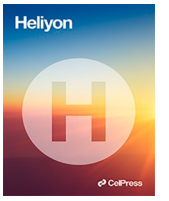
Heliyon 10 (2024) e32563

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Flavonoids: Potential therapeutic agents for cardiovascular disease

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ARTICLE INFO

Keywords:
Flavonoid
Cardiovascular disease
Bioavailability
Inflammation
Antioxidant

ABSTRACT

Flavonoids are found in the roots, stems, leaves, and fruits of many plant taxa. They are related to plant growth and development, pigment formation, and protection against environmental stress. Flavonoids function as antioxidants and exert anti-inflammatory effects in the cardiovascular system by modulating classical inflammatory response pathways, such as the TLR4-NF-κB, PI3K-AKT, and Nrf2/HO-1 signalling pathways. There is increasing evidence for the therapeutic effects of flavonoids on hypertension, atherosclerosis, and other diseases. The potential clinical value of flavonoids for diseases of the cardiovascular system has been widely explored. For example, studies have evaluated the roles of flavonoids in the regulation of blood pressure via endothelium-dependent and non-endothelium-dependent pathways and in the regulation of myocardial systolic and diastolic functions by influencing calcium homeostasis and smooth muscle-related protein expression. Flavonoids also have hypoglycaemic, hypolipidemic, anti-platelet, autophagy, and antibacterial effects. In this paper, the role and mechanism of flavonoids in cardiovascular diseases were reviewed in order to provide reference for the clinical application of flavonoids in the future.

1. Introduction

Cardiovascular disease (CVD) accounts for the highest proportion of disease-related deaths in China [1]. Globally, 17.8 million people died from CVD-related events in 2017 [2], with an increase to 18.6 million in 2019 [3]. Ischemic heart disease accounts for about 50 % of these cases [4]. CVDs mainly include atherosclerosis, hypertension, and cardiomyopathy [5]. Smoking, hypertension, hyperlipidemia, diabetes and hyperinsulinemia are the important causes of increased cardiovascular burden[6,7].In addition to the above risk factors, poor diet is also an important factor leading to cardiovascular disease, and the impact is more significant in young people. Analysis of NHANES data suggests that approximately 64 % of cardiometabolic deaths in people aged 25–34 years are related to poor diet [8].Studies have shown that total intake of fruits and vegetables is inversely associated with cardiovascular disease risk, with folic acid, plant fiber, and flavonoids considered to be the main reasons for dietary benefits [9].

Flavonoids, abundant in many foods, are polyphenolic compounds generated by plant secondary metabolism [10]. They are found

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https://doi.org/10.1016/j.heliyon.2024.e32563
Received 12 December 2023; Received in revised form 5 June 2024; Accepted 5 June 2024
Available online 6 June 2024

in a variety of plants and plant parts (e.g. fruits, grains, flowers, roots, and seeds) and are related to the formation of plant pigments [11–13].They have various pharmacological effects, such as immunomodulatory, hypoglycaemic, antibacterial, and anti-tumour invasion and metastasis effects, and have therapeutic effects in many chronic diseases [14]. In recent years, more studies have demonstrated the remarkable effects of flavonoids on cardiovascular diseases, taking anthocyanins, a representative subgroup of flavonoids, as an example, anthocyanins play a positive role in antihypertensive, anti-inflammatory and other aspects. Known systematic reviews and meta-analyses have shown that anthocyanin intake is positively associated with a reduced risk of hypertension in the study population [15], and at physiological concentrations (0.1–2 μM), Anthocyanins reduce monocyte adherence to TNF-α-activated endothelial cells, which may be an important pharmacological target for their anti-inflammatory effects[16,17]. In addition to anthocyanins, other flavonoid subgroups also have their own unique anti-cardiovascular disease targets [18]. Consequently, this paper focuses on the role and mechanism of flavonoids and cardiovascular diseases. In particular, we provide an overview of the structure, synthesis, and biological properties of flavonoids, followed by descriptions of their effects on CVD and related diseases, especially their lipid lowering, anti-inflammatory, and antioxidant effects [19]. This review of the literature on the role of flavonoids in cardiovascular diseases provides an important basis for future research and may guide the development of therapeutic strategies.

1.1. Flavonoids

1.1.1. Molecular structure

Flavonoids consists of two benzene rings with a phenolic hydroxyl group (i.e. the A ring and B ring) and a heterocyclic C ring connected through the central carbon atom (Fig. 1) [20]. According to the chemical modifications of their carbon units, such as hydroxylation, methylation, glycosylation, acylation, and isoprene attachment, flavonoids are mainly divided into anthocyanins, proanthocyanidins, flavonols, flavonoids, flavanones, isoflavones, and phlobaphenes. These subgroups are further divided according to the degree of oxidation, resulting in thousands of similar chemical compounds with unique biological properties.

1.1.2. Biosynthesis

The enzymes involved in flavonoid synthesis may be related to the ripening process of berries [21]. Flavonoids, along with lignin and other aromatic compounds, are commonly synthesised in plants via the phenylpropanoid pathway. In the first three steps of the phenylpropanoid pathway, phenylalanine is converted into *p*-coumaroyl-CoA. P-coumaroyl-CoA enters the flavonoid biosynthesis pathway, initiates the synthesis of specific flavonoids, and generates chalcone, the first key intermediate product in the flavonoid metabolism pathway, providing the basic framework for downstream flavonoid synthesis[22,23]. With chalcone as the first enzyme in the pathway, downstream enzymes catalyse the formation of different classes of flavonoids (Fig. 2) . For example, chalcone isomerase catalyses chalcone to form flavanone (including naringenin, liquiritigenin, pentahydroxyflavanone, and eriodictyol) [24]. Flavonoid synthases further catalyse flavanone to flavone (including apigenin, dihydroxyflavone, and luteolin).

