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Review

# Oxidative Stress-Mediated Cardiac Injury and Cardioprotective Potential of Medicinal Plants with Special Reference to Operculina Turpethum: A Comprehensive Review

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**Abstract:**
Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide, with oxidative stress playing a pivotal role in myocardial injury. Reactive oxygen species (ROS) induce lipid peroxidation, protein oxidation, and DNA damage, leading to cardiomyocyte dysfunction and apoptosis. Biomarkers such as CK-MB, troponins, and lactate dehydrogenase are essential for early detection and monitoring of cardiac injury. In-vitro models using cardiomyocytes allow mechanistic studies of oxidative injury and screening of cardioprotective agents. Medicinal plants, particularly *Operculina turpethum*, have demonstrated significant antioxidant, anti-apoptotic, and anti-inflammatory activities, highlighting their potential in cardioprotection. This review summarizes the molecular mechanisms of oxidative stress-mediated cardiac injury, in-vitro screening models, and the cardioprotective potential of *O. turpethum*, while identifying research gaps and future directions.

**Keywords:** Cardioprotection; *Operculina turpethum*; oxidative stress; reactive oxygen species; myocardial injury; medicinal plants



## 1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of global mortality, accounting for approximately 17.9 million deaths annually, which represents 32% of all global deaths [1]. The burden is especially high in low- and middle-income countries, including India, where rapid urbanization, lifestyle changes, and increased prevalence of risk factors such as hypertension, diabetes, and dyslipidemia have contributed to a surge in CVD-related morbidity and mortality [2].

Myocardial injury in CVD is often mediated by oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) generation and antioxidant defense systems. Excess ROS can induce lipid peroxidation, protein oxidation, and DNA damage, ultimately leading to cardiomyocyte apoptosis or necrosis [3,4].

Early detection of myocardial injury relies on sensitive and specific biomarkers, including creatine kinase-MB (CK-MB), cardiac troponins, lactate dehydrogenase (LDH), and brain natriuretic peptide (BNP), which provide crucial information for diagnosis, prognosis, and therapeutic monitoring [5,6].

Medicinal plants have historically been a rich source of cardioprotective agents. Phytochemicals such as flavonoids, phenolics, alkaloids, and glycosides exhibit

antioxidant, anti-inflammatory, and anti-apoptotic properties, making them attractive candidates for preclinical and clinical evaluation [7,8]. Among these, *Operculina turpethum* has emerged as a promising cardioprotective plant, showing efficacy in reducing oxidative stress and preserving myocardial function in experimental models [9–11].

This review provides a comprehensive overview of oxidative stress- mediated cardiac injury, molecular mechanisms, in-vitro cardioprotective models, and the role of medicinal plants, with a particular emphasis on *O. turpethum*. Research gaps and future directions for cardioprotective drug development are also discussed.

## 1. Oxidative Stress and Myocardial Injury

Oxidative stress is defined as an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense systems, leading to cellular damage. In the myocardium, excessive ROS production is a key mediator of ischemia–reperfusion injury, myocardial infarction, and heart failure [12,13].

### 1.1 Sources of Reactive Oxygen Species in the Heart

ROS are generated from multiple sources within cardiomyocytes, including:

1. **Mitochondrial electron transport chain (ETC):** Leakage of electrons at complex I and III produces superoxide anions ($O_2^-$) [14].
2. **NADPH oxidases (NOX):** Membrane-bound enzymes that generate superoxide during stress responses [15].
3. **Xanthine oxidase:** Converts hypoxanthine to xanthine, generating ROS during ischemic reperfusion [16].
4. **Uncoupled nitric oxide synthase (NOS):** Produces superoxide instead of nitric oxide under pathological conditions [17].

