Review Article

Advances in Chinese herbal medicine in modulating mitochondria to treat myocardial ischemia-reperfusion injury: a narrative review

Yushi Tian[1]^, Xiaoyang Hu[1], Tingyu Zhang[2], Bojia Li[1], Qiang Fu[1], Ji Li[1]

[1]School of Basic Medicine, Heilongjiang University of Chinese Medicine, Harbin, China; [2]Acupuncture and Tuina Science, Liaoning University of Chinese Medicine, Shenyang, China

Contributions: (I) Conception and design: Y Tian, Q Fu; (II) Administrative support: J Li, X Hu; (III) Provision of study materials or patients: Y Tian, B Li; (IV) Collection and assembly of data: Y Tian, B Li; (V) Data analysis and interpretation: Y Tian, B Li, T Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ji Li, MD, PhD. School of Basic Medicine, Heilongjiang University of Chinese Medicine, No. 24 Heping Road, Xiangfang District, Harbin 150040, China. Email: 626753714@qq.com.

Background and Objective: The urgent need to identify pathways that can mitigate myocardial ischemia-reperfusion injury (MIRI) has become a central focus in cardiovascular treatment. Chinese herbal medicine (CHM), renowned for its multi-component, multi-channel, and multi-target therapeutic properties, holds significant promise in the management of MIRI. Mitochondria, as pivotal players in MIRI, have been shown to be effectively modulated by CHM through various mechanisms. The objective of this narrative review is to underscore the critical role of mitochondria in MIRI and to provide an up-to-date overview of the latest research advancements in utilizing CHM to treat MIRI by targeting mitochondrial morphology and function.

Methods: The PubMed and the China National Knowledge Infrastructure (CNKI) databases were searched using keywords related to MIRI. Relevant English-language articles published from January 2019 to July 2024 were included in this narrative review.

Key Content and Findings: Mitochondria are intimately linked to MIRI. The mechanisms involve the regulation of mitochondrial biogenesis and energy metabolism, the functionality of the mitochondrial respiratory chain, resistance to oxidative stress-induced damage, the maintenance of mitochondrial homeostasis, the modulation of calcium ion homeostasis, the preservation of mitochondrial membrane potential, the opening of adenosine triphosphate (ATP)-sensitive potassium channels, and the effective control over the opening of the mitochondrial permeability transition pore, all of which contribute to the balance between autophagy and apoptosis in cardiomyocytes. Various effective monomers of CHM, extracts of CHM, compounds, and proprietary Chinese medicine have demonstrated promising therapeutic potential in basic research, among them, tonic and blood-activating CHMs account for the largest proportion.

Conclusions: The prospect of CHM targeting mitochondria for the treatment of MIRI is promising, yet it necessitates overcoming challenges such as low bioavailability and inadequate mechanistic research. By integrating traditional Chinese medicine theories with modern scientific technologies, it is imperative to delve deeper into and optimize the pharmacodynamics, pharmacokinetics, and clinical applications of these herbs.

Keywords: Mitochondria; myocardial ischemia-reperfusion injury (MIRI); monomers of Chinese herbal medicine (monomers of CHM); extracts of Chinese herbal medicine (extracts of CHM)

Submitted Jul 22, 2024. Accepted for publication Nov 28, 2024. Published online Feb 25, 2025.
doi: 10.21037/cdt-24-346
View this article at: https://dx.doi.org/10.21037/cdt-24-346

^ ORCID: 0009-0004-9923-9659.

Introduction

Background

Acute myocardial infarction (AMI) is the most serious ischemic heart disease caused by the rupture of coronary atherosclerotic plaques (1). It is one of the major diseases with high morbidity and mortality in the world (2). At present, the main treatment methods include percutaneous coronary intervention, thrombolysis, anticoagulation, and coronary artery bypass grafting, with the aim of promptly resolving thrombus occlusion and restoring coronary blood flow (3,4). However, a growing body of evidence demonstrated that when the interrupted myocardial blood supply is restored within a certain period, it may cause more serious damage to the original ischemic myocardium, known as myocardial ischemia-reperfusion injury (MIRI), manifested as myocardial stunning, reperfusion arrhythmia, microvascular dysfunction, and fatal myocardial reperfusion injury (5). Therefore, how to reduce additional heart damage has become one of the urgent problems to be solved in the treatment of cardiovascular diseases. Mitochondria are the main site of adenosine triphosphate (ATP) generation, which can support the metabolism and function of myocardial cells. Mitochondrial structural disorder and dysfunction during reperfusion are the key factors of cell death after AMI (6,7). To date, relevant studies have shown that Chinese herbal medicine (CHM) is an effective treatment to alleviate MIRI by regulating the structure and function of mitochondria (8,9). Currently, the primary therapeutic approaches for clinical management of MIRI encompass: (I) pharmacological therapy: the mitochondrial protector cyclosporine A can maintain the function of the mitochondrial permeability transition pore (mPTP) (10). (II) Gene therapy: *CRISPR/Cas9* gene editing is employed for targeted modification of genes involved in mitochondrial function or oxidative stress pathways (11). (III) Cellular therapy: mitochondrial transplantation directly transfers healthy mitochondria into damaged cells to restore their functionality (12). (IV) Physical therapy: ischemic preconditioning and postconditioning (13). In comparison to these therapeutic approaches, CHMs typically contain a multitude of active compounds that target various aspects of the disease process through multiple mechanisms, making them particularly beneficial for complex diseases such as MIRI, which may be induced by multiple factors (14). The combination of CHMs can generate synergistic effects, enhancing the overall therapeutic efficacy (15). Compared to pharmacological treatments, CHMs generally harbor complex compounds capable of mutual balance, reducing the likelihood of adverse reactions, and thus, CHMs often exhibit milder side effects (14).

Rationale and knowledge gaps

Traditional Chinese medicine (TCM), including CHM, has a long history of treating cardiovascular diseases with a holistic approach. Recent studies have suggested that CHM may alleviate MIRI by modulating mitochondrial function and structure, offering a promising therapeutic avenue. However, a comprehensive review of the current literature on the mitochondria-related cardioprotective effects and underlying mechanisms of CHM in MIRI is lacking.

Objective

This study conducted a narrative review of both domestic and international literature from 2019 to 2024, focusing on the mitochondria-related cardioprotective effects and potential mechanisms of monomers and extracts of CHM, compounds, and proprietary Chinese medicine in the context of MIRI. The review aimed to provide new insights into the basic research and drug development of MIRI. We present this article in accordance with the Narrative Review reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-346/rc).

Methods

To conduct this narrative review, a search was conducted in the PubMed and the China National Knowledge Infrastructure (CNKI) databases to retrieve research articles published in peer-reviewed journals between January 2019 and July 2024. The search strategy details are provided in *Table 1* and the terms used for the search are listed in *Table 2*. A total of 653 articles were reviewed by two senior authors based on their abstracts. Ultimately, 55 research articles met the inclusion criteria for this article.

The role of mitochondria in the MIRI mechanism

The heart is the most energy-consuming organ in the body (16). Mitochondria are the main organelles for ATP production and provide energy for the myocardium (17). In addition, mitochondria also have important biological functions, including regulation of intracellular calcium homeostasis and lipid metabolism, oxygen

Table 1 The search strategy summary

Items	Specification
Date of search	1 February 2024 to 2 July 2024
Databases searched	PubMed/CNKI
Search terms used	See *Table 2* for details
Timeframe	January 2019 to July 2024
Inclusion and exclusion criteria	Inclusion criteria: (I) the articles are mainly focused on the role, mechanisms, or interventional measures of mitochondria in MIRI; (II) the articles are published in full text in peer-reviewed journals; (III) the research data are complete, the statistical methods are appropriately applied, and the results are significant; (IV) the language of the articles is restricted to English and Chinese. Exclusion criteria: the primary focus of the study is not on MIRI but rather on other cardiac diseases or pathological processes
Selection process	The selection process was conducted by two senior authors (Y.T. and B.L.)

CNKI, China National Knowledge Infrastructure; MIRI, myocardial ischemia-reperfusion injury.

Table 2 Details of the search strategy in the PubMed

("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitochondria)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (Chinese herbal medicine)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mechanism)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitochondrial biogenesis)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitochondrial energy metabolism)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitochondrial respiratory chain)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitochondrial oxidative stress)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitochondrial dynamics)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitochondrial ATP-sensitive potassium channel)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitochondrial permeability transition pore)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitochondrial membrane potential)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitochondrial calcium overload)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitophagy)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitochondrial apoptosis)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (traditional Chinese medicine)
("Chinese herbal medicine"[MeSH Terms]) AND (history)
("mitochondria"[MeSH Terms]) AND (traditional Chinese medicine)
("myocardial ischemia-reperfusion injury"[MeSH Terms]) AND (mitophagy)

radical production, apoptosis and autophagy, and cell signalling (18). Under normal conditions, approximately 95% of myocardial ATP is derived from mitochondrial oxidative phosphorylation (OXPHOS) to maintain the systolic and diastolic function and ion pump function of cardiomyocytes (19). Mitochondrial dysfunction represents important pathological mechanisms of MIRI (20). When myocardial cells are damaged by ischemia and hypoxia, the energy supply mode changes from aerobic OXPHOS to anaerobic glycolysis (*Figure 1*), resulting in lactic acid, H^+ and $NADH^+$ accumulation, and decreased cytoplasmic pH (21). During reperfusion, cells need to discharge

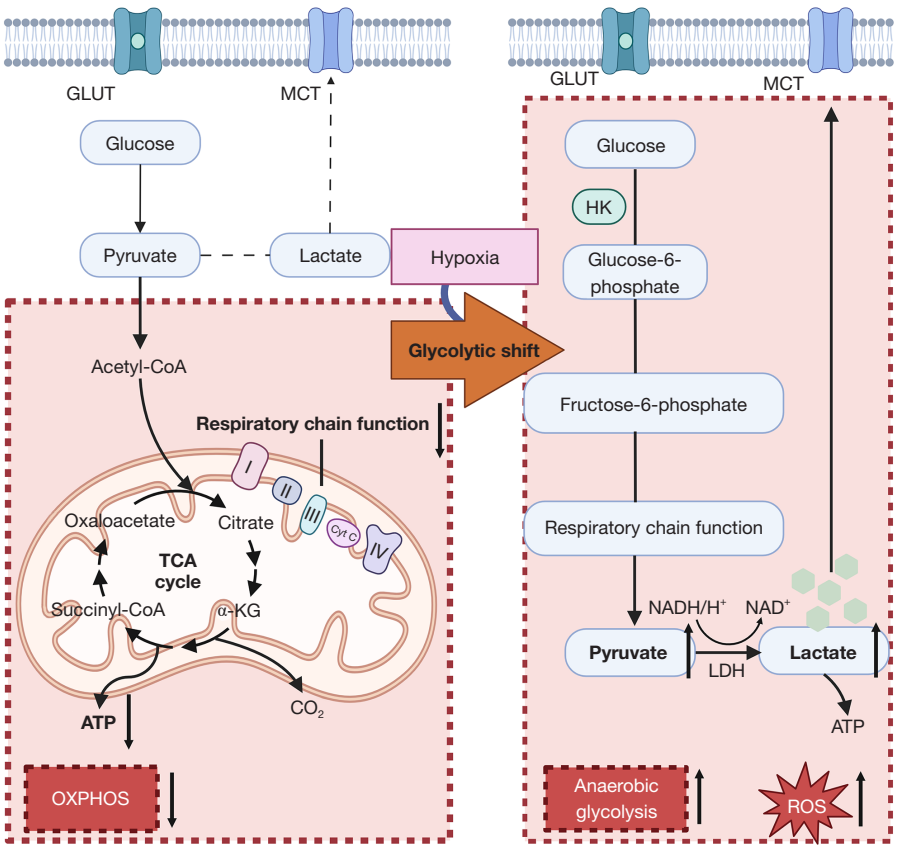

Figure 1 Metabolic changes of myocardial cells during ischemia. Under ischemic and hypoxic conditions, inadequate oxygen supply inhibits the function of the mitochondrial respiratory chain, leading to a reduction in ATP production via the OXPHOS pathway. To compensate for this ATP deficiency, cardiomyocytes promptly activate the anaerobic glycolysis pathway. This pathway directly converts glucose into pyruvate, which is further metabolized into lactate, accompanied by the release of a small amount of ATP. Normally, pyruvate generated from glycolysis enters mitochondria for oxidative decarboxylation and entry into the TCA cycle. However, under hypoxic conditions, pyruvate is unable to enter mitochondria and thus accumulates in the cytoplasm. The accumulated pyruvate is then reduced to lactate by lactate dehydrogenase, with NADH being oxidized to NAD^+, resulting in an imbalance in the NADH/NAD^+ ratio, which disrupts other NAD^+-dependent metabolic pathways within the cell. Moreover, mitochondrial electron transport chain dysfunction under hypoxic conditions may lead to electron leakage onto oxygen molecules, generating ROS. Additionally, ROS can also be produced during anaerobic glycolysis. The accumulation of ROS further exacerbates cellular oxidative stress and damage. GLUT, glucose transporter; MCT, monocarboxylate transporter; Acetyl-CoA, acetyl coenzyme A; Cyt c, cytochrome c; TCA, tricarboxylic acid; Succinyl-CoA, succinyl coenzyme A; α-KG, α-ketoglutarate; ATP, adenosine triphosphate; OXPHOS, oxidative phosphorylation; HK, hexokinase; NADH, nicotinamide adenine dinucleotide; LDH, lactate dehydrogenase; ROS, reactive oxygen species.

excess H^+ through the Na^+/H^+ exchanger and Na^+/HCO_3^{2-} transporter to reconstruct intracellular acid-base balance (22). However, this process may cause extracellular Na^+ influx, resulting in the increased intracellular Na^+ (23). When blood flow is restored and oxygen is regained, ATP synthesis is restored, and the Na^+ concentration difference between inside and outside the cell is increased. The Na^+/H^+ exchanger is then activated, and the cellular Na^+/Ca^{2+} exchange is increased, Ca^{2+} influx is promoted, and intracellular calcium overload is caused (24). During local ischemia, the citrate cycle metabolite succinic acid accumulates. After reperfusion, the accumulated succinic acid is rapidly reoxidized by succinate dehydrogenase, which drives a large amount of reactive oxygen species (ROS) production through reverse electron transfer at mitochondrial complex I (25). The early

release of active metabolites leads to a significant decrease in endogenous antioxidant defense ability, induces enzyme denaturation and direct deoxyribonucleic acid (DNA) damage, causes lipid peroxidation, destroys cell membranes, and results in cell necrosis (26). Sustained disruption of calcium homeostasis, the accumulation of ROS, and the recovery of pH during reperfusion will activate mPTP (27). The opening of mPTP disrupts the integrity of the mitochondrial inner membrane, resulting in swelling of the mitochondrial matrix. Due to the unrestricted passage of a multitude of ions across the mitochondrial membrane, depolarization of the mitochondrial membrane potential (MMP) ensues (28). MMP, serving as the potential difference formed by the asymmetric distribution of protons and other ions across the inner membrane, is a prerequisite for maintaining mitochondrial OXPHOS and ATP synthesis (29). Recent research has indicated that the decrease in MMP is considered as a landmark event of early apoptosis (30). Concurrently, the opening of mPTP facilitates the release of intermembrane proteins such as cytochrome C (Cyt c) and apoptosis-inducing factor into the cytoplasm. These proteins can initiate caspase-dependent or caspase-independent cascade reaction mechanisms, thereby inducing apoptosis in cells (31). The mitochondrial pathway plays a pivotal role in mediating myocardial cell apoptosis during MIRI (32) (*Figure 2*).

