Plant Foods for Human Nutrition (2020) 75:307–315
https://doi.org/10.1007/s11130-020-00832-0

REVIEW ARTICLE

Molecular and Biological Functions of Quercetin as a Natural Solution for Cardiovascular Disease Prevention and Treatment

Liaosadat Mirsafaei[1] · Željko Reiner[2] · Rana Shafabakhsh[3] · Zatollah Asemi[3]

Published online: 25 June 2020

Abstract

Cardiovascular disease (CVD) is a worldwide health problem with growing up rates of mortality and morbidity. Many risk factors, including high blood pressure, cigarette smoking, diabetes, obesity, and dyslipidemia are responsible for CVD. CVD can be prevented by some simple and cost-effective steps such as smoking cessation, normalizing body weight, regular physical activity, and dietary changes, including decreasing saturated fats, increasing the intake of vegetables and fruits, and reducing sugar intake. In the last decades, growing up number of studies were performed to explain the possible function of non-nutrient substances from the diet which might prevent CVD. One of these natural compounds is quercetin which is widely present in vegetables, tea, fruits and wine. Many *in vitro, in vivo* and clinical studies have indicated the cardioprotective functions of quercetin. They can be explained by quercetin's reducing blood pressure, antioxidant potential and some other activities. This review evaluates the experimental and clinical studies that have studied the effect of quercetin in CVD and summarizes the molecular mechanisms of action as well as clinical effects of quercetin in CVD.

Keywords Cardiovascular disease · Quercetin · Signaling pathway · Inflammatory markers · Metabolic profiles

Abbreviations

CVD	Cardiovascular disease
WHO	World Health Organization
ROS	Reactive oxygen species
IL-1	Interleukin-1
IFN-γ	Interferon-γ
TNF-α	Tumor necrosis factor-α
TNF-β	Tumor necrosis factor-β
MCP-1	monocyte chemoattractant protein-1
IL-8	Interleukin-8
VCAM-1	Vascular cell adhesion molecule-1
PDGF	Platelet-derived growth factor
TGF-β	Transforming growth factor-β
SMC	Smooth muscle cell
CRP	C-reactive protein
NO	Nitric oxide
SOD	Superoxide dismutase
CAT	Catalase
MI	Myocardial infarction
MDA	Malondialdehyde
PC	Protein carbonyl
Nox	Nitrite and nitrate
iNOS	Inducible nitric oxide synthase
GSH	Glutathione
GSSG	Oxidized glutathione
TLRs	Toll-like receptors

✉ Rana Shafabakhsh
r.shafabakhsh@gmail.com

✉ Zatollah Asemi
asemi_r@yahoo.com

Liaosadat Mirsafaei
Liaosadat.mirsafaei@gmail.com

Željko Reiner
zeljko.reiner@kbc-zagreb.hr

[1] Department of Cardiology, Ramsar Campus, Mazandaran University of Medical Sciences, Sari, Iran

[2] Department of Internal Medicine, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia

[3] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, IR, Iran

Introduction

Atherosclerotic cardiovascular disease (CVD) is the principal cause of mortality and morbidity worldwide [1, 2]. Over 80% of all CVD-related death happens in developing countries [3].

The World Health Organization states that about 75% of CVD mortality may be prevented by preventing strategies [4]. During the past decades, different advances in the prevention and medication of CVD have decreased death rates of CVD by 50% [5]. Simple and cost-effective steps such as smoking cessation, achieving healthy body weight, regular physical activity, and dietary changes, including decreasing the consumption of saturated fats, increasing the intake of vegetables and fruits, and reducing sugar intake may prevent CVD development [6]. Several factors are important in atherosclerotic CVD pathogenesis. Atherosclerosis is a heterogeneous disease in which risk factors such as dyslipidemia, arterial high blood pressure, smoking, diabetes, chronic inflammation, and obesity play the key roles [7, 8].

Recently, patient's demand for non-pharmacological options became a reality. Therefore, it is necessary for physicians to be aquainted with the safety and effectiveness of these options [9, 10]. In the last decades, more and more studies have been published concerning the function of non-nutrient substances in the diet which might have some effects on preventing CVD [11]. Some of these natural compounds are flavonoids which exist in fruits and vegetables as well as some beverages and supplementations. Quercetin is a well-known flavonoid which is one of the most famous dietary antioxidants. It is widely present in vegetables, tea, fruits and wine [12]. The name is derived from *quercetum* (oak forest), after *Quercus* [13]. Chemical structure of quercetin is an unconjugated aglycone that does not have a carbohydrate moiety [13]. A quercetin glycoside is constructed by binding a glycosyl group (mostly glucose, rhamnose, or rutinose) as a substitutive for one of the OH groups [13]. Taken strictly, the term quercetin should be applied to the aglycone only [13, 14]. Both types of molecules are easily bioavailable but the glycoside form causes better bioavailability than its aglycone type [13–15]. All derivatives of quercetin are absorbed in the upper segment of small intestine [16, 17]. In the plasma, quercetin is transported to the liver by albumin [18, 19]. In the liver, it is transformed to its metabolites, including isorhamnetin, tamarixetin and kaempferol. The half-lives of quercetin and its metabolites are 11 to 28 h suggesting considerable plasma concentrations of quercetin after its consumption [20]. A large number of studies have been carried out to elucidate the mechanism of action and toxicological properties of quercetin. Evidence from experimental and clinical studies has suggested the cardiovascular protective effects of quercetin. It has been documented that quercetin might have effects on CVD by reducing blood pressure, by its antioxidant, interference with the renin-angiotensin-aldosterone system, and/or improving vascular function in an endothelium-dependent [11].

