Review

Natural compounds as antiatherogenic agents

Uzma Saqib[1], Masood A. Khan[2], Manikandan Alagumuthu[3], Suraj P. Parihar[4*], Mirza S. Baig[3*]

[1] Discipline of Chemistry, Indian Institute of Technology Indore (IITI), Simrol, Indore, India

[2] Department of Basic Health Sciences, College of Applied Medical Sciences, Qassim University, Buraydah, Saudi Arabia

[3] Discipline of Biosciences and Biomedical Engineering (BSBE), Indian Institute of Technology Indore (IITI), Simrol, Indore, India

[4] Wellcome Centre for Infectious Diseases Research in Africa (CIDRI-Africa) and Institute of Infectious Diseases and Molecular Medicine (IDM), Division of Medical Microbiology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

*Correspondence to: suraj.parihar@uct.ac.za; msb.iit@iiti.ac.in

Abstract: Atherosclerosis (AS) is a widespread pathological coronary heart disease (CHD), which, along with other cardiovascular diseases (CVDs), is the primary cause of global mortality. It is initiated by the accumulation of cholesterol-laden macrophages in the artery wall, thereby forming the foam-cells, the hallmark of AS. Increased influx of oxidized LDL and decreased efflux of free cholesterol from macrophages constitute major factors that mediate the progression of AS. Natural compounds treatment and prevention of AS being an effective approach for a long time. Currently, as interests in medicinally important natural products increased that including medicinal herbs, numerous studies on natural compounds effective forAS have been reported. In the current review, we shed light on the available plant-based natural compounds as AS modulators with underlying mechanisms that may lead to potential therapeutic implications.

Key words: Cardiovascular diseases; Atherosclerosis; Macrophage; Low-density lipoprotein (LDL); Natural compounds.

Introduction

Atherosclerosis (AS) is a disease stemming from the endothelial cell inflammatory signalling of the vessel wall. An estimated 17.9 million deaths occur globally due to cardiovascular diseases (CVDs) owing to the complications associated with AS (1, 2). The hardening and narrowing of arteries due to the formation of "foam cells" is the crucial process which leads to the blockage of blood flow in the arteries. Hence, atherosclerotic cardiovascular disease remains the foremost source of strokes, heart attacks, and peripheral vascular diseases. In the chronic inflammatory state of the AS, macrophages play a vital role and can suppress immune reactions and other associated processes by releasing cytokines to the cellular environment (3). The M1 macrophages, which release proinflammatory cytokines, get attracted to the lipid and cholesterol deposits or plaques in the blood vessel wall (4-6). This further progresses until the development of foam cells that consequently hardens to form a sclerotic lesion (*athero "artery" and sclerosis "hardening"). Atherosclerosis (*AS) could be attributed due to many factors, including smoking, alcohol, a high-fat diet with no physical activity, obesity, or other congenital disorder associated with hereditary patterns or racial ancestry.

For the past few years, numerous synthetic-based chemical entities have been analysed for their efficacy as anti-inflammatory agents by targeting the macrophage foam cell formation (7, 8); however, their safety remains a concern. Meanwhile, plant-based modulators are involved in alleviating multiple diseases, including AS (9). For example, the phytoestrogen-rich drug karinat (garlic powder, an extract of green tea leaves, α-tocopherol, grape seeds, β-carotene, hop cones, and ascorbic acid) stops the progress of Carotid Atherosclerosis in postmenopausal women (10). Extended treatment with allicor (garlic powder) produced a direct anti-atherosclerotic effect on carotid AS even in asymptomatic men. Fig. 1 displays natural compounds that are reported as antiatherogenic modulators. Phytochemicals have come a long way and proven to be safer alternates to conventional synthetic drugs. In our previous review, we discussed the role of diverse phytochemicals on macrophage modulation by facilitating the conversion of proinflammatory M1 to anti-inflammatory M2 phenotype by targeting diverse pathways (11). The natural compounds display their beneficial effects by contributing to the modulation of the crucial actions of the oxLDL–macrophage interphase, including; (i) the atheroligand formation, (ii) expression of atheroreceptor (iii) transformation of foam cells, and (iv) pro-oxidant/ proinflammatory macrophage response. In the current review, we discuss how the natural plant-based chemicals modulate the AS foam cell formation by targeting various signalling pathways.

Ellagic Acid (EA)

Ellagic Acid (EA) is a polyphenol present in several plant foods, including pomegranates, berries, and nuts (12). Multiple studies describe the antiatherogenic functions of EA shown to prevent oxidized LDL-induced endothelial disfunction by weakening lectin-like oxidized

Figure 1. Illustration of the few naturally obtained antiatherogenic agents.
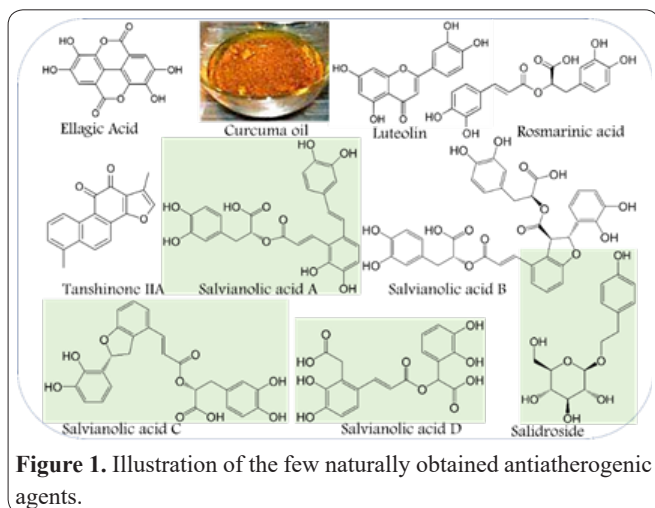
LDL receptor-1–mediated signalling pathways (13). A study showed that EA effectively condensed rat aortic smooth muscle cell proliferation persuaded by oxidized LDL through inactivation of the ERK pathway (14). Interestingly, other than EA, pomegranate phenolics of punicalagin, punicalin, gallic acid reduced AS lesions, and elevated cellular paraoxonase 2 activity in peritoneal macrophages of atherosclerotic ApoE-/- mice and J774A1 murine macrophages (15). EA also enhanced macrophage cholesterol handling by enhancing the PPARγ-LXRα-ABCA1 pathway to clear excess cholesterol loaded by oxidized LDL (16).

