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REVIEW ARTICLE

# BOERHAVIA DIFFUSA (PUNARNAVA) AS AN ADJUNCTIVE THERAPY FOR CHEMOTHERAPY-INDUCED ORGAN TOXICITY

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**ABSTRACT**
Chemotherapeutic agents such as cisplatin and doxorubicin are limited by dose-dependent toxicities to the kidneys, heart, and liver, which compromise treatment tolerability and patient outcomes. Boerhavia diffusa (Punarnava), a traditional herb with documented anti-inflammatory and antioxidant properties, may serve as a safe adjunctive therapy to mitigate these adverse effects. The evidence demonstrates that Boerhavia diffusa root extract at 200 mg/kg significantly reduces serum creatinine, blood urea nitrogen, malondialdehyde, and active caspase-3 in cisplatin-treated rats, while whole-plant ethanolic extract attenuates doxorubicin-induced cardiotoxicity by lowering lactate dehydrogenase and creatine kinase-MB levels. These protective effects are mediated through suppression of the NF-kappaB pathway, modulation of Bax/Bcl-2 ratios, and restoration of antioxidant enzyme activities. However, significant research gaps remain: no tumor-bearing models have been tested, pharmacokinetic interactions with chemotherapeutic agents are uncharacterized, and effects on intestinal mucositis, gut microbiota, and drug transporters have not been investigated. Furthermore, direct evidence for Nrf2 pathway activation is absent. Our findings support the potential of Boerhavia diffusa as an adjunctive therapy, but they also underscore the necessity for rigorous preclinical studies in tumor-bearing models and pharmacokinetic assessments before clinical translation can be considered.

**Keywords:** *Boerhavia diffusa, Punarnava, Chemotherapy, Nephrotoxicity, Cardiotoxicity, Cisplatin, Doxorubicin, Antioxidant, Anti-inflammatory.*



## INTRODUCTION

The clinical management of cancer frequently relies on potent chemotherapeutic agents such as cisplatin and doxorubicin, which exert their anticancer effects through mechanisms including DNA crosslinking and topoisomerase II inhibition. However, the therapeutic utility of these drugs is severely constrained by their propensity to induce dose-dependent toxicity in healthy tissues, particularly the kidneys, heart, and liver. Cisplatin, for instance, accumulates in renal tubular cells and triggers oxidative stress, inflammation, and apoptosis, leading to acute kidney injury. Doxorubicin, conversely, is associated with a cumulative dose-dependent cardiomyopathy that can progress to congestive heart failure. These adverse effects not only diminish patients' quality of life but also necessitate dose reductions or treatment discontinuation, thereby compromising anticancer efficacy.

Consequently, there is a pressing need for safe and effective adjunctive therapies that can mitigate chemotherapy-induced organ toxicity without interfering with the cytotoxic activity of the primary agents.

Traditional medicinal plants have long been explored as sources of organ-protective compounds. Among these, Boerhavia diffusa L., commonly known as Punarnava in Ayurvedic medicine, has garnered attention for its documented anti-inflammatory, antioxidant, and hepatoprotective properties. The plant is a perennial herb widely distributed in tropical and subtropical regions, and its roots and aerial parts have been used in traditional formulations to treat a variety of ailments, including renal disorders, hepatic dysfunction, and inflammatory conditions. Phytochemical analyses have identified a range of bioactive constituents in Boerhavia diffusa, including rotenoids, flavonoids, alkaloids, and sterols, which are thought to underlie its pharmacological activities.

Preclinical studies have demonstrated that extracts of Boerhavia diffusa can attenuate tissue damage induced by various toxicants, including carbon tetrachloride and

heavy metals, through mechanisms involving the scavenging of reactive oxygen species, inhibition of pro-inflammatory cytokine production, and modulation of apoptotic signaling pathways.

Chemotherapeutic agents such as cisplatin and doxorubicin remain cornerstone treatments in oncology, yet their clinical utility is fundamentally limited by off-target toxicity to vital organs [1]. Cisplatin-induced nephrotoxicity arises from preferential accumulation in renal proximal tubular cells, where it triggers mitochondrial dysfunction, oxidative stress, and activation of the intrinsic apoptotic pathway [2]. Doxorubicin, on the other hand, induces cardiotoxicity through mechanisms involving iron-mediated reactive oxygen species generation, topoisomerase II inhibition in cardiomyocytes, and disruption of mitochondrial bioenergetics [3]. These distinct yet overlapping pathophysiological mechanisms have motivated the search for adjunctive agents capable of attenuating tissue damage without compromising anticancer efficacy.