Pathogenesis of Atherosclerosis and CVD: Mechanisms

The development of the levels of atherosclerosis from an early fatty streak lesion to a highly hazardous rupture-prone plaque is due to the many molecular and cellular events at each level. One of the important processes involved in atherogenesis is endothelial dysfunction and oxidative stress which leads to reactive oxygen species (ROS) generation, including superoxide anion, lipid peroxides, hydrogen peroxide and peroxynitrite. Antioxidants in diet and enzymes like glutathione peroxidase inactivate ROS and therefore low concentrations of these enzymes act as pro-atherosclerotic factors [21]. High amounts of oxidative stress which is mediated by several factors, including abnormal salt control of kidney, elevated levels of angiotensin II, and smoking also occur in hypertension [22].

In the subendothelial space, elevated levels of ROS cause the oxidation of LDL particles which is one of the first steps towards atherosclerosis [23]. Monocytes enter the subendothelial space and get transformed into macrophages oxidized LDL particles rich in cholesterol and transform into foam cells. This process is accompanied by a low-grade chronic inflammation. Many cytokines, including interleukin-1 (IL-1), interferon-γ (IFN-γ), tumor necrosis factor-β (TNF-β) and angiotensin II as well as several chemokine's containing monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), CXC cytokines and eotaxin elevate adhesion molecules expression such as vascular cell adhesion molecule-1 (VCAM-1), P- and E-selectin and thereby attract inflammatory and immune cells, including monocytes, T and B lymphocytes, leukocytes and mast cells from the blood flow [24].

Leukocytes attached to the adhesion molecules enter the subendothelial space. Growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β) induce smooth muscle cell (SMC) to migrate from intima to media, to proliferate and secrete collagen leading to fatty-fibrous lesion or atherosclerotic plaque. These lesions develop by remodeling and neo-vascularisation which can cause CVD events. The stable plaques have a thick fibrous cap with a smaller lipid core and have low concentrations of inflammatory cells and cytokines. Lipid-lowering therapy can conquer such plaques [25]. The unstable plaques have a thinner fibrous cap, more lipids in the core and a higher content of inflammatory cells and are prone to extreme inflammation. Lipid-lowering therapy can transform such plaques into stable lesions [25]. Also several pro-apoptotic cytokines including TNF-β, matrix metalloproteinases, which digest collagen molecules, and IFN-γ, which suppress collagen secretion, are produced by inflammatory cells. The accumulation of cholesterol from LDL particles induces apoptosis in macrophages which is prone to develop atherosclerosis by cholesterol transfer to

endoplasmic reticulum membranes and signaling cholesterol-induced apoptosis [26]. Rupture of the plaques occurs often without any symptoms. In such situation, the thrombus which is formed on the place of rupture is absorbed into the plaques. PDGF and TGF-β stimulate the growth of the plaques which together induce SMC proliferation and the formation of a dense collagen matrix thus thickening the cap of the plaque. On the other hand, new micro-vessels within the plaque are prone to break which results in intra-plaque hemorrhage contributing to plaque instability [27].

Risk Factors of CVD and their Molecular Mechanisms

Multiple studies suggested that hypertension leads to atherosclerosis by several synergistic processes which involve oxidative stress and inflammation in the arterial wall [28, 29]. Many environmental and genetic factors may modulate the effect of hypertension on CVD. It has been confirmed that blood pressure lowering strategies are effective in delaying the formation of atherosclerosis lesions and CVD [30]. Smoking is another factor which is the major cause of CVD [31]. Contents of cigarette such as nicotine and carbon monoxide impair the structure of the arteries; stimulate developing of the atherosclerotic plaques, and elevate concentrations of circulating non-esterified fatty acids which increase inflammatory response. Smoking generates ROS leading to oxidative stress and increased levels of oxidized LDL that promotes atherosclerosis. Advanced CVD is often more found in patients with diabetes in comparison with patients without diabetes and diabetes is accepted as an important risk factor for CVD [32]. Multiple mechanisms in diabetes are responsible for this such as oxidative stress, abnormal vessels reactivity, renal dysfunction, which all participate in atherogenesis and increase the risk of CVD [33]. Another important risk factor CVD is obesity. Obesity is one of the most principal components of the metabolic syndrome which also promotes atherosclerosis [34]. Multiple molecules activated in obesity influence oxidative stress and inflammation and therefore CVD. IL-6 which is produced in adipocytes is increased by increased number of adipocytes. Increased concentrations of IL-6 induce C-reactive protein (CRP) production in the liver which decreases the levels of nitric oxide (NO) leading to vasoconstriction, increased vascular resistance and finally endothelial dysfunction [35]. Dyslipidemia, and particularly elevated LDL-C levels, has also a key role in CVD. One of the primary causes of damage to the artery wall is elevated LDL-C in the blood [36]. Higher levels of LDL-C lead to adhesion of leukocytes to the endothelium and the production of foam cells. Foods rich in saturated fats and *trans*-fatty acids and abnormal LDL receptors are the most often causes of hypercholesterolemia and therefore of atherosclerosis [37]. There are several markers for CVD, including CRP, CD40 ligand, and troponin. CRP is one of the principal markers of inflammation and atherosclerosis which is independent of other markers [38]. It is formed in the liver by induction of cytokines such as IL-6. CRP is present in lesions where binds to oxidized LDL and acts as a chemo-attractant by increasing the expression of adhesion molecules. During myocardial injury, the cytoplasm of cardiomyocytes release myofilament troponin. Acute coronary syndrome especially microinfarction can be recognized by elevated cardiac troponin [39]. Soluble CD40 ligand is another predictive marker of acute coronary syndromes. The expression of soluble CD40 is found in leukocytes, smooth muscle cells, endothelial cells and activated platelets. Increased levels of soluble CD40 ligand shows the activation of platelet and thereby elevated risk of cardiovascular events [40, 41].

