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Pharmacological Evaluation of the Cardioprotective Effect of *Selaginella bryopteris* in Experimental Myocardial Infarction Induced by Isoproterenol

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ABSTRACT

Cardiovascular diseases (CVDs) remain the leading cause of global mortality, accounting for nearly one-third of all deaths worldwide (World Health Organisation [WHO], 2023; Roth et al., 2020). Among them, myocardial infarction (MI) is a major manifestation of ischemic heart disease characterised by irreversible cardiac muscle injury caused by prolonged ischemia, oxidative stress, inflammation, mitochondrial dysfunction, and calcium overload (Ibanez et al., 2018; Hausenloy & Yellon, 2013). Although current therapies such as β-blockers, statins, ACE inhibitors, and reperfusion strategies have improved survival, persistent oxidative-inflammatory injury and ventricular dysfunction continue to limit complete recovery (Benjamin et al., 2019).

Medicinal plants have gained attention as potential cardioprotective agents because of their multitarget pharmacological properties. *Selaginella bryopteris*, commonly known as "Sanjeevani booti" or the "resurrection plant," possesses significant antioxidant, anti-inflammatory, and cytoprotective activities attributed to its flavonoids, biflavonoids, phenolic compounds, terpenoids, and alkaloids (Sah et al., 2015; Li et al., 2020).

The Isoproterenol-induced myocardial infarction model is widely used for evaluating cardioprotective agents because it closely mimics oxidative stress, calcium dysregulation, inflammation, and myocardial necrosis observed in human infarction (Wexler, 1978; Madamanchi & Runge, 2013). Experimental evidence suggests that *Selaginella bryopteris* may protect the myocardium by enhancing antioxidant defences, reducing lipid peroxidation, preserving mitochondrial function, and suppressing inflammatory and apoptotic pathways (Ma, 2013; Testai et al., 2017). This review highlights the phytochemistry, pharmacological mechanisms, and cardioprotective potential of *Selaginella bryopteris* in experimental myocardial infarction.

Keywords: Cardioprotection, Myocardial Infarction, Isoproterenol, Oxidative Stress, Flavonoids, Biflavonoids, Antioxidants, Experimental Pharmacology, Medicinal Plants, *Selaginella bryopteris*

1. Introduction

Cardiovascular disease remains one of the greatest global public health challenges of the modern era. Epidemiological data consistently indicate that ischemic heart disease remains the leading cause of death worldwide, contributing substantially to disability-adjusted life years, premature mortality, and chronic morbidity across both developed and developing nations (WHO, 2023; Roth et al., 2020). Myocardial infarction is a major clinical consequence of coronary artery disease. It represents a pathophysiological event characterised by acute interruption of coronary blood flow, resulting in ischemia, metabolic collapse, and irreversible cardiomyocyte necrosis (Ibanez et al., 2018).

The pathological consequences of myocardial infarction extend well beyond acute ischemic cell death. Post-infarction injury frequently progresses into ventricular remodelling, myocardial fibrosis, arrhythmogenesis, endothelial dysfunction, chronic neurohormonal activation, and progressive heart failure, ultimately contributing to reduced quality of life and long-term mortality (Hausenloy & Yellon, 2013; Benjamin et al., 2019). The biochemical basis of myocardial infarction is multifactorial, involving oxidative stress, inflammatory cytokine activation, mitochondrial dysfunction, calcium overload, nitric oxide imbalance, apoptotic signalling, and extracellular matrix remodelling (Madamanchi & Runge, 2013).

Oxidative stress is particularly recognised as a central molecular determinant of myocardial injury. Excessive generation of reactive oxygen species (ROS) during ischemia and reperfusion results in lipid peroxidation, oxidation of membrane proteins, DNA fragmentation, mitochondrial permeability transition, activation of inflammatory transcription factors such as nuclear factor-kappa B (NF-κB), and stimulation of apoptosis through Bax-dependent pathways (Hausenloy & Yellon, 2013; Ma, 2013). These biochemical disturbances amplify myocardial damage and worsen functional cardiac decline.

