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Review article

Therapeutic potential of quercetin as a cardiovascular agent

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ABSTRACT

Flavonoids are integral components of various vegetation and in foods; consequently, they represent an inevitable part of the diet. Historical and epidemiological proof recommend that diet plans consisting of flavonoids such as quercetin have positive health benefits, especially on the heart. Flavonoids have been proven to be active against hypertension, inflammation, diabetes and vascular diseases. Quercetin exhibits significant heart related benefits as inhibition of LDL oxidation, endothelium-independent vasodilator effects, reduction of adhesion molecules and other inflammatory markers, the protective effect on nitric oxide and endothelial function under conditions of oxidative stress, prevention of neuronal oxidative and inflammatory damage and platelet antiaggregant effects. Searching for experimental evidence to validate the cardioprotective effects of quercetin, we review here the recent detailed *in vivo* studies. Quercetin and its derivatives lead to an enhancement in heart features, indicating the prospective for quercetin to be used therapeutically in the treatment of cardiac diseases. Several evidence-based studies suggest mechanisms to observe cardiovascular diseases such as aging effects, hypertension, angiotensin-converting enzyme activity and endothelial-dependent and independent functions. Different animal models including human are also used to elucidate the *in vivo* role of quercetin in cardiovascular diseases. The role of quercetin and its derivatives may go beyond their existence in food and has potential as a lead molecule in drug development programs.

Contents

Abbreviation: CVD, Cardiovascular disease; eNOS, endothelial nitric oxide synthase; BcL2, B-cell lymphoma 2; MDA, malonaldehyde; TNFα, tumor necrosis factor α; IL-6, Interleukin 6; PPARα, Peroxisome proliferator-activated receptor α; HDL, high density lipoprotein; LDL, low density lipoprotein; pgc1α, Peroxisome proliferator-activated receptor gamma coactivator 1 α; CYP7A1, cholesterol 7 alpha hydroxylase; VCAM-1, vascular endothelial adhesion molecule-1; ICAM-1, intercellular cell adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; AMPK, adenosine monophosphate kinase; LOX-1, Lectin-like oxidized receptor 1; Ang II, angiotensin II; AT1R, angiotensin II type 1 receptor; ET-1, endothelin-1; ACE, angiotensin converting enzyme; CRP, C-reactive protein; SIRT1, Sirtuin 1; Tfam, mitochondrial transcription factor A; SOD, super oxide dismutase; COX 1, Cyclooxygenase 1; NADPH oxidase, nicotinamide adenine dinucleotide phosphate-oxidase; VSMC apoptosis, vascular smooth muscle cell apoptosis; ROS, reactive oxygen species; cGMP, cyclic guanosine monophosphate; PKC, protein kinase C; AACQ, abdominal aortic constriction + quercetin; AAC, abdominal aortic constriction; L-NAME, N^{ω}-Nitro-L-arginine methyl ester hydrochloride; PKC, Protein kinase C; ADMA, asymmetric dimethylarginine; VSMC, vascular smooth muscle cell; AP-1, activator protein 1; ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; BK, bradykinin; MDA, plasma malonaldehyde; NADPH, Nicotinamide adenine dinucleotide phosphate; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; FMD, flow-mediated vasodilation; GTN, glyceryl trinitrate; SNP, sodium nitroprusside.

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1. Introduction

Throughout the drug discovery evolution, till date, more than 250000 entries of natural substances have been reported [1]. The vast variety of chemical structures, for example, polyketides, carbohydrates, flavonoids, terpenes-terpenoids, steroids, alkaloids, amino acids, peptides and so on [2], derived from natural resources have gained a great deal of attention in the medicinal therapeutics collection. Efforts to build the desired functionally featured generation of these classes of natural analogues are also ongoing for several years [3,4], thus reducing the chance of drug resistance with wide structural variety.

For the last several years, there have been tremendous growth in a variety of research targeted by the action of non-nutritional compounds present in the diet, that have been able to avoid the incident of degenerative illnesses, for example, cardiovascular pathologies. These heterogeneous types of elements, generally known as phytochemicals, contain natural vitamins (carotenoids) and food polyphenols, such as flavonoids, phytoalexins, phenolic chemicals, indoles and sulfur-rich substances They exist typically in fruits, vegetables, beverages (tea, wine, beer) and also in most dietary supplements and herbal remedies. However, what attracts typically scientists' attention is the possible variety of ingredients available in such naturally occurring phytochemicals existing in nature. Flavonoids signify the important type of polyphenolics and are apparently capable of delivering anticipated cardioprotective action in cardiovascular diseases and aging through the mechanism of action as described below (Fig. 1) [5].

Flavonoids usually consist of several million plant-derived substances sharing a common skeleton of phenylchromane. This basic framework allows several different replacement structures resulting in several flavonoid subclasses such as flavonols, flavones, flavanones, catechins, isoflavones, anthocyanidins, dihydroflavonols, and chalcones (Fig. 2). They have anti-viral, anti-microbial, anti-inflammatory and anti-allergic potential that can be indicated in different cell types, both in animal and human models. The attention in nutritional flavonoids has expanded in the last many decades after the publication of several epidemiological researchers displaying an inverse connection between nutritional intake of flavonols and flavones and reduced occurrence and death rate from cardiac disorders (its related diseases as well as cancer) [6,7]. The first medical property described for flavonoids was related to the hurdle function of the endothelium [8]. Due to their effect on capillary permeability, flavonoids were formerly considered as natural vitamins. The phrase "vitamin P" (for Permeability) was stopped in the 1950s [9]. Recently, a lot of experimental and some clinical data have been collected regarding the consequences of flavonoids on the endothelium under physical and pathological

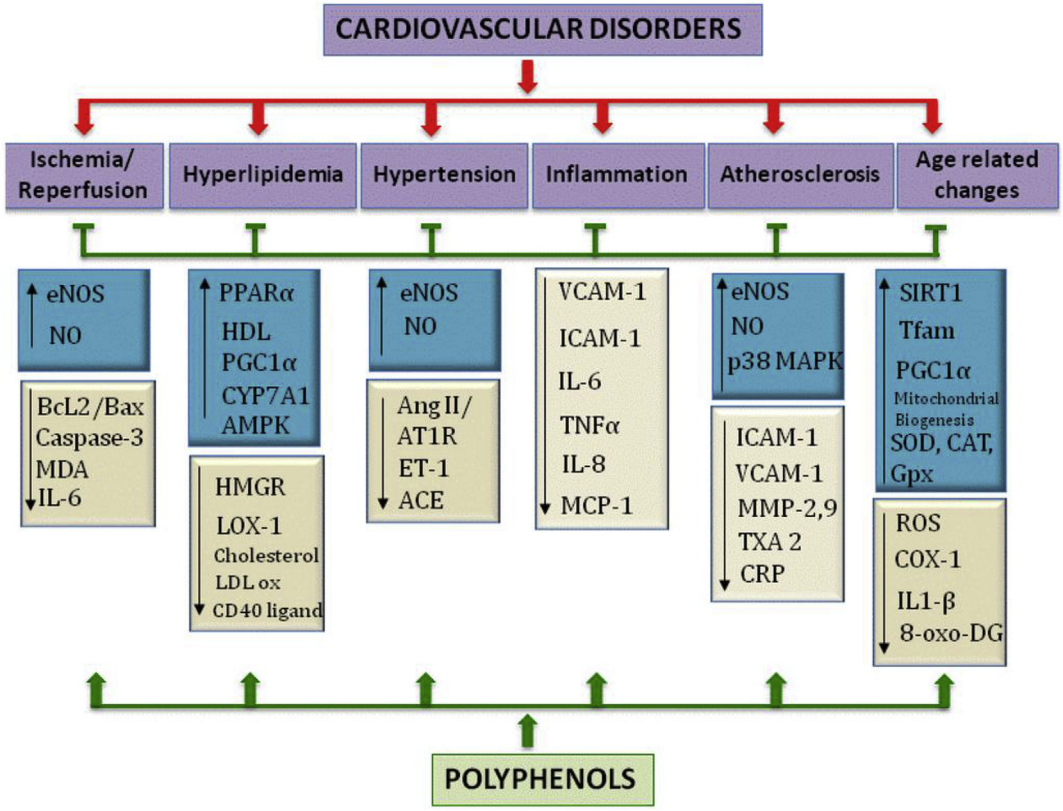
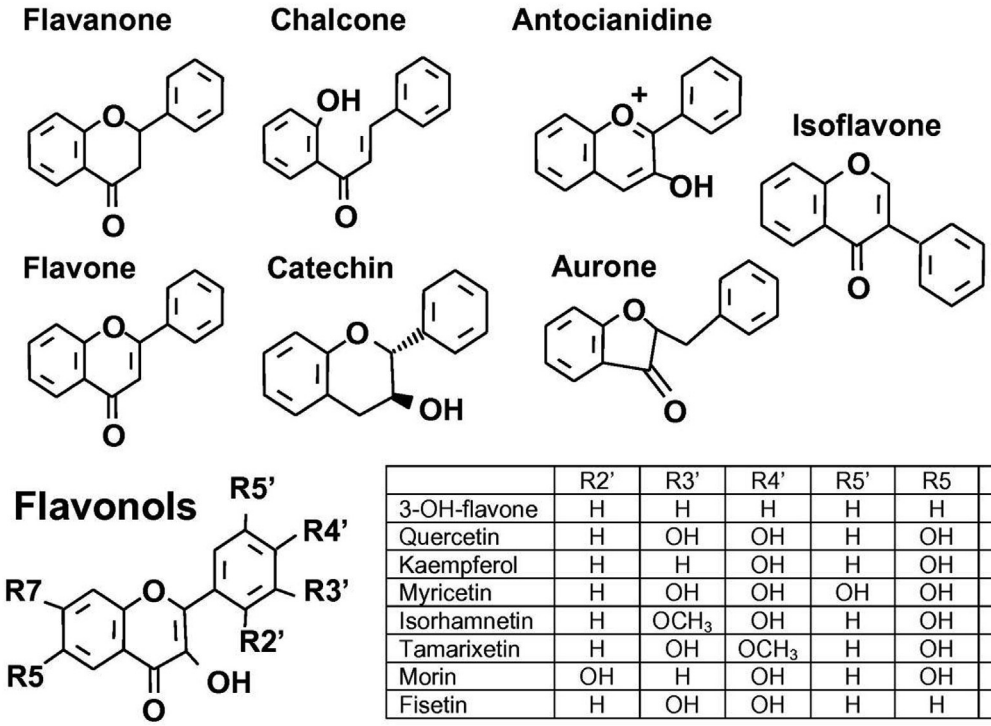


Fig. 1. Mechanisms of protection by polyphenols. **Source**: Reproduced from Ref [5b].



