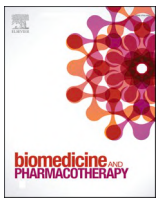
Biomedicine & Pharmacotherapy 164 (2023) 114999

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Review

Cardiovascular disease treatment using traditional Chinese medicine : Mitochondria as the Achilles' heel

Jie Gao, Tianshu Hou *

Chengdu Integrated TCM and Western Medicine Hospital and Chengdu University of Traditional Chinese Medicine, Chengdu 610041 China

ARTICLE INFO

Keywords:
Cardiovascular disease (CVD)
Mitochondria
Oxidative stress
Traditional Chinese medicine (TCM)

ABSTRACT

Cardiovascular disease (CVD), involving the pathological alteration of the heart or blood vessels, is one of the main causes of disability and death worldwide, with an estimated 18.6 million deaths per year. CVDs are caused by a variety of risk factors, including inflammation, hyperglycemia, hyperlipidemia, and increased oxidative stress. Mitochondria, the hub of ATP production and the main generator of reactive oxygen species (ROS), are linked to multiple cellular signaling pathways that regulate the progression of CVD and therefore are recognized as an essential target for CVD management. Initial treatment of CVD generally focuses on diet and lifestyle interventions; proper drugs or surgery can prolong or save the patient's life. Traditional Chinese medicine (TCM), a holistic medical care system with an over 2500-year history, has been proven to be efficient in curing CVD and other illnesses, with a strengthening effect on the body. However, the mechanisms underlying TCM alleviation of CVD remain elusive. Recent studies have recognized that TCM can alleviate cardiovascular disease by manipulating the quality and function of mitochondria. This review systematically summarizes the association of mitochondria with cardiovascular risk factors, and the relationships between mitochondrial dysfunction and CVD progression. We will investigate the research progress of managing cardiovascular disease by TCM and cover widely used TCMs that target mitochondria for the treatment of cardiovascular disease.

1. Introduction

Cardiovascular disease (CVD), a kind of disease that affects the heart or blood vessels, causes poor survival prognosis and high economic costs [1]. It mainly includes coronary artery disease (CAD), hypertension, cardiomyopathy, heart failure, atherosclerosis, dyslipidemia, hyperglycemia, strokes and transient ischemic attack, and other related diseases [2]. The progression of CVD is usually associated with an increase in blood clots and fatty deposits inside the arteries (atherosclerosis). It can also be involved in damage to arteries in organs [3]. Therefore, many CVDs are accompanied by a series of irreversible damages that lead to organic and vascular complications. Most CVD affects older adults, the older group with the higher incidence rate [4]. CVD might be caused by a variety of risk factors that elicit severe oxidative stress, such as smoking, excessive drinking, lack of exercise, poor diet, obesity, and poor sleep [5]. Moreover, high blood pressure, high blood cholesterol, and diabetes mellitus are intrinsically associated with CVD [6] (Fig. 1). CVD may be preventable and treatable via proper diet and lifestyle interventions. Agents such as aspirin, ACE inhibitors, beta-blockers, statins and antibiotics, and surgical or procedural interventions can save someone's life or prolong it [7,8]. Regarding surgical interventions, replacing the valve is a first option for heart valve problems, a pacemaker can help reduce abnormal heart rhythms for arrhythmias, and coronary angioplasty and coronary artery bypass surgery are two strategies for a heart attack [9]. Nevertheless, CVD remains a serious threat to human health and simultaneously brings heavy social and economic burdens to the world. Therefore, it is very important to explore novel agents and new strategies for CVD management.

Mitochondria are highly dynamic organelles that generate adenosine triphosphate (ATP) and produce heat by driving electron transport chain (ETC)-coupled oxidative phosphorylation (OXPHOS). It is derived from bacteria and retains its own genome, which contains 13 polypeptide-encoding genes, 22 tRNA genes, and 2 rRNA genes. In addition, it is composed of the mitochondrial matrix, inner mitochondrial membrane, outer mitochondrial membrane, and intermembrane space [10]. Mitochondria act as signaling hubs by producing proper levels of reactive oxygen species (ROS) to modulate cellular movements when signals reach cellular components such as the membrane and the nucleus. They

* Corresponding author.
E-mail address: houtianshu@cdutcm.edu.cn (T. Hou).

https://doi.org/10.1016/j.biopha.2023.114999
Received 8 April 2023; Received in revised form 30 May 2023; Accepted 7 June 2023
Available online 11 June 2023

manage their number, morphology, quantity, and location to maintain cellular homeostasis and fitness to satisfy physiological needs according to different living environments. Under stress conditions, the homeostasis of mitochondria is disrupted, causing mitochondrial dysfunction and cell fate alteration, which is closely associated with the occurrence and development of many diseases, such as tumors, neurological diseases, and CVD [11]. Currently, a large body of evidence indicates that the occurrence and development of CVD are usually accompanied by mitochondrial dysfunction. Multiple aspects of mitochondria, including defects/mutations in mtDNA, mitochondrial ion channel dysfunction, and abnormities in mitochondrial structure and volume, can lead to dysfunction of mitochondria and are reported to be closely related to CVDs [12]. For example, a recent study reported that aging-elevated IL-6 and mitochondrial dysfunction upregulated the protein level of Parkin and associated mitophagy in the aorta to exacerbate atherogenesis upon acute hyperlipidemia [13]. In addition, dual-specificity tyrosine-regulated kinase 1B (DYRK1B) could drive cardiac hypertrophy and heart failure by directly binding with signal transducer and activator of transcription 3 (STAT3, regulator that mediates cellular responses to interleukins, KITLG/SCF, LEP and other growth factors) to impair mitochondrial bioenergetics [14]. Obviously, these emerging findings may provide new therapeutic options for CVD management.

Traditional Chinese medicine (TCM), a major component of the Chinese medical system, has been in use for over 2500 years. It is characterized by diagnosing diseases through inspection, auscultation, olfaction, inquiry, pulse-taking and palpation to investigate the "*Yin-Yang*" and "*Qi-Xue*" of patients [15] and curing diseases using a large number of herbal medicines, medicinal animal materials, medicinal minerals, or their extracts. In addition, several nonmedicine therapeutic strategies, including acupuncture, moxibustion, TuiNa (massage), Taichi and Gua Sha (skin scraping), have been widely applied to intervene in acupressure points or meridians [16]. TCM treatment modulates "multi-targets and multi-pathways" with their "multi-components", therefore realizing a holistic equilibrium and improvement of the whole body [17], rather than eliminating a specific lesion. Even though there are shortcomings, a good portion of patients chose TCM as their favorite [18], and most patients preferred the combination of Western medicine and TCM after having experienced Western medicine, TCM, or integrative medicine. In Western countries, TCM has also gradually become complementary or alternative medicine. Furthermore, TCM is increasingly applied in the prevention and treatment of multiple diseases in which huge unmet needs remain for disease control with Western medicine, including cancer and COVID-19, particularly CVD [19]. Intriguingly, multiple Chinese herbals and natural medicines could protect myocardial cells and endothelial cells by regulating mitochondria and related signaling pathways, thus benefiting CVD patients with limited side effects.

This review investigates the underlying molecular mechanisms involved in the progression of CVD from a mitochondria-centric perspective. We summarize recent findings on the pharmacological management of CVD by TCM based therapeutics, with an emphasis on their molecular actions on regulating mitochondria and related signaling pathways.

2. Cardiovascular disease resulting from mitochondrial dysfunction

While a proper level of reactive oxygen species (ROS) facilitates fine function of the cell, excessive levels of ROS cause oxidative stress [20], resulting in damage to cellular macromolecules and eventually apoptotic or necrotic cell death [21]. CVD, the most lethal disease worldwide, has been documented to be linked with excess production of ROS [22,23]. Increased ROS not only impair nitric oxide availability and vasoconstriction to promote arterial hypertension but also induce hypertrophic signaling or apoptosis to cause arrhythmia and augment cardiac remodeling [24]. In addition, ROS play a pivotal role in the development of atherosclerosis by promoting atherosclerotic plaque formation [25]. Mitochondria, the main drivers of intracellular ROS, can easily be affected by risk factors, including atherosclerosis, inflammation [26], hyperglycemia [27], and hyperlipidemia [28], leading to ROS overproduction and the death of smooth muscle cells (SMCs) and endothelial cells (ECs), thereby resulting in CVDs [29]. The homeostasis of mitochondria depends on the balance of a series of dynamic processes, including fusion and fission, mitophagy and mitochondrial biogenesis

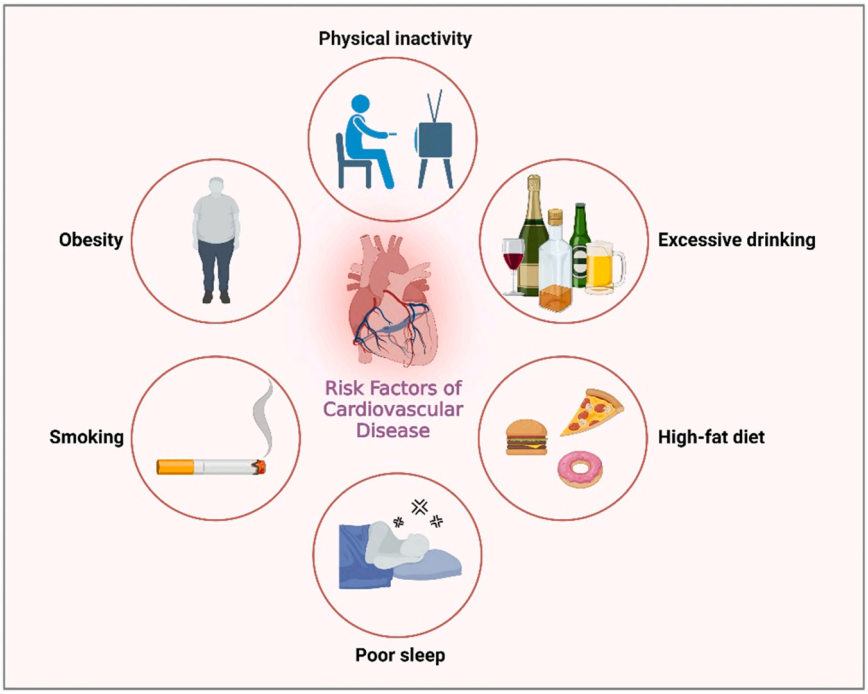


Fig. 1. Risk factors associated to cardiovascular disease. A variety of risk factors that elicit severe oxidative stress, such as smoking, excessive drinking, lack of exercise, poor diet, obesity, and poor sleep, are intrinsically associated with the progression of cardiovascular disease.

[30]. Recently, the association between mitochondria and other cellular organelles, mitochondrial-derived peptides, and mitochondrial trafficking/transfer have also been proven to play essential roles in maintaining cellular homeostasis [31]. In addition, disability in all aspects of mitochondrial DNA (mtDNA), including loss in copy number and mtDNA mutation/deletion, could inherently cause bioenergetic disorder [32]. Undoubtedly, these mitochondrial-related events are intrinsically related to the progression of CVDs.

2.1. mtDNA disorders and cardiovascular disease

Mitochondrial dysfunction may result from mtDNA disorders, including mtDNA damage, mutation/deletion, and loss in copy number [32,33]. These mtDNA disorders cause a broad spectrum of cardiovascular events. mtDNA lacks histones and has a minor capacity for repair and is thus particularly prone to oxidative damage (Fig. 2). Mitochondrial DNA damage can trigger a vicious cycle of ROS production and reduce the stabilization of an adequate ATP supply, thus leading to the development of CVDs [34,35]. For instance, proprotein convertase subtilisin/Kexin type 9 (PCSK9, acting to enhance the degradation of the hepatic low density lipoprotein receptor) was observed to cause mtDNA damage and activate NACHT, LRR and PYD domains-containing protein 3 (NLRP3, sensor component of the NLRP3 inflammasome that mediates inflammasome activation) inflammasome signaling, resulting in Caspase-1-dependent pyroptosis in HL-1 cardiomyocytes [36]. In addition, Knut H and his coworkers revealed that mtDNA damage connects to cardiac dysfunction by reducing NAD^+ levels and causing mitochondrial dysfunction. They demonstrated that high levels of cardiomyocyte mtDNA damage cause impaired activation of NAD^+-dependent SIRT3 in a transgenic model [37]. These results provide convincing evidence for the link between CVDs and mtDNA damage.

