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Review

The Protective Effects of Myricetin against Cardiovascular Disease

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Summary Cardiovascular disease (CVD) is the leading cause of death globally, except Africa, and poses a severe health burden worldwide. Both in vitro and in vivo studies have demonstrated the protective effects of myricetin for preventing CVD. For this review, we have assessed the literature from 2009 to 2019 at home and abroad to uncover the protective roles of myricetin for preventing CVD. Myricetin exhibits cardioprotective, anti-hypertensive, anti-atherosclerotic, anti-hyperglycemic, and anti-hyperlipidemic effects. In addition, myricetin may alleviate some of the complications caused by adult-onset diabetes. The combined functions of myricetin allow for the prevention of CVD. This review describes the possible therapeutic benefits of myricetin, along with its potential mechanisms of action, to support the clinical use of the myricetin for the prevention of CVD.

Key Words cardioprotective, hypertensive, atherosclerotic, hypoglycemic, hypolipidemic

1. Biological Sources and Functions of Myricetin

Myricetin (Myr), chemically named 3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl) chromen-4-one, is a natural polyhydroxy flavonoid compound extracted from the bark and leaves of *Myrica rubra* (*1*). Myr is widely distributed beyond the *Myricaceae* family, including *Polygonum bellardii* (*2*), *Primulaceae* (*3*), *Anacardiaceae* (*4*) and *Pinaceae* (5). Myr is a common component of many foods and beverages, including fruits, vegetables, berries, and teas (*6*). In addition, Myr is also found in honey and grapes, specifically the grapes used to create red wine (*7*) (Fig. 1). The health benefits of Myr have been thoroughly investigated in over the last decade. Currently, Myr is known display the following biological properties: antioxidant (*8*), antimicrobial (*9*), antiviral (*10*), anti-inflammatory (*11*), anti-tumor (*12*), analgesic (*13*), hepatoprotective (*14*), hypoglycemic (*15*), hypolipidemic (*16*), cardioprotective (*17*), and neurological damage inhibition (*18*). Recently, the cardioprotective role of Myr has attracted attention from the research community due to its potential clinical impact (Fig. 2).

Chinese traditional medicine has been closely concerned with the treatment of cardiovascular disease (CVD), including coronary heart disease, heart failure, and stroke. The use of naturally-occurring plant extracts has become increasingly popular over the past decade. While only a few clinical and epidemiological researchers have assessed the health benefits of Myr on the cardiovascular system, several in vitro and in vivo studies have verified the protective effects of Myr against CVD. For this review, we have summarized the most relevant work published in the past ten years on the cardiovascular system-associated protective effects of Myr. In addition, we have described the underlying molecular mechanisms of Myr, which will support the clinical use of Myr for preventing CVD.

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2. Cardioprotective Effects of Myr

Myr exhibits several cardioprotective effects on lipopolysaccharide (LPS) or endotoxin-induced inflammatory myocardial injury, ischemia/reperfusion (I/R)-induced myocardial injury, and isoproterenol (ISO)-induced myocardial infarction. Using an LPS-induced myocardial injury mouse model, Myr (100 mg/kg) was given orally twice daily to reduce the levels of inflammatory cytokines in the serum and heart tissues of mice. In addition, this concentration of Myr was shown to inhibit NF-κB/P65 signaling and oxidoreductase activity, including that of superoxide dismutase (SOD) and glutathione peroxidase (GPx) (*19*). In another study, Chen and Fan (*20*) showed that Myr could inhibit the expression of IL-1β, IL-6, and TNF-α in cultured H9c2 cardiomyocytes, while also protecting against endotoxin-induced early inflammatory reactions through the regulation of ROS and IκB kinase/NF-κB signaling. Therefore, these findings suggest that Myr may display cardioprotective effects again CVD through its anti-inflammatory effects.