Curcumin and curcuma oil

Curcumin is a natural polyphenolic compound that shows protective effects against AS. It exerts an anti-atherosclerotic effect by inhibiting the inflammatory response of monocytes as well as the intracellular cholesterol accretion (17). Studies established the capability of curcumin mediating the anti-inflammatory M2 phenotype in murine macrophages *in vitro* (18). Meanwhile, Curcuma oil exhibited a dose-dependent inhibition of OxLDL-induced cholesterol accretion and improved the mRNA expression of lipid-related genes involved in cellular cholesterol metabolism and efflux (19). Curcuma oil was found to reduce the expression of scavenger receptor CD36 in both mouse peritoneal and human THP-1 macrophages (20). It plays an important role in the prevention of lipid accumulation in macrophages by regulating the overexpression of PPARα, ABCA1, ABCG1, and LXRα genes involved in AS development (21).

Andrographolide

Andrographolide (AG) is a labdane diterpenoid obtained from the plant *Andrographis paniculata*. A recent study was reported to reduce the tendency of oxLDL-induced lipid accretion in macrophage foam cells (22). Furthermore, the authors also reported the decreased expression of CD36 both at mRNA and protein levels following AG treatment. AG was found to increase the mRNA and protein expression of the Transcription factor liver X receptor (LXR) and improved its nuclear translocation and DNA binding effect (22). AG-loaded PEG-PPS micelle was found to synchronically ease the

inflammation and oxidative stress, which provides a promising and innovative strategy against AS (23).

Luteolin

Luteolin (3,4,5,7-tetrahydroxy-flavone) is a polyphenolic compound that is naturally occurring and is found in many medicinal herbs, vegetables, and fruits. It restricts plaque formation and lipid deposits in the abdominal aorta by reducing macrophage inflammation during AS mediated by AMPK-SIRT1 signalling (24). It was reported that 100 mg/kg of dietary luteolin ameliorated AS plaque development and lipid accretion in the abdominal aorta. Additionally, triglyceride, total cholesterol, and LDL-cholesterol levels were reduced in the plasma of luteolin-fed mice while comparing to the western diet-fed animals (24). It decreases foam cell formation and suppresses macrophage apoptosis by triggering autophagy. It also defends against vascular inflammation in mice and TNF-α-induced monocyte union to endothelial cells by conquering the IKBα/NF-κB signalling pathway (25, 26).

Ampelopsin/Dihydromyricetin

Dihydromyricetin (DHM) is a flavonoid-rich in *Ampelopsis grossedentata*. It enriches foam cell formation via LXRα-ABCA1/ABCG1-dependent cholesterol efflux in macrophages (27). In HFD-fed LDLr-/- mice, DHM enriched hyperlipidemia, reduced serum ox-LDL, IL-6, and TNF-α amounts and curbed hepatic lipid accretion. DHM inhibited AS-lesion growth and improved topographies of plaque stability, and controlled hepatic and aortic inflammation, as demonstrated by the decreased IL-6 and TNF-α mRNA expression. DHM abridged the hepatic and aortic oxidative stress by regulating activities of liver antioxidant enzymes and suppressing reactive oxygen species (ROS) generation and NADPH oxidase isoform 2 (NOX2) protein expression in both liver and aorta (28). DHM in amalgamated with D-tagatose stops the progress of hyperlipidemia, and AS in ApoE-/- knockout mice fed a Western (high fat, high cholesterol, and high sucrose) diet (29).

Dansameum

Dansameum (DSE) shows anti-atherosclerotic properties by regulating foam cell formation. It is a mixture of *Salvia miltiorrhiza* root extract (40g), *Amomumxanthioides* fruit extract (4g), and *Santalum album* lignum extract (4g). DSE reduced the expression of CD36 and PPAR-γ in oxLDL-stimulated RAW264.7 cells along with effectively reducing heme oxygenase-1 in ApoE-/- mice (30). Thus, DSE may be effective in the prevention of Atherosclerosis since it reduces the development of early atherosclerotic lesions and lipid accumulation in the aorta of ApoE-/-mice fed a high-fat diet (30).

Salidroside

Salidroside (rhodioloside), a glucoside of tyrosol, is a major active element extracted from *Rhodiola rosea*. It decreased the expression of VCAM-1, ICAM-1, and MCP1 in the aortic tissue in an LDL−/− mice model

(31). It also inhibited the ox-LDL–induced upsurge in the phosphorylation of ERK1/2, JNK, and p38 MAPK in the human THP1 cells. A recent study has revealed the highly beneficial effects of Salidroside in AS, including the suppression of oxidative stress by upregulating ABCA1 and downregulating LOX1 which thereby reverses cholesterol transport/efflux promotion. This study has also reported that MAPK and Akt pathways are highly involved in the salidroside-induced Nrf2 nuclear translocation, which was showed by the upregulation of Nrf2 in the THP1 cells (32). Mechanistically, shear stress is distressed at junctions, bowed segments of arteries or distal to areas of stenosis, NO bioavailability reduces, $O_2\bullet$ generation upsurges, and Nrf2-activated genes are reduced, producing the endothelium to become inclined to atherogenesis.