Mitochondrial DNA copy number (mtDNA-CN), the number of mitochondrial genomes in each mitochondrion, has long been regarded as a biomarker of mitochondrial function [38]. Levels of mtDNA-CN have been reproducibly associated with various diseases, especially age-related diseases such as cardiovascular disease, and it significantly impacted overall mortality [39]. For instance, lower baseline mtDNA-CN is reported to be relevant to incident CVD (including coronary heart disease, abdominal aortic aneurysm, and stroke). Furthermore, their study showed that mtDNA-CN may have a mediating effect on the association between T2D and CVD, since the total effect of T2D on future risk of CVD was reduced after controlling for mtDNA-CN [40]. Moreover, a study aimed to investigate the association between mtDNA-CN and peripheral arterial disease (PAD) showed that low mtDNA-CN relates to all-cause mortality in PAD patients with intermittent claudication [41]. Intriguingly, mtDNA-CN may influence CVDs through modification of nuclear DNA (nDNA) methylation, thus regulating the expression of nuclear genes. As reported by Christina A et al., over half of CpGs were linked to phenotypes that were associated with mtDNA-CN, including cardiovascular disease, coronary heart disease, and mortality. Additionally, experimental modulation of mtDNA-CN led to alterations in nDNA methylation and gene expression [42]. Together, these observations demonstrate that changes in mtDNA-CN may modulate human health and disease through finely regulated cell signaling.

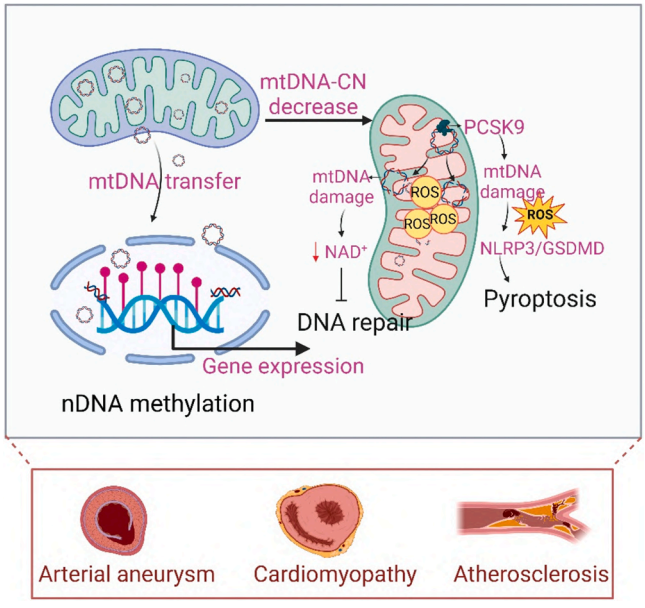


Fig. 2. mtDNA disorders are generally linked to cardiovascular disease. mtDNA disorders, including mtDNA damage, mutation/deletion, and loss in copy numbers, have been well demonstrated to cause cardiovascular disease.

Recently, mtDNA deletions/mutations have been considered potential disease markers. A study investigating 770 patients with known or suspected stable CAD revealed that two emerging hallmarks of aging, mitochondrial DNA deletion ($mtDNA^{4977}$) and leucocyte telomere length (LTL), have predictive value for adverse cardiovascular outcomes [43]. Although there is not much direct evidence showing the association between mtDNA mutation and CVD at present, a plethora of studies have shown that mtDNA mutation indirectly affects the progression of CVD or damages the cardiovascular system by regulating other diseases [44–46]. Further study on the associated dysfunction of mtDNA deletion/mutation may open new perspectives for CVD treatment [47].

2.2. Mitochondrial fusion/fission and cardiovascular disease

Mitochondria maintain homeostasis through dynamic fusion and fission [48,49]. Mitochondrial fusion is executed by mitofusin 1 and 2 (Mfn1/2) and optic atrophy 1 (OPA1) to achieve the exchange of intramitochondrial materials, whereas the fission process is mediated by dynamin-related protein 1 (Drp1) to produce multiple differently sized mitochondria, allowing the division of mtDNA and the isolation of damaged organelles [50,51]. Imbalances in mitochondrial fission and fusion cause disorders in mitochondrial morphology and function, damaging cardiomyocytes and thereby disturbing the structure and function of the heart, which is closely involved in the initiation and progression of cardiovascular diseases such as diabetic cardiomyopathy, septic cardiomyopathy, and ischemia—reperfusion injury (IRI) [52]. The robust evidence demonstrating the critical role of mitochondrial fusion and fission in CVDs is that aberrance in the expression of related proteins results in the development of a cardiovascular disorder [11,53,54] (Fig. 3).

Several other molecules and signaling pathways can also influence the occurrence and progression of CVD by directly or indirectly regulating mitochondrial dynamics. For instance, miR-34a-3p regulated epigenetic dysregulation of MiD49 and MiD51, two classical Drp1 binding partners, was found to increase Drp1-mediated mitotic mitochondrial fission and promote pulmonary arterial hypertension (PAH), thus providing new therapeutic targets for PAH [55]. In addition, DNA-dependent protein kinase catalytic subunit (DNA-PKcs) was demonstrated to promote cardiac IRI by disturbing BI-1-mediated mitochondrial homeostasis. Ablation of DNA-PKcs could counter cardiac ischemia reperfusion (IR)- or hypoxia-reoxygenation (HR)-elevated oxidative stress that results from mPTP opening, mitophagy failure and mitochondrial apoptosis [56]. Furthermore, Chen et al. found that in a hypoxia/reoxygenation (H/R) model, ROS could stimulate JNK-governed mitochondrial fission via Drp1 phosphorylation. Reduction of ROS induces mitochondrial fission to preserve mitochondrial function under H/R injury. Further results indicated that H/R injury induced damage in endothelial cells through the ROS-JNK-Drp1 signaling pathway [57]. Wang et al. found that the nuclear factor of

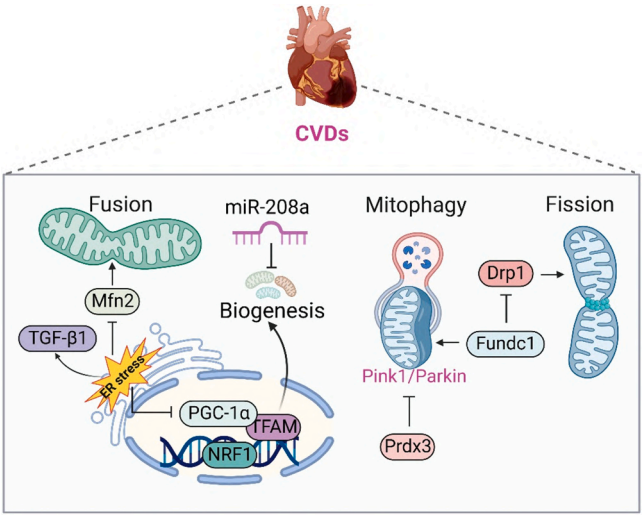


Fig. 3. Mitochondrial dynamics and cardiovascular disease. Imbalances in mitochondrial fusion/fission and biogenesis/degradation disturb mitochondrial homeostasis and result in cardiovascular disease.

activated T-cells, cytoplasmic 3 (NFATc3, a regulator involves in the inducible expression of cytokine genes in T-cells) induces the expression of miR-153–3p to promote mitochondrial fragmentation in cardiac hypertrophy when suffering isoprenaline (ISO) insult. This signaling pathway represents a novel therapeutic target for the prevention and treatment of cardiac hypertrophy [58]. In a dilated cardiomyopathy (DCM) model induced by activation of Toll-like receptor 4 (TLR4, mediating the innate immune response to bacterial lipopolysaccharide (LPS)), fragments of mitochondria with damaged cristae in the ultrastructure were observed. Further study revealed that aggravation of aberrated mitochondria in the DCM model was mainly associated with OPA1 downregulation caused by TLR4-mediated TNF-α upregulation and ROS elevation. Taken together, these findings indicate that TLR4 activation induces OPA1 dysfunction to cause mitochondrial dynamic imbalance, which may contribute to the progression of DCM [59].

Notably, mitochondrial dynamics-regulated proteins can also participate in the progression of CVDs through cellular communication between adjacent cells. For instance, the role of Drp1 in macrophages, an essential player promoting various vascular diseases, was investigated, and the results indicated that macrophage Drp1 promotes macrophage-mediated inflammation to accelerate intimal thickening, suggesting macrophage Drp1 as a potential therapeutic target for vascular diseases [60]. Further investigations focusing on the role of mitochondrial fusion and fission and their regulators would facilitate the understanding of the molecular mechanisms underlying CVD progression and offer potential targets for CVD treatment.

2.3. *Mitochondrial biogenesis and degradation in cardiovascular disease*

In addition to fusion and fission, mitochondrial biogenesis and degradation are two other pivotal processes in the mitochondrial quality control (MQC) system. Dysfunctional mitochondria compromise ATP synthesis and generate excessive ROS. The timely biogenesis of healthy mitochondria and degradation of damaged mitochondria are of great importance for cardiovascular protection. Signals are transmitted to the nucleus for transcriptional upregulation of mitochondrial biogenesis-related genes when the mitochondrial network suffers damage [61], whereas degradation-related proteins are recruited to eliminate damaged mitochondria [62]. Impairment of the MQC system results in accumulation of abnormal mitochondria, which is one of the major contributors to the pathogenesis of multiple cardiac disorders [62]. Herein, this section provides an overview of the role of mitochondrial biogenesis and degradation in the progression of CVD (Fig. 3).

Mitochondrial biogenesis is elaborated by peroxlsome proliferator-activated receptor-γ coactivator-1α (PGC-1α)-regulated transcription of mitochondrial nuclear genes and mitochondrial transcription factor A (TFAM)-mediated mitochondrial transcription and translation, which replenishes healthy mitochondria to furnish OXPHOS and ATP production [63]. Abnormal expression of these proteins inevitably leads to mitochondrial dysfunction and is involved in cardiovascular disorders. Recently, endoplasmic reticulum (ER) stress, which generally occurs when protein unfolding or calcium handling fails, has been recognized as a pathogenic factor in cardiovascular diseases [64]. Further results suggested that ER stress induced connexin 43 (CX43) translocations to mitochondria by upregulating profibrotic factor transforming growth factor-β1 (TGF-β1) and downregulating mitochondrial biogenesis protein PGC-1a and mitochondrial fusion protein mitofusin-2 (MFN2), thereby eventually causing mitochondrial dysfunction. In addition, damage to mitochondrial metabolism contributes to the progression of cardiovascular disease. For example, it has been discovered that miR 208a inhibits mitochondrial biogenesis asscociated signaling pathway and respiratory properties when faced with metabolic challenges, offering a therapeutic target to encourage mitochondrial biogenesis in cardiovascular disease, including metabolic cardiomyopathy [65]. Furthermore, the results showed that nuclear respiratory factor 1 [Nrf1, transcription factor that activates the expression of the EIF2S1 (EIF2-alpha) gene] in the paraventricular nucleus (PVN) is linked to the onset of one-clip (2K1C)-induced hypertension and that Nrf1 knockdown in the PVN can reduce hypertension by promoting mitochondrial biogenesis and restoring the balance between superoxide production and removal [66]. Together, these results suggested that mitochondrial biogenesis and related regulators may be prospective targets for reducing the risk of CVD.

