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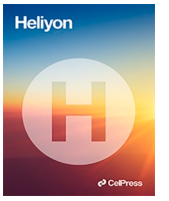

Review article

Citrus flavonoids and adhesion molecules: Potential role in the management of atherosclerosis

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ABSTRACT

Atherosclerosis as a chronic inflammatory disorder is accompanied with oxidative stress which causes a high morbidity and mortality. Adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), P-selectin, and E-selectin, are amongst the most important contributors in atherosclerosis. In such cases, dietary interventions with functional foods containing natural antioxidant and anti-inflammatory constituents are of a great interest. Citrus fruits are rich sources of flavonoids as natural pigments with potent antioxidant and anti-inflammatory activities. This study aims to review current evidence regarding the role of citrus flavonoids in the management of atherosclerosis with a focus on their effect on adhesion molecules. Electronic databases including PubMed, Scopus, and Web of Science were searched with the names of adhesion molecules and flavonoids from inception until January 2023. The included articles highly support the beneficial effects of citrus flavonoids in preclinical models of atherosclerosis. Quercetin, naringin and naringenin, hesperidin and hesperetin, nobiletin, rutin, luteolin, apigenin, and kaempferol are the most common flavonoids in citrus fruits which could modulate adhesion molecules including ICAM-1, VCAM-1, E-selectin, and P-selectin. Additionally, markers of chronic inflammation such as interleukins, tumor necrosis factor-α, nuclear factor-κB, and nitric oxide signaling, as well as oxidative stress markers like superoxide dismutase and glutathione were all normalized upon administration of citrus flavonoids. Conclusively, this review confirms the modulatory role of flavonoids on adhesion molecules in atherosclerosis based on the preclinical evaluations. Thus, citrus fruits can be further studied in atherosclerotic patients regarding their activity in reducing adhesion molecules.

1. Introduction

1.1. Atherosclerosis: etiology and pathophysiology

Atherosclerosis has been characterized as a chronic and progressive inflammatory disease that leads to threatening cardiovascular

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events such as coronary artery disease, peripheral vascular disease, strokes, and ischemic heart disease, resulting in a high global morbidity and mortality [1]. Accumulation of plaques in the intima of vessels occurs as a result of inflammatory processes in response to fatty streaks in medium-sized and large arteries [2]. Athermanous plaques cause abnormal narrowing and wall stiffness of blood vessels. Several risk factors participate in the occurrence of atherosclerosis such as blood lipids (hypercholesterolemia), cigarette smoking, diabetes mellitus, hypertension, chronic kidney disease, and adiposity [2]. Hemodynamic and chemical irritant risk factors disturb the function and permeability of vascular endothelial cells (EC) which are the closest layer to the bloodstream [3]. Excess permeability due to high plasma cholesterol levels, mainly low-density lipoprotein (LDL-C), allows this lipoprotein to enter EC which will oxidized in these cells. Oxidized-LDL-C (ox-LDL-C) stimulate the expression of adhesion molecules on EC which attract circulating dispense monocytes in blood that pass through EC. In response to macrophage colony-stimulating factor (M-CSF), monocytes convert to macrophages in sub-endothelial layers. Subsequently, abnormally-high production of some cytokines and chemokines and burst of inflammatory mediators occurs in the intima [4]. These macrophages uptake ox-LDL-C and form "foam cells". Ox-LDL-C initiates apoptotic processes of accumulated foam cells and eventually, produces the necrotic core of plaque. Also, proliferation and migration of smooth muscle cell (SMC) from media layer to intima cause expansion of vascular endothelium and reduce space of lumen. Because of plaque instability, rupture may occur and cause cardiovascular events like thrombosis [3,5].

Current approved treatments of atherosclerosis include a wide variety of conventional medicines which target different causes of the disease. Antihyperlipidemic agents (i.e., statins and fibrates, antihypertensive drugs (e.g., β-blockers, calcium channel blockers, Angiotensin-converting-enzyme inhibitors, and Angiotensin II receptor blockers), antidiabetic medicines (metformin, sulfonylureas, and thiazolidinediones), and blood thinners (such as aspirin) are amongst the drug categories administered for patients with atherosclerosis according to the baseline conditions. In spite of the diversity of the available drugs, incomplete response to treatment, side effects, and cost-effectiveness of the current therapies are still a matter of debate. On the other hand, evidence from observational and interventional studies on Mediterranean diets or other diets rich in herbs supports the benefits of dietary interventions with vegetables, fresh herbs, fruits, and other sources of natural herbal ingredients to lower the risk of mortality in patients with atherosclerosis [6].

1.2. Role of adhesion molecules in atherosclerosis

Adhesion molecules are a large group of mediators responsible for cellular interactions and their dysregulation is involved in the pathogenesis of several human diseases including gestational diabetes [7], fibrotic diseases [8], malignancies [9], autoimmune diseases [10], and cardiovascular disorders [11]. It has been demonstrated that upregulation of different adhesion molecules stimulates a cascade of several inflammatory processes and, if not being controlled properly, causes a chronic inflammatory status [10]. In other words, dysregulation of any of the categories of adhesion molecules results in specific inflammatory and immune-related disorders which can affect different tissues/organs and as mentioned above, has various clinical manifestations.

In the earlier stages of atherosclerosis, migration of monocytes through EC is associated with adhesion molecules present on the vascular endothelial cells. These important protein molecules are involved in the sticking of leukocytes to the surface of EC. Generally, adhesion molecules have five main families, i.e., immunoglobulin superfamily, selectins, integrins, cadherins, and others [8]. Three main groups of adhesion molecules in the plaque structure are integrins (β_1, β_2 Integrin), members of immunoglobulins superfamily including intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), and selectins (P, E, or L selectin) [12,13].

ICAMs, such as ICAM-1, are expressed in endothelial cells and leukocytes and stimulate leukocyte migration. Another form of ICAM-1 called sICAM-1 (Soluble ICAM-1) found in serum, can be generated by proteolytic cleavage or intermittent splicing of RNA messenger named mICAM-1 [14]. ICAM-1 functions as a counter receptor for the β_2-integrins CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1) and facilitate leukocyte transmigration across the endothelium. After the leukocytes adhere firmly, they will migrate through the vessel's endothelium by LFA-1/ICAM-1 and VLA-4/VCAM-1, and they pass through gap junctions [15].

Adhesion molecules and released chemokines in the inflammatory process invocate leukocytes and bind to endothelial cells. Selectins, addressins, low-affinity receptors, and leukocyte a4b1-integrin help leukocytes to do "rolling" activation. A 90-kDa glycoprotein was named as vascular cell adhesion molecule-1 (VCAM-1or CD106) have a low affinity to bind to leukocyte a4b1-integrin. Some factors such as TNF-α, ROS generation, ox-LDL-C, high glucose concentration, toll-like receptor agonists, and shear stress cause the expression of VCAM-1 by endothelial cells. VCAM-1 has six or seven immunoglobulin domains, a transmembrane domain, and a cytoplasmic domain. After binding to the receptor, cascade pathways are set up that ultimately reduce the tendency of endothelial cells to adhere to each other and facilitate the migration of leukocytes toward them [16–18].

The selectin glycoproteins family (E−, L- and P-selectin) with lectin domains can bind to ligands. These three selectins are produced by different cells. L-selectin is produced in granulocytes, monocytes, and most lymphocytes. P-selectin are available in platelets and Weibel–Palade bodies of endothelial cells; while production of E-selectin is induced by inflammatory cytokines [19,20].

Expression of adhesion molecules due to ox-LDL-C accumulation occurs in EC. First of all, selectins cause rolling and tethering of leukocytes. Then, firm attachments take place with ICAM and VCAM expression and as a result, leukocytes enter the intima. Identifying and evaluating the expression of these molecules in atherosclerotic lesions in different studies is used as an indicator of the effectiveness of various anti-thrombotic drugs [5,21].