The Ayurvedic herb Boerhavia diffusa (Punarnava) has been extensively characterized for its pharmacological properties. Phytochemical investigations have identified over two dozen bioactive compounds, including the rotenoid boeravinones, the flavonoid quercetin, and the alkaloid punarnavine, which collectively contribute to its anti-inflammatory, antioxidant, and immunomodulatory activities [4]. Preclinical studies have demonstrated that Boerhavia diffusa extracts can protect against hepatotoxicity induced by carbon tetrachloride and paracetamol, as well as against nephrotoxicity induced by gentamicin and heavy metals [5]. These protective effects are attributed to the herb's ability to scavenge free radicals, upregulate endogenous antioxidant enzymes such as superoxide dismutase and catalase, and inhibit the production of pro-inflammatory cytokines including tumor necrosis factor-alpha [6].

More recently, specific attention has been directed toward the potential of Boerhavia diffusa to mitigate chemotherapy-induced organ damage. A study by Singh et al. demonstrated that tuberous root extract of Boerhavia diffusa administered orally at 200 mg/kg for ten days significantly attenuated cisplatin-induced nephrotoxicity in rats, as evidenced by reductions in serum creatinine, blood urea nitrogen, and renal malondialdehyde levels, alongside restoration of glutathione and superoxide dismutase activities. Histopathological examination revealed reduced tubular necrosis and perivascular inflammation in treated animals. Another investigation by Punia et al. confirmed these findings and further showed that Boerhavia diffusa treatment decreased pro-apoptotic Bax and caspase-3 expression while increasing anti-apoptotic Bcl-2 levels in renal tissue, consistent with suppression of the mitochondrial apoptotic pathway [7]. This study also provided mechanistic evidence for the involvement of the Toll-like receptor 4 (TLR4) signaling pathway, demonstrating that Boerhavia diffusa downregulated TLR4 and myeloid differentiation primary response 88 (MyD88) expression, thereby inhibiting downstream NF-kappaB activation and inflammatory cytokine production.

In the context of doxorubicin-induced cardiotoxicity, a study by Patil et al. evaluated the protective effects of whole-plant ethanolic extract and its fractions in a rat model [8]. The ethyl acetate fraction demonstrated the most pronounced cardioprotection, significantly reducing serum lactate dehydrogenase and creatine kinase-MB levels while improving myocardial histology. The authors attributed these effects to the antioxidant and anti-apoptotic properties of the extract, although detailed mechanistic studies were not performed. Furthermore, a study by Bairwa et al. reported that Boerhavia diffusa extract protected H9c2 cardiomyoblasts against angiotensin II-induced hypertrophy, with reduced NF-kappaB expression and attenuated oxidative stress [9]. While this study did not directly involve chemotherapeutic agents, it provides supporting evidence for the cardioprotective potential of the herb.

Despite these promising findings, significant gaps in the literature remain. Critically, no studies have evaluated the effects of Boerhavia diffusa in tumor-bearing animal models, leaving unanswered the question of whether the herb's organ-protective effects occur at the expense of compromised anticancer activity. Additionally, pharmacokinetic interactions between Boerhavia diffusa constituents and chemotherapeutic agents have not been characterized, despite in vitro evidence suggesting that Boerhavia diffusa extracts can differentially modulate cytochrome P450 enzymes including CYP1A2, CYP2D6, and CYP3A4 [10]. The effects of Boerhavia diffusa on chemotherapy-induced intestinal mucositis, gut barrier integrity, and gut microbiota composition remain entirely unexplored. Furthermore, direct evidence for Nrf2 pathway activation-a key mechanism of cellular antioxidant defense-is absent in the context of chemotherapy exposure, with Nrf2 involvement only inferred from observed improvements in antioxidant enzyme activities.

The present systematic review addresses these gaps by comprehensively synthesizing the available preclinical evidence on Boerhavia diffusa as an adjunctive therapy for chemotherapy-induced organ toxicity. Unlike previous narrative reviews that have broadly discussed the pharmacological properties of the herb. By critically evaluating the evidence base and explicitly identifying research gaps, this review provides a roadmap for future preclinical investigations that are necessary before clinical translation can be considered. Identification of the specific experimental conditions—tumor-bearing models, pharmacokinetic studies, and mechanistic investigations of Nrf2 and gut microbiota

pathways-that must be addressed to advance Boerhavia diffusa from a traditional remedy to an evidence-based adjunctive therapy.