Mitophagy, the mainstream mitochondrial degradation pathway, is triggered to eliminate dysfunctional, damaged, and superfluous mitochondria to maintain a healthy mitochondrial population and participates in the pathological process of cardiovascular diseases [67]. Mitophagy receptors are essential for mitophagy signaling, and the most well-known pathway involves phosphatase and tensin homolog kinase 1 (PINK1)/E3 ubiquitin kinase (Parkin). Additionally, Bcl-2 E1B 19-kDa interacting protein 3 (BNIP3), BNIP3-like (BNIP3L, also known as NIX), Bcl2-like protein 13 (Bcl2-L-13), and FUN14 domain containing protein 1 (FUNDC1) are also reported to be involved in mitophagy. Deficiency in these mitophagy receptors and disruption in mitophagy signaling always cause disruption of mitophagy signaling and may result in the progression of CVD [68,69]. For instance, a lack of thioredoxin-dependent peroxide reductase (Prdx3, thiol-specific peroxidase that catalyzes the reduction of hydrogen peroxide and organic hydroperoxides) directly Nrf1causes heart failure through mitochondrial malfunction caused by a breakdown in PINK1/Parkin-mediated mitophagy. The role of Prdx3 in mitophagy regulation and mitochondrial oxidative stress removal clarifies the process of MQC and offers fresh information for creating a treatment plan for cardiovascular conditions linked to mitochondria [70]. By suppressing Drp1-mediated mitochondrial fission, ischemia preconditioning-triggered Fundc1-dependent mitophagy is necessary for ischemia preconditioning to provide renoprotection in ischemic acute kidney injury (AKI) [71]. Furthermore, tamoxifen-induced cardiac-specific Drp1 mutant mice accumulated damaged mitochondria and suppressed mitophagy. Suppressed mitophagy results in mitochondrial malfunction, which in turn promotes heart dysfunction and increases ischemia reperfusion vulnerability [72]. The modulation of the mitophagy pathway offers a potential therapeutic method for the management of CVD, and these observations described the molecular, functional, and prospective significance of mitophagy in the pathogenesis of CVD.

2.4. Mitochondria-derived peptides in cardiovascular disease

Short peptides with biological activity called mitochondria-derived peptides (MDPs) are encoded by mitochondrial DNA's tiny open reading frames (ORFs) [73]. Humanin (HN), MOTS-c, and SHLP1–6 are three types of MDPs that have been found to sustain mitochondrial function and cell viability under stress. As a result, they play a role in a variety of physiological processes and illnesses, including aging, senescence, inflammation, and carcinogenesis [73]. It is interesting to note that current research has demonstrated numerous methods by which MDPs contribute to pathogenic alterations in CVD [74]. MDPs often exert cardioprotective effects by inhibiting apoptosis, combating oxidative stress, protecting the endoplasmic reticulum from damage, and suppressing inflammatory responses [75] (Fig. 4). For instance, a significant aging-related drop in plasma levels of MDPs (such as HN, SHLP2, and mots-c) was observed, suggesting a link between the loss of MDPs and the deteriorating biological processes related to aging and age-related disorders [76]. HN has recently been implicated in the formation and progression of atherosclerosis, primarily through endothelial cell protection, oxidative stress reduction, and anti-inflammatory responses [77]. The endothelial cell layer of human arteries was also shown to express HN, and it has a cytoprotective impact against oxidized LDL-induced oxidative stress [78]. Additionally, MOTS-c was said to inhibit diet-induced obesity and insulin resistance by activating 5′-AMP-activated protein kinase catalytic subunit alpha-1 (AMPK, an energy sensor protein kinase that plays a key role in regulating cellular energy metabolism) and promoting the expression of its downstream glucose transporters (GLUTs) [79].

Accordingly, supplementation with these MDPs may protect ECs and myocardial cells from oxidative damage. A powerful analog of HN called HNG, for instance, has been shown to improve cardiac function by increasing left ventricular ejection fraction and maintaining post-ischemic left ventricular dimensions (end-diastolic and end-systolic). Mechanistically, HNG dramatically decreased Bcl-2-associated X (BAX) protein and B-cell lymphoma-2 levels and elevated endothelial nitric oxide synthase (eNOS) and AMPK phosphorylation in the heart (Bcl-2) [79]. For a better knowledge of the function and underlying mechanisms of MDPs in CVD, more thorough research is needed.

2.5. Other mitochondrial events in cardiovascular disease

In addition to the mitochondrial dynamics mentioned above, multiple newly reported mitochondrial events were observed to be associated with CVD progression (Fig. 5). For instance, the mitochondrial-associated endoplasmic reticulum (ER) membrane (MAM), the most thoroughly investigated membranous system, is in constant interaction with other intracellular organelles and has been proven to be crucial for maintaining mitochondrial function, including mitophagy and fission [80]. Recently, these membrane systems have also been reported to be involved in CVD processes [81]. Furthermore, the integrity of the mitochondrial membrane was also linked to CVD. It has been discovered that the low-density lipoprotein (LDL) subtype ApoE colocalizes with the mitochondrial voltage-dependent anion channel (VDAC) and induces enlargement of the mitochondria both *in vitro* and *in vivo*. Atherosclerosis and cardiovascular disorders are likely linked to this mitochondrial dysfunction caused by the opening of the mitochondrial permeability transition pore [82]. Herrington et al. used mass spectrometry to analyze coronary artery and aortic specimens from 100 autopsied young adults to investigate the human arterial proteome and proteomic characteristics. The findings indicated significant declines in the number of mitochondrial proteins in early atherosclerosis and identified a collection of plasma proteins that are highly predictive of coronary disease as defined by angiograms [83].

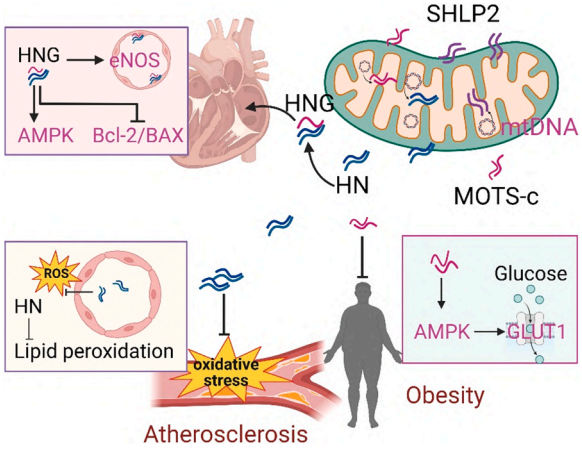


Fig. 4. Mitochondria-derived peptides protect cardiovascular cells from damage. Mitochondria-derived peptides have been recognized to maintain mitochondrial function and cell viability under stress conditions, thereby protecting endothelial cells and myocardial cells from damage.

In addition to being powerhouses within cells, mitochondria are released into the extracellular space in free form or contained in a carrier to act as intercellular signals and mediate cell-to-cell communication [83]. Extracellular mitochondria are emerging as a major regulator in the development of cardiovascular disease because they maintain the healthy operation of the heart. Recent research on the existence and types of mitochondrial transfer between cells, as well as the impacts of these mitochondria on vascular inflammation and ischemic myocardium, was summarized in a systematic review, leading to the conclusion that mitochondrial transplantation is a novel treatment paradigm for people with acute cardiovascular accidents [84]. Circulating cell-free nucleic acids (cf-NAs) have the potential to be a new noninvasive tool for the early identification of a variety of diseases because they are crucial for sustaining healthy physiological functioning and controlling the emergence of pathological changes [85]. The presence of cf-NAs in specimens, including cell-free genomic DNA, mtDNA, mRNA, miRNA, and long noncoding RNA in CVDs, is now well documented. They open up new possibilities for accurate diagnosis and therapy monitoring of CVDs because they are released in free, extracellular vesicle (EV)-encapsulated or protein-bound forms in an active, triggered or passive manner [86]. Extensive research on mitochondria-associated movement will be conducive to an in-depth understanding of the pathogenesis of CVD and facilitate CVD management by targeting mitochondria.

3. Targeting mitochondria by traditional Chinese medicine for cardiovascular disease management

Targeting mitochondria for the management of cardiovascular disease has garnered significant interest across the globe and has demonstrated excellent application prospects because of the essential role that mitochondria play in the development of cardiovascular disease [87, 88]. A plethora of agents [89], including aspirin, melatonin, leptin and so forth, have been reported to protect the cardiovascular system from oxidative damage through mitochondrial-related pathways. Due to the complex pathogenic mechanisms of cardiovascular diseases and the diminished efficacy of Western medicine, modes for treatment of CVD using modern medicine in combination with TCM have now been established as a main method in China and other countries, with TCM even dominating in some instances [90]. In this section, we discuss the most well-documented Chinese Herbal Medicines (CHMs) that have proven to be efficient against CVDs. Strategies that promote the delivery of TCM to mitochondria for targeting CVDs will be briefly introduced.

3.1. Chinese herbal medicines and their active ingredients

The properties of CHMs mainly depend on their active ingredients, which are generally categorized into polyphenols, flavonoids,

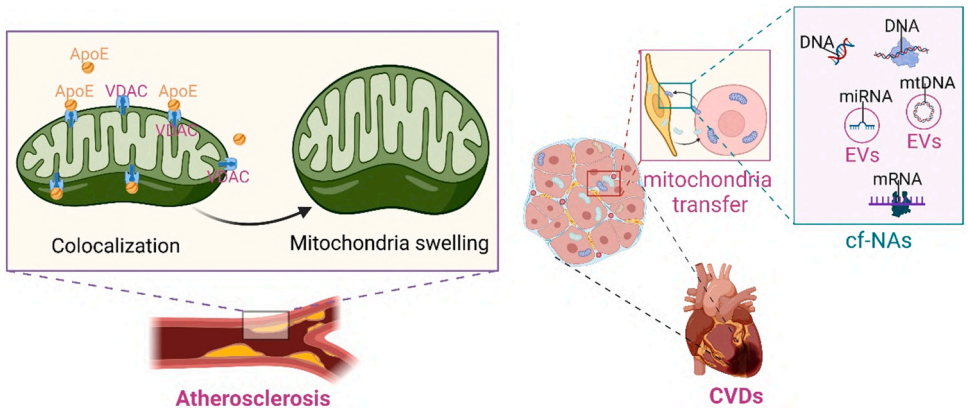


Fig. 5. Other mitochondrial events and cardiovascular disease. Several newly recognized mitochondrial events, including mitochondrial-associated endoplasmic reticulum (ER) membrane (MAM), mitochondrial membrane integrity, and mitochondrial transfer, have been observed to be associated with CVD progression.

polysaccharides, glycosides, diterpenoids, phenolic acids, saponins and so on [91]. Active ingredients of CHMs can confront CVD by maintaining the balance of vasoactive factors and calcium, removing free radicals, protecting mitochondrial functions to protect cardiomyocytes and promote angiogenesis (Fig. 6). At present, there are various types of CHMs used in CVD.