1.3. Flavonoids and their benefits in atherosclerosis

Flavonoids are a large group of polyphenol compounds with two phenyls and one heterocyclic ring. Over 9000 compounds belong

to this group and are classified as flavones, isoflavones, flavanols, flavan-3-ols, flavanones, and anthocyanidins. Flavonoids are abundant in fruits and vegetables, including in citrus fruits. Various studies have been performed on the therapeutic effect of these natural compounds, demonstrating the effectiveness of flavonoids in many diseases such as hypertension, hyperlipidemia, insulin resistance, and oxidative damage [22]. Some studies have investigated the antioxidant role of various flavonoids [23], showing their role as radical scavengers and inhibitors of reactive oxygen species (ROS) formation. Oxidative stress is known as an initial trigger for the beginning of thrombotic process. Radicals and non-radical forms of oxygen agents (ROS) are generated during the routine physiological activities of EC. If some factors, like LDL-C accumulation, induces oxidative stress, excessive amounts of ROS cause an imbalance in the production and removal of oxygen free radicals. The subsequent oxidative stress causes an increase in adhesion molecules expression, followed by the beginning of an atherosclerotic plaque formation. Fig. 1 shows a schema of anti-inflammatory effects of flavonoids in different diseases. Anti-inflammatory features of flavonoids and different mechanisms for each flavonoid in influencing the expression of adhesion molecules have been discussed in several previous literatures; however, there is no review available on this topic [24,25].

Plants from the genus *Citrus* (family Rutaceae) are globally cultivated due to the pleasant taste of the fruits, making them a popular part of diet and culinary all over the world. Lemon, orange, tangerine, bergamot, and grapefruit are amongst the most famous citrus fruits which can be found in almost all parts of the world. On the other hand, citrus fruits are a rich source of flavonoids. As these fruits are globally available, they can be considered as highly valuable functional foods with preventive/therapeutic role in the inflammation- and oxidative stress-related disorders, e.g., atherosclerosis.

Several previous studies discussed the role of flavonoids in the primary and secondary prevention of atherosclerosis considering different underlying mechanisms, such as antioxidant properties or their effects on pro-inflammatory cytokines; however, discussions regarding their effects on the adhesion molecules are limited [23–25]. As explained above, adhesion molecules are involved in the primary stages of atherosclerosis and thus, modulating the activity of these molecules has a critical role in the prevention and treatment of atherosclerosis. Accordingly, this paper aims to review current pharmacological investigations regarding the role of citrus flavonoids in the primary and secondary prevention of atherosclerosis with a focus on their role in regulation of adhesion molecules.

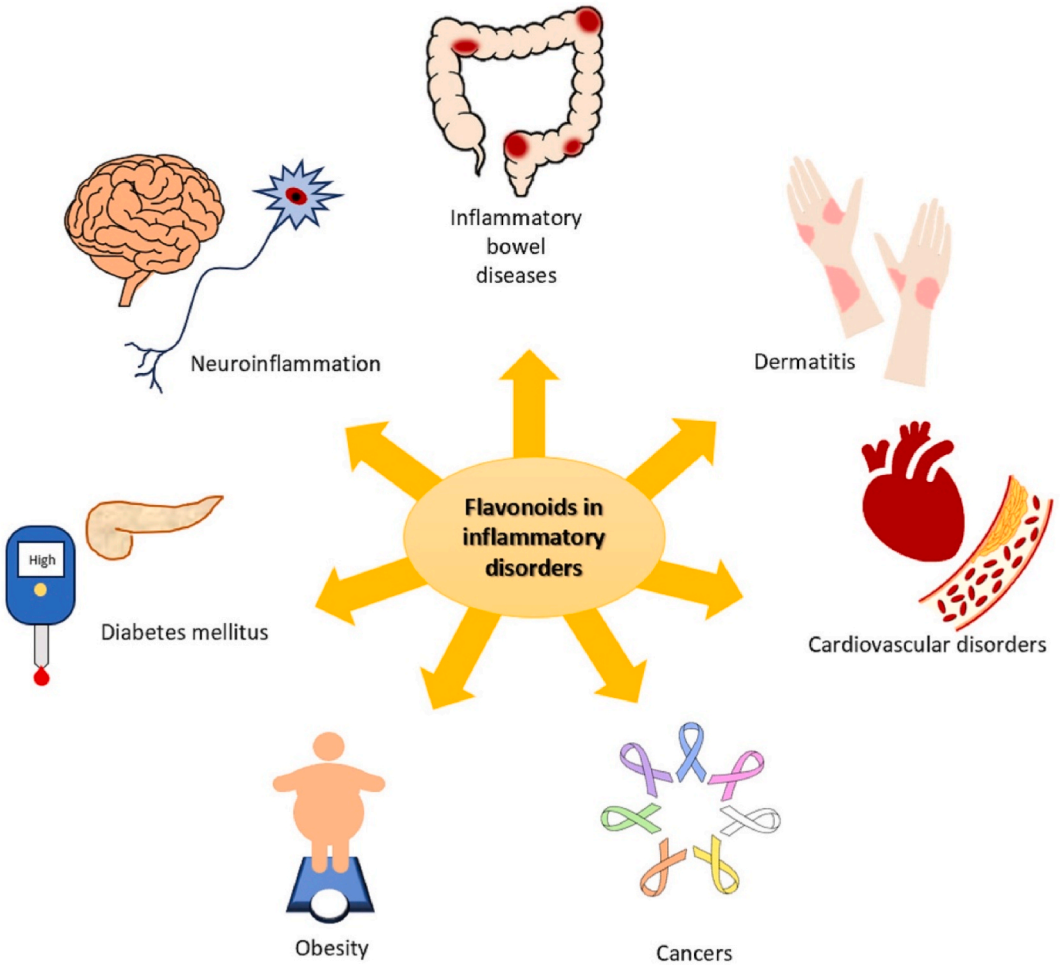

Fig. 1. An overview of the role of flavonoids in inflammatory disorders based on the available literature.

Table 1
Summary of the studies assessing the effect of citrus flavonoids on atherosclerosis via modulation of adhesion molecules.

Flavonoid Name	Model	Dosage & route of administration	Duration of treatment	Outcomes	Reference
Quercetin	In vitro: HUVECs treated with ox-LDL-C In vivo: rat on HCD diet	In vitro: 0.5, 10, 25, 50, 100 μM In vivo: 25 mg/kg p.o.	12 & 24 h 60 d	Without cytotoxic effects, ↓VCAM-1& ↓ICAM-1, Inhibited NF-κB, Inhibited TLR expression, ↓COX, ↓LOX-5, ↓NOS activity, ↓CRP, ↓ IL-6, ↓leukocyte infiltration, ↓Pro oxidant & generation by MPO enzyme	[26]
Naringin & Naringenin	HUVECs treated with LPS	Naringin: 0.2, 0.4, 0.6 μg/mL Naringenin: 0.1, 0.2, 0.4 μg/mL	1, 3, 6 h	Without cytotoxic effects, ↓cell injury, naringenin was more effective than naringin, ↑cell viability, ↓apoptotic & necrotic cells, ROS, Calcium concentration, ↓AP-1 & NF-κB & COX-2, ↓Cytochrome, ↓IL-1, ↓IL-6, ↓ICAM-1, ↓VCAM-1, ↓TNF-α, ↓caspase-3, -7, -9 ↓p-ERK & *p*-JNK & p-p38	[27]
Quercetin	HUVECs treated with high-dose glucosamine	5, 10, 20, 50 μM	24 h	↓Cell viability, ↓ICAM-1, ↓VCAM-1, ↓ET-, ↓CHOP, ↓GRP78, ↓Cleaved caspase-3, ↓p-JNK & p-PERK thus restoring ER homeostasis.	[28]
Naringin	In vivo: Mice on HF-HC diet & Sponataneous atherosclerotic mouse model apoE(−/−) In vitro: HUVECs stimulated with TNF-α	0.02 % (wt/wt) p.o. 1 μM	18 w 24 h	In vivo:↓atherosclerotic lesions, ↓non-HDL-C, ↓TAG, ↓TC,↑TC/HDL-C, ↓E-selectin, ↓I-CAM-1, no change in IL-6 & FRAP & urinary 15-isoprostane F2, down-regulated 703 genes & up-regulated 714 genes, ↓monocyte adhesion, ↓cell number in isolated ASMCs	[29]
Naringin	Rabbits on HCD	500 mg/kg/day p.o.	8 w	↓Fatty streak area in aorta, inhibited neointimal foam-cell infiltration, ↓ICAM-1, inhibited macrophage infiltration ↓ALT, ↓serum alanine aminotransferase Levels, Inhibited hepatocyte destruction & fat infiltration	[30]
Flavonoids: (flavanols: epigallocatechin gallate, catechin, Flavonols: quercetin, myricetin, flavanones: naringenin, naringin, hesperetin, Flavones: luteolin, apigenin)	HUVEC stimulated with TNF-α	1–50 μM	30 min	The flavones were the most potent flavonoids. The flavanols and flavanones did not prevent monocyte adherence on TNF-α activated endothelial cells. The flavones, luteolin and apigenin, almost completely blocked the expression of VCAM-1 & ICAM-1 & E-selectin. The flavonol quercetin ↓expression CAM. Activated NF-κB binding was attenuated by treatment with quercetin, luteolin, or apigenin.	[31]
Quercetin	Primary endothelial cells from porcine pulmonary aorta treated with PCB77	10 μM	30 min	↓CYP1A1 & VCAM-1 & E-selectin & P-selectin mRNA & Cav-1 protein & caveolin-1 phosphorylation	[31]
Quercetin, Epicatechin	Randomized double-blind, placebo-controlled crossover design on 37 apparently healthy prehypertensive men and women	160 mg/d, p.o. 100 mg/day, p.o.	4 w	Quercetin: ↓plasma E-selectin, ↓IL-1β, ↓z-score for biomarkers Epicatechin: ↓plasma E-selectin, no significant change in other markers	[32]