Quercetin-3-glucuronide (Q3GA)

Quercetin-3-glucuronide (Q3GA) is a natural flavonoid bound to sugars mostly as β-glycosides. Quercetin glycosides are richin apples,broccoli, and particularly in onions. *In vitro* studies with murine macrophage cell lines unveiled that the Q3GA taken up and deconjugated into active aglycone, which was further transformed to the methylated form in the activated macrophages. Furthermore, the mRNA expression of the class A scavenger receptor and CD36was suppressed by Q3GA. The above-mentioned processes play an imperative role in the development of foam cells. These results also propose that injured/inflamed arteries with activated macrophages are the probable targets of the metabolites of dietary quercetin (33). These data also provide new insights into the bioavailability of dietary flavonoids, especially of Q3GA, and their role in the prevention of AS and CVD.

Diosgenin

Diosgenin (Dgn),a structural analogue of cholesterol, remarkably up-regulates the expression of ATP-binding cassette transporter A1 (ABCA1) protein in human THP-1 macrophages (34). The potential mechanism of diosgenin (10-80 mM) in decreasing foam cell development as well as in atherogenesis over the inhibition of miRNA-19b. Furthermore, cholesterol transport assays showed that Dgn itself or combined with miR-19b inhibitor remarkably improved ABCA1-dependent cholesterol efflux, subsequent in reduced free cholesterol, total intracellular cholesterol, and cholesterol ester (35). Moreover, mice treated with Dgn alone or together with antagomiR-19b elevated plasma high-density lipoprotein levels whilst reducing low-density lipoprotein levels. Consequently, aortic lipid deposition and plaque area were condensed, and collagen content and ABCA1 expression were amplified (35).

Coenzyme Q10

Coenzyme Q10 (CoQ10, ubiquinone, ubiquinol) is a compound synthesized in the body and stored in the mitochondria. CoQ10 is abundant in the heart, liver, and kidney and meat products such as pork, beef, and chicken. Fatty fish such as trout, herring, mackerel, and sardine are the other animal sources of CoQ10—vegetables such as spinach, cauliflower, and broccoli, and fruits such as oranges and strawberries. Additionally, legumes like soybeans, lentils and peanuts, nuts, and seeds such as sesame seeds and pistachios, and oils like soybean and canola oil are the main sources of CoQ10 from plants (36, 37). CoQ10 enhanced reverse cholesterol transport (RCT) and reduced AS through a novel miR-378 regulatory module. A study identified that the activator protein-1/miR-378/ATP-binding cassette transporter G1 act as a novel target for CoQ10 in facilitating macrophage cholesterol efflux *in vitro* and *in vivo* (38). Mechanistically, CoQ10 inhibits the expression of c-Jun, and thus the activity of the AP-1 complex, which is a transcriptional activator of miR-378, which in turn directly targets ABCG1. The loss of miR-378 suppression resulted in increased cholesterol efflux and atheroprotection in mice (39).

Protocatechuic acid (PCA)

Anthocyaninsare most abundant in various vegetables, red wine, colourful fruits, and grains. They are flavonoids. The effect of protocatechuic acid (PCA) in the treatment of AS was determined by examining its effect in promoting macrophage reverse cholesterol transport (RCT) and exhibited the presence of a novel mechanism by which PCA limits miR-10b expression, upsurges ABCA1 and ABCG1 expression, and increases macrophage RCT in the ApoE$^{-/-}$ mice model (40).

Betulinic acid

Betulinic acid (BA) is a naturally occurring triterpenoid extensively present in all over the plant kingdom. A recent study suggests new visions into the defensive consequence of BA in improving cholesterol efflux over up-regulating ABCA1 expression facilitated by inhibiting the NF-κB signalling pathway and miR-33 expression (41). In addition to this, BA treatment improved the endothelial nitric oxide synthase (eNOS) expression reduction. This eases the inhibition of intracellular adhesion molecule 1 (ICAM-1) and endothelin 1 (ET-1) expression andthusstops endothelial dysfunction (42).

(−)-Epigallocatechin-3-gallate (EGCG)

The (−)-epigallocatechin-3-gallate (EGCG) is available as a component of green tea (Camellia Sinensis). Cai et al., have established that EGCG attenuates *Porphyromonas gingivalis* induced AS effectively (43). It has also been demonstrated that EGCG effectively protects against ox-LDL-induced endothelial cell impairment in the Jagged-1-mediated Notch pathway (44). Reports also suggest that EGCG-mediates its anti-atherosclerotic effects through modulation of the LXR/SREBP-1 pathway via the modulation of hepatic TTC39B expression, accountable for lipid metabolism syndrome in ApoE-/- mice (45).

Vitamin E & D

Vitamin E is a set of compounds formed by plants from homogentisic acid. These compounds comprise

two groups of tocopherols and tocotrienols each of which comprises α, β, δ, γ compounds. Tocotrienols decrease plasma cholesterol amounts and thus enriching hypercholesterolemia by interfering with cholesterol synthesis in the liver by inhibiting the HMG-CoA reductase, a key enzyme in cholesterol biosynthesis (46). Many other studies demonstrating the long-term effect of Vit-E consumption in decreasing AS (47, 48).

