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Review

Mitochondrial dysfunction: a new target for traditional Chinese medicine in the treatment of chronic heart failure

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ABSTRACT

Chronic heart failure (CHF) remains a global health challenge with limited therapeutic options. Mitochondrial dysfunction is a key pathological feature, and traditional Chinese medicine (TCM) shows unique potential in targeting this mechanism. Evidence from human and animal models of heart failure indicates that TCM can restore mitochondrial function by regulating mitochondrial Ca^{2+} homeostasis, oxidative stress, energy metabolism, mitochondrial dynamics, and mitophagy. TCM-based treatment of CHF offers notable clinical advantages, including improved therapeutic efficacy, enhanced cardiac function, and reduced incidence of major cardiovascular events. Experimental studies demonstrate that TCM decoctions and monomers modulate signaling pathways such as PPAR–RXRα, NF-κB, and PI3K/AKT to alleviate oxidative stress. TCM also increases AMPK activity *via* phosphorylation of PGC-1α, indirectly promoting mitochondrial biogenesis; attenuates calcium influx and enhances Ca^{2+} reuptake, thereby ameliorating myocardial mitochondrial dysfunction in CHF; and improves CHF by rebalancing mitochondrial dynamics and autophagy.

1. Introduction

Chronic heart failure (CHF) is a complex clinical syndrome caused by structural or functional cardiac abnormalities that impair ventricular systolic and/or diastolic function [1]. The main pathophysiological manifestation is reduced cardiac output due to the heart's inability to pump blood effectively, often accompanied by structural remodeling and fluid retention. Typical clinical symptoms include dyspnea (on exertion, at rest, or paroxysmal nocturnal dyspnea), fatigue, peripheral edema (e.g., lower limb edema), and cough (sometimes with pink frothy sputum). Common signs include jugular venous distension, pulmonary rales, hepatomegaly, positive hepatojugular reflux, and abnormal heart sounds. Patients with CHF frequently exhibit reduced exercise tolerance and poor quality of life and may develop complications such as arrhythmias, renal insufficiency, thromboembolism, and cachexia. By 2024, more than 60 million individuals worldwide were estimated to be living with CHF, with incidence expected to rise further due to population aging and improved survival from cardiovascular diseases. The overall prevalence of CHF in developed countries is approximately 2%–4%, rising to as high as 11.8% in individuals aged ≥ 60 years. In the Asia–Pacific region, prevalence varies substantially, with estimates of about 1.3% in China, 1% in India, and up to 6% in Taiwan [2]. Traditional Chinese medicine (TCM) has been used for decades in the management of CHF, mainly through strategies such as replenishing Qi and nourishing Yin, promoting blood circulation, and resolving blood stasis to improve cardiac function. Concepts related to CHF can be traced back to classical texts such as the *Huangdi Neijing* (*Inner Canon of Huangdi*) and Shang Han Lun (Treatise on Febrile Diseases). The *Inner Canon of Huangdi* states "Yang transforms Qi, Yin shapes the body". In modern terms, "Yang transforms Qi" parallels the generation of $NADH/FADH_2$ in the tricarboxylic acid (TCA) cycle (redox reactions), while "Yin shapes the body" corresponds to fatty acid synthesis (anabolic processes) *via* the conversion of citrate to acetyl-CoA in fatty acid metabolism. Furthermore, the classic notion that "the Qi of the chest accumulates in the chest and passes through the lungs, connecting the heart and vessels" aligns with modern findings that myocardial mitochondria account for 20%–35% of cardiomyocyte volume, much higher than other organelles, highlighting the central relationship between myocardial energy generation, mitochondrial function, and effective cardiac output. In recent years, multiple studies have confirmed the importance of TCM in treating heart failure. Compared with the predominantly single-target effects and long-term dependence associated with Western medicines, TCM can modulate multiple pathological processes *via* multi-target regulation. In TCM, the principle of treatment based on syndrome differentiation allows for individualized formulations tailored to each patient's constitution and disease etiology, thereby achieving holistic therapeutic effects. Recent evidence indicates that TCM improves key pathological mechanisms of CHF by regulating mitochondrial dynamics, calcium homeostasis, and endoplas-

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mic reticulum–mitochondrial interactions. For example, Xin-Ji-Er-Kang has been shown to facilitate ERα nuclear translocation, upregulate SIRT3, and restore the balance of mitochondrial fusion and fission [3]. Xin-Fu-Kang Oral Liquid protects against chronic hemodynamic overload by modulating NR4A1-dependent functional coupling between the endoplasmic reticulum and mitochondria in cardiomyocytes, thereby preserving mitochondrial function and preventing apoptosis [4]. Another study demonstrated that Jin-Xin-Kang modulates the CaN/Drp1 pathway *in vitro* and *in vivo*, alleviating mitochondrial dysfunction [5]. Clinical studies also indicate that Chinese traditional patent medicines (CTPMs) confer significant benefits in reducing major adverse cardiovascular and cerebrovascular events (MACCEs) in patients with CHF. For example, Qili Qiangxin Capsules reduce the composite outcome of heart failure hospitalization and cardiovascular death, and improve New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), 6-minute walk distance (6MWD), and quality-of-life scores [6, 7]. Other CTPMs, such as Qishen Yiqi Dropping Pills, have been shown to improve exercise tolerance and quality of life with good tolerability. Adverse effects reported in the context of TCM treatment for CHF are generally mild, including fatigue, hypotension, dizziness, and nausea. Despite these therapeutic advances, the global burden of CHF continues to rise. Further improving treatment efficacy and delaying disease onset and progression remain key challenges that have attracted substantial research interest. In this context, mitochondrial dysfunction has emerged as a promising, mechanistically grounded therapeutic target for TCM interventions.

2. Current status and advantages of Chinese medicine in the treatment of CHF

2.1. Understanding CHF from the TCM perspective

From the perspective of TCM, the core pathogenesis of CHF is characterized by “root deficiency with superficial excess” and “intermingled deficiency and excess”. The fundamental deficiency (root) is primarily Qi deficiency, often combined with Yin and Yang deficiency; the excess (superficial) mainly manifests as blood stasis, phlegm retention, and obstruction in the heart and vessels. Excess is a key driving factor determining the course of CHF, while deficiency is a dynamic factor influencing changes in disease severity. The interplay between deficiency and excess governs the progression and evolution of CHF. Modern research supports the view that CHF is a progressive disease with stage-dependent pathophysiological mechanisms and therapeutic priorities. According to Supplementary Table 1, 19 high-quality randomized controlled trials (RCTs) were included, covering five TCM decoctions, seven Chinese patent medicines (CPMs), three TCM injections, and four TCM-based adjunct therapies. As shown in Fig. 1, the clinical evidence suggests that TCM for CHF can 1) improve LVEF; 2) reduce the incidence of MACE; 3) ameliorate inflammatory factors; 4) regulate negative emotions; 5) modulate energy metabolism; 6) improve exercise tolerance; 7) reduce systemic edema.

