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Nature's Defense: Cardioprotective Potential of Convolvulus prostratus Against Doxorubicin-Induced Toxicity

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ABSTRACT

Doxorubicin is a widely used chemotherapeutic agent effective against various malignancies; however, its clinical application is significantly limited by its dose-dependent cardiotoxicity. This adverse effect, primarily mediated through oxidative stress, mitochondrial dysfunction, and apoptosis, underscores the urgent need for cardioprotective interventions. In recent years, the exploration of plant-based compounds with antioxidant and cytoprotective properties has gained substantial momentum. Convolvulus prostratus, a traditional medicinal herb known for its neuroprotective, antioxidant, and anti-inflammatory properties, has shown promising pharmacological potential in preclinical models. This review critically examines the available literature on the cardioprotective effects of ethanolic extracts of Convolvulus prostratus in the context of doxorubicin-induced cardiotoxicity. We explore its phytochemical profile, focusing on flavonoids, alkaloids, and glycosides that may contribute to its cardioprotective actions. The review also discusses possible mechanisms, including attenuation of oxidative stress, modulation of apoptotic pathways, and stabilization of myocardial membrane integrity. Furthermore, evidence from in vivo studies in rat models suggests a significant mitigation of biochemical and histopathological markers of cardiac injury following treatment with C. prostratus extracts. Although the data are encouraging, further mechanistic studies and clinical investigations are essential to establish its efficacy and safety in humans. This review highlights the potential of Convolvulus prostratus as a natural adjunct in protecting against chemotherapy-induced cardiac damage, paving the way for future translational research in cardio-oncology.

Keywords: *Convolvulus prostrates, Doxorubicin, Cardiotoxicity, Phytotherapy, Oxidative stress.*

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide. Among various chemotherapeutic agents, doxorubicin (DOX) has emerged as a cornerstone in the treatment of a wide spectrum of cancers, including leukemias, lymphomas, breast cancer, and sarcomas.[1-2] Despite its broad-spectrum antitumor activity, the clinical utility of doxorubicin is significantly hampered by its dose-dependent cardiotoxicity, which may manifest as arrhythmias, cardiomyopathy, or congestive heart failure. The underlying mechanisms of doxorubicin-induced cardiotoxicity are multifactorial and involve oxidative stress, mitochondrial dysfunction, lipid peroxidation, and the induction of apoptosis in cardiomyocytes. These adverse effects necessitate the search for novel cardioprotective agents that can mitigate the cardiac damage associated with doxorubicin without compromising its anticancer efficacy.[3-6]

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In recent years, considerable attention has been given to natural products and plant-derived compounds for their therapeutic potential in managing various diseases, including chemotherapy-induced toxicities. Herbal medicines have traditionally been used across cultures for their healing properties, and recent scientific exploration has validated many of these traditional claims through pharmacological investigations.[7-8] Among these, *Convolvulus prostratus*, also known as Shankhpushpi in Ayurvedic medicine, has emerged as a plant of interest due to its wide range of pharmacological activities, including neuroprotective, antioxidant, anti-inflammatory, and adaptogenic effects. Native to the Indian subcontinent, *C. prostratus* has been used in traditional systems of medicine for enhancing memory, alleviating stress, and promoting general well-being.[9-10]

The therapeutic properties of *Convolvulus prostratus* are attributed to its rich phytochemical composition, which includes alkaloids, flavonoids, glycosides, and phenolic compounds. These constituents are known to exert strong antioxidant activity, which could counteract the oxidative stress induced by doxorubicin.[11-12] Additionally, its anti-inflammatory and anti-apoptotic properties may provide a multifaceted protective mechanism against the cascade of events leading to cardiotoxicity. Preliminary pharmacological evaluations in animal models suggest that ethanolic extracts of *C. prostratus* may significantly reduce biochemical markers of cardiac injury and improve histopathological outcomes in doxorubicin-induced cardiotoxicity models.[13-15]

This review aims to provide a comprehensive analysis of the cardioprotective potential of *Convolvulus prostratus* in the context of doxorubicin-induced toxicity. We begin with an overview of doxorubicin's mechanism of action and the pathophysiology of its cardiotoxic effects. This is followed by a detailed examination of the phytochemical profile and pharmacological properties of *C. prostratus*, with a focus on its antioxidant and cardioprotective mechanisms. The review further discusses experimental evidence from preclinical studies, highlighting the efficacy of ethanolic extracts of the plant in mitigating doxorubicin-induced cardiac damage in rat models. We also explore the proposed molecular pathways through which *C. prostratus* exerts its effects, including modulation of oxidative stress, inhibition of lipid peroxidation, and prevention of apoptosis in cardiac tissue.

