

# AMPK Signalling Pathway: A Potential Strategy for the Treatment of Heart Failure with Chinese Medicine

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**Abstract:** Heart failure (HF) is a complex clinical syndrome that represents the advanced stage of cardiovascular disease, characterized by systolic and diastolic dysfunction of the heart. Despite continuous updates in HF treatment drugs, the morbidity and mortality rates remain high, necessitating ongoing exploration for new therapeutic targets. Adenosine monophosphate-activated protein kinase (AMPK) is the serine/threonine protein kinase which responds to adenosine monophosphate (AMP) levels. Activation of AMPK shifts cellular metabolic patterns from synthesis to catabolism, enhancing energy metabolism in pathological conditions such as inflammation, ischemia, obesity, and aging. Numerous studies have identified AMPK as a vital target for HF treatment, with herbal monomers/extracts and compounds affecting key signaling factors including rapamycin targeting protein (mTOR), silencing regulator protein 1 (SIRT1), nuclear transcription factor E2-related factor 2 (Nrf2), and nuclear transcription factor- $\kappa$ B (NF- $\kappa$ B) through regulation of the AMPK signaling pathway. This modulation can achieve the effects of improving metabolism, autophagy, reducing oxidative stress and inflammatory response in the treatment of heart failure, with the advantages of multi-targeting, comprehensive action and low toxicity. The modulation of the AMPK pathway by Traditional Chinese Medicine (TCM) has emerged as a crucial research direction for the prevention and treatment of HF, but a systematic summary and generalization in this field is lacking. This article provides an overview of the composition, regulation, and mechanism of the AMPK signaling pathway's influence on HF, as well as a summary of current research on the regulation of the AMPK pathway by TCM for HF prevention and treatment. The aim is to serve as a reference for the diagnosis and treatment of HF using TCM and the development of new drugs.

**Keywords:** AMPK signalling pathway, Chinese medicine, heart failure, mechanism of action, review

## Introduction

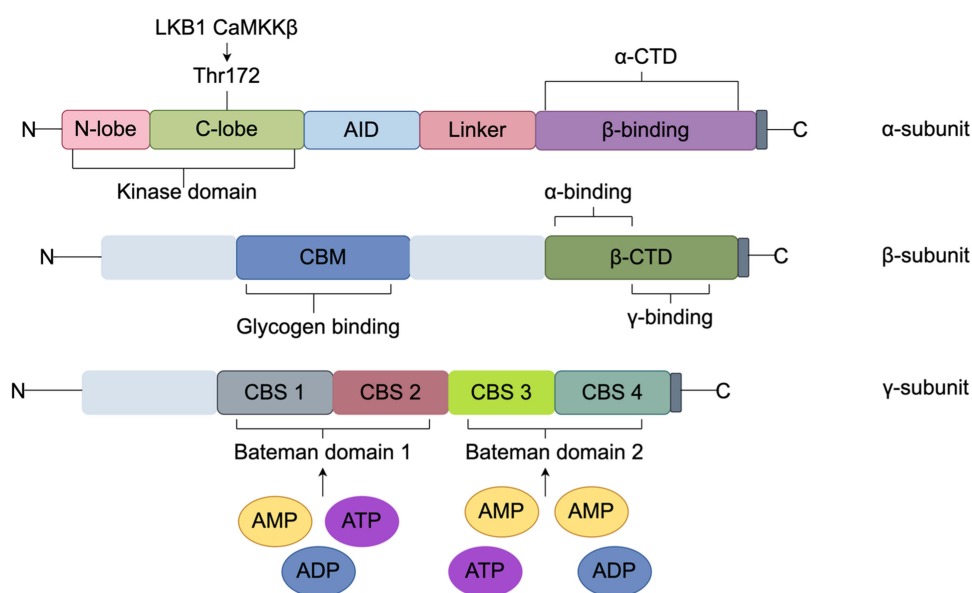
Heart failure (HF) is a complex clinical syndrome characterised by a decrease in the heart's ability to pump and/or fill with blood.<sup>1</sup> It is a progressive disease and is the endpoint of the vast majority of cardiovascular diseases. In recent years, the survival rate of HF has gradually increased due to population aging, advances in medical technology, and improved health care policies, but its morbidity and mortality rates have not declined, which indirectly leads to an increase in hospitalisation rates, and an increase in the cost of health care.<sup>2,3</sup> HF continues to be a growing public health problem on a global scale. According to statistics, the prevalence of heart failure is expected to increase by 46% from 2012 to 2030, and the proportion of the total population with heart failure is projected to rise from 2.4% to 3.0%.<sup>4,5</sup> Western medicine in the drug treatment of this disease mainly uses cardiotonic, diuretic, vasodilator, etc. In the acute or advanced stage of heart failure, there are many non-pharmacological treatments, including cardiac resynchronisation therapy, implantable cardiac defibrillator, cardiac transplantation, total artificial heart, gene and cell therapy.<sup>6-8</sup> Although western medical treatment is perfect and can achieve certain efficacy and prolong the life span of patients to a certain extent, there are still some limitations in clinical treatment because of its many adverse reactions, poorer prognosis, and poorer results.<sup>9</sup> Therefore, finding drugs that target key pathological aspects of HF, improving and optimising therapeutic regimens, reducing mortality and recurrence rates, and improving clinical outcomes are key to current research into the treatment of heart failure.

Adenosine monophosphate-activated protein kinase (AMPK) serves as an “energy sensor” regulating cellular metabolism.<sup>10,11</sup> It is a highly conserved serine/threonine protein kinase that is widely expressed in eukaryotic organisms and various organs, allowing it to sense changes in the cellular ratio of adenosine monophosphate (AMP) to adenosine triphosphate (ATP). AMPK plays a crucial role in regulating multiple metabolic pathways and maintaining cellular ATP homeostasis, making it the “master metabolic switch” of the body.<sup>12–14</sup> By restoring energy supply, regulating autophagy, and improving cardiac ventricular remodeling, AMPK contributes to the restoration of cardiac function and the slowing of disease progression in heart failure.<sup>15,16</sup>

In recent years, the role of Chinese medicines in the prevention and treatment of HF has become more and more prominent, and the number of studies exploring the targets of Chinese medicines in intervening in HF and their mechanisms of action based on AMPK signalling has also increased.<sup>17,18</sup> Numerous pharmacological studies have shown that Chinese medicines have the advantages of good safety and precise efficacy in the prevention and treatment of HF, and the AMPK signalling pathway is one of the key pathways through which the active ingredients of Chinese medicines and Chinese medicinal extracts can play a role in improving the outcomes in HF.<sup>19–21</sup> This article will review the existing pharmacological and experimental research results of TCM intervention in AMPK signalling pathway to improve HF in recent years.

## AMPK Signaling Pathway Composition

AMPK is a key regulator of cellular metabolism in eukaryotes.<sup>22</sup> It functions as an energy-sensitive heterotrimeric protein kinase complex consisting of catalytic ( $\alpha$ ) and regulatory ( $\beta$ ,  $\gamma$ ) subunits.<sup>12</sup> This complex plays a crucial role in maintaining energy homeostasis by modulating ATP catabolism and anabolism.<sup>22,23</sup> In mammals, there are 12 different heterotrimeric combinations of AMPK, depending on the subunit composition ( $\alpha 1/\alpha 2$ ,  $\beta 1/\beta 2$ ,  $\gamma 1/\gamma 2/\gamma 3$ ).<sup>23</sup> These combinations determine the nucleotide activation and sensitivity to phosphorylation. The  $\alpha$ -subunit contains the kinase structural domain and a crucial Thr172 residue that is phosphorylated by upstream kinases CAMKK2 and LKB1. The  $\beta$ -subunit contains a carbohydrate-binding module for glycogen binding and a C-terminal structural domain for binding the  $\alpha$ - and  $\gamma$ -subunits. The  $\gamma$ -subunit comprises four tandem cystathionine- $\beta$ -synthases (CBS) domains that directly bind ATP and adenosine diphosphate (ADP), enabling AMPK to respond to changes in the ATP-to-AMP ratio.<sup>24–26</sup> (See Figure 1.)



**Figure 1** Subunit structure of AMPK.

## AMPK Signaling Transduction

AMPK signaling is activated in response to low energy levels, typically occurring under stressful conditions. The catalytically active  $\alpha$  subunit of AMPK undergoes phosphorylation at threonine 172 (T172), which leads to the activation of AMPK signaling.<sup>27</sup> Upstream mediators such as calcium/calmodulin-dependent protein kinase  $\beta$  (CaMKK $\beta$ ), transforming growth factor  $\beta$ -activated kinase 1, and liver kinase B1 (LKB1) induce T172 phosphorylation in response to activated AMPK.<sup>24,28</sup> Metabolic stress triggers AMPK signaling by increasing AMP levels and decreasing ATP levels. This process is intriguing because elevated levels of AMP and adenosine diphosphate during metabolic stress bind to the  $\gamma$ -subunit, leading to AMPK activation and T172 phosphorylation.<sup>29</sup> It's important to note that AMPK can also be activated independently of AMP levels. Calcium signaling and its accumulation in cells can induce T172 phosphorylation, resulting in CaMKK $\beta$ -dependent upregulation of AMPK.<sup>30</sup> Additionally, there are endogenous inhibitors of AMPK signaling. Protein phosphatases such as protein phosphatase 2A, protein phosphatase 2C $\alpha$ , and magnesium/manganese-dependent protein phosphatases can inhibit AMPK by dephosphorylating T172 and inhibiting its activation.<sup>31</sup>

## Mechanisms Associated with AMPK Amelioration of Heart Failure

### AMPK Improves Interstitial Fibrosis in Heart Failure

Myocardial fibrosis (MF) is a pathological process characterized by the excessive deposition of extracellular matrix proteins due to the transformation of cardiac fibroblasts into myofibroblasts. It plays a significant role in the development of heart failure.<sup>32,33</sup> Among the isoforms of TGF- $\beta$ , TGF- $\beta$ 1 is predominantly expressed in the heart and is a potent fibrogenic cytokine.<sup>34</sup> It regulates cell proliferation, inflammation, collagen fiber deposition, and cardiac fibroblast activation.<sup>35</sup> The TGF- $\beta$ /Smad3 signaling pathway, with Smad2/3 as downstream effectors, is crucial in pressure overload-induced myocardial fibrosis.<sup>36</sup> TGF- $\beta$ 1 additionally activates Smad-independent signaling pathways such as ERK, JNK, and p38 MAPK, all of which are implicated in fibroblast activation.<sup>37</sup>

AMPK activation has been shown to ameliorate myocardial fibrosis. In cardiac fibroblasts, AMPK activation inhibits the expression of hepatocyte nuclear factor (HNF-4), thereby regulating TGF- $\beta$  transcription.<sup>38</sup> It also inhibits ERK, an essential regulator of cardiac fibroblast growth and proliferation.<sup>36</sup> Furthermore, AMPK inhibits JNK/NF- $\kappa$ B signaling, attenuating inflammation, reactive oxygen species (ROS), and cell death while protecting cardiomyocytes.<sup>39</sup>

Based on these findings, it can be inferred that AMPK attenuates myocardial fibrosis and exerts a beneficial effect on heart failure.

### AMPK Improves Energy Metabolism and Maintains Mitochondrial Homeostasis in Heart Failure

The heart, as a highly energy-demanding organ, requires a substantial amount of energy to fulfill the needs of the body.<sup>40</sup> In a physiological state, the heart obtains energy through the oxidation of various substrates such as fatty acids, glucose, and lactate. These substrates are metabolized to acetyl coenzyme A through processes like  $\beta$ -oxidation and glycolysis. Acetyl coenzyme A then enters the tricarboxylic acid cycle and oxidative phosphorylation in the mitochondria, effectively providing energy for the heart.<sup>41–43</sup> However, when myocardial hypertrophy occurs, ATP production efficiency decreases, leading to a shift in the heart's fuel preference from fatty acids to glucose and an increase in glycolysis, resulting in lactate accumulation.<sup>44</sup>

On the other hand, AMPK plays a crucial role in regulating enzymes involved in ATP production and promotes mitochondrial biogenesis, thereby enhancing energy supply in heart failure.<sup>45</sup> Under pathological conditions, AMPK is activated in myocardial tissues through phosphorylation. This activation facilitates the transport of GLUT4 protein from the cytoplasm to the membrane, contributing to improved glucose uptake and utilization under pathological conditions, which provides some protection to the heart.<sup>46</sup> Additionally, AMPK inhibits GLUT4 endocytosis, ensuring that GLUT4 remains in the active site.<sup>47</sup> Moreover, AMPK increases fatty acid uptake and oxidation by promoting the membrane transport of fatty acid transporter protein CD36, facilitating fatty acid uptake by cardiomyocytes. CPT-1, a key enzyme that regulates  $\beta$ -oxidation, is activated by AMPK, which inhibits acetyl-coenzyme A carboxylase (ACC) and reduces the production of malonyl-coenzyme A. This, in turn, increases CPT-1 activity and promotes fatty acid oxidation.<sup>48,49</sup>

AMPK also directly influences mitochondrial biosynthesis by interacting with peroxisome proliferator-activated receptor (PPAR)  $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ), leading to increased mitochondrial synthesis or maintenance of mitochondrial function stability. Both AMPK and PGC-1 $\alpha$  are considered potent activators of mitochondrial biosynthesis in the heart.<sup>50</sup> PGC-1 $\alpha$  activates estrogen-related receptor (ERR), which promotes transcription of genes associated with mitochondrial biosynthesis.<sup>51</sup> Additionally, AMPK can stimulate mitochondrial biosynthesis directly by phosphorylating the serine of PGC-1 $\alpha$  or indirectly by activating Sirtuin 1 (Sirt1).<sup>52,53</sup> These combined actions ultimately result in increased ATP production, alleviating the energy supply-demand imbalance in heart failure and improving its condition.

## AMPK Improves Oxidative Stress in Heart Failure

Excessive production of reactive oxygen species (ROS) during oxidative stress can cause damage to cardiomyocytes, leading to cardiac remodeling and ultimately heart dysfunction and heart failure (HF). In recent years, several pharmacological studies have shown that activating AMPK in the myocardium can protect the heart from oxidative stress.<sup>54</sup> For example, resveratrol has been found to inhibit NADPH oxidase-mediated ROS production and enhance the activity of cardiac antioxidant enzymes through AMPK activation, thereby reducing cardiomyocyte damage caused by oxidative stress. Junlong et al<sup>55</sup> demonstrated that selegiline can reduce mitochondrial superoxide production by activating the AMPK-endothelial nitric oxide synthase axis, thereby protecting endothelial cells from oxidative stress injury.

The beneficial effects of AMPK activation are mediated through mitochondria, particularly the inhibition of mitochondrial permeability transition pore (PTP) opening.<sup>56</sup> Although PTP opening is a well-known phenomenon that occurs in response to oxidative stress, the molecular identity of the pore complex is not yet clear. It has been well established that cyclophilin D (CypD) plays an important role in regulating of PTP opening.<sup>57,58</sup> It has been found that metformin-induced activation of AMPK has been shown to prevent acute oxidative stress in mitochondria by blocking the interaction between peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ ) and CypD, which ultimately prevents PTP formation. In addition, AMPK increases the expression of mitochondrial superoxide dismutase (SOD), thereby reducing ROS production.<sup>59</sup> In conclusion, certain drugs can attenuate oxidative stress-induced cardiomyocyte injury by activating AMPK. However, the specific mechanism of the protective effect of AMPK against oxidative stress needs further investigation.

## AMPK Improves Inflammation in Heart Failure

Inflammation resulting from myocardial ischemia and infection plays a crucial role in the development of heart failure (HF). Extensive research has demonstrated the significance of inflammation as a mechanism in HF development.<sup>60,61</sup> Initially, low levels of inflammation act as an early response to ischemic injury, promoting healing and cardiac tissue remodeling. However, persistent or heightened inflammation is the primary cause of HF exacerbation.<sup>62</sup> Previous studies have revealed that AMPK downregulates acetylation levels of targets such as nuclear factor KB (NF-KB), AP-1, and histones through SIRT1, thus inhibiting the expression of inflammation-related genes and attenuating the inflammatory response.<sup>63</sup> Additionally, AMPK demonstrates a protective effect against TNF- $\alpha$ -induced cardiomyocyte necrosis and inflammatory cell infiltration in ischemic cardiomyopathy, as TNF- $\alpha$  acts as a pro-inflammatory cytokine that stimulates the cascade of inflammation in vivo.<sup>64</sup> Empagliflozin, a sodium-glucose cotransporter protein 2 inhibitor, has been shown to activate AMPK and reduce the inflammatory response in macrophages treated with lipopolysaccharide.<sup>65</sup> Moreover, liraglutide has been demonstrated to activate AMPK, protecting cardiomyocytes from metabolic disorders and mitochondrial dysfunction induced by interleukin 1 $\beta$ .<sup>66</sup> Berberine, an important inflammatory regulator, can downregulate the expression of galactoglucon-3 through the regulation of NF- $\kappa$ B and AMPK signaling pathways, thus reducing macrophage activation induced by oxidized LDL and attenuating inflammation.<sup>67</sup> Collectively, these findings indicate that AMPK's participation in the attenuation of the inflammatory response contributes to delaying the progression of HF.

## AMPK Regulates Autophagy in Heart Failure

AMPK activation can play a cardioprotective role by inducing autophagy in the heart.<sup>68</sup> mTOR, known as an energy sensor, regulates the balance between nutritional status and cell growth. Normally, mTOR inhibits autophagy and promotes cell growth under conditions of adequate nutrition. However, during nutrient deficiency or disease, mTOR is inactivated, leading to increased autophagy.<sup>69</sup> Conversely, inhibiting mTOR complex 1 (mTORC1) enhances autophagy, thereby protecting the heart and improving cell survival.<sup>70</sup> Studies have demonstrated that AMPK attenuates pressure overload-induced cardiac hypertrophy by inhibiting mTORC1 and promoting autophagy.<sup>71</sup> AMPK phosphorylates tuberous sclerosis complex 2 (TSC2), a negative regulator of mTORC1, leading to mTORC1 inhibition and subsequent autophagy induction through its downstream target, p70S6K.<sup>72</sup> Autophagy, regulated by AMPK, plays a crucial role in maintaining cardiac function under stress conditions.<sup>73</sup> Additionally, AMPK directly enhances autophagy by phosphorylating the Unc-51-like kinase 1 (ULK1) kinase complex.<sup>74</sup> Both autophagy and cardiac hypertrophy influence the development of heart failure, suggesting that AMPK's promotion of autophagy may ameliorate heart failure. However, it is important to note that autophagy's effects on heart failure can be dual. While low levels of autophagy are cardioprotective under pressure overload, excessive autophagy can worsen heart failure by causing increased susceptibility to injury and dysfunction. Studies have shown that inhibiting the CaMKK $\beta$ -AMPK-mTOR pathway down-regulates autophagy, exhibiting protective effects in hypertrophied hearts.<sup>75</sup> Moreover, significantly increased autophagy levels impair cardiac function, indicating that prolonged autophagy activation may be detrimental to the heart.<sup>76</sup> Therefore, these findings suggest that although autophagy can ameliorate heart failure and protect the heart, excessive autophagy can contribute to heart failure progression by degrading functional proteins and organelles and inducing cardiomyocyte death.

## AMPK Improves Endoplasmic Reticulum Stress in Heart Failure

The endoplasmic reticulum is a multifunctional organelle that is essential for protein synthesis, folding, translocation and calcium homeostasis, and lipid synthesis. In the presence of hypoxia, elevated protein synthesis and calcium overload can lead to dysfunction and cause endoplasmic reticulum stress.<sup>77–79</sup> In cardiomyocytes, if endoplasmic reticulum stress is induced for a prolonged period of time, the expression of C/EBP homologous protein (CHOP) can be upregulated, which can lead to apoptosis in cardiomyocytes during the transition from hypertrophy to heart failure.<sup>80</sup> The activation of AMPK can influence endoplasmic reticulum stress. Studies have shown<sup>81</sup> that activation of AMPK inhibits cardiac dysfunction and cardiomyocyte apoptosis induced by endoplasmic reticulum stress and increases BNP levels. Xu et al<sup>82</sup> demonstrated that nickel-stripe protein-like METRNL attenuates apoptosis of cardiomyocytes by attenuating endoplasmic reticulum stress, and that its mechanism is related to the activation of AMPK-PAK2 signalling. Park et al<sup>83</sup> confirmed that AMPK can reduce the accumulation of unfolded proteins by inhibiting mTOR activity, thereby reducing endoplasmic reticulum stress. However, the mechanism by which AMPK reduces endoplasmic reticulum stress in heart failure has not been fully elucidated.

## AMPK Improves Ferroptosis in Heart Failure

Ferroptosis is a novel form of cell death characterized by iron overload and accumulation of lipid peroxides.<sup>84</sup> It plays a significant role in the processes of cell proliferation, differentiation, aging, and death, and has been shown to be involved in heart failure (HF).<sup>85</sup> The occurrence of ferroptosis is accompanied by a decrease in the levels of glutathione (GSH) and glutathione peroxidase 4 (GPX4). Studies have indicated that during myocardial infarction, interference with small interfering RNA (siRNA) or the ferroptosis inducer RSL3 inhibiting GPX4 may result in the accumulation of lipid peroxides, leading to the conclusion that GPX4 can prevent ferroptosis during acute myocardial infarction.<sup>86</sup> Nrf2 is a transcription factor with antioxidant properties, and heme oxygenase-1 (HO-1) and GPX4 are downstream genes of Nrf2.<sup>87</sup> When the body is under oxidative stress, Nrf2 is released from the Kelch-like ECH-associated protein 1 (Keap-1) binding site and rapidly translocates into the nucleus, where it interacts with antioxidant response element (ARE) in the promoter region of target genes.<sup>88</sup> Research has shown that activation of the AMPK/glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ )/Nrf2 pathway can upregulate the expression of GPX4 to inhibit lipid peroxidation and ferroptosis, thereby reducing



myocardial ischemia-reperfusion injury (MIRI).<sup>89</sup> Therefore, modulation of the AMPK pathway can suppress ferroptosis and protect cardiomyocytes in HF.

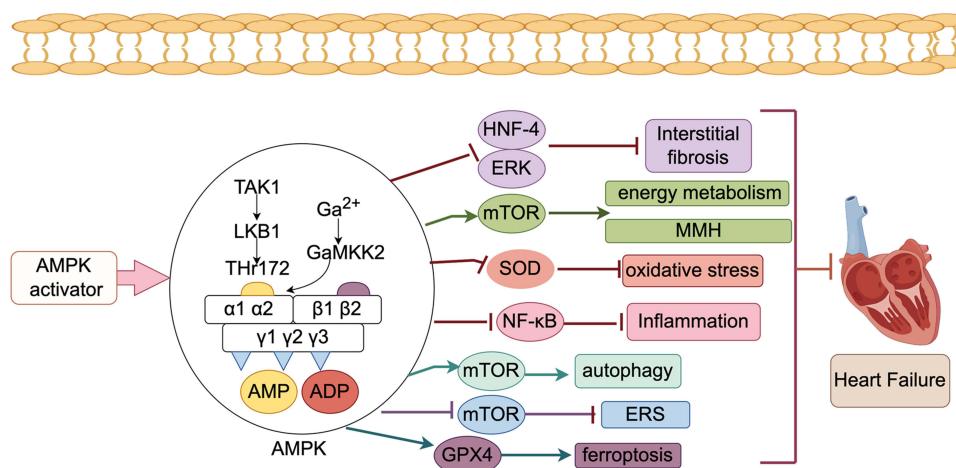
The pathogenesis of the specific AMPK signaling pathway in HF is shown in Figure 2.

## Chinese Medicine Intervenes in HF Through the AMPK Signalling Pathway

It is urgent to find effective drugs to treat HF, and studies have shown that the above pathophysiological processes play an important role in the treatment of HF. Due to its advantages of multi-components, multi-targets and few adverse effects, several studies have demonstrated that Chinese medicine combinations and active ingredients and extracts of Chinese medicine can protect cardiomyocytes and alleviate HF by up-regulating or inhibiting the expression of relevant target genes through regulating the AMPK signalling pathway.

## Herbal Monotherapy Ameliorate HF Through the AMPK Signalling Pathway

Astragaloside and astragalus polysaccharide are active ingredients derived from the dried root of *Astragalus membranaceus*, a traditional Chinese medicine. These components have various biological effects, including delaying cellular aging, inhibiting inflammatory mediators, and providing organ protection.<sup>90,91</sup> Song et al<sup>92</sup> discovered that astragalus polysaccharide activates the AMPK-related pathway, increases FAT/CD36 translocation and CPT1 expression, facilitates myocardial uptake and utilization of free fatty acids (FFA), and improves myocardial metabolism in chronic heart failure rats, thus ameliorating the condition. Similarly, Xinwei et al<sup>93</sup> found that astragaloside effectively inhibits mitochondrial autophagy and cardiomyocyte apoptosis in rats with acute heart failure, with its regulatory mechanism involving the CaMkk $\beta$ /AMPK signaling pathway. Luo Han Guo flavonoids, derived from the ripe fruit of Luo Han Guo, have been shown by Weibin et al<sup>94,95</sup> to enhance the activity of energy metabolism enzymes CK, LDH, and SDH, upregulate PPAR $\alpha$  mRNA expression, and improve energy metabolism and myocardial tissue damage. Ginsenoside, the main active ingredient in ginseng, has been found to regulate ventricular remodeling and enhance fatty acid  $\beta$ -oxidation in heart failure rats through the activation of AMPK in a study on adriamycin-induced heart failure rats.<sup>96,97</sup> Paeoniflorin, an active compound extracted from the dried root of *Paeonia lactiflora*, exerts cardioprotective effects by combating oxidative stress, inhibiting cardiomyocyte apoptosis, suppressing myocardial inflammation, and regulating autophagy.<sup>98</sup> Yuqin et al<sup>99</sup> demonstrated that paeoniflorin promotes AMPK $\alpha$  phosphorylation, reduces inflammatory factor levels in myocardial tissue, and protects myocardial endothelial cells. Tanshinone IIA, derived from dried tansy rhizomes, has multiple clinical effects, including cardiovascular protection, hepatoprotection, anti-inflammation, anti-oxidant, anti-tumor, and antifibrotic effects.<sup>100</sup> Zhang et al<sup>101</sup> discovered that tanshinone IIA administration to heart failure rats with ligated left anterior descending branches activates the AMPK/mTOR pathway, enhances autophagy (as observed through autophagy-associated factor proteins LC3, p62, and Beclin1), and improves cardiac function. Panax



**Figure 2** Pathogenesis of AMPK signaling pathway in HF.

ginseng total saponin, the primary active component of Panax ginseng, exhibits pharmacological effects such as anti-inflammatory, lipid-lowering, and anti-tumor effects.<sup>102</sup> Wang et al<sup>103</sup> experimentally demonstrated that Panax ginseng total saponin protects the hearts of mice with left anterior descending ligation by enhancing glucose metabolism through phosphorylation of AMPK Thr172 and CaMKII Thr287 in cardiomyocytes under deprivation-induced autophagy. Additionally, berberine has been shown<sup>104</sup> to inhibit cardiomyocyte hypertrophy through AMPK pathway-mediated promotion of autophagy, as evidenced by down-regulation of p62 expression and up-regulation of LC3II activity. Puerarin is extracted from the rhizome of Pueraria lobata. Zhou et al<sup>105</sup> found that puerarin inhibits cardiomyocyte apoptosis and iron death by promoting AMPK phosphorylation, thereby alleviating inflammation and oxidative damage in myocardial tissues and exerting cardioprotective effects. Furthermore, Ma et al<sup>106</sup> observed activation of AMPK $\alpha$ /mTOR and inhibition of endoplasmic reticulum stress in hypertrophied hearts treated with gardenia glycosides. They also found that knockdown of compound C (CpC) or AMPK- $\alpha$  limited the activation of mammalian target of rapamycin and ERK induced by hypertrophic stimuli, which suggests that gardenia jasminoides can inhibit endoplasmic reticulum stress through activation of the GLP-1 receptor/AMPK- $\alpha$  pathway, thus preventing cardiac hypertrophy. (See Table 1.)

**Table 1** Mechanism of Action of Chinese Herbal Monomers Modulating AMPK Signalling Pathway to Improve HF

Chinese Medicine Monomer	Composition	Research Subject	Dose	Times	Mechanism of Action	Reference
Astragalus	Astragaloside	ADR-induced heart failure in rats	4ng/L	4 weeks	Activation of AMPK-related pathways, Improvement of myocardial metabolic substrates	[92]
	Astragalus polysaccharide	TAC-induced heart failure in rats	16.7, 33.3, 66.7 mg/kg	8 weeks	Activation of AMPK-related pathways, Inhibition of mitochondrial autophagy and apoptosis in cardiomyocytes	[93]
Luo Han Guo	Luo Han Guo flavonoids	TAC-induced heart failure in rats	7.5, 15, 30 mg/kg	4 weeks	Activation of AMPK-related pathways, Improvement of energy metabolism	[95]
Ginseng	Ginsenoside	AAS-induced heart failure in rats	20mg/kg	4 weeks	Activation of AMPK-related pathways, Improvement of cardiomyocyte oxidative stress	[97]
Paeonia lactiflora	Paeoniflorin	ADR-induced heart failure in rats	100, 200mg/kg	8 weeks	Activation of AMPK-related pathways, Suppression of inflammatory response	[99]
Salvia miltiorrhiza	Tanshinone IIA	SHR-induced heart failure in rats	10mg/kg	6 weeks	Activation of AMPK-related pathways, Enhances autophagy, improves cardiac function	[101]
Panax ginseng	Panax ginseng total saponin	TAC-induced heart failure in rats	30, 60, 120mg/kg	4 weeks	Activation of AMPK-related pathways, Enhances autophagy, improves cardiac function	[103]
Coptis	Berberine	ISO-induced heart failure in rats	4, 8, 16mg/kg	8 weeks	Activation of AMPK-related pathways, Enhances autophagy and inhibits cardiomyocyte hypertrophy	[104]
Pueraria lobata	Puerarin	TAC-induced heart failure in rats	10, 30, 100mg/kg	4 weeks	Activation of AMPK-related pathways, Inhibition of ferroptosis, apoptosis	[105]
Gardenia	Gardenia glycosides	TAC-induced heart failure in rats	20mg/kg	4 weeks	Activation of AMPK-related pathways, Inhibition of endoplasmic reticulum stress to prevent atrial hypertrophy	[106]

**Abbreviations:** ADR, Adriamycin; TAC, Transverse aortic constriction; SHR, Spontaneously hypertensive rats; ISO, Isoproterenol; AAS, ascending aortic stenosis.

## Chinese Herbal Compound Improves HF Through AMPK Signalling Pathway

Lingui Zhugan soup, which has the efficacy of warming heart yang, strengthening spleen qi, and resolving water-drinking, has been widely used in the treatment of CHF in clinics with precise and reliable efficacy.<sup>107,108</sup> Juan et al<sup>109</sup> experimentally found that Lingui Zhugan soup could alleviate oxidative stress and apoptotic injury of cardiomyocytes and improve mitochondrial function in HF rats, and its effect was related to mitochondrial fission-fusion and activation of Sirt3/AMPK signalling pathway. Yixintai is a commonly used clinical formula with the effect of benefiting qi, activating blood and inducing diuresis. After more than twenty years of clinical use of the drug has proved that it has an anti-ventricular remodelling effect, and it is safe, effective and without adverse reactions, which is worthy of clinical promotion and application.<sup>110–112</sup> Yun et al<sup>111</sup> experimentally found that Yixintai granules can promote the increase of AMPK protein expression, increase ATPase activity, inhibit fatty acid oxidation, reduce serum NT-pro BNP levels, and improve heart failure. Yixintai tablets have the efficacy of benefiting qi and nourishing yin, activating blood and inducing diuresis, and are effective in clinical practice.<sup>113</sup> The results of Ren et al<sup>114</sup> showed that Yangxin Kang Tablets had the effect of improving the ultrastructure of cardiomyocytes and regulating the level of cardiomyocyte autophagy in a rabbit model of heart failure after myocardial infarction, and the cardioprotective effect of Yangxin Kang Tablets was reduced after specific blockade of the Akt/AMPK-mTOR signalling pathway, which indicated that the effects of Yangxin Kang Tablets in improving ventricular remodeling were mediated by interfering with the Akt/AMPK-mTOR signaling pathway, suggesting that the improvement of ventricular remodeling by Yangxin Kang Tablets was achieved by interfering with the Akt/AMPK-mTOR signaling pathway and regulating the autophagy level of cardiomyocytes.

Xinshuai Ning Combination has the efficacy of benefiting qi and warming yang, promoting blood circulation and inducing diuresis, and has been used in clinical practice for a long time with remarkable efficacy and no obvious toxic side effects.<sup>115,116</sup> Studies have shown that Xinshuai Ning Combination can improve cardiac function, regulate myocardial energy metabolism, intervene in ventricular remodelling, and anti-myocardial fibrosis in CHF rats.<sup>117,118</sup> Yuanli et al<sup>119</sup> found that Xinshuai Ning Combination can significantly reduce the degree of myocardial fibrosis in CHF rats, reduce the serum BNP level, reduce the serum and myocardial FFA level, increase the level of PPAR $\alpha$  mRNA and protein expression, reduce the level of AMPK mRNA and protein expression, regulate the myocardial energy metabolism substrate of CHF rats, and delay the occurrence and development of CHF, and its mechanism is related to the regulation of myocardial energy metabolism. Occurrence and development, and its mechanism is related to the regulation of PPAR $\alpha$  and AMPK expression, which in turn improves FFA levels. Chenghao et al<sup>120</sup> found that Wenyang Yiqi Soup was able to improve myocardial function in post-infarction heart failure rats, and its mechanism of action was related to the inhibition of AMPK-mediated mitochondrial autophagy. The tonifying yang and returning five soup is a famous formula for the treatment of qi deficiency and blood stasis syndrome, which has the efficacy of benefiting qi, activating blood, and clearing the veins, and is widely used in the treatment of HF.<sup>121</sup> Zhen et al<sup>122</sup> found that Buyang Huanwu Soup could activate AMPK and up-regulate the expression of PPAR $\alpha$  and PGC-1 $\alpha$ , which could preliminarily confirm that Buyang Huanwu Soup could improve energy metabolism of the failing heart and delay the progression of HF by improving the function of cardiomyocytes' mitochondria, promoting energy production of failing hearts and up-regulating the expression of AMPK/PPAR $\alpha$  signalling pathway, promoting mitochondrial biogenesis, and thus improving energy metabolism of failing hearts. This will improve the energy metabolism of the failing heart and delay the progression of HF.

Shihai et al<sup>123</sup> found that Shenkui Tongxin granules could regulate the AMPK-mt TFA-PINK1 signalling axis, promote mitochondrial autophagy in cardiomyocytes, enhance mitochondrial production, attenuate mitochondrial damage, and improve the disorders of energy metabolism, which could in turn alleviate the progression of HF. Fan et al<sup>124</sup> found that Shenfu Qiangxin Soup may activate the AMPK-PGC-1 $\alpha$  signalling pathway, increase the expression of p-AMPK and PGC-1 $\alpha$  to regulate fatty acid oxidation metabolism and glucose transport, and thus improve the energy metabolism of the myocardium in heart failure rats, thus playing a therapeutic role in the treatment of heart failure. Wei et al<sup>125</sup> found that Shenfu Xiongze Soup could increase the expression of AMPK and GLUT4 proteins and the content of serum CK and CK-MB in myocardial tissues, reduce the content of serum FFA, alleviate the pathological damage of myocardial tissues, and improve the effects of heart failure. Xianwei et al<sup>126</sup> showed that ginseng injection could activate AMPK, reduce the content of IL-6 and TNF- $\alpha$  in myocardial tissues of rats with heart failure, inhibit inflammatory reactions, and delay



ventricular remodelling and myocardial hypertrophy. Qiong et al<sup>127</sup> experiments showed that Huanglian Jiandu soup could protect inflammation-injured endothelial cells by affecting AMPK and ICAM-1.(See Table 2)

## Conclusion and Outlook

The pathogenesis of HF is complex, and the AMPK signalling pathway plays an important role in its pathogenesis. By regulating the AMPK pathway, HF can be alleviated by inhibiting inflammatory response, oxidative stress, autophagy,

**Table 2** Mechanism of Action of Chinese Herbal Medicine Combinations Regulating the AMPK Signalling Pathway to Improve Heart Failure

Chinese Medicine Compound	Composition	Research Subject	Dose	Times	Mechanism of Action	Reference
Linggui Zhugan soup	Cassia twig, Atractylodes rhizoma, Poria cocos	ADR-induced heart failure in rats	2.43, 4.86g/kg	4 weeks	Activation of AMPK-related pathways, Inhibits oxidative stress and improves mitochondrial function	[109]
Yixintai granules	Ginseng, Radix Ophiopogonis, Schisandrae, Rhizoma anemarrhenae, Angelica, calamus	AAS-induced heart failure in rats	1.76, 3.56, 5.58 g/kg	6 weeks	Activation of AMPK-related pathways, Inhibits fatty acid oxidation and increases ATPase activity	[111]
Yangxin Kang Tablets	Ginseng, polygonum multiflorum, panax notoginseng	TAC-induced heart failure in rats	3.78, 7.56, 15.12g/kg	4 weeks	Activation of AMPK-related pathways, Modulation of cardiomyocyte autophagy	[114]
Xinshuai Ning Combination	Mulberry bark, Rhizoma alismatis, plantaginis, Astragalus	ISO-induced heart failure in rats	11.1, 22.2g/kg	5 weeks	Regulation of PPAR $\alpha$ , AMPK expression and consequently improvement of FFA levels	[119]
Wenyang Yiqi Soup	Aconite, cinnamon, Astragalus, Poria, Atractylodes rhizoma	ADR-induced heart failure in rats	1.188g/mL	8 weeks	Inhibition of AMPK-mediated mitochondrial autophagy	[120]
Buyang Huanwu Soup	Angelica sinensis, wild land, RHIZOMA Chuanxiong, Astragalus membranaceus, Paeonia lactiflora	SHR-induced heart failure in rats	9, 18, 36g/kg	4 weeks	Activation of AMPK-related pathways, Enhances autophagy and improves mitochondrial metabolism	[122]
Shenkui Tongxin granules	Salvia miltiorrhiza, RHIZOMA Chuanxiong, Radix Puerariae	AAC-induced heart failure in rats	0.375, 0.75, 1.5g/kg	4 weeks	Activation of AMPK-related pathways, Enhanced mitochondrial autophagy and improved energy metabolism in cardiomyocytes	[123]
Shenfu Qiangxin Soup	Ginseng, Aconite, mulberry white skin, descurainia	ISO-induced heart failure in rats	12.6g/kg	6 weeks	Activation of AMPK-related pathways, Regulation of fatty acid oxidative metabolism and glucose transport	[124]
Shenfu Xiongze Soup	Ginseng, Aconite, RHIZOMA Chuanxiong, Rhizoma alismatis	SHR-induced heart failure in rats	6.61, 13.22, 26.44g/kg	2 weeks	Activation of AMPK-related pathways, Reduces serum FFA levels	[125]
Ginseng injection	Ginseng, Aconite, salvia miltiorrhiza, Bupleurum	TAC-induced heart failure in rats	3.71, 7.42g/kg	5 weeks	Activation of AMPK-related pathways, Suppression of the inflammatory response	[126]
Huanglian Jiandu soup	Scutellaria baicalensis, Rhizoma coptidis, Phellodendron angustifolia, Gardenia jasminoides	ISO-induced heart failure in rats	10mL/kg	6 weeks	Activation of AMPK-related pathways, Suppression of inflammatory response	[127]

**Abbreviations:** ADR, Adriamycin; TAC, Transverse aortic constriction; SHR, Spontaneously hypertensive rats; ISO, Isoproterenol; AAS, ascending aortic stenosis; AAC, abdominal aortic coarctation.

apoptosis and ferroptosis, etc. Currently, there is some research on the efficacy of Chinese herbal compounds, Chinese herbal active ingredients and Chinese herbal extracts in the treatment of HF, and the mechanism of action of the relevant drugs has been studied to some extent. Therefore, this paper reviewed the connection between the AMPK signalling pathway and the pathogenesis of HF, as well as the current progress of Chinese medicines in attenuating HF by interfering with the AMPK signalling pathway, with a view to better understanding the pathogenesis of HF and providing some theoretical basis for the treatment of HF with Chinese medicines. It is therefore concluded that traditional Chinese medicine can protect cardiomyocytes to attenuate HF by regulating the AMPK signalling pathway.

In summary, targeting the AMPK signalling pathway for the treatment of HF may be an effective means, and current research has achieved some results in modulating the AMPK signalling pathway in traditional Chinese medicine to alleviate HF. However, there are still shortcomings in the existing research, firstly, the current research on the AMPK signalling pathway of HF is mostly based on animal experiments, lack of relevant clinical research and a single research method, the future can be a combination of clinical research and experimental research to better elucidate its effectiveness and safety. Secondly, there are few studies that explore the complex relationship between the active ingredients of TCM and its compound and the mechanism of HF from the level of molecular mechanism. In the future, modern science and technology, such as network pharmacology and biological information, can be combined to conduct in-depth excavation, and further research can be carried out to explore the specific mechanisms in order to lay the foundation for the alleviation of HF.

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## Disclosure

All the authors declare that they have no conflicts of interest.

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