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Review Article

Quercetin and Heart Health: From Molecular Pathways to Clinical Findings

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Cardiovascular diseases (CVD) are the leading causes of global death, increasing over time. Despite current novel improvements, it is still a major medical challenge. Quercetin (QU) is a flavonoid with anti-inflammatory, vasodilatory, antihypertensive, antiarrhythmogenic, and antiapoptotic effects. It can reduce low-density lipoprotein (LDL) and cholesterol oxidation and prevent endothelial dysfunction in CVD. Also, it can protect myocardial cells against oxidative stress and inflammation caused by free radicals. An updated review of the literature on the cardiovascular effects of quercetin was performed using PubMed, Embase, and Science Direct databases. The aim of this review is to summarize the various effects of quercetin on the cardiovascular system.

1. Introduction

Quercetin (QU) (3,3′,4′, 5,7-pentahydroxyflavone) is a natural compound and it belongs to the flavonoids that greatly exist in the daily diet and various vegetables, fruits, and plants including onion, asparagus, berries, buckwheat, and broccoli. Flavonoids are important kinds of polyphenols with cardioprotective properties in cardiovascular disease (CVD) [1]. This compound is known as a functional food that is used in medical supplements. QU may have beneficial impacts on several disorders such as CVD and cancers due to its antioxidant and anti-inflammatory properties [2]. Nowadays interests are attended to the chemical structures derived from natural products as a lead compound of novel drugs. This may be because of a vast range of activities, low drug resistance, and fewer side effects. This may reduce the prevalence of CVD [3]. As CVD is still the main cause of global death with an increasing rate of expansion over the world, it is necessary to find novel medicines to reduce the risk of CVD incidence. Qu has potential benefits for CVD in both animals and humans [4]. There is a direct relationship between a higher intake of quercetin and a reduction in CVD incidence. Qu was the first flavonoid discovered with high existence in our diet. This valuable compound was discovered after a publication in 1936 written by Albert Szent-Gyorgyi who showed that a patient recovered after receiving a Hungarian red pepper extraction which they called vitamin P for permeability [5]. Recently, The World Health Organization (WHO) declared that CVD mortality is preventable by 75% via reducing the use of smoke, sugar, and fat, utilizing a healthy diet, and regular physical activities [6]. Following these statements, more and more research had been done to evaluate the effects of non-nutrient substances such as quercetin on CVD prevention [7]. In this review, we have summarized the cardioprotective effects of Qu and its molecular pathway along with its pharmacokinetic and clinical studies in this area (Figure 1).

2. Review Methodology

This updated review covers the cardioprotective effects and potential alternative therapeutic options of Qu in cardiovascular disorders. Scientific data on the cardioprotective

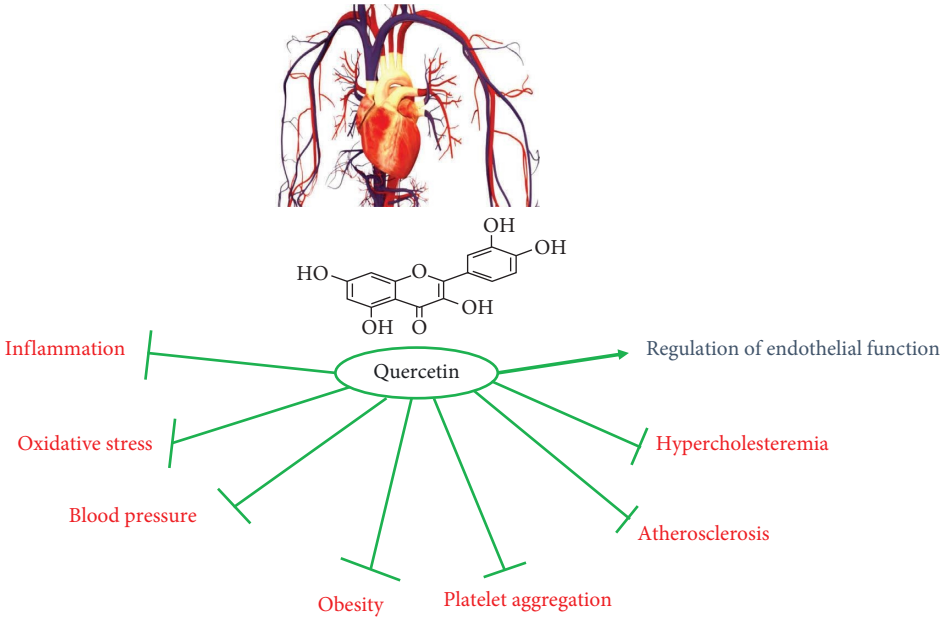

Figure 1: Summary of the beneficial effects of quercetin on cardio vascular system.

effects of Qu were collected from online databases such as PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Science Direct (http://www.sciencedirect.com/), and Google Scholar (https://scholar.google.com/).

