REVIEW

Molecular Mechanisms and Promising Role of Dihydromyricetin in Cardiovascular Diseases

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Received April 11, 2022
Accepted September 8, 2022
Epub Ahead of Print November 25, 2022

Summary
Vine tea, a Chinese herbal medicine, is widely used in traditional Asian medicine to treat common health problems. Dihydromyricetin (DMY) is the main functional flavonoid compound extracted from vine tea. In recent years, preclinical studies have focused on the potential beneficial effects of dihydromyricetin, including glucose metabolism regulation, lipid metabolism regulation, neuroprotection, and anti-tumor effects. In addition, DMY may play a role in cardiovascular disease by resisting oxidative stress and participating in the regulation of inflammation. This review is the first review that summaries the applications of dihydromyricetin in cardiovascular diseases, including atherosclerosis, myocardial infarction, myocardial hypertrophy, and diabetic cardiomyopathy. We also clarified the underlying mechanisms and signaling pathways involved in the above process. The aim of this review is to provide a better understanding and quick overview for future researches of dihydromyricetin in the field of cardiovascular diseases, and more detailed and robust researches are needed for evaluation and reference.

Keywords
Dihydromyricetin • Cardiovascular disease • Atherosclerosis, Myocardial infarction • Myocardial hypertrophy

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Introduction

Vine tea (*Ampelopsis grossedentata* [Hand.-Mazz.] W. T. Wang), a Chinese herbal medicine, is widely used in traditional Asian medicine to treat common health problems such as fever and cough [1]. Dihydromyricetin (DMY), myricetin, and quercetin are the main functional flavonoid compounds extracted from vine tea [2]. DMY comprises over 30 % of the dry weight of the leaves and stems of vine tea [3].(2R,3R)-3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphenyl)-2,3-dihydro-chromen-4-one is the chemical name of DMY. The chemical structure of DMY was shown in Figure1. The pharmacological effects, such as anti-inflammatory and anti-oxidation, underlie the potential clinical applications of DMY, including glucose metabolism regulation, lipid metabolism regulation, neuroprotection, antitumour effects, and cardiovascular protection [4]. Emerging preclinical researches have focused on the beneficial effects of DMY in a variety of cardiovascular diseases, including atherosclerosis (AS), myocardial infarction, myocardial hypertrophy, and diabetic cardiomyopathy (DCM). This review will summarize the pharmacological properties and the effects of DMY on cardiovascular diseases.

Pharmacological properties and toxic effects

The molecular weight of DYM is 320.25, and

the pKA is 7.38±0.60. DMY possesses two kinds of enantiomers, including dextroisomer and laevoisomer [5]. DMY is soluble in ethanol and DMSO. Solubility of DMY in water is 0.2 mg/ml at 25 °C and 0.9 mg/ml at 37 °C [6]. Hydroxypropyl-β-cyclodextrin, PVP K30, and PEG6000 help to enhance the water-solubility of dihydromyricetin [7]. In addition, enzyme-acylated product of dihydromyricetin improves its lipid-solubility [5].

Tong and colleagues reported that DMY was partially absorbed by oral administration [8]. After oral administration at a dose of 100 mg/kg in rats, DMY rapidly distributed into stomach, small intestine, heart, liver, spleen, lung, kidney, and brain, with the highest concentration in gastrointestinal tract [9]. Liquid chromatography-mass spectrometry analysis showed the maximum serum concentration (C_{max}) was 21.63 ± 3.62 ng/mL at approximately 2.67 h after oral administration at a dose of 20 mg/kg, and the drug half-life ($t_{1/2}$) was 3.70 ± 0.99 h correspondingly [8]. Researchers used the human intestinal Caco-2 cell model to predict the absorption properties of DMY and found that passive diffusion mechanism conducted the uptake and transport process, which might partially give explanation to the relative low administration bioavailability of DMY when taken orally. Time, concentration, pH, and efflux transporters may affect its uptake and transport processes [10].

