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The multifaceted anti-atherosclerotic properties of herbal flavonoids: A comprehensive review

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ABSTRACT

Atherosclerosis (AS) is a major etiological factor underpinning a spectrum of cardiovascular diseases, leading to cerebral infarction, coronary artery disease, and peripheral vascular disease. The chronic progression of AS, spanning from initial plaque formation to the occurrence of acute cardiovascular events, underscores the complexity of AS and the challenges it presents in terms of treatment. Currently, the clinical management of AS relies predominantly on statins and proprotein convertase subtilisin/kexin type 9 inhibitors, which primarily aim to reduce low-density lipoprotein levels and have demonstrated some therapeutic efficacy. Nevertheless, due to their potential side effects, there is a pressing need to actively investigate alternative treatment approaches.

Abbreviations: ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; ABCG8, ATP binding cassette subfamily G member 8; ACAT, acyl-CoA:cholesterol acyltransferase; ACLY, ATP citrate lyase; Akt, protein kinase B; AMPK, adenosine 5'-monophosphate activated protein kinase; Ang II, angiotensin II; ApoA-I, apolipoprotein A-I; ApoE$^{-/-}$, apolipoprotein E knockdown; AREs, antioxidant response elements; AS, atherosclerosis; ATG, autophagy-related protein; ATP, adenosine triphosphate; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; CAT, catalase; CD36, cluster of differentiation 36; CDK, cyclin-dependent kinase; CETP, cholesterol ester transfer protein; CHF, chronic heart failure; CPT-1, carnitine acyl transferase I; CYP7A1, cholesterol 7alpha-hydroxylase; Db/db mice, diabetes mouse; DHFR, dihydrofolate reductase; EC, endothelial cell; ENOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; FC, free cholesterol; FGF15, fibroblast growth factor-15; FXR, farnesoid X receptor; GCH1, GTP cyclohydrolase 1; GPER, G-protein coupled estrogen receptor; GSH-Px, glutathione peroxidase; GTC, Ge Gen Tongluo capsule; HDL, high-density lipoprotein; HFD, high-fat diet; HO-1, heme oxygenase-1; H_2O_2, hydrogen peroxide; HUVEC, human umbilical vein endothelial cell; ICAM-1, intercellular cell adhesion molecule-1; IKK, inhibitor of kappa B kinase; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; IL-1, interleukin-1; IL-8, interleukin-8; IL-10, interleukin 10; IS, ischemic stroke; JAK2, janus kinase 2; LAD, left anterior descending branch; LC3, microtubule-associated protein 1 A/1B-light chain 3; LDL, low-density lipoprotein; Ldlr$^{-/-}$, low-density lipoprotein receptor knockdown; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; LXRα, liver X receptor alpha; MAPK., p38 mitogen-activated protein kinase.; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; Mef2c, myocyte enhancer factor 2 C; MLKL, mixed lineage kinase domain-like protein; MMP, matrix metalloproteinase; MSR1, macrophage scavenger receptor 1; MTOR, mammalian target of rapamycin; MIRI, myocardial ischemia-reperfusion injury; MYH9, myosin heavy chain 9; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; NLRP3, NOD-like receptor family pyrin domain-containing 3; NO, nitric oxide; NOXS, NADPH oxidase; Nrf2, nuclear factor erythroid 2-related factor 2; Notch, neurogenic locus notch homolog protein; O^{2-}, superoxide anions; OH·, hydroxyl radicals; Ox-LDL, oxidized low-density lipoprotein; PCNA, proliferating cell nuclear antigen; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol 3-kinase; PPARα, peroxisome proliferator-activated receptor alpha; PPARγ, peroxisome proliferator-activated receptor gamma; P38 MAPK, p38 mitogen-activated protein kinase; RASMCs, rat aortic smooth muscle cells; RCT, reverse cholesterol transport; ROO·, peroxyl radicals; ROS, reactive oxygen species; RXR, retinoid X receptor; SOD, superoxide dismutase; SIRT1, sirtuin 1; SIcam-1, soluble intercellular adhesion molecule-1; Smad2, SMAD family member 2; Smad3, SMAD family member 3; Sp1, specificity protein 1; SR-A, scavenger receptor A; SR-B, scavenger receptor class B; SREBP-1c, sterol regulatory element-binding protein 1; SREBP2, sterol-regulatory element binding protein 2; STAT3, signal transducer and activator of transcription 3; TFEB, transcription factor EB; TGF-β, transforming growth factor-beta; TGFR, transforming growth factor receptor; TNF-α, tumor necrosis factor-alpha; THP-1, human monocytic-leukemia cells; ULK, unc-51-like kinase; VCAM-1, vascular cell adhesion molecule-1; VLDL, very low-density lipoprotein; VSMC, vascular smooth muscle cell; XO, xanthine oxidase.

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Researches on natural compounds derived from herbal medicines, such as flavonoids, hold significant promise in combating AS by regulating lipid metabolism, reducing oxidative stress and inflammation, inhibiting the proliferation of vascular smooth muscle cells, modulating autophagy and additional pathways. Various targets participate in these physiological processes, encompassing acyl-CoA: cholesterol acyltransferase (ACAT), ATP citrate lyase (ACLY), nuclear factor erythroid 2-related factor 2 (Nrf2), krüppel-like factor 2 (KLF2), NOD-like receptor protein 3 (NLRP3), transcription factor EB (TFEB) and so on. This comprehensive review endeavors to synthesize and analyse the most recent findings on herbal flavonoids, shedding light on their anti-atherosclerotic potential and the underlying protective mechanisms and related-targets, which might pave the way for the development of novel drug candidates or the optimization of flavonoid-based therapies.

1. Introduction

Atherosclerosis (AS) is recognized as the quintessential malady of the cardiovascular system, predominantly driving the development of cerebral infarction, coronary artery disease, and peripheral vascular disease [1]. The onset of AS is widely acknowledged to stem from a confluence of factors, both genetic and environmental in nature. In Asia, and Central and South America, shifts in traditional dietary patterns have occurred in tandem with burgeoning population growth and economic prosperity. Concurrently, there has been a marked increase in smoking prevalence, alongside an upswing in obesity and diabetes rates. These factors contribute to a higher susceptibility to atherosclerotic cardiovascular diseases in these regions, thereby presenting formidable challenges to public health [2]. Additionally, hypertension stands out as a major independent risk factor for atherosclerotic cardiovascular diseases. Studies have consistently reported a substantial elevation in cardiovascular risk among hyperlipidemic patients suffering from hypertension. While hypercholesterolemia is a crucial initiator for the genesis and development of AS, hypertension acts as an "accelerator" that exacerbates its progression [3]. Growing evidence further suggests the involvement of the immune system, with emerging factors such as inflammation and the clonal hematopoiesis which cause by the somatic mutations in stem cells being identified as independent risk factor of AS [4]. The intricate etiology of AS has been progressively deciphered through various investigative approaches, such as lipid infiltration, inflammation, oxidative stress, monocyte/macrophage activity, and immune mechanisms [5–7]. Recent insights posit that AS is intertwined with various mechanisms, including clonal hematopoiesis, epigenetics and non-coding RNA [8,9], angiogenesis, aging, copper dyshomeostasis [10], glycolysis, gut microbiome, and additional pathways.

The enduring nature of AS and the absence of highly effective or curative treatments place a considerable financial and emotional strain on affected individuals. Currently, the Food and Drug Administration endorses a range of medications for AS treatment, such as statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors, bempedoic acid, and inclisiran which are formulated to reduce Low-density lipoprotein (LDL) levels or to target specific proteins, thereby diminishing the risks associated with atherosclerotic cardiovascular diseases [11,12]. Despite their intended benefits, these treatments tend to offer only modest and transient effects on disease management and are unable to fully prevent, stop, or reverse the progression of AS. Moreover, long-term use of statins has been associated with undesirable side effects, such as muscle pain, hepatic dysfunction, and even black urine, which mandated consistent medical supervision [13,14]. Hence, there is an urgent need to find alternative treatment strategies.

Over the past several decades, extensive researches have been conducted to evaluate the anti-atherosclerotic properties of natural compounds derived from herbal medicines. Flavonoids, a significant class of these natural substances, are found in more than 400 plant species. They are particularly prevalent in plant families such as *Rutaceae*, *Leguminosae*, *Rosaceae*, *Umbelliferae*, and *Labiatae*, as well as in gymnosperms including *Sapiaceae* and *Pinaceae*. These compounds play diverse and crucial roles in plant physiology. Flavonoids significantly contribute to plant defense against oxidative stress, acting as robust ultraviolet filters that protect plants from both biotic and abiotic stresses [15]. Additionally, flavonoids function as detoxifying agents and showcase potent antimicrobial properties [16]. In recent years, numerous studies have substantiated the diverse biological activities and pharmacological effects of flavonoids and flavonoid-rich herbs, particularly in the context of atherosclerotic cardiovascular diseases prevention and treatment. Studies have indicated that kaempferol, a flavonoid naturally presents in a variety of fruits and vegetables and particularly abundant in traditional Chinese medicine such as *Ginkgo biloba*, demonstrates antioxidant, anti-inflammatory, and cardio-protective attributes, positioning it as a promising pharmaceutical candidate for the prevention and treatment of AS [17]. Hawthorn, a functional food and medicinal herb, is rich in flavonoids. It serves as an example of "medicine-food homology", offering potential preventive and therapeutic effects on AS [18].

This review delivers a thorough synthesis of the latest progress of flavonoid monomers and total flavonoids extracted from herbal medicines in combating AS, exploring their multifaceted roles as modulators of lipid profiles, antioxidants, anti-inflammatory agents, inhibitors of vascular smooth muscle cell (VSMC) proliferation and migration, inducers of autophagy and other pathways. The roles of various targets, including acyl-CoA: cholesterol acyltransferase (ACAT), ATP citrate lyase (ACLY), nuclear factor erythroid 2-related factor 2 (Nrf2), krüppel-like factor 2 (KLF2), NOD-like receptor protein 3 (NLRP3), transcription factor EB (TFEB) in these physiological processes are comprehensively summarized. These insights may pave the way for innovative therapeutic strategies that leverage the natural bounty of flavonoids, offering patients more effective and safer options for the management of atherosclerotic cardiovascular diseases.

2. Basic structure and classification of flavonoids

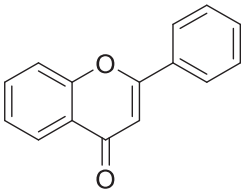
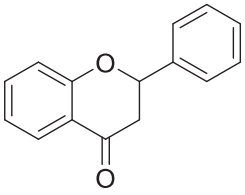
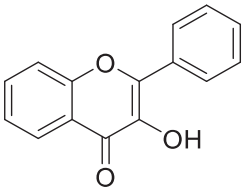
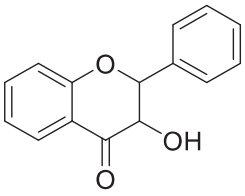
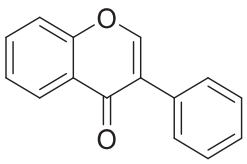
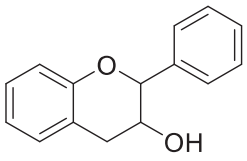
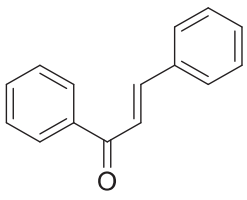
Flavonoids are a diverse class of polyphenolic compounds, characterized by a distinctive molecular structure known as the C_6-C_3-C_6 skeleton. This structure consists of two six-carbon aromatic rings, labelled as rings A and B, which are interconnected by a three-carbon chain known as C-ring. The classification of flavonoids is based on various factors, including the oxidation state of the C-ring, the exact point at which the B-ring is attached to the C-ring, and the presence or absence of a heterocyclic ring formed by the C-ring. Flavonoids often exhibit chromophores such as hydroxyl groups (-OH) and methyl groups (-CH_3) on their molecular scaffolding [19]. The presence of these functional groups can result in various colours, ranging from yellow and orange to red and blue, depending on the specific flavonoid and its chemical environment [20].