Quercetin and CVD

Antioxidant Effects of Quercetin in CVD

As already mentioned, oxidative stress is one of the main processes in atherogenesis and CDV. Quercetin has the most potent antioxidant properties compared with curcumin. Presence of the hydroxyl (-OH) replacements and the catechol-type B-ring in the structure of quercetin provides its potent antioxidant features [42, 43]. A large number of studies have suggested that quercetin is able to reduce oxidative injury in several tissues including brain, liver, aorta, kidney, and cardiac muscle tissue [44]. Quercetin increases the cellular antioxidant function via the Nrf2 pathway [45]. Quercetin can also enhance the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT). Quercetin has anti-diabetic effects as well as protects tissues such as heart to oxidative injury induced by diabetes [46]. Hertog et al. [47] observed reduced both total and LDL-C levels when plasma levels of quercetin are elevated. Another study showed that consumption of quercetin-rich foods decreased the mortality related to coronary heart disease [48]. An experimental study reported that pretreatment with quercetin decreased the serum creatine kinase activity, lactate dehydrogenase, heart mitochondrial lipid peroxidation products and increased mitochondrial antioxidants. Moreover, quercetin improves activities of the enzymes involved in tricarboxylic acid cycle and respiratory chain in rats with myocardial infarction (MI) [49]. Chiş et al. [50] analyzed the effect of quercetin on the cardiac hypoxia-induced oxidative stress biomarkers, including malondialdehyde (MDA), protein carbonyl (PC) content, nitrite and nitrate (NOx) generation, inducible nitric oxide synthase (iNOS) expression and antioxidant enzymes, including SOD, and CAT in rats exposed to intermittent hypobaric hypoxia. The results showed that in heart tissue of these rats

MDA, PC, NOx, and iNOS expression decreased and the activity of SOD and CAT increased as a result of quercetin administration. This study indicated that increased hypoxia-induced oxidative stress in heart tissue could be ameliorated by quercetin. Another study suggested a cardioprotective effect of quercetin in rats with cadmium induced oxidative cardiotoxicity and dyslipidemia in rats by increasing several antioxidant enzymes including SOD, CAT, and gluthation peroxidase [51].

Quercetin reduced cardiac diastolic dysfunction and cardiac cholesterol accumulation in diabetic rats with hypercholesterolemia. It also decreased lipid peroxidation and PC content and prevented alterations in peroxisome proliferator-activated receptor gamma expression, decreased cardiac oxidative stress via increasing the glutathione (GSH)/oxidized glutathione (GSSG) ratio, the nuclear translocation of Nrf2 and the activity of antioxidant enzymes [52]. An experimental study evaluated the effects of quercetin on trauma-induced secondary cardiac damage. Quercetin pretreatment potentially enhanced post-traumatic cardiomyocyte apoptosis and cardiac dysfunction. Additionally, quercetin caused increased cell viability and decreased TNF-α levels, and it reduced ROS and Ca^2+ in myoblastic cells. Thus, quercetin may reverse post-traumatic cardiac dysfunction by decreasing oxidative stress, inflammation and apoptosis [53]. Oyagbemi et al. [54] reported that quercetin in rats with hypertension decreased blood pressure by improving antioxidant defense system. In rat models, hypertension and oxidative stress were induced by deoxycorticosterone acetate-salt. In these rats quercetin treatment improved diastolic blood pressure and cardiac hypertrophy as well as antioxidant defense system, restored GSH concentrations in liver and heart. Thus, this study indicated the anti-hypertensive and antioxidant roles of quercetin in a rat model of hypertension [55] (Table 1).

Anti-Inflammatory Effects of Quercetin in CVD

Inflammatory response is a complex biological mechanism which involves microvesels, molecular mediators and immune cells stimulated by pathogens, irritants, damaged cells, etc. [56]. Inflammation can clear up injured necrotic cells and trigger the repair of damaged tissues. One of the most significant properties of quercetin is its modulatory effect on inflammation. Quercetin can suppress inflammatory enzymes including cyclooxygenase and lipooxygenase as well as pro-inflammatory mediators [57, 58]. Pro-inflammatory cytokines which are produced in stressful situations promote inflammation [59]. As mentioned above, inflammation is a key player in CVD.

Lu et al. [60] reported that quercetin decreased atherosclerotic plaques in atherosclerotic mice. It was shown that quercetin may reduce inflammatory process via suppressing endothelial leukocyte adhesion and NF-kB signaling pathway in endothelial cells and reduce the inflammatory response in atherosclerotic rats and that it can inhibit atherosclerotic plaque development [61]. Another study examined the influence of quercetin on mice with lipopolysaccharide-induced cardiac abnormalities. Quercetin had cardiovascular protective effect by inhibiting the pro-inflammatory cytokines such as TNF-α and IL-1β and suppressing IκB kinase phosphorylation [62]. Quercetin supplementation suppressed the nuclear translocation of NF-kB and cytokines release induced by ox-LDL *in vitro*. Quercetin also decreased the gene expression of TNF-α and toll-like receptors (TLRs) in atherosclerotic rats suggesting that quercetin could be a promising agent in prevention and medication of atherosclerosis by preventing inflammation [63]. Ma et al. [64] evaluated the effect of isoquercetin on a rat model of acute MI. They observed that isoquercetin improved MI size, creatine kinase, and the activity of lactic dehydrogenase. Moreover, quercetin suppressed inflammation, oxidative stress and apoptosis of heart cells. Quercetin also elevated endothelial NOS, decreased iNOS and inhibited TLR4 NF-kB signaling pathway. This study indicated the protective role of quercetin against acute myocardial infarction by its anti-inflammatory and anti-apoptosis properties. In another recent study, quercetin decreased lipid peroxidation and reduced the expression of VCAM-1 and E-selectin. Quercetin also inhibited atherosclerosis by reducing inflammatory response [65]. In diabetic rats quercetin administration led to reduced blood pressure, reduced serum concentrations of TNF-α and CRP and inhibited aortic NF-kB. The authors of this study suggested that quercetin could be an effective candidate to prevent vascular disorders of diabetes by its inhibitory effects on inflammation, particularly NF-kB signaling [66] (Table 1).

