Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 370-376 | ISSN:2251-6727

To Investigate the Nephroprotective Activity of Plant-Derived Alkaloids Against Drug-Induced Kidney Injury

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(Received: 05 January 2026 Revised: 15 February 2026 Accepted: 05 March 2026)

KEYWORDS

Plant- derived alkaloids, Nephroprot ection, Drug- induced kidney injury, Oxidative stress, Renal toxicity, Antioxidan t activity, Inflammati on, Kidney function

ABSTRACT:

Drug-induced kidney injury is a common side effect of many medicines such as antibiotics, painkillers, and anticancer drugs. It mainly occurs due to oxidative stress, inflammation, and damage to kidney cells, which leads to reduced kidney function.

The aim of this study is to investigate the nephroprotective activity of plant-derived alkaloids against drug-induced kidney injury. Plant alkaloids are known for their antioxidant and anti- inflammatory properties, which may help protect kidney tissues from damage.

In this study, selected plant-derived alkaloids are evaluated for their protective effects on kidney function. Their activity is assessed by measuring biochemical markers such as serum creatinine and blood urea nitrogen, along with oxidative stress parameters and histopathological changes in kidney tissue.

The findings suggest that plant-derived alkaloids may reduce oxidative stress, decrease inflammation, and protect kidney structure and function from drug-induced damage.

Thus, plant-derived alkaloids may serve as promising natural agents for preventing and managing drug-induced kidney injury.

1. Introduction

The kidney is an essential organ responsible for maintaining physiological homeostasis through filtration of blood, removal of metabolic waste, regulation of fluid and electrolyte balance, acid–base equilibrium, and detoxification of endogenous and exogenous substances. Due to its high blood flow, active transport systems, and role in drug metabolism and excretion, the kidney is particularly vulnerable to toxic injury caused by pharmacological agents **(Perazella, 2019)**.

Drug-induced kidney injury (DIKI) has emerged as a significant contributor to acute kidney injury (AKI) and is responsible for approximately 20–30% of AKI cases globally **(Perazella, 2019)**. A wide range of commonly used therapeutic drugs are associated with nephrotoxicity. These include chemotherapeutic agents such as cisplatin, aminoglycoside antibiotics like gentamicin, non-steroidal anti-inflammatory drugs (NSAIDs), and excessive doses of widely used analgesics such as paracetamol **(Yuan et al., 2020)**. The nephrotoxic effects of these drugs are mediated through multiple pathological mechanisms including oxidative stress, mitochondrial dysfunction, inflammatory responses, and apoptosis of renal tubular epithelial cells **(Zhang et al., 2018; Yang et al., 2020)**.

Oxidative stress plays a central role in drug-induced renal injury by increasing the production of reactive oxygen species (ROS), which leads to lipid peroxidation, protein damage, and DNA injury **(Zhang et al., 2018)**. Additionally, inflammatory pathways involving cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins contribute significantly to the progression of renal damage **(Liu et al., 2019)**. Persistent injury may ultimately impair renal function, leading to elevated serum creatinine and blood urea nitrogen levels, which are hallmark indicators of kidney dysfunction **(Yuan et al., 2020)**.

In recent years, there has been growing interest in the use of natural products as protective agents against organ toxicity. Among these, plant-derived alkaloids have gained considerable attention due to their diverse

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JCHR (2026) 16(2), 370-376 | ISSN:2251-6727

pharmacological properties including antioxidant, anti-inflammatory, anti-apoptotic, and cytoprotective effects **(Khan et al., 2021)**. Alkaloids such as berberine, piperine, and tetrandrine have demonstrated significant potential in mitigating drug-induced renal damage in experimental studies by reducing oxidative stress and preserving renal structural integrity **(Imenshahidi & Hosseinzadeh, 2019)**.

Therefore, plant-derived alkaloids represent promising therapeutic candidates for the prevention and management of drug-induced kidney injury. Understanding their protective mechanisms may contribute to the development of safer and more effective nephroprotective strategies.