At present, conventional therapeutic strategies—including antiplatelet drugs, statins, β-blockers, ACE inhibitors, nitrates, thrombolytic therapy, and mechanical reperfusion—remain central to myocardial infarction management (Ibanez et al., 2018). However, these interventions do not fully eliminate oxidative-inflammatory myocardial injury or prevent progressive ventricular remodelling, highlighting the need for novel adjunctive cardioprotective therapies (Libby, 2021). Plant-derived phytopharmaceuticals possessing multitarget antioxidant and anti-inflammatory actions have therefore attracted considerable pharmacological interest (Testai et al., 2017).

Among such candidates, *Selaginella bryopteris* has emerged as a promising medicinal plant due to its extraordinary biochemical resilience, rich phytochemical composition, and broad traditional medicinal relevance (Sah et al., 2015; Singh et al., 2018).

2. Botanical and Ethnomedicinal Profile

Selaginella bryopteris belongs to the family Selaginellaceae, one of the oldest surviving vascular plant lineages among primitive pteridophytes (Pandey et al., 2012). It is distributed in rocky mountainous terrains of India, particularly in central Indian forests, Vindhyan ecological zones, and selected Himalayan habitats characterised by severe environmental fluctuations, intense sunlight exposure, and prolonged water scarcity (Sah et al., 2015).

The plant is widely known as a “resurrection plant” because of its remarkable ability to survive extreme dehydration and rapidly restore physiological function upon rehydration. This phenomenon is biologically significant because desiccation tolerance requires highly efficient endogenous defence systems including antioxidant accumulation, membrane stabilisation, osmoprotective signalling, mitochondrial preservation, and protein stabilisation mechanisms (Singh et al., 2018). Such biochemical resilience strongly parallels mechanisms relevant in myocardial cytoprotection during oxidative injury.

In traditional Indian medicinal systems, *Selaginella bryopteris* has long been valued for rejuvenative, wound-healing, vitality-enhancing, anti-inflammatory, and restorative medicinal properties (Sah et al., 2015). Ethnomedicinal usage includes treatment of fatigue, heat stress, weakness, inflammatory disorders, and tissue injury. These traditional applications align mechanistically with modern understanding of antioxidant pharmacology, mitochondrial preservation, and inflammatory modulation, thereby supporting scientific exploration of its cardioprotective potential (Singh et al., 2018).

3. Phytochemical Composition and Pharmacological Significance

The pharmacological value of *Selaginella bryopteris* is fundamentally linked to its chemically diverse phytoconstituent profile. Phytochemical investigations reveal abundant flavonoids, biflavonoids, phenolic acids, terpenoids, alkaloids, glycosides, tannins, saponins, phytosterols, and antioxidant polysaccharides (Sah et al., 2015; Singh et al., 2018).

Flavonoids represent one of the most pharmacologically important groups because of their polyphenolic redox-active structure, enabling direct scavenging of superoxide radicals, hydroxyl radicals, and lipid peroxyl radicals while also chelating catalytic transition metals involved in hydroxyl radical generation (Panche et al., 2016). These compounds additionally inhibit LDL oxidation, suppress inflammatory cytokine release, improve endothelial nitric oxide signalling, and enhance endogenous antioxidant enzymes including superoxide dismutase, catalase, and glutathione peroxidase (Testai et al., 2017).

A distinctive phytochemical feature of *Selaginella* species is their abundance of biflavonoids such as amentoflavone-type and hinokiflavone-related compounds. These molecules possess enhanced radical stabilisation, potent anti-inflammatory activity, mitochondrial protective effects, calcium regulatory influence, and anti-apoptotic pharmacology, making them especially attractive in cardiovascular protection (Li et al., 2020).

Phenolic acids and polyphenols further contribute by activating the Nrf2 antioxidant response pathway, increasing expression of detoxifying enzymes, heme oxygenase-1, catalase, and glutathione-related antioxidant systems, thereby improving myocardial resistance against oxidative injury (Ma, 2013). Terpenoids, alkaloids, tannins, and glycosides provide additional anti-inflammatory, membrane-stabilising, vasorelaxant, and cytoprotective activity (Zhang et al., 2019).

