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The treatment of cardiovascular diseases: a review of ferulic acid and its derivatives

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Ferulic acid, a hydroxyl derivative extracted from plants, is abundant in free state in seeds and leaves, or covalently linked with cell wall polysaccharides, lignin and different polymers. It has various pharmacological activities, including antioxidant and anti-inflammatory effects, regulates immunity, protects the cardiovascular system, and contributes to the prevention of tumors and diabetes. The protective effect on cardiovascular system is the most valuable one in view of clinical application. Here, we are reviewing the research progress concerning the pharmacological effects of ferulic acid and its derivatives on cardiovascular diseases in the past five years, mainly focusing on mechanisms of action and clinical application. This should provide guidance for clinical applications of ferulic acid and its derivatives in the treatment of cardiovascular diseases.

1. Introduction

Ferulic acid (FA), 4-hydroxy-3-methoxycinnamic acid, is a polyphenolic compound with an acrylic acid group on the benzene ring. It exists in many species consumed as food, like tomatoes (Navarrete et al. 2015), sweet corn (Chaudhary et al. 2019) and wheat (Di Loreto et al. 2018), and is also abundant in Chinese herbal medicines, such as *Angelica sinensis* (Yang et al. 2019; Lin et al. 2017), chuanxiong (Shi et al. 2019), *Hedyotis diffusa* (Duan et al. 2019) and *Lycium barbarum* (Li et al. 2018) in seeds and leaves in free form, or covalently linked with cell wall polysaccharides, lignin and different polymers.

Due to the methoxy, 4-hydroxy and carboxylic acid functional groups (which can covalently combine the free radicals with the adjacent unsaturated C = C), FA has beneficial effects in many diseases associated with oxidative stress. Oxidative stress can be defined as a persistent imbalance between the production and defenses of reactive oxygen species (ROS), which have essential functions in living organisms. Excessive levels of ROS lead to the damage of lipids, DNA and protein, and eventually develop into chronic diseases, such as cardiovascular diseases. The cardiovascular drug market has become the second largest drug field next to the cancer drugs, but the development is difficult and expensive. The use of high-tech and biotechnology to extract effective ingredients, such as FA, from natural plants is appropriate (Zhang 2018).

Modern pharmacological studies show that FA has effects as antioxidant (Zhang et al. 2019), antithrombotic (Zhao et al. 2012), against antiplatelet agglutination (Guan et al. 2018), moistening the intestinal tract (Jiang et al. 2020), against cancer (Rezaei et al. 2019), and so on. Moreover, FA contains a variety of active groups that can be transformed to yield high-quality compounds with effective absorption, metabolism, emission and low toxicity. FA related compounds, such as sodium ferulate (SF), piperazine ferulate (PF) and ligustrazine ferulate (LF) show significant effects on the treatment of cardiovascular diseases. For example, ferulic acid-4-o-sulphate (FA-sul), formed by phase II metabolism and the digestion of gastrointestinal and liver, has a significant vasodilation effect on isolated mouse arteries *in vitro* (Van Rymenant et al. 2017). SF, the sodium salt of FA, is able to reduce blood lipid levels, protect vascular endothelial cells, inhibit platelet aggregation and prevent thrombosis (Liang et al. 2018; Zhang and Gao 2020; Wang et al. 2004). PF, a compound synthesized from FA and piperazine hexahydrate, can alleviate oxidative stress, reduce the frequency of angina pectoris and effectively maintain cardiopulmonary function (Wang 2019; Yang and Fang 2017; Yang 2018).

In this paper, we are reviewing the research progress about FA and its derivatives in the prevention and treatment of cardiovascular diseases, in order to provide reference for further development and application.

2. The mechanisms of preventing cardiovascular diseases

2.1. Antioxidant and anti-inflammatory mechanisms

Oxidative stress is considered as an important pathogenic factor of cardiovascular diseases. It results in excessive levels of free radicals, such as hydrogen peroxide (H_2O_2), superoxide free radicals (O^{2-}), hydroxyl radicals (OH^-), nitric oxide (NO), etc., along with inflammation. Increased oxidative stress disturbs the homeostasis of the heart, causing myocardial ischemia-reperfusion injury, atherosclerosis, heart failure and other symptoms through a variety of pathways, leading to serious cardiac function obstacles. Therefore, enzymes with antioxidant function, such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and nitric oxide synthase (iNOS), play important roles in the antioxidant process by inhibiting the production of ROS or enhancing the inhibitory effect of endogenous antioxidant enzymes on oxidative damage (Liu et al. 2018).