The wide range of biological activities and potential health benefits of flavonoids are closely related to their chemical and structural characteristics. These natural compounds, harnessed for their utility in addressing atherosclerotic cardiovascular diseases, are meticulously categorized into seven distinct subclasses: flavones, flavanones, flavonols, flavanonols, isoflavones, flav-3-ols, chalcones and biflavonoids (Table 1) [21].

2.1. Flavones

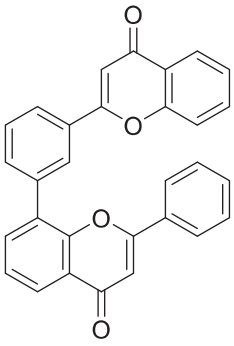
Flavones, a subclass of flavonoids, are characterized by the presence of 2-phenyl chromogenic ketones as the core structure, with the notable absence of oxygen-containing substituents at the C_3 position. They are ubiquitous in dietary sources such as celery, honeysuckle, and chamomile flower tea [22]. Luteolin, a prominent member of the flavone family, has been the subject of numerous studies due to its potential hypotensive effects. Specifically, it has been demonstrated to reduce blood pressure in hypertensive rats, enhance vasodilation in aortic rings,

Table 1
Classification and pharmacological activities of representative flavonoids related to atherosclerotic cardiovascular diseases.

Type	Skeleton	Representative compound	Pharmacological activity	Reference
Flavones		luteolin, baicalin, chrysin, baicalein	antioxidant, anti-inflammatory, hypolipidemic, vasodilatory, anti-hypotensive	[23,24, 58–62,64]
Flavanones		hesperitin, liquiritigenin, liquiritin	anti-inflammatory, antioxidant, hypolipidemic, anti-fibrosis, myocardial blood flow-increasing	[65–69]
Flavonols		quercetin, kaempferol, myricetin, rutin	anti-inflammatory, antioxidant, antithrombotic, antiplatelet-activating, anti-hypotensive, hypolipidemic	[30,63, 70–75]
Flavanonols		dihydroquercetin, dihydromorin	anti-inflammatory, antioxidant	[33,76–78]
Isoflavones		genistein, puerarin, daidzin	antioxidant, anti-inflammation, anti-thrombotic, anti-hypotensive, anti-arrhythmic	[79–82]
Flavan−3-ols		catechin, epicatechin, epigallocatechin gallate	anti-hypertensive, anti-inflammatory, antioxidant, anti-atherogenic	[40,41,84, 85]
Chalcones		hydroxysafflor yellow A	anti-inflammatory, antioxidant, anti-angiogenic, anti-hypotensive, anti-anginal, anti-arrhythmic	[86–88]

(continued on next page)

Table 1 (*continued*)

Type	Skeleton	Representative compound	Pharmacological activity	Reference
Biflavonoids	* 	amentoflavone, bilobetin, sciadopitysin, ginkgetin, isoginkgetin	anti-inflammatory, antioxidant, antioxidant, anti-angiogenic , hypolipidemic , anti-apoptosis	[46–58]

* Different skeletons are present in biflavonoids, with the amentoflavone-type being the sole example listed in this table.

and augment cyclic adenosine monophosphate (cAMP) accumulation by inhibiting cAMP-specific phosphorylation during rats' pregnancy [23]. Concurrently, baicalin, another flavone, undergoes hydrolysis to yield quinone derivatives, which have been reported to possess antibacterial, antiviral, and antihypertensive properties [24].

2.2. Flavanones

Flavanones are a subclass of flavonoids distinguished by their saturated C_2- C_3 bond, which are prevalent in plant families, including *Rosaceae*, *Rutaceae*, *Compositae*, *Ginger*, and *Rhododendroaceae*. Hesperetin, a flavanone particularly abundant in citrus fruits, is recognized for its metabolites that contribute to their anti-hypertensive properties and impeding the progression of atherosclerotic plaques through significant anti-inflammatory mechanisms [25]. Furthermore, the antioxidative properties of hesperetin are also pivotal, as they enhance nitric oxide (NO) production and reduce calcium ion concentrations, collectively promoting relaxation of the smooth muscle within blood vessels [26]. Liquiritigenin stands out as a promising candidate for the treatment of chronic heart failure (CHF). Its therapeutic effects are realized by alleviating doxorubicin-induced CHF through the upregulation of ARHGAP18 expression and the suppression of ras homolog gene family member A /rho-associated protein kinase 1 pathway [27].

2.3. Flavonols

Flavonols are characterized by the presence of hydroxyl groups or other oxygen-containing groups attached to the C_3 position of the flavonoid backbone. They are abundant in dicotyledonous plants and can be found in various plant families such as *Rosaceae* and *Leguminosae*. Two prevalent examples of flavonols are quercetin and rutin. Quercetin is renowned for its diverse health benefits, including improving endothelial function, regulating vascular smooth muscle contraction, and modulating the renin-angiotensin-aldosterone system to reduce blood pressure [28]. Moreover, quercetin's capacity to counteract oxidative stress is beneficial for the heart and kidney, supporting its overall health and function [29]. Rutin exhibits a vitamin P-like effect, which contributes to the maintenance of vascular resistance, reduction in permeability, mitigation of brittleness, and anti-inflammatory effects [30].

2.4. Flavanonols

Flavanonols are a class of compounds that arise from the hydrogenation of the C_2-C_3 double bond in flavonols. They are commonly observed in conjunction with their corresponding flavonols within the same plant. For instance, *Rhododendron dauricum* L. contains both dihydroquercetin and quercetin [31], while *Morus alba* L. contains both dihydromorin and morin [32]. It has been shown that dihydroquercetin alleviates myocardial ischemia-reperfusion injury (MIRI) by activating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway, leading to a decrease in oxidative stress and apoptosis induced by endoplasmic reticulum stress [33].

2.5. Isoflavones

Isoflavones, a group of natural compounds featured with a 3-phenyl chromone core structure, are subject to various modifications, including oxygen substitution, alkylation, and glycosylation, which contribute to their diverse biological activities. Diadzein, a prominent isoflavone found in soybeans and soy-based products, is recognized for its protective role against oxidative stress-induced damage. Additionally, it is known to enhance NO synthesis, reduces low-density lipoprotein oxidation, and promotes prostaglandin production [34]. Genistein, another isoflavone found in soybeans and select legumes, has been the focus of scientific research. Studies have substantiated its potential as a promising anti-hypertensive agent with results observed across different experimental models [35].

2.6. Flavan-3-ols

Flavan-3-ols encompass a group of flavonoid compounds found in various plant species, especially in tannin-rich woody plants. The basic structure of flavan-3-ols consists of two aromatic rings (A and B rings) connected by a three-carbon chain. Catechins are a subgroup of flavan-3-ols that exist as monomeric constituents and include epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate [36]. These compounds have been extensively studied for their potential health benefits. Extensive research has demonstrated the advantageous impact of catechins on vascular function as well as their cardioprotective properties [37,38]. Furthermore, investigations have revealed the potential of these compounds to mitigate both systolic and diastolic blood pressure levels [39]. Epicatechin has been shown to possess anti-hypertensive properties, as supported by its capacity to decrease systolic and diastolic blood pressures when consumed in the form of epicatechin-rich chocolate [40]. Additionally, recent studies have demonstrated its potential to alleviate myocardial rigidity in rats afflicted with hypertrophic cardiomyopathy. Furthermore, epigallocatechin gallate, which is prominently found in green tea, possesses anti-inflammatory, antioxidant, and anti-atherogenic properties [41].

2.7. Chalcones

Chalcones are characterized by their structure, where two benzene rings are connected by a three-carbon chain containing carbonyl groups.

Typically, chalcones are converted into flavonoids through the action of an enzyme known as chalcone isomerase. This enzyme catalyzes the isomerization of chalcones, rearranging the double bond within the molecule to form the characteristic flavonoid structure [42]. Although chalcones are less abundant than other flavonoid compounds in plants, they serve crucial roles as primary constituents of pigments found in flowers. Safflor yellow A is a typical chalcone component. It has been shown the potential to protect vascular endothelial cells (ECs) from damage induced by oxidized low-density lipoprotein (ox-LDL) via modulating the activation of the adenosine 5'-monophosphate activated protein kinase (AMPK) pathway [43].

2.8. Biflavonoids

Biflavonoids, comprising two monoflavonoid residues, can be categorized into types such as AA, BB, AB, and CC based on the configuration of their two rings. These compounds demonstrate a diverse array of biological activities relevant to atherosclerotic cardiovascular diseases, encompassing anti-inflammatory, antioxidant, and vasodilatory effects. In specific cases, the biological efficacy of biflavonoids exceeds that of the individual monomers [44]. Biflavonoids play a significant role as constituents of ginkgo phytopharmaceuticals. Presently, ginkgo is known to contain 13 biflavonoids, with amentoflavone, bilobetin, sciadopitysin, ginkgetin, and isoginkgetin being among the most prevalent ones [45]. Among these, amentoflavone stands out as the most extensively studied. Studies have indicated that amentoflavone has the potential to inhibit the renin-angiotensin system and alleviate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-induced oxidative stress, resulting in decreased blood pressure and improved cardiovascular function [46]. Furthermore, it has been reported that amentoflavone prevents ox-LDL-induced lipid accumulation by suppressing the proliferator-activated receptor gamma (PPARγ)/cluster of differentiation 36 (CD36) signaling pathway [47]. Additionally, amentoflavone exhibits cardioprotective effects by suppressing apoptosis and inflammation in both *in vitro* and *in vivo* models of MIRI [48]. Ginkgetin has been reported to enhance the integrity of the thoracic aortic intima, reduce intima-media thickness and the intima/-media ratio, and alleviate lipid deposition in the aorta of atherosclerotic rats [49]. Furthermore, it effectively mitigates apoptosis and inflammation responses through the nuclear factor-κB (NF-κB) signaling pathway in MIRI [50]. Other biflavonoids, such as bilobetin [51], isoginkgetin [52], morelloflavone [53,54], sciadopitysin [55,56], and taiwaniaflavone [57], have also shown protective potential in the field of cardiovascular management.

3. Mechanisms underlying anti-atherosclerotic effects of herbal flavonoids

3.1. Lipid metabolism regulation

The basis of atherosclerotic lesions lies in the abnormal lipid metabolism that occurs in patients, and the "cholesterol theory" is one of the primary theories explaining the cause of AS [89]. During the progression of AS, LDL cholesterol accumulates within the endothelium, initiating the development of lipid plaques. Ox-LDL triggers the activation of macrophage receptors, such as scavenger receptor A (SR-A), scavenger receptor B (SR-B)/ CD36, and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), leading to a heightened uptake of ox-LDL. Subsequently, ox-LDL undergoes digestion in macrophage lysosomes, releasing free cholesterol. This cholesterol can be esterified by the endoplasmic reticulum enzyme cholesterol esterase ACAT and ultimately stored as cytosolic lipid droplets, forming foam cells. This process exacerbates the progression of plaque formation. Research findings indicate that hesperidin [90], hawthorn leaf flavonoids [91], isoliquiritigenin [92], naringin [93], nobiletin [94], and xanthohumol [95] demonstrate significant efficacy in inhibiting lipid uptake, thereby reducing the formation of foam cells.