Annurca polyphenolic extracts (AAE)

Annurca polyphenolic extracts (AAE) isa nutraceutical found in Annurca, an apple native to Southern Italy enriched in procyanidin B2 (49). AAE showed inhibition of *de-novo* synthesis of cholesterol in HuH7 cells by stopping utilizing the intermediate metabolites for lipogenesis and cholesterogenesis. The cells then twitch to acquire FAs from lipid stores and process TGs available in intracellular lipid droplets and plasma membrane lipids or the extracellular medium (50).

Avenanthramides

Avenanthramides (anthranilic acid amides) are phenolic alkaloids found in oats (51, 52). They have been analysed for Antiatherogenic activity by investigating their properties on adhesion of monocytes to human aortic endothelial cell (HAEC) monolayers, production of proinflammatory cytokines and chemokines, and expression of adhesion molecules. Further, pre-incubation of HAEC's with AEM expressively reduced IL-1β-stimulated expressions of intracellular adhesion molecule-1 (ICAM-1), E-selectin and the secretion of proinflammatory cytokines IL-6, vascular cell adhesion molecule-1 (VCAM-1), chemokines IL-8 and monocyte chemoattractant protein (MCP)-1 (53).

Resveratrol

Resveratrol (RS) is a polyphenol present in grapes and also red wine (54). Oxidative stress influences CVD risk, including AS, by obstructing the development of free radicals and the oxidation of LDL. Reactive oxygen species (ROS) are the reason for the generation and accretion of oxidized LDL at the site of AS lesions (55, 56). Oxidative stress also increasingly leads to the progress of AS by contributing to macrophage foam cell development and enhancing endothelial dysfunction (57). RS expressively reduces oxidative stress markers, including serum glycated albumin and urinary 8-hydroxyguanosine in stroke-prone impulsively hypertensive rats (58). RS also improves the activities of catalase and decreases ROS construction in the cardiac tissue of guinea pigs. A study has shown a reduction in oxidized LDL in high fat diet-fed rats treated with RS for 45 days at a dose of 1 mg/kg per day (59). Overall, these results propose that RS efficiently inhibits lipid peroxidation *in vivo*. The anti-oxidative properties of RS were recommended as the mechanism underlying its varied properties including antiatherogenic activity (60, 61).

Salvianolic acid B

Salvianolic acid B (SAB) is a bioactive compound from *S. miltiorrhiza.* Its antiatherogenic activity has been assessed on platelet-induced inflammation in endothelial cells (62). SAB inhibits macrophage uptake of altered low-density lipoprotein (LDL) in a scavenger receptor CD36-dependent way. SAB abridged oxLDL-induced CD36 gene expression in the cell lines and primary macrophages. SAB also abridged CD36 expression competently in ApoE KO mice fed a high-fat diet and lipid intake in macrophages is indicating its ability to antagonize CD36 pathways *in vivo* (63, 64).

Atractylenolides

Antiplatelet drugs are extensively used in the treatment of coronary artery disease and atractylodes lactone compounds inhibit platelet activation (65). Platelets play a vital role in the development of atherosclerosis-thrombosis.Atractylenolides I, II, and III are the major ingredient of the herb *Atractylodes macrocephala.* Heme oxygenase-1 (HO-1) is an Nrf2-regulated gene that plays a serious role in the stoppage of vascular inflammation. HO-1 enabled vascular defense may be due to a amalgamation of systemic and vascular local possessions. Atractylenolide I restore HO-1 expression and inhibit Ox-LDL-induced vascular smooth muscle cells (VSMCs) migration,proliferation, and inflammatory responses *in vitro*. Atractylenolides II and III attenuated agonist-induced platelet accumulation and ATP release from platelet dense granules. Atractylenolides II and III displayed suppressive effects similar to those of acetylsalicylic acidon platelet activation in response to agonists (66, 67).

Toddalolactone

Toddalolactone is the main component of orange climber or *Toddalia asiatica.* A recent report stated that toddalolactone showed Plasminogen activator inhibitor-1 (PAI-1) inhibitory effects (68). PAI-1is related to fibrin deposition, which develops into organ fibrosis and AS. Toddalolactone suppresses the binding of PAI-1 with urokinase-type plasminogen activators (uPA) and consequently attenuated the development of the PAI-1/uPA complex (68).

Piper

Piper beetle ethanolic extract and of its active component, eugenol, were analysed in an animal model of chronic hypercholesterolemia. In the results, the histopathological valuation exposed the protective effect of Piper beetle extract on the hepatic and aortic tissues of atherogenic diet-fed (presumed atherosclerotic) rats (69). On the other hand, Oleuropein, a chief glycoside, presents in olives and is responsible for the characteristic bitter taste of immature olives (Fig.2). Cell culture experiments using olive oil phenolics remarkably induce a noteworthy decrease in the secretion of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 and protect against cytotoxic effects of hydrogen peroxide and oxidized LDL (70).
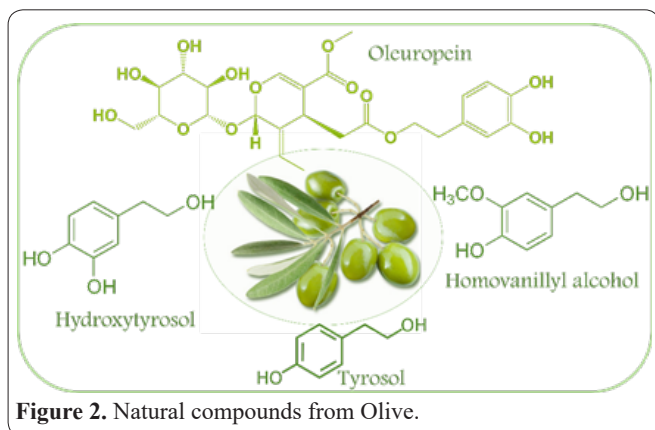
Figure 2. Natural compounds from Olive.

