



Review paper

The potential of herbal drugs to treat heart failure: The roles of Sirt1/AMPK

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ABSTRACT

Heart failure (HF) is a highly morbid syndrome that seriously affects the physical and mental health of patients and generates an enormous socio-economic burden. In addition to cardiac myocyte oxidative stress and apoptosis, which are considered mechanisms for the development of HF, alterations in cardiac energy metabolism and pathological autophagy also contribute to cardiac abnormalities and ultimately HF. Silent information regulator 1 (Sirt1) and adenosine monophosphate-activated protein kinase (AMPK) are nicotinamide adenine dinucleotide (NAD⁺)-dependent deacetylases and phosphorylated kinases, respectively. They play similar roles in regulating some pathological processes of the heart through regulating targets such as peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α), protein 38 mitogen-activated protein kinase (p38 MAPK), peroxisome proliferator-activated receptors (PPARs), and mammalian target of rapamycin (mTOR). We summarized the synergistic effects of Sirt1 and AMPK in the heart, and listed the traditional Chinese medicine (TCM) that exhibit cardioprotective properties by modulating the Sirt1/AMPK pathway, to provide a basis for the development of Sirt1/AMPK activators or inhibitors for the treatment of HF and other cardiovascular diseases (CVDs).

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1. Introduction

One of the leading causes of mortality in the world is heart failure (HF), which is characterized by the inability of the heart to effectively pump enough blood to meet the needs of the body for nourishment and oxygen [1]. Over 64.34 million people were affected by HF in 2020. The annual global economic burden of the disease is more than \$300 billion. Between 1992 and 2020, the prevalence of HF increased by 3.9% in elderly people [2]. The median survival of patients with HF was only 2.1 years despite therapeutic advances, and the 5-year mortality hazard ratio of hospitalized patients with HF was approaching 76% [3,4]. People

with HF typically show symptoms of exercise intolerance, and some with tension, concern, shortness of breath, and lack of energy [5,6].

HF is a clinical syndrome with complex pathophysiology, characterized by phenotypes including insufficient myocardial contractility, diminished response to stresses, loss of cardiomyocytes, and increased fibrosis [7]. Impaired energy metabolism is one of the cornerstones in the pathophysiology of HF. Compromised mitochondrial oxidative phosphorylation leads to multiple defects in both energy supply and demand within the failing heart, resulting in an organ that is both energy-depleted and dysfunctional [8]. Oxidative stress is also an essential pathophysiological mechanism of HF, abnormalities in the oxidative and antioxidant states causing oxidative stress were found in HF of various etiologies [9]. Excessive intracellular reactive oxygen species (ROS) accumulation directly impairs the physiological function of cardiomyocytes (including electrophysiology and the contractile machinery), subsequently promoting heart fibrosis [10]. In normal hearts, autophagy can mediate the iteration of organelles by eliminating ROS producers like dysfunctional mitochondria [11]. But impaired autophagy accelerates cardiomyocyte loss, adverse ventricular remodeling, and

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HF progression [12]. In addition, excessive autophagy has also been proposed as a maladaptive response that contributes to HF progression. An important example is toll-like receptors (TLRs), which are immunoreceptors involved in host defense against invading microbes. Overexpression of TLRs could contribute to persistent autophagy and thus promote the development of HF [13]. Apoptosis, as a genetically programmed event in normal cells, is also another pivotal promoter of cardiac cell fate and plays an important role in the development and progression of HF. The overexpression of apoptosis might create a deadly dilated cardiomyopathy. Apoptotic cells were detected by the number of myocardial nuclei labeled with fluorescein, the levels of apoptosis in cardiomyocytes increased 232 times in HF [14]. In addition, severe HF is associated with elevated levels of apoptosis related factors such as B-cell lymphoma-2 (Bcl-2)-associated x (Bax). Overexpression of the BH4 domain of the anti-apoptosis Bcl-2-related gene long isoform (Bcl-xl) protein could avert the onset of HF [15].

Sirtuins belong to a family of nicotinamide adenine dinucleotide (NAD⁺)-dependent protein deacetylases, which include silent information regulator (Sirt1)-7 [16]. Sirt1 is one of the most deeply and widely studied sirtuins in heart and is intimately connected to adenosine monophosphate-activated protein kinase (AMPK) [7]. Under the pathogenic circumstances, Sirt1 was activated to support cardiac cell survival. Levels of HF indicators that include atrial and brain natriuretic peptides are increased in Sirt1 knockout mice, and inhibition of endogenous Sirt1 enhanced apoptosis accumulation [17]. Sirt1 was downregulated in the HF samples compared with healthy cardiomyocytes and was accompanied by an increased oxidative stress index [18]. Similar investigations showed that Sirt1 was connected with autophagy and energy metabolism [19,20]. AMPK, a heterotrimeric complex made up of the three subunits that are α , β and γ , responds to HF by maintaining energy homeostasis, promoting the production of autophagosomes, and limiting cardiac apoptosis and oxidative stress [21,22]. AMPK and Sirt1 are vital in an orchestrated network controlling cellular homeostasis and largely need each other as “transit stations” to act. A prominent example is that AMPK and Sirt1 directly activate proliferator-activated receptor γ coactivator 1 α (PGC-1 α) through phosphorylation (AMPK) and deacetylation (Sirt1), respectively. However, the PGC-1 α mutation that lacks the two AMPK-phosphorylation sites reduces deacetylation of PGC-1 α [23]. It may be that phosphorylation of PGC-1 α constitutes a priming signal for subsequent deacetylation by Sirt1. Furthermore, the regulatory effect of Sirt1 on mammalian target of rapamycin (mTOR) may be partially mediated by AMPK, which is mentioned in Section 2.3 [24]. In addition, there is a feedforward relationship between AMPK and Sirt1 in the heart. In both sham and ischemia conditions, AMPK silenced hearts revealed significantly decreased Sirt1 activity compared with wild-type rat hearts. FK866, a nicotinamide phosphoribosyl transferase (Nampt) inhibitor that decreases the level of NAD⁺ to inhibit Sirt1 activity, decreased cardiac AMPK activation in ischemia [25]. Hence, when treatment with AMPK or Sirt1 activators or inhibitors alone is not adequate to treat cardiovascular diseases (CVDs), therapy based on the synergistic effect of AMPK and Sirt1 may make up for the defects. Previous research has confirmed that in the regulation of glucose and lipid metabolism in mice, leucine, a Sirt1 activator, co-treated with metformin (AMPK activator) not only reduced the dosage of metformin by 83% and improved drug tolerability, but also improved efficacy by 66% compared to full-dose metformin (AMPK activator) monotherapy [26]. Although these two targets have been extensively studied and their roles in specific diseases (such as non-alcoholic fatty liver) extensively explained, the magnitude and significance of a synergistic interaction between AMPK and Sirt1 in heart are seldom reported [27,28].

At present, the traditional treatments for HF include angiotensin converting enzyme inhibitors (ACEIs), β -adrenergic blockers, and diuretics. Although these interventions can extend survival, the quality of life of patients still needs to be raised. Clinical trials investigating the treatment of HF have revealed severe side effects such as hypotensive, hyperkalemia, and dizziness with these drugs [29]. Moreover, patients still face great challenges with treatment or prevention due to the possible conflict between excessive diuretic doses and ACEIs [30]. In essence, at certain stages of development of HF, existing methods and these drugs may not be enough. Traditional Chinese medicine (TCM) is characterized by having multi-components and multi-targets, such as the ginseng in TCM, which not only contains a large number of ginsenosides (including ginsenoside Rb1, ginsenoside Rg1, and ginsenoside Rd), but also acts on various targets to play a role (such as anti-inflammatory by the NOD-like receptor protein 3 (NLRP3) target, and anti-apoptosis by the Bax and Bcl-2 targets [31]). Many TCM formulas have been widely used in the treatment of HF (e.g., Danqi tablets and Qiliqiangxin capsules) [32]. A particular instance is a randomized double-blind controlled trial that indicated that Qiliqiangxin capsule may effectively improve quality of life in patients with chronic HF by decreasing the plasma N-terminal pro-brain natriuretic peptide level and increasing left ventricular ejection fraction [33]. With the development of society, complementary therapy based on TCM can be recommended as an attractive treatment. Herbal medicine and constituents from TCM, such as flavonoids and polyphenols, protect the heart by modulating the Sirt1/AMPK pathway.

Consequently, the retrieved literature was consulted from 2013 to 2023 using the PubMed, Google Scholar, Chinese National Knowledge Infrastructure (CNKI), and Web of Science databases, and considering the following keywords: Sirt1, AMPK, plant extracts, traditional Chinese medicine, and heart failure. We summarized the herbal medicines showing protective properties in CVDs via activation of Sirt1/AMPK signaling. We hope to provide a reference for follow-up studies on the development and utilization of targeted therapy with Sirt1/AMPK and herbal medicines for treating HF and other CVDs.

2. Sirt1 and AMPK collaborate in HF

Sirt1 exhibits a widespread distribution across the heart, brain, and liver [34,35]. In the adult mouse heart, Sirt1, expressed in both the cytoplasm and nucleus, maintains the appropriate subcellular localization by nucleocytoplasmic shuttling, to perform proper functions in a given physiological context. Sirt1 catalytic activity is regulated by post-translational modifications, including small ubiquitin-related modifier (SUMO)ylation at lysine-73 [36–38]. By binding to target proteins and deacetylating acetyl-lysine residues in them, Sirt1 might modulate the activities of target proteins as well as their intracellular localizations and stabilities [39]. It catalyzes NAD⁺-dependent lysine deacetylation to produce nicotinamide, deacetylated proteins, and 2'-O-acetyl-ADP-ribose (OAADPr, a small signaling metabolic molecule). Nicotinamide is a negative-feedback inhibitor of Sirt1, and OAADPr is converted into adenosine diphosphate ribose to regulate ROS [40–42]. Sirt1 deacetylates several substrates, such as PGC-1 α , peroxisome proliferator-activated receptors (PPARs), and forkhead box family and subfamily O of transcription factors (FOXOs), in response to a range of physiological events [43–45].

AMPK is a highly conserved sensor of intracellular adenosine nucleotide levels. Previous research has shown that an increase in adenosine monophosphate (AMP) triggers AMPK γ subunits to bind AMP, boosting the catalytic activity of the complex and enhancing the phosphorylation of key residue (Thr172 in the mice α -subunits) [46,47]. AMPK can also be directly phosphorylated by upstream activators such as liver kinase B1 (LKB1) (at AMPK α -Thr172). In

[62]. Therefore, it may be that early metabolic improvement drives a beneficial effect in HF. For example, a clinical trial found that trimetazidine controlled resting whole body energy metabolism to improve functional class and left ventricular function in patients [63,64]. In addition, metformin (a typical anti-diabetic drug) decreased cardiac remodeling and maintained left ventricular function by improving the myocardial energy metabolic status in HF [65].

