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Mitochondrial function: A new direction for the targeted treatment of cardiovascular diseases with Chinese herbal medicine

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ABSTRACT

Mitochondria play a central role in cardiovascular diseases, primarily by providing cellular energy and facilitating various cardiac functions. Excessive fat accumulation, circadian rhythm disturbances, viral infections, and persistent inflammation can lead to myocarditis, fibrosis, and infarction, thereby exacerbating the progression of cardiovascular diseases. As essential organelles for energy production, mitochondria exhibit remarkable dynamic adaptability and can integrate diverse cellular signaling pathways, endowing myocardial cells with both bioenergetic and biosynthetic versatility. Consequently, targeting mitochondria for cardiovascular disease therapy has gained increasing attention and is applicable to various cardiovascular conditions. Numerous mitochondrial adaptive mechanisms, including dynamics, metabolic processes, and apoptosis regulation, have emerged as promising therapeutic targets. Nevertheless, contemporary investigations into mitochondrial biology have unveiled their intricate structural and functional characteristics, as well as their complex roles within cellular systems, which present obstacles to the clinical implementation of mitochondria-focused cardiovascular therapies. Recent studies have found that traditional Chinese medicine (TCM) possesses the potential to effectively address cardiovascular diseases while enhancing the structural integrity and functional capacity of mitochondria. This review aims to offer a comprehensive analysis of the modulatory effects of TCM on cardiac mitochondria and its therapeutic ramifications for cardiovascular conditions.

1. Introduction

Cardiovascular disease encompasses a complex group of disorders, primarily characterized by metabolic imbalances, viral infections, parasitic infections, and immune system abnormalities that lead to inflammation. These conditions can progress to myocardial fibrosis, myocardial hypertrophy, myocardial infarction, and ventricular remodeling. Etiologically, cardiovascular diseases can be classified into types such as hypertension, coronary artery disease, heart failure, arrhythmias, pulmonary hypertension, and cardiomyopathies.[1–5] These diseases share common features of progressive inflammation and fibrosis in cardiac tissue, leading to impaired heart function and potentially severe consequences.[6–9] (see Table 1) Epidemiological studies have revealed a strong association between major cardiovascular diseases—such as cardiomyopathies, arrhythmias, and coronary atherosclerosis—and metabolic disorders, including abnormal blood glucose and lipid levels, as well as non-alcoholic fatty liver disease. This connection poses a significant global health challenge. Extensive research suggests that the development of these diseases is closely linked to metabolic dysregulation, with energy metabolism playing a central role in this process. Traditional Chinese Medicine (TCM), with its holistic approach, has demonstrated remarkable potential in regulating overall health. This article aims to explore the novel directions and unique advantages of TCM in the targeted treatment of cardiovascular diseases, focusing on multiple dimensions and therapeutic targets.

Mitochondria are one of the most evolutionarily conserved intracellular organelles, comprising the outer mitochondrial membrane (OMM) and the highly folded inner mitochondrial membrane (IMM).[10] The two

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Table 1
Herbs (herb's preparation) and their compounds alleviate the process of cardiovascular disease through mitochondria.

Herb (herb's preparation)	Active ingredient	Mechanisms of influence	Result	Reference
Shenmai Injection	Ginsenoside Rb1	Opa1↑ Drp1↓	Reduces mitochondrial mitosis and promotes the recovery of mitochondrial membranes; Inhibits the overload of mitochondria with calcium ions	49 150 151 138
Ginseng	Ginsenoside Rb1	AMPK↑ Mff↑ Drp1↓ TGF-β1/Smad/Akt↑	Alleviate mitochondrial dysfunction in response to energy stress and inhibition of mitophagy; Inhibits mitochondrial calcium overload	140 139,141 152
Houttuynia cordata	Houttuynic acid	MMP2↑ p38↑	Selective degradation of damaged mitochondria	8
Eleutherococcus senticosus	Eleutheroside	NF-κB↓	Degradation of damaged mitochondria reduces the production of reactive oxygen species and inhibits oxidative stress	35
Salvia	Salvianolic acid B Tanshinone IIA	LC3II/LC3I↑ SIRT1/PGC↑	Promotes the restoration of mitochondrial structure and function; Inhibits mitochondrial permeability conversion porosity	142 155 156
Horny Goat Weed	Icariin	TGF-β1/Smad2↑ Bcl-2↑ Keap1-Nrf2/HO-1↑	Inhibits mitochondrial apoptosis; Regulates mitophagy and reduces inflammation	143 140
Yangxinshi Tablet	Salvianolic acid A Ferulic acid Icariin Ginsenoside Rb1	PI3K/Akt/mTOR/ Rps6/HIF-1α↑ AMPK/PGC1α/ GLUT4↑	Improves mitochondrial function and energy metabolism	144
Aconite	Aconitine Hypoaconitine Isoaconitine	cAMP↑	Improves mitochondrial energy metabolism	145,146
Xintong Capsule	Panax notoginseng saponins	miR-3158-3p↓ Nur77↓	Enhance the activity of mitochondrial respiratory chain complex I-IV, repair the electron transport chain, restore electrical signaling, and restore mitochondrial biosynthesis	148,149 147
Radix astragali	Astragaloside IV	lncRNA4012/9456↓	Regulates Ca^{2+} pump activity in sarcoplasmic reticulum	89,153, 154
Musk	Muskone	NLRP3/GSDMD↓	Inhibits oxidative stress and enhances mitochondrial energy production	65
Histamine-gingerol	Higenamine	LKB1/AMPKα/ SIRT1↑	Enhances mitochondrial energy production and promotes energy metabolism	157,158
Turmeric	Tetrahydroberberrubine	SIRT3↑	Inhibits oxidative stress and enhances mitochondrial energy metabolism	159,88
Honeysuckle	Chlorogenic acid	SLC7A11/GPX4↑	Inhibits the production of mitochondrial lipid peroxides and reactive oxygen species	160
Qishen Yiqi granules	Salvianolic acid B Notoginsenoside R1 Ginsenoside Rg1 Astragaloside IV	UCP2↓	Promotes the restoration of mitochondrial membrane potential, increases energy production; Regulates fatty acid and glucose metabolism	165
Valerian	Valerenic acid	PPARα↑	Inhibits glycolysis and restores mitochondrial function	166,167

membranes are separated by the intermembrane space (IMS), and there are notable differences in their lipid composition and permeability. It is worth noting that the IMM invaginates into the mitochondrial matrix to form cristae, which are critical structures for mitochondrial function.[11] To ensure the continued functionality of these structures, mitochondria engage in a range of intricate processes, including fission and fusion, to adapt mitochondrial performance in response to external cues.[12] It has been demonstrated that the primary function of mitochondria is to supply energy. In the process of energy production, mitochondria integrate multiple metabolic pathways, including the tricarboxylic acid (TCA) cycle, fatty acid oxidation (FAO), amino acid oxidation, and others. This integration allows mitochondria to provide not only the majority of cellular ATP but also intermediate metabolites that support various physiological functions of the organism.[13] In cardiomyocytes, mitochondria are the most abundant organelle, providing the majority of the energy required for cardiac activity and functional changes.[6,14,15] A reduction in ATP production resulting from cardiovascular disease has a considerable impact on the myocardium, leading to a deficiency in energy supply and affecting normal cardiac function.[16,17] A lack of energy can result in the myocardium losing its metabolic flexibility, preventing it from effectively switching between different metabolic substrates and failing to meet the heart's energy demands.[18]