Spiromastixones

Spiromastixones are obtained from deep sea-derived fungus, *Spiromastix sp*. They have been shown to possesses lipid-lowering activity and inhibition of foam cell formation in RAW264.7 macrophages (71). Investigations reveal that Spiromastixones promote cholesterol efflux through upregulation of the PPARγ-ABCA1/G1 pathway and inhibition of cholesterol uptake via down-regulation of the scavenger receptors CD36 and SR-A1 (71). Therefore, spiromastixones could be potentially developed further to combat Atherosclerosis.

Mycoepoxydiene

Mycoepoxydiene (MED) is polyketide obtained from a marine fungus present in the mangrove forest. MED is connected with numerous activities, including antitumor and anti-inflammatory activities. A recent study examined the properties of MED on oxidized low-density lipoprotein (ox-LDL)-induced macrophage foam cell formation and activation, and on the high-fat diet (HFD)-induced Atherosclerosis in ApoE-deficient (ApoE-/-) mice. MED found to be effectiveto inhibit macrophage foam cell formation by inhibiting NF-κB activation, thereby protecting ApoE-/- mice froma high-fat diet(HFD)-induced AS (72).

Chlorogenic acid

Chlorogenic acid (CGA, 5-caffeoylquinic acid), arich polyphenols in the human diet, present in tomato,peach, sweet potato, oilseeds,carrot, apple, prune, and coffee (73). It effectively decreasesASprogress in ApoE$^{-/-}$ mice. The potential anti-atherosclerotic actions of CGA responsible for the protection against AScomprisea reduction of serum lipid, promotion of cholesterol efflux and suppression of vascular inflammation from macrophages (74). Upregulation of PPARγ, LXRα, ABCA1, and ABCG1 transcription and PPARγ activity may be involved in the stimulating consequence of CGA on cholesterol efflux from macrophages (75).

Chrysin

Chrysin (5,7-dihydroxyflavone) present in propolis, honey, and plant extracts (76) is a flavonoid. It is effectively inhibit foam cell development by inhibiting cholesterol accretion induced by ox-LDL, stimulat-ing cholesterol efflux, and stopping cholesterol uptake in RAW264.7 macrophages (77). Up-regulation of PPARγ–LXRα–ABCA1/ABCG1 pathway may contain the promoting effect of chrysin on cholesterol efflux and down-regulation of SR-A1 and SR-A2 may involving in the inhibition effect of chrysin on cholesterol uptake.

Kyolic

AGE (aged garlic extract) Kyolic roots a reduction in aortic tissue cholesterol fatty streak formation and atherosclerotic plaque formed in the balloon-injured carotid arteryin a rabbit model of AS (78) (Fig.3). Poly-datin isone of the major active ingredients of a Chinese herbal medicine Rhizoma *Polygoni cuspidati*. It inhibits the development of peritoneal macrophage-derived foam cells of ApoE$^{-/-}$ mice. Further examination has revealed that Polydatin has anti-inflammatory effects and controls the metabolism of intracellular lipid, possibly over PPAR-γ signalling pathway (79).

Berberine (BBR)

Berberine (BBR)is an alkaloid isolated from *Coptidis Rhizoma* (Huanglian) and *Cortex Phellodendri* (Huangbai), the traditional Chinese medicinal herbs. BBR inhibits ox-LDL-induced foam cell formation and cholesterol accretion in macrophages (80). Treatment with BBR augmented the expression of SIRT1 and reduced the expression of PPAR-γ at both the protein and mRNA amounts in the macrophages in a dose-dependent manner, thereby controlling lipid accretion (80).

Puerarin

Puerarin is an isoflavone, a naturally occurring product from Kudzu roots. It was recognized from reports that puerarin reduces ox-LDL induced proinflammatory gene expression along with downregulation of TLR4 and phospho-IκBα/IκBαdose-dependently. Furthermore, puerarin reduced oxLDL-mediated lipid deposition and foam cell formation related with the downregulation of scavenger receptor CD36. Flow cytometry analysis displayed that it abridged the number of premature apoptotic cells of macrophages persuaded by
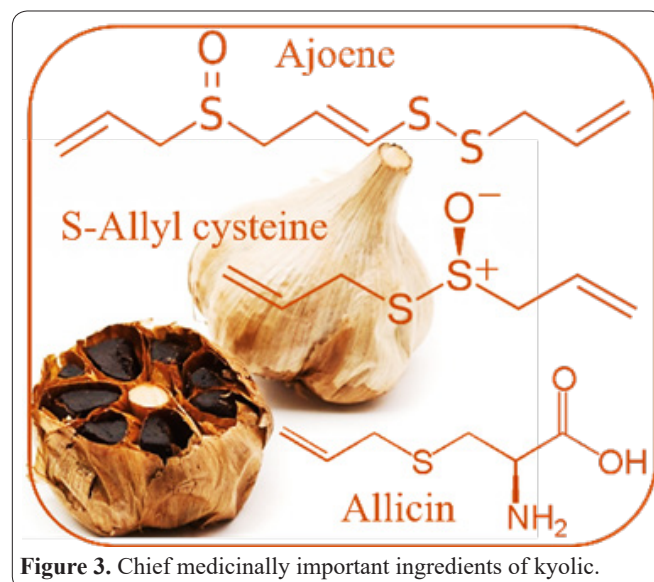

Figure 3. Chief medicinally important ingredients of kyolic.

ox-LDL (81).