3.1.1. *Salvia miltiorrhiza (SM)*

Salvia miltiorrhiza (SM), also known as Danshen in Chinese, has a number of biological properties, including antioxidative stress, anti-inflammation, and antithrombosis, which make it a popular treatment for circulatory illnesses, including cardiovascular and cerebrovascular diseases [92]. According to prior research, the most common chemical classes in SM's bioactive components are hydrophilic phenolic acids and lipophilic terpenoids [93]. It is well recognized that the lipophilic diterpene tanshinone IIA, which is extracted from SM, is advantageous for cardiovascular health. According to research, pretreatment with tanshinone IIA shields H9c2 cells from anoxia-reoxygenation (A/R) damage by increasing the expression of 14–3–3 (Adapter protein that binds to and modulate the activity of a large number of partners) and promoting the translocation of apoptosis regulator Bcl-2 to the mitochondrial outer membrane, which prevents the opening of the mitochondrial permeability transition pore and lowers cytochrome c release and caspase-3 activation [94]. Tanshinone IIA can also stimulate the NAD-dependent protein deacetylase sirtuin-1/ Peroxisome proliferator-activated receptor gamma coactivator 1-alpha

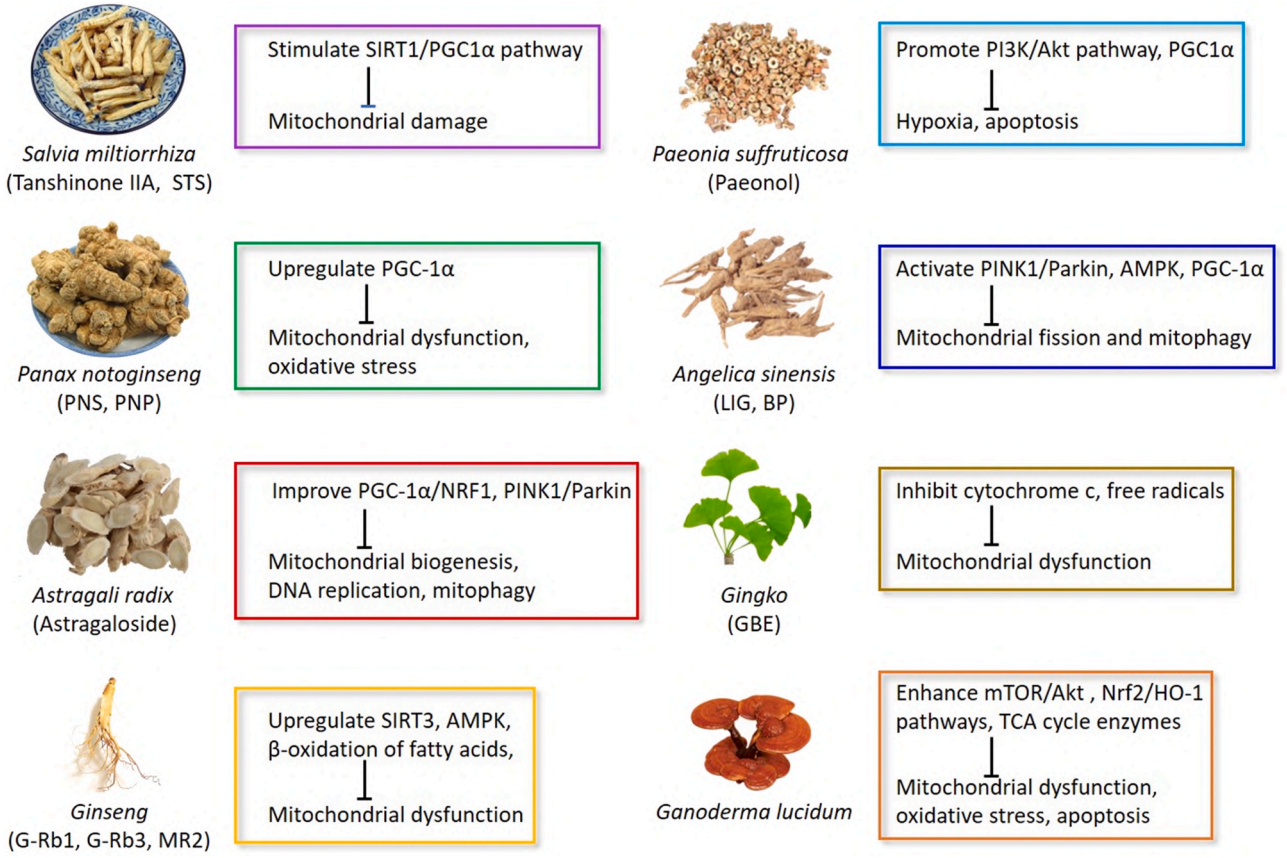


Fig. 6. Traditional Chinese medicine exhibits potential efficacy for cardiovascular disease by targeting mitochondria. A variety of Chinese herbal medicines and their active ingredients have been reported to protect the cardiovascular system from oxidative damage by regulating mitochondrial-related pathways.

(SIRT1/PGC1) pathway to inhibit mitochondrial damage, giving cardiac microvascular endothelial cells (CMECs) a survival advantage and protecting the structure and function of the microvascular system, according to research by Zhong et al. [95]. Notably, the mitochondria targeting group triphenylphosphine (TPP) developed a mitochondrion-targeting tanshinone IIA derivative that may reduce cardiac hypoxia reoxygenation injury by blocking SDH activity, reducing oxidative damage, and controlling ATP levels to maintain energy output [96]. Cardiovascular disorders are frequently treated with sodium tanshinone IIA sulfonate (STS), a water-soluble tanshinone IIA derivative. It is claimed to lessen the apoptosis caused by cigarette smoke in alveolar epithelial cells (AECs) by boosting the SIRT1 pathway and improving mitochondrial activity [97]. The maintenance of mitochondrial homeostasis and suppression of excessive generation of mitochondrial ROS in atherosclerosis by STS treatment also significantly reduced the overexpression of important proteins in aortic artery wall plaques and characteristic pyroptosis [98]. Several other active components of SM, such as salvianic acid (Danshensu) and ursolic acid, have also shown promising effects on protecting the cardiovascular system by modulating mitochondrial function [99,100]. These studies indicate that SM possesses robust cardiovascular health protective efficacy.

3.1.2. *Panax notoginseng*

In China, *Panax notoginseng* has a long history and is frequently utilized in clinical settings. In China, Panax notoginseng saponins (PNSs), a key active ingredient that has potent antioxidant benefits, are frequently utilized to treat cardiovascular conditions, including stroke [100,101]. It has a significant ability to reverse the downregulation of fork-head box O3a (FOXO3) and Mn-SOD, increase the expression of PGC-1 and mitophagy to lessen ROS-mediated oxidative damage, alleviate aging-related mitochondrial dysfunction and morphological changes in the rat myocardium, and inhibit the apoptosis of cardiomyocytes [102]. PNS also reduced lipotoxicity, controlled oxidative stress, and enhanced mitochondrial activity in diabetic mice, preventing the development of diabetic cardiomyopathy [103]. PNS also stopped the increase in cardiomyocyte apoptosis in aging rats, greatly improved the morphological alterations in the myocardium, and alleviated mitochondrial dysfunction-related aging in a dose-dependent manner [103]. Intriguingly, Li et al. discovered that Panax notoginseng polysaccharides (PNP), another active component of Panax notoginseng, had a protective effect on ischemia/reperfusion (I/R) injury in rats. This effect was primarily demonstrated by increasing brain tissue antioxidant capacity and inhibiting the excessive production of inflammatory cytokines [103]. Overall, *Panax notoginseng* reduced oxidative damage by regulating mitochondria function, sparing the cardiovascular system from harm.

3.1.3. *Astragali Radix*

Astragali Radix (AR) has historically been used by the Chinese for "Qi-invigoration" due to its tonic properties in strengthening biological tissues and promoting energy metabolism [104,105]. Huang et al. developed a systemic method using an extracellular flow analyzer to assess mitochondrial respiration in cultured H9C2 cardiomyocytes. The tonic effects of AR extracts and their primary compounds were assessed, and the results demonstrated that highly polar AR extracts, particularly astragaloside-enriched extracts, have better tonic effects on the mitochondrial bioenergetics of cultured cardiomyocytes than extracts with a lower polarity [106]. Additionally, the active ingredient in AR, calycosin, has been shown to improve triptolide-induced cardiotoxicity by enhancing PGC-1/NRF1-dependent cardiac mitochondrial biogenesis and respiration, providing a druggable mechanism for reducing cardiotoxicity [106]. In cultured cardiomyoblasts, the herbal mixture Danggui Buxue Tang (DBT), which contains AR and Angelicae Sinensis Radix (ASR), can increase the transcript expression of genes involved in mitochondrial biogenesis and DNA replication [106]. When utilized for the clinical treatment of diabetic nephropathy (DN), Huangqi-Danshen decoction (HDD), which is made up of AR (Huang-qi) and Dan-shen, exhibits good efficacy. According to previous studies, treatment for HDD dramatically reduces increased mitochondrial fission and PINK1/Parkin-mediated mitophagy in db/db mice, preventing type 2 diabetes-related kidney damage [107]. These findings showed that mitochondrial energy metabolism is a key potential mechanism underlying AR against CVD.

3.1.4. *Ginseng*

Ginseng, a well-known traditional medicine and tonic, has long been regarded as panacea. Abundant evidence suggests that its antioxidant property plays a central role in preventing biological aging and promoting longevity [108]. It has been demonstrated that the main active ingredients of Panax ginseng, ginsenoside Rb1, protects neurons from ischemia injury by inactivating astrocytes and transferring mitochondria. The potential for targeting astrocytes for pharmacological interventions in ischemic brain injury is suggested to involved in inhibiting nicotinamide adenine dinucleotide (NADH) dehydrogenase in mitochondrial complex I to block reverse electron transport-derived ROS production from complex I and inactivated astrocytes to protect the mitochondria [109]. Additionally, the natural supplement ginsenoside Rb3 (G-Rb3), which is derived from ginseng, has cardioprotective properties by increasing the production of important enzymes for the oxidation of fatty acids and the main mitochondrial deacetylase, sirtuin 3 (SIRT3) [109]. By regulating mitochondrial activity and biogenesis, majonoside-R2 (MR2), a major saponin present in Vietnamese ginseng that has several biological functions [109], can shield cardiomyocytes from hypoxia/reoxygenation harm [110]. By controlling mitophagy through the AMPK pathway, ginseng-sanqi-chuanxiong (GSC) AMPK extracts ameliorate diabetes-induced endothelial cell senescence. It is not unexpected that ginseng-sanqi-chuanxiong (GSC) extracts were found to delay the senescence of endothelial cells induced by diabetes by controlling mitophagy through the AMPK pathway [111]. By controlling intestinal flora and mitochondrial dysfunction, ginseng Dingzhi decoction was reported to ameliorate myocardial fibrosis and high glucose-induced cardiomyocyte damage [112]. Taken together, ginseng modulates mitochondrial function to preserve cardioprotective effects.

3.1.5. *Paeonia suffruticosa*

Traditional medicine has used *Paeonia suffruticosa* extensively to treat conditions such as diabetes [113], arthritis [114], and cancer [115]. For the treatment of atherosclerotic cardiovascular disease, paeonol, an active component isolated from Cortex Moutan (the root bark of Paeonia suffruticosa), is frequently employed [116]. Paeonol was discovered to protect primary human pulmonary artery SMCs (PASMCs) from damage caused by hypoxia and to stop pulmonary vascular remodeling in a prior study by inhibiting mitochondrial damage and enhancing ATP generation by IRI upregulating PGC-1 [116]. Paeonol may have a protective impact on the myocardium in IRI, according to additional research [117], which was associated with the activation of the PI3K/Akt pathway and the suppression of cell apoptosis [118]. In conclusion, preserving mitochondria and preventing apoptosis are both key components of the cardiovascular protective impact of paeonol.

