal nephropathy through distinct mechanisms. Sulfadiazine-induced crystal nephropathy has re-emerged as a critical issue associated with sulfadiazine use, particularly in treating toxoplasmosis. This condition leads to crystal formation in the kidneys, often presenting with flank pain, nausea, and acute kidney injury, characterized by "sheaves of wheat" crystals in acidic urine [27]. Indinavir, a protease inhibitor used for HIV treatment, also unequivocally leads to crystal formation.

A study examining crystalluria and urinary tract abnormalities in patients taking indinavir showed that its poor solubility in urine directly results in the formation of characteristic crystals. This crystalluria is closely linked to a range of urologic problems, including nephrolithiasis and indinavir-related crystal nephropathy, manifesting as intrarenal sludge and renal parenchymal defects [28]. Acyclovir is another documented cause of crystal nephropathy. Intratubular crystal deposition occurs due to its poor solubility in urine, especially under conditions of high concentration and low urine flow. Acyclovir is rapidly filtered and secreted, leading to nephron obstruction, increased renal

resistance, and elevated serum creatinine (sCr) levels. The rapid rise in sCr typically occurs within 24 hours of intravenous acyclovir administration [29].

A case of ciprofloxacin-induced nephropathy demonstrated unequivocal bilateral ureteral obstruction due to calculi composed of 85% ciprofloxacin in acidic urine, contrary to prior expectations. The presence of uric acid crystals (15%) within the calculus suggested they acted as a nidus for ciprofloxacin crystal precipitation [30]. The study "High Incidence of Amoxicillin-Induced Crystal Nephropathy in Patients Receiving High Doses of Intravenous Amoxicillin" highlights the substantial risk of amoxicillin-induced crystal nephropathy (AICN) in patients receiving high intravenous doses (≥8 g/day, with a median of 12 g/day), reporting an incidence rate of 4.5%. The study identifies crystalluria as a primary mechanism, where birefringent needle-shaped crystals form within the renal tubules, causing obstruction and damage. Key risk factors include high urine drug excretion, poor diuresis, and female gender [31].

Finally, crystal nephropathy due to high-dose methotrexate occurs when methotrexate and its metabolites precipitate within the renal tubules. This micro-precipitation causes nephrotoxicity, with outcomes ranging from mostly grade 1–2 toxicity to severe grades that can lead to significant morbidity and mortality [32]. The precipitation occurs as methotrexate is acidic and has lower solubility in acidic urine. The resulting crystal formation obstructs the tubules and directly damages the renal tubular epithelium, leading to AKI [33].

D. Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) is a medical condition identified by damage to the endothelium, accumulation of platelets, and thrombosis in microvessels. The insufficient blood supply results in organ damage that specifically affects the kidneys as well as other body parts. Given that drug-induced TMA (DITMA) stands as a major factor that causes both AKI and CKD during nephrotoxicity cases. The condition displays three primary symptoms, which include hemolytic anemia together with thrombocytopenia, and renal dysfunction according to research [34].

TMA-related nephrotoxicity has two possible outcomes: it can develop into thrombotic thrombocytopenic purpura (TTP) or atypical hemolytic uremic syndrome (aHUS), depending on which underlying cause takes effect. TTP develops because of ADAMTS13 protease deficiency or inhibition that prevents von Willebrand factor cleavage, thus promoting excessive platelet aggregation and microvascular occlusion [35]. The development of aHUS occurs because of complement dysregulation that persistently damages endothelial tissue and promotes thrombus formation [36].

Various drugs trigger TMA by different mechanisms, which involve DITMA conditions from gemcitabine and quinine and tacrolimus medication, while VEGF inhibition-related TMA develops from ranibizumab treatments, and clinically complement-mediated TMA occurs in patients exposed to interferons. Gemcitabine, a chemotherapy agent, is known to be associated with TMA. Two notable cases of gemcitabine-induced TMA that illustrate its potential severity: a 55-year-old man with pancreatic adenocarcinoma developed thrombocytopenia, microangiopathic hemolytic anemia, and elevated LDH after receiving 18,354 mg of gemcitabine. Similarly, a 75-year-old woman with the same cancer experienced seizures, hypertension, and AKI following treatment (with a total dose of 31,860 mg), subsequently leading to thrombocytopenia and anemia [37]. Quinine-induced TMA signifies a serious immune-related response that results in microangiopathic hemolytic anemia, low platelet count, and acute kidney injury (AKI).

A case series from the Oklahoma TTP-HUS Registry (1989–2015) documented 19 patients with quinine-induced TMA, many of whom were misdiagnosed as having TTP or HUS [38]. Moreover, VEGF inhibition can lead to TMA by disrupting the integrity of the glomerular endothelium, resulting in microvascular injury. Research conducted in a mouse model showed that the deletion of VEGF in podocytes induced thrombotic glomerular damage. A case report highlighted a patient who developed acute kidney dysfunction, microangiopathic hemolytic anemia, and thrombocytopenia after receiving intravitreal injections of ranibizumab, illustrating this risk [39]. Tacrolimus, similar to cyclosporine, can also cause renal dysfunction, despite binding to different cytosolic proteins. A report described a 60-year-old lung transplant recipient who developed hemolytic uremic syndrome (HUS) while on tacrolimus; the symptoms included thrombocytopenia, schistocytes, and kidney dysfunction [40].

Interferon (IFN) therapy, although considered an unusual cause, can also result in TMA as an adverse effect. One case report detailed a 62-year-old woman with chronic myeloid leukemia (CML) who had been treated with alpha-interferon and hydroxyurea for 10 years. Subsequently, it developed TMA, showing neurological, cardiac, and renal manifestations [41].

E. Rhabdomyolysis

Rhabdomyolysis-induced nephrotoxicity is a significant cause of AKI, due to the massive release of intracellular muscle components into the bloodstream [42]. Myoglobin, a key mediator, contributes to nephrotoxicity through several mechanisms, including direct tubular toxicity, intratubular cast formation, and oxidative stress [43].