Metabolic Effects of Quercetin in CVD (Clinical Studies)

Quercetin due to anti-hypertensive, anti-atherosclerotic, anti-platelet activity, and lipid-lowering effects has positive effects on CVD. Consumption of the extract of red grape polyphenol which is rich in quercetin causes an elevation of flow-mediated dilation of main arteries indicating an improvement in endothelial function [67]. Already a relatively old study indicated that LDL oxidation is lower in people who take quercetin and an alcohol-free red wine extract, containing quercetin [68]. Quercetin also inhibits accumulation of fat in human fat cells and initiates apoptosis in these cells [69, 70]. In other studies quercetin also inhibited glucose uptake from the blood, the production of fat cells, and increased necrosis of fat cells [71, 72].

In a randomized double-blinded placebo-controlled crossover clinical trial 70 overweight-to-obese patients with pre-hypertension were selected to receive quercetin 162 mg *per* day or placebo. The findings indicated that quercetin could

Table 1 Experimental studies of quercetin in CVD

Doses	Problem	Model	Findings	Ref
30 mg/kg	Hypoxia	*In vivo*	Decreased MDA, PC, NOx and iNOS, increased activity of SOD, CAT	[50]
50 mg/kg	Oxidative cardiotoxicity and dyslipidemia	*In vivo*	Increased SOD, CAT, decreased lipid peroxidation and PC content	[51]
0.5% w/w	Diabetic myocardiopathy	*In vivo*	Decreased cardiac diastolic dysfunction, cardiac cholesterol accumulation, and cardiac oxidative stress, increased GSH/GSSH ratio, nuclear translocation of Nrf2, and activity of antioxidant enzymes	[52]
20 mg/kg	Trauma-induced secondary cardiac injury	*In vivo* *In vitro*	Ameliorated posttraumatic cardiomyocyte apoptosis and cardiac dysfunction Increased viability, decreased TNF-α, ROS and Ca^{2+}	[53]
50 and 100 mg/kg	Hypertension	*In vivo*	Decreased blood pressure, improved antioxidant defense system	[54]
10 mg/kg	Hypertension	*In vivo*	Ameliorate diastolic blood pressure and cardiac hypertrophy, improved antioxidant defense system	[55]
50 and 100 mg/kg	Atherosclerosis	*In vivo* *In vitro*	Decreased atherosclerotic plaque size Decreased inflammation and apoptosis	[60]
25 mg /kg 25 μM	Atherosclerosis	*In vivo* *In vitro*	Decreased COX, MPO, CRP and IL-6 Decreased VCAM-1, ICAM-1, MCP-1 and nuclear translocation of NF-kB p65 subunit	[61]
25 mg /kg	LPS-induced cardiac abnormalities	*In vivo*	Decreased TNF-α and IL-1β, inhibited activation of I-kB phosphorylation	[62]
50 mg/kg	Atherosclerosis	*In vivo* *In vitro*	Decreased expression of TNF-α and TLRs Inhibited nuclear translocation of NF-kB	[63]
–	Acute mayocardial infarction	*In vivo*	Improved myocardial infarct size, creatine kinase, and activity of LDH, decreased inflammation, oxidative stress and apoptosis, increased endothelial NOS, decreased iNOS, inhibited TLR4 NF-kB signaling pathway	[64]
0.1%, w/w	Atherosclerosis	*In vivo*	Decreased lipid peroxidation, expression of VCAM-1 and E-selectin	[65]
50 mg/kg	Diabetic myocardiopathy	*In vivo*	Decreased blood pressure, serum levels of TNF-α and CRP, inhibited aortic NF-kB	[66]

CVD cardiovascular disease, *COX* cyclooxygenase, *MPO* myeloperoxidase, *ROS* reactive oxygen species, *IFN-*γ interferon-γ, *TNF-*α tumor necrosis factor-α, *MCP-1* monocyte chemoattractant protein-1, *IL-1* interleukin-1, *VCAM-1* vascular cell adhesion molecule-1, *TGF-*β transforming growth factor-β, *CRP* C-reactive protein, *NO* nitric oxide, *SOD* superoxide dismutase, *CAT* catalase, *MDA* malondialdehyde, *PC* protein carbonyl, *Nox* nitrite and nitrate, *iNOS* inducible nitric oxide synthase, *LDH* lactate dehydrogenase, *NOS* nitric oxide synthase, *GSH* glutathione, *TLRs* toll-like receptors

reduce ambulatory blood pressure suggesting the cardioprotective role of quercetin [73]. Pfeuffer et al. [74] assessed the influence of quercetin on atherosclerosis risk factors, biomarkers of oxidative stress and inflammation in healthy subjects with different APOE genotypes. These authors reported that quercetin significantly reduced postprandial systolic blood pressure without any changes on endothelial function. Quercetin consumption also significantly decreased postprandial triglycerides levels and increased HDL-cholesterol levels when compared with placebo group. Quercetin moderately elevated TNF-α levels as well. The authors suggested that quercetin supplementation may improve some CVD risk factors. The effects of quercetin on hypertension, lipid metabolism, markers of inflammation and oxidative stress were analyzed in overweight or obese patients with metabolic syndrome. Quercetin supplementation reduced serum levels of HDL-cholesterol whereas total cholesterol, triglycerides, LDL/HDL-cholesterol and triglycerides/HDL-cholesterol ratios were not changed. On the other hand, quercetin potentially reduced plasma levels of ox-LDL, while TNF-α and CRP were not altered in comparison to those in placebo group. Despite disappointing results concerning lipids, this study showed that there might be some possible beneficial effects of quercetin concerning CVD [75]. In another study, drinking quercetin rich onion juice could significantly suppressed cholesterol and elevate total antioxidant capacity levels [76].