Myr has also been found to protect against myocardial injury induced by I/R. For example, Qiu et al. (*21*) used an acute I/R-induced myocardial injury mouse model to study the biological effects and molecular mechanism of Myr in protecting against CVD. An effective dose of Myr (5 μM) was shown to reduce the infarct size and down-regulate the apoptosis of cardiomyocytes (*21*). Myr was also found to exhibit protective effects against I/R-induced myocardial injury through its antioxidant effects and its inhibitory effects of signal transducer

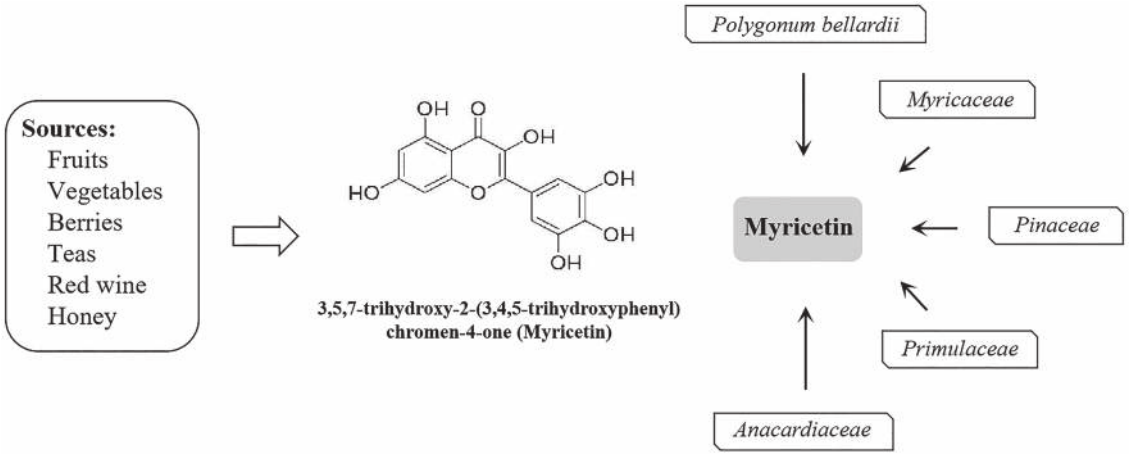

Fig. 1. Myricetin comes from several biological sources, such as fruits and berries, and may be found in several plant species. The chemical structure of myricetin consists of 3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl) chromen-4-one.

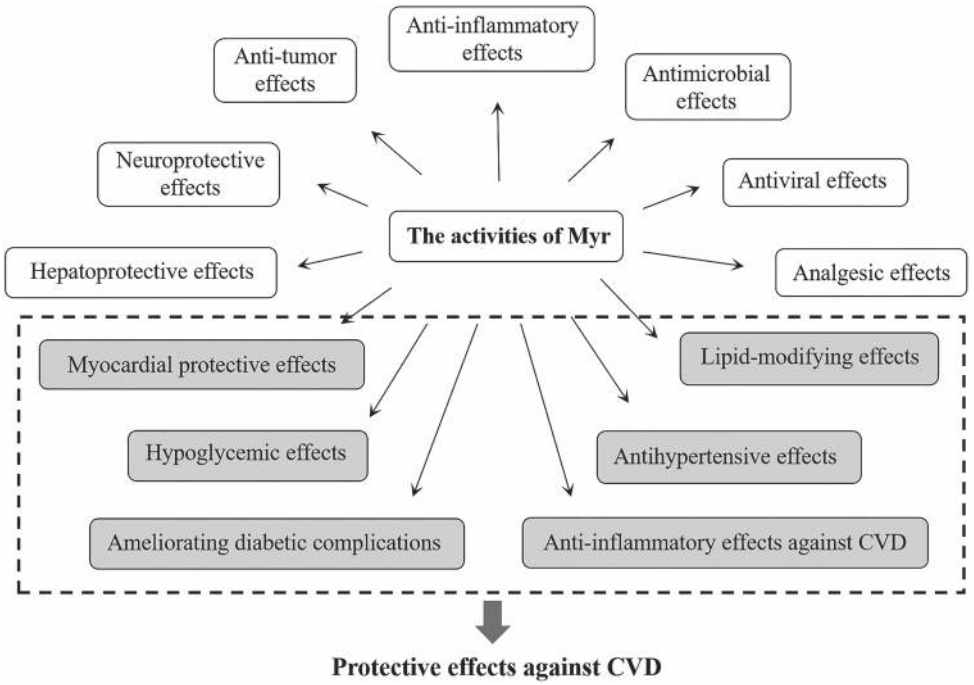

Fig. 2. Biological properties of myricetin, many of which contribute to its cardioprotective effects. Myr, myricetin; CVD, cardiovascular disease.

and activator of transcription 1 (STAT1) activation (*21*, *22*). Myr acted as a selective coronary dilator to induce coronary dilation directly, without producing any myocardial effects or influencing the contractility or relaxation of the coronary artery. The selective vasodilation produced by Myr can protect the heart from injury in cases of CVD (*23*).