All these mechanisms can play a role in the pathogenesis of acute renal failure. There are various causes of rhabdomyolysis, which can be classified as traumatic (crush syndrome), nontraumatic (drug abuse, alcohol withdrawal, metabolic disturbances, and enzyme deficiencies), and ischemic (resulting from arterial obstruction in the limbs) [44].

The first reported case of daptomycin-induced rhabdomyolysis in humans contrasted with the low incidence of myopathy (0.2%) and CPK elevations (2.8%) in clinical trials [45]. Research has shown that atorvastatin, pravastatin, and simvastatin monotherapy carry a low, comparable risk of hospitalized rhabdomyolysis.

However, cerivastatin monotherapy presents a significantly higher risk. When statins are combined with fibrates, the risk of rhabdomyolysis generally increases, especially with the cerivastatin and fibrate combination, which

poses a dramatically elevated risk. Additionally, older age and diabetes mellitus have been identified as risk factors for rhabdomyolysis with statin monotherapy. Most statins are metabolized by the cytochrome P450 system, except pravastatin [46]. Ethanol has the potential to cause rhabdomyolysis by impairing the operation of the adenosine triphosphatase pump, damaging the muscle membrane, and modifying the sarcoplasmic reticulum.

A case report describes a 55-year-old man who developed alcohol-induced rhabdomyolysis, with his creatine kinase (CK) level reaching 401,280 U/L despite aggressive fluid repletion [47].

F. Interstitial nephritis

Drug-induced acute interstitial nephritis (DI-AIN) is a common cause of AKI, also resulting from immune reactions in humans, which can be either cell-mediated or antibody-mediated. In humans, most instances are likely associated with cell-mediated immunity, as renal biopsies generally do not reveal immune deposits. Rather, interstitial infiltrates usually consist of a high proportion of T-cells and might even develop granulomas.

However, antibody-mediated immunity can also play a role, as evidenced by occasional observations of anti-tubular basement membrane (TBM) antibodies or immune complexes on renal biopsies, such as in methicillin-induced AIN. DI-AIN typically develops about two weeks after starting the causative drug and is often characterized by symptoms such as fever, cutaneous rash, arthralgias, eosinophilia, hematuria, pyuria, and renal failure [48].

While any medication has the potential to result in DI-AIN, antibiotics, non-steroidal anti-inflammatory medications (NSAIDs), and proton pump inhibitors (PPIs) are the ones most frequently associated. In one patient case, after showing clinical improvement with ceftriaxone and azithromycin therapy, the patient experienced a rise in serum creatinine. Although acute kidney injury was considered in the differential diagnosis, along with acute infectious glomerulonephritis and DI-AIN, ceftriaxone was determined to be the most likely cause of the diagnosis of diffuse acute interstitial nephritis (AIN) [49]. NSAIDs can lead to a unique form of acute tubulointerstitial nephritis, often accompanied by glomerulopathy. This condition, termed acute interstitial nephritis with glomerulopathy (AING), is characterized by renal failure and proteinuria, frequently in the nephrotic range. It is more common in elderly women and is often associated with long-term NSAID use for musculoskeletal issues.

Similarly, fenoprofen has been implicated in a significant percentage of reviewed cases [50]. Another study describes a unique case in which a 14-year-old boy developed acute renal failure, with kidney biopsy results showing acute tubulointerstitial nephritis (ATIN) and intense granular deposits of polyclonal IgG and C3 in the TBM [51]. Celecoxib, a selective COX-2 inhibitor, has been linked to acute allergic interstitial nephritis (AIN) through an idiosyncratic mechanism. One hypothesis suggests that COX inhibition shifts the arachidonic acid pathway toward leukotriene production, which increases glomerular permeability and contributes to nephrotic-range proteinuria and interstitial nephritis. A case report details a 59-year-old diabetic man who developed AIN and nephrotic syndrome after a year of celecoxib use for joint disease [52].

Similarly, a case report describes a patient who developed AIN. Although a drug-induced lymphocyte stimulation test, rifampicin was strongly suspected as the cause of DI-AIN [53]. PPIs are also associated with AIN, likely due to an idiosyncratic hypersensitivity reaction. A retrospective study conducted at two Australian hospitals identified 18 biopsy-proven cases of PPI-induced AIN causing acute renal failure, making it the most extensive hospital-based case series on this issue. Additionally, a review of national registry data (TGA) found 31 more biopsy-confirmed cases linked to omeprazole, pantoprazole, esomeprazole, and rabeprazole [54].

G. *Glomerulonephritis*

Drug-driven glomerular damage, although frequently overlooked, may arise from direct cell toxicity or immune-related harm. Numerous drugs can negatively impact endothelial, mesangial, or podocyte cells, resulting in ailments such as TMA, focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), and membranous nephropathy (MN).

Some drugs cause structural damage to glomeruli, while others trigger immune responses, leading to antibody-mediated injury or autoimmunity. Several medications, including gold therapy, hydralazine, interferon-alfa, lithium, NSAIDs, propylthiouracil, and pamidronate, have been implicated in drug-induced glomerulopathies [7,55].

Certain drugs directly damage glomerular structures, particularly the podocytes and endothelial cells. Pamidronate, a bisphosphonate used in multiple myeloma and metastatic cancer, has been linked to collapsing FSGS. In a study of seven patients (six with multiple myeloma and one with metastatic breast cancer), high-dose pamidronate therapy led to acute renal failure and nephrotic-range proteinuria. Renal biopsies showed collapsing FSGS with podocyte foot process effacement, confirming drug-induced injury [56].