3. Chemical Structure and Pharmacokinetics

The molecular formulation of Qu is C15H10O7. Quercetin can be in salt form by reacting oxygen basic atoms on the first carbon with powerful acids [8]. Quercetin mostly is used in its free form and the aglycone type, in supplements, while natural quercetin in foods, fruits, and vegetables is in glycoside type. In dietary supplements, recommended daily doses of quercetin aglycone are usually in the range of up to 1000 mg (most commonly 500 mg) [9]. Qu has poor bioavailability in oral treatments due to the first-pass metabolism. Qu is ingested in glycosides form and converted to the aglycone structure. Qu is absorbed into erythrocytes by b-glycosidase enzymes [10]. Human subjects can absorb significant amounts of quercetin from food or supplements; however, the oral bioavailability of quercetin in humans is 1%. Elimination is quite slow, with a reported half-life ranging from 11 to 28 h [11, 12]. New formulations of quercetin can develop drug delivery of quercetin and also improve its bioavailability. For example, the phytosome-based formulation promotes more absorption of QU. QU is a low stable compound that cannot persist in temperature and PH, in combination with other substances. QU can be hydrolyzed in several steps, such as in the mouth under reaction with proteins and enzymes, especially salivary gland proteins and phenolic group hydrolysis due to low PH, affected by β-glucosidase, and produces metabolites [13]. The glycosyl group increases the water solubility of quercetin. Both forms of quercetin are absorbed with passive diffusion in small intestinal tissues or by onion transporter peptide carriers. Novel formulations and modifications had been designed to enhance the bioavailability, permeability, instability, and solubility of quercetin [14]. Various absorptions had been shown from quercetin formulations based on the type of sugar attachment. Glucuronic and sulfonic glucuronidation makes easy absorption of quercetin. Absorption happens in the upper segment of the small intestine. QU metabolites are in several organs such as the intestine, colon, liver, and kidney. QU is conjugated into different metabolites by colonic micro-organisms and colonic endothelial cell enzymes. QU accumulated in organs and in mitochondria of cells. When we increased the dose of quercetin, its level rose in urine as kidneys are the main organs for quercetin excretion. Very high doses of quercetin may damage the kidneys [15]. Another main organ in excretion of quercetin is the lung. Oral bioavailability of QU was promoted by combination with Vit C, folate, and other flavonoids [16].

4. Cardioprotective Effects of Quercetin

4.1. Quercetin and Hypertension. QU has vasodilation effect in the isolated arteries of rats. It can reduce the severity of high blood pressure according to laboratory findings from hypertensive rat models such as high-sucrose feeding rats and salt-sensitive, angiotensin-induced hypertensive rats. Human epidemiological research has shown that quercetin has powerful cardio-protection consequences. In consumers with more than 29 mg of treatment with quercetin, the rate of death is 68% less than in consumers treated with less than 10 mg. Quercetin can reduce arterial blood pressure; however, QU cannot reduce BP in prehypertensive and normotensive models [17]. QU progresses the reduction in BP dose-dependently. QU prevents oxidative stress-induced pathological changes in the heart, kidney, and vessel cells [18–20]. It can result in decreasing the level of inflammatory factors such as TNF-a, IL-1b, and IL-17 [21]. Continuous

