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Research progress of quercetin in cardiovascular disease

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Quercetin is one of the most common flavonoids. More and more studies have found that quercetin has great potential utilization value in cardiovascular diseases (CVD), such as antioxidant, antiplatelet aggregation, antibacterial, cholesterol lowering, endothelial cell protection, etc. However, the medicinal value of quercetin is mostly limited to animal models and preclinical studies. Due to the complexity of the human body and functional structure compared to animals, more research is needed to explore whether quercetin has the same mechanism of action and pharmacological value as animal experiments. In order to systematically understand the clinical application value of quercetin, this article reviews the research progress of quercetin in CVD, including preclinical and clinical studies. We will focus on the relationship between quercetin and common CVD, such as atherosclerosis, myocardial infarction, ischemia reperfusion injury, heart failure, hypertension and arrhythmia, etc. By elaborating on the pathophysiological mechanism and clinical application research progress of quercetin's protective effect on CVD, data support is provided for the transformation of quercetin from laboratory to clinical application.

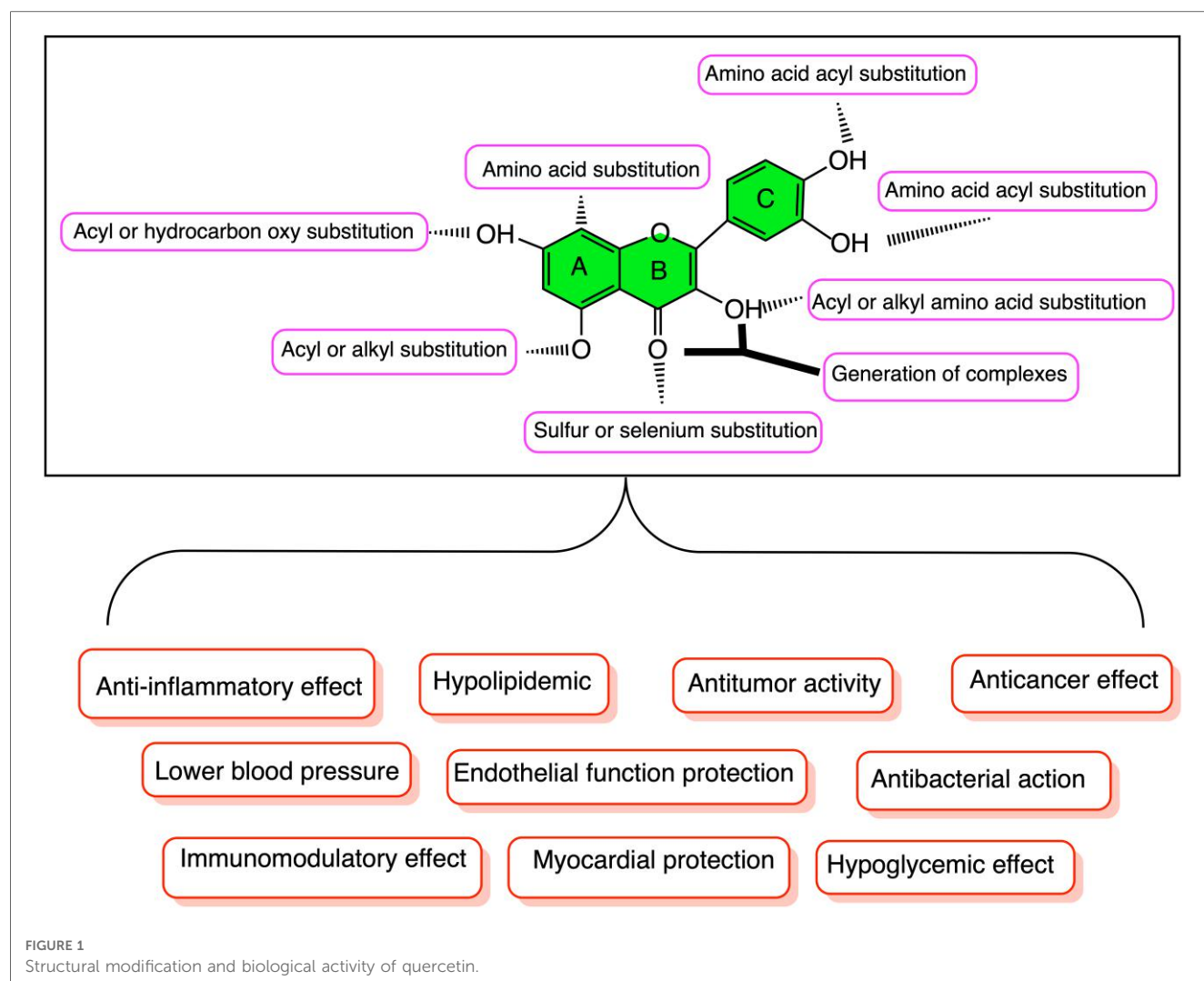
KEYWORDS

quercetin, cardiovascular disease, antioxidant, lipid-lowering, myocardial protection

1. Introduction

Cardiovascular disease is a global chronic disease with high mortality and disability rates, and its pathogenic factors are complex and diverse, such as oxidative stress, inflammation, and arterial plaques (1, 2). Antioxidant, anti-inflammatory, and lipid-lowering treatment strategies are considered one of the treatment methods for preventing and treating CVD. Although Western medicine has a clear therapeutic effect on CVD, its target is relatively single. The research and development process of western medicine is slow and complex, requiring a significant investment of time, energy, and financial resources. Therefore, more and more researchers are paying attention to the therapeutic value of natural molecular compounds in CVD.

Quercetin, which has existed for a hundred years in the history of traditional Chinese medicine, belongs to a natural flavonoid compound. Quercetin is found in high concentrations in a variety of foods, including fruits, onion, tea, and red wine (3). As is well known, most of the chemotherapy drugs approved by the Food and Drug Administration (FDA) are extracted from natural products such as plants and marine organisms (4). As an important natural drug molecule, quercetin has been used alone or in combination for the treatment of various diseases, including malignant tumors, CVD, autoimmune diseases, metabolic diseases, etc (5–8). Human research on quercetin has



never stopped, and by continuously improving its biological activity and bioavailability, more patients can benefit from it.

Recently, a large number of *in vitro* and *in vivo* studies have shown that quercetin has various functions such as anti-inflammatory, antioxidant, antihypertensive, hypoglycemic, neurovascular protection, anticancer, anti-aging, and immune enhancement (7, 9–11) (**Figure 1** and **Table 1**). Quercetin has prominent medicinal value in CVD, such as antioxidation, antiplatelet aggregation, reducing myocardial fibrosis, improving ventricular remodeling and cardiac function, protecting vascular endothelium, anti-arrhythmia, anti-heart failure, preventing ischemia reperfusion injury, and regulating blood pressure. This study will mainly describe the research progress of quercetin in CVD.

2. Structure and metabolic pathway of quercetin

Quercetin has a structure of 3,3', 4', 5,7-pentahydroxyflavones, which are naturally present in the form of quercetin glycosides (24, 25). Quercetin is composed of two benzene rings (A ring and

B ring) and a closed pyran ring (C-ring). The A ring has two hydroxyl groups that belong to the m-diphenol structure, the B ring has two hydroxyl groups that belong to the o-diphenol structure, and the C ring has one hydroxyl group that belongs to an enol structure, with a total of five hydroxyl groups (**Figure 1**). Its glycosylation can occur on any hydroxyl group, and by combining with glucose, xylose, or rutin sugar, various forms of quercetin glycosides are produced (26). As medical research continues to deepen, researchers have found that compounds obtained from natural products, such as quercetin, are more effective in treating and preventing diseases (27, 28). Although poor water solubility and low bioavailability limit the clinical application of quercetin, its metabolic derivatives can effectively clear the active substances in the body, making it considered by epidemiologists and nutritionists as a natural compound with the most promising application in disease prevention and treatment (29–31). The derivatives of quercetin mainly include O-glycosides, C-glycosides, ethers, and derivatives containing alkyl substituents (11, 25) (**Figure 2**).

Quercetin, as a relatively low molecular weight polyphenol compound, has broad pharmacological effects and therapeutic

TABLE 1 Clinical trials of quercetin and CVD.