Lithium, commonly used in psychiatric disorders, has been associated with glomerular and tubulointerstitial nephropathy, particularly with long-term use. Studies show a higher prevalence of sclerotic glomeruli in patients on chronic lithium therapy, with the risk increasing with prolonged and frequent dosing [57]. Certain medications induce autoimmune responses, leading to glomerulonephritis. Propylthiouracil, an antithyroid drug, has been linked to (antineutrophil cytoplasmic antibodies) ANCA-positive rapidly progressive glomerulonephritis. While the exact mechanism is unclear, propylthiouracil is believed to induce myeloperoxidase (MPO)-ANCA production, which contributes to disease progression [58].

Hydralazine, a vasodilator used for hypertension, has been associated with pauci-immune glomerulonephritis and drug-induced lupus. In a case series of four elderly women who had been taking ≥150 mg of hydralazine for over 12 months, all presented with acute kidney injury, nephritic urine sediment, and high p-ANCA titres. Kidney biopsies revealed crescentic

or necrotizing glomerulonephritis without immune complex deposits, highlighting the overlapping features of drug-induced lupus and vasculitis [59].

Gold therapy, previously used for rheumatoid arthritis, can cause membranous glomerulonephritis. This is characterized by subepithelial electron-dense deposits and IgG deposits along the glomerular basement membrane, as observed in a patient who developed the condition after oral gold therapy with auranofin [60].

Understanding the mechanisms of DIN is crucial for identifying potential risks and developing effective interventions. Various drugs have been implicated in renal toxicity through distinct pathways, including oxidative stress, inflammation, and immune-mediated damage. TABLE I summarizes different nephrotoxic drugs, their mechanisms, affected renal structures, and associated clinical manifestations, providing a comprehensive reference for their impact on kidney function.

TABLE I. Common drugs causing nephrotoxicity [24,25,39,40,41,56,61-80]

S. No.	Drug name	Mechanism	Target site in the kidney	Pathophysiological effect	Clinical manifestation
1	Adenofir	ATN, fanconi syndrome	Proximal tubules	Mitochondrial DNA depletion, impaired cellular oxidative respiration	↑serum creatinine (scr), fanconi syndrome with phosphate wasting, ARF, glycosuria, ↓serum bicarbonate
2	Cidofovir	Dose-dependent proximal tubular cell injury	Proximal tubules	Dose-dependent proximal tubular cell injury	Proteinuria, glucosuria
3	Acyclovir	Crystalluria leading to obstructive nephropathy	Renal collecting tubules	Obstructive nephropathy caused by crystallization	Malaise, nausea, vomiting, anorexia, headache, irritability, confusion, flushing, metallic taste, ↑scr
4	Amphotericin B	Direct renal vasoconstriction	Afferent arterioles	↓GFR, renal vasoconstriction, tubular dysfunction	↑urine flow, urinary chloride excretion, and mean arterial pressure
5	Methotrexate	Mitochondrial dysfunction and oxidative stress	Proximal tubules	Renal tubular degeneration, retraction of glomeruli, interstitial inflammation, and vascular congestion	↑BUN, scr, causes hypokalemia, hypophosphatemia, ↑ROS, lipid peroxidation, ↓glutathione
6	Cisplatin	ATN	Distal and collecting tubules, proximal tubules	Dilation of tubules, formation of casts, focal ATN, cytoplasmic vacuolization	↑BUN, scr, proteinuria and hyperuricemia
7	Mitomycin C	Endothelial injury, HUS	Endothelium	Microangiopathy	Hemolytic-uremia
8	Cyclosporine	Vasoconstriction, endothelial damage, tubular toxicity	Renal microvasculature, glomerulus, tubules, endothelial, mesangial cells	Tubulointerstitial fibrosis and vascular lesions, isometric vacuolization, glomerular thrombosis	↓GFR and renal blood flow, progressive nephropathy
9	Tacrolimus	Hemolytic uremic syndrome	Tubular epithelial cells, afferent arterioles	Microangiopathic hemolysis, thrombocytopenia, and renal failure	Headache, nausea, malaise, ↑BUN and scr levels, ↓hemoglobin and platelet count, schistocytes on the peripheral smear
10	Celecoxib	AIN	Macula densa cells, glomerular podocytes, afferent arterioles, medullary interstitium	Interstitial infiltration with interstitial edema and mild interstitial fibrosis	Body weakness, malaise, arthralgias, leg pain, subnephrotic proteinuria, and ARF
11	Naproxen	Renal papillary necrosis	Renal papilla	Necrosis of the inner medulla, damage, death of tubular cells, Inflammation in the interstitium, mild mesangial proliferation	↑BUN and Cr, abdominal pain, ↓oral intake, and potential dehydration, hematuria
12	Pamidronate	Epithelial injury	Glomeruli, tubules	Glomerulosclerosis, tubule atrophy, luminal ectasia, loss of brush border, cytoplasmic vacuolization, and mild-to-severe interstitial fibrosis	Nephrotic proteinuria, low blood pressure, ↓urine output, pitting edema
13	Zoledronate	ATN	Proximal tubules	Luminal ectasia, loss of brush border, enlarged hyperchromatic nuclei, apoptotic and mitotic figures	↑scr, proteinuria
14	Vancomycin	ATN, AIN	Tubules, interstitial tissue	Diffuse interstitial infiltrates of mononuclear inflammatory cells, tubular dilatation, tubular epithelial thinning	↑scr, oliguria, proteinuria, hematuria
15	Amikacin	ARF	Renal cortex	Mitochondrial dysfunction and enhanced production of free radicals	↑scr and urea, ↓urine output and creatinine, glomerular damage, tubular necrosis, interstitial inflammation, ↑leucocytic infiltration
16	Rifampin	ATN	Tubules, interstitium	Immune-mediated injury to the tubular membrane	Fanconi syndrome, muscle weakness, reticular opacities,