	R2'	R3'	R4'	R5'	R5	R7
3-OH-flavone	H	H	H	H	H	H
Quercetin	H	OH	OH	H	OH	OH
Kaempferol	H	H	OH	H	OH	OH
Myricetin	H	OH	OH	OH	OH	OH
Isorhamnetin	H	OCH_3	OH	H	OH	OH
Tamarixetin	H	OH	OCH_3	H	OH	OH
Morin	OH	H	OH	H	OH	OH
Fisetin	H	OH	OH	H	H	OH

Fig. 2. Chemical structures of the main flavonoid classes and the most common flavonol aglycones. **Source**: Reproduced from ref [11].

conditions. They apply their qualities both as purified aglycone molecules and as plant extracts. Many of the consequences revealed quercetin as probably the most diffused and known nature-derived flavonol [10].

Flavonols and flavanols are the most widely distributed and greatly abundant in nature when compared to other flavonoids. Flavonols can be found, usually as different glycosides, in huge quantities in our regular diet. The prototypical flavonol quercetin is very largely researched and is the most abundant one. Other common flavonols include morin, myricetin, fisetin, isorhamnetin, kaempferol and tamarixetin (Fig. 2) [11]. The bioavailability of quercetin relies upon on the characteristics of attached sugars and the components of the food matrix (ethanol, fat, and emulsifiers) which may impact its solubility. Quercetin is quickly conjugated with glucuronic acid and/or sulfate during first-pass metabolism (intestine–liver) and a portion of the metabolites are also methylated and, therefore, the significant metabolites of quercetin in human plasma are quercetin-3-glucuronide, quercetin-3-sulfate and isorhamnetin-3-glucuronide. Furthermore, research indicates that flavonols displays higher vasodilator effects amongst several associate flavonoids in isolated endothelium-intact rat aorta than flavones and flavanols [12].

Quercetin is one of a group of over 4000 naturally available plant phenolic compounds whose isolation and biological recognition were first described by Szent-Gyorgyi in 1936 [8]. It is also, a member of the flavonoids family and one of the most popular nutritional anti-oxidants. It ubiquitously exists in foods such as vegetables, fruits, tea, and wine as well as plenty of nutritious products [13] and continuous protection not only against various illnesses such as osteoporosis, certain types of melanoma, lung and heart illnesses but also against aging. Especially the capability of quercetin to feed on extremely sensitive varieties such as peroxynitrite and the hydroxyl radical is recommended to be engaged in these valuable health results. Consequently, several pieces of research have been conducted to collect medical proof **of** these facts as well as information regarding the actual procedure of activity and possible toxicological factors of this flavonoid. Like many other compounds, quercetin affects resistance and swelling by performing mainly on leukocytes and focusing on many intracellular signaling kinases and phosphatases, enzymes and membrane proteins, which are often crucial for a cellular specific function. Quercetin is considered to prevent several degenerative illnesses by avoiding fat peroxidation. However, the amount and technique of quercetin consumption *in vivo* have yet to be recognized. It is believed that the frequently occurring glucoside form is modified to the aglycone, which is then amended to one of several quercetin metabolites. Features and research of quercetin metabolites are vital to exploring how quercetin features as an antioxidant. The reason for this analysis is to elucidate the possible health-beneficial outcomes of the antioxidant quercetin, for example, blood pressure reducing agent [14]. The current evaluation mainly concentrates on the general biological results of quercetin. In doing this, we say sorry in advance for the many details left out and wish that these comments may help to estimate future improvements in the area. However, concerning cardioprotective function; there is a body of proof from cell-based assays, trial creature designs, and human medical studies that facilitate its performance. Consequently, the procedures by which quercetin may function as a cardioprotective agent (tested both *ex vivo* and *in vivo*) are also elaborated. Potential mechanisms by which quercetin exerts its cardioprotective effects is shown in Fig. 3 [15].

Quercetin is the most popular of the dietary flavonoids and the wealthiest resources are shown in Fig. 4. The chemical structure of pure quercetin is an unconjugated aglycone that doesn't have a carbohydrate moiety. Quercetin in foods, for example, onions, has a sugar group in its structure, which is known as a glycoside form. Additional types of quercetin are usually quercetin aglycone; although some items have little amounts of a glycoside called rutin as well. The bioavailability of quercetin mainly relies on the way of its consumption. Though, researchers discovered that both types

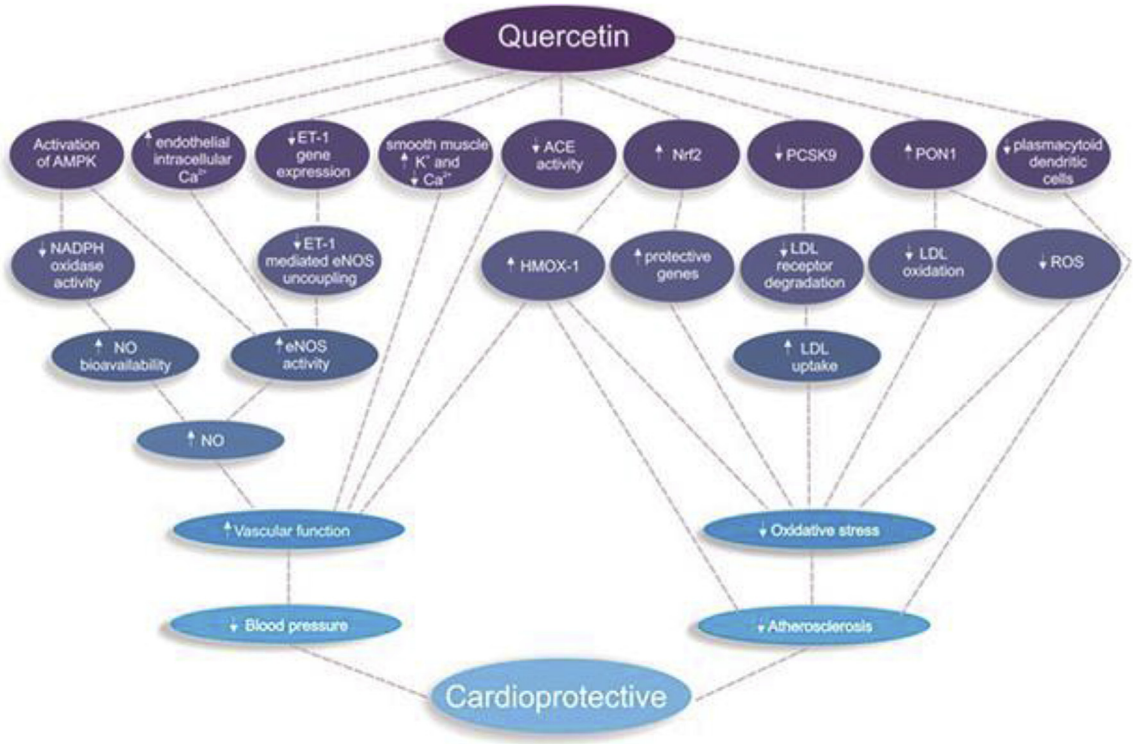


Fig. 3. Potential mechanisms by which quercetin exerts its cardioprotective effects. ACE angiotensin-converting enzyme, AMPK adenosine monophosphate-activated protein kinase, eNOS endothelial nitric oxide synthase, ET-1 endothelin-1, HMOX-1 heme oxygenase-1, LDL low-density lipoprotein, NADPH nicotinamide adenine dinucleotide phosphate, NO nitric oxide, Nrf2 nuclear factor erythroid 2-related factor 2, PCSK9 proprotein convertase subtilisin/kexin 9, PON1 paraoxonase 1, ROS reactive oxygen species. **Source**: Reproduced from ref [15].

are easily bioavailable [16–18], the glycoside types of quercetin leads to better consumption than quercetin aglycone. All kinds of quercetin (aglycone and quercetin with glycosides) are consumed in the small intestine and digestive tract. *In vivo* studies indicate that quercetin glycosides are hydrolyzed before absorption by an enzyme, lactase-phlorizin hydrolase whereas quercetin aglycone is absorbed as it is [19–23]. Once in the plasma, quercetin is bound to albumin [24] and transported to the liver [25]. In the liver, quercetin (aglycone or with glycosides) is quickly transformed to one or more metabolites such as isorhamnetin, kaempferol, and tamarixetin. In the perspective of the future medical use of the compound, quercetin's half-life and tissue distribution offer useful details. The half-

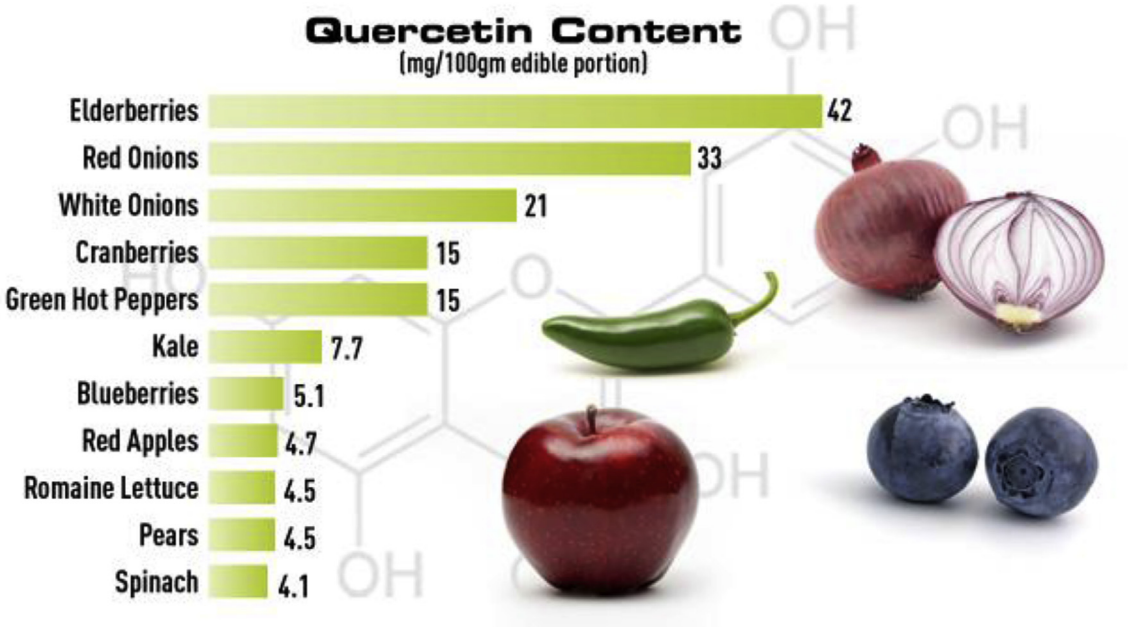


Fig. 4. Quercetin content in different foods. **Source**: http://drjockers.com.

lives of the molecule and its metabolites range between 11 and 28 h thus suggesting the chance of considerably improving plasma concentrations upon ongoing supplements [26,27].