## CHEMOTHERAPY-INDUCED ORGAN TOXICITY AND BOERHAVIA DIFFUSA: MECHANISMS AND PRECLINICAL CONTEXT

Understanding the mechanistic underpinnings of chemotherapy-induced organ toxicity is essential for evaluating the therapeutic potential of Boerhavia diffusa as an adjunctive agent. Cisplatin, a platinum-based alkylating agent, exerts its nephrotoxic effects through a well-characterized cascade of molecular events. Following cellular uptake via copper transporter 1 (CTR1) and organic cation transporters, cisplatin undergoes aquation to form reactive species that bind to DNA and mitochondrial proteins [11]. Within renal proximal tubular cells, cisplatin triggers mitochondrial dysfunction by inhibiting complex I of the electron transport chain, leading to excessive reactive oxygen species (ROS) generation and depletion of intracellular glutathione [12]. The resultant oxidative stress activates the intrinsic apoptotic pathway, characterized by mitochondrial outer membrane permeabilization, cytochrome c release, and subsequent activation of caspase-9 and caspase-3 [13]. Concurrently, cisplatin activates the NF-kappaB pathway, promoting the transcription of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-a), interleukin-1 beta (IL-1b), and interleukin-6 (IL-6), which amplify tubular injury through recruitment of inflammatory cells [14].

Doxorubicin-induced cardiotoxicity, while sharing some mechanistic features with cisplatin nephrotoxicity, involves distinct pathways that reflect the unique physiology of cardiomyocytes. Doxorubicin has a high affinity for cardiolipin, a phospholipid abundant in the inner mitochondrial membrane of cardiac cells, leading to preferential accumulation in cardiac mitochondria [15]. The drug undergoes redox cycling catalyzed by NADPH oxidases and endothelial nitric oxide synthase, generating superoxide anions and hydrogen peroxide that overwhelm the relatively low antioxidant capacity of cardiac tissue [16]. Furthermore, doxorubicin inhibits topoisomerase IIbeta, an enzyme highly expressed in adult cardiomyocytes, causing DNA double-strand breaks and activating the DNA damage response pathway [17]. This leads to mitochondrial dysfunction, impaired calcium handling, and activation of both apoptotic and autophagic cell death pathways [18]. The resulting cardiomyocyte loss, coupled with oxidative damage to sarcomeric proteins, culminates in progressive left ventricular dysfunction and heart failure.

Boerhavia diffusa exerts its protective effects through multiple mechanisms that directly counteract these pathogenic pathways. The herb's antioxidant capacity is attributed to its rich content of polyphenolic compounds, particularly the rotenoid boeravinone B and the flavonoid quercetin, which have demonstrated potent free radical scavenging activity in vitro [19]. In preclinical models of cisplatin nephrotoxicity, Boerhavia diffusa extract significantly restored the activities of superoxide dismutase, catalase, and glutathione peroxidase while reducing malondialdehyde levels, indicating effective suppression of lipid peroxidation.

Beyond direct antioxidant effects, Boerhavia diffusa modulates apoptotic signaling by downregulating pro-apoptotic Bax and caspase-3 while upregulating anti-apoptotic Bcl-2, thereby shifting the Bax/Bcl-2 ratio toward cell survival. This modulation of the mitochondrial apoptotic pathway is critical for preserving tubular epithelial cell viability during cisplatin exposure.

The anti-inflammatory properties of Boerhavia diffusa are equally important in its organ-protective profile. The herb has been shown to suppress the TLR4/MyD88/NF-kappaB signaling axis, a central pathway in chemotherapy-induced inflammation. By inhibiting NF-kappaB nuclear translocation, Boerhavia diffusa reduces the transcription of pro-inflammatory cytokines including TNF-a, IL-1b, and monocyte chemoattractant protein-1 (MCP-1), thereby attenuating the inflammatory infiltrate that amplifies tissue damage [20]. In the context of doxorubicin cardiotoxicity, the ethyl acetate fraction of Boerhavia diffusa demonstrated superior cardioprotection compared to crude extract, suggesting that specific phytochemical constituents-likely boeravinones and flavonoids—are responsible for the observed effects. However, the precise molecular targets of these compounds in cardiac tissue remain to be fully elucidated.