					↑echogenicity
17	Ciprofloxacin	Crystal nephropathy	Tubules	Acute tubular damage, intratubular crystals, birefringent crystals	ARF, ↑scr levels, ↓urine output, few red blood cells in urine sediment
18	Alpha interferon	TMA	Glomeruli, arterioles, vessel walls	Thickening of arteriolar walls, arteriolar thrombi, interstitial fibrosis, diffuse endothelial swelling, ischemia	Proteinuria, renal failure, nephrotic syndrome, ↑lactate dehydrogenase, end-stage renal failure
19	VEGF inhibitors	TMA	Glomerular endothelium	Segmental duplication of the glomerular basement, endothelial swelling, recanalized arteriolar thrombi, and fibrinogen deposits	Microangiopathic hemolytic anemia, thrombocytopenia, weakness, edema, hypertension, proteinuria, hypoalbuminemia
20	Lithium	ATN	Distal tubule, collecting duct	Lesions in the distal tubule and collecting duct, diminished brush border staining, and flattening of cells in both tubules	Hyponatremia, concentrated urine, lower extremity swelling, ↑abdominal girth
21	HMG CoA reductase	Renal tubular toxicity	Renal tubules	ATN results in rhabdomyolysis, irregular vacuolated renal tubular cells with denudation of tubular basement membranes	Proteinuria, ↑plasma Cr, renal tubular casts, haematuria, myalgia, arthralgia
22	Triamterene	ATI, AIN, and crystalline nephropathy	Tubular lumina	Yellow-tan crystals, tubular atrophy, interstitial fibrosis, and mild mononuclear cell interstitial inflammation	Crystalluria and kidney calculi, reversible hemodynamic, AKI, acute oliguric kidney injury
23	Checkpoint inhibitors	AKI	Tubule interstitium	ATIN, glomerulonephritis	Pyuria, hematuria, and proteinuria
24	Proton pump inhibitors	AIN	Renal interstitium	Inflammatory infiltrate that leads to ARF	Fever and chills, ↑erythrocyte sedimentation rate and C-reactive protein, sterile pyuria
25	ACE inhibitors	ARF	Glomeruli, renal tubules	Vasodilation of the postglomerular efferent arterioles, ↓proximal tubule, and aldosterone-dependent collecting duct sodium reabsorption	↑scr, hyperkalemia
26	Corticosteroids	AIN	Renal interstitium	Cell-mediated immunity, inflammatory cell infiltrate	Oliguria, arthralgia, fever, rash

A thorough understanding of the mechanisms of drug-induced nephrotoxicity is essential to developing effective interventions. Building upon these pathogenic insights, the following sections explore therapeutic strategies that aim to mitigate renal injury, ranging from traditional herbal remedies to synthetic agents and cutting-edge technologies.

III. Treatment Strategies

A. Herbal drug approaches in the rat model of DIN

Given the high prevalence of DIN, there is growing interest in alternative therapeutic approaches to protect renal function. Herbal medicines have gained attention due to their antioxidant, anti-inflammatory, and cytoprotective properties, which may help counteract nephrotoxic effects by modulating oxidative stress, inflammation, and apoptotic pathways [81].

Traditional medicinal plants have been used for centuries to treat renal disorders, and preclinical studies, particularly in animal models, suggest their potential efficacy in mitigating nephrotoxicity. However, despite promising findings in experimental settings, concerns regarding safety, efficacy, and potential nephrotoxicity persist, necessitating further clinical validation [82]. While phytomedicines have demonstrated protective effects in *in vitro* and *in vivo* studies, the lack of human trials limits their application in clinical practice.

Additionally, more than 100 herbal formulations have been linked to nephrotoxicity, emphasizing the need for cautious use and regulatory oversight [83]. Given these uncertainties, further investigation through well-designed clinical trials is crucial to establish the safety and therapeutic potential of herbal medicines in preventing and treating drug-induced nephrotoxicity. TABLE II. provides a comprehensive overview of various herbal treatments studied for their nephroprotective potential.

B. Synthetic Pharmacological Interventions in DIN

Synthetic pharmacological agents are being actively explored for their potential to mitigate DIN, particularly in human subjects. These drugs aim to counteract key pathogenic mechanisms involved in DIN. While several synthetic compounds have shown encouraging renoprotective effects in clinical settings, their widespread adoption is still limited by the need for further validation in larger, controlled human studies. Although early results are promising, the evidence remains heterogeneous, and their efficacy is not yet conclusively established for routine clinical use. TABLE III. summarizes synthetic drugs evaluated in human studies for the treatment or prevention of DIN, along with their proposed mechanisms and reported outcomes. However, these therapeutic strategies should be interpreted with caution, as further research is necessary to confirm their clinical utility and optimize dosing, timing, and safety profiles.

C. Novel and Advanced Strategies for DIN

With advancements in nephrology and pharmacology, several novel and advanced therapeutic strategies have emerged to mitigate DIN. These approaches aim to provide early detection, targeted therapy, and renal regeneration, offering promising alternatives to traditional nephroprotective measures.

TABLE II. Plant-based interventions for DIN in rat models [84-97].