3.1.6. *Angelica sinensis*

Chinese medicine practitioners have employed *Angelica sinensis*, often called female ginseng or Dang Gui (in Chinese), for thousands of years. As its "meridian tropism" encompasses the liver, heart, and spleen channels, TCM theory states that it has therapeutic benefits on ailments by boosting blood circulation, regulating menstruation, reducing pain, and exerting laxative action. Since the 1980 s, ischemic cardiovascular disease has been treated with angelica sinensis extract and its active ingredients [113]. It has been demonstrated that the major active component of Angelica sinensis, liggustilide (LIG), plays a crucial role in the control of mitochondrial fission and mitophagy in an AMPK-dependent manner, reducing the severity of ischemic stroke

injury by enhancing mitochondrial activity [114]. LIG may also lessen neuronal damage from ischemic stroke by encouraging mitophagy via PINK1/Parkin [120]. By encouraging the interaction of AMPK with PGC-1 and increasing multilocular lipid droplet levels, AMP-activated protein kinase (AMPK) signaling (AMPK/acetyl-CoA carboxylase/SIRT1), and increasing multilocular lipid droplet levels, N-butylidenephthalide (BP), a natural derivative from Angelica sinensis, was shown to improve the metabolic profiles of mice with high-fat diet-induced obesity [121].

3.1.7. Others

A plethora of TCM herbs might benefit CVDs by targeting mitochondrial function through a series of actions. For thousands of years, *Ginkgo biloba* seeds and leaves have been used as a traditional herb, and its leaf extract (GBE) exerts vascular protection functions. The degree of exogenous cytochrome c-induced respiration stimulation decreased free radical production in the mitochondria, attenuated ischemia-induced V3 drop, and uncoupled mitochondrial oxidation from phosphorylation are all factors contributing to GE's cardioprotective effects [115]. In particular, a class of bioactive constituents of GBE, terpene lactones, has been widely used as an add-on therapy in patients with ischemic cardiovascular and cerebrovascular diseases [116].

The mushroom lingzhi, also known as *ganoderma lucidum*, is commonly consumed in Asia and is gaining popularity in Western nations as a supplemental treatment for cardiovascular health [117,118]. By directly scavenging free radicals and boosting the activities of TCA cycle enzymes and respiratory chain complexes, it was said to greatly protect mitochondria [119]. Additionally, *Amauroderma rugosum* (AR), a different genus of mushroom from the Ganodermataceae family with infrequently reported medicinal value, was shown by Li et al. to have remarkable cardioprotective effects against Dox-induced cardiotoxicity by upregulating the serine/threonine-protein kinase mTOR/Akt and nuclear factor erythroid 2-related factor 2/ heme oxygenase 1 (Nrf2/HO-1)-dependent pathways and lowering oxidative stress, mitochondrial dysfunction, and cardiomyocyte apoptosis [119]. Further study investigating the efficacy and underlying mechanisms of the Ganodermataceae family would provide promising therapeutics for CVD.

3.2. Traditional Chinese medicine decoction and patented drugs

Generally, a variety of Chinese medicinal materials are used together in the form of a "Formula" to treat diseases (Table 1) [120]. Different components of a formula complement each other to achieve a harmonious and unified disease treatment effect. Sini decoction (SND), a well-known formula of traditional Chinese medicine derived from "Treatise on Febrile Diseases", consists of roasted licorice, dried ginger, and aconite. It has been used to treat kidney Yang deficiency as a warming agent to dispel the cold and restore adversity [121] and has been applied to treat cardiovascular disease for many years [122,123]. For instance, SND pretreatment was found to protect the myocardium possibly by modulating the nuclear factor kappa-B (NF-κB) signaling pathway and regulating phospholipid and bile acid metabolism [124]. Dan-Shen-Yin (DSY), a famous Chinese herbal formula consisting of sandalwood *Fructus amomi* and *Salvia miltiorrhiza*, is extensively used for treating coronary heart disease [125]. DSY potentially retards endothelial-to-mesenchymal transition (EndMT), which plays an essential role in the pathogenesis of atherosclerosis, by modulating the LASP1/PI3K/AKT pathway [126]. Bao-Xin-Tang (BXT), another Chinese herbal compound mainly containing *Codonopsis pilosula*, *Atractylodes macrocephala*, *Astragalus*, and *Fructus crataegi*, has been verified to ameliorate blood circulation and protect the myocardium and is therefore extensively used to treat coronary heart disease. The effects of BXT may be associated with its anti-inflammatory and antioxidative properties [127].

Many of these formulas have gained patents and are produced in different preparations, including pills, tablets, injections, capsules and so on (Table 1). The therapeutic effects and good safety profile of Qiliqiangxin capsules have been well demonstrated in patients with chronic heart failure. Cardiac improvement might be achieved by ameliorating abnormal Ca^{2+} transients, attenuating fibrosis and decreasing apoptosis [128,129]. YiQiFuMai powder injection (YQFM), a Chinese medicinal formula extracted from *Panax ginseng*, *Ophiopogon japonicus*, and *Schisandra chinensis*, is widely used to treat angina and ischemic heart failure. Previous studies have illustrated that its protective effect is related to the modulation of autophagy, mitochondrial function, apoptosis, and oxidant stress by regulating ROS generation, p38 and ERK1/2 MAPK signaling, and CaMKII signaling pathways [130,131]. Tongxinluo (TXL) is a prescription compound of Chinese medicine used to ameliorate ischemic heart diseases primarily attributed to its anti-inflammatory, lipid-lowering, and antioxidant effects [132,133]. Intriguingly, a recent study revealed that TXL could ameliorate myocardial ischemia—reperfusion injury by activating Parkin-mediated mitophagy and downregulating the ubiquitin—proteasome system [134].

However, more research is needed to determine their impact on the long-term outcomes of patients with chronic heart failure. Numerous TCM medicines, including Nuanxin, Shencaotongmai, and Yangxinkang, have been shown to be successful in enhancing cardiac function in these patients [135,136]. Moreover, the Jiangzhitongluo capsule and Zhibitai capsule, for example, may be used as alternatives to Western

Table 1
List of TCM decoction and patented drugs mentioned in this article.

Name	Components	Functions	Mechanisms	Refs
Sini decoction (SND)	Roasted licorice, Dried ginger, Aconite	Protect myocardium	Modulating NF-κB signaling pathway, regulating phospholipid and bile acid metabolisms	[124]
Dan-Shen-Yin (DSY)	*Sandalwood Fructus amomi* and *Salvia miltiorrhiza*	Retards endothelial-to-mesenchymal transition (EndMT)	Modulating the LASP1/PI3K/AKT pathway	[126]
Bao-Xin-Tang (BXT)	*Codonopsis pilosula*, *Atractylodes macrocephala, Astragalus*, and *Fructus crataegi*	Ameliorate blood circulation and protect the myocardium	Anti-inflammatory and anti-oxidative stress	[127]
Qiliqiangxin capsule	Aconite, *Astragalus*, Ginseng, Rhizoma alismatis, *Salvia miltiorrhiza*, and Psoralea corylifolia L.	Improve cardiac function	Ameliorating abnormal Ca^{2+} transients, attenuating fibrosis and decreasing apoptosis	[128, 129]
YiQiFuMai powder injection (YQFM)	*Panax ginseng*, *Ophiopogon japonicus*, and *Schisandra chinensis*	Treat angina and ischemic heart failure	Regulating ROS generation, p38 and ERK1/2 MAPKs signaling, and CaMKII signaling pathways	[130, 131]
Tongxinluo (TXL)	Ginseng, Paeoniaeradixrubra, Ziziphispinosae semen, Dalbergiaeodoriferae lignum, Santali albi lignum, Olibanum, Hirudo, Scorpio, Scolopendra, Cicadae periostracum, EupolyphagaSteleophaga, and Borneolum	Ameliorate myocardial ischemia-reperfusion	Activating Parkin-mediated mitophagy and downregulating ubiquitin-proteasome system	[134]

medications for the treatment of dyslipidemia considering currently available data. These TCM medications are effective in lowering serum lipid levels [137,138]. However, more thorough, extensive research is required to determine whether these beneficial effects could lead to a decrease in cardiovascular events.

3.3. Strategies that facilitate targeting mitochondria via TCMs for CVD management

To promote the applications of TCM worldwide, a series of technologies and strategies have been developed to achieve quality control, storage, target screening and precision delivery of TCM [88]. The active components of TCM are separated and characterized using chromatography (CG), capillary electrophoresis (CE), mass spectrometry (MS), and NMR so that the quality of TCM can be guaranteed [139]. In recent years, advances in omics strategies have assisted in deciphering cellular targets and mechanisms of action from multiple perspectives, including chromosomes, DNA, RNA, proteins, and metabolites. In this regard, scientific evidence is increasingly gathered and therefore provides important fundamental information about specific TCM formulations to promote their clinical validation. In addition to being applied in single-herb preparations or prescription formulas, TCM herbs are always developed into purified natural products or multicomponent preparations for different purposes. Purified natural components can easily oxidize, which greatly attenuates their stability. Additionally, the insufficient bioavailability, low water solubility, and lackluster selectivity of natural components are what essentially restrict their pharmaceutical usefulness [140]. Natural component bioactivities can be improved by structural changes such esterification and glycosylation that prevent degradation [129]. For instance, glycosylation of polyphenols increased their stability and shielded them against oxidants, light deterioration, and digestive conditions that are acidic [130]. The stability and targeting capacity of recently developed nano-techniques have been extensively demonstrated. For instance, the antioxidant molecule MitoQ10 is conjugated to lipophilic molecules to selectively target mitochondria [141]. It enhances blood pressure and endothelial NO bioavailability, preventing the onset of hypertension, enhancing endothelial function, and reducing cardiac hypertrophy in young spontaneously hypertensive rats predisposed to stroke, providing a new therapeutic intervention for human cardiovascular disease. Additionally, it has been shown that the GLSO@P188/PEG400 nanosystem (NS) can be rationally manufactured to obtain good water solubility and improved protection against radiation-induced heart disease [132]. As expected, the improved free radical scavenging ability of GLSO@P188/PEG400 NSs allows them to reduce the high ROS levels brought on by X-rays. Taken together, these findings suggest that TCM has great potential for treating cardiovascular diseases.

4. Conclusion and perspective

Mitochondria are a target for CVD therapy due to their involvement in the dysregulation of the cell cycle, oxidative stress, hyperuricemia, altered calcium signaling, and vascular inflammation, which are implicated in the onset and progression of EC senescence and vascular disease in aging [142]. According to TCM interpretation, researchers believe that mitochondria are Qi (Chi), which roughly translates as vital force or energy [134]. In this respect, yang-invigorating herbs may improve ATP synthesis by enhancing mitochondrial electron transport and leading to increases in antioxidant capacity, whereas yin-nourishing herbs may reduce the capacity of myocardial ATP synthesis [135]. Therefore, it is crucial to think carefully about when and how to apply a TCM technique to control mitochondrial function for the treatment of CVD. It is obvious that new therapeutic approaches and unidentified mitochondrial mechanisms for the treatment of CVD by TCM should be thoroughly surveyed. It is important to note that the intricate makeup of TCM herbs serves as a reminder to build stringent *in vitro* and *in vivo* screening systems prior to daily use as well as in-depth ways to investigate dosage accuracy and pharmacokinetics. TCM herbs will not be an ideal treatment for daily use unless clinical data are gathered.

Funding

This work was supported by the special project of TCM Scientific Research of Sichuan Administration of Traditional Chinese Medicine (2021MS359) and the "Xinglin Scholar" discipline personnel scientific research promotion program of Chengdu University of Traditional Chinese Medicine (YYZX2021119).

Ethics statement

Not applicable.

CRediT authorship contribution statement

Jie Gao: Conceptualization, Writing – original draft, Funding acquisition. **Tianshu Hou:** Review & Editing, Supervision, Funding acquisition.

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.

Data availability

No data was used for the research described in the article.

Acknowledgements

Figures in this review were created with the BioRender platform.