Flavonoid synthesis is regulated at the transcriptional level by multiple transcription factors [25]. The MBW complex composed of bHLH, MYB, and WD40 is the main transcriptional regulator of the flavonoid biosynthesis pathway and functions by activating the

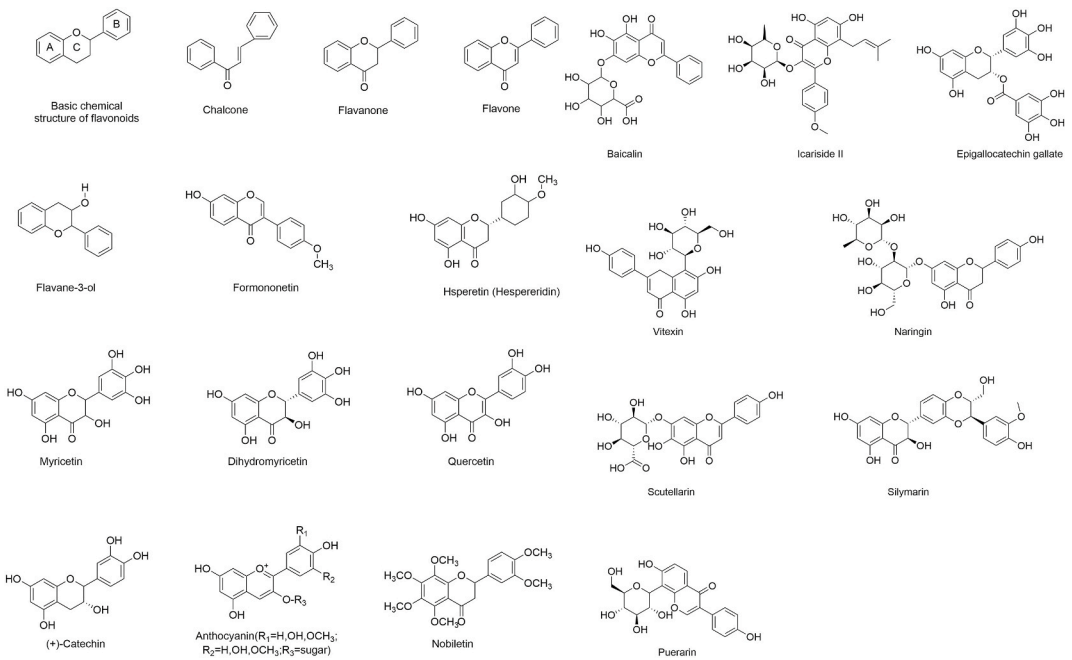

Fig. 1. Diagram of molecular structure of substances in the pathway of flavonoid synthesis.

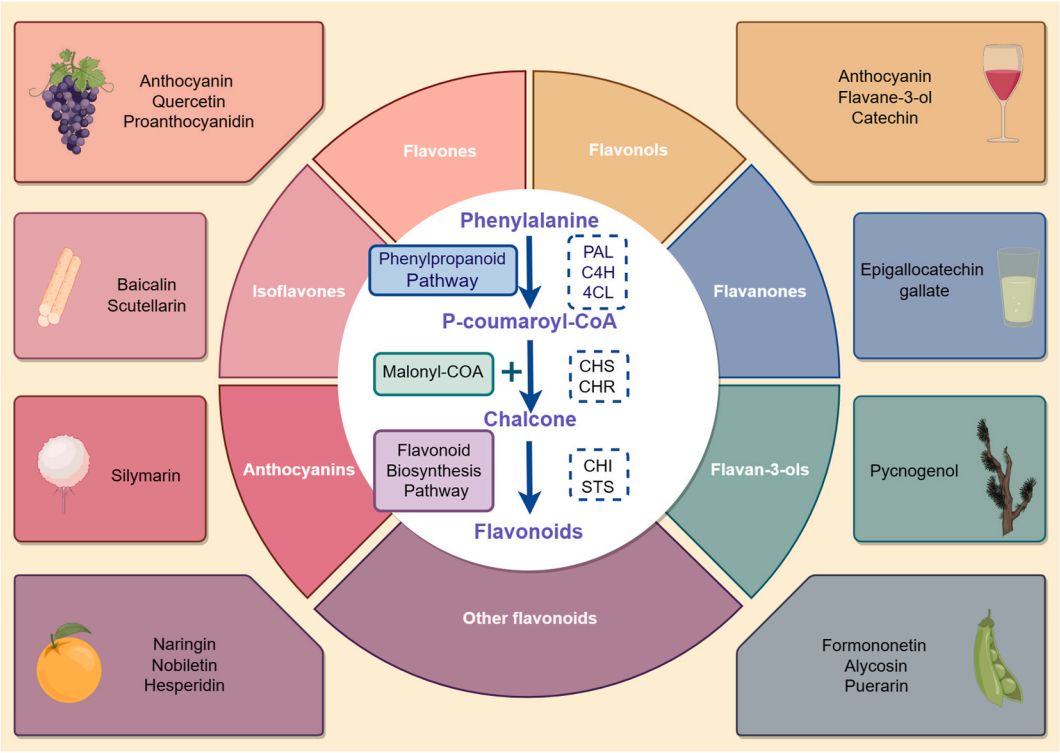

Fig. 2. Biosynthesis process and source of flavonoids. Phenylalanine is converted to *p*-coumaroyl-CoA under the action of phenylalanine ammonia lyase (PAL), cinnamic acid 4-hydroxylase (C4H), 4-coumarate: CoA ligase (4CL). *p*-coumaroyl-CoA and malonyl-COA generate Chalcone under the action of chalcone synthase (CHS) and chalcone reductase (CHR). chalcone provides the basic framework for downstream flavonoids, which are produced by different enzymes such as chalcone isomerase (CHI), Stilbene synthase (STS), etc. Flavonoids are divided into Flavones, Flavonols, Flavanones, Flavan-3-ols, Anthocyanins, Isoflavones, etc., mainly derived from red wine, green tea, baicalensis root, purple grape, citrus, soybean, milk thistle and other foods or plants. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

expression of LBG[26–28]. TT1, TT2, TT8, TT16, TTG1, TTG2, and other TT genes encoding transcriptional regulators have been shown to be related to flavonoid biosynthesis [29]. Furthermore, flavonoid synthesis is often affected by environmental stress during the growth of plants and seeds, with effects of temperature, light, pressure, and other conditions[30–32].

