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TARGETING MITOCHONDRIAL DYSFUNCTION IN CARDIOVASCULAR DISEASES: EMERGING ROLE OF CARDIOPROTECTIVE HERBAL MEDICINES

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ABSTRACT

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, with mitochondrial dysfunction emerging as a central contributor to their pathogenesis. Mitochondria play a pivotal role in cardiac energy metabolism, redox homeostasis and apoptosis regulation. Disruption of mitochondrial dynamics, oxidative phosphorylationand mitochondrial membrane integrity leads to cardiomyocyte injury, particularly during ischemia-reperfusion and heart failure. While pharmacological strategies targeting mitochondrial dysfunction are under investigation, growing evidence highlights the potential of herbal medicines in modulating mitochondrial function and offering cardioprotection. This review explores the molecular mechanisms by which cardioprotective herbsincluding *Curcuma longa*, *Panax ginseng*, *Salvia miltiorrhiza* and *Withania somnifera* exert their beneficial effects via mitochondrial pathways. Key mechanisms include attenuation of oxidative stress, inhibition of mitochondrial permeability transition pore (mPTP) opening, enhancement of mitochondrial biogenesisand modulation of apoptosis-related signaling. By integrating insights from preclinical and emerging clinical studies, we highlight the promise of herbal medicines as adjunct or alternative strategies in managing mitochondrial dysfunction in CVDs. The review also discusses current challenges, such as variability in herbal formulations and the need for translational research, to pave the way for mitochondria-targeted phytotherapeutics in cardiovascular care.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death globally, accounting for approximately 17.9 million deaths annually about 32% of all global deaths, according to the World Health Organization [1]. Despite advances in pharmacotherapy and interventional cardiology, the morbidity and mortality associated with CVDs remain high, primarily due to the complex molecular mechanisms underlying disease progression and limited efficacy of current treatments in addressing those root causes.Among these mechanisms, mitochondrial dysfunction has emerged as a central player in the pathogenesis of various cardiovascular conditions, including ischemic heart disease, myocardial infarction, heart failure and cardiomyopathies [2-3]. Mitochondria are not only critical for energy production in cardiomyocytes through oxidative phosphorylation but also regulate calcium homeostasis, reactive oxygen species (ROS) generation and apoptosis. Damage to mitochondrial structure or function leads to excessive ROS production, mitochondrial DNA (mtDNA) damage and the activation of cell death pathways, exacerbating cardiac injury [4].

In recent years, interest has grown in natural products and herbal medicines for their potential cardioprotective effects, particularly their ability to modulate mitochondrial function

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[5]. Several traditional medicinal herbs including *Curcuma longa* (turmeric), *Salvia miltiorrhiza* (Danshen), *Panax ginseng* and *Withania somnifera* (ashwagandha) have shown promise in preclinical studies for improving mitochondrial health, reducing oxidative stressand preserving cardiomyocyte viability under stress conditions [6-7].

Given this emerging evidence, this review aims to explore the mitochondria targeted mechanisms by which cardioprotective herbal medicines exert their effects in cardiovascular diseases. We focus on mitochondrial biogenesis, oxidative stress attenuation, inhibition of mitochondrial permeability transition pore (mPTP) opening and modulation of apoptosis, drawing from experimental and translational studies. This mechanistic understanding could open new avenues for integrating herbal medicine into mitochondria-centered therapies for cardiovascular health.

Burden of CVDs

Cardiovascular diseases (CVDs) remain the leading cause of death globally, accounting for an estimated 17.9 million deaths per year, which represents approximately 32% of all global deaths. Of these, over 85% are due to heart attacks and strokes, according to the World Health Organization [1]. The global burden of CVD is not only reflected in mortality but also in rising disability-adjusted life years (DALYs), reduced quality of life and increasing healthcare costs.

CVDs are driven by a combination of modifiable risk factorsincluding hypertension, diabetes, smoking, obesity, physical inactivity and unhealthy dietsand non-modifiable factors such as age and genetics. Rapid urbanization, lifestyle transitions and increased life expectancy have contributed to a surge in CVD prevalence, particularly in low and middle-income countries, which now account for more than 75% of CVD-related deaths [8].In addition to the human toll, the economic burden of CVDs is substantial. The global costincluding direct healthcare expenses and loss of productivityis projected to exceed $1 trillion annually by 2030 [9]. Despite existing interventions, recurrent cardiovascular events and progressive heart failure remain common. Highlighting the need for novel therapeutic strategies that target the underlying molecular and cellular mechanisms of cardiac injury.