Mitochondrial biogenesis in MIRI

Mitochondrial quality control regulates and maintains mitochondrial homeostasis by coordinating various processes such as biogenesis, mitochondrial fission, fusion, mitochondrial proteolysis, and mitophagy degradation (33). Mitochondrial biogenesis is a regenerative process that maintains the number of mitochondria, replacing old and damaged mitochondria with new and healthy mitochondria (34). It is a complex process that requires the co-regulation of mitochondrial DNA (mtDNA) and nuclear DNA (nDNA), and is regulated by multiple transcription factors (35). Sirtuin 1 (SIRT1) and peroxisome proliferator-activated receptor γ coactivator 1-alpha (PGC-1α) are key regulators of mitochondrial biogenesis. Nuclear respiratory factor 1 (NRF1) and nuclear respiratory factor 2 (NRF2) are key factors in the downstream of mitochondrial biogenesis. SIRT1 activates PGC-1α by deacetylation. PGC-1α can bind to and promote the transcription of NRF1/2, upregulate the expression of mitochondrial transcription factor A (TFAM), and directly increase mtDNA transcription and replication, thereby initiating mitochondrial biogenesis (36). In addition, adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), $Ca2^{+}$/calmodulin-dependent protein kinase (CaMK), and cyclic-AMP response binding protein (CREB) are also involved in the regulation of mitochondrial biogenesis (35). After MIRI, the mtDNA copy number is drastically reduced, together with diminished phospho-AMPK, PGC-1α, peroxisome proliferator-activated receptor alpha (PPARα) and TFAM protein levels (37). Additionally, hypoxia/reoxygenation (H/R) inhibits the AMPK pathway and downregulates PGC-1α, NRF1, NRF2, TFAM and SIRT3 levels, in association with altered mitochondrial biogenesis, mitochondrial dysfunction, disrupted the mitochondrial morphology, and activated mitochondrial apoptosis (38).

Mitochondrial energy metabolism in MIRI

Mitochondria are the main organelle of energy supply, and the correlation between MIRI and abnormal mitochondrial energy metabolism has become a general consensus (39). Fatty acids, glucose, and other energy substrates enter mitochondria through protein-mediated transport, metabolism, and other pathways to produce acetyl-CoA. Under the promotion of various enzymes, ATP is synthesized by OXPHOS (40). Therefore, mitochondrial OXPHOS serves as the central hub for cellular energy metabolism. During myocardial ischemia-reperfusion (I/R), mitochondria are damaged, and the pathway of energy metabolism changes from OXPHOS to anaerobic glycolysis, which reduces ATP synthesis, disrupts mitochondrial energy metabolism, leads to cardiomyocyte apoptosis or necrosis, and aggravates MIRI (41).

Mitochondrial respiratory chain in MIRI

The mitochondrial respiratory chain, also known as the electron transport chain (ETC), is distributed on the mitochondrial inner membrane in the form of protein complexes to participate in OXPHOS (42). The five enzyme complexes on ETC include complex I [also known as CI or nicotinamide adenine dinucleotide (NADH):ubiquinone oxidoreductase], complex II (also known as CII or succinate dehydrogenase), dimer complex III2 (also known as CIII2 or cytochrome bc1 oxidoreductase), and complex IV (also known as CIV or cytochrome c oxidase). The proton gradient generated by complex I–IV is then used by complex V, that is, ATP synthase, to phosphorylate

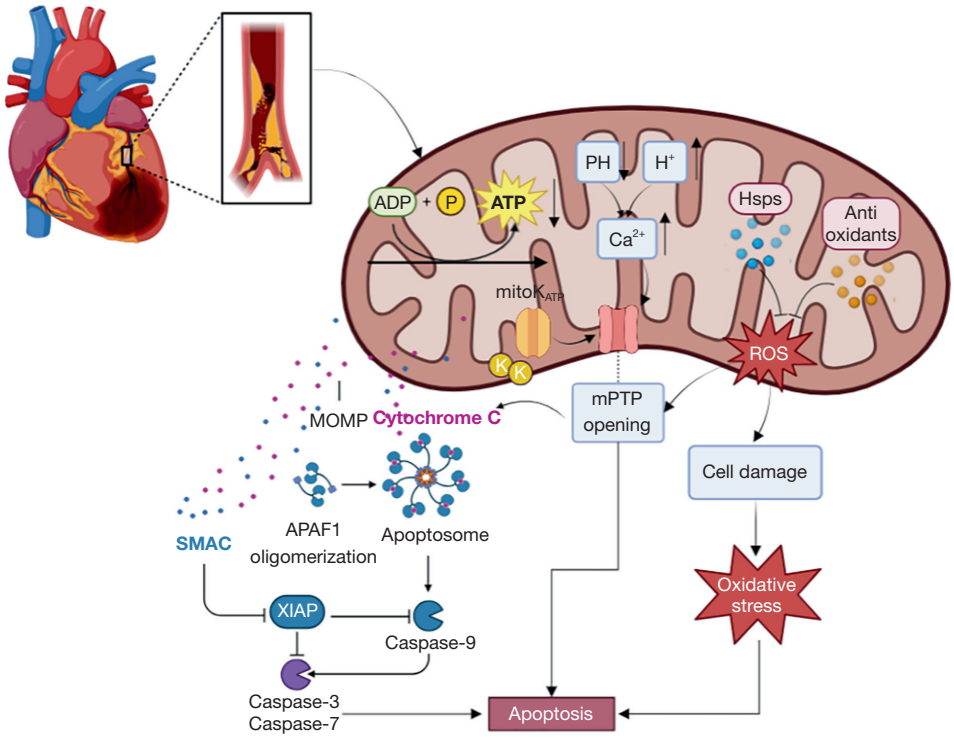

Figure 2 Mitochondrial pathway-mediated apoptosis after myocardial infarction. During ischemia, cardiomyocytes undergo anaerobic metabolism, which results in decreased ATP levels and pH, which increase levels of intracellular Ca^{2+}. The oxidative stress caused by calcium overload and ROS overload can exacerbate mitochondrial damage, amplify mitochondrial dysfunction and lead to energy metabolism disorders, and stimulate mPTP opening. The opening of mPTP leads to depolarization of mitochondrial membrane potential and matrix swelling. This causes the intermembrane protein cytochrome C to be released into the cytoplasm. The release of cytochrome C is a key step in the initiation of the mitochondrial apoptotic pathway. It binds to APAF1 to form apoptotic bodies, which in turn activates the Caspase protease system. The activation of Caspase promotes the execution of apoptosis. ADP, adenosine diphosphate; ATP, adenosine triphosphate; pH, pondus hydrogenii; Hsps, heat shock proteins; ROS, reactive oxygen species; mitoKATP, mitochondrial KATP; KATP, ATP-sensitive potassium channel; MOMP, mitochondrial outer membrane permeabilisation; APAF1, apoptotic protease activating factor-1; SMAC, second mitochondria-derived activator of caspases; XIAP, X-linked inhibitor of apoptosis protein; Caspase, cysteinyl aspartate specific proteinase; mPTP, mitochondrial permeability transition pore.

adenosine diphosphate to ATP (43). Under normal circumstances, mitochondrial respiratory chain function depends on the activity of membrane protein complexes, and it regulates MMP to affect mitochondrial function, thereby interfering with OXPHOS (44). However, ischemia and hypoxia disrupt the electron transport of ETC, disrupt the function of OXPHOS, reduce ATP production, cause ROS accumulation, and MMP collapse, and ultimately lead to mitochondrial dysfunction and cell death (45).

Mitochondrial oxidative stress in MIRI

ROS is considered as a toxic by-product of aerobic metabolism (46). Excessive ROS accumulation in mitochondria is closely associated with the occurrence of MIRI (47). During myocardial ischemia, mitochondrial OXPHOS is disturbed, and the intracellular energy supply is insufficient, resulting in the increased ROS production rate, and the balance between ROS scavenging enzyme systems [e.g., superoxide dismutase (SOD), catalase, and glutathione peroxidase] is broken, resulting in oxidative stress (48). Oxidative stress causes cell death by directly destroying macromolecules, including proteins, DNA, and lipids (49). Excessive ROS may induce mPTP opening, causing mitochondrial swelling, rupture, and release of Cyt c, which may in turn result in cardiomyocyte death

and affect cardiac function (50). In addition, ROS-induced mitochondrial dysfunction may further aggravate the production of ROS, forming a vicious cycle, known as "ROS-induced ROS release", resulting in continuous oxidative stress damage (51).

Mitochondrial dynamics in MIRI

Under physiological conditions, mitochondria are in a dynamic equilibrium state of continuous division and fusion to control their number, distribution and morphology (52). These dynamic processes are called mitochondrial dynamics, which are important for mitochondrial inheritance, maintenance of mitochondrial functions, transmission of energy status and control of cell quality (53). Mitochondrial fission is a process of self-maintenance and repair (54). Mitochondrial fission occurs when mitochondria are irreversibly damaged and potentially harmful for the cell. It is characterized by the fragmentation of the damaged mitochondrion into small sphere-shaped organelles that are then isolated and digested by mitophagy (55). Mitochondrial fusion allows a dynamic repair of reversibly damaged portions of mitochondria and re-enter into the mitochondrial network, forming functional elongated organelles (56). These two processes are coordinated by mitochondrial fission and fusion proteins, respectively (57). Mitofusin 1 (MFN1) and mitofusin 2 (MFN2) are the effectors of the GTPase family responsible for mitochondrial outer membrane fusion, and optic atrophy protein 1 (OPA1) is the main regulatory protein for mitochondrial inner membrane fusion (58). Five fission-related proteins were dynamin-related protein 1 (Drp1), mitochondrial fission protein 1 (Fis1), mitochondrial dynamics proteins of 49 and 51 and mitochondrial fission factor (Mff), divide a single mitochondria into two separate broken mitochondria (59). However, when MIRI occurs, the dynamic balance of mitochondria is destroyed and tends to fission, which affects mitochondrial function and aggravates MIRI (60).

Mitochondrial ATP-sensitive potassium channel in MIRI

Mitochondrial KATP (mitoKATP) is an inward rectifier K^+ channel located in the mitochondrial inner membrane, which is mainly regulated by intracellular ATP concentration (61). Under normal circumstances, mitoKATP is in a closed state. When cells are ischemic and hypoxic, the ability of mitochondria to synthesize ATP is reduced, and mitoKATP is gradually opened (62). Studies have indicated that opening of mitoKATP can increase ATP content, and reduce Na^+/H^+ exchange, thereby reducing mitochondrial calcium concentration, preventing mitochondrial calcium overload, decreasing MMP, attenuating mitochondrial structural damage, preventing the release of Cyt c from mitochondria, and protecting damaged myocardium during reperfusion (63,64).

mPTP in MIRI

Notably, mPTP is a non-specific channel composed of the inner and outer membranes of mitochondria (65). In the process of MIRI, ROS, Ca^{2+}, and rapid recovery of pH in cardiomyocytes are considered as the key activators to promote the opening of mPTP (66), leading to the free entry and exit of various ions and protein molecules in mitochondria (67), causing MMP collapse, depolarization of MMP, uncoupling of electron transfer of respiratory chain and OXPHOS, mitochondrial damage, termination of ATP synthesis, depletion of NAD^+, an increase in ROS, and outflow of Ca^{2+} in cell matrix (68). It may eventually result in mitochondrial swelling, rupture of the outer membrane, and subsequent release of various apoptosis factors, ultimately leading to myocardial cell death (69).

Mitophagy in MIRI

Autophagy is a self-protective mechanism of cells, removing senescent or abnormally folded proteins and damaged organelles in cells. Mitophagy is a special subtype of autophagy. It is a process in which cells selectively remove damaged mitochondria through autophagy, which is essential for maintaining mitochondrial and cell homeostasis (70). Mitophagy mainly includes four processes: (I) under the action of ROS, nutrient deficiency, cell aging, and other external stimuli, mitochondria depolarize and lose membrane potential, which is the prerequisite for the occurrence of mitophagy (71). (II) Mitochondria are wrapped by autophagosomes to form mitochondrial autophagosomes. Firstly, the double-membrane phagophores that surround the mitochondria to be degraded begin to initiate and elongate. Subsequently, the phagophore is enclosed in double-membrane vesicles called autophagosomes (72). (III) After the formation of mitochondrial autophagosomes, they are transported to lysosomes and fused with them to form autophagic lysosomes. (IV) Lysosomes or vacuolar acid hydrolases flow

into autophagosomes to degrade mitochondria. During the degradation process, the contents of mitochondria are hydrolyzed into small molecules, which are then recycled by cells (73). During myocardial I/R, a large amount of ROS and other oxidative stress products are generated. High levels of ROS can disrupt the function and stability of autophagy-related proteins, thereby inhibiting the normal process of mitophagy. Calcium overload can affect the normal function of mitochondria, including OXPHOS and ATP generation, which in turn affects the energy supply and signal transduction of mitophagy (74). Proper mitophagy maintains cellular homeostasis by removing defective mitochondria in MIRI. However, uncontrolled or overactivated autophagy may lead to a shortage of functional or healthy mitochondria required for ATP production, thereby increasing the degree of myocardial injury (75). Therefore, the impact of mitophagy on MIRI has a double-sided effect (76).

Mitochondrial apoptosis in MIRI

Apoptosis is a form of programmed cell death regulated by multiple genes, and mitochondria play an important role in the execution of apoptosis (63). The mitochondrial apoptotic pathway is triggered by mitochondrial swelling and mitochondrial outer membrane rupture, facilitating the release of pro-apoptotic factors such as Cyt c from the membrane gap to the cytoplasm. Cyt c protein enters the cytoplasm and interacts with cytoplasmic apoptotic protease activating factor-1 (APAF1), resulting in the activation of caspase-9. The cleavage of active caspase-9 causes pro-caspase-3 to produce active caspase-3 and causes a cascade reaction by shearing other caspase substrates to control apoptosis (77). In addition, several studies have demonstrated that increased mitochondrial fission in ischemic hearts contributes to the induction of apoptosis and infarction (78,79). Irreversible damage to cardiac function occurs due to myocardial cell apoptosis caused by MIRI, as myocardial cells have a limited regenerative capacity (80).

The effects of CHM regulating mitochondria on MIRI

Understanding of "MIRI" in TCM

There is no disease name of MIRI in TCM. Based on the lesion site and the clinical symptoms of chest pain, palpitations and chest tightness, MIRI is classified as "chest paralysis" and "true cardiac pain" in TCM. The name "chest paralysis" was first found in Zhang Zhongjing's "The Essentials of Golden Killing", which summarises the pathogenesis of the disease as "yang wei yin string". A deficiency of yang energy in the upper jiao and an abundance of yin cold energy in the lower jiao. That is, the heart vessels stasis caused by exogenous or endogenous etiological, as well as the pain caused by blockages in the veins and channels (81,82). The nature of the disease has two aspects of deficiency and excess, that is, the essence of the disease is deficiency, the pathogenic factor is excess pathogens and combined deficiency and excess. This deficiency is often due to deficiencies of qi, blood, yin and yang in the heart, while excess pathogen is often due to blockages in the veins and channels caused by qi impediment, phlegm retention, blood stasis, cold retention and other pathogens (83). Specifically, from the perspective of TCM, MIRI constitutes an intricate pathological process encompassing disruptions in the circulation of qi and blood, dysfunction of zang-fu organs, and overall disharmony between yin and yang. During myocardial ischemia, insufficient blood supply to the heart leads to deficiency of heart-qi, impeding the smooth flow of blood and fostering blood stasis. This blood stasis further obstructs the circulation of qi and blood, depriving the myocardium of adequate nourishment and oxygen supply, thereby exacerbating injury. Prolonged myocardial ischemia culminates in the exhaustion of heart-blood, with qi collapse following heavy blood loss, yielding a pathological state characterized by dual deficiency of qi and blood. In this context, inadequacy of heart-qi and insufficient nourishment of the heart by blood exacerbate myocardial damage and dysfunction. Additionally, MIRI primarily involves dysfunction of zang-fu organs such as the heart, spleen, and kidneys, notably heart-qi insufficiency, splenic malfunction, and kidney water insufficiency, collectively contributing to impairments in the production and circulation of qi and blood. During ischemia and reperfusion, the body's yin-yang equilibrium is disrupted by multiple factors including qi and blood deficiency, and organ dysfunction, manifesting as either yin deficiency leading to fire hyperactivity or deficiency of both yin and yang. At this juncture, the body falls into a state of profound weakness, significantly compromising its resistance to disease and capacity for recovery (84). The treatment principles are to treat the symptoms first and then treat the deficiency pattern. The treatment method is to dissipate cold, circulate blood,

transform phlegm, regulate qi, clear heat and tonify the deficiency of heart qi, blood, yin and yang (85).