In addition, Myr has shown protective effects in an ISO-induced myocardial infarction rat model. Myr (100 or 300 mg/kg, orally for 21 d) significantly improved the heart rate, serum enzyme levels, vascular reactivity, and electrocardiograph patterns of rats with myocardial infarctions. These findings suggested that Myr could inhibit the cardiotoxicity of ISO and may hold promise in the clinical treatment of myocardial infarctions in the future (*17*). In another study, Myr exerted an anti-arrhythmic effect by inhibiting the ultra-rapid delayed rectifier potassium current (I_{kur}) and human Kv1.5 (hKv1.5) expression in HEK293 cells in a time-, dose-, and frequency-dependent manner (*24*).

3. Anti-Hypertensive Effects of Myr

Myr displayed anti-hypertensive effects in a fructose-induced rat model of hypertension. Myr (100 and 300 mg/kg/d, orally for 6 wk) reduced systolic blood pressure changes and vascular reactivity to catecholamines. In addition, Myr also reversed the fructose-induced metabolic changes (*25*), suggesting that Myr may prevent or limit the development of high blood pressure in some cases. The chronic administration of

Myr (100 and 300 mg/kg, orally for 4 wk) could effectively treat hypertension and oxidative stress caused by deoxycorticosterone acetate (DOCA)-salts in rats. DOCA increased the levels of thio-barbituric acid reactive substances and reduced the levels of catalase, superoxide dismutase, urinary sodium excretion, and glutathione in the heart. However, Myr also decreased systolic blood pressure and changes in vascular reactivity, while even reversing the DOCA-induced changes. In another study, Myr was verified to show anti-hypertensive and antioxidant effects in a DOCA-induced hypertension mouse model (*26*).

4. Anti-Hyperglycemic Effects of Myr

4.1. Protection of islet β cells

Cytokine-induced cell death is the primary cause of progressive β cell loss in humans. Ding et al. (*27*) reported on the protective effects of Myr (10 μM and 20 μM) in preventing insulin-secreting RIN-m5f β cell death. Myr increased cell viability and decreased cytokine (TNF-α, IL-1β, and IFN-γ)-induced cell apoptosis. Moreover, Myr (20 μM) effectively inhibited NF-κB, nitric oxide (NO), cytochrome C, and reactive oxygen species (ROS) levels in RIN-m5f β cells (*27*). Aggregation of islet amyloid polypeptide (IAPP) is known to play a direct role in the death of pancreatic β-islet cells in patients with type 2 diabetes mellitus (T2DM), also known as adult-onset diabetes (*28*). Previously, Zelus et al. (*28*) described the inhibitory effects of Myr on IAPP aggregation and found that the drug could rescue mammalian cells from the toxic effects of IAPP. In addition, IAPP was found to be a potent inhibitor of IAPP amyloid formation and was an excellent therapeutic target for the treatment of amyloid diseases.

4.2. Promotion of insulin secretion

Glucagon-like peptide 1 (GLP-1) is a potential therapeutic target for the treatment of T2DM as it regulates blood glucose levels by improving insulin secretion after glucose consumption. Previously, Myr (3 μM) was found to increase glucose-dependent insulin secretion from Wistar rat islets in vitro. In addition, the oral administration of Myr (250 μg/kg) increased glucoregulatory activity in rats. In another study, Myr activated the GLP-1 receptor (GLP-1R), which stimulated the secretion of insulin (*29*), further indicating that Myr may be an excellent small-molecule GLP-1R agonist for the treatment of T2DM.