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Table 1 (*continued*)

Flavonoid Name	Model	Dosage & route of administration	Duration of treatment	Outcomes	Reference
Nobiletin, 4-demethyl-nobiletin, 3, 4-didemethyl-nobiletin & 3-demethyl-nobiletin	Human monocyte derived THP-1 cells stimulated with TPA	20 μM	30 min	Suppressed SR-A, LOX-1 & CD-36 mRNA, Inhibited AP-1 & NF-κB expression	[33]
Nobiletin	Human monocyte-derived THP-1 cells stimulated with TPA	100 μM	30 min	↓LOX-1 mRNA expression, ↓TPA-induced LOX-1 expression, ↓AP-1 transactivation Blocked activation of ERK1/2 & JNK1/2 but not p38 MAPK, ↓c-Jun but not affect c-Fos, ↓SR-1 & SR-PSOX, CD-36 & CD-11b, CD-18 & CD68, no uptake of Dil-acLDL	[34]
Naringin	HUVEC stimulated with TNF-α	50,100, 200 μg/mL	18 & 24 h	no cytotoxic effect, inhibited adhesion of monocytes, ↓ICAM-1 & VCAM-1 & E-selectin mRNA & protein levels, down regulated Fractalkine, MCP-1, RANTES, ↓NF-κB Nuclear translocation, ↓phosphorylation of IκB-α & IKKα/β & NF-κB, inhibited IKK-NF-κB	[35]
Hyperoside	MOVAS-1 stimulated with TNF-α	0–10 μg/mL	2 h	No cytotoxic effect ↓MDA &VCAM-1, ↓Phosphorylation of p38 & MAPK & ERK & JNK, ↓p65, ↓p-IκB & Suppression of NF-κB, ↓TNFR-1 expression, ↓monocyte adhesion rate	[36]
Flavones: luteolin & apigenin Flavanols: epigallocatechin gallate & catechin, Flavonols: quercetin & rutin, Flavanones; naringin, naringenin, hesperidin, hesperetin	HUVECs treated with ox-LDL-C	25 μM	5 h	Flavones: ↓monocyte adhesion & ↓VCAM-1 expression, ↓E-selectin expression, ↓mRNA levels of VCAM-1 & E-selectin, ↓LOX-1, ↓uptake of ox-LDL-C	[37]
Luteolin	In vitro: EA.hy926 cells and HUVECs stimulated with TNF-α In vivo: TNF-α- induced inflammation in male C57BL/6 mice	0.5–20 μM 0.6 % p.o.	1 h 1 w	In vitro: ↓monocyte adhesion, ↓ICAM-1 & VCAM-1 & MCP-1, inhibited NF-κB, inhibited degradation of IκBα, inhibited IKKβ expression, In vivo: blocked adhesion of monocytes, ↓MCP-1/JE, KC & sICAM-1 Blocked F4/80-positive, disruption of aortic elastin fiber in mouse cells.	[38]
Quercetin	In vivo: ApoE(−/−) & C57 mice on HFD In vitro: HUVECs treated with ox-LDL-C	In vivo: 20 mg/kg/d (intragastrically) In vitro: 3,1,0.3 μg/mL	8 w 48 h	↓sICAM-1 & VCAM-1 & Sirt1, ↓senescence rate in HAECs, ↑viability of the cells, ↓cell apoptosis, ↓ROS generation & Δφm ,↑regulation of 254 DE mRNA, ↓regulated 144 DE mRNA	[39]
Quercetin and its metabolite	HUVECs treated with ox-LDL-C	1–10 μg/mL	12 h	Suppress CAV-1 mRNA expression, ↓VCAM-1 & ICAM-1	[40]
Flavonols: Myricetin, quercetin kaempferol, galangin	HUVECs stimulated with IL-1β	5,10,15,50 μM	20 h	Nontoxic at special concentration of each flavenols, Antioxidant activity: myricetin = quercetin > kaempferol = galangin, Quercetin & myricetin: more effective to suppress the intracellular antioxidant activity & inhibited angiogenesis & more powerful suppressing the adhesion interaction & ↓cell proliferation & ↓VCAM-1, ↓ICAM-1, ↓E-selectin, Myricetin: was more effective at inhibiting adhesion to HUVEC.	[41]

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Table 1 (*continued*)

Flavonoid Name	Model	Dosage & route of administration	Duration of treatment	Outcomes	Reference
Naringin, hesperidin	HUVECs treated with HG	1–30 μM	0–8 h	Inhibited production of ICAM-1 but not of VCAM-1 and E -selectin, ↓p38 MAPK phosphorylation	[42]
Quercetin	In vitro: HUVECs treated with TNFα In vivo: 1) human CRP transgenic mice treated with IL-1β 2) ApoE*3 Leiden mice on HCD	In vitro: 10 or 30 μM In vivo: 1) 0.1 % (w/w) 2) 0.1 % (w/w) p.o.	24 h 2 w 15 w	In vitro: ↓lipid peroxidation, ↓E-selectin, ↓NF-κB activation In vivo: ↓CRP, ↓IL-1β, ↓SAA ↓fibrinogen, no effect on cholesterol & LDL-C & HDL-C, TAG level, ↓atherosclerotic lesion area but no effect on lesion number, ↓STAT3, ↓SP3, ↓PPARα, ↓RXRα, ↓IL-1 receptor, ↓IKK, ↓IL-7, ↑IRS, ↑PI3K, ↑AKT, ↑GLUT4, ↓PDGF receptor, ↓PCNA	[43]
Kaempferol	NZW male rabbits on HCD	30, 150 mg/kg/day p.o.	10 w	↓TC & TAG & HDL-C & LDL-C, ↓TNF-α, & IL-1β, ↓MDA, ↑SOD, ↓diameter of plaques, ↓plaques area, ↓lipid accumulation, ↓intima damage, ↓foam cells and macrophages, ↓ICAM-1, ↓VCAM-1, ↓E-selectin, ↓MCP-1, ↓mRNA levels of ICAM-1 & VCAM-1 & MCP-1 & E-selectin	[44]
Hyperoside	In vitro: HUVECs treated with HG In vivo: HG-induced male C57BL/6 mice	In vitro: up to 50 μM In vivo: 4.6, 9.3, 18.6, or 46.4 μg/mouse (i.v.)	24 h 6 h	↓Endothelial disruption & hyperpermeability, has no effect on cell viability, inhibited THP-1 adhesion, ↓ICAM-1& VCAM-1 & E-selectin, ↓MCP-1 & IL-8, ↓H_2O_2 levels, ↓p65 NF-κB levels	[45]
Quercetin	In vitro: Macrophages derived from bone marrow of C57BL/6 mice & stimulated with different stimuli (LDL-C, ox-LDL-C, LPS, or cholesterol crystals) In vivo: apoE (−/−) mice on HFD	In vitro: 20 μM In vivo: 50 mg/kg p.o.	12 h 12 w	In vitro: ↓DiI-ox-LDL-C cells ↓uptake of ox-LDL-C & cholesterol & ox-LDL-C-mediated foam cell & its receptor ↓CD-36 expression, ↓ lipid body formation and accumulation of macrophage, modulated TLR-Dependent pathway, ↓ROS production, ↓IL-6 secretion, ↓IL-1β, ↓MCP-1, ↓IL-12p70, ↓TNF-α, ↓MIP-1α, inhibited NLRP3 activation, In vivo: ↓macrophage and T-cell infiltration, ↓plasma cholesterol, ↓MDA serum level, no cytotoxic effect om mice	[46]
Naringin and naringenin	NZW male rabbits on HCD	1 % naringin or 0.05 % naringenin p.o.	8 w	↑Body weight, no effect on HDL-C and triglyceride levels, ↓atherosclerotic lesions, ↓macrophage infiltration, ↓intimal thickening, ↓hepatic ACAT activity, ↓VCAM-1 & MCP-1	[47]
Rutin	In vivo: Female ICR mice In vitro: HUVEC stimulated with LPS	10 μg/mouse p.o. 20 nM	6 h 6 h	No cytotoxic effects, ↓barrier dysfunction, ↓vascular permeability, ↓expression of TLR4, ↓ICAM-1, ↓VCAM-1, ↓E-selectin, ↓leukocytes infiltration & macrophage adhesion, ↓TEM, ↓NF-κb, ↓Iκb-p, ↓TNF-α, ↓ hyper permeability	[48]
Quercetin	HAEC stimulated with LPS	5,10,20 μM	18 h	No cytotoxic effect, ↓adhesion molecules mRNA levels, ↓ICAM-1, ↓E-selection mRNA, ↓ICAM-1, ↓E-selectin, inhibited oxidant generation, ↓basal level of oxidants, no effect on NF-κb,↑Nrf2 DNA- binding Activity,↑Nrf2 translocation,↑HO-1 transcription, ↑GCLM, p38 phosphorylation	[49]