One such emerging area is the role of mitochondrial dysfunction in the pathophysiology of CVDs, which offers promising avenues for mitochondria-targeted therapies, including those derived from cardioprotective herbal medicines.

Emerging importance of mitochondrial health in cardio-protection

Mitochondria are fundamental to cardiac cell survival and function due to their pivotal role in ATP production, calcium homeostasis, redox balance and the regulation of apoptotic signaling. The heart, with its high metabolic demand, relies heavily on healthy mitochondrial function to sustain contractile activity and overall performance. Disruption of mitochondrial integrity is now recognized as a key pathological feature in numerous cardiovascular diseases (CVDs), including myocardial infarction, ischemia-reperfusion (I/R) injury, heart failure and cardiomyopathies [3-2].

During cardiovascular stress, such as ischemia or oxidative insult, mitochondria become major sources of reactive oxygen species (ROS)which can cause oxidative damage to mitochondrial DNA (mtDNA), lipids and proteins. This leads to impaired oxidative phosphorylation and opening of the mitochondrial permeability transition pore (mPTP), ultimately triggering cell death pathways such as apoptosis and necrosis[4]. Additionally, imbalances in mitochondrial dynamic snamely, fission, fusion, mitophagy and biogenesis further contribute to the decline in mitochondrial and cardiac function. Recent advances have highlighted the therapeutic potential of targeting mitochondrial pathways to mitigate cardiac injury. Interventions that preserve mitochondrial membrane potential, inhibit mPTP opening, reduce oxidative stress and promote mitochondrial biogenesis have been shown to attenuate myocardial damage and improve cardiac outcomes [10-11].

In this context, the role of natural products and herbal medicines has gained attention, as several plant-derived compounds have been found to exert mitochondria-targeted cardioprotective effects. These effects include enhancing mitochondrial antioxidant capacity, modulating pro- and anti-apoptotic signaling and promoting energy metabolism. Understanding these mechanisms provides a promising strategy for developing novel, mitochondria-focused therapies for CVDs, especially those based on traditional medicine systems.

Mitochondrial Dysfunction in CVDs

Mitochondria are central to cardiac function, generating over 90% of the adenosine triphosphate (ATP) required by the heart through oxidative phosphorylation. Beyond their role in energy production, mitochondria are critical regulators of cell death, calcium signaling and redox balance, making them key determinants of cardiomyocyte survival. In cardiovascular diseases (CVDs), mitochondrial dysfunction has emerged as a fundamental contributor to both the initiation and progression of myocardial injury [12-2].

One hallmark of mitochondrial dysfunction in CVDs is excessive production of reactive oxygen species (ROS). Under normal conditions, low levels of ROS act as signaling molecules; however, in pathological states such as ischemia-reperfusion (I/R) injury, uncontrolled ROS production leads to oxidative damage of mitochondrial DNA (mtDNA), lipids and proteins [4]. This oxidative stress not only impairs mitochondrial respiratory chain complexes but also triggers downstream apoptosis.Another critical event is the opening of the mitochondrial permeability transition pore (mPTP). This non-selective pore, when opened persistently, results in loss of mitochondrial membrane potential ($\Delta\psi m$), uncoupling of oxidative phosphorylation, matrix swelling and ultimately cell death. mPTP opening is a key mediator of myocardial necrosis during reperfusion after ischemia [13].

Additionally, disturbances in mitochondrial dynamics, including fission, fusion, mitophagy and biogenesis, contribute to CVD pathogenesis. An imbalance in these processes disrupts mitochondrial quality control, leading to the accumulation of damaged mitochondria and further aggravation of cardiac injury[14]. For example, excessive mitochondrial fission promotes apoptosis, while impaired mitophagy leads to the persistence of dysfunctional mitochondria, exacerbating oxidative damage and metabolic inefficiency.

Moreover, mitochondrial metabolic inflexibility especially impaired fatty acid oxidation and reduced pyruvate utilizationis observed in heart failure, contributing to energy starvation in cardiomyocytes[15].Collectively, these mitochondrial impairments not only compromise cardiomyocyte energy metabolism and survival but also initiate maladaptive remodeling, fibrosis and contractile dysfunction. As such, targeting mitochondrial dysfunction presents a compelling strategy in the treatment and prevention of CVDs.