Mitochondrial quality control is typically maintained by three distinct mechanisms: mitochondrial biogenesis, mitochondrial dynamics (fusion and fission), and mitophagy. Mitochondrial fusion and fission play a role in fibroblasts during cardiac fibrosis.[19] In mitochondrial dynamics, dynamin-related protein 1 (Drp1), mitochondrial fusion protein 2 (Mfn2), and optic atrophy 1 (Opa1) regulate the dynamic cycle of fission and fusion, forming a plastic network to maintain mitochondrial function.[20] As a key protein involved in mitochondrial fission, Drp1 is present in the cytoplasm when inactive. Once activated, it translocates to the outer membrane and forms a ring-like polymer by binding to molecules, which contracts and divides the mitochondria, resulting in mitochondrial fission.[21] Opa1, also known as optic atrophy1, is a GTPase located in the IMM. It contains a GTPase domain, an intermediate transmembrane region, and a GTPase effector domain at the C-terminal of the peptide chain, which regulates IMM fusion.[22] Mitophagy is a specific form of cellular autophagy.[23] Mitochondria can respond to external stress by selectively removing excess or dysfunctional mitochondria, thereby ensuring mitochondrial quality and maintaining mitochondrial function. To prevent mitochondrial damage in cells, damaged or injured mitochondria are selectively degraded, maintaining cellular homeostasis.[24] Mitophagy involves four key steps: First, the damaged mitochondria undergo depolarization and lose their membrane potential. Second, autophagosomes envelop the mitochondria, forming mitophagosomes. The third step involves the fusion of mitophagosomes with lysosomes. Finally, the lysosomes degrade the mitochondrial contents.[24]

It is therefore essential to target the relevant structures and functions of mitochondria in order to ensure the effective treatment of cardiovascular disease. The TCM approach has evolved in response to the distinctive natural and social environments of the Chinese population. TCM is a profound and comprehensive system that employs four diagnostic methods and integrates the pharmacological activities of herbal medicine. The combination of monarch, minister, assistant, and envoy herbs works synergistically to maximize their effectiveness.[25–28] In TCM, chronic heart failure is the result of a complex interplay between external and internal factors.[29–32] External factors include viral, bacterial, and

parasitic infections, while internal factors involve metabolism, emotions, and congenital issues.[33–37] Herbal medicine is an important tool in addressing the underlying causes of these diseases and is a key component in the management of cardiovascular conditions.[38–40] This article examines the potential applications of herbal medicine in the treatment of cardiovascular diseases, with a particular focus on the mechanisms by which mitochondria regulate this condition.

2. Mitochondrial function

2.1. Mitochondrial fission

Mitochondrial fission is dependent on the activation of Drp1 in the cytosol, which results in the translocation of Drp1 to the mitochondria. Once there, it binds to receptors on the OMM. The process of mitochondrial fission results in the formation of sub-mitochondrial structures with varying membrane potentials. This function facilitates the selective degradation of damaged mitochondria through autophagy, thereby maintaining cellular homeostasis.[41] During the process of mitosis, the distribution of damaged mitochondria to daughter cells is ensured by the fission process.[42] In response to stress conditions, Drp1 in the cytosol is transported to the fission sites on the OMM by four mitochondrial dynamics proteins (Mff, Fis1, Mid49 and Mid51), forming a ring-like structure that stimulates mitochondrial membrane constriction and promotes mitochondrial fission.[43] Drp1 is primarily responsible for regulating mitochondrial fission in mammals and interacts with a number of other organelles.[44] Dynamin 2 plays a role in mitochondrial fission, but its absence does not prevent this process from occurring.[45] It is therefore evident that Drp1 plays a pivotal role in membrane constriction and separation.[46] Once Drp1 has been translocated to the mitochondria, it accumulates and wraps around the mitochondria, leading to mitochondrial fission.[47] The *Drp1* gene is subject to regulation at the level of transcription and protein degradation. Small RNA molecules, such as microRNAs, have the potential to influence the expression of the *Drp1* gene.[48]

2.2. Mitochondrial fusion

Mitochondrial fusion represents a potential repair process for mildly damaged mitochondria. This process is divided into two relatively independent steps: outer membrane fusion and inner membrane fusion. The former involves mitochondrial fusion proteins 1 and 2 (Mfn1/Mfn2), while the latter involves optic atrophy protein 1 (Opa1). In the initial phase of mitochondrial fusion, Mfn1/Mfn2 on the outer membranes of two adjacent mitochondria connect with each other, subsequently stimulating OMM fusion in a GTPase-dependent manner.[49] The process of IMM fusion is initiated immediately by Opa1 following the completion of OMM fusion.[50] Opa1 can be processed into two forms, long (L-Opa1) and short (S-Opa1), which can work together to accomplish IMM fusion. The function of Opa1 is contingent upon Mfn1[51] The absence of Opa1 has a dual impact on mitochondrial function. Firstly, it reduces the ability of mitochondria to fuse. Secondly, it leads to mitochondrial fragmentation and an abnormal cristae structure.

2.3. Mitochondrial autophagy

Mitochondrial autophagy represents a novel selective phagocytic

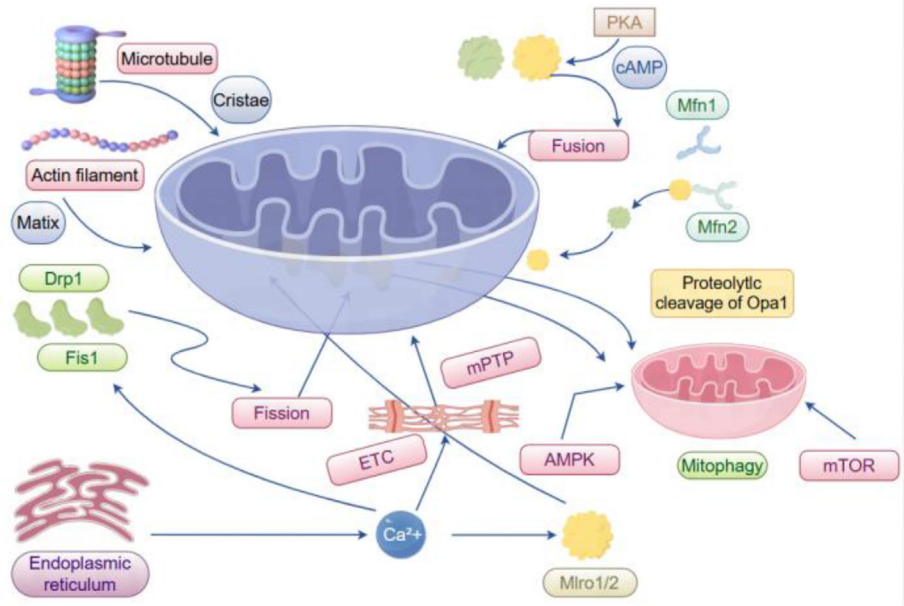

Fig. 1. This image illustrates the structure and function of mitochondria within cells, as well as their interactions with processes such as the cytoskeleton and cell signaling. The image includes the internal structure of mitochondria (such as cristae), the cytoskeleton (microtubules and microfilaments), the molecular mechanisms of mitochondrial fission and fusion (such as Drp1, Fis1, Mfn1, and Mfn2), the mitochondrial permeability transition pore (mPTP), calcium ion signaling, mitophagy, and interactions with the endoplasmic reticulum. Mitochondria have cristae, which are folded structures of the mitochondrial membrane that increase surface area, aiding energy metabolism.[63] Mitochondria interact with microtubules and microfilaments, affecting their distribution and movement within the cell. Mitochondrial fission is regulated by molecules such as Drp1 and Fis1, while mitochondrial fusion is controlled by molecules like PKA, cAMP, Mfn1, and Mfn2.[41] Opening of the mPTP leads to loss of mitochondrial membrane potential, promoting the release of cytochrome C and activating apoptotic signaling. Mitochondria help regulate intracellular calcium (Ca^{2+}) signaling by absorbing Ca^{2+} from the endoplasmic reticulum, influencing cellular function and apoptosis. Mitophagy, the process by which cells eliminate damaged mitochondria, is regulated by molecules such as mTOR and AMPK. There is a close interaction between mitochondria and the endoplasmic reticulum, affecting calcium ion signaling and cell function.[52] Mitochondria also participate in cell signaling, influencing apoptosis and cell function through the release of apoptotic factors and regulation of calcium ion signaling. Mitochondria have various functions within cells, including energy metabolism, cytoskeletal regulation, fission and fusion, permeability transition pore regulation, calcium signaling, autophagy, and interactions with the endoplasmic reticulum.[64] These functions are interrelated and work together to maintain normal cellular physiological states.