PGC-1 α and PPAR α serve as key transcriptional regulators of cellular energy metabolism [66]. PGC-1 α has been shown to regulate the expression of a variety of coactivated genes, including the nuclear receptors (PPARs family and estrogen receptor related receptors (ERRs)) and non-nuclear receptors (nuclear respiratory factors family (Nrfs)), thereby controlling genes that mediate the transfer of myocardial fuel substrates and are involved in mitochondrial oxidative phosphorylation and the electron transport chain [67–70]. Sirt1 can bind to PGC-1 α in the central regulatory region between amino acids 200 and 400 and subsequently deacetylate PGC-1 α , thereby promoting mitochondrial oxidative phosphorylation and production of adenosine triphosphate (ATP) [71]. After treatment with nicotinamide in cardiomyocytes *in vitro*, the acetylation level of PGC-1 α is increased and its activity is decreased [72]. PGC-1 α in the hypoxia-induced H9c2 cells is similarly reliant on the AMPK signaling pathway, since after AMPK knockdown, the upregulation of PGC-1 α was abolished [73]. In 2007, with coimmunoprecipitation experiments and mass spectrometry analysis, Jäger et al. [74] found that AMPK directly phosphorylated the PGC-1 α protein at threonine-177 and serine-538. The PPAR family of transcription factors, which includes PPAR α , PPAR β and PPAR γ , stimulates fuel substrate utilization via improving mitochondrial function and fatty acid oxidative pathways [75]. However, the mechanism by which PPAR is regulated is not entirely clear in the context of HF. For instance, PPAR α activation promotes fatty acid uptake and oxidation, and fenofibrate (PPAR α artificial ligands) protects against endothelin-induced HF [76]. In contrast, persistent PPAR α activation induces insulin resistance, lipid accumulation, and lipotoxicity [77]. However, cardiomyocyte specific PPAR γ knockout and agonist both induced cardiac hypertrophy in mice [78]. Sirt1 mediated regulation of PPAR seems also complex. It was revealed that PPAR α bound and recruited Sirt1 to the ERR response element, thereby suppressing ERR target genes, and thereafter facilitating the process of cardiac hypertrophy [40]. ERR are recognized as pleiotropic regulators of heart function. The gene disruption of ERR α in mice led to HF and impaired mitochondrial ATP production [79]. However, another study revealed that in a phenylephrine-induced neonatal cardiomyocyte hypertrophy model, PPAR α is activated by Sirt1 overexpression, thereby upregulating fatty acid oxidation and inhibiting cardiomyocyte hypertrophy [80]. All in all, PPAR is necessary for the heart, but too high or too low stock of PPAR will do some damages to the heart. The heart also responds to external stimuli through adaptive regulation, and the full panoply of effector mechanisms remains to be elucidated. In addition, AMPK also seems to modulate the transcriptional activity of PPAR. PPAR α and PPAR γ agonists significantly enhanced glucose uptake in the papillary muscle of rat hearts, while this effect was blocked after AMPK was inhibited [81]. Whether this effect is mediated by Sirt1 remains to be elucidated. In addition, earlier investigations have revealed that the Compound C (AMPK inhibitor) restricts the protein expression and transcriptional activity of Sirt1, accompanied by the recovery of cardiac hypertrophy and the blocking of fatty acid oxidation, which confirms that AMPK regulates energy metabolism partly through the Sirt1 pathway [82].

In addition, AMPK mediates glucose metabolism in cardiomyocytes potentially through other pathways. For example, phosphofructokinase (PFK-2), as one of the isoforms of PFK, could

convert fructose 6-phosphate to 2,6-bisphosphate in glycolysis to promote glucose metabolism [83]. AMPK, *in vitro* cardiomyocytes, can directly phosphorylate and activate PFK-2 at Ser466 [84]. Furthermore, the regulatory effect of AMPK on glucose metabolism in cardiomyocytes is presumably mediated via modifying glucose transporters. An example of this is the study carried out by Li et al. [85] in which AMPK is involved in the glucose transporter type 4 (GLUT4) translocation and leads to GLUT4 transport from intracellular compartments to the plasma membrane of cardiomyocytes, thereby increasing glucose absorption.

2.2. Regulation of apoptosis by Sirt1 and AMPK in HF

During the progression of HF, cardiomyocyte apoptosis is of great significance [86]. Accumulating evidence established that myocardial apoptosis was one of the critical indicators linked with early symptomatic post-infarction HF [87]. In both *in vivo* and *in vitro* experiments, apoptosis was confirmed to positively correlate with the severity of cardiac dysfunction [88]. Cardiomyocyte viability is dependent upon the action of opposing apoptotic and survival pathways. Thus, the possibility of reducing cardiomyocyte loss by inhibiting apoptosis has potentially important implications for the treatment of HF. For example, by suppressing mitochondrial cytochrome c to attenuate activation of the caspase cascade to anti-apoptosis, carvedilol can contribute to the beneficial effects in patients with HF [89].

The upstream targets for regulating cardiomyocyte apoptotic markers (such as Bax and Bcl-2) include p53, MAPKs family, and nuclear factor-kappa-B (NF- κ B). p53 is a potent inducer of apoptosis. It can directly bind and inhibit anti-apoptotic Bcl-2 protein and induce transcription of the pro-apoptotic Bax [90]. A study found that replication-defective adenovirus infected cardiomyocytes could result in an increase in p53 transcriptional activity and protein accumulation, eventually causing apoptosis-specific morphological changes [91]. Sirt1 mediated deacetylation antagonizes p53-dependent transcriptional activation, inhibiting p53-dependent apoptosis [92]. An increment of p53 protein acetylation, when the dominant negative form of Sirt1 was overexpressed, activated p53 binding to the promoter of Bax and upregulated Bax expression [17,93]. Furthermore, AMPK was identified to directly phosphorylate p53 at Ser 15. However, conflicting results have been reported regarding the regulation of apoptosis by AMPK/p53 pathway. Jones et al. [94] reported that AMPK improves cell survival through phosphorylation of p53 under energy stress conditions. In contrast, another study found that AMPK dependent phosphorylation of p53 led to cellular apoptosis under similar carbon source depletion [95]. These findings could be due to different cell types and treatment durations. NF- κ B super family is an important regulator of apoptosis and consists of some genes encoding the members, such as RelA/p65, RelB, p50 and p52 [96]. Functional loss of NF- κ B signaling in cardiac myocytes increases cardiomyocyte susceptibility to tumor necrosis factor- α (TNF- α)-induced apoptosis [97]. Sirt1 can regulate the transcription of NF- κ B by combining with the RelA/p65 subunit of NF- κ B to deacetylate it at lysine 310, thereby protecting against apoptosis [98]. Although the NF- κ B subunits are not direct phosphorylation targets of AMPK, AMPK has a similar inhibitory effect on NF- κ B, and the effect of NF- κ B by AMPK is partly mediated by Sirt1 [99]. MAPK family members, including p38 MAPK, extracellular signal-regulated kinase (ERK) and c-jun nh2-terminal kinase (JNK), play essential roles in oxidative stress-induced apoptosis and other forms of apoptosis [100]. p38 MAPK activation leads to cell apoptosis through alterations in the expression of proteins involved in apoptosis, including Bcl-2 and Bax. These targets are also involved in the pro-apoptosis function of JNK. Similarly,

phosphorylated ERK interacts with downstream effectors Bcl-2 and caspase signaling pathways to adjust cell proliferation and apoptosis. Blockade or deletion of cardiac ERK1/2 will increase the susceptibility of the heart to HF under external stimulation and with an increase in myocyte apoptosis [101]. It has been demonstrated that Sirt1, by enhancing Akt phosphorylation, can inhibit p38 and JNK and enhance ERK1/2 phosphorylation to alleviate apoptosis in ischemia-reperfusion (I/R) rats [102]. The specific mechanisms may be that Sirt1 can activate Akt by binding the pleckstrin homology (PH) domain and deacetylating Lys14 and Lys20, and subsequently, Akt phosphorylates ASK1 that acts upstream of JNK and p38 MAPK. Acetylation of Akt prevents subsequent phosphorylation of Akt [103]. Another study reported that palmitic acid induced cardiomyocyte apoptosis and increased the phosphorylation of stress-activated protein kinase (SAPK)/JNK, and these effects were completely inhibited after treatment with aminoimidazole carboxamide ribotide (AICAR) (AMPK agonist) [104]. It is worth noting that AMPK could directly phosphorylate Akt at Thr308 [105]. Possibly, this effect is also mediated through the Akt pathway. In addition, there are several downstream effector molecules (including autophagy-related mTOR) in tandem with Akt, which is mentioned in Section 2.4.

2.3. The role of Sirt1/AMPK-mediated oxidative stress in HF

ROS refers to all the reactive chemical species derived from oxygen. Superoxide that is generated by mitochondrial respiration is dismasted by manganese-superoxide dismutase (SOD) to form hydrogen peroxide and further originate the highly reactive hydroxyl radical via the Fenton reaction [106]. Excessive ROS buildup may lead to oxidative stress and then result in cardiac damage. Antioxidant defense systems guarantee a balance between the production and neutralization of ROS to maintain a normal heart [107]. The important contribution of ROS to the pathophysiology of HF may indicate that therapeutic strategies aimed at reducing oxidative stress within the myocardium may beneficially influence the course of the disease. For example, vitamin C, as an optimal antioxidant, protects cardiac function and structure by lowering oxidative stress in doxorubicin (DOX)-induced HF [108].

Oxidative stress is one of the driving events of apoptosis, and many upstream effectors share the regulation of oxidative stress and apoptosis. As indicated before, the MAPK family is regulated by Sirt1 and AMPK, playing a role in anti-apoptosis as well as producing the effect of antioxidant stress [109]. In addition, Mn-SOD and catalase are well-characterized targets of the FOXO family of transcription factors, including FOXO1a, FOXO3a, and FOXO4 [110]. FOXO3a contributes to anti-oxidative stress by directly raising the quantities of Mn-SOD messenger RNA and protein [111,112]. Chromatin immunoprecipitation confirmed that FOXO4 binds to and regulates ubiquitin specific peptidase 10 (USP10), leading to a reduction in the content of SOD and an enhancement in the malondialdehyde (reflecting the antioxidant potential) [113]. Some studies have reported that Sirt1 binds and deacetylates FOXO3 and FOXO4 in response to oxidative stress and increases the antioxidant stress capabilities of FOXO3 and FOXO4 [114–116]. *In vitro* kinase assays, AMPK can phosphorylate FOXO3 at serine and threonine, subsequently promoting FOXO3 translocation into the nucleus, then promoting FOXO3 binding and activating thioredoxin (a major antioxidant system) [117]. Nuclear factor erythroid2-related factor 2 (Nrf2) regulates the transcription of enzymatic antioxidant defense proteins, including heme oxygenase 1 (HO-1), SOD, and NAD(P)H dehydrogenase quinone 1 (NQO1) [118]. Sirt1 can physically interact with Nrf2 *in vitro*, and significantly promote the deacetylation of Nrf2, accompanied by a decrease in the level of oxidative stress [119]. AMPK phosphorylated Nrf2 at the Ser550

residue and promoted gene transactivation driven by the antioxidant response element of Nrf-2 [120]. In the *in vitro* kinase and peptide competition assays, inhibition of AMPK remarkably reduced the expression of Nrf2 and HO-1 in the diabetic cardiomyocytes, therefore increasing oxidative stress damage [121]. It may be that AMPK was also an upstream target of Nrf2.