1.1.3. Metabolism, decomposition, and bioavailability

Most flavonoids ingested by humans are derived from food sources (Table 1). The gastrointestinal tract is the main site for the absorption of flavonoids, and absorption is closely related to the molecular structure, intestinal permeability, and intestinal microorganisms. Flavonoids often exist as glycosylated macromolecules and therefore require glycosidases synthesised by gut microorganisms to break down into glycosides or phenolic acids for absorption [33]. In the case of hesperidin, for example, hesperidin is more easily degraded proximal to the colon than the stomach and small intestine, thanks to the microbiota decomposition activity in the colon, and α-rhamnosidase is the key to its metabolism[34,35].Based on the chemical structure, flavonoids are highly lipophilic. Therefore, they have low solubility [36], and this contributes to the low bioavailability of many common flavonoids. For example, the bioavailability of hesperidin is about 4.1–5.4 % [37],epigallocatechin gallate (EGCG), which is abundant in green tea, showed a maximum plasma concentration of 156 ng/ml after a single oral dose of 97 mg in rats, with a bioavailability of less than 1 % [38], and the bioavailability of anthocyanins was estimated to be 1–2% [39]. However, there is recent evidence that some specific flavonoids have a better bioavailability than was previously recognized; for example, the absorption rate of quercetin bound to glycosides can reach 50 % or more [40]. The absorption and transport of flavonoids is another important factor affecting their bioavailability. In plant cells, the concentration gradient is the main driving force for flavonoid transport and is mediated by membrane transport proteins. Dietary flavonoids are absorbed and transported by vesicles and transporters [41]. For example, dihydrodaidzein and tetrahydrodaidzein, which are metabolites of daidzein in vivo, are more permeable than daidzein and are actively transported in the gut, however, daidzein, as a known efflux protein substrate, is easily recognized by the efflux system, thus limiting its absorption in the gut [42].Flavonoids are mainly bound to serum albumin in vivo, and this binding is often inhibited by fatty acids. Dietary flavonoids are partially metabolised in the intestine; however, after being absorbed into the blood, they undergo extensive metabolism again through the liver, kidney, and other organs and are rapidly cleared through the plasma, affecting their bioavailability to a large extent [43]. However, methods to improve the bioavailability of flavonoids are needed, and many approaches have been evaluated, such as

Table 1
Sources of flavonoids and the therapeutic mechanisms for cardiovascular diseases.

Source	Flavonoids	Mechanism	Preventing Cardiovascular Diseases	Reference
Red wine	Anthocyanin, flavane-3-ol, catechin	Antioxidant, anti-inflammatory，antifibrosis，calcium homeostasis	Antihypertensive，anti-cardiomyopathy	[47,48,49]
Baicalensis root	Baicalin, scutellarin	Antibacterial, anti-inflammatory，antifibrosis，calcium Homeostasis	Antihypertensive，anti-myocarditis，anti-endocarditis，anti-heart failure	[50,51]
Purple grape	Anthocyanin, quercetin, proanthocyanidin	Anti-hypertensive, antioxidant，antiplatelet, anti-atherosclerosis，hypolipidemic，anti-myocardial remodelling，antibacterial，calcium homeostasis	Antihypertensive，anti-atherosclerosis，anti-myocarditis，anti-endocarditis， anti-heart failure	[52,53,54,55]
Citrus	Naringin, nobiletin，hesperidin	Hypolipidemic，antiplatelet, anti-atherosclerosis	Anti-atherosclerosis，Anti-ischemia reperfusion	[56,57]
Pinnatifida Bunge	Vitexin	Anti-inflammatory	Anti-atherosclerosis，Anti-ischemia reperfusion	[58]
Pinus maritima	Pycnogenol	Hypolipidemic，anti-atherosclerosis	Anti-atherosclerosis，anti-ischemia reperfusion	[59]
Soybean	Formononetin, alycosin, puerarin	Promote autophagy，hypolipidemic，anti-inflammatory	Anti-atherosclerosis，Anti-ischemia reperfusion	[60,61,62]
Milk Thistle	Silymarin	Hypolipidemic，anti-inflammatory	Anti-cardiomyopathy	[63]
Green tea	Epigallocatechin gallate	Antiapoptotic，anti-aging	Anti-heart failure	[64]
Icariin	Icariside II	Anti-inflammatory，antifibrosis，anti-myocardial remodelling	Anti-heart failure，anti-cardiomyopathy	[65]
Ampelopsis grossedentata	Dihydromyricetin, Myricetin	Anti-inflammatory，anti-myocardial remodelling，antiapoptotic	Anti-heart failure，anti-cardiomyopathy	[66,67,68]

intraportal drug delivery during surgery and drug delivery through new nanomaterials[44,45]. At present, there have been relevant studies on the administration of flavonoids through nanomaterials. Drug administration through lipid material embedding can greatly avoid the status of flavonoid bioutilization being limited by intestinal biological factors, which will be one of the keys to the clinical application of flavonoids [46].

1.2. Effects of flavonoids on cardiovascular disease

As early as 1936, Rusznyak and Szent-Gyorgyi proposed that flavonoids have a protective effect on peripheral blood vessels. Subsequent studies proved that flavonoids can reduce the risk of CVD [69]. For example, quercetin and catechin (which are abundant in tea) are beneficial in patients with coronary heart disease, puerarin can slow down the process of pathological heart remodelling [70], and hesperidin in citrus has a therapeutic effect on hypertension [60]. We summarise the mechanisms by which flavonoids contribute to the prevention and treatment of CVD (Fig. 3, Table 2).