Diseases	Number of patients	Dosage regimen	Experiment Type	Primary outcomes	References
MI	88	500 mg/day orally for 8 weeks	Double blind, placebo-controlled, randomized clinical trial	↓Inflammatory factors, TAC; ↑QOL	(Dehghani et al.) (12)
Hypertension	22	162 mg/day orally for 6 weeks	Randomized, double-blind, placebo-controlled, crossover trial	BP and endothelial function→	(Brüll et al.) (13)
Hypertension	84	1,000 mg orally 2 times per day for 6 months, and then 500 mg 2 times per day for 6 months	Non randomized clinical trials	↑Left ventricular diastolic function, purine metabolism; ↓BP	(Kondratiuk et al.) (14)
Hypertension	41	730 mg/day orally for 28 days	Randomized, double-blind, placebo-controlled, crossover trial	↓BP; oxidative stress→	(Edwards et al.) (15)
Hypertension	18	25 mg/day orally for 28 days	Double-blinded, placebo-controlled, crossover trial	↓Diastolic pressure; ↑eNOS and NO	(Biesinger et al.) (16)
Hypertension	17	Total orally 1,095mg	Randomized, double-blind, crossover, placebo-controlled study	↓BP; ACE and ET-1→	(Larson et al.) (17)
Hypertension	186	150 mg/day orally for 6 weeks	Double-blinded, placebo-controlled cross-over trial	↓BP; TNF- α , CRP→	(Egert et al.) (18)
High CVD risk phenotype	72	500 mg/day orally for 10 weeks	Double-blind randomized clinical trial	↓BP; LDL-C, TG, TNF- α , IL-6→	(Zahedi et al.) (19)
APOE genotype healthy male	49	150 mg/day orally for 8 weeks	Double-blind crossover study	↑TNF- α , waist circumference, postprandial systolic BP	(Pfeuffer et al.) (20)
Volunteers	22	30 mg/day orally for 2 weeks	Randomized, placebo controlled	↓ox-LDL	(Chopra et al.) (21)
Healthy volunteers	15	200 mg or 400 mg/day orally for 3 weeks	Double blind, randomized, placebo-controlled trial	Induce vasodilator effects	(Perez et al.) (22)
CHD	85	120 mg/day orally for 12 months	Randomized controlled trial	↑Left ventricular systolic and diastolic function, protect the heart	(Chekalina et al.) (23)

ACE, Angiotensin-converting enzyme; APOE, Apolipoprotein E; BP, Blood pressure; CHD, Coronary heart disease; CRP, C-reactive protein; CVD, Cardiovascular diseases; ET-1, Endothelin-1; eNOS, Endothelial nitric oxide synthase; IL-6, Interleukin-6; LDL-C, Low-density lipoprotein cholesterol; MI, Myocardial infarction; NO, Nitric oxide; ox-LDL, Oxidized low-density lipoprotein; QOL, Quality of life; TAC, Total antioxidant capacity; TAG, Triacylglycerol; TNF- α , Tumor necrosis factor α ; TxA2, Thromboxane A2; TG, Triglycerides; ↑, Increase or increase, ↓, Down or down; →, Stable or no change.

potential mainly through interactions with gut microbiota or key cell signaling proteins (32) (Figure 3). After oral administration, the quercetin is absorbed into the bloodstream by the small intestine in the form of glycosides, then bound to serum albumin and transported to the liver for metabolism (33, 34). Quercetin binds with methyl, sulfate, or glucuronic acid in the body to produce active metabolites such as isorhamnetin, kaempferol, and tamarind (35). These metabolites have a half-life of up to 28 h, and after being released, they reach the blood and lymph nodes of the whole body, and finally enter different organs such as the liver and kidneys for catabolism, which is ultimately discharged through feces or urine for 24 to 28 h (25, 36–40) (Figure 4).

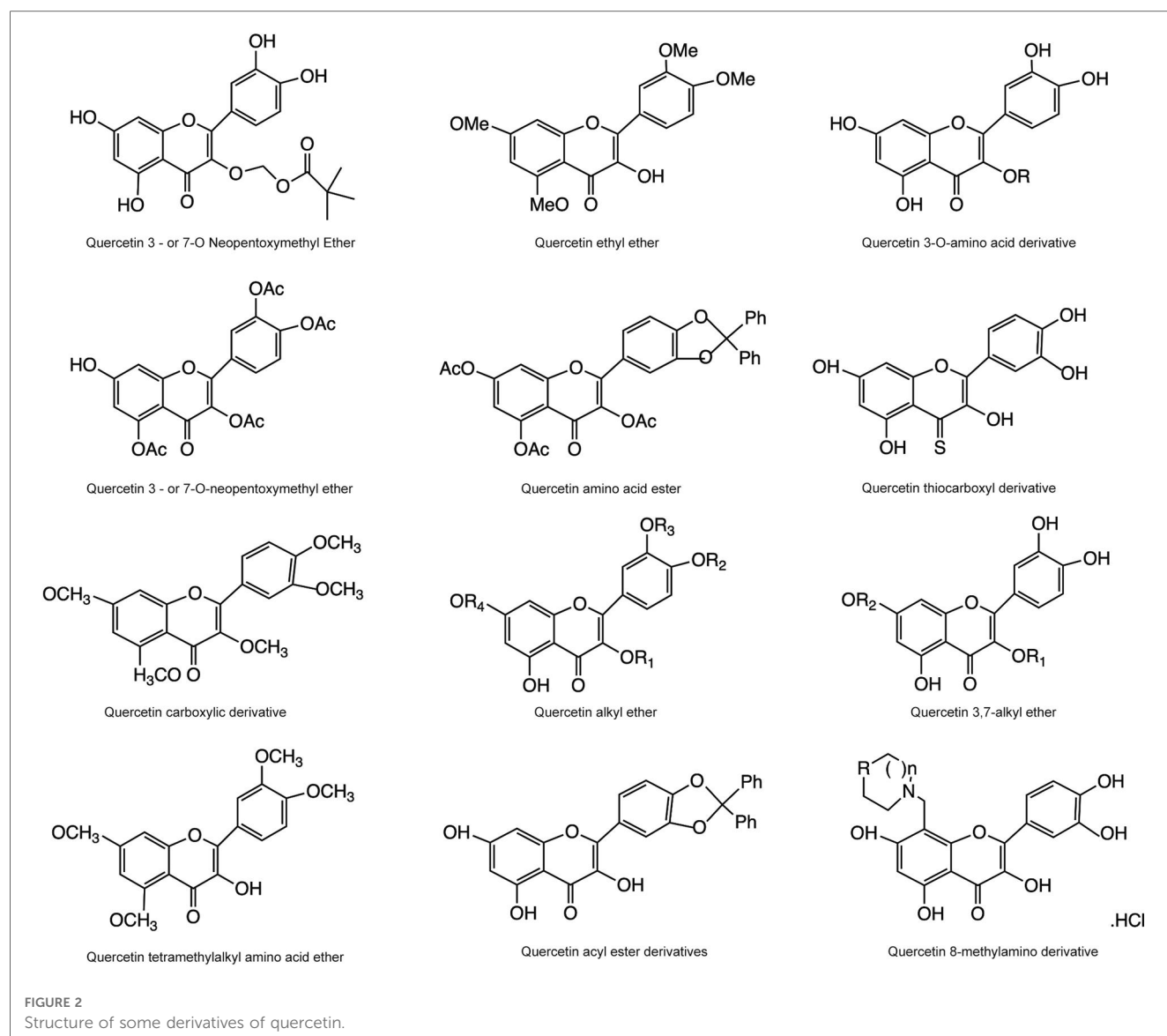
3. The relationship between quercetin and CVD

3.1. Antioxidant effect

The antioxidant effect of quercetin is mainly achieved by directly clearing reactive oxygen species, chelating metal ions, and inhibiting LDL oxidative damage. Quercetin, as a natural antioxidant, can remove hydroxyl radicals, hydrogen peroxide (H₂O₂), and superoxide anions accumulated in cells both *in vivo* and *in vitro*, thereby increasing oxygen atoms to stabilize the structure of the benzene ring (41, 42). Quercetin can also induce the production of the antioxidant enzyme heme oxygenase-1 (HO-1), thereby enhancing cellular defense against oxidative damage (43). The

antioxidant capacity of quercetin is mainly related to its ability to scavenge free radicals (44). We know that cellular oxidative stress damage caused by reactive oxygen species (ROS) is mainly related to signaling pathways such as nuclear factor carotenoid derivative 2 (NRF2), adenosine monophosphate activated protein kinase (AMPK), mitogen-activated protein kinase (MAPK), extracellular regulated protein kinases (ERK), p38, and c-Jun N-terminal kinase (JNK). Quercetin can just scavenge ROS, which is involved in maintaining intracellular oxidation balance. Zhang et al. (45) found that quercetin can clear ROS in cardiac fibroblasts and inhibit cell proliferation, which is related to inhibiting the activation of the MAPK signaling pathway to reduce the phosphorylation levels of ERK, p38, and JNK. Lu et al. (46) showed that quercetin can also activate caspase-3 and nuclear factor (NF) regulated by Phosphatidylinositol-3-kinase (PI3K)/protein kinase κ B pathway (Akt- κ B) to reduce ROS production, thereby improving atherosclerosis.