treatment with quercetin reduces vascular smooth muscle cells (VSMC) which directly attenuated CVD progression. Also, quercetin decreased the level of NADPH oxidase, ROS, superoxide anion, and free radicals that exhibit anti-inflammatory and antihypertensive properties. The level of MMP-2 is observed to increase in hypertension, which activates mostly by stress oxidation. Quercetin can decrease the raised level of MMP-2 activity in hypertension rat models which ameliorates vascular remodeling [22]. It seems that low and moderate doses of quercetin had no significant reduction in blood pressure while high doses of that can reduce BP meaningfully. QU revealed the antihypertensive properties via modulating the arachidonic acid (AA) in kidneys. The main metabolites of AA are 20-HETE and EETs which regulate arterial blood pressure [23]. QU is a strong scavenger of radical oxygen and nitrogen species. Quercetin significantly increases the level of CAT, SOD, and GSH and decreases the level of MDA, AOPP, and H2O2 levels in the kidney. All these biomarkers indicate that quercetin has antioxidant effects. Ameliorating inflammation results in upgrading the NO production. NO is an endogenous vasodilator that can relax the smooth muscles of blood vessels [24]. QU considerably induces PGI2 and increases the level of COX2, hence reducing blood pressure. ROS influences blood pressure by reducing NO production. It affects mostly the last stages of hypertension in severe high blood pressure than the early stage. Quercetin scavenges ROS thereby promoting the functions of endothelial cells. Quercetin suppresses the ACE function in a dose-dependent manner. ACE is a metalloprotease enzyme that transforms angiotensin I to angiotensin II. Qu mainly inhibits angiotensin II and destructs bradykinin resulting in decreasing blood pressure [25]. The main antihypertensive impact of quercetin is due to its attenuation in renin-angiotensin-aldosterone (RAAS) and VSMC contraction. However, quercetin can reduce high blood pressure in diabetic, metabolic diseases, and various rat models. It has been reported that QU performs as a Ca^{2+} channel inhibitor. In addition, QU ameliorates endothelial impairments by activating Ca^{2+-} activated K^{+} channels which particularly cause hyperpolarizing of cells. Increasing NO synthesis involving Ca2+-activated K+ channels-dependent membrane hyperpolarization-induced capacitive Ca^{2+} is responsible for this effect [26, 27].

4.2. Quercetin and Atherosclerosis. Endothelial cells act as first-line in hemostasis in cardiovascular events. Endothelial senescence promotes atherosclerosis. QU has benefits in blood flow in vessels as a vascular protector. Also, quercetin suppresses lipid aggregation and decreases serum levels of LDL, TNF-a, IL-1B, IL-18, and IL-6. Suppressing ROS properties of quercetin may help inhibit atherosclerosis plaques. Administrating 20 mg/kg/d QU for 8 weeks effectively ameliorates lipid impairments in vessels intima and develops atherosclerosis treatments. In endothelial cells senescence, SIRT1 plays a key component in enhancing cell aging and autophagy. Quercetin increases the level of SIRT1 while reducing soluble intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) which worsens atherosclerosis conditions [28]. Clinical studies demonstrated that quercetin reduces the level of total cholesterol, LDL-C, and C-reactive protein but did not find a significant effect on triglycerides and HDL levels [29]. It increases antioxidant capacity via reducing LDL oxidation related to atherosclerosis. Some new derived compounds from quercetin have more antiatherosclerosis properties compared to quercetin such as quercetin 7-O-sialic acid which is combined with quercetin and N-acetylneuraminic acid [30]. Another study showed that NADPH oxidase plays a crucial role in the formation of atherosclerotic lesions in animals. As this evidence, it was evaluated and found that quercetin can regulate the NADH-oxidase function. Heme oxygenase-1 (HO-1) is an antioxidant enzyme that suppresses NADH-oxidase activities. Quercetin feeding in mice enhances the expression of HO-1 in this pathway to prevent atherosclerosis plaques [31]. Oxidized cholesterol promotes the expression of ATP binding cassette transporter A1 (ABCA1) protein. IL-6 inhibits the expression of ABCA1. Also, quercetin can regulate the level of ABCA1. In this way, quercetin speeds up cholesterol efflux and inhibits the formation of foam cells from macrophages. Quercetin increases the level of LXRs as a cholesterol metabolism receptor that can organize lipid metabolism. With the same function, PCSK9 is a lipid metabolism regulator which promptly affects vessel walls and PCSK9 regulates LDL-C and expresses inflammatory cytokines in atherosclerotic mice. Previous study has shown that quercetin reduces PCSK9 expression [32]. Between various molecule pathways for antiatherosclerosis effects of quercetin, a new signaling pathway was found related to suppressing inflammation. It has been reported that 100 mg/kg quercetin for 16 weeks suppressed NLRP3 inflammatory activities in macrophages. Furthermore, QU inhibits the expression of galectin-3, a compound which promotes atherosclerosis plaques [33]. Ameliorating atherosclerosis with QU is attributed to regulating autophagy. Macrophages and T cells are most cells involved in atherosclerosis. Incorporating quercetin with docosahexaenoic acid inhibits expressions of NF-KB; however, quercetin can suppress translocation of NF-KB lonely which makes it a reasonable candidate in atherosclerosis prevention [34].

