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A REVIEW ON: PHARMACOLOGICAL EVALUATION OF CYPERUS ROTUNDUS_ON DOXORUBICIN-INDUCED CARDIOTOXICITY IN EXPERIMENTAL RATS

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ABSTRACT

Doxorubicin is commonly used against solid and haematological malignancies but causes **cardio toxicity** marked by elevated cardiac biomarkers, oxidative stress, structural heart tissue damage, and eventual heart failure. Key mechanisms include **reactive oxygen species (ROS) generation**, lipid peroxidation, inflammatory cytokine upregulation, and apoptotic signaling in cardiomyocytes. Enhancing antioxidant and anti-inflammatory defenses remains a promising approach to mitigate these effects. *Cyperus rotundus* (nutgrass), widely used in Ayurvedic, Chinese, and traditional medicines, possesses **antioxidant, anti-inflammatory, vasodilator, and cardioprotective** activities linked to its rich phytochemical profile.

KEYWORDS: Chemotherapy, cardiotoxicity, and phytochemicals.

INTRODUCTION

Cardiotoxicity is a broad term that refers to the negative effects of toxic substances on the heart. Cancer drugs can cause cardiotoxicity by effects on heart cells, thromboembolic events, and/or hypertension that can lead to heart failure. Rheumatoid arthritis biologics may interfere with ischemic preconditioning and cause/worsen heart failure. Long-term and heavy alcohol use can result in oxidative stress, apoptosis, and decreased contractile protein

function. Cocaine use results in sympathetic nervous system stimulation of heart and smooth muscle cells and leads to cardiotoxicity and evolution of heart failure. The definition of cardiotoxicity is likely to evolve along with knowledge about detecting subclinical myocardial injury.

Doxorubicin-Induced Cardiotoxicity: Mechanisms of Injury

DOX cardiotoxicity involves multiple interacting pathways:

- **Oxidative stress**: DOX undergoes redox cycling, generating free radicals and depleting endogenous antioxidants, which leads to lipid, protein, and DNA damage in cardiac tissue.
- **Inflammation**: Elevated proinflammatory cytokines (e.g., TNF-α, IL-1β) contribute to myocardial injury.
- **Apoptosis**: Activation of caspase-dependent pathways results in cardiomyocyte death.
- **Functional and biochemical changes**: Increases in cardiac biomarkers (CK-MB, LDH, and troponin) and histopathological damage are characteristic.

These mechanisms make DOX cardiotoxicity a target for interventions that reinforce **antioxidant defenses, modulate inflammation, and preserve cellular integrity**.

***Cyperus rotundus*: Phytochemistry and Pharmacological Profile**

Phytochemical Constituents

C. rotundus rhizomes contain **essential oils, flavonoids, polyphenols, sesquiterpenes** (e.g., α-cyperone), and other compounds that contribute to biological activity.

These constituents are associated with radical scavenging, lipid peroxidation inhibition, and modulation of cellular signaling pathways relevant to oxidative and inflammatory stress.

Pharmacological Activities.

Experimental studies on *C. rotundus* reveal several activities relevant to cardioprotection.

- **Antioxidant activity:** Extracts exhibit DPPH radical scavenging, metal chelation, nitric oxide scavenging, and protection against oxidative macromolecular damage.
- **Anti-inflammatory and immunomodulatory effects:** Bioactive fractions reduced inflammatory responses and enhanced lymphocyte proliferation in rodent models.
- **Vasodilator and calcium channel modulation:** Extracts demonstrated vasorelaxant properties in isolated vascular tissues, which could be relevant to cardiomyocyte stress responses.

In a myocardial injury model (isoproterenol-induced infarction), polyphenolic *C. rotundus* extracts modulated cardiac markers and reduced tissue necrosis, supporting potential cardioprotective effects beyond traditional uses.

Potential Mechanisms of Cardioprotection by *C. rotundus*

Although no direct studies on DOX and *C. rotundus* currently exist, based on its pharmacological profile, the following mechanisms may underlie cardioprotective potential.

Attenuation of Oxidative Stress

The antioxidant compounds in *C. rotundus* could reduce ROS generation and lipid peroxidation, a primary driver of DOX cardiotoxicity. Restoring antioxidant enzyme activity (e.g., SOD, catalase) is protective in many DOX models.

Anti-Inflammatory Modulation

Sesquiterpenes like α-cyperone have been shown to inhibit pro-inflammatory cytokine expression and NF-κB signaling. Similar pathways are implicated in DOX cardiac injury, suggesting *C. rotundus* could reduce inflammatory damage.