The history and benefits of CHM

China is the birthplace of CHM. The history of the use of Chinese medicines can be traced back to thousands of years ago. At present, there are about 12,000 kinds of Chinese medicines in China, including herbal medicines (roots, stems, leaves, flowers, fruits), medicinal animal materials and medicinal minerals (86). As an inseparable part of Chinese culture, Chinese medicines have unique advantages and play a vital role in the prevention and treatment of cardiovascular-related diseases (87). With the application of modern technological means in the extraction of CHM components, as well as the study of the action and mechanism of single herbs and compounds, more effective components in CHM and their respective action mechanism are clear. This will help people understand and correctly recognize the significant value of TCM and CHM. So that people will pay attention to and participate in the research and development of CHM. Only then can CHM be rapidly developed and applied for the benefit of mankind.

Explore of "mitochondria" in TCM theory

The theory of "Qi and Blood smooth flow" comes from "Yellow Emperor's Inner Canon". Qi is an abstract concept, including both innate and acquired qi, as well as qi of meridians and qi of the zang-fu organs. There are Yuan-primordial qi and Zong-pectoral qi in the innate qi. Zong-pectoral qi fills the heart vein to run qi and blood, and the heart governs the blood and vessels, and the heart qi drives the blood to run in the vein. The vessel is the channel of human blood circulation. Whether the vessel is sufficient or not plays a key role in the function of the body. In modern research, the vessel corresponds to the human circulatory system, including the veins, arteries and capillaries except the heart. The vascular network plays an important role in transporting blood, distributing blood and material exchange (88). Therefore, the theory of "Qi and Blood smooth flow" is quite consistent with the occurrence and development of cardiovascular disease.

Mitochondria, as the power source and energy supply of cells, are related to qi in TCM. The material properties of "qi" is equivalent to the mitochondria of modern medicine, and the function of mitochondria in modern medicine is equivalent to the role of "qi" in TCM. The functions of qi such as promotion, warmth and facilitation are very similar to the functions of mitochondria in maintaining energy metabolism, regulating immunity and regulating the functions of cells (89). The occurrence of abnormal energy metabolism, oxidative stress, autophagy and apoptosis caused by mitochondrial homeostasis imbalance is a dynamic process, which reflects the molecular biological mechanism of the pathogenesis evolution from "unfavorable pulse" to "blocked pulse" (90). The theory of "qi" in TCM echoes the mitochondria in modern medicine, which further confirms the scientific nature of applying TCM to intervene MIRI.

Monomers of CHM for regulating mitochondria in MIRI

Tonic CHM

As shown in *Table 3*, tonic CHM is suitable for chest paralysis caused by insufficient yin, yang, qi and blood of the heart. *Panax ginseng* C. A. Mey. is derived from the root of *P. ginseng*, and it contains a variety of ginsenosides. It has the effects of nourishing qi, nourishing body fluid, and nourishing blood. It is mainly combined with other CHM to treat chest paralysis and other diseases. Huang *et al.* (91) found that ginsenoside Rc pretreatment significantly promoted mitochondrial biogenesis in H9c2 and PC12 cells, as well as in neurons through SIRT1-mediated PGC-1α acetylation, and it increased the activity of ETC complex II–IV, thereby reducing mitochondrial damage and apoptosis in heart and neuron models induced by MIRI. Ginsenoside Rb1 is the most abundant ginsenoside in *P. ginseng*, which reduces ROS production and alleviate MIRI by inhibiting NADH dehydrogenase activity in mitochondrial complex I (92). Calenduloside E (93) and cordycepin (94) have remarkable cardioprotective effects *in vivo* and *in vitro*, and their mechanism is related to mitochondrial dynamics. In addition, the protective effects of other tonic CHM active ingredients such as atractylolactone I (95) on MIRI are attributed to increasing MMP, inhibiting mitochondrial Ca^{2+} overload and decreasing cardiomyocyte apoptosis rate. Warming yang herbs such as *Morinda officinalis* How. and *Curculigo orchioides Gaertn*., mainly treat chest paralysis and true cardiac pain by warming meridians, unblocking collaterals and dissipating cold. Modern studies have found that Morinda officinalis oligose (96) and curculigoside (97) have protective effects against MIRI-induced cardiac dysfunction.

Table 3 Active constituents, acting on mitochondria, used to decrease ischemia-reperfusion injury in the past 5 years

Active constituent	Source	Model	Dosage	Finding	Target	Reference
Ginsenoside Rc	*Panax ginseng* C. A. Mey.	SD rats; H9c2 cells, PC12 cells	10 mg/kg; 6.25, 12.5, 25, 50 μmol/L	↑: electron-transport chain complex II–IV, MMP, ATP, hexokinase I/II, glucose uptake, pyruvate carrier I/II, Bcl-2/Bax, SIRT1 ↓: apoptosis rate, Cyt c, the infarction sizes of heart and brain tissue	Mitochondrial quality control, energy metabolism, MMP, mitochondrial apoptosis	(91)
Ginsenoside Rb1	*Panax ginseng* C. A. Mey.	C57BL/6J male mice; primary cardiomyocytes	50 mg/kg; 10 μM	↑: ATP, MMP, Bcl-2 ↓: mitochondrial complex I activity, myocardial infarct size, mPTP, ROS, Bax, Bak, Ndufv1, Ndufv2, Ndufs1, Ndufs4, Ndufa12	Energy metabolism, MMP, mPTP	(92)
Calenduloside E	*Aralia elata* (Miq.) Seem.	SD rats; H9c2 cells	15 mg/kg; 12.5 μM	↑: cell viability, ATP, MMP, OPA1, MFN1/2 ↓: LDH, cTnI, mPTP, myocardial infarct size, apoptosis rate, Cyt c, Bax, cleaved caspase-3, cleaved-PARP, Drp1	Mitochondrial dynamics, MMP, mPTP, mitochondrial apoptosis	(93)
Cordycepin	*Cordyceps mushrooms*	Mfn2loxp mice, C57BL/6 mice; H9c2 cells, primary cardiomyocytes	10 mg/kg; 20 μmol/L	↑: MFN2, ATP, MMP, glutathione, p-AMPK ↓: myocardial infarct size, CK, LDH, EF, FS, Cyt c, cleaved caspase-3, cleaved caspase-9, ROS	Mitochondrial dynamics, oxidative stress, MMP, mitochondrial apoptosis	(94)
Atractylenolide I	*Atractylodes macrocephala*	SD rats; rat cardiomyocytes	10, 50, 250 μg	↑: Bcl-2, MMP, SOD ↓: CK-MB, CK, cTnI, MB, apoptosis rate, myocardial infarct size, Bax, caspase-3, cleaved caspase-3, cleaved caspase-9, ROS, Ca^{2+}	MMP, calcium overload, mitochondrial apoptosis	(95)
Morinda officinalis oligose	*Morinda officinalis How*.	SD rats	0.07, 0.21 g/mL	↑: ATP, ADP, AMP, TAN, EC	Energy metabolism	(96)
Curculigoside	*Curculigo orchioides Gaertn*.	Wistar rats; H9c2 cells	5, 10, 15 mg/kg; 5, 10, 15 μM	↑: MMP, Bcl-2/Bax ↓: LDH, myocardial infarct size, apoptosis rate, Cyt c, mPTP, APAF1, caspase-9, caspase-3	MMP, mPTP, mitochondrial apoptosis	(97)
Tanshinone I	*Salvia miltiorrhiza Bunge*	SD rats; H9c2 cells	10, 20 mg/kg; 0.125, 0.25, 0.5, 1, 2 μM	↑: MMP, Nrf2, HO-1, NQO-1, SOD ↓: LDH, necroptosis, ROS, MDA, TNF-α, IL-6, p-RIP1, p-RIP3, p-MLKL	Mitochondrial apoptosis, oxidative stress, MMP	(98)
Hydroxysafflor yellow A	*Carthamus tinctorius* L.	SD rats; NPCMs	30 mg/kg; 2.5, 5, 10 μM	↑: Bcl-2 ↓: LDH, AST, CK-MB, Bax, caspase-3, caspase-9, calcium overload	Calcium overload, mitochondrial apoptosis	(99)
Ferulic acid	*Angelica sinensis* (Oliv.) Diels, *Ligusticum chuanxiong* Hort.	H9c2 cells	6.25, 12.5, 25, 50, 100, 200 μM	↑: cell viability, ATP, MMP, p62 ↓: ROS, LC3II/LC3I, Parkin, PINK1, apoptosis rate, cleaved caspase-3	Mitochondrial apoptosis, energy metabolism, MMP, mitophagy	(100)
Ligustrazine	Ligusticum chuanxiong Hort.	SD rats	3 mg/L	↑: LVDP, HR, $\pm dp/dt_{max}$, CF, MMP, SOD, JAK2, STAT3, Bcl-2 ↓: MMP, MDA, H2O2, Bax, apoptotic rate, myocardial infarct size	MMP, oxidative stress, mitochondrial apoptosis, mitophagy	(101)
Anisodamine	*Anisodus tanguticus* (Maxim.) Pascher	SD rats; NRVMs	0.3 mM; 0.01 μM	↑: ATP, MMP, SOD ↓: cTnI, myocardial infarct size, MDA	Energy metabolism, MMP, mitoKATP, oxidative stress	(102)
Notoginsenoside R1	*Panax notoginseng*	SD rats	1 mg/kg	↑: ATP 5D, ATP/ADP, ATP/AMP ↓: complex V activity, MPO, MDA, 8-OhdG, 9-myocardial infarct size, Bcl-2/Bax, caspase-3, caspase-9, cleaved caspase-3, cleaved caspase-9	Energy metabolism, oxidative stress, mitochondrial apoptosis	(103)
Salidroside	*Rhodiola rosea*	SD rats; H9c2 cells	5 mg/kg; 30 μM	↑: HR, LVDP, $\pm dp/dt_{max}$, pAMPK/AMPK, Bcl-2, ATP ↓: LDH, CK, LVEDP, mitochondrial fission, Bax, cleaved caspase-3, p-PERK, p-eIF2, CHOP, myocardial infarct size	Energy metabolism, mitochondrial apoptosis, mitochondrial dynamics	(104)
Sappanone A	*Caesalpinia sappan* L.	Wistar rats	10, 100, 1,000 μM	↑: ATP, MMP, mtDNA, PGC-1α, Mfn2, p62, Parkin ↓: CK-MB, LDH, cTnI, mPTP, ROS, myocardial infarct size, Drp1, LC3II/LC3I, PINK1	Mitochondrial quality control, MMP, mPTP	(105)

Table 3 (*continued*)

Table 3 (*continued*)

Active constituent	Source	Model	Dosage	Finding	Target	Reference
Vitexin	*Crataegus pinnatifida*	SD rats; H9c2 cells	1, 3, 10 μM; 1, 3, 10, 30, 50 μM	↑: LVSP, HR, CF, dP/dt, Bcl-2/Bax, ATP, MMP, cell viability, MFN2, COX IV, SDHB ↓: LDH, LVEDP, ROS, NOX4, cleaved caspase-3, cleaved caspase-9, Cyt c, Drp1	Oxidative stress, MMP, mitochondrial dynamics, energy metabolism, mitochondrial apoptosis	(106)
Protocatechuic aldehyde	*Salvia miltiorrhiza root*	SD rats, C57BL/6 rats; NRVMs, H9c2 cells	20, 40, 80 mg/kg; 5, 10 μmol/L	↑: Bcl-2 ↓: CK-MB, LDH, ROS, mPTP, apoptosis rate, Bax, cleaved caspase-3, Cyt c	Oxidative stress, mPTP, mitochondrial apoptosis	(107)
Morin	*Morus alba* L.	Wistar rats	0.25, 0.5, 1 mg/L	↑: mitoK ATP ↓: LDH, MDA, ROS, myocardial infarct size	mitoKATP, oxidative stress	(108)
Tilianin	*Dracocephalum moldavica* L.	H9c2 cells	2.5, 5, 10 μg/mL	↑: cell viability, MMP ↓: mPTP, ROS, LDH, SOD	MMP, mPTP, necroptosis	(109)
Baicalein	*Scutellaria baicalensis* Georgi	C57BL/6 mice; H9c2 cells	25, 40 mg/kg; 50 μM	↑: MARCH5, LC3-II, KLF4 ↓: apoptosis rate, LC3-II, Drp1	Oxidative stress, mitochondrial quality control, mitochondrial apoptosis	(110)
Berbamine	Berberis	C57/BL6 mice	10 mg/kg	↑: SOD, p-AMPK, p-ACC, NQO-1, HO-1, Nrf2, LVEF, LVFS ↓: CK, LDH, MDA, ROS, myocardial infarct size, cleaved caspase-3, Cyt c	Oxidative stress, mitochondrial apoptosis	(111)
Cryptochlorogenic acid	*Saxifraga tangutica* (*S. tangutica*)	ICR mice	5 μM	↑: LVDP, RPP, +dP/dt, −dP/dt, SIRT1, PGC-1α, NRF1, TFAM, MFN2, Drp1	Mitochondrial quality control	(112)
L-theanine	*Camellia sinensis* (L.) *Kuntze*	Wistar mice	250 mg/kg	↑: SOD, CAT, oxygen consumption, MMP, SOD1, Nrf2, PPARα ↓: myocardial infarct size, ROS, MDA, Ca^{2+}	Oxidative stress, calcium overload, MMP	(113)
Allicin	Garlic	Mini-musk swines; primary cardiomyocytes	5, 10, 20, 40 μg/mL	↑: cell viability, MMP, Bcl-2, PGC-1α, eNOS ↓: IL-6, TNF-α, ROS, Cyt c, apoptosis rate, Bax, cleaved caspase-3, HIF-1α, ET1, TGF-β	Oxidative stress, MMP, mitochondrial apoptosis	(114)
Lycopene	*Carthamus tinctorius* L.	Wistar rats	5, 20 mg/kg	↑: AKT, ERK1/2, GSK-3β ↓: LDH, CK-MB, mPTP, GRP78, CHOP, Cyt c, cleaved caspase-9, cleaved caspase-3	mPTP, mitochondrial apoptosis	(115)
Breviscapine	*Scutellariae Radix*, *Scutellariae Barbatae Herba*, *Oroxyli Semen*, *Perilla Frutescens*	SD rat	100, 200 mg/kg	↑: LVSP, MAP, LVEF, mTOR, p-PI3K/PI3K, p-Akt/Akt ↓: TC, TG, LDL-C, IL-1β, IL-6, TNF-α, HR, LVEDP, LC3-II/LC3-I, Beclin1	Mitophagy	(116)
Asiatic acid	*Centella asiatica*	C57BL/6 mice; NRVMs	100 mg/kg; 20 μM	↑: SOD, MMP, Bcl-2 ↓: MDA, ROS, Bax, Cyt c, apoptosis rate, myocardial infarct size, p-p38, p-JNK, cleaved caspase-9, cleaved caspase-3	Oxidative stress, mitochondrial apoptosis	(117)