2. Drug-Induced Kidney Injury: Pathophysiology

Drug-induced kidney injury (DIKI) is a complex process involving multiple interrelated cellular and molecular mechanisms that ultimately impair renal structure and function. Nephrotoxic drugs such as cisplatin, aminoglycosides, NSAIDs, and certain chemotherapeutic agents initiate a cascade of pathological events that damage renal tubular cells and compromise kidney filtration capacity **(Yuan et al., 2020)**.

The major mechanisms involved in drug-induced nephrotoxicity include oxidative stress, inflammation, apoptosis, and mitochondrial dysfunction.

2.1 Oxidative Stress

Oxidative stress is one of the primary mechanisms of renal injury. Many nephrotoxic drugs increase the production of reactive oxygen species (ROS), which overwhelm the endogenous antioxidant defense system. This leads to lipid peroxidation, protein oxidation, and DNA damage, resulting in cellular dysfunction and structural injury to renal tissues **(Zhang et al., 2018)**.

2.2 Inflammation

Nephrotoxic agents stimulate inflammatory pathways by activating immune mediators and cytokines. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) play a crucial role in promoting renal inflammation, tissue damage, and fibrosis **(Liu et al., 2019)**.

2.3 Apoptosis

Drug-induced toxicity can trigger programmed cell death (apoptosis) in renal tubular epithelial cells. This process involves activation of apoptotic signaling pathways that lead to structural damage and loss of functional kidney cells **(Yang et al., 2020)**.

2.4 Mitochondrial Dysfunction

Mitochondria are essential for ATP production and cellular energy balance. Nephrotoxic drugs impair mitochondrial function, reducing ATP synthesis and increasing oxidative damage. This results in energy depletion and eventual renal tissue injury **(Yuan et al., 2020)**.

Table-1

3. Plant-Derived Alkaloids

Alkaloids are naturally occurring nitrogen-containing secondary metabolites widely present in medicinal plants. They exhibit diverse pharmacological properties uch as antioxidant, anti-inflammatory, anti-apoptotic, and cytoprotective activities. These biological effects make them promising candidates for protecting renal tissues against drug-induced damage.

Several plant-derived alkaloids have demonstrated significant nephroprotective effects in experimental models of kidney injury by reducing oxidative stress, suppressing inflammation, and preserving renal structure and function **(Imenshahidi & Hosseinzadeh, 2019)**.

Table-2

4. Mechanisms of Nephroprotection

Plant-derived alkaloids protect renal tissues against drug-induced injury through multiple interconnected molecular and cellular pathways. Their nephroprotective action is mainly attributed to antioxidant defense enhancement, suppression of inflammatory responses, inhibition of apoptosis, and preservation of mitochondrial function.

4.1 Antioxidant Action

Oxidative stress is a primary driver of drug-induced kidney injury. Many nephrotoxic drugs increase the generation of reactive oxygen species (ROS), which

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JCHR (2026) 16(2), 370-376 | ISSN:2251-6727

damage cellular lipids, proteins, and DNA, ultimately leading to renal dysfunction.

Plant-derived alkaloids play a crucial role in combating oxidative stress by:

i. Scavenging excess ROS
ii. Inhibiting lipid peroxidation
iii. Enhancing endogenous antioxidant defense systems

These compounds significantly upregulate key antioxidant enzymes such as:

1. **Superoxide dismutase (SOD)** – neutralizes superoxide radicals
2. **Catalase** – decomposes hydrogen peroxide into water and oxygen
3. **Glutathione (GSH)** – protects against oxidative cellular damage

By restoring the antioxidant balance, alkaloids help maintain cellular integrity and prevent oxidative injury to renal tubular cells **(Bhardwaj & Verma, 2020; Zhang et al., 2018)**.