As for the intravenous use, DMY reached C_{max} of 165.67 ± 16.35 ng/mL at a dose of 2 mg/kg for intravenous administration, and $t_{1/2}$ was 2.05 ± 0.52 h correspondingly for rats [8]. In another study, mice were administered with 50 mg/kg DMY by intraperitoneal injection or oral gavage. After 15 minutes, DMY could be detected in serum and brain tissue [1]. The calculated effective permeability coefficient (Peff) is an important parameter that determines the rate and degree of drug absorption in vivo. Peff of DMY was calculated to be $(1.84 \pm 0.37) \times 10^{-6}$ cm/s [5].

DMY could be metabolized and eliminated in the intestinal tract [8], and it's metabolites could be eliminated through the digestive and urinary systems within 12 hours. Metabolites with different retention time have been identified in urine, feces and plasma [1]. DMY could be degraded by a variety of digestive enzymes [11]. The stability of the gastrointestinal environment and transport proteins influenced the metabolic rate of DMY, which meant that bioavailability of DMY could be influenced by gastrointestinal pH [12]. Some proteins might modulate the intake and transport of DMY. Inhibition of multidrug resistance protein 2 with probenecid and inhibition of breast cancer resistance (BCRP) protein with Ko143 resulted in the significant uptake of DMY [10]. Besides, five metabolic pathways of DMY have been proposed, including dehydroxylation, methylation, glucuronidation, sulfation and reduction [13].

Since the low solubility, short half-life period, and instability limit clinical applications of DMY, different complex formulations and delivery systems have been used to improve the bioavailability of DMY, such as microemulsions, inclusion complexes, nanoencapsulation, soluble cocrystals, and phospholipid complexes [2, 14].

The toxic effect of plant flavonoids could be an important issue for its further clinical applications, but few studies have raised concerns to the adverse effects of DMY. Currently toxicological studies indicated that DMY is safe. Nanoencapsulation-loaded DMY maintained its antioxidant capacity in peripheral blood mononuclear cells at the concentration of 150 μM [15]. Continuous administration showed little influence on metabolism and development for rats [16, 17]. In a subacute toxicity assessment for rats, mortality, food and water consumption, body weight changes, and absolute organ weights were observed. Herbal mixture extracts complex rich in DMY exhibited little toxicological signs for rats. The content of DMY in herbal mixture was 362.7 ± 12.5 mg/g and the administration dose of herbal mixture was 1998mg/kg, and the maximum tolerated dose in rats is 5-10 g/kg [18]. In another toxicity assessment research of DMY, no liver toxicity or kidney toxicity was observed, as well as blood cell damage [19]. DMY has been reported to show little cytotoxicity to normal hepatocytes [20]. Additional animal and clinical trials are needed to further evaluate the safety of DMY in human.

DMY can inhibit the increase of body weight and fat mass, preventing non-alcoholic fatty liver disease in mice [1]. In rats, DMY supplementation did not affect appetite and energy intake, suggesting that weight loss was related to changes in metabolism [18]. DMY administration decreased the triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) contents in mouse serum [2]. A study of hamsters also showed that DMY attenuated the high-fat-induced increase in body weight, liver lipid deposition, serum triglycerides and total cholesterol levels [3]. Moreover, DMY reduced

fasting blood glucose and delayed the onset of hyperglycemia by 4 weeks in rats [4]. DMY reduced the fasting blood glucose, serum insulin, and glycated hemoglobin levels and the insulin resistance index in mice. In the oral glucose tolerance test (OGTT), mice demonstrated a significant suppressed of elevated plasma glucose levels 30, 60, 120, and 180 min after the ingestion of a single high dose of glucose [5]. According to a double-blind clinical trial, adult nonalcoholic fatty liver disease patients took dihydromyricetin twice daily for three months. The serum levels of glucose and the homeostasis model assessment of insulin resistance (HOMA-IR) index were significantly decreased in the dihydromyricetin group compared with the placebo group [6]. DMY was found to increase glucose uptake and decrease adipogenesis in mouse fibroblast 3T3-L1 cells [7]. It is a shortcoming that most studies remain in the animal or cell experimental stage, and further investigation should be carried out.

