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Review

Role of Chinese Herbal Medicines in Regulation of Energy Metabolism in Treating Cardiovascular Diseases*

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ABSTRACT Recently, studying myocardial energy metabolism pathways or improving myocardial metabolism through drugs is another effective strategy for treating ischemic heart disease. Many active components of Chinese herbal medicines (CHMs) have been found to modulate energy metabolism in myocardial cells, cerebral vascular cells, endothelial cells and tumour cells. This paper reviews the advances in studies on the active components of CHMs that modulating energy metabolism in treating cardiovascular diseases over the past five years.

KEYWORDS biologically active ingredient, Chinese herbal medicine, cardiovascular disease, ischemic heart disease, heart failure

According to the Global Burden Disease estimates, cardiovascular diseases were the top 5 leading causes of total years of life lost in 2016.[1] Cardiovascular disease is the leading cause of death worldwide, and its incidence is considered to be an important economic burden on patients and their society. Although the incidence and mortality of cardiovascular disease have dropped significantly in several high-income countries in the past few decades, income growth rates in low- and middle-income countries are still very fast, and these accounts for nearly 80% of the global burden.[2,3] Therefore, the treatment of cardiovascular diseases has become a hot issue.

Progress in medical science has demonstrated the pathogenesis of cardiovascular disease to be complicated, with a wide variety of underlying factors. So far, in the treatment of myocardial ischemia strategies are more concerned about the intervention or thrombolysis method to make coronary artery patency, but changes in myocardial energy metabolism is also an important factor inducing or aggravating myocardial ischemia.[4,5] Alterations of myocardial energy metabolism and redox-status can be depicted together as a fatal cocktail, dramatically propelling the cardiovascular diseases to its lethal outcome. Therefore, the study of myocardial energy metabolism and effective regulation, or through drugs to improve myocardial metabolic status, is the treatment of ischemic heart disease (IHD) is another effective strategy.

Indeed, recent several studies have shown that metabolic therapy can be a potential and promising approach in dealing with IHD and heart failure (HF).[6-8] Metabolic therapy functions by modulating metabolism, shift the energy production pathway from fatty acid to glucose in the presence of decreased oxygen supply. As these agents function without affecting the hemodynamic alterations, they would not add further to the side effects already produced by heavy multiple hemodynamically acting agents.

Recent studies have found that some Chinese herbal medicines (CHMs) and their active ingredients can regulate a variety of energy metabolism processes.[9,10] This article summarizes the past five years of researches on the use of CHMs and their active ingredients to treat cardiovascular disease and other chronic diseases by regulating energy metabolism.

Application of Plant Products in IHD

The heart needs a lot of energy to maintain its

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normal physiological function. According to reports, myocardial metabolic disorders are associated with the onset of myocardial ischemia/reperfusion injury (MIRI).[11] Myocardial ischemia reduces myocardial aerobic metabolism and anaerobic metabolism becomes the main route. Anaerobic metabolism produces a large amount of acidic products, which in turn induces intracellular acidic toxicity, thereby impairing the cellular microstructure. At the same time, the production of adenosine triphosphate (ATP) decreased rapidly, which reduced the mitochondrial activity of Ca^{2+}-ATPase and Mg^{2+}-ATPase. Therefore, mitochondrial Ca^{2+} levels increased significantly.

Under normal conditions, the heart oxidizes from free fatty acids (FFAs) to produce most of the energy, and the rest comes from glucose oxidation and lactic acid. Compared to glucose, the number of moles of ATP produced per mole of carbon oxides is about 29% higher than FFA. In hypoxia, glucose is preferred for energy production because it is compared to the production of glycogen per mole of ATP. The solution requires less oxygen and FFA oxidation. The number of moles of ATP consumed per mole of oxygen is 12% higher than that of glucose FFA. Increased use of glucose and lactate can increase myocardial oxygen utilization and efficiency by 16%–26%. Therefore, the production of energy is more dependent on glucose metabolism (Figure 1).[12]

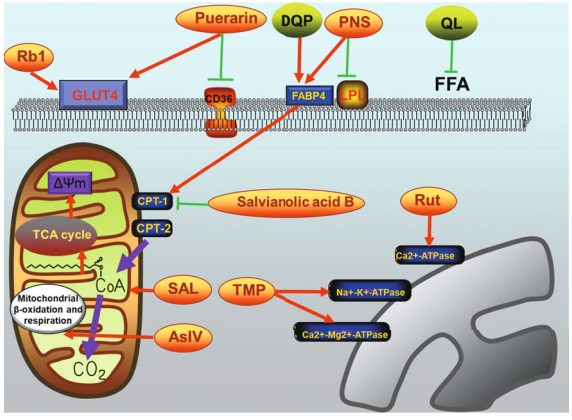

Figure 1. Schematic Overview of Proposed in Regulation of Energy Metabolism in Treating Cardiovascular Diseases Mechanism of Each Natural Drug Agent

Notes: Rb1: ginsenoside Rb1; DQT: Danqi Tablet; SAL: salidroside; AsⅣ: astragaloside Ⅳ; TMP: tetramethylpyrazine; Rut: rutaecarpine; QL: Qili Qiangxin Capsule; PNS: panax notoginseng saponins

Current medical therapies for IHD involve anticoagulants, thrombolytic and percutaneous coronary intervention which aim to improve the blood supply of the heart. However, these treatments will irreversibly cause myocardial injury. Over the last 30 years, researches demonstrate that partial inhibition of myocardial fatty acid oxidation, with mutual activation of carbohydrate oxidation, is an effective treatment for myocardial injury. Some studies suggest that some CHMs have exhibited promising benefit effects on IHD.[13]

Alkaloids

Rutaecarpine

Evodia rutaecarpa (*E. rutaecarpa*), a CHMs, is used in the treatment of headache, hypertension, and gastrointestinal disorders.[14] Rutaecarpine (Rut), an indolopyridoquinazolinone alkaloid isolated from the unripe fruit of *E. rutaecarpa*, has been shown to have various biological activities such as antithrombotic activities and anti-inflammatory effects.[15] Various pharmacological effects have been reported for Rut, including analgesic effects, anti-inflammatory activity,[16] atherosclerosis suppression,[17] inotropic action on cardiomyocytes[18] and vasodilatory effects.[19]

Recently, Xue, et al[20] reported that Rut attenuated myocardial infarct size induced by MIRI, improved metabolism disorders between fatty acid and glucose, increased the content of ATP, Ca^{2+}-ATPase activity and reduced the content of peroxisome proliferator-activated receptor α (PPARα) protein level. Rut may regulate the glycolipid substrate metabolism to protect cardiac myocytes and delay heart ischemia/reperfusion (I/R) injury development process.

Tetramethylpyrazine

Tetramethylpyrazine (TMP) is a biologically active ingredient isolated from the CHM *Ligusticum chuanxiong* Hort, which is widely used in China for the treatment of cardiovascular problems[6,21] It has been previously reported to increase coronary blood flow and systemic circulation by protecting mitochondria and improving energy metabolism,[22] scavenging oxygen free radicals in order to inhibit lipid peroxidation, inhibition of apoptosis and protection of myocardial cells, reducing the inflammatory reaction, mitigating cell injury, and protecting myocardial cells.

Wang, et al[23] reported that TMP can ameliorate

MIRI by increasing energy production in myocardial cells. A proposed mechanism is that TMP can reduce the degradation of myocardial ATP and increase ATP generation. Though this pathway, energy storage in myocardial cells is increased, which could protect high-energy phosphate compounds in the myocardium.

Zhu, et al[24] reported that Na^+-K^+-ATPase in myocardial tissues is not sensitive to ischemic injury but is sensitive to reperfusion injury. TMP could protect the Na^+-K^+-ATPase activity of ischemic myocardial tissues afer reperfusion. Shi, et al[25] using molecular biological methods, observed that TMP could increase the absorption of ^{3}H-leucine and ^{3}H-uridine under oxygen- and deficiency of glucose deprivation in myocardial cells. TMP could also stimulate the synthesis of protein and RNA as well as increase expression of nitric oxide synthase in oxygen- and sugar-defcient myocardial cells to enhance their tolerance of these deficiencies.

Based on a study of key respiratory enzymes of mitochondria *in vivo*, Wan, et al[26] reported that TMP strongly antagonized the reduction of activity of succinate dehydrogenase and cytochrome oxidase during MIRI. Li, et al[27] reported that the protective effect of TMP in a rat model of myocardial ischemic injury could be related to the increased activity of Ca^{2+}-ATPase and Ca^{2+}-Mg^{2+}-ATPase and regulation the expression of Bcl-2 gene.

Glycoside

Panax notoginseng saponins

Panax notoginseng saponins (PNS) were extracted from a CHM, *Panax notoginseng* (Burkill) F.H. Chen (Araliaceae), which has been extensively used in treating coronary heart disease (CHD), ischemic cerebrovascular disease and hemorrhagic disorders in China for more than 1,000 years.[28]

Coronary artery disease is closely related to lipid metabolic disorders, specifically including increased, low-density lipoprotein (LDL-C), and serum total cholesterol (TC). PNS could markedly reduce TC, triglyceride, and LDL-C and increase high-density lipoprotein cholesterol (HDL-C) significantly.[29] carnitine palmitoyl transterase-1 (CPT-1)A is a key enzyme in the process of fatty acid oxidation, while the fatty acid transporter protein 4 (FATP4) is associated with long chain fatty acid.[30] FABP4 and CPT-1A were downregulated in ischemic zone of the heart. PNS could regulate lipid metabolism by increasing the expressions of FABP4 and CPT-1A.

Research has shown that PNS could depress the level of TC by elevating liver X receptor alpha (LXR α) alpha, member 1 of human transporter sub-family ABCA (ABCA1), and ATP-binding cassette, sub-family G member 1 (ABCG1) and reducing nuclear factor (NF)-κB. In addition, PNS could regulate lipid metabolism by inhibiting LPL and increasing FABP4 and CPT-1A. Furthermore, lipidosis is closely related to inflammation, which PNS have diverse effects on.[31]

Salvianolic acid B

Radix salviae miltiorrhizae Bge. is CHM. It has been widely used for the treatment of IHD and other cardiovascular diseases. Salvianolic acid B is derived from the roots and rhizomes of the *Salvia Miltiorrhiza* Bge. There is some evidence to suggest that salvianolic acid B could ameliorate the function of heart by increasing coronary blood flow and scavenging oxygen-free radicals.[32] Recent researches show that salvianolic acid B decreases myocardium apoptosis via activating the JAK2/STAT3, NF-κB pathways and may protect myocardium via a redox-sensitive PKC ε/mK (ATP) pathway.[33]

Research has shown that the drug mechanism of salvianolic acid B may be related with pathways of energy metabolism, especially tricarboxylic acid cycle (TCA) and β-oxidation of fatty acids. Besides, the protein expressions of p-AMPK and p-ACC in salvianolic acid B group were significantly elevated, while the levels of CPT-1 was dramatically reduced by salvianolic acid B. The evidence from this study suggests that salvianolic acid B pretreatment could ameliorate MIRI by intervening energy metabolism, especially TCA cycle and β-oxidation of fatty acids metabolism.[35]

Compounds

Danqi Tablet

Danqi Tablet (丹七片, DQT) is prescribed widely in China. It composed of *Radix Salvia Miltiorrhiza* and *Panax notoginseng* and has definite cardioprotective effect on CHD. One of such studies has proved that DQT could regulate plasma levels of HDL-C and LDL-C.

In a study by Chang, et al[36], DQT could up-

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regulate the mRNA expression of LPL. Membrane proteins involved in lipid transport and uptake, such as FABP4 and CPT-1A, were down-regulated in ischemic heart tissues. Treatment with DQT regulated lipid metabolisms by up-regulating expressions of FABP4 and CPT-1A. DQT also suppressed expression of cytochrome P450. Furthermore, transcriptional factors, such as PPARα, PPARγ, retinoid X receptor alpha (RXRA) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) were down-regulated in ischemic model group, and up-regulated by DQT.

Application of Plant Products in HF

HF is a clinical syndrome characterized by the low contractile ability of the myocardium. In the United States, more than 5 million people suffer from HF.[37] In addition, in spite of significant declines in mortality, the 5-year survival rate is still 50% worse than cancers. Recently, the role of impaired cardiac energetic status in HF has gained increasing recognition with the identification of reduced metabolic capacity for carbohydrates and fatty acids, impaired function of the electron transport chain, reduced capacity to transfer ATP to the cytosol, and inefficient utilization of the energy produced.[38] These nodes in the genesis of cardiac energetic impairment provide potential therapeutic targets, and there is promising data from recent experimental and early-phase clinical studies evaluating modulators such as carnitine palmitoyltransferase Ⅰ inhibitors, partial fatty acid oxidation inhibitors and mitochondrial-targeted antioxidants. Metabolic modulation may provide significant symptomatic and prognostic benefit for patients suffering from HF above and beyond guideline-directed therapy, but further clinical trials are needed.[39]

Flavonoid

Puerarin

Et kudzu radix (Pueraria lobata) has been used to treat cardiovascular diseases for thousands of years. Puerarin, a known isoflavone, was commonly found as an important component in the *Et kudzu radix*. It is the 8-c-glucoside of daidzein 1 and has been widely prescribed in clinic in China to treat cardiac diseases such as heart failure, ischemia, angina pectoris,[40] cardiac infarction and arrhythmia. Puerarin has been examined as monotherapy for HF.[41] One of such studies showed that puerarin improved cardiac function after MI in diabetic mice through regulation of energy metabolism, the possible mechanism responsible for the effect of puerarin was increasing the expression and translocation of glucose transporter 4 (GLUT4) while attenuating the expression and translocation of C luster of differentiation 36 (CD36).[42]

Glycoside

Salidroside

Salidroside (SAL) is separated and purified from *Rhodiola rosea*, which has been documented to show the wide range of pharmacological features, including protective effects against death induced by various stresses. Many studies have confirmed that SAL shows various pharmacological effects, including anti-cancer, cardioprotective, anti-hypoxic injury and preventing high altitude reaction effects.[43,44] Meanwhile, many studies have found that SAL participated in several signaling pathways to antagonize hypoxic cytotoxic effects, including repressing mammalian target of rapamycin (mTOR) signaling and Fas-dependent apoptosis[45,46] and increasing glutathione peroxidase-1 and vascular endothelial growth factor expression.[47,48]

In a study by Xu, et al[49] SAL showed a positive protective function involving the acetyl-CoA metabolic, TCA cycle using bioinformatics analysis. They also demonstrated that SAL plays a critical role in restoring the TCA cycle and protecting cardiomyocytes from oxidative injury via upregulation expressions of PDHE1-B, ACO2, SUCLG1, SUCLG2 and down-regulation of MDH2. SAL also inhibited H9c2 cell apoptosis by inhibiting the activation of pro-apoptotic molecules caspase 3 and caspase 9 as well as activation of the anti-apoptotic molecular Bcl-2. Additionally, SAL also improved mitochondrial membrane potential ($\triangle\Psi$m), reduced reactive oxygen species (ROS) and intercellular Ca^{2+} concentration ($[Ca^{2+}]i$) accumulation and inhibited the excessive consumption of ATP in H9c2 cells.

Ginsenoside Rb1

Ginseng is a perennial plant that belongs to Panax genus of Araliaceae family.[50] The bioactive components of ginseng are ginsenosides. Ginsenoside Rb1 is one of the most important members among the identified ginsenosides and has been reported to attenuate I/R injury in multiple organs. Li, et al[51] have demonstrated that ginsenoside Rb1 protected against I/R and hypoxia/reoxygenation (H/R) injury via Akt, GSK-3β and mitochondrial permeability transition pore. Wang, et al[52] have found that ginsenoside

Rb1 inhibited isoproterenol-induced apoptosis of rat cardiomyocytes and H9c2 cells. Jiang, et al[53] have showed that ginsenoside Rb1 alleviated monocrotaline-induced cardiac hypertrophy in rats and protected cardiomyocytes from prostaglandin F2α-induced cardiac hypertrophy.

A number of studies examined the use of ginsenoside Rb1 in HF. In one such study, ginsenoside Rb1 decreased mitochondrial membrane potential and enhanced the translocation of GLUT4 to plasma membrane. The transforming growth factor-β1 (TGF-β1)/Smad and extracellular regulated protein kinases (ERK) signaling pathways were inhibited and the Akt pathway was activated. These findings suggest that ginsenoside Rb1 might restore cardiac/mitochondrial function, increase glucose uptake and protect against cardiac remodeling via the TGF-β1/Smad, ERK and Akt signaling pathways.[54]

Astragaloside Ⅳ

Radix Astragalus (RA) is a CHM that possesses various important pharmacological effects for the cardiovascular system.[55] There are multiple forms of RA remedies applied in the clinical treatment of HF. Recently, extensive clinical and experimental researches, regarding the mechanism of RA in treating HF, have been carried out from organic, cellular and molecular levels with some progress. Astragaloside Ⅳ (AsⅣ) is an extract of the monomer astragaloside. AsⅣ produces various effects, including protection against cerebral I/R injury.[56] Certain protective effects of AsⅣ on cardiovascular disease have also been suggested. In addition to providing cardioprotection during myocardial ischemia, AsⅣ has also been demonstrated to limit endothelial dysfunction induced by oxidative stress and inhibit compensatory hypertrophy of myocardial cells. The results obtained in these previous studies provided the impetus to study the protection mechanism of AsⅣ during reperfusion. AsⅣ could reduce the survival of cardiocytes, release lactic dehydrogenase and stimulate the ROS production, increase mitochondrial membrane potential (△Ψm) and intracellular calcium increase and increase apoptosis.[57] Treatment with As also reversed the ang Ⅱ-induced increase in the production of ROS, the increase in NADPH oxidase and xanthine oxidase activity, as well as the decrease in △Ψm and manganese superoxide dismutase (Mn-SOD) activity.[58]

Interestingly, some studies indicate that, AsⅣ regulated energy metabolism by increasing ATP production and enhancing mitochondrial function, attributable to increased oxygen consumption and slightly increased mitochondrial Ca^{2+} uptake *in vitro*.[59,60] In HF, AsⅣ switched glycolysis to fatty acid β-oxidation, as confirmed by reduced anaerobic glycolysis and an increased oxygen consumption ratio. These results suggest that AsⅣ can stimulate fatty acid β-oxidation and improve mitochondrial function, which may present a novel cardioprotective treatment that inhibits the progress of HF.

Componds

Qili Qiangxin Capsule

Qili Qiangxin Capsule (芪苈强心胶囊, QQC) was developed under the guidance of CM theory of collateral disease. It is a drug of Chinese medicine for the treatment of HF, registered in the Chinese State Food and Drug Administration in 1996, and has been used in clinical practice for more than a decade. Previous studies have shown that QQC was able to inhibit ang Ⅱ and aldosterone levels, improve hemodynamics and cardiac function, inhibit ventricular remodeling, and reduce the concentration of plasma vasopressin and cardiac stress.[61] The main active pharmaceutical ingredients of QQC included *Astragalus*, *Ginseng*, *Salvia miltiorrhiza*, *Pepperweed Seed*, *Rhizoma Alismatis*, *Polygonatum odoratum*, *Ramulus Cinnamomi*, *Carthamus tinctorius*, *Cortex Periplocae*, *Tangerine Peel*, and *other herbs*.[62]

The present study explored the role of and mechanism by which the herbal compounds QQC act on energy metabolism, *in vivo*, in pressure overload heart failure[6]. QQC significantly inhibited cardiac hypertrophy due to ascending aortic constriction and improved hemodynamics. This effect was linked to the expression levels of the signaling factors in connection with upregulated energy and the regulation of glucose and lipid substrate metabolism and with a decrease in metabolic intermediate products and the protection of mitochondrial function. It is concluded that QQC may regulate the glycolipid substrate metabolism by activating AMPK/PGC-1α axis and reduce the accumulation of FFAs and lactic acid, to protect cardiac myocytes and mitochondrial function.

Disscussion

Cardiovascular disease is the leading cause

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of death worldwide. Potential serious adverse reactions to therapeutic drugs have led to increasing awareness of the role of CHM in the treatment of cardiovascular diseases.[64] Since ancient times, CHM has been widely used in many countries, especially China; however, the mechanism of action of herbs in the prevention and treatment of cardiovascular diseases is not yet clear. In this review, we summarize the research progress in the regulation of energy metabolism in the treatment of cardiovascular disease by CHM active ingredients over the past five years (Table 1). The key examples reviewed and the latest developments clearly demonstrate the great potential and future prospects of natural products in the treatment or prevention of cardiovascular and metabolic diseases.

However, there are the following limitations in the treatment of cardiovascular diseases with natural medicines. First of all, although in CM, therapeutic strategies are generally made by using well organized herbal formulas which are based on a unique CM theory with the strategies of multiple components and ingredients to act on multiple signal pathways, the exact active compounds and molecular targets are unclear. Second, the active ingredients in CM materials are relatively low. Therefore, Chinese and Western medicine should make full use of

Table 1. Natural Drug Therapies in Regulation of Energy Metabolism in Treating Cardiovascular Diseases

Active ingredients	Chemical structure	Natural drug	Molecular formula	Mechanism of action	State of evidence	Cardiovascular diseases	References
Alkaloid	Pyrazines alkaloids	Tetramethylpyrazine	$C_8H_{12}N_2$	Increasing ATP generation, protecting the Na^+-K^+-ATPase activity, increasing activity of Ca^{2+}-ATPase and Ca^{2+}-Mg^{2+}-ATPase	*In vitro*/*vivo* models	Ischemia-reperfusion	21–29
	Alkaloids	Rutaecarpine	$C_{19}H_{17}N_3O$	Improving metabolism disorders between fatty acid and glucose, increasing the content of ATP, Ca^{2+}-ATPase activity	*In vivo* models	Ischemia-reperfusion	14–20
Glycoside		Ginsenoside Rb1	$C_{54}H_{92}O_{23}$	Decreasing mitochondrial membrane potential and enhancing the translocation of GLUT4 to plasma membrane	*In vitro*/*vivo* models	Heart failure	50–54
		Panax notoginseng saponins	$C_{59}H_{10}0O_{27}$	Regulating lipid metabolism by inhibiting LPL and increasing FABP4 and CPT-1A	*In vitro*/*vivo* models	Ischemia-reperfusion	28–31
		Salidroside	$C_{14}H_{20}O_7$	Protecting acetyl-CoA metabolic, TCA cycle, improving $\triangle\Psi$m, reducing ROS and $[Ca^{2+}]^i$ accumulation and inhibiting the excessive consumption of ATP	*In vitro* models	Heart failure	43–49
		Astragaloside Ⅳ	$C_{41}H_{68}O_{14}$	Improving $\triangle\Psi$m, reducing ROS, increasing ATP production, stimulating fatty acid β-oxidation and improving mitochondrial function	*In vitro*/*vivo* models	Heart failure	55–60
Flavonoid		Puerarin	$C_{21}H_{20}O_9$	Increasing the expression and translocation of GLUT4, while attenuating the expression of CD36	*In vivo* models	Heart failure	40–42
Phenolic acid		Salvianolic acid B	$C_{36}H_{30}O_{16}$	Intervening energy metabolism, especially TCA cycle and β-oxidation of fatty acids metabolism	In vitro/ vivo models	Ischemia-reperfusion	32–35
Danqi Tablet				Regulating lipid metabolisms by up-regulating expressions of FABP4 and CPT-1A	*In vitro*/*vivo* models	Ischemia-reperfusion	33–35
Qili Qiangxin Capsule				Regulating the glycolipid substrate metabolism, reducing the accumulation of free fatty acids and lactic acid	*In vitro*/*vivo* models	Heart failure	62–63

Notes: GLUT4: glucose transporter 4; $\triangle\Psi$m: mitochondrial membrane potential; ROS: reactive oxygen species; $[Ca^{2+}]^i$: intercellular Ca^{2+} concentration

the advantages of integrated Chinese and Western medicine to achieve both blood pressure and blood lipid levels, but also from the overall function. Third, CM resources are a rich natural product resource, and the commonly used natural medicines used are very limited. Based on the homology of the known active ingredients of CM, they can find more medicinal resources; at the same time, they can also based on the known active ingredient chemistry structure, through chemical synthesis, developed more new drugs. Last but not least, treatment of cardiovascular drugs is monotonous and can develop a variety of dosage forms to getting results quickly. Therefore, studies on the therapeutic strategies of CHM not only provide novel cue to find active compounds to prevent myocardial ischemia and protect myocardial cells from ischemic injury, but introduce a new strategy for drug development targeting multiple cardiovascular diseases pathways.

Conflict of Interest

All authors declare that they have no conflicts of interest.

Author Contributions

Li J performed the data analyses and wrote the manuscript,Guan XK helped perform the analysis with constructive discussions, Liu RX contributed to the conception of the study.

REFERENCES

1. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1151-1210.
2. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol 2009;8:355-369.
3. Mensah GA, Roth GA, Sampson UK, Moran AE, Feigin VL, Forouzanfar MH, et al. Mortality from cardiovascular diseases in sub-Saharan Africa, 1990–2013: a systematic analysis of data from the Global Burden of Disease Study 2013. Cardiovasc J Afr 2015;26:S6-S10.
4. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation 2017;135:e146-e603.
5. Tao L, Bei Y, Lin S, Zhang H, Zhou Y, Jiang J, et al. Exercise training protects against acute myocardial infarction via improving myocardial energy metabolism and mitochondrial biogenesis. Cell Physiol Biochem 2015;37:162-175.
6. Gorbunova ML, Vilkova AV. Assessment of efficacy and safety of metabolic therapy with trimetazidine MB in patients with ischemic heart disease and chronic heart failure. Kardiologiia 2016;56:67-72.
7. Cheng ML, Wang CH, Shiao MS, Liu MH, Huang YY, Huang CY, et al. Metabolic disturbances identified in plasma are associated with outcomes in patients with heart failure: diagnostic and prognostic value of metabolomics. J Am Coll Cardiol 2015;65:1509-1520.
8. Hunter WG, Kelly JP, McGarrah RW 3rd, Kraus WE, Shah SH. Metabolic dysfunction in heart failure: diagnostic, prognostic, and pathophysiologic insights from metabolomic profiling. Curr Heart Fail Rep 2016;13:119-131.
9. Guo J, Yong Y, Aa J, Cao B, Sun R, Yu X, et al. Compound Danshen Dripping Pills modulate the perturbed energy metabolism in a rat model of acute myocardial ischemia. Sci Rep 2016;6:37919.
10. Wang JR, Zhou H, Yi XQ, Jiang ZH, Liu L. Total ginsenosides of *Radix Ginseng* modulates tricarboxylic acid cycle protein expression to enhance cardiac energy metabolism in ischemic rat heart tissues. Molecules 2012;17:12746-12757.
11. Miri R, Sajjadieh A, Parsamahjoob M, Hajibaratali B, Shekarchizadeh M, Kolahi AA, et al. Relationship between metabolic syndrome and angiographic severity of coronary artery disease. ARYA Atheroscler 2016;12:220-225.
12. Kolwicz SC Jr, Tian R. Glucose metabolism and cardiac hypertrophy. Cardiovasc Res 2011;90:194-201.
13. Zhan S, Fan X, Zhang F, Wang Y, Kang L, Li Z. A proteomic study of Shengmai Injection's mechanism on preventing cardiac ischemia-reperfusion injury via energy metabolism modulation. Mol Biosyst 2015;11:540-548.
14. Schramm A, Hamburger M. Gram-scale purification of dehydroevodiamine from *Evodia rutaecarpa* fruits, and a procedure for selective removal of quaternary indoloquinazoline alkaloids from Evodia extracts. Fitoterapia 2014;94:127-133.
15. Li YJ, Zhang F, Gong QH, Wu Q, Yu LM, Sun AS. Rutaecarpine inhibits angiotensin Ⅱ-induced proliferation in rat vascular smooth muscle cells. Chin J Integr Med 2014;20:682-687.
16. Yarosh DB, Galvin JW, Nay SL, Pena AV, Canning MT, Brown DA. Anti-inflammatory activity in skin by biomimetic of *Evodia rutaecarpa* extract from traditional Chinese medicine. J Dermatol Sci 2006;42:13-21.
17. Heo SK, Yun HJ, Yi HS, Noh EK, Park SD. Evodiamine and rutaecarpine inhibit migration by LIGHT via suppression of NADPH oxidase activation. J Cell Biochem 2009;107:123-133.
18. Jia S, Hu C. Pharmacological effects of rutaecarpine as a cardiovascular protective agent. Molecules 2010;15:1873-1881.
19. Son J K, Chang H W, Jahng Y. Progress in studies on rutaecarpine. Ⅱ.–Synthesis and structure-biological activity

relationships. Molecules 2015;20:10800-10821.

20. Xue H, Cheng Y, Wang X, Yue Y, Zhang W, Li X. Rutaecarpine and evodiamine selected as beta1-AR inhibitor candidates using beta1-AR/CMC-offline-UPLC/MS prevent cardiac ischemia-reperfusion injury via energy modulation. J Pharm Biomed Anal 2015;115:307-314.
21. Cao X, Nakamura Y, Wada T, Kishie T, Enkhsaikhan A, Izumi-Nakaseko H, et al. Assessment of the anti-anginal effect of tetramethylpyrazine using vasopressin-induced angina model rats. Biol Pharm Bull 2016;39:1370-1373.
22. Qian W, Xiong X, Fang Z, Lu H, Wang Z. Protective effect of tetramethylpyrazine on myocardial ischemia-reperfusion injury. Evid Based Complement Altern Med 2014;2014:107501.
23. Wang WT, Wang FY, Wang W. Effect of ligustrazine and L-arginine on function of mitochondria in myocardial cell in the reperfusion injury afer myocardial ischemia in rabbits. Chin J Arteriosclerosis (Chin) 2006;14:955.
24. Zhu HB, Wang MM, Zhang B. Effect of myocardial ischemia reperfusion in rabbits on Na^+-K^+-ATPase and protective effect of ligustrazine pretreatment. Hubei J Tradit Chin Med (Chin) 2010;32:5-6.
25. Shi DZ, Chen KJ, Zhong P. The effects of ligustrazine on synthesis of protein and RNA, and NOS gene expression in cultural myocardial cells with hypoxia and lack of sugar. Chin Pharm J (Chin) 1998;33:724-726.
26. Wan FS, Liu B, Zhao XM. Effects of ligustrazine on respiratory enzymes in the myocardial mitochondria of the ischemia-reperfusion rats. Chin J Pathophysiol (Chin) 2001;17:58.
27. Li Y, Wan FS, Wan YF. Protective effects of ligustrazine against myocardial ischemia injury of rat. Chin Tradit Patent Med (Chin) 2003;25:646-648.
28. Luo H, Sun C, Sun Y, Wu Q, Li Y, Song J, et al. Analysis of the transcriptome of *Panax notoginseng* root uncovers putative triterpene saponin-biosynthetic genes and genetic markers. BMC Genomics 2011;12 (Suppl 5):S5.
29. Liu Y, Zhang HG, Jia Y, Li XH. *Panax notoginseng* saponins attenuate atherogenesis accelerated by zymosan in rabbits. Biol Pharm Bull 2010;33:1324-1330.
30. Hall AM, Wiczer BM, Herrmann T, Stremmel W, Bernlohr DA. Enzymatic properties of purified murine fatty acid transport protein 4 and analysis of acyl-CoA synthetase activities in tissues from FATP4 null mice. J Biol Chem 2005;280:11948-11954.
31. Liu J, Wang Y, Qiu L, Yu Y, Wang C. Saponins of *Panax notoginseng*: chemistry, cellular targets and therapeutic opportunities in cardiovascular diseases. Expert Opin Invest Drugs 2014;23:523-539.
32. Zhou GJ, Wang W, Xie XM, Qin MJ, Kuai BK, Zhou TS. Post-harvest induced production of salvianolic acids and significant promotion of antioxidant properties in roots of *Salvia miltiorrhiza* (Danshen). Molecules 2014;19:7207-7222.
33. Liu CH, Shyu WC, Fu RH, Huang SJ, Chang CH, Huang YC, et al. Salvianolic acid B maintained stem cell pluripotency and increased proliferation rate by activating Jak2-Stat3 combined with EGFR-Erk1/2 pathways. Cell Transplant 2014;23:657-668.
34. Xu H, Wang D, Peng C, Huang X, Ou M, Wang N, et al. Rabbit sera containing compound Danshen Dripping Pill attenuate leukocytes adhesion to TNF-alpha-activated human umbilical vein endothelial cells by suppressing endothelial ICAM-1 and VCAM-1 expression through NF-kappaB signaling pathway. J Cardiovasc Pharmacol 2014;63:323-332.
35. Mu F, Duan J, Bian H, Zhai X, Shang P, Lin R, et al. Metabonomic strategy for the evaluation of Chinese medicine *Salvia miltiorrhiza* and *Dalbergia odorifera* Interfering with myocardial ischemia/reperfusion injury in rats. Rejuvenation Res 2017;20:263-277.
36. Chang H, Wang Q, Shi T, Huo K, Li C, Zhang Q, et al. Effect of Danqi Pill on PPARalpha, lipid disorders and arachidonic acid pathway in rat model of coronary heart disease. BMC Complement Alternat Med 2016;16:103.
37. Rogers C, Bush N. Heart failure: pathophysiology, diagnosis, medical treatment guidelines, and nursing management. Nurs Clin North Am 2015;50:787-799.
38. Heggermont WA, Papageorgiou AP, Heymans S, van Bilsen M. Metabolic support for the heart: complementary therapy for heart failure? Eur J Heart Fail 2016;18:1420-1429.
39. Siddiqi N, Singh S, Beadle R, Dawson D, Frenneaux M. Cardiac metabolism in hypertrophy and heart failure: implications for therapy. Heart Fail Rev 2013;18:595-606.
40. Ai F, Chen M, Yu B, Yang Y, Xu G, Gui F, et al. Puerarin accelerates cardiac angiogenesis and improves cardiac function of myocardial infarction by upregulating VEGFA, ang-Ⅰ and ang-Ⅱ in rats. Int J C lin Exp Med 2015;8:20821-20828.
41. Liu B, Zhao C, Li H, Chen X, Ding Y, Xu S. Puerarin protects against heart failure induced by pressure overload through mitigation of ferroptosis. Biochem Biophys Res Commun 2018;497:233-240.
42. Xu H, Zhao M, Liang S, Huang Q, Xiao Y, Ye L, et al. The effects of puerarin on rat ventricular myocytes and the potential mechanism. Sci Rep 2016;6:35475.
43. Fang DL, Chen Y, Xu B, Ren K, He ZY, He LL, et al. Development of lipid-shell and polymer core nanoparticles with water-soluble salidroside for anti-cancer therapy. Int J Mol Sci 2014;15:3373-3388.
44. Zhu L, Wei T, Gao J, Chang X, He H, Luo F, et al. The cardioprotective effect of salidroside against myocardial ischemia reperfusion injury in rats by inhibiting apoptosis and inflammation. Apoptosis 2015;20:1433-1443.
45. Zhong X, Lin R, Li Z, Mao J, Chen L. Effects of salidroside

on cobalt chloride-induced hypoxia damage and mTOR signaling repression in PC12 cells. Biol Pharm Bull 2014;37:1199-1206.
46. Lai MC, Lin JG, Pai PY, Lai MH, Lin YM, Yeh YL, et al. Protective effect of salidroside on cardiac apoptosis in mice with chronic intermittent hypoxia. Int J Cardiol 2014;174:565-573.
47. Qian EW, Ge DT, Kong SK. Salidroside promotes erythropoiesis and protects erythroblasts against oxidative stress by up-regulating glutathione peroxidase and thioredoxin. J Ethnopharmacol 2011;133:308-314.
48. Zhang J, Liu A, Hou R, Zhang J, Jia X, Jiang W, et al. Salidroside protects cardiomyocyte against hypoxia-induced death: a HIF-1alpha-activated and VEGF-mediated pathway. Eur J Pharmacol 2009;607:6-14.
49. Xu ZW, Chen X, Jin XH, Meng XY, Zhou X, Fan FX, et al. SILAC-based proteomic analysis reveals that salidroside antagonizes cobalt chloride-induced hypoxic effects by restoring the tricarboxylic acid cycle in cardiomyocytes. J Proteomics 2016;130:211-220.
50. Yang L, Yu QT, Ge YZ, Zhang WS, Fan Y, Ma CW, et al. Distinct urine metabolome after Asian ginseng and American ginseng intervention based on GC-MS metabolomics approach. Sci Rep 2016;6:39045.
51. Li YH, Li YY, Fan GW, Yu JH, Duan ZZ, Wang LY, et al. Cardioprotection of ginsenoside Rb1 against ischemia/reperfusion injury is associated with mitochondrial permeability transition pore opening inhibition. Chin J Integr Med 2016 Jan 6. Epnb aheadof print.
52. Wang XF, Liu XJ, Zhou QM, Du J, Zhang TL, Lu YY, et al. Ginsenoside Rb1 reduces isoproterenol-induced cardiomyocytes apoptosis *in vitro* and *in vivo*. Evid Based Complement Alternat Med 2013;2013:454389.
53. Jiang QS, Huang XN, Yang GZ, Jiang XY, Zhou QX. Inhibitory effect of ginsenoside Rb1 on calcineurin signal pathway in cardiomyocyte hypertrophy induced by prostaglandin F2alpha. Acta Pharmacol Sin 2007;28:1149-1154.
54. Zheng X, Wang S, Zou X, Jing Y, Yang R, Li S, et al. Ginsenoside Rb1 improves cardiac function and remodeling in heart failure. Exp Anim 2017;66:217-228.
55. Fu J, Wang Z, Huang L, Zheng S, Wang D, Chen S, et al. Review of the botanical characteristics, phytochemistry, and pharmacology of *Astragalus membranaceus* (Huangqi). Phytother Res 2014;28:1275-1283.
56. Ren S, Zhang H, Mu Y, Sun M, Liu P. Pharmacological effects of astragaloside Ⅳ: a literature review. J Tradit Chin Med 2013;33:413-416.
57. Guan FY, Yang SJ, Liu J, Yang SR. Effect of astragaloside Ⅳ against rat myocardial cell apoptosis induced by oxidative stress via mitochondrial ATP-sensitive potassium channels. Mol Med Rep 2015;12:371-376.
58. Xu C, Tang F, Lu M, Yang J, Han R, Mei M, et al. Pretreatment with astragaloside Ⅳ protects human umbilical vein endothelial cells from hydrogen peroxide induced oxidative stress and cell dysfunction via inhibiting eNOS uncoupling and NADPH oxidase - ROS - NF-kappaB pathway. Can J Physiol Pharmacol 2016;1-9.
59. Jiang XG, Sun K, Liu YY, Yan L, Wang MX, Fan JY, et al. Astragaloside Ⅳ ameliorates 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis implicating regulation of energy metabolism. Sci Rep 2017;7:41832.
60. Dong Z, Zhao P, Xu M, Zhang C, Guo W, Chen H, et al. Astragaloside Ⅳ alleviates heart failure via activating PPARalpha to switch glycolysis to fatty acid beta-oxidation. Sci Rep 2017;7:2691.
61. Zhang J, Wei C, Wang H, Tang S, Jia Z, Wang L, et al. Protective effect of Qiliqiangxin Capsule on energy metabolism and myocardial mitochondria in pressure overload heart failure rats. Evid Based Complement Alternat Med 2013;2013:378298.
62. Wang J, Li Z, Wang Y, Zhang J, Zhao W, Fu M, et al. Qiliqiangxin enhances cardiac glucose metabolism and improves diastolic function in spontaneously hypertensive rats. Evid Based Complement Alternat Med 2017;2017:3197320.
63. Cui X, Zhang J, Li Y, Sun Y, Cao J, Zhao M, et al. Effects of Qili Qiangxin Capsule on AQP2, V2R, and AT1R in rats with chronic heart failure. Evid Based Complement Alternat Med 2015;2015:639450.
64. Seto SW, Kiat H, Lee SM, Bensoussan A, Sun YT, Hoi MP, et al. Zebrafish models of cardiovascular diseases and their applications in herbal medicine research. Eur J Pharmacol 2015;768:77-86.

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