ACAT plays a pivotal role in the regulation of cholesterol metabolism by catalyzing the esterification of free cholesterol within cells. It has been reported that ACAT activity is slightly low in rabbits fed naringin (5.0 %) and naringenin (15.0 %) compared to the controls [96]. ACAT1 exhibits broad expression across various tissues, notably in macrophage foam cells, where it facilitates cholesteryl ester accumulation. Proanthocyanidins show the potential to increase miR-9 expression, leading to the inhibition of ACAT1 expression, thus exerting inhibitory effects on macrophage foam formation [97]. On the other hand, ACAT2 is predominantly expressed in intestinal enterocytes and hepatocytes. Inhibiting ACAT2 activity can lead to reduced serum cholesterol levels and impaired cholesterol absorption. For example, luteolin is demonstrated to alleviate hepatic impairment in HFD-induced rats by amelioration of oxidative stress and downregulation of ACAT2 and sterol regulatory element-binding protein 2 [98].

Additionally, as an enzyme that plays a crucial role in cellular metabolism, ACLY catalyzes the conversion of citrate and CoA into acetyl-CoA and oxaloacetate. Acetyl-CoA is a key molecule in many metabolic pathways, including fatty acid synthesis and cholesterol biosynthesis. Recently, several flavonoids have been reported to function as potent inhibitors of ACLY, including herbacetin, luteolin, quercetin, and gossypetin [99]. Furthermore, bergamot flavonoids effectively inhibit the synthesis of fatty acids by downregulating ACLY expression [100].

Cholesterol efflux is critical to maintaining the homeostasis of intracellular cholesterol. Reverse cholesterol transport (RCT) is a crucial process in maintaining cholesterol homeostasis and preventing AS development [101,102]. Flavonoids are found to promote cholesterol efflux through their involvement in the regulation of RCT pathways. It has been reported that hawthorn leaf flavonoids can downregulate AS development in apolipoprotein E knockdown ($ApoE^{-/-}$) mice by inhibiting foam cell formation and promoting RCT *in vivo* [103].

Many proteins are involved in RCT regulation, among which ATP-binding cassette transporter A1 (ABCA1) and G1 (ABCG1) are essential [104]. Both are integral membrane proteins that utilize ATP as an energy source for transmembrane transport of lipids and other metabolites. Flavonoids, such as quercetin [70,72], kuwanon G [105] and baicalein [62], are involved in lipid metabolism through the regulation of the ABCA1 and ABCG1. By upregulating the expression of ABCA1 and ABCG1, flavonoids facilitate the efflux of excess cholesterol from macrophages, promoting its transport to high-density lipoprotein (HDL) particles [106]. HDL subsequently transports cholesterol back to the liver for further metabolism and excretion from the body. Furthermore, flavonoids also modulate the expression and activities of other RCT-related proteins, such as SR-B1 [107] and cholesterol ester transfer protein (CETP) [108]. SR-B1 facilitates the selective uptake of cholesterol from HDL particles, while CETP mediates the transfer of cholesterol esters between lipoproteins.

Moreover, ABCA1 and ABCG1 can be regulated fully or partially through the peroxisome PPARγ/liver X receptor alpha (LXRα)-dependent pathway. PPARγ and LXRα are nuclear receptors that play crucial roles in lipid metabolism and cholesterol homeostasis. Activation of PPARγ leads to the upregulation of ABCA1 and ABCG1 gene expression. PPARγ forms a heterodimer with the retinoid X receptor (RXR) and binds to specific response elements in the promoter regions of ABCA1 and ABCG1 genes [109]. This binding activates the transcription of these transporters, resulting in increased cholesterol efflux from cells. It is found that isoliquiritigenin can enhance PPARγlevel and reverse the downregulated ABCA1 expression in ox-LDL-treated macrophages by regulating PPARγ-dependent signaling, thus facilitating lipid metabolism [65]. Similarly, LXRα activation also contributes to the regulation of ABCA1 and ABCG1. LXRα forms a heterodimer with RXR and binds to specific response elements in the promoter regions of the ABCA1 and ABCG1 genes [110]. This binding induces the transcription of these transporters, enhancing cholesterol efflux. *Hibiscus sabdariffa*

leaf polyphenolic extract, which is rich in flavonoids, can remove cholesterol from macrophages and delay AS by regulating LXRα/ABCA1 pathway [111]. The upregulation of ABCA1 and ABCG1 expression by dihydromyricetin is found to be dependent on LXRα level, and the inhibitory effects of dihydromyricetin on cholesterol and lipid accumulation in macrophages can be reversed by LXRα siRNA [77]. Additionally, by modulating PPARγ/LXRα-dependent pathway, flavonoids can enhance cholesterol efflux, reduce foam cell formation, and mitigate AS progression. Baicalin exerts anti-atherosclerotic effects through PPARγ-LXRα-ABCA1/ABCG1 pathway, promoting cholesterol efflux from macrophages and delaying foam cells formation [112]. In human monocytic-leukemia cells (THP-1) macrophage-derived foam cells, treatment with biochanin A promotes cholesterol efflux and reduces intracellular cholesterol concentration by activating the PPARγ/LXRα and PPARγ/heme oxygenase-1 (HO-1) pathways and upregulating ABCA1 and ABCG1 expression [113]. Chrysin can inhibit intracellular cholesterol accumulation by activating the PPARγ-LXRα-ABCA1/ABCG1 pathway and downregulating SR-A1 and SR-A2 [114].

These findings suggest that certain flavonoids from herbal medicines can achieve anti-atherosclerotic effects by regulating certain key molecules involved in cholesterol influx, esterification and efflux (Fig. 1). Understanding the intracellular metabolic pathways might provide insights into the development of therapeutic strategies for managing lipid disorders and AS.

3.2. Anti-oxidative stress effect

Oxidative stress refers to an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms. ROS are highly reactive molecules generated as natural byproducts of cellular metabolism [115]. Under normal physiological conditions, ROS are essential for cell signaling, gene expression, defense against foreign microbial invasion, and maintenance of normal cell growth. However, when there is an excessive production of ROS or a weakened antioxidant defense, oxidative stress occurs, which leads to various biological systems damages, involving proteins, lipids, and DNA, contributing to the development and progression of various diseases [116].

Oxidative stress intricately influences the onset and progression of AS through diverse mechanisms [117–119]. Oxidative stress leads to the oxidation of LDL cholesterol particles, increasing the particles' propensity for uptake by macrophages and the formation of foam cells, a hallmark of early atherosclerotic lesions [120]. Furthermore, oxidative stress promotes endothelial dysfunction, which is characterized by impaired NO bioavailability and increased production of pro-inflammatory molecules [121]. Endothelial dysfunction is a key step in AS development by fostering immune cells adhesion, facilitating smooth muscle cells migration, and contributing to atherosclerotic plaques formation. Oxidative stress also influences the vascular wall remodeling, boosting the proliferation and migration of smooth muscle cells and aiding in the deposition of extracellular matrix proteins [122], which further contribute to the development of atherosclerotic lesions.

Several specific flavonoids commonly found in herbal medicines have been studied for their antioxidant capacity. For example, quercetin has been shown to possess strong antioxidant activity, which is shown to scavenge free radicals, inhibit lipid peroxidation, and protect against oxidative DNA damage [73]. Other flavonoids, such as catechins, epicatechin, and proanthocyanins commonly found in green tea and other herbal medicines [84,85,123], also demonstrate antioxidant potentials, including scavenging free radicals, inhibiting oxidative damage to lipids and proteins, and protecting against oxidative stress-induced cell death. The relative antioxidant activity mechanisms are as follows:

First, flavonoids can directly scavenge ROS by acting as hydrogen atom donors for free radicals, such as superoxide anions ($O_2^{\cdot-}$), hydroxyl radicals (OH·) and peroxyl radicals (ROO·), thereby reducing LDL oxidation and attenuating vascular endothelial inflammation [124]. Myricitrin protects ECs from ROS-induced apoptosis and prevent AS formation by scavenging ROS, reducing lipid peroxidation, blocking NO release, and maintaining the mitochondrial transmembrane potential [125]. Isoflavone-rich extracts from *Pueraria lobata* (kudzu) roots can act as vascular EC protectors against intracellular ROS-mediated apoptosis and mitochondrial damage [126]. Safflor yellow A protects human

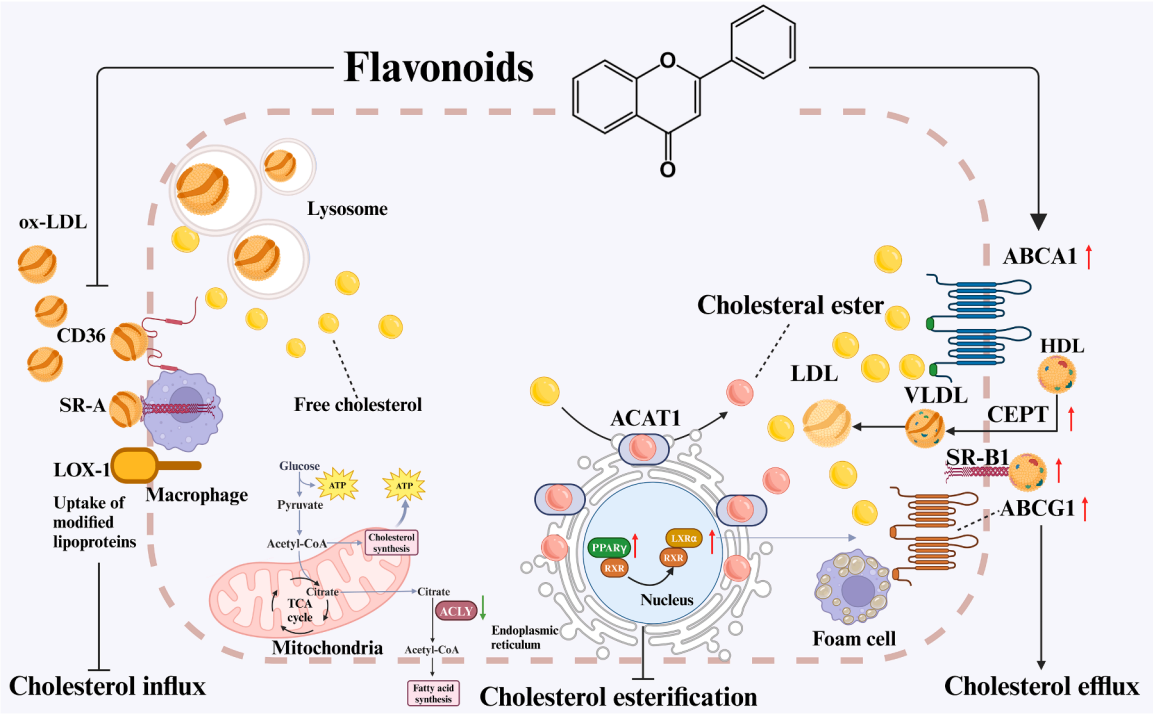


Fig. 1. Mechanism of flavonoids regulating certain key molecules involved on cholesterol influx, esterification and efflux. Red arrow: activation effect of flavonoids. Green arrow: inhibitory effect of flavonoids.

umbilical vein endothelial cells (HUVECs) from oxidative damage by directly antagonizing ox-LDL-mediated upregulation of ROS and downregulation of NO in HUVECs [88]. Total flavonoids from *Astragalus membranaceus* effectively scavenge superoxide and hydroxyl radicals in isolated hearts in a dose-dependent manner, which might be one of the potential mechanisms underlying the anti-atherosclerosis effect of *Astragalus* [127].