In the oxidative stress model induced by hydrogen peroxide, quercetin pretreatment significantly reduced intracellular ROS levels (47). This indicates that quercetin can reduce intracellular reactive oxygen species and protect cells from oxidative damage. Researchers also found that quercetin significantly increased cell viability by reversing oxidative stress induced by hydrogen peroxide, while the expression levels of oxidative stress-related proteins induced by hydrogen peroxide also decreased. The direct scavenging effect of quercetin on reactive oxygen species may be related to the abundance of phenolic hydroxyl groups in the structure. Phenolic hydroxyl groups can exert antioxidant effects



by providing active hydrogen to inactivate free radicals while being oxidized to highly stable free radicals (48).

In addition, antioxidant enzymes such as catalase (CAT) and superoxide dismutase (SOD) play an important role in clearing superoxide anion free radicals in the body. A study found that quercetin can protect the myocardium from damage by increasing the activity of antioxidant enzymes in rats with acute myocardial infarction, including SOD, catalase and glutathione peroxidase (49). Quercetin can significantly reduce the levels of oxidative stress biomarkers such as malondialdehyde (MDA) and nitric oxide synthase (iNOS) in hypoxic induced myocardial tissue of rats, while increasing the activity of SOD and CAT. In a cadmium induced cardiovascular disease rat model, quercetin can also protect the heart by increasing SOD, CAT, and glutathione peroxidase (50).

The steady state destruction of metal iron and copper in the body is also one of the reasons for the increase of free radicals in the body (51). Quercetin has a strong ability to chelate metal ions, thereby blocking the Fenton reaction and ROS production

(52). In stable chelating complexes, quercetin exhibits stronger antioxidant effects. Research has found that catechol in the molecular structure of quercetin can chelate with Cu^{2+} and Fe^{2+} to exert antioxidant effect (53). In the model of alcoholic liver disease, quercetin inhibits Fe^{2+} induced lipid peroxidation by chelating Fe^{2+} , ultimately inhibiting iron overload and oxidative damage caused by alcoholic liver disease (54). Pękal et al. (55) found through spectral analysis that under the action of Cu^{2+} , quercetin can be oxidized into benzoquinone products with stable structures, and Cu^{2+} also loses its ability to mediate lipid oxidation. In addition, Jomova et al. (56) found that the chelation of quercetin with copper can significantly inhibit the ability of copper to induce hydroxyl radical formation, and quercetin can also protect DNA from reactive oxygen species by inhibiting the formation of reactive oxygen species.

The increase of oxidized low-density lipoprotein (ox-LDL) *in vivo* will not only lead to the necrosis or apoptosis of vascular endothelial cells, inflammatory cells, fibroblasts and smooth muscle cells, but also promote the development of atherosclerosis

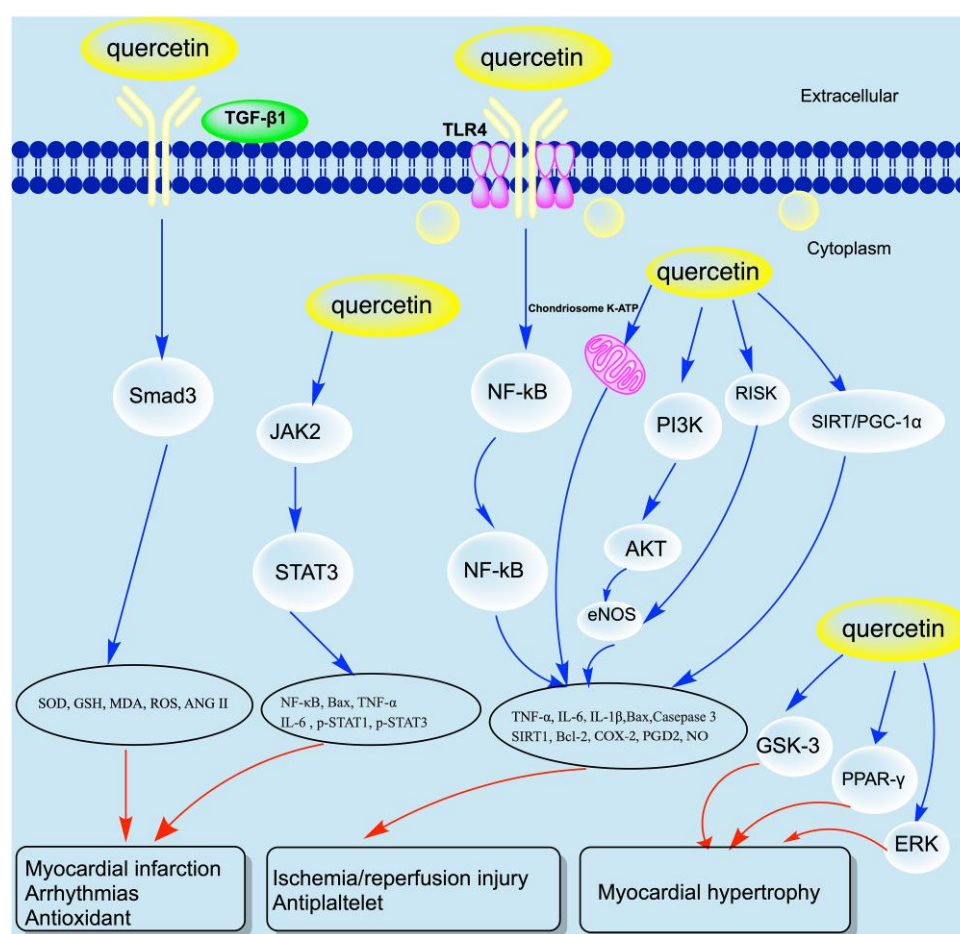


FIGURE 3

Molecular mechanism of quercetin in CVD. COX, cyclooxygenase; ERK, Extracellular regulated protein kinases; MDA, Malondialdehyde; NF-κB, Nuclear Factor Kappa Beta; NO, Nitric oxide; PDG2, Prostaglandin E2; PGC-1α, GSH, Glutathione; Peroxisome proliferator-activated receptor-γ Coactivator-1α; RISK, Reperfusion Injury Salvage Kinases; SOD, Superoxide dismutase; SIRT1, Silencing information regulator 1; STAT, Signal transducer and activator of transcription; TNF-α, Tumor necrosis factor α.