4. Pathophysiology of Myocardial Infarction

Myocardial infarction is a complex pathobiological process characterised by irreversible necrosis of cardiomyocytes secondary to prolonged ischemia and oxygen deprivation (Ibanez et al., 2018). Although coronary artery occlusion is the primary initiating event in clinical myocardial infarction, the resulting myocardial damage involves multiple interdependent biochemical, inflammatory, metabolic, and electrophysiological disturbances (Hausenloy & Yellon, 2013).

Under normal physiological conditions, the myocardium relies heavily on aerobic oxidative phosphorylation for ATP production, with mitochondria generating nearly 95% of myocardial energy requirements through oxidation of fatty acids and glucose (Stanley et al., 2005). During ischemia, oxygen supply declines abruptly, resulting in impaired oxidative phosphorylation, ATP depletion, lactic acid accumulation, intracellular acidosis, membrane depolarisation, and ionic pump failure. Loss of ATP-dependent ion transport mechanisms promotes sodium accumulation and intracellular calcium overload, both of which contribute significantly to myocardial dysfunction and cell death (Hausenloy & Yellon, 2013).

Oxidative stress is widely recognised as a central mechanism underlying myocardial injury. Excessive generation of reactive oxygen species—including superoxide anion, hydroxyl radicals, hydrogen peroxide, and peroxynitrite—results from mitochondrial electron leakage, catecholamine autoxidation, NADPH oxidase activation, xanthine oxidase activity, and activated inflammatory cells (Madamanchi & Runge, 2013). These radicals initiate lipid peroxidation, protein oxidation, mitochondrial membrane injury, DNA fragmentation, and activation of inflammatory signalling pathways.

A major consequence of oxidative stress is membrane lipid peroxidation, which damages phospholipid bilayers and produces toxic aldehydic products such as malondialdehyde (MDA) and 4-hydroxynonenal. These secondary oxidation products further amplify oxidative injury by modifying proteins, enzymes, ion channels, and mitochondrial membranes (Madamanchi & Runge, 2013). Concurrently, oxidative injury activates inflammatory transcription factors such as NF-κB, leading to increased expression of tumour necrosis factor-

alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), inducible nitric oxide synthase, and cyclooxygenase-2 (Hausenloy & Yellon, 2013).

Mitochondrial dysfunction is another major determinant of infarct progression. Oxidative injury destabilises mitochondrial membranes, disrupts electron transport chain function, increases ROS production, and promotes opening of the mitochondrial permeability transition pore (mPTP), resulting in cytochrome c release and caspase-mediated apoptosis (Hausenloy & Yellon, 2013). Simultaneously, calcium overload activates phospholipases, proteases, and hypercontracture pathways, further contributing to myocardial necrosis and arrhythmogenesis.

Collectively, these interconnected processes culminate in cardiomyocyte death, inflammatory amplification, fibrosis, ventricular remodelling, and progressive cardiac dysfunction. Therefore, pharmacological agents capable of suppressing oxidative stress, preserving mitochondria, inhibiting inflammatory signalling, stabilising calcium homeostasis, and attenuating apoptosis possess strong cardioprotective potential (Testai et al., 2017).

5. Isoproterenol-Induced Experimental Myocardial Infarction Model

Among experimental models used for cardioprotective drug screening, the Isoproterenol-induced myocardial infarction model remains one of the most extensively validated and widely employed systems because of its reproducibility, low procedural complexity, and strong biochemical resemblance to catecholamine-mediated myocardial injury in humans (Wexler, 1978).

Isoproterenol is a synthetic non-selective β-adrenergic agonist that induces severe myocardial necrosis through multiple interrelated mechanisms including catecholamine autoxidation, calcium overload, mitochondrial dysfunction, tachycardia-induced oxygen demand, oxidative stress, and inflammatory activation (Wexler, 1978; Madamanchi & Runge, 2013). Following administration, Isoproterenol markedly increases heart rate and myocardial contractility through β_1-adrenergic stimulation, resulting in elevated oxygen consumption and ischemic imbalance between oxygen demand and coronary perfusion.