ROS production*:* Reactive oxygen species (ROS) are by-products of mitochondrial oxidative phosphorylation, primarily generated at complexes I and III of the electron transport chain (ETC). Under physiological conditions, low levels of ROS serve essential roles in redox signaling, cellular adaptation and vascular tone regulation. However, during pathological stresssuch as ischemia-reperfusion (I/R) injury, heart failure, or hypertrophy mitochondrial ROS production becomes excessive and uncontrolled **[16]**.

In CVDs, mitochondrial ROS overproduction leads to oxidative damage of mitochondrial DNA (mtDNA), proteins and lipids, impairing mitochondrial function and creating a vicious cycle of further ROS generation. This oxidative stress disrupts ATP synthesis, opens the mitochondrial permeability transition pore (mPTP) and activates apoptotic signaling pathways**[4]**. Notably, mitochondrial ROS also modulate inflammation by activating redox-sensitive transcription factors such as NF-κB and NLRP3 inflammasome, contributing to cardiac remodeling and fibrosis[17].

Additionally, excessive ROS can cause depolarization of the mitochondrial membrane potential (Δψm), promoting cytochrome c release and caspase-dependent apoptosis. These events collectively result in cardiomyocyte injury, contractile dysfunction and eventual progression to heart failure. Importantly, emerging evidence suggests that herbal medicines can modulate ROS levels by enhancing endogenous antioxidant defensessuch as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalaseor directly scavenging free radicals. Compounds from herbs like *Curcuma longa* (curcumin), *Ginkgo biloba* (ginkgolides) and *Panax ginseng*(ginsenosides) have been shown to attenuate ROS-mediated damage and restore mitochondrial function [6].

Mitochondrial permeability transition pores (mPTP)

The mitochondrial permeability transition pore (mPTP) is a non-specific, high-conductance channel that forms in the inner mitochondrial membrane under pathological conditions. Normally closed in healthy cells, mPTP opening is triggered by calcium overload, oxidative stress, ATP depletion and high mitochondrial membrane potential (Δψm) conditions that are frequently present during ischemia-reperfusion (I/R) injury and heart failure **[15-18]**.

Persistent or prolonged opening of the mPTP leads to the loss of mitochondrial membrane potential, uncoupling of oxidative phosphorylation, mitochondrial swelling and ultimately rupture of the outer mitochondrial membrane. This results in the release of pro-apoptotic factors such as cytochrome c, which activate caspase-dependent apoptosis and contribute to cardiomyocyte death **[19]**. In the setting of I/R injury, the sudden reintroduction of oxygen leads to a burst of mitochondrial ROS and calcium influx, both of which are potent inducers of mPTP opening. This process is a major contributor to reperfusion injury, often responsible for more damage than the ischemia itself [20]. As a result, inhibition of mPTP has been recognized as a viable therapeutic strategy for reducing infarct size and preserving cardiac function.

Recent studies suggest that natural products and herbal medicines may modulate mPTP opening. For example, curcumin (from *Curcuma longa*) and tanshinones (from *Salvia miltiorrhiza*) have shown the ability to prevent mPTP opening in cardiomyocytes, likely by reducing oxidative stress and modulating mitochondrial calcium handling [6-7]. These findings highlight the potential of phytochemicals to target mPTP as part of a broader strategy to maintain mitochondrial integrity in cardiovascular conditions.

Mitochondrial dynamics and biogenesis

Mitochondrial quality and function are tightly regulated by dynamic processes that include fission, fusion, mitophagy and biogenesis. Collectively referred to as mitochondrial dynamics, these processes are essential for maintaining mitochondrial integrity, adapting to cellular energy demands and removing damaged organelles. In the heart a highly energy-dependent organ imbalances in mitochondrial dynamics contribute significantly to the pathogenesis of cardiovascular diseases (CVDs) such as ischemic injury, heart failure and cardiomyopathies[14-21].

Mitochondrial Fission and Fusion

Fission facilitates mitochondrial division and is crucial for mitophagy, the removal of dysfunctional mitochondria. However, excessive fission leads to mitochondrial fragmentation, ROS overproductionand apoptosis. Key Proteins: Dynamin-related protein 1 (Drp1), Fis1.