4.3. Development of insulin resistance

Obesity-associated insulin resistance is a strong risk factor for T2DM. Recently, Choi et al. (*30*) reported that Myr (0.12% of the total high-sucrose diet, for 12 wk after a 1-wk adaptation) significantly reduced the body weight and serum glucose levels of mice, effectively treating the sucrose-induced hypertriglyceridemia and hypercholesterolemia. Myr displayed protective effects against diet-induced obesity and insulin resistance in mice fed with a high fat and sugar diet. The alleviation of insulin resistance was partly attributed to the reduction of serum proinflammatory cytokine levels and weight management (*30*). β-Endorphin, an endogenous opioid neuropeptide and peptide hormone, was previously shown to play an important role in the amelioration of insulin resistance in rats (*31*). Myr treatment (1 mg/kg, three times a day for 14 d) could increase β-endorphin levels in fructose-induced insulin-resistant rats. The increase of β-endorphin secretion activated peripheral μ-opioid receptors (MOR) and alleviated the impaired signaling intermediates downstream of the insulin receptors (*31*).

There are two forms of adipose tissue in mammals, including white adipose tissue (WAT) and brown adipose tissue (BAT). The activation of BAT is correlated with systemic energy metabolism. Previously, Hu et al. (*32*) assessed whether Myr could activate BAT in leptin receptor-deficient db/db male mice. Myr (400 mg/kg, given by oral gavage for 14 wk) alleviated the systemic insulin resistance and hepatic steatosis of mice. In addition, Myr promoted the formation of beige fat, increased thermogenic protein levels, and activated mitochondrial biogenesis. Lastly, Myr prevented obesity and systemic insulin resistance by activating BAT and increasing adiponectin expression. Moreover, Ding et al. (*33*) reported on a putative link between hyperinsulinemia and insulin resistance in C2C12 skeletal muscle cell line. Myr stimulated glucose uptake and attenuated hyperinsulinemia-induced insulin resistance in the skeletal muscle cells.

4.4. Inhibition of α-amylase and α-glucosidase activity

Specific inhibitors of human pancreatic α-amylase have the potential for controlling blood glucose levels in the treatment of T2BM and obesity. Myr was identified as a competitive inhibitor of pancreatic α-amylase through high throughput screening of 30,000 crude biological extracts from terrestrial and marine origins (*34*). Meng and colleagues (*35*) investigated the inhibitory effects of Myr on α-amylase and α-glucosidase to alleviate postprandial hyperglycemia. Myr effectively inhibited α-amylase and α-glucosidase activity with IC_{50} values of 662 μg/mL and 3 μg/mL, respectively. The inhibitory effects of Myr on α-amylase were all reversible and competitive, and reversible but non-competitive for α-glucosidase. Hence, Myr may be used to alleviate postprandial hyperglycemia in patients with T2DM.

4.5. Alleviation of complications associated with adult-onset diabetes

Many studies have explored the anti-hyperglycemic and renal protective effects of Myr in recent years. In streptozotocin (STZ) and cadmium (Cd)-induced diabetic nephrotoxic rat models, the administration of Myr (1.0 mg/kg/d, intraperitoneally once a day for 12 wk) could suppress the extracellular mesangial matrix expansion, interstitial fibrosis, and glomerulosclerosis. Myr exhibited remarkable protective effects on STZ-Cd-induced changes in lipid metabolism and attenuated diabetic nephropathy (*36*). In the STZ-Cd-induced diabetic nephrotoxic rat model, intraperitoneal administration of Myr (1.0 mg/kg/d for 30 d) showed significant protective effects on several biochemical parameters, including plasma glucose, glycosylated hemoglobin, plasma insulin, urea, creatinine, uric acid, and albumin. Myr subsequently increased glucose utilization and

enhanced renal functioning in diabetic STZ-Cd-induced nephrotoxic rats (*37*, *38*). Besides, Myr (6 mg/d, intraperitoneal injections every 12 h for 10 d) also restored the altered activities of GPx and xanthine oxidase (XO) in the renal tissues of STZ-induced diabetic rats (*39*). Histopathology of liver and kidney tissues verified that Myr exhibited protective effects in STZ-Cd-induced diabetic nephrotoxic rats by regulating an oxidative mechanism (*40*). These data suggest that Myr may be useful in the treatment of diabetic nephropathy.