References

[1] S. Smith, F. Horgan, E. Sexton, et al., The cost of stroke and transient ischaemic attack in Ireland: a prevalence-based estimate, Age Ageing 41 (3) (2012) 332–338.
[2] C.C. Low Wang, C.N. Hess, W.R. Hiatt, A.B. Goldfine, Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations, Circulation 133 (24) (2016) 2459–2502.
[3] Boffa R.J., Constanti M., Floyd C.N., Wierzbicki A.S. , Hypertension in adults: summary of updated NICE guidance, BMJ Clin. Res., 367, l5310 (2019).
[4] L.M. Behlke, E.J. Lenze, R.M. Carney, The cardiovascular effects of newer antidepressants in older adults and those with or at high risk for cardiovascular diseases, CNS Drugs 34 (11) (2020) 1133–1147.
[5] K. Lechner, C. von Schacky, A.L. McKenzie, et al., Lifestyle factors and high-risk atherosclerosis: pathways and mechanisms beyond traditional risk factors, Eur. J. Prev. Cardiol. 27 (4) (2020) 394–406.
[6] N. Jeremic, P. Chaturvedi, S.C. Tyagi, Browning of white fat: novel insight into factors, mechanisms, and therapeutics, J. Cell. Physiol. 232 (1) (2017) 61–68.
[7] R.C.F. Pena, M.A. Hofmann Bowman, M. Ahmad, et al., An assessment of the current medical management of thoracic aortic disease: a patient-centered scoping literature review, Semin. Vasc. Surg. 35 (1) (2022) 16–34.
[8] E.A. Russell, W.F. Walsh, B. Costello, et al., Medical management of rheumatic heart disease: a systematic review of the evidence, Cardiol. Rev. 26 (4) (2018) 187–195.
[9] M.Y. Desai, S. Windecker, P. Lancellotti, et al., Prevention, diagnosis, and management of radiation-associated cardiac disease: JACC Scientific Expert Panel, J. Am. Coll. Cardiol. 74 (7) (2019) 905–927.
[10] E. Kummer, N. Ban, Mechanisms and regulation of protein synthesis in mitochondria, Nat. Rev. Mol. Cell Biol. 22 (5) (2021) 307–325.
[11] M. Adebayo, S. Singh, A.P. Singh, S. Dasgupta, Mitochondrial fusion and fission: the fine-tune balance for cellular homeostasis, FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 35 (6) (2021), e21620.
[12] V.Y. Glanz, I.A. Sobenin, A.V. Grechko, S.F. Yet, A.N. Orekhov, The role of mitochondria in cardiovascular diseases related to atherosclerosis, Front. Biosci. (Elite Ed.) 12 (1) (2020) 102–112.
[13] D.J. Tyrrell, M.G. Blin, J. Song, et al., Age-associated mitochondrial dysfunction accelerates atherogenesis, Circ. Res. 126 (3) (2020) 298–314.

[14] L. Zhuang, K. Jia, C. Chen, et al., DYRK1B-STAT3 drives cardiac hypertrophy and heart failure by impairing mitochondrial bioenergetics, Circulation 145 (11) (2022) 829–846.
[15] C.C. Li, X.S. Yan, M.H. Liu, G.F. Teng, Current status of objectification of four diagnostic methods on constitution recognition of Chinese medicine, Chin. J. Integr. Med. 28 (12) (2022) 1137–1146.
[16] P.E. Ferrara, S. Codazza, S. Cerulli, G. Maccauro, G. Ferriero, G. Ronconi, Physical modalities for the conservative treatment of wrist and hand's tenosynovitis: a systematic review, Semin. Arthritis Rheum. 50 (6) (2020) 1280–1290.
[17] D. Zhang, Y. Zhang, Y. Gao, et al., Translating traditional herbal formulas into modern drugs: a network-based analysis of Xiaoyao decoction, Chin. Med. 15 (2020) 25.
[18] P. Hao, F. Jiang, J. Cheng, L. Ma, Y. Zhang, Y. Zhao, Traditional chinese medicine for cardiovascular disease: evidence and potential mechanisms, J. Am. Coll. Cardiol. 69 (24) (2017) 2952–2966.
[19] H.V. Lakhani, S.S. Pillai, M. Zehra, I. Sharma, K. Sodhi, Systematic review of clinical insights into novel coronavirus (CoVID-19) pandemic: persisting challenges in U.S. rural population, Int. J. Environ. Res. Public Health 17 (12) (2020).
[20] U. Krengel, S.Biochemistry Törnroth-Horsefield, Coping with oxidative stress, Science 347 (6218) (2015) 125–126.
[21] S.I. Liochev, Reactive oxygen species and the free radical theory of aging, Free Radic. Biol. Med. 60 (2013) 1–4.
[22] A. Samman Tahhan, P.B. Sandesara, S.S. Hayek, et al., Association between oxidative stress and atrial fibrillation, Heart Rhythm 14 (12) (2017) 1849–1855.
[23] A.J. Kattoor, N.V.K. Pothineni, D. Palagiri, J.L. Mehta, Oxidative stress in atherosclerosis, Curr. Atheroscler. Rep. 19 (11) (2017) 42.
[24] S.I. Hashem, C.N. Perry, M. Bauer, et al., Brief report: oxidative stress mediates cardiomyocyte apoptosis in a human model of Danon disease and heart failure, Stem Cells 33 (7) (2015) 2343–2350.
[25] T. Senoner, W. Dichtl, Oxidative stress in cardiovascular diseases: still a therapeutic target? Nutrients 11 (9) (2019).
[26] A. Meyer, G. Laverny, L. Bernardi, et al., Mitochondria: an organelle of bacterial origin controlling inflammation, Front. Immunol. 9 (2018) 536.
[27] S. Rovira-Llopis, N. Apostolova, C. Bañuls, J. Muntané, M. Rocha, V.M. Victor, Mitochondria, the NLRP3 inflammasome, and sirtuins in type 2 diabetes: new therapeutic targets, Antioxid. Redox Signal. 29 (8) (2018) 749–791.
[28] Z. Safiedeen, R. Andriantsitohaina, M.C. Martinez, Dialogue between endoplasmic reticulum and mitochondria as a key actor of vascular dysfunction associated to metabolic disorders, Int. J. Biochem. Cell Biol. 77 (Pt A) (2016) 10–14.
[29] Y. Zhang, C. Wang, Y. Jin, et al., Activating the PGC-1α/TERT pathway by catalpol ameliorates atherosclerosis via modulating ROS production, DNA damage, and Telomere function: implications on mitochondria and Telomere link, Oxid. Med. Cell. Longev. 2018 (2018) 2876350.
[30] N.N. Wu, Y. Zhang, J. Ren, Mitophagy, mitochondrial dynamics, and homeostasis in cardiovascular aging, Oxid. Med. Cell. Longev. 2019 (2019) 9825061.
[31] P. Jin, J. Jiang, L. Zhou, et al., Mitochondrial adaptation in cancer drug resistance: prevalence, mechanisms, and management, J. Hematol. Oncol. 15 (1) (2022) 97.
[32] Y. Li, X. Xia, Y. Wang, J.C. Zheng, Mitochondrial dysfunction in microglia: a novel perspective for pathogenesis of Alzheimer's disease, J. Neuroinflamm. 19 (1) (2022) 248.
[33] Y. Quan, Y. Xin, G. Tian, J. Zhou, X. Liu, Mitochondrial ROS-modulated mtDNA: a potential target for cardiac aging, Oxid. Med. Cell. Longev. 2020 (2020) 9423593.
[34 A.S. Manolis, A.A. Manolis, T.A. Manolis, et al., Mitochondrial dysfunction in cardiovascular disease: current status of translational research/clinical and therapeutic implications, Med. Res. Rev. 41 (1) (2021) 275–313.
[35] Y. Mikhed, A. Daiber, S. Steven, Mitochondrial oxidative stress, mitochondrial DNA damage and their role in age-related vascular dysfunction, Int. J. Mol. Sci. 16 (7) (2015) 15918–15953.
[36] X. Wang, X. Li, S. Liu, et al., PCSK9 regulates pyroptosis via mtDNA damage in chronic myocardial ischemia, Basic Res. Cardiol. 115 (6) (2020) 66.
[37] K.H. Lauritzen, M.B. Olsen, M.S. Ahmed, et al., Instability in NAD(+) metabolism leads to impaired cardiac mitochondrial function and communication, eLife 10 (2021).
[38] F.N. Ashar, Y. Zhang, R.J. Longchamps, et al., Association of mitochondrial DNA copy number with cardiovascular disease, JAMA Cardiol. 2 (11) (2017) 1247–1255.
[39] P. Yue, S. Jing, L. Liu, et al., Association between mitochondrial DNA copy number and cardiovascular disease: current evidence based on a systematic review and meta-analysis, PLoS One 13 (11) (2018), e0206003.
[40] K. Sundquist, J. Sundquist, K. Palmer, A.A. Memon, Role of mitochondrial DNA copy number in incident cardiovascular diseases and the association between cardiovascular disease and type 2 diabetes: a follow-up study on middle-aged women, Atherosclerosis 341 (2022) 58–62.
[41] A. Koller, F. Fazzini, C. Lamina, et al., Mitochondrial DNA copy number is associated with all-cause mortality and cardiovascular events in patients with peripheral arterial disease, J. Intern. Med. 287 (5) (2020) 569–579.
[42] C.A. Castellani, R.J. Longchamps, J.A. Sumpter, et al., Mitochondrial DNA copy number can influence mortality and cardiovascular disease via methylation of nuclear DNA CpGs, Genome Med. 12 (1) (2020) 84.
[43] C. Vecoli, A. Borghini, S. Pulignani, et al., Independent and combined effects of telomere shortening and mtDNA(4977) deletion on long-term outcomes of patients with coronary artery disease, Int. J. Mol. Sci. 20 (21) (2019).
[44] J. Kim, R. Gupta, L.P. Blanco, et al., VDAC oligomers form mitochondrial pores to release mtDNA fragments and promote lupus-like disease, Science 366 (6472) (2019) 1531–1536.
[45] A.M. Markin, V.A. Khotina, X.G. Zabudskaya, et al., Disturbance of mitochondrial dynamics and mitochondrial therapies in atherosclerosis, Life 11 (2) (2021).
[46] A. Stoccoro, F. Coppedè, Mitochondrial DNA methylation and human diseases, Int. J. Mol. Sci. 22 (9) (2021).
[47] A.N. Orekhov, A.V. Poznyak, I.A. Sobenin, N.N. Nikifirov, E.A. Ivanova, Mitochondrion as a selective target for the treatment of atherosclerosis: role of mitochondrial DNA mutations and defective mitophagy in the pathogenesis of atherosclerosis and chronic inflammation, Curr. Neuropharmacol. 18 (11) (2020) 1064–1075.
[48] S. Rovira-Llopis, C. Bañuls, N. Diaz-Morales, A. Hernandez-Mijares, M. Rocha, V. M. Victor, Mitochondrial dynamics in type 2 diabetes: pathophysiological implications, Redox Biol. 11 (2017) 637–645.
[49] A. Picca, R.T. Mankowski, J.L. Burman, et al., Mitochondrial quality control mechanisms as molecular targets in cardiac ageing, Nat. Rev. Cardiol. 15 (9) (2018) 543–554.
[50] A.W. El-Hattab, J. Suleiman, M. Almannai, F. Scaglia, Mitochondrial dynamics: biological roles, molecular machinery, and related diseases, Mol. Genet. Metab. 125 (4) (2018) 315–321.
[51] G. Siasos, V. Tsigkou, M. Kosmopoulos, et al., Mitochondria and cardiovascular diseases-from pathophysiology to treatment, Ann. Transl. Med. 6 (12) (2018) 256.
[52] Y. Tan, F. Xia, L. Li, et al., Novel insights into the molecular features and regulatory mechanisms of mitochondrial dynamic disorder in the pathogenesis of cardiovascular disease, Oxid. Med. Cell. Longev. 2021 (2021) 6669075.
[53] A.R. Hall, N. Burke, R.K. Dongworth, D.J. Hausenloy, Mitochondrial fusion and fission proteins: novel therapeutic targets for combating cardiovascular disease, Br. J. Pharmacol. 171 (8) (2014) 1890–1906.
[54] S.B. Ong, D.J. Hausenloy, Mitochondrial morphology and cardiovascular disease, Cardiovasc. Res. 88 (1) (2010) 16–29.
[55] K.H. Chen, A. Dasgupta, J. Lin, et al., Epigenetic DYsregulation of the Dynamin-related Protein 1 Binding Partners MiD49 and MiD51 increases mitotic mitochondrial fission and promotes pulmonary arterial hypertension: mechanistic and therapeutic implications, Circulation 138 (3) (2018) 287–304.
[56] H. Zhou, S. Toan, P. Zhu, J. Wang, J. Ren, Y. Zhang, DNA-PKcs promotes cardiac ischemia reperfusion injury through mitigating BI-1-governed mitochondrial homeostasis, Basic Res. Cardiol. 115 (2) (2020) 11.
[57] Y. Chen, C. Liu, P. Zhou, et al., Coronary endothelium no-reflow injury is associated with ROS-modified mitochondrial fission through the JNK-Drp1 signaling pathway, Oxid. Med. Cell. Longev. 2021 (2021) 6699516.
[58] T. Wang, M. Zhai, S. Xu, et al., NFATc3-dependent expression of miR-153-3p promotes mitochondrial fragmentation in cardiac hypertrophy by impairing mitofusin-1 expression, Theranostics 10 (2) (2020) 553–566.
[59] B. Wu, J. Li, H. Ni, et al., TLR4 activation promotes the progression of experimental autoimmune myocarditis to dilated cardiomyopathy by inducing mitochondrial dynamic imbalance, Oxid. Med. Cell. Longev. 2018 (2018) 3181278.
[60] R. Umezu, J.I. Koga, T. Matoba, et al., Macrophage (Drp1) dynamin-related protein 1 accelerates intimal thickening after vascular injury, Arterioscler. Thromb. Vasc. Biol. 40 (7) (2020) e214–e226.
[61] S.H. Jeong, H.K. Kim, I.S. Song, et al., Echinochrome a increases mitochondrial mass and function by modulating mitochondrial biogenesis regulatory genes, Mar. Drugs 12 (8) (2014) 4602–4615.
[62] F.G. Tahrir, D. Langford, S. Amini, T. Mohseni Ahooyi, K. Khalili, Mitochondrial quality control in cardiac cells: mechanisms and role in cardiac cell injury and disease, J. Cell. Physiol. 234 (6) (2019) 8122–8133.
[63] R. Ventura-Clapier, A. Garnier, V. Veksler, Transcriptional control of mitochondrial biogenesis: the central role of PGC-1alpha, Cardiovasc. Res. 79 (2) (2008) 208–217.
[64] J. He, M. Gong, Z. Wang, et al., Cardiac abnormalities after induction of endoplasmic reticulum stress are associated with mitochondrial dysfunction and connexin43 expression, Clin. Exp. Pharmacol. Physiol. 48 (10) (2021) 1371–1381.
[65] N. Mekala, J. Kurdys, A.P. Vicenzi, et al., MiR 208a regulates mitochondrial biogenesis in metabolically challenged cardiomyocytes, Cells 10 (11) (2021).
[66] Y. Li, X.J. Yu, T. Xiao, H.L. Chi, G.Q. Zhu, Y.M. Kang, Nrf1 knock-down in the hypothalamic paraventricular nucleus alleviates hypertension through intervention of superoxide production-removal balance and mitochondrial function, Cardiovasc. Toxicol. 21 (6) (2021) 472–489.
[67] L. Montava-Garriga, I.G. Ganley, Outstanding questions in mitophagy: what we do and do not know, J. Mol. Biol. 432 (1) (2020) 206–230.
[68] P.E. Morales, C. Arias-Durán, Y. Ávalos-Guajardo, et al., Emerging role of mitophagy in cardiovascular physiology and pathology, Mol. Asp. Med. 71 (2020), 100822.
[69] Y. Yang, T. Li, Z. Li, N. Liu, Y. Yan, B. Liu, Role of mitophagy in cardiovascular disease, Aging Dis. 11 (2) (2020) 419–437.
[70] S.K. Sonn, E.J. Song, S. Seo, et al., Peroxiredoxin 3 deficiency induces cardiac hypertrophy and dysfunction by impaired mitochondrial quality control, Redox Biol. 51 (2022), 102275.
[71] J. Wang, P. Zhu, R. Li, J. Ren, H. Zhou, Fundc1-dependent mitophagy is obligatory to ischemic preconditioning-conferred renoprotection in ischemic AKI via suppression of Drp1-mediated mitochondrial fission, Redox Biol. 30 (2020), 101415.