Comprehensive Analysis of the Cardioprotective Potential of *Convolvulus prostratus* in the Context of Doxorubicin-Induced Toxicity

Doxorubicin (DOX), a potent anthracycline antibiotic, remains a cornerstone chemotherapeutic agent for a wide spectrum of malignancies. However, its clinical efficacy is marred by dose-dependent cardiotoxicity, leading to irreversible cardiomyopathy and congestive heart failure. The pathogenesis of doxorubicin-induced cardiotoxicity (DIC) is multifactorial, primarily involving oxidative stress, mitochondrial dysfunction, lipid peroxidation, and apoptosis of cardiomyocytes.[16] In recent years, interest has grown in identifying natural compounds with cardioprotective properties to mitigate these adverse effects. Among them, *Convolvulus prostratus* (CP), commonly known as Shankhpushpi, has emerged as a promising candidate owing to its broad spectrum of pharmacological properties, particularly its antioxidant and anti-inflammatory potential.[17] *Convolvulus prostratus* is a traditional medicinal herb used in Ayurveda, primarily for its nootropic and adaptogenic effects. The plant is rich in bioactive constituents such as flavonoids, alkaloids, coumarins, and glycosides, which contribute to its diverse therapeutic activities. Its antioxidant activity is of particular interest in the context of DIC, as reactive oxygen species (ROS) generation is a major contributing factor to DOX-induced myocardial damage.[18] Studies have demonstrated

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that CP can scavenge free radicals and enhance endogenous antioxidant enzyme systems, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), thereby attenuating oxidative stress.[19-20]
Preclinical studies evaluating the cardioprotective potential of CP in DOX-induced models reveal promising outcomes.[21] CP extracts have been shown to significantly reduce serum biomarkers of cardiac injury such as creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), and troponin-T in DOX-treated animals. Histopathological analysis further supports these findings, showing that CP mitigates DOX-induced myocardial degeneration, cellular infiltration, and necrosis. The plant's anti-apoptotic effects, potentially through modulation of Bcl-2 family proteins and inhibition of caspase-3 activity, further contribute to its cardioprotective mechanism.[22-23] Additionally, the anti-inflammatory properties of CP also play a critical role in cardioprotection. DOX induces an inflammatory response characterized by elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. CP has been reported to suppress these cytokines, likely via inhibition of the NF-κB signaling pathway. By dampening inflammation, CP helps to preserve myocardial architecture and function.[24]

Moreover, the neuroprotective and adaptogenic properties of CP may offer indirect cardiovascular benefits by mitigating stress-induced autonomic imbalance, which often exacerbates cardiotoxic effects. CP's influence on nitric oxide pathways and calcium homeostasis could further contribute to its protective profile, although these mechanisms require more focused investigation.[25] *Convolvulus prostratus* presents a compelling case for further investigation as a cardioprotective agent against doxorubicin-induced toxicity. Its multifaceted actions—antioxidant, anti-inflammatory, and anti-apoptotic—address the core mechanisms underlying DIC. While preclinical data are encouraging, comprehensive clinical trials are warranted to validate its efficacy and safety in human subjects. Integrating such phytotherapeutics with conventional chemotherapy regimens may offer a strategic advantage in improving patient outcomes and quality of life.[26-28]

What is Doxorubicin-Induced Toxicity?
Doxorubicin-induced toxicity refers to the harmful side effects caused by the chemotherapy drug doxorubicin, particularly its damaging effects on the heart (cardiotoxicity), liver, kidneys, and other tissues. Among these, cardiotoxicity is the most serious and limiting factor in its clinical use. It may lead to cardiomyopathy, heart failure, or even death if not managed appropriately.[29]

Mechanism of Doxorubicin-Induced Toxicity[31]
Oxidative Stress and ROS Generation
- Doxorubicin undergoes redox cycling, generating reactive oxygen species (ROS) like superoxide and hydrogen peroxide.
- These ROS damage cellular components—lipids, proteins, and DNA—especially in cardiomyocytes, which have lower antioxidant capacity.

Mitochondrial Dysfunction
- Doxorubicin accumulates in mitochondria and disrupts the electron transport chain, leading to ATP depletion and further ROS production.
- Mitochondrial DNA damage triggers apoptosis (programmed cell death).

Lipid Peroxidation

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- ROS react with polyunsaturated fatty acids in cell membranes, causing lipid peroxidation, leading to loss of membrane integrity and cellular leakage.

Iron Interaction
- Doxorubicin chelates iron, forming doxorubicin-iron complexes that catalyze ROS formation via the Fenton reaction, exacerbating oxidative stress.

Topoisomerase IIβ Inhibition
- In cardiomyocytes, doxorubicin inhibits Topoisomerase IIβ, leading to DNA double-strand breaks, mitochondrial dysfunction, and cell death.

Reasons for Occurrence[32-33]
- **High cumulative dose**: Risk increases with cumulative doses >400–550 mg/m^2.
- **Age**: Children and elderly are more vulnerable.
- **Preexisting cardiac conditions**: Patients with heart disease are at higher risk.
- **Genetic predisposition**: Polymorphisms in genes related to oxidative stress or drug metabolism can influence toxicity.
- **Concurrent radiation or other cardiotoxic drugs**: Enhances cardiac risk.
- **Poor antioxidant defense in heart tissue**: The heart has fewer detoxifying enzymes compared to other organs.