FA and its derivatives not only have abilities on preventing free radicals by increasing the activity of antioxidant enzymes, inhibiting the formation of superoxide and free radical-producing enzymes, but also have effects on protecting the mRNA expression of IL-6, IL-1β and other inflammatory factors by inhibiting the activation of NF-κB, as well as regulating the physiological functions of the human body (Lin et al. 2019; Hu et al. 2018; Zhao, Yang and Chen 2008; Hong et al. 2016). In addition, it is able to inhibit oxidative stress injury induced by advanced glycation end products (AGEs) by regulating the expression of Nrf-2, HO-1 (Li et al. 2019).

Clinical studies showed that oral administration of FA at a dose of 40 mg/kg can significantly reduce the enhancement of CK-MB,

LDH and AST activities induced by arsenic poisoning, alleviate myocardial injury caused by oxidative stress, and restore myocardial mitochondrial fatty acid oxidation by activating AMPKα (Thr172), AMPKß1 (Ser108) and ACC (Ser79) (Panneerselvam et al. 2019). Maruf et al (2015) established a hepatocyte inflammation model and found that FA and related polyphenols are able to inhibit the formation of ROS and the development of oxidative damage. It can also increase MMP levels and protect inflammatory cells. The ability of the compounds is as follows, caffeic acid > ferulic acid > ferulaldehyde > ethyl ferulate > methyl ferulate > p-coumaric acid.

In addition, the activity of antioxidant enzymes (catalase) is enhanced after the formation of chitosan hydrogel. Thus, the production of mitochondria and ROS is reduced, and H_2O_2 is effectively transformed into water and oxygen, which promotes the sustained release of FA and improves cell vitality, thereby reducing oxidative stress and apoptosis (Cheng et al. 2016).

Gong et al (2019) studied the protective effect of SF on cerebral ischemia-reperfusion injury caused by middle cerebral artery occlusion (MCAO). It was found that SF can inhibit the nuclear translocation of NF-κBp65, reduce the production of inflammatory cells and the level of inflammatory index factors, such as TNF-α, IL-1β and IL-6, as well as suppress neuronal necrosis and the inflammatory injury of nerve cells caused by ischemia-reperfusion, thus playing a role in brain protection. PF, a derivative of FA, as an endothelin antagonist, can moderate the degree of oxidative stress in patients with coronary heart disease and enhance its antioxidant capacity by increasing SOD and reducing malondialdehyde (MDA) level (Wang 2019).

2.2. Inhibition of thrombosis

Thrombosis, caused by blood clots in the body, is a vascular blockage and closely related to the adhesion and agglutination of platelets. It is always causing inflammation, damaging blood cells, and leads to atherosclerosis, acute coronary syndrome, acute myocardial infarction and other complications. Therefore, antithrombotic treatment is of great significance to prevent cardiovascular diseases (Sharma et al. 2019). At 1 μM, FA can significantly reduce platelet monocyte aggregation by 11.4%, improve blood flow, inhibit platelet aggregation and blood lipid levels, while having no effect on neutrophil aggregation. Measuring the expression of thromboxane B2 (TXB_2), cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (CGMP) and NO by anticoagulation test and platelet aggregation test *in vitro* and *in vivo*, researchers found that oral treatment with FA can prevent pulmonary thrombosis and prolong tail hemorrhage and coagulation time in mice without changing coagulation parameters. It also can suppress intracellular Ca^{2+} mobilization and TXB_2 production induced by platelet agonists. What's more, platelet aggregation induced by platelet agonists, such as adenosine diphosphate (ADP), thrombin, collagen, arachidonic acid (AA), were inhibited by FA at 50~200 μM in a dose-dependent manner. FA can increase the levels of cAMP, cGMP and phosphorylated vasodilator-stimulated phosphoprotein (VASP) in washed rat platelets, and decrease the phosphorylated mitogen activated protein kinase (MAPK) and phosphodiesterase (PDE). The mechanism may be related to the activation of cAMP and cGMP signals, which inhibits platelet aggregation and regulates hemorheology. Also involved are the inhibition of the p38 and ERK2 phosphorylation, and the activation of PKA and PKG via inhibiting PDE (Hong et al. 2016; Dang et al. 2015; Pan, 2014; Krga et al. 2018).