Protective effects of DMY

Antioxidative effects

Oxidative stress is involved in the pathological process of cardiovascular diseases. During the oxidative process, the formation of ROS and their immediate interaction with other substances is increased. When the respiratory chain complexes are dysfunctional, ROS production is simultaneously increased and pathological process is accelerated [21].

Antioxidant stress is one of the main strategies for the treatment of cardiovascular diseases [22]. DMY could affect the formation of free radicals in the respiratory chain and accelerated their elimination, leading to the reduction of intracellular malondialdehyde (MDA). In lipopolysaccharide (LPS)-induced sepsis rat model, DMY decreased the serum level of nitric oxide (NO) and MDA, and eventually ameliorated the impaired contractility of the rat aorta [23]. In the meanwhile, in 2,2′-azobis (2-amidinopropane) dihydrochloride (AAPH)-induced oxidative stress damage of human erythrocytes model DMY treatment significantly increased the level of superoxide dismutase (SOD), which catalysed the removal preocess of superoxide anion radicals [24]. The oxidative-stress prevention effect of DMY has also been demonstrated in mouse brain tissue. DMY could improve Pb-induced cognitive functional impairment by decreasing the levels of lipid peroxidation and protein carbonyl and increasing the activities of SOD and catalase [25].

In addition, DMY might participate in the activation of genes that regulate detoxifying and antioxidant enzymes. Mitochondrial oxidative stress, as well as the decreased mitochondrial DNA (mtDNA) copy number, leads to mtDNA damage, which indicating serious mitochondrial dysfunction [26]. Sirtuin 3 (SIRT3), a mitochondrial enzyme, participates in metabolism and the oxidative stress response [27]. Hou *et al.* reported that the protective effect of DMY was mediated by mitochondrial apoptotic pathways [28]. DMY enhanced SIRT3 protein expression as well as mtDNA copy number in thoracic aorta of diabetic mice. Knocking out SIRT3 abolished the positive effects of DMY on mitochondrial function, which indicated that DMY improved endothelial dysfunction via oxidative stress inhibition in a SIRT3-dependent manner [29]. Moreover, SIRT3-mediated Atg4b deacetylation following DMY treatment induced cell autophagy, suggesting that SIRT3 and Atg4b were involved in DMY-induced benefits [26].

DMY regulates several proteins that have been reported to be involved in antioxidative response as well. Oxidized low-density lipoprotein (Ox-LDL) injured human umbilical vein endothelial cells (HUVECs) were treated with DMY, resulting in the activation of protein kinase B (Akt) and extracellular regulated protein kinases 1/2 (Erk1/2), as well as the upregulation of antioxidant enzymes and antiapoptotic proteins, including cysteinyl aspartate specific proteinase-3 (caspase-3), B-cell lymphoma 2 (Bcl-2) and Bcl-2-associated X protein (Bax) [30]. Besides, Zhang reported that DMY could promote the expression of phosphorylated forkhead box O3 (FoxO3) and Akt, and modulate the nuclear localization of FoxO3, thereby protecting HUVECs from oxidative stress [31]. DMY inhibited cell apoptosis, lipid accumulation and oxidative stress in cellular model of steatosis by suppressing the expression of peroxisome proliferators-activated receptors-γ (PPAR-γ) and the phosphorylation of Akt [25], and promoted the phosphorylation of adenosine 5‘-monophosphate-activated protein kinase (AMPK) [32].

In conclusion, DMY play a role in various cardiovascular diseases and other diseases by regulating key products of oxidative stress, mitochondrial antioxidant enzymes and oxidative stress-related proteins. Further research is needed to expand the application range of DMY.