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Table 1 (*continued*)

Flavonoid Name	Model	Dosage & route of administration	Duration of treatment	Outcomes	Reference
Naringin or quercetin	HUVECs treated with TNF-α	Naringin: 21.5, 43, 86 μM Quercetin: 20 μM	24 h	↑SOD, ↓MDA & LDH, ↓ROS production & Nox4 expression & p22phox, ↓ICAM-1 & VCAM-1, ↓p–NF–κB/p65, ↑p-Akt, activating PI3K/Akt signaling pathway, inhibit apoptosis through reduction of caspase-3, -9 & activation of anti-apoptotic protein Bcl-2	[50]
Apigenin, chrysin, quercetin, epicatechin, kaempferol, galangin	HAECs stimulated with TNF-α	5–50 μM	18 h	↓VCAM-1, ICAM-1 & E-selectin expression, apigenin and chrysin, galangin, kaempferol, quercetin inhibit endothelial adhesion molecule expression, whereas flavone, chromone, the flavanone, naringenin, and the flavanol, epicatechin, were ineffectual.	[51]
Quercetin	In vitro: Dendritic cells and endothelial cells stimulated with ox-LDL-C In vivo: 8 healthy male volunteers	10 μmol/L 500 mg p.o.	24 h 4 w	↓apoptosis & necrosis, DC adhesion & CD11a expression, ↓Receptor-mediated phagocytosis, no effect on maturation & differentiation of DC, ↓NF-κb activity, ↓ BDCA2 expression, ↑HDL-C, no effect on LDL-C, ↓serum ox-LDL-C, ↓ADMA	[52]
Quercetin	Collagen-induced platelet aggregation	12.5–100 μM	1,3,5 min	↓platelet aggregation, ↓ P-selectin secretion, ↓ATP release, ↓Calcium mobilization, ↓fibrinogen binding to integrin, ↓MAPK, & ERK & JNK, ↓p38, inhibits PI3K and Akt phosphorylation	[53]
Kaempferol, apigenin, galangin, chrysin, luteolin, hesperidin	HUVECs stimulated with Benzo[*a*]pyrene-	5 μM	16 h	↓ICAM-1, ↓cytokine-induced adhesion molecule expression	[54]
Quercetin	Porcine pulmonary artery endothelial cells treated with linoleic Acid & H2O2	10, 25, 50 μM	6 h	↓Generation of free radicals, ↓NF-κb & AP-1 DNA binding, ↓VCAM-1,IL-6, ↓PPARγ DNA binding	[55]
Apigenin and naringenin	In vivo: HFD & STZ-induced diabetes in male Sprague-Dawley rats In vitro: PA-induced damage in HUVECs	In vivo: 50, 100 mg/kg/d p.o. In vitro: 3 or 30 μM	6 w 30 min	Apigenin group gained body weight but naringenin has no effect on body weight, ↓FBG level, ↑ glucose tolerance, ↓GSP level, ↓blood glucose, ↓TC, TAG & LDL-C & FFA, ↑ HDL-C, ↓MDA, ↓ICAM-1, ↑ SOD, ↓IRI, inhibits insulin resistance, ↓phenylephrine-induced contraction, ↑ acetylcholine-induced relaxation, ↑ insulin-mediated relaxation, ↓aortic damage, ↓NO production, ↓NF-κb activation, ↓ICAM-1 mRNA levels	[56]
Hesperetin and hesperidin	In vitro: BAEC cell stimulated with TNF-α clinical study: placebo-controlled, double-blind crossover design in individuals with metabolic syndrome	In vitro: 10 μM clinical: 500 mg/d p.o.	5 h 3 w	↑pAkt, pAMPK & peNOS, NO production, H2O2 production, ↓TNF-α activity, ↓endothelial dysfunction Improvement in FMD, ↓hsCRP, ↓SAA protein, ↓E-selectin, ↓TC, ↓apoB,↑HDL-C, improving insulin resistance, no significant effect on LDL-C & apoA & TAG	[57]
Hesperidin	Randomized, double-blind, placebo-controlled, parallel-group study in healthy overweight individuals with high fat meal	450 mg/d p.o.	6 w	No effect on fasted FMD & fasted brachial FMD, protected the postprandial FMD, ↓sVCAM-1, ↓sICAM-1, ↓sP-selectin, ↓SBP, ↓DBP, no significant effect on LDL-C & HDL-C & TAG	[58]
Luteolin	TNF-α-induced inflammation in HUVECs	40 μm	24 h	↓ICAM-1	[59]

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Table 1 (*continued*)

Flavonoid Name	Model	Dosage & route of administration	Duration of treatment	Outcomes	Reference
Quercetin & its metabolites (quercetin 3 -sulfate, quercetin 3- glucuronide & 3-methylquercetin 3-glucuronide)	LPS & TNF-α- induced inflammation in HUVECs	2–10 μM	45 min	Quercetin and quercetin 3-glucuronide: ↓ICAM-1 & ↓VCAM-1. Other metabolites have effects only on VCAM-1. ↓MCP-1 with isorhamnetin 3- glucuronide	[60]
Quercetin	Co-culture between HUVEC & human HepG2 hepatic cells or human LHCN-M2 muscle cells	5 μM	18 h	Downregulated PDK-4, ↑glucose uptake just in HepG2 cells	[61]
Quercetin	LPS-induced inflammation in intestinal-endothelial-monocyte/macrophage coculture	10 μM	24 h	↓monocyte adhesion to endothelium, ↓macrophage migration through endothelium, ↓sVCAM-1, IL-6, IL-8, TNF-α	[62]
Quercetin & its metabolites (quercetin-3′ sulfate, quercetin-3-glucronide, isorhamnetin-3-glucronide)	HUASMCs stimulated with TNF-α	2,10 μM	1 h	Quercetin inhibited cell proliferation, ↓ICAM-1 & VCAM-1 & ↓MCP-1 but its metabolites do not have this effect	[63]
Luteolin	HUVECs stimulated with TNF-α	6.25,12.5,25 μM	12 & 22 h	↓LDH production, ↑ SOD activity, ↑ GSH levels, ↓ROS generation, ↓Nox4, ↓p22phox mRNA expression, ↓Nox4 and p22phox, ↓caspase 3 & 9, inhibits TNF-α apoptosis, ↑ Bcl-2, ↓ICAM-1, ↓VCAM-1 mRNA expression & protein expression, ↓monocyte adhesion, inhibited NF-κb/p65 translocation, inhibited IκB-α, ↓p38 phosphorylation, ↓ERK1/2 phosphorylation	[64]
Apigenin	ISO-HAS human endothelial cells treated with TMAO	10,30,50 μM	1–48 h	↓ICAM-1 & VCAM-1 & CCL-2 & OLR1 & CXCL16 & ↓CCL-2, ↓ICAM-1, ↓VCAM-1, ↓SCARF1, ↓OLR1, CXCL16, ↓uptake of acetylated LDL-C, ↓PYCARD, ↓NLRP3, ↓TXNP1, ↓LOX-1	[65]
Apigenin, chromone, chrysin, epicatechin, flavone, kaempferol, quercetin, naringenin, galangin	ISO-HAS treated with TNF-α in HG conditions	10,30,50 μM	0–24 h	↓LOX-1, Apigenin: ↓COX-2 & VCAM-1	[66]
Apigenin, chrysin, quercetin, kaempferol	ISO-HAS treated with TNF-α in HG conditions	10,30,50 μM	0–24 h	Chrysin & apigenin inhibited the expression of VCAM-1& MCP-1, kaempferol ↓MCP-1, VCAM-1, chromone and naringenin does not have this effect, flavonoids ↑occludin but flavones ↓occludin, apigenin ↓VCAM-1, ↓adhesion cells apigenin, quercetin ↓IKKα, apigenin, chromone, kaempferol & quercetin ↓IKKε/IKKi apigenin inhibited both IKKα, IKKε/IKKi	[67]
Quercetin	HUVECs treated with different concentration of H_2O_2	0, 30, 60, 90, 120, 150, 180, 210 μM	12 h	no cytotoxic effect, ↓cell damage, ↑cell viability, vascular protective effects, ↓VCAM-1	[68]
Luteolin	In vitro: EA.hy 926 cells stimulated with TNF-α, In vivo: TNF-α injected-C57BL/6 mice	In vitro: Luteolin: 0.1, 0.5, 1,5 μM curcumin: 0.1, 1.5, 10 μM In vivo: 500 mg/kg p.o.	20 h 1 w	In vitro: ↓monocyte adhesion, ↓VCAM-1, ↓MCP-1, ↓p65 translocation In vivo: ↓vascular inflammation, blocked adhesion of monocytes to the endothelium, ↓VCAM-1 & MCP-1	[69]