2.2. Clinical evidence of TCM for CHF

2.2.1. TCM decoctions for CHF treatment

The primary advantages of TCM decoctions in CHF lie in their individualized and holistic treatment approach. First, formulations can be flexibly adjusted according to the patient’s specific syndrome pattern and clinical status, with dynamic modification of composition and dosage to optimize efficacy. Second, treatment based on syndrome differentiation enables simultaneous treatment of cardiac dysfunction and comorbid organ impairment, promoting systemic balance and reducing the risk of collateral damage associated with narrow, single-target pharmacotherapy.

In a prospective cohort study involving 116 CHF patients, Xuefu Zhuyu Decoction significantly improved TCM symptom scores, cardiac function, and inflammatory markers [high-sensitivity C-reactive protein (hs-CRP), monocyte chemoattractant protein-1 (MCP-1), and matrix metalloproteinase 9 (MMP-9)] and ameliorated negative emotions and depressive symptoms. Another prospective RCT investigating Shenfu Decoction found that patients in the Shenfu group showed more pronounced improvements in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores and liver function compared with controls. Subgroup analyses indicated greater improvements in both physical and emotional dimensions. Shenfu Decoction also improved NYHA class, LVEF, and serum alanine aminotransferase (ALT), suggesting simultaneous cardioprotective and hepatoprotective effects [8]. Chinese herbal tonics also play an important role in improving exercise tolerance and energy metabolism in CHF. A prospective, single-blind, single-center RCT evaluated Yangyin Shuxin Decoction (YYSXD) using cardiopulmonary exercise testing (CPET). After two weeks, peak VO_2, eQ-visual analog scale (EQ-VAS) score, and maximum voluntary ventilation (MVV) of the YYSXD group were significantly higher than those of the control group. The effect of YYSXD also improved scores on the TCM Four-Dimensional Diagnostic Information Scale (TCMFDIS), with no serious adverse events (AEs) reported [9]. In a multicenter, double-blind RCT of 80 CHF patients, Buyang Huanwu Decoction (BYHWD) had a significant effect on improving NYHA functional classification, TCM syndrome scores, and NCHS scores and decreasing NT-ProBNP by more than 30%. In a multicenter, double-blind RCT of 80 CHF patients, BYHWD significantly improved NYHA class, TCM syndrome scores, and NCHS scores, and reduced NT-proBNP levels by more than 30%. In CHF rat models, BYHWD also regulated energy metabolism indicators such as adenosine diphosphate (ADP) and adenosine triphosphate (ATP), supporting its role in improving myocardial energy metabolism. Other decoctions have similarly been shown to enhance exercise tolerance, optimize energy metabolism, and improve fluid status in heart failure. For example, a prospective RCT demonstrated that Zhuling Decoction significantly improved urine output, NT-proBNP, NYHA class, and MLHFQ scores in CHF patients, indicating beneficial effects on volume overload and quality of life [10].

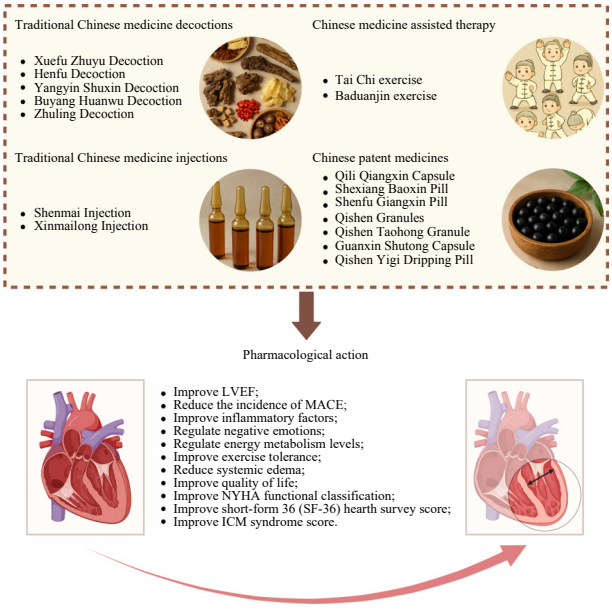

Fig. 1 Clinical advantages of TCM in the prevention and treatment of CHF.

2.2.2. CPMs for CHF treatment

CPMs offer unique advantages in the long-term management of chronic diseases such as CHF. First, through multi-component formulations, CPMs act on multiple targets and pathways to regulate systemic function and improve overall efficacy. Second, sustained use can stabilize disease, reduce relapse, and support long-term management. Third, CPMs tend to have favorable safety profiles and good tolerability.

CHF is strongly associated with increased mortality and re-hospitalization. A multicenter, double-blind RCT demonstrated that Qili Qiangxin Capsules significantly reduced the risk of CHF hospitalization and mortality compared with control, with similar rates of all-cause mortality and adverse events, indicating good safety [7]. Elevated NT-proBNP is common in CHF, and multiple studies have shown that CPMs effectively reduce NT-proBNP and improve exercise capacity [e.g., 6-minute walk test (6MWT)], TCM symptom scores, and echocardiographic indices [11].

In a randomized, double-blind controlled trial, patients were assigned to three groups: group A received standard heart failure therapy plus home-based exercise plus Shexiang Baoxin Pills; group B received standard therapy plus home-based exercise; and group C received standard therapy alone, all for 12 weeks. All groups showed improvements in peak oxygen uptake (peak VO_2), anaerobic threshold (AT), 6MWT, Pittsburgh Sleep Quality Index (PSQI), and SF-36 scores, but group A exhibited the greatest improvement in physical function, role physical, vitality, and mental health domains, indicating that Shexiang Baoxin pills further enhanced quality of life [12]. Consistent findings have been reported in other multicenter, randomized, double-blind, placebo-controlled trials, in which Guanxin Shutong Capsules and Qishen Yiqi Dropping Pills significantly improved 6MWD and quality-of-life metrics (NYHA class, MLHFQ, and echocardiographic indices compared with placebo [13–14].

2.2.3. TCM injections for CHF treatment

TCM injections provide significant advantages in managing acute and chronic conditions. Intravenous administration bypasses gastrointestinal absorption, enables rapid onset, and is particularly suitable for acute decompensation. Modern extraction techniques allow concentration of active ingredients, improving bioavailability and reducing impurities and side effects. In addition, standardized formulations facilitate precise dosing and quality control.

In a double-blind, multicenter study of 240 CHF patients, Shenmai Injection (SMI) significantly improved the NYHA functional class compared with placebo after 1 week of treatment. The SMI group also showed greater improvements in 6MWD, SF-36 scores, TCM syndrome scores, LVEF, and B-type natriuretic peptide [15]. A single-blind controlled trial further found that SMI modulated energy metabolism: after 7 days of treatment, serum free fatty acids (FFAs), glucose, lactic acid (LA), pyruvate (PA), and branched-chain amino acids (BCAAs) improved significantly compared with controls [16]. In another randomized, double-blind, placebo-controlled study including 100 CHF patients, Xinmailong Injection significantly improved NYHA class and LVEF after 5 days of treatment, with no deaths and no significant difference in adverse event incidence between groups [17].

