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Review of Saponins in Treating Heart Failure

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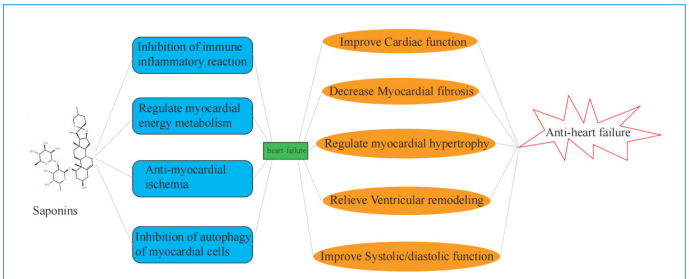
Abstract

Traditional Chinese Medicine (TCM) has a long history and rich experience in treating Heart Failure (HF), with good clinical effect and little side effects. Saponins, as one of the active substances in TCM, have a variety of pharmacological activities, wide sources and low toxicity, and their functions can not be ignored. Further research on the role of saponins in the treatment of HF found that saponins have the advantages of multi-level, multi-target and multi-channel comprehensive regulation effects, which has important research and development value in the treatment of HF. Through the analysis and summary of the related literatures on the mechanism of treating HF with saponins, it is found that saponins can improve heart function mainly by inhibiting inflammatory reaction, regulating energy metabolism disorder, resisting myocardial ischemia, inhibiting myocardial apoptosis and other ways. The purpose of this paper is to further explore the mechanism of saponin in treating different HF, and to provide further ideas and references for the research and drug development and application of TCM in preventing and treating HF.

Keywords: Saponins; Ginsenoside; Astragalus saponin; Panax notoginseng saponins; Heart failure.



Graphical abstract.

Introduction

Heart Failure (HF) is the terminal stage of the development of a variety of cardiovascular diseases, and it is a group of clinical symptoms that the ejection function is impaired due to changes of heart structure and function. The incidence is mainly related to hypertension, myocardial infarction, diabetes and ischemic heart disease [1]. In recent years, its incidence, recurrence and readmission rate and mortality have gradually increased [2]. According to the pathogenesis of HF, at present, the related treatment and research mainly focuses on diuretics, Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB) and statins, which can effectively improve the heart function and relieve the corresponding discomfort symptoms. However, the mortality, prognosis and quality of life of the patients have not improved within three years, and there are still some problems in clinical treatment, such as high ex-

amination cost, serious side effects of drugs such as electrolyte exhaustion, body fluid exhaustion and hypotension. Therefore, it is particularly important to find better way to diagnose and treat HF and to develop new drugs.

Tradition Chinese Medicine (TCM) has been used to treat HF with great curative effects for thousands of years. With the progress and development of modern science and technology, as well as the in-depth study of traditional Chinese medicine, it is found that compared with traditional drugs for treating HF, the active components of traditional Chinese medicine include saponins, polysaccharides, alkaloids, flavonoids, volatile oil, etc., which have the characteristics of multi-target synergy and less toxic side effects. Clinical data show that the side effect of western medicine treatment is 9.81%, while that of TCM treatment is only 4.08% [3]. Many studies have discussed the pharmacological mechanism of TCM in treating HF. The dosage forms of TCM studied include single drug, Chinese medicine extract and prescription. Relevant experimental studies in vitro and in vivo show that TCM has the characteristics of anti-fibrosis, anti-inflammation, anti-oxidation, anti-apoptosis, promoting angiogenesis and regulating metabolism [4]. Saponins are widely found in all kinds of TCM. In recent years, people have done a lot of research on saponins in TCM, and found that saponins can prevent and treat cardiovascular diseases by reducing the level of oxidative stress, inhibiting myocardial cell apoptosis, inhibiting inflammation, regulating autophagy, regulating myocardial energy metabolism and so on, thus playing a role in protecting the heart [5]. Thus, the development of active ingredients from Chinese herbal medicine is the direction of treating HF in the future.

TCM or its effective components can play a role through various channels and targets, effectively regulating the complex pathological mechanism of HF, which is also the advantage of the application of TCM [6]. Saponins not only have the advantages of TCM, but also its effective components are easy to be identified and extract, which has become a hot spot in modern medical research. Therefore, based on the obvious anti-HF effect of saponins, the saponins of TCM with heart protection function are classified and summarized, the internal relationship between saponins and HF is discussed, and the mechanism of treating HF is analyzed, so as to provide ideas and references for the in-depth research and drug development and application of TCM to prevent and treat HF.

Pathogenesis of HF: Modern medicine believes that HF is the terminal stage of the development of many cardiovascular diseases, such as valvular heart disease, cardiomyopathy, myocarditis, myocardial infarction, etc. It is a change of heart structure and function, which eventually leads to the weakening of ventricular pumping and filling function, and then leads to a series of symptoms of heart failure, mainly manifested as shortness of breath, fatigue, palpitation, edema of lower limbs and so on [7]. Common pathogenic factors of HF are respiratory infection, anemia, arrhythmia, hyperthyroidism, pregnancy, childbirth, excessive physical activity and emotional excitement, digitalis poisoning and other diseases. Cardiac output is one of the main features of heart failure. According to the difference of ejection fraction, the American Heart Association Foundation (ACCF)/ American Heart Association (AHA) defined ejection fraction ≤40% as HF with reduced Ejection Fraction (HFrEF), the ejection fraction between 41% and 49% as HF with moderately reduced Ejection Fraction (HFmrEF) and the ejection fraction ≥50% as HF with preserved Ejection Fraction (HFpEF) [8]. Although the diagnosis of HFrEF, HFpEF and HFmrEF is different, they can all cause cardiac dysfunction by causing changes in myocardial structure and activating several molecular signaling pathways, such as myocardial autophagy, endothelial dysfunction, oxidative stress, interstitial fibrosis and cardiac inflammatory response [9]. At the same time, many cardiovascular diseases will lead to HF at the end stage, such as myocardial infarction, myocardial ischemia, cardiovascular damage, increased hemodynamic load and other reasons, which can all cause damage to the structure and function of the heart [10].

Saponins and their pharmacological effects: Saponins are a common class of bioactive glycosides in TCM, mainly including triterpenoid saponins and steroidal saponins, which have many biological activities such as protecting cardiovascular function, improving energy metabolism, anti-inflammatory and anti-oxidation [11]. Modern pharmacological research shows that ginsenoside, astragaloside, notoginseng saponin, dioxin and other saponin compounds have many effects on improving heart function, with high medicinal value and definite curative effect.

The source of saponins: The word “Saponin” is a free translation of English saponin. The name “saponin” is derived from the Latin word “sapo”, meaning soap-like foam-generating ability, and the amphiphilic properties derived from the structure containing an isoprenoid-derived aglycone (a sapogenin) attached to one or more sugar chains by either an ether or ester linkage [12]. Saponins are compounds with complex structures in glycosides, which are widely found in Araliaceae, Umbelliferae, Leguminosae, Dioscoreaceae, Liliaceae and other medicinal materials, such as Ginseng, Astragalus, Notoginseng Radix, Dioscorea, etc., and mainly exist in a wide variety of plants with complex components.

Chemical structure of TCM saponins: Saponins are complex compounds composed of triterpenoid or steroid aglycone molecular skeleton combined with glycosyl [13]. The common sugars that constitute saponins are glucose, arabinose, xylose, galactose and galacturonic acid. Saponins can be divided into monosaccharide chain saponins, disaccharide chain saponins and trisaccharide chain saponins according to the number of sugar chains connected by aglycone, and triterpene saponins and steroid saponins according to aglycone.

Chemical structure of steroid saponins: Saponins with glycine as spirostane (C-27 steroids) are called steroid saponins. Steroidal saponins are a kind of spirocyclic steroid compounds containing oligosaccharide structural fragments, which mainly exist in Dioscorea, Liliaceae and Scrophulariaceae. The sapogenin skeleton of steroidal saponins is a derivative of spirosterane, which consists of 27 carbon atoms, and its mother nucleus is cyclopentane-doxene. According to the configuration of C-25 position in the spirostane structure and the cyclization state of the ring, it can be divided into spirostanol, isostanol, deformed spirostanol and furastanol saponin, among which spirostanol saponin is the most common, and its structural diversity also contributes to its extensive pharmacological activities.

Chemical structure of triterpenoid saponins: Saponins containing triterpenoid aglycone are called triterpenoid saponins, which mainly exist in Umbelliferae, Araliaceae, Polygalaceae, Leguminosae and Cucurbitaceae. Triterpenoids are terpenoids with 30 carbon atoms, and their basic nucleus consists of six isoprene units (C5H8). Triterpenoid saponins can be divided into linear triterpenoids, bicyclic triterpenoids, tricyclic triterpenoids, tetracycline triterpenoids and pentacyclic triterpenoids

according to its basic carbon skeleton. There are mainly tetracycline triterpenoids and pentacyclic triterpenoids in plants, among which tetracycline triterpenoids are mainly cyclic atun type, dammarane type, cucurbitacine type, lanolin type, etc., and pentacyclic triterpenoids are mainly oleanane type, lupane type, Wusu type, etc [14].

Pharmacological effects of TCM saponins

Anti-inflammatory effect: Inflammation and immune response explain the human body's defense against injury and stimulation from different perspectives. The response of the body to the stimulus of injury leads to the release of immune mediators by the immune system, which leads to inflammatory reactions [15]. The immune system is a dynamic balance between pro-inflammatory and anti-inflammatory responses. With the immune activation of HF, it is actually an immune disorder. The contents of proinflammatory factors and corresponding anti-inflammatory factors in serum and myocardium of patients with heart failure are out of balance [16]. Excessive inflammatory response inhibits myocardial contraction through various mechanisms, leading to myocardial remodeling, myocardial hypertrophy, fibrosis and other pathological changes [17]. At the same time, studies have shown that ginsenoside, panax Noto ginseng saponin and other traditional Chinese medicine saponins have pharmacological effects of alleviating inflammatory reaction [18,19]. It can be seen that it has a certain anti-HF effect by reducing the inflammatory reaction of myocardial cells and the damage of inflammatory immune regulation to myocardial cells.

Regulation of energy metabolism disorder: The heart is a high energy-consuming organ of the body, and it needs to continuously consume ATP to maintain its contraction and relaxation functions. However, due to the lack of energy storage structure, the myocardium uses the productivity of fatty acids, glucose, lactic acid, ketone bodies and amino acids to maintain high energy conversion efficiency [20]. In the process of heart failure, the energy metabolism of the heart is opposite to that of the fetus in a hypoxic environment. Glucose oxidation is the main energy supply, and its production efficiency is significantly higher than fatty acid oxidation. Patients with HF are often accompanied by insufficient energy supply, such as substrate absorption and utilization, oxidative phosphorylation and ATP shuttle disorder [6,21]. Regulating substrate metabolism and relieving the disorder of myocardial energy metabolism are of great significance to improve myocardial mechanical function and delaying the process of heart failure. It was found that astragaloside IV, ginsenoside and other traditional Chinese medicine saponins can significantly improve the disorder of myocardial energy metabolism and alleviate HF process [22-24].

Anti-myocardial ischemia effect: Myocardial ischemia is a pathological state in which the blood perfusion of the heart is reduced, resulting in insufficient blood supply and oxygen supply to the heart, and the energy metabolism of the whole heart cannot be carried out normally. Almost all the energy needed for heart activity comes from aerobic metabolism, and the oxygen demand brought by myocardial blood supply is high. Therefore, it is very important to maintain the oxygen uptake required by myocardium to ensure the normal work of the heart for effective myocardial blood supply [25]. If the myocardium is ischemic, it may lead to myocardial cell necrosis due to lack of oxygen, so that the heart cannot work normally, and sudden death may occur. Long-term myocardial ischemia will cause ischemic cardiomyopathy, and myocardial cell necrosis and apoptosis will cause myocardial fibrosis after myocardial ischemia. When myocardial ischemia develops to a certain extent, it will enlarge the heart, weaken the myocardial contractility and eventually lead to heart failure. Therefore, measures must be taken as soon as possible to treat myocardial ischemia, increase myocardial blood supply, reduce the burden on the heart, and prevent myocardial ischemia from getting worse [26]. Studies have found that saponins of traditional Chinese medicine, such as panax Noto ginseng saponins, astragaloside IV, ginsenoside, etc., can relieve the symptoms of myocardial ischemia [27-29].

Inhibition of myocardial cell apoptosis: Apoptosis of myocardial cells is an important pathogenesis of heart failure. Apoptosis is a complex series of pathophysiological changes. Under the control of related genes, cells contract and chromatin accumulates until cells decompose and swallow. Apoptosis occurs all the time in the body, and myocardial apoptosis exists in all stages of the development of many cardiovascular diseases. Myocardial cells do not have the ability to regenerate, and the number of surviving myocardial cells decreases after myocardial apoptosis, which further aggravates ventricular remodeling and promotes the progress of heart failure [30]. Therefore, inhibiting myocardial cell apoptosis is of great significance for preventing and treating heart failure. It has been found that saponins of TCM, such as Astragalus saponin, Ginsenoside and Gynostemma pentaphyllum saponin, can effectively inhibit cardiomyocyte apoptosis [31-33].

Mechanism of action of saponins in treating HF

Triterpenoid saponins

Ginsenoside: Ginseng is a TCM for invigorating qi and nourishing viscera, which can significantly replenish the body's vitality, and at the same time, it can play the roles of restoring pulse and removing blood stasis, nourishing the heart and generating blood, and warming and nourishing Yuanyang. Ginsenosides in ginseng can excite myocardium, increasing myocardial blood flow, protecting myocardial ischemia and hypoxia injury, reducing myocardial oxygen consumption and regulate blood pressure, thus effectively preventing the occurrence and development of HF [34]. Rat HF model was induced by abdominal aortic coarctation, and then ginsenoside Rb 1 (Gs-Rb 1) was used to intervene. It was found that Gs-Rb 1 could alleviate myocardial hypertrophy and fibrosis, restore mitochondrial function and improve heart function by inhibiting TGF-β 1/Smad and ERK pathways and activating Akt pathways [35]. At the same time, another study shows that Gs-Rb 1 can also inhibit the autophagy of myocardial cells in HF rats by regulating Rho/ROCK and PI 3K/mTOR signaling pathways, thus exerting anti-HF effects [36]. In addition, ginsenoside Rg 3 (Gs-Rg3) was used to interfere with HF model mice induced by abdominal aorta constriction. Comparing heart function with mitochondrial function, it was found that the mechanism of Gs-Rg 3 improving heart function in mice with heart failure may be related to activating AMPK pathway, improving insulin resistance and regulate glucose metabolism [37]. The rat HF model induced by adriamycin was used, and the prognosis was made by Gs-Rb 1. The activities of high-energy phosphate, free L-carnitine, malonyl-coenzyme A and FAO-related enzymes in rat myocardium were compared. It was found that Gs-Rb 1 could regulate cardiac metabolic remodeling and improve cardiac function by activating AMPK pathway, thus improving myocardial fatty acid β oxidation in rats with HF [38].

Astragaloside: Astragalus membranaceus is one of the commonly used TCM for treating HF. Astragaloside IV is the main

active ingredient in Astragalus membranaceus. Many pharmacological studies show that astragaloside IV plays a significant role in improving cardiac function, inhibiting inflammatory response, improving myocardial energy metabolism, protecting myocardium and inhibiting ventricular remodeling [39]. Astragalus saponins can improve myocardial hypoxia and ischemia in CHF rats after myocardial infarction, and its mechanism may be by regulating AT 1-PLC pathway, down-regulating the expression level of AT 1 protein and mRNA in myocardial tissue, and reducing the activity of myocardial PLC, thus reducing the intracellular calcium concentration of myocardial cells and alleviating the damage of calcium overload to cells [31]. Astraloside IV (AS-IV) has the functions of protecting myocardial ischemia, promoting angiogenesis, improve energy metabolism, inhibiting myocardial hypertrophy and fibrosis, and reduce myocardial cell apoptosis, which is of great significance for improving heart function of HF model [31]. AS-IV can protect the heart from HF by regulating Nrf-2 pathway and reducing the apoptosis of myocardial cells and mitochondrial dysfunction induced by Adriamycin [40]. AS-IV can increase the expression of PARα, MCAD and MCPT 1 in myocardium of CHF rats, improve the utilization ratio of FFA, inhibit ventricular remodeling and improve the cardiac function of CHF rats [41]. AS-IV can prevent cardiac hypertrophy by increasing the activity of SIKE inhibiting TBK1/PI3K/AKT [42]. At the same time, AS-IV can protect myocardial cells from oxidative damage by regulating the activity of histone Heacetylase (HDAC), thus reversing the low eNOS level caused by OxLDL, which is manifested by the decrease of BNP concentration [43]. In addition, AS-IV can also regulate JAK-STAT 3 pathway to activate VEGF promoter, promote angiogenesis, and thus relieve the symptoms of HF rats [44].

Notoginsenoside: Panax notoginseng, the dried root and rhizome of Araliaceae plants, is a common and precious Chinese medicine for treating cardiovascular diseases, which has the effect of removing blood stasis and stopping bleeding. Panax notoginseng saponins is one of the main active ingredients extracted from it, which has the functions of improving myocardial ischemia-reperfusion injury, increase blood circulation and improve blood supply. The protective effect of PNS on MIRI is mainly due to its ability to enhance mitochondrial autophagy in myocardial tissue through the HIF-1α/NIP3 pathway [45]. At the same time, it has also been found that PNS can protect the heart by inducing autophagy of myocardial cells, preventing platelet aggregation, enhancing endothelial cell migration and angiogenesis [46]. In addition, PNS can also prevent HF by regulating PPAR signaling pathway [47].

Gynostemma pentaphyllum saponin: Gynostemma pentaphyllum is a plant of Gynostemma in Cucurbitaceae, and its effective components have the functions of regulating blood lipid, antioxidation and anti-apoptosis. It was found that Gynostemma pentaphyllum saponin I can reduce oxidative stress, inflammation and myocardial hypertrophy induced by Isoproterenol (ISO), reduce myocardial fibrosis and improve cardiac

Table 1: The mechanism of triterpenoid saponins in the treatment of HF.

Triterpenoid saponin components	Experimental model	Mechanism	References
Ginsenoside	Rat model of HF induced by abdominal aortic coarctation.	Inhibit TGF-β1/Smad and ERK pathways, and activate Akt pathway.	ZHENG [35]
	DOX-induced HF rat model	Activating AMPK pathway	KONG [38]
	Rat model of HF induced by ligation of left anterior descending coronary artery	Regulating Rho/ROCK and PI3K/mTOR Signal Pathways	YANG [36]
	Mice model of HF induced by abdominal aortic coarctation	Activating AMPK pathway	NI [37]
Astragaloside	DOX-induced HF rat model	Regulation of Nrf-2 pathway	FENG [40]
	Rat model of CHF induced by abdominal aortic coarctation.	Increase the expression of PPARα, MCAD and MCPT1 in myocardium.	TANG [41]
	Myocardial hypertrophy model induced by coarctation of aorta in mice.	Increase the expression of SIKE and inhibit the activity of TBK1/PI3K/AKT.	LIU [42]
	Cardiomyocyte injury model induced by ox-LDL	Regulating HDAC activity	ZHANG [43]
	HF rats	Regulation of JAK-STAT3 pathway	SUI [44]
Notoginsenoside	MIRI rats model	Regulating HIF-1α/BNIP3 pathway and increasing the expression of HIF-1α, BNIP3, Atg5 and Beclin-1.	LIU [45]
	Mice model of HF induced by ligation of left anterior descending coronary artery	Up-regulate the expression of AMPK Thr172 and CaMKII Thr287.	WANG [46]
	Mice model of HF induced by ligation of left anterior descending coronary artery	egulating PPAR signaling pathway	CHEN [47]
Gynostemma saponin	ISO-induced injury model of H9C2 cardiomyocytes	Inhibition of TLR4/NF-κB/NLRP3 signal pathway	LI [48]
	Mice model of MI induced by ligation of left anterior descending coronary artery	Inhibit apoptosis and autophagy induced by ERS, and improve the expression of ATG5, LC3A/B and BAX.	SU [33]
Sanguisorba saponin	H_2O_2-induced injury model of H9C2 cardiomyocytes	Activating ERK1/2 signal pathway, promoting the expression of Bestrophin3 and inhibiting the expression of Bax, Caspase-3 and Caspase-9.	RU [48]
Momordica saponins	DOX-induced HF rat model	Decrease the expression level of Caspase-8, Caspase-3, MMP-2, TNF-α and NT-proBNP protein and mRNA, decrease the expression, and increase the expression of Bcl-2 protein and mRNA.	HUANG [54-56]

function by inhibiting TLR4/NF-κB/NLRP3 signaling pathway [48]. Gynostemma pentaphyllum saponin can also improve the health of rats by inhibiting oxidative stress and inflammatory cytokines [49]. It is found that Gynostemma Pentaphyllum XVII (GP-17) can protect the heart by inhibiting ERS-induced apoptosis, autophagy, oxidative stress and mitochondrial division [33].

Sanguisorba saponin: Sanguisorba officinalis belongs to Rosaceae, which has anti-inflammatory, anti-virus and anti-oxidation effects. Sanguisorba saponin Ⅱ is a triterpenoid saponin compound separated from Sanguisorba officinalis. Studies have shown that Sanguisorba officinalis saponin Ⅱ has the effects of resisting oxidative stress and inhibiting apoptosis. It can activate ERK 1/2 signal pathway, promoting the expression of Bestrophin 3, inhibit oxidative stress, inhibit the expression of apoptosis-related proteins Bax, Caspase-3 and Caspase-9, and effectively inhibit H_2O_2-induced myocardial cell apoptosis [50].

Momordica saponins: Momordica charantia has the effects of clearing away heat and relieving summer heat, diuresis and cooling blood, benefiting qi and strengthening yang. Total saponins of momordica charantia are a kind of saponin compounds extracted from momordica charantia. It was found that total saponins of momordica charantia can reduce the expression levels of Caspase-8, Caspase-3, MMP-2, TNF-α and NT-proBNP, increase the expression of Bcl-2 protein and mRNA, delay the apoptosis of myocardial cells, inhibit inflammatory reaction, protect myocardium damaged by CHF, and thus improve the cardiac function of CHF rats [51-53]. We have classified and summarized the mechanism of the above triterpenoid saponins in HF in Table 1.

Steroidal saponins

Diosgenin: Dioscorea zingiberensis has the function of relaxing muscles and activating blood circulation. Diosgenin is the main component of Dioscorea, and it is a natural steroidal saponins compound. Modern pharmacological studies have shown that dioxin have pharmacological effects such as protecting vascular endothelial function, alleviating myocardial ischemia/reperfusion injury, and can effectively improve hypertrophic cardiomyopathy, arrhythmia, myocardial I/r injury and cardiotoxicity caused by Adriamycin [54-56]. Studies show that diosgenin can prevent myocardial hypertrophy and fibrosis induced by angiotensin II (AngII) by regulating MAPK, Akt/GSK 3β/mTOR and PKCε/ERK pathways [57,58]. In a study, Doxorubicin (Dox) was employed to induce HF model and HL-1 cell damage model. It was found that dioxin could reverse cell apoptosis and autophagy by activating Akt/mTOR pathway mediated by PDK 1, regulating the levels of key molecules related to autophagy (including Atg 5 and Berlin 1) and apoptosis-related proteins (including Bcl-2 and caspase-3), thus alleviating cardiac function damage [59]. Diosgenin can also reduce DOX-induced cardiotoxicity by regulating myocardial oxidative stress mediated by miR-140-5p [60]. In addition, related studies also found that dioxin can enhance mitochondrial Kreb circulation and respiratory chain enzyme activity, promote antioxidant enzyme activity to reduce ROS, relieve mitochondrial dysfunction, and inhibit myocardial cell apoptosis, thus improving the heart function of mice with myocardial infarction [61].

Ophioposide: Ophioposide (OPD) is a saponin extracted from Ophiopogon japonicus, which has many biological activities, such as anti-inflammatory, anti-oxidation, enhancing cardiovascular function and so on [62]. Studies have shown that OPD has obvious cardioprotective effect on DOX-induced CHF. It can delay the onset of CHF by inhibiting inflammatory cytokines and reducing oxidative stress through p38 MAPK activity [63]. OPD can also induce the expression of CYP2J2 and CYP2J3, treat ISO-induced HF in rats and protect myocardial cells [64]. We have classified and summarized the mechanism of the above steroidal saponinsin HF in Table 2.

Table 2: The mechanism of steroidal saponins in the treatment of HF.

Triterpenoid saponin components	Experimental model	Mechanism	References
Diosgenin	AngII-induced HF mice model	Regulating MAPK, Akt/GSK3β/mTOR pathways	CHEN [57-58]
	ISO-induced HF rat model, ISO-induced H9C2 cell model and primary myocardial cell model.	Regulating PKCε/ERK pathway	LI [57-58]
	Dox-induced HF model and HL-1 cell injury model	Activation of Akt/mTOR pathway mediated by PDK 1	YUAN [59]
	Adriamycin-induced H9C2 cell injury and myocardial injury model in rats and mice.	Activation of Nrf2 and Sirt2 signal pathways reduces the expression of miR-1-1p.	ZHAO [60]
ophioposide	DOX-induced CHF rat model	Activating p38 MAPK activity, inhibiting inflammatory cytokines, reducing oxidative stress, etc.	WU [63]
	ISO-induced HF rat model, H9C2 cell injury model.	Up-regulating the expression of CYP2J3 and CYP2J3	LIN [64]

Summary and prospect

Treating HF with TCM has the unique advantages of less side effects, safety and effectiveness. With the advancement of modernization of TCM, saponins have been proved to play an anti-HF role in many ways, including inhibiting inflammatory reaction, inhibiting myocardial cell apoptosis and improving myocardial energy metabolism. Ginsenoside, Astragaloside, Notoginsenoside, dioxin and so on Can improve heart function and prevent heart failure by inhibiting inflammatory reaction, myocardial cell apoptosis, myocardial fibrosis, myocardial energy metabolism and hypertrophy. However, there are still many problems to be solved and improved in the research of preventing and treating HF with saponins of TCM.

① The research on the mechanism of saponin in treating HF mainly focuses on animal experiments and cell experiments, lacking clinical research, and there are few reports on its in vivo process and safety. The research on its plasma concentration, metabolic pathway, duration, blood-brain barrier and in vivo toxicology is still in its infancy.

② There are few studies on the dose-effect-toxicity relationship of traditional Chinese medicine saponins, which makes it difficult to popularize in clinic.

③ There are few studies on the mechanism of Chinese medicine saponin components intervening heart failure and the

integration of Chinese medicine theory. How to intervene heart failure by using saponin components combined with Chinese medicine theory on the basis of syndrome differentiation and treatment needs further exploration.

④ The mechanism of Chinese medicine saponin intervening HF is complicated, and the function and connection between signal pathway and the synergistic and antagonistic effects of various pharmacological mechanisms need further systematic study.

Generally speaking, the active components of saponins have been proved to play an important role in HF and its complications, which has a rich preliminary foundation and broad research prospects. In the follow-up, we should further expand the related research on the intervention of TCM on HF, promote the development and utilization of TCM resources, and help the research and development of new drugs for HF.

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