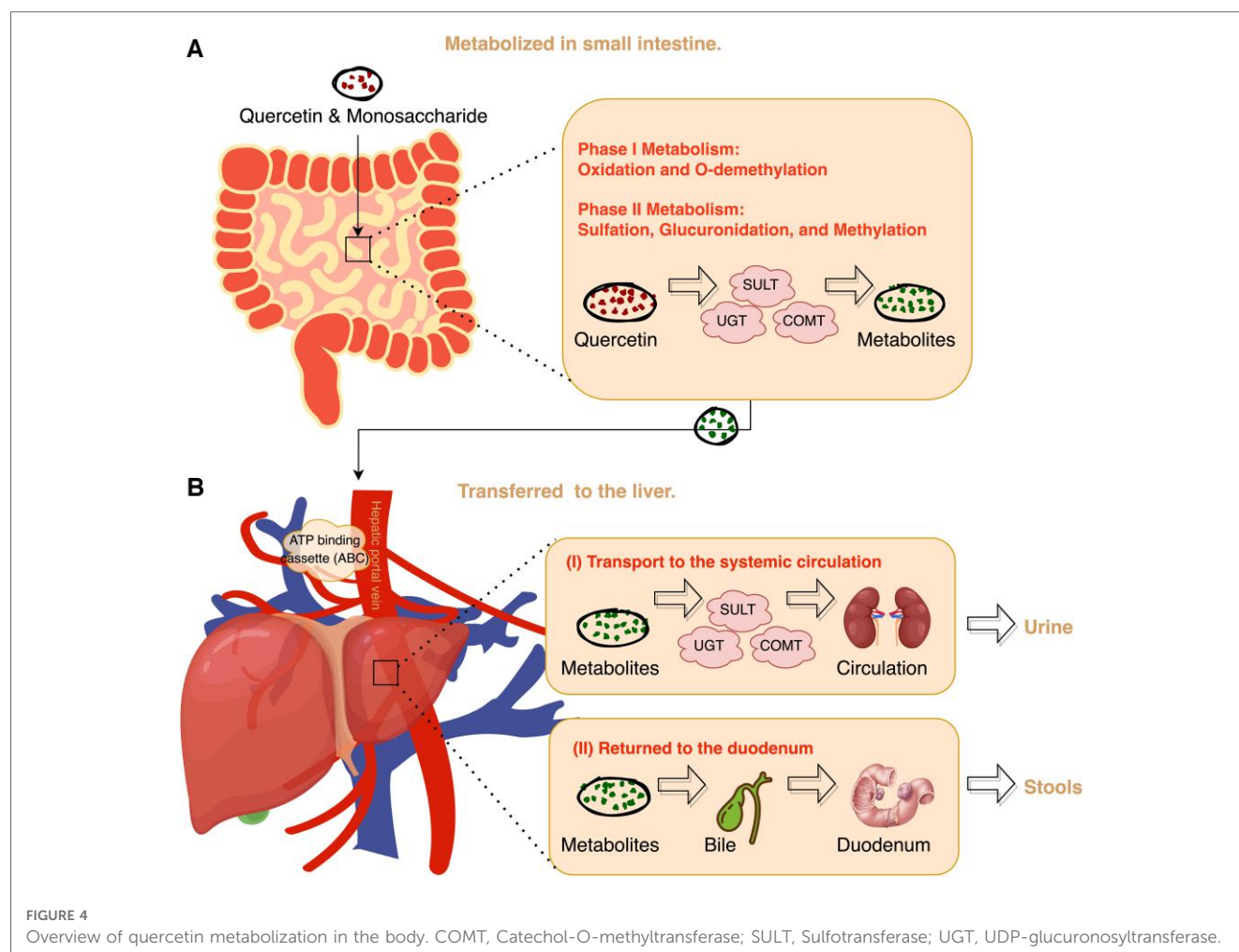
and other CVD (57–59). Quercetin can achieve antioxidant effects by inhibiting LDL oxidation and reducing intracellular ROS content (60). Hertog et al. (61) observed that when plasma levels of quercetin increase, both total cholesterol and low-density lipoprotein cholesterol levels decrease. This may be related to quercetin upregulating MAPK and ERK phosphorylation to promote autophagy, thereby promoting cell survival. In addition, quercetin inhibits ox-LDL induced oxidative stress by downregulating the expression of toll like receptor 4 (TLR4) in the ROS/TLR4 signaling pathway, thereby reducing ox-LDL induced cell calcification and osteogenic differentiation of vascular smooth muscle cells (62).

3.2. Anti atherosclerotic effect

Atherosclerosis is a chronic vascular inflammatory disease related to ox-LDL (63). With the continuous stimulation of inflammatory factors in the arterial wall and the accumulation of lipids in the intima, vascular endothelial cells can be damaged, leading to dysfunction (64). Although the use of anti-lipid drugs

has certain preventive and therapeutic effects on atherosclerosis, the incidence of cardiovascular events is still high. In recent years, researchers have found that combined use of anti-inflammatory drugs can effectively alleviate and treat arterial Congee. Reducing blood lipids and cholesterol in atherosclerotic plaques is an important treatment to inhibit the progression of atherosclerosis.

As a purely natural drug, quercetin has a strong anti-inflammatory effect, mainly inhibiting inflammatory factors such as interleukin (IL) - 6, IL-1β, monocyte chemotactic protein 1 (MCP-1), and vascular endothelial growth factor (VEGF) (65). Quercetin can activate caspase-3 and NFK-β factor and paraoxonase 1 gene expression (46), and inhibition of endoplasmic reticulum stress chop pathway to inhibit the development of atherosclerosis (66). In addition, quercetin can also inhibit the release of inflammatory factors in macrophages. Zhang et al. (67) found that quercetin can reduce the inflammatory factor IL-1 in a rat model of cerebral ischemia caused by IL-1β and IL-6 to alleviate the severity of cerebral ischemia. Si et al. (68) found that quercetin can regulate Nuclear Factor Kappa Beta (NF-κB) and MAPK signaling pathways inhibit the secretion of prostaglandin E2 (PGD2), cyclooxygenase-2 (COX-2), and nitric oxide (NO). It



was also found in animal models that quercetin could reduce the expression levels of matrix metalloproteinase (MMP)-1 and MMP-9 by inhibiting ERK signaling pathway, thus stabilizing atherosclerotic plaque (69, 70).

In the ApoE knockout mouse model, quercetin can significantly reduce the atherosclerotic plaque area in the hyperlipidemia group, and alleviate the oxidative stress response of various systems by blocking the activation of Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (71). In addition, quercetin can significantly increase the activity of nitric oxide synthase and the expression of HO-1 protein in endothelial cells (72). In cell and animal models of atherosclerosis induced by high fructose or lipopolysaccharide, quercetin indirectly affects PI3K/Akt pathway mainly by regulating ROS, thereby inhibiting the occurrence of inflammation and apoptosis, and ultimately reducing the degree of atherosclerosis (46). In other mouse models, exercise and quercetin can reduce the formation of atherosclerotic plaques by 78% (73), which may be related to the effect of quercetin on blood lipid (74).

3.3. Myocardial infarction

Myocardial infarction (MI) is a heart disease with high mortality and disability rates caused by the blockage of blood in

a certain part of the heart, leading to the death of myocardial tissue (75). MI can cause systemic and local inflammatory reactions in the body, increasing the release of inflammatory factors, which in turn exacerbates further damage to the myocardium. Ischemic myocardial tissue can recruit a large number of neutrophils, thereby increasing the production of ROS (12). Myocardial fibrosis and ventricular remodeling are common pathological changes in the late stages of MI (76–78). The quality of life of patients with MI has also significantly decreased. In addition to existing medication, many traditional Chinese medicine health foods are also recommended for adjuvant treatment of MI (79).

Angiotensin II (Ang II) is an important fibrogenic factor leading to myocardial fibrosis. Some studies have found that quercetin can reduce the effects of Ang II on myocardial fibrosis and hypertrophy, and reverse mouse ventricular remodeling (80, 81). In the rat model of ventricular hypertrophy, quercetin was found to be responsible for the inhibition of Silencing information regulator 1 (SIRT1)/NF- κ B pathway alleviates left ventricular hypertrophy in rats (82, 83). Lacerda et al. (84) also found that quercetin can reduce ROS production by increasing the content of endogenous antioxidants in mice, thereby reversing myocardial hypertrophy and improving cardiac function. In the rat heart failure model, quercetin was also found

to improve cardiac function by increasing the expression of NRF2 to restore reconstructed cardiomyocytes (85). The transforming growth factor (TGF) β 1 superfamily is also an important factor that causes myocardial fibrosis and apoptosis after MI. In another preclinical study on rats with MI, it was found that quercetin can inhibit the TGF β 1/Smad3 signaling pathway to eliminate ROS and enhance the myocardial antioxidant, anti-inflammatory, and anti-fibrosis capabilities, thereby reversing ventricular remodeling (86).

In addition, Janus kinase (JAK)/signal converter and transcription activating factor (STAT) signaling pathways may also be involved in the protective effect of quercetin on MI. Oral administration of 50 mg/kg quercetin in rats with acute MI can significantly increase the expression levels of IL-6, Bax, NF- κ B p65, tumor necrosis factor α (TNF- α) through the JAK/STAT signaling pathway, while reducing the expression of p-STAT1 (Ser727) (87). Li et al. (49) also found that quercetin has a protective effect on acute MI in both low and high dose groups and can significantly reduce TNF- α and IL-1 β while increasing antioxidant capacity.

Although quercetin has achieved promising results at both the cellular and animal levels, its potential benefits in preventing and managing human MI have not been well confirmed. While there have been a few small human studies exploring the effects of quercetin supplementation on heart health, the results have been inconsistent, and more well-designed clinical trials are needed to fully evaluate the potential benefits of this polyphenol. A double-blind, placebo-controlled, randomized clinical trial showed that after 8 weeks of oral treatment with 500 mg quercetin or placebo in 88 MI patients, the serum total antioxidant capacity (TAC) of the quercetin group was significantly improved, while the inflammatory factor TNF- α was also significantly reduced (12). However, there were no significant changes in IL-6, C-reactive protein (CRP), and blood pressure in both groups of patients (12). Lu et al. (88) demonstrated that onion juice containing quercetin can significantly inhibit the regulation of lipid status and antioxidant status in patients with mild hypercholesterolemia. However, some studies have shown that quercetin has no significant impact on serum TAC, TNF- α , and IL-6 levels in patients (89–91). This may be related to the varying nature of the disease. Overall, there are currently very few clinical trials of quercetin for MI. It can be seen that more carefully designed clinical trials are needed to further explore the protective effects and mechanisms of quercetin on MI (Table 2).