2.2.4. TCM-assisted therapy

Traditional health exercises such as Tai Chi and Baduanjin represent important TCM-based adjunct therapies for CHF rehabilitation. These low-to-moderate intensity aerobic exercises gradually enhance cardiopulmonary function without imposing excessive hemodynamic load, thereby improving exercise tolerance and quality of life. The slow, coordinated movements promote Qi and blood circulation, reduce cardiac congestion, and improve myocardial oxygen supply. Additionally, the emphasis on mind–body integration helps alleviate anxiety and depression and improves autonomic regulation. A single-blind, multicenter, parallel-group RCT involving 100 CHF patients showed that a 12-week Tai Chi program significantly improved quality of life, mood, and exercise self-efficacy compared with controls [18]. Another study reported that Tai Chi significantly improved quality of life and reduced SCL-90-R depression scores [19]. In a randomized controlled trial of Baduanjin, patients in the intervention group practiced Baduanjin three times per week for 12 weeks at home, supported by a demonstration video, educational brochure, and practice log, whereas controls received routine care only. After 12 weeks, the intervention group exhibited significant improvements in fatigue and quality of life compared with controls [20]. Other studies have shown that *Baduanjin* improves 6MWD and other functional indices in CHF patients [21].

In summary, TCM-based treatment of CHF offers clear clinical advantages, including: 1) improved LVEF; 2) reduced incidence of major adverse cardiovascular events; 3) regulation of negative emotions (including SCL-90-R depression scores); 4) improved energy metabolism (ADP, ATP, FFAs, LA, PA, BCAAs); 5) enhanced exercise tolerance (EQ-VAS, MVV, peak VO, peak VO_2, AT, 6MWT); 6) modulation of inflammatory markers (hs-CRP, MCP-1, MMP-9); 7) improved quality-of-life measures (e.g., SF-36 physical function, vitality, and mental health). These clinical benefits may be closely related to the regulation of myocardial energy metabolism, particularly mitochondrial energy metabolism, the mechanisms of which are elaborated in detail below.

3. The relationship between mitochondria and TCM

Mitochondria are the cellular “energy factories”, responsible for ATP production and centrally involved in metabolism, redox balance, and regulation of intracellular Ca^{2+} homeostasis. In recent years, the role of mitochondria in chronic and age-related diseases has attracted considerable attention [22]. In traditional Chinese medicine (TCM), the concepts of Qi and Essence (Jing) show notable parallels with mitochondrial function, and accumulating evidence suggests that TCM interventions can modulate mitochondrial activity. First, mitochondria and the TCM concept of Qi share important conceptual similarities. TCM holds that Qi is the fundamental driving force behind all life activities and that adequate and harmoniously circulating Qi is essential for health. Mitochondria generate ATP through oxidative phosphorylation (OXPHOS), supplying the biochemical energy required for cellular functions. Accordingly, mitochondrial energy metabolism can be viewed as the material basis of Qi in TCM. Many disease patterns in TCM, such as “Qi deficiency”, “Qi stagnation”, “Qi collapse”, and “Qi desertion”, reflect disturbances of Qi movement. From a modern biological perspective, these may correspond to varying degrees of mitochondrial dysfunction. Multiple studies have shown that impaired mitochondrial function can lead to insufficient cellular energy supply, disruption of the TCA cycle, decreased efficiency of the electron transport chain (ETC), increased production of reactive oxygen species (ROS), and reduced ATP synthesis, ultimately resulting in tissue and organ dysfunction [23]. These changes mirror TCM descriptions of disturbed Qi dynamics. Accordingly, TCM therapies aimed at regulating Qi may, at least in part, exert their effects by improving mitochondrial function.

Second, mitochondrial damage is closely associated with functional decline in aging and chronic disease, which resonates with the TCM concept of Essence (Jing). In TCM theory, Essence is the fundamental substance that sustains growth, development, and reproduction. With advancing age, depletion of Essence leads to manifestations such as fatigue, dizziness, weakness, and memory impairment. Qi and Essence are mutually transformable: Qi generates and consolidates Essence, while Essence nourishes

and promotes the generation of Qi. Insufficiency of Essence may therefore be accompanied by mitochondrial dysfunction, and the two interact synergistically to influence mitochondrial status. With aging, mitochondrial DNA mutations and oxidative damage accumulate, impairing mitochondrial function and promoting apoptosis, tissue injury, and senescence. Modern research has demonstrated that certain tonic Chinese herbal medicines, such as *Polygonatum sibiricum* [24] and Ginseng [25], enhance mitochondrial antioxidant capacity and promote mitochondrial biogenesis, thereby delaying aging-related decline. These mechanisms support the TCM view that "nourishing Essence" can ameliorate conditions associated with functional degeneration. In addition, many TCM herbs exhibit unique actions in protecting and restoring mitochondrial function. For example, Astragali Radix [26], *Salvia miltiorrhiza* [27], and *Ligusticum chuanxiong* possess antioxidant, anti-inflammatory, and anti-apoptotic properties that help maintain the structural integrity of mitochondrial membranes and alleviate mitochondrial dysfunction [28]. The regulatory effects of these herbs exemplify the TCM principle of modulating Qi and Essence through pharmacological interventions, providing a mechanistic basis for the scientific interpretation of TCM in terms of mitochondrial regulation (Fig. 2).

In summary, mitochondrial activity is closely related to core TCM concepts such as Qi and Essence, offering a new perspective for modern research on TCM. TCM may achieve its therapeutic effects by improving mitochondrial function, thereby aligning the classical notion of "treating disease before its onset" with modern cellular and molecular biology. Based on clinical and experimental observations, the core pathways through which TCM improves CHF can be analyzed from the perspective of mitochondrial function.

4. Mechanism of mitochondrial dysfunction inducing CHF

4.1. Overview of mitochondrial functions

Mitochondria are essential organelles in eukaryotic cells, recognized for their central roles in energy production and inter-organelle communication. They are often referred to as the "powerhouses" of the cell because they generate ATP *via* oxidative phosphorylation (OXPHOS), supplying the energy needed for growth, proliferation, differentiation, and diverse physiological processes. ATP production in mitochondria is primarily driven by the TCA cycle and the ETC. In the TCA cycle, substrates such as glucose, fatty acids, and amino acids are oxidized to produce reduced cofactors, including nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$). These electron donors transfer electrons to the ETC, driving proton pumping across the inner mitochondrial membrane and generating a proton gradient. This electrochemical gradient powers ATP synthase to convert ADP to ATP. Oxidative phosphorylation accounts for more than 80% of the energy requirements in most cells.