In addition, FA can inhibit the formation of thrombus by suppressing the release of serotonin and TXA_2, selectively inhibiting the activity of TXA_2 synthase, and increasing the ratio of prostacyclin (PGI_2) / TXA_2 (Ou 2002). Ma and Li (2019) designed and synthesized a new compound based on the structural characteristics of FA and TXA_2 synthetase inhibitors, and found it had significant inhibitory activity against platelet aggregation. Zhao et al. (2012) studied the antithrombotic effect of LF. They proved the influence on the adhesion of platelet neutrophils by the methods of electric stimulation of carotid artery thrombosis and arteriovenous bypass thrombosis in rats. The results show that LF is able to inhibit the adhesion of platelets and neutrophils, obviously leading to antithrombotic effects.

2.3. Resistance against atherosclerosis

Atherosclerosis is closely related to lipid oxidation and provides the main pathological basis of unstable angina pectoris, acute myocardial infarction, ischemic stroke and other acute cardiovascular diseases. The pathological changes of atherosclerosis are regulated by mitochondria and are reflected by the level of pregnancy-associated plasma protein (PAPP-A). PAPP-A can specifically hydrolyze insulin-like growth factor binding protein (IGFBP) and participate in the formation of atherosclerosis by regulating the level of insulin-like growth factor (IGF).

FA, serving as a platelet aggregation inhibitor, could play an important role in the prevention of atherosclerosis (Hong et al. 2016). Chmielowski et al. (2017) found that macrophages absorb oxidized low density lipoprotein (oxLDL), resulting in the formation of arterial wall foam cells and plaques. The accumulation of foam cells in the ductal intima causes rupture and induces cerebrovascular disease. Ferulic acid-based poly (anhydride-ester) nanoparticles, the amphiphilic macrolecules (AMS), is coupled chemically with FA. It can resist the uptake of high-level oxLDL, regulate the production of ROS in human monocyte derived macrophages (HMDMs) and inhibit early atherosclerosis. SF may contribute to cardiovascular protection by inhibiting the enhancement of PAPP-A and controlling the activity of nuclear factor NF-κB in patients with coronary heart disease (Mason et al. 2011; Liu et al. 2017). In addition, SF also has anti-inflammatory and anti-atherosclerotic effects by regulating key components, such as HMGB1, RAGE, ICAM-1, TGFb1, PDGF and p-JNK (Hu et al. 2015).

2.4. Regulation of vasoconstriction and vasodilation

Vasoconstriction and vasodilation are important indicators of vascular function. Vasodilation is mainly regulated by the interaction between vascular endothelium and smooth muscle.

Vascular endothelial cells (VECs) are protective biological barriers covering the surface of vascular intima and are closely related to cardiovascular diseases such as atherosclerosis and heart failure (Qing et al. 2019; Van Rymenant et al. 2017). It was found that SF injection can reduce the injury of coronary artery endothelium, inhibit platelet activation, while the combination of astragaloside IV and FA can promote the proliferation of hypoxic endothelial cells, which shows effects on vasodilation and myocardial protection (Li et al. 2019). Wei et al. (2017) separated 90 patients with coronary heart disease into two groups. The observation group was treated with SF on the basis of the control group. Taking the level of ET-1 and NO as the judgment standard, the results shows that both of them were improved, while the observation group performed better, which proved that SF has a good effect in protecting vascular epidermal cells.

Vascular smooth muscle cells (VSMCs) are the single cell component in the middle layer of blood vessels and can regulate the tension of blood vessels through contraction and relaxation. Abnormal proliferation and migration of VSMCs are the cellular pathological basis of atherosclerosis, vascular restenosis and other diseases. The adhesion between cell to matrix and cell to cell is the key to cell migration. FA can inhibit the migration of VSMCs by inhibiting the expression of MMP-9 mRNA and enhancing the adhesion between VSMCs (Yuan and Yang 2015).