↑, an increase/rise in data values, indicating an upward trend; ↓, a decrease/reduction in data values, indicating a downward trend. SD, Sprague-Dawley; MMP, mitochondrial membrane potential; ATP, adenosine triphosphate; Bcl-2, B-cell lymphoma-2; Bax, Bcl-2-associated X protein; SIRT1, sirtuin 1; Cyt c, cytochrome c; mPTP, mitochondrial permeability transition pore; ROS, reactive oxygen species; Bak, Bcl2 antagonist/killer; Nduf, NADH:ubiquinone oxidoreductase core subunit; NADH, nicotinamide adenine dinucleotide; ETC, electron transport chain; OPA1, optic atrophy protein 1; MFN1, mitofusin 1; MFN2, mitofusin 2; LDH, lactate dehydrogenase; cTnI, cardiac troponin I; PARP, poly ADP-ribose polymerase; Drp1, dynamin-related protein 1; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; CK, creatine kinase; EF, ejection fraction; FS, fractional shortening; Caspase, cysteinyl aspartate specific proteinase; ADP, adenosine diphosphate; AMP, adenosine monophosphate; TAN, total adenine nucleotide; EC, energy charge; APAF1, apoptotic protease activating factor-1; NRF, nuclear respiratory factor; HO-1, heme oxygenase-1; NQO-1, NAD(P)H quinone oxidoreductase 1; SOD, superoxide dismutase; MDA, malondialdehyde; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; RIP1, receptor-interacting protein kinase 1; MLKL, mixed lineage kinase domain-like protein; AST, aspartate transaminase; LC3II, LC3-phosphatidylethanolamine conjugate; Parkin, E3 ubiquitin-protein ligase parkin; PINK1, PTEN-induced putative kinase 1; LVDP, left ventricular developed pressure; HR, heart rate; CF, coronary flow; JAK2, janus kinase2; STAT3, signal transducer and activator of transcription3; MPO, myeloperoxidase; LVEDP, left ventricular end-diastolic pressure; PERK, protein kinase RNA-like endoplasmic reticulum kinase; eIF2, eukaryotic initiation factor; CHOP, C/EBP-homologous protein; mtDNA, mitochondrial DNA; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-alpha; p62, SQSTM1; LVSP, left ventricular systolic pressure; NOX4, NADPH oxidase 4; mitoKATP, mitochondrial KATP; MARCH, membrane associated Ring-CH; KLF4, Krüppel-like factor 4; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; TFAM, mitochondrial transcription factor A; RPP, rate pressure product; +dP/dt, maximal left ventricular pressure rising rate; −dP/dt, maximal left ventricular pressure decline rate; CAT, catalase; HIF-1α, hypoxia-inducible factor-1α; ET1, endothelin-1; TGF-β, transforming growth factor-β; Akt, protein kinase B; ERK1/2, extracellular regulated protein kinases 1/2; GSK-3β, glycogen synthase kinase 3β; GRP78, glucose regulated protein 78kD; MAP, mitogen-activated protein; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol3-kinase; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; JNK, c-Jun N-terminal kinase.

Blood-activating CHM

Salvia miltiorrhiza Bunge has been proved to play an important role in the prevention of MIRI and the treatment of cardiovascular diseases. It is known for its effects of circulating blood, transforming stasis and alleviating pain. Recent study has demonstrated that tanshinone I, a major ingredience in *Salvia miltiorrhiza* Bunge, has the effects of anti-mitochondrial oxidative stress injury, increasing MMP, and reducing mitochondrial apoptosis (98). It has been indicated that *Carthamus tinctorius* L. has the effects of dilating blood vessels, improving microcirculation, lowering blood pressure, and anti-arrhythmia. Hydroxysafflor yellow A has been identified as the most potent water-soluble component of *C. tinctorius*, which exerts a protective effect on MIRI by inhibiting mitochondrial calcium overload and apoptosis (99). Ferulic acid is one of the effective components of *Angelica sinensis* (Oliv.) Diels and *Ligusticum chuanxiong* Hort., which are commonly utilized in the treatment of cardiovascular diseases. It exhibits antioxidant, anti-inflammatory, anti-thrombotic, hypolipidemic properties and reduce myocardial oxygen consumption. An experimental study indicated that it could alleviate H/R injury in H9c2 cells by inhibiting PINK1/Parkin-mediated mitophagy signaling pathway (100). The protective effect of ligustrazine (101), the active ingredient of *L. chuanxiong*, on MIRI may be achieved by regulating janus kinase2 (JAK2)/signal transducer and activator of transcription3 (STAT3) signaling pathway and mitophagy. *Anisodus tanguticus* (Maxim.) Pascher has the effects of analgesia and relieves convulsions, circulates blood, as well as transforms stasis, stops bleeding and regenerates new tissues. *In vivo* experiments have shown that anisodamine could significantly improve the hemodynamic parameters of the isolated heart, reduce the area of myocardial infarction and the release of myocardial injury marker cTnI, reduce the occurrence of ventricular reperfusion arrhythmia, increase the content of metabolic index ATP, increase the activity of oxidative stress index SOD, reduce the level of MDA, and improve the ultrastructure of myocardial tissue. In addition, the mitoKATP blocker could antagonize the protective effect of anisodamine above. The results of *in vitro* experiments were consistent with those of *in vivo* experiments, which suggests that to open mitoKATP could play an important role in the protective effect of anisodamine against MIRI (102). The active ingredients of other circulate blood and transform stasis CHM include notoginsenoside R1 (103), salidroside (104), sappanone A (105), vitexin (106), protocatechuic aldehyde (107), and morin (108) have exhibited promising anti-MIRI effects.

Interior heat-clearing CHM

Dracocephalum Moldevica L. is a CHM, possessing the effects of clear heat and eliminating dampness, cooling liver and hemostasis. Tilianin, the primary active ingredient in the total flavonoids of *D. Moldevica*, possesses anti-inflammatory, antioxidant, and myocardial protective effects. Study has indicated that tilianin inhibits the opening of mPTP and programmed necrosis, thereby demonstrating anti-MIRI effects (109). Baicalein derived from *Scutellaria baicalensis* Georgi has demonstrated cardiovascular protective effects by inhibiting mitochondrial fission, promoting mitophagy, reducing oxidative stress injury, and inhibiting apoptosis (110). Furthermore, berbamine, primarily derived from Berberis, has exhibited notable properties, such as blood pressure reduction, anti-arrhythmic effects and anti-myocardial ischemia effects, which has been extensively utilized in clinical settings. Its enhancement of cardiac function primarily stems from improvements in antioxidant capacity, regulation of mitophagy, and inhibition of apoptosis (111). *Saxifraga tangutica* (*S. tangutica*) is one of the commonly used traditional Tibetan medicines. *S. tangutica* is bitter and cold in taste and is used to clear the heat of liver and gallbladder fever and to treat acute otitis media. The *ex vivo* MIRI assay demonstrated that cryptochlorogenic acid significantly improved hemodynamic function, hemodynamic function-related indices, and cell morphology in I/R myocardium tissues, and significantly increased mitochondrial biogenesis in I/R myocardial tissues (112). *Camelia sinensis* is sweet, bitter, and slightly cold in taste and is used to clear heat and reduce fire, strengthen the heart and diuretic. L-theanine, a non-protein amino acid isolated from *C. sinensis*, could prevents I/R-induced cardiac injury, increases mitochondrial respiration, prevents loss of inner MMP and buffers calcium overload by upregulating antioxidant defenses (113).

Other CHM

In the history of CHM's treatment of MIRI, circulating blood, transforming stasis, tonifying the body and warming yang CHM have shown promising therapeutic effects. In addition, other types of CHM have also shown positive therapeutic effects. Recent research has unveiled the cardioprotective effects of allicin, the principal active ingredient found in garlic. Allicin has demonstrated the ability to enhance myocardial cell viability, decrease

the expression levels of apoptosis-related proteins, such as Bax, cleaved caspase-3, and Cyt c, and reduce the apoptosis rate. It also increases the expression level of Bcl-2, significantly lowers intracellular ROS production, and enhances MMP (114). Lycopene (115), breviscapine (116), asiatic acid (117) have been found to participate in various mechanisms, contributing to their protective effects on the heart.

Extracts of CHM for regulating mitochondria in MIRI

Many extracts have been shown to protect the heart by regulating mitochondrial morphology and function, as detailed in *Table 4*. *Astragali Radix* is recognized as one of the traditional CHM used in the treatment of cardiovascular diseases. Clinically, it is often used in large quantities to replenish qi and move blood, so that the blood can circulate normally throughout the body. Flavonoids and astragalosides in *A. Radix* are two main active beneficial compounds that exert the pharmacological activities and therapeutic effects. Extensive *in vivo* and *in vitro* studies have demonstrated the protective effects of astragaloside IV derivative (LS-102) on MIRI (118). *Herba Siegesbeckiae* is a CHM used for rheumatism, joint health, and detoxification purposes. The study conducted by Wei *et al.* (119) demonstrated, for the first time, that *H. Siegesbeckiae* pretreatment exerted a protective effect on cardiac dysfunction induced by MIRI. This effect is achieved through enhancing mitochondrial biogenesis, increasing mitochondrial respiratory chain complex activity, reducing oxidative stress injury, and inhibiting NOD-like receptor thermal protein domain associated protein 3 (NLRP3)-mediated inflammatory response, thereby restoring mitochondrial function and improving MIRI. *Corydalis yanhusuo* W. T. Wang has been used as an analgesic in TCM for hundreds of years. Besides, it can also circulate blood, transform stasis and circulate qi. It has a variety of pharmacological effects such as softening blood vessels, improving blood rheology, promoting blood circulation, anti-arrhythmia and anti-thrombosis. The combined use of *P. ginseng*, *S. miltiorrhiza* and *C. yanhusuo* reflects the therapeutic principles of supplementing "qi" and activating blood circulation to dissipate blood stasis in the treatment of cardiovascular diseases. The results (120) showed that the total saponins of the *P. ginseng*, total phenolic acids of the *S. miltiorrhiza* and the total alkaloids of the *C. yanhusuo* reduced the infarction area and no-flow area, improved cardiac function, mitigated pathological alterations, increased endothelial nitric oxide synthase expression, protected endothelial function, and attenuated microvascular damage after MIRI. They also affect cardiac microvascular endothelial cells migration and angiogenesis, reduce MMP damage, inhibit membrane opening, restore mitochondrial fission to normal levels and inhibit mitochondrial apoptosis. Hawthorn leaves are known for their blood pressure-lowering properties and therapeutic effects on cardiovascular and cerebrovascular diseases. Its extract, Hawthorn leaves flavonoids (121), exhibited a protective effect on myocardial mitochondrial respiratory function in myocardial I/R rats. This effect may be attributed to the inhibition of mitochondrial Ca^{2+} overload and the maintenance of mitochondrial membrane stability. *Sorbus tianschanica* Rupr. is a commonly used folk medicine in Xinjiang. Flavonoids present in *S. tianschanica* have been reported to possess strong antioxidant activity and anti-myocardial ischemia effects. Li *et al.* (122) found the anti-MIRI effect of *S. tianschanica* was mainly attributed to enhancing myocardial systolic and diastolic functions, reducing myocardial infarction area, mitigating oxidative stress injury in myocardial tissue, and inhibiting mPTP opening by targeting translocator protein receptors and reducing mitochondrial edema in myocardial cells.

In addition to the aforementioned CHM extracts that exhibited a protective role in MIRI, several other extracts have also shown beneficial effects. These include total flavonoid *Dracocephalum Moldavica* L. (123), crocin (124), fangchinoline (125), tetrandrine (126), hirsutine (127), Panax notoginseng saponins and Panax quinquefolius saponin compatibility (128), Danshen-Honghua extracts (129).

Compounds for regulating mitochondria in MIRI

We have summarised 10 species of compounds that regulate mitochondria to exert protective effects on MIRI in *Table 5*. Wenxin prescription is a TCM compound created by Professor Cao Hongxin through years of clinical practice and research on the basis of the understanding of the basic pathogenesis "yang deficiency and phlegm stasis" of coronary heart disease. It is composed of *P. ginseng*, *Rhizoma*, *Ophiopogon* japonicus (Linn.f.) Ker-Gawl., *Coptidis* Rhizoma, *L. chuanxiong*, *Trichosanthes Kirilowii* Maxim, *Allium Azureum* Ledeb., *Pinelliae*, *Radix Paeoniae Rubra* and *Cinnamomi Ramulus*. Liu *et al.* (130) found that Wenxin prescription improved myocardial mitochondrial energy metabolism by regulating the SIRT1/PGC-1α/ERRα signaling pathway, thereby playing a protective role in MIRI. Huoxue Huatan Decoction is composed of *S.*

Table 4 Extracts of Chinese herbal medicines, acting on mitochondria, used to decrease ischemia-reperfusion injury in the past 5 years

Extracts of Chinese herbal medicines	Source	Model	Dosage	Finding	Target	Reference
Astragaloside IV derivative	*Astragali Radix*	SD rats; H9c2 cells	2.5, 5, 10 mg/kg; 20 μM	↑: cell viability, MMP, Bax/Bcl-2, p-PI3K, p-Akt, ATP, SOD ↓: myocardial infarct size, apoptosis rate, ROS, CK-MB, LDH, Bax, cleaved caspase-3, Drp1	Mitochondrial dynamics, MMP, mitochondrial apoptosis	(118)
Herba Siegesbeckiae	*Herba Siegesbeckiae*	SD rats	1, 2, 4 g/kg	↑: +dp/dt$_{max}$, LVSP, electron-transport chain complex I–V, ATP5A ↓: ROS, RNS, MDA, 8-OHdG, −dp/dt$_{max}$, CK-MB, cTnT, LDH, ALT, AST, RNS, NO, IL-1β, IL-18, TNF-α, IL-6, apoptosis rate, myocardial infarct size, NLRP3, ASC, caspase-1	Biogenesis, oxidative stress, mitochondrial apoptosis, energy metabolism	(119)
The total saponins of the ginseng, total phenolic acids of the Salvia miltiorrhiza and the total alkaloids of the *Corydalis*	*Panax ginseng C. A. Mey*, *Salvia miltiorrhiza Bunge*, *Corydalis yanhusuo W. T. Wang*	SD rats; cardiac microvascular endothelial cells	45, 90, 180 mg/kg; 25 μg/mL	↑: EF, FS, SV, CO, APTT time, eNOS, MMP, transendothelial electrical resistance ↓: the peak time of myocardial perfusion, myocardial no-reflow area, myocardial infarct size, CK, CK-MB, LDH, FIB content, ET-1, inflammatory cell, muscle bundle gaps, perivascular edema, cross-sectional area of myocardial cells, NR4A1, Mff, Drp1, VDAC1, HK2, mPTP, Cyt c, caspase-9	Mitochondrial dynamics, mitochondrial apoptosis	(120)
Hawthorn leaves flavonoids	Hawthorn leaves	SD rats	25, 50, 100 mg/kg	↑: R3, RCR, NADPH, ATP, Na^+-K^+-ATP, MMP ↓: Ca^{2+}-ATP, R4, Ca^{2+}, mPTP	Calcium overload, MMP, mPTP	(121)
Flavonoids in *Sorbus tianschanica* Rupr.	*Sorbus tianschanica* Rupr.	SD rats	0.5, 1.5 mg/L	↑: SOD, GSH/GSSG, CAT ↓: myocardial infarct size, MDA, mPTP	Oxidative stress, mPTP	(122)
Total flavonoid *Dracocephalum moldavica* L.	*Dracocephalum moldavica* L.	SD rats	60 mg/kg	↑: SOD, AMPK, SIRT1, PGC-1α ↓: myocardial infarct size, ROS, MDA	Oxidative stress	(123)
Crocin	*Crocus sativus* L.	Wistar rats	5, 25, 50 mg/L	↑: LVDP, HR, ±dp/dt$_{max}$, SOD, GSH-Px, ATP, ADP ↓: MDA, LDH, Cyt c, caspase-3, caspase-9, Bax, Bax/Bcl-2	Oxidative stress, mitochondrial apoptosis	(124)
Fangchinoline	*Stephania tetrandra* S. Moore	SD rats	10 mg/kg	↑: LVSP, MAP, SOD, GSH, Bcl-2, c-Myc ↓: Mb, CK-MB, MDA, myocardial pathological changes, apoptosis rate, cleaved caspase-3, Bax, p-P38, p-MAPK, p-ERK1/2	Oxidative stress, mitochondrial apoptosis	(125)
Tetrandrine	Stephania tetrandra S. Moore	SD rats; H9c2 cells	50 mg/kg; 1.5 μmol/L	↑: MMP ↓: ROS, mPTP, Ca^{2+}, TRPV2	Calcium overload, MMP, mPTP	(126)
Hirsutine	Uncaria rhynchophylla	SD rats	5, 10, 20 mg/kg	↑: LVEF, LVFS, SOD, MFN2, ATP, mitochondrial respiratory complex (I–IV) activity, Bcl-2 ↓: myocardial infarct size, LVEsD, LVEDD, ROS, LDH, MDA, apoptotic cells, Drp1, p-CaMKII, p-Akt, p-ASK-1, p-p38, Bax, caspase-3	Oxidative stress, energy metabolism, mitochondrial dynamics, mitochondrial apoptosis	(127)
Panax notoginseng saponins, Panax quinquefolius saponin	*Panax Notoginseng* (Burk.) F. H. Chen Ex C. Chow, *Panacis Quinquefolii* Radix	H9c2 cells	40, 80, 160 mg/kg	↑: cell viability, MMP, autolysosome, HIF-1α ↓: apoptosis rate, ROS, BNIP3	MMP, mitophagy	(128)
Danshen-Honghua extracts	*Radix Salviae, Carthami Flos*	SD rats	1.2, 2.4, 4.8 g/kg	↑: Bcl-2, MMP ↓: myocardial infarct size, apoptosis rate, Cyt c, Bax/Bcl-2, cleaved caspase-3, cleaved caspase-9, mPTP, mitochondrial damage	MMP, mPTP, mitochondrial apoptosis	(129)