process within the autophagy family of mechanisms. It serves as the primary means for lysosomal degradation of damaged and dysfunctional mitochondria. Mitochondrial autophagy comprises four stages: the formation of phagophores, the recognition of damaged mitochondria by the phagophores, the fusion of both to form an autophagosome, and the fusion of the autophagosome with the lysosome to create an autolysosome. In summary, it is the process of forming and clearing autophagic vesicles. Mitochondrial autophagy is a vital component of the mitochondrial quality control system, ensuring the maintenance of intracellular homeostasis. From Fig. 1 we mention that mitophagy, the process by which cells eliminate damaged mitochondria, is regulated by molecules such as mTOR and AMPK. There is a close interaction between mitochondria and the endoplasmic reticulum, affecting calcium ion signaling and cell function.[52] Mitochondrial autophagy can be classified into two main categories: ubiquitin-dependent and receptor-dependent. The distinction between these two types hinges on the manner in which the phagophores recognise damaged mitochondria.[52]

There are several pathways for mitochondrial autophagy; however, the PTEN-induced kinase 1 (PINK1)/Parkin pathway is the most well-known form of mitochondrial autophagy. PINK1 accumulates on the OMM, and then the mitochondrial membrane potential is reduced, leading to phosphorylation and recruitment of cytosolic Parkin. The activated Parkin binds LC3II through the recruitment of autophagy receptor proteins (such as p62/SQSTM1), thus initiating mitochondrial autophagy.[53] The PINK1/Parkin pathway is the primary mechanism for ubiquitin-dependent mitochondrial autophagy. This pathway involves the actions of PTEN-induced putative kinase 1 (PINK1), a serine/threonine kinase, and its downstream target Parkin, an E3 ubiquitin ligase. In normal circumstances, PINK1 enters the IMM with the assistance of transport proteins from the translocase of the outer mitochondrial membrane (TOM) complex and is then linked to the inner membrane via transport proteins from the translocase of the inner mitochondrial membrane (TIM) complex. PINK1 is cleaved by the rhomboid protease PARL and released into the cytosol, where it is degraded by a series of proteases. This process ensures that PINK1 is maintained at low levels in normal mitochondria.[54] Mitochondrial dysfunction impacts the aforementioned degradation process of PINK1, resulting in its accumulation in the OMM. In addition to OMM proteins, several autophagy receptors are also present at other mitochondrial locations.[55] ULK1 is a serine/threonine kinase and a homolog of the autophagy-related protein.[56] Notably, the activity of ULK1 is regulated by phosphorylation through AMP-activated protein kinase (AMPK) and the mammalian target of rapamycin (mTOR). AMPK activates *ULK1* through phosphorylation, thereby initiating autophagy.[57] ULK1 controls the initiation of general autophagy or the specific targeting of mitochondrial degradation,[58] therefore, impairing ULK1 function weakens mitochondrial autophagy.[59] The non-ubiquitin-dependent pathway refers to the presence of several receptors involved in mitochondrial autophagy in the mitochondria. In mammals, these receptors include NIP3-like protein X (NIX), Bcl2-interacting protein 3 (BNIP3), and FUN14 domain-containing 1 (FUNDC1), among others. These receptors serve as autophagy mediators by directly binding LC3 without being ubiquitinated as a mechanism for mitochondrial autophagy.[60] NIX is located on the OMM and acts as a mitochondrial autophagy receptor under developmental or pathological conditions. There is a close relationship between mitochondrial autophagy and autophagy: they can occur simultaneously under the same stimuli and depend on the same autophagy receptor, NIX.[61] Specifically, NIX regulates the binding of Sp1 to the *NIX* promoter and is modulated by Gαq signaling and protein kinase Cα. NIX plays a role in heart disease, and its role in cardiomyocyte apoptosis has been confirmed *in vivo*.[62]

2.4. Mitochondrial oxidative phosphorylation

The energy produced from adenosine triphosphate (ATP) is the source of vitality for cardiomyocytes, primarily generated through the process of oxidative phosphorylation in the mitochondria. Furthermore, in acute situations, cardiomyocytes also contribute to ATP production through glycolysis, enabling the body to meet changes in energy demand.[65] From Fig. 2 we mention that the energy produced from ATP is the source of vitality for cardiomyocytes, primarily generated through the process of oxidative phosphorylation in the mitochondria. In hypoxic conditions, the efficiency of mitochondrial oxidative phosphorylation is reduced, which in turn results in a decrease in the synthesis of ATP.[66] Oxidative phosphorylation is driven by the electron transport chain, which generates ATP and produces heat. The mitochondrial genome can be traced back to ancient bacteria, which retained their own genome. This genome contains 13 polypeptide-coding genes, 22 tRNA genes, and 2 rRNA genes. These genes are essential for the function and biosynthesis of the mitochondria themselves.[67,68] ATP produced by mitochondria

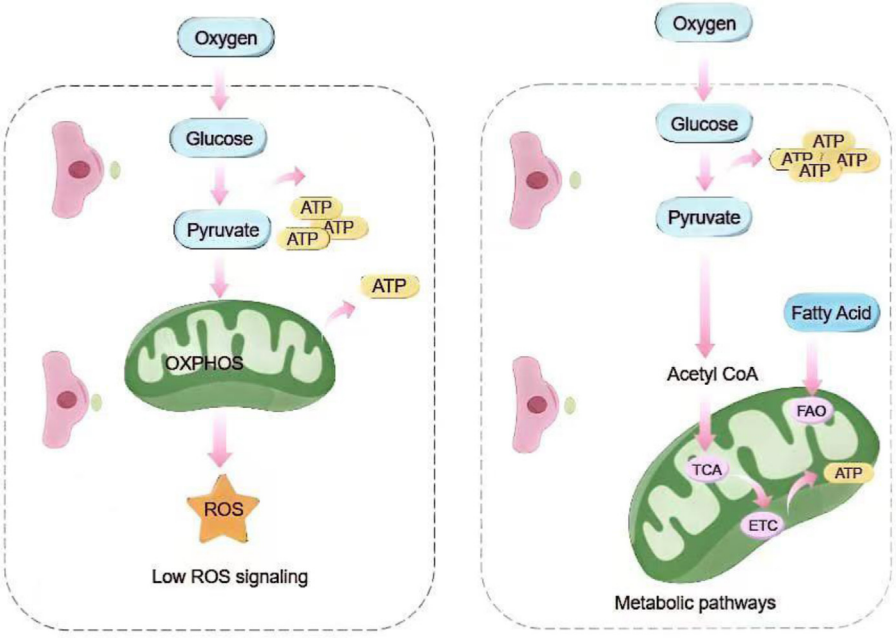

Fig. 2. The image illustrates two different metabolic pathways. The diagram on the left shows the process of oxidative phosphorylation, where oxygen and glucose participate in reactions that ultimately produce ATP and low levels of ROS. The diagram on the right displays metabolic pathways including glucose metabolism, FAO, the TCA cycle, and the electron transport chain, all of which also generate ATP. The energy produced from ATP is the source of vitality for cardiomyocytes, primarily generated through the process of oxidative phosphorylation in the mitochondria. In hypoxic conditions, the efficiency of mitochondrial oxidative phosphorylation is reduced, which in turn results in a decrease in the synthesis of ATP.[66] Furthermore, hypoxia also results in the excessive production of ROS within the mitochondria. Fatty acids represent the most energy-rich substrates, the cytosolic activation of fatty acids to acylcarnitine derivatives, transport into the mitochondrial matrix via CPT, and the formation of acyl-CoA, and their metabolism has been preserved through evolution, making them crucial for the cellular function of organs that require large amounts of ATP on a constant basis.[77]

serves two vital functions. Firstly, it acts as a form of energy storage for the cell. Secondly, it plays a pivotal role in metabolic processes such as the citric acid cycle and fatty acid β-oxidation.[69] Ischemia and hypoxia can have a significant impact on mitochondrial function, leading to reduced energy production and impaired cellular metabolism. In hypoxic conditions, the efficiency of mitochondrial oxidative phosphorylation is reduced, which in turn results in a decrease in the synthesis of energy ATP. Furthermore, hypoxia also results in the excessive production of reactive oxygen species (ROS) within the mitochondria. This can lead to additional damage to mitochondrial DNA and proteins, which in turn affects their normal metabolic function.[70–75]