Preservation of Cellular Integrity

By reducing oxidative and inflammatory insults, *C. rotundus* components may stabilize cardiomyocyte membranes, lower biomarker leakage (CK-MB, LDH), and prevent apoptosis—mechanisms seen with other natural cardioprotectants.

Mechanism of cardio toxicity

First: What is Doxorubicin?

Doxorubicin is a strong anticancer drug used in chemotherapy.

It kills cancer cells.

But it can also accidentally damage heart cells.

That heart damage = **cardiotoxicity**.

How Does Doxorubicin Damage the Heart?

Imagine your heart is a **factory that never stops working**.

It needs clean energy and healthy workers (heart cells).

Doxorubicin causes trouble in 5 main ways.

Free Radical Formation

Doxorubicin creates **bad molecules called free radicals** (Reactive Oxygen Species – ROS).

Think of them like tiny sparks inside the cell.

These sparks

- Damage cell membrane
- Damage proteins
- Damage DNA
- Damage mitochondria (energy factory of the cell)

Heart cells are very sensitive because

- They need LOTS of oxygen
- They have weak antioxidant defense

So they get injured easily.

This is called **oxidative stress**

Mitochondrial Damage

Mitochondria = battery of the heart cell.

Doxorubicin

- Enters mitochondria
- Disturbs energy production
- Reduces ATP

No energy = weak heart contraction.

Lipid Peroxidation

Free radicals attack fats in the cell membrane.

This causes.

- Membrane leakage
- Loss of cell structure
- Cell death

In experiments, this increases

- MDA (malondialdehyde)

Calcium Overload

Doxorubicin disturbs calcium balance.

Too much calcium inside heart cells

- Causes abnormal contraction
- Leads to arrhythmia
- Triggers cell death

Apoptosis (Programmed Cell Death)

Doxorubicin activates:

- Caspases
- Pro-apoptotic proteins

So heart cells commit "suicide".

Too many cells die → Heart becomes weak → Cardiomyopathy.

What Happens Finally?

All these lead to:

- Myocardial degeneration
- Reduced ejection fraction
- Dilated cardiomyopathy
- Increased CK-MB, LDH
- ECG changes

In severe cases → Heart failure.

Summary Table

Mechanism	Drug Examples	Effect on Heart
Oxidative stress	Doxorubicin, Cisplatin	Lipid/protein/DNA damage
Mitochondrial dysfunction	Anthracyclines	ATP depletion, apoptosis
Ion channel disruption	Antiarrhythmics, TKIs	Arrhythmia

Doxorubicin-induced cardio toxicity

Introduction

Doxorubicin is an **anthracycline antibiotic** widely used as a chemotherapeutic agent for various cancers. Despite its efficacy, its clinical use is limited due to **cardiotoxicity**, which can lead to **heart failure**.

Key features of doxorubicin cardiotoxicity.

- Can be **acute**, **early-onset chronic**, or **late-onset chronic**.
- Dose-dependent: risk increases significantly with cumulative doses > 450–550 mg/m².
- Manifests as **left ventricular dysfunction**, arrhythmias, or cardiomyopathy.

2. Mechanism of Doxorubicin-Induced Cardio toxicity

Several mechanisms are involved:

a) Free Radical Formation Oxidative Stress &

- Doxorubicin undergoes **redox cycling** in cardiomyocytes → generates **reactive oxygen species (ROS)**.
- ROS damage **lipids, proteins, and DNA**, leading to cell death.
- Cardiomyocytes are particularly sensitive due to **low levels of antioxidant enzymes**.

b) Iron Chelation

- Doxorubicin binds to iron → forms **doxorubicin-iron complexes** → catalyze ROS production via **Fenton reaction**.

c) Mitochondrial Dysfunction

- Accumulates in mitochondria → inhibits **electron transport chain** → decreased ATP production.
- Leads to **apoptosis** and cardiomyocyte necrosis.

d) Topoisomerase IIβ Inhibition

- Doxorubicin inhibits **Topoisomerase IIβ in cardiomyocytes** → DNA double-strand breaks → triggers **cell death pathways**.

e) Calcium Dysregulation

Disrupts **calcium homeostasis** → impairs cardiac contraction.

Pathology of Cyprus Rotundus_On Doxorubicin-Induced Cardiotoxicity

Doxorubicin damages the heart via multiple mechanisms.