↑, an increase/rise in data values, indicating an upward trend; ↓, a decrease/reduction in data values, indicating a downward trend. SD, Sprague-Dawley; MMP, mitochondrial membrane potential; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; PI3K, phosphatidylinositol3-kinase; Akt, protein kinase B; ATP, adenosine triphosphate; SOD, superoxide dismutase; ROS, reactive oxygen species; CK-MB, creatine kinase MB; LDH, lactate dehydrogenase; Caspase, cysteinyl aspartate specific proteinase; Drp1, dynamin-related protein 1; +dp/dt$_{max}$, left ventricular maximum upstroke velocity; LVSP, left ventricular systolic pressure; ATP5A, ATP synthase subunit alpha of complex V; RNS, reactive nitrogen species; MDA, malonaldehyde; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; −dp/dt$_{max}$, left ventricular maximum descent velocity; cTnT, troponin T; ALT, alanine transaminase; AST, aspartate transaminase; NO, nitric oxide; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; NLRP3, NOD-like receptor thermal protein domain associated protein 3; ASC, apoptosis-associated speck-like protein with a caspase-recruitment domain; EF, ejection fraction; FS, fractional shortening; SV, stroke volume; CO, cardiac output; APTT, activated partial thromboplastin time; eNOS, endothelial nitric oxide synthase; FIB, fibrinogen; ET-1, endothelin-1; NR4A1, nuclear receptor subfamily 4 group A member 1; Mff, mitochondrial fission factor; VDAC1, voltage-dependent anion channel protein 1; HK2, hexokinase 2; mPTP, mitochondrial permeability transition pore; Cyt c, cytochrome c; RCR, respiration control ratio; NADPH, nicotinamide adenine dinucleotide phosphate; GSH/GSSG, glutathione,reduced/glutathione,oxidized; CAT, catalase; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-alpha; LVDP, left ventricular developed pressure; HR, heart rate; ADP, adenosine diphosphate; LVSP, left ventricular systolic pressure; MAP, mean arterial pressure; c-Myc, myc proto-oncogene protein; Mb, myoglobin; MAPK, mitogen-activated protein kinase; ERK1/2, extracellular regulated protein kinases 1/2; TRPV2, transient receptor potential vanilloid type-2; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; MFN2, mitofusin 2; LVEsD, left ventricular end-diastolic diameter; LVEDD, left ventricular end-diastolic diameter; CaMKII, calmodulin-stimulated protein kinase II; HIF-1α, hypoxia-inducible factor-1α; BNIP3, BCL2 interacting protein 3.

Table 5 Compounds, acting on mitochondria, used to decrease ischemia-reperfusion injury in the past 5 years

Compounds	Composition	Model	Dosage	Finding	Target	Reference
Wenxin prescription	*Panax Ginseng* C. A. Mey., *Rhizoma, Ophiopogon japonicus (Linn.f.) Ker-Gawl., Coptidis Rhizoma, Chuanxiong Rhizoma, Trichosanthes Kirilowii Maxim, Allium Azureum Ledeb., Pinelliae, Radix Paeoniae Rubra, Cinnamomi Ramulus*	Wistar rats	0.99, 1.98, 3.96 g/kg	↑: ATP, CCO, SDH, SIRT1, PGC-1α, ERRα, TFAM ↓: myocardial infarct size, CK-MB, LDH	Energy metabolism	(130)
Huoxue Huatan Decoction	*Salvia miltiorrhiza Bunge, Ginkgo biloba* L., *Astragalus mongholicus* Bunge, *Panax notoginseng* (Burkill) F. H. Chen, *Trichosanthes kirilowii* Maxim., *Allium macrostemon* Bunge, *Ziziphus jujuba* Mill	Wistar rats	0.9, 1.8, 3.6 g/kg	↑: LVEF, T-SOD, SDH, CuZn-SOD, GSH-Px, PGC-1a, PPARa, NRF1, mtTFA, mtDNA ↓: myocardial infarct size, CK-MB, LDH, LVIDd, LVIDs, MDA	Biogenesis, oxidative stress	(131)
Danshen Decoction	*Radix Salviae, Santalum Album* L., *Amomum Aurantiacum* H. T. Tsai Et S. W. Zhao	Wistar rats	2.4, 4.2, 8.4 g/kg	↑: SAP, LVSP, LV +dp/dt_{max}, ATP, ADP, EC, ATP/ADP, Bcl-2/Bax ↓: LVEDP, apoptosis rate, Cyt c, cleaved caspase-3	Energy metabolism, mitochondrial apoptosis	(132)
Tongmai formula	*Salvia miltiorrhiza*, Chuanxiong, *Pueraria lobata*	SD rats; NRVMs	1,060, 2,012, 3,018 mg/kg; 15, 30, 60 μg/mL	↑: left ventricular contractile function, FS%, EF%, dP/dt_{max}, Bcl-2, MMP, GSH-Px, SOD, MFN2 ↓: myocardial infarct size, Bax, cTnI, CK, LDH, mPTP, Ca^{2+}, AIF, Cyt c, ROS, DRP1, MDA	MMP, mPTP, calcium overload, oxidative stress, mitochondrial dynamics, mitochondrial apoptosis	(133)
Xuefu Zhuyu Decoction	*Angelicae Sinensis* Radix, *Persicae Semen, Rehmannia glutinosa* (Gaetn.) Libosch. ex Fisch. et Mey., *Chuanxiong Rhizoma, Carthami Flos, Aurantii Fructus,* licorice, *Achyranthis Bidentatae* Radix, *Radix Bupleuri, Radix Paeoniae Rubra, Platycodon Grandiforus*	SD rats	3.51, 7.02, 14.04 g/kg	↑: MFN1 ↓: myocardial infarct size, degree of edema of cardiomyocytes, inflammatory cell infiltration, degree of cardiomyocyte necrosis, MFN2	Mitochondrial dynamics	(134)
Bawei Chenxiang Powder	*Linderae Radix, Myristicae Semen, Choerospondiatis* Fructus, Shí Huī Huá, *Gossampiniflos, Chebulae* Fructus, *Olibanun*, Aucklandiae Radix	HCM cells	Aqueous extracts: 15, 30, 60 μg/mL; alcohol extract: 7.5, 15, 30 μg/mL	↓: ROS, Ca^{2+}	Calcium overload, oxidative stress	(135)
Shen Yuan Dan	Salvia miltiorrhiza Bge, Astragalus membranaceus Bge, root of Pilose Asiabell, Radix Scrophulariae, Hirudo nipponica (Whitman), Lumbricus, Eupolyphaga sinensis (Walker), and Rhizoma Corydalis	H9c2 cells	100 μg/mL	↑: MMP, ATP, SOD, the distribution and number of mitochondria, MFN1, MFN2, OPA1, PGC-1α, PINK1, Parkin ↓: MDA, Drp1, Fis1	Mitochondrial quality control, oxidative stress	(136)
Guizhi Gancao Decoction	*Cinnamomum cassia (L.) C. Presl, Glycyrrhiza uralensis Fisch.*	SD rats	3 g/kg	↑: SOD, p-ERK1/2 ↓: myocardial infarct size, LDH, CK-MB, MDA, p38, p-JNK	Oxidative stress, mitochondrial apoptosis	(137)
Baijinfang	*Trichosanthes Kirilowii* Maxim, Allium *Azureum* Ledeb., *Hypericum attenuatum* Choisy	SD rats	7 g/kg	↑: PINK1, Parkin ↓: CK, LDH	Mitophagy	(138)
Gualou Xiebai Banxia Decoction	*Trichosanthes Kirilowii Maxim, Allium Azureum* Ledeb.*Arum Ternatum Thunb*., Huangjiu	SD rats	6.5, 13 g/kg	↑: MFN2 ↓: LDH, CK-MB, Beclin-1, P62, Pink1, Parkin	Mitophagy	(139)

↑, an increase/rise in data values, indicating an upward trend; ↓, a decrease/reduction in data values, indicating a downward trend. ATP, adenosine triphosphate; CCO, cytochrome-c oxidase; SDH, succinate dehydrogenase; SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-alpha; ERR, estrogen-related receptor; TFAM, mitochondrial transcription factor A; CK-MB, creatine kinase MB; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; PPARa, peroxisome proliferator-activated receptor alpha; NRF, nuclear respiratory factor; mtDNA, mitochondrial DNA; LVIDd, left ventricular internal dimension-diastole; LVIDs, left ventricular internal dimension in systole; MDA, malondialdehyde; SAP, systolic arterial pressure; LVSP, left ventricular systolic pressure; ADP, adenosine diphosphate; EC, energy charge; Bcl-2, B-cell lymphoma-2; Bax, Bcl-2-associated X protein; LVEDP, left ventricular end-diastolic pressure; Cyt c, cytochrome c; SD, Sprague-Dawley; NRVMs, neonatal rat ventricular cardiomyocytes; FS, fractional shortening; EF, ejection fraction; +dp/dt_{max}, left ventricular maximum upstroke velocity; MMP, mitochondrial membrane potential; cTnI, cardiac troponin I; mPTP, mitochondrial permeability transition pore; AIF, apoptosis inducing factor; MDA, malondialdehyde; MFN1, mitofusin 1; MFN2, mitofusin 2; ROS, reactive oxygen species; OPA1, optic atrophy protein 1; Drp1, dynamin-related protein 1; Fis1, fission 1; ERK1/2, extracellular regulated protein kinases 1/2; JNK, c-Jun N-terminal kinase; PINK1, PTEN-induced putative kinase 1; Parkin, E3 ubiquitin-protein ligase parkin.

miltiorrhiza, *Ginkgo biloba* L., *Astragalus mongholicus* Bunge, *Panax notoginseng* (Burkill) F. H. Chen, *T. kirilowii*, *Allium macrostemon* Bunge, *Ziziphus jujuba* Mill. It is a commonly prescribed medicine for the treatment of coronary heart disease with phlegm-blood stasis syndrome, and has been used clinically for more than 20 years. It has the effects of invigorating qi and activating blood, resolving phlegm, and removing blood stasis. Experimental studies have shown that Huoxue Huatan Decoction promote the mRNA expression and protein transcription of PGC-1α-NRF1-TFAM mitochondrial biosynthesis-related genes, enhances antioxidant capacity, facilitates mtDNA synthesis, mitigates mitochondrial damage, preserves mitochondrial structure and function, reduces I/R-induced damage and improves cardiac function (131). In addition to *S. miltiorrhiza*, Danshen decoction also contains *Santalum Album* L. and *Amomum Aurantiacum* H. T. Tsai Et S. W. Zhao. Danshen decoction (132) pretreatment has been found to improve left ventricular function in I/R rats, enhance myocardial energy metabolism, reduce myocardial cell apoptosis, and provide cardiac protection against MIRI. Tongmai formula, composed of *S. miltiorrhiza*, *L. chuanxiong*, and *Pueraria lobata*, is a classic prescription used for nourishing blood, and unblocking meridians. Xuefu Zhuyu decoction has the effects of circulating blood and transforming stasis, circulating qi and alleviating pain. Mainly contains *Angelicae Sinensis* Radix, *L. chuanxiong*, *Carthami Flos* and other CHMs. The two prescriptions are commonly used in the clinical treatment of cardiovascular diseases caused by obstruction or failure. Zhao *et al.* (133) demonstrated that Tongmai exhibited protective effects on rats with MIRI and neonatal rat ventricular cardiomyocytes (NRVMs) H/R. It restored MMP, inhibited mPTP opening, mediated mitochondrial dynamics regulators, downregulated Drp1 expression level, upregulated MFN2 expression level, and improved cardiac dysfunction caused by MIRI. Xuefu Zhuyu Decoction (134) also promoted mitochondrial fusion in rat myocardial cells and reduced myocardial ischemic injury by downregulating the MFN2 expression level and upregulating the MFN1 expression level. Bawei Chenxiang Powder, a Tibetan medicine, has the effects of clearing heart heat, calming and settling the mind, awakening the brain and opening the orifices, is commonly used for the clinical treatment of coronary heart disease and angina pectoris. Recent research (135) has found that Bawei Chenxiang Powder could improve mitochondrial function by inhibiting ROS production, reducing Ca^{2+} overload, and inhibiting apoptosis, thereby protecting cardiomyocytes from H/R injury. Shen Yuan Dan has been broadly applied in clinical for the treatment of coronary heart disease by invigorating qi and removing blood stasis. It mainly includes Salvia miltiorrhiza Bge, Astragalus membranaceus Bge and root of Pilose Asiabell. It was discovered that Shen Yuan Dan pretreatment elevated MMP in H/R injury cardiomyocytes, enhanced ATP content, activated SOD activity, and reduced MDA level. Shen Yuan Dan treatment increased the mRNA levels of MFN1, MFN2, OPA1 and PGC-1α decreased the mRNA levels of Drp1 and Fis1, and reduced the protein levels of LC3, PINK1, and Parkin. The results demonstrate that Shen Yuan Dan pretreatment significantly increases mitochondrial antioxidant capacity, alleviates the mitochondrial damage caused by H/R, regulates mitochondrial fission and fusion, upregulates mitochondrial biogenesis, and downregulates excessive mitophagy, thereby protecting cardiomyocytes from MIRI (136). Guizhi Gancao decoction is Zhang Zhongjing's classic prescription for the treatment of heart yang deficiency pattern. *Cinnamomum cassia (L.) C. Presl* is pungent flavour and hot, could warm and promote heart yang, and *Glycyrrhiza uralensis Fisch.* is sweet flavour and neutral property, could tonify qi and nourish blood. The two CHMs are compatible with pungent and sweet transform into yang (xin-gan-hua-yang), which is suitable for heart yang deficiency syndrome. Modern clinical practice mostly uses this prescription as the basis for the treatment of "Palpitations" and other related diseases. Studies have found that Guizhi Gancao decoction can significantly reduce myocardial infarction area, restores myocardial cell structure, improves myocardial mitochondrial ultrastructural damage, protects myocardial tissue from oxidative damage by increasing the level of antioxidant enzymes, significantly increases the level of p-ERK1/2 in myocardial tissue after MIRI, reduces the level of p-JNK and p38, regulates MAPK signaling pathway, and exerts anti-MIRI effects (137). Additionally, Baijinfang (138) and Gualou Xiebai decoction (139) alleviate MIRI by inhibiting excessive activation of mitophagy mediated via the PINK1/Parkin pathway.