Table 3: Antioxidant Mechanism of Plant Alkaloids in Nephroprotection

4.2 **Anti-Inflammatory Action**

Inflammation plays a central role in the progression of drug-induced kidney injury. Nephrotoxic drugs stimulate the release of pro-inflammatory cytokines, which amplify renal damage.

Plant-derived alkaloids help suppress inflammation by:

i. Inhibiting pro-inflammatory cytokines such as:
1. Tumor necrosis factor-alpha (TNF-α)
2. Interleukin-1 beta (IL-1β)
3. Interleukin-6 (IL-6)
ii. Reducing immune cell infiltration into renal tissues
iii. Preventing inflammatory signaling pathways

By controlling inflammatory responses, alkaloids minimize tissue damage and prevent the progression of renal dysfunction **(Liu et al., 2019)**.

Table 4: Anti-Inflammatory Effects of Plant Alkaloids

4.3 Anti-Apoptotic Action

Apoptosis, or programmed cell death, is a major mechanism involved in drug- induced renal toxicity.

Plant alkaloids exert anti-apoptotic effects by:

i. Inhibiting activation of apoptotic pathways
ii. ii. Preventing renal tubular cell death
iii. Stabilizing cellular survival signaling mechanisms

This helps maintain renal cellular structure and prevents functional deterioration **(Yang et al., 2020)**.

Table 5: Anti-Apoptotic Role of Alkaloids

4.4 Mitochondrial Protection

Mitochondrial dysfunction is a critical factor in nephrotoxicity, as it leads to reduced ATP production and increased oxidative stress.

Plant-derived alkaloids help maintain mitochondrial health by:

i. Protecting mitochondrial membrane integrity
ii. Enhancing A TP synthesis
iii. Reducing mitochondrial ROS production

This ultimately preserves renal cellular energy balance and prevents tissue damage **(Yuan et al., 2020).**

Table 6: Mitochondrial Protective Mechanisms

5. Histopathological Protection

Histopathological studies provide structural evidence of renal protection offered by plant- derived alkaloids in drug-induced kidney injury models. These compounds play a crucial role in maintaining the integrity of renal tissues by minimizing structural damage caused by nephrotoxic agents.

Experimental findings suggest that alkaloids contribute to:

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1. Prevention of tubular necrosis
2. Reduction of glomerular damage
3. Preservation of overall renal architecture

By protecting renal tubules and glomeruli from degeneration, alkaloids help maintain normal kidney morphology and functional stability **(Yang et al., 2020)**.

Table 7: Histopathological Protective Effects of Alkaloids

6. Conclusion

Plant-derived alkaloids demonstrate significant protective effects against drug-induced kidney injury through their antioxidant, anti-inflammatory, and anti-apoptotic properties. By reducing oxidative stress, suppressing inflammatory responses, and preventing renal cell damage, these natural compounds help preserve kidney structure and function.

Overall, plant-derived alkaloids represent promising therapeutic agents for nephroprotection. However, further clinical studies are required to validate their safety, efficacy, and potential application in the prevention and management of drug-induced kidney injury.

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Table-1

Mechanism	Pathological Effect	Outcome on Kidney Function	References
Oxidative Stress	Increased ROS, lipid peroxidation, DNA damage	Tubular injury and cell dysfunction	Zhang et al., 2018
Inflammation	Activation of TNF-α, IL-1β, IL-6	Renal inflammation and fibrosis	Liu et al., 2019
Apoptosis	Programmed cell death of tubular cells	Loss of renal structural integrity	Yang et al., 2020
Mitochondrial Dysfunction	Reduced ATP production and energy imbalance	Renal tissue injury	Yuan et al., 2020

Table-2

S.NO.	Alkaloid	Source Plant	Nephrotoxic Drug Model	Protective Mechanism	Evidence / Outcome	Reference