In addition to its anti-hyperglycemic and renoprotective effects, Myr can be used for the treatment of diabetic retinopathy, diabetic erythrocytes damage, and diabetic skin damage. Advanced glycation end products (AGE) are involved in the development of diabetic retinopathy, and the loss of retinal pericytes is the result of pericytes migration and an early indicator of diabetic retinopathy in the clinic (*41*). An injection of Myr, at 10 μM in bovine retinal pericytes or 50–100 μM by intravitreal injection in Sprague-Dawley rats with AGE, could inhibit AGE-induced cell migration of the retinal pericytes via phosphorylation of the extracellular regulated protein kinases (ERK1/2), paxillin, and focal adhesion kinase 1 (FAK-1) (*41*). Pandey and colleagues (*42*) reported that micromolar concentrations of Myr could protect against *tert*-butyl hydroperoxide (*t*-BHP)-induced oxidative stress in diabetic erythrocytes. The imbalance of oxidative stress caused by high glucose levels may play a role in dermal fibroblasts alterations. High glucose altered the ratio of metalloproteinase-1 (TIMP-1) to matrix metalloproteinase (MMP), which is used in the clinic for the detection of diabetic foot ulcerations (*43*). Treatment with Myr (3 μM) balanced the TIMP1/MMP ratio and reduced oxidative stress levels in the diabetic dermal fibroblasts (*43*).

5. *Anti-Hyperlipidemic Effects of Myr*

Myr may prevent obesity and obesity-related metabolic complications, while also exhibiting reversing hepatic steatosis caused by high-fat diets. Previously, Chao et al. (*44*) reported on the anti-obesity effects of Myr using male Sprague-Dawley rats that were fed a high-fat diet for 8 wk and administrated 1, 5, or 10 mg/L of Myr. In this study, Myr reduced the weight gain, blood lipid levels, and the size and weight of the epididymal and perirenal adipose tissues. The anti-obesity effects of Myr may be associated with the upregulation of adropin and β-endorphin levels. Previously, Su et al. (*45*) reported that in high fat diet-induced obese C57BL/6 mice, Myr (150 mg/kg/d, orally for 10 wk) significantly decreased the levels of serum glucose, triglycerides, cholesterol, and body weight. In addition, the treatment improved the obesity-associated oxidative stress, including GPx activity and total antioxidant capacity levels. Similarly, Chang et al. (*46*) drew the same conclusions in Myr (300 mg/kg/d, orally for 8 wk)-treated Wistar rat as the drug produced anti-obesity and anti-hyperlipidemic effects, which were mediated by the up-regulation of peroxisome proliferator-activated receptor α (PPARα) and down-regulation of sterol regulatory element-binding protein (SREBP) expression in the liver of rats receiving a high-fat diet. Myr might exhibit a regressive impact on pre-existing hepatic steatosis induced by high-fat diets. Besides, C57BL/6 mice were fed with high-fat diets and Myr (0.12% in the diet, w/w, for 12 wk) to explore the therapeutic effects of Myr on hepatic steatosis. Myr effectively inhibited the high-fat diet-induced steatosis and hepatic lipid accumulation, and Myr may be an effective treatment for high-fat diet-induced hepatic steatosis through the activation of Nrf2 and PPAR signaling pathways (*47*).

Myr produces anti-obesity effects through the inhibition of preadipocyte differentiation into adipocytes and promotion of fat decomposition in mature adipocytes. Previously, Wang et al. (*48*) found that Myr (100 μM) could inhibit the differentiation of 3T3-L1 preadipocytes in a concentration-dependent manner. In addition, Myr decreased the levels of adipogenic transcription factors and increased the release of glycerol in fully differentiated adipocytes, suggesting that Myr has stimulatory effects on adipocyte lipolysis.

The oxidative modification of low-density lipoprotein (LDL) and endothelium might play a prominent role in atherogenesis. Previously, Myr was shown to exhibit significant protective effects against oxidized LDL and ROS production in human umbilical vein endothelial cells (HUVEC) (*49*). Myr showed significant anti-atherogenesis activities by inhibiting H_2O_2-induced oxidative injury in HUVEC (*49*).