1.2.1. Hypertension

Hypertension is divided into primary and secondary hypertension. The aetiology of essential hypertension is unknown; however, known risk factors include hyperlipidaemia, insulin resistance, and obesity. Secondary hypertension refers to an increase in blood pressure with known causes, including kidney-related diseases (renal failure), vascular diseases (coarctation of aorta), and endocrine disorders (primary hyperaldosteronism) [84]. Flavonoids have been shown to exert antihypertensive effects by a variety of mechanisms[85,86]. Quercetin, a flavonol, has a significant effect on blood pressure. Quercetin lowers diastolic blood pressure in patients with hypertension and lowers systolic blood pressure in subjects with normal blood pressure [87]. Other studies have shown that moderate consumption of chocolate (in which flavanols are the main active ingredient) may reduce the risk of high blood pressure[71,88].

Activation of the renin-angiotensin-aldosterone (RAAS) system is the main mechanism underlying essential hypertension, which involves the promotion of arterial media thickening, increased blood volume, and vascular endothelial injury [89]. Anti- RAAS agents are a key link in the treatment of hypertension, and AngII inhibits the RAAS system. AngII can promote the generation of reactive oxygen species (ROS) by triphosphopyridine nucleotide (NADPH) and promote vasoconstriction caused by vascular endothelial

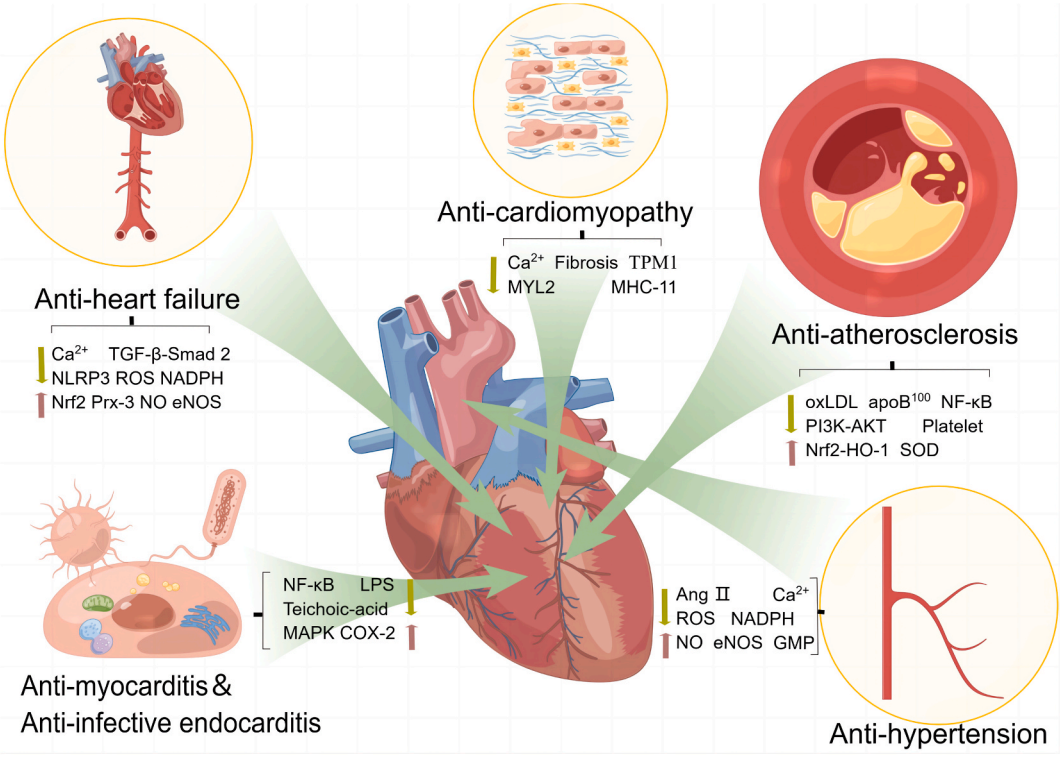

Fig. 3. Effects of flavonoids on cardiovascular disease. Anti-heart failure： inhibiting the expressions of Ca2+, TGF-β/Smad signaling pathway, NLRP3, ROS and NADPH, increasing the expressions of Nrf2, PRX-3, NO and eNOS.Anti-cardiomyopathy：inhibiting the expression of Ca2+, TPM1, MYL2 , MHC-11 and myocardial fibrosis. Anti-myocarditis and endocarditis: inhibiting the expression of NF-κB, LPS and Teichoic-acid, increasing the expression of MAPK and COX-2. Anti-hypertension：inhibiting the expression of AngII, Ca2+, ROS and NADPH, increasing the expression of NO, eNOS and GMP.Anti-atherosclerosis：inhibiting the expression of ox-LDL, apoB100, NF-Kb, PI3K-AKT signaling pathways and anti-platelet generation, increasing the expression of Nrf2/HO-1 pathway and SOD.

Table 2
Regulatory targets and functions of flavonoids.

Flavonoids Target	Expression	Functions	Reference
NADPH oxidase	↓	Antioxidant	[71]
ROS	↓	Antioxidant	[47]
Ang II	↓	Antioxidant	[47]
Ca^{2+}	↓	Vasodilation	[50]
NO	↑	Vasodilation	[52]
Bradykinin	↑	Vasodilation	[52]
eNOS	↑	Vasodilation	[72]
RCT	↑	Hypolipidemic	[73,74]
AMPK	↓	Hypolipidemic	[53]
KLF4	↓	Hypolipidemic	[75]
SAR	↓	Hypolipidemic	[56]
ApoB100	↓	Hypolipidemic	[76]
NF-κB	↓	Anti-inflammatory	[58]
ADRP	↓	Hypolipidemic	[77]
H0-1	↑	Anti-inflammatory	[78]
MLKL	↓	Promote Autophagy	[61]
AKT、mTOR	↓	Anti-inflammatory	[62]
PDI	↓	Antiplatelet	[79]
ANRIL	↓	Anti-ischemia reperfusion	[80]
TPM1、MYH11、MYL2	↑	Anti-myocardial remodelling	[63]
MAPK、COX-2	↓	Antibacterial	[81]
Lipoteichoic acid	↓	Antibacterial	[82]
TGF-β1、Smad	↓	Antifibrosis	[83]
Prx-3	↑	Antioxidant	[54]
NLRP3	↓	Anti-inflammatory	[68]