Second, some flavonoids can chelate metal ions, for example, iron and copper, which are involved in the generation of ROS. By binding to these metal ions, flavonoids inhibit their participation in redox reactions, thereby reducing ROS production and oxidative stress. Chrysin exerts an antioxidant effect by enhancing the antioxidant system, suppressing pro-oxidant enzymes, scavenging free radicals, and chelating redox-active transition metal ions [60]. It is reported that amentoflavone exhibits strong metal chelation abilities, particularly in the chelation of copper ions (Cu^{2+}), which demonstrates a high affinity for binding with flavonoids. By chelating copper ions, amentoflavone inhibits these redox reactions, reducing ROS generation and oxidative stress [128].

Furthermore, the mechanism of ROS scavenging by flavonoids is also related to the inhibition of several enzymes that generate superoxide radicals, such as xanthine oxidase (XO) and NADPH oxidase (NOXS). For example, quercetin can effectively suppress NOXS-derived ROS formation and oxidant-induced endothelial dysfunction in vascular ECs through upregulation of HO-1 expression [83]. In addition, although endothelial nitric oxide synthase (eNOS) primarily produces NO under certain conditions, it can also generate superoxide radicals. Flavonoids have been found to modulate eNOS activity and prevent eNOS uncoupling, which refers to the aberrant production of superoxide instead of NO. By preserving eNOS function, flavonoids help maintain the balance between NO and superoxide production, reducing oxidative stress. Genistein treatment can reverse eNOS uncoupling induced by ox-LDL in HUVECs. This reversal is achieved by activating the sirtuin 1 (SIRT1) pathway. By restoring eNOS function, genistein may contribute to the protective effects against AS [129].

Moreover, flavonoids can also neutralize or block the damage caused by oxidative stress via activating certain antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px), which are important to help detoxify ROS. Vaccarin is found to enhance the activity of SOD, which may protect the vascular endothelium from dysfunction induced by hydrogen peroxide (H_2O_2) [130]. Farrerol has been demonstrated to increase SOD and GSH-Px activities, leading to the inhibition of H_2O_2-induced cell viability loss [131]. Baicalin is reported to upregulate the activities of SOD, CAT, and GSH-Px while downregulate the activity of the oxidative parameter malondialdehyde (MDA), indicating a significant antioxidant effect [132]. Other flavonoids, such as chrysin [58], scutellarin [133], and dihydromyricetin [76], have also been shown to improve the antioxidant capacity of the body by upregulating the activities of antioxidant enzymes. By activating these antioxidant enzymes, flavonoids enhance cellular defense capacity against oxidative stress and reduce ROS accumulation.

Nrf2 is considered as a classical antioxidant transcription factor due to its central role in regulating the expression of various antioxidants. When cells experience oxidative stress, Nrf2 is activated and translocates to the nucleus where it binds to antioxidant response elements (AREs) in the promoter region to initiate the transcriptionof downstream antioxidant genes such as HO-1 and catalase to reduce ROS [134]. Alpinetin has been demonstrated to facilitate Nrf2 phosphorylation and nuclear translocation, leading to the heightened Nrf2 transactivation within RAW264.7 macrophages, which subsequently culminates in the inhibition of macrophage infiltration and AS progression [135]. Dihydromyricetin can prevent HUVECs from ox-LDL-induced oxidative injury through activation of the Nrf2/HO-1 pathway mediated by Akt and extracellular signal-regulated kinases (ERK) [136]. The protective mechanism of kaempferol against AS involves the activation of the PI3K/AKT/Nrf2 pathway through the stimulation of G protein-coupled oestrogen receptor [137]. Various flavonoids, such as anthocyanins [138], epigallocatechin gallate [139], puerarin [140], and theaflavin [141], have also exhibited promise in attenuating AS, with obvious efficacy attributed to Nrf2 pathway modulation.

Overall, oxidative stress plays a significant role in AS pathogenesis and flavonoids exhibit antioxidant activity through varied mechanisms (Fig. 2). Understanding the underlying mechanisms will help identify potential targets for therapeutic interventions aiming at reducing the burden of this atherosclerotic cardiovascular diseases.

3.3. Anti-inflammatory effect

AS appears to be a progressive vascular inflammatory process [142]. Endothelial dysfunction leads to the upregulation of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular cell adhesion molecule-1 (ICAM-1), E-selectin, and P-selectin [143]. These molecules facilitate the adhesion of circulating monocytes to endothelial cells and their migration into the subendothelial layer. The adhered monocytes in the subendothelial layer differentiate into macrophages. Macrophages exert a pivotal influence in the pathogenesis of AS. On the one hand, these macrophages engulf ox-LDL particles and transform into foam cells, which are hallmarks of early atherosclerotic lesions or fatty streaks. On the other hand, inflammatory macrophages release cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-alpha (TNF-α) [144,145], interacting with other immune cells to impact plaque development and stability.

Studies have shown that herbal flavonoids reduce cellular communication between inflammatory cells involved in AS and inhibit adhesion molecule activity while regulating the secretion and expression of inflammatory cytokines. For instance, Morin reduces the levels of inflammatory cytokines such as TNF-α and ICAM-1. In animal studies using $ApoE^{-/-}$ mice, morin inhibits the formation of atherosclerotic plaques [146]. Genistein is found to significantly inhibit the production of adhesion molecules and chemokines induced by TNF-α, including ICAM-1, VCAM-1, E-selectin, MCP-1, IL-8, and other molecules. By attenuating vascular inflammation, genistein inhibits AS progression [81]. Puerarin has shown potential in reducing atherosclerotic lesions by reducing the ox-LDL-induced adhesion between monocytes and HUVECs. Puerarin also inhibits the expression of adhesion-related genes, such as VCAM-1, ICAM-1, MCP-1, and IL-8, in HUVECs. In another study with $apoE^{-/-}$ mice, puerarin is also shown to reduce atherosclerotic lesions [80]. These findings indicate that flavonoids present in herbal medicines have anti-inflammatory effects and modulate the cellular and molecular processes involved in AS. By reducing inflammation, inhibiting adhesion molecule activity, and regulating cytokine secretion, such flavonoids prevent or postpone the progression of atherosclerotic plaques.

Additionally, dysfunctional efferocytosis, characterized by impaired clearance of apoptotic cells, can lead to the formation of necrotic cores within plaques, promoting inflammation and increasing plaque vulnerability [147]. Flavonoids play diverse roles in efferocytosis, crucial for modulating immune responses, aiding tissue repair, and mitigating inflammatory pathways. Although the role of flavonoids in enhancing efferocytosis in AS has been limitedly reported, it has been documented in other diseases. For example, baicalein has been shown to promote M2 macrophage polarization, enhancing efferocytosis to reduce inflammation and alleviate liver damage [148]. Baicalin increases efferocytosis by acting as an antioxidant via a RhoA-dependent pathway and regulates macrophage polarization, thus promoting inflammatory resolution [149]. Isoliquiritigenin accelerates efferocytosis and angiogenesis, leading to quicker wound closure and enhanced tissue repair in diabetic mouse wounds [150]. Daidzein may possess therapeutic potential in the treatment of inflammatory diseases by upregulating TG2 and Rac1 to boost efferocytosis capacity [151]. Further

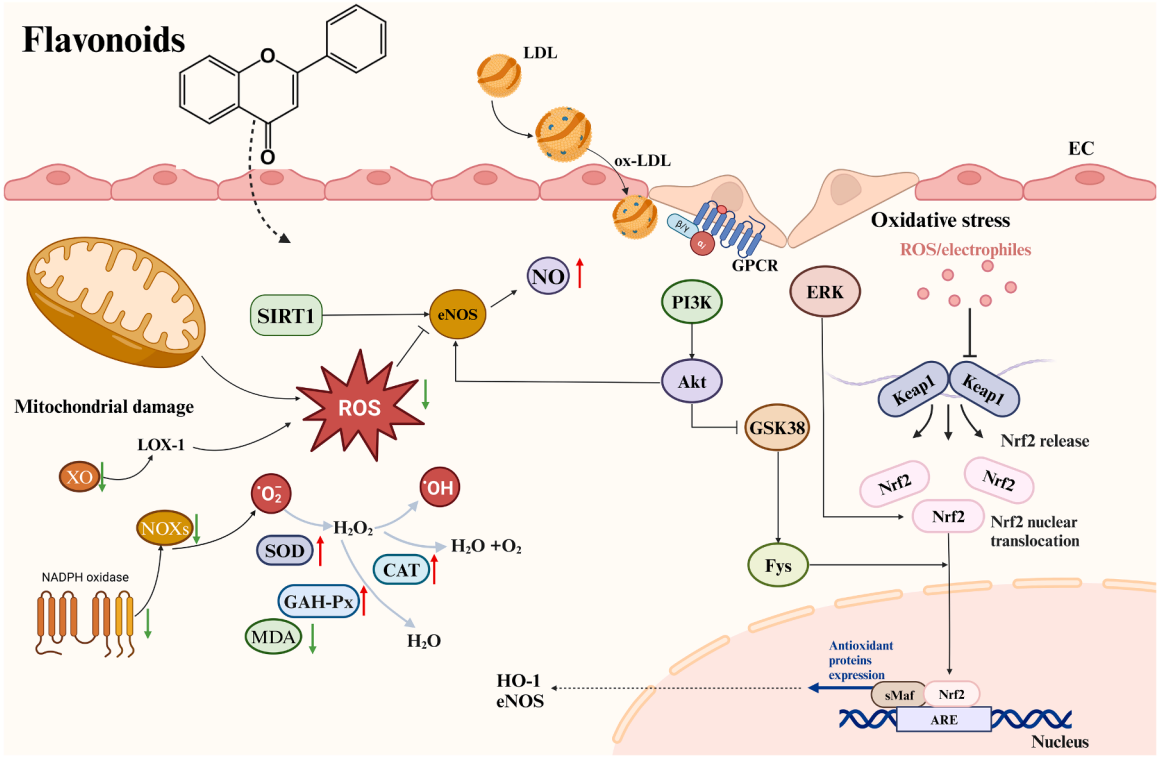


Fig. 2. Mechanism of flavonoids in anti-oxidative stress effect. Red arrow: activation effect of flavonoids. Green arrow: inhibitory effect of flavonoids.

research could explore the regulatory effects of flavonoids on efferocytosis mechanisms, thereby enhancing our understanding of the processes that support flavonoid-based therapeutics.

NF-κB is a transcription factor prevalent in eukaryotic cells and influence the inflammatory response through cytokines, adhesion factors, and receptors. It plays a pivotal role as a transcription factor in various inflammatory signaling pathways within AS, exerting regulatory control over the growth and rupture of atherosclerotic plaques via the NF-κB signaling pathway. Several flavonols [152,153], flavones [154,155], and isoflavones [156,157] have been shown to have anti-atherosclerotic inflammatory effects and are intricately associated with the modulation of the NF-κB signaling pathway. The related mechanisms involve modulating the expression of the p65 subunit, inhibiting the nuclear translocation of NF-κB, and influencing the activation of inhibitor of kappa B kinase (IKK). Myricitrin has been shown to inhibit the expression of adhesion molecules such as VCAM-1 and ICAM-1 by inhibiting TNF-α-induced NF-κB p65 expression and the degradation of IκBα. By preventing the translocation of NF-κB into the nucleus, myricitrin effectively suppress the inflammatory response [152]. Luteolin inhibits TNF-α-induced NF-κB transcriptional activity, IκBα degradation, and subsequent nuclear translocation of NF-κB p65 in ECs. By suppressing the expression of such NF-κB pathway components, luteolin effectively reduces the expression of MCP-1 and adhesion molecules, such as ICAM-1 and VCAM-1, thus ameliorating vascular inflammation [61].