4.3. Quercetin and Myocardial Infarction. Acute myocardial infarction (AMI) is the basis of coronary artery disease which leads to coronary artery blocking, suppressing, and interrupting blood supply to the heart tissues that causes myocardial necrosis. Novel studies indicated that oxidative stress is a crucial factor for AMI progression. QU is a flavonoid compound with attractive properties, for instance, it scavenged ROS species, lowers BP, protects the heart tissues against ischemia, prevents ischemia-reperfusion injury, modulates the immune system capacity, and promotes antioxidant activities. The strong antioxidative stress properties of QU can be utilized for AMI prevention. It can inhibit TNF-α, IL-1β, and other mediators over products in AMI conditions. QU regulates intracellular molecular

pathways involved in AMI [35]. In a study, MI had been induced by chronic unpredictable stress (CUS) for 21 days, and then the preventable effect of QU had been investigated in rats. CUS causes heart abnormalities and promotes inflammation and oxidation. QU suppressed all kinds of heart impairment caused by CUS. QU inhibits CUS-ST segment elevation in rats. QU blocks GPx antioxidant enzyme reduction elicited by CUS. QU inhibits myocardial muscle cell death in MI induced in rats [36]. Pretreatment of QU before ischemia protects the heart's myocardial tissue against inflammation and oxidation. Though it is not exactly clear whether QU postconditioning protects against reperfusion or not, QU protects against ischemia/reperfusion by PI3K/Akt signaling pathway and alleviates apoptosis in this way. QU postconditioning considerably decreased the infarct size and myocardial cell apoptosis following infarction. QU enhances functional recovery. It reduces the myocardial damage caused by ischemia. QU increases Bcl-2 and decreases Bax expression. The ratio of Bcl-2/Bax had been increased. PI3K/Akt activation may be the reason for these results. QU can modulate the expression of Bcl-2 and Bax. Also, it can attenuate myocardial injury via PI3K/Akt activation [37]. QU supplements (500 mg) daily for 8 weeks in 88 post-MI patients results in inflammatory factor improvements and increase in antioxidant capacity and quality of life. QU reduces TNF-α in blood plasma. Also, QU decreases the level of hs-CRP in blood serum. Experimental research indicates that QU protects against stress-induced anxiety via regulating the serotonergic and cholinergic neurotransmission. The most crucial challenge in these studies is the lack of measuring of QU metabolites in urine and plasma, and the second challenge is the duration of the study [38]. QU exhibits antiischemic properties in chronic administration. QU not only protects the heart against MI injury but also reversed damages caused by MI consisting of apoptosis, structural changes, and matrix metalloproteinase-2 activation. Therefore, QU or QU supplements present as a cardioprotestant agent against myocardial infarction [39].

4.4. Quercetin and Coronary Artery Disease (CAD). CAD is one of the reasons for mortality in the world. The prevalence of CAD is increasing over time, leading to stable angina pectoris and heart failure in the end-stage [40]. Inflammation is an essential factor for CAD progression. Increased levels of proinflammatory cytokines activate immunocompetent and endothelial cells. IL-1β, TNF-α, and NF-kB activations are involved in CAD development. QU is associated with decreased expression of NF-kB genes accompanied by IL-1β reduction. QU activates protein sirtuin 1 (SIRT1) and prevents inflammatory gene expression. QU suppressed endothelial cell damages mediated by SIRT1 protein. Also, QU prevents lipid peroxidation damages and demonstrates positive effects in CAD healing. Administration of QU 120 mg daily for 2 months in 85 patients with CAD indicates beneficial properties in patients [41]. Atherosclerotic plaques are the main factor for CAD incidence. QU eliminates free radicals in the body and reduces the oxidation of low-density lipoproteins. Two months of treatment with QU in 80 hyperlipidemia patients protects cells against oxidative damages [42]. 250 my/day QU prescription for 8 weeks in 24 men with CAD after percutaneous coronary intervention (PCI) leads to improving stress oxidative, blood pressure, ventricular function, and aerobic power. However, p wave depression (PWD) was not different between QU and control groups [43]. QU at a dose of 3 gr per day per os for two months reduces endothelial cell degeneration and necrosis factor in CAD patients. QU potentiates the statin drug's effectiveness and is recommended as a promising angioprotector agent [44].