3.4. Ischemia/reperfusion injury

As one of the main risk factors for coronary heart disease (CHD), ischemia and reperfusion injury (I/R) can produce a large amount of ROS, leading to myocardial cell death, arrhythmia, and dysfunction (93, 94). Therefore, protecting ischemic myocardium is crucial in the treatment of CHD and angina pectoris. As a polyphenolic compound, quercetin has been proven to have protective effects on a variety of cells in I/R, such as myocardial cells, liver cells, and kidney cells (44).

However, the mechanism by which quercetin protects myocardial cells from I/R is not fully understood. Sanhueza et al. (95) found that quercetin can prevent the decrease of the xanthine dehydrogenase/xanthine oxidase ratio, thereby reducing the oxidative damage caused by I/R in myocardial cells. Chen et al. (96) found that quercetin protects cardiomyocytes by reducing Src kinase, STAT3, caspase 9, Bax, intracellular reactive oxidation products, and inflammatory factors. In a study where young rats (4 weeks) and adult rats (12 weeks) were treated with quercetin at a dose of 20 mg/kg per day for 4 weeks, the isolated hearts were subjected to ischemia for 25 min and then reperfusion for 40 min. The results showed that quercetin improved left ventricular end-diastolic pressure in young rats after ischemia but had no effect on adult rats (97). This suggests that the dose and duration of quercetin use in CVD should consider age as a factor.

Similarly, in another isolated I/R injury model, it was found that quercetin can improve myocardial injury through the high mobility group box 1 (HMGB1) pathway (98). The addition of quercetin to the myocardial ischemia-reperfusion solution of male Wistar rats significantly reduce IL-1 β , TNF- α and IL-6 level through mitochondrial adenosine triphosphate (ATP) sensitive potassium channels and NO systems (99). In an I/R model induced by coronary artery occlusion for 30 min and reperfusion for 2 h, quercetin significantly reduced the MI area, inhibited cardiomyocyte apoptosis and caspase-3 immune response, and decreased serum creatine kinase and lactate dehydrogenase levels (100). In addition, quercetin can also increase Akt phosphorylation and Bcl-2 expression through the PI3K/Akt signaling pathway, as well as reduce Bax expression (101). This result has also been further confirmed by Liu's study (101). There are also studies using quercetin (1.0 mg/kg, i.v.) to treat isolated rat heart I/R injury, and the results showed that serum TNF- α and IL-10 expression decreased significantly (102). In

TABLE 2 Preclinical studies of quercetin and MI.

Animal	Study design	Signal pathway	Outcomes	References
Rat	50 mg/kg orally for 30 days	TGF- β 1/Smad3	IL-6 and TNF- α →; ↓SOD, GSH, MDA, ROS and ANG II	(Albadrani et al.) (86)
Rat	50 mg/kg orally for 7 days	JAK2/STAT3	↓ NF- κ B, Bax, TNF- α ; ↑IL-6, p-STAT1 and p-STAT3	(Albadrani et al.) (87)
Rat	Total 100 mg/kg or 400 mg/kg gavage	/	↓TNF- α , IL-1 β , MDA, SOD and CAT	(Li et al.) (49)
Rat	5 mg/kg or 10 mg/kg i.p 10 min before reperfusion	/	↑SOD and CAT	(Annapurna et al.) (92)

ANG II, Angiotensin II; CAT, Catalase; i.p, Intraperitoneal perfusion; IL-6, Interleukin-6; IL-1 β , Interleukin-1 β ; GSH, Glutathione; JAK2/STAT3, Janus kinase signal transducers 2 and activator of transcription 3; MDA, Malondialdehyde; MI, Myocardial infarction; p-STAT, phosphorylated Signal Transducer And Activator Of Transcription; ROS, Reactive oxygen species; SOD, Superoxide dismutase; NF- κ B, Nuclear Factor Kappa Beta; TGF- β 1, Transforming growth factor β 1, TNF- α , Tumor necrosis factor α ; ↑, Increase or increase, ↓, Down or down; →, Stable or no change.

addition, quercetin in combination with amlodipine can increase cardiac function, ATP, and reduced glutathione (GSH) levels while reducing the levels of creatine kinase (CK), thiobarbituric acid reactive substances (TBARS) and total nitrate/nitrite (x) (103). Wan et al. (104) also found that quercetin can reduce the levels of Nitrogen oxide compound (NOX) and nitrous oxide system (NOS) proteins and mRNA to protect against myocardial injury in the I/R rabbit model. Brookes et al. (105) found that taking quercetin (0.033 mg/kg per day, gavage for 4 days) in rats can stabilize mitochondrial function and protect myocardial I/R.

However, in the I/R model of type 2 diabetes rats, although quercetin upregulates the expression of endothelial nitric oxide synthase (eNOS) in young rats and protein Kinase C (PKC) Epsilon in old rats, it does not activate the entire PI3K/Akt pathway (23). Therefore, it has not shown any cardiac protective effect, and even worsened the cardiac function of rats over 1 year old. It can be seen that although quercetin has shown good myocardial protection in I/R animal models, it still needs further verification in I/R animal models with other diseases such as diabetes.

Although there is sufficient evidence in preclinical studies of quercetin in the treatment of simple I/R diseases, there are still few studies actually used in clinical trials. In a study comparing quercetin and aspirin in the treatment of patients with myocardial ischemia, it was found that after 2 months of treatment with 120 mg/kg quercetin, cardiac function, hemodynamics, and symptoms of myocardial ischemia were significantly improved (106). In addition, among 55 patients with chronic ischemic heart disease with metabolic syndrome, 35 patients receiving quercetin treatment significantly reduced the incidence and duration of myocardial ischemia, reduced supraventricular extrasystole to 5%, and significantly reduced the incidence of arrhythmia (107) (Table 3).

3.5. Myocardial hypertrophy

Myocardial hypertrophy is a compensatory response to increased stress in the myocardial wall, but as pressure continues to increase, it gradually becomes decompensated, leading to heart failure. Reversing myocardial hypertrophy is an important treatment for preventing heart failure. Cardiac hypertrophy is associated with many signal pathways and gene expression, including MAPK, JAK/STAT, and Activator protein-1 (AP-1) (110, 111). Ultimately, it leads to an increase in the concentration of Ca^{2+} in myocardial cells to promote myocardial hypertrophy. Quercetin can prevent myocardial hypertrophy by reducing the oscillation frequency of Ca^{2+} in rat cardiomyocytes (112).

In rats with constricted abdominal aorta, adding 1.5 g/kg of quercetin to their diet can lower blood pressure and reduce myocardial hypertrophy (113). Both *in vivo* and *in vitro* experiments have confirmed that quercetin can inhibit Ang II induced myocardial hypertrophy by enhancing PPAR-1 expression and inhibiting AP-1 activity (110). Similarly, quercetin can also inhibit Ang II induced myocardial hypertrophy through PKC and tyrosine protein kinase (TPK) signaling pathways (114). Han et al. (115) demonstrated that quercetin can inhibit the cardiac hypertrophy by inhibiting the ERK1/2, p38 MAP kinase, Akt and GSK-3 β activities in pressure overload rats.

Hypercholesterolemia is another risk factor for hypertrophic cardiomyopathy. In Apo E knockout mice, continuous oral administration of 0.1 μ mol/kg quercetin for 6 weeks significantly reduced total cholesterol and very low-density lipoprotein (VLDL) in peripheral blood, thereby inhibiting ventricular hypertrophy (116). Quercetin can also inhibit cardiomyocyte hypertrophy and apoptosis in rats through the NOX2/GAPDH pathway (116). Although these preclinical studies confirm that quercetin can

TABLE 3 Preclinical studies of quercetin and I/R.