Simultaneously, autoxidation of catecholamines generates superoxide radicals, semiquinones, hydrogen peroxide, and quinones that produce intense oxidative stress and membrane lipid peroxidation (Madamanchi & Runge, 2013). Intracellular calcium overload further activates phospholipases, proteases, endonucleases, and hypercontracture pathways, accelerating myocardial degeneration and necrosis.

The Isoproterenol model reproduces characteristic biochemical and histopathological features of myocardial infarction, including elevated serum CK-MB, LDH, AST, ALT, cardiac troponins, inflammatory cytokines, and malondialdehyde levels, along with depletion of endogenous antioxidant enzymes such as SOD, CAT, GPx, and GSH (Wexler, 1978). Histological examination commonly reveals myocardial necrosis, oedema, inflammatory infiltration, myofibrillar degeneration, haemorrhage, and fibrosis, while electrocardiographic changes include ST-segment elevation, arrhythmias, tachycardia, and conduction abnormalities.

Because these pathological alterations closely resemble oxidative-inflammatory cardiac injury in humans, the Isoproterenol model serves as a highly suitable experimental platform for evaluating phytomedicinal cardioprotective agents including *Selaginella bryopteris*.

6. Molecular Mechanisms of Cardioprotection by *Selaginella bryopteris*

The cardioprotective potential of *Selaginella bryopteris* is strongly supported by mechanistic convergence between its phytochemical profile and the molecular biology of myocardial injury. Its bioactive constituents exert multitarget actions involving antioxidant defence, anti-inflammatory modulation, mitochondrial

preservation, membrane stabilisation, endothelial protection, and inhibition of apoptosis (Li et al., 2020; Testai et al., 2017).

6.1 Antioxidant and Redox Regulation

One of the most important mechanisms of cardioprotection involves restoration of oxidative balance. Flavonoids and biflavonoids in *S. bryopteris* directly scavenge reactive oxygen species while also chelating transition metals that catalyse hydroxyl radical formation (Panche et al., 2016). These compounds may additionally activate the Nrf2 antioxidant response pathway, increasing transcription of endogenous antioxidant enzymes including SOD, CAT, GPx, glutathione reductase, and heme oxygenase-1 (Ma, 2013).

$$ROS \uparrow \rightarrow Nrf2 \uparrow \rightarrow SOD,\ CAT,\ GPx,\ HO\text{-}1 \uparrow$$

Restoration of endogenous antioxidant defences reduces oxidative membrane damage, improves cellular redox balance, and enhances myocardial resistance against ischemic injury.

6.2 Inhibition of Lipid Peroxidation

Oxidative injury causes extensive lipid peroxidation of cardiomyocyte membranes, generating toxic products such as malondialdehyde that amplify cellular damage (Madamanchi & Runge, 2013). Polyphenolic compounds in *S. bryopteris* may interrupt lipid radical chain reactions, preserve membrane phospholipids, reduce membrane permeability, and prevent leakage of cardiac biomarkers such as CK-MB and LDH (Testai et al., 2017).

6.3 Mitochondrial Preservation and Anti-apoptotic Effects

Mitochondrial integrity is essential for ATP generation, calcium buffering, and cell survival. During myocardial infarction, mitochondrial permeability transition leads to cytochrome c release and activation of apoptotic cascades (Hausenloy & Yellon, 2013). Bioactive constituents in *S. bryopteris* may stabilise mitochondrial membranes, preserve respiratory enzyme function, inhibit mPTP opening, and reduce apoptosis.

$$mPTP\ opening \rightarrow Cytochrome\ c\ release \rightarrow Caspase\ activation \rightarrow Apoptosis$$

The plant may additionally regulate Bax/Bcl-2 signalling balance, thereby reducing programmed cardiomyocyte death.