4.5. Quercetin and Heart Arrhythmias. Cardiac arrhythmia is one of the most prevalent cardiovascular diseases worldwide, which can occur alone or be triggered by other diseases, and it can be fatal in severe cases [45]. A growing number of in vitro experiments and in vivo animal studies have shown that QU significantly inhibits mitochondrial oxidative stress, cardiac fibrosis, inflammatory responses, and apoptosis, regulates autophagic responses, improves ischemia/reperfusion injury in cardiomyocytes, and regulates gut microbiota, thereby attenuating or preventing structural and electrical remodeling in the heart [45, 46].

Furthermore, QU activates mitoKATP channels which play an important role in heart health. MitoKATP channels are a kind of potassium channel that regulate cell activities and protect cardiac cells against free radical damages. QU may exert antiarrhythmic effects in this way [46, 47] Zhang et al. demonstrated that QU can counteract ventricular arrhythmias in rats by inhibiting Na+ inward flow, reducing the activity of fast-responding cells such as atrial conduction tissue and the atrioventricular bundle Purkinje system, and prolonging the refractory period [48]. Similarly, Wallace et al. proved that QU and its analogs could block ATXII-induced late sodium currents in rat ventricular myocytes and improve calcium handling and contractility of cardiomyocytes to exert antiarrhythmic effects [49]. Thus, QU may exert antiarrhythmic and cardioprotective effects as cardiac voltage-gated sodium channels (VGSCs) inhibitor [50].

4.5.1. Quercetin and Myocarditis. Myocarditis is defined as cardiac inflammation. It is attributed to cardiac cell necrosis and cell degeneration. There is no exact medication for myocarditis but autoinflammation has been recognized to play a critical role in its pathogenesis. Releasing cytokines from macrophages and T cells are included in experimental autoimmune myocarditis (EAM) induction. Moreover, QU modulates nitric oxide generation in activated macrophages. Medication for EAM is a massive challenge and an important clinical problem. It is related to the fact that autoimmune systems play a critical role in its pathology. It has been reported that QU is effective in autoimmune-related diseases. Three weeks administration of QU attenuated autoimmune myocarditis considerably. QU decreases the severity of inflammation by inhibiting proinflammatory cytokines consisting of TNF-α and IL-17 and upregulating IL-10 [51]. TNF-α expression is higher in myocarditis

Table 1: Clinical finding about the effects of QU in CVD.

Model	Number of patients	Effects	Results	References
Double-blind randomized QU administered 500 mg/day for 8 weeks	Seventy-two patients	QU administration reduced the concentration of TNF-α and IL-6	QU administration decreased systolic hypertension, no significant changes in blood lipids (HDL-C, LDL-C, TG)	[55]
QU 1 gr/day was administered in healthy humans for 28 days	—	QU had no significant effects on healthy participants in reducing cardiovascular risk	No significant modifications were observed in blood pressure, heart rate, and thrombogenic risk factors	[56]
Administration of QU (3 gr/day) for 2 months	30 CAD patients	QU inhibited NF-κB-dependent gene expression and decreases the level of TNF-α	QU potentiates the potency of statins and decreases the endothelium degeneration in CAD patients	[44]
Addition of QU as an ultralowering agent in patients with gout and hypertension for 12 months	43 patients with gout and essential hypertension	QU stimulates the Na+-K+-2Cl-cotransporter 1 (NKCC1) which is one main agent in Cl regulation	QU administration developed echocardiographic parameter of diastolic function left ventricular and normalized blood pressure	[57]
QU 150 mg/day administration in CHD patients for 2 months	85 patients with CHD	QU improves the bioavailability of NO and increases myocardial blood flow, prevents apoptosis, and inhibits MMPs and NF-Kβ	Systolic and diastolic LV function improved in this study. QU had advantages in patients with stable CHD patients	[58]
QU 120 mg/day administered for 2 months	85 patients with CAD	Levels of IL-1β and TNF-α were decreased and IL-10 levels had been tended to decrease	QU has protective effects and antioxidative properties in myocardial cells and it enhances membrane rigidity and prevents risk of cardiovascular events	[41]
QU/QU supplements 250 mg/day administered for 10 weeks	34 men with hypertension and CAD after PCI aged 40–60 years	—	Left ventricular systolic and diastolic function increased by QU consumption	[59]
QU 150 mg/day administered for 6 weeks	93 overweight-obese volunteers	QU greatly reduced plasma oxidized LDL and tumor necrosis factor-α	QU reduced the blood pressure in overweight humans	[60]
QU 162 mg/day administered from onion skin extract powder for 6 weeks treatment	70 overweight-to-obese patients with prehypertension and stage I hypertension	QU supplements were not influenced inflammation and oxidative stress parameters in this study	QU significantly decreased 24 h systolic ABP	[61]
150 mg or 300 mg quercetin-4¢-O-b-D-glucoside supplement administration	—	QU has inhibitory effects on platelet aggregation which reduce the risk of cardiovascular events	QU reduced the risk of thrombosis	[62]