Quercetin ($C_{15}H_{10}O_7$, 3,3′,4′,5,7-penthahydroxy-2-phenyl-chromen-4-one) is a participant of these naturally sourced polyphenolic compounds that share a common flavone nucleus created up of two benzene rings connected through a heterocyclic pyrone one. Quercetin is synthesized in plants starting from the amino acid phenylalanine. Phenylalanine (**1**) is transformed to 4-Coumaroyl-Coenzyme A (2) in a sequence of steps recognized as the general phenylpropanoid pathway using phenyl ammonia lyase, cinnamate-4-hydroxylase, and 4-coumaroyl-CoA ligase [28]. The metabolite 4-coumaroyl-CoA (**2**) is included to three molecules of malonyl-CoA (**3**) to form tetrahydroxychalcone (**4**) using 7,2′-dihydroxy, 4′-methoxyisoflavanol synthase. Tetrahydroxychalcone is then converted to naringenin (5) using chalcone isomerase. Naringenin is then turned into eriodictyol (6) using flavonoid 3′ hydroxylase, and eriodictyol is then converted to into dihydroquercetin (7) with flavanone 3-hydroxylase, which finally yielded that is then turned into quercetin using flavonol synthase [29] (Fig. 5).

Given the pre-established cardioprotective potential of quercetin molecules, we review here the *ex vivo* and *in vivo* evidence chronologically from its history to have a glimpse of its' potent cardio-friendly action.

2. Cardio-protective effects of quercetin

A quick glance at the pharmacological study of the quercetin, a flavonol compound, suggests that it has the capacity for cardioprotection against many diseases. Therefore, the intuitive explanation of the hypothesis that quercetin and its derivatives have cardio-protective role has no further doubt. There is no alternative assumption on the action of this compound on cardiac functions. In this review paper, we discuss studies on the cardioprotective role of quercetin and functions of its derivatives. Based on the available bioassay evidence, we hypothesize that the quercetin and its derivatives have a medicinal role in diseases related to the heart. It can work on the healthy heart in protecting it from diseases and in disease state as medicine. To assist this hypothesis, we first evaluated primary information about the heart and its features, which highly indicates that the quercetin responses to cardiac protection. We take a look at the discrepancy in the medicinal role of quercetin. Most of the evidence studied here was derived from experiments in the heart of mice, rats, rabbits or humans; other animals that have the same cardiac physiology also exhibit the same functional capacity for quercetin. Moreover, researchers have reviewed that quercetin is essential to reduce blood pressure (Fig. 6) [32] and has potent antioxidant potential [31] as well as some cardio friendly action [30]. Moreover, some efforts have been recently made to summarize cardiovascular effects of

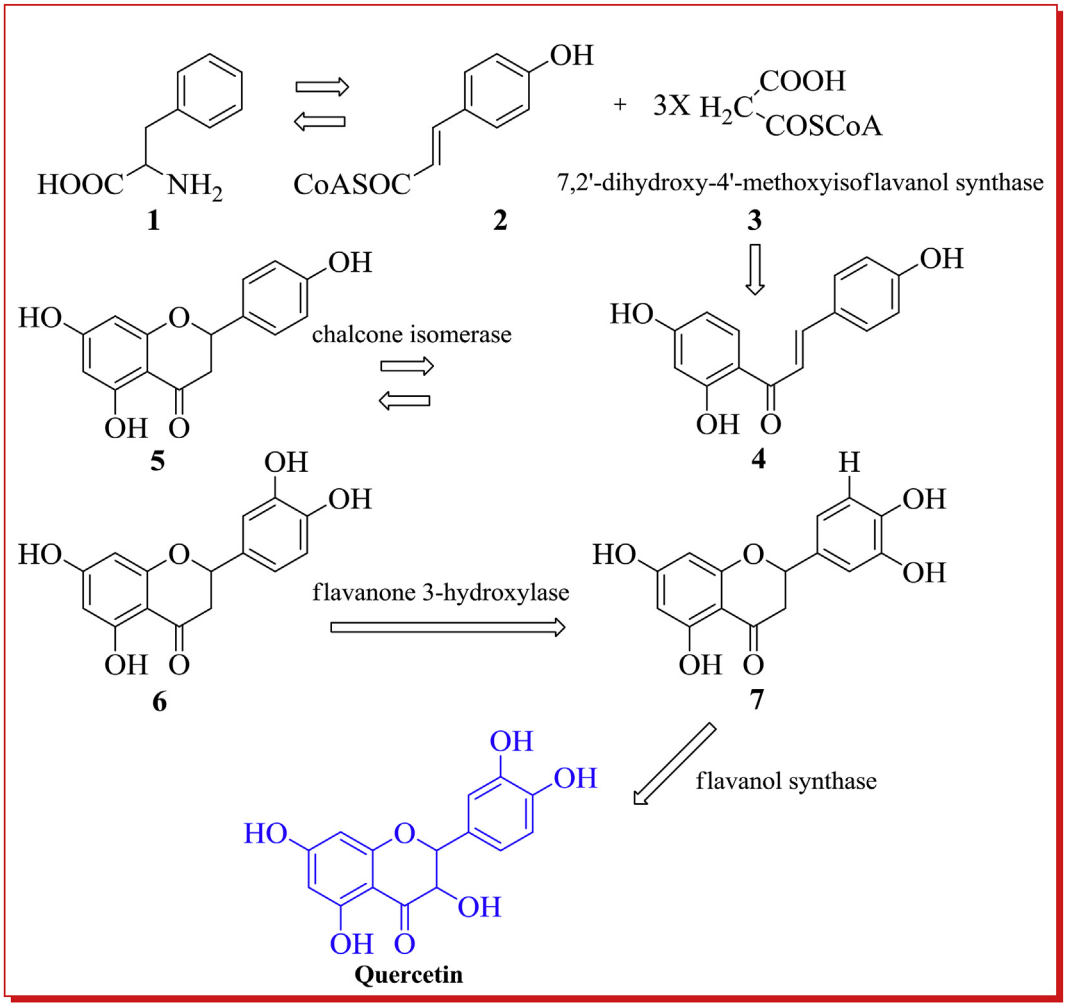


Fig. 5. A summary of main pathway of quercetin biosynthesis in plants.

this plant flavonoid [33]. However, we describe here in detail how quercetin effects on cardiac problems.

An explanation of the role of quercetin on cardiac functions was provided with a first double-blind study report on plasma quercetin concentration [34], serum fatty acid levels and its relation to cardiac diseases in a controlled interventional trial in which a quercetin diet was given for a specified period [35]. This study was conducted on healthy men and women with no history of any heart diseases with cholesterol levels of 4.0–7.2 mmol/l. The individual subject under investigation consumed either quercetin-containing supplement in a capsule form that is equal to 1.0 g quercetin/d or rice flour placebo for 28 days. It was noticed in this study that there is a 23-fold increase in the plasma concentration of the quercetin in individuals taking quercetin capsules than the controlled group. No modification of total serum, triglyceride and cholesterol levels was observed in these subjects. The two scientists emphasized that there was no change in the risk factors for heart diseases in such matters and Quercetin supplementation did not alter serum cholesterol or triglyceride levels. The researchers expected that extended consumption of quercetin (1 g for 28 days) brought up 14-fold plasma quercetin level, i.e., 1.5 μmol/L of mean. Quercetin supplementation in the control group under study did not help in maintaining the serum cholesterol levels.

They claimed that no change noticed in other risk factors was mainly associated with the cardiovascular disease. In their experimental study, Conquer & Maiani increased the dietary intake of the quercetin to 50 folds than the normal. Other risk factors like platelet thromboxane B2 production, resting heart rate, aggregation of platelets and blood pressure also shows no improvement. The research also exposed that there was no impact of quercetin supplements on the polyunsaturated body fat stages in the serum [36] Conquer & Maiani concluded with experimental evidence that quercetin-containing capsules could enhance its concentration in the plasma, but it has no effects on risk factors associated with cardiovascular diseases [37].

Rendig et al. [38] later incorporated a dynamic study on the concentration of quercetin in the blood, which suggested endothelium-independent vasorelaxation of the coronary vessels due to higher levels of quercetin in animal models. This vasorelaxation was more significant in the resistance vessels than in the conductance vessels. Assuming the fact that red wine and alcohol is beneficial in reducing the risk factors for coronary heart diseases, Symons et al. [39] checked the effects of quercetin, ethanol and red wine as an active flavonoid compound in red wine, on the coronary resistant (80–150 p.m. i.d.) and conductance vessels (300–525 Jim. i.d.) in rabbit model. Hence, quercetin can be considered as a key factor in treating cardio-diseases as in this study at an alcohol concentration (14 mM) equivalent to average intake of red wine which evoked a small, transient constrictor impact in level of resistance and conductance veins ($9 \pm 4\%$, $n = 5$; $8 \pm 1\%$, $n = 7$, respectively; $p < 0.05$), ethanol alone at this concentration was without effect as well as quercetin (5.6, 8, and 30 μM) considerably relaxed level of resistance ($-32 \pm 4\%$, $n = 10$; $-47 \pm 2\%$, $n = 7$; $-82 \pm 6\%$, $n = 8$, respectively) and conductance ($-20 \pm 3\%$, $n = 8$; $-32 \pm 4\%$, $n = 8$; $-72 \pm 7\%$, $n = 8$, respectively) coronary arteries.