Animal	Study design	Signal pathway	Outcomes	References
Rat	50 mg/kg orally for 5 days	HMGB1-TLR4-NF- κ B	$\downarrow$ TNF- α , IL-6 and IL-1 β	(Dong et al.) (98)
Rat	100 ng/ml cardiac perfusion for 10 min	NO, Mitochondrial K-ATP Channels	$\downarrow$ IL-1 β , TNF- α , IL-6	(Liu et al.) (99)
Rat	40 μ mol/L for 10 days	JAK2/STAT3	$\downarrow$ Apoptosis and oxidative stress, MI area; $\uparrow$ Ventricular remodeling and biochemical indicators, recovery of cardiac blood flow	(Liu et al.) (108)
Rat	10 mg/kg <i>ip</i> 5 min before reperfusion	PI3K/Akt	$\downarrow$ MI area, cardiomyocyte apoptosis and caspase-3, CK, LDH and Bax; $\uparrow$ Akt phosphorylation and Bcl-2	(Wang et al.) (100)
Rat	20 mg/kg orally for 6 weeks	RISK, NO	$\uparrow$ eNOS in younger rats, $\uparrow$ PKC ϵ in older rats, did not activate PI3K/Akt pathway	(Ferenczyova et al.) (23)
Rat	1.0 mg/kg i.v. once total	/	$\downarrow$ TNF- α , IL-10	(Jin et al.) (102)
Rat	25 mg/kg or 50 mg/kg or 100 mg/kg by gavage for 1 weeks before operation	SIRT1/PGC-1 α	$\uparrow$ SIRT1, PGC-1 α , Bcl-2; $\downarrow$ Bax	(Tang et al.) (109)
Rat	20 mg/kg orally for 4 weeks	/	$\downarrow$ Left ventricular end-diastolic pressure	(Bartekova et al.) (97)
Rat	250 mg/kg orally for 10 days	PI3K/Akt	$\downarrow$ TNF- α , CRP, IL-1 β , Bax, $\uparrow$ Bcl-2	(Liu et al.) (101)
Rat	5 mg/kg orally for 1 week before the operation	/	$\uparrow$ Cardiac function, ATP, and GSH; $\downarrow$ CK, TBARS and nitrate/nitrite (x)	(Ahmed et al.) (103)
Rabbit	1 mg/kg i.v. 5 min before ligation, once total	NOX and NOS	$\downarrow$ NOX2, eNOS, iNOS	(Wan et al.) (104)

ATP, Adenosine triphosphate; Akt, protein kinase κ B pathway; Bcl-2, B-cell lymphoma-2; CK, Creatine kinase; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; HF, Heart failure; HMGB1, High mobility group box 1; i.v., Injected intravenously; i.p., Intraperitoneal perfusion; IL-6, Interleukin-6; IL-1 β , Interleukin-1 β ; JAK2/STAT3, Janus kinase signal transducers 2 and activator of transcription 3; LDH, Lactate dehydrogenase; MI, Myocardial infarction; MDA, Malondialdehyde; NF- κ B, Nuclear Factor Kappa Beta; NO, Nitric oxide; NOS, nitrous oxide system; NOX, Nitrogen oxide compound; PI3K, Phosphatidylinositol-3-kinase; PGC-1 α , Peroxisome proliferator-activated receptor- γ Coactivator - 1 α ; PKC ϵ , Protein Kinase C Epsilon; iNOS, inducible nitric oxide synthase; SIRT1, Silencing information regulator 1; TBARS, Thiobarbituric acid reactive substances; TLR4, Toll like receptor 4; TNF- α , Tumor necrosis factor α ; VLDL, Very low-density lipoprotein; $\uparrow$, Increase or increase, $\downarrow$, Down or down; $\rightarrow$, Stable or no change.

inhibit the development of ventricular hypertrophy, unfortunately, there are currently no relevant clinical trials to confirm its role in patients with ventricular hypertrophy. We hope there will be real event studies on the prevention and treatment of myocardial hypertrophy diseases with quercetin in the future (Table 4).

3.6. Hypertension

With the acceleration of the global population aging, the prevalence of hypertension in developing countries is also increasing year by year, and most of them are hypertension of unknown etiology (118). Hypertension is a chronic disease associated with endothelial dysfunction, smooth muscle cell contraction, and hyperlipidemia. Over time, hypertension can lead to various complications such as heart failure, myocardial hypertrophy, stroke, and CHD (119). Although there are many clinical options for antihypertensive drugs, some patients still have poor antihypertensive effects, and even develop refractory hypertension. Therefore, drug update and development in the treatment of hypertension is particularly important. In recent years, studies have found that quercetin has a unique pharmacological activity in reducing blood pressure.

Kim et al. (120) found that quercetin can inhibit the contraction of vascular smooth muscle through AMPK signaling pathway, thereby playing a role in reducing blood pressure. Lin et al. (121) have found that quercetin has a hypotensive effect by promoting autophagy of endothelial cells. Pereira et al. (122) found that quercetin can improve vascular remodeling and endothelial oxidative stress, thereby reducing systolic blood pressure. In a rat model of hypertension induced by renin angiotensin aldosterone (RAAS), quercetin can reduce blood pressure by increasing urine and promoting sodium excretion (123). In spontaneously hypertensive rats, continuous oral administration of quercetin (10 mg/kg) for 5 weeks significantly reduced blood pressure and malondialdehyde levels, and increased glutathione peroxidase activity (124, 125). In addition, quercetin also has a hypotensive effect in pregnancy induced hypertension, which may be related to the regulation of endothelin 1 (ET-1) and endothelin 1A receptor (ETAR) (126).

In the treatment of hypertension, quercetin can reduce hypertension induced aortic remodeling, oxidative stress, and MMP-2 activity (122). Quercetin can also reduce systolic and

diastolic blood pressure in rats by reducing oxidative stress and NF- κ B (127, 128). In a sodium fluoride induced hypertension model, quercetin can reduce blood pressure in rats by regulating the hsp70/ERK/PPAR pathway (129). Quercetin can reduce the activity of NADPH oxidase and vascular superoxide in hypertensive rat models, thereby improving vascular endothelial function and lowering blood pressure (13, 14). Even in sodium chloride induced hypertension, quercetin is superior to nifedipine in improving hemodynamics, redox, and metabolic imbalances (15).

In a clinical study of quercetin in the treatment of grade 2 hypertension, it was found that quercetin can significantly reduce the levels of nitric oxide, CRP, IL-1, and lipid profile in patients' peripheral blood (16). Adding quercetin to the treatment regimen for patients with hypertension and gout can improve left ventricular diastolic function, purine metabolism, and lower blood pressure (17). However, in a randomized, double-blind, controlled, crossover dietary study, adding 162 mg of quercetin to the diet per day did not improve blood pressure in hypertensive patients (18). In addition, in 93 overweight or obese individuals, quercetin reduced blood pressure in overweight subjects, but had no effect on TNF- α and C-reactive protein (19). Although quercetin can reduce systolic blood pressure in patients, it has no significant effects on other cardiovascular risk factors such as cholesterol, low density lipoprotein cholesterol (LDL-C), triglycerides, TNF- α and IL-6 (20). But the results of another randomized clinical trial were exactly the opposite. The waist circumference, triacylglycerol and postprandial systolic blood pressure of healthy men with apolipoprotein E (APOE) genotype significantly decreased after oral administration of quercetin, while the level of TNF- α and high-density lipoprotein cholesterol (HDL-C) significantly increased (21).

Another randomized, double-blind, crossover clinical study found that 41 hypertensive patients had a significant decrease in blood pressure after 28 days of continuous administration of 730 mg quercetin, while the measured oxidative stress index in plasma and urine remained unchanged, which was contrary to previous animal experimental studies (22). Similarly, another study also found that although quercetin can reduce blood pressure, it has nothing to do with angiotensin converting enzyme (ACE) activity and ET-1 (130). Therefore, the mechanism of quercetin in reducing hypertension still needs further in-depth research and exploration (Table 5).

TABLE 4 Preclinical studies of quercetin and myocardial hypertrophy.

Animal	Study design	Signal pathway	Outcomes	References
Rat	5 mg/kg or 10 mg/kg or 20 mg/kg orally for 8 weeks	GSK-3 Pathway	↓AKT, LKB1/AMPK α , ERK, histone H3, β -catenin, and GATA4	(Chen et al.) (117)
Rat	5 mg/kg or 10 mg/kg by gavage for 12 weeks	PPAR- γ and AP-1	↓Cardiac hypertrophy	(Yan et al.) (110)
Rat	In the drinking water at 5 mg or 10 mg/head for 3 weeks	ERK1/2, p38 MAP kinase, Akt and GSK-3 β	↓Cardiac hypertrophy	(Han et al.) (115)
Rat	120 mg/kg i.v. for 5 days	Myocardial [Ca $^{2+}$] i-oscillation	↓Heart rate, hypertrophy	(Wang et al.) (112)
Rat	0.1 μ mol/kg oral for 6 weeks	/	↓Cholesterol and VLDL	(Ulasova et al.) (116)
Rat	5 mg/kg by gavage for 3 weeks	Nox2/GAPDH	↓NADPH oxidase gene, myocardial hypertrophy and apoptosis	(Mao et al.) (116)

Akt, Serine/threonine kinase; AMPK α , Adenosine monophosphate activated protein kinase α ; AP-1, Activator protein-1; ERK, Extracellular regulated protein kinases; GAPDH, Glyceraldehyde-3-phosphate dehydrogenase; GSK-3, Hepatocyte Synthesis Kinase 3; i.v., Injected intravenously; PPAR- γ , Peroxisome proliferator-activated receptor γ ; LKB1, Liver kinase B1; MAP, Mitogen-activated protein; NADPH, Nicotinamide adenine dinucleotide phosphate; NOX, Nitrogen oxide compound; VLDL, Very low-density lipoprotein; ↑, Increase or increase, ↓, Down or down; →, Stable or no change.