2.4. Regulation of autophagy by Sirt1 and AMPK in HF

Autophagy is an endogenous protective process that helps maintain the quality of the intracellular environment by eliminating misfolded proteins and malfunctioning organelles. However, autophagy has been proposed as a “double-edged sword” in heart tissue. The level of autophagy in the heart may determine whether the autophagy will be protective or deleterious. On the one hand, the loss of autophagy can destabilize proteostasis and elevate intracellular oxidative stress, which is critically involved in the development of HF [122]. For instance, injection of Tat-Becn1 (a potent inducer of autophagy) attenuated cardiac injury by resorting to mitochondrial autophagy. In a transverse aortic constriction (TAC)-induced HF mouse model, knockout of Eva-1 homologue A (a protein that can activate cell autophagy) generated myocardial contractile dysfunction and cardiac hypertrophy in mice [123,124]. On the other hand, excessive autophagosome production leads to insufficient lysosomes that bind to autophagosomes and to incomplete degradation of autophagosomes, which in turn impairs autophagic flux, causing further damage to cells. An HF mouse model study showed that isoprenaline (ISO) led to a sustained increase in autophagy accompanied cardiac dysfunction [125].

The mTOR protein is a serine/threonine kinase that exists in two distinct complexes (mTORC1 and mTORC2). One of the functions of mTORC1 is to negatively regulate autophagy via phosphorylating activators of autophagy, such as phosphatidylinositol 3-kinase catalytic subunit type 3/vacuolar protein sorting 34 [126]. mTORC2, through its downstream target kinase Ypk1, inhibits the Ca²⁺ and Cnd1/calmodulin-dependent phosphatase, calcineurin, to enable the activation of the amino acid-sensing eukaryotic translation initiation factor 2 subunit alpha (EIF2S1/eIF2a) kinase, Gcn2, and promote autophagy [127]. An investigation discovered that AICAR could increase autophagy by negatively affecting the mTORC1 target and lowering the phosphorylation of the mTORC1 substrates (eukaryotic initiation factor 4E binding protein-1 (4EBP1) and ribosomal S6 kinase (S6K)) [22]. This mechanism of the effect may be that AMPK phosphorylates the tuberous sclerosis complex 2 (TSC2), the upstream suppressor of mTORC1, thereby suppressing mTORC1 [128]. In addition, another study reported that AMPK inhibits mTORC1 via phosphorylating raptor (inhibitory phosphorylation of an essential mTORC1 protein) on two conserved serine residues, Ser 722 and Ser 792 [129]. Noticeably, Sirt1 was a negative regulator of mTORC1 in mouse and human cells; depleting Sirt1 in HeLa cells presented higher phosphorylation of 4EBP1 and S6K, and this change was reversed by a TSC2 knockdown [130]. It may be attributed to the direct interaction of Sirt1 with TSC2 or the regulation of mTORC2 via the AMPK pathway. In addition, another study found that AMPK phosphorylated Akt (the mTORC2 effector) at Ser 473 to subdue autophagy and attenuate cardiac hypertrophy in HF related to mTORC2 activation [107]. The likely explanation for this paradoxical outcome was that AMPK has a bidirectional influence on autophagy regulation, whether AMPK triggers or suppresses autophagy during HF depends on the degree of autophagy. Autophagy is mediated by a cascade reaction of the autophagy-related genes (Atgs), and decreased expression of key Atgs, such as Atg5, Atg6, Atg7, and Atg12, would substantially inhibit the autophagic process [131]. Previous research has found that Sirt1 could bind with Atg5, Atg7, and Atg8 and directly deacetylate them,

thus improving autophagy to protect cells [132]. In addition, elongation factor-2 (eEF2) is phosphorylated and activated by eEF2-kinase (eEF2K) and thereby mediates autophagy [133]. Sirt1 could enhance autophagy by promoting eEF2 phosphorylation to enhance cardiomyocyte survival. After Sirt1 expression was inhibited by EX257, phosphorylation of eEF2 by eEF2K returned to the basic level. However, co-immunoprecipitation assay revealed that Sirt1 was not associated with eEF2 or eEF2K, but eukaryotic initiation factor-2 α (eIF2 α) was co-immunoprecipitated with eEF2K [134]. Previous studies demonstrated that Sirt1 can physically interact with and deacetylate eIF2 α at lysine K143 [135]. Therefore, the activation of the eEF2K/eEF2 pathway by Sirt1 may involve eIF2 α . By analyzing the labeled peak by nano electrospray ionization tandem mass spectrometry (ESI-MS/MS), Browne et al. [136] found that AMPK can directly phosphorylate eEF2K and that the major site of phosphorylation is Ser-78 in a regulatory domain of eEF2K. Unc-51-like kinase 1 (ULK1) is a protein kinase that is motivated by autophagy; upon autophagy induction, the ULK1 complex translocates for autophagy initiation and regulates the autophagy process [137]. AMPK could bind to the PS domain of ULK1 and promote autophagy [138]. ULK1 may also be one of the upstream targets of Sirt1. In a study, it was found that endothelial nitric oxide synthase may favorably control Sirt1, but this effect was blocked in vascular endothelial cells with ULK1 knockout [139]. This may offer another route for AMPK to influence Sirt1. In addition, mTOR and ULK1 are key pathways in the regulation of mitophagy (a selective autophagy mode that controls mitochondrial quality by removing damaged or aging mitochondria). AMPK and Sirt1 can mediate mitochondrial autophagy through mTOR and ULK1 targets [140]. In addition, PTEN-induced kinase 1 (PINK1), as a molecular sensor of mitochondrial health, is a serine/threonine kinase that recruits and activates parkin and mediates ubiquitination of mitochondrial substrates when it detects mitochondrial damage, then induces mitochondrial autophagy. AMPK α can promote mitochondrial autophagy and prevent the progression of HF via directly phosphorylating and activating PINK1 at Ser495 [141]. Furthermore, in hypoxic cardiomyocytes, activation of Sirt1 could improve autophagic flux and reduce apoptosis, but Compound C abolished the effect of Sirt1 on autophagy activation. This study demonstrated that Sirt1 promotes autophagy partly via AMPK activation, thereby protecting cardiomyocytes [142].

3. Herbal medicines protect against HF by regulating Sirt1/AMPK signaling pathway

More and more reports have comprehensively investigated the effects of herbal medicines on HF. Increasing results illustrated that the extracts or monomers obtained from natural herbal medicines exerted excellent protective effects on HF via activation of Sirt1/AMPK signaling. In the following section, the beneficial effects and molecular mechanisms of herbal medicine and its constituents on HF are detailed.

3.1. Herbal medicine formula

It has been previously established that ischemic heart disease is the primary cause of HF [143]. Ligation of the left anterior descending (LAD) coronary artery is a common method of inducing cardiac ischemic injury in mice. Perfusion is then used to construct various disease models. Permanent ligation is applied to create myocardial ischemia and HF models while ligation and reperfusion are performed to produce an ischemia-reperfusion injury model. The latter differs from HF models. Nevertheless, ischemia-reperfusion injury exacerbates myocardial damage and accelerates the transition to HF. The administration of Danqi tablets

upregulated AMPK, Sirt1 and PGC-1 α proteins, thereby improving ATP production and heart function in a LAD-induced ischemic injury model [144]. Similarly, Danqi tablets in LAD-induced HF rats restored autophagy and protected against cardiomyocyte injury by upregulating AMPK phosphorylation and reducing mTOR in a rat LAD-induced HF model [145]. Tongxinluo is a Chinese patent medicine that is widely administered to treat various CVDs. Li et al. [146] found that it increased the ejection fraction and improved cardiac function in a LAD-induced myocardial infarction (MI) model. Potential mechanisms of Tongxinluo included the upregulation of AMPK phosphorylation and the downregulation of the mTOR. While Xuefuzhuyu decoction affected hypoxia/reoxygenation (H/R)-induced H9c2 cells injury in the same manner as Danqi tablet and Tongxinluo, its mode of action nonetheless differed from theirs. Xuefuzhuyu decoction reduced AMPK phosphorylation, upregulated mTOR, and inhibited autophagy. This mechanism is consistent with the fact that AMPK bidirectionally regulates autophagy as previously described [147]. *In vitro*, Xuefuzhuyu oral liquid also prevented ischemia-induced cardiac apoptosis by regulating Sirt1 and its associated genes FOXO1, FOXO2, and NF- κ B [148]. In a LAD-induced HF rat model, Linggui Zhugan Decoction improved cardiac energy metabolism by upregulating Sirt1 and AMPK phosphorylation [149]. Shenfu formula consists of ginseng and aconite. In a TAC-induced rat HF model, it improved oxygen consumption and normalized aberrant energy metabolic pathways by modulating the AMPK/PPAR α /PGC-1 α pathway [150]. Nuanxin capsule consists of red ginseng, Coicis Semen, Citri Exocarpium Rubrum, and Radix Aconite Lateralis Praeparata. It inhibited oxidative stress and apoptosis by activating the AMPK/JNK pathway in the same model [151]. The above herbal medicine formulas effects are summarized in Table 1 [144–151].

3.2. Plant extracts

Hongjingtian injection is derived from *Rhodiola wallichiana* var. *cholaensi* and inhibited autophagy and lower cardiac cell apoptosis, downregulated AMPK, and upregulated mTOR protein in a LAD-induced myocardial ischemia-reperfusion injury (MI/RI) model [152]. In the same model, Zhao et al. [153] found that total flavonoids from *Dracocephalum moldavica* alleviated energy metabolism dysregulation via AMPK/Sirt1/PGC-1 α pathway. In a mouse LAD-induced MI injury model, saponins from *Panax japonicus* minimized myocardial necrosis and improved ischemia-induced heart systolic via dose-dependent Sirt1 upregulation and TNF- α downregulation [154]. In a rat LAD-induced HF model, saponins from *Panax notoginseng* increased cardiomyocyte autophagy by promoting AMPK Thr172 and calmodulin-dependent protein kinase II phosphorylation [155]. A *Houttuynia cordata* herbal extract upregulated AMPK, Nrf-2, and PGC-1 α proteins and reduced cardiac oxidative stress in hyperlipidemic mice [156]. In a rat DOX-induced cardiotoxicity model, *Glycyrrhiza glabra* (licorice) root extract upregulated Sirt1 and PPAR α proteins, thereby reducing oxidative stress [157]. In 2016, Chang et al. [158] demonstrated that the TCM drug Alpinate *Oxyphyllae Fructus* improved rat heart function by upregulating Sirt1, AMPK, and PGC-1 α that had been previously downregulated via *D*-galactose treatment. Pomegranate flower extracts normalized cardiac energy metabolism and mitigated cardiac fatty acid oxidation by regulating the AMPK/PPAR α signaling pathway in Zucker diabetic fatty rats [159]. The above plant extracts effects are summarized in Table 2 [152–159], and Fig. 2.

3.3. Constituents from herbal medicines

Flavonoids have a broad range of bioactivity in CVDs. They regulate and normalize oxidative stress, energy metabolism, and

Table 1
Protective effects of herbal medicine formulas on cardiovascular diseases.