S. No.	Plant name	Extract/ plant part	Experimental model	Species, dose, route, no. of days	Outcomes
1	*Hygrophila spinosa*	methanol extract (whole plant)	cisplatin-induced nephrotoxicity	male Wistar rats, extract (250 mg/kg and 500 mg/kg, p.o., 10 days), on 11th-day cisplatin (7.5 mg/kg, i.p.)	pretreatment significantly ↓blood urea, sCr levels, attenuated cisplatin-induced ↑MDA, ↓ GSH, CAT, SOD, and GSH, histopathological examination
2	*Costus afer*	aqueous extract (leaf)	cyclosporine A (CsA) - induced nephrotoxicity	male Wistar rats, extract (375, 750, and 1125 mg/kg, p.o.,1st-5th day), CsA (50 mg/kg, p.o.,6th -10th day)	prevented oxidative impairments, ↓plasma Cr, BUN, K+, MDA, ↑GSH, SOD, CAT, GST serum electrolytes, ↓severity of renal cellular damage
3	*Moringa oleifera*	seed oil	gentamicin-induced oxidative nephrotoxicity	male Wistar rats, seed oil (5ml/kg, p.o., 16 days), gentamicin (100mg/kg, i.p. injected from day 11 to day 16)	seed oil ↓sCr and urea levels, depressed oxidative stress, restored renal content of IL-1b, IL-6, TNF-a, and NO, and ameliorated histopathological alterations
4	*Melia Azadirachta*	Ethanol extract (leaf)	acetaminophen-induced nephrotoxicity in male albino Wister rats	male albino Wister rats, extract (250 and 500 mg/kg, p.o.), acetaminophen (750mg/kg, p.o.)	extract restored serum urea, and Cr levels, and showed a mild degree of necrosis and degeneration compared to acetaminophen
5	*Achillea millefolium*	ethanol extract (aerial part)	doxorubicin-induced renal injury in rats	male rats, extract (100, 200 mg/kg/day, p.o., 28 days), doxorubicin (5 mg/kg/week i.p., 4 weeks)	extract of 200 mg/kg reversed the effects of ↑sCr, urea, uric acid, and pro-inflammatory cytokines and suppressed inflammation
6	*Hedera helix*	leaf extract	paracetamol-induced nephrotoxicity in mice	male Swiss albino mice, extract (50,100,200, and 300 mg/kg, p.o. twice a day, every 12 hours, 7 days), paracetamol (600 mg/kg, i.p.) on 8th day	leaf extract ↓ BUN, Cr, and uric acid levels, histological alterations, 200 mg/kg group showed effective treatment
7	*Sonchus asper*	methanol extract (whole plant)	CCl4-induced nephrotoxicity in Sprague–Dawley male rats	male Sprague–Dawley rats, extract (100, 200 mg/kg, intragastric, 4 weeks), CCl4 (3 ml/kg, i.p. biweekly, 4 weeks)	extract ameliorated the alterations induced by CCl4 in lipid peroxidation, antioxidant defenses, biochemical markers, genotoxicity, and renal lesions
8	*Boerhaava diffusa*	methanol extract (root)	lead acetate-induced nephrotoxicity in rats	male albino rats, extract (150 mg/kg, p.o., 21 days), lead acetate (200 mg/kg, p.o., 21 days)	lead exposure ↓protein levels and ↑urea, uric acid, Cr, and TBARS, while extract treatment reversed these effects
9	*Amomum compactum*	powdered plant	gentamicin-induced AKI in rats	male Wistar rats, powder plant (low dose 1.54 g/kg, high-dose 3.08 g/kg, p.o. for 15 days)	Plant treatment exhibited strong protective effects against AKI, in the high-dose group symptoms of tubular atrophy were relieved, and sCr, and BUN levels ↓significantly
10	*Curcuma longa*	methanol extract (rhizome)	acetaminophen-induced nephrotoxicity	male NMRI mice, extract (400, 800, and 1000 mg/kg), and acetaminophen (500 mg/kg) both administered in single dose by gavage	acetaminophen caused renal injury by ↑Cr, BUN, and uric acid levels, damage to glomeruli and proximal tubules while extract (1000 mg/kg) reduced these markers and preserved kidney structure
11	*Artocarpus heterophyllus*	ethanol extract (leaf)	neomycin-induced nephrotoxicity in rats	Albino Wistar rats, extract (200 and 400 mg/kg p.o., 14 days), neomycin (80 mg/kg, i.p. for last 8 days)	extract ↓ the levels of renal function markers and histopathological improvements compared to the toxic control group
12	*Alhagi maurorum*	methanol extract (aerial parts)	lead-induced nephrotoxicity in rats	male Wistar rats, extract (100mg/kg and 200 mg/kg, p.o., 28 days), lead acetate (15 mg/kg, p.o.,28 days)	extract ameliorated lead-induced nephrotoxicity by improving kidney function, ↓oxidative stress, and inflammation, and modulating apoptosis.
13	*Limonium duriusculum*	ethyl acetate extract (aerial part)	cyclosporine-induced nephrotoxicity	male Wistar rats, extract (*invivo*-200 mg/kg, p.o., 14 days, *invitro*-5, 25, and 50 µg/ml), cyclosporine (*in vivo*-25 mg/kg, p.o., 14 days, *in vitro*-10 µg/ml for 6h)	extract inhibits renal dysfunction, suppresses oxidative stress, ↓endoplasmic reticulum stress, and inflammation, restores cell morphology, maintains renal redox homeostasis
14	*Bryophyllum pinnatum*	aqueous extract (leaf)	ketamine-induced kidney injury in Wistar rats	male Wistar rats, extract (50, 100, and 200 mg/kg, p.o., 21 days), ketamine (20 mg/kg, i.p., 7 days)	extract 100, and 200 mg/kg significantly ↓ the levels of kidney function biomarkers, histological analysis also revealed extract attenuated ketamine-induced renal damage

1. Mitochondria-targeted Therapy

Mitochondria play a central role in cellular energy metabolism, reactive oxygen species (ROS) regulation, and apoptosis. In the kidneys, mitochondrial dysfunction is a key driver of drug-induced nephrotoxicity, leading to oxidative stress, impaired ATP production, and activation of cell death pathways [15].

Recent research recognizes mitochondria-focused medicines as an effective method to protect kidneys from damage through improved mitochondrial health and decreased oxidative cell destruction. According to research findings, the preclinical application of mitochondria-targeted antioxidants along with enhanced mitochondrial biogenesis has demonstrated promise [108].

TABLE III. Synthetic drugs in the management of DIN from human studies [98-107]

S. No	Drug	Study type	Dose	Mechanism of action	Outcome
1	Pentoxifylline	prospective, randomized, single-blind, single-center clinical trial	400 mg	mitigating inflammation and oxidative stress, as well as improving blood flow	prevention of contrast-induced nephropathy (CIN) in patients undergoing coronary angioplasty
2	Methylprednisolone, prednisone	retrospective multicentre study	250-500mg, 1 mg/kg	reduce the inflammatory response in the kidney and prevent the development of interstitial fibrosis	recovery of renal function and preventing long-term damage in patients with drug-induced ATIN
3	Sodium bicarbonate, N-acetylcysteine	prospective, double-blind, randomized trial	Sodium bicarbonate (154mEq/L, 3mL/kg, 1mL/kg), NAC (1200mg)	NAC (antioxidant, improves renal hemodynamic), Sodium bicarbonate (alkalinizes renal tubular fluid, scavenges reactive species, buffers H^+ in the proximal tubule)	prophylactic prevention of CIN in patients with chronic kidney disease
4	Theophylline	prospective, randomized trial	200 mg	glomerular adenosine antagonist counteracts adenosine-induced vasoconstriction of afferent arterioles, offers tubular protection, and possesses antioxidant properties	prophylactic reduction of CIN in patients with chronic renal insufficiency
5	Statins	nonrandomized analysis	nil	pleiotropic effects, including antioxidant, anti-inflammatory, and antithrombotic properties, and reduced endothelin secretion	pre-procedure statin use is associated with a lower incidence of CIN
6	Ascorbic acid	randomized, double-blind, placebo-controlled trial	3g and 2g	antioxidant neutralizes reactive oxygen species generated by contrast agents	ascorbic acid may protect against CIN in patients undergoing a coronary procedure
7	Erythropoietin	prospective, randomized, double-blind, placebo-controlled trial	300 U/kg	tissue-protective, non-hematopoietic actions such as anti-apoptotic or anti-inflammatory effects	↓ the incidence of AKI and improved postoperative renal function in patients undergoing coronary artery bypass grafting
8	Natriuretic peptide	randomized controlled trial	0.025 μg/kg	inhibition of the intrarenal renin-angiotensin-aldosterone system (RAAS)	renal protective effects during cardiac surgery and ↓ the incidence of AKI after ischemia-reperfusion surgery
9	Probenecid	observational study	500 mg	inhibits the human organic anion transporter 1	↓nephrotoxicity associated with tenofovir disoproxil fumarate-related nephrotoxicity
10	Acetazolamide	case report	1500 mg	inhibits bicarbonate resorption, leading to alkaline diuresis this alkalinization improves myoglobin solubility and excretion	Treatment of rhabdomyolysis-induced myoglobinuric renal failure

1.1. Mitochondria-Targeted Antioxidants

The derivative coenzyme Q10 compound MitoQ achieves high accumulation levels in mitochondria because it combines coenzyme Q10 with the triphenylphosphonium cation's lipophilic character. Studies have shown MitoQ succeeds in protecting the kidneys from injury by both decreasing mitochondrial ROS production and improving mitochondrial function during nephrotoxicity models.

Additionally, SkQ1 functions as an antioxidant to protect kidneys through its ability to preserve mitochondrial health and minimize tissue oxidative stress [109,110]. Similarly, SS-31 functions as an antioxidant peptide that protects mitochondria by reducing ROS production and restoring their structure. Renal function benefits from SS-31 treatment because patients show decreased serum creatinine and blood urea nitrogen (BUN) levels. However, another study indicates that SS-31 protects mice from CI-AKI by functioning as an antioxidant and reducing cell death while affecting the mitochondrial ROS-NLRP3 pathway [111].

1.2. Enhancement of Mitochondrial Biogenesis

Restoring mitochondrial function along with enhancing cellular energy status depends on the strategy of promoting mitochondrial biogenesis. The compound resveratrol, together with other compounds, has shown its ability to activate mitochondrial biogenesis. The polyphenolic compound resveratrol, which exists in grapes along with berries, enables the activation of mitochondrial biogenesis through its stimulation of Sirtuin 1 (SIRT1) and Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) pathways. Resveratrol administration improved kidney protection along with enhanced mitochondrial function when given to experimental injury models, according to research [112,113].

Researchers have discovered that nicotinamide riboside (NR) demonstrates promising results for restoring mitochondrial function because it functions as a vitamin B3 natural precursor of Nicotinamide Adenine Dinucleotide (NAD+). The rise in NAD+ levels provoked by NR causes new mitochondria to develop and improves ATP production capabilities [114].

1.3. Inhibition of the Mitochondrial Permeability Transition Pore (mPTP)

mPTP opens excessively in cells, becoming a critical regulator of death. This causes mitochondrial swelling and loss of membrane potential, followed by apoptosis. Preventing mPTP opening demonstrates potential as an effective method

to protect renal tissue from damage in conditions of nephrotoxicity.

Research shows that Cyclosporine A (CsA) functions as a well-established mPTP inhibitor, which decreases nephrotoxicity, especially in ischemia-reperfusion injury models. The protective abilities of CsA in renal tissue depend heavily on the administration time and dosage of the drug received, according to research findings. Another study [115] established that strategic pretreatment with CsA at optimal doses produces greater mPTP prevention to safeguard rat model mitochondria from ischemia-reperfusion damage. Studies demonstrate that therapeutic interventions that direct treatment toward mitochondria show great potential for defending the kidneys from drug-caused damage.

Ongoing studies and proper clinical trial investigations are necessary to understand how these compounds perform in humans regarding safety and efficacy, as well as their long-term impact on human health

2. Regenerative Medicine & Stem Cell Therapy

2.1. Mesenchymal stem cells (MSCs)

MSCs demonstrate strong protective effects on the kidneys through three mechanisms, which consist of immune response adjustment, along with fibrosis prevention and renal tissue healing promotion. The therapeutic mechanisms of MSCs rely on their paracrine factor release that includes cytokines and growth factors, which drive angiogenesis and protect cells against apoptosis while enhancing endogenous cell proliferation for renal function recovery and fibrosis reduction [116].

Additionally, Human umbilical cord-derived MSCs (hUC-MSCs) demonstrate potential for early diabetic nephropathy prevention because they lower a fibrotic protein and help restore kidney autophagy responsible for self-cleaning. The research confirms that MSCs represent a valuable therapeutic option for kidney diseases through direct targeting of persistent inflammation and fibrosis [117].

2.2. Exosome-Based Therapy

The specialized microvesicular subset called exosomes transfers mRNA along with miRNA between cells for enabling crucial intercellular communication. These nano-sized bodies emerge from different cell types, especially mesenchymal stem cells, while showing evidence of contributing to tissue regeneration along with immune regulation systems and delivering drugs precisely.

Scientific evidence demonstrates that microvesicles originating from Mesenchymal Stem Cells act to defend against AKI and delay the development of CKD during ischemia-reperfusion injury conditions. The administration of these MVs alone after injury resulted in decreased kidney tissue destruction and boosted cell growth while preventing cellular death. The RNA content inside these vesicles functions as a main protector for the development of fibrosis and chronic injury [118]. The antioxidant properties of exosomes produced by human Wharton's jelly mesenchymal stromal cells (WJ-MSCs) make them effective at combating renal ischemia-reperfusion injury (IRI). The exosomes control oxidative stress through their mechanism of inhibiting NOX2/gp91(phox), which functions as an essential enzyme in ROS formation. The reduction of oxidative damage through this process protects renal functions and prevents apoptosis and supports tissue regeneration [119].

3. RNA-Based Therapy

3.1. MicroRNA-Based Treatments

MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression and play a key role in kidney disease progression. Multiple miRNAs have been associated with renal fibrosis and nephropathy, positioning them as potential therapeutic targets.

microRNA 192 (miR-192): upregulated in diabetic nephropathy and contributes to renal fibrosis. One study demonstrated that inhibiting miR-192 with LNA-anti-miR-192 in diabetic mouse models significantly reduced renal fibrosis and improved proteinuria, highlighting its potential as a therapeutic target [120].

microRNA 29 (miR-29): The miR-29 family is a well-characterized regulator of transforming growth factor beta 1 (TGF-β1)-mediated fibrosis across various tissues. Another study investigated miR-29's role in renal fibrosis using a mouse model of obstructive nephropathy and in vitro cell cultures. The results indicated that miR-29 is negatively controlled by the TGF-β/Smad3 signaling pathway and functions as a downstream suppressor of fibrosis. Importantly, reinstating miR-29 levels in fibrotic kidneys halted disease progression, emphasizing its promise as an antifibrotic treatment [121].

microRNA 21 (miR-21): Similarly, another study identified a distinct miRNA signature associated with UUO-induced renal fibrosis, with miR-21 being significantly upregulated in fibrotic kidneys, particularly in distal tubular epithelial cells. Importantly, in vivo inhibition of miR-21 effectively reduced fibrosis, suggesting its potential as a novel therapeutic target for renal fibrosis treatment [122].

microRNA 709 (miR-709): In another study, miR-709 was significantly upregulated in acute kidney injury (AKI), where it contributes to mitochondrial dysfunction and tubular cell death by targeting transcription factor A, mitochondrial (TFAM). Experimental studies demonstrated that inhibiting miR-709 or restoring TFAM expression effectively mitigated AKI severity in a mouse model, highlighting a potential therapeutic strategy for preserving mitochondrial integrity and renal function [123].

3.2. Small Interfering RNA (siRNA) Therapies

Small interfering RNA (siRNA) therapies have emerged as a promising strategy for targeting key molecular pathways implicated in kidney diseases, including inflammation, fibrosis, and apoptosis. By silencing specific mRNAs, siRNAs effectively modulate disease progression and mitigate renal injury.

One study explored the therapeutic potential of siRNA targeting the p53 protein in AKI. Intravenous administration of p53-specific siRNA in animal models significantly reduced both ischemia- and cisplatin-induced AKI. This renoprotective effect was achieved by downregulating p53 expression, suppressing apoptotic signaling in proximal tubule cells, and

ultimately preserving renal function [124]. Another study explored siRNA treatment of mitogen-activated protein kinase 1 (MAPK1) in glomerulonephritis patients. Nanocarriers made with poly(ethylene glycol)-poly(L-lysine) (PEG-PLL) delivered MAPK1 siRNA through targeted delivery routes when injected repeatedly into the peritoneal cavity, which successfully decreased MAPK1 expression in glomeruli. Scientists demonstrated through this therapy that kidney performance improved and proteinuria decreased while glomerular sclerosis diminished substantially [125].

Future stability advances and delivery system development in siRNA-based medicine will strengthen their effectiveness as precise therapeutic agents against kidney disorders.

4. Artificial Intelligence and Machine Learning

Artificial intelligence (AI) and machine learning (ML) systems use numerous data sources to detect elaborate patterns connected with nephrotoxicity, thereby constructing more precise AKI predictions. The use of AI/ML models has shown success in early DIKI prediction for drug development that both improves safety outcomes and enhances productivity rates. The predictive accuracy of Random Forest and Neural Networks depends on their ability to analyze physicochemical properties and off-target interactions as per ML algorithms. A combination of AI/ML algorithms delivering both features produced improved DIKI prediction accuracy with AUROC equaling 0.87.

Research showed PSA together with pKa and gene interactions (such as PDE4A and CASP3) to be important predictors for AI-based nephrotoxicity screening [126]. Similarly, ML models have shown high accuracy in predicting drug-induced nephrotoxicity. A study using the Random Forest algorithm on hiPSC-derived renal cells achieved 87.0% test accuracy, outperforming primary human renal cells. The model classified toxic and non-toxic compounds with 100% accuracy while minimizing donor variability.

Automated classification based on interleukin-6 (IL6) and interleukin-8 (IL8) expression changes, coupled with robust validation, underscores its potential as a reliable in vitro nephrotoxicity screening tool [127]. Further, a comparative study of ML algorithms found that the Random Forest model was the most effective for AKI prediction. It identified key clinical features such as SOFA score and eGFR as highly relevant to AKI development, demonstrating ML's potential in risk stratification and early intervention for patients with heart failure [128].

The prediction of AKI benefits from AI and ML systems through diverse data unification and complex detection of nephrotoxicity patterns. Traditional monitoring systems can create a lot of unnecessary false alarms, which can be exhausting for clinicians. To tackle this issue, researchers developed a recurrent neural network with gated recurrent units (RNN-GRU) that predicts AKI within 48 hours after a patient is exposed to high levels of nephrotoxins. This innovative model has increased accuracy, with a precision rate of 0.60, and reduced the number of false alerts from 2.5 to just 0.7 for each AKI event. Important factors that were used for predictions included hemoglobin levels, blood pressure, and white blood cell count, highlighting how machine learning can enhance AKI prevention efforts [129].

Additionally, machine learning is also being used in pharmacovigilance to track which medications might lead to AKI in older patients. A study of health databases found that about 9% of prescribed medications could potentially harm the kidneys. Some of the drugs linked to a higher risk of AKI included angiotensin II receptor blockers, certain antibiotics, diuretics, NSAIDs, iron supplements, and xanthine oxidase inhibitors. This highlights ML's potential to prevent medication-induced nephrotoxicity through improved drug monitoring and risk assessment [130].

5. Kidney-on-a-chip

Organ-on-a-chip technology represents a groundbreaking advancement in biomedical engineering, offering microfluidic platforms that replicate the complex architecture and physiological functions of human organs. Among these, kidney-on-a-chip models have been specifically developed to mimic the structural, mechanical, and functional properties of the human kidney's proximal tubule [131]. These microdevices cultivate human kidney epithelial cells under fluidic flow conditions, enhancing cell polarization and key functional activities such as albumin transport and glucose reabsorption. A primary application of kidney-on-a-chip technology is nephrotoxicity assessment, which provides a more accurate and dynamic evaluation of DIKI compared to traditional methods. Unlike static culture systems, these microfluidic models enable real-time monitoring of cellular responses to nephrotoxic agents, making them valuable tools in preclinical drug screening.

High-throughput platforms like Nephroscreen further enhance nephrotoxicity testing efficiency, improving drug safety assessments and reducing reliance on animal models [132]. Several studies have demonstrated the effectiveness of kidney-on-a-chip systems in replicating renal toxicity mechanisms. Similarly, one study cultured primary human kidney proximal tubular epithelial cells within a microfluidic device under controlled shear stress, successfully enhancing cell polarization and in vivo-like functional activities. Their model effectively simulated cisplatin-induced nephrotoxicity, reinforcing its potential for preclinical drug evaluations. Further advancements include the development of co-culture kidney-on-a-chip models [133].

A research team built a microfluidic device that combined renal proximal tubular epithelial cells (RPTECs) with peritubular capillary endothelial cells (PCECs into three separate layers. The improved system led to better cell development and functional capabilities than what static culture methods could deliver. The researchers recorded substantial improvement in protecting against cisplatin-related kidney damage when patients received cimetidine treatment in their study for therapeutic screening [134]. Expanding on these findings, researcher developed a nephrotoxicity model by using injection-molded polycarbonate chips as they combined human renal proximal tubular epithelial cells (HRPTECs) with human umbilical vein endothelial cells (HUVECs). The simulated model duplicated nephrotoxicity

caused by cisplatin and gentamicin through its ability to reduce cellular survival along with toxicity marker escalation. This platform provides a toxicity test platform based on human cells to decrease disparities between animal tests and human subjects frequently present in experimental data. The application of kidney-on-a-chip technology extends beyond pharmaceutical research because researchers have utilized this technology to evaluate environmental toxic substances [135]. A study created a three-compartment microfluidic device, which became the foundation for studying cadmium-induced nephrotoxicity. The toxicity effects of cadmium could be analyzed in real time by using primary rat glomerular endothelial cells in their barrier model. Open literature demonstrated a dose-dependent toxicity mechanism while showing increased permeability properties of the platform for environmental toxicology applications [136]. Additionally, the Nephroscreen platform functions as a 3D microfluidic system that assesses the detection of DIKI. The system showed exceptional stability together with high sensitivity in drug-transporter tests and nephrotoxicity applications, thus supporting pharmaceutical research [137].

IV. Conclusion

Nephrotoxic outcomes from medication usage represent an elaborate problem that medical authorities increasingly recognize in preclinical and clinical settings. This review has assembled a detailed understanding of DIN pathogenesis through research conducted on human studies, together with experimental animal models. The review examines present-day therapeutic options that combine plant extracts with synthetic drug compounds in addition to sophisticated medical technologies used to decrease renal tissue damage frequency and severity.

Renal protection, along with tissue regeneration, benefits from the recent advancements, which include mitochondria-targeted therapeutics and mesenchymal stem cells, as well as exosome-based treatments along with RNA-targeted strategies. Artificial intelligence and machine learning tools now transform nephrotoxicity prediction and monitoring capabilities simultaneously as scientists develop organ-on-a-chip systems that include kidney-on-a-chip technology for better preclinical drug evaluations.

Despite these advancements, significant translational gaps persist. Most herbal remedies lack robust clinical validation, synthetic agentsrequire larger-scale trials for widespread adoption, and newer technologies face regulatory and implementation challenges before routine integration into clinical practice. Ongoing research, cross-disciplinary collaboration, and funding in tailored medicine will be essential to close the divide between laboratory and clinical practice.

Ultimately, DIN is not only preventable but also potentially manageable through a multifaceted approach that combines mechanistic insight, evidence-based interventions, and technological innovation. Integrating traditional knowledge with cutting-edge science will help pave the way toward safer pharmacotherapy, improved patient outcomes, and a future where renal toxicity is no longer a limiting factor in drug development.

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Conflict of Interest

The authors declare that there are no conflicts of interest related to the content of this manuscript.

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