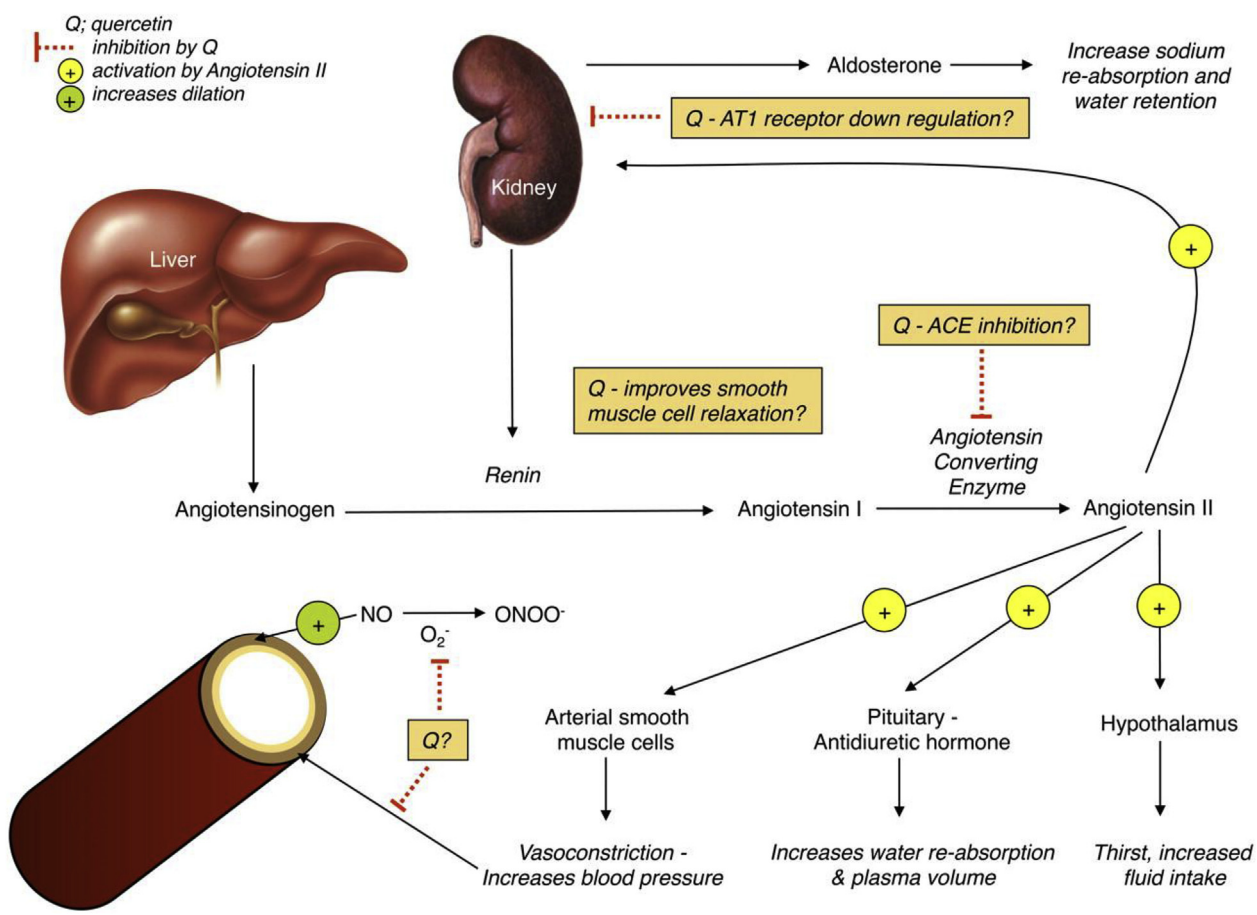


Fig. 6. Overview of possible mechanisms based on available *in vitro* and *in vivo* evidence by which quercetin (Q) may interact with the renin-angiotensin-aldosterone system to decrease blood pressure. **Source**: Reproduced from ref [30].

This cardio friendly action of quercetin was endothelium-independent and was considerably more significant in the level of resistance than in conductance veins. These data recommend that red wine and ethanol do not stimulate pleasure in the small coronary bloodstream at levels associated with average intake. In addition, Quercetin brings about noticeable endothelium-independent coronary vasorelaxation. However, the concentrations of quercetin necessary to accomplish this activity are not achieved with regular red wine intake.

Moreover, the vessel wall tension was measured before and after the consumption of these substances. Vessel wall tension was assessed in small and isolated segments controlled in a myograph (37 °C) which is pre-constricted with 30 mM K. It was studied that red wine induced little transient constrictor effect in blood vessels. Ethanol is not so helpful in producing any such effect if used alone, and the role of quercetin is very significant as a vaso-relaxer. This study strongly suggests that the red wine and ethanol do not have any direct role in the relaxation of the coronary vessels at a moderate level of consumption, so higher concentrations are required to attain concrete results. However, according to this study, quercetin-induced marked vasorelaxation in the coronary vessels [40,41].

In later years, several researchers worked on the inhibitory action of quercetin on different enzymes. Hackl et al. (2002) revealed the inhibitory effect of quercetin on angiotensin-converting enzyme activity by converting bradykinin and angiotensin I. The scientists found through experiment that effect of bradykinin was significant on the blood pressure in experimental anesthetized rats after pretreatment with captopril or quercetin as quercetin pretreatment (88.7 μmol/kg p.o, 45 min; 14.7 μmol/kg i.v., 5 min) considerably potentiated the hypotensive impact of bradykinin (10 nmol/kg i.v.) [42,43]. They claimed that quercetin and captopril have a similar mechanism of action if given orally or intravenously [44]. BK gave intravenously (10 nmol/kg) to experimental rats had a significant hypotensive effect (18.0 ± 0.7 mm Hg). In those rats pretreated with captopril (10 nmol/kg Lv.), an intravenous injection of BK or pretreatment with captopril in higher dose (100 nmol/kg p.o.), showed marked hypotensive response to BK (27.6 ± l.9and29.7 ± 1.8 mmHg, respectively).

To understand the effect of quercetin as an angiotensin-converting-enzyme inhibitor, scientists examined two groups of rats one treated with normal saline and other with the quercetin. Results showed that the animals treated with quercetin had a marked inhibition of the ACE enzyme. This study also revealed that the hypertensive response to angiotensin I was reduced by quercetin in a particular dose [45].

The subsequent studies gave a clear picture of the concept that quercetin and its derivatives found in onions and berries can help in reducing blood pressure in hypertensive animals. Quercetin and its derivatives are used to inhibit the pathway of the signals that induce cardiac hypertrophy. Researchers have demonstrated on a rat model that aortic constriction in rats on Q-supplemented diets had attenuated cardiac hypertrophy and relatively lowered the blood pressure. These changes had no evident effects on cardiac or vascular functions. In this study it gave standard or Q-supplemented chow (1 .5 g Q/kg chow) for 7 days before any abdominal aorta constriction or sham surgery (SHAM, n = 15; AAC, n = 15; SHAMQ, n = 15; AACQ, n = 14). The plasma and liver quercetin concentrations were raised ($P < 0.05$) with a decline in hepatic lipid oxidation levels ($P < 0.05$) after 14th postoperative day. The comparison was established between treated and non-treated rats. Cardiac protein kinase C 1311 translocation was also at normal levels ($P < 0.05$) in abdominal aortic constriction + quercetin (AACQ) versus abdominal aortic constriction (AAC) [46,47]. Carotid hypertrophy, as well as arterial blood pressure, were attenuated ($P < 0.05$) in the treated rats. There is no evident change in the values of extracellular regulated kinase 1/2 phosphorylation in both groups of rats. Cardiac hypertrophy has an increased risk of heart failure in animals. Significantly, quercetin handled mice did not display any unhealthy changes in myocardial operate (echocardiography). The scientists also demonstrated that the quercetin reduces thickening of the medial wall of the aorta and normalized cardiac translocation [48]. Hence, these changes were not accompanied by harmful effects on any cardiac or vascular function [49]. This study supports a significant anti-hypertensive and anti-hypertrophic role of quercetin in animal models without any effects on echocardiography.

The theoretical limit of the study fits well with an observation on the use of quercetin for prevention of cardiovascular diseases. Sanchez et al. (2007) provided evidence-based results that quercetin and isorhamnetin help in preventing AngII-induced endothelial dysfunction [50]. In a separate study, scientists tried to discover the effects of the flavonoid quercetin in mice after serious self-consciousness of nitric oxide supplements (NO) features with N^{ω}-nitro-L-arginine methyl ester. The researchers claimed with evidence that long-term use of quercetin reduced the risk of elevation in the levels of systolic arterial pressure (SBP) in spontaneously hypertensive rats (STR).

The progress of systolic hypertension, morphological factors, proteinuria, plasma malondialdehyde and nitrite and nitrate levels, hepatic glutathione and malondialdehyde content, glutathione enzyme action and general reactivity at the end of the research were evaluated. The outcomes became fixed after therapy with quercetin (5 mg/kg p.o or 10 mg/kg p.o.) for 5 several weeks in Wistar-Kyoto mice (WEEKY). There was a marked reduction in the mean arterial pressure (−12%) and heart rate (in STR) after 13 weeks of treatment with quercetin. The changes were noticed in the WEEKY as quercetin considerably restricted the growth of $N^{(\omega)}$-Nitro-L-arginine methyl ester hydrochloride (L-NAME) induced high blood pressure.

This impact was associated with a limited or full protection of most of the consequences caused by L-NAME such as (1) enhancing of the remaining ventricular and kidney weight indices; (2) proteinuria; (3) renal histological lesions, such as hyaline arteriopathy and thickening of the vascular wall with regular lack of the lumen; (4) improved endothelium dependent contraction; (5) increased thromboxane vascular B2 (TXB2) synthesis; (6) reduced plasma concentrations of nitrates plus nitrates (NOx); (7) increased plasma and hepatic malondialdehyde (MDA) concentrations; and (8) reduced glutathione peroxidase activity. In most situations, these results were amount reliant, but none of them was seen in normotensive creatures. Quercetin and its derivative inhibit the overexpression of P47P and result in increased O_2 production, thereby increasing nitric oxide bioavailability [51]. Quercetin and other flavonoids are theoretically documented as broad protein kinase inhibitors [52].

Following the well-established findings stated above were, a study by Edwards et al. (2007) came as a hallmark in hypertensive patients [14]. They established in an epidemiological study on rodents that quercetin supplementation reduces blood pressure and risk of stroke in already hypertensive cases [53]. To our knowledge, this was the first established literature that suggests that quercetin reduces blood pressure in cases of stage I hypertensive patients [54]. Researchers used a placebo-controlled models for this double-blinded study to analyze the effectiveness of 730 mg quercetin/d for 28 d vs. placebo and reductions in ($P < 0.01$) systolic (−7±2 mm Hg), diastolic (−5±2 mm Hg), and mean arterial pressures (−5±2 mm Hg) were seen in level 1 hypertensive sufferers after quercetin therapy.

However, indices of oxidant stress found in the plasma and urine were not affected by quercetin [55]. Hence, the quercetin

supplementation is highly effective in reducing the blood pressure. The researcher suggested the extrapolation of this study to human subjects in homogenous cohort studies. Later the data explained the important role of this flavonoid compound to be used as adjunct dietary therapy to control and maintain blood pressure [56]. Moreover, quercetin plays a key part in vasodilatation as the control in blood vessels pressure level is the vital for high blood pressure. Furthermore, large conductance Ca^{2+}-activated K^+ programs (BKCa) controls heart tone *in vivo*, which plays a crucial part in blood vessels' pressure level control. The related research also suggested that quercetin might stimulate BK_{Ca} channel in isolated myocytes from the coronary rat bloodstream and that this mechanism might be engaged in its heart relaxant results. These studies represent that quercetin (>0.1 μM) improved the frequency of spontaneous transient outward currents (STOCs) carried by BK_{Ca} channels and the outward currents in addition to cell membrane hyperpolarization. These results were eliminated by the particular BKCa blocker iberiotoxin and by catalase. Quercetin improved dichlorofluorescein fluorescence in the coronary bloodstream in a polyethylene glycol-catalase-sensitive manner, showing that it improved cytosolic H_2O_2.