Hubbard et al. [77] measured platelets isolated from subjects who ingested quercetin-4'-O-beta-D-glucoside supplement to analyze cell signaling and aggregation stimulated by

Table 2 Clinical trials of quercetin in CVD

Form of quercetin	Doses	Subjects	Findings	Ref
Quercetin	162 mg/d	Pre-hypertension/ overweight-to-obese	Decreased ambulatory blood pressure	[73]
Quercetin	150 mg/d	Men with different APOE isoforms	Decreased postprandial systolic blood pressure, decreased postprandial TAC, increased HDL-cholesterol, increased TNF-α	[74]
Quercetin	150 mg/d	Overweight or obese subjects with metabolic syndrome	Decreased serum HDL-cholesterol, decreased ox-LDL	[75]
quercetin-4'-O-beta-D-glucoside	150 or 300 mg	Healthy	Inhibited platelet cell signaling and thrombus formation	[77]
Quercetin	730 mg/d	Pre-hypertensive subjects Stage 1 hypertensive subjects	Unaltered blood pressure Decreased blood pressure	[78]

CVD cardiovascular disease, *TNF-α* tumor necrosis factor-α, *TAC* total antioxidant capacity

collagen. The results indicated that quercetin inhibits platelet cell signaling and thrombus formation. The effect of quercetin on human hypertension was evaluated by Edwards et al. [78]. Nineteen subjects with pre-hypertension and 22 subjects with stage 1 hypertension were receiving 730 mg quercetin or placebo daily for 28 days. After quercetin treatment, blood pressure of pre-hypertensive subjects was not changed while the blood pressure of stage 1 hypertensive subjects was reduced. Another study also confirmed the blood pressure lowering effect of quercetin. This study reported that quercetin decreased blood pressure via a mechanism which is not dependent on angiotensin-converting enzyme, endothelin-1 or NO (Table 2).

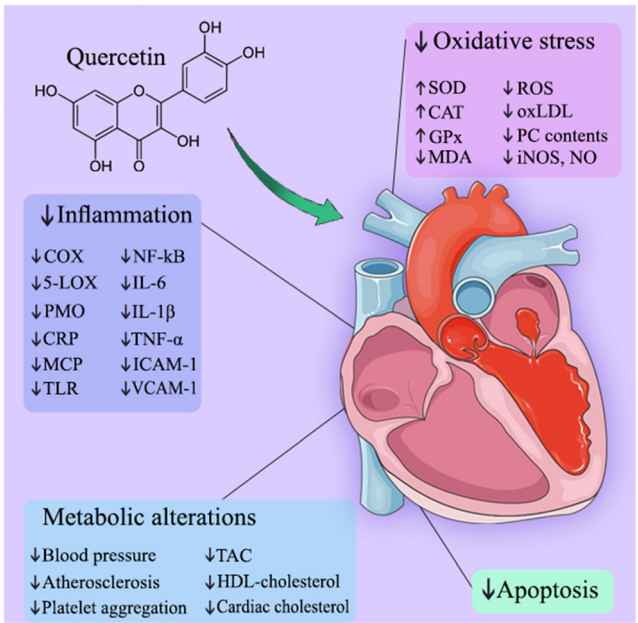

Fig. 1 Schematic representation in targeting different signaling and metabolic pathways using quercetin as a novel therapeutic strategy in cardiovascular disease prevention and treatment

Conclusions

Nowadays, CVD is a worldwide health controversy with a high rate of mortality and morbidity. Several risk factors containing high blood pressure, smoking, diabetes, obesity, and dyslipidemia are involved. Each of these factors can promote several mechanisms and pathways by which atherosclerosis and atherosclerotic CVD can develop. The main molecular processes involved in CVD are including oxidative stress, inflammation, apoptosis and endothelial dysfunction. Quercetin as a natural compound has been considered to be effective in the prevention and treatment of CVD (Fig. 1). In the last two decades, several *in vitro, in vivo* and clinical trials have been conducted in order to try to explain the mechanisms of action of quercetin in CVD. The results have confirmed some possible antiatherosclerotic effects of quercetin. However, the details of molecular mechanisms by which quercetin might achieve such effects have not yet been completely clarified. Some authors have suggested that this is because of its antioxidant, anti-inflammatory, and anti-apoptotic activities, protective effect on NO, anti-aggregation effect, blood pressure lowering effects, and beneficial effects on endothelial dysfunction. It could be concluded that quercetin seems to be a promising therapeutic agent in preventing CVD are needed, particularly those clinical with CVD outcomes. This is particularly important since there is no proof so far that quercetin might prevent CVD morbidity and mortality.

Author Contributions ZA contributed in conception, design and drafting of the manuscript.
RS, ZR and LM contributed in data collection and manuscript drafting.
All authors approved the final version for submission.
ZA oversaw the study.

Compliance with Ethical Standards

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare no conflict of interest.