Anti-inflammatory effects

Inflammatory process is the common feature of cardiovascular disorders. Some in vivo and in vitro studies have shown that DMY participated in the regulation of inflammation, implying potential medicinal value of DMY in immune-related and inflammation-related diseases. However, the anti-inflammatory mechanism of DMY remains unclear. According to existing studies, it can be explained from two aspects, including inflammatory cells and inflammatory cytokines

DMY might contribute to immune regulation by affecting macrophage polarization. M1 macrophages are involved in the pro-inflammatory response while M2 macrophages are responsible for immune regulation and resolution of inflammation [33]. Atomic force microscope scanning proved that DMY prevented morphological change and membrane alterations of RAW 264.7 macrophages caused by LPS stimulation, suppressed M1 macrophage activation. In addition, DMY inhibits lipid accumulation in macrophages and promotes cholesterol excretion. So, DMY could prevent ox-LDL induced the transformation of macrophages into foam cells [34].

During the macrophage polarization process, cyclooxygenase-2 (COX-2) protein expression and p65 phosphorylation were inhibited by DMY [35], and inhibition of COX-2 enzyme contribute to anti-inflammatory effects in cardiovascular diseases [33]. Cox-2 was usually upregulated at inflammatory sites and catalyzed the initial step of arachidonic acid metabolism and prostaglandin synthesis. COX-2 active products are involved in hemodynamics and blood pressure, thromboresistance, pain and inflammation [36]. Abdolahi also confirmed that COX-2 expression were suppressed by DMY in a dose-dependent manner in vivo, showing the potent anti-inflammatory effect of DMY [37].

On the other hand, the inflammation suppression roles of DMY may be related with its effects on regulating inflammatory factors. DMY inhibited the activation of nuclear factor-kappa B (NF-κB) /the toll-like receptor 4/myeloid differentiation primary response gene 88/ nuclear factor-kappa B (TLR4/MyD88/NF-κB) pathway [38], and subsequently inhibiting the expression of proinflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6 and IL-18 [39]. Inflammation index such as IL-2 and IL-6 were modulated by DMY in hippocampal neurons [40].

Besides, a growing number of studies have focused on the inhibitory effect of DMY on the nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3 (NLRP3) inflammasome [41], which is a critical component of the innate immune system. NLRP3 mediates caspase-1 activation and the secretion of proinflammatory cytokines IL-1β/IL-18 in response to cellular damage. DMY was reported to reduce microglia-mediated neuroinflammation by suppressing NLRP3 inflammasome activation [42]. In an acute lung injury (ALI) model, the role of DMY has also been verified. DMY protects against ALI by inhibiting NLRP3 inflammasome activation and subsequent pyroptosis [23]. Studies on the anti-inflammatory effect of DMY have mainly focused on the observations and summaries of the phenomenon, and more in-depth mechanistic explorations still needs to be performed.

Application of DMY in cardiovascular diseases

Atherosclerosis

AS is a chronic inflammatory disease of the blood vessels, characterized by atherosclerotic lesion formation. DMY might be a potential therapeutic for the treatment of atherosclerosis, which has been shown to inhibit atherosclerotic plaque formation and maintain plaque stability in vivo and in vitro. The mechanisms of DMY against AS might include antioxidant, regulation of lipid metabolism, and regulation of pyroptosis.

Endothelial dysfunction is a risk factor for the development of AS. Endothelial nitric oxide synthase (eNOS) catalyses the formation of NO, inhibiting vascular sclerosis and maintaining vascular homeostasis [43]. DMY acted as a potential therapeutic adjuvant for endothelial dysfunction. Yang's research team revealed that DMY attenuated TNF-α induced endothelial dysfunction mediated by decreasing the expression of microRNA-21 and increasing eNOS/NO expression, as evidenced by increased tube formation and migration and increased NO concentration [44]. In apolipoprotein E-deficient (Apoe-/-) mice, DMY treatment significantly inhibited atherosclerotic lesion formation and increased nitric oxide (NO) production and improves lipid metabolism [44,45]. However, overexpression of microRNA-21 can significantly inhibit the cardiovascular protective effect of DMY and increase the circulating lipid level.