Fusion allows mixing of mitochondrial contents, diluting damaged components and preserving function.Key Proteins: Mitofusins (Mfn1, Mfn2) and Optic atrophy 1 (Opa1). In CVD, there is often upregulation of fission and downregulation of fusion, leading to mitochondrial dysfunction and cardiomyocyte death [22]. Inhibiting Drp1 or enhancing Mfn2 expression has shown protective effects in myocardial injury models.

Mitochondrial Biogenesis

Mitochondrial biogenesis refers to the synthesis of new mitochondria and their components, a process critical for replacing damaged mitochondria and maintaining energy production. It is regulated by a complex network of signaling molecules:

- Peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α)
- Nuclear respiratory factors (NRF1, NRF2)
- Mitochondrial transcription factor A (TFAM)

In heart failure and other CVDs, suppressed biogenesis contributes to reduced mitochondrial number and impaired energy metabolism[23]. Activating PGC-1α or enhancing TFAM expression has been linked to improved mitochondrial function and cardioprotection.

Herbal Medicines and Mitochondrial Dynamics

Several cardioprotective herbal medicines have been reported to modulate mitochondrial dynamics and biogenesis:

- Resveratrol (from *Polygonum cuspidatum*): Activates PGC-1α and SIRT1, promoting biogenesis and improving cardiac function [24].
- Ginsenosides (from *Panax ginseng*): Improve mitochondrial fusion/fission balance and upregulate PGC-1α expression.
- Curcumin (from *Curcuma longa*): Enhances NRF2-mediated antioxidant response and mitochondrial biogenesis [25].
- Tanshinone IIA (from *Salvia miltiorrhiza*): Modulates Drp1/Mfn2 balance and supports mitochondrial integrity.

These phytochemicals offer promising therapeutic avenues by restoring mitochondrial homeostasis and improving energy efficiency in stressed cardiomyocytes.

Overview of Cardioprotective Herbal Medicines

Herbal medicines have been used for centuries in various traditional systems such as Ayurveda, Traditional Chinese Medicine (TCM) and Kampo to treat cardiovascular diseases (CVDs). Recently, scientific research has begun to validate many of these herbs, uncovering their bioactive compounds and molecular mechanisms underlying their cardioprotective effects. These natural products offer a rich source of multi-targeted therapeutic agents that may complement or provide alternatives to conventional CVD treatments with fewer side effects (**Zhou et al., 2019**).

Key Cardioprotective Herbs and Their Bioactive Compounds

- ***Curcuma longa* (Turmeric)**: Contains curcumin, a potent antioxidant and anti-inflammatory agent that improves endothelial function, inhibits oxidative stressand modulates mitochondrial function [25].
- ***Panax ginseng***: Rich in ginsenosides, known to enhance cardiac contractility, reduce ischemia-reperfusion injuryand improve mitochondrial biogenesis and dynamics [26].
- ***Salvia miltiorrhiza* (Danshen)**: Contains tanshinones and salvianolic acids, which exhibit antioxidant, anti-inflammatory and anti-apoptotic effectsand have been shown to inhibit mitochondrial permeability transition pore (mPTP) opening [7].
- ***Ginkgo biloba***: Its flavonoids and terpenoids improve microcirculation, reduce platelet aggregationand protect mitochondria from oxidative damage [27].
- **Hawthorn (*Crataegus* spp.)**: Rich in oligomeric proanthocyanidins and flavonoids, hawthorn extracts improve myocardial energy metabolism and exhibit vasodilatory and antioxidant properties[28].