2.5. Mitochondrial fatty acid oxidation

It is a well-established fact that mitochondria interact with the cell nucleus on a continuous basis, exerting a considerable influence on cellular phenotype and function. Mitochondria have the capacity to utilize a range of substrates, including amino acids, carbohydrates, and fatty acids. Fatty acids represent the most energy-rich substrates, and their metabolism has been preserved through evolution, making them crucial for the cellular function of organs that require large amounts of ATP on a constant basis.[76] The utilization of fatty acids is a highly intricate process. The process includes the cellular uptake of fatty acids, the cytosolic activation of fatty acids to acylcarnitine derivatives, transport into the mitochondrial matrix via carnitine palmitoyl transferase (CPT), and the formation of acyl-CoA.[77] From Fig. 2 we mention that Fatty acids represent the most energy-rich substrates, the cytosolic activation of fatty acids to acylcarnitine derivatives, transport into the mitochondrial matrix via CPT, and the formation of acyl-CoA, and their metabolism has been preserved through evolution, making them crucial for the cellular function of organs that require large amounts of ATP on a constant basis.[77]

The process involves four consecutive reactions with long-chain acyl-CoA dehydrogenase, enoyl-CoA hydratase, 3-hydroxyacyl-CoA dehydrogenase, and 3-ketoacyl-CoA thiolase. This results in the shortening of acyl-CoA through respiratory and synthetic pathways.[78] The activity of fatty acid oxidation is dependent on the acetylation of the relevant enzymes.[79]

2.6. Mitochondrial calcium ions

Mitochondrial Ca^{2+} signaling is closely related to cell growth and metabolism. It activates multiple components of the TCA cycle (IDH, α-KGDH, and PDH), thereby providing nutrients for the electron transport chain and ATP production. This pro-survival mechanism is essential for maintaining cellular processes.[80] This signaling pathway represents a fundamental mechanism that can initiate apoptosis by opening the mitochondrial permeability transition pore (mPTP) and releasing cytochrome C. From Fig. 1 we mention that Opening of the mPTP leads to loss of mitochondrial membrane potential, promoting the release of cytochrome C and activating apoptotic signaling. Mitochondria help regulate intracellular calcium (Ca^{2+}) signaling by absorbing Ca^{2+} from the endoplasmic reticulum, influencing cellular function and apoptosis. It serves as a key program in determining cell fate, and therefore represents a key area of focus for further research.[64] Furthermore, calcium plays a role in regulating the mechanisms that drive mitochondrial energy production and metabolic activity. To illustrate, calcium oversees the activity of metabolic enzymes within the TCA cycle, including pyruvate dehydrogenase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase.[81] The TCA cycle produces reducing equivalents (such as NADH and FDH2) that are used by proton pumps to establish membrane potential and alkalise the mitochondrial matrix relative to the cytosol. This in turn shifts ATP synthase from its more favourable ATP hydrolysis setting towards an operational mechanism favouring ATP production through oxidative phosphorylation.[82] It is therefore evident that in tissues with high energy demands, where cells are continuously exposed to transient calcium signals, calcium homeostasis is intrinsically linked with ATP production via the TCA cycle and oxidative phosphorylation. This, in turn, regulates cellular bioenergetics.

2.7. Mitochondrial dynamics

Mitochondrial motility is the term used to describe the dynamic repositioning and morphological changes of mitochondria in response to a variety of developmental, bioenergetic, and environmental stress sources. This process is aimed at maintaining cellular homeostasis. Mitochondrial transfer, which encompasses both intercellular and intracellular movement, occurs through the formation of tunneling nanotubes by cytoplasmic and cell membrane-derived microvesicles. It is worth noting that intracellular mitochondrial movement is closely associated with actin dynamics.[63] Actin is a dynamic protein that plays a crucial role in coordinating the movement of organelles and intracellular substances. From a morphological standpoint, actin exists in two forms: symmetric and asymmetric. Each form serves a distinct function. Symmetric actin is located in the mitochondrial matrix and on the OMM. It establishes direct contact with mitochondria, anchoring them in specific locations and significantly promoting energy metabolism and mitochondrial fission.[83] It is essential that mitochondria are positioned in axons, dendrites, and synaptic terminals, as these sites rely heavily on ATP and calcium buffering for signal transmission.[84] It is therefore essential to implement a robust system to ensure the continued health of mitochondria in distal regions. It is important to note that mitochondria contain outer membrane Rho GTPase proteins, namely Miro1 and Miro2, as well as adaptor proteins TRAK1 and TRAK2 (also known as Milton1/2). These are essential for binding to kinesin and dynein/dynactin motor proteins, which are responsible for mitochondrial transport within the cell.[85] The transport and delivery of mitochondria are regulated by calcium binding in Miro1, which is a key regulatory mechanism in this process. The release of mitochondria into postsynaptic neurons is induced by high calcium levels, which serve to supply energy and buffer calcium.[86] Furthermore, TRAK1 may possess the capacity to directly interact with microtubules, thereby facilitating the navigation of motor protein complexes for the long-distance relocation of mitochondria.[87]

3. Mitochondrial function in cardiovascular disease

3.1. Mitochondrial fusion

In patients with advanced heart failure, there is a notable decline in mitochondrial activity. This is accompanied by a reduction in fusion capacity and an increase in fission function. Concurrently, antioxidant capability is diminished, while reactive oxygen species production rises. These changes result in the further activation of apoptotic factors, which in turn induce cardiomyocyte death and exacerbate cardiac dysfunction.[97] During cardiac ischemia/reperfusion (I/R), mitochondria, as the primary source of cellular energy, undergo significant structural and functional changes to meet the demands of cell survival. While this adaptation is intended to protect cells, it often leads to a series of issues, such as abnormal mitochondrial fusion that further reduces ATP synthesis, decreases utilization, and disrupts metabolic functions.[93,94] From Fig. 3 we mention that Severe mitochondrial damage triggers fusion processes mediated by the proteins Mfn1, Mfn2 and Opa1, whereas mild mitochondrial damage triggers fission processes regulated by Drp1 and Fis1. It has been established that mutations in mitochondrial fusion-related proteins are associated with myocardial dysfunction. The relationship is more pronounced for Opa1 than for Mfn1 or Mfn2. The conditional double knockout of *Mfn1/Mfn2* in adult hearts has been observed to induce mitochondrial fragmentation, cardiomyocyte and mitochondrial respiratory dysfunction, and a rapid progression to lethal dilated cardiomyopathy (DCM).[98] The evidence indicates that *Mfn2* knockout can mitigate mitochondrial Ca^{2+} overload, impede lethal Drp1-induced mitochondrial fission and PINK1/Parkin-induced