9-Cis β-Carotene

9-cis β-carotene isomer, obtained from the alga *Dunaliella*, effectively inhibit macrophage foam cell development upon its alteration to retinoids (82). 9-cis β-carotene, developed in macrophages and can be locally cleaved by endogenous BCMO1 (β,β-Carotene monooxygenase 1) to form 9-cis retinoic acid and other retinoids. Subsequently, these retinoids trigger the nuclear receptor retinoid X receptor (RXR) that, along with supplementary nuclear receptors, can disturb numerous metabolic pathways, including those involved in foam cell development and Atherosclerosis (82).

Phenylpropanoid glucosides

Phenylpropanoid glucosides (PPGs)obtained from *Tadehagi triquetrum*antagonize ox-LDL-induced foam cell development by controlling cholesterol homeostasis observed in RAW264.7 macrophages. PPGs significantly down-regulate the expression of scavenge receptors 1 (SR-1) and CD36 and simultaneously up surging the expression of ATP-binding cassette transporters A1 and G1 (ABCA1 and ABCG1). This indicates them as effective regulators of cholesterol influx/efflux and anti-atherosclerotic agents (83).

Tetramethylpyrazine

Tetramethylpyrazine (TMP), extracted from *Ligusticum wallichii*, showed effective athero-protective activity. A study has examined the athero-protective effect of TMP and basic mechanisms in RAW264.7 macrophages and apolipoprotein E-deficient (ApoE-/-) mice (87). TMP treatment remarkably augmented the cholesterol efflux and inhibited oxidized low-density lipoprotein (ox-LDL) uptake, consequently, improving lipid accretion in macrophages. TMP amplified the protein and mRNA expression of ATP-binding cassette transporters A1 (ABCA1) and G1 (ABCG1) while conquering the protein and mRNA expression of class A scavenger receptor (SR-A) and CD36 (84). Moreover, the properties of TMP on the upregulation of the expression of ABCA1 and ABCG1, the downregulation of the expression of CD36 and SR-A, the upsurge of cholesterol efflux and the reduction of lipid accumulation as well as the uptake of ox-LDL were arbitrated by the inactivation of PI3K/Akt and p38 MAPK pathway. Also, TMP upregulated the protein stability of ABCA1 deprived ofupsetting ABCG1 (84). Therefore, TMP regulated the expression of SR-A, CD36, ABCA1, and ABCG1 in aortas of ApoE-/- mice, which look like the verdicts observed in macrophages. TMP treatment was also delayed the progress of AS in ApoE-/- mice. These results exposed that TMP downregulates scavenger receptors and upregulates ATP-binding cassette transporters via PI3K/Akt and p38 MAPK signalling, thus overwhelming lipid accretion in macrophages.

Thymoquinone

Thymoquinone (TQ), a main component of *Ni-gella sativa* seeds, displayed potent antioxidant and anti-inflammatory properties (85, 86). Earlier studies displayed that TQ is protective against drug-induced cardiac toxicity by inhibiting the lipid peroxidation and inflammation (87, 88). Furthermore, it also inhibited the levels of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α in heart tissue homogenates.ApoE$^{-/-}$ deficient mice fed with a high cholesterol diet exhibited higher levels of total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-c), which were up turned by TQ administration. Also, TQ inhibited the expression of LOX-1 that plays an significant role in ox-LDL uptake and foam cell development. This study also exposed that TQ abridged the infiltration of macrophages in the heart of ApoE$^{-/-}$ deficient mice. In another study, Nader et. al disclosed that TQ in combination with propolis abridged the risk of AS by lowering the levels of total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and triglycerides (89). Moreover, this combination was also effective in reversing the effect of high cholesterol-induced endothelial damage and foam cell thickening (89). TQ also reduced hyperlipidemia- and cyclosporin-induced formation of atherosclerotic plaques by modulating the oxidative stress and lipid profile parameters. The exact mechanism by which TQ shows its therapeutic effects against AS is poorly known. Therefore, further studies using appropriate disease models should be conducted to understand the anti-atherosclerotic activity of TQ at the molecular level that may lead to the development of a more effective therapeutic formulation of TQ. Besides, a combination of TQ with lipid-lowering statins may be considered to potentiate the efficacy of statin to counter the progression of AS. However, the above-mentioned findings suggest that TQ exerts anti-atherosclerotic action by modulating the status of oxidative stress, proinflammatory cytokines, macrophage infiltration, and foam cell formation. We have summarised all the compounds discussed along with the mechanism of action in table 1.

Discussion

Atherosclerosis (AS) is a prevalent and chronic progressive arterial disease that has been viewed as one of the major causes of global mortality. Natural products are used as one of the most significant sources for the treatment and prevention of CVD's for a long time. In the recent era, interest in natural products, including medicinal herbs, has enlarged, many studies using natural compounds as active antiatherogenic agents, have been steered. The main aim of this review is to offer an overview of natural compounds used for the treatment and prevention of Atherosclerosis. Although most of the known compounds have at least one known mechanism of action, certain compounds like salvianolic acid B (SAB), Cryptotanshinone, and protocatechuic acid (PCA) did not show not specific MOAs, despite having a clear-cut role in inhibiting foam cell formation and AS.

The following factors have been demonstrated to contribute to the development of Atherosclerosis: coagulation system, inflammation, hyperlipidemia, and environmental factors. Besides that, the conducted studies on AS have demonstrated the active effects of

Table 1. Suggested natural supplements and products to treat Atherosclerosis.