Ox-LDL accumulation contributes to the

formation of atherosclerotic lesions. DMY provided cytoprotective effects by suppressing ox-LDL-induced endothelial cell apoptosis and caspase-3 activation. Moreover, DMY ameliorated mitochondrial dysfunction and inhibited ROS generation in ox-LDL injured HUVEC model. Nuclear transcription factor-erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) signalling pathway was activated during this process, and antioxidant enzymes and anti-apoptotic proteins were up-regulated [30]. In LDL receptor deficient mice fed with high fat diet, the effects of DMY were further studied. DMY increased the expression of cholesterol-regulating proteins (PPAR-α, liver X receptor-α and adenosine triphosphate (ATP) binding cassette subfamily A member 1), reduced IL-6 and TNF-α expression, and prevented hepatic and aortic inflammation. Therefore, DMY inhibited AS lesion formation and favoured features of plaque stability [46].

In addition, regulation of pyroptosis might contribute to the protective effects of DMY. Pyroptosis is a recently discovered type of programmed cell death, which participates in the pathological process of AS. This process is accompanied by the release of a large amount of proinflammatory factors [47,48]. Caspase-1 plays a key role during pyroptosis. Hyperlipidaemia induced the production of cholesterol crystal and promoted atherogenesis [49], while caspase-1 promoted endothelial cell activation and monocyte recruitment to the arterial intima in hyperlipidaemia [50,51]. DMY pre-treatment inhibited palmitic acid-induced pyroptotic cell death by increasing cell viability and eliminating caspase-1 cleavage and subsequent IL-1β maturation. As a result, the percentage of propidium iodide (PI) positive cells was decreased, indicating the loss of plasma membrane integrity [52]. Emerging evidence indicated that DMY can mediate vascular endothelial cell pyroptosis through pathways we mentioned above, including the Nrf2 signalling pathway and NLRP3 signalling pathway [30, 52].

Myocardial infarction and ischaemia-reperfusion injury

Myocardial ischaemia/reperfusion (I/R) injury refers to the aggravated metabolic dysfunctions and structural damages when blood flow is restored after myocardial ischemia and reperfusion. Due to calcium overload, free radical production, and inflammatory cell infiltration, blood supply reperfusion can cause severe damage to the ischaemic myocardium, even result in arrhythmia and enlarged infarct size [53]. In general, research model of I/R injury can be induced by left anterior descending coronary artery occlusion in animal models and hypoxia/reoxygenation (H/R) injury in cardiomyocytes in vitro [54, 55]. DMY was reported to have beneficial effects against I/R dysfunction. In this part, we summarized beneficial effects of DMY against I/R injury, and we focused on the effects of DMY on myocardial dysfunction and mitochondrial dysfunction.

Myocardial dysfunction is one of the manifestations during myocardial infarction. Liu and colleagues demonstrated that DMY had cardioprotective effects by decreasing I/R-induced apoptosis and necrosis. In a rat I/R model, the S-T segment elevation was diminished and myocardial infarct size was decreased by pretreatment with DMY (150 mg/kg). In this study, PI3K/Akt and hypoxia inducible factor-1α (HIF-1α) played crucial protective effects. PI3K inhibitor LY294002 effectively inhibited the protective effects of DMY against I/R-induced injury [56]. Besides, Dong Wang reported that DMY significantly improved the recovery of left ventricular developed pressure and maximum up/down rate of left ventricular pressure in vitro model of cold cardioplegia in isolated working rat hearts [57]. The present study provided preliminary evidence that DMY may have potential clinical applications in cardiac transplantation. Mitochondrial dysfunction can be considered one of the major mechanisms in the pathogenesis of I/R injury [58]. Mitochondrial functional impairments lead to loss of myocyte during the acute ischemic stage, as well as the decline of surviving myocytes during the subacute and chronic stages. Mitochondrial dysfunction was alleviated by DMY treatment. The mitochondrial injury was alleviated after DMY treatment, and DMY resulted in an increase in mitochondrial membrane potential in response to the H/R in cardiomyocytes. The above beneficial function of DMY might be associated with the upregulation of SIRT3 [59].

In addition, irisin is a myokine reducing endothelial damage by inhibiting inflammation and oxidative stress in the early phase of post-myocardial infarction [60]. Oral administration of DMY (100 mg/kg/d) could promote irisin secretion and increased serum irisin concentration 1.9-fold compared to sedentary rats, resulting in improvement of cardiac remodeling in myocardial infarction rats, and the heart rate variability domains increased back to normal.