oxidative stress. Studies have demonstrated that red wine polyphenols can inhibit the generation of ROS in blood vessels and the expression of NADPH oxidase and inhibit the vasoconstriction induced by angiotensin II (AngII) [47,90]. Interestingly, the main components of red wine polyphenols are flavonoids (including anthocyanin, flavan-3-ol, catechin, and resveratrol), and these results were verified in studies of another flavonoid, proanthocyanidin, in the treatment of hypertension in pregnant mice [48]. AngII also increases free calcium ions in vascular smooth muscle cells by promoting the influx of extracellular calcium ions and the release of intracytoplasmic calcium ions, triggering the electromechanical coupling pathway in smooth muscle. Flavonoids can regulate non-endothelium-dependent vasodilation via calcium ion antagonism. The flavonoid baicalin extracted from *Scutellaria baicalensis* root can inhibit intracellular calcium ion release via the myosin light chain kinase (MLCK) pathway and alleviate endothelial thickening to a certain extent [50]. In addition, the vasodilatory effect of quercetin associated with elevated cyclic guanosine monophosphate (cGMP) was observed in treated pig coronary arteries, again demonstrating the direct regulatory effect of flavonoids on vascular smooth muscle [91].

The activation of RAAS also has an impact on vascular endothelial-dependent blood pressure regulation. Vascular endothelial cells can release a variety of cytokines to contract and relax blood vessels, thereby playing an important role in vascular tone, and NO is the main substance for vascular relaxation. Endothelial dysfunction results in impaired endothelial-dependent vasodilation. The regulation of NO synthesis by flavonoids is an important mechanism for the regulation of blood pressure. Kaempferol , the flavonoid component in purple grape enhances platelet-derived NO release in a dose-dependent manner, and decreased platelet aggregation and superoxide reduction have been detected in the plasma of healthy subjects [52]. During the activation of the RAAS system, angiotensin-converting enzyme (ACE) not only promotes the production of angiotensin but also inactivates bradykinin, which regulates vascular tension mainly by regulating NO production [72]. Flavonoids can significantly enhance bradykinin-mediated vasodilating effects. On the other hand, an increase in ROS levels in endothelial cells promotes the uncoupling of endothelial nitric oxide synthase (eNOS) and reduces NO production. Flavonoids can activate eNOS and increase NO levels in endothelial cells [92]. In red wine polyphenols, resveratrol can significantly increase the promoter activity of eNOS, and the increased synthesis of eNOS and NO has been detected in human umbilical vein endothelial cells treated with red wine polyphenols [49]. Gabriele Carullo et al. treated isolated rat aortas with red wine polyphenols and detected an increase in the NO content. The same endothelium-dependent vasodilatory effect was observed in rats fed the red wine polyphenol extract [93]. Other flavonoids through different pathways also influence the expression of eNOS, direct activation of eNOS/NO by myricetin [66] , total flavonoids activating the Akt/eNOS pathway [94], baicalin through targeted HSP70/90 adjusting eNOS expression [95].

Pulmonary hypertension is a condition caused by abnormally high pressure in the pulmonary arteries, which is a cause of heart failure, often secondary to thrombotic disease, chronic heart disease, chronic lung disease, and so on [96]. Flavonoids can prevent the formation of pulmonary hypertension and have a positive therapeutic effect on cardiopulmonary impairment caused by pulmonary hypertension [97]. The mechanism by which flavonoids exert beneficial effects in pulmonary hypertension is similar to that in hypertension described above. Nobiletin inhibits pulmonary hypertension through PI3K/Akt/STAT3 pathway [98]. Under oxidative stress, vascular smooth muscle cells transition to a synthetic dedifferentiated phenotype characterized by enhanced proliferation and migration[99,100]. In addition, elevated ROS levels decrease NO levels and induce endothelial cell dysfunction [101], and isoquercitrin alleviates pulmonary hypertension by inhibiting the proliferation of lung smooth muscle cells [102].It is worth mentioning

that recent studies have shown that flavonoids provide the basis for new diagnostic and treatment approaches for pulmonary hypertension by inhibiting pulmonary vascular endothelial mesenchymal transformation and pulmonary vascular remodelling [103].

1.2.2. Atherosclerosis

Atherosclerosis is caused by lipid deposition and involves endothelial cells and inflammatory cells. It is the main cause of cardiovascular events, such as myocardial infarction, stroke, and peripheral vascular disease [104]. Epidemiological analysis suggested that flavonoids had a protective effect on coronary heart disease [105]. A study of ethnic dietary differences in the United States found that total dietary intake of flavonoids was negatively associated with the risk of coronary heart disease, with anthocyanin and proanthocyanidin intake significantly reducing the incidence of coronary heart disease [105]. Similarly, the Zuphen Elderly Study, which followed 805 men for five years, found that those with higher flavonoid intake had lower rates of coronary heart disease mortality and myocardial infarction [106].