Proprietary Chinese medicine for regulating mitochondria in MIRI

As shown in *Table 6*, Xuefuzhuyu capsule is primarily composed of blood-activating CHMs such as *Angelicae Sinensis* Radix, *Radix Paeoniae Rubra*, *Carthami Flos* and *L. chuanxiong*. Kong *et al.* (140) found that Xuefuzhuyu capsule pretreatment could improve mitochondrial

respiratory function and reduce MIRI by restoring the level of mitochondrial complex I/II OXPHOS in the I/R rat model. In addition to *Radix Salviae* and Codonopsis Radix, Ershen granules also contain qi-circulating CHMs such as *L. chuanxiong*a, *Schisandrae Chinensis* Fructus, *Corydalis* Rhizoma and *Aucklandiae* Radix. Ershen granules have been shown to inhibit $CoCl_2$-induced ROS levels in cardiomyocytes, activate the SIRT1/PGC-1α/PPARα signaling pathway, improve tissue morphology, reduce myocardial fibrosis in rats with myocardial ischemia, enhance the activity of mitochondrial respiratory chain complexes, promote ATP production, and subsequently reduce oxidative stress-mediated cardiomyocyte apoptosis and improve cardiac function (141). Xinmai'an tablets are a compound Chinese medicine developed from accumulated clinical experience and evolved from the classic prescription Sheng Mai San. They comprise Ginseng Radix et *Rhizoma*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Aastragali Radix*, *Ophiopogonis Radix*, Paeoniae Radix Rubra, and *Borneolum Syntheticum*. Research demonstrated that Xinmai'an tablet enhanced glucose uptake, improved mitochondrial function, and inhibited vascular endothelial damage, oxidative stress, and apoptosis, subsequently improving myocardial energy metabolism and alleviating MIRI. These protective effects were partially attributed to the AMPK/SIRT1/PGC-1α pathway (142). Wenxin Granule (143) is known for its blood circulation-promoting and blood-stasis-removing effects, and is commonly used to treat palpitations, chest tightness and chest pain caused by heart blood stasis. It is mainly composed of *Codonopsis* Radix, Polygonati Rhizoma, *Notoginseng* Radix Et Rhizoma, *Ambrum* and *Nardostachyos* Radix Et Rhizoma. Experimental studies have shown that Wenxin Granule can significantly reduce ROS production, maintain MMP, mitigate oxidative stress injury, decrease cardiomyocyte apoptosis rate, and improve mitochondrial function to treat MIRI. Danhong injection is frequently used in the treatment of cardiovascular diseases, such as coronary atherosclerotic heart disease, ischemic stroke, and chronic heart failure. It possesses blood-stasis-removing and collateral-dredging properties, promoting blood circulation and relaxing collaterals. Zhang *et al.* (144) conducted *in vivo* and *in vitro* experiments and found that Danhong injection could significantly increase ATP production in mitochondria, inhibit ROS production, maintain MMP, reduce oxidative stress injury, decrease apoptosis rate, and improve mitochondrial dysfunction, thereby playing a cardioprotective role. Shuangshen Ningxin capsule contains three CHMs of *P. ginseng*, *Radix Salviae* and *Corydalis* Rhizoma, which possesses the functions of benefiting qi, activating blood circulation, removing blood stasis, and relieving pain. It is used for the treatment of coronary heart disease, coronary microcirculation disorders, angina pectoris, and other related conditions. Relevant experiments have confirmed that the Shuangshen Ningxin capsule could improve myocardial mitochondrial MMP by opening mitoKATP channels to stabilize mitochondria, reduce myocardial cell damage caused by mitochondrial dysfunction (145).

Strengths and limitations

Strengths

In the experimental studies conducted *in vivo* and *in vitro*, CHM has shown significant progress in the prevention and treatment of MIRI by targeting mitochondria. CHM offers advantages, such as low toxicity, minimal side effects, stable therapeutic effects, and diverse mechanisms. Various effective monomers of CHM, extracts of CHM, compounds, and proprietary Chinese medicine have demonstrated promising therapeutic potential in basic research, among them, tonic and blood-activating CHMs account for the largest proportion. This paper presents a compilation and summary of information on effective monomers of CHM, extracts of CHM, compounds, and proprietary Chinese medicine, medicinal sources, models, doses, experimental results, related mechanisms and references in the form of tables. This aims to provide theoretical support for the screening and development of safe, efficient, and low-toxicity anti-MIRI drugs.

Limitations

Many studies on the anti-MIRI effects of CHM remain limited to basic research, with few clinical trials conducted. Furthermore, CHM exhibits inherent characteristics, such as limited bioavailability, rapid metabolic rate, and a lack of targeted administration. Its full drug potential has not been fully utilized in clinical practice, resulting in relatively low practical value. These observations suggest that there are still several challenges to be addressed. Firstly, although existing experimental studies have identified different active ingredients of CHM that can target the same MIRI-related proteins and pathways, research is scarce on the deeper aspects of related protein channels and genes. Additionally, the design of indices in these studies is relatively simplistic.

Table 6 Proprietary Chinese medicines, acting on mitochondria, used to decrease ischemia-reperfusion injury in the past 5 years

Proprietary Chinese medicines	Composition	Model	Dosage	Finding	Target	Reference
Xuefuzhuyu capsule	Radix Bupleuri, *Angelicae Sinensis* Radix, *Rehmannia glutinosa* (Gaetn.) Libosch. ex Fisch. et Mey., *Radix Paeoniae Rubra*, Carthami Flos, *Persicae Semen*, licorice, *Aurantii Fructus*, *Chuanxiong Rhizoma*, *Achyranthis Bidentatae* Radix, *Platycodon Grandiforus*	Wistar rats	1.6 g/kg	↑: LVDP, +dp/dt$_{max}$, −dp/dt$_{max}$, p-ERK, mitochondrial complex I/II, p-Akt ↓: myocardial infarct size	Energy metabolism	(140)
Ershen granules	*Radix Salviae*, Codonopsis Radix, *Dalbergiae Odoriferae Lignum*, *Schisandrae Chinensis* Fructus, *Chuanxiong Rhizoma*, *Allium Azureum* Ledeb., *Corydalis* Rhizoma, *Aucklandiae* Radix, *Ophiopogon japonicus* (Linn. f.) Ker-Gawl.	SD rats; H9c2 cells	4.05, 8.1, 16.2 g/kg; 50, 100, 200 μg/mL;	↑: cell viability, SOD, Bcl-2/Bax, ATP, MMP, complex I, II, III, V, SIRT1, PGC-1α, PPARα ↓: LDH, CK, MDA, ROS, apoptosis, cleaved caspase-3, cleaved caspase-9, cleaved-PARP	Energy metabolism, MMP, oxidative stress, mitochondrial apoptosis	(141)
Xinmai'an tablets	*Ginseng Radix et Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Aastragali Radix, Ophiopogonis Radix, Paeoniae Radix Rubra,* and *Borneolum Syntheticum*	SD rats	0.5, 1, 2g/kg	↑: LVEF, LVFS, CO, SV, NO, SOD, ATP, Na^+-K^+-ATPase, Ca^{2+}-Mg^{2+}-ATPase activities, HK, PFK, PK, GLUT4, Bcl-2, SIRT1, PGC-1α, p-AMPK ↓: myocardial infarct size, AST, CK-MB, LDH, cTnI, ET-1, MDA, GLUT1, Bax, caspase-1, caspase-9	Energy metabolism, oxidative stress, mitochondrial apoptosis	(142)
Wenxin Granule	*Codonopsis* Radix, Polygonati Rhizoma, *Notoginseng* Radix Et Rhizoma, *Ambrum*, *Nardostachyos* Radix Et Rhizoma	The H9c2 rat embryonic cardiomyocyte cell line	5 mg/kg	↑: cell viability, SOD, GSH/GSSG, ATP, MMP, Bcl-2 ↓: LDH, MDA, ROS, mPTP, Cyt c, Bax, cleaved caspase-3, apoptosis rate	Energy metabolism, MMP, mPTP, oxidative stress, mitochondrial apoptosis	(143)
Danhong injection	*Salvia miltiorrhiza* Bge, *Carthamus tinctorius* L.	SD rats; H9c2 cells	1, 2 mL/kg; 5, 10, 20, 40, 80, 100 μL/mL	↑: SOD, GSH/GSSG, ATP, MMP, Nrf2, Bcl-2/Bax ↓: myocardial infarct size, apoptosis rate, ROS, p-JNK, Keap1, Cyt c, cleaved caspase-3	Oxidative stress, MMP, mitochondrial apoptosis	(144)
Shuangshen Ningxin capsule	*Panax Ginseng* C. A. Mey., *Radix Salviae*, *Corydalis* Rhizoma	SD rats	90 mg/kg	↑: MMP ↓: CK, CK-MB, LDH, myocardial infarct size	MMP, mitoKATP	(145)

↑, an increase/rise in data values, indicating an upward trend; ↓, a decrease/reduction in data values, indicating a downward trend. LVDP, left ventricular developed pressure; +dP/dt, maximal left ventricular pressure rising rate; –dP/dt, maximal left ventricular pressure decline rate; ERK, extracellular regulated protein kinases; SD, Sprague-Dawley; SOD, superoxide dismutase; Bcl-2, B-cell lymphoma-2; Bax, Bcl-2-associated X protein; ATP, adenosine triphosphate; MMP, mitochondrial membrane potential; SIRT1, sirtuin 1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1-alpha; PPARa, peroxisome proliferator-activated receptor alpha; LDH, lactate dehydrogenase; MDA, malondialdehyde; ROS, reactive oxygen species; Caspase, cysteinyl aspartate specific proteinase; PARP, poly ADP-ribose polymerase; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; CO, cardiac output; SV, stroke volume; NO, nitric oxide; HK, hexokinase; PFK, phosphofructokinase; PK, pyruvate kinase; GLUT, glucose transporter; SIRT1, sirtuin 1; AMPK, adenosine 5'-monophosphate (AMP)-activated protein kinase; AST, aspartate transaminase; CK-MB, creatine kinase MB; cTnI, cardiac troponin I; ET-1, endothelin-1; mPTP, mitochondrial permeability transition pore; Cyt c, cytochrome c; GSH/GSSG, glutathione,reduced/glutathione,oxidized; Nrf2, nuclear factor erythroid 2-related factor 2; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1.

There is a tendency for repeated detection of the same indices and verification of the same active ingredients. This approach fails to elucidate the distinct effects of these active ingredients on mitochondrial-related mechanisms, thereby missing the opportunity to highlight the multi-channel and multi-target advantages of CHM in MIRI mechanisms. To overcome this limitation, it is important to clarify the material basis and main mechanisms of CHM and its components in the prevention and treatment of MIRI. This will contribute to the objective understanding and further development of TCM theory. Secondly, although China possesses abundant CHM resources, the content of confirmed effective monomeric components in basic research is relatively low. The purification and identification of these components can be challenging, hindering the development of artificial synthesis methods aiming at increasing the content of active ingredients. Without addressing this issue, there may be a decline in meeting future clinical demands. Therefore, a multidisciplinary integration approach should be adopted to tackle these challenges and establish a solid foundation for the development of highly efficient and low-toxicity anti-MIRI drugs derived from CHM. Thirdly, the components present in CHM extracts, compounds, and proprietary Chinese medicine are often complex. The therapeutic activity against MIRI is usually attributed to the synergistic effect of multiple chemicals, while the interactions among these components remain elusive. This lack of understanding limits in-depth research and clinical applications of CHM in the treatment of MIRI. Therefore, it is necessary to identify the active components responsible for the anti-MIRI effects, such as effective parts or component groups. Technologies, such as quantum computing, molecular docking, and molecular dynamics simulation can aid in the exploration of mitochondrial-targeted drugs and facilitate the translation of basic research findings into potential clinical treatment methods. Fourthly, it is crucial to combine basic research with both TCM theory and modern MIRI pathological mechanisms. At present, most of the basic research refers to the model of Western medicine, and the integration of TCM theory is insufficient, which leads to blindness in clinical practice. In clinical practice, MIRI presents multi-dimensional manifestations, while basic research animal models only exhibit the characteristics of MIRI disease without considering the principles of TCM's "Treatment based on pattern identification" theory. This mismatch between basic research and TCM theory can lead to limitations and blind spots in clinical practice. To address this issue, it is important to integrate the "holistic concept" and "treatment based on pattern identification" theory of TCM. By combining the disease differentiation of Western medicine with the syndrome differentiation of TCM, a comprehensive understanding of MIRI can be achieved. This approach allows for the exploration of the organic combination of disease, syndrome, and prescription, aligning with the principles of TCM theory. Fifthly, although some basic research has been conducted, there is a need for closer integration with clinical practice. Conducting scientific studies with larger sample sizes, multi-center designs, and clinical observations is necessary. Additionally, the results of clinical research can be utilized to optimize the compatibility, dosage, administration time, and administration methods of effective components of CHM.

Conclusions

CHM shows promise in the prevention and treatment of MIRI through targeting mitochondria, but further research is needed to fully realize its potential. Addressing limitations such as limited clinical trials, bioavailability issues, simplistic research designs, and lack of integration with TCM theory is crucial for advancing the field. Multidisciplinary integration and the application of new technologies, such as quantum computing and molecular docking, can aid in exploring mitochondrial-targeted drugs and translating basic research findings into clinical practice. There is a need for closer integration of basic research with clinical practice, utilizing clinical research results to optimize CHM's compatibility, dosage, and administration methods. As understanding of MIRI pathogenesis deepens, further investigation into the pharmacodynamics, pharmacokinetics, toxicology, and mechanisms of CHM anti-MIRI is necessary to promote its in-depth research and clinical application.

Acknowledgments

We are grateful to the funding of the National Natural Science Foundation of China, to the image materials provided by Biorender. We would like to thank Yin Fu for her help in polishing our paper, and Peiyao Qin, Lihua Tian and Shuxian Wang for participating in the communication during the manuscript submission and peer review process.