S. No.	Natural products	Type/Source/part used	Responsible ingredient for medicinal value	The therapeutic mechanism of action
1	Alpha-linolenic acid (ALA)	Plants (flaxseed oil, and in canola, soy, perilla, and walnut oils)	Omega-3 long-chain polyunsaturated fatty acids	Attenuates AS lesions, inhibits the proliferation of vascular smooth muscle cells by targeting the Ras/MEK/ERK signalling pathway (90).
2	Barley	Grass/Cereal grain/ Dietary fibres	Caffeic, p-coumaric & diferulic acid, prodelphinidin B3, saponarin, catechin, procyanidin, hordenine.	Acting as antioxidant and hypolipidemic activities (91).
3	Beta-sitosterol	Fruits, vegetables, nuts, and seeds, oral supplements, and some margarine	Phytosterols or plant sterols, Plant sterol ester.	Lowering blood cholesterol levels and reducing the risk of coronary heart disease (CHD) (92).
4	Black tea	More oxidized than oolong, green, and white teas	Polyphenols (flavonoids)	Inhibit AS by lipid, antioxidant, and fibrinolytic mechanisms (93).
5	Blond psyllium	Found in seed and the outer covering of the seed (husk)	Husk fibres	Decrease serum and LDL-Cholesterol & increase HDL-Cholesterol (94).
6	Calcium	Milk, cheese, broccoli, cabbage and okra, soya beans, tofu, soya drinks with added calcium, nuts.	Co-factor for many enzymes	Calcium mineralization of the lumen in the atherosclerotic artery promotes and solidifies plaque formation causing narrowing of the vessel (95).
7	Cocoa	A most concentrated source of flavonols (flavonoids) also found in tea and red wine.	Flavonoids, liquor polyphenols, etc.	Improves hyperlipidemia and AS mediated through the suppression of hepatic endoplasmic reticulum stress (96).
8	Cod liver oil	Extracted from Atlantic cod livers	Omega 3 fatty acids (EPA and DHA), vitamin A and vitamin D.	Dietary cod-liver oil retards the development of CAD through changes in prostaglandin metabolism (97, 98).
9	Coenzyme Q10	Carbon-containing non-protein molecules such as vitamins, vitamin derivatives, or form from nucleotides.	Ubiquinone or coenzyme Q10	Decreasing circadian rhythms of cardiac events, oxidative damage as well as an increase in HDL cholesterol (99).
10	Folic acid	B vitamins	Folic acid converted into Folate or vitamin B_9 and folacin a dietary supplement	Prevents AS by modifying DNA methylation via methionine cycle, refines DNA methyltransferase activity & restrict expression of AS-related genes (100).
11	Oat bran	Found in oatmeal and whole oats	Soluble fibre (β-glucan), vitamin E, phytic acid, phenolics, Avenanthramides (Avns)	Reducing total blood cholesterol levels and lesions in the descending aorta (101).
12	Sitostanol	Found in a variety of plant sources as phytosterol and margarine (Benecol)	Stigmastanol (Sitostanol)	Reducing LDL-Cholesterol, decreasing cholesterol absorption markers, β-sitosterol and hydrogenation of stigmasterol (102).
13	Vitamin C	Citrus fruits, broccoli, tomatoes, etc.	Ascorbic acid	Protect arteries against damage, slowing down AS through monocyte adhesion to the vascular endothelium & LDL oxidation (103, 104).

medicinal plants and plant-based compounds in decreasing and ameliorating Atherosclerosis with remarkable therapeutic effects in decreasing glucose, fibrinogen, Ox-LDL, and MDA, decreasing the production of free radicals, preventing LDL NADPH oxidase activity and cholesterol oxidation, decreasing hyperlipidemia and high antioxidant activity, producing prostaglandins, and dilating vessels and aorta (9, 105, 106). Table 2 indicates the effect of the natural compounds, their source, therapeutic effect, and their targets to control the plaque formation in Atherosclerosis.

Studying and introducing these food ingredients and plant-based compounds with potential antioxidant properties can contribute to preventing the formation of free radicals and decreasing lipid levels, plaques, Atherosclerosis, cardiovascular disease, and ischemia. Phenolic and polyphenolic compounds, flavonoids, kaempferol, anthocyanin, catechin, quercetin, sterol, carotenoid, caffeic acid, beta-carotene, and gallic acid are the most important active compounds with these properties (119). In conclusion, many reports suggest that plant-based compounds are effective in the treat-

Table 2. Effects of medicinal herbs on plaque formation.