### 1.2 Mechanisms of ROS-Induced Myocardial Injury

Excess ROS mediates cardiac injury through multiple mechanisms:

- **Lipid peroxidation:** ROS attack membrane lipids, disrupting cellular and mitochondrial membranes, leading to cardiomyocyte death [18].
- **Protein oxidation:** ROS modify proteins, impairing enzymatic function and structural integrity [19].
- **DNA damage:** Oxidative stress induces DNA strand breaks and activates pro-apoptotic pathways [20].
- **Apoptosis and necrosis:** Activation of caspase cascades and mitochondrial permeability transition pore (mPTP) opening leads to programmed cell death [21].

**Role of Oxidative Stress in Ischemia–Reperfusion Injury**

During myocardial ischemia, limited oxygen supply reduces mitochondrial ATP production. Upon reperfusion, a sudden influx of oxygen generates ROS, triggering oxidative damage and inflammation [22]. This phenomenon is central to myocardial infarction and is a key target for cardioprotective interventions.

### 1.3 Antioxidant Defense Systems

The heart is equipped with enzymatic and non-enzymatic antioxidants to neutralize ROS:

- **Enzymatic:** Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx)
- **Non-enzymatic:** Glutathione (GSH), vitamin C, vitamin E, flavonoids [23]

An imbalance between ROS generation and these antioxidant defenses results in oxidative stress, contributing to myocardial injury and progression of CVD.

**Table 1: Common Sources and Effects of ROS in the Heart**

| Source | ROS Produced | Mechanism of Damage | References |
|---|---|---|---|
| Mitochondrial ETC | Superoxide ($O_2^-$) | Lipid peroxidation, mitochondrial dysfunction | [14] |

| | | | |
|---|---|---|---|
| NADPH oxidase (NOX) | Superoxide | Protein oxidation, inflammatory signaling | [15] |
| Xanthine oxidase | Superoxide, $H_2O_2$ | DNA damage, apoptosis | [16] |
| Uncoupled NOS | Superoxide | Endothelial dysfunction, reduced NO availability | [17] |

## 2. Molecular Mechanisms of ROS-Mediated Cardiac Damage

Reactive oxygen species (ROS) are central mediators of cardiac injury, not only causing direct macromolecular damage but also triggering signaling cascades that promote apoptosis, inflammation, and fibrosis [24,25]. Understanding these molecular mechanisms is essential for developing cardioprotective strategies.

### 2.1 Mitochondria-Mediated Apoptosis

Mitochondria are both a major source and target of ROS in cardiomyocytes. Excess ROS induces:

- **Mitochondrial permeability transition pore (mPTP) opening:** Leads to loss of mitochondrial membrane potential and cytochrome c release [26].
- **Caspase activation:** Cytochrome c activates caspase-9 and caspase-3, promoting apoptosis [27].
- **Bcl-2 family regulation:** Increased Bax/Bak and decreased Bcl- 2 levels favor apoptosis [28].

### 2.2 ROS-Induced Signaling Pathways

ROS act as signaling molecules modulating several pathways:

1. **NF-κB pathway:** Activated by ROS, leading to transcription of pro-inflammatory cytokines such as TNF-α and IL-6 [29].
2. **MAPK pathway (ERK, JNK, p38):** ROS-induced phosphorylation promotes apoptosis and hypertrophic signaling [30].
3. **Nrf2 pathway:** ROS activate Nrf2 translocation to the nucleus, upregulating antioxidant defense genes (SOD, CAT, GPx) as a protective response [31].

### 2.3 Lipid Peroxidation and Membrane Damage

ROS-mediated peroxidation of membrane lipids generates malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which further impair membrane integrity, ion transport, and mitochondrial function, exacerbating cardiomyocyte death [32].

### 2.4 ROS-Induced Inflammatory Response

Excessive ROS triggers activation of inflammatory mediators:

- **Cytokine release:** TNF-α, IL-1β, IL-6
- **Activation of NLRP3 inflammasome:** Promotes pyroptosis in cardiomyocytes
- **Recruitment of immune cells:** Neutrophils and macrophages amplify tissue injury [33,34]

Collectively, ROS-mediated molecular pathways contribute to myocardial apoptosis, necrosis, fibrosis, and ultimately, progression of heart failure.