TABLE 5 Preclinical studies of quercetin and hypertension.

Animal	Study design	Signal pathway	Outcomes	References
Rat	10 mg/kg orally for 6 weeks	Endothelial autophagy	↓BP	(Lin et al.) (121)
Rat	10 mg/kg i.p. for 4 weeks	RAAS	↓BP	(Mackraj et al.) (123)
Rat	10 mg/kg orally for 5 weeks	/	↓BP and malondialdehyde; ↑glutathione peroxidase activity	(Duarte et al.) (124, 125)
Rat	10 mg/kg or 20 mg/kg or 50 mg/kg by gavage for 5 days	ET-1, sFlt-1	↓BP	(Sun et al.) (126)
Rat	10 mg/kg by gavage for 3 weeks	Oxidative stress	↓Vascular remodeling, oxidative stress and MMP-2 activity	(Pereira et al.) (122)
Rat	10 mg/kg by gavage for 2 weeks	NF-κB	↓Systolic and diastolic BP	(Ajibade et al.) (127)
Rat	50 mg/kg or 100 mg/kg by gavage for 1 week	HSP 70/ERK/PPARγ	↓BP	(Oyagbemi et al.) (129)
Rat	50 mg/kg by gavage for 3 weeks	Nitrite and nitroso	↓NADPH oxidase activity and vascular superoxide production	(Montenegro et al.) (13)
Rat	10 mg/kg orally by 13 weeks	↓NADPH oxidase, ↑eNOS activity	↓BP	(Sánchez et al.) (14)

BP, Blood pressure; eNOS, endothelial nitric oxide synthase; ET-1, Endothelin-1; ERK, Extracellular regulated protein kinases; HSP, Heat Shock Protein; i.p., Intraperitoneal perfusion; MMP-2, Matrix metalloproteinase; NF-κB, Nuclear Factor Kappa Beta; PPAR-γ, Peroxisome proliferator-activated receptor γ; RAAS, Renin-angiotensin-aldosterone; sFlt-1, Soluble fms-like tyrosine kinase-1; ↑, Increase or increase, ↓, Down or down; →, Stable or no change.

3.7. Heart failure

Heart failure (HF) is one of the serious CVD in clinical practice, and the main therapeutic drugs are β Receptor blockers, angiotensin converting enzyme inhibitors, or Ang II receptor antagonists. HF is closely related to cardiac hypertrophy and oxidative stress caused by ROS. Many studies have confirmed that quercetin, a ROS scavenger, can improve redox balance and mitochondrial homeostasis by blocking H₂O₂ and reversing mitochondrial Mn SOD activity, thereby reducing myocardial hypertrophy (84). Tan et al. (131) analyzed the network pharmacology system and found that quercetin may further improve the pathophysiological changes of HF by regulating the AKT1-eNOS-MMP9 pathway to resist apoptosis. In an *in vitro* experiment of cisplatin induced cardiac toxicity, it was found that H9c2 cardiomyocytes treated with 40 μM quercetin significantly decreased their myocardial cytotoxicity, which may be related to the Nrf2/HO-1 and P38MAKP/NF-κBp65/IL-8 signal pathway (132). Furthermore, quercetin can prevent myocardial hypertrophy through proteasome GSK-3 Pathway, which may be related to upstream liver kinase B1/AMP activated protein kinase (LKB1/AMPK α), protein kinase B and downstream hypertrophy factors such as extracellularly ERK, histone H3, β-Catenin, and GATA binding protein 4 (GATA4) (133). In a mouse model of HF, quercetin promotes the de succinylation of isocitrate dehydrogenase (IDH2) through SIRT5, maintains mitochondrial homeostasis, and improves myocardial

fibrosis, thereby reducing the incidence of HF (134). Although there are currently no human experimental studies on the correlation between quercetin and HF, we believe there will be breakthroughs in the near future (Table 6).

3.8. Arrhythmia

Arrhythmias are a common disease with complex etiology in clinical practice. The inducing factors include changes in myocardial tissue, conduction bundle, intense exercise, drug stimulation, electrolyte disorders, and so on (139). Arrhythmias have seriously affected the quality of life of the people. Currently, the main methods for treating arrhythmia include radiofrequency ablation, artificial pacemakers, and drug therapy (140). However, the current treatment of arrhythmia drugs and therapeutic efficacy are very limited. As one of the drugs that can effectively prevent and treat CVD, quercetin also has an important therapeutic effect on arrhythmia.

Quercetin (25 mg/kg) can be passed through TGF-β/Smads pathway inhibits myocardial fibrosis, thereby achieving the effect of treating arrhythmia (135). Quercetin can inhibit myocardial fibrosis and improve atrial fibrillation by regulating the expression of miR-223-3p/ Fork head Box Protein O3 (FOXO3) and activating autophagy (136) (Table 6). Pretreatment with quercetin 2 min before reperfusion arrhythmia can inhibit platelet aggregation and thromboxane A2 (TXA2) formation,

TABLE 6 Preclinical study of quercetin and HF, AF, CHD and hyperlipidemia.

Animal	Diseases	Study design	Signal pathway	Outcomes	References
Rat	HF	50 mg/kg i.p. for 4 weeks	SIRT5	↑IDH2, ↓HF	(Chang et al.) (134)
Rat	AF	25 mg/kg by gavage for 3 weeks	TGF-β/Smads pathway	↓miR-135b, ↓AF	(Wang et al.) (135)
Rat	AF	25 mg/kg by gavage for 3 weeks	miR-223-3p/FOXO3	↑Autophagy	(Hu et al.) (136)
Rat	CHD	50 mg/kg or 100 mg/kg or 200 mg/kg/times i.v. or i.p., 3 times/week for 2 weeks	HMG-CoA	↓HMG-CoA	(Khamis et al.) (137)
Rat	Hyperlipidemia	4.0 g/kg supplement diet orally for 5 weeks	CYP7A1	Promote cholesterol-to-bile acid conversion	(Zhang et al.) (138)

AF, Atrial fibrillation; CHD, Coronary heart disease; CYP7A1, Cytochrome P450 7A1 protein; FOXO3, Fork head Box Protein O3; HF, Heart failure; HMG-CoA, 3-hydroxy-3-methyl glutaryl coenzyme A reductase; IDH, isocitrate dehydrogenase; i.p., Intraperitoneal perfusion; i.v., Injected intravenously; RISK, Reperfusion injury salvage kinases; SIRT5, Sirtuin 5; SOD, Superoxide dismutase; TGF, Transforming growth factor; ↑, Increase or increase, ↓, Down or down; →, Stable or no change.

thereby achieving the effect of preventing arrhythmia (141). As a commonly used antineoplastic drug, doxorubicin mainly increases cardiac toxicity by increasing LDH, iNOS, and NO. In the doxorubicin induced myocardial injury model, quercetin can significantly reduce the incidence of arrhythmia by increasing SOD activity, inhibiting iNOS and myocardial cell apoptosis (142). In addition, in the rat cardiomyopathy model, it was found that adding quercetin to drinking water can prevent the occurrence of lipid peroxidation in serum, thereby reducing arrhythmia (143). It can be seen that quercetin has sufficient experimental evidence in the treatment and prevention of arrhythmia, and the road from laboratory to clinical is not far away.

3.9. Antiplatelet

Antiplatelet therapy, an essential tool in the arsenal against myocardial infarction (MI) or heart attack, remains a critical component of modern cardiovascular medicine (144). Antiplatelet agents act as vital prophylactic and therapeutic measures by preventing the aggregation of platelets, crucial elements in clot formation and arterial blockage (145). Antiplatelet therapy encompasses a range of medications, such as aspirin, P2Y₁₂ inhibitors and glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, which have demonstrated their effectiveness in reducing MI and thrombotic complications risk (146). Furthermore, the potential of traditional Chinese medicine as an adjuvant treatment for MI is an emerging area of interest, with numerous studies investigating the therapeutic effects of various compounds and herbal formulations (147). By combining conventional antiplatelet therapies with alternative treatments, to ultimately reduce the global burden of MI and improve patient outcomes.