6. *Conclusions*

CVD is the most common cause of death in people over the age of 65, making it a substantial global health burden for families, governments, and healthcare providers (*50*). The majority of studies conducted more than a decade ago focused on the anti-hyperglycemic effects Myr alone (*51*–*55*). A non-controlled, pilot study reported that *Eugenia punicifolia* (Kunth) DC (*Myrtaceae*), which is rich in Myr, could be used as adjuvant therapy for T2DM (*56*). However, a prospective study showed that none of the total flavonols and flavones, quercetin, kaempferol, myricetin, apigenin, or luteolin, were significantly associated with an increased risk of T2DM (*57*). In the past decade, researchers have found that Myr exhibits several biological properties in mammals, including cardioprotective, anti-hypertensive, anti-atherosclerotic, anti-hyperglycemic, and anti-hyperlipidemic effects. All of these functions likely contribute to the drugs protective effects against CVD, such as atherosclerosis, hypertension, hyperglycemia and hyperlipidemia (Fig. 3). While Canada et al. (*58*) reported that Myr could be toxic to intestinal cells, the safety of Myr has been verified through several in vitro and in vivo studies (*59*–*61*). Myr is an important active ingredient and additive in many foods, including several nutritional foods found in Europe.

Based on the current findings, Myr clearly shows powerful protective effects and offers a considerable amount of promise as a novel drug for preventing CVD. However, several questions remain unanswered and further

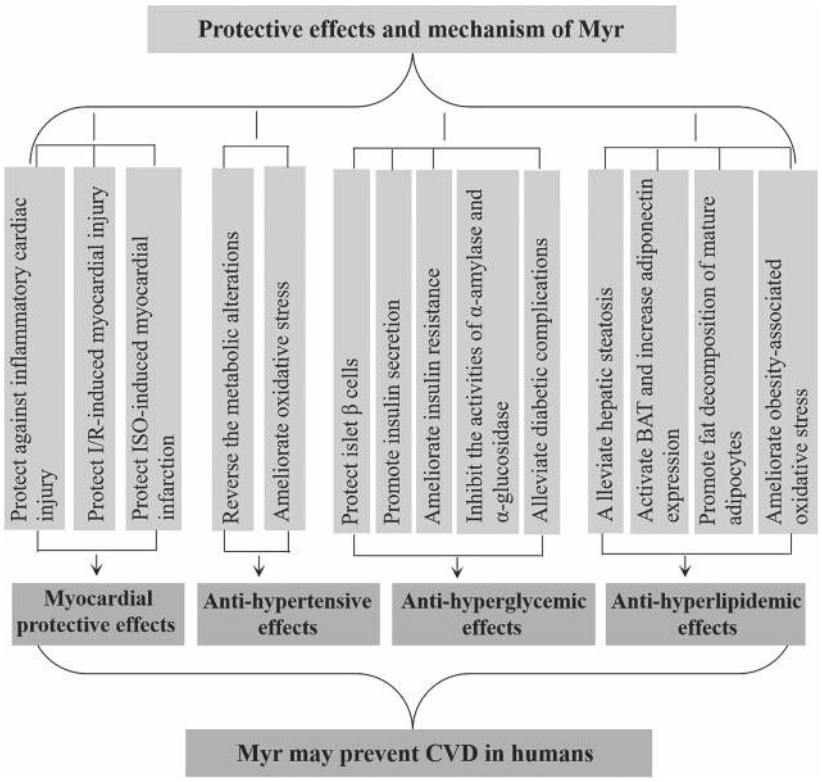

Fig. 3. Myrcetin offers a considerable amount of promise as a novel drug for preventing CVD. Myr, myrcetin; I/R, ischemia/reperfusion; ISO, isoproterenol; BAT, brown adipose tissue; CVD, cardiovascular disease.

in vitro and in vivo studies are needed to fully elucidate the molecular mechanism through which Myr protects against CVD. In addition, randomized trials need to be performed to determine whether Myr can be used as a drug or dietary strategy for decreasing the risk of CVD in patients. However, Myr remains an excellent therapeutic candidate for the prevention and possible treatment of CVD in the clinic.

Disclosure of state of COI

The authors confirm they have no conflicts of interest.

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