Abbreviations: TPA: 12-*O*-tetradecanoylphorbol-13-acetate, ICAM-1: Intercellular adhesion molecule 1, VCAM-1: vascular cell adhesion molecule 1, MCP-1: Monocyte chemoattractant protein-1, TNF-α: tumor necrosis factor α, NF-κB: nuclear factor κB, COX: cyclooxygenase, LOX: lipoxygenase, H_2O_2: hydrogen peroxide, HUVEC: Human umbilical vein endothelial cells, NLRP: Nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing, CXCL: C-X-C motif chemokine ligand, NO: nitric oxide, ET: endothelin, SOD: superoxide dismutase, GSH: reduced glutathione, ROS: reactive oxygen species, IL: interleukin, AMPK: AMP-activated protein kinase, SBP: systolic blood pressure, DBP: diastolic blood

pressure, FMD: flow mediated dilation, PPAR: Peroxisome proliferator-activated receptor, PI3K: Phosphoinositide 3-kinase, MAPK: mitogen-activated protein kinase, ERK: extracellular signal-regulated kinase, JNK: c-Jun N-terminal kinase, TLR: toll-like receptors, NOS: nitric oxide synthase, CRP: C-reactive protein, MPO: myeloperoxidase, FRAP: ferric reducing antioxidant potential, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, TAG: triacylglycerol, ox-LDL-C: oxidized LDL, MDA: malondialdehyde, i.v.: intravenous, p.o.: per oral, HF-HC: high-fat high-cholesterol.

2. Search strategy

Electronic databases, including PubMed, Scopus, and Web of Science, were searched with the following search formula:

((((((((((plant) OR (extract)) OR (herb)) OR (flavonoid)) OR (polyphenol)) OR (phenolic compound)) AND ((((((("adhesion molecule"[Title/Abstract]) OR ("adhesion molecules"[Title/Abstract])) OR (ICAM[Title/Abstract])) OR (VCAM[Title/Abstract])) OR (PECAM[Title/Abstract])) OR (selectin[Title/Abstract])))) AND ((((((("adhesion molecule"[Title/Abstract]) OR ("adhesion molecules"[Title/Abstract])) OR (ICAM[Title/Abstract])) OR (VCAM[Title/Abstract])) OR (PECAM[Title/Abstract])) OR (selectin[Title/Abstract])))) AND ((((atherosclerosis[Title/Abstract]) OR (atherosclerotic[Title/Abstract])) OR (arterial intima[Title/Abstract])) OR ("endothelial dysfunction"[Title/Abstract])))

Articles were searched from inception until January 2023. Only papers with an English full-text were considered for this review article. Primary search results were screened based on the title and abstract by two independent investigators. Only papers assessed common flavonoids of citrus fruits were considered. All in vitro, in vivo, and clinical studies evaluating the effect of one of the citrus flavonoids along with their mechanisms of action were included in this paper. Data from the finally-included articles, including the name of the assessed compound, animal/cell model, dose/concentration, route of administration, duration of treatment, and outcomes with a focus on mechanisms are summarized in Table 1. Fig. 2 shows a general overview of the role of flavonoids for the management of atherosclerosis.

3. Results: role of citrus flavonoids to modify adhesion molecules in atherosclerosis

3.1. Quercetin

Quercetin is a flavonol-type flavonoid which appears as aglycone or different glycosylated forms in numerous plants and foods of human diet. Quercetin is a powerful antioxidant and several animal and human studies have shown its anti-inflammatory activity in a variety of diseases. Also, it plays a modulating, biphasic and regulatory role in inflammation [70,71].

Quercetin and epicatechin are two of the few phytochemicals with clinical evidence on their role as antiatherosclerotic

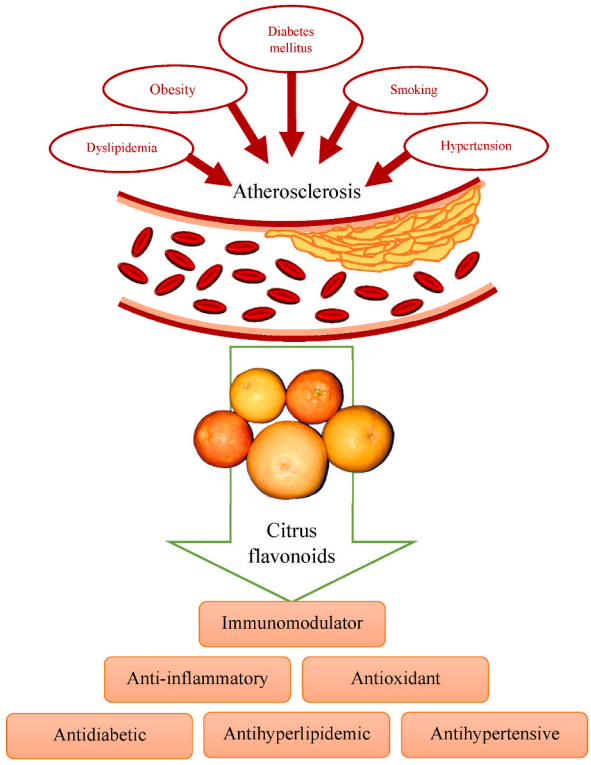

Fig. 2. Role of citrus flavonoids for the primary and secondary prevention of atherosclerosis.

supplements via reduction of adhesion molecules. Thirty-seven pre-hypertensive participants, including men and women, participated in a randomized, double-blind, placebo-controlled crossover clinical trial. Over 4 weeks, they were given 160 mg/day of quercetin-3 glycosides or 100 mg/dL of epicatechin. It was found that epicatechin and quercetin significantly decreased E-selectin concentrations in comparison to placebo; while quercetin could also reduce IL-1β and z score for inflammation [32].

An in vitro evaluation assessed the anti-inflammatory effects of quercetin in human umbilical vein endothelial cells (HUVECs) stimulated with ox-LDL-C. Indirect Enzyme-Linked Immunosorbent Assay (ELISA) was performed to determine VCAM-1 and ICAM-1 mRNA levels as markers of inflammation. As compared to the negative control, quercetin could significantly suppress the ox-LDL-C-induced upregulation of ICAM-1 and VCAM-1 activities [26].

In another study in HUVEC cells, glucosamine was used as HUVECs-atherosclerosis stimulating factor. HUVECs pre-treated with 15 μM glucosamine were incubated with 5, 10, 20, 50 μM of quercetin for 24 h. ICAM-1 expression was increased by glucosamine; however, quercetin at all concentrations could significantly inhibit the expression of VCAM-1 and ICAM-1 [28].