Beyond energy production, mitochondria are crucial for maintaining cellular redox balance. During ATP generation, a fraction of electrons leaks from the ETC, leading to ROS formation. At physiological levels, ROS participate in cell signaling, but at high levels, they damage proteins, lipids, and DNA. Under normal conditions, cellular antioxidant systems effectively clear ROS and maintain redox homeostasis. When ROS accumulate excessively, oxidative stress occurs, promoting mitochondrial dysfunction and contributing to pathological processes such as aging, inflammation, and neurodegenerative diseases [29]. Mitochondria also play a pivotal role in intracellular Ca^{2+} homeostasis. The spatial and temporal dynamics of Ca^{2+} inside and outside the cell are fundamental to many signaling pathways. Mitochondria take up and release Ca^{2+} through mechanisms such as the mitochondrial

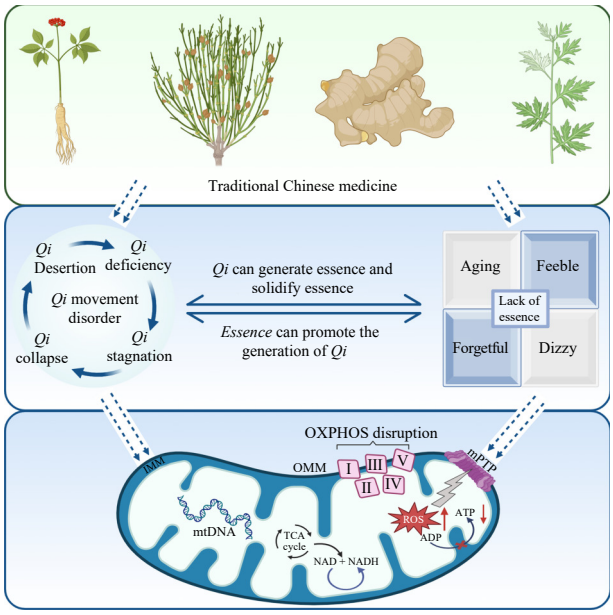

Fig. 2 The interaction between TCM and mitochondrion.

calcium uniporter (MCU) and mitochondrial Ca^{+} exchangers. Mitochondrial Ca^{2+} uptake can stimulate TCA cycle enzymes, enhance ATP production, and enable the cell to meet increased energy demands under stress. Mitophagy, the selective autophagic removal of damaged or dysfunctional mitochondria, is essential for regulating mitochondrial quantity, maintaining energy homeostasis, and adapting to metabolic fluctuations. By eliminating abnormal mitochondria under conditions such as dynamic imbalance, hypoxia, toxin exposure, or aging, mitophagy promotes cell survival and functional adaptation. Mitochondrial dynamics, continuous fusion and fission, are equally critical for maintaining normal function. Fusion supports the mixing of mitochondrial contents, repair of damaged mitochondrial DNA, and equilibration of metabolic components, whereas fission is important for quality control, segregation of damaged segments, and appropriate distribution during cell division. Loss of balance between fusion and fission compromises mitochondrial function, disrupts metabolism, and can contribute to diseases such as neurodegenerative disorders [30].

4.2. Mitochondria and CHF

The role of mitochondria in CHF has become a major focus of cardiovascular research. Mitochondria are deeply involved in key pathological processes, including oxidative stress, disturbed energy metabolism, Ca^{2+} homeostasis imbalance, altered mitophagy, and abnormal mitochondrial dynamics. Basic and clinical studies have established that mitochondrial dysfunction constitutes an important mechanistic basis for CHF and a promising target for novel therapies.

As the principal source of ATP in cardiomyocytes, mitochondria are crucial for maintaining the heart's contractile function. In health, cardiomyocytes generate large amounts of ATP through OXPHOS to sustain the continuous pumping of blood. In heart failure, however, mitochondrial oxidative phosphorylation efficiency is significantly reduced, resulting in diminished ATP synthesis and inadequate energy supply relative to cardiac workload. Mitochondrial oxidative stress is also prominent in CHF [31]. Under physiological conditions, ROS produced by mitochondria at low levels contribute to normal signaling and immune responses. In CHF, ROS production in cardiomyocytes is markedly elevated, and antioxidant defense capacity is overwhelmed, leading to lipid peroxidation of mitochondrial membranes and damage to

mtDNA, further aggravating mitochondrial dysfunction. Clinical studies indicate that ROS levels in the serum and myocardial tissue of CHF patients correlate positively with the severity of cardiac dysfunction, suggesting that oxidative stress is a critical driver of CHF progression [32].

Experimental studies have characterized mitochondrial dysfunction in CHF at the molecular and cellular levels. In mouse models of heart failure, activities of mitochondrial respiratory chain complexes are significantly reduced, indicating impaired mitochondrial function and insufficient energy generation. ROS are central in this pathological process: mitochondrial abnormalities increase ROS production, which in turn exacerbates oxidative damage and apoptosis in cardiomyocytes. In a mouse heart failure model exposed to high-fat conditions and in H9c2 cardiomyocytes stimulated with palmitic acid, phosphorylated adenosine 5'-monophosphate (AMP)-activated protein kinase (p-AMPK) and peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) were downregulated; apoptotic signaling was activated; mitochondrial ROS (mtROS) levels increased; and mitochondrial homeostasis was disrupted. Berberine treatment upregulated p-AMPK and PGC-1α, restored mitochondrial homeostasis, and reduced mtROS by modulating the AMPK/PGC-1α pathway [33].

Mitochondrial Ca^{2+} homeostasis has also received considerable attention in CHF models. Doxorubicin (ADR) administration in rats induced overactivation of Na^+/H^+ exchanger 1 (NHE1), increased intracellular Ca^{2+} levels, and activation of p38 and its downstream NHE1 signaling. Puerarin treatment reduced NHE1 activity and attenuated mitochondrial damage caused by Ca^{2+} overload by inhibiting p38 and its downstream signaling, thereby protecting the myocardium [34]. In addition, Ca^{2+} leakage from the sarcoplasmic reticulum causes mitochondrial Ca^{2+} overload, leading to a 60%–70% decrease in mitochondrial membrane potential and promotion of cardiomyocyte apoptosis. Ca^{2+} overload can also induce pathological hypertrophy by triggering mPTP opening and activating the Ca^{2+}/CaMKII/calcineurin pathway [35]. These findings suggest that regulating Ca^{2+} homeostasis may represent a promising therapeutic strategy in CHF.