KLF2, is another transcription factor that plays a crucial role in various biological processes, including the regulation of endothelial function, vascular homeostasis, and inflammation. Existing researches suggest that certain flavonoids targeting KLF2 signaling pathways may have the potential for therapeutic interventions aiming at combating atherosclerotic cardiovascular diseases. Calycosin can protect against AS and enhance plaque stability via promoting autophagy to inhibiting inflammation and oxidant stress through KLF2-mixed lineage kinase domain-like protein signaling pathway modulation [158]. It has been reported that fisetin can ameliorate oxLDL-induced EC death, inflammation and dysfunction via downregulation of extracellular signal-regulated kinase 5 (ERK5)/ myocyte enhancer factor 2c-KLF2 signaling pathway [159]. Juglanin has the potential to prevent the adhesion of THP-1 monocytes to ECs by inhibiting the expression of VCAM-1 and E-selectin induced by oscillatory shear stress. Such effect may be associated with its effect on decreasing KLF2 expression [160]. Puerarin can reduce monocyte adhesion to ECs and atherosclerotic lesion formation in apolipoprotein E-deficient mice through the activation of ERK5/KLF2 [80]. Other researches suggest that the anti-inflammatory effect of trans-chalcone on AS is characterized by the upregulation of KLF2 gene expression, potentially resulting in the induction of eNOS expression [161]. Therefore, utilizing flavonoids to regulate KLF2 expression might be a promising approach in interventions aimed at combating AS.

Besides, the inflammasome serves as a critical component of the innate immune system, assuming a pivotal role in initiating inflammation upon recognition of exogenous pathogens or signals of injury. Among these inflammasomes, the NLRP3 inflammasome is essential in various disease processes, including AS [162]. Certain herbal flavonoids have been found to possess anti-inflammatory properties that can specifically target the NLRP3 inflammasome. It has been reported that dihydromyricetin [163], quercetin [164,165], and baicalin [64] may inhibit the activation of the NLRP3 inflammasome, thereby attenuating inflammation in blood vessel walls and potentially impacting AS progression.

Therefore, the anti-inflammatory effect of herbal flavonoids in the context of AS involves the regulation of various inflammatory cytokines and complex signaling pathways (Fig. 3). These signaling pathways, facilitated by the related signaling molecules, may serve as a robust foundation for elucidating the specific targets involved in the anti-inflammatory mechanism of flavonoids.

3.4. Inhibition of VSMC proliferation and migration

VSMC, located in the mid-membrane of the vessel wall, is the primary cell that forms the blood vessel wall. Under normal conditions,

VSMCs are involved in physiological processes such as vasoconstriction and blood pressure regulation to maintain a contractile phenotype. When blood vessels are damaged or in response to certain cytokines and growth factors, VSMCs shift to a synthetic phenotype, proliferate and migrate, thicken the vessel wall and cause luminal narrowing, thereby expediting the progression of AS [166].

Flavonoids have been shown to modulate cell cycle progression in VSMCs by inhibiting the activity of cyclin-dependent kinases (CDKs) and cyclins, which are the key regulators of the cell cycle. By interfering with cell cycle progression, flavonoids suppress VSMC proliferation. Glyceollins is found to block the progression of VSMCs from the G0/G1 phase to the S phase of the cell cycle by downregulating the expression of CDK2 and cyclin D. It can also increase the expression of CDK inhibitors such as p27kip1 and p53. CDK inhibitors act as negative regulators of the cell cycle, further contributing to the inhibition of VSMC proliferation [167]. It is reported that tangeretin inhibits cell proliferation by downregulating the expression of cyclin D1 and cyclin E, which contributes to the induction of cell cycle arrest in the G0/G1 phase, effectively halting cell proliferation [168].

In addition, flavonoids can interfere with the signaling pathways activated by growth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β). These growth factors play important roles in VSMC proliferation and migration. Flavonoids can inhibit the activation of downstream signaling molecules, such as ERKs and Akt, thus impeding VSMC growth factor responses. For instance, puerarin has been reported to inhibit the formation and development of AS plaques and suppress the proliferation and migration of rabbit VSMCs by reducing the expression of proliferating cell nuclear antigen (PCNA) and PDGF [169]. Recent studies have demonstrated that cardamonin effectively inhibits Ang II-induced proliferation and migration of rat VSMCs by downregulating key signaling molecules, such as P38 AMPK, Akt and ERK [170]. Besides, it is suggested that tilianin has the potential to modulate the TGF-β/Smad pathway, thereby influencing the proliferation and migration of rat VSMCs induced by Ang II [171].

Moreover, flavonoids affect the production and remodeling of the extracellular matrix (ECM) in VSMCs. They can inhibit the synthesis of ECM components, such as collagen and fibronectin, and modulate the activity of matrix metalloproteinases (MMPs), which are involved in ECM degradation. By influencing ECM composition and structure, flavonoids can impact VSMC migration. Morin has been shown to possess anti-metastatic properties and inhibit the activity of MMP-9. By suppressing MMP-9 activity, morin impedes ECM degradation and inhibits the migration and invasion of VSMCs [172].

Furthermore, in response to injury or pathological stimuli, VSMCs can switch to a synthetic phenotype. This phenotype is characterized by increased proliferation, migration, production of ECM components, and a decrease in contractile protein expression. The phenotypic switch of VSMCs is crucial in vascular remodeling, AS, and other vascular diseases. Certain flavonoids may be possible to modulate the phenotypic switch of VSMCs to mitigate vascular disease progression. Previous studies have indicated that hydroxysafflor yellow A may possess inhibitory properties against differentiated phenotype of VSMCs, thus suppressing PDGF-BB-stimulated VSMC proliferation [173].

Understanding the mechanisms by which these factors induce damage and activate signal pathways in VSMCs is crucial for unraveling the complex pathophysiology of AS (Fig. 4).

3.5. Activation of autophagy

Autophagy is a cellular process involved in the degradation and recycling of cellular components. It serves as a mechanism for maintaining cellular homeostasis and removing damaged organelles and proteins [174]. Autophagy has both protective and detrimental effects on AS. Under certain conditions, autophagy promotes cells survival within plaques and maintains plaque stability. However, excessive or dysregulated autophagy leads to cell death and contributes to plaque vulnerability. Frequently, autophagy and apoptosis manifest an

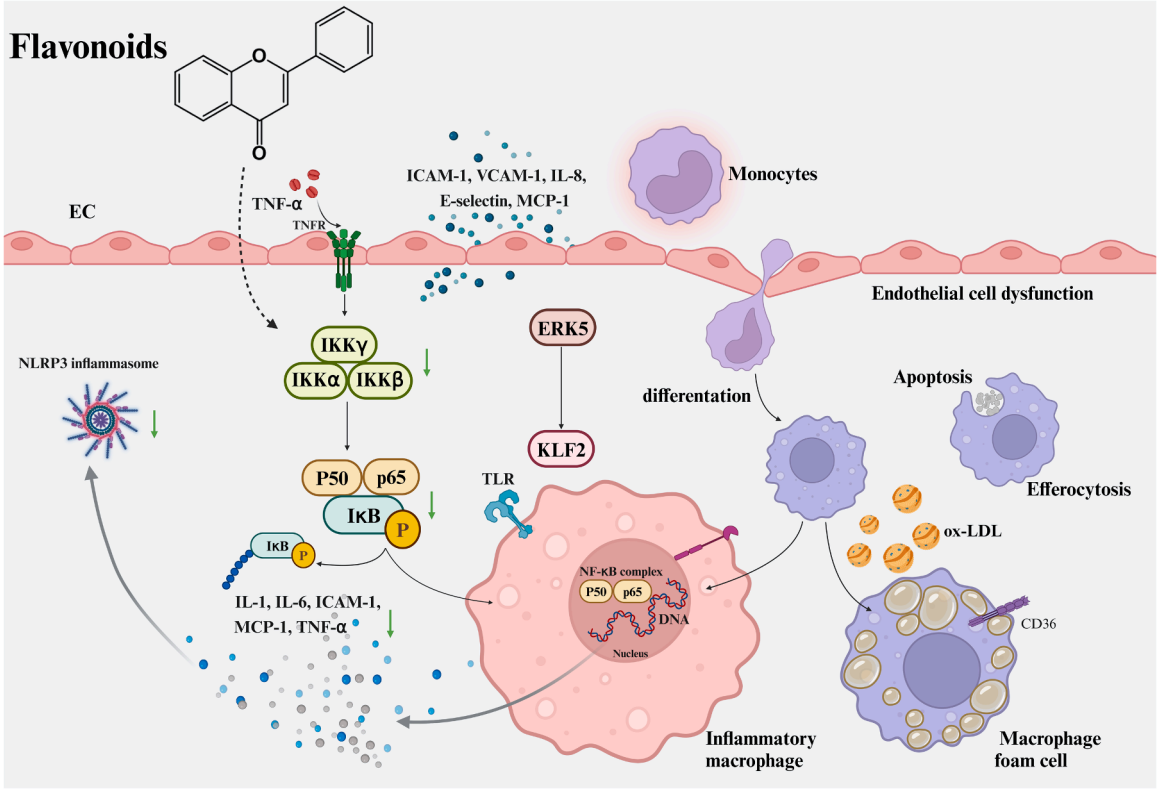


Fig. 3. Mechanism of flavonoids in anti-inflammatory effect. Green arrow: inhibitory effect of flavonoids.

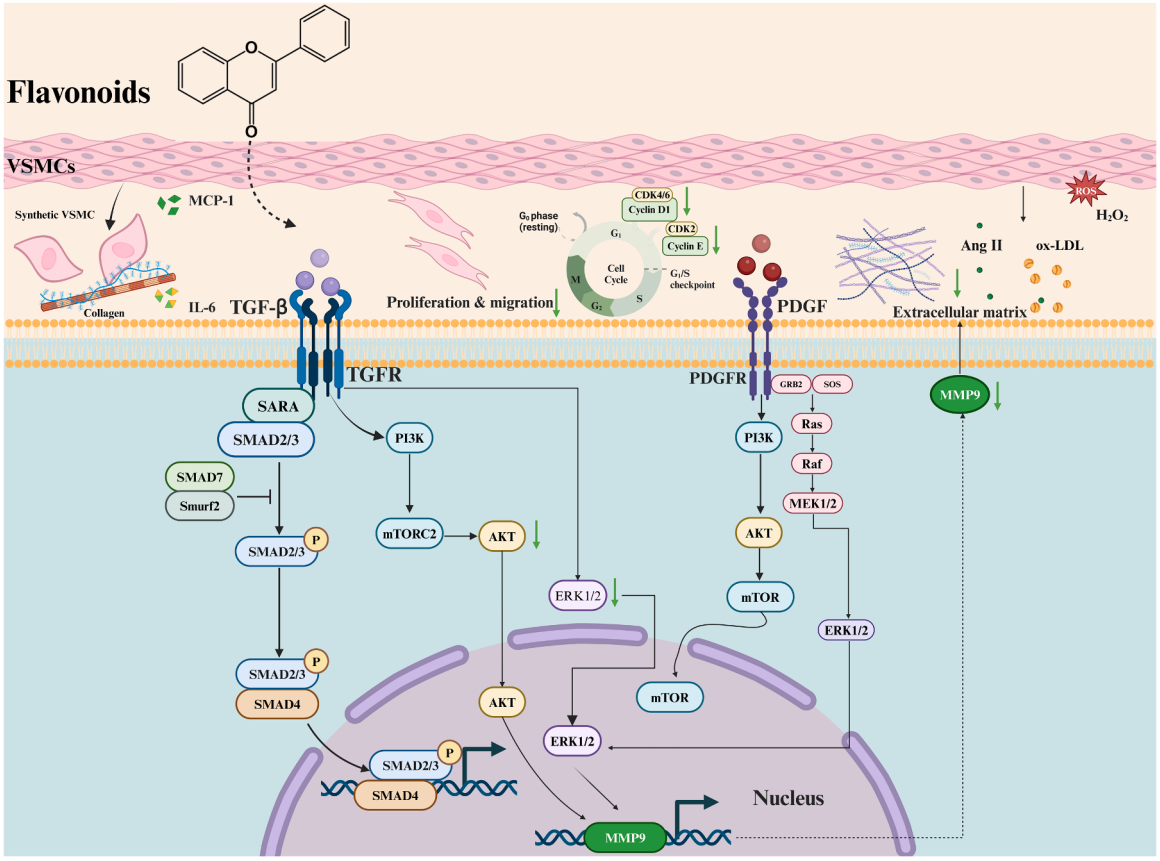


Fig. 4. Mechanism of flavonoids inhibiting the proliferation and migration of VSMCs. Green arrow: inhibitory effect of flavonoids.

antagonistic interplay [175]. Activation of autophagy impedes apoptosis, thus conferring a safeguarding influence on the organism. The balance between apoptosis and autophagy in AS is influenced by various factors, including oxidative stress, inflammation, lipid accumulation, and cellular signaling pathways. Dysregulation of these processes contributes to AS progression and vulnerable plaque formation. Recent studies provided new evidence that flavonoids possess the potential to postpone AS development through the activation of the autophagy pathways.