The membrane-permeable analog of H_2O_2 *t*-butyl hydroperoxide resembled the consequences of quercetin on external outward currents. Hence, it was determined that quercetin improved BKCa voltages via production of intracellular H_2O_2 [57]. This impact is engaged, at least partly, in the vasodilator coronary results of quercetin. In a separate randomized research on STZ-induced suffering from diabetes Male Wistar-Kyoto mice, the impact of chronic oral management of quercetin (10 mg kg-1 body weight, by mouth for 6 weeks) on blood glucose, vascular function and oxidative stress was analyzed. Quercetin treatment decreased plasma malonaldehyde (MDA) plus 4-hydroxyalkenals (4-HNE) content while improving superoxide dismutase activity; total antioxidant capacity in suffering from diabetes mice. From the present research, it can be determined that quercetin management to suffering from diabetes mice regenerates vascular function, probably through improvement in the bioavailability of endothelium-derived nitric oxide products supplements products mixed to reduced blood vessels sugar level and oxidative pressure [58].

An intuitive consequence of the facts mentioned above was well studied in later studies. In a study published in 2008, Kawai et al. [59] gave new insight into the bioavailability of the quercetin and its derivatives and stated that the injured or inflamed arteries are the potential targets of dietary quercetin. Most of the studies previously conducted by researchers were on cultured cells to support our hypothesis. In those *in vitro* studies, scientists used higher concentrations of quercetin to induce anti-atherosclerotic effects. Moreover, same group of researchers conducted an evidence-based study *in vivo* to resolve immunohistochemical data showing the presence of different target sites of quercetin and its derivatives. The scientists suggested further studies to understand the molecular mechanism for the effects of the quercetin on the cardiovascular system [60–62]. Modulating outcomes on gene expression profile of rat cardiomyocyte by quercetin was examined by Angeloni et al. adopting DNA microarrays [63].

Results revealed unique short-term changes in gene expression due to quercetin and an impressive upregulation of phase 2 enzymes, introducing quercetin capability to act also with an oblique anti-oxidant procedure. Quercetin is accountable for L-type Ca^{2+} channel activation in cardioprotective operates as was examined by Saponara et al. [64] in vascular smooth muscle cells. L-type Ca^{2+} currents [$I_{Ca}(L)$] were documented in freshly isolated rat tail main artery myocytes using the Whole-cell patch-clamp method, and the same was in assessment to (S)-(−)-methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)pyridine-5-carboxylate (Bay K 8644). It was discovered that pre-incubation of myocytes with levels of quercetin *per se* ineffective as an L-type Ca^{2+} channel activator (0.1 and 0.3 μM) restricted considerably the biggest possible reaction evoked by Bay K 8644, but without altering its efficiency. Quercetin (0.1 μM) avoided the hyperpolarizing move of the steady-state inactivation flip due to 0.1 μM Bay K 8644 and its stimulation of $I_{Ca}(L)$ tail current intensity without modifying Bay K 8644-induced outcomes on $I_{Ca}(L)$ activation, inactivation, deactivation kinetics as well as on use-dependence and restoration from inactivation. Quercetin at nutritionally essential levels restricted the responsiveness of typical L-type Ca^{2+} channels to the pharmacological stimulation managed by Bay K 8644. This information improves a better knowing of quercetin outcomes on experimental *in vivo* cardioprotection.

Research confirms the counterintuitive observation on human subjects that quercetin and its derivatives improve endothelial functions and hence improve the cardiac functions [65]. An endothelial dysfunction is a primary event in the pathogenesis of atherosclerosis and its consequences [66]. The author of this publication gave substantive data regarding the role of dietary quercetin and its derivative epicatechin in improving the endothelial function. These flavonoids modulate the concentration of nitric oxide in the blood and hence enhance vascular activity [67]. The effects of flavonoids are exerted by inhibition of NADPH oxidase that activates eNOS. Though this study was conducted for a short period, it helps in investigating the molecular mechanism after the intake of dietary quercetin [68].

Quercetin has the ability to control dyslipidemia. Variations in fat hepatic functions are crucial to the management of serum fat levels, and outcomes of quercetin on lipogenesis in rat liver cells were examined by Gnoni et al. [69]. In this research, the impact of quercetin on the amount of synthesis of neutral lipids, fatty acids, phospholipids, cholesterol, and very-low-density lipoproteins were examined in rat hepatocyte revocation. Inhibition of fatty acid synthesis took place within 30 min of quercetin addition to the hepatocytes at a concentration level of 25 μM. A loss in label development mainly into TAG was noticed. The palmitic acid formation was considerably reduced within new synthesized fatty acids which suggested that during *de novo* fatty acid synthesis, enzymatic step(s) was affected. Overall, in hepatocytes normal rats, the quercetin decreased in both *de novo* fatty acid, and triacylglycerol (TAG) synthesis, with a major loss of VLDL-TAG formation, may represent a potential process resulting in the exposed hypotriacylglycerolemic effect of quercetin. Another research exposed that quercetin restricted the improved necessary protein kinase C inhibitory activity due to endothelin-1.

The result indicated that ET-1-induced NADPH oxidase upregulation and eNOS uncoupling via Protein kinase C (PKC) resulting in endothelial breakdown were prevented by quercetin [70]. Hence it can be mentioned that quercetin stops general superoxide production due to endothelin-1.93 Overweight or obese mature subjects with age between 25 and 65 years with metabolic problem features were exposed to a double-blinded, placebo-controlled cross-over test with 6-week treatment times to examine the repercussions of quercetin products (150 mg quercetin/d) on veins pressure levels, fat metabolic rate, signs of oxidative pressure, swelling, and composition [71]. Bioassay outcomes confirmed that mean fasting plasma quercetin concentrations improved from 71 to 269 nmol/L ($P < 0.001$) during quercetin treatment. Contrary to glucose tablet, quercetin reduced systolic veins pressure levels (SBP) by 2.6 mmHg ($P < 0.01$) in the entire research group, by 2.9 mmHg ($P < 0.01$) in the sub-group of hypertensive subjects and by 3.7 mmHg ($P < 0.001$) in the subgroup of young grownups mature 25–50 years. Quercetin also reduced serum HDL-

cholesterol levels ($P < 0.001$) while total cholesterol levels, TAG, and the LDL: HDL-cholesterol and TAG: HDL-cholesterol rates were unaltered.

Quercetin significantly reduced plasma concentrations of atherogenic oxidized LDL, but did not impact TNF-α and C-reactive protein when compared with placebo. Blood parameters of liver and kidney function, hematology and serum electrolytes did not expose any negative outcomes of quercetin. In summary, quercetin reduced SBP and plasma oxidized LDL concentrations in overweight subjects with a high-CVD risk phenotype. These results offer further proof that quercetin may protect us against CVD. Annapurna et al. [72] tried to examine the cardioprotective actions of quercetin in ischemia-reperfusion-induced myocardial infarction in both normal and diabetic rats. In this study, staining agent 2,3,5-triphenyltetrazolium chloride was employed to obtain myocardial infarct size. Serum and tissue malondialdehyde levels and superoxide dismutase and catalase in heart tissue were estimated spectrophotometrically.

A lead II electrocardiogram was monitored at various intervals throughout the experiment. The results confirmed the larger infarct sizing, improved fat peroxidation, restricted decrease of antioxidant nutrients and excessive fall in heart rate in diabetic hearts exposed to *in vivo* ischemia–reperfusion in evaluation to frequent rats exposed to ischemia–reperfusion. Furthermore, quercetin significantly boundaries the infarct sizing in both frequent and suffering from diabetic issues, significantly attenuate the fat peroxidation and reasonably improved the beat quantity in both types. Delicate fresh air types (ROS), endothelial nitric oxide synthase (eNOS), and inducible nitric oxide supplements products synthase (iNOS) are required in the pathophysiology of myocardial ischemia-reperfusion harm (MIRI). A research has confirmed that quercetin offers a safety effect against MIRI as its impact on NOX_2, eNOS, and iNOS was examined by Wan et al. [73] after MIRI in rabbits. Management of quercetin reduced NOX_2, eNOS, and iNOS mRNA and necessary protein overall look both in management and in I/R (ischemia/reperfusion), middle ($P < 0.01$). Gene and protein expression of NOX2 and iNOS were improved after MIRI. Quercetin not only restricted myocardial ischemia-reperfusion-induced NOX2 and iNOS mRNA and protein expression, but also restricted eNOS mRNA and protein expression.

Han et al. [74] examined whether quercetin products could attenuate the development of center hypertrophy due to pressure overload. The study revealed complete self-consciousness of center hypertrophy and malondialdehyde production due to pressure overload which was protected up by quercetin. The actions of extracellular signal-regulated kinase (ERK1/2), p38 MAP kinase, Akt and GSK-3β were considerably enhanced with pressure overload and attenuated by quercetin therapy. Hence, it was recognized that quercetin seemed to avoid the growth of cardiac hypertrophy induced by pressure overload in rats. Moreover, it was also discovered that quercetin could add advantages to the cardioprotective impact of amlodipine against damage activated in the heart by ischemia/reperfusion [75].

The impact of quercetin on the heart was analyzed by Mezesova et al. [76] after 4-week supplements in the amount of 20 $mgkg^{-1}day^{-1}$ to young male normotensive control (C) and to automatically hypertensive rats (SHR) over the period of their 5th-8th week of age. The research was targeted on the impact of quercetin on the qualities of the kidney Na, K-ATPase, a critical program in keeping the homeostasis of sodium in the organism. Spontaneous hypertension by itself enhanced the action of Na+/K + -ATPase probably as an impact of a greater variety of effective active enzyme molecules, as observed by the 15% increase of V_{max}, along with enhanced appreciation to ATP, as indicated by the 30% loss of the value of Michaelis-Menten constant K_m between without treatment SHR vs. without treatment normotensive rats.