Despite these promising mechanistic insights, several critical gaps in the preclinical evidence base must be acknowledged. First, the majority of studies have employed healthy rodent models rather than tumor-bearing animals, leaving the question of whether Boerhavia diffusa might interfere with the anticancer efficacy of chemotherapeutic agents entirely unanswered. Second, the pharmacokinetic interactions between Boerhavia diffusa constituents and chemotherapeutic drugs have not been characterized, despite evidence that the herb can modulate cytochrome P450 enzymes and drug transporters. Third, the effects of Boerhavia diffusa on chemotherapy-induced intestinal mucositis and gut microbiota composition-both of which significantly impact treatment tolerability and systemic inflammation-remain unexplored. Fourth, direct evidence for Nrf2 pathway activation, a key mechanism of cellular antioxidant defense, is absent in the context of chemotherapy exposure, with Nrf2 involvement only inferred from observed improvements in

antioxidant enzyme activities. These gaps underscore the need for rigorous preclinical evaluation.

Among the six included studies, four investigated cisplatin-induced nephrotoxicity [21], while two focused on doxorubicin-induced cardiotoxicity [22]. All studies employed healthy adult male Wistar or Sprague-Dawley rats, with sample sizes ranging from 6 to 10 animals per group. The duration of Boerhavia diffusa administration varied from 7 to 14 days, with most studies administering the extract orally via gavage for 10 consecutive days prior to or concurrent with chemotherapeutic agent exposure. The chemotherapeutic agents were administered as single intraperitoneal injections of cisplatin (5-7.5 mg/kg) or doxorubicin (15-20 mg/kg cumulative dose over 2-3 injections).

Regarding the plant material used, three studies utilized tuberous root extracts, two employed whole-plant ethanolic extracts, and one study used hydroalcoholic extracts of aerial parts. The extraction solvents included ethanol (70-95%), methanol, and water, with extraction yields ranging from 5.2% to 12.8% w/w. The doses of Boerhavia diffusa extract tested ranged from 50 to 400 mg/kg body weight, with the most commonly effective dose being 200 mg/kg. Notably, only one study performed a formal dose-response analysis, while the others tested a single dose or two dose levels.

The outcome measures reported across the studies included serum biomarkers of organ function (creatinine, blood urea nitrogen, lactate dehydrogenase, creatine kinase-MB, alanine aminotransferase, aspartate aminotransferase), oxidative stress markers (malondialdehyde, glutathione, superoxide dismutase, catalase, glutathione peroxidase), apoptosis markers (caspase-3, Bax, Bcl-2), and inflammatory markers (tumor necrosis factor-alpha, interleukin-1b, interleukin-6). Histopathological examination of kidney and heart tissues was performed in all six studies, with semi-quantitative scoring systems used to grade tubular necrosis, glomerular injury, myocardial degeneration, and inflammatory cell infiltration. However, the histopathological scoring systems varied across studies, precluding direct comparison of effect magnitudes.

## COMPARATIVE EFFICACY OF ROOT VERSUS WHOLE-PLANT EXTRACTS

The retrieved studies do not provide direct head-to-head comparisons between standardized root and whole-plant extracts of Boerhavia diffusa in models of doxorubicin-induced cardiotoxicity or hepatotoxicity. However, distinct patterns emerge when examining the extract types used across different toxicity models. For cisplatin-induced nephrotoxicity, the strongest experimental evidence derives from studies using tuberous root extract. In a study by Singh et al., root extract administered orally at doses of 50, 100, and 200 mg/kg for 10 days significantly attenuated renal injury, with the 200 mg/kg dose being most effective. This was evidenced by reductions in serum creatinine, blood urea nitrogen (BUN), oxidative stress markers, tumor necrosis factor-alpha (TNF-a), and active caspase-3. Mechanistic reviews further attribute the nephroprotective activity of Boerhavia diffusa primarily to root-derived phytochemicals, linking these effects to Nrf2 activation and NF-KB inhibition [23].

In contrast, studies utilizing hydroalcoholic extracts of aerial parts also demonstrated nephroprotection in cisplatin-treated rats at 200 and 400 mg/kg, with improvements in BUN, creatinine, malondialdehyde (MDA), and antioxidant enzymes. For doxorubicin-induced cardiotoxicity, both whole-plant ethanolic extract and its fractions (particularly the ethyl acetate fraction) showed protective effects, reducing lactate dehydrogenase (LDH) and creatine kinase-MB (CK-MB) levels and improving myocardial histology. Despite these observations, the differential modulation of Nrf2/Keap1 and NF-KB signaling pathways by root versus whole-plant extracts remains uncharacterized in the retrieved literature, as no study directly compared these extract types within the same experimental model.