References

1. Murray CJ, Lopez AD (1997) Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet (London, England) 349:1498–1504
2. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglu L, Verschuren WM, Vlachopoulos C, Wood DA, Zamorano JL (2016) 2016 ESC/EAS guidelines for the management of dyslipidaemias: the task force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis 253:281–344
3. Van Camp G (2014) Cardiovascular disease prevention. Acta Clin Belg 69:407–411
4. Nishida C, Uauy R, Kumanyika S, Shetty P (2004) The joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases: process, product and policy implications. Public Health Nutr 7:245–250
5. Leong DP, Joseph PG, McKee M, Anand SS, Teo KK, Schwalm JD, Yusuf S (2017) Reducing the global burden of cardiovascular disease, part 2: prevention and treatment of cardiovascular disease. Circulation Res 121:695–710
6. Haynes RB, McDonald HP, Garg AX (2002) Helping patients follow prescribed treatment: clinical applications. JAMA 288:2880–2883
7. Glass CK, Witztum JL (2001) Atherosclerosis. The road ahead. Cell 104:503–516
8. Kopelman PG (2000) Obesity as a medical problem. Nature 404:635–643
9. Aggarwal M, Aggarwal B, Rao J (2017) Integrative medicine for cardiovascular disease and prevention. Med Clin North Am 101:895–923
10. Cicero AFG, Colletti A, Bajraktari G, Descamps O, Djuric DM, Ezhov M, Fras Z, Katsiki N, Langlois M, Latkovskis G, Panagiotakos DB, Paragh G, Mikhailidis DP, Mitchenko O, Paulweber B, Pella D, Pitsavos C, Reiner Ž, Ray KK, Rizzo M, Sahebkar A, Serban MC, Sperling LS, Toth PP, Vinereanu D, Vrablík M, Wong ND, Banach M (2017) Lipid-lowering nutraceuticals in clinical practice: position paper from an international lipid expert panel. Nutr Rev 75:731–767
11. Larson AJ, Symons JD, Jalili T (2012) Therapeutic potential of quercetin to decrease blood pressure: review of efficacy and mechanisms. Adv Nutr 3:39–46
12. Oboh G, Ademosun AO, Ogunsuyi OB (2016) Quercetin and its role in chronic diseases. Adv Exp Med Biol 929:377–387
13. Manach C, Williamson G, Morand C, Scalbert A, Remesy C (2005) Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. Am J Clin Nutr 81:230s–242s
14. Egert S, Wolffram S, Bosy-Westphal A, Boesch-Saadatmandi C, Wagner AE, Frank J, Rimbach G, Mueller MJ (2008) Daily quercetin supplementation dose-dependently increases plasma quercetin concentrations in healthy humans. J Nutr 138:1615–1621
15. Olthof MR, Hollman PC, Vree TB, Katan MB (2000) Bioavailabilities of quercetin-3-glucoside and quercetin-4′-glucoside do not differ in humans. J Nutr 130:1200–1203
16. Crespy V, Morand C, Besson C, Manach C, Demigne C, Remesy C (2001) Comparison of the intestinal absorption of quercetin, phloretin and their glucosides in rats. J Nutr 131:2109–2114
17. Day AJ, DuPont MS, Ridley S, Rhodes M, Rhodes MJ, Morgan MR, Williamson G (1998) Deglycosylation of flavonoid and isoflavonoid glycosides by human small intestine and liver beta-glucosidase activity. FEBS Lett 436:71–75
18. Manach C, Morand C, Texier O, Favier ML, Agullo G, Demigne C, Regerat F, Remesy C (1995) Quercetin metabolites in plasma of rats fed diets containing rutin or quercetin. J Nutr 125:1911–1922
19. Nijveldt RJ, van Nood E, van Hoorn DE, Boelens PG, van Norren K, van Leeuwen PA (2001) Flavonoids: a review of probable mechanisms of action and potential applications. Am J Clin Nutr 74:418–425
20. Boots AW, Haenen GR, Bast A (2008) Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol 585:325–337
21. Blankenberg S, Rupprecht HJ, Bickel C, Torzewski M, Hafner G, Tiret L, Smieja M, Cambien F, Meyer J, Lackner KJ (2003) Glutathione peroxidase 1 activity and cardiovascular events in patients with coronary artery disease. N Engl J Med 349:1605–1613
22. Friedman AN (2002) Renovascular hypertension, endothelial function, and oxidative stress. N Engl J Med 347:1528–1530 author reply 1528-1530
23. Wentworth P Jr, Nieva J, Takeuchi C, Galve R, Wentworth AD, Dilley RB, DeLaria GA, Saven A, Babior BM, Janda KD, Eschenmoser A, Lerner RA (2003) Evidence for ozone formation in human atherosclerotic arteries. Science 302:1053–1056
24. Taleb S (2016) Inflammation in atherosclerosis. Arch Cardiovasc Dis 109:708–715
25. Alavi A, Hood JD, Frausto R, Stupack DG, Cheresh DA (2003) Role of Raf in vascular protection from distinct apoptotic stimuli. Science 301:94–96
26. Feng B, Yao PM, Li Y, Devlin CM, Zhang D, Harding HP, Sweeney M, Rong JX, Kuriakose G, Fisher EA, Marks AR, Ron D, Tabas I (2003) The endoplasmic reticulum is the site of cholesterol-induced cytotoxicity in macrophages. Nat Cell Biol 5:781–792
27. Kolodgie FD, Gold HK, Burke AP, Fowler DR, Kruth HS, Weber DK, Farb A, Guerrero LJ, Hayase M, Kutys R, Narula J, Finn AV, Virmani R (2003) Intraplaque hemorrhage and progression of coronary atheroma. N Engl J Med 349:2316–2325
28. Li JJ, Chen JL (2005) Inflammation may be a bridge connecting hypertension and atherosclerosis. Med Hypotheses 64:925–929
29. O'Keefe JH, Carter MD, Lavie CJ (2009) Primary and secondary prevention of cardiovascular diseases: a practical evidence-based approach. Mayo Clin Proc 84:741–757
30. Tropeano AI, Saleh N, Hawajri N, Macquin-Mavier I, Maison P (2011) Do all antihypertensive drugs improve carotid intima-media thickness? A network meta-analysis of randomized controlled trials. Fundam Clin Pharmacol 25:395–404
31. Piano MR, Benowitz NL, Fitzgerald GA, Corbridge S, Heath J, Hahn E, Pechacek TF, Howard G (2010) Impact of smokeless tobacco products on cardiovascular disease: implications for policy, prevention, and treatment: a policy statement from the American Heart Association. Circulation 122:1520–1544
32. Donahoe SM, Stewart GC, McCabe CH, Mohanavelu S, Murphy SA, Cannon CP, Antman EM (2007) Diabetes and mortality following acute coronary syndromes. JAMA 298:765–775
33. Barnett AH (2008) The importance of treating cardiometabolic risk factors in patients with type 2 diabetes. Diab Vasc Dis Res 5:9–14
34. Kachur S, Lavie CJ, de Schutter A, Milani RV, Ventura HO (2017) Obesity and cardiovascular diseases. Minerva Med 108:212–228

35. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH (2006) Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity, and metabolism. Circulation 113:898–918
36. Libby P (2006) Inflammation and cardiovascular disease mechanisms. Am J Clin Nutr 83:456s–460s
37. Young A, Koduri G, Batley M, Kulinskaya E, Gough A, Norton S, Dixey J (2007) Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology 46:350–357
38. Mosca L (2002) C-reactive protein–to screen or not to screen? N Engl J Med 347:1615–1617
39. Aviles RJ, Askari AT, Lindahl B, Wallentin L, Jia G, Ohman EM, Mahaffey KW, Newby LK, Califf RM, Simoons ML, Topol EJ, Berger P, Lauer MS (2002) Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. N Engl J Med 346:2047–2052
40. Lindberg S (2014) Prognostic utility of the soluble CD40 ligand in acute coronary syndrome. Coron Artery Dis 25:548–549
41. Freedman JE (2003) CD40 ligand–assessing risk instead of damage? N Engl J Med 348:1163–1165
42. Rice-Evans CA, Miller NJ, Paganga G (1996) Structure-antioxidant activity relationships of flavonoids and phenolic acids. Free Radic Biol Med 20:933–956
43. Wang L, Tu YC, Lian TW, Hung JT, Yen JH, Wu MJ (2006) Distinctive antioxidant and antiinflammatory effects of flavonols. J Agric Food Chem 54:9798–9804
44. Dogan Z, Kocahan S, Erdemli E, Kose E, Yilmaz I, Ekincioglu Z, Ekinci N, Turkoz Y (2015) Effect of chemotherapy exposure prior to pregnancy on fetal brain tissue and the potential protective role of quercetin. Cytotechnology 67:1031–1038
45. Gutteridge JM (1995) Lipid peroxidation and antioxidants as biomarkers of tissue damage. Clin Chem 41:1819–1828
46. Zhang M, Swarts SG, Yin L, Liu C, Tian Y, Cao Y, Swarts M, Yang S, Zhang SB, Zhang K, Ju S, Olek DJ Jr, Schwartz L, Keng PC, Howell R, Zhang L, Okunieff P (2011) Antioxidant properties of quercetin. Adv Exp Med Biol 701:283–289
47. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D (1994) Dietary flavonoids and cancer risk in the Zutphen elderly study. Nutr Cancer 22:175–184
48. Knekt P, Jarvinen R, Reunanen A, Maatela J (1996) Flavonoid intake and coronary mortality in Finland: a cohort study. BMJ 312:478–481
49. Czepas J, Gwozdzinski K (2014) The flavonoid quercetin: possible solution for anthracycline-induced cardiotoxicity and multidrug resistance. Biomed Pharmacother 68:1149–1159
50. Chis IC, Baltaru D, Dumitrovici A, Coseriu A, Radu BC, Moldovan R, Muresan A (2018) Protective effects of quercetin from oxidative/nitrosative stress under intermittent hypobaric hypoxia exposure in the rat's heart. Physiol Int 105:233–246
51. Milton Prabu S, Muthumani M, Shagirtha K (2013) Quercetin potentially attenuates cadmium induced oxidative stress mediated cardiotoxicity and dyslipidemia in rats. Eur Rev Med Pharmacol Sci 17:582–595
52. Castillo RL, Herrera EA (2018) Quercetin prevents diastolic dysfunction induced by a high-cholesterol diet: role of oxidative stress and bioenergetics in hyperglycemic rats. Oxid Med Cell Longev 2018:7239123
53. Jing Z, Wang Z, Li X, Li X, Cao T, Bi Y, Zhou J, Chen X, Yu D, Zhu L, Li S (2016) Protective effect of quercetin on posttraumatic cardiac injury. Sci Rep 6:30812
54. Oyagbemi AA, Omobowale TO, Ola-Davies OE, Asenuga ER, Ajibade TO, Adejumobi OA, Arojojoye OA, Afolabi JM, Ogunpolu BS, Falayi OO, Hassan FO, Ochigbo GO, Saba AB, Adedapo AA, Yakubu MA (2018) Quercetin attenuates hypertension induced by sodium fluoride via reduction in oxidative stress and modulation of HSP 70/ERK/PPARgamma signaling pathways. BioFactors 44:465–479
55. Galisteo M, Garcia-Saura MF, Jimenez R, Villar IC, Zarzuelo A, Vargas F, Duarte J (2004) Effects of chronic quercetin treatment on antioxidant defence system and oxidative status of deoxycorticosterone acetate-salt-hypertensive rats. Mol Cell Biochem 259:91–99
56. Ferrero-Miliani L, Nielsen OH, Andersen PS, Girardin SE (2007) Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1beta generation. Clin Exp Immunol 147:227–235
57. Xiao X, Shi D, Liu L, Wang J, Xie X, Kang T, Deng W (2011) Quercetin suppresses cyclooxygenase-2 expression and angiogenesis through inactivation of P300 signaling. PLoS One 6:e22934
58. Warren CA, Paulhill KJ, Davidson LA, Lupton JR, Taddeo SS, Hong MY, Carroll RJ, Chapkin RS, Turner ND (2009) Quercetin may suppress rat aberrant crypt foci formation by suppressing inflammatory mediators that influence proliferation and apoptosis. J Nutr 139:101–105
59. Takahashi K, Fukushima S, Yamahara K, Yashiro K, Shintani Y, Coppen SR, Salem HK, Brouilette SW, Yacoub MH, Suzuki K (2008) Modulated inflammation by injection of high-mobility group box 1 recovers post-infarction chronically failing heart. Circulation 118:S106–S114
60. Lu XL, Zhao CH, Yao XL, Zhang H (2017) Quercetin attenuates high fructose feeding-induced atherosclerosis by suppressing inflammation and apoptosis via ROS-regulated PI3K/AKT signaling pathway. Biomed Pharmacother 85:658–671
61. Bhaskar S, Sudhakaran PR, Helen A (2016) Quercetin attenuates atherosclerotic inflammation and adhesion molecule expression by modulating TLR-NF-kappaB signaling pathway. Cell Immunol 310:131–140
62. Wei X, Meng X, Yuan Y, Shen F, Li C, Yang J (2018) Quercetin exerts cardiovascular protective effects in LPS-induced dysfunction *in vivo* by regulating inflammatory cytokine expression, NF-kappaB phosphorylation, and caspase activity. Mol Cell Biochem 446:43–52
63. Bhaskar S, Helen A (2016) Quercetin modulates toll-like receptor-mediated protein kinase signaling pathways in oxLDL-challenged human PBMCs and regulates TLR-activated atherosclerotic inflammation in hypercholesterolemic rats. Mol Cell Biochem 423:53–65
64. Ma C, Jiang Y, Zhang X, Chen X, Liu Z, Tian X (2018) Isoquercetin ameliorates myocardial infarction through anti-inflammation and anti-apoptosis factor and regulating TLR4-NF-kappaB signal pathway. Mol Med Rep 17:6675–6680
65. Kleemann R, Verschuren L, Morrison M, Zadelaar S, van Erk MJ, Wielinga PY, Kooistra T (2011) Anti-inflammatory, anti-proliferative and anti-atherosclerotic effects of quercetin in human *in vitro* and *in vivo* models. Atherosclerosis 218:44–52
66. Mahmoud MF, Hassan NA, El Bassossy HM, Fahmy A (2013) Quercetin protects against diabetes-induced exaggerated vasoconstriction in rats: effect on low grade inflammation. PLoS One 8: e63784
67. Lekakis J, Rallidis LS, Andreadou I, Vamvakou G, Kazantzoglou G, Magiatis P, Skaltsounis AL, Kremastinos DT (2005) Polyphenolic compounds from red grapes acutely improve endothelial function in patients with coronary heart disease. Eur J Cardiovasc Prev Rehabil 12:596–600
68. Chopra M, Fitzsimons PE, Strain JJ, Thurnham DI, Howard AN (2000) Nonalcoholic red wine extract and quercetin inhibit LDL oxidation without affecting plasma antioxidant vitamin and carotenoid concentrations. Clin Chem 46:1162–1170
69. Park HJ, Yang JY, Ambati S, Della-Fera MA, Hausman DB, Rayalam S, Baile CA (2008) Combined effects of genistein,