Quercetin caused a damage of Na, K-ATPase action when all ATP and Na^+ levels examined. Moreover, in another research, quercetin (10 mg/kg) was applied orally as pretreatment to Wistar mice every day for seven times. After pretreatment, mice were caused by myocardial infarction by subcutaneous hypodermic injection of isoproterenol (100 mg/kg) at a period of 24 h for two times. Quercetin pretreatment considerably ($P < 0.05$) reduced the ST-segment level and decreased the stages of fat peroxidation products in plasma and heart in isoproterenol handled cardiotoxic mice. Quercetin pretreatment also considerably ($P < 0.05$) decreased the levels of free fatty acids in serum, serum phospholipids, total cholesterol, triglycerides and heart and heart mitochondria in isoproterenol-treated cardiotoxic mice. Considerably ($P < 0.05$) a higher level of heart and heart mitochondrial phospholipids were seen in quercetin pretreated isoproterenol handled cardiotoxic mice. It is the pretreatment which significantly ($P < 0.05$) decreased the stages of serum low-density lipoprotein and very low-density lipoprotein-cholesterol and apparently ($P < 0.05$) improved serum high-density lipoprotein-cholesterol in isoproterenol handled cardiotoxic rats. Moreover, quercetin considerably ($P < 0.05$) reduced the activity of 3-hydroxy-3-methyl glutaryl-coenzyme A reductase in plasma and liver and significantly ($P < 0.05$) improved the activity of the liver organ lecithin cholesterol stages acyltransferase in isoproterenol handled cardiotoxic mice. *In vitro* research on complete anti-oxidant activity confirmed the anti-oxidant property of quercetin. It is the antioxidant activity of quercetin that stops fat peroxidation as well as and stops building up of fats, modifications in lipoproteins and electrocardiogram in isoproterenol handled cardiotoxic mice [77]. Furthermore, the impact of quercetin on vasoconstrictor and vasodilator reactions in the porcine separated heart were identified by Suri et al. [78] and quercetin improved both the cyclic GMP content of the artery and cyclic GMP-dependent relaxations to GTN and SNP as well as restricted receptor-mediated contractions of the porcine separated heart by an endothelium-independent activity.

Scientists have found that oral supplements with quercetin (50 mg/kg bw/d) for 4 weeks in Cd intoxicated rats considerably ($P > 0.05$) has reduced the plasma levels including total cholesterol, the activity of hydroxyl-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), triglycerides (TGs), thiobarbituric acid reactive substances (TBARS), lipid hydroperoxides (LOOH), low-density lipoprotein cholesterol (LDLC), phospholipids (PL), very low density lipoprotein cholesterol (VLDL-C), free fatty acids (FFA) and significantly ($P > 0.05$) raised the action of LCAT and the plasma levels of HDL-C. The oral supplementation also considerably ($P > 0.05$) decreased the FFA, hepatic oxidative stress markers, TGs, cholesterol and significantly ($P > 0.05$) enhanced the lecithin cholesterol acyltransferase activity and the phospholipids in liver [79].

Research exposed that quercetin considerably attenuated 2K1C-hypertension improved in NADPH oxidase activity and general superoxide manufacturing ($P < 0.05$). In the 2K1C model, one renal artery is narrowed to constantly reduce renal perfusion, while the other renal artery continues to be fresh. Hence, quercetin regenerates plasma nitrite and nitroso species levels in renovascular hypertension, and such studies help to understand the probable mechanism of action (Fig. 7) by which quercetin acts as antihypertensive agent [80].

Kleemann et al. [81] examined the quercetin's effect on heart threat indicators such as individual C-reactive proteins (CRP) and on coronary artery illness using transgenic humanized designs of cardiac arrest as quercetin (0.1%, w/w in diet) was given to individual CRP transgenic rats, a humanized inflammation and atherosclerosis models, and ApoE*3Leiden transgenic mice. In this

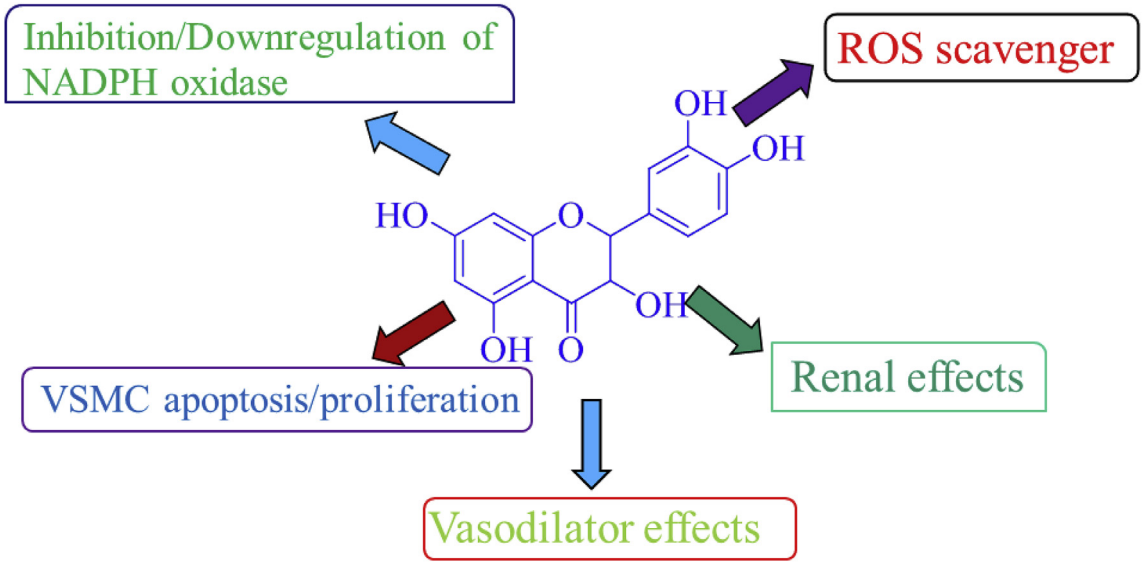


Fig. 7. Mechanisms of antihypertensive action of quercetin. **Source**: Adopted from Ref [80b].

experiment, in cultured human endothelial cells, quercetin secured against H_2O_2-induced fat peroxidation and decreased the cytokine-induced cell-surface appearance of VCAM-1 and E-selectin.

Quercetin also reduced the transcriptional action of NFkB in human hepatocytes. In human CRP transgenic mice (quercetin plasma concentration: 12.9 ± 1.3 μM), quercetin quenched IL1β-induced CRP appearance, as sodium salicylate effected. In ApoE*3Leiden mice, quercetin (plasma concentration: 19.3 ± 8.3 μM) significantly attenuated coronary artery illness by 40% (sodium salicylate by 86%). Quercetin did not show the impact on atherogenic plasma lipids or lipoproteins, but it significantly reduced the distributing information related risks SAA and fibrinogen. Mixed histological and microarray research of aortas exposed that quercetin impacted vascular cell proliferation is thereby decreasing sore atherosclerotic development. Quercetin also reduced the gene expression of particular aspects suggested in local vascular inflammation. Hence, quercetin decreases the appearance of individual CRP and heart risks (SAA, fibrinogen) in rats *in vivo*. Coronary artery illness is known to be an inflammation-related illness. Dendritic tissues (DCs) are important for the control of the defense mechanisms. The impact of the flavonol quercetin on DC action and difference *in vivo* was analyzed [82] among eight healthier men volunteers with the management of 500 mg of quercetin twice every day over 4 several weeks. It was found that quercetin decreased DC bond (−42%; $p < 0.05$) and appearance of CD11a (−21%; $p < 0.05$).

Lastly, it was determined that quercetin decrease circulating plasmacytoid DCs and systemic asymmetric dimethylarginine (ADMA) levels. The immunoregulatory results of quercetin may promote the anti-atherosclerotic perspective of flavonols. The safety impact of quercetin against arteriosclerosis was reported by Ishizawa et al. [83] and lately confirmed that quercetin 3-O-β-D-glucuronide (Q3GA) is one of the significant quercetin conjugates in human plasma. Due to this effort, platelet-derived development factor–caused cell migration and proliferation were restricted by Q3GA in VSMCs. Q3GA attenuated angiotensin II-induced vascular smooth muscle cell (VSMC) hypertrophy through its inhibitory effect on JNK and the AP-1 signaling pathway. Q3GA scavenged 1,1-diphenyl-2-picrylhydrazyl radical recorded by the electron paramagnetic resonance method. Also, immunohistochemically studies with monoclonal antibody 14A2 focusing on the Q3GA confirmed that the beneficial discoloration particularly builds up in individual atherosclerotic patches, but not in the regular aorta. These results recommend Q3GA would be an effective metabolite of quercetin in plasma and may have precautionary results on arteriosclerosis appropriate to VSMC problems. Furthermore mixture of quercetin with α-tocopherol shows improved aerobic safety results on isoproterenol-induced myocardial infarcted mice [84].

Additionally, quercetin caused a more efficient concentration-dependent relaxant impact than catechin in the separated rat aorta, and the isobolographic research of the mixtures showed no complete or opposed results between them, i.e. their results were preservative. Quercetin was more efficient in mesenteric than in lung bloodstream. Catechin had poor results in these veins and did not change the consequences of quercetin. The endothelial malfunction caused by improved oxidative stress by the superoxide dismutase chemical diethyldithiocarbamate was avoided by quercetin, whereas catechin revealed a poor impact and the 1:1 combination advanced effects in contrast to the genuine substances. Quercetin but not catechin revealed a pro-oxidant and NO-scavenging impact, which was not avoided by catechin. In summary, catechin was less effective than quercetin as a vasodilator, pro-oxidant or to prevent endothelial malfunction, and there was no complete synergistic interaction between quercetin and catechin [85]. Lee et al. [86] confirmed that quercetin-rich supplements, based on onion peel extract, enhances cardiometabolic risk components in healthy male smokers in double blinded, placebo-controlled randomized, parallel designs.

Arbitrarily allocated subjects were directed to take either the placebo ($n = 43$) or 100 mg quercetin supplements each day ($n = 49$) for 10 weeks. Quercetin-rich supplements considerably reduced serum levels of total cholesterol levels ($P < 0.05$) and LDL-cholesterol ($P < 0.01$) in comparison to control therapy. In addition, changes in HDL-cholesterol were considerably greater in subjects getting quercetin-rich supplements than the placebo as well as both systolic ($P < 0.05$) and diastolic hypertension ($P < 0.01$) reduced significantly in the quercetin-rich supplements group. As a result, it can be stated that daily quercetin-rich supplements from onion peel extract has positive effects on glucose and blood pressure levels as well as on lipid levels, indicating a valuable contribution for quercetin as a protection against heart risk. Angelone et al. [87] analyzed quercetin affect on mammalian basal

myocardial and coronary function in isolated and Langendorff perfused rat hearts under both basal conditions and α- and β-adrenergic stimulation. Quercetin caused biphasic inotropic and lusitropic effects, positive at lower levels and negative at higher levels.