1. **Oxidative Stress**
   - DOX generates reactive oxygen species (ROS)
   - Causes lipid peroxidation in cardiomyocyte membranes
   - Leads to mitochondrial dysfunction

2. **Apoptosis**
   - Activation of caspase pathways
   - DNA fragmentation in cardiomyocytes
3. **Inflammation**
   - Elevated pro-inflammatory cytokines (TNF-α, IL-6)
   - Myocardial inflammation and edema
4. **Histopathological Changes**
   - Myocyte vacuolization
   - Necrosis and fibrosis
   - Disruption of cardiac architecture
5. **Biochemical Markers**
   - ↑ Serum CK-MB (Creatine kinase-MB)
   - ↑ LDH (Lactate dehydrogenase)
   - ↑ Troponin levels

3. Pharmacological Role of ***Cyperus rotundus***

- **Active constituents:** flavonoids, terpenoids, polyphenols
- **Mechanisms of cardioprotection**:

1. **Antioxidant activity**: scavenges ROS, reduces lipid peroxidation
2. **Anti-inflammatory effect**: suppresses TNF-α, IL-6
3. **Anti-apoptotic effect**: stabilizes mitochondrial membrane, reduces caspase activation
4. **Preservation of cardiac enzymes**: prevents rise in CK-MB, LDH
5. **Histological protection**: reduces myocardial vacuolization, necrosis, and fibrosis.

4. Pathological Observations in Experimental Rats

Control (Doxorubicin only)

- Myocardial fiber disarray
- Cytoplasmic vacuolation
- Inflammatory cell infiltration
- Fibrosis in interstitial tissue

Treatment (*Cyperus rotundus* extract + Doxorubicin)

- Reduced vacuolization
- Maintained myocyte integrity
- Decreased inflammatory infiltration

Noralization of cardiac

Experimental Approaches to Validate Cardioprotective Effects

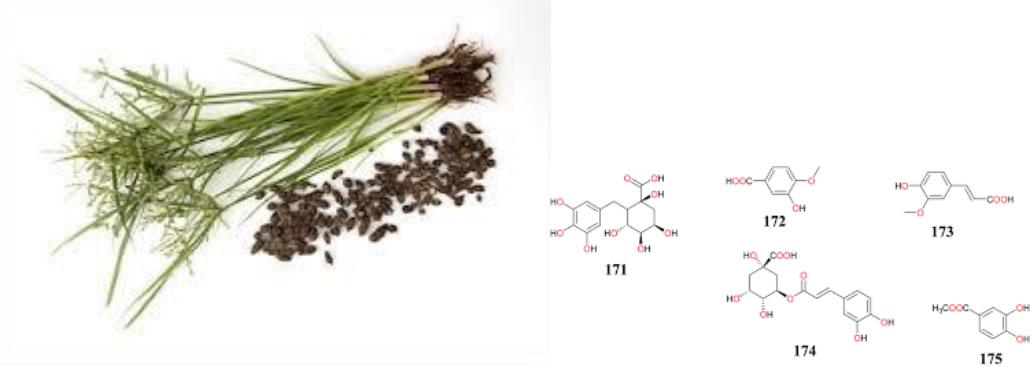
To confirm *C. rotundus* efficacy against DOX-induced cardiotoxicity, experimental designs should include.

- **Animal model**: Wistar or Sprague-Dawley rats with cumulative DOX dosing to induce cardiotoxicity.
- **Treatment groups**: Control, DOX only, *C. rotundus* extract alone, and DOX + *C. rotundus* (multiple doses).
- **Biochemical markers**: Measurement of CK-MB, troponin I, LDH, AST, and oxidative stress markers (MDA, SOD, catalase).
- **Histopathology**: Examination of cardiac tissue for vacuolization, necrosis, and inflammatory infiltration.
- **Molecular assays**: Assessment of inflammatory cytokines and apoptotic markers.

  Such a design would provide comprehensive evidence of pharmacological effects.

1. DRUG PROFILE

Cyperus rotundus-Chemical Structure and Biological Activities.



Cyperus rotundus

1. Botanical & General Information

- **Common Names:** Nutgrass, Purple Nutsedge
- **Scientific Name:** *Cyperus rotundus*
- **Family:** Cyperaceae
- **Parts Used:** Rhizomes (underground stems), roots
- **Traditional Uses:** Anti-inflammatory, digestive aid, antioxidant, cardioprotective.

Safety and Toxicological Considerations

Existing data indicate that *C. rotundus* extracts exhibit acceptable safety profiles in rodents at therapeutic doses, with no significant toxicity up to several hundred mg/kg. However, specific safety studies in the context of DOX co-administration are necessary.

CONCLUSION AND FUTURE DIRECTIONS

C. rotundas exhibits **antioxidant, anti-inflammatory, and vascular modulatory activities**, suggesting potential as a cardio protective agent against DOX-induced cardiac injury. While direct evidence is currently lacking, the plant's photochemistry aligns with mechanisms that counteract DOX cardio toxicity. Well-designed experimental studies are needed to validate these hypotheses and support translational applications.

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