quercetin, and resveratrol in human and 3T3-L1 adipocytes. J Med Food 11:773–783
70. Ahn J, Lee H, Kim S, Park J, Ha T (2008) The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. Biochem Biophys Res Commun 373:545–549
71. Strobel P, Allard C, Perez-Acle T, Calderon R, Aldunate R, Leighton F (2005) Myricetin, quercetin and catechin-gallate inhibit glucose uptake in isolated rat adipocytes. Biochem J 386:471–478
72. Yang JY, Della-Fera MA, Rayalam S, Ambati S, Hartzell DL, Park HJ, Baile CA (2008) Enhanced inhibition of adipogenesis and induction of apoptosis in 3T3-L1 adipocytes with combinations of resveratrol and quercetin. Life Sci 82:1032–1039
73. Brull V, Burak C, Stoffel-Wagner B, Wolffram S, Nickenig G, Muller C, Langguth P, Alteheld B, Fimmers R, Naaf S, Zimmermann BF, Stehle P, Egert S (2015) Effects of a quercetin-rich onion skin extract on 24 h ambulatory blood pressure and endothelial function in overweight-to-obese patients with (pre-)hypertension: a randomised double-blinded placebo-controlled cross-over trial. Br J Nutr 114:1263–1277
74. Pfeuffer M, Auinger A, Bley U, Kraus-Stojanowic I, Laue C, Winkler P, Rüfer CE, Frank J, Bösch-Saadatmandi C, Rimbach G, Schrezenmeir J (2013) Effect of quercetin on traits of the metabolic syndrome, endothelial function and inflammation in men with different APOE isoforms. Nutr Metab Cardiovasc Dis 23:403–409
75. Egert S, Bosy-Westphal A, Seiberl J, Kürbitz C, Settler U, Plachta-Danielzik S, Wagner AE, Frank J, Schrezenmeir J, Rimbach G, Wolffram S, Müller MJ (2009) Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. Br J Nutr 102:1065–1074
76. Lu TM, Chiu HF, Shen YC, Chung CC, Venkatakrishnan K, Wang CK (2015) Hypocholesterolemic efficacy of quercetin rich onion juice in healthy mild hypercholesterolemic adults: a pilot study. Plant Foods Hum Nutr 70:395–400
77. Hubbard GP, Wolffram S, Lovegrove JA, Gibbins JM (2004) Ingestion of quercetin inhibits platelet aggregation and essential components of the collagen-stimulated platelet activation pathway in humans. J Thromb Haemost 2:2138–2145
78. Edwards RL, Lyon T, Litwin SE, Rabovsky A, Symons JD, Jalili T (2007) Quercetin reduces blood pressure in hypertensive subjects. J Nutr 137:2405–2411