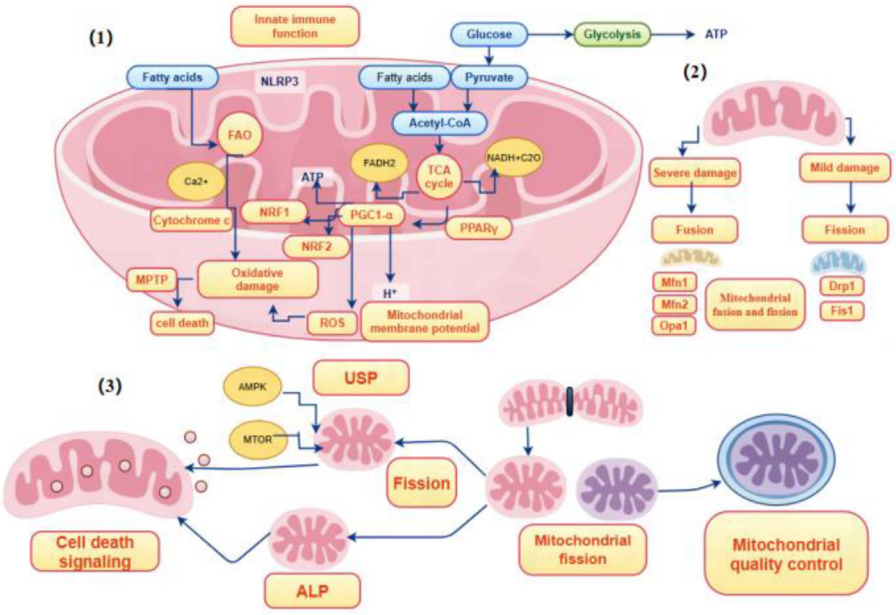

Fig. 3. (1) This figure illustrates the intracellular metabolic and signaling regulatory network, highlighting the interplay between NLRP3, PGC1-α, NRF2, and the TCA cycle. It describes several metabolism-related pathways involved in energy metabolism and inflammatory responses, including FAO, glycolysis, and the TCA cycle.[88–91] Key molecules and signaling pathways are labeled, including PGC1-α, NRF2, and NLRP3 inflammatory vesicles. In addition, the image illustrates how these molecules and pathways ultimately affect cell survival and death by regulating cell fate, oxidative stress, and inflammatory responses. Key molecular components and signaling pathways are annotated, such as the NLRP3 inflammasome, PGC1-α, NRF2 and mitochondrial membrane potential. In addition, the diagram illustrates how these molecules and pathways regulate cell fate, oxidative stress and inflammatory responses, ultimately influencing cell survival and death.[92] (2) This schematic illustrates the regulatory mechanisms of mitochondrial homeostasis, primarily divided into fusion and fission pathways. Severe mitochondrial damage triggers fusion processes mediated by the proteins Mfn1, Mfn2 and Opa1, whereas mild mitochondrial damage triggers fission processes regulated by Drp1 and Fis1.[93,94] These proteins critically maintain mitochondrial health and functionality by dynamically balancing structural integrity and cellular energy requirements. (3) The diagram shows a simplified flowchart of intracellular metabolic regulation and mitochondrial quality control. Key molecular components include AMPK, mTOR, USP, and ALP, as well as mitochondrial dynamic processes. AMPK and mTOR regulate mitochondrial dynamics through modulation of USP. AMPK is activated under low energy conditions, inhibiting the mTOR signaling pathway and consequently affecting downstream USP activity. The USP is involved in the regulation of mitochondrial fission, thereby affecting mitochondrial quality control.[95,96] Mitochondria maintain normal function by maintaining a balance between fission and fusion. The figure shows that after mitochondrial fission, a subset of mitochondria undergoes quality control processes, while others may participate in cell death signaling cascades.

mitophagy, and reduce partial damage caused by hypoxic conditions in cardiac microvascular endothelial cells (CMEC).[99]

3.2. Mitochondrial fission

In advanced heart failure, increased mitochondrial fragmentation due to reduced myocardial viability leads to damage to their morphology and function, affecting cellular energy metabolism and overall cardiac function.[100] Abnormal mitochondrial fission induced by Drp1 disruption can lead to mitochondrial elongation and inhibit mitophagy, resulting in mitochondrial dysfunction that promotes cardiomyocyte dysfunction.[101] Similarly, downregulation of mitophagy can induce mitochondrial dysfunction and heart failure (HF), whereas its restoration can attenuate the progression of HF in pressure overload mouse models, in which endogenous Drp1 is critical for mediating mitophagy and maintaining mitochondrial and cardiac function.[102] The important role of endogenous Drp1 is further demonstrated in cardiomyocytes from adult mice with ablated Drp1, which leads to significant changes in mitochondrial fission and promotes mitochondrial depletion, resulting in lethal cardiomyopathy.[103] A recent study helps to unravel the effects of pathological fission and mitochondrial depletion in sepsis-induced cardiomyopathy, focusing on the role of the Drp1's mitochondrial anchoring protein Fission 1 (Drp1/Fis1) interaction. P110, a peptide inhibitor specific for the Drp1/Fis1 interaction, was found to suppress lipopolysaccharide (LPS)-induced oxidative stress and mitochondrial fission in H9c2 cells and Balb/c mice, thereby improving cardiac function and reducing mortality.[104]

3.3. Mitochondrial dynamics

Mitochondrial dynamics in cardiomyocytes are fundamental mechanisms by which cells adapt to metabolic demands. Mitochondria undergo a coordinated cycle of fission and fusion to maintain energy homeostasis and respond to changes in nutrient availability.[48] Alterations in mitochondrial dynamics are important factors in myocardial injury and are key reasons for the decreased ATP production and increased mitochondrial ROS in heart failure, which subsequently alters the transcriptional regulation of mitochondrial proteins and increases post-translational modifications of proteins.[105] Research suggests that changes in mitochondrial function in heart failure are influenced by mitochondrial biogenesis. Alterations in mitochondrial biogenesis may lead to further impairment of mitochondrial number and function, exacerbating energy metabolism disorders and oxidative stress in the heart.[106] Under nutrient-rich conditions, mitochondrial fragmentation can prevent energy waste, reduce bioenergetic efficiency, and increase mitochondrial uncoupling, leading to increased nutrient storage.[107] Conversely, under

conditions of nutrient starvation, increased fusion leads to elongated mitochondria.[108]

3.4. Mitochondrial oxidative phosphorylation

Mitochondrial dysfunction is closely associated with the development of cardiovascular disease. Mitochondrial oxidative metabolism is the primary source of energy for the heart, responsible for producing the majority of ATP. To adapt to dynamic changes in the homeostasis of the cardiomyocyte environment, a complex network of enzymes and signaling pathways regulates the metabolic flux of substrates. This regulation effectively mediates mitochondrial oxidative phosphorylation, ensuring that ATP is produced to meet the energy demands of cardiomyocytes.[66] The inability of mitochondria to efficiently produce and transfer energy has long been considered the primary mechanism linking mitochondrial dysfunction to cardiovascular disease.[18] Research has shown that ATP levels in patients with end-stage heart failure can be as much as 30% lower than in healthy hearts. This significant decrease not only affects the contractile function of the myocardium, but also disrupts cellular energy metabolism and overall cardiac function, further exacerbating the pathological changes in cardiovascular disease. As mentioned above, the high production of ATP relies on the structural and functional homeostasis of the mitochondria and the normal process of oxidative metabolism. However, the phenomenon of energy deficiency is often associated with impaired mitochondrial structure and function, leading to reduced oxidative capacity.[109–111] Indeed, alterations in myocardial redox regulation are an important feature of heart failure, with increased oxidative stress at its core.[112] The accumulation of ROS depletes antioxidants, leading to lipid peroxidation, which further damages mitochondrial DNA and reduces ATP production.[113] Studies have shown that *N*-acetyl-L-cysteine (NAC) can reduce oxidative damage by inhibiting the production of ROS.[114,115]

3.5. Mitochondrial autophagy

Mitochondrial autophagy plays a crucial bridging role in maintaining normal myocardial function by removing damaged mitochondria to balance mitochondrial homeostasis. In the mid-stages of heart failure, the processes of mitochondrial fission and fusion are altered, affecting the regulation of mitochondrial autophagy. Activation of mitochondrial autophagy not only leads to the removal of damaged mitochondria, but can also mediate apoptotic signals, leading to cardiomyocyte apoptosis and further exacerbating cardiac dysfunction.[68,116] In advanced stages of cardiovascular disease, the number of damaged mitochondria increases significantly, leading to the activation of autophagy to deal with this damage. However, excessive autophagy can lead to a significant reduction in the number of mitochondria, affecting ATP production and energy homeostasis. This imbalance further triggers autophagy and apoptotic processes, leading to cell death and exacerbating mitochondrial damage. Impaired mitochondrial autophagy not only fails to effectively remove damaged mitochondria, but can also activate mitochondrial-mediated apoptotic signaling.[117] Mitochondrial autophagy maintains a dynamic balance by degrading dysfunctional and damaged mitochondria, effectively alleviating heart failure. From Fig. 3 we mention that AMPK and mTOR regulate mitochondrial dynamics through modulation of USP. AMPK is activated under low energy conditions, inhibiting the mTOR signaling pathway and consequently affecting downstream USP activity. The ubiquitin-proteasome system (UPS) and the autophagy-lysosome system are the primary mechanisms for degrading abnormally synthesised proteins.[95,96] Misfolded proteins are typically removed by the UPS system, while damaged mitochondria are selectively degraded by autophagy. These two processes are complementary and work together in cellular quality control. Heart failure is primarily characterised by inadequate energy metabolism in the body, which affects the function and tolerance of the heart.[118]