$$\frac{Bax}{Bcl\text{-}2} \uparrow \rightarrow Apoptosis \uparrow$$

6.4 Anti-inflammatory Activity

Inflammatory amplification significantly contributes to infarct expansion. Polyphenols and biflavonoids from *S. bryopteris* may inhibit NF-κB activation and suppress inflammatory mediators including TNF-α, IL-6, IL-1β, and cyclooxygenase-2 (Li et al., 2020). Reduced cytokine release limits leukocyte infiltration, oedema, oxidative burst, and extracellular matrix degradation.

$$NF\text{-}\kappa B \downarrow \rightarrow TNF\text{-}\alpha,\ IL\text{-}6,\ COX\text{-}2 \downarrow$$

6.5 Calcium Homeostasis and Endothelial Protection

Calcium overload is a major contributor to myocardial necrosis and arrhythmogenesis in catecholamine-induced cardiac injury. Antioxidant and membrane-stabilising phytochemicals in *S. bryopteris* may improve calcium homeostasis by preserving ATP-dependent calcium transport and reducing oxidative calcium channel

dysfunction (Hausenloy & Yellon, 2013). Additionally, polyphenols may improve endothelial nitric oxide bioavailability and enhance coronary microvascular function (Testai et al., 2017).

7. Experimental Pharmacological Evidence

Experimental evaluation of cardioprotective agents involves integrated biochemical, molecular, electrocardiographic, hemodynamic, and histopathological assessment. Although dedicated large-scale cardioprotective studies specifically involving *Selaginella bryopteris* remain limited, its phytochemical composition and established antioxidant pharmacology strongly support therapeutic plausibility (Sah et al., 2015; Singh et al., 2018).

A cardioprotective response would be expected to demonstrate reduction in serum CK-MB, LDH, AST, ALT, troponins, inflammatory cytokines, and malondialdehyde levels alongside restoration of SOD, CAT, GPx, and glutathione activity. Histologically, reduced necrosis, oedema, inflammatory infiltration, and fibrosis with preservation of myocardial architecture would indicate effective myocardial protection. Functional improvement may include normalisation of ECG abnormalities, reduced tachycardia, and preservation of ventricular function.

Several medicinal plants, including *Curcuma longa*, *Withania somnifera*, *Terminalia arjuna*, and *Camellia sinensis,* have demonstrated cardioprotective effects through antioxidant and anti-inflammatory pathways similar to those proposed for *S. bryopteris* (Testai et al., 2017). Given its remarkable biochemical stress tolerance and biflavonoid richness, *S. bryopteris* warrants further translational cardiovascular investigation.

8. Conclusion

Selaginella bryopteris has emerged as a scientifically significant medicinal plant with considerable potential in cardiovascular pharmacology, particularly in the prevention and management of myocardial infarction. The cardioprotective relevance of the plant is strongly supported by the close relationship between its phytochemical composition and the molecular pathways involved in myocardial injury. The presence of flavonoids, biflavonoids, phenolic acids, terpenoids, alkaloids, glycosides, and antioxidant polysaccharides provides a broad spectrum of biological activities including antioxidant, anti-inflammatory, anti-apoptotic, mitochondrial protective, endothelial stabilising, and membrane-preserving effects (Li et al., 2020; Panche et al., 2016).

Experimental evidence indicates that oxidative stress plays a central role in Isoproterenol-induced myocardial infarction through excessive generation of reactive oxygen species, lipid peroxidation, calcium overload, mitochondrial dysfunction, inflammatory cytokine activation, and apoptosis (Madamanchi & Runge, 2013). The phytoconstituents of Selaginella bryopteris appear capable of modulating many of these pathological mechanisms simultaneously. Restoration of endogenous antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and reduced glutathione may significantly improve myocardial resistance to oxidative injury, while suppression of NF-κB-mediated inflammatory pathways may reduce cytokine-induced myocardial damage (Ma, 2013; Testai et al., 2017).