**Table 2: Key Molecular Pathways in ROS-Mediated Cardiac Injury**

| Pathway/Mechanism | ROS Effect | Downstream Outcome | Reference s |
|---|---|---|---|
| Mitochondrial apoptosis | mPTP opening, cytochrome c release | Caspase activation, apoptosis | [26–28] |
| NF-κB signaling | ROS-mediated phosphorylation | Cytokine production, inflammation | [29] |
| MAPK signaling | ERK, JNK, p38 activation | Apoptosis, hypertrophy | [30] |
| Nrf2 antioxidant response | Nuclear translocation of Nrf2 | SOD, CAT, GPx upregulation, ROS neutralization | [31] |
| Lipid peroxidation | MDA, 4-HNE formation | Membrane damage, mitochondria l dysfunction | [32] |

## 3. Cardiac Biomarkers

Cardiac biomarkers are vital tools for the **early diagnosis, prognosis, and monitoring of myocardial injury**. They reflect the extent of cardiomyocyte damage and help guide therapeutic interventions [35,36].

### 3.1 Classification of Cardiac Biomarkers

1. **Enzymatic markers**
   - **Creatine kinase-MB (CK-MB):** Released within 4–6 hours of myocardial injury; peaks at 18–24 hours. Sensitive for early detection [37].
   - **Lactate dehydrogenase (LDH):** Peaks later (24–48 hours); useful in late diagnosis or reinfarction [38].
2. **Protein markers**
   - **Cardiac troponins (cTnI, cTnT):** Highly specific and sensitive; released 3–6 hours post-injury; remain elevated for up to 10 days [39].
3. **Other markers**
   - **Aspartate aminotransferase (AST) & Alanine aminotransferase (ALT):** Indicative of myocardial damage but less specific [40].
   - **Brain natriuretic peptide (BNP) & NT-proBNP:** Reflect myocardial stress and heart failure progression [41].

### 3.2 Role in Experimental and Clinical Studies

In preclinical studies, measurement of biomarkers like CK-MB, LDH, and troponins is critical for evaluating cardioprotective interventions, including herbal extracts, antioxidants, and pharmacological agents. These biomarkers provide quantitative data on myocardial injury and therapeutic efficacy [42].

**Table 3: Common Cardiac Biomarkers and Their Clinical Relevance**

| Biomarker | Type | Time of Elevation Post-Injury | Pea k Tim e | Specificity | Clinical Use | References |
|---|---|---|---|---|---|---|
| CK-MB | Enzyme | 4–6 h | 18–24h | Moderate | Early MI detection | [37] |
| LDH | Enzyme | 12–24 h | 24–48h | Low | Late MI detection, reinfarction | [38] |
| Troponin I/T | Protein | 3–6 h | 12–24h | High | Diagnosis and prognosis of | [39] |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | MI | |
| AST | Enzyme | 6–8 h | 24 h | Low | Adjunct marker of myocardial injury | [40] |
| ALT | Enzyme | 6–8 h | 24 h | Low | Adjunct marker | [40] |
| BNP/NT-proBNP | Peptide | 1–2 h (heart failure) | N/A | Moderate | Heart failure evaluation | [41] |

## 4. In-Vitro Cardioprotective Screening Models

In-vitro models provide a controlled platform for studying mechanisms of cardiotoxicity and screening potential cardioprotective agents before in-vivo studies. These models allow mechanistic insights into oxidative stress, apoptosis, and drug efficacy [43].