3.6. Mitochondrial calcium ions

Calcium ions play a crucial role in mitochondrial metabolism, and calcium deficiency can reduce the activity of metabolic synthesis enzymes. However, excess calcium can also activate apoptotic pathways, inducing cell death and exacerbating the progression of cardiovascular disease.[119,120] When mitochondria experience an imbalance in calcium homeostasis due to internal and external stimuli, damage to the electron transport chain disrupts electrical signaling, leading to the accumulation of ROS. These ROS trigger electrophysiological dysfunction through the mPTP and the inner membrane anion channel (IMAC), further exacerbating cardiac dysfunction.[121,122] Under physiological conditions, inhibition of mPTP opening can effectively reduce the release of ROS. The key transcriptional regulator of mitochondrial biogenesis, PGC1-alpha, promotes the transcriptional expression of the nuclear respiratory factors NRF-1 and NRF-2, which encode genes related to mitochondrial replication and electron transport chain proteins. However, in heart failure, PGC1-α activation is suppressed, leading to reduced mitochondrial biogenesis and consequently reduced ATP production.[88–91] In addition, post-translational modifications of mitochondrial proteins further impair the oxidative capacity of mitochondria, exacerbating the pathological progression of heart failure.[123] Mitochondrial dysfunction is a key factor in cardiovascular disease, so maintaining calcium ion homeostasis within the mitochondria is crucial.

3.7. Mitochondrial fatty acid oxidation

There is increasing evidence that disturbances in cardiac energy metabolism and mitochondrial function are important driving factors in the pathological remodeling of heart failure. Fatty acids, as the primary energy substrate for the heart, play a critical role in maintaining cardiac function through their oxidation process. In the early stages of heart failure, significant changes occur in the transcriptional regulation of FAO. This alteration leads to the downregulation of fatty acid oxidation pathways, resulting in the accumulation of incompletely oxidized fatty acids in cardiomyocytes. This phenomenon indicates that the metabolic regulation of fatty acids is impaired, which adversely affects the energy supply to the heart.[92] From Fig. 3 we mention that the intracellular metabolic and signaling regulatory network, highlights the interplay between NLRP3, PGC1-α, NRF2, and the TCA cycle. It describes several metabolism-related pathways involved in energy metabolism and inflammatory responses, including FAO, glycolysis, and the TCA cycle. FAO not only provides sufficient energy substrates but also effectively maintains mitochondrial function under conditions of pressure overload. By optimizing fatty acid oxidation, the heart can better adapt to metabolic demands and prevent metabolic failure.[124] The transcription factor PPARα is a key subtype in the regulation of cardiac fatty acid oxidation. In certain forms of HFpEF, particularly those associated with diabetes and obesity, activation of PPARα leads to a decrease in the expression of genes involved in fatty acid uptake and oxidation. This reduction in expression may further affect cardiac energy metabolism.[125] While increased FAO is generally considered beneficial in heart tissue, it is relatively poorly tolerated in situations of increased lipid delivery.[126–133] Partial replacement of fatty acid oxidation with ATP produced from glucose can help improve myocardial oxygen delivery and energy metabolism.[134,135] This metabolic reprogramming not only improves the energy status of the heart, but also helps to alleviate cardiac dysfunction and promote recovery in heart failure patients.[136,137]

4. Modulation of function by traditional Chinese medicine in cardiovascular disease

4.1. Mitochondrial fusion

4.1.1. Shenmai Injection

Shenmai Injection reduces mitochondrial fission by increasing Opa1

levels and inhibiting Drp1, thereby promoting mitochondrial membrane repair. This process reduces mitochondrial structural damage caused by hypoxia-reoxygenation and increases mitochondrial oxygen consumption and ATP generation, providing sufficient energy for cells, thereby slowing cell damage and preventing apoptosis.[49,138]

4.1.2. Ginseng

The antioxidant properties of ginseng play a central role in preventing biological aging and promoting longevity. The main active component of ginseng, ginsenoside Rb1, works by inactivating astrocytes and transferring mitochondria.[139] TAMPK can signal to the mitochondrial fission factor (MFF), a Drp1 receptor required to recruit Drp1 to the mitochondrial membrane and induce mitochondrial fission.[140] This signaling alleviates the dysfunction of the mitochondrial response to energy stress and protects cardiomyocytes from hypoxia/reoxygenation injury, controlling mitochondrial autophagy through the AMPK pathway ameliorates myocardial fibrosis and high glucose-induced cardiomyocyte damage.[139,141]

4.2. Mitochondrial fission

4.2.1. Houttuynia cordata

Houttuynia cordata acid from *Houttuynia cordata*, one of the major chemical constituents of Houttuynia *cordata*, has been shown to protect against cardiomyocyte injury. It selectively degrades damaged mitochondria by binding to MMP2 and p38, thereby maintaining cellular homeostasis and reducing cardiac fibroblast activation and proliferation. This action helps to inhibit cardiac fibrosis, regulate blood homeostasis and slow the progression of heart failure.[8]

4.2.2. Eleutherococcus senticosus

Eleutheroside E from *Eleutherococcus senticosus* is a compound isolated from the dried roots and rhizomes or stems of *Eleutherococcus senticosus*. According to traditional Chinese medicine, it is known for its ability to nourish the heart and calm the mind. Research has shown that it can reduce the generation of reactive oxygen species by breaking down damaged mitochondria, thereby reducing oxidative stress, inhibiting the activation of NF-κB and improving metabolism. These effects contribute to the reduction of myocardial ischemia/reperfusion injury, aiding in the treatment and recovery of cardiovascular disease.[35]

4.3. Mitochondrial autophagy

4.3.1. Salvia

Salvianolic acid B from Salvia has been shown in *in vitro* cell experiments to inhibit the impairment of cardiomyocyte viability caused by hypoxia/reoxygenation when administered in advance. In addition, the elevated ratio of mitochondrial autophagy-related protein LC3II/LC3I is suppressed, leading to a reduction in autophagy levels. This effect promotes the recovery of mitochondrial structure and function while increasing ATP production levels, thereby protecting cardiomyocytes from damage.[142]

4.3.2. Horny Goat Weed

Icariin from Horny Goat Weed has been shown *in vitro* and *in vivo* studies to significantly enhance gelatinase activity by activating the TGF-β1/Smad2 signaling pathway, thereby promoting the degradation of excess extracellular matrix.[140] We also found that Icariin can reduce the activation of mitochondrial apoptosis by Bcl-2.[143] Our previous research has shown that Icariin can mediate p62-dependent Keap1 degradation and activate nuclear factor erythroid 2-related factor 2 (Nrf2) to inhibit oxidative stress. This mechanism reduces cellular inflammation through the Keap1-Nrf2/HO-1 axis in a manner dependent on mitochondrial autophagy, thereby restoring cardiomyocyte function.[143]

4.4. Mitochondrial dynamics

4.4.1. Yangxinshi Tablet

Yangxinshi Tablet improves mitochondrial function and energy metabolism by activating related targets, stimulating glucose consumption and oxygen utilization, while inhibiting the production of reactive oxygen species. These effects help to suppress myocardial fibrosis and hypertrophy, thereby slowing the progression of heart failure and improving cardiac function.[144]

4.4.2. Aconite

The major constituents of aconite, such as aconitine, mesaconitine, and hypaconitine, can improve ventricular compliance by activating the cAMP signaling pathway in cardiomyocytes. This modulation improves cardiac contractility and enhances mitochondrial energy metabolism, reduces the surface area of hypertrophied cardiomyocytes, increases cardiac capillary density, and increases cardiomyocyte activation levels, thereby inhibiting cardiomyocyte apoptosis.[145,146]