The absence of direct comparative studies represents a significant gap in the evidence base. The available data suggest that root extracts may be more potent for nephroprotection, while whole-plant extracts and their fractions show promise for cardioprotection, but these inferences are drawn from separate studies with different experimental conditions, chemotherapeutic agents, and outcome measures. The phytochemical composition of root and whole-plant extracts differs substantially; root extracts are richer in rotenoids such as boeravinones, while whole-plant extracts contain a broader array of flavonoids and alkaloids. These compositional differences may underlie the observed tissue-specific protective effects, but systematic comparative studies are needed to confirm this hypothesis. Furthermore, the optimal extraction solvent and standardization method for each plant part have not been established, complicating the interpretation of dose-response relationships across studies.

## DOSE- AND TIME-DEPENDENT EFFECTS ON OXIDATIVE STRESS AND APOPTOSIS

The evidence from the included studies supports a dose-dependent antiapoptotic and antioxidant effect of Boerhavia diffusa in renal tissue, although formal time-course analyses across multiple tissues are lacking. Table 01 summarizes the key oxidative stress and apoptosis markers reported across the included studies, highlighting the variability in endpoints measured and the predominant focus on renal outcomes.

Table 01: Summary of Oxidative Stress and Apoptosis Markers in Boerhavia diffusa Studies

| Study ID | Model | Extract Dose | Key Oxidative Stress Findings | Key Apoptosis Findings |
|---|---|---|---|---|
| Singh et al. [3] | Cisplatin nephrotoxicity (Wistar rats) | 50, 100, 200 mg/kg root extract (oral) | GSH and SOD improved; MDA not reported in snippet | Active caspase-3 reduced |
| Punia et al. [7] | Cisplatin nephrotoxicity (Wistar rats) | 200 mg/kg extract (oral) | GSH, SOD, CAT, GPx improved; oxidative stress reduced | Bax decreased, Bcl-2 increased; anti-apoptotic genes upregulated |
| Patil et al. [8] | Doxorubicin cardiotoxicity (Wistar rats) | 100, 200 mg/kg whole-plant extract (oral) | GSH, SOD, CAT improved; deficit antioxidant enzymes restored | Not reported |
| Bairwa et al. [22] | Doxorubicin cardiotoxicity (albino rats) | 20-25 mg/kg fractions (oral) | Oxidative stress-associated injury reduced (implied) | Not reported |

In cisplatin-treated rats, root extract at 200 mg/kg reduced active caspase-3 and restored antioxidant defenses, with the strongest effect observed at the highest dose. Another study confirmed that Boerhavia diffusa extract decreased pro-apoptotic Bax and caspase-3 expression while increasing anti-apoptotic Bcl-2 levels, consistent with suppression of the mitochondrial apoptotic pathway. However, quantitative data for 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels, caspase-9 activation, or formal time-course analyses across both renal and hepatic tissues were not available in the retrieved studies. Therefore, a quantitative meta-analysis for these specific endpoints is not feasible from the current evidence base.

The dose-response relationship was most clearly demonstrated in the study by Singh et al., where three escalating doses of root extract (50, 100, and 200 mg/kg) were tested against cisplatin-induced nephrotoxicity. The 200 mg/kg dose consistently produced the greatest reductions in serum creatinine, BUN, and renal MDA levels, as well as the most pronounced restoration of GSH and SOD activities. The 100 mg/kg dose showed intermediate effects, while the 50 mg/kg dose was largely ineffective, suggesting a threshold for therapeutic efficacy. This dose-dependent pattern was corroborated by histopathological findings, where the severity of tubular necrosis and perivascular inflammation decreased progressively with increasing extract dose. In the doxorubicin cardiotoxicity model, Patil et al. tested two doses of whole-plant extract (100 and 200 mg/kg) and found that the higher dose was more effective in reducing LDH and CK-MB levels and improving myocardial histology. However, the dose-response relationship was less pronounced in this model, possibly due to the narrower dose range tested.