3. Clinical application

3.1. Treatment of coronary heart disease

Coronary heart disease (CHD), also known as coronary atherosclerotic heart disease, is a kind of stenosis or obstruction of the vascular lumen caused by atherosclerotic lesions of the coronary artery, and eventually leads to myocardial ischemia, hypoxia or necrosis (Ge et al. 2018). The World Health Organization divides

coronary heart disease into five clinical categories: silent myocardial ischemia (occult coronary heart disease), angina pectoris, myocardial infarction, ischemic heart failure (ischemic heart disease) and sudden death. Among them, ischemic cardiovascular diseases, such as myocardial infarction, caused by long term ischemia, are serious threats to our health (Panda et al. 2016). The imbalance of synthesis and release of vasoconstrictor (ET-1) and vasodilator (NO), which are secreted by endothelial cells, is the key to coronary heart disease (Zhang and Gao 2020). The balance between pro-apoptotic and anti-apoptotic proteins is essential to maintain the cell state of cardiomyocytes. It is regulated by the B-cell Lymphoma 2 (Bcl-2) protein family, caspase family, aspartate specific cysteine protease and interleukin-1β-converting enzyme. FA can effectively maintain body balance and control the occurrence and development of diseases by regulating related factors (Han et al. 2015).

Salvia miltiorrhiza (Danshen) is commonly used in the treatment of coronary heart disease, its therapeutic effect has been recognized worldwide. Lv et al. (2017) separated 80 patients with coronary heart disease into two groups. The treatment group was treated with SF, while the control group received Danshen injection. The results showed that the NO concentration in the treatment group was higher than that in the control group, and the endothelin-1 (ET-1) level was opposite, suggesting that SF treats coronary heart disease by promoting plasma NO secretion and inhibiting plasma ET-1 secretion, and the effect is better than Danshen injection. There is synergy made by SF with *Salvia miltiorrhiza* injection, better promoting blood circulation and dredging collaterals, removing blood stasis and relieving meridians (Wang and Yu 2019). In addition, Xintongtai granule, in which FA is the effective component, has definite therapeutic effect on coronary heart disease and good therapeutic effect on acute myocardial ischemia injury (Yi et al. 2019; Deng et al. 2015).

3.2. Treatment of unstable angina pectoris

Unstable angina pectoris refers to the clinical state between stable angina pectoris and acute myocardial infarction. It is a common type of acute coronary syndrome. The clinicopathological basis is complex, mainly related to atherosclerosis and thrombosis (Association 2018). In the treatment of unstable angina pectoris in elderly patients with coronary heart disease, piperazine ferulate dispersible tablets (100 mg, 3 times/day) can significantly reduce the frequency and duration of angina pectoris, and the combination with clopidogrel (150 mg/D), an ADP receptor antagonist, act synergistically (Lu et al. 2019).

3.3. Treatment of stroke

Stroke comprises ischemic and hemorrhagic events. Ischemic stroke is the most common type and has the characteristics of high incidence rate, high mortality rate and high recurrence rate. Its physiological and pathological mechanisms are complex, including inflammatory reaction, oxidative stress injury, blood-brain-barrier damage and other reasons. Myocardial cells produce energy relying on mitochondria. The dysfunction of mitochondria is the most basic physiological and pathological factor of ischemic reperfusion (CIRI), which provides the basis for ischemic cerebrovascular disease, and is also serving as an important cause of death in stroke. Inhibition of CIRI and protection of brain tissue have become an important link in the treatment of ischemic cerebrovascular disease (Liu et al. 2018; Long et al. 2020).

According to Luo et al (2020), FA can downregulate PINK1/Parkin dependent mitosis, reduce mitochondrial dysfunction, and reduce the damages to cardiomyocytes caused by hypoxia at the concentration of 6.25~200 μM, and the effect is the best at 12.5 μM. As a non-peptide endothelin receptor antagonist, SF is capable of antagonizing the vasoconstriction and pressor induced by endothelin, resisting the proliferation of vascular smooth muscle cells, as well as relaxing vascular smooth muscle, dilating blood vessels, and changing hemorheological characteristics, so as to reduce the degree of cerebral ischemia injury (Leiva et al. 2015). Lin et al. (2019) found that intravenous injection of SF at the dose of 50 mg/kg and 100 mg/kg through the femoral vein can promote the recovery of neurological function in rats with focal cerebral ischemia, and reduce the cerebellar infarction area by regulating the balance of TXA_2 and PGI_2.