It was found that therapy with 10 mg/kg quercetin defends from the development of experimental autoimmune myocarditis (EAM) to dilated cardiomyopathy (DCM) [88]. To further validate this speculation, Arumugam et al. [89] used the rat design of EAM caused by porcine heart myosin and recognized that the post-myocarditis rats experienced from raised endoplasmic reticulum (ER) stress and negative heart modified by means of myocardial fibrosis, whereas the rats handled with quercetin have been secured from these changes as confirmed by the reduced myocardial stages of ER stress and fibrosis indicators when in contrast to the vehicle-treated DCM rats. Moreover, the myocardial measurements and cardiac function were maintained considerably in the quercetin-treated rats in evaluation with the DCM rats handled with vehicle alone. Remarkably, the rats treated with quercetin revealed significant suppression of the myocardial endothelin-1 and also the mitogen-activated protein kinases (MAPK) indicated that the protection by quercetin treatment against the development of EAM includes the modulation of MAPK signaling cascade. Larson et al. hypothesized that acute quercetin aglycone management decreases blood veins stress stages in hypertensive men by reducing angiotensin-converting compound (ACE) action and by decreasing the rate of distributing endothelin-1 (ET-1) to nitric oxide supplements and that these modifications will enhance endothelial operate. In this research, using a double-blind, placebo-controlled, cross-over design quercetin or placebo was applied to normotensive men ($n = 5$; 24 ± 3 years; 24 ± 4 kg/m2) and level 1 hypertensive men ($n = 12$; 41 ± 12 years; 29 ± 5 kg/m2). In level 1 hypertensive individuals, lcd quercetin increased (0.6 ± 0.4 vs. 0.05 ± 0.02 μmol/L), and mean BP reduced (103 ± 7 vs 108 ± 7 mmHg; both $P < 0.05$) 10 h after quercetin vs placebo, respectively. Hence, it was determined that a single dose of quercetin aglycone decreased BP in hypertensive men through a procedure that is separated from changes in ACE action (ET-1), or nitric oxide supplements bioavailability and without impacting general reactivity [90].

Shen et al. examined the consequences of supraphysiological stages of quercetin and its methyl and glucuronide metabolites (3′-O-methyl- quercetin, and quercetin-3-O-glucuronide) on initial of adenosine proteins kinase (AMPK) and endothelial nitric oxide supplements synthase (eNOS) in individual aortic endothelial tissues (HAECs) and endothelial operate in separated aortic rings from C57BL mice. It was found that 5 and 10 μM quercetin and its metabolites, and pretreatment of arteries with quercetin and its metabolites can secure veins against hypochlorous acid-induced endothelial malfunction in separated arteries ($P < 0.05$). It was noticed that inhibition of AMPK obstructed these safety results. It was also perceived that 5 and 10 μM quercetin and its metabolites could generate initial of AMPK and eNOS in individual aortic endothelial tissues, and lead to an increase in the stages of S-nitrosothiols and nitrite in cell culture media ($P < 0.05$). These outcomes further supported by the cardioprotective effects of specific nutritional flavonoids [91]. Liu et al. analyzed the impact of quercetin on myocardial oxidative stress and immunity function incapacity caused by isoproterenol (70 mg/kg) in Wistar rats. In this experiment, blood immunity index, cardiac marker enzymes and antioxidative parameters in hearts were calculated. It was found that the levels of blood AST, creatine kinase, NO, NOS, IL-10, IL-1, IL-8, and lactate dehydrogenase in isoproterenol-treated rats were considerably improved. The mice administrated with isoproterenol revealed the decreases in myocardial antioxidant enzymes activities and management of quercetin considerably ameliorated myocardial oxidative damage and immunity function impairment caused by isoproterenol [92].

The metabolic problem is a risk aspect of cardiovascular disease and nonalcoholic fatty liver disease (NAFLD). Panchal et al. [93] examined the reactions to the quercetin in men Wistar mice (8–9 week old) separated into four categories. Two classes were given either high-carbohydrate or high-fat (H) or corn starch-rich (C) diet for 16 weeks; the remaining two groups were given either a C or H diet for 8 weeks followed by further 8 weeks quercetin (0.8 g/kg) supplementation (CQ and HQ, respectively). It was discerned that comparison between C mice, the H mice had higher dyslipidemia, body weight, higher systolic blood pressure, cardiovascular remodeling, affected glucose tolerance, NAFLD, and abdominal obesity. The H mice had a lower protein expression of carnitine palmitoyltransferase 1 (CPT1), heme oxygenase-1 (HO-1) and nuclear aspect (erythroid-derived 2)-related factor-2 (Nrf2) with greater expression of NF-kB in both the liver and heart as well as less appearance of caspase-3 in the liver than in C rats. HQ mice had the higher appearance of Nrf2, HO-1, and CPT1 and reduced appearance of NF-kB than H mice in both the heart and the liver. HQ rats had reduced abdominal fat and lower systolic hypertension along with attenuation of changes in structure and function of the middle and the liver body organ contrary to H mice, although body weight and dyslipidemia did not vary between the H and HQ mice. Thus, quercetin therapy attenuated most of the signs of a metabolic problem, such as abdominal obesity, NAFLD and cardiovascular renovating with the most likely systems being reduced in oxidative stress and inflammation.

He et al. [94] examined the *in vivo* and *in vitro* safety results of pentamethyl quercetin (PMQ); a participant of poly methoxy flavonoids (PMFs) in heart hypertrophy. An *in vivo* heart hypertrophy recognized by stomach aorta banding strategy in mice was handled with PMQ in improving doses (2.5, 5, and 10 mg kg^{-1} d^{-1}). During the research, it was observed that daily oral administration of PMQ (2.5, 5, and 10 mg/kg for 7 weeks) avoided this histology, gene and proteins change additional to AAC process. Moreover, the up-regulated inflammation aspects such as TNF-α and IL-6, and the down-regulated PPAR α and PPAR β were normalized by PMQ therapy. Hence, it can be determined that PMQ has important safety results on heart hypertrophy through up-regulating the mRNA and proteins stages of PPAR α and PPAR β engaged in the procedure of inflammation response and cardiac fibrosis. Furthermore Galindo et al. [95] analyzed spontaneously hypertensive rats (SHR) were arbitrarily allocated to four trial treatments for five weeks treatment: (1) 10 mg/kg quercetin by orally once daily and 2% DMSO i.p.; (2) 1 mL of 1% methylcellulose orally and 10 mg/kg quercetin i.p. injection. (3) 1 mL of 1% methylcellulose orally and 2% DMSO i.p. (control group); (4) 10 mg/kg quercetin orally divided in two daily doses ($5 + 5$ at 12 h intervals) and 2% DMSO i.p. Individual amount and two every day amounts, in a long-term oral therapy, were similarly efficient, both repairing the affected aortic endothelium-dependent vasodilatation and decreasing mesenteric contractile reaction to phenylephrine, systolic hypertension, pulse amount, and center and renal hypertrophy. Attenuation of general NADPH oxidase-driven O_2^- production was also discovered in orally treated rats. In summary, oral quercetin was excellent to intraperitoneal management of the security from heart problems in SHR.

Redondo et al. [96] explored the impact of quercetin, catechin, and the combination, on Angiotensin II (AngII)-induced redox-dependent signaling pathways and cell behavior. Mesenteric smooth muscle cells (MesSMC) from spontaneously hypertensive rats were incubated with AngII (0.1 μ mol/L) alone or with the mixture of low concentrations of quercetin and catechin. AngII-increased ROS production was reduced by the mixture of the

separately ineffective low concentration of quercetin (15 μ mol/L) plus catechin (20 μ mol/L). This mixture decreased AngII-stimulated NAD(P)H oxidase activation and p47phox translocation to the cell membrane, without affecting Nox2 expression. Coincubation of quercetin plus catechin considerably restricted AngII-induced migration and growth. These results were separate of *p*-ERK1/2 and relevant with decreased p38MAPK phosphorylation and confirmed that low levels of singly non-effective flavonoids when are mixed apply a complete impact in suppressing AngII-induced redox-sensitive signaling pathways.

Yan et al. [97] hypothesized that quercetin prevents heart hypertrophy by preventing activator protein 1 (c-fos, c-jun proteins) and initiating PPAR-γ signaling pathways. It was confirm during *in vivo* research; AP-1 (c-fos, s-jun) initial was covered up in the quercetin-treated number of spontaneously hypertensive rats, as was the downstream hypertrophy gene, including mRNA levels of ANP and BNP ($P < 0.05$, vs. SHRs). Furthermore, both western blotting and real time-PCR verified that PPAR-c protein and mRNA were enhanced in the myocardium and AP-1 proteins and mRNA were considerably reduced in the quercetin-treated team ($P < 0.05$, vs. SHRs). Besides, European blotting and actual time-PCR research also revealed that transfection with PPAR-c siRNA considerably improved AP-1 signaling and changed the consequences of quercetin self-consciousness on mRNA appearance stages of genetics such as atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) in hypertrophic H9C2 tissues. Lately, it was also observed that the organic flavonoid quercetin calms the rat end primary artery partially via a PKG-mediated activation of sleek and muscular KCa1.1 channels [98]. The elevated circulating lipid levels are known risks for heart illnesses and to analyze the consequences of quercetin on lipid metabolism, Hil et al. [99] handled rats with a mild-high-fat diet plan without (control) or with supplements of 0.33% (w/w) quercetin for 12 several weeks. The body weight, energy intake and hepatic lipid build-up did not vary considerably between the quercetin and control group. In the serum of quercetin-fed mice, triglycerides (TG) were reduced with 14% ($p < 0.001$) and level of total polyunsaturated fatty acids (PUFA) was positively improved with 13% ($p < 0.01$). Oleic acid, palmitic acid, and linoleic acid were all reduced by 9–15% ($p < 0.05$) in quercetin-administered mice. Both palmitic acid and oleic acid can be oxidized by Omega (ω)-oxidation. Gene expression profiling revealed that quercetin improved hepatic fat metabolic rate, especially v-oxidation. At the gene level, this was proven by the up-regulation of cytochrome P450 (Cyp) 4a10, Cyp4a14, Cyp4a31 and Acyl-CoA thioesterase 3 (Acot3). The transcription factor constitutive androstane receptor and cytochrome P450 oxidoreductase regulators were also upregulated in the quercetin-fed rats. Hence, it was identified that quercetin consumption improved hepatic fat v-oxidation and reduced corresponding distributing fat stages, which may promote prospective benefits on CVD.