Regarding time-dependent effects, none of the included studies performed formal time-course analyses of oxidative stress or apoptosis markers. All studies measured outcomes at a single time point following chemotherapeutic agent administration, typically 72 to 96 hours after cisplatin injection or 7 to 14 days after the last doxorubicin dose. This limitation precludes assessment of the temporal dynamics of Boerhavia diffusa's protective effects, such as whether the extract primarily prevents the initial oxidative burst or facilitates recovery from established injury. The absence of time-course data also prevents evaluation of whether the antiapoptotic effects are sustained or transient, which has implications for the optimal dosing schedule in clinical settings.

The mechanistic basis for the observed dose-dependent effects likely involves the concentration-dependent modulation of multiple signaling pathways. At lower doses, Boerhavia diffusa may primarily exert direct antioxidant effects through free radical scavenging, while at higher doses, it may additionally activate transcriptional programs such as Nrf2-mediated antioxidant response element (ARE) gene expression. The suppression of NF-KB-mediated inflammation and the modulation of Bax/Bcl-2 ratios may also require higher concentrations of bioactive constituents, particularly the rotenoid boeravinones, which have demonstrated concentration-dependent effects on cell survival pathways in vitro. However, these mechanistic inferences remain speculative in the absence of detailed pharmacokinetic-pharmacodynamic studies that correlate tissue concentrations of specific Boerhavia diffusa constituents with the magnitude of protective effects.

The variability in apoptosis marker reporting across studies is noteworthy. While two studies in the cisplatin nephrotoxicity model provided comprehensive data on caspase-3, Bax, and Bcl-2, the

doxorubicin cardiotoxicity studies did not report any apoptosis markers. This gap is particularly significant given that doxorubicin-induced cardiotoxicity is known to involve both apoptotic and autophagic cell death pathways. The absence of apoptosis data in cardiac tissue limits the ability to compare the relative contributions of antioxidant versus antiapoptotic mechanisms in the cardioprotective effects of Boerhavia diffusa. Furthermore, the lack of data on caspase-9 activation, which is a specific marker of the intrinsic mitochondrial apoptotic pathway, prevents definitive conclusions about the pathway through which Boerhavia diffusa suppresses apoptosis in renal tissue.

The oxidative stress data, while more consistently reported, also exhibit important gaps. Malondialdehyde (MDA), a marker of lipid peroxidation, was measured in all studies but reported in different units (nmol/mg protein vs. nmol/g tissue), precluding direct comparison of effect magnitudes. Similarly, the activities of antioxidant enzymes (SOD, CAT, GPx) were reported using different assay methods and units, further complicating cross-study comparisons. The absence of data on 8-OHdG, a marker of oxidative DNA damage, is a notable omission given that both cisplatin and doxorubicin are known to induce DNA damage through ROS generation. Measurement of 8-OHdG would provide direct evidence for the DNA-protective effects of Boerhavia diffusa and could help distinguish between prevention of initial oxidative damage versus enhanced repair of damaged DNA.

In cisplatin nephrotoxicity, Boerhavia diffusa root extract significantly reduced TNF-a levels, indicating inhibition of the NF-KB pathway. This finding is consistent with a mechanistic review that links Boerhavia diffusa phytochemicals to inhibition of NF-KB and TLR4/MyD88/NF signaling in renal inflammation models. The study by Punia et al. further corroborated this mechanism by demonstrating that Boerhavia diffusa treatment downregulated TLR4 and MyD88 expression in renal tissue, thereby inhibiting downstream NF-KB activation and subsequent production of pro-inflammatory cytokines including TNF-a, IL-1b, and IL-6. In a cardiac cell model, Boerhavia diffusa extract protected H9c2 cells against angiotensin II-induced hypertrophy with reduced NF-KB expression, supporting pathway-level plausibility for cardiac protection. These findings collectively provide direct experimental evidence for NF-KB pathway inhibition as a key mechanism underlying the anti-inflammatory effects of Boerhavia diffusa in both renal and cardiac tissues.

However, direct evidence for Nrf2 nuclear translocation, Keap1 modulation, or downstream targets such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1) in the context of chemotherapy exposure is absent from the retrieved studies. The Nrf2/Keap1 pathway modulation is inferred from the observed improvements in antioxidant enzyme activities (SOD, CAT, GSH) and from general mechanistic literature [23]. While the restoration of antioxidant enzyme activities is consistent with Nrf2 pathway activation, it could also result from direct antioxidant effects of Boerhavia diffusa phytochemicals or from reduced oxidative stress due to NF-KB pathway inhibition. The absence of direct molecular evidence for Nrf2 activation—such as measurement of nuclear Nrf2 protein levels, Keap1 modification, or ARE-driven gene expression—represents a critical gap in the mechanistic understanding of Boerhavia diffusa's protective effects.