4.4.3. Xintong Capsule

Xintong Capsule enhances the activity of mitochondrial respiratory chain complexes I–IV, repairs the electron transport chain to restore electrical signal conduction, promotes mitochondrial biogenesis, and reduces the production of reactive oxygen species. This action inhibits cardiomyocyte apoptosis, thereby restoring mitochondrial membrane structure and function.[147] This drug effectively protects cardiomyocytes under hypoxia-reoxygenation conditions, preventing cell damage.[148,149]

4.5. Mitochondrial calcium ions

4.5.1. Shenmai Injection

Shenmai Injection restores mitochondrial function, reduces the production of ROS, and lowers levels of nicotinamide adenine dinucleotide (NADH) and malondialdehyde (MDA). This effectively inhibits mitochondrial calcium overload and reduces myocardial stress.[138,150] It also mediates calcium homeostasis by activating the Drp1 signaling pathway, which inhibits apoptosis in cardiomyocytes.[151] Ginsenoside Rb1 promotes the recovery of cardiac mitochondrial function and increases glucose uptake by activating the TGF-β1/Smad and *Akt* signaling pathways. This effectively inhibits mitochondrial calcium overload and prevents cardiac remodeling, and further improves heart failure.[152]

4.5.2. Radix astragali

Astragaloside IV from Radix astragali has demonstrated significant cardioprotective effects in both *in vivo* and *in vitro* studies. Under pathological conditions, it promotes myocardial perfusion and regulates the activity of calcium pumps in the sarcoplasmic reticulum, thereby optimizing the balance of calcium ions within cardiomyocytes. In addition, Astragaloside IV induces angiogenesis in the myocardium, helps restore energy metabolism, reduces the number of damaged organelles, and alleviates apoptosis in cardiomyocytes.[89,153,154]

4.5.3. Salvia

Tanshinone IIA from Salvia pretreatment regulates the translocation of the anti-apoptotic factor Bcl-2 to the OMM, thereby protecting H9c2 cells from hypoxia/reoxygenation (H/R) injury. This action prevents the opening of the mitochondrial permeability transition pore, reducing cytochrome C release and caspase-3 activation.[155] Tanshinone IIA can also stimulate the NAD^+-dependent deacetylase sirtuin-1/peroxisome proliferator-activated receptor γ coactivator 1-α (SIRT1/PGC1) pathway to inhibit mitochondrial damage, providing a survival advantage to cardiac microvascular endothelial cells (CMECs) and protecting the structure and function of the microvasculature.[156]

4.6. Mitochondrial oxidative phosphorylation

4.6.1. Musk

Musk has the ability to open the orifices, awaken the spirit, and promote circulation, particularly benefiting the heart by improving blood flow. Research has shown that musk can ameliorate the damage caused by myocardial infarction by reducing the production of ROS to inhibit oxidative stress, promoting vascular regeneration, and increasing ATP breakdown to boost metabolism, ultimately reducing the risk of heart failure and improving cardiac function.[65]

4.6.2. Histamine-gingerol

Histamine-gingerol can attenuate doxorubicin (DOX)-induced cardiotoxicity by improving cardiac function. This protective effect is achieved primarily through activation of the LKB1/AMPKα/SIRT1 signaling pathway, which increases ATP degradation and promotes energy metabolism in cardiomyocytes.[157,158]

4.6.3. Turmeric

Tetrahydrocurcumin inhibits oxidative stress by activating the SIRT3 pathway, preserving mitochondrial function, and improving post-infarction cardiac dysfunction and remodeling. This mechanism effectively improves mitochondrial energy metabolism, thereby slowing the progression of heart failure.[88,159]

4.7. Mitochondrial fatty acid oxidation

4.7.1. Honeysuckle

Honeysuckle can clear heat and detoxify, belonging to the heart, lung, and stomach meridians. It contains the bioactive polyphenolic compound chlorogenic acid, which studies have shown can improve cardiac function in pathological conditions through the *SLC7A11/GPX4* signaling pathway. It also reduces the secretion of lipid peroxides and reactive oxygen species in cardiomyocytes, further alleviating ferroptosis in these cells.[88,160]

4.7.2. Qishen Yiqi granules

Qishen Yiqi granules inhibit the generation of reactive oxygen species by reducing the expression of UCP2, thereby regulating fatty acid and glucose metabolism in the myocardium of heart failure rats.[161–164] At the same time, it increases mitochondrial membrane potential and ATP synthesis, thereby reducing cell damage, preventing cardiomyocyte apoptosis, and ultimately improving cardiac function.[88,165]

4.7.3. Valerian

Valerenic acid from Valerian effectively alleviates pathological cardiac hypertrophy by promoting the utilisation of various substrates in mitochondrial energy metabolism, inhibiting glycolysis, and accelerating FAO. This mechanism may protect cardiac function and inhibit the progression of heart failure by improving the energy supply and metabolic flexibility of cardiomyocytes.[166,167]

5. Discussion

TCM has been a valuable resource for treating cardiovascular diseases (CVD) throughout history. Based on centuries of empirical use, TCM formulations can be rapidly applied to clinical practice, whereas biochemical preparations often require prolonged scrutiny.[176] Numerous examples and clinical evidence attest to the distinctive features of TCM, including its diverse range of ingredients, unique therapeutic effects, and broad applicability.[177] From Fig. 4 we mention that TCM can regulate and tonify qi, warm and strengthen heart yang, promote blood circulation and remove stasis, and resolve turbid phlegm, thereby treating cardiac pathology, improving blood flow, reducing internal and external pressure differences, and alleviating swelling, ultimately enhancing cardiac function. These characteristics have significantly improved cardiac function in CVD patients, alleviated associated symptoms, and reduced mortality rates. Encouragingly, it has been reported that dozens of herbal formulas, hundreds of medicinal herbs, and their extracts or active components exhibit pharmacologically validated bioactivities against CVD. Through the synergistic use of herbs in formulas adhering to the TCM principles of Jun-Chen-Zuo-Shi (sovereign, minister, assistant, and envoy), the pharmacological activities of these herbs can be maximized.[178] Jun-Chen-Zuo-Shi is one of the fundamental principles in the formulation of TCM prescriptions. Its core idea is to achieve therapeutic effects through the rational combination of medicinal herbs. In this principle, the "Jun" herb is the primary ingredient, targeting the main symptoms and playing the principal therapeutic role; the "Chen" herb assists the "Jun" herb by enhancing its efficacy or addressing secondary symptoms; the "Zuo" herb reduces or eliminates the toxicity of both the "Jun" and "Chen" herbs, while also helping with treatment; and the "Shi" herb guides the other herbs to the affected area or harmonizes the overall formula.[179–181] From Fig. 5 we mention that the impact of different traditional Chinese medicines on regulating mitochondrial function in

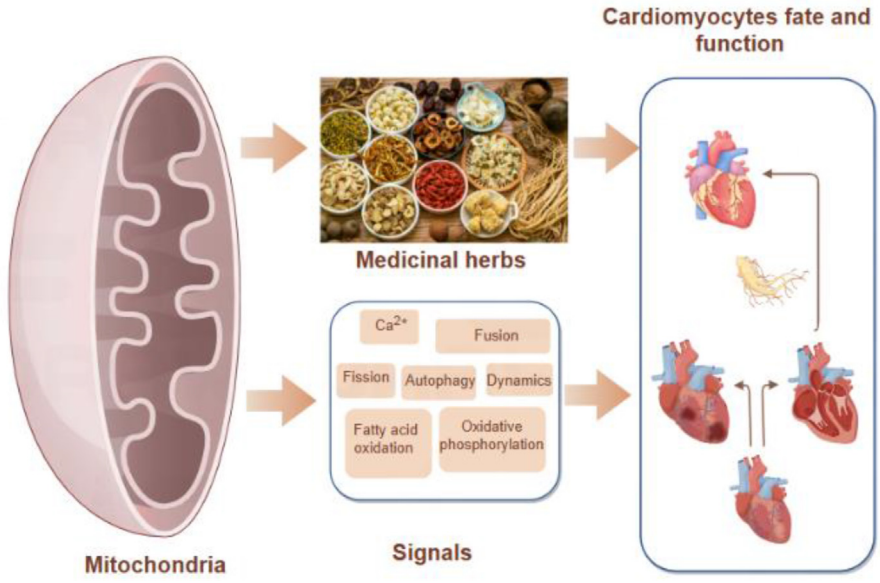

Fig. 4. TCM offers a variety of options for disease treatment through its multi-pathway, multi-signal, and multi-connection characteristics. TCM can regulate and tonify qi, warm and strengthen heart yang, promote blood circulation and remove stasis, and resolve turbid phlegm, thereby treating cardiac pathology, improving blood flow, reducing internal and external pressure differences, and alleviating swelling, ultimately enhancing cardiac function.[29–32] In various experimental studies of TCM, both in animal and cellular models, the results consistently show that TCM significantly improves mitochondrial energy metabolism in cardiomyocytes.