### 4.1 Types of In-Vitro Models

1. **Primary Cardiomyocytes**
   - Isolated from neonatal or adult rodents
   - Maintain physiological properties of cardiac cells
   - Useful for mechanistic studies of ROS-mediated injury [44]
2. **H9c2 Cell Line**
   - Derived from rat embryonic heart tissue
   - Widely used due to ease of culture and reproducibility
   - Can mimic hypoxia/reoxygenation and oxidative stress injury [45]
3. **Stem Cell–Derived Cardiomyocytes**
   - Induced pluripotent stem cells (iPSC) differentiated into cardiomyocytes
   - Closely resemble human cardiomyocytes
   - Useful for translational studies and drug screening [46]
4. **Cardiomyocyte-Like Cell Lines**
   - HL-1 (mouse atrial) or AC16 (human ventricular) cells
   - Allow high-throughput screening and mechanistic studies [47]

### 4.2 Induction of Oxidative Injury

Cardiomyocyte injury in-vitro is typically induced by:

- **Hydrogen peroxide ($H_2O_2$):** Direct ROS generation
- **Hypoxia/Reoxygenation (H/R):** Mimics ischemia–reperfusion
- **Isoproterenol or Doxorubicin treatment:** Drug-induced cardiotoxicity [48,49]

These models are essential for assessing antioxidant, anti-apoptotic, and cytoprotective potential of medicinal plant extracts such as *O. turpethum*.

**Table 4: Common In-Vitro Cardioprotective Screening Models**

| Model | Description | Injury Induction Method | Advantages | Limitations | References |
|---|---|---|---|---|---|
| Primary cardiomyocytes | Isolated from neonatal/ adult rodents | $H_2O_2$, H/R | Physiologically relevant | Difficult to culture, limited lifespan | [44] |
| H9c2 cells | Rat embryonic heart- derived cell line | $H_2O_2$, Isoproterenol | Easy to culture, reproducible | Less human relevance | [45] |
| iPSC- derived cardiomyocytes | Human stem cell-derived | H/R, $H_2O_2$ | Human- like response, translational | Expensive, technically challenging | [46] |

| | | | | | |
|---|---|---|---|---|---|
| HL-1/AC16 cell lines | Mouse/human cardiomyocyte lines | Doxorubicin, $H_2O_2$ | High-throughput, mechanistic studies | May differ from primary cardiomyocytes | [47] |

**1. Medicinal Plants with Cardioprotective Activity**

Medicinal plants have been extensively studied for their **cardioprotective potential**, primarily due to their **antioxidant, anti-inflammatory, anti-apoptotic, and lipid-lowering effects**.

Phytochemicals such as flavonoids, phenolics, alkaloids, saponins, and glycosides play crucial roles in protecting cardiomyocytes against oxidative stress-induced injury [50,51].

**1.1 Mechanisms of Cardioprotection by Plants**

1. **Antioxidant activity:** Scavenging ROS and enhancing endogenous antioxidant enzymes (SOD, CAT, GPx)
2. **Anti-apoptotic effect:** Modulation of Bcl-2/Bax ratio, inhibition of caspase activation
3. **Anti-inflammatory activity:** Suppression of NF-κB, TNF-α, and IL-6 signaling
4. **Lipid regulation:** Reduction of cholesterol, triglycerides, and prevention of atherosclerosis

These mechanisms have been demonstrated in both **in-vitro and in- vivo studies**, highlighting the therapeutic potential of plant-derived compounds in cardiovascular diseases.

**2. Detailed Focus on *Operculina turpethum***

*Operculina turpethum* (Family: Convolvulaceae), commonly known as **Indian Jalap**, is a medicinal plant traditionally used in **cardiovascular, gastrointestinal, and inflammatory disorders** [57]. Recent studies highlight its **cardioprotective potential**, primarily due to its **antioxidant, anti-apoptotic, and anti-inflammatory properties**.