Additionally, the plant's biflavonoids and polyphenolic compounds may preserve mitochondrial integrity, reduce membrane lipid peroxidation, stabilise intracellular calcium homeostasis, and attenuate apoptosis through regulation of Bax/Bcl-2 signalling pathways. These multitarget pharmacological actions are particularly important because myocardial infarction is a highly complex disorder involving interconnected oxidative, inflammatory, metabolic, and apoptotic pathways rather than a single pathogenic mechanism.

The Isoproterenol-induced myocardial infarction model provides strong experimental support for evaluating natural cardioprotective agents because it reproduces several biochemical, histopathological, and electrophysiological alterations observed in human myocardial injury (Wexler, 1978). In this context, Selaginella bryopteris demonstrates promising therapeutic potential as a natural cardioprotective candidate. Although current evidence is encouraging, more comprehensive pharmacological and translational investigations are necessary before clinical application can be considered.

Overall, the integration of traditional ethnomedicinal knowledge with modern experimental pharmacology highlights Selaginella bryopteris as a potentially valuable adjunctive therapeutic agent for reducing myocardial injury and improving cardiovascular outcomes.

9. Future Directions

Despite significant advances in understanding the pharmacological properties of Selaginella bryopteris, several important areas require further investigation to establish its therapeutic applicability in cardiovascular medicine. Future research should focus on the following directions:

1. Standardisation of Phytochemical Composition

One of the major limitations in herbal pharmacology is variability in phytochemical composition due to geographical location, climate, harvesting conditions, extraction methods, and plant maturity. Standardised extraction protocols and quantitative phytochemical profiling are essential to ensure reproducibility, consistency, and pharmacological reliability of S. bryopteris preparations.

2. Isolation and Characterisation of Active Compounds

Although flavonoids and biflavonoids are considered major bioactive constituents, the exact compounds responsible for cardioprotection remain insufficiently characterised. Advanced chromatographic and spectroscopic studies should be conducted to isolate, identify, and evaluate specific phytochemicals responsible for antioxidant, anti-inflammatory, and mitochondrial protective effects.

3. Molecular Mechanistic Studies

Further molecular investigations are required to validate the intracellular signalling pathways involved in cardioprotection. Particular emphasis should be placed on pathways associated with:

- Nrf2-mediated antioxidant regulation
- NF-κB inflammatory signalling
- Bax/Bcl-2 apoptotic balance
- Mitochondrial permeability transition
- Calcium homeostasis
- Endothelial nitric oxide signalling

Understanding these mechanisms in greater detail may help establish precise pharmacodynamic targets.

4. Pharmacokinetic and Bioavailability Studies

Limited information is available regarding the absorption, distribution, metabolism, and excretion of phytoconstituents from S. bryopteris. Pharmacokinetic studies are necessary to determine bioavailability, tissue distribution, metabolic stability, plasma half-life, and optimal therapeutic dosage.

5. Toxicological and Safety Evaluation

Comprehensive acute, subacute, and chronic toxicity studies are required to evaluate long-term safety. Toxicological assessment should include hepatic, renal, haematological, reproductive, and genotoxicity evaluation to establish safe therapeutic ranges for future clinical use.

6. Advanced Experimental and Translational Research

Most available evidence remains preliminary and experimental. Future studies should include:

- Large-scale in vivo cardioprotection studies
- Comparative studies with standard cardioprotective drugs
- Dose-response evaluations
- Histopathological and ultrastructural analysis
- Biomarker-based molecular investigations
- Studies involving diabetic and hypertensive cardiac injury models

Such investigations would strengthen translational relevance.

7. Clinical Research and Therapeutic Development

Ultimately, controlled clinical studies will be necessary to evaluate efficacy, safety, tolerability, and therapeutic outcomes in human subjects. Development of standardised phytopharmaceutical formulations, nanoparticle-based delivery systems, or combination therapies may further enhance clinical applicability.

8. Integration of Traditional Knowledge with Modern Medicine

The longstanding ethnomedicinal use of Selaginella bryopteris provides an important foundation for modern scientific exploration. Integrating traditional medicinal knowledge with evidence-based pharmacological research may contribute to the discovery of safer, multitarget cardioprotective therapies for myocardial infarction and related cardiovascular disorders.

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