An individual research conducted by Wang et al. [100] examined whether quercetin postcondition has any safety results on myocardial ischemia/reperfusion (I/R) damage *in vivo* with its prospective cardioprotective systems. It was documented that male Sprague-Dawley rats were arbitrarily assigned to five categories: sham, I/R, quercetin postconditioning, Que + LY294002 [a phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway inhibitor], and LY294002 + I/R. I/R was produced from 30-min coronary occlusion followed by 2-h reperfusion. Additionally, Western blotting identified the phosphorylation of Akt, protein expression of Bcl- 2 and Bax. Quercetin post conditioning considerably decreased infarct size and serum levels of creatine kinase and lactate dehydrogenase in contrast to the I/R group (all $P < 0.05$). Furthermore, Apoptotic cardiomyocytes and caspase-3 immunoreactivity were also covered up in the Q postconditioning group compared with the I/R group (both $P < 0.05$). Akt phosphorylation and Bcl-2 expression improved after Q postconditioning, but Bax expression decreased while LY294002 restricted these effects. The information indicates that Q postconditions can generate cardio-protection by initiating the PI3K/Akt signaling process and modulating the expression of Bcl-2 and Bax proteins. Recently, *in vitro* research recommended that quercetin mitochondrion tropic derivatives antagonize nitrate tolerance, and endothelial dysfunction of isolated rat aorta rings [101]. Zahedi et al. [102] performed a double-blind randomized clinical test on 72 women with type 2 diabetes for 10 weeks and assigned to quercetin and placebo groups employing a permutated block randomization of size two.

The amount of Quercetin was specified to participants as a 500 mg capsule daily and biochemical factors were calculated at baseline and the end of the study, and changes were compared using appropriate mathematical techniques. Consequently, in contrast to placebo, quercetin consumption reduced systolic hypertension considerably (-8.8 ± 9.3 vs. -3.5 ± 11.7, $P = 0.04$) and high-density lipoprotein cholesterol levels (HDL-C) was significantly reduced in both categories while changes in complete cholesterol levels, low-density lipoprotein cholesterol levels (LDL-C), triglycerides (TG) and rate of TG/HDL-C and LDL-C/HDL-C were not important between and within categories. Quercetin supplements considerably decreased the serum concentration of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) ($P = 0.01$ and $P < 0.0001$, respectively).

Moreover, Tang et al. [103] exposed that one of the systems of quercetin defending cardiomyocytes from A/R damage might improve the appearance of PKCε proteins and then improve the action of its downstream pathway. Lindane is a man-made organochlorine pesticide used to kill pests used for farming reasons and encourages oxidative pressure (OS) by interacting with the cell membrane, which activates the creation of ROS, and toxic creation mediates lindane-induced poisoning. The results recommend that gallic acid and quercetin offer protection against lindane-induced myocardial damage, possibly through keeping levels of endogenous antioxidant enzymes and membrane-bound ATPase activity, as well as suppressing fat peroxidation [104].

In the latest research, healthy men (44 ± 10 years, $n = 23$) were exposed to 4.3 g of onion extract (containing 51 mg of quercetin) once a day for 30 days. The response of the chronic onion extract consumption were analyzed, using fasting and postprandial flow-mediated vasodilation (FMD) analysis. It was observed that maltose loading significantly decreased FMD both before and after chronic onion extract intake ($p = 0.000037$ and $p = 0.0035$, respectively). The chronic onion extract consumption did not considerably impact fasting FMD ($p = 0.069$) but enhanced the postprandial FMD considerably from $5.1\% \pm 2.2\%$–$6.7\% \pm 2.6\%$ ($p = 0.00015$). Additionally, the chronic onion extract consumption did not modify systemically and forearm hemodynamics. Furthermore, in guinea pig ventricular cardiomyocytes, quercetin depresses the action potential duration and inhibited the underlying ionic currents I_{CaL}., I_{Krec}.I_{K1} in cardiomyocytes. In rat aorta, quercetin (0.1–100 μM) relaxed the contraction induced by pretreatment with 5 μM norepinephrine (NE) in a concentration-dependent manner. Finally, it was concluded that quercetin induces [Ca2+]i elevation, leading to NO production and K_{Ca} channel activation in endothelium cell. The hyperpolarization induced by the activation of K_{Ca} channel inhibits Ca channel in smooth muscle cell. Moreover, modulation of gap junction aggravates the vasodilatation (Fig. 8) [105]. These results recommend that chronic onion extract intake ameliorate postprandial endothelial dysfunction in healthy men and may be beneficial for enhancing heart health [106].

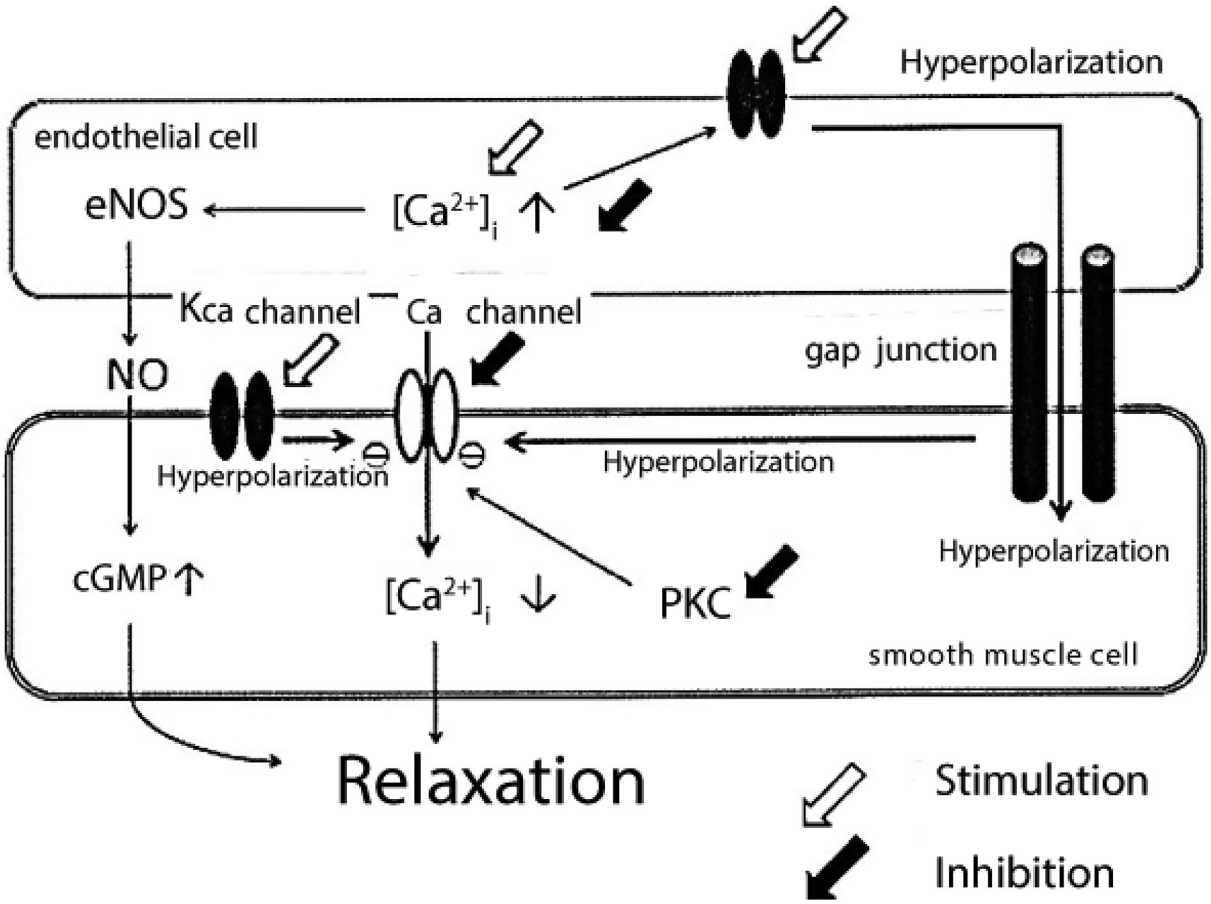


Fig. 8. Diagram for the mechanism of quecetin-induced vasorelaxation. **Source**: Reproduced from Ref. [105].

Table 1
Prediction of drug-like properties of quercetin.

Name	miLogP	TPSA (A°)	No. of atoms	No of rotatable bonds	Volume
Quercetin	1.68	131.35	22	1	240.08

3. Druggable properties of quercetin

The druggable properties and bioactivity score (Tables 1 and 2) of Quercetin were calculated using Molinspiration software (http://www.molinspiration.com/). Properties such as partition coefficient (LogP) gives information about the partitioning of a molecule between aqueous and lipophilic phases.LogP plays a vital role in maintaining the Hydrophilic-Lipophilic Balance (HLB) during the drug formulation stage [107,108]. Total Polar Surface Area (TPSA) is a variable that is useful in predicting the cell permeability of a molecule in the drug discovery process. A molecule with a TPSA value of less than 140 A° considered to be crossing the Blood Brain Barrier (BBB).

The molecules having bioactivity score higher than 0.00 are considered to have good biological significance, whereas scores between −0.50 and 0.00 are reasonably active and if the value is less than −0.50 it will be considered as inactive [109]. Since, most of the predicted scores are in between −0.50 and 0.00, it is worthwhile investigating Quercetin as a potential molecular for deeper biological studies.

4. Conclusion

Numerous attempts were conducted in the successive years to understand the basic mechanism of action of quercetin in reducing the risks of cardiovascular diseases. Each subsequent year provides extensive evidence-based study to elucidate our hypothesis. Several randomized, double-blind, placebo-controlled, crossover studies on animals as well as human with different stages of the cardiac disease have shown that treatment with high-dose quercetin and its derivatives led to an impvrovement in cardiac functions, suggesting the potential for quercetin to be used therapeutically in the treatment of cardiac diseases although relevant details of the molecular mechanism have not yet been fully elucidated. It can possibly connect to many of the molecular objectives known to engage in the pathophysiology of ischemic cardiovascular disease and stroke. Several evidence-based studies suggest mechanisms to observe cardiovascular diseases such as

Table 2
Bioactivity score.

Name	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear Receptor Ligand	Protease inhibitor	Enyme inhibitor
Quercetin	−0.06	−0.19	0.28	0.36	−0.25	0.28

aging effects, hypertension, angiotensin-converting enzyme activity and endothelial-dependent and independent functions. Moreover to its anti-oxidant impact, there is an amazing variety of enzymes whose action is modulated (mostly inhibited) by quercetin. Thus, it can be expected that a large variety of pathological/physiological processes and biochemical signaling pathways can be influenced by this flavonol. In a summary, quercetin exhibits significant heart related benefits as inhibition of LDL oxidation, endothelium-independent vasodilator effects, reduction of adhesion molecules and other inflammatory markers, the protective effect on nitric oxide and endothelial function under conditions of oxidative stress, prevention of neuronal oxidative and inflammatory damage and platelet antiaggregant effects. The objective of this review is to evaluate the therapeutic role of quercetin and its derivatives in cardiovascular diseases. This article provides proof assisting the perspective that quercetin should be considered a potential healing agents against a variety of cardiovascular diseases, giving rise to novel applications in their protection and therapy.

Conflicts of interest

The authors declare no conflict of interest.

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