Footnote

Reporting Checklist: The authors have completed the

Narrative Review reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-346/rc

Peer Review File: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-346/prf

Funding: This study was funded by the National Natural Science Foundation of China (No. 81874426).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-346/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. Lancet 2017;389:197-210.
2. World Health Organization. The top 10 causes of death (August 7, 2024). Available online: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
3. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237-69.
4. Heusch G. Myocardial ischaemia-reperfusion injury and cardioprotection in perspective. Nat Rev Cardiol 2020;17:773-89.
5. Yang CF. Clinical manifestations and basic mechanisms of myocardial ischemia/reperfusion injury. Tzu Chi Med J 2018;30:209-15.
6. Song R, Dasgupta C, Mulder C, et al. MicroRNA-210 Controls Mitochondrial Metabolism and Protects Heart Function in Myocardial Infarction. Circulation 2022;145:1140-53.
7. Ramachandra CJA, Hernandez-Resendiz S, Crespo-Avilan GE, et al. Mitochondria in acute myocardial infarction and cardioprotection. EBioMedicine 2020;57:102884.
8. Mou YL, Zhao R, Lyu SY, et al. Crocetin protects cardiomyocytes against hypoxia/reoxygenation injury by attenuating Drp1-mediated mitochondrial fission via PGC-1α. J Geriatr Cardiol 2023;20:68-82.
9. Chen M, Zhong G, Liu M, et al. Integrating network analysis and experimental validation to reveal the mitophagy-associated mechanism of Yiqi Huoxue (YQHX) prescription in the treatment of myocardial ischemia/reperfusion injury. Pharmacol Res 2023;189:106682.
10. Hefler J, Marfil-Garza BA, Campbell S, et al. Preclinical systematic review & meta-analysis of cyclosporine for the treatment of myocardial ischemia-reperfusion injury. Ann Transl Med 2022;10:954.
11. Zaib S, Saleem MA, Khan I. CRISPR-Cas9 Genome Engineering: Trends in Medicine and Health. Mini Rev Med Chem 2022;22:410-21.
12. McCully JD, Del Nido PJ, Emani SM. Mitochondrial transplantation for organ rescue. Mitochondrion 2022;64:27-33.
13. Wu X, Liu L, Zheng Q, et al. Dihydrotanshinone I preconditions myocardium against ischemic injury via PKM2 glutathionylation sensitive to ROS. Acta Pharm Sin B 2023;13:113-27.
14. Gan X, Shu Z, Wang X, et al. Network medicine framework reveals generic herb-symptom effectiveness of traditional Chinese medicine. Sci Adv 2023;9:eadh0215.
15. Zhang S, Yan F, Luan F, et al. The pathological mechanisms and potential therapeutic drugs for myocardial ischemia reperfusion injury. Phytomedicine 2024;129:155649.
16. Vela D. Keeping heart homeostasis in check through the balance of iron metabolism. Acta Physiol (Oxf) 2020;228:e13324.
17. Kuznetsov AV, Javadov S, Margreiter R, et al. The Role of Mitochondria in the Mechanisms of Cardiac Ischemia-Reperfusion Injury. Antioxidants (Basel) 2019;8:454.
18. Zhang X, Xie F, Ma S, et al. Mitochondria: one of the vital hubs for molecular hydrogen's biological functions. Front Cell Dev Biol 2023;11:1283820.
19. Manolis AS, Manolis TA, Manolis AA. Ketone Bodies and Cardiovascular Disease: An Alternate Fuel Source to the Rescue. Int J Mol Sci 2023;24:3534.
20. Sun Y, Zhang P, Li Y, et al. Light-Activated Gold-Selenium Core-Shell Nanocomposites with NIR-II

Photoacoustic Imaging Performances for Heart-Targeted Repair. ACS Nano 2022;16:18667-81.
21. Xia D, Liu Y, Wu P, et al. Current Advances of Mitochondrial Dysfunction and Cardiovascular Disease and Promising Therapeutic Strategies. Am J Pathol 2023;193:1485-500.
22. Sanada S, Komuro I, Kitakaze M. Pathophysiology of myocardial reperfusion injury: preconditioning, postconditioning, and translational aspects of protective measures. Am J Physiol Heart Circ Physiol 2011;301:H1723-41.
23. Liu T, Juan Z, Xia B, et al. HSP70 protects H9C2 cells from hypoxia and reoxygenation injury through STIM1/IP3R. Cell Stress Chaperones 2022;27:535-44.
24. Wang R, Wang M, He S, et al. Targeting Calcium Homeostasis in Myocardial Ischemia/Reperfusion Injury: An Overview of Regulatory Mechanisms and Therapeutic Reagents. Front Pharmacol 2020;11:872.
25. Figueroa-Juárez E. Uncovering the origin of oxidative damage in ischaemia-reperfusion injury in the heart. Nat Rev Endocrinol 2023;19:560.
26. Tahrir FG, Langford D, Amini S, et al. Mitochondrial quality control in cardiac cells: Mechanisms and role in cardiac cell injury and disease. J Cell Physiol 2019;234:8122-33.
27. Pedriali G, Ramaccini D, Bouhamida E, et al. Perspectives on mitochondrial relevance in cardiac ischemia/reperfusion injury. Front Cell Dev Biol 2022;10:1082095.
28. Endlicher R, Drahota Z, Štefková K, et al. The Mitochondrial Permeability Transition Pore-Current Knowledge of Its Structure, Function, and Regulation, and Optimized Methods for Evaluating Its Functional State. Cells 2023;12:1273.
29. Lee JH, Amarsanaa K, Wu J, et al. Nobiletin attenuates neurotoxic mitochondrial calcium overload through K(+) influx and ΔΨ(m) across mitochondrial inner membrane. Korean J Physiol Pharmacol 2018;22:311-9.
30. Davidson SM, Adameová A, Barile L, et al. Mitochondrial and mitochondrial-independent pathways of myocardial cell death during ischaemia and reperfusion injury. J Cell Mol Med 2020;24:3795-806.
31. Del Re DP, Amgalan D, Linkermann A, et al. Fundamental Mechanisms of Regulated Cell Death and Implications for Heart Disease. Physiol Rev 2019;99:1765-817.
32. Li P, Dong XR, Zhang B, et al. Molecular mechanism and therapeutic targeting of necrosis, apoptosis, pyroptosis, and autophagy in cardiovascular disease. Chin Med J (Engl) 2021;134:2647-55.
33. Zhou H, Dai Z, Li J, et al. TMBIM6 prevents VDAC1 multimerization and improves mitochondrial quality control to reduce sepsis-related myocardial injury. Metabolism 2023;140:155383.
34. Zhou H, Ren J, Toan S, et al. Role of mitochondrial quality surveillance in myocardial infarction: From bench to bedside. Ageing Res Rev 2021;66:101250.
35. Belosludtseva NV, Matveeva LA, Belosludtsev KN. Mitochondrial Dyshomeostasis as an Early Hallmark and a Therapeutic Target in Amyotrophic Lateral Sclerosis. Int J Mol Sci 2023;24:16833.
36. Popov LD. Mitochondrial biogenesis: An update. J Cell Mol Med 2020;24:4892-9.
37. Qi X, Wang J. Melatonin improves mitochondrial biogenesis through the AMPK/PGC1α pathway to attenuate ischemia/reperfusion-induced myocardial damage. Aging (Albany NY) 2020;12:7299-312.
38. Zhang Q, Dang YY, Luo X, et al. Kazinol B protects H9c2 cardiomyocytes from hypoxia/reoxygenation-induced cardiac injury by modulating the AKT/AMPK/Nrf2 signalling pathway. Pharm Biol 2023;61:362-71.
39. Tian L, Cao W, Yue R, et al. Pretreatment with Tilianin improves mitochondrial energy metabolism and oxidative stress in rats with myocardial ischemia/reperfusion injury via AMPK/SIRT1/PGC-1 alpha signaling pathway. J Pharmacol Sci 2019;139:352-60.
40. Ziemann M, Lim SC, Kang Y, et al. MicroRNA-101-3p Modulates Mitochondrial Metabolism via the Regulation of Complex II Assembly. J Mol Biol 2022;434:167361.
41. Xue Y, Huang W, Wan B, et al. Effects of electroacupuncture pretreatment on mitochondrial energy metabolism in rats with myocardial ischemia reperfusion. World Journal of Acupuncture - Moxibustion 2020;30:120-4.
42. Cogliati S, Lorenzi I, Rigoni G, et al. Regulation of Mitochondrial Electron Transport Chain Assembly. J Mol Biol 2018;430:4849-73.
43. Vercellino I, Sazanov LA. The assembly, regulation and function of the mitochondrial respiratory chain. Nat Rev Mol Cell Biol 2022;23:141-61.
44. Zhao RZ, Jiang S, Zhang L, et al. Mitochondrial electron transport chain, ROS generation and uncoupling (Review). Int J Mol Med 2019;44:3-15.
45. Papatheodorou I, Makrecka-Kuka M, Kuka J, et al. Pharmacological activation of PPARβ/δ preserves mitochondrial respiratory function in ischemia/reperfusion via stimulation of fatty acid oxidation-linked respiration and PGC-1α/NRF-1 signaling. Front Endocrinol

(Lausanne) 2022;13:941822.
46. Cadenas S. ROS and redox signaling in myocardial ischemia-reperfusion injury and cardioprotection. Free Radic Biol Med 2018;117:76-89.
47. Chen YR, Zweier JL. Cardiac mitochondria and reactive oxygen species generation. Circ Res 2014;114:524-37.
48. Farías JG, Molina VM, Carrasco RA, et al. Antioxidant Therapeutic Strategies for Cardiovascular Conditions Associated with Oxidative Stress. Nutrients 2017;9:966.
49. Zhang S, Lin Y, Kim YS, et al. c-Jun N-terminal kinase mediates hydrogen peroxide-induced cell death via sustained poly(ADP-ribose) polymerase-1 activation. Cell Death Differ 2007;14:1001-10.
50. Chen CL, Zhang L, Jin Z, et al. Mitochondrial redox regulation and myocardial ischemia-reperfusion injury. Am J Physiol Cell Physiol 2022;322:C12-23.
51. Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol Rev 2014;94:909-50.
52. Kondadi AK, Anand R, Reichert AS. Functional Interplay between Cristae Biogenesis, Mitochondrial Dynamics and Mitochondrial DNA Integrity. Int J Mol Sci 2019;20:4311.
53. García-Niño WR, Zazueta C, Buelna-Chontal M, et al. Mitochondrial Quality Control in Cardiac-Conditioning Strategies against Ischemia-Reperfusion Injury. Life (Basel) 2021;11:1123.
54. Tokuyama T, Yanagi S. Role of Mitochondrial Dynamics in Heart Diseases. Genes (Basel) 2023;14:1876.
55. Forte M, Schirone L, Ameri P, et al. The role of mitochondrial dynamics in cardiovascular diseases. Br J Pharmacol 2021;178:2060-76.
56. Ong SB, Kalkhoran SB, Cabrera-Fuentes HA, et al. Mitochondrial fusion and fission proteins as novel therapeutic targets for treating cardiovascular disease. Eur J Pharmacol 2015;763:104-14.
57. Dai W, Jiang L. Dysregulated Mitochondrial Dynamics and Metabolism in Obesity, Diabetes, and Cancer. Front Endocrinol (Lausanne) 2019;10:570.
58. El-Hattab AW, Suleiman J, Almannai M, et al. Mitochondrial dynamics: Biological roles, molecular machinery, and related diseases. Mol Genet Metab 2018;125:315-21.
59. Pagliuso A, Cossart P, Stavru F. The ever-growing complexity of the mitochondrial fission machinery. Cell Mol Life Sci 2018;75:355-74.
60. Wang J, Zhou H. Mitochondrial quality control mechanisms as molecular targets in cardiac ischemia-reperfusion injury. Acta Pharm Sin B 2020;10:1866-79.
61. Kulawiak B, Bednarczyk P, Szewczyk A. Multidimensional Regulation of Cardiac Mitochondrial Potassium Channels. Cells 2021;10:1554.
62. Wojtovich AP, Williams DM, Karcz MK, et al. A novel mitochondrial K(ATP) channel assay. Circ Res 2010;106:1190-6.
63. Jang YH, Kim JH, Lee YC. Mitochondrial ATP-Sensitive Potassium Channels Play a Role in Reducing Both Myocardial Infarction and Reperfusion Arrhythmia in Remote Ischemic Preconditioned Hearts. Anesth Pain Med 2017;7:e42505.
64. Lukowski R, Cruz Santos M, Kuret A, et al. cGMP and mitochondrial K(+) channels-Compartmentalized but closely connected in cardioprotection. Br J Pharmacol 2022;179:2344-60.
65. Halestrap AP, Richardson AP. The mitochondrial permeability transition: a current perspective on its identity and role in ischaemia/reperfusion injury. J Mol Cell Cardiol 2015;78:129-41.
66. Seidlmayer LK, Juettner VV, Kettlewell S, et al. Distinct mPTP activation mechanisms in ischaemia-reperfusion: contributions of Ca2+, ROS, pH, and inorganic polyphosphate. Cardiovasc Res 2015;106:237-48.
67. Penna C, Perrelli MG, Pagliaro P. Mitochondrial pathways, permeability transition pore, and redox signaling in cardioprotection: therapeutic implications. Antioxid Redox Signal 2013;18:556-99.
68. Morciano G, Bonora M, Campo G, et al. Mechanistic Role of mPTP in Ischemia-Reperfusion Injury. Adv Exp Med Biol 2017;982:169-89.
69. Di Lisa F, Canton M, Carpi A, et al. Mitochondrial injury and protection in ischemic pre- and postconditioning. Antioxid Redox Signal 2011;14:881-91.
70. Li YZ, Wu XD, Liu XH, et al. Mitophagy imbalance in cardiomyocyte ischaemia/reperfusion injury. Acta Physiol (Oxf) 2019;225:e13228.
71. Lu Y, Li Z, Zhang S, et al. Cellular mitophagy: Mechanism, roles in diseases and small molecule pharmacological regulation. Theranostics 2023;13:736-66.
72. Yoo SM, Jung YK. A Molecular Approach to Mitophagy and Mitochondrial Dynamics. Mol Cells 2018;41:18-26.
73. Zhang R, Krigman J, Luo H, et al. Mitophagy in cardiovascular homeostasis. Mech Ageing Dev 2020;188:111245.
74. Liu C, Li Z, Li B, et al. Relationship between ferroptosis and mitophagy in cardiac ischemia reperfusion injury: a mini-review. PeerJ 2023;11:e14952.
75. Zhang Y, Whaley-Connell AT, Sowers JR, et al. Autophagy