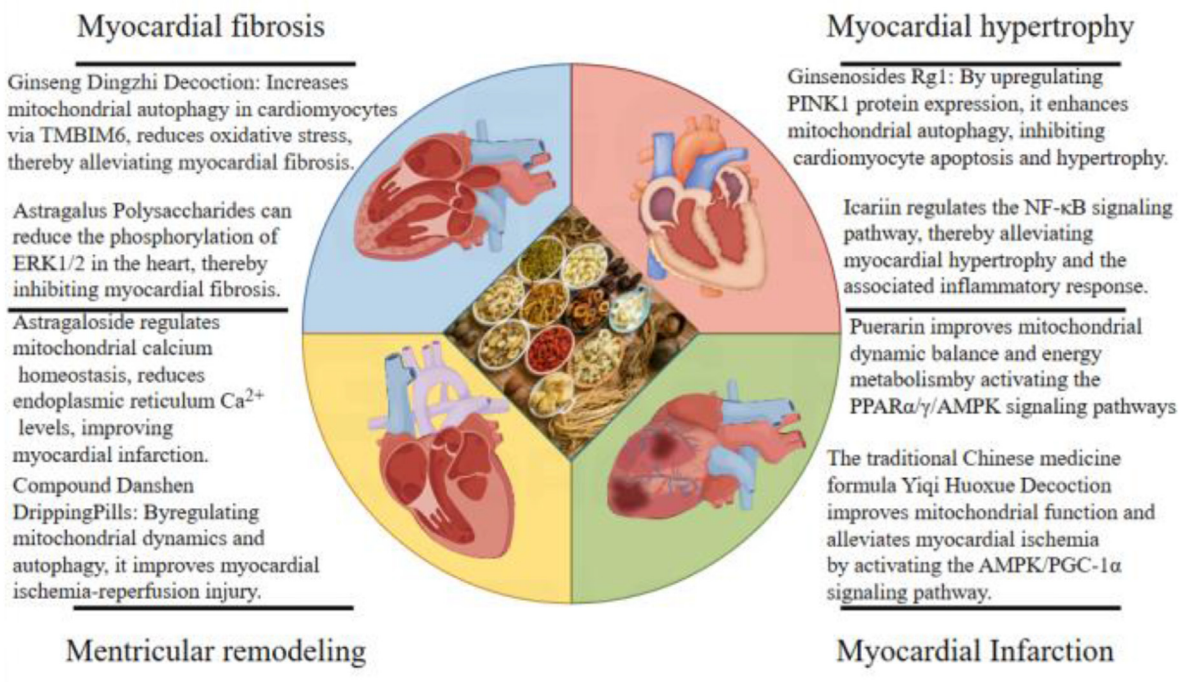

Fig. 5. This figure illustrates the impact of different traditional Chinese medicines on regulating mitochondrial function in cardiac diseases, specifically including four aspects: myocardial fibrosis, myocardial hypertrophy, myocardial infarction, and ventricular remodeling.[168–175]

cardiac diseases, specifically including four aspects: myocardial fibrosis, myocardial hypertrophy, myocardial infarction, and ventricular remodeling.

In recent years, significant progress has been made in studying the therapeutic effects of herbs and their natural active compounds on CVD via mitochondrial modulation. The above discussion highlights how herbs can influence the progression of CVD by directly or indirectly modulating mitochondrial function. As mitochondria are critical organelles for cardiac function, their instability or dysfunction can trigger significant stress responses. Most current research focuses on the relationship between mitochondrial activity and cardiac health. First, leveraging mitochondrial function as a target offers a promising avenue to regulate CVD.[182] This approach enhances our understanding of how herbs can prevent and treat CVD through mitochondrial pathways, paving the way for developing more effective anti-aging drugs and therapeutic strategies. Second, analyzing the active components in herbal extracts can aid in identifying and isolating other compounds to create more potent and effective medications for preventing CVD.[183] These efforts will enable researchers to elucidate the molecular mechanisms by which TCM mitigates the progression of CVD through mitochondrial targeting, providing new insights and methodologies for future investigations.

TCM regulates mitochondrial quality control through multiple targets and pathways, including mitochondrial biogenesis, dynamics, and autophagy, which can inhibit cardiomyocyte apoptosis and slow down the progression of cardiovascular diseases.[184] TCM formulas regulate mitochondrial function through mechanisms such as antioxidant stress response, calcium homeostasis regulation, and anti-apoptosis, which have potential therapeutic effects on cardiovascular diseases.[185] TCM shows unique advantages in treating myocardial injury, such as alleviating cardiomyocyte damage by regulating mitochondrial dynamics and autophagy processes.[186] The specific mechanisms of TCM in regulating mitochondrial function are not yet clear, lacking systematic research and clinical trial data to support its effectiveness.[187] The components of TCM are complex and diverse, with varying effects on mitochondrial damage, making it difficult to accurately assess their therapeutic effects. Existing research mainly relies on animal experiments, and there is insufficient clinical evidence to support the use of TCM in cardiovascular diseases.[188,189] TCM has a certain theoretical foundation and practical advantages in regulating mitochondrial function and treating cardiovascular diseases, but further research is needed to improve its scientific basis and clinical application value.[185,189]

The journey of research into suppressing CVD progression has evolved from *in vivo* and *in vitro* cellular studies toward holistic approaches, reflecting deeper understandings of CVD mechanisms in both traditional Chinese and Western medicine. This progress has enabled researchers to explore the molecular mechanisms of CVD more comprehensively.[190] Numerous studies indicate that Western medicine treatments often exhibit dose-dependent effects and common side effects. In contrast, TCM, with its functions such as promoting blood circulation, removing stasis, and regulating lipid metabolism, improves mitochondrial function through multiple pathways, effectively inhibiting CVD progression.[191] This widens the therapeutic scope for CVD, offering unique advantages and enhanced efficacy. These findings demonstrate that TCM can intervene in CVD from multiple perspectives, levels, and methodologies, potentially achieving its effects by regulating the expression of related genes. TCM has shown remarkable results in improving myocardial energy metabolism, enhancing cardiac function, and providing novel strategies for treating CVD.[192] By integrating this comprehensive approach with modern research findings, TCM better meets patient needs. Overall, we find that herbal medicines targeting mitochondrial function play a pivotal role in treating CVD.

CRediT authorship contribution statement

Lin Yang: Writing – original draft. **Liang Wang:** Software. **Baofeng Yang:** Conceptualization. **Yue Zhang:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

TCM, Traditional Chinese medicine; ROS, Reactive oxygen species; ATP, adenosine triphosphate; UPS, ubiquitin-proteasome system; NADH, Nicotinamide adenine dinucleotide; MDA, malondialdehyde; FAO, fatty acid oxidation; ALPR, Aconiti Lateralis radix Praeparata; MPTP, mitochondrial permeability transition; NAC, *N*-acetyl-L-cysteine; CPT, carnitine palmitoyltransferase; PINK1, PTEN-induced putative kinase 1; MFF, mitochondrial fission factor; OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; CVD, Cardiovascular disease.

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