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1	Berberine	*Berberis vulgaris*	Cisplatin	Antioxidant & anti-inflammatory	Reduced oxidative stress & serum creatinine	Imenshahidi & Hosseinzadeh, 2019
2	Piperine	*Piper nigrum*	Gentamicin	ROS inhibition & cytoprotection	Improved renal antioxidant defense	Khan et al., 2021
3	Tetrandrine	*Stephania tetrandra*	Cisplatin	Anti-inflammatory & anti-apoptotic	Reduced tubular necrosis	Zhou et al., 2020
4	Boldine	*Peumus boldus*	NSAIDs	Free radical scavenging	Preserved renal histology	Bhardwaj & Verma, 2020
5	Palmatine	*Coptis chinensis*	Cisplatin	Anti-inflammatory & antioxidant	Reduced renal inflammation	Liu et al., 2019
6	Magnoflorine	*Tinospora cordifolia*	Gentamicin	Anti-apoptotic	Prevented renal cell death	Yang et al., 2020
7	Sinomenine	*Sinomenium acutum*	Cisplatin	Anti-inflammatory	Decreased cytokine levels	Zhou et al., 2020
8	Harmine	*Peganum harmala*	Paracetamol overdose	Antioxidant	Reduced lipid peroxidation	Zhang et al., 2018
9	Colchicine	*Colchicum autumnale*	Drug-induced fibrosis model	Anti-inflammatory & anti-fibrotic	Reduced renal fibrosis	Khan et al., 2021
10	Vinpocetine	*Vinca minor*	Ischemic renal injury	Cytoprotective	Improved renal function markers	Bhardwaj & Verma, 2020
11	Sanguinarine	*Sanguinaria canadensis*	Cisplatin	Antioxidant & anti-inflammatory	Reduced ROS and renal inflammation	Zhang et al., 2018
12	Chelerythrine	*Chelidonium majus*	Gentamicin	Anti-apoptotic	Prevented tubular cell apoptosis	Yang et al., 2020

Table 3: Antioxidant Mechanism of Plant Alkaloids in Nephroprotection

Mechanism	Effect on Kidney Cells	Outcome	Reference
ROS Scavenging	Reduces oxidative damage	Protects renal tissue	Zhang et al., 2018
Increased SOD Activity	Neutralizes free radicals	Prevents cellular injury	Bhardwaj & Verma, 2020

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Catalase Activation	Breaks down hydrogen peroxide	Reduces oxidative stress	Khan et al., 2021
Glutathione Enhancement	Improves cellular defense	Maintains renal function	Yang et al., 2020

Table 4: Anti-Inflammatory Effects of Plant Alkaloids

Mechanism	Effect on Kidney Tissue	Outcome	Reference
TNF-α Suppression	Reduces inflammatory response	Prevents renal injury	Liu et al., 2019
IL-1β Inhibition	Limits cytokine-mediated damage	Protects tubular cells	Khan et al., 2021
IL-6 Reduction	Prevents fibrosis progression	Maintains renal integrity	Zhou et al., 2020

Table 5: Anti-Apoptotic Role of Alkaloids

Mechanism	Effect on Renal Cells	Outcome	Reference
Apoptotic pathway inhibition	Prevents tubular cell death	Preserves kidney structure	Yang et al., 2020
Cellular survival support	Enhances cell viability	Improves renal function	Khan et al., 2021

Table 6: Mitochondrial Protective Mechanisms

Mechanism	Effect	Outcome	Reference
Mitochondrial stabilization	Maintains energy balance	Prevents renal injury	Yuan et al., 2020
Reduced mitochondrial ROS	Limits oxidative damage	Protects renal cells	Zhang et al., 2018

Table 7: Histopathological Protective Effects of Alkaloids

Protective Effect	Histological Outcome	Functional Benefit	Reference
Prevention of tubular necrosis	Maintains tubular integrity	Supports filtration function	Yang et al., 2020
Reduced glomerular damage	Protects glomerular structure	Prevents renal dysfunction	Khan et al., 2021
Preservation of renal architecture	Maintains tissue organization	Enhances overall kidney health	Liu et al., 2019