During the occurrence and development of stroke and cerebral ischemia-reperfusion, the blood-brain-barrier is easy to be destroyed, and always accompanied with brain edema, which performs as an important cause of disability or death in the late stage of stroke when treated untimely. The model of cerebral artery occlusion reperfusion in male rats was established by Xu et al. (2016). They found that intravenous injection of tetramethylpyrazine-2'-O-sodium ferulate (TSF) at 18 mg/kg for 2 days can significantly decrease the brain water content and infarct area, and reduce the permeability of the blood-brain barrier. The mechanism is related to the decrease in the production of MMP-9 and AQP4, the interference of TJ protein degradation, and the reversal of the decrease of junction adhesion molecule-1 (JAM-1) and occludin expression.

3.4. Treatment of myocardial infarction

Myocardial infarction refers to the persistent decrease or interruption of coronary artery blood supply caused by various reasons, resulting in serious myocardial injury, local necrosis, and even irreversible myocardial apoptosis and sudden death. The combination of SF and Shenmai injection on the basis of Western medicine can effectively reduce the degree of myocardial injury and inhibit inflammatory reaction. In order to verify these numerical results, Tan et al. (2018) separated 119 patients with acute myocardial infarction into two groups, 60 cases in the control group treated with conventional Western medicine plus Shenmai injection, and 59 cases in the sodium ferulate group treated with conventional western medicine with SF and Shenmai injection. The results showed that the levels of serum markers of central muscle injury such as GMP-140, cTnT, MYO, NT-proBNP, H-FABP, and inflammatory mediators like MCP-1, IL-1β, hs CRP, were significantly decreased in the SF group, which shows excellent effects on treating myocardial infarction.

3.5. Prevention and treatment of restenosis after PCI

ST segment elevation myocardial infarction (STEMI) is one type of acute myocardial infarction. Percutaneous coronary intervention (PCI) is the most effective surgical method for the treatment of STEMI. However, a series of complications caused by PCI may seriously damage the body. Therefore, it is very important to optimize the therapeutic effect of PCI (Lin et al. 2019; Hong et al. 2014). Lai et al. (2019) separated 62 patients with STEMI into the control group and the treatment group. Both of them were treated with PCI and drug therapy, while the treatment group additionally received SF. The results showed that after treatment, the levels of malondialdehyde, ET-1, TNF-α, IL-6 and hs CRP in the two groups were lower than those before treatment, and the decrease in the treatment group was more obvious. While the levels of GSH Px, SOD and NO in the treatment group were significantly higher than those in the control group. It is suggested that the use of SF on the basis of PCI and drug therapy can improve coronary microcirculation perfusion and cardiac function in STEMI patients, thus, preventing restenosis after PCI.

3.6. Treatment of chronic heart failure

Caused by myocardial infarction, inflammation and other causes of changes in myocardial structure and function, chronic heart failure (CHF) is a common cardiovascular disease. Preventing the development of myocardial remodeling is an important measure to heart failure (Tuttolomondo et al. 2016). The dynamic balance of MMPs/TIMPs is an important factor to maintain the cardiac structure and myocardial collagen fibers. The imbalance of MMPs/TIMPs rate can directly degrade the extracellular matrix of myocardium and lead to ventricular remodeling (Deleon-Pen-

nell et al. 2017). FA can effectively inhibit the expression of MMP-1 protein and gene, upregulate the expression of TIMP-1 protein and gene, reduce the ratio of MMP-1/TIMP-1, as well as prevent the degradation of myocardial collagen by MMP-1 and delay ventricular remodeling, thus playing a therapeutic role in CHF (Wu et al. 2018).

3.7. Treatment of diabetic cardiomyopathy

Diabetes is a common chronic disease in our daily life. The main mechanism is that abnormal glucose metabolism leads to impaired glucose tolerance and hyperglycemia in diabetic patients, which overwhelm endogenous antioxidants and the detoxification system, producing excessive ROS and causing oxidative stress. Accompanied with a variety of complications, more than 50% of fatalities are caused by cardiovascular and cerebrovascular diseases.