as an emerging target in cardiorenal metabolic disease: From pathophysiology to management. Pharmacol Ther 2018;191:1-22.
76. Deng J, Liu Q, Ye L, et al. The Janus face of mitophagy in myocardial ischemia/reperfusion injury and recovery. Biomed Pharmacother 2024;173:116337.
77. Ong SB, Samangouei P, Kalkhoran SB, et al. The mitochondrial permeability transition pore and its role in myocardial ischemia reperfusion injury. J Mol Cell Cardiol 2015;78:23-34.
78. Yang M, Linn BS, Zhang Y, et al. Mitophagy and mitochondrial integrity in cardiac ischemia-reperfusion injury. Biochim Biophys Acta Mol Basis Dis 2019;1865:2293-302.
79. Zhang P, Guan P, Ye X, et al. SOCS6 Promotes Mitochondrial Fission and Cardiomyocyte Apoptosis and Is Negatively Regulated by Quaking-Mediated miR-19b. Oxid Med Cell Longev 2022;2022:1121323.
80. Li YF, Wei TW, Fan Y, et al. Serine/Threonine-Protein Kinase 3 Facilitates Myocardial Repair After Cardiac Injury Possibly Through the Glycogen Synthase Kinase-3β/β-Catenin Pathway. J Am Heart Assoc 2021;10:e022802.
81. Bi Y, Wang X, Wang S, et al. Times evolution and modern understanding of the connotation of'weak pulse at yang but stringy pulse at yin'as the pathogenesis of chest paralysis. China Journal of Traditional Chinese Medicine and Pharmacy 2023;38:5266-70.
82. Song Z, Yang Z, Tian L, et al. Targeting mitochondrial circadian rhythms: The potential intervention strategies of Traditional Chinese medicine for myocardial ischaemia–reperfusion injury. Biomed Pharmacother 2023;166:115432.
83. Tong XY, Xu Y, Feng N, et al. Discussion on the teaching ideas of difficult points of 'chest paralysis' in 'Internal Medicine of Traditional Chinese Medicine'. Jiangsu J Tradit Chin Med 2017;49:70-2.
84. Li J. The experimental and clinical research on protective effect and mechanism of Sofren on myocardial ischemia-reperfusion injury. Nanjing University of Chinese Medicine; 2014.
85. Liu Y, Zhu Y. Efficacy of Rhodiola rosea in the adjuvant treatment of elderly patients with unstable angina pectoris and its effect on serum inflammatory factors. Mod J Integr Tradit Chin West Med 2019;28:3836-9.
86. Xu JY, Yan LW, Tang SK, et al. Traditional Chinese medicine used as anti-aging agent by targeting nuclear factor erythroid 2-related factor 2 signaling pathway. Sheng Li Xue Bao 2023;75:877-86.
87. Niu P, Fan Y, Lu F, et al. Effects of liquorice extract on cardiac fibroblasts fibrosis induced by TGF-β1. Chinese Journal of Clinical Pharmacology and Therapeutics 2022;27:129-35.
88. Xiang Y, Xu T, Guo L, et al. Application of Treating Qi and Blood together in Abnormal Myocardial Energy Metabo-lism under the Guidance of Theory of Qi and Blood Smooth Flow in"Yellow Emperor's Inner Canon". Journal of Guizhou University of Traditional Chinese Medicine 2023;45:23-8.
89. Gao RY, Gao JR, Zhao HY, et al. Mechanism of tonifying Qi by traditional Chinese medicine from mitochondrial dynamics. Zhongguo Zhong Yao Za Zhi 2023;48:3684-92.
90. Ma XD, Qu CH, Wang DC, et al. Briefly on the TCM connotation of atherosclerosis endothelial injury based on the theory of "Unsmooth Vessels". Chin J Ethnomedicine and Ethnopharmacy 2022;31:5-7.
91. Huang Q, Su H, Qi B, et al. A SIRT1 Activator, Ginsenoside Rc, Promotes Energy Metabolism in Cardiomyocytes and Neurons. J Am Chem Soc 2021;143:1416-27.
92. Jiang L, Yin X, Chen YH, et al. Proteomic analysis reveals ginsenoside Rb1 attenuates myocardial ischemia/reperfusion injury through inhibiting ROS production from mitochondrial complex I. Theranostics 2021;11:1703-20.
93. Wang M, Wang RY, Zhou JH, et al. Calenduloside E Ameliorates Myocardial Ischemia-Reperfusion Injury through Regulation of AMPK and Mitochondrial OPA1. Oxid Med Cell Longev 2020;2020:2415269.
94. Yu H, Hong X, Liu L, et al. Cordycepin Decreases Ischemia/Reperfusion Injury in Diabetic Hearts via Upregulating AMPK/Mfn2-dependent Mitochondrial Fusion. Front Pharmacol 2021;12:754005.
95. Sun C, Zhang X, Yu F, et al. Atractylenolide I alleviates ischemia/reperfusion injury by preserving mitochondrial function and inhibiting caspase-3 activity. J Int Med Res 2021;49:300060521993315.
96. Wang ZH, Cheng LX, Huang D, et al. Preventive effects of morinda officinalis oligose on myocardial energy metabolism disorder and cell structure injury in ovariectomized rats after myocardial ischemia-reperfusion injury. Journal of Zhengzhou University (Medical Sciences) 2022;57:472-6.
97. Zhao Y, Guo Y, Chen Y, et al. Curculigoside attenuates myocardial ischemia reperfusion injury by inhibiting the opening of the mitochondrial permeability transition pore. Int J Mol Med 2020;45:1514-24.

98. Zhuo Y, Yuan R, Chen X, et al. Tanshinone I exerts cardiovascular protective effects in vivo and in vitro through inhibiting necroptosis via Akt/Nrf2 signaling pathway. Chin Med 2021;16:48.
99. Ye J, Wang R, Wang M, et al. Hydroxysafflor Yellow A Ameliorates Myocardial Ischemia/Reperfusion Injury by Suppressing Calcium Overload and Apoptosis. Oxid Med Cell Longev 2021;2021:6643615.
100. Luo C, Zhang Y, Guo H, et al. Ferulic Acid Attenuates Hypoxia/Reoxygenation Injury by Suppressing Mitophagy Through the PINK1/Parkin Signaling Pathway in H9c2 Cells. Front Pharmacol 2020;11:103.
101. Chen C, Chen T, Xu Y. Mechanism of ligustrazine on mitochondrial autophagy reducing myocardial ischemia reperfusion injury through JAK2/STAT3 signaling pathway. Chinese Journal of Immunology 2021;37:819-23.
102. Bai S, Wang X, Wu H, et al. Cardioprotective effect of anisodamine against ischemia/reperfusion injury through the mitochondrial ATP-sensitive potassium channel. Eur J Pharmacol 2021;901:174095.
103. Yan L, Pan CS, Liu YY, et al. The Composite of 3, 4-Dihydroxyl-Phenyl Lactic Acid and Notoginsenoside R1 Attenuates Myocardial Ischemia and Reperfusion Injury Through Regulating Mitochondrial Respiratory Chain. Front Physiol 2021;12:538962.
104. Tian X, Huang Y, Zhang X, et al. Salidroside attenuates myocardial ischemia/reperfusion injury via AMPK-induced suppression of endoplasmic reticulum stress and mitochondrial fission. Toxicol Appl Pharmacol 2022;448:116093.
105. Shi X, Li Y, Wang Y, et al. Pharmacological postconditioning with sappanone A ameliorates myocardial ischemia reperfusion injury and mitochondrial dysfunction via AMPK-mediated mitochondrial quality control. Toxicol Appl Pharmacol 2021;427:115668.
106. Xue W, Wang X, Tang H, et al. Vitexin attenuates myocardial ischemia/reperfusion injury in rats by regulating mitochondrial dysfunction induced by mitochondrial dynamics imbalance. Biomed Pharmacother 2020;124:109849.
107. Wu X, Liu L, Zheng Q, et al. Protocatechuic aldehyde protects cardiomycoytes against ischemic injury via regulation of nuclear pyruvate kinase M2. Acta Pharm Sin B 2021;11:3553-66.
108. Rameshrad M, Omidkhoda SF, Razavi BM, et al. Evaluating the possible role of mitochondrial ATP-sensitive potassium channels in the cardioprotective effects of morin in the isolated rat heart. Life Sci 2021;264:118659.
109. Yang J, Zheng R, Du Y, et al. The mechanism of tilianin against ischemia-reperfusion injury of H9c2 cells. Acta Pharmaceutica Sinica 2021;56:1070-8.
110. Li Q, Yu Z, Xiao D, et al. Baicalein inhibits mitochondrial apoptosis induced by oxidative stress in cardiomyocytes by stabilizing MARCH5 expression. J Cell Mol Med 2020;24:2040-51.
111. Xu C, Liu Y, Yang J, et al. Effects of berbamine against myocardial ischemia/reperfusion injury: Activation of the 5' adenosine monophosphate-activated protein kinase/nuclear factor erythroid 2-related factor pathway and changes in the mitochondrial state. Biofactors 2022;48:651-64.
112. Tong Y, Li G, Shi X, et al. Protection against myocardial ischemia/reperfusion injury in mice by 3-caffeoylquinic acid isomers isolated from Saxifraga tangutica. RSC Adv 2024;14:6642-55.
113. García-Niño WR, Correa F, Zúñiga-Muñoz AM, et al. L-theanine abates oxidative stress and mitochondrial dysfunction in myocardial ischemia-reperfusion injury by positively regulating the antioxidant response. Toxicol Appl Pharmacol 2024;486:116940.
114. Deng X, Yang P, Gao T, et al. Allicin attenuates myocardial apoptosis, inflammation and mitochondrial injury during hypoxia-reoxygenation: an in vitro study. BMC Cardiovasc Disord 2021;21:200.
115. Duan L. The research on the effect and mechanism of lycopene on myocardial ischemia-reperfusion injury in ischemia postconditioning hypercholesterolemia rats. China Medical University; 2020.
116. Yang NN, Cui ZH, Zhang B, et al. Reduction of breviscapine on myocardial ischemia-reperfusion injury in diabetic rats by activating mitochondrial autophagy. Drugs & Clinic 2021;36:219-25.
117. Yi C, Song M, Sun L, et al. Asiatic Acid Alleviates Myocardial Ischemia-Reperfusion Injury by Inhibiting the ROS-Mediated Mitochondria-Dependent Apoptosis Pathway. Oxid Med Cell Longev 2022;2022:3267450.
118. Chen L, Chen XY, Wang QL, et al. Astragaloside IV Derivative (LS-102) Alleviated Myocardial Ischemia Reperfusion Injury by Inhibiting Drp1(Ser616) Phosphorylation-Mediated Mitochondrial Fission. Front Pharmacol 2020;11:1083.
119. Wei X, Wu Y, Pan H, et al. Proteomics Revealed That Mitochondrial Function Contributed to the Protective Effect of Herba Siegesbeckiae Against Cardiac Ischemia/Reperfusion Injury. Front Cardiovasc Med 2022;9:895797.
120. Liu Z, Han X, You Y, et al. Shuangshen ningxin formula

attenuates cardiac microvascular ischemia/reperfusion injury through improving mitochondrial function. J Ethnopharmacol 2024;323:117690.
121. Zhen Z, Chan L, Wang G, et al. Effect of Hawthorn Leaves Flavonoids on Mitochondrial Respiratory Function in Rats with Myocardial Ischemia-reperfusion. Chinese Journal of Integrative Medicine on Cardio/Cerebrovascular Disease 2021;19:2000-3.
122. Li H, Pang K, Li L, et al. Effect of flavones of Sorbus tianschanica against myocardial ischemia reperfusion injury. Chinese Traditional and Herbal Drugs 2020;51:5243-53.
123. Li C, Ma XL, Wen ZP, et al. Protective effects of Dracocephalum moldavica total flavonoids on oxidative stress and mitochondria in rats with myocardial ischemia-reperfusion injury. Chin Tradit Pat Med 2022;44:390-5.
124. Zhang DM, Wu WD, Xu XH, et al. Effect of crocin improves myocardial ischemia-reperfusion injury in rats by restoring mitochondrial function. Clinical Res Practice 2021;6:14-7.
125. Li C, Wang A, Xiao Y, et al. Fangchinoline inhibits P38 MAPK and ERK1/2 phosphorylation and mitigates myocardial cell apoptosis and mitochondrial oxidative damage in myocardial ischemia/reperfusion rats. Chinese Journal of Pharmacology and Toxicology 2020;34:336-42.
126. Jiang L, Zhou X, Zhao X, et al. Tetrandrine downregulates TRPV2 expression to ameliorate myocardial ischemia/reperfusion injury in rats via regulation of cardiomyocyte apoptosis, calcium homeostasis and mitochondrial function. Eur J Pharmacol 2024;964:176246.
127. Jiang W, Zhang Y, Zhang W, et al. Hirsutine ameliorates myocardial ischemia-reperfusion injury through improving mitochondrial function via CaMKII pathway. Clin Exp Hypertens 2023;45:2192444.
128. Xia JY. Mechanism of Yiqihuoxue drugs regulating mitophagy to improve hypoxia-reoxygenation injury of cardiomyocytes. Beijing University of Chinese Medicine; 2021.
129. Bai J, Wang X, Du S, et al. Study on the protective effects of danshen-honghua herb pair (DHHP) on myocardial ischaemia/reperfusion injury (MIRI) and potential mechanisms based on apoptosis and mitochondria. Pharm Biol 2021;59:335-46.
130. Liu Y, Wang Z, Shen L, et al. Protective Effect of Wenxin Prescription on Mitochondrial Energy Metabolism in Rats with Myocardial Ischemia-reperfusion Injury. Chinese Journal of Experimental Traditional Medical Formulae 2022;28:52-9.
131. Lin F, Tan YQ, He XH, et al. Huoxue Huatan Decoction Ameliorates Myocardial Ischemia/Reperfusion Injury in Hyperlipidemic Rats via PGC-1α-PPARα and PGC-1α-NRF1-mtTFA Pathways. Front Pharmacol 2020;11:546825.
132. Hu M, Li X, Jin J, et al. Effects of Danshen Decoction pretreatment on cardiac hemodynamics and mitochondrial energy metabolism in rats with myocardial ischemia reperfusion injury. Chinese Traditional Patent Medicine 2022;44:2119-25.
133. Zhao Y, Guo R, Li L, et al. Tongmai formula improves cardiac function via regulating mitochondrial quality control in the myocardium with ischemia/reperfusion injury. Biomed Pharmacother 2020;132:110897.
134. Yang Y, Li L, Su C, et al. Study on effect and mechanism of Xuefu Zhuyu Decoction against myocardial ischemia injury based on mitochondrial fusion. Lishizhen Med Mater Med Res 2022;33:1564-8.
135. Xu B, Nie B, Jokyab Tsering. Study on Effects of Bawei Chenxiang Powder on Levels of Reactive Oxygen and Calcium Ions in Myocardial Cells with Ischemia Reperfusion Injury. Liaoning Journal of Traditional Chinese Medicine 2021;48:157-60.
136. Zhang Z, Zhou M, Liu H, et al. Protective effects of Shen Yuan Dan on myocardial ischemia-reperfusion injury via the regulation of mitochondrial quality control. Cardiovasc Diagn Ther 2023;13:395-407.
137. Li LY, Chen LL, Liu P. Mechanism of Guizhi Gancao Decoction against myocardial ischemia-reperfusion injury based on network pharmacology and experimental verification. Zhongguo Zhong Yao Za Zhi 2024;49:798-808.
138. Sun H, Liu K, Cai GF, et al. To explore the myocardial protective effect and mechanism of Baijinfang on MIRI rats based on mitophagy. Lishizhen Med Mater Med Res 2020;31:539-42.
139. Li X, Zhang HM, Cui HF, et al. Effects of Gualou Xiebai Decoction on autophagy and PINK1/parkin pathway in rats with myocardial ischemia-reperfusion injury.v. J Basic Chin Med 2020;26:1626-30.
140. Kong CE, Cheng XX, Xu ZL. Protective effect of Xuefuzhuyu capsules pretreatment on myocardial ischemia/reperfusion injury in rats. Chin J Clin Pharmacol Ther 2021;37:2007-10.
141. Chai JM. Study on the Protective Effect of Ershrn Granules on Myocardial Ischemia Modei Based on Mitochondrial Function and Related Mechanisms. Changchun University of Chinese Medicine; 2021.
142. Zhang W, Chen R, Xu K, et al. Protective effect

of Xinmai'an tablets via mediation of the AMPK/SIRT1/PGC-1α signaling pathway on myocardial ischemia-reperfusion injury in rats. Phytomedicine 2023;120:155034.
143. Jin Q, Jiang Y, Fu L, et al. Wenxin Granule Ameliorates Hypoxia/Reoxygenation-Induced Oxidative Stress in Mitochondria via the PKC-δ/NOX2/ROS Pathway in H9c2 Cells. Oxid Med Cell Longev 2020;2020:3245483.
144. Zhang L, Wang Y, Li C, et al. Dan Hong Injection Protects Against Cardiomyocytes Apoptosis by Maintaining Mitochondrial Integrity Through Keap1/Nuclear Factor Erythroid 2-Related Factor 2/JNK Pathway. Front Pharmacol 2020;11:591197.
145. Zhao YW, Fu JH, Li L, et al. Effect of Shuangshen Ningxin Capsule in Alleviating Myocardial Ischemia/Reperfusion Injury in Rats by Regulating Mitochondrial ATP-sensitive Potassium Channel. Chin J Exp Tradit Med Formulae 2020;26:104-10.

Cite this article as: Tian Y, Hu X, Zhang T, Li B, Fu Q, Li J. Advances in Chinese herbal medicine in modulating mitochondria to treat myocardial ischemia-reperfusion injury: a narrative review. Cardiovasc Diagn Ther 2025;15(1):207-232. doi: 10.21037/cdt-24-346