**2.1 Botanical Description**

- **Habit:** Perennial climbing vine
- **Leaves:** Simple, ovate
- **Flowers:** Small, funnel-shaped
- **Roots:** Thick, tuberous, used for medicinal purposes
- **Geographical Distribution:** India, Sri Lanka, Southeast Asia [57]

**2.2 Phytochemistry**

The root extract of *O. turpethum* contains a rich array of bioactive compounds, including:

- **Glycosides:** Turpethin, operculinoside
- **Flavonoids:** Quercetin, kaempferol derivatives
- **Triterpenoids and steroids:** Betulinic acid, sitosterol
- **Phenolic compounds:** Catechins, tannins [58,59]

**In-Vivo Studies:**

- **Isoproterenol-induced myocardial injury in rats:** *O. turpethum* significantly reduced serum CK-MB, LDH, and troponin levels, while enhancing antioxidant enzymes SOD, CAT, and GSH [9,10].
- **Histopathological improvements:** Reduced myocardial necrosis, edema, and inflammatory infiltration [9].
- **In-Vitro Studies:**
- **H9c2 cardiomyocyte models:** Root extracts scavenged ROS and prevented $H_2O_2$-induced apoptosis, as indicated by decreased Bax/Bcl-2 ratio and caspase-3 activity [11].

These findings suggest a **multi-targeted cardioprotective mechanism**, making *O. turpethum* a promising candidate for therapeutic development.

**Table 6: Pharmacological Activities of *Operculina turpethum***

| Study Type | Model / Method | Observed Effect | Mechanism Involved | References |
|---|---|---|---|---|
| In- vivo | Isoproterenol- induced MI in rats | ↓ CK-MB, LDH, troponin; ↑ SOD, CAT, GSH | Antioxidant, anti-apoptotic | [9,10] |
| In- vivo | Histopathology | Reduced myocardial necrosis and edema | Anti- inflammatory | [9] |
| In- vitro | H9c2 cardiomyocytes + $H_2O_2$ | ↓ ROS generation, ↓ caspase-3 activity | ROS scavenging, anti-apoptotic | [11] |
| In- vitro | DPPH radical scavenging assay | $IC_{50}$ 45–50 µg/mL | Free radical scavenging | [58] |

**Research Gaps and Future Perspectives**

Despite growing evidence supporting the cardioprotective potential of *Operculina turpethum* and other medicinal plants, several research gaps remain:

**2.3 Limitations in Current Studies**

1. **Preclinical focus:** Most studies are limited to rodent models or in-vitro systems; human clinical data are scarce [60].
2. **Standardization issues:** Variability in extraction methods, plant parts, and bioactive content reduces reproducibility [61].
3. **Mechanistic clarity:** While antioxidant and anti-apoptotic effects are documented, detailed molecular signaling pathways remain underexplored.
4. **Long-term safety and toxicity:** Limited data exist on chronic use, pharmacokinetics, and potential drug interactions.

**2.4 Future Directions**

1. **Clinical trials:** Well-designed randomized controlled trials to validate efficacy and safety in humans.
2. **Standardized extracts:** Isolation and characterization of bioactive compounds for dose optimization.
3. **Multi-target studies:** Investigation of molecular mechanisms beyond ROS scavenging, including epigenetic regulation and mitochondrial dynamics.
4. **Formulation development:** Novel delivery systems (nanoparticles, liposomes) to enhance bioavailability and therapeutic outcomes [62].

Addressing these gaps will accelerate the translation of *O. turpethum* from traditional use to evidence-based cardioprotective therapy.

**Conclusion**

Cardiovascular diseases remain a major global health challenge, with oxidative stress playing a pivotal role in myocardial injury. Early detection through cardiac biomarkers and mechanistic insights from in-vitro models are critical for evaluating cardioprotective interventions.

Medicinal plants, particularly *Operculina turpethum*, exhibit significant antioxidant, anti-apoptotic, and anti-inflammatory properties, highlighting their therapeutic potential. However, most evidence is preclinical, and further research, including clinical trials, is needed to validate efficacy and ensure safety.

Overall, *O. turpethum* represents a promising candidate for **multi- targeted cardioprotective therapy**, and future studies focusing on molecular mechanisms, standardized extracts, and translational research may pave the way for its clinical application.

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