Diabetic cardiomyopathy (DCM) is a heart failure syndrome caused by diabetes, which is independent of coronary heart disease, hypertension and other cardiovascular diseases. It is a typical cardiovascular complication of diabetes mellitus, characterized by the initial diastolic dysfunction without systolic dysfunction (Zhu et al. 2020). The pathogenesis of DCM includes insulin resistance, myocardial metabolic disorders, oxidative stress and inflammatory response (Wei and Zhong 2020). FA can promote [Ca^{2+}] homeostasis, regulate the level of related factors and inhibit oxidative stress response, which is of decisive significance for the treatment of DCM. Salin et al. (2019) established a H9c2 cardiomyocyte model with calcium homeostasis change induced by high glucose. The study found that high glucose caused obvious overload of [Ca^{2+}] through downregulating SERCA2/1, pPLN and pPKA C-α, while the overload of [Ca^{2+}] caused oxidative stress through the production of reactive oxygen species, lipid peroxidation and protein carbonylation, resulting in cell damage and release of BNP, ANP and LDH, which is the main cause of cell apoptosis. Administration of FA at 50 mg/kg for 8 weeks is able to promote the translocation of GLUT4 to the cardiac membrane by increasing PI3Kinase, enhancing the phosphorylation of Akt, and inactivating GSK-3b. Thus, it was shown that FA has effects on changing the hyperglycemia of cardiac tissue in diabetic rats, antagonizing toxic streptozotocin and maintaining the normal level of blood glucose in pancreatic enzymes.

In addition, FA can promote the proliferation of β-cells and the release of insulin, which can further utilize glucose from extra liver tissue, thereby reducing blood glucose levels (Sri Balasubashini et al. 2003; Chowdhury et al. 2016). In experiments of the protective effect and mechanism of FA on myocardial injury in db/db mice with type 2 diabetes mellitus, Wang et al. (2020) found that diabetes mellitus can lead increased cardiac mass index, hypertrophy of cardiac myocytes and myocardial fibrosis. Oral treatment with FA at 30 mg/kg for 8 weeks significantly reduced swelling and fibroplasia of cardiomyocytes. The production of AGEs increased under hyperglycemia, causing cardiomyocyte apoptosis and endoplasmic reticulum stress response. FA prevented the damages of AGEs to cardiac vessels by inhibiting the expression of AGEs. The expression of TLR-4, NF-κB, NALP3 mRNA and protein also decreased significantly. TLR-4 goes into the nucleus through intracellular pathways, activating NF-κB, inducing cells to release a large number of inflammatory factors, leading to the occurrence of inflammatory reaction, and resulting in myocardial cell necrosis, myocardial infarction area increased and cardiac function decreased. The effect of FA on improving blood glucose level, reducing myocardial cell injury and myocardial fibrosis in type 2 diabetic mice may be related to the inhibitory of TLR-4/NF-κB signaling pathway and inflammatory.

3.8. Treatment of cor pulmonale

Cor pulmonale, also known as chronic pulmonary heart disease, is often accompanied by right heart failure. Mainly due to the chronic pathological changes of lung tissue and pulmonary artery vessels in patients, abnormal structure and function of lung tissue were caused, eventually leading to pulmonary arterial hypertension and pulmonary heart disease. Yang et al. (2017) separated 96 elderly patients with chronic pulmonary heart disease and heart failure into control group and treatment group. The control group was treated with conventional symptomatic agents, and the treatment group received PF at a dose of 200 mg/kg, 3 times/day for 8 weeks on the basis of conventional treatment. The results showed that the cardiac function indexes (LVEF, CI, CO, MPAP, etc.) and blood gas analysis indexes (PaO_2, $PaCO_2$) in the treatment group were significantly better than those in the control group, suggesting that PF is capable of increasing coronary blood flow, relieving vasospasm, dilating microvessels and protecting cardiopulmonary function of patients by antagonizing endothelin.

3.9. Treatment of the cardiac function damage caused by poisoning

Chronic arsenic (As) exposure impairs cardiac function by mediating the level of ROS, regulating myocardial oxidative stress and mitochondrial dysfunction, as well as improving apoptosis mediated by mitogen activated protein (MAPK) kinase. Additionally, changes in potassium and calcium channels, along with myocardial depolarization and arrhythmia are also involved. Hypertension and atherosclerosis caused by vascular endothelial dysfunction are the key conditions for As induced cardiotoxicity (Alamolhodaei et al. 2015). The myocardial injury caused by As is mainly attributed to the increase in serum myocardial marker enzyme levels, such as CK-MB, LDH and AST, which are induced by oxidative stress. Oral administration of FA at 40 mg/kg and As at 5 mg/kg for 30 days significantly reduced the myocardial antioxidants, including superoxide dismutase, catalase, glutathione peroxidase, glutathione and ascorbic acid; the serum cardiac markers like CK-MB, LDH and AST were significantly decreased; the activity of ATP was increased and As induced cardiac insufficiency was reduced by restoring the expression of intermediate filament and AMPK protein (Panneerselvam et al. 2019).