First, flavonoids may activate autophagy by inhibiting the mammalian target of rapamycin (mTOR) signaling pathway. As a key regulator of cell growth and metabolism, mTOR serves as a negative regulator of autophagy. Flavonoids can modulate mTOR levels, leading to the activation of autophagy. It has been discovered that kaempferol effectively mitigates ox-LDL-induced apoptosis in HUVECs by inhibiting the PI3K/Akt/mTOR pathway and promoting autophagy [176]. Hydroxysafflor yellow A is reported to induce an autophagic response via the PI3K/Akt/mTOR pathway and inhibit inflammation by reducing ROS in THP-1 macrophages [177]. Rutin has also been found to modulate the PI3K/Akt/ mTOR pathway, which contributes to its inhibitory effects on ox-LDL-mediated macrophage inflammation and foam cell formation [178]. Additionally, the total flavonoids of *Engelhardia roxburghiana* Wall. alleviates AS progression *in vivo* and *in vitro* through reducing foam cell formation and inflammatory responses, while the possible mechanism may be due to macrophage autophagy activation by inhibiting AKT and mTOR phosphorylation [179].

Second, flavonoids may activate autophagy by stimulating the AMPK pathway. AMPK is an energy-sensing enzyme that plays a role in cellular energy homeostasis, and can directly phosphorylate Unc-51-like kinase (ULK1) at multiple sites, including Ser556 and Ser757, leading to ULK1 activation. This phosphorylation enhances the kinase activity of ULK1 and promotes autophagy induction. Delphinidin-3-glucoside has been shown to protect HUVECs against injury induced by ox-LDL through the induction of autophagy via the AMPK/SIRT1 signaling pathway [180].

Moreover, flavonoids modulate the expression and activity of autophagy-related proteins, such as Beclin-1 and microtubule-associated protein 1 A/1B-light chain 3 (LC3). Beclin-1 is involved in the nucleation of autophagosomes, while LC3 is involved in the elongation and closure of autophagosomes. Flavonoids may promote autophagy by upregulating the expression of such proteins. It has been reported that *Hibiscus sabdariffa* leaf, rich in epicatechin gallate, can activate the class III PI3K/Beclin-1 signaling pathway, leading to a suppression of ox-LDL-induced HUVEC injury and apoptosis [181]. Epigallocatechin-3-gallate has been reported to inhibit VCAM-1 expression and apoptosis induction associated with LC3 expression in TNFα-stimulated human ECs [182]. It has been shown that quercetin inhibits the formation of foam cells induced by ox-LDL. The ability of quercetin to increase the expression of LC3-II/I and Beclin1 is related to its role in promoting autophagy [183]. Luteolin has been shown to have significant effects on apoptosis and autophagy. In a study conducted on RAW264.7 cells, luteolin is found to significantly decrease the expression of apoptosis-related proteins, such as Bcl-2-associated X protein (Bax), cleaved caspase-9, and cleaved caspase-3. Moreover, luteolin can increase the ratio of microtubule-associated LC3-II to LC3-I, indicating its capacity to enhance autophagy. This enhancement is attributed to the increased formation of autophagosomes and the activation of Beclin-1 [184].

TFEB is a master regulator of lysosomal biogenesis and autophagy, which is crucial in coordinating the expression of genes involved in lysosomal function, autophagy, and cellular clearance processes. Formononetin is reported to restore TFEB nuclear translocation, which is subsequently followed by lysosome biogenesis, autophagosome-lysosome fusion and lipophagy, alleviating lipid accumulation in an AMPK-dependent manner [185]. Homoplantaginin can effectively

upregulate the protein expression of *p*-AMPK and TFEB, enhance autophagy, reduce apoptosis, and alleviate vascular injury [186]. Procyanidin B2 shows to mechanistically promote lipid degradation by modulating TFEB through the lysosomal pathway [187]. Additionally, hyperoside may play a role in the coordination of white fat browning and autophagy via the cyclin-dependent kinase 6-TFEB pathway [188]. Therefore, modulating TFEB activity has emerged as a potential therapeutic strategy for AS.

Autophagy is essential for maintaining cellular homeostasis and removing damaged proteins and organelles. Understanding the molecular mechanisms through which flavonoids regulate autophagy can provide valuable insights for the development of novel therapeutic strategies targeting AS (Fig. 5).

3.6. Others

In recent years, various other flavonoids, such as quercetin, naringin, and dihydromyricetin, have also been reported to alleviate AS through multiple pathways. These compounds engage novel mechanisms, including the modulation of cell senescence, gut microbiota remodeling, regulation of non-coding RNA, inhibition of M1 macrophage polarization, and so on. Studies have shown that quercetin can modulate oxidized LDL-induced endothelial cellular senescence and suppress oxidized LDL-induced senescence in plaque macrophages by inhibiting the p38MAPK/p16 pathway [189,190]. Research has also indicated that naringin's amelioration of AS in ApoE$^{-/-}$ mice is linked to the modulation of bile acid biosynthesis from cholesterol through alterations in cytochrome P450 family 7 subfamily A member 1 and farnesoid X receptor/fibroblast growth factor 15 expression, influenced by changes in the abundance of *Bacteroides*, *Bifidobacterium, Clostridium, and Eubacterium* via gut microbiota remodeling [191,192]. Furthermore, quercetin treatment has been shown to lower lipid levels, atherosclerotic lesion areas, and plaque size, while also modifying the gut microbiota composition and reducing atherogenic lipid metabolites [193]. Additionally, dihydromyricetin inhibits M1 macrophage polarization in AS by modulating the miR-9-mediated SIRT1/NF-κB signaling pathway [194].

In conclusion, flavonoids exhibit promising anti-atherosclerotic effects through diverse pharmacological actions targeting multiple pathways (summarized in Table 2), offering potential strategies for the prevention and management of AS and related cardiovascular diseases.

4. Clinical applications of herbal flavonoids in atherosclerotic cardiovascular diseases

Currently, certain flavonoid monomers, flavonoid-rich herbs, and proprietary Chinese medicines are in clinical use for treating atherosclerotic cardiovascular diseases such as coronary heart disease (CHD), ischemic stroke (IS), HF and hypertension.

4.1. CHD

In a study involving 143 patients presenting with first anterior ST-segment elevation myocardial infarction within 6 hours of symptom onset, individuals were randomly allocated to receive either quercetin infusions (n = 70) or standard treatment (n = 73). The quercetin group received infusions before reperfusion and for the subsequent 5 days, in conjunction with standard care. Results showed that the median early CK-MB AUC was significantly lower in the quercetin group, indicating a reduction in infarct size. Moreover, intravenous administration of quercetin was associated with a reduced occurrence of reperfusion-induced intramyocardial hemorrhage by Day 3, exhibiting a marked contrast between the quercetin group and the control group (11.1 % vs. 53.3 %, $p < 0.024$) [195]. Additionally, in another randomized controlled trial of 80 patients with CHD, compared with the control group, *Ginkgo biloba* extract showed significant improvements in

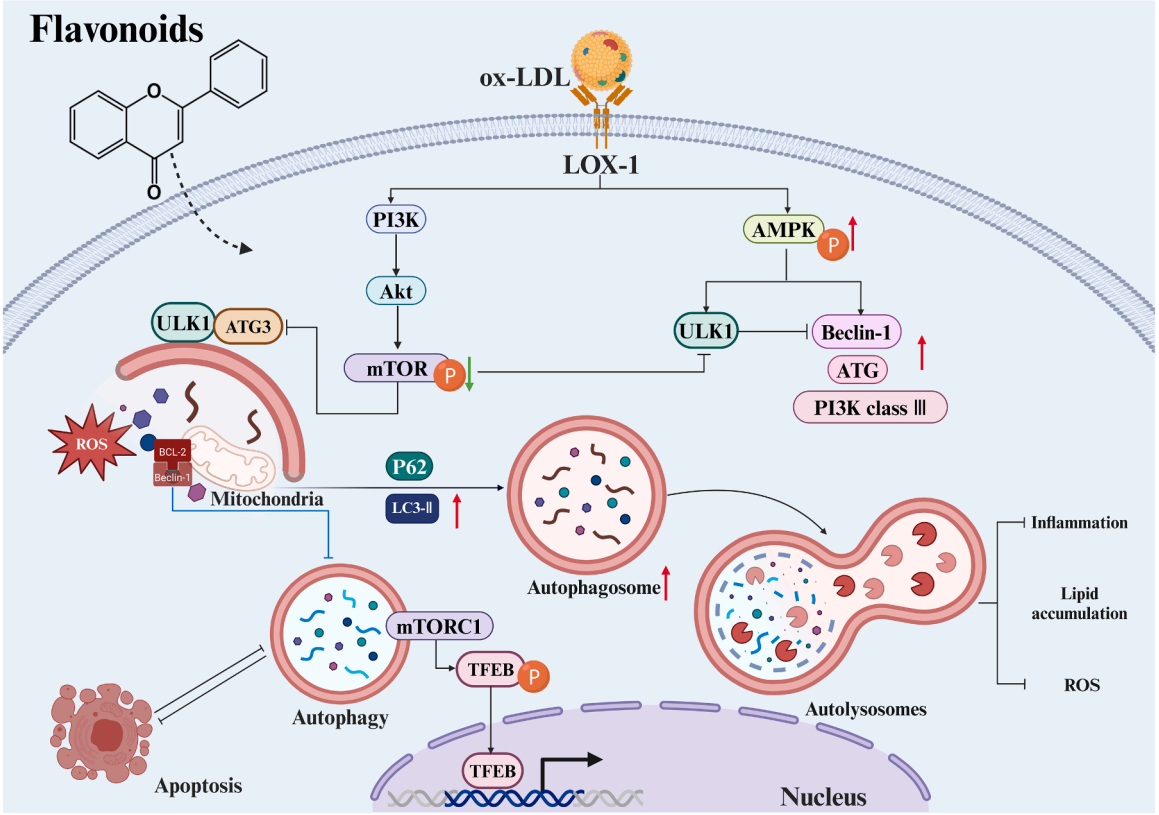


Fig. 5. Mechanism of flavonoids activating autophagy. Red arrow: activation effect of flavonoids. Green arrow: inhibitory effect of flavonoids.