4.3. Mitochondrial Dysfunction in CHF

Under physiological conditions, fatty acids are the primary substrates for mitochondrial OXPHOS in cardiomyocytes. In a healthy heart, ATP synthesis must match ATP consumption to sustain continuous contraction, because endogenous ATP reserves alone can only support cardiac activity for a short period [36]. In an energy homeostatic system, pathological remodeling, including structural changes, neurohormonal activation, and impaired Ca^{2+} handling, disrupts the balance between energy supply and demand, increasing energy consumption. Therapies that reduce cardiac energy expenditure, such as β-blockers and vasodilators, are supported by clinical evidence and improve survival, whereas positive inotropes, which increase energy demand, are associated with higher rates of MACEs. Various strategies have therefore been explored to improve ATP utilization efficiency. In failing hearts, high-energy phosphate content is often reduced. Levels of phosphocreatine (PCr), a key energy reserve, decrease, leading to a reduced PCr/ATP ratio [37]. Cardiomyocytes may attempt to utilize alternative substrates (e.g., glucose, amino acids, ketone bodies) to support ATP production, but due to mitochondrial dysfunction and reduced enzyme activity, oxidation efficiency remains limited, resulting in a state of "energy starvation". Over time, myocardial metabolism shifts from fatty acid oxidation toward glucose utilization to reduce oxygen consumption, which may temporarily reduce cardiac burden but ultimately accelerates functional deterioration and progression of heart failure, contributing to MACEs [38]. Thus, improving ATP regeneration efficiency, maintaining cardiomyocyte energy balance, and restoring normal energy conversion pathways are key goals in end-stage heart disease treatment. Overall, mitochondrial dysfunction can lead to CHF *via* five major mechanisms (Fig. 3).

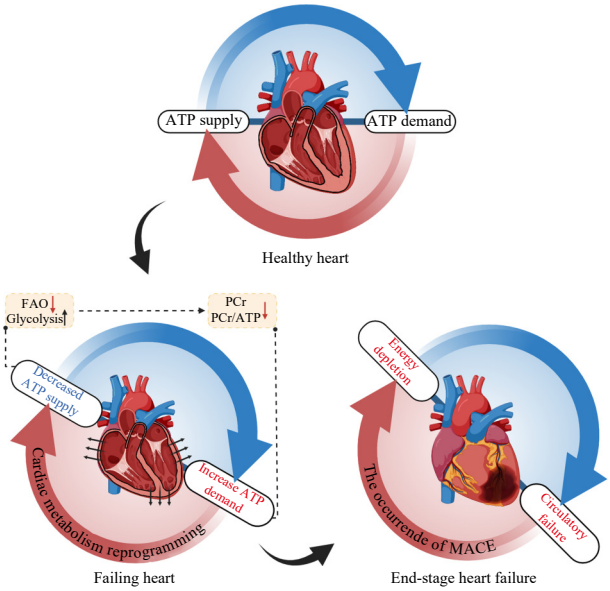

Fig. 3 Energy supply and demand balance and the progression of chronic heart failure.

4.3.1. MtROS and disordered energy metabolism

MtROS play a critical role in CHF pathogenesis. Mitochondria are the central hub of energy metabolism in cardiomyocytes, where ATP is generated *via* OXPHOS to maintain contraction, ionic balance, and signal transduction. Under normal conditions, small amounts of ROS generated during ATP production serve physiological signaling roles, and antioxidant systems, such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), maintain redox homeostasis [39]. In heart failure, however, ROS production exceeds clearance capacity under stressors such as inflammation and hypoxia, resulting in oxidative stress and extensive cardiac injury, which in turn exacerbates mitochondrial oxidative damage [40]. Moreover, excessive generation of ROS can cause oxidative damage to mitochondrial DNA, lipids, and proteins, compromising mitochondrial structure and function and subsequently diminishing the efficacy of mitochondrial ATP synthesis. Furthermore, as oxidative stress aggravates, the resulting mitochondrial dysfunction can induce cardiomyocyte apoptosis or necrosis and trigger an inflammatory response, such as a disturbance in inflammatory factors such as interleukin-1β, 2,6 (IL-1β, IL-2, and IL-6). ROS not only directly damages cardiomyocytes but also activates various signaling pathways, such as PI3K/AKT, NF-κB, and MAPK pathways, which regulate the antioxidant response, cell cycle, and apoptosis, further aggravating structural and functional abnormalities [41]. Myo-inositol, an endogenous metabolite, is significantly elevated in the plasma of heart failure patients. Myo-inositol enters cardiomyocytes *via* the sodium myo-inositol cotransporter 1 and may activate NADPH oxidase 2, leading to increased ROS production, mitochondrial dysfunction, and cell death [42]. Persistent cell death and inflammation drive fibrotic remodeling, ultimately resulting in ventricular remodeling and progressive loss of cardiac function. Mitochondria are at the heart of energy metabolism in cardiomyocytes, and their main function is to provide ATP *via* OXPHOS to maintain myocardial contraction, ionic homeostasis, and signal transduction. The primary energy sources for the heart are glucose, fatty acids, and ketone bodies. Due to the heart's limited ability to retain these energy

substrates intracellularly, they must be perpetually sourced from the bloodstream. Approximately 40%–60% of mitochondrial ATP is derived from fatty acid oxidation, with the remainder produced from the oxidation of amino acids, ketone bodies, and pyruvate (derived from glucose and lactate) [43]. Fatty acids are normally esterified to create fatty acyl-CoA after being absorbed by cardiomyocytes. Enzymes like carnitine palmitoyl transferase 1 and 2 (CPT-1 and CPT-2) subsequently convert fatty acids to carnitine to create long-chain acylcarnitine, which is then delivered to the mitochondria. Beta-oxidation is a cyclic process consisting of four recurring enzymatic reactions that break down fatty acyl-CoA in the mitochondrial matrix. In each cycle, removal of a two-carbon unit generates acetyl-CoA, which enters the TCA cycle to produce NADH and $FADH_2$, thereby driving oxidative phosphorylation and promoting the conversion of ADP to ATP in the presence of oxygen. Peroxisome proliferator-activated receptor alpha (PPARα) is a key regulator of lipid metabolism. In failing hearts, PPARα expression is reduced. Activation of PPARα can increase expression of CPT-1 and long-chain acyl-CoA dehydrogenase and modulate substrate preference, thereby influencing mitochondrial fatty acid uptake and oxidation [44]. Glucose is transported into cardiomyocytes *via* GLUT1 and GLUT4 and then metabolized through glycolysis to pyruvate. Pyruvate is converted by pyruvate dehydrogenase (PDH) to acetyl-CoA, which enters the TCA cycle and supports ETC function and ATP production. Ketone bodies also serve as important energy substrates, especially in heart failure. Mitochondrial dysfunction in visceral adipose tissue, manifested as decreased *β*-oxidation, reduced TCA enzyme activity, and disrupted lipid metabolism, can worsen systemic insulin resistance and compromise cardiac energy supply *via* circulating lipids and inflammatory mediators such as FGF-21 and adiponectin, thereby contributing to CHF [45]. PGC-1α and AMPK are critical regulators of mitochondrial biogenesis and energy metabolism. PGC-1α promotes mitochondrial DNA transcription and replication *via* interactions with transcription factors such as PPARs and NRF-1, increasing mitochondrial mass and function. AMPK, activated when the ATP/AMP ratio falls, phosphorylates and activates PGC-1α, thereby indirectly promoting mitochondrial biogenesis [46]. From this perspective, a core pathway for TCM improvement of CHF involves regulation of mitochondrial ROS and energy metabolism.