S. No.	Compounds	Natural/Plant source	Therapeutic effect and target	References
1	Curcumin and Curcuma oil	*Curcuma longa*	CD36, PPARα, ABCA1, ABCG1 and LXRα	(107)
2	Andrographolide	*Andrographis paniculate*	Transcription factor liver X receptor (LXR) depended on ABCA1 & ABCG1	(108, 109)
3	Luteolin	*Reseda luteola*	IKBα/NF-κB signalling pathway	(24)
4	Ampelopsin/ Dihydromyricetin	*Ampelopsis grossedentata*	LXRα-ABCA1/ABCG1	(27)
5	Dansameum Extract (DSE)	A mixture of *Salvia miltiorrhiza* root, *Santalum album* lignum, and *Amomumxanthioides* fruit	CD36 and PARP-γ	(30)
6	Salidroside	*Rhodiola rosea*	MCP1, ICAM-1, VCAM-1, ABCA1 LOX1, MAPK and Akt pathways	(31)
7	Diosgenin	*Dioscorea wild yam*	ATP-binding cassette transporter A1 (ABCA1) protein	(34, 35)
8	(−)-Epigallocatechin-3-gallate (EGCG)	*Camellia Sinensis*	Lxrβ, Abcg5, Abcg8, Abca1, Srebf1, Scd1, Scd2, Fas, Elovl5, Mylip; 67kD laminin receptor (67LR)	(43, 44)
9	Protocatechuic acid (PCA)	*Hibiscus sabdariffa*	miR-10b, ABCA1 and ABCG1	(110)
10	Avenanthramides	*Avena sativa*	Avenanthramides ICAM-1, VCAM-1	(52)
11	Atractylenolide	*Rhizoma atractylodes*	Monocyte chemoattractant protein-1 (MCP-1)	(111)
12	Toddalolactone	*Zanthoxylum nitidum*	Plasminogen activator inhibitor-1 (PAI-1)	(68)
13	Salvianolic acid B	*Salvia miltiorrhiza*	P-selectin, NF-κB	(62, 112)
14	Cryptotanshinone	Danshen	LOX-1, MMP-9, ROS, NF-κB, ICAM-1, VCAM-1	(113, 114)
15	Atractylodes lactone	*Atractylodes macrocephala*	ATP release, Ser473, phospho-p38 MAPK	(67)
16	1,6-Di-O-caffeoyl-β-D-glucopyranoside	*Callicarpa nudiflora* Hook	αIIbβ3 integrin, 5-HT, TXA2, RhoA, P2Y12, PI3K/Akt/GSK3β,	(69)
17	Protocatechualdehyde	*Salvia miltiorrhiza*	PDGF, PI3K/Akt, MAPK, cyclin D2, ROS	(40)
18	Ellagic acid	Strawberries, Raspberries, Blackberries, Cherries, and Walnuts	NF-E2-related factor 2, ABCA1, ABCG1, VCAM-1, MCP-1, PECAM-1, F4/80, ERK & PPARg-LXRaABCA1 pathway	(115-117)
19	Thymoquinone	*Nigella sativa* seed or black seed or black cumin	LOX1, IL-1β, IL-6, TNF-α,	(118)

ment of Atherosclerosis. The active ingredients present in plants comprising flavonoids and other phenolic compounds with antioxidant activity can scavenge free radicals and would be effective against Atherosclerosis. There are still many issues about Atherosclerosis which we have limited information on and therefore deserve much further investigation.

Competing Interests
The authors declare no competing interests.

Availability of data and materials
Not applicable, all information in this review can be found in the reference list.

Ethics approval and consent to participate
No ethics approval was required for this review that did not involve patients or patient data.

Consent for publication
All authors consent to publication.

References

1. Ferrero-Miliani L, Nielsen OH, Andersen PS, Girardin SE. Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1beta generation. Clinical and experimental immunology. 2007;147(2):227-35.
2. Li X, Fang P, Li Y, Kuo YM, Andrews AJ, Nanayakkara G, et al. Mitochondrial Reactive Oxygen Species Mediate Lysophosphatidylcholine-Induced Endothelial Cell Activation. Arteriosclerosis,

thrombosis, and vascular biology. 2016;36(6):1090-100.

3. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. Frontiers in immunology. 2014;5:491.

4. Buttari B, Profumo E, Businaro R, Saso L, Capoano R, Salvati B, et al. Oxidized Haemoglobin–Driven Endothelial Dysfunction and Immune Cell Activation: Novel Therapeutic Targets for Atherosclerosis. Current medicinal chemistry. 2013;20(37):4806-14.

5. Choy PC, Siow YL, Mymin D, O K. Lipids and atherosclerosis. Biochemistry and cell biology = Biochimie et biologie cellulaire. 2004;82(1):212-24.

6. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature. 1993;362(6423):801-9.

7. Alagumuthu M, Srivastava V, Shah M, Arumugam S, Sonaimuthu M, Arumugam NA. Pro- and Anti-Inflammatory Cytokine Expression Levels in Macrophages; An Approach to Develop Indazolpyridin-Methanones as a Novel Inflammation Medication. Anti-inflammatory & anti-allergy agents in medicinal chemistry. 2020;19(4):425-35.

8. Dennis Bilavendran J, Manikandan A, Thangarasu P, Sivakumar K. Synthesis and discovery of pyrazolo-pyridine analogs as inflammation medications through pro- and anti-inflammatory cytokine and COX-2 inhibition assessments. Bioorganic chemistry. 2020;94:103484.

9. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: process, indicators, risk factors and new hopes. International journal of preventive medicine. 2014;5(8):927-46.

10. Orekhov AN. Direct anti-atherosclerotic therapy; development of natural anti-atherosclerotic drugs preventing cellular cholesterol retention. Current pharmaceutical design. 2013;19(33):5909-28.

11. Saqib U, Sarkar S, Suk K, Mohammad O, Baig MS, Savai R. Phytochemicals as modulators of M1-M2 macrophages in inflammation. Oncotarget. 2018;9(25):17937.

12. Derosa G, Maffioli P, Sahebkar A. Ellagic Acid and Its Role in Chronic Diseases. Advances in experimental medicine and biology. 2016;928:473-9.

13. Lee WJ, Ou HC, Hsu WC, Chou MM, Tseng JJ, Hsu SL, et al. Ellagic acid inhibits oxidized LDL-mediated LOX-1 expression, ROS generation, and inflammation in human endothelial cells. Journal of vascular surgery. 2010;52(5):1290-300.

14. Chang W-C, Yu Y-M, Chiang S-Y, Tseng C-Y. Ellagic acid suppresses oxidised low-density lipoprotein-induced aortic smooth muscle cell proliferation: studies on the activation of extracellular signal-regulated kinase 1/2 and proliferating cell nuclear antigen expression. British journal of nutrition. 2008;99(4):709-14.

15. Aviram M, Volkova N, