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Review Article

Nephroprotective Role of *Boerhavia diffusa*: A Mechanistic Review of Gene Expression and Signaling Cascades

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ABSTRACT

Drug induced nephrotoxicity is a major clinical challenge, arising from diverse therapeutic agents such as cisplatin, aminoglycosides, streptozotocin, NSAIDs, antivirals, methotrexate, calcineurin inhibitors, and radiocontrast media. These agents damage renal tissue through overlapping mechanisms including oxidative stress, mitochondrial dysfunction, apoptosis, inflammation, and fibrosis, leading to acute kidney injury and progression to chronic kidney disease. Conventional mitigation strategies remain limited, prompting growing interest in plantderived secondary metabolites with multitargeted protective effects. *Boerhavia diffusa* Linn. (Punarnava), a traditional herb, has demonstrated nephroprotective potential through its diverse phytoconstituents such as *boeravinones, punarnavine*, flavonoids, saponins, and phenolic acids. These compounds modulate key signaling pathways including Nuclear Factor Erythroid 2Related Factor 2/ Antioxidant Response Elements (Nrf2/ARE), Nuclear Factor Kappa B (NFκB), MitogenActivated Protein Kinase, Phosphoinositide 3Kinase/ Protein Kinase B (MAPK, PI3K/Akt), and Transforming Growth Factor Beta (TGFβ/Smad), thereby attenuating oxidative damage, suppressing inflammation, regulating apoptosis, and reducing fibrosis. This review synthesizes mechanistic insights into druginduced nephrotoxicity and highlights the translational relevance of *B. diffusa* as a multitarget nephroprotective agent.

Key words: Kidney, Nephroprotection, NFκb, MAPK, Nrf2/ARE, PI3K/Akt, TGFβ/Smad.

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INTRODUCTION

Druginduced nephrotoxicity remains a main clinical problem, because, kidney is highly susceptible to xenobiotic injury having its role in drug metabolism and excretion. Renal damage is commonly caused by therapeutic drugs such as cisplatin, aminoglycosides, streptozotocin, NSAIDs, antivirals, methotrexate, calcineurin inhibitors, and radiocontrast agents, through diverse mechanisms such as oxidative stress, mitochondrial dysfunction, apoptosis of Renal tissue, inflammation of tubules, crystal deposition, and fibrosis of the renal parenchyma (Pabla *et al*., 2008; Manohar *et al*., 2018; Gumbar *et al*., 2023; Li *et al*., 2024; Pansare *et al*., 2025; Khatlan *et al*., 2024). All these clinical conditions are manifested as Acute Renal failure, proteinuria, electrolyte imbalances, leading to Chronic Kidney Disease (CKD), frequently resulting in treatment complications and finally limit the usage of drugs (Ahsan *et al*., 2025; Rodríguez-Novoa *et al*., 2010; Widemann *et al*., 2006).

Therefore, it is crucial to mitigate nephrotoxicity in order to maintain renal function and to guarantee safe and efficient medication. Partial protection is offered by traditional methods like dose modification and hydration, although natural compounds and secondary metabolites with anti-inflammatory, anti-fibrotic, and antioxidant qualities are receiving more attention (Howard *et al*., 2016, Nageh *et al*., 2025, Persson *et al*., 2005). Plant-derived drugs have demonstrated potential in reversing drug-induced kidney impairment by altering important signaling pathways, such as Nrf2/ARE, NF κB, MAPK, PI3K/Akt, and TGF β/Smad (Cho *et al*., 2022; Patel *et al*., 2024).

Among these, the popular Ayurvedic medicinal herb *B. diffusa* Linn. (*Punarnava*) (Figure 2) has become a powerful nephroprotective agent (Kaur, 2019). The phytoconstituents *boerhavinones, punarnavine*, flavonoids, and saponins present in *B. diffusa* Linn. Scavenge free radicals, reduce inflammatory mediators, modulate apoptosis, and attenuate fibrosis to provide protective benefits (Varsha *et al*., 2025; Oseni *et al*., 2024; Patel *et al*., 2025; Nayak *et al*., 2016; Yadav *et al*., 2024).

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Since it enables the logical incorporation of phytochemicals into nephroprotective methods and offers translational insights for clinical application, an understanding of these pathways is essential. Thus, the purpose of this review is to build a framework connecting pharmacological impairment with phytochemical intervention, define the molecular basis of drug-induced nephrotoxicity, and emphasize the protective role of *B. diffusa* and its secondary metabolites. This study aims to increase awareness on *Punarnava's* function in reducing kidney damage and guiding the development of new treatments by integrating mechanistic toxicology and ethnopharmacology.

METHODOLOGY

The extensive literature search was carried out in the largest scientific databases such as PubMed, Scopus, Web of Science, and Google Scholar. The keywords used to search included the combinations of the following terms: *Boerhavia diffusa, Punarnava*, nephrotoxicity, nephroprotection, oxidative stress, Nrf2/ARE, NF-kB, MAPK, PI3K/Akt, and TGF-b/Smad. The inclusion criteria were limited to peer-reviewed research that examined the molecular pathways of the drug-induced kidney injury and the nephroprotective properties of the plant-based phytochemicals. To combine the traditional knowledge with the evidence of modern mechanisms, ethnopharmacological surveys as well as analytical studies on *Boerhavia diffusa* were also taken into account.

REVIEW OF LITERATURE

Phytochemistry of *Punarnava*

In Ayurveda and ethnomedicine, *Boerhavia diffusa* Linn. is a well-known medicinal plant with a variety of therapeutic uses, especially for renal conditions (Wudali *et al.*, 2020). Modern analytical methods like GC-MS and thorough phytochemical profiling, which uncover a wide range of bioactive ingredients, have validated its phytochemical richness (Juneja *et al.*, 202).

B. diffusa leaf extract was found to contain flavonoids and alkaloids, particularly punarnavine, a quinolizidine alkaloid. According to qualitative and quantitative GC-MS analysis (Saraswati *et al.*, 2013; Rai *et al.*, 2024), phenolic acids, terpenoids, sterols, saponins, and other secondary metabolites are present in various extracts of *B. diffusa* that add to its therapeutic value, as well as rotenoids/lignans, specifically boeravinones A-H (Chaudhary *et al.*, 2011, Wang *et al.*, 2023; Bhattarai *et al.*, 2024; Kumar *et al.*, 2025) (Table 1). Ethnomedicinal surveys among indigenous communities in the Indian subcontinent further highlight the plant's traditional use in kidney ailments, edema, and inflammatory conditions, attributing these effects to its phytochemical diversity (Pandey, 2025; Ahmed *et al.*, 2024). These compounds are mechanistically linked to antioxidant, anti-inflammatory, anti-apoptotic, and anti-fibrotic activities (Gaur, 2022; Santhosh *et al.*, 2023).

Drug Induced Nephrotoxicity

Diverse substances that cause renal damage through overlapping mechanisms can lead to drug-induced nephrotoxicity. Here, a few mechanisms have been described (Figure 1). Cisplatin, a popular chemotherapeutic medicine (Figure 3), disrupts the functions of the endoplasmic reticulum and mitochondria and causes oxidative stress damaging proximal convoluted tubules. This causes DNA adhesion formation, reactive oxygen species generation, inflammatory cytokine release, and renal tubule necrosis, which can result in Acute Kidney Injury (AKI) or chronic kidney injury (Miller *et al.*, 2010; Tang *et al.*, 2023). Gentamicin, an aminoglycoside on accumulation in lysosomes of renal tissue causes Tubular necrosis and ultimately renal impairment, which activates phospholipids and produces reactive oxygen species (Gumbar *et al.*, 2023). Streptozotocin, a chemotherapeutic agent commonly used in research to induce diabetes in rats, causes glomerular damage through oxidative stress and advanced glycation end products resulting from hyperglycemia, ultimately leading to diabetic nephropathy (Li *et al.*, 2024; Pansare *et al.*, 2025). Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) reduce prostaglandin synthesis, lower renal blood flow, and heighten the likelihood of ischemic injury, which can lead to necrosis of the renal papilla (Ahsan *et al.*, 2025). Antivirals such as tenofovir and acyclovir are associated with mitochondrial toxicity and crystal nephropathy, manifesting as obstructive tubular injury and chronic dysfunction (Rodríguez-Novoa *et al.*, 2010). Methotrexate, particularly at high doses, can precipitate within renal tubules causing crystal nephropathy and direct tubular toxicity, which delays drug clearance and leads to systemic toxicity (Howard *et al.*, 2016). Calcineurin inhibitors (cyclosporine, tacrolimus) induce vasoconstriction, endothelial dysfunction, and interstitial fibrosis, contributing to chronic nephrotoxicity (Nageh *et al.*, 2025). Radiocontrast agents precipitate acute tubular injury through oxidative stress, vasoconstriction, and TLR4/MyD88mediated inflammation (Cho *et al.*, 2022).

Antiviral medications like tenofovir and acyclovir are associated with mitochondrial toxicity and crystal nephropathy, manifesting as obstructive tubular injury and chronic dysfunction. Methotrexate, particularly in higher doses, can precipitate within renal tubules, causing crystal nephropathy and direct toxicity to the tubules, which hinders drug clearance and results in systemic toxicity. Calcineurin inhibitors lead to vasoconstriction, endothelial dysfunction, and interstitial fibrosis, all of which contribute to chronic nephrotoxicity. Radiocontrast agents can cause acute tubular injury.

Mechanisms of Nephroprotection

Nrf2/ARE signaling in Nephroprotection

Nrf2 inhibit lipid peroxidation and regain the antioxidant enzyme activity in gentamicin induced renal failure proved to recover the activity of SOD and catalase (Das *et al.*, 2023)

(Figure 1). Nrf2 is a transcription factor that is usually bound by Keap1 at the cytoplasm, which facilitates its ubiquitination and degradation by proteasomes (Lin *et al.*, 2023). On the exposure of phytochemicals or oxidative stress Nrf2 dissociates with Keap1 and translocates to the nucleus (Nezu *et al.*, 2020). Nrf2 binding to Antioxidant Response Elements (AREs) and activating HO 1 and NQO1 genes is found in the nucleus (Guerrero-Hue *et al.*, 2020; Hafez *et al.*, 2019). This signaling pathway improves antioxidants, decreases ROS and prevents oxidative damage in renal tissue (Molaei *et al.*, 2021).

Activators of Nrf2 have been well established to be natural products such as flavonoids and phenolic acids (Mohan *et al.*, 2020). Phytochemicals stimulating the Nrf2 signaling pathway with subsequent HO 1 and NQO1 upregulation have been reported in *B. diffusa*, including *quercetin* derivatives, caffeic acid, and *boeravinones* (Santhosha *et al.*, 2021).

NFκB signaling in Nephroprotection

NFκB is a transcription factor which is normally held in the cytoplasm by inhibitory proteins (IkBs), inhibiting its nuclear activity (White *et al.*, 2020). IkB is phosphorylated, degraded upon stress signal stimulation (via ROS, cytokines or by TOLL-like receptors) and NFκB (p65/p50) translocate into the nucleus (Na *et al.*, 2024). NFκB also binds to kB response elements in the nucleus and transcription of pro-inflammatory mediators such as TNFα, IL-6, COX-2, and adhesion molecules (Altindag, 2022). This signaling cascade intensifies inflammation, directly stimulates renal fibrosis, and increases the speed of nephrotoxic damage

Natural substances, like *umbelliferone, sulbutiamine, silymarin, kaempferol,* and *berberine*, have been found to inhibit the action of NFκB, thus decreasing the release of cytokines and preserving renal tissue (Ali *et al.*, 2021; Ghaiad *et al.*, 2023; Alshehri *et al.*, 2022; Zhu *et al.*, 2018). There are claims of phytochemicals in *Boerhavia diffusa* like *punarnavine, boeravinones*, flavonoids and saponins to inhibit NF kB signaling resulting in reduced TNFα and IL-6 expression. These substances inhibit inflammatory processes and recover renal activity in models of cisplatin and gentamicin induced nephrotoxicity.

MAPK signaling in Nephroprotection

The Mitogen-Activated Protein Kinase (MAPK) signaling pathway is a key regulator of cellular stress responses that mediate inflammation, apoptosis and fibrosis in chronic kidney disease. MAPKs, including p38, JNK, and ERK, are activated in response to oxidative stress and nephrotoxic insults, which results in the activation of pro-inflammatory cytokines and pro- apoptotic genes transcription (Zhang *et al.*, 2018; Jiang *et al.*, 2020). This signaling cascade is involved in tubular damage, glomerulosclerosis and diabetic and toxic nephropathy progression.

Natural antioxidants have been found to regulate the MAPK activity and thus safeguard the renal tissue. As an example, *Fangchinoline* mitigates the effect of diabetic nephropathy by inhibiting the MAPK signaling pathways and renal inflammation. Salvianolic acid A prevents kidney disease in nephrectomized rats with 5/6 kidneys and suppresses NFκB and p38 MAPK intricate. *Mangiferin* prevents cisplatin-induced acute kidney injury by regulating MAPK signaling, inhibiting apoptosis and oxidative stress (Sahu *et al.*, 2019). Correspondingly, an isoflavone dietary antioxidant called daidzein reduces oxidative, apoptotic, and inflammatory response of cisplatin-induced nephrotoxicity by regulating the MAPK pathway (Tomar *et al.*, 2020).

PI3K/Akt Signaling in Nephroprotection

The phosphoinositide 3kinase PI3K/Akt signaling is one of the main regulators of cell survival, metabolic response and stress in renal tissue. The PI3K, on activation, phosphorylates Akt, which then regulates downstream targets, including mTOR and GSK3b, facilitating anti apoptotic signaling and cellular resilience (Liu *et al.*, 2015). The dysregulation of this pathway can also be found to cause apoptosis, inflammation, and nephrotoxicity progression in ischemic and diabetic models (Hasan *et al.*, 2020).

Natural compounds have also shown nephroprotective effect by the regulation of PI3K/Akt signaling. Activation of PI3K/Akt during ischemia/reperfusion injury suppressed oxidative stress and apoptosis, and polydatin inhibited these phenomena. Extracts of *Celastrus paniculatus* attenuate the lead acetate induced nephrotoxicity through PI3K/Akt activation, which regains the renal architecture and function (Balaji *et al.*, 2021). *Phillygenin* enhances diabetic nephropathy by suppressing inflammatory diseases and apoptosis by regulating TLR4/MyD88/ NFκB and PI3K/Akt/ GSK3β-signaling (Feng *et al.*, 2025). *Quercetin* also protects the kidneys during ischemia/reperfusion injury through the Akt/mTOR axis and consequently the apoptosis and oxidative injury. Likewise, andrographolide is a multi-target therapeutic agent that has a protective effect on diabetic nephropathy and its mechanism is mediated by changes in the pathways of STAT3 and PI3K/Akt (Yin *et al.*, 2025).

TGFβ/Smad Signaling in Nephroprotection

A key mediator of renal fibrosis and Epithelial to Mesenchymal Transition (EMT) is the transforming growth factor β) TGFβ/ Smad pathway. When activated, the TGF β attaches to receptors and the Smad2/3 are phosphorylated and translocate to the nucleus and activate the transcription of pro fibrotic genes including collagen and fibronectin. This signaling pathway facilitates extracellular matrix, tubular atrophy and transition of acute kidney injury to chronic kidney disease (Zou *et al.*, 2025).

Attack on TGF β /Smad signaling has proven to alleviate the effects of fibrosis and to recover renal function. *Azilsartan* improves nephroprotective properties of adipose tissue derived

Table 1: Phytochemical Classes and Mechanistic Roles of *Boerhavia diffusa* Constituents in Nephroprotection.

Class	Representative Compounds	Plant Part / Extract	Analytical Method	Mechanistic / Therapeutic Relevance
Alkaloids	Punarnavine	Root, leaf	Phytochemical screening, FTIR	Anti-inflammatory, immunomodulatory, nephroprotective
Rotenoids / Lignans	Boeravinones A-H	Root	GC-MS, LC-MS	Antioxidant, anti-apoptotic, anti-fibrotic
Flavonoids	Quercetin, kaempferol derivatives	Leaf	GC-MS, FTIR	ROS scavenging, cytoprotection
Phenolic acids	Caffeic acid, hydroxycinnamates	Leaf	GC-MS	Nrf2 activation, antioxidant defense
Saponins	Steroidal saponins	Whole plant	Phytochemical screening	Anti-fibrotic (↓ TGFβ/Smad), immunomodulatory
Terpenoids and Sterols	Stigmasterol, β-sitosterol	Leaf	GC-MS	Anti-inflammatory, membrane stabilizing
Lipids and Fatty acids	Palmitic acid, linoleic acid	Leaf	GC-MS	Energy metabolism, membrane roles
Carbohydrates and Glycoproteins	Polysaccharides, glycoprotein fractions	Whole plant	Phytochemical screening	Supportive metabolic and immunomodulatory roles
Proteins	Bioactive protein fractions	Whole plant	Phytochemical screening	Structural and enzymatic roles
Other metabolites	Amino acids, sugars	Leaf/root	Phytochemical screening	Supportive metabolic roles

mesenchymal stem cells (AT-MSCs) against cisplatin triggered EMT by inhibiting oxidative stress and preventing TGF β /Smad stimulation at the same time. *Rhubarb* prevents tubulointerstitial fibrosis in chronic kidney disease by suppressing TGF β /Smad signaling and restoring abnormal metabolomic changes (Fawzy *et al*., 2023). *Chrysophanol* also alleviates interstitial fibrosis in the kidney by inhibiting the TGF β /Smad pathway, which diminishes the collagen accumulation and scarring of tissues (Zhang *et al*., 2018).

Suppression of Caspase Mediated Apoptosis in Nephrotoxicity

Apoptosis is a highly controlled form of cellular homeostasis, which may cause tubular cell death and nephrotoxicity progression when over-activated in the renal tissue. Mitochondrial dysfunction and caspase-9 activation are caused by the intrinsic pathway, which is mediated by cytochrome c release, whereas death receptor signaling and caspase-8 activation are caused by the extrinsic one. Both of them converge to caspase-3, which leads to fragmentation of DNA and programmed cell death (Zou *et al*., 2025).

The Bcl-2/Bax ratio is a determining factor of mitochondrial integrity. Anti apoptotic Bcl 2 stabilizes the mitochondrial membrane and inhibits the release of cytochrome c, but pro apoptotic Bax facilitates the mitochondrial outer Membrane Permeabilization (MOMP) and apoptosis. There are also changes of Bax dominance in nephrotoxic model which results in mitochondrial dysfunction and tubular injury (Palabiyik AA 2025; Saddam *et al*., 2024).

Pharmacological agents and natural compounds have been demonstrated to reduce the apoptosis in models of kidney injury. *Azilsartan* increases the nephroprotective ability of Adipose Tissue derived Mesenchymal Stem Cells (AT-MSCs) in cisplatin induced EMT by decreasing oxidative stress and inhibiting apoptotic process via regulating TGFβ /Smad signaling. *Rhubarb* prevents tubulointerstitial fibrosis in chronic kidney disease by inhibiting apoptosis in addition to suppressing TGFβ /Smad signaling (Zhang *et al*., 2018). *Chrysophanol* suppresses renal interstitial fibrosis by attenuating pro apoptotic genes and by preventing Smad-dependent transcription (Dou *et al*., 2020).

Phytochemicals including *boeravinones, punarnavine* and *quercetin* analogs have been suggested to elevate Bcl-2 and decrease Bax in *B. diffusa* to preserve mitochondrial integrity and minimize caspase 3 activation (Mayurya *et al*., 2023).

TLR4/MyD88/NFκB Signaling in Nephroprotection

Toll like receptor 4 (TLR4)/MyD88/ NFκB pathway is a mediator of innate immune responses in the kidney. When TLR4 is triggered by danger signals (lipopolysaccharide, contrast agents

or oxidative stress), MyD88, an adaptor protein, targets the TLR4 and triggers downstream phosphorylation cascades leading to the activation of NFκB. This triggers the pro inflammatory cytokines such as TNFα, IL-1 β and IL-6 transcription, and worsens renal inflammation and is one of the causes of tubular injury and fibrosis (Wang *et al.*, 2020; Yue *et al.*, 2017).

Kidney injury inhibited with the help of natural compounds and pharmacological agents was demonstrated to affect this pathway. Indicatively, *Phillygenin* enhances diabetic nephropathy by suppressing inflammatory and apoptotic processes by modulating TLR4/MyD88/ NFκB and PI3K/Akt/GSK3 β signaling. Atorvastatin decreases contrast induced acute kidney injury by inhibiting TLR4/MyD88 signaling, which inhibits the release of cytokines and oxidative stress (Yue *et al.*, 2017). Inflammatory kidney injury induced by lipopolysaccharide is prevented by Dioscin through the microRNA let-7i/TLR4/MyD88 pathway, which revealed the involvement of microRNA regulation in nephroprotection (Qi *et al.*, 2016).

Other phytochemicals including *boeravinones and punarnavine* have been reported to inhibit TLR4/MyD88/NF signaling in *B. diffusa*, which suppresses the expression of pro inflammatory cytokines and has been shown to improve renal function in nephrotoxic models (Pal *et al.*, 2025; Mishra *et al.*, 2014).

Risk Factors for DrugInduced Nephrotoxicity

Patient and treatment related risk factors are very strong determinants of the severity of drug induced nephrotoxicity. Old age, renal impairment that exists beforehand, diabetes, and hypertension predispose to the renal injury. Cumulative dosage, long term treatment and combination with other nephrotoxic agents increase risk further. Patients are also vulnerable to acute kidney injury due to such clinical conditions as dehydration, sepsis, or perioperative stress. Inter individual differences in renal toxicity could be attributed to genetic variation in the metabolism of drugs and the activity of drug transporters. The need to identify these risk factors is fundamental in customizing preventive measures and the need to consider adjunctive nephroprotective measures like *B. diffusa* in the vulnerable groups.

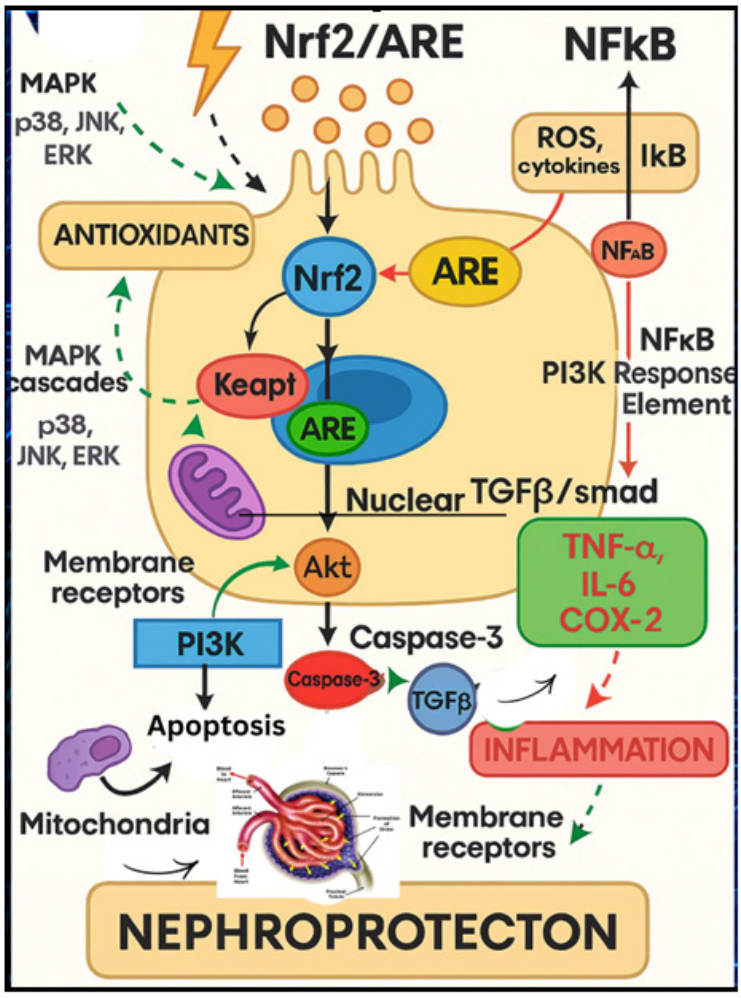

Figure 1: Mechanism of Nephrotoxicity.

Figure 2: Image of the plant *B. diffusa*.

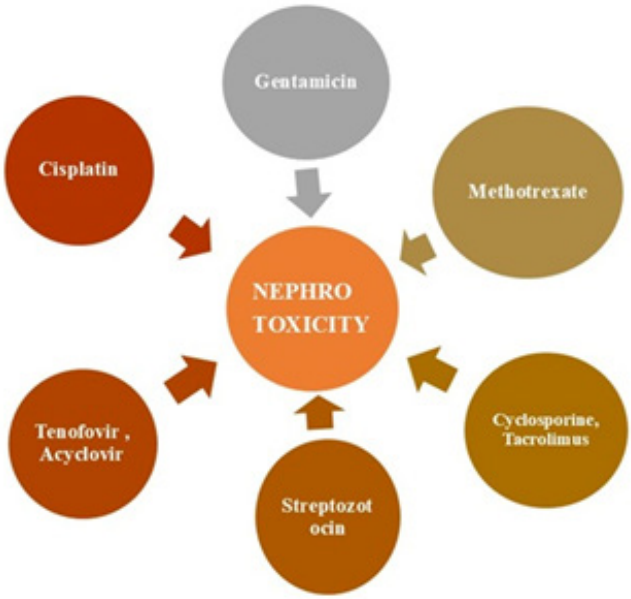

Figure 3: Drug induced Nephrotoxicity.

CONCLUSION

Drug induced nephrotoxicity reflects the convergence of multiple pathological signals, making singletarget interventions insufficient for durable renal protection. Thus, *Boerhavia diffusa* (*Punarnava*), with its diverse phytoconstituents, offers coordinated protection by enhancing antioxidant defenses, suppressing inflammation, preserving mitochondrial integrity, and limiting fibrosis. This multitargeted activity validates traditional claims and highlights *Punarnava's* translational potential as a model plant for nephroprotection.

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ABBREVIATIONS

AKI: Acute Kidney Injury; **ARE:** Antioxidant Response Elements; **AT-MSCs:** Adipose Tissue Derived Mesenchymal Stem Cells; **Bax:** Bcl-2 Associated X Protein; **Bcl-2:** B Cell Lymphoma 2; **CKD:** Chronic Kidney Disease; **COX-2:** Cyclooxygenase 2; **EMT:** Epithelial to Mesenchymal Transition; **ERK:** Extracellular Signal Regulated Kinase; **FTIR:** Fourier Transform Infrared Spectroscopy; **GC-MS:** Gas Chromatography-Mass Spectrometry; **GSK3β:** Glycogen Synthase Kinase 3 Beta; **HO-1:** Heme Oxygenase 1; **IL-6:** Interleukin 6; **IκB:** Inhibitor of κB; **JNK:** c-Jun N-Terminal Kinase; **MAPK:** Mitogen Activated Protein Kinase; **MOMP:** Mitochondrial Outer Membrane Permeabilization; **mTOR:** Mammalian Target of Rapamycin; **MyD88:** Myeloid Differentiation Primary Response 88; **NF-κB:** Nuclear Factor Kappa B; **NQO1:** NAD(P)H Quinone Dehydrogenase 1; **NSAIDs:** Nonsteroidal Anti-Inflammatory Drugs; **Nrf2:** Nuclear Factor Erythroid 2 Related Factor 2; **PI3K:** Phosphoinositide 3 Kinase; **ROS:** Reactive Oxygen Species; **SOD:** Superoxide Dismutase; **STAT3:** Signal Transducer and Activator of Transcription 3; **TGF-β:** Transforming Growth Factor Beta; **TLR4:** Toll Like Receptor 4; **TNF-α:** Tumor Necrosis Factor Alpha.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUTURE DIRECTIONS

Although *Boerhavia diffusa* exhibits considerable multi-target nephroprotective effects, there is a considerable gap in the literature focus on the simple standardization of phytoconstituent extractions of the plant to be used in clinical practice. Meeting this promise requires the next step, which is to perform large-scale dose-response research and adequately designed, large-scale clinical trials. These are important to transform *B. diffusa* into evidence-based clinical practice of reducing drug-induced renal injury rather than the traditional ethnomedicine.

SUMMARY

All the evidence that has been collected thus far demonstrates that drug induced nephrotoxicity is not a process that has only one pathway but an active interaction of oxidative, inflammatory, apoptotic, and fibrotic signals. Such complexity portrays the importance of interventions that are broader as opposed to narrow. In this respect, *B. diffusa* is a unique example, with its wide range of phytoconstituents, *punarnavine, boeravinones*, flavonoids and saponins acting at more than ten molecular entry points, demonstrating a multifactorial response that resembles the multifactorial nature of renal injury. This review places *B.*

diffusa at the interface of the traditional ethnomedicine and recent mechanistic studies and preconditions the emergence of the translational usefulness of this model plant in terms of multi target nephroprotection.

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