Mechanisms of Cardioprotection act via multiple pathways,as shown in figure

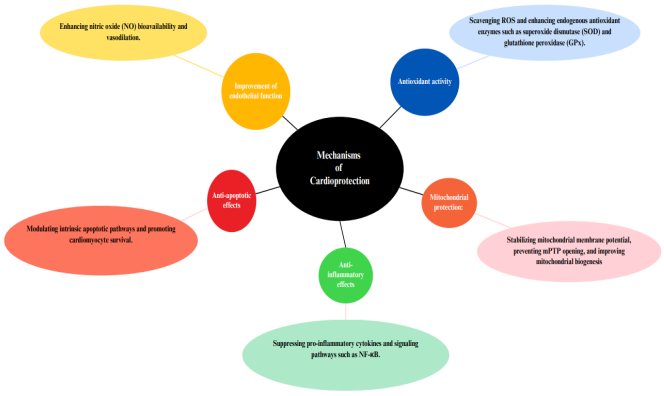

Figure 1. Mechanisms of Cardio-protection

Clinical Relevance and Future Perspectives: Several herbal extracts and isolated compounds have demonstrated efficacy in preclinical models of myocardial ischemia, heart failureand hypertension. Some, such as ginseng and Danshen, have progressed to clinical trials, showing beneficial effects on cardiac function and patient outcomes [29]. Despite promising results, challenges remain in standardization, bioavailability and understanding herb-drug interactions. Ongoing research focusing on mitochondria-targeted effects of herbal medicines may unlock novel cardioprotective therapies with improved efficacy and safety profiles.

Table.1: Common Cardioprotective Herbs

Herb Name	Key Active Compounds	Cardioprotective Mechanisms	Clinical Evidence Level*	Comments / Key References
Curcuma longa (Turmeric)	Curcumin	Antioxidant, anti-inflammatory, mitochondrial protection, inhibits mPTP opening	Moderate: Several RCTs in CVD risk factors, some clinical trials on endothelial function	[25-30]
Panax ginseng	Ginsenosides	Enhances mitochondrial biogenesis, improves cardiac contractility, anti-apoptotic	Moderate: Clinical trials in heart failure and ischemia; meta-analyses available	[26-31]
Salvia miltiorrhiza (Danshen)	Tanshinones, salvianolic acids	Antioxidant, anti-inflammatory, inhibits mPTP, improves microcirculation	Moderate to High: Used in TCM; RCTs showing efficacy in angina and myocardial ischemia	[7-32]

Ginkgo biloba	Flavonoids, terpenoids	Antioxidant, improves endothelial function, reduces platelet aggregation	Moderate: RCTs in peripheral vascular disease and cognitive function	[27-33]
Crataegus spp. (Hawthorn)	Oligomeric proanthocyanidins, flavonoids	Vasodilatory, antioxidant, improves myocardial metabolism	High: Multiple RCTs in chronic heart failure, safe and effective	[28-34]
Allium sativum (Garlic)	Allicin, ajoene	Anti-hypertensive, antioxidant, lipid-lowering, antiplatelet	Moderate: Meta-analyses supporting BP reduction, lipid improvement	[35]
Camellia sinensis (Green Tea)	Catechins (EGCG)	Antioxidant, improves endothelial function, anti-inflammatory	Moderate: Epidemiological and clinical trial support in CVD prevention	[36]
Terminalia arjuna	Arjunolic acid, tannins	Antioxidant, improves cardiac muscle function, anti-inflammatory	Low to Moderate: Traditional use supported by small clinical trials	[37-]
Hibiscus sabdariffa	Anthocyanins, flavonoids	Antihypertensive, antioxidant, diuretic effects	Moderate: RCTs showing BP lowering effects	[38]
Zingiber officinale (Ginger)	Gingerols, shogaols	Anti-inflammatory, antioxidant, improves lipid profile	Low to Moderate: Limited clinical trials, mainly on lipid and inflammation modulation	[39-40]

Common herbs with known cardioprotective effects

***High:** Multiple randomized controlled trials (RCTs) and meta-analyses supporting efficacy and safety in cardiovascular conditions. **Moderate:** Some RCTs and clinical studies with positive outcomes; traditional use supported by emerging clinical data. **Low:** Limited clinical data; mostly preclinical or small clinical studies; further research needed.

These herbs exert their cardioprotective effects mainly through antioxidant activity, mitochondrial protection, anti-inflammatory actions, improving endothelial functionand modulating lipid metabolism. Many have been shown in experimental models and some clinical studies to reduce risk factors such as hypertension, ischemia-reperfusion injuryand heart failure progression.

Mechanistic Focus: Herbal Modulation of Mitochondrial Pathways:

Mitochondria are central to cardiac cell survival and function, making them critical targets for cardioprotective interventions. Numerous herbal medicines exert their beneficial effects by modulating key mitochondrial pathways involved in energy production, oxidative stress, apoptosisand mitochondrial quality control. Understanding these mechanisms highlights how phytochemicals can preserve mitochondrial integrity and function in cardiovascular diseases (CVDs).

Antioxidant Activity and ROS Scavenging

Excessive mitochondrial reactive oxygen species (ROS) production contributes to oxidative damage in cardiomyocytes. Herbal compounds such as curcumin (*Curcuma longa*), resveratrol (*Polygonum cuspidatum*) and ginsenosides (*Panax ginseng*) upregulate endogenous antioxidant defenses including superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx), thereby reducing oxidative stress and mitochondrial DNA damage [24-25].

Inhibition of Mitochondrial Permeability Transition Pore (mPTP) Opening

The opening of mPTP leads to loss of mitochondrial membrane potential and initiation of apoptosis. Phytochemicals such as tanshinones (*Salvia miltiorrhiza*) and curcumin have been shown to inhibit mPTP opening, preventing mitochondrial swelling and cytochrome-c release, thus protecting cardiomyocytes from ischemia-reperfusion injury [6-7].

Regulation of Mitochondrial Dynamics

Herbal medicines modulate the balance between mitochondrial fission and fusion, essential for maintaining mitochondrial morphology and function. For example, ginsenosides promote mitochondrial fusion by upregulating mitofusin proteins (Mfn1, Mfn2) and downregulating fission mediators like Drp1, reducing mitochondrial fragmentation and apoptosis [22]. Similarly, curcumin enhances mitochondrial fusion and mitophagy, contributing to mitochondrial quality control [25].

Enhancement of Mitochondrial Biogenesis

Activation of mitochondrial biogenesis increases mitochondrial mass and improves cardiac energetics. Key regulators such as PGC-1α, NRF1/2and TFAM are upregulated by compounds like resveratrol and ginsenosides, leading to improved oxidative phosphorylation capacity and resistance to cardiac stress [24-26].

Modulation of Apoptotic Pathways

Mitochondria-mediated apoptosis is critical in cardiomyocyte loss during CVD. Herbal compounds can modulate the balance of pro and anti-apoptotic proteins. For instance, curcumin

and tanshinones increase anti-apoptotic Bcl-2 expression and inhibit pro-apoptotic Bax and caspase activation, thus reducing cell death [7].

Synergistic Approaches: Combining Herbs with Mitochondrial-Targeted Drugs

Mitochondrial dysfunction plays a central role in the pathogenesis of cardiovascular diseases (CVDs), including heart failure, myocardial infarctionand ischemia-reperfusion injury. Therapeutic agents that specifically target mitochondrial pathways (e.g., antioxidants, permeability transition pore inhibitors, biogenesis enhancers) have emerged as promising interventions. Meanwhile, several plant-derived compounds commonly used in traditional medicinehave demonstrated cardioprotective effects through mitochondrial mechanisms. A synergistic approach, combining herbal compounds with mitochondrial-targeted pharmacological agents, may provide enhanced efficacy through multi-targeted, complementary mechanisms.

Rationale for Combining Herbal Medicines with Mitochondrial Drugs are, Multifactorial benefits: Herbal compounds often affect multiple mitochondrial processesROS regulation, membrane potential stabilization and dynamics offering additive or synergistic effects with synthetic drugs. Overcoming bioavailability issues: Nano-formulations and mitochondrial-targeted delivery systems can improve the stability and bioavailability of herbal phytochemicals. Minimizing side effects: Combination strategies may reduce the required doses of conventional drugs, decreasing potential toxicity [41].

Table.2: Mechanistic Basis of Synergy

Mitochondrial Target	Herbal Agent	Drug	Combined Effect
ROS scavenging	Resveratrol, Quercetin	MitoQ, SkQ1	Enhanced antioxidant defense
mPTP inhibition	Berberine, Tanshinone IIA	Cyclosporin A	Reduced apoptosis during reperfusion
Biogenesis stimulation	Ginsenosides, Curcumin	PGC-1α activators	Improved mitochondrial renewal
Dynamics (fission/fusion)	Salvia miltiorrhiza (Danshen)	DRP1 inhibitors	Stabilization of mitochondrial morphology
Mitophagy activation	Astragaloside IV	Urolithin A	Enhanced clearance of damaged mitochondria

Examples of polyherbal formulations or integration with conventional therapy

Resveratrol + Mitochondria-targeted Nanoparticles

Resveratrol has limited bioavailability, but encapsulation in ischemic myocardial-targeted nanoparticles (IMTPMCTDNPs) has shown increased delivery to mitochondria, reduced ROS, improved ATP productionand lowered infarct size in animal models [42].

Tanshinone IIA + Conventional Cardiovascular Therapy

Tanshinone IIA, derived from *Salvia miltiorrhiza*, combined with standard drugs like nitrates or beta-blockers, improves left ventricular function and reduces infarct size post-MI. It modulates mitochondrial apoptosis and calcium handling [43].

Berberine + Trimetazidine

In hypertensive cardiac patients, berberine combined with trimetazidine improved endothelial nitric oxide synthase (eNOS) expression and mitochondrial integrity. This combo regulated mitochondrial calcium overload and oxidative stress more effectively than either alone [44].

Curcumin + PGC-1α Activators

Curcumin can activate Nrf2 and PGC-1α pathways, improving mitochondrial biogenesis and antioxidant response. When used with pharmacological PGC-1α activators, the combination augments mitochondrial replication and functional recovery after ischemic injury [45].

Limitations, Challengesand Future Directions

Limitations related to polyherbal formulations such as poor bioavailability and stability, lack of standardization, limited clinical evidence or non-specific mechanisms of action Many herbal compounds (e.g., resveratrol, quercetin) suffer from low solubility, rapid metabolismand poor systemic absorption, limiting their effectiveness *in vivo*[46-47].

Lack of Standardization: Herbal formulations vary in concentration, purityand composition due to differences in cultivation, extractionand processing, which affects reproducibility and comparability across studies [45].

Limited Clinical Evidence: Most evidence is derived from preclinical studies; human clinical trials are scarce, small-scaleand lack long-term follow-up [48].

Non-specific Mechanisms of Action: Herbal compounds often act on multiple cellular targets. While this can be beneficial, it complicates mechanistic understanding and raises concerns about off-target effects [49].

Challenges

Translational Gap: Positive findings in rodent or cell models do not always translate to human success due to differences in metabolism, disease progressionand mitochondrial dynamics [17]

Complexity of Cardiovascular Disease: CVDs involve multifactorial and systemic dysfunctions. Targeting only mitochondrial pathways may not be sufficient for holistic treatment [50].

Delivery to Mitochondria: Current delivery systems often fail to target mitochondria efficiently. Technologies like TPP-conjugated molecules and nanocarriers are still experimental [51].

Safety and Toxicity: Long-term effects, toxicityand drug–herb interactions are not well studied, especially in elderly or polymedicated patients.

Future Directions

Development of Mitochondria-Targeted Delivery Systems: Design of nanocarriers, liposomesand conjugates (e.g., triphenylphosphonium) that can specifically deliver herbal bioactives into mitochondria [51].

Integration of Omics and Precision Medicine: Using genomics, metabolomics and mitochondrial biomarkers to tailor herbal interventions to specific patient populations[42].

Standardized Formulations and Dosing: Creating pharmaceutical-grade standardized herbal extracts with clear pharmacokinetic profiles to improve reproducibility and efficacy.

Robust Clinical Trials: Large-scale, randomized, controlled trials are needed to confirm efficacy, determine optimal dosages, assess long-term safety and understand interactions with conventional drugs.

Combining Herbal and Synthetic Therapies: Exploring synergistic effects between herbal compounds and conventional drugs or mitochondrial-targeted agents like elamipretide or MitoQ.

CONCLUSION

Targeting mitochondrial dysfunction presents a promising avenue in the prevention and treatment of cardiovascular diseases (CVDs) and herbal medicines offer unique potential due to their multitarget effects and natural origin. Numerous phytochemicals such as resveratrol, quercetin, curcuminand ginsenosides have demonstrated the ability to modulate mitochondrial dynamics, reduce oxidative stress and enhance mitochondrial bioenergetics in preclinical models. However, the translation of these findings into clinical success is hindered by significant limitations. These include poor bioavailability, lack of standardized formulations, insufficient human trials and challenges in mitochondrial-specific drug delivery. Moreover, the complex pathophysiology of CVDs demands a systems-level approach rather than isolated interventions. To overcome these barriers, future research should focus on: developing advanced mitochondria-targeted delivery systems,standardizing herbal compounds for pharmaceutical use,conducting large-scale, biomarker-guided clinical trials and integrating herbal therapies with conventional or emerging mitochondrial medicines. In conclusion, while cardioprotective herbal medicines show great promise in targeting mitochondrial dysfunction, realizing their full therapeutic potential will require multidisciplinary efforts involving pharmacology, systems biology, nanotechnology and clinical science.

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