Hyperlipidaemia is the main risk factor for the occurrence of atherosclerotic lesions, and other identified risk factors include smoking, hypertension, hyperglycaemia, vascular endothelial injury, and vascular inflammation [107]. Under the influence of pathological factors, such as lipid deposition and inflammatory injury, macrophages and smooth muscle cells take up lipids to form foam cells, and a large number of collagen fibres gather at the injured site to form fibrous caps, which eventually form atherosclerotic plaques. The site, degree of plaque stability, and degree of vascular occlusion determine the clinical severity and prognosis of the disease [108]. Flavonoids can inhibit inflammation in fat tissue [104],at present, lowering blood lipids is an important part of the treatment of atherosclerotic diseases, and the atherosclerotic protective effect of flavonoids is partially mediated by an increase in reverse cholesterol transport and reduction in blood lipids[73,74]. Flavonoids are beneficial in fighting atherosclerosis caused by a high-fat diet [109]. Proanthocyanidins inhibit macrophage uptake of oxidized low den-sity lipoprotein (oxLDL) and promote cholesterol outflow via the serine/threonine kinase AMP-activated protein kinase/mammalian target of rapamycin （AMPK/mTOR）pathway [53]. Naringenin also promotes the outflow of cholesterol by promoting the expression of the transcription factor Krüppel-like factor 4 (KLF4) [75]. Formononetin inhibited the expression of the cholesterol inflow-related gene *SRA* and antagonised the uptake of cholesterol and ox-LDL by SRA-mediated macrophages and vascular smooth muscle cells [56]. The extrahepatic transport of low-density lipoprotein and very low-density lipoprotein plays a significant role in the occurrence of hyperlipidaemia. Apolipoprotein B (apoB) is the key protein in the transport of low-density lipoprotein and very low-density lipoprotein in vivo and is an important indicator to evaluate hyperlipidaemia. An increase in the apoB100 concentration is the characteristic change in lipoprotein profile associated with atherosclerosis. Nobiletin, an abundant flavonoid in citrus, inhibits the secretion of apoB100 by activating the MAPK signalling pathway [57]. Other flavonoids, such as anthocyanins also inhibit apoB secretion [76].

The inflammatory response after vascular endothelial injury greatly promotes the formation of atherosclerosis, and the anti-inflammatory, antioxidant, and other effects of flavonoids have been studied extensively [110]. Flavonoids can inhibit the inflammatory response in atherosclerosis by a variety of mechanisms, thereby playing a vasoprotective role. The nuclear factor kappa B（NF-κB）family of pro-inflammatory transcription factors is involved in the anti-inflammatory effects of flavonoids [111]. Vitexin has been shown to inhibit the expression of NF-κB in endothelial cells by targeting Apurinic-Apyrimidinic Endonuclease I (APEX1) [58]. Pycnogenol antagonises lipid deposition of foam cells mediated by adipose differentiation-related adipocyte differentiation-related protein（ADRP）via the TLR4-NF-κB pathway, preventing the progression of atherosclerosis [77].

In addition, flavonoids can effectively inhibit vascular endothelial inflammation caused by increased intracellular reactive oxygen species（ROS）and oxidative stress[112–114]. Quercetin is a widely studied flavonoid that can promote the expression of Heme oxygenase 1 (HO-1) by activating the phosphatidylinositol 3-kinas/protein kinase B (PI3K-AKT) signalling pathway and can activate nuclear factor erythroid2-related factor 2/Heme oxygenase 1 (Nrf2/HO-1), participating in the antioxidant reaction and inhibits ROS production, which is related to the production of superoxide dismutase (SOD) [78].

In recent years, autophagy has been found to play an important protective role in the process of atherosclerosis. In the early stage of coronary atherosclerosis, macrophages are transformed into foam cells after oxidative stress, and the inflammatory necrosis of foam cells leads to plaque instability and rupture, while the occurrence of autophagy prevents this process. Flavonoids can regulate the occurrence of autophagy under vascular stress. Calycosin, a flavonoid present in legume species functions via Krüppel-like factors (KLF2) to inhibits the negative regulator of autophagy mixed lineage kinase domain-like protein (MLKL), thereby promoting autophagy; flavonoids also regulate the outflow of cholesterol and are related to functional autophagy [61]. In addition, the PI3K/AKT/mTOR signalling pathway is a key pathway in the regulation of cell growth, proliferation, and metabolism and inhibits autophagy. Flavonoids extracted from yellow berries (mainly composed of formononetin and calynoisoflavone) can inhibit the phosphorylation of AKT and mTOR, regulate the autophagy of macrophages, and exert a vascular protective effect.Different from the previously mentioned flavonoids acting on the AKT/eNOS signaling pathway to alleviate mitochondrial damage in response to oxidative stress, the AKT/mTOR pathway mainly acts on cellular lysosomes, thereby promoting the protective autophagy response of cells to the body [62].

Coronary heart disease is a common cause of myocardial ischemia [115]. The role of food-derived flavonoids in human health has been studied extensively. A prospective meta-analysis has shown that dietary flavonoid intake is inversely associated with the risk of coronary heart disease [116]. Myocardial infarction is myocardial necrosis caused by acute, persistent coronary ischemia and hypoxia, platelet aggregation, and thrombosis; flavonoids can reduce platelet aggregation. Clinical experiments have proven that anthocyanins can reduce platelet hyperactivity in patients with dyslipidaemia [116]. When platelets are activated, protein disulphide isomerase (PDI) is released to the surface of platelets, which binds to the transmembrane protein αIIbβ3 to function as a reductase, promoting platelet adhesion and thrombosis. Flavonoids act as PDI inhibitors and inhibit the rapid activation caused by platelet degranulation by regulating the level of calcium ions in platelets[79,117]. Ischemia-reperfusion injury often occurs after myocardial infarction,

aggravating the area of myocardial necrosis, and flavonoids inhibit myocardial ischemia-reperfusion injury by regulating the expression of the NF-κB epigenetic regulatory gene ANRIL [80].

1.2.3. Cardiomyopathy

Cardiomyopathy hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC) and is usually divided into two categories: primary and secondary cardiomyopathy. The aetiology of primary cardiomyopathy is not clear; however, it is mainly related to genetic factors[118,119]. Cardiomyopathy is an important cause of heart failure and sudden cardiac death in young patients [120]. Secondary cardiomyopathy is often secondary to infectious diseases, ischemic diseases, endocrine diseases, etc. There is evidence of the role of flavonoids in the treatment of cardiomyopathy, and the Children's Hospital of Chongqing Medical University study found that after 12 months of oral catechin capsules were given to 12 children with diastolic dysfunction, the children's heart stroke volume and left ventricle end diastolic Volume has been significantly improved (the initial dose was 15 mg/kg daily and was added to 50 mg/kg daily within 3 months after the first dosing) [64].