[72] Y. Ikeda, A. Shirakabe, Y. Maejima, et al., Endogenous Drp1 mediates mitochondrial autophagy and protects the heart against energy stress, Circ. Res. 116 (2) (2015) 264–278.
[73] B. Robson, Computers and preventative diagnosis. A survey with bioinformatics examples of mitochondrial small open reading frame peptides as portents of a new generation of powerful biomarkers, Comput. Biol. Med. 140 (2021), 105116.
[74] Z. Gong, E. Tas, R. Muzumdar, Humanin and age-related diseases: a new link? Front. Endocrinol. 5 (2014) 210.
[75] Z. Gong, E. Goetzman, R.H. Muzumdar, Cardio-protective role of Humanin in myocardial ischemia-reperfusion, Biochim. Biophys. Acta Gen. Subj. 1866 (2) (2022), 130066.
[76] L.J. Cobb, C. Lee, J. Xiao, et al., Naturally occurring mitochondrial-derived peptides are age-dependent regulators of apoptosis, insulin sensitivity, and inflammatory markers, Aging 8 (4) (2016) 796–809.
[77] P.O. Bonetti, L.O. Lerman, A. Lerman, Endothelial dysfunction: a marker of atherosclerotic risk, Arterioscler. Thromb. Vasc. Biol. 23 (2) (2003) 168–175.
[78] A.R. Bachar, L. Scheffer, A.S. Schroeder, et al., Humanin is expressed in human vascular walls and has a cytoprotective effect against oxidized LDL-induced oxidative stress, Cardiovasc. Res. 88 (2) (2010) 360–366.
[79] Y. Yang, H. Gao, H. Zhou, et al., The role of mitochondria-derived peptides in cardiovascular disease: recent updates, Biomed. Pharmacother. 117 (2019), 109075.
[80] I. Genovese, M. Carinci, L. Modesti, G. Aguiari, P. Pinton, C. Giorgi, Mitochondria: insights into crucial features to overcome cancer chemoresistance, Int. J. Mol. Sci. 22 (9) (2021).
[81] Y. Hu, H. Chen, L. Zhang, et al., The AMPK-MFN2 axis regulates MAM dynamics and autophagy induced by energy stresses, Autophagy 17 (5) (2021) 1142–1156.
[82] W.Y. Chen, Y.F. Chen, H.C. Chan, et al., Role of apolipoprotein E in electronegative low-density lipoprotein-induced mitochondrial dysfunction in cardiomyocytes, Metab. Clin. Exp. 107 (2020), 154227.
[83] D.M. Herrington, C. Mao, S.J. Parker, et al., Proteomic architecture of human coronary and aortic atherosclerosis, Circulation 137 (25) (2018) 2741–2756.
[84] Y. Xu, Y. Yu, B. Yang, et al., Extracellular mitochondrial components and effects on cardiovascular disease, DNA Cell Biol. 40 (9) (2021) 1131–1143.
[85] O. Biró, O. Hajas, E. Nagy-Baló, B. Soltész, Z. Csanádi, B. Nagy, Relationship between cardiovascular diseases and circulating cell-free nucleic acids in human plasma, Biomark. Med. 12 (8) (2018) 891–905.
[86] B. Soltesz, B. Nagy, Quantification of mtDNA in extracellular vesicles, Methods Enzymol. 645 (2020) 119–140.
[87] F.F. Cox, A. Misiou, A. Vierkant, et al., Protective effects of curcumin in cardiovascular diseases-impact on oxidative stress and mitochondria, Cells 11 (3) (2022).
[88] M. Bonora, M.R. Wieckowski, D.A. Sinclair, G. Kroemer, P. Pinton, L. Galluzzi, Targeting mitochondria for cardiovascular disorders: therapeutic potential and obstacles, Nat. Rev. Cardiol. 16 (1) (2019) 33–55.
[89] K. Zekri-Nechar, J.J. Zamorano-León, M. Cortina-Gredilla, et al., Mitochondrial mitophagy protection combining rivaroxaban and aspirin in high glucose-exposed human coronary artery endothelial cell. An in vitro study, Diabetes Vasc. Dis. Res. 19 (5) (2022) (14791641221129877).
[90] H. Yuan, Q. Ma, L. Ye, G. Piao, The traditional medicine and modern medicine from natural products, Molecules 21 (5) (2016).
[91] L. Wu, F. Li, C. Zhao, et al., Effects and mechanisms of traditional chinese herbal medicine in the treatment of Ischemic cardiomyopathy, Pharmacol. Res. 151 (2020), 104488.
[92] Y.C. Cheng, I.L. Hung, Y.N. Liao, W.L. Hu, Y.C. Hung, Salvia miltiorrhiza protects endothelial dysfunction against mitochondrial oxidative stress, Life 11 (11) (2021).
[93] H. Pang, L. Wu, Y. Tang, G. Zhou, C. Qu, J.A. Duan, Chemical analysis of the herbal medicine Salviae miltiorrhizae Radix et Rhizoma (Danshen), Molecules 21 (1) (2016) 51.
[94] Z. Zhang, H. He, Y. Qiao, et al., Tanshinone IIA pretreatment protects H9c2 cells against anoxia/reoxygenation injury: involvement of the translocation of Bcl-2 to mitochondria mediated by 14-3-3η, Oxid. Med. Cell. Longev. 2018 (3583921) (2018).
[95] J. Zhong, H. Ouyang, M. Sun, et al., Tanshinone IIA attenuates cardiac microvascular ischemia-reperfusion injury via regulating the SIRT1-PGC1α-mitochondrial apoptosis pathway, Cell Stress Chaperon. 24 (5) (2019) 991–1003.
[96] Y.P. Zhao, F. Wang, W. Jiang, et al., A mitochondrion-targeting tanshinone IIA derivative attenuates myocardial hypoxia reoxygenation injury through a SDH-dependent antioxidant mechanism, J. Drug Target. 27 (8) (2019) 896–902.
[97] R. Guan, H. Yao, Z. Li, et al., Sodium Tanshinone IIA sulfonate attenuates cigarette smoke extract-induced mitochondrial dysfunction, oxidative stress, and apoptosis in alveolar epithelial cells by enhancing SIRT1 pathway, Toxicol. Sci. Off. J. Soc. Toxicol. 183 (2) (2021) 352–362.
[98] J. Zhu, H. Chen, J. Guo, C. Zha, D. Lu, Sodium Tanshinone IIA sulfonate inhibits vascular endothelial cell pyroptosis via the AMPK signaling pathway in atherosclerosis, J. Inflamm. Res. 15 (2022) 6293–6306.
[99] D. Jia, T. Li, X. Chen, et al., Salvianic acid A sodium protects HUVEC cells against tert-butyl hydroperoxide induced oxidative injury via mitochondria-dependent pathway, Chem. Biol. Interact. 279 (2018) 234–242.
[100] C.T. Wu, J.S. Deng, W.C. Huang, P.C. Shieh, M.I. Chung, G.J. Huang, Salvianolic Acid C against acetaminophen-induced acute liver injury by attenuating inflammation, oxidative stress, and apoptosis through inhibition of the Keap1/Nrf2/HO-1 signaling, Oxid. Med. Cell. Longev. 2019 (2019) 9056845.
[101] F. Yang, Q. Ma, M.G. Matsabisa, H. Chabalala, F.C. Braga, M. Tang, Panax notoginseng for cerebral Ischemia: a systematic review, Am. J. Chin. Med. 48 (6) (2020) 1331–1351.
[102] Z. Zhou, J. Wang, Y. Song, et al., Panax notoginseng saponins attenuate cardiomyocyte apoptosis through mitochondrial pathway in natural aging rats, Phytother. Res. PTR 32 (2) (2018) 243–250.
[103] C. Zhang, B. Zhang, X. Zhang, M. Wang, X. Sun, G. Sun, Panax notoginseng saponin protects against diabetic cardiomyopathy through lipid metabolism modulation, J. Am. Heart Assoc. 11 (4) (2022), e023540.
[104] K.K.L. Kwan, T.T.X. Dong, K.W.K. Tsim, Danggui Buxue Tang, a Chinese herbal decoction containing Astragali Radix and Angelicae Sinensis Radix, improves mitochrondial bioenergetics in osteoblast, Phytomed. Int. J. Phytother. Phytopharmacol. 88 (2021), 153605.
[105] H.F. Su, S. Shaker, Y. Kuang, M. Zhang, M. Ye, X. Qiao, Phytochemistry and cardiovascular protective effects of Huang-Qi (Astragali Radix), Med. Res. Rev. 41 (4) (2021) 1999–2038.
[106] Y. Huang, K.K.L. Kwan, K.W. Leung, et al., The extracts and major compounds derived from astragali radix alter mitochondrial bioenergetics in cultured cardiomyocytes: comparison of various polar solvents and compounds, Int. J. Mol. Sci. 19 (6) (2018).
[107] X. Liu, J. Lu, S. Liu, et al., Huangqi-Danshen decoction alleviates diabetic nephropathy in db/db mice by inhibiting PINK1/Parkin-mediated mitophagy, Am. J. Transl. Res. 12 (3) (2020) 989–998.
[108] S.W. Lim, Y.J. Shin, K. Luo, et al., Ginseng increases Klotho expression by FoxO3-mediated manganese superoxide dismutase in a mouse model of tacrolimus-induced renal injury, Aging 11 (15) (2019) 5548–5569.
[109] X.C. Ni, H.F. Wang, Y.Y. Cai, et al., Ginsenoside Rb1 inhibits astrocyte activation and promotes transfer of astrocytic mitochondria to neurons against ischemic stroke, Redox Biol. 54 (2022), 102363.
[110] V.T. Thu, N.T.H. Yen, N.H. Tung, P.T. Bich, J. Han, H.K. Kim, Majonoside-R2 extracted from Vietnamese ginseng protects H9C2 cells against hypoxia/reoxygenation injury via modulating mitochondrial function and biogenesis, Bioorg. Med. Chem. Lett. 36 (2021), 127814.
[111] X. Wang, J.Q. Zhang, C.K. Xiu, J. Yang, J.Y. Fang, Y. Lei, Ginseng-Sanqi-Chuanxiong (GSC) extracts ameliorate diabetes-induced endothelial cell senescence through regulating mitophagy via the AMPK Pathway, Oxid. Med. Cell. Longev. 2020 (2020) 7151946.
[112] J. Wang, P. Chen, Q. Cao, W. Wang, X. Chang, Traditional Chinese medicine Ginseng Dingzhi decoction ameliorates myocardial fibrosis and high glucose-induced cardiomyocyte injury by regulating intestinal flora and mitochondrial dysfunction, Oxid. Med. Cell. Longev. 2022 (2022) 9205908.
[113] Y. Han, Y. Chen, Q. Zhang, et al., Overview of therapeutic potentiality of Angelica sinensis for ischemic stroke, Phytomed. Int. J. Phytother. Phytopharm. 90 (2021), 153652.
[114] Q. Wu, J. Liu, Z. Mao, et al., Ligustilide attenuates ischemic stroke injury by promoting Drp1-mediated mitochondrial fission via activation of AMPK, Phytomed. Int. J. Phytother. Phytopharm. 95 (2022), 153884.
[115] J. Bernatoniene, D. Majiene, R. Peciura, et al., The effect of Ginkgo biloba extract on mitochondrial oxidative phosphorylation in the normal and ischemic rat heart, Phytother. Res. PTR 25 (7) (2011) 1054–1060.
[116] X.W. Liu, J.L. Yang, W. Niu, et al., Human pharmacokinetics of ginkgo terpene lactones and impact of carboxylation in blood on their platelet-activating factor antagonistic activity, Acta Pharmacol. Sin. 39 (12) (2018) 1935–1946.
[117] N.L. Klupp, D. Chang, F. Hawke, et al., Ganoderma lucidum mushroom for the treatment of cardiovascular risk factors, Cochrane Database Syst. Rev. 2015 (2) (2015) Cd007259.
[118] X.Q. Geng, A. Ma, J.Z. He, et al., Ganoderic acid hinders renal fibrosis via suppressing the TGF-β/Smad and MAPK signaling pathways, Acta Pharmacol. Sin. 41 (5) (2020) 670–677.
[119] N.P. Sudheesh, T.A. Ajith, K.K. Janardhanan, Ganoderma lucidum ameliorate mitochondrial damage in isoproterenol-induced myocardial infarction in rats by enhancing the activities of TCA cycle enzymes and respiratory chain complexes, Int. J. Cardiol. 165 (1) (2013) 117–125.
[120] X. Luan, L.J. Zhang, X.Q. Li, et al., Compound-based Chinese medicine formula: from discovery to compatibility mechanism, J. Ethnopharmacol. 254 (2020), 112687.
[121] N. Tang, L. Liu, H. Qiu, W. Shi, D. Mao, Analysis of gene expression and functional changes of adrenal gland in a rat model of kidney yang deficiency syndrome treated with Sini decoction, Exp. Ther. Med. 16 (4) (2018) 3107–3115.
[122] H. Zhang, S. Ma, Z. Feng, et al., Cardiovascular disease chemogenomics knowledgebase-guided target identification and drug synergy Mechanism study of an herbal formula, Sci. Rep. 6 (2016) 33963.
[123] W. Zhang, H. Zhang, S. Sun, et al., Comparative pharmacokinetics of hypaconitine after oral administration of pure hypaconitine, Aconitum carmichaelii extract and Sini Decoction to rats, Molecules 20 (1) (2015) 1560–1570.
[124] J. Zhou, X. Ma, M. Shi, et al., Serum metabolomics analysis reveals that obvious cardioprotective effects of low dose Sini decoction against isoproterenol-induced myocardial injury in rats, Phytomed. Int. J. Phytother. Phytopharm. 31 (2017) 18–31.
[125] R.R. Wang, T.Y. Yuan, D. Chen, et al., Dan-Shen-Yin granules prevent hypoxia-induced pulmonary hypertension via STAT3/HIF-1α/VEGF and FAK/AKT signaling pathways, Front. Pharmacol. 13 (2022), 844400.
[126] M. Hong, Y. Wu, H. Zhang, et al., Network pharmacology and experimental analysis to reveal the mechanism of Dan-Shen-Yin against endothelial to mesenchymal transition in atherosclerosis, Front. Pharmacol. 13 (2022), 946193.