However, the reason why DMY promoted irisin secretory was not clearly clarified [61].

In the mouse carotid artery ligation model, intraperitoneal injection of DMY (40 mg/kg) every 2 days significantly protect vascular by attenuating injury-induced carotid artery neointimal formation two weeks after surgery. DMY promoted smooth muscle cell differentiation and inhibited its proliferation and migration via induction of nuclear receptor 4A subfamily member (TR3), which mediated SMC phenotypic switch [62].

Cardiac hypertrophy

Hypertrophic growth of cardiomyocytes is an adaptive and reversible response to haemodynamic stress. Cardiac hypertrophy refers to an irreversible form of pathological hypertrophy caused by chronic stress overload. Hypertension and valvular disease are the most common causes of cardiac hypertrophy. Cardiac hypertrophy is characterized by an excessive increase in ventricular dimensions, accompanied by myocardial dysfunction and fibrosis [63, 64]. Increased myocardial oxygen consumption in the hypertrophic myocardium leads to multiple cardiovascular accidents, such as arrhythmia and myocardial infarction. Inflammation, oxidative stress, and humoral stimuli have been found to induce cardiomyocyte hypertrophy and pathological remodelling [65]. Transverse aortic constriction surgery (TAC) could be applied to generate an animal model of myocardial hypertrophy induced by pressure overload [66]. The current study found that DMY can attenuate myocardial hypertrophy in vitro and in vivo via oxidative stress inhibition.

Intragastric administration of DMY (250 mg/kg/day) decreased interventricular septum and left ventricular posterior wall thickness, reduced the cardiomyocyte cross-sectional areas and the cardiac index of cardiac hypertrophy model after TAC. In Ang II-induced cardiomyocyte hypertrophy model, DMY treatment can reduce expression of ROS and MDA in mRNA level and increase SOD activity, indicating that oxidative stress was inhibited during this process [67].

Neonatal rat cardiomyocytes incubated with angiotensin II (100 nM) for 24h could be used as a model of cardiomyocyte hypertrophy in vitro. DMY administration enhances the SIRT3 pathway in cellular model, as measured by SIRT3 activity in the myocardium [68].

Diabetic cardiomyopathy

DCM was first observed in 1972 in four patients with diabetic glomerulosclerosis who suffered from congestive heart failure and arrhythmia without obvious coronary arterial and valvular disease, neither congenital heart disease or hypertension [69]. Diabetic patients have a high prevalence of DCM and high mortality due to heart failure. DCM causes cardiac microvascular disease, myocardial metabolic disorder, and myocardial fibrosis, leading to left ventricular hypertrophy and cardiac dysfunction, and eventually develops into congestive heart failure [70, 71]. According to present researches, DMY may act on DCM by regulating glucose uptake, insulin metabolism, insulin resistance in skeletal muscle, and mitochondrial autophagy.

DMY participated in the regulation of glucose metabolism. AMPK is a key regulator involved in energy sensing to the metabolic manipulation. AMPK modulation has shown beneficial effects against diabetes and cardiovascular complications. AMPK signalling pathway maintains the normal function of mitochondria and energy homeostasis [72]. In the diabetic encephalopathy model, DMY protected PC12 cells against apoptosis and glucose metabolism disorders by restraining the hyperactivation of phospho-AMPK and normalizing the translocation of glucose transporter protein 4 (GLUT4), resulting in the rebalance in glucose uptake [73].

In the meanwhile, DMY played a role in the regulation of insulin resistance as well. According to a study of rats with HFD-induced insulin resistance, DMY promoted the phosphorylation of AMPK, which significantly increased insulin-independent glucose uptake and the maintenance of glucose homeostasis [74]. Shi and colleagues reported that DMY induced insulin sensitivity improvement and activated insulin signalling in skeletal muscle in vitro and in vivo. DMY increased the glucose uptake capacity in palmitate-treated L6 myotubes under insulin stimulation. The beneficial effects of DMY in skeletal muscle insulin resistance might be associated with the autophagy induction and the up-regulation of AMPK [75,76].