Cardiac systolic and diastolic restriction is a common clinical manifestation of cardiomyopathy, and calcium ions are a major factor in cardiac remodelling. Flavonoids can inhibit the dysregulation of Ca2+ sensitivity induced by troponin I phosphorylation[121,122]. Catechins alleviate diastolic dysfunction in cardiomyopathy to a certain extent by improving Ca2+ hypersensitivity caused by myofibrillar protein mutations [64]. In addition, flavonoids have a direct effect on myocardial myofilament movement-related proteins, and the flavonoid lignan silymarin can regulate myocardial contraction and diastolic function by inducing the expression of tropomyosin 1 (TPM1), myosin light chain 2 (MYL2), myosin heavy chain 11 (MYH11), and other proteins in cardiomyocytes, thereby protecting against myocardial steatosis via its lipid-lowering effect [63].

1.2.4. Myocarditis and infective endocarditis

Myocarditis can be divided into infectious and non-infectious types according to the aetiology. Infectious factors include viruses, bacteria, and fungi, among which viral infection is the most common. Non-infectious factors include immune-related and drug-related. Myocarditis contributes to the development of DCM [123]. NF-κB is a common pro-inflammatory factor and an important factor in the development of myocarditis. In the rat myocarditis model, treatment of catechin significantly inhibits the expression of NF-κB and improves the inflammatory infiltration and fibrosis of myocardial cells [124]. Other flavonoids, such as pycnogenol and cocoa polyphenols, also inhibit the development of myocarditis in mice via similar anti–NF–κB effects [125].

Infective endocarditis is divided into acute and subacute types, which are mainly caused by pathogen invasion, particularly *Staphylococcus aureus* and viridans streptococci[126–128]. The incidence of infective endocarditis is lower than those of other CVDs. In most cases, the occurrence of infective endocarditis is related to oral inflammatory diseases. A variety of pathogenic bacteria in plaque invade the blood during the occurrence of periodontitis and oral mucosal damage. Flavonoids have a wide range of anti-inflammatory activities, effectively inhibit the inflammatory reaction in periodontal tissue, and significantly reduce the occurrence of periodontal disease [129]. After gram-negative *Bacillus* enters the bloodstream, it releases lipopolysaccharide (LPS) and induces an inflammatory response. Flavonoids have a significant inhibitory effect on LPS-induced MAPK pathway activation and COX-2 expression [81]. *Staphylococcus aureus* is the most common gram-positive bacteria that causes infective endocarditis; flavonoids can prevent its biofilm formation [130]. They exert an antibacterial effect mainly by inhibiting the cell wall component lipoteichoic acid [82].

1.2.5. Heart failure

Heart failure is the manifestation of end-stage cardiovascular disease, and more and more epidemiological evidence confirms that dietary flavonoids are effective in preventing the occurrence of heart failure. The NHANES study found that among 15,869 participants, those who consumed more anthocyanins in their diets showed a lower risk of heart failure [131]. In addition, there is a clinical basis for the therapeutic value of flavonoids in the course of heart failure. A clinical study of 209 patients with heart failure (NYHA class III) was randomized to Crataegus extract WS 1442 (procyanidines) 1800mg/900 mg or placebo for 16 weeks. Activity tolerance in patients treated with WS 1442 improved significantly compared to patients given placebo and was positively correlated with drug dose [132].

Almost all CVDs lead to changes in the structure and function of the heart. Myocardial systolic and diastolic functions are the basis for maintaining the pumping function of the heart, and calcium is the key ion that triggers the electromechanical coupling of the heart [133]. In end-stage heart failure, environmental disturbances lead to the instability of intracellular ion channels, and the accumulation of calcium ions often leads to malignant arrhythmias[134,135]. Mitochondria are the source of cellular energy, and the accumulation of calcium ions in cells leads to calcium ion overload, oxidative stress, and a loss of original mitochondrial functions, in turn affecting the physiological functions of cardiomyocytes[136–138]. Flavonoids regulate the expression of Cav1.2 and NCX1 plasma transporters to maintain calcium homeostasis in cardiomyocytes, thus protecting mitochondrial apoptosis [139]. Flavonoids may prevent heart failure by reducing oxidative dysfunction and inhibiting the transition of mitochondrial permeability [140].A recent study has shown that flavonoids can prolong the life span of rats with heart failure by inhibiting damage to mitochondrial and anti-cell aging [141].

Myocardial fibrosis is a typical pathological change in the advanced stage of CVD; due to the deposition of collagen fibres and the proliferation of interstitial cells, the original structure and function of the heart are destroyed and the heart pump function is accelerated[142,143]. Transforming growth factor β (TGF-β) plays an important role in the pathogenesis of cardiac fibrosis [144]. TGF-β1 is believed to be directly related to the production of cardiac collagen. Studies have shown that Ang II directly promotes the production and deposition of collagen fibres in fibroblasts by up-regulating the expression of TGF-β1 [145]. Studies have demonstrated the therapeutic effect of flavonoids on myocardial fibrosis and have shown that the flavonoid scutellarin, extracted from *Scutellaria*

baicalensis, has a direct inhibitory effect on Ang II and TGF-β1 [51]. Moreover, TGF-β1/Smad is an important regulatory pathway in the endothelial-mesenchymal transition (End-MT), and the flavonoid Icariside II can inhibit the activation of the TGF-β1/Smad2 pathway and exert anti-myocardial fibrosis and anti-cardiac remodelling effects [83]. Other flavonoids have similar anti-fibrotic effects, such as liquiritinapioside, quercetin, neohesperidin, and resveratrol[146–148]. Inflammation, oxidative stress, and other types of damage contribute to the occurrence of myocardial fibrosis. Flavonoids have antioxidant-like therapeutic effects and exert an antifibrotic effect by the regulation of key factors, such as Nrf2 and NF-κB [149]. For example, quercetin upregulates the expression of antioxidant Prx-3 by the regulation of Nrf2 transcription factors, reducing oxidative damage in mitochondria[54,55]. Myricetin alleviated myocardial hypertrophy and fibrosis in mice by the regulation of Nrf2/NF-κB [67]. 8-Formylophiopogonone B regulates the NF-κB pathway by the inhibition of HO-1, inhibiting myocardial damage and cardiac fibrosis [150]. In addition, 17-methoxyl-7-hydroxy-benzene-furanchalcone, a flavonoid monomer, has been shown to promote the expression of eNOS and NO by activating the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, thereby exerting an anti-remodelling effect[151,152].

In the advanced stages of heart failure, cardiomyocytes often exhibit increased ROS, an ion imbalance, and lysosomal instability due to the disruption of internal environmental homeostasis, resulting in an irreversible inflammatory response[153,154]. Flavonoids clear ROS by activating Nrf2 transcription factors [155].NADPH is the main source of ROS production, and flavonoids can interfere with the subunit synthesis of NADPH, inhibit NADPH oxidation activity, and inhibit ROS production via the Ang II/ROS/NO axis and the MAPK pathway[156,157]. Furthermore, the inflammasome is also involved in the inflammatory response in cardiomyocytes [158]. The inflammasome is an important part of the innate immune system [159]. Previous studies have shown that NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome is strongly associated with cardiomyocyte inflammatory injury responses. Flavonoids inhibit NLRP3 activation. For example, dihydromyricetin has been shown to inhibit NLRP3 inflammasome activity by activating the SIRT pathway, which shows anti-apoptotic activity, thereby inhibiting cellular inflammatory responses and apoptosis [68]. There is sufficient evidence for the positive effects of flavonoids on heart function in patients with heart failure [160] as well as their ability to reverse drug-related cardiac impairment, supporting the therapeutic potential of flavonoids for clinical heart failure [161].

2. Conclusion

At present, the research on the medicinal value of flavonoids is increasingly extensive in the field of cardiovascular system diseases and other system diseases, and flavonoids are considered to be a kind of herbal medicine that is beneficial to human health. Existing epidemiological and clinical studies have confirmed the preventive and therapeutic effects of flavonoids, and a large number of basic experiments support this conclusion. In this paper, the potential mechanism of flavonoids for cardiovascular diseases was discussed based on the current research progress of flavonoids.

By inhibiting the synthesis and secretion of related inflammatory factors, flavonoids inhibit vascular endothelial injury and myocardial inflammation, promote the synthesis and release of vascular active factors, such as NO and eNOS, promote autophagy, and inhibit platelet aggregation and thrombosis. They have a therapeutic effect on inflammatory damage in hypertension, coronary atherosclerotic heart disease, myocarditis, and other diseases. In addition, flavonoids are involved in the regulation of ion channels to maintain the stability of plasma concentrations of sodium and calcium ions in the myocardium. Through the regulation of ions and related myofilament, flavonoids are involved in the regulation of myocardial contractile activity, which can improve the restrictive diseases, such as DCM and HCM, and affect the contractile function and diastolic function of vascular smooth muscle. Moreover, flavonoids have a significant therapeutic effect on hyperlipidaemia. They function by regulating the reverse transport of liver lipids, inhibiting the synthesis of lipid transporters (e.g. low-density lipoprotein and very low-density lipoprotein), promoting macrophage fat outflow, and inhibiting the progression of diseases with high blood lipids as a risk factor (such as hypertension and coronary heart disease).

In summary, we believe that flavonoids are a promising alternative treatment option for CVD. However, the toxicity and side effects of the drugs, as well as ways to improve the pharmacokinetics of flavonoids, need to be further explored.

Funding

This work was supported by the National Natural Science Foundation of China (81903000), Natural Science Foundation of Sichuan Province (2023NSFSC1846) , Sichuan Science and Technology Program (2022YFS0636–B4, 2022YFS0636–C4), Foundation of Southwest Medical University (00031742, 2021ZKQN093).

Data availability statement

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

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Yingxue Liu: Writing – original draft, Conceptualization. **Jing Luo:** Writing – original draft, Formal analysis, Data curation. **Lin Peng:** Validation, Software, Investigation. **Qi Zhang:** Supervision, Software. **Xi Rong:** Visualization, Methodology. **Yuhao Luo:** Writing – review & editing, Funding acquisition, Conceptualization. **Jiafu Li:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to acknowledge the Editage for manuscript editing service, we also acknowledge the grant of National Natural Science Foundation of China, Natural Science Foundation of Sichuan Province , Sichuan Science and Technology Program, Foundation of Southwest Medical University.

Abbreviations

CAD Cardiovascular disease
EGCG epigallocatechin gallate
RAAS renin-angiotensin-aldosterone
NADPH triphosphopyridine nucleotide;
AngII angiotensin II
ACE angiotensin-converting enzyme
MLCK myosin light chain kinase
cGMP cyclic guanosine monophosphate
oxLDL, oxidized low den-sity lipoprotein
AMPK/mTOR serine/threonine kinase AMP-activated protein kinase/mammalian target of rapamycin
KLF4 Krüppel-like factor 4
Enos endothelial nitric oxide synthase
ROS reactive oxygen species
apoB Apolipoprotein B
APEX1 Apurinic-Apyrimidinic Endonuclease I
HO-1 Heme oxygenase 1
Nrf2 nuclear factor erythroid2-related factor 2
SOD superoxide dismutase
KLF2 Krüppel-like factors
MLKL, mixed lineage kinase domain-like protein
PDI protein disulphide isomerase
HCM hypertrophic cardiomyopathy
DCM dilated cardiomyopathy
RCM restrictive cardiomyopathy
ARVC arrhythmogenic right ventricular cardiomyopathy
TPM1 tropomyosin 1;
MYL2 myosin light chain 2
MYH11 myosin heavy chain 11
LPS lipopolysaccharide;
TGF-β, Transforming growth factor β
End-MT endothelial-mesenchymal transition
NLRP3, NOD LRR- and pyrin domain-containing 3
COVID-19 Corona Virus Disease 2019

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