patients. Its activation results in a signal transducer and activator of transcription 1 (STAT1) stimulation which causes cell damage. QU inhibited the activation of STAT1 induced by TNF-α. Also, TNF-α activates the MAPK pathway. QU prevented this metabolism [52]. Endoplasmic reticulum (ER) stress has been recently identified as a major factor in cardiovascular disorders. ER results in cardiac dysfunction and impairment [53]. Under ER, stress cells stimulate unfolded proteins. QU can modulate ER stress and shows to be a novel therapeutic medicine in this attractive pathway [54].

5. Clinical Findings of the Effects of Quercetin on Heart Health

As it had been suggested according to a bow writings, quercetin is a protective agent in cardiovascular diseases. Due to the inverse relation of taking flavones and flavonoids with the death rate of cardiovascular events, several clinical research studies have been done. These studies considered the effect of QU on the physical and pathological situations in heart-related events. QU had been applied as a purified aglycone molecular or in plant-extracted forms. Results of these clinical findings revealed a promising heart-friend agent that protects the heart against harmful conditions. Table 1 exhibits the protective effects of QU in heart diseases in clinical researches [3].

6. Conclusion

Nowadays, high rates of mortality and morbidity make cardiac disorders as one of the challenges facing humanity. Multiple elements increase the risk of heart events including hypertension, smoking, obesity, and dyslipidemia. These elements promote cardiovascular diseases such as atherosclerosis. Inflammation, oxidation, apoptosis, and endothelium dysfunctions are the crucial molecular mechanism involved in heart diseases. QU is a plant heart-friend pigment from the flavonoid group of polyphenols which exists in many plants, fruits, and food such as green tea, apples, and berries. Various research studies consisting of in vitro, in vivo, and clinical trials had been performed to clarify the mechanism actions of QU in heart diseases. Findings have proved the beneficial effects of QU in CVD by its blood pressure lowering effects, positive effects on endothelial functions, anti-inflammation, and antioxidant properties, antiapoptotic activities, antiplatelet aggregation functions, and dyslipidemia controlling benefits. It seems that QU can act as a favorable remedial agent in CVD prevention. In this research, we discuss QU's numerous mechanisms in different types of cardiovascular diseases and consider its effects in clinical studies. This is especially important to investigate possibly greater benefits of QU/QU supplements in heart health [63].

Abbreviations

CVD: Cardiovascular diseases
QU: Quercetin
LDL: Low-density lipoprotein
TNF alpha: Tumor necrosis factor alpha
IL: Interleukin
BP: Blood pressure
ROS: Reactive oxygen species
CAT: Catalase
GPx: Glutathione peroxidase
SOD: Super oxide dismutase
GSH: Glutathione
COX: Cyclooxygenase.

Data Availability

No data were used for the research described in the article.

Additional Points

Quercetin is a flavonoid which greatly exists in the daily diet and various vegetables. The various pharmacological properties of quercetin make this natural flavonoid a beneficial compound for cardiovascular diseases. In this paper, we have summarized the beneficial effects of quercetin for cardiovascular diseases.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

FNK conceptualized the study and wrote the manuscript; MGB supervised the study and revised the manuscript.

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