In an animal study, specific pathogen-free (SPF) Apo-E (−/−) deficient mice were fed with a fat-rich diet for 12 weeks. Wild-type C57BL/6J (C57) mice were included in the study as a control group. Apo-E (−/−) mice were randomly given either 20 mg/kg/day of quercetin or normal saline for 8 weeks. Immunohistochemical staining (IHC) demonstrated significant reduction of sICAM upon treatment with quercetin. In the in vitro experiment, ox-LDL-C- induced senescence in human aortic endothelial cells (HAECs) were treated by different concentrations of quercetin (3, 1, or 0.3 mM). Both in vitro and in vivo evaluations revealed that quercetin significantly reduced sICAM-1. Also, there was a significant decrease in senescence-associated β-galactosidase and the pro-inflammatory cytokine IL-6, as well as an increase in mitochondrial membrane potential, all of which confirm the anti-atherosclerotic properties of quercetin [39]. In a study by Kamada et al., one of the metabolites of quercetin referred to as quercetin-3-*O*-β-glucuronide (Q3GA) was evaluated in lysophosphatidyl choline (lysoPC)-induced damage in HUVECs. LysoPC is one of the ox-LDL-C species which was used to induce caveolin-1, a structural protein in plasma membrane contributing in the development of atherosclerosis. Incubation of cells with 1–10 μg/mL of quercetin or Q3GA could significantly decrease ICAM-1 and VCAM-1 mRNA levels, as well as caveolin-1, showing the protective effect of these compounds through suppression of adhesion molecules and improvement of caveolae function [40].

In another study in ox-LDL-induced damage in cultured macrophages derived from ApoE-deficient C57BL/6 mice, pretreatment with 20 μM quercetin could suppress ROS production and pro-inflammatory cytokines [46].

In LPS-induced inflammation in HAECs, pre-incubation with or without 5, 10, or 20 μM quercetin for 18 h could significantly decrease mRNA and protein levels of ICAM-1 and E-selectin in a dose-dependent manner [49].

Dendritic cells (DC) are a kind of antigen-presenting cell to stimulate T-cells in an immune response and become increased in inflammatory processes such as atherosclerosis. Quercetin pretreatment with a concentration of 10 μM showed a significant reduction of inflammation in ox-LDL-induced damage in DCs through reduction of CD11a expression as an adhesion receptor. Also, in a human study in eight healthy men, 500 mg of quercetin was administered twice a day for 4 weeks which could significantly decrease plasma DCs, as well as DC differentiation in comparison to untreated controls [52].

HUVECs were pretreated with 2–10 μM quercetin and its metabolites for 45 min and then, inflammation was induced by addition of LPS and TNF-α for 24 h. Flow cytometer was used to determine surface adhesion molecules and gene expression was analyzed by real-time RT-PCR. A significant decrease in ICAM-1 and VCAM expression was observed upon treatment with quercetin and quercetin 3-glucuronide; while all human metabolites of quercetin could reduce VCAM surface expression at 2 μM [60].

In another study, HUVECs were co-cultured with or without HepG2 cells to examine its effect on metabolism and glucose transport in HUVECs, then 5 μM quercetin was added to the culture, after 4 and 18 h HUVECs has been examined. Quercetin could upregulate heme oxygenase-1 (HO-1) and decrease PDK-4 expression [61].

Human umbilical artery smooth muscle cells (HUASMCs), pre-treated with TNF-α, were exposed to 2 and 10 μM quercetin or its metabolites (quercetin 3-sulfate, quercetin 3-glucuronide and, isorhamnetin 3-glucuronide). RT-PCR analysis revealed that treatment with 10 μM of quercetin significantly decreased ICAM-1 and VCAM-1 gene expression; however, no such effect was observed with 2 μM concentration. Additionally, quercetin metabolites did not show a significant influence on ICAM-1 and VCAM-1 neither at 2 nor at 10 μM concentrations [63].

In another in vitro experiment in H_2O_2-induced injury, HUVECs were treated with 0–210 μM quercetin, where it could significantly decrease H_2O_2-induced ICAM-1, VCAM-1 and CD80 expression and cellular morphological changes [68].

Polychlorinated biphenyls (PCBs) and halogenated aromatic hydrocarbons (HAHs) porcine are environmental pollutants with previously demonstrated negative impact on cardiovascular disease and promotion of oxidative stress [72]. Cell culture of endothelial pulmonary cells was pretreated for 30 min with 10 μm quercetin, followed by 2.5 μm of PCB for 6 h. Quercetin significantly suppressed mRNA expression of VCAM-1, E-selectin, and P-selectin [31].

In another study, endothelial cells were derived from porcine pulmonary artery. Cells were treated with 10, 25, 50 μmol/L quercetin, 90 μmol/L linoleic acid (as a poly unsaturated fatty acid that mediated oxidative stress for vessel endothelial cells) for 6 h and treated with vitamin E (antioxidant) for 18 h before that fatty acid was added. The RT-PCR results revealed that quercetin reduced ROS, free radical, and VCAM-1 gene expression in a concentration-dependent manner [55].

In another study, cultured HUVECs were pretreated with 1–100 μmol/L of quercetin for 18 h, then treated with inflammation stimulating factor (100U/ml of TNF-α). Analyses of mRNA expression showed that quercetin could suppress the production of VCAM-1 and E-Selectin [43]. Also, in rat-derived platelets stimulated with 2.5 μg/mL collagen, 10 μM ADP, and 0.1U/mL thrombin, pre-treatment with 12.5–100 μM of quercetin could decrease platelet aggregation and collagen-induced P-selectin [53].

3.2. Naringin and naringenin

Naringenin and its glycosylated form, naringin, are other popular citrus flavonoids with a flavanone structure and previously demonstrated anti-inflammatory and antioxidant activities [73,74]. Naringin and naringenin were evaluated in LPS-induced inflammation in HUVECs with different concentration (0.2, 0.4 and 0.6 μg/mL and 0.1, 0.2 and 0.4 μg/mL, respectively). It was found that both flavonoids could significantly decrease apoptosis and inflammation; while naringenin was more effective. The compounds act through suppression of ICAM-1, VCAM-1, COX-2, NF-κB, and pro-inflammatory cytokines, as well as several markers of apoptosis such as caspase enzymes, *p*-ERK, *p*-JNK, and p-p38 [27]. In an in vivo study, two mouse models of dyslipidemia, wild-type (WT) mice were fed with high-fat/high-cholesterol diet (HF-HC) and Apo lipoprotein E-knockout mice (ApoE−/−), were fed with 0.02 % wt/wt dietary naringin for 18 weeks. As a result, naringin decreased atherogenic plasma lipids in WT mice with an HF-HC diet; while could not improve lipid profile in ApoE−/− mice which suggests the possible role of naringin in removal of cholesterol via apo E receptors. Also, adhesion of cultured monocytes to TNF-α-induced inflammation in HUVECs was significantly decreased upon treatment with naringin. The concentrations of adhesion molecules including sE-selectin and sICAM-1 were significantly reduced both in vitro and in vivo [29]. Another study also confirms the anti-inflammatory properties of naringin at 50, 100 and, 200 g/mL concentrations in the same in vitro model via reduction of VCAM-1, ICAM-1 and E-selectin, as well as chemokines like fractalkine, monocyte chemoattractant protein-1 (MCP-1), and regulated upon activation, normal T cell expressed and presumably secreted (RANTES), possibly through suppression of NF-κB pathway [35]. Another in vitro study in TNF-α-induced damage in HUVECs showed the inhibitory effect of relatively lower naringin concentrations on the reduction of ICAM-1 and VCAM-1 via suppression of NF-κB and activation of phosphatidylinositol 3-kinase/Akt (PI3K/Akt) [50].

In high-cholesterol diet-induced atherogenesis in New Zealand white rabbits, 500 mg/kg dose of naringin was compared with lovastatin, both of which could decrease total cholesterol and triglyceride levels compared with untreated group. IHC examination of endothelial cells in the aorta of animals determined a lower leukocyte adhesion and macrophage infiltration due to decreased ICAM-1 expression [30].