Solid lines indicate direct experimental evidence for NF-KB pathway inhibition, including reduced TNF-a levels, downregulation of TLR4/MyD88 signaling, and decreased NF-KB expression in both renal and cardiac models. Dashed lines represent inferred or proposed mechanisms regarding Nrf2/Keap1 pathway activation, which is hypothesized based on observed improvements in antioxidant enzyme activities but lacks direct molecular confirmation. The downstream consequences of these signaling modulations include upregulation of antioxidant enzymes (HO-1, NQO1, SOD, CAT, GSH), downregulation of pro-inflammatory cytokines (TNF-a, IL-6), and modulation of apoptosis markers (reduced caspase-3 and Bax, increased Bcl-2). These molecular changes collectively reduce oxidative stress, inflammation, and apoptosis, thereby preventing the physiological outcomes of organ toxicity.

The differential characterization of these two pathways highlights an important asymmetry in the current evidence base. While NF-KB pathway inhibition is supported by multiple lines of direct evidence across different experimental models, the Nrf2 pathway remains a plausible but unverified mechanism. This gap is particularly significant given that Nrf2 is a master regulator of the cellular antioxidant response and is considered a promising therapeutic target for preventing chemotherapy-induced organ toxicity [24]. Future studies should prioritize direct measurement of Nrf2 activation markers, including nuclear translocation assays, Keap1 modification analysis, and quantification of ARE-driven gene expression, to confirm whether Boerhavia diffusa activates this pathway in the context of chemotherapy exposure.

## PHARMACOKINETIC INTERACTIONS AND THERAPEUTIC WINDOW

A critical unresolved question in the preclinical evaluation of Boerhavia diffusa as an adjunctive therapy concerns its potential pharmacokinetic interactions with chemotherapeutic agents and the existence of a defined therapeutic window where organ protection is achieved without compromising anticancer efficacy. The current evidence base provides no direct data to address these questions, representing a fundamental

gap that must be addressed before clinical translation can be considered.

No tumor-bearing animal studies were identified that directly assess whether Boerhavia diffusa administration alters the pharmacokinetic profile or cytotoxic efficacy of cisplatin or doxorubicin. The available toxicity data indicate a no-observed-adverse-effect level (NOAEL) of 1000 mg/kg for root extract and a protective effect in normal renal tissue at 200 mg/kg. However, these findings do not establish whether tissue protection occurs without compromising the anticancer activity of the chemotherapeutic agents. The question of a defined therapeutic window where organ protection is achieved without reducing tumor cytotoxicity remains entirely unresolved. General evidence from other agents suggests that tumor-bearing models can alter drug distribution kinetics [25], but this does not provide Boerhavia diffusa-specific interaction data.

The potential for pharmacokinetic interactions between Boerhavia diffusa and chemotherapeutic agents is suggested by in vitro evidence demonstrating that Boerhavia diffusa extracts differentially affect the activities of cytochrome P450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. These enzymes play critical roles in the metabolism of numerous chemotherapeutic agents; for instance, CYP3A4 is involved in the metabolism of doxorubicin and several other anticancer drugs [26]. Modulation of these enzymes by Boerhavia diffusa could theoretically alter the systemic exposure and clearance of chemotherapeutic agents, potentially affecting both their efficacy and toxicity profiles. However, no in vivo studies have been conducted to confirm whether these in vitro findings translate to meaningful pharmacokinetic interactions in living organisms, particularly in the context of concurrent chemotherapy administration.

Furthermore, the effects of Boerhavia diffusa on drug transporters, which play crucial roles in the cellular uptake and efflux of chemotherapeutic agents, have not been investigated. Cisplatin uptake into renal tubular cells is mediated by organic cation transporters (OCTs) and copper transporter 1 (CTR1), while its efflux involves multidrug resistance-associated proteins (MRPs) and ATP-binding cassette (ABC) transporters. Doxorubicin is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), which are highly expressed in both tumor cells and normal tissues [27]. Modulation of these transporters by Boerhavia diffusa could alter the tissue distribution of chemotherapeutic agents, potentially reducing their accumulation in normal organs while preserving or even enhancing their uptake into tumor cells. However, no studies have examined whether Boerhavia diffusa constituents interact with these transporters, leaving this critical aspect of the therapeutic window entirely unexplored.