Table 2
The effects of flavonoids in AS and related molecular targets.

Flavonoids/Source	Animal/cells	Effects	Related molecular targets		References
			Activation	Inhibition	
Naringin	High cholesterol-fed rabbit	Inhibit free cholesterol		ACAT, VCAM−1, MCP−1	[96]
	foam cell formation in THP−1 and RAW264.7	Inhibit macrophage foam cell formation by regulating metabolic phenotypes and inflammation	ABCA1, ABCG1, SR-B1; IL−10	MSR1, CD36;IL−1β , IL−6, TNF-α	[93]
	ApoE$^{-/-}$ mice	Alleviate atherosclerosis	gut microbiota-FXR/FGF15-CYP7A1 pathway, ABCA1		[191,192]
Proanthocyanidins	THP−1	Lessen the intracellular lipid accumulation and inhibit the macrophage foam formation	MiR−9	ACAT1	[97]
Luteolin	HFD-induced rats	amelioration of oxidative stress		ACAT2, SREBP2, PPARα	[98]
	TNF-α administration-mice	Ameliorate vascular inflammation	IκBα	NF-κB, MCP−1, ICAM−1, VCAM−1	[61]
	RAW264.7 macrophage	Promote autophagy, attenuate foam cell formation and macrophage apoptosis	LC3-II/LC3-I	Bax, cleaved caspase−9, and cleaved caspase−3	[184]
Hawthorn leaf flavonoids	ApoE$^{-/-}$ mice	Inhibit foam cell formation and promote RCT	ABCA1		[103]
Quercetin	Macrophage	Increase cholesterol efflux	ABCA1, Sp1, LXRα		[70]
	ApoE$^{-/-}$ mice	Promote RCT and lipid-lowering	ABCA1, ABCG1		[72]
	HFD-fed ApoE$^{-/-}$ mice	antioxidant	HO−1	NADPH oxidase	[83]
	ApoE$^{-/-}$ mice	Inhibit foam cell formation and inflammation		IL−6, NLRP3, IL−1β	[164]
	ApoE$^{-/-}$ mice	Anti-inflammation		Galectin−3-NLRP3 pathway, IL−1β	[165]
	RAW264.7 Macrophage	Promote autophagy, inhibit the formation of foam cells and delay senescence	LC3-II/I, Beclin−1		[183]
	ApoE$^{-/-}$ mice, HAECs	Inhibit cell senescence and reduce atherosclerosis lesion	SIRT1	SICAM−1, IL−6, VCAM−1	[189]
	ApoE$^{-/-}$ mice, RAW264.7 Macrophage	Inhibit cell senescence and reduce atherosclerosis lesion		p38 MAPK/p16 signaling pathway	[190]
	Ldlr$^{-/-}$ mice	Alter the gut microbiota and reduce atherogenic lipid metabolites			[193]
Kuwanon G	ApoE$^{-/-}$ mice, RAW264.7 Macrophage	Inhibit foam cell formation and inflammatory, reduce atherosclerosis lesion	LXRα, ABCA1, ABCG1	NF-κB	[105]
Isoliquiritigenin	ApoE$^{-/-}$ mice	Facilitate lipid metabolism, anti-inflammation, antioxidation	PPARγ	IL−6, TNF-α, MCP−1, SR-BI, ABCA1, ABCG8	[65]
Hibiscus sabdariffa leaf polyphenolic	J774A.1 macrophage	Reduce cholesterol, delay atherosclerosis	LXRα/ABCA1 pathway		[111]
Dihydromyricetin	THP−1 macrophage, ApoE$^{-/-}$ mice	Inhibit the cholesterol and lipid accumulation	ABCA1, ABCG1, LXRα		[77]
	HUVECs	Provide cytoprotective effects	Akt, ERK1/2, Nrf2/HO−1 pathway		[76]
	HUVECs	Inhibit oxidative injury	Akt, Nrf2/HO−1 pathway		[136]
	HUVECs	Inhibit pyroptosis	Nrf2	NLRP3, IL−1β	[163]
	ApoE$^{-/-}$ mice	Inhibit macrophage polarization	miR−9	SIRT1/NF-κB pathway	[194]
Baicalin	macrophage	Promote cholesterol efflux and delay foam cell formation	PPARγ, LXRα, ABCA1, ABCG1		[112]
	ApoE$^{-/-}$ mice	Anti-inflammation		NLRP3, IL−1, IL−18, ROS, ICAM−1, VCAM−1	[64]
	ApoE$^{-/-}$ mice	Antioxidant, anti-inflammation and anti-adipogenic	PPARα, CPT−1, SOD, CAT, GSH-Px	NF-κB, p38 MAPK pathway; SREBP−1c; MDA, IL−6 , TNF-α , sVE-cadherin	[132]
Biochanin A	ApoE$^{-/-}$ mice, THP−1 cells	Promote cholesterol efflux and reduce intracellular cholesterol	PPARγ-LXRα, PPARγ-HO−1, ABCA1, ABCG1		[113]
Chrysin	RAW264.7 macrophages	Inhibit intracellular cholesterol accumulation	PPARγ-LXRα-ABCA1/ABCG1	SR-A−1, SR-A−2	[114]
Scutellarin	HUVECs, HFD-rats	Antioxidant	SOD1, Nox4		[133]
Alpinetin	RAW264.7 Macrophage	Inhibit macrophage infiltration and atherosclerosis progression	Nrf2		[135]
Genistein	HUVECs	Reverse eNOS uncoupling	SIRT1, GCH1, DHFR	Nox4	[129]
Vaccarin	EA hy926 cell	Reduce vascular endothelium dysfunction	SOD	caspase−3, Notch	[130]
Farrerol	EA hy926 cell	Inhibition of cell viability loss	SOD, GSH-Px, Bcl2	Bax, p38MAPK, caspase−3	[131]
Morin	HUVECs	Induce autophagy		p-AMPK, p-mTOR, ICAM−1, VCAM−1, IL−6, IL−1β	[146]
	VSMC	Inhibit VSMC proliferation and migration		PDGF, Akt, MMP−9	[172]

(*continued on next page*)

Table 2 (*continued*)

Flavonoids/Source	Animal/cells	Effects	Related molecular targets		References
			Activation	Inhibition	
Theaflavin	HFD-fed mice	Antioxidant	miR−24, Nrf2/HO−1 pathway		[141]
Puerarin	THP−1, HUVECs, ApoE$^{-/-}$ mice	Reduce cell adhesion and atherosclerotic lesions	ERK5/KLF2	VCAM−1, ICAM−1, MCP−1, IL−8	[80]
	Acrolein-fed mice, HUVECs	Anti-inflammation, antioxidant	MYH9, SIRT1/Nrf2	NLRP3	[140]
	rabbit	Inhibit atherosclerosis plaque formation, VSMC proliferation and migration		PCNA, PDGF	[169]
Myricitrin	MOVAS−1 VSMC	Suppress the inflammation	IκBα	NF-κB p65, VCAM−1, ICAM−1	[152]
	HFD-fed ApoE$^{-/-}$ mice	Prevent the apoptosis induced by oxidative stress injury	caspase−3 and the MAPK signaling pathway	p53	[125]
Calycosin	ApoE$^{-/-}$ mice	Enhance autophagy	KLF2-MLKL signaling pathway		[158]
Fisetin	HUVECs	Ameliorate EC death, inflammation, and dysfunction		Erk−5/Mef2c-KLF2 signaling pathway	[159]
Juglanin	HAECs, THP−1	Prevent cell adhesion and anti-inflammation		KLF2, VCAM−1. E- selectin	[160]
Glyceollins	VSMC	Inhibit VSMC proliferation	P27kip1, p53	CDK2, cyclin d	[167]
Tangeretin	RASMCs	halting cell proliferation		PI3K/Akt, cyclin D1, cyclin E	[168]
Cardamonin	Ang II-induce rat VSMCs	VSMC proliferation and migration		p38MAPK, Akt, ERK	[170]
Tilianin	Ang II-induce rat VSMCs	VSMC proliferation and migration		TGF-β, Smad2, Smad3, Smad2/3, P-Smad2/3, ICAM−1, VCAM−1, MMP−2, MMP−9	[171]
Kaempferol	ApoE$^{-/-}$ mice, HAECs	Protect atherosclerosis	PI3K/Akt/Nrf2 pathway, GPER		[137]
	HUVECs	Promote autophagy, and inhibit apoptosis		PI3K/Akt/mTOR signaling pathway	[176]
Hydroxysafflor yellow A	VSMC	Inhibit VSMC proliferation		Akt	[173]
	THP−1	Promote autophagy, and inhibit inflammatory		PI3K/Akt/mTOR signaling pathway	[177]
Rutin	Macrophage	Anti-inflammation		PI3K/Akt/mTOR signaling pathway	[178]
Total flavonoids of *Engelhardia roxburghiana* Wall.	Macrophage	Inhibit foam cell formation and inflammation, and promote autophagy		Akt, mTOR	[179]
Delphinidin−3-glucoside	HUVECs	Promote autophagy	AMPK/SIRT1 signaling pathway		[180]
Epicatechin gallate	ApoE$^{-/-}$ mice	Reduce atherosclerosis plaque formation	Nrf2, HO−1		[123]
	HUVECs	Inhibition of cell injury and apoptosis	PI3K/Beclin−1 signaling pathway		[181]
Epigallocatechin−3-gallate	ECs	Inhibition of apoptosis		VCAM−1, LC3	[182]
Homoplantaginin	HUVECs, db/db mice	Promote autophagy, induce apoptosis, and alleviate vascular injury	p-AMPK, mTORC1, TFEB		[186]
Hyperoside	HFD-induced obesity mice	Prevent obesity	CDK6-TFEB		[188]