In another experiment, male white rabbits were assessed in an in vivo study in which they consumed either 0.1 % naringin or 0.05 % naringenin along with 1 % cholesterol for eight weeks. In addition, the activity of the hepatic cholesterol acyltransferase (ACAT) was evaluated. Reduced ACAT activity and lower aortic fatty streak regions were observed in animals treated with the two flavonoids, along with a reduction of LDL-C. Additionally, a significant downregulation of VCAM-1 and MCP-1 gene expression were observed in the intervention groups [47].

3.3. Nobiletin

Nobiletin and its metabolites such as 4-dimethyl-nobiletin, 3, 4-didemethyl-nobiletin and 3-demethyl-nobiletin with polymethylated flavone structures are other major flavonoids of citrus fruits such as *Citrus sinensis* (L.) Osbeck and *Citrus x aurantium* L.

One of the important anti-atherosclerotic mechanisms suggested for nobiletin is reducing the expression of scavenger receptors (SRs). SRs are important membrane proteins that participate in the irreversible formation of foam cells by scavenging ox-LDL-C [75]. In a study by Eguchi et al., the expression of SRs was induced by addition of phorbol ester to THP-1 human monocytic leukemia cell line. Nobiletin treatment at a concentration of 100 μM could significantly decrease the expression of SRs, such as Lectin-like oxidized LDL-C receptor 1 (LOX-1) gene [34]. Also, incubation of the cells with 20 μM of nobiletin and its metabolites, 3′-demethyl nobiletin, 4′-demethyl nobiletin, and 3′, 4′-didemethyl nobiletin, caused a significant downregulation in the mRNA expression of SRs, including LOX-1. There was also a significant decrease in the expression level of CD11b and CD18 [33], β2-integrin subunits which are considered as soluble adhesion molecules expressed on the surface of leukocytes and act as ICAM-1 ligands [76,77].

3.4. Luteolin

Luteolin is a flavonoid present in many plants such as celery, spinach, lettuce, and citrus fruits. Previous studies showed that luteolin has antioxidant, anti-inflammatory, and cytoprotective effects and thus, is useful in inflammatory disorders such as atherosclerosis [78].

In an in vitro experiment, luteolin (0.5–20 μM) could significantly reduce the adhesion of THP-1 cells to TNF-α-stimulated EA.hy 926 endothelial cells through the reduction of ICAM-1, VCAM-1, and MCP-1. The inhibitory effect of luteolin on the production of adhesion molecules observed in the in vitro assessment was also confirmed in an in vivo study. In a mouse model of TNF-α-induced production of adhesion molecules, administration of 0.6 % dietary luteolin for one week could decrease ICAM-1 and VCAM-1 expression. Also, ex vivo adhesion of mouse WEHI 78/24 monocyte to the endothelium of mouse treated with luteolin was significantly lower in comparison to the negative control [38]. In TNF-α-induced production of adhesion molecules in HUVECs, incubation with 6.5, 12.5, 25 μM of luteolin could decrease ICAM-1 and VCAM-1 protein and mRNA expression. There was also a significant reduction in NADPH oxidase-4 (Nox4), ROS formation, NF-κB, and pro-apoptotic markers such as Casp enzymes [64]. Although luteolin is available to a lower extent in human diet in comparison to quercetin, it has a more acceptable safety due to lower possibility of pro-oxidant activity [78] and thus, can be a promising candidate for future development of anti-inflammatory natural supplements.

3.5. Apigenin

Apigenin is another citrus flavonoid that has several therapeutic aspects, including prevention of CVD. The anti-inflammatory

effects of apigenin on atherosclerosis is due to inhibition of glucose-induced expression of LOX-1 and adhesion molecules, LDL-C oxidation, ROS formation, and induction of NO production [79].

Trimethylamine oxide (TMAO) is derived from the metabolism of gut microbiota on choline, lecithin, and carnitine which are abundant in foods such as red meat, eggs, dairy products, and salt-water fish and is involved in the vascular inflammation and atherosclerosis. In TMAO-induced damage in ISO-HAS endothelial cells, treatment with apigenin with 10, 30, 50 μM concentrations could reduce TMAO-induced ICAM-1 and VCAM-1 gene and protein expression, as well as SRs and NLRP3 inflammosomes [65].

In HFD and streptozotocin-induced diabetes in rats, four-week administration of apigenin with the doses of 50 and100 mg/kg/day caused a significant decrease in serum concentration of ICAM-1. To assess the mechanisms, an in vitro experiment was conducted using palmitic acid-induced damage in HUVECs which were pretreated with 3 or 30 μM of apigenin. As a result, ICAM-1 mRNA expression was significantly decreased. Authors concluded that the higher potency of apigenin in comparison to other evaluated flavonoids is probably due to the existence of a double bond between C-2 and C-3 in the C-ring of apigenin [56].

3.6. Rutin

Rutoside or rutin is a glycosylated form of quercetin found in many plants and vegetables, like buckwheat, forsythia, hydrangea, and viola. Some studies showed its pharmacological effects like antimicrobial, antioxidant, anti-allergic, and antitumor aspects [80]. In an in vitro study using LPS-induced inflammation in HUVECs, incubation with 20 nM of rutin could significantly inhibit ICAM-1, VCAM-1, and E-selectin expression [48].

3.7. Hyperoside

Hyperoside or quercetin-3-*O*-galactoside is another flavonol compound named upon *Hypericum* spp.; however, is also abundantly found in citrus fruits. Studies demonstrated significant antioxidant, anticancer, antihyperglycemic, and anti-inflammatory properties for this flavonoid [81]. An in vivo experiment was performed using high glucose-induced vascular inflammation in C57BL/6 mice. Animals were pretreated with 4.6, 9.4, 18.6, 46.4 μg/mouse of hyperoside which resulted in a significant decrease in glucose-induced vascular permeability, expressions of cell adhesion molecules, ROS, NF-κB activity, and monocyte adhesion. Also, in high glucose-induced inflammation in HUVECs, incubation with 5,10,20,50 μM of hyperoside could decrease VCAM-1, ICAM-1, and E-selectin expression, as well as NF-κB activation in a dose-dependent manner [45]. In another in vitro study in TNF-α-induced mouse vascular smooth muscle (MOVAS)-1 cells, incubation with 10 μg/mL hyperoside for 2 h could significantly downregulate VCAM-1 mRNA and protein expression [36].

3.8. Kaempferol

Kaempferol as another flavonoid with numerous reports its beneficial biological activities [82]. In high cholesterol-induced atherosclerosis in white rabbits, 30 or 150 mg/kg/day of kaempferol was administered for ten weeks. Kaempferol showed a significant decrease in the mRNA expression of E-selectin, ICAM-1, VCAM-1; however, there was no difference between the low and high dose [44].

3.9. Hesperidin and hesperetin

Hesperidin is another flavanone glycoside component of citrus fruits with the aglycone hesperetin which is formed upon bacterial digestion of the glycoside by gut microbiota. Both structures have shown various biological activities [83]. In a randomized, double-blind, placebo-controlled clinical trial, 68 volunteers were randomly divided into hesperidin and placebo groups. Standard high-fat meal and two 250 mg capsules of hesperidin were administered for the treatment group; while the placebo group received two 250 mg of microcrystalline cellulose for 6 weeks. Hesperidin could decrease deterioration in flow-mediated dilation (FMD) immediately after consumption high-fat diet but had no significant effect on basal or postprandial FMD. Also, there was a significant reduction of sVCAM-1, sICAM-1, and sE-selectin by hesperidin compared with the placebo group [65]. In another double-blind, placebo-controlled, crossover study, adults suffering from metabolic syndrome were administered with 500 mg/day of hesperetin for three weeks. There was a significant improvement in FMD, HDL-C, and insulin resistance, along with a remarkable decrease in hs-CRP and E-selectin [57]. Authors of this trial also performed an in vitro study in TNF-α-induced inflammation in bovine aortic endothelial cells (BAEC) cells. Pretreatment with 10 μM of hesperetin significantly suppressed TNF-α activity and H_2O_2 production, as well as an improvement in the endothelial function [57].

4. Discussion

Atherosclerosis is a chronic inflammatory disorder which causes life-threatening cardiovascular events. Adhesion molecules have a critical role in the progression of the disease and thus, can be an important therapeutic target in these patients. Plants have long been used as a reliable source of active components with valuable pharmacological effects, including cardioactive compounds. Previous human studies demonstrated the role of several phytochemicals in the management of atherosclerosis [84,85].