[127] Y. Wang, W. Wang, W. Peng, et al., Cardioprotective roles of the chinese medicinal formula Bao-Xin-Tang on acute myocardial infarction in rats, Afr. J. Tradit., Complement., Altern. Med.: AJTCAM 14 (2) (2017) 65–74.
[128] H. Chen, L. Lou, D. Zhang, et al., Qiliqiangxin capsule improves cardiac function and attenuates cardiac remodeling by upregulating miR-133a after myocardial infarction in rats, Evid. Based Complement. Altern. Med. eCAM 2019 (2019) 7528214.
[129] Y. Li, Z. Zhang, X. Hao, T. Yu, S. Li, Qiliqiangxin capsule modulates calcium transients and calcium sparks in human induced pluripotent stem cell-derived cardiomyocytes, Evid. Based Complement. Altern. Med. eCAM 2022 (2022) 9361077.
[130] S. Lv, Y. Wang, W. Zhang, H. Shang, The chemical components, action mechanisms, and clinical evidences of YiQiFuMai injection in the treatment of heart failure, Front. Pharmacol. 13 (2022) 1040235.
[131] Y. Zhang, L. Zhang, Y. Zhang, et al., YiQiFuMai powder injection attenuates coronary artery ligation-induced heart failure through improving mitochondrial function via regulating ROS generation and CaMKII signaling pathways, Front. Pharmacol. 10 (2019) 381.
[132] Y. Wang, X. Kuang, Y. Yin, et al., Tongxinluo prevents chronic obstructive pulmonary disease complicated with atherosclerosis by inhibiting ferroptosis and protecting against pulmonary microvascular barrier dysfunction, Biomed. Pharmacother. 145 (2022), 112367.
[133] Y. Xiong, , et al.R. Tang, J. Xu, Tongxinluo-pretreated mesenchymal stem cells facilitate cardiac repair via exosomal transfer of miR-146a-5p targeting IRAK1/NF-κB p65 pathway, Stem Cell Res. Ther. 13 (1) (2022) 289.
[134] H.X. Yang, P. Wang, N.N. Wang, S.D. Li, M.H. Yang, Tongxinluo ameliorates myocardial ischemia-reperfusion injury mainly via activating Parkin-mediated mitophagy and downregulating ubiquitin-proteasome system, Chin. J. Integr. Med. 27 (7) (2021) 542–550.
[135] T. Lou, J. Ma, Y. Xie, et al., Nuanxin capsule enhances cardiac function by inhibiting oxidative stress-induced mitochondrial dependent apoptosis through AMPK/JNK signaling pathway, Biomed. Pharmacother. 135 (2021), 111188.
[136] P.H. Ren, Z.M. Zhang, P. Wang, H.P. Zhu, Z.Q. Li, Yangxinkang tablet protects against cardiac dysfunction and remodelling after myocardial infarction in rats through inhibition of AMPK/mTOR-mediated autophagy, Pharm. Biol. 58 (1) (2020) 321–327.
[137] C. Wang, W. Pang, X. Du, et al., Efficacy and safety of zhibitai in the treatment of hyperlipidemia: a systematic review and meta-analysis, Front. Pharmacol. 13 (2022), 974995.
[138] Y. Xie, Y.B. He, S.X. Zhang, et al., [Treatment of combined hyperlipidemia patients by jiangzhi tongluo soft capsule combined atorvastatin calcium tablet: a clinical study], Zhongguo Zhong xi yi jie he za zhi Zhongguo Zhongxiyi jiehe zazhi Chin. J. Integr. Tradit. West. Med. 34 (9) (2014) 1059–1063.
[139] D.I. Sánchez-Vidaña, R. Rajwani, M.S. Wong, The use of omic technologies applied to traditional chinese medicine research, Evid. Based Complement. Altern. Med. eCAM 2017 (2017) 6359730.
[140] L. Li, P. Jin, Y. Guan, et al., Exploiting polyphenol-mediated redox reorientation in cancer therapy, Pharmaceuticals 15 (12) (2022).
[141] D. Graham, N.N. Huynh, C.A. Hamilton, et al., Mitochondria-targeted antioxidant MitoQ10 improves endothelial function and attenuates cardiac hypertrophy, Hyperten. (Dallas, Tex.: 1979) 54 (2) (2009) 322–328.
[142] G. Jia, A.R. Aroor, C. Jia, J.R. Sowers, Endothelial cell senescence in aging-related vascular dysfunction. Biochim. Biophys. Acta Mol. Basis Dis. 1865 (7) (2019) 1802–1809.