For peripheral tissues, muscle tissue is the main component in which insulin regulates glucose uptake. Insulin resistance in skeletal muscle participates in the onset of type 2 diabetes. The ratio of the fast-twitch fibres and slow-twitch fibres in skeletal muscle plays a regulatory role in insulin resistance [77, 78]. Slow-

twitch fibres exhibit a stronger capacity for glucose transport and homeostasis maintenance than fast-twitch fibres [79]. Folliculin (FLCN) and folliculin-interacting protein 1 (FNIP1) regulated the differentiation of muscle fibre types [80]. It was reported that treating obese mice with DMY increased the proportion of slow-twitch fibres and improved insulin resistance. In vitro experiments using mouse skeletal muscle C2C12 myoblast cells showed that palmitate treatment decreased the expression of slow-twitch fibre and enhanced insulin resistance, concomitant with increases in FLCN/FNIP1 expression and decreases in peroxlsome proliferator—activated receptor-γ coactlvator—1α (PGC-1α) expression. These effects could be suppressed by knockdown of FLCN or DMY administration [81].

Activated mitochondrial autophagy might participate in the protection process against diabetes-related myocardial damage. As an important response mechanism by which cells respond to changes in internal and external environments, autophagy degrades and clears damaged organelles and misfolded proteins, thereby stabilizing cellular morphology and structure [82]. DMY might be engaged in the autophagy process in a regulated manner. DMY decreased the expression of miR-34a and abrogated the impairment in autophagy in high glucose-induced cardiomyocytes and in the heart tissue from diabetic mice. Moreover, DMY reduced the myocardial fibrosis and collagen deposition, and reorganized the collagen network [83]. DMY administration restored the LC3 II/LC3 I ratio, as well as the expression of Beclin1 and autophagy related 7 (Atg7) in the hearts of diabetic mice [84]. Besides, DMY treatment enhanced the phosphorylation of AMPK and unc-51 like kinase 1 (ULK1) in diabetic mice. It was confirmed that AMPK promoted autophagy by activating ULK1 through phosphorylation of Ser 317 and Ser 777 [85]. Taken together, DMY might prevent cardiac dysfunction in diabetic mice by restoring autophagy through AMPK/ULK1 activation, and this phenomenon have been confirmed by Shi's research team [76].

Summary and prospects

In this review, we summarized the beneficial effects of DMY in cardiovascular diseases, including antioxidant stress, anti-inflammatory, and cardioprotective effects (Fig. 1). Besides, the main results of the in vivo studies have been provided in Table 1. These research results show the great clinical potentiality of DMY in the treatment of cardiovascular diseases. More detailed and robust research is needed for evaluation and reference. For example, research on the pharmacokinetics, toxicology, and safety of DMY remains insufficient, and approaches to ameliorate the short half-life, poor bioavailability and low aqueous solubility are needed. Although we have a basic understanding of the protective effects of DMY on cells, DMY is not efficiently absorbed orally, so it is necessary to improve the method to ensure the pharmacological effects of Vine tea (that is taken orally) in vivo. And the in-depth mechanisms by which DMY protects the cardiovascular system have not been systematically and clearly confirmed. In addition, clinical trials for DMY, especially the randomized, double-blind, placebo-controlled trial, are still lacking, and safety analyses in the human body need further verification.