Extracts	Main compositions	Animal/cells	Models	Dose/Concentration	Effects	Related molecular targets		Refs.
						Up-regulation	Down-regulation	
DQ	Chinese herbs <i>Salvia miltiorrhiza</i> Bunge and <i>Panax notoginseng</i>	SD rats	LAD-induced ischemic	1.5 g/kg	Improving heart function and production of ATP; Protecting structure of heart	AMPK, Sirt1, PGC-1 α	–	[144]
DQ		SD rats	LAD-induced HF	1.5 g/kg	Improving cardiac function; Increasing the information of autophagosomes	Beclin1, Atg3, AMPK	mTOR, ULK1	[145]
TXL	<i>Radix ginseng</i> , <i>Buthus martensi</i> , <i>Hirudo</i> , <i>Eupolyphaga seusteleophaga</i> , <i>Scolopendra subspinipes</i> , <i>Periostracum cicadae</i> , etc.	SD rats	LAD-induced MI	4 mg/kg/day	Increasing ejection fraction and cardiac function; Reducing myocardial infarction, fibrosis, inflammation and apoptosis	AMPK, Bcl-2	mTOR, Bax	[146]
XFZY	Chinese <i>Angelica</i> , Dried <i>Rehmannia</i> root, Peachseed, Safflower, <i>Radix Paeoniae Rubra</i> , <i>Radix Bupleuri</i> , etc.	SD Rats, H9c2 cells	H/R-induced cardiomyocyte injury	4.5, 9, 18, 36, 72 mg/mL	Inhibiting apoptosis and autophagy of cardiomyocytes	mTOR	AMPK, Beclin1	[147]
XFZYOL		H9c2 cells	Cobalt chloride induced H9c2 ischemic		Reducing apoptosis	Sirt1	FOXO1, FOXO3, NF- κ B	[148]
LGZG	<i>Poria cocos</i> , <i>Neolitsea cassia</i> , <i>Glycyrrhiza</i> and <i>Atractylodes</i>	SD rats	LAD-induced HF	5.4 g/kg	Improving the cardiac function; Enhancing myocardial antioxidant capacity	Sirt1, AMPK, PGC-1 α	–	[149]
SFF	<i>Panax Ginseng</i> and <i>Radix Aconitum carmichaelii</i>	C57 mice	TAC-induced HF	2.5, 5, 10 g/day	Protecting myocardial contraction and diastolic function; Alleviating myocardial necrosis, fibrosis and hypertrophy	AMPK α , PGC-1 α , GLUT4, PPAR α	–	[150]
NX	Red ginseng, <i>Coicis Semen</i> , <i>Citri Exocarpium Rubrum</i> and <i>Radix aconiti lateralis preparata</i>	C57BL/6J mice, H9c2 cells	TAC-induced HF	0.64 g/kg	Improving cardiac function; Inhibiting apoptosis and oxidative stress; Protecting mitochondrial function	AMPK, Bcl-2	Bax, JNK	[151]

SD: Sprague Dawley; DQ: Danqi tablet; TXL: Tongxinluo capsule; XFZY: Xuefuzhuyu decoction; XFZYOL: Xuefuzhuyu oral liquid; LGZG: Lingguizhugan decoction; SF: Shen-fu formulas; NX: Nuanxin capsule; LAD: ligation of the left anterior descending coronary artery; AMPK: adenosine monophosphate activated protein kinase; Sirt1: silent information regulator 1; PGC-1 α : peroxisome proliferator-activated receptor γ coactivator 1 α ; HF: heart failure; Atg: autophagy-related genes; mTOR: mammalian target of rapamycin; ULK1: unc-51-like kinase 1; MI: myocardial ischemia; Bcl-2: B-cell lymphoma-2; Bax: Bcl2-associated x; H/R: hypoxia/reoxygenation; FOXO1: forkhead box family and subfamily O of transcription factor 1; FOXO3: forkhead box family and subfamily O of transcription factor 3; NF- κ B: nuclear factor-kappa-B; TAC: transverse aortic constriction; GLUT4: glucose transporter type 4; PPAR α : peroxisome proliferator-activated receptor α ; JNK: c-Jun NH2-terminal kinase.

apoptosis [160]. In a mouse LAD-induced HF model, tanshinone IIA extracted from *Salvia miltiorrhiza* upregulated AMPK phosphorylation and Bcl-2 and Beclin1 [161]. It also activated Sirt1 and PGC-1 α , thereby ameliorating microvascular and mitochondrial damage [162]. Hence, tanshinone IIA upregulates both AMPK and Sirt1. Acacetin extracted from *Acacia farnesiana* upregulated AMPK phosphorylation and Sirt1 in a rat angiotensin II (Ang II)-induced HF model. Compound C inhibited acacetin-mediated AMPK phosphorylation but not Sirt1 upregulation. In Sirt1 knockdown cells, however, acacetin failed to upregulate AMPK or PGC-1 α . Acacetin also increased the intracellular NAD⁺/NADH ratio [163]. The anti-inflammatory, anti-cancer, anti-obesity, and cardioprotective effects of acacetin have been reported [164]. Acacetin also upregulated Sirt1 and mediated the AMPK/Nrf2 pathway in a rat DOX-

induced cardiomyopathy model and a mouse D-galactose-induced aging model [165,166]. Rhizoma *Anemarrhenae* contains the diphenyl pyrone flavonoid mangiferin. In HF mice, mangiferin alleviated cardiomyocyte apoptosis by upregulating Sirt1 and promoting FOXO3a deacetylation. However, it produced no such effects in Sirt1 knockout mice [167]. Tilianin is a flavonoid glycoside with an extensive range of biological actions, and it ameliorated a mouse LAD-induced MI/RI model. It upregulated the AMPK, Sirt1, and PGC-1 α proteins which, in turn, shrank the cardiac infarcts and minimized cellular swelling and rupture. In contrast, Compound C or EX-527 reversed the foregoing effects [168,169]. Luteolin is a flavonoid in *Lonicera japonica thunb* and *Perillae Folium*. It upregulated Sirt1 and downregulated NLRP3 in a mouse LAD-induced MI/RI model [170]. The flavonol quercetin has multiple biological

Table 2
Protective effects of herbal medicine extracts on cardiomyocytes.

Extracts	Animal/Cells	Models	Dose/Concentration	Effects	Related molecular targets		Refs.
					Up-regulation	Down-regulation	
HJT	C57BL/6 J mice; H9c2 cells	LAD-induced MI/RI	28 μ L/10 g	Attenuating I/R-induced infarct size; Alleviating cardiac cell apoptosis; Limiting over-expression of autophagy	mTOR	AMPK	[152]
DMF	SD rats	LAD-induced MI/RI	60 mg/kg/d	Ameliorating heart disease	AMPK, Sirt1, PGC-1 α	–	[153]
PGS	SD rats	LAD-induced MI	50, 100 mg/kg	Reducing necrotic myocardium; Ameliorating cardiac function	Sirt1, ERK1/2, p38MAPK, Bcl-2	Bax, TNF- α , NF- κ B	[154]
PNs	C57BL/6J mice	LAD-induced HF	10, 100 μ g/mL	Improving survival ratio of MI mice; Preserving cardiac function; Elevating the autophagy of cardiomyocytes	AMPK, CaMKII	ULK1	[155]
HHA	C57BL/6J mice	P407-induced hyperlipidemic	200 mg/kg/day	Improving cardiac remodeling; Attenuating oxidative stress; Promoting mitochondrial biogenesis	AMPK, PGC-1 α	–	[156]
Gg	H9c2 cells	DOX-induced cardiotoxicity	40 μ g/mL	Reducing oxidative stress; Improving cardiac morphology	Sirt1, PPAR α	–	[157]
AOF	SD rats	D-galactose-induced aging mice	50, 100, 150 mg/kg	Improving heart function; Reducing apoptosis	Bcl-2, PI3K, AMPK, Sirt1, PGC-1 α	Bax	[158]
PF	Zucker lean rats	Zucker diabetic fatty rats	500 mg/kg	Reducing cardiac TG content and plasma level	–	PPAR α , AMPK α 2	[159]

SD: Sprague Dawley; HJT: Hongjingtian injection; DMF: *dracocephalum moldavica* total flavonoids; PGS: saponins extract from panax japonicus; PNs: panax noto ginseng saponins; HHA: *Houttuynia cordata* herbal extract; Gg: glycyrrhiza glabra; AOF: alpinate oxyphyllae fructus; PF: pomegranate flower; LAD: ligation of the left anterior descending coronary artery; MI/RI: myocardial ischemia-reperfusion injury; mTOR: mammalian target of rapamycin; AMPK: adenosine monophosphate activated protein kinase; Sirt1: silent information regulator 1; PGC-1 α : peroxisome proliferator-activated receptor γ coactivator 1 α ; MI: myocardial ischemia; ERK1/2: extracellular signal-regulated kinase; p38 MAPK: protein 38 mitogen-activated protein kinase; Bcl-2: B-cell lymphoma-2; Bax: Bcl2-associated x; TNF- α : tumor necrosis factor α ; NF- κ B: nuclear factor-kappa-B; HF: heart failure; CaMK II: calmodulin dependent protein kinase II; ULK1: unc-51-like kinase 1; HF: heart failure.

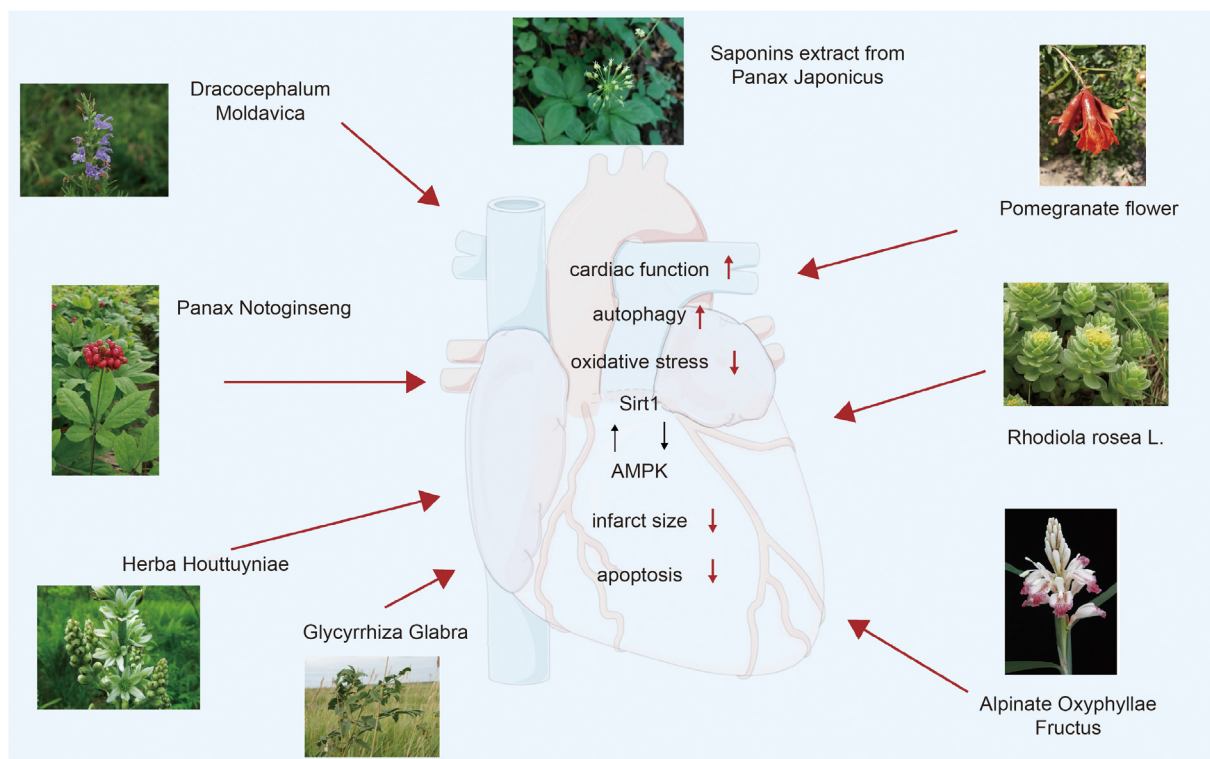


Fig. 2. The protective effects of traditional Chinese medicine extract on heart through silent information regulator 1 (Sirt1)/adenosine monophosphate activated protein kinase (AMPK) pathway. Some common herbal drugs extracts active ingredients work to improve heart autophagy, lower cardiomyocytes apoptosis, and reduce oxidative stress by regulating the Sirt1/AMPK signal pathways. As a result, cardiac function is improved, the size of heart infarct is reduced, and therefore progression of heart failure (HF) is slowed. The above herbal pictures are reprinted from GBIF.org (year) citation guidelines. Available from <https://www.gbif.org/citation-guidelines> with permission and was partly generated using Servier Medical Art, provided by Servier, licensed under a creative commons attribution 3.0 unported license.