Treatment and Therapies for Doxorubicin-Induced Toxicity[34-35]

Preventive Approaches
- **Dose Limitation**: Keeping cumulative doses within safe limits.
- **Liposomal Doxorubicin**: Encapsulated form reduces heart exposure.
- **Dexrazoxane**: FDA-approved cardioprotective agent that chelates iron and reduces ROS formation.

Antioxidant Therapy
- **Natural Antioxidants**: Such as *Convolvulus prostratus*, curcumin, resveratrol, and vitamin E.
- **Synthetic Antioxidants**: N-acetylcysteine (NAC), coenzyme Q10.

Cardioprotective Drugs
- **Beta-blockers (e.g., carvedilol)**: Reduce oxidative damage.
- **ACE inhibitors (e.g., enalapril)**: Improve heart function.
- **Statins**: May reduce inflammation and oxidative stress.

Monitoring and Early Detection
- **Echocardiography and ECG**: Regular cardiac function monitoring.
- **Biomarkers**: Troponin I, NT-proBNP, and CK-MB to detect early damage.

Regenerative Therapy (Experimental)
- **Stem cell therapy** and **gene therapy** are under investigation for reversing cardiac damage.

Convolvulus prostratus (also known as *Convolvulus pluricaulis*), commonly referred to as Shankhpushpi, is a well-known medicinal herb in traditional Indian medicine, particularly

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Ayurveda and Unani systems. It is widely valued for its nootropic (memory-enhancing) and neuroprotective properties.

Botanical Information
Scientific Name: *Convolvulus prostratus* / *Convolvulus pluricaulis*
Family: Convolvulaceae
Common Names: Shankhpushpi, Aloe weed, Morning Glory
Habitat: Commonly found in India, especially in dry plains and open grasslands.

Morphology:

- It is a **perennial herb** that grows low and spreads across the ground.
- Leaves are **small, simple, alternate**, and ovate or lanceolate.
- Flowers are **blue or violet**, funnel-shaped, and bloom singly.

Phytochemical Constituents
Contains **alkaloids** (shankhapushpine), **glycosides**, **coumarins**, **flavonoids**, and **phenolic compounds**. Also contains **beta-sitosterol**, **caffeic acid**, and **scopoletin**.

Traditional Uses

- Memory Enhancer: Widely used in Ayurvedic formulations to improve memory, concentration, and learning.
- Anxiolytic & Antidepressant: Helps reduce stress, anxiety, and depression symptoms.
- Nervine Tonic: Supports cognitive functions and helps in calming the nervous system.
- Anticonvulsant: Used in epilepsy and convulsions.
- Adaptogen: Helps the body adapt to stress and restore balance.

Pharmacological Activities

- Nootropic
- Neuroprotective
- Antioxidant
- Anti-anxiety
- Anti-depressant
- Anti-ulcer
- Anti-inflammatory

Formulations

- Commonly found in syrups, powders, and tablets as a **brain tonic**.
- Often used in combination with other herbs like **Brahmi (Bacopa monnieri)** and **Ashwagandha (Withania somnifera)**.

Major Chemical Constituents of *Convolvulus prostratus*:
Alkaloids

- **Shankhpushpine** (a major bioactive alkaloid)
- Evolvine
- Convolvine
- Convolamine
- Scopoletin (a coumarin derivative)

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Flavonoids

- Kaempferol
- Quercetin
- Rutin
- Luteolin

  These are known for their antioxidant and neuroprotective properties.

Glycosides

- Coumarin glycosides
- Iridoid glycosides

  Help in cognitive enhancement and adaptogenic effects.

Sterols

- **β-sitosterol**
- Stigmasterol

- These contribute to anti-inflammatory and antioxidant activity.

Phenolic Compounds

- Caffeic acid
- Ferulic acid

  These are powerful antioxidants and support neuroprotection.

Volatile Oils

- Present in small amounts; contribute to aroma and potential CNS effects.

CONCLUSION

Doxorubicin-induced toxicity, particularly its cardiotoxic effects, remains a major limitation in the long-term use of this highly effective chemotherapeutic agent. Its toxicity arises primarily from oxidative stress, mitochondrial dysfunction, and apoptotic cell death, especially in cardiac tissues. The heart's limited antioxidant defense makes it especially susceptible to damage. A combination of preventive strategies—including dose monitoring, cardioprotective agents like dexrazoxane, antioxidant supplementation, and natural phytotherapeutics such as *Convolvulus prostratus*—offers a promising approach to mitigating this toxicity. Continued research into these protective mechanisms and the development of integrative therapies is essential to enhance patient safety and sustain the therapeutic benefits of doxorubicin in cancer treatment.

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