Several TCM preparations have been reported to mitigate mitochondrial ROS and improve ATP synthesis. Di'ao Xinxuekang Capsule [47], Shenyuandan Capsule [48], liquiritin [49], and Huoxin Pill [50] reduce ROS production in cardiomyocytes, enhance mitochondrial ATP generation, increase SOD, GSH-Px, and glutathione reductase (GR) activities, upregulate HIF-1α, and downregulate NF-κB p65, thereby repairing myocardial injury and treating CHF. Regarding oxidative stress–related genes, Longshengzhi Capsule [51] and steroidal saponins [52] inhibit doxorubicin-induced apoptosis, reduce inflammatory cytokines, and modulate SOD1, SOD2, peroxidase, and GSH-Px to rebalance oxidative stress. In left anterior descending (LAD)-induced HF and OGD/R-induced H9c2 models, ginsenoside Rb_3 protected cardiac function by activating the PPAR–RXRα pathway, inhibiting OGD/R-induced ROS production, upregulating RXRα and SIRT3, and increasing intracellular ATP levels [53]. Several studies have demonstrated the potential of traditional Chinese medicine formulation and compounds to relieve oxidative stress to protect cardiac function. Luhong formula reduced ROS levels by inhibiting HIF-1α in a rat post–myocardial infarction heart failure model [54]. In Ang II-stimulated human cardiac fibroblasts, salsolinol modulated the STAT3/Notch1 pathway, decreased TNF-α and IL-6, and reduced ROS [55]. Other interventions, including Shexiang Baoxin Pill [56], Zhenwu Decoction [57], *Panax ginseng* [58], HuoXin Pill (HXP) [59], Tongxinluo [60], exert anti-oxidative effects *via* PI3K/AKT signaling. Baoyuan Decoction [61], Yiqi Fumai [62], Guanxintai [63], and vaccarin [64] attenuate oxidative stress by modulating the p38 MAPK pathway. These findings are summarized in Fig. 4 and Supplementary Table 2.

In vivo and *in vitro* CHF models studies and RNA-seq data analysis have found that Qiangxin Formula can activate the transcription factor recombinant kruppel-like factor 5, intestinal (KLF5), upregulate the expression of hexokinase2 (HK2), GLUT1, and GLUT4, which are key enzymes in glucose metabolism, and ultimately promote glucose metabolism. These regulated mechanisms may contribute to improving mitochondrial metabolism disorders [65]. Other studies have shown that Xinbao Pill [66], Linggui Zhugan Decoction [67], Yangxinshi Tablet [68], Shengxian Decoction [69], and Shengmai Injection [70] can regulate glucose metabolism and lipid-acid imbalance and control the balance of glucose and lipid metabolism (Fig. 4 and Supplementary Table 2).

4.3.2. Mitochondrial calcium disorder

Disturbances in Ca^{2+} are central to CHF pathophysiology. Under normal conditions, mitochondria regulate calcium influx and efflux to maintain intracellular Ca^{2+} balance, support energy metabolism, and sustain OXPHOS and myocardial contractility. [71]. In CHF, prolonged hemodynamic overload, ischemia, and inflammation impair mitochondrial Ca^{2+} handling, leading to either excessive accumulation or insufficient Ca^{2+} in the mitochondrial matrix. In heart failure, increased SR Ca^{2+} leak *via* ryanodine receptors and reduced SR Ca^{2+} reuptake (e.g., diminished SERCA2a function) decrease cytosolic Ca^{2+} transients and alter excitation–contraction coupling. The mitochondrial Ca^{2+} uniporter (MCU) mediates Ca^{2+} influx into the matrix, positively regulating three Ca^{2+}-dependent TCA cycle enzymes (pyruvate dehydrogenase, isocitrate dehydrogenase, and *α*-ketoglutarate dehydrogenase) and thereby sustaining ATP synthesises [72]. Under pathological conditions, however, excessive mitochondrial Ca^{2+} uptake promotes mPTP opening, leading to loss of membrane potential and cell death. Ca^{2+} may play a part in the development of heart failure and is necessary for the control of mitochondrial activity. Constructing a CHF model in C57BL/6J mice through *in vivo* thoracic aortic constriction, ventricular myocytes were isolated from the hearts of C57BL/6J mice by Langendorff crossflow perfusion system. the studies showed that stachydrine hydrochloride can improve cardiac function and calcium transient amplitude, inhibit SR leakage and the number of electrical sparks, and block excessive phosphorylation of CaMKII, RyR2, and PLN [73]. In a rat model of CHF induced by LAD and cell hypoxia of 24-hour oxygen glucose deprivation (OGD), Yiqi Fumai Powder injection was shown to downregulate the expression of calcium voltage-gated channel subunit α1C (CACNA1C) and the phosphorylation of calmodulin-dependent protein kinase II (p-CaMKII), regulate the opening of mPTP, inhibit ROS production and CaMKII signaling pathways [74]. Other TCM interventions, including Qiangxinyin Formula [75], Jin-Xin-Kang [5], AACO Formula [76], Qishen Granule [77], and tanshinone IIA [78], have been shown to block calcium influx, increase Ca^{2+} reuptake rate, and alleviate mitochondrial dysfunction in CHF myocardium (Fig. 4 and Supplementary Table 2).

4.3.3. Mitochondrial dynamics and mitophagy

Mitochondrial dynamics is the process by which mitochondria dynamically regulate their morphology and function through continuous fusion and fission. It is essential for cellular metabolism, energy generation, and signal transduction [79]. Mitophagy is a specialized autophagy pathway that selectively removes damaged mitochondria, thereby maintaining mitochondrial quality and functional integrity. Fusion facilitates content mixing and repair of minor damage, whereas fission segregates severely damaged segments for autophagic clearance. Key proteins such as Drp1 and the receptor FUNDC1 can activate mitophagy signaling. Defects in autophagy lead to the accumulation of damaged mito-