activities. *In vivo*, it reduced cardiac cell apoptosis by modulating Sirt1 and PGC-1 α expression [171]. In an *in vitro* H/R model, quercetin also ameliorated mitochondrial oxidative stress by upregulating Sirt1. However, these effects were counteracted by Sirt1 silencing [172]. The flavonoid glycoside icaritin reduced apoptosis by upregulating Sirt1 in the same model [173]. Similar effects were reported for H₂O₂ challenged H9c2 cells treated with naringenin [174]. The flavonoid glycoside rutin reduced apoptosis in an H/R-induced myocardial injury model by upregulating Sirt1 [175]. The isoflavone derivative puerarin was detected in the TCM *Pueraria*. In a LAD-induced MI model, it upregulated Sirt1 and ameliorated myocardial infarction [176].

Sun et al. [177] reported that dihydromyricetin inhibited apoptosis in a rat DOX-induced cardiotoxicity model and the H9c2 cell injury model by upregulating Sirt1. Jaceosidin is an active flavonoid in the TCMs, *Artemisiae Argyi Folium* and *Eupatorii Lindleyani Herba*. It mitigated DOX-induced cardiotoxicity in rats by upregulating Sirt1 [178]. Oroxylin A is a major active flavonoid in *Scutellariae Radix*. It has anti-cancer, anti-inflammatory, and neuroprotectant efficacy [179]. Oroxylin A ameliorated DOX-induced cardiotoxicity by mitigating oxidative damage and apoptosis *in vivo* through the regulation of Sirt1 and Nrf2 expression [180]. In a mouse Ang II-induced cardiac injury model, kaempferol mitigated cardiac oxidative stress by regulating AMPK expression [181]. It also modulated Sirt1 expression and reduced the ROS levels in an *in vitro* anoxia/reoxygenation (A/R) model [182]. The propiophenoid phloretin and the flavonoid isorhamnetin in *Hippophae fructus* ameliorated an *in vivo* mouse streptozotocin-induced diabetes model and an *in vitro* A/R-induced cardiomyocyte injury model by upregulating Sirt1 [183,184]. The β -adrenergic agonist ISO induces MI by promoting apoptosis and downregulating Sirt1 and Nrf2. However, hesperetin from *Citri Reticulatae Pericarpium* reversed these effects and improved myocardial injury in a rat ISO-induced MI model [185]. The flavonoid silibinin in *Silybum marianum* has multiple modes of action in the treatment of hematological disorders and cancers [186]. In an *in vitro* ISO-induced MI model, silibinin inhibited cardiac death and protected against mitochondrial dysfunction in myocardial cells by regulating Sirt1 expression [187]. In an H₂O₂-induced H9c2 cell injury model, liquiritin reduced the ROS levels, attenuated apoptosis and oxidative stress and upregulated AMPK and Sirt1. Nevertheless, Compound C downregulated Sirt1 [188]. Daidzein is extracted from *Pueraria lobata* root. It upregulated AMPK and Sirt1, protected cardiomyocytes from oxidative damage, and reduced oxidative stress in a rat streptozotocin-induced diabetes model [189].

Terpenoids are the largest and most diverse group of secondary metabolites in plants. They have antitumor, anti-inflammatory, and neuroprotectant efficacy. Triterpenoids have the highest pharmaceutical potential of all terpenoid subclasses [190–194]. However, the monoterpenoid oxypaeoniflorin derived from *Paeoniae Radix Alba* and *Paeoniae Radix Rubra* alleviated cardiac damage in a rat LAD-induced MI/RI model possibly by upregulating Sirt1 and downregulating FOXO1 acetylation [195]. The pentacyclic triterpenoid betulin alleviated myocardial inflammation by upregulating Sirt1 in a rat LAD-induced MI/RI model [196]. The monoterpenoid bakuchiol isolated from *Psoralea corylifolia* seeds reduced apoptosis by activating the Sirt1 and PGC-1 α pathways in a rat MI/RI model. The foregoing effects were reversed by Sirtinol (a Sirt1 inhibitor) [197]. Bakuchiol also reduced oxidative stress and upregulated Sirt1 and Nrf2 proteins in a mouse high-fat diet-induced diabetic cardiomyopathy model [198]. The iridoid geniposide isolated from *Gardenia jasminoides* attenuated high-fat diet-induced myocardial inflammation and apoptosis in rats by upregulating Sirt1 and increasing AMPK α phosphorylation, respectively. Whereas AMPK deficiency did not affect cardiomyocyte pro-

inflammatory factor biosynthesis, Sirt1 knockout promoted it [199]. In 2021, Hou et al. [200] demonstrated that geniposide downregulated mitochondrial energy metabolism markers, regulated energy metabolism, and reduced myocardial injury in spontaneously hypertensive rats possibly by upregulating phosphorylation of the AMPK/Sirt1 pathway. AMPK silencing reversed the preceding effects. The sodium salt of isosteviol, a diterpenoid derived from *Stevia rebaudiana*, reduced oxidative stress by upregulating AMPK phosphorylation and Sirt1 in a rat high fat/high cholesterol-induced myocardial dysfunction model [201]. Isosteviol sodium reversed myocardial hypertrophy in an H9c2 cell model by upregulating AMPK phosphorylation and Sirt1. Sirt1 expression was higher in response to a combination of the polyphenol resveratrol and isosteviol sodium than resveratrol alone. In contrast, EX-257 treatment significantly downregulated Sirt1 [202]. The diterpene lactone ginkgolide B is derived from the dried roots and leaves of *Ginkgo biloba*. In AngII-treated H9c2 cells, it activated autophagy and reduced oxidative stress by upregulating Sirt1 and FOXO1 proteins [203].

Polyphenols have a wide range of biological and pharmacological effects on CVDs, brain injury, and gut microbiota metabolism [204]. Resveratrol is extracted from giant knotweed rhizome. It significantly upregulated both Sirt1 and AMPK, improved cardiac function, and lowered mortality in a rat LAD-induced HF model. In contrast, nicotinamide reversed the foregoing effects [205]. However, resveratrol neither upregulated AMPK nor protected cardiomyocyte mitochondria in Sirt1 knockout mice [206]. Hence, Sirt1 mediated the action of resveratrol on AMPK. In a rat DOX cardiotoxicity model, the stilbene polyphenol pterostilbene, a resveratrol derivative, alleviated mitochondrial damage and oxidative stress in a dose-dependent manner. Nevertheless, PGC-1 α was not activated and the preceding effects were partially reversed in the presence of AMPK knockout or EX257 treatment [207]. Punicalagin counteracted cardiomyocyte apoptosis and inflammation in a rat LAD-induced MI/RI model by upregulating the Sirt1/Nrf2 pathway while downregulating inhibitory kappa B alpha phosphorylation and TNF- α [208]. The low-molecular-weight polyphenol curcumin extracted from *Curcuma longa* L. reduced cardiac apoptosis and alleviated oxidative stress in MI rats by modulating Sirt1 and FOXO1 expression [209]. Curcumin demonstrated comparable effects in a mouse diabetic cardiomyopathy model [210]. The polyphenolic antioxidant ellagic acid occurs in various fruits and vegetables. It upregulated Sirt1 and FOXO1 deacetylation and prevented oxidative stress in a rat diabetic cardiomyopathy model [211]. In the same model, rosmarinic acid mitigated cardiomyocyte mitochondrial damage by upregulating Sirt1 and PGC-1 α . However, Sirt1 knockout counteracted these effects [212].

The saponins in various TCM formulations have neuroprotectant and anti-cancer efficacy and attenuate nerve pain [213–215]. The ginsenosides Rc and Rb2 enhanced cardiac mitochondrial biosynthesis and glucose uptake, improved energy metabolism, and upregulated Sirt1 in a rat I/R model. Both foregoing substances are saponins derived from ginseng (*Araliaceae*) [216,217]. Araloside C extracted from the root bark of *Aralia elata* prevented cytotoxicity by upregulating AMPK protein in an *in vitro* H9c2 cardiomyocyte damage model [218].

Numerous other plant natural products also have cardioprotective efficacy mediated by Sirt1/AMPK signaling. In a mouse arsenic trioxide injection-induced MI model, 6-gingerol derived from *Zingiberis Rhizoma Recens* (ZRR; Sheng Jiang) suppressed oxidative stress and attenuated myocardial mitochondrial damage by upregulating AMPK, Sirt1, and PGC-1 α proteins [219]. In addition, Li et al. [220] reported that the phenolic compound salvianolic acid B from *Salviae miltiorrhizae* ameliorated cardiac function and reduced myocardial apoptosis in a rat LAD-induced MI model. Nevertheless,

EX257 addition reversed the preceding effects and downregulated AMPK phosphorylation and Sirt1 protein. Salvianolic acid B upregulated the AMPK/Phosphoinositide 3-kinase (PI3K) pathway, reduced infarct size, and improved cardiac function. The same study also showed that the mechanism of tanshinone IIA resembled that of salvianolic acid B [221]. In a rat LAD-induced AMI/R model and a myocardial cell oxygen-glucose deprivation-induced injury model, arctigenin inhibited cardiomyocyte apoptosis, oxidative stress, and inflammation and upregulated Sirt1 and AMPK phosphorylation in a dose-dependent manner. Compound C downregulated AMPK and Sirt1 whereas the Sirt1 inhibitor Sirt1-IN-1 did not alter AMPK phosphorylation. Hence, arctigenin upregulated Sirt1 by activating AMPK [222]. The bioactive alkaloid berberine isolated from various TCM formulations has antimicrobial, antidiabetic, and anti-cancer efficacy [223]. LAD-induced I/R injury is associated with excessive autophagy. However, berberine mitigates autophagy by downregulating mTORC2 and AMPK phosphorylation [224]. In a mouse DOX-induced aging heart model, berberine protected against oxidative stress and apoptosis by upregulating Sirt1 [225]. In a rat ISO-induced HF model, the phenylethanol glycoside echinacoside from *Cistanche Herba* mitigated mitochondrial oxidative damage and apoptosis by upregulating Sirt1 and FOXO3a [226]. The anthraquinone rhein is anti-inflammatory, antitumor, and hepatoprotective. In a mouse Ang II-induced cardiac remodeling model, it upregulated AMPK and suppressed oxidative stress [227]. Thymoquinone is derived from *Nigellae Semen*. In an *in vitro* MI/R model, it improved cardiac function, reduced apoptosis, attenuated oxidative stress damage, and upregulated Sirt1 protein in a concentration-dependent manner [228]. The phenolic hydroxyl honokiol is extracted from *Magnoliae Officinalis Cortex*. In a rat LAD-induced MI/RI model, it reduced oxidative stress and inhibited cardiac apoptosis by upregulating the Sirt1/Nrf2 pathway [229]. The alkaloid capsaicin is isolated from chili pepper. In an *in vitro* H/R model, it reduced oxidative stress by upregulating Sirt1 [230]. The ester crocin is extracted from *Crocus sativus*. Wang et al. [231] reported that in a rat LAD-induced I/R injury model, crocin reduced cardiac apoptosis and endoplasmic reticulum stress and protected myocardial cells against I/R injury by upregulating Sirt1 and Nrf2. However, the preceding effects were reversed by nicotinamide. Above constituents from herbal medicines effects were summarized in Table 3 [161–163,165–167,169–178,180–185,187–189,195–203,206–212,216–222,224–231], and Fig. 3.

4. Discussion and perspectives

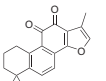
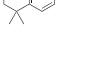
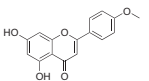
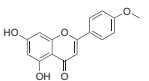
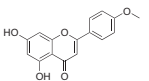
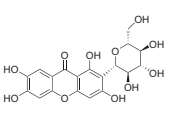
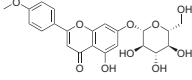
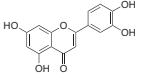
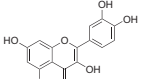
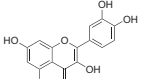
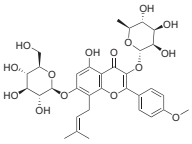
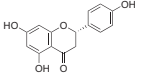
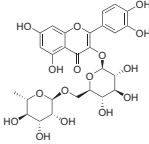
The present review demonstrated that the numerous target molecules can affect the fuel-sensing Sirt1/AMPK pathway that is evolutionarily conserved among different cell types. Sirt1 and AMPK regulate PGC-1 α , thereby improving cardiac fatty acid and glucose metabolism, regulating p53 targets, and alleviating apoptosis. They also decrease ROS by regulating FOXOs and improve autophagy by mediating mTOR. Sirt1 and AMPK may also protect against HF by modulating other targets. Here, we summarized the natural constituents including flavonoids, terpenoids, polyphenols, and saponins in herbal medicines and their extracts that have demonstrated prophylactic efficacy against HF. Most of these substances alleviate apoptosis and oxidative stress, increase autophagy, and improve energy metabolism in HF. The primary mechanism common to all these therapeutic effects is the activation of the Sirt1/AMPK signaling pathway. The present review provided a theoretical and practical reference for the development of natural products that treat cardiovascular disorders by targeting Sirt1/AMPK.

AMPK is a heterotrimeric complex comprising ≤ 12 distinct proteins that are formed by assorting various subunits. In humans, $\gamma 2$ missense mutations cause glycogen-storage cardiomyopathy. In pigs,

however, a $\gamma 3$ mutation causes muscle glycogen accumulation [232]. Thus, the arrangement of AMPK subunits in humans may differ from those in other animals. The use of suitable and appropriate animal models may determine whether the AMPK activators being investigated could, in practice, improve cardiovascular function *in vivo*. Sirt1 is known as a longevity gene. In mice, both Sirt1 overexpression and silencing downregulated nuclear-encoded mitochondrial genes [233]. Hence, only a low Sirt1 expression level may be required to induce the foregoing genes in cardiac mitochondria. Future research should investigate agonists and inhibitors targeting AMPK or Sirt1 for the treatment of HF and other CVDs. Nevertheless, Sirt1 and AMPK expression levels may change in response to aging and/or disease [93,227,234]. Thus, it might be more successful to combine with treatment of Sirt1 and AMPK activators or inhibitors when the endogenous Sirt1 or AMPK is too high or too low. This gives us a promise. In the foregoing overview of TCM, some drugs play their role through Sirt1-mediated AMPK, some regulate Sirt1 through AMPK. Thus, the compatibility of combinations of multiple medications may have to be evaluated. A Sirt1 activator might upregulate AMPK just as an AMPK activator might upregulate Sirt1. A prior study showed that Sirt1 downregulation impeded AMPK activation in aging hearts [25]. Moreover, Sirt1 and AMPK may operate in tandem to treat various conditions and disorders. They are indispensable targets in the treatment of acute renal injury, renal fibrosis, and other kidney diseases [235]. They also play important roles in the chemotherapeutic resistance of patients with gastric cancer, Sirt1 inhibits chemoresistance and cancer stemness of gastric cancer by initiating an AMPK/FOXO3 positive feedback loop [236]. HF is a complex clinical syndrome. Except when it is the result of mechanical injury, its co-morbidities may include vascular and skeletal muscle dysfunction. The compounds described herein demonstrated protective efficacy against certain heart diseases. Nonetheless, the pleiotropic effects of these substances on multiple organ systems merit further exploration.

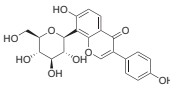
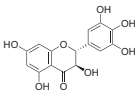
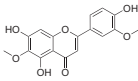
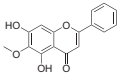
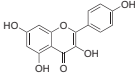
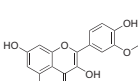
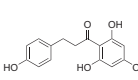
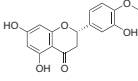
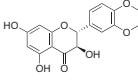
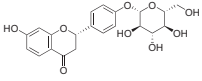
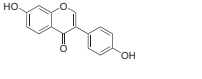
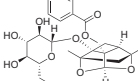

The relative efficacies of the aforementioned natural compounds as Sirt1/AMPK activators in the prevention and therapy of HF and other CVDs are widely variable. Some of the flavonoids described in this paper have considerable disparities in bioavailability because of their distinct forms of existence. On the one hand, due to their hydrophilicity, flavonoid glycosides could not rapidly diffuse across the intestinal membrane during ingestion. On the other hand, although flavonoid aglycons have high permeability, their oral bioavailability is low due to their poor solubility [237]. Other phenolic compounds confront the same problems in cardiovascular disease, they not only have low oral bioavailability, but also have poor water solubility. Therefore, in order to expand their clinical application, one alternative method, just as some other TCM constituents also face low bioavailability is to make derivatives (structural modifications) and modify dosage forms [238]. Such as pterostilbene, a dimethyl derivative of resveratrol, which has improved bioavailability and similar pharmacological effects [207]. Another study revealed that solid orally delivered lipid resveratrol-loaded nanoparticles had 8.035-fold higher bioavailability than resveratrol suspension [239]. Nevertheless, the pharmacological effects and efficacy of structurally and dosage form-modified drugs must be carefully evaluated. Furthermore, many of these natural plant products are pleiotropic. For this reason, it is difficult to determine whether it is their direct biological modes of action or their side effects that ameliorate cardiopathy. In addition, it remains to be established whether it is the parent compounds or their metabolites that have prophylactic or therapeutic efficacy against CVDs. For example, although the protective effects of polyphenols on HF have been reviewed, polyphenols are extensively metabolized by cytochrome P450 and UDP-glucose pyro-phosphorylase in the liver and intestinal epithelium [240,241].

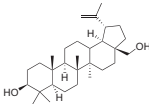
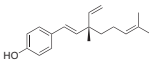
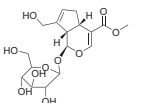
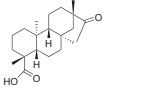
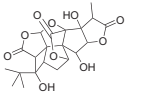
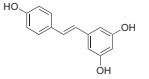
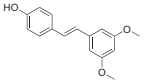
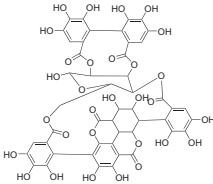
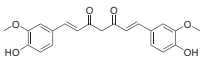
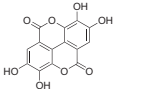
Table 3
Protective effects of constituents from herbal medicine on cardiomyocytes.

Classification /Constituents	Chemical structure	Animal/Cells	Models	Dose/Concentration	Effects	Related molecular targets		Refs.
						Up-regulation	Down-regulation	
Tanshinone IIA		SD rats; H9c2 cells	LAD-induced HF	1.5 mg/kg; 5 μM	Reversing pathological changes; Reducing the ratio of apoptosis; Upregulating autophagy	AMPK, Bcl-2, Beclin1	Bax	[161]
Tanshinone IIA		C57BL/6 mice	LAD-induced HF	5, 25 mg/kg	Reducing microvascular damage, apoptosis and mitochondrial damage of cardiomyocytes	Sirt1, PGC-1α	–	[162]
Acacetin		SD rats; H9c2 cells	Ang II-induced HF	10 mg/kg; 0.3, 1, 3 μM	Protecting cardiomyocyte hypertrophy; Reducing ROS production and apoptosis; Increasing anti-oxidation	PGC-1α, PPARα, AMPK, Sirt1	BNP	[163]
Acacetin		C57BL/6 mice; H9c2 cells	Dox-induced cardiomyopathy rats	15 mg/kg; 0.3, 1, 3 μM	Improving cardiac function and cell viability; Reducing ROS levels	Sirt1, AMPK, Nrf2, HO-1,	Bax, cleaved caspase-3	[165]
Acacetin		C57BL/6 mice; H9c2 cells	D-galactose induced aging mouse	10, 20, 50 mg/kg; 0.3, 1, 3 μM	Improving heart function; Decreasing myocardial senescence markers	PINK1, Parkin, Sirt6, Sirt1, AMPK	–	[166]
Mangiferin		C57BL/6 mice; H9c2 cells	LAD-induced HF	40 mg/kg/day; 20 μM	Alleviating cardiomyocyte apoptosis; Improving cell viability	Sirt1, FOXO3α	–	[167]
Tilianin		SD rats	LAD-induced MI/RI	5 mg/kg	Reducing cardiac infarct size; Improving swollen and ruptured of cells	AMPK, Sirt1, PGC-1α, FOXO1	–	[169]
Luteolin		SD rats	LAD-induced MI/RI	20, 40 mg/kg	Reducing myocardial infarction area; Improving myocardial pathological	Sirt1	TNF-α, IL-6, NLRP3	[170]
Quercetin		SD rats	LAD-induced I/R	25, 50, 100 mL/L	Reducing the pathological changes and apoptosis	Sirt1, PGC-1α, Bcl-2	Bax	[171]
Quercetin		Human cardiomyocytes	Vitro H/R model	50, 100, 150, 200, 250 mg/L	Improving the vulnerability of cardiomyocytes; Ameliorating mitochondrial oxidative stress	Sirt1, PINK1, Atg5, TMBIM6, Bcl-2	–	[172]
Icariin		C57BL/6 mice	Vitro H/R model	2, 4, 8 μM	Reducing cell death and apoptosis; Inhibiting oxidative stress; Restoring mitochondrial dysfunction	Sirt1, FOXO1, Bcl-2, Sirt6	Bax, caspase-3	[173]
Naringenin		H9c2 cells	H ₂ O ₂ induced cardiomyocyte injury	10, 30, 100, 300 μM	Reducing ROS levels and inflammatory; Alleviating cardiac fibrotic remodeling	Sirt1	TNF-α, IL-6	[174]
Rutin		H9c2 cells	Vitro H/R model	50 μM	Protecting cell viability; Attenuating myocardial injury and apoptosis	Sirt1	caspase-3	[175]

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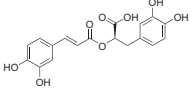
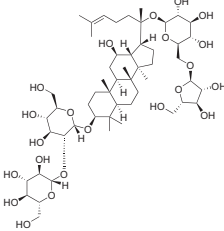
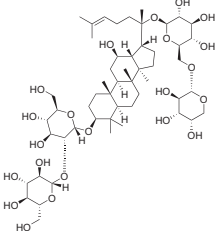
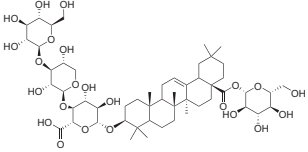
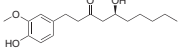

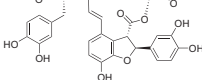
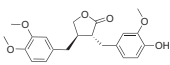
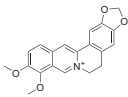
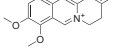
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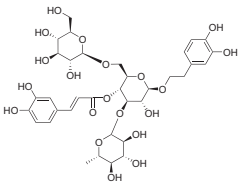
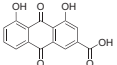

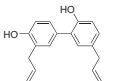
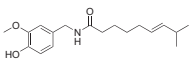
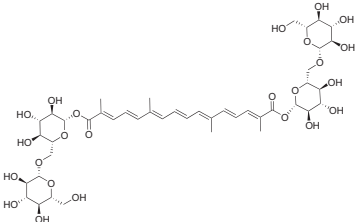
Classification /Constituents	Chemical structure	Animal/Cells	Models	Dose/Concentration	Effects	Related molecular targets		Refs.
						Up-regulation	Down-regulation	
Puerarin		C57BL/6 mice	LAD-induced MI	100 mg/kg	Reducing myocardial infarct size; Improving cardiac structural damage	Sirt1	NLRP3, NF-κB, IL-18, IL-1β	[176]
Dihydromyricetin		SD rats; H9c2 cells	Dox-induced cardiotoxicity rats	100, 200 mg/kg/day; 0.5, 1, 2, 5, 10 μM	Preventing cardiac damage; Attenuating the left ventricle dysfunction; Inhibiting apoptosis	Bcl-2, Sirt1	Bax, NLRP3, IL-1β	[177]
Jaceosidin		C57BL/6 mice; neonatal rat cardiac myocytes	Dox-induced cardiotoxicity rats	4 mg/kg; 2.5, 5, 10, 15 μM	Suppressing cardiac ROS; Inhibiting inflammation and cell loss; Attenuating cardiac injury and oxidative stress	Sirt1, Bax	NF-κB, TNF-α, MCP-1, Bcl-2	[178]
Oroxylin A		C57BL/6 mice; H9c2 cells	Dox-induced cardiotoxicity rats	40 mg/kg; 40 μM	Suppressing cardiac injury and cardiac dysfunction; Alleviating oxidative damage and apoptosis	Sirt1, Nrf2, HO-1, NQO1	TNF-α, IL-6, IL-1β, MMP-2, MMP-9	[180]
Kaempferol		C57BL/6 mice	Ang II-induced mice cardiac injury	2.5, 10 mM	Attenuating cardiac dysfunction; Reducing inflammation and oxidative stress of cardiac	AMPK, Nrf-2	ERK, TNF-α, IL-6	[181]
Kaempferol		H9c2 cells	Vitro A/R model	20 μM	Increasing the viability of cardiac; Decreasing ROS level	Sirt1, Bcl-2	Caspase-3	[182]
Isorhamnetin		SD rats; H9c2 cells	Vivo A/R model	10, 20, 40 mM	Improving cell viability; Reducing oxidative stress and apoptosis	Sirt1	caspase-3	[183]
Phloretin		rats	Streptozotocin-induced diabetic mouse model	20 mg/kg	Preventing cardiomyocyte injury; Attenuating fibrotic response, apoptotic death	Sirt1	IL-6, TNF-α, ANP, TGF-β	[184]
Hesperetin		Kunming mice	ISO-induced MI	25, 50 mg/kg/day	Antagonizing the myocardial injury; Improving myocardial injury	Bcl-2, Nrf-2, Sirt1, NQO-1, HO-1	IL-6, TNF-α, Bax, caspase-3	[185]
Silibinin		H9c2 cells	Vitro ISO induced myocardial cells injury	0.3, 0.5 mM	Inhibiting cardiac death; Protecting mitochondrial function	Bcl2, Sirt1	–	[187]
Liquiritin		H9c2 cells	H ₂ O ₂ induced cardiomyocyte injury	5, 10, 20 μM	Promoting cells proliferation; Reducing ROS level and oxidative stress	AMPK, Sirt1	NF-κB	[188]
Daidzein		SD rats	Streptozotocin-induced diabetes rats	25, 50, 100 mg/kg	Improving cardiac function; Reducing oxidative stress	AMPK, Sirt1	–	[189]
Oxypaeoniflorin		C57BL/6 mice	LAD-induced MI/RI	10, 20, 40 mg/kg	Improving cardiac function; Ameliorating cardiac damage; Protecting cardiomyocytes	Sirt1, Bcl-2	Bax, cleaved caspase-3, FOXO1	[195]

Betulin		Wistar rats	LAD-induced MI/RI	20, 40 mg/kg	Alleviating myocardial inflammatory; Relieving myocardial function changes	Sirt1, NLRP3	IL-6, TNF- α , IL-18	[196]
Bakuchiol		C57BL/6 mice	LAD-induced MI/RI	0.25, 0.5, 1 μ M	Reducing myocardial dysfunction and cardiac hypertrophy; Alleviating oxidative stress	Sirt1, PGC-1 α , Bcl2	Bax, cleaved Caspase3	[197]
Bakuchiol		SD rats	High-fat diet-induced diabetic rats	60 mg/kg	Improving the functional recovery; Reducing apoptosis and oxidative stress	Sirt1, Nrf2	TGF- β 1	[198]
Geniposide		Wistar-Kyoto and SHR rats	High-fat diet-induced diabetic rats	25, 50 mg/kg/day	Reducing myocardial injury; Improving the systolic function of the left ventricle and myocardial hypertrophy	AMPK, FOXO1, Sirt1	Bax	[199]
Geniposide		C57/B6J mice	Spontaneously hypertensive rats	50 μ M	Improving left ventricular function; Inhibiting myocardial inflammation and apoptosis	AMPK, Sirt1	cleaved caspase-3, NF- κ B, TNF- α , IL-1	[200]
Isosteviol sodium		SD rats	High fat/high cholesterol-induced rats	1, 10, 20 mg/kg/day	Improving cardiac function; Relieving myocardial fibrosis and oxidative stress	AMPK, Sirt1	—	[201]
Isosteviol sodium		H9c2 cells	High glucose and ISO induced H9c2	5, 10, 50 μ M	Reducing ROS accumulation; Protecting cells against cardiomyocyte hypertrophy	Sirt1, PGC-1 α , AMPK	—	[202]
Ginkgolide B		H9c2 cells	AngII-induced H9c2 cells hypertrophy	10, 30, 50, 100 μ M	Preventing cardiomyocyte hypertrophy; Promoting autophagy; Inhibiting oxidative stress	Beclin-1, Sirt1, FOXO1	—	[203]
Resveratrol		SD rats; H9c2 cells	LAD-induced HF	2.5 mg/kg; 50, 100 μ M	Improving cardiac function; Reducing mortality of HF	AMPK, Sirt1	—	[206]
Pterostilbene		C57BL/6 mice; H9c2 cells	Dox-induced cardiotoxicity	10 mg/kg/day; 10 μ M	Alleviating cell viability inhibition, mitochondrial damage and oxidative stress	AMPK, Sirt1, PGC-1 α , NRF1, UCP2	—	[207]
Punicalagin		SD rats	LAD-induced MI/RI	20, 40, 80 mg/kg/day	Reducing apoptosis, inflammation and myocardial infarct size	Sirt1, Nrf2, HO-1, NQO-1	caspase-3	[208]
Curcumin		SD rats; H9c2 cells	LAD-induced MI	100 mg/kg/day	Reducing apoptosis and oxidative stress; Improving cardiac function	Sirt1, PI3K, Akt, FOXO1, Bcl-2	Bax	[209]
Curcumin		C57BL/6J mice	Streptozotocin-induced diabetes rats	100 mg/kg/day	Alleviating cardiac fibrosis	Sirt1	MMP-2, MMP-9	[210]
Ellagic acid		Wistar rats	High-glucose induced diabetic cardiomyopathy mice	20, 50, 100, 200 mg/kg	Preserving cardiac systolic and diastolic function; Preventing oxidative stress	Sirt1, FOXO1	IL-6, NF- κ B	[211]

(continued on next page)

Table 3 (continued)

Classification /Constituents	Chemical structure	Animal/Cells	Models	Dose/Concentration	Effects	Related molecular targets		Refs.
						Up-regulation	Down-regulation	
Rosmarinic acid		C57BL/6 mice	High-glucose induced diabetic cardiomyopathy mice	20 mM	Ameliorating cardiac function; Preventing mitochondrial injury	Sirt1, PGC-1 α	cleaved caspase-3	[212]
Ginsenoside Rc		SD rats	LAD-induce I/R	10 mg/kg	Enhancing mitochondrial biosynthesis and glucose uptake of cardiac; Inhibiting mitochondrial damage	Sirt1, GLUT4, HK-1/II, PFK, PGC-1 α	Bax	[216]
Ginsenoside Rb2		Wistar rats	LAD-induce I/R	10, 20 mg/kg	Reducing oxidative stress and inflammation response; Improving cardiac dysfunction	Sirt1, Bcl-2	IL-1 β , IL-6, TNF- α	[217]
Araloside C		H9c2 cells	H ₂ O ₂ induced cardiomyocyte injury	6.5, 12.5, 25 μ M	Inhibiting H9c2 cardiomyocytes mitochondriocytes damage and cytotoxicity of H ₂ O ₂ -induced	AMPK, Bcl2	Bax	[218]
6-Gingerol		KunMing mice	As ₂ O ₃ -induced MI	10, 20 mg/kg	Ameliorating heart injury; Suppressing oxidative stress; Attenuating myocardial mitochondrial damage	Bcl-2, AMPK, Sirt1, PGC-1 α	TNF- α , IL-6, Bax	[219]
Salvianolic acid B		SD rats; H9c2 cells	LAD-induced MI	8, 32 mg/kg	Ameliorating cardiac function; Reducing infarct size and myocardial apoptosis	Sirt1, AMPK, PGC-1 α	NLRP3, Caspase-1	[220]
Salvianolic acid B		C57BL/6 mice	LAD-induced MI	40 mg/kg	Attenuating cardiac infraction sizes; Improving cardiac function	AMPK, eNOS, PI3K, Akt	—	[221]
Arctigenin		SD rats; H9c2 cells	LAD-induce AMI/R	100 μ mol/kg; 0, 25, 50, 100, 200, 400 μ M	Inhibiting apoptosis of cardiomyocytes, oxidative stress and inflammatory; Improving cardiac functions	AMPK, Sirt1, Bcl-2, I- κ B	NF- κ B, Caspase3	[222]
Berberine		C57BL/6 mice; H9c2 cells	LAD-induced I/R	5, 10 mg/kg; 5, 20 μ M	Restoring cardiac function; Protecting cell death and inhibiting autophagy	—	AMPK, mTORC2, Sirt1	[224]
Berberine		SD rats; H9c2 cells	Dox-induced aging mice	100, 200 mg/kg	Reducing ratio of senescent cells; Improving cell viability	Bcl-2, Sirt1	Bax	[225]

Echinacoside		SD rats; AC16 cells	ISO-induced HF	20 µg/g; 50 µM	Reversing myocardial remodeling; Inhibiting mitochondrial oxidative damage and apoptosis	Sirt1, FOXO3a	—	[226]
Rhein		C57BL/6 J mice	Ang II-induced cardiac remodeling mice	50, 100 mg/kg	Inhibiting cardiac hypertrophy and cardiac fibroblasts; Improving cardiac function; Suppressing oxidative stress	AMPK	FGF-23	[227]
Thymoquinone		SD rats	LAD- induce MI/R	2.5, 5, 10 µM	Improving cardiac function; Reducing apoptosis oxidative stress damage	Sirt1, Bcl-2	Bax, cleaved caspase-3	[228]
Honokiol		SD rats; H9c2 cells	LAD-induced MI/RI	5 mg/kg/day; 5 µM	Alleviating cardiac damage; Reducing oxidative stress apoptosis	Sirt1, Nrf2, Bcl-2	Bax	[229]
Capsaicin		Sprague Dawley rats	Vitro H/R model	20 µM	Improving viabilities of cardiomyocytes; Reducing oxidative stress	Bcl-2, Sirt1	Caspase-3	[230]
Crocin		newborn C57BL/6 mice	LAD-induced I/R	50 mg/kg/day; 10 µM	Reducing apoptosis and ER stress	Bcl-2, Sirt1, Nrf2, HO-1	Caspase-3, Bax	[231]

SD: Sprague Dawley; LAD: ligation of the left anterior descending coronary artery; HF: heart failure; AMPK: adenosine monophosphate activated protein kinase; Bcl-2: B-cell lymphoma-2; Bax: Bcl2-associated x; Sirt1: silent information regulator 1; PGC-1 α : peroxisome proliferator-activated receptor γ coactivator 1 α ; Ang II: angiotensin II; PPAR α : peroxisome proliferator-activated receptor α ; BNP: brain natriuretic peptide; DOX: doxorubicin; Nrf2: nuclear factor erythroid2-related factor 2; HO-1: heme oxygenase-1; PINK: PTEN-induced kinase 1; Sirt6: silent information regulator 6; FOXO3: forkhead box family and subfamily O of transcription factor 3; MI/RI: myocardial ischemia-reperfusion injury; FOXO1: forkhead box family and subfamily O of transcription factor 1; TNF- α : tumor necrosis factor α ; IL-6: interleukin 6; NLRP3: NOD-like receptor protein 3; I/R: ischemia-reperfusion; H/R: hypoxia/reoxygenation; Atg5: autophagy-related gene 5; TMBIM6: transmembrane BAX inhibitor motif containing 6; NF- κ B: nuclear factor-kappa-B; IL-1: interleukin 1; IL-18: interleukin 18; MCP-1: monocyte chemotactic protein-1; NQO1: NAD(P)H-quinone oxidoreductase 1; MMP-2: matrix metalloproteinase 2; MMP-9: matrix metalloproteinase 9; ERK: extracellular signal-regulated kinase; ANP: atrial natriuretic peptide; TGF- β : transforming growth factor- β ; NRF-1: nuclear respiratory factor-1; UCP2: uncoupling protein 2; PI3K: phosphoinositide 3-kinase; Akt: protein kinase B; GLUT4: glucose transporter type 4; HK-I/II: hexokinase-I/II; PFK: phosphofructokinase; eNOS: endothelial nitric oxide synthase; I- κ B: inhibitor kappa B; mTORC2: mammalian target of rapamycin compound 2; ISO: isoprenaline; FGF-23: fibroblast growth factor.

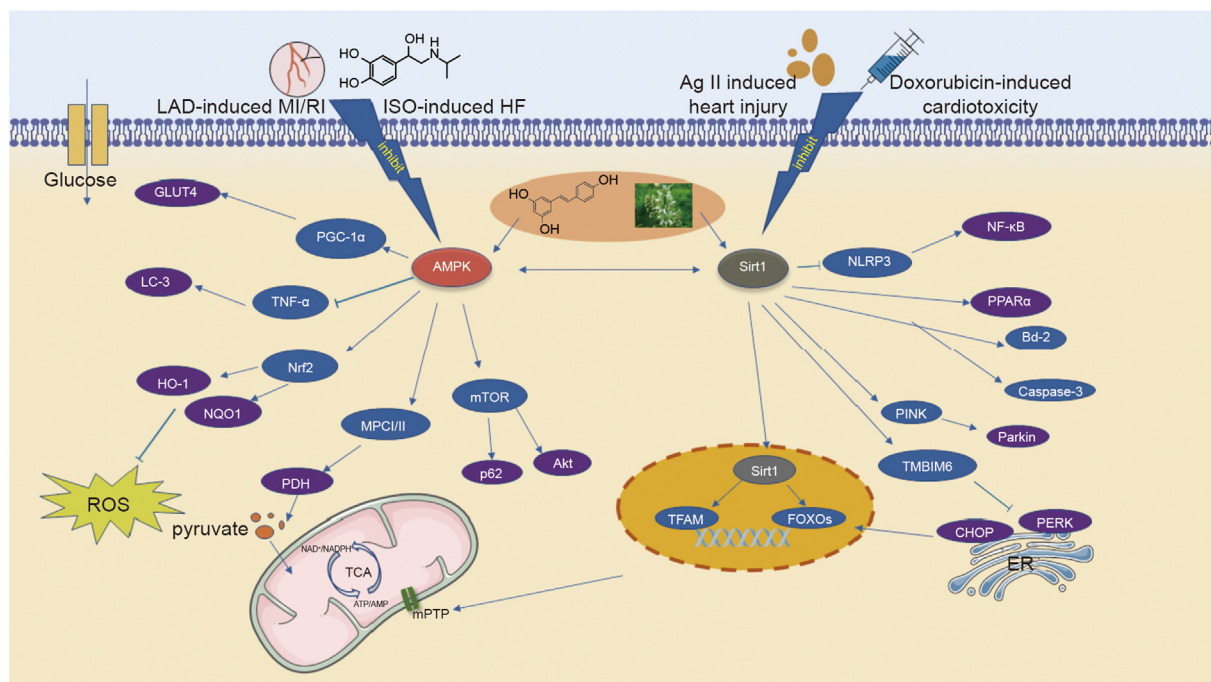


Fig. 3. The possible molecular mechanisms for constituents from herbal medicines to treat HF via activation of AMPK/Sirt1 signaling. Some monomer compounds of traditional Chinese medicine, such as resveratrol, up-regulate the expression of the GLUT4 protein to promote glucose transport, promote the expression of Bcl-2 to inhibit apoptosis, and up-regulate the expression of the Nrf2 protein to reduce the level of oxidative stress in the heart by activating Sirt1 and AMPK. In addition, these compounds also regulate the tricarboxylic acid cycle through the Sirt1/AMPK pathway to combat the imbalance of myocardial energy metabolism, regulate the opening of mPTP channels to maintain mitochondrial function, regulate autophagy, and inhibit endoplasmic reticulum oxidative stress to maintain normal cell physiological function. Where represents \longrightarrow indicates stimulation/promoting, \longleftarrow indicates reduction/inhibition. LAD: ligation of the left anterior descending coronary artery; MI/RI: myocardial ischemia-reperfusion injury; ISO: isoprenaline; HF: heart failure; Ag II: angiotensin II; GLUT4: glucose transporter type 4; PGC-1 α : peroxisome proliferator-activated receptor γ coactivator 1 α ; AMPK: adenosine monophosphate activated protein kinase; LC-3: light chain 3; TNF- α : tumor necrosis factor α ; HO-1: heme oxygenase-1; Nrf2: nuclear factor erythroid2-related factor 2; NQO1: NAD(P)H-quinone oxidoreductase 1; PDH: pyruvate dehydrogenase; MPC I/II: mitochondrial pyruvate carrier I/II; p62: sequestosome 1; mTOR: mammalian target of rapamycin; Akt: protein kinase B; Sirt1: silent information regulator 1; NLRP3: NOD-like receptor protein 3; NF- κ B: nuclear factor-kappa-B; PPAR α : peroxisome proliferator-activated receptor α ; JNK: c-Jun NH2-terminal kinase; Bcl-2: B-cell lymphoma-2; PINK: PTEN-induced kinase 1; TMBIM6: transmembrane BAX inhibitor motif containing 6; CHOP: C/EBP-homologous protein; PERK: protein kinase R (PKR)-like endoplasmic reticulum kinase; TFAM: mitochondrial transcription factor A; FOXOs: forkhead box family and subfamily O of transcription factors; TCA: tricarboxylic acid; mPTP: mitochondrial permeability transition pore; Bcl-2: B-cell lymphoma-2; Bax: Bcl-2-associated x. The above herbal pictures are reprinted from Reprinted from [GBIF.org](https://www.gbif.org) (year) citation guidelines. Available from <https://www.gbif.org/citation-guidelines> with permission and was partly generated using Servier Medical Art, provided by Servier, licensed under a creative commons attribution 3.0 unported license.

Steady progress has been made in identifying the constituents of natural plant products that are cardioprotective by activating Sirt1/AMPK signaling. However, preclinical and clinical trials will be required to detect and validate the safety and efficacy of novel plant secondary metabolites for the prevention and treatment of HF.

CRediT author statement

Tao Zhang: Investigation, Data curation, Writing - Original draft preparation, Reviewing and Editing; **Lei Xu:** Writing - Original draft preparation; **Xiaowei Guo:** Investigation, Data curation; **Honglin Tao:** Investigation, Data curation; **Yue Liu:** Supervision; **Xianfeng Liu:** Writing - Reviewing and Editing; **Yi Zhang:** Resources, Writing - Reviewing and Editing, Supervision, Funding acquisition; **Xianli Meng:** Resources, Writing - Reviewing and Editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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