In vitro studies have shown that quercetin can inhibit platelet aggregation by several mechanisms. Firstly, it can effectively inhibit platelet activators adenosine diphosphate (ADP) and TXA₂, thereby reducing the release of platelet particles (148). Second, it can inhibit the activation of platelet integrins, such as GPIIb/IIIa, which are essential for platelet aggregation (149). Third, it can interfere with the signaling pathways involved in platelet activation, such as the PI3K/Akt and MAPK pathways (150, 151). In addition, quercetin can also reduce platelet aggregation and thrombosis by inhibiting the PI3K/Akt and MAPK pathways (152).

Zaragoza et al. (153) found that quercetin has significant antiplatelet effects and a higher degree of COX enzyme inhibition. Perez et al. (154) investigated quercetin's vasodilatory, antiplatelet, and antiproliferative effects in hypertensive models. In a double-blind trial with 15 healthy volunteers, oral quercetin administration led to dose-dependent increases in quercetin-3-O-glucuronide (Q3GA) levels. No blood pressure changes were observed, but quercetin-induced brachial artery diameter increases were found to correlate with Q3GA levels and plasma glucuronidase activity. The study highlights quercetin's acute vasodilatory effects in individuals with normal blood pressure and cholesterol levels, consistent with Q3GA metabolite deconjugation.

In conclusion, quercetin has been shown to have antiplatelet effects *in vitro* and *in vivo*, by inhibiting platelet aggregation and thrombus formation through various mechanisms, including the inhibition of platelet granule release, integrin activation, and signaling pathways involved in platelet activation. These effects suggest that quercetin may have potential as a natural supplement to complement antiplatelet therapy and reduce the risk of adverse side effects associated with these medications. However, more clinical trials are needed to confirm these findings in humans and to determine the optimal dose and duration of quercetin supplementation. Further research is also needed to investigate the potential interactions between quercetin and antiplatelet medications, as well as the long-term effects of quercetin supplementation on cardiovascular outcomes.

3.10. CHD

CHD result from the narrowing or blockage of the coronary arteries responsible for supplying oxygen and nutrients to the heart muscle. This narrowing or blockage is primarily caused by the accumulation of plaque, consisting of cholesterol, fatty substances, and cellular waste products, within the arterial walls (155). CHD can lead to various complications such as complication is angina, characterized by chest pain or discomfort due to inadequate blood flow to the heart muscle. In more severe cases, CHD can result in myocardial infarction, heart failure, or even sudden cardiac death (156). The pathophysiology of CHD involves a complex interplay of processes, such as endothelial dysfunction, inflammation, and oxidative stress (157). Treatment for CHD typically involves a combination of lifestyle modifications, pharmacological interventions, and, in some cases, surgical procedures. Additionally, the role of specific micronutrients and functional foods, such as omega-3 fatty acids, antioxidants, and plant-based compounds, is being investigated for their potential cardioprotective properties (158–160).

Quercetin can inhibit the formation of CHD by attenuating oxidative stress and reducing the expression of adhesion molecules. It also can promote the vitality, migration, and angiogenesis of human microvascular endothelial cells by downregulating the expression of intercellular cell adhesion molecule-1 and Vascular cell adhesion molecule-1, and inhibit cell apoptosis (161). Abnormal lipid metabolism is one of the important risk factors for coronary heart disease. Quercetin can also regulate lipid metabolism by regulating the expression of key enzymes involved in cholesterol synthesis, such as 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA) reductase, and is a new candidate drug for future development of cholesterol lowering drugs (137).

Although some studies have shown that quercetin has no impact on cardiovascular or thrombotic risk factors in healthy patients (162). However, other studies have found that treatment with 120 mg/day of quercetin can improve the ejection fraction of 88 CHD patients and reduce the frequency of ST segment changes and ventricular premature beats (106). However, more research is needed to confirm the optimal dosage and duration of quercetin. Furthermore, it is currently unclear whether there is

a potential interaction between quercetin and existing cardiovascular drugs (Table 6).

3.11. Hyperlipidemia

Persistent hyperlipidemia can cause the recruitment of inflammatory cells and the production of ROS by damaging the vascular endothelial function, thus leading to a series of cardiovascular and cerebrovascular events such as atherosclerosis, arterial stenosis, thrombosis and stroke (157, 163–165). Although lipid-lowering therapy is the main treatment for hyperlipidemia, these drugs can also cause side effects and are not sufficient to completely lower blood lipids (21, 166). Therefore, people are increasingly interested in alternative and complementary therapies for hyperlipidemia, including the use of traditional Chinese medicine and functional foods (167).

Zhang et al. (138) randomly divided 20 male Wistar rats into a control group and a quercetin supplementation group, and found that quercetin supplementation significantly increased the activity of hepatic cholesterol 7 α -hydroxylase and the expression of ATP binding cassette transporter G1 mRNA and protein in the liver. Furthermore, it has been proven that quercetin can promote cholesterol efflux and promote the conversion of cholesterol into bile acids, thereby regulating liver cholesterol metabolism through these pathways.

Quercetin can also reduce the oxidation of low-density lipoprotein, thereby reducing the risk of developing hyperlipidemia (168). Janisch et al. (169) found that LDL oxidation lag time was increased by up to four times by low (<2 μ M) concentrations of quercetin-3-glucuronide. Gnoni et al. (170) found that the formation of palmitic acid in rat hepatocytes treated with quercetin was significantly reduced after 30 min, indicating that quercetin has an inhibitory effect on fatty acid synthesis. The decrease in *de novo* synthesis of fatty acids and triacylglycerol (TAG) induced by quercetin, subsequently leading to a reduction in the formation of VLDL, may represent a potential mechanism underlying quercetin's ability to lower triacylglycerol levels.

Despite promising results *in vitro* and *in vivo* studies, there are relatively few clinical trials of quercetin for the prevention or treatment of human hyperlipidemia. A meta-analysis of five randomized controlled trials showed that quercetin did not significantly affect plasma LDL-C, HDL-C, and triglycerides (171). During subgroup analysis, it was also found that only plasma triglyceride levels were significantly correlated with the dosage and supplementation time of quercetin. Overall, the impact of quercetin on blood lipid levels is still uncertain, and its lipid-lowering effect may depend on the dosage and duration of supplementation.

4. Conclusion and outlook

Flavonoids are the main bioactive components of quercetin, which have multiple functions such as antioxidant, anti-inflammatory, myocardial protection, lipid lowering, blood pressure lowering, and improvement of myocardial ischemia and

arrhythmia. However, the current research results on the mechanism and target of quercetin in the treatment of CVD are not uniform. The complex pharmacological actions and targets limit the application of quercetin in clinical patients. In addition, quercetin has the disadvantages of poor water solubility and low bioavailability. In order to further increase the pharmacological effects of quercetin, many structural modifications have been made to quercetin, mainly including the modification of hydroxyl groups to generate ethers and esters, the modification of carbonyl groups to generate carbonyl oxygen substituted products, and the modification of quercetin A and B rings. Quercetin derivatives with good solubility, high bioavailability, and significant biological activity were obtained through optimized modification (24, 172). Preparation of new dosage forms can also increase the pharmacological effects of quercetin, such as micro lotion, liposome encapsulation and nanocrystals.

In addition, the potential toxic side effects of quercetin may also be one of the reasons limiting its clinical application. However, in fact, among numerous published human intervention studies, the adverse reactions after supplementation with quercetin have been rarely reported, and even the reported adverse reactions are very mild (3). Although there are very few studies showing that prolonged and high-dose supplementation of quercetin can increase the risk of nephrotoxicity, it has not been found in human intervention experiments that quercetin increases nephrotoxicity in subjects with metabolic syndrome characteristics (19). Overall, oral administration of quercetin in humans appears to be well tolerated, with only a very low incidence of adverse reactions observed so far. However, this does not necessarily mean that quercetin has no toxic side effects, and more research is needed to confirm this.

Although researchers have made significant contributions to improving the bioavailability of quercetin. Many *in vitro* and *in vivo* studies have shown that quercetin has the effect of treating and preventing CVD, but there are still few clinical trials of quercetin in CVD, especially heart failure, myocardial infarction, ischemia reperfusion, myocardial hypertrophy, myocarditis, and other diseases. Even the doses and research results of quercetin used in clinical patients are uneven. In addition, it is not entirely clear which components of quercetin have practical applications, so it is necessary to further explore the monomer of traditional Chinese medicine. It can be seen that quercetin still needs a long way to be truly used in the treatment of patients with CVD. Firstly, it is necessary to focus on how to further improve the water solubility and oral bioavailability of quercetin. Secondly, the efficacy, mechanism of action, and unified application standards of quercetin in combination with other drugs. Finally, multicenter, large sample randomized controlled clinical trials are needed to further evaluate the safety and effectiveness of quercetin in CVD.

Author contributions

MD and YR conceived the topic and carried out manuscript editing. FY, WZ, and YZ drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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