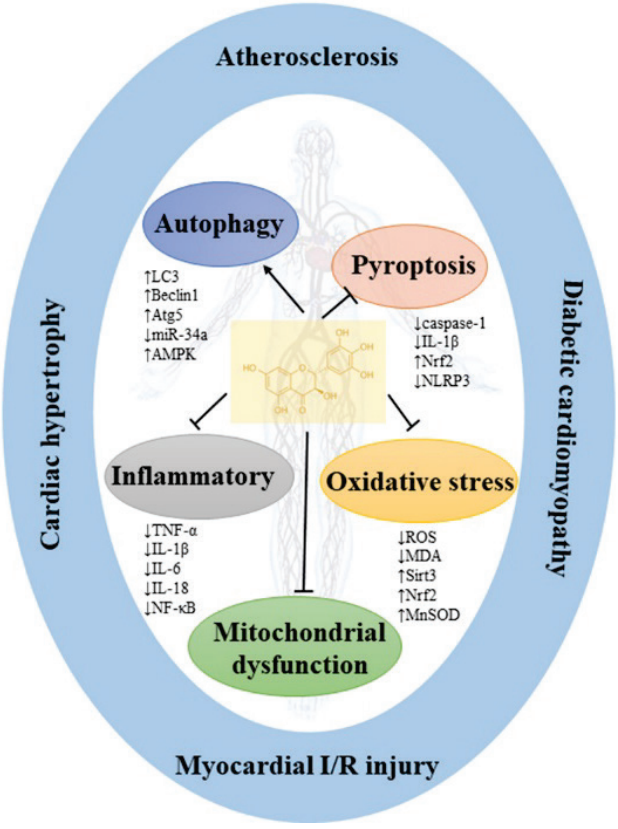

Fig. 1. The chemical structure and beneficial effects of DMY in cardiovascular diseases.

Table 1. Main results of in vivo trials of DMY efficacy

Clinical disease	Experimental models	Route, dose and time of administration	Main findings	Ref
Sepsis	Sprague-Dawley (SD) rats induced by lipopolysaccharide (LPS)	intravenous injection, 5 μg/kg/d, 7 days	DMY administration ameliorated LPS-induced vascular hyporesponsiveness and DMY decreased the serum concentrations of cytokines and oxidative stress.	23
Atherosclerosis	Apoe$^{-/-}$ mice on a 1.25 % high cholesterol diet	intragastric gavage, 50 mg/kg/d, 12 weeks	DMY treatment significantly inhibited atherosclerotic lesion formation, proinflammatory gene expression by increasing NO production and improving endothelial function in Apoe$^{-/-}$ mice.	45
Atherosclerosis	High Fat Diet fed LDLr$^{-/-}$ mice	intragastric gavage, 250 or 500 mg/kg/d, 8 weeks	DMY inhibited atherosclerotic lesion formation, favoured features of plaque stability, aortic inflammation and oxidative stress in HFD-fed LDLr−/− mice.	46
Myocardial ischemia-reperfusion injury	rats treated with the surgery of ligation the Left anterior descending coronary artery	intragastric gavage, 150 mg/kg/d, 7 days	DMY had cardioprotective effects against I/R-induced oxidative stress and apoptosis, and enhanced antioxidant capacity in cardiac tissues.	56
Myocardial infarction	rats induced by subcutaneous injection of isoproterenol	intragastric gavage, 100 mg/kg/d, 8 weeks	DMY improved heart function and the course of wound healing by stimulating irisin secretion in post MI rats. Exercise training was superior to DMY in improving hemodynamic parameters.	61
Injury-induced vascular diseases	ligation-induced carotid artery neointimal formation in mice	intraperitoneal injection, 40,100 or 300 mg/kg, per two days up to 10 week	Ligation-induced carotid artery neointimal formation and inflammatory in mice could be significantly attenuated by DMY treatment which can lead to expression of TR3.	62
Myocardial Hypertrophy	Transverse aortic constriction (TAC) induced myocardial hypertrophy mice	intragastric gavage, 250 mg/kg/d, 2 weeks	DMY improved myocardial structure and reduced cardiomyocyte cross-sectional area and cardiac index by suppressing the hypertrophic genes expression in mice after TAC.	68
Diabetic Cardio-myopathy	Diabetes mice with intraperitoneal injection of streptozotocin	intragastric gavage, 100 mg/kg/d, 13 weeks	DMY ameliorated cardiac function by rescuing impaired autophagy through miR-34a suppression in diabetic mice.	83

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This work was supported by National Key R&D Program of China (Project 2020YFC2008000), Hubei Provincial Natural Science Foundation of China (Project 2021CFB067) and National Natural Science Foundation of China (Project 81873811).

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