ECs: endothelial cell; THP-1, human monocytic-leukemia cells; HUVECs, human umbilical vein endothelial cells; db/db mice, diabetes mouse; RASMCs, rat aortic smooth muscle cells;ApoE$^{-/-}$, apolipoprotein E knockdown; Ldlr$^{-/-}$low-density lipoprotein receptor knockdown; Ang II, Angiotensin II; HFD, high-fat diet; RCT, reverse cholesterol transport; VSMCs, vascular smooth muscle cells; ABCA1, ATP-binding cassette transporter A1; ABCG1, ATP-binding cassette transporter G1; SR-B1, scavenger receptor class B type 1; IL-10, interleukin 10; MSR1, macrophage scavenger receptor 1; CD36, cluster of differentiation 36; IL-1β, interleukin IL-1β, interleukin 6, TNF-α, tumor necrosis factor-alpha; ACAT, acyl-CoA cholesterol acyltransferase; VCAM-1, vascular cell adhesion molecule-1; MCP-1,monocyte chemoattractant protein-1; FXR, farnesoid X receptor; FGF15, fibroblast growth factor-15; CYP7A1, cholesterol 7 alpha-hydroxylase; ACAT1, acyl-CoA: cholesterol acyltransferase 1; ACAT2, acyl-CoA: cholesterol acyltransferase2; SREBP2, sterol-regulatory element binding protein 2; PPARα, peroxisome proliferator-activated receptor alpha; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; NF-κB, nuclear factor kappa-B; ICAM-1, intercellular cell adhesion molecule-1; LC3, microtubule-associated protein 1 A/1B-light chain 3, Bax, Bcl-2-associated X protein; Sp1, specificity protein 1; LXRα, liver X receptor alpha; HO-1, heme oxygenase-1; NLRP3, NOD-like receptor protein 3; SIRT1, sirtuin 1; sIcam-1, soluble intercellular adhesion molecule-1;MAPK, p38 mitogen-activated protein kinase; PPARγ, peroxisome proliferator-activated receptor gamma, SR-BI, scavenger receptor class B type I; ABCG8, ATP binding cassette subfamily G member 8; Akt, protein kinase B; ERK1/2, extracellular signal-regulated kinases 1/2; Nrf2, nuclear factor erythroid 2-related factor 2;;IL-18, interleukin 18; ROS, reactive oxygen species; CPT-1, carnitine acyl transferase I; SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase;SREBP-1c, sterol regulatory element-binding protein 1; MDA, malondialdehyde, SR-A-1, Scavenger receptor-A 1; SR-A-2, Scavenger receptor-A 2; SOD1, superoxide dismutase; Nox4, NADPH oxidase 4; GCH1, GTP cyclohydrolase 1; DHFR, dihydrofolate reductase; Notch, Neurogenic locus notch homolog protein;Bcl2, B-cell lymphoma 2; AMPK, adenosine 5′-monophosphate activated protein kinase; mTOR; PDGF, platelet-derived growth factor; MMP-9,matrix metalloproteinase 9; ERK5, extracellular signal-regulated kinase 5; KLF2, krüppel-like factor 2; MYH9, Myosin Heavy Chain 9; PCNA, proliferating cell nuclear antigen; p65,RELA; MLKL, mixed lineage kinase domain-like protein; Mef2c, myocyte enhancer factor 2 C; CDK2, cyclin-dependent kinases 2; TGF-β, transforming growth factor-beta; Smad2, SMAD family member 2; Smad3,SMAD family member 3; MMP-2,matrix metalloproteinase 2; PI3K, phosphatidylinositol 3-kinase;GPER, G-protein coupled estrogen receptor; mTORC1, mechanistic target of rapamycin complex 1; TFEB, transcription factor EB; CDK6, cyclin-dependent kinase 6;eNOS, endothelial nitric oxide synthase.

maximum peak diastolic velocity, maximum peak systolic velocity and diastolic time velocity integral; increased distal blood flow in the left anterior descending branch of the coronary artery; and improved NO/endothelin balance and coronary circulation [196]. These studies highlight the advantages of herbal flavonoids for the treatment of CHD.

4.2. IS

In a randomized controlled study including 200 patients with IS, soy isoflavone (isoflavone extract consisting mainly of 55 % genistein, 23 % soy flavonoids and 14 % glycine) reduced the damage produced by brachial artery flow-mediated vasodilation, significantly increased erythrocyte-derived 2-like 2 and SOD levels and significantly reduced serum C-reactive protein, 8-isoprenaline, MDA, IL-6 and TNF-α levels. These results suggested that soy isoflavones improved ischemic symptoms by enhancing the antioxidant capacity of stroke patients [197]. Additionally, in a multicentred randomized controlled trial that included 348 acute stroke patients, patients treated with *Ginkgo biloba* extract demonstrated improved memory function, executive function, neurological function and daily living. Moreover, safety data analysis showed that *Ginkgo biloba* extract did not increase the incidence of adverse events. Compared to the controls, *Ginkgo biloba* extract treatment significantly improved neurological function in mean National Institutes of Health Stroke Scale scores and modified Rankin scale scores. These data suggested that *Ginkgo biloba* extract was effective and could be used to treat acute IS [198]. These findings further confirm the clinical relevance of herbal flavonoids in the treatment of IS.

4.3. HF

WS 1442 is a flavonoid component derived from hawthorn leaves that is used to treat chronic stable HF. In a randomized controlled study that included 209 patients with advanced HF (New York Heart Association [NIHA] class III), patients treated with 1800 mg WS 1442 were found to have a statistically significant increase in maximum tolerable workload during cycling and the lowest incidence of adverse events, particularly symptoms such as dizziness and vertigo. WS 1442 reduced typical HF symptoms in patients to a greater extent compared to placebo [199]. Another randomized controlled study that included 78 patients with chronic HF showed that puerarin treatment improved clinical cardiac function, increased left ventricular ejection, and reduced ox-LDL levels [200]. Moreover, a randomized controlled study that included 84 patients with sexual HF found that long-term administration of *Ginkgo biloba* tablets improved left ventricular systolic and diastolic function in patients with chronic HF and had a better cardioprotective effect [201]. These findings corroborate the basic research and prove that flavonoids in herbal medicines have positive effects on improving HF.

4.4. Hypertension

Hypertension is a risk factor for cardiovascular events. In a randomized, positive drug and placebo-controlled double-blind trial that included 477 patients, the clinical recovery rate of NIHSS score and the overall effective rate of NIHSS were significantly improved after treatment with Ge Gen Tongluo capsules (GTC, consisting of total flavonoids of Ge Gen), and the blood pressure control rate was significantly higher in the GTC group than in the *Ginkgo biloba* and placebo groups, indicating that GTC demonstrated significant efficacy in improving patients' quality of life, neurological function and control of hypertension [202]. In addition, in a series of randomized controlled trials involving 587 patients, quercetin was administered at doses ranging from 100 to 1000 mg/day over supplementation periods of 4–10 weeks to evaluate its effect on blood pressure. Oral quercetin administration was well-tolerated in all trials, with no reports of serious adverse events. Significant reductions in both systolic and diastolic blood pressure were observed following quercetin supplementation, especially at doses of 500 mg/day or higher [203]. The results of the above clinical studies indicated that herbal flavonoids have positive implications for the control of hypertension and could be potential anti-hypertensive agents.

Furthermore, clinical studies also showed that flavonoid extracts from herbal medicines and their proprietary Chinese medicines could be used to improve the symptoms and reduce the complications of diabetes [204,205], non-alcoholic fatty liver disease [206] and osteoporosis [207], which can prolong the life span of patients and improve their quality of life.

5. Discussion and conclusions

Flavonoids, abundant and diverse compounds in nature, exhibit complex structures, varied biological activities, low toxicity, and extensive medicinal properties. Specific flavonoids in herbs such as baicalin in *Scutellaria baicalensis*, puerarin in *Pueraria lobata*, and hesperidin in *Citri Reticulatae* Pericarpium are piotal for quality control in traditional Chinese medicine. The bioactive constituents present in the herbs form the basis for the therapeutic effects of herbal medicines, showcasing their clinical significance. Therefore, it is imperative and advantageous to undertake comprehensive investigations of the functional roles, mechanisms of action, and safety profiles of flavonoids.

Flavonoids are pivotal in the prevention and treatment of cardiovascular diseases through multiple pathways, notably demonstrating potent anti-atherosclerotic effects. The underlying mechanisms of flavonoids in ameliorating AS are related to the regulation of lipid metabolism, anti-oxidative stress, anti-inflammatory effects, the inhibition of VSMC proliferation and migration, and the activation of autophagy. As previously discussed, flavonoids exert their effects through a variety of mechanisms, including the activation or inhibition of kinase activity (MAPK, ERK1/2, AMPK, PI3K, Akt, mTOR), modulation of metabolically associated proteins (ACAT1, SIRT1, ACLY), upregulation of key integrated membrane proteins (ABCA1), ATP-binding proteins (ABCG1) involved in RCT. They also activate the NLRP3 inflammasome, downregulate cell adhesion molecules (VCAM-1, ICAM-1), reduce inflammatory mediators such as interleukins (IL-6, IL-1), pro-inflammatory cytokines, and chemokines, as well as transcription factors like NF-κB (involved in oxidative stress and autophagy), Nrf2 (related to oxidative stress), KLF2, TFEB, PPARγ, among others. Continued exploration of these associated targets is essential for elucidating the molecular mechanisms by which flavonoids act against AS. In clinical practice, flavonoids have shown potential in improving atherosclerotic cardiovascular diseases, with certain individual flavonoid compounds and specific flavonoid-rich herb formulations being used to treat disorders such as CHD, IS, HF, and hypertension. Additionally, flavonoids are key components in the convergence of medicine and food, which serve as vital antioxidants in the diet. Extensive research has identified over 4000 flavonoids present in various food sources, including onions, mulberries, chocolate, tea, coffee, and red wine [208]. Regular consumption of these flavonoid-rich foods has been reported to help individuals guard against atherosclerotic cardiovascular risk factors and lower the risk of atherosclerotic cardiovascular events [209–211].

However, there are still some limitations in the study of flavonoids. One limitation is the variability in solubility among different types of flavonoids. Free flavonoid glycosides and sugar-bound flavonoid glycosides exhibit different solubilities, affecting their bioavailability and efficacy. This solubility diversity poses challenges in formulating effective and bioavailable flavonoid-based treatments [212]. Another limitation is the slow efficacy and low bioavailability of flavonoids. These compounds often suffer from low oral bioavailability and can be rapidly metabolized and eliminated from the body. This limits their clinical application and effectiveness. Strategies to enhance the bioavailability and pharmacokinetic properties of flavonoids, such as nanoparticle formulations or prodrugs, are being explored to overcome these limitations [213]. Additionally, in contrast to abundant *in vitro* and animal studies, clinical research on flavonoids is sparse. While *in vitro* and

animal studies provide valuable insights into the potential mechanisms of action of flavonoids, rigorous clinical trials are vital to assess their safety and efficacy in humans. Further well-designed clinical trials are necessary to confirm the therapeutic potential of flavonoids in atherosclerotic cardiovascular diseases. Furthermore, there exists a persistent lack of comprehensive understanding regarding the precise mechanisms through which flavonoids exert their effects. Presently, the identification of molecular targets for flavonoid compounds encompasses a range of methodologies. For instance, the utilization of biotin-labeled flavonoid compound probes enables the capture of target proteins through affinity interactions, followed by the application of several techniques, such as immunoprecipitation and mass spectrometry, for target identification [214]. Besides, the amalgamation of photoaffinity labeling techniques involves activating the photoaffinity probe with ultraviolet light to irreversibly interact with target proteins, enabling the capture of these proteins. Subsequent validation is conducted through surface plasmon resonance and biochemical assays [215]. Moreover, computational chemistry methods like molecular docking and molecular dynamics simulations can forecast the interaction between flavonoid compounds and potential targets [216]. In the case of specific flavonoid compounds and their derivatives, the intricate structure of the compound with the target protein can be elucidated using X-ray co-crystallization techniques to pinpoint the binding site accurately [217]. Additionally, technologies such as microarrays [218], transcriptome and proteome sequencing [219], gene editing techniques (e.g. CRISPR-Cas9) [220] play a pivotal role in the identification and screening of potential molecular targets both *in vivo* and *in vitro* post-treatment with flavonoid compounds. The application of these comprehensive methods significantly contributes to understanding the action mechanisms and targets of flavonoid compounds to a certain extent. However, the understanding of flavonoids is not exhaustive, highlighting the imperative need to further explore the molecular targets that flavonoids engage to exert their therapeutic effects.

In conclusion, the promise of flavonoids in clinical settings is compelling and justifies an in-depth exploration of their utility in both the prophylaxis and therapy of AS. As we approach the brink of novel findings, this review aims to summarize the existing knowledge and stimulate forthcoming research that will ultimately enhance the clinical domain of cardiovascular medicine. Future research efforts are suggested to focus on overcoming the limitations and challenges in flavonoid studies. This includes enhancing their solubility and bioavailability, conducting additional high-quality clinical trials, standardizing research protocols, and gaining a deeper understanding of their mechanisms of action. These efforts will enable us to unleash the medicinal potential of flavonoids and create innovative therapeutic approaches for the prevention and treatment of atherosclerotic cardiovascular diseases.

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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.

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Data Availability

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

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