Current pharmaceutical market provides several drug categories to manage the condition of patients with atherosclerosis; however, there are several limitations regarding the use of these medicines [6]. High price of the Branded drugs causes a high burden to the

patients and healthcare system. Also, side effects of conventional drugs, such as the ACE-inhibitor-induced cough which may even result in switching to a replacement therapy, limits their use. Additionally, polypharmacy in patients with other background diseases is always a challenge, especially in geriatrics.

In this paper, we reviewed the preclinical and clinical evidence of flavonoids abundant in citrus fruits in atherosclerosis with a focus on adhesion molecules. Fig. 3(a–j) shows the molecular structure of citrus flavonoids with modulatory activity on adhesion molecules in different models of atherosclerosis [86].

Citrus fruits are a group of widely-available fruits which can be grown and found in almost all parts of the world. This feature makes citrus fruits largely available as fresh fruits. Additionally, due to the pleasant flavor and fragrance of these fruits, they attract a lot of attention from food industries. There are numerous food products in the market, such as juices, jams, and compotes, which are made with citrus fruits. Furthermore, several other food products like cakes, jellies, and sweets, contain citrus fruits as flavoring agents.

The popularity of citrus fruits, both as fresh fruit or as processed food products, in one hand, and the high content of nutraceuticals on the other hand, make them valuable functional foods which can be included in a healthy diet for the primary and secondary prevention of several diseases, including atherosclerosis. A growing body of evidence support the health benefits of citrus fruits in atherosclerotic patients. Bergamot [87], grapefruit [88], lime [89], and orange [90] are amongst the most-studies citrus fruits in preclinical and clinical studies regarding their role on the modulation of hypertension, dyslipidemia, and inflammation.

Amongst different categories of active components in the citrus fruits, flavonoids have always been in the center of attention. Quercetin, hesperidin and hesperetin, naringin and naringenin, rutin, and nobiletin are flavonoid structures abundantly found in citrus fruits [91]. Although these compounds can also be found in several other herbal sources, citrus fruits are considered as their rich source. Studies support the beneficial effects of citrus flavonoids in cardiovascular parameters via different mechanisms, including activation of hepatic Peroxisome proliferator-activated receptor (PPAR)γ-coactivator 1 α (PGC1α) and PPARα [90], reduction of NF-κB and Nrf2, improvement of endogenous antioxidants, and vasodilatory activity [92].

Reviewing the current literature on the effect of citrus flavonoids on adhesion molecules in atherosclerosis provided a new point of view for the pharmacological basis of health benefits of citrus flavonoids in cardiovascular diseases.

Included studies confirmed the capability of citrus flavonoids on the reduction of different adhesion molecules, including ICAM-1, VCAM-1, P-selectin, and E-selectin, in various in vitro and in vivo models (Table 1). Addition of flavonoids to different cells involved in the progression of atherosclerosis, such as endothelial cells, monocytes, and macrophages stimulated by inflammatory factors like TNF-α, interleukins, and LPS, could significantly modulate the production of adhesion molecules, as well as other inflammatory mediators. Also, administration of citrus flavonoids to animals with atherosclerosis induced by different methods, including high-fat diet, high-glucose diet, TNF-α, streptozotocin, and genetically-susceptible animals, could successfully decrease the serum levels of the adhesion molecules.

As previously mentioned, several categories of adhesion molecules are involved in the pathogenesis of atherosclerosis; however, the studies included in our review have mostly focused on the effect of flavonoids on ICAM-1 and VCAM-1. It seems that researchers believe these two adhesion molecules have the highest contribution in the development and progression of atherosclerosis and thus, have mostly tried to evaluate the effect of flavonoids on the level of these two molecules. Considering the involvement of other adhesion molecules in atherosclerosis, future studies can also consider other families of these molecules, such as integrins and selectins, to be also assessed.

One of the unanswered questions is the comparative effectiveness of each of the flavonoids in modification of adhesion molecules. Since the phytochemical profile of fruits is highly dependent on the cultivation area and plant chemotype, one specific species may contain various profiles of flavonoids based on different geographical location. Accordingly, citrus food products may have different flavonoids as major component. It is not yet clear which flavonoid has the highest activity against adhesion molecules and

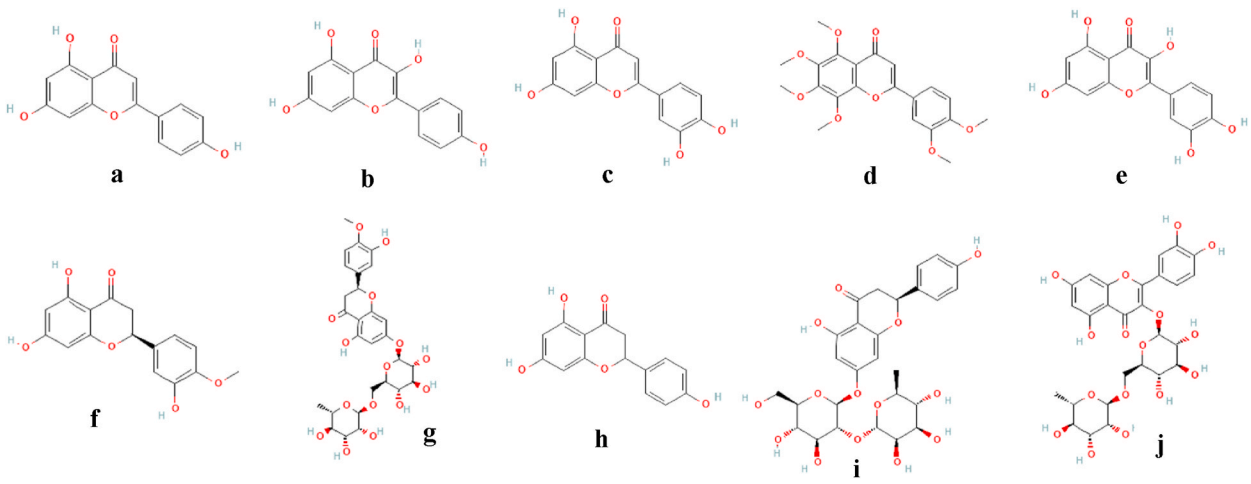

Fig. 3. Molecular structure of citrus flavonoids with modulatory activity on adhesion molecules in atherosclerosis: a: apigenin, b: kaempferol, c: luteolin, d: nobiletin, e: quercetin, f: hesperetin, g: hesperidin, h: naringenin, i: naringin, j: rutin.

atherosclerosis plaque formation. Comparison of the pharmacological activity of different citrus flavonoids can be helpful to define the suitable flavonoid as a marker for the standardization of citrus fruits food and pharmaceutical products which provides a better uniformity in the clinical efficacy.

Another issue is the low oral bioavailability of flavonoids [93]. Several previous studies have discussed this problem as a major limitation against the clinical efficacy of flavonoids in oral administration [93,94]. The percentage of oral bioavailability of each flavonoid depends on the number of hydrophilic/hydrophobic functional groups on the basic skeleton. On the other hand, most flavonoids are available in the glycosylated form in nature which makes the molecular structure larger and thus, decreases the oral bioavailability. In spite of all these facts, studies showed that metabolism of flavonoids, either by human metabolic enzymes or the gut microbiota, results in the production of flavonoid derivatives with a better intestinal absorption; while showing an acceptable pharmacological activity [93]. Additionally, recent studies have suggested strategies like nanoformulation of flavonoids as novel approaches to improve their bioavailability [93,94]. Thus, assessment of food products enriched with optimized formulations of flavonoids can be the subject of future studies to evaluate the effect of these compounds in primary and secondary prevention of atherosclerosis.

5. Conclusions

Taken together, the beneficial effects of citrus fruits as a rich source of flavonoids are supported by a growing body of evidence. Due to popularity of these fruits, their pleasant taste, and high safety, citrus fruits can be recommended as a medicinal food for the primary and secondary prevention of atherosclerosis in the diet of susceptible individuals. Future clinical studies using standardized citrus fruit products, as well as measurement of serum concentration of adhesion molecules in human studies are suggested to better confirm the clinical efficacy of these compounds.

Data availability

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

CRediT authorship contribution statement

Farnaz Ebrahimi: Writing – original draft, Methodology, Investigation, Conceptualization. **Mohammad Mahdi Ghazimoradi:** Writing – original draft, Methodology, Investigation. **Ghizal Fatima:** Writing – review & editing, Supervision. **Roodabeh Bahramsoltani:** Writing – review & editing, Supervision, Project administration, 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.

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