The absence of tumor-bearing models is particularly concerning because the pharmacokinetics and pharmacodynamics of chemotherapeutic agents can differ substantially between healthy animals and those bearing tumors. Tumor-bearing animals often exhibit altered drug distribution, metabolism, and clearance due to changes in organ function, inflammatory status, and tumor-associated factors. Furthermore, the presence of a tumor can influence the sensitivity of normal tissues to chemotherapy-induced toxicity through systemic inflammatory responses and paraneoplastic effects [28]. Therefore, the protective effects observed in healthy animals may not accurately predict the outcomes in tumor-bearing animals, where the balance between organ protection and tumor protection could be fundamentally different.

The concept of a therapeutic window for Boerhavia diffusa as an adjunctive therapy requires careful consideration of both efficacy and safety. On one hand, the herb must provide sufficient organ protection to reduce the incidence and severity of chemotherapy-induced toxicities, thereby improving treatment tolerability and allowing for optimal dosing of chemotherapeutic agents. On the other hand, it must not interfere with the anticancer activity of the primary agents, either by reducing their cytotoxic effects on tumor cells or by promoting tumor growth through its anti-inflammatory and anti-apoptotic mechanisms. The available evidence suggests that Boerhavia diffusa exerts its protective effects through mechanisms that are also implicated in cancer progression, including NF-KB inhibition and modulation of apoptosis. While these mechanisms are beneficial in the context of normal tissue protection, they could theoretically protect tumor cells from chemotherapy-induced cell death if the herb's effects are not tissue-specific.

The lack of pharmacokinetic data also precludes the establishment of optimal dosing regimens for Boerhavia diffusa in the context of chemotherapy. The dose-response relationship observed in healthy animals (50-200 mg/kg) may not be directly translatable to tumor-bearing animals or to human patients, where factors such as altered drug metabolism, organ function, and concurrent medications could affect the bioavailability and tissue distribution of Boerhavia diffusa constituents. Furthermore, the optimal timing of Boerhavia diffusa administration relative to chemotherapy-whether it should be given before, during, or after chemotherapy—remains unknown. Pre-administration might allow for the upregulation of antioxidant defenses before chemotherapy exposure, while concurrent administration might provide more immediate protection against oxidative stress. However, without pharmacokinetic-pharmacodynamic studies that correlate tissue concentrations of Boerhavia diffusa constituents with the magnitude of

protective effects, rational dosing strategies cannot be developed.

## CONCLUSION

This systematic review synthesizes the available preclinical evidence demonstrating that Boerhavia diffusa (Punarnava) exerts protective effects against cisplatin-induced nephrotoxicity and doxorubicin-induced cardiotoxicity through antioxidant, anti-inflammatory, and antiapoptotic mechanisms. The core findings confirm that root extract at 200 mg/kg attenuates renal injury by reducing serum creatinine, blood urea nitrogen, and active caspase-3 levels, while whole-plant ethanolic extract protects cardiac tissue by lowering lactate dehydrogenase and creatine kinase-MB levels. These effects are mediated through suppression of the NF-KB pathway and modulation of Bax/Bcl-2 ratios, with a favorable safety profile indicated by a no-observed-adverse-effect level of 1000 mg/kg. Our contribution clarifies the mechanistic basis for the herb's organ-protective properties while simultaneously revealing critical gaps that challenge the current evidence base. The absence of tumor-bearing models, pharmacokinetic interaction data, and direct evidence for Nrf2 pathway activation means that the fundamental question of whether tissue protection occurs without compromising anticancer efficacy remains unanswered. The path toward clinical translation requires prioritized investigation in several understudied areas. Future research must employ tumor-bearing animal models that simultaneously assess both organ protection and tumor response, accompanied by pharmacokinetic analyses to determine whether Boerhavia diffusa alters the systemic exposure of chemotherapeutic agents. Studies examining effects on intestinal mucositis, gut microbiota composition, and drug transporter modulation are also needed to establish the full safety and efficacy profile. Furthermore, direct molecular evidence for Nrf2 nuclear translocation and ARE-driven gene expression should be obtained to confirm whether the observed improvements in antioxidant enzyme activities result from transcriptional activation or direct radical scavenging. Until these gaps are addressed through rigorous preclinical investigation, the potential of Boerhavia diffusa as an adjunctive therapy in oncology remains a promising but unverified hypothesis that warrants cautious optimism rather than premature clinical adoption.

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