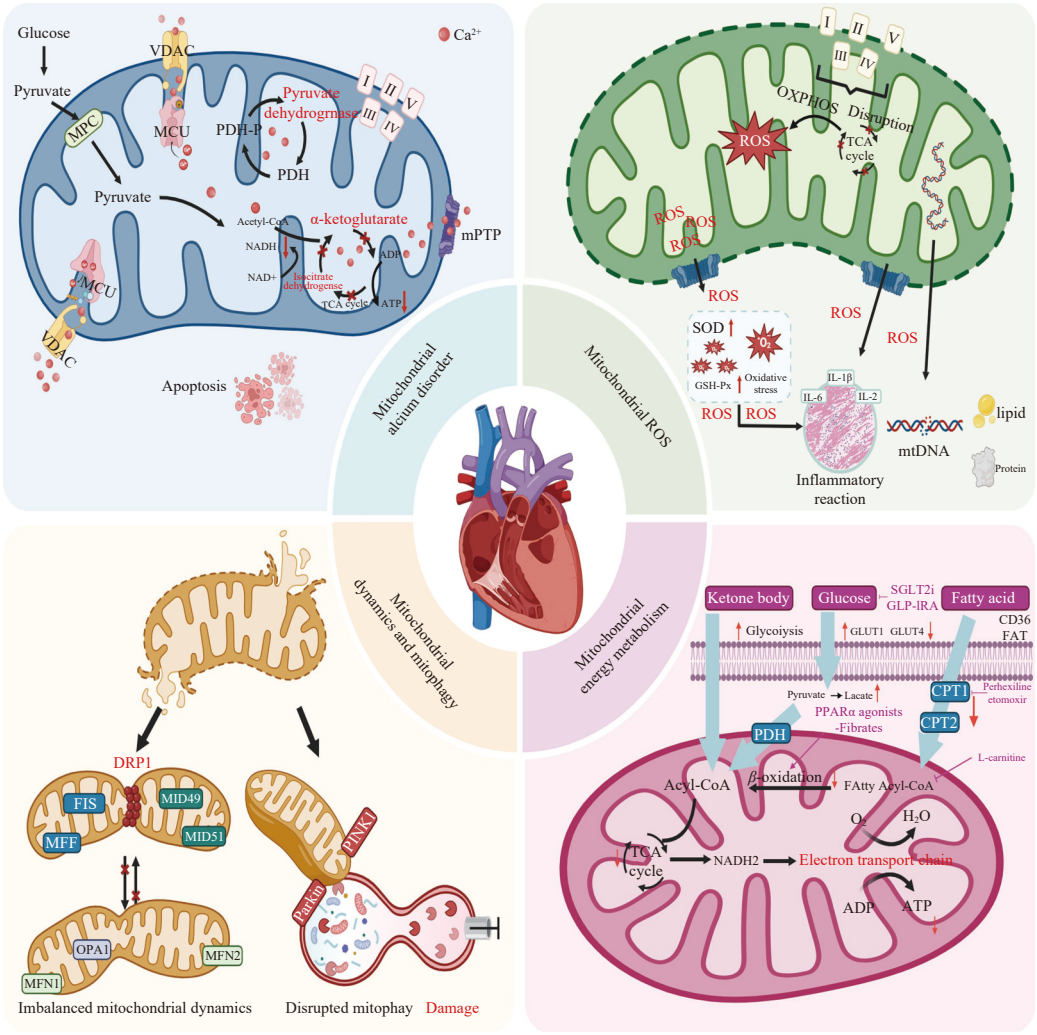

Fig. 4 Chronic heart failure due to mitochondrial dysfunction.

chondria, disrupting energy metabolism and cell survival. In CHF, mitochondrial dysfunction and dynamic imbalance are major contributors to abnormal energy metabolism. Under physiological conditions, fusion proteins such as OPA1, MFN1, and MFN2 preserve mitochondrial network integrity and functional stability, enabling mtDNA sharing and repair. Fission proteins including Drp1 and Fis1 promote mitochondrial division and distribution, helping isolate damaged organelles [30]. In CHF, persistent stressors such as oxidative stress and energy deficiency disrupt this balance. Overactivation of fission causes mitochondrial fragmentation, loss of membrane potential, and increased apoptosis and necrosis, whereas downregulation of fusion proteins impairs network function and metabolic adaptability [80]. Restoring the fusion–fission equilibrium and mitochondrial quality may thus represent a novel therapeutic approach. For example, Mdivi-1 (Drp1 inhibitor) significantly reduced mitochondrial fragmentation and cardiomyocyte death in animal models, while upregulation of Mfn2 expression by gene editing increased mitochondrial network stability. Under normal circumstances, cardiomyocytes can maintain mitochondrial quality and function through mitophagy. When mitochondria are damaged by oxidative stress, calcium overload, or other metabolic disorders, damaged mitochondria are recognized by specific marker molecules such as microtubule-associated protein light chain 3 (LC3), autophagy-related gene 7 (ATG7), and p62, and are transported into autophagosomes, where they are then degraded by lysosomes [81, 82]. This process removes dysfunctional mitochondria and supports renewal of healthy organelles. In CHF, mitophagy is often impaired. Decreased mitophagic activity leads to accumulation of damaged mitochondria and progressive decline in cardiac function [83]. PINK1/Parkin and mTOR are key regulatory pathways in mitophagy. Following mitochondrial depolarization, PINK1 accumulates on the outer membrane and recruits the E3 ligase Parkin to ubiquitinate mitochondrial proteins, thereby labeling damaged mitochondria and recruiting adaptor proteins such as OPTN, CALCOCO2, and p62 for autophagic degradation [84]. mTOR integrates energy and nutrient signals: under energy-sufficient conditions, mTORC1 inhibits Unc-51-like kinase 1 (ULK1) and suppresses autophagosome formation. Under nutrient deprivation or energy deficiency, reduced mTORC1 activity releases ULK1 inhibition and activates autophagy, promoting clearance of damaged mitochondria [85]. Dysregulated mitophagy thus exacerbates mitochondrial dysfunction and contributes to cardiac pathology.

Several TCM interventions modulate mitochondrial dynamics and mitophagy in CHF models. In LAD-induced CHF rats and OGD/R-injured cardiomyocytes, Shenqi Lixin reduced myocardial injury, increased PGC-1α, Mfn2, and Opa1 expression, and inhibited Drp1 and Fis1 [86]. Similarly, in the heart failure model induced by LAD, ShengmaiSan mitigates mitochondrial-dependent cardiomyocyte death *via* the Ca^{2+}/Drp1 signaling pathway and enhances mitochondrial function by elevating mitochondrial membrane potential and cellular ATP levels [87]. Meanwhile, Qili Qiangxin inhibits H_2O_2-induced mitochondrial fragmentation, mitochondrial permeability transition pore (MPTP) opening, and mitochondrial membrane potential (MMP) decrease, thereby ameliorating oxidative stress-induced mitochondrial-dependent

apoptosis of cardiomyocytes， and it can improve the cardiac function and attenuate oxidative stress-induced myocardial apoptosis of rats with heart failure induced by LAD [88]. In a TAC model, JinXinKang combined with the Drp1 inhibitor Mdivi-1 had synergistic effects on reversing ventricular remodeling and improving mitochondrial structure and function [5]. In the future, these precision treatment strategies based on mitochondrial dynamics are expected to become a new therapy for CHF (Fig. 4 and Supplementary Table 2).

In terms of mitophagy regulation, epirubicin-treated rats receiving Xinmailong (XML) injection for 14 days exhibited inhibited Beclin1 and ATG7 accumulation through upregulation of PI3K/AKT and inhibition of p38 MAPK and ERK1/2 phosphorylation [89]. In CHF models induced by doxorubicin, CLP, or LAD, Yangxinxue granule [90], Poge Jiuxin decoction [91], and Nuanxinkang [84] can improve mitochondrial function and structure by regulating the PINK1/Parkin pathway signal pathway to promote ATP synthesis and reduce the expression of autophagy-related molecules to treat CHF. Meanwhile, tanshinone IIA [92], Qili Qiangxin Capsule [93], Yangxinkang Tablet [94], and oridonin [95] all inhibit excessive autophagy *via* the AMPK/mTOR pathway and regulate key autophagy markers (LC3-II, ATG7, p62), thereby protecting cardiomyocytes and improving cardiac structure and function in CHF. In addition, pretreatment studies with ROS modulators showed that Luhong formula inhibited excessive autophagy by reducing intracellular ROS [54] (Fig. 4 and Supplementary Table 2).

5. Conclusion and perspectives

CHF is fundamentally a bioenergetic disease arising from an inability to compensate for multifactorial cardiac injury. Current Western medical therapies primarily alleviate symptoms and improve prognosis but are limited by side effects and the need for long-term treatment adherence. TCM offers advantages in individualized, holistic, and multi-target regulation. However, its efficacy and safety are highly dose-dependent. For example, low-dose astragaloside IV (e.g., < 25 $mg \cdot kg^{-1}$) does not significantly enhance mitochondrial biogenesis, whereas high-dose (> 100 $mg \cdot kg^{-1}$) can ameliorate septic cardiomyopathy by modulating mitochondrial homeostasis [96]. Herb–drug interactions also require careful evaluation: Salvia miltiorrhiza combined with warfarin increases bleeding risk; *Pausinystalia yohimbe* with tricyclic antidepressants elevates hypertension risk; and *Panax ginseng* with mixed antidepressants may precipitate manic episodes [97]. These examples underscore the need for precise dosing and interaction screening in TCM practice. Subtherapeutic doses may lack efficacy, whereas excessive doses risk toxicity. Future research should therefore emphasize standardized dose ranges for key TCM components based on pharmacokinetic–pharmacodynamic (PK–PD) modeling and rigorously designed clinical trials.

The "energy factories" of cells are called mitochondria. The role of mitochondria in heart failure has drawn much attention lately. Its dysfunction directly leads to insufficient energy supply to cardiomyocytes, which is a key pathologic link in the development of CHF. Compared with other mechanisms (e.g., inflammation, oxidative stress, fibrosis, etc.), mitochondrial dysfunction is an early event in CHF, and the improvement of mitochondrial function not only relieves the symptoms of CHF at an early stage, but also delays the progression of the disease. For example, by enhancing mitochondrial biosynthesis and kinetics, the energy supply and functional stability of cardiomyocytes can be maintained in the long term. In addition, mitochondria not only maintain energy homeostasis, but also regulate various physiological processes such as apoptosis, oxidative stress, and calcium homeostasis. Therefore, regulating mitochondrial disorders can improve the energy metabolism of cardiomyocytes from the source and has more direct therapeutic implications. TCM's Qi and Essence theories show similarities to mitochondrial functions, which has sparked much interest in both scientific and clinical studies. This study consolidates information from human and animal models of heart failure, demonstrating that TCM can rectify defective mitochondria through the modulation of mitochondrial Ca^{2+} homeostasis, oxidative stress, energy metabolism, mitochondrial dynamics, and mitochondrial autophagy. Pharmacological targets of TCM for mitochondrial regulation are described, and beneficial effects on cardiac performance are discussed.

Looking forward, several directions merit emphasis: For elderly patients, Qi-tonifying herbs (such as Astragalus membranaceus) may be prioritized, whereas women may benefit from additional blood-nourishing agents (such as Angelica sinensis). For patients with comorbidities, appropriate combination therapies should be carefully evaluated for optimum outcomes. For CHF patients with diabetes or hypertension, herbal medicines with metabolic regulation effects (such as *Coptis chinensis*) or blood activating and stasis removing drugs (such as *Salvia miltiorrhiza*) can be used together, while avoiding interaction with western medicines (such as ginseng should be used with anticoagulants). In terms of stage-based intervention, treatment of mild to moderate heart failure should primarily focus on tonifying Qi and promoting blood circulation (e.g., Shengmai San), whereas in advanced or severe heart failure, these principles should be combined with strategies to promote diuresis and reduce edema (e.g., *Poria cocos* and *Alisma*), with dynamic dose adjustment to balance efficacy and safety. In addition, for evidence-based stratification, subgroup analyses (such as by NYHA class or biomarker levels) are recommended to evaluate differential therapeutic effects of specific prescriptions across patient subgroups and thereby promote more precise TCM practice.

This review also introduces several novel aspects compared with previous work: 1) It is, to our knowledge, the first to systematically explore CHF treatment with TCM specifically from the perspective of mitochondrial dysfunction. 2) It integrates clinical evidence on TCM decoctions, injections, and adjunct therapies in CHF. 3) It provides a comprehensive summary of mitochondrial dysfunction in CHF and the multi-level benefits of TCM intervention from whole-animal to cellular studies. Nonetheless, important limitations remain: 1) Clinical research on TCM targeting mitochondrial dysfunction is still limited; most evidence derives from animal and cellular studies. 2) Many studies focus on specific mitochondrial functions, with relatively less emphasis on mitochondrial ultrastructure and morphology. 3) Differences in international regulatory frameworks restrict the global application of TCM. 4) Health policy and cultural barriers hinder broader dissemination and acceptance. Based on the above shortcomings, it is suggested that future research focus on the following aspects: 1) It is recommended to conduct a multicenter, randomized, double-blind, placebo-controlled clinical trial that includes a large sample of NYHA II-III grade CHF patients. The primary endpoints may be LVEF, NT proBNP levels, and 6-minute walking distance to evaluate the effect of TCM on mitochondrial function markers (such as ATP content and ROS levels). The course of treatment should be at least 6 months, and the incidence of cardiovascular events should be followed up for 1 year. 2) For patients with heart failure complications, such as diabetes patients with heart failure (HbA1c ≥ 7%), through cardiac magnetic resonance combined with myocardial biopsy, the dynamic changes of mitochondrial ultrastructure (such as electron microscopic observation of ridge morphology, mitochondrial volume density) after the intervention of TCM may be analyzed, and the expression level of targets was correlated to clarify the therapeutic mechanism of specific populations. 3) Using single-cell RNA sequencing to analyze the expression profile of mitochondrial-related genes (such as PINK1 and Parkin) in peripheral blood mononuclear cells of heart failure patients, combined with or-

ganoid models, screening for Chinese herbal monomers that can activate related pathways, and further verifying their cardioprotective effects in animal models. 4) The plant equivalence method using LC-MS/MS fingerprinting combined with bioactivity determination enhances the evidence chain between TCM theory and modern medicine, and improves cross-cultural adaptability. 5) Development of cross-cultural diagnostic mapping for the WHO International Classification of Traditional Medicine can support regulatory approval of TCM products by agencies such as the U.S. FDA and EMA. 6) Cross-border collaborations should be encouraged to advance evidence-based TCM research and develop clinical practice guidelines that account for cultural differences and regulatory environments.

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Supporting information

Supplementary data associated with this article can berequested by sending E-mail to the corresponding authors.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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