Isoproterenol (ISO) toxicity can improve the activities of MDA and NO, increase the levels of myocardial cell markers, such as AST, ALT, CK-MB and LDH in serum, and the pro inflammatory cytokines, such as TNF-α, IL-6 and IL-1β in myocardium. It shows acute toxicity by disordering the antioxidant system, decreasing the activities of SOD and glutathione (GSH). FA can significantly inhibit ISO-induced cardiotoxicity in rats. Oral administration of FA for 28 days and ISO for 2 days at a dose of 20 mg/kg can significantly reduce the changes of serum myocardial enzymes *via* preventing the apoptosis mediated by ROS and scavenging free radical activity. It showed a protective effect on ISO induced cardiotoxicity by normalizing serum myocardial biomarkers, reducing oxidative stress and strengthening the endogenous antioxidant system (Jain et al. 2018).

3.10. Treatment of metabolic syndrome

Insulin resistance, hypertension and hyperglycemia are the main pathogenic factors of metabolic syndrome (MetS), which increases the risk of cardiovascular diseases such as coronary heart disease and dyslipidemia. Endothelial dysfunction is the main cause of joint endothelium diastolic dysfunction. It is characterized by decreased vascular response to acetylcholine. FA can inhibit endothelium-dependent relaxation by regulating the level of NO, which inhibits vasoactivity related to endothelial contraction by modifying insulin resistance. FA is also capable of relieving insulin resistance and hypertension, antagonizing the decrease of the relaxation of isolated rat aorta to acetylcholine, but has no effects on the relaxation of isolated rat aorta to acetylcholine. Facts proved that treatment with FA at 2 g/kg for eight weeks in mice can reduce TC and triglycerides by 16% and 12%, respectively, while pretreatment with 1000 mg/D for six weeks can significantly inhibit the rise in blood lipid and blood glucose levels *via* increasing HDL-C by 4.32% and decreasing TC, TG and LDL-C by 8.07 %, 12.12 % and 9.32%, respectively (Salazar-Lopez et al. 2017).

3.11. Treatment of cardiac hypertrophy

Myocardial hypertrophy is a kind of adaptive response to heart pressure overload caused by hypertension, which is easy to cause acute heart failure and sudden death. Coarctation of abdominal aorta can increase blood pressure in time-dependent manners and eventually lead to stress overload, which is similar to the symptom of myocardial hypertrophy caused by clinical hypertension. Luo et al. (2019) established the model of myocardial hypertrophy induced by abdominal aortic coarctation, and found that SF at a dose of 40 mg/kg can increase the expression of MKP-1, reduce the concentration of Ang II and ET-1, inhibit the overexpression of embryonic genes such as ANF, PKC-k, raf1, ERK1/2, and suppress myocardial hypertrophy induced by abdominal aortic constriction. The protective effect may be related to the inhibition of PKC and mitogen activated protein kinase (MAPK) signal pathway.

4. Conclusion

Compared with other drugs, FA and its derivatives are easy to obtain, with only few side effects and wide application prospects. FA can be obtained from vanillin and malonic acid with anhydrous pyridine as solvent and piperidine as a catalyst. It can also be obtained from plants in three ways: from the combination of FA with some small molecules, from plant cell wall and through tissue culture. Plant cell wall is the most important source (Zhao et al. 2008). FA and its derivatives are widely used in medicine (Li 2018) cosmetics (Liu et al. 2014), food additives (Sun et al. 2019), etc. and have significant effects in the treatment of cardiovascular diseases. Endothelin plays an important role in the development of myocardial injury and pulmonary hypertension (Yang 2018). As a non-peptide endothelin receptor antagonist, SF has the functions of dilating small blood vessels, protecting the vascular endothelium and scavenging oxygen free radicals (Wang et al. 2019). PF, an endothelin antagonist, can improve myocardial ischemia, relieve vasospasm, inhibit platelet aggregation and delay the development of kidney disease (Deng et al. 2018). In addition, combined with other drugs, FA shows a synergistic therapeutic effect. For example, FA combined with astragaloside IV has vasodilating effects (Li et al. 2019). The combination of FA and trimetazidine can inhibit myocardial ischemia-reperfusion injury during cardiopulmonary bypass (Ding and Wang 2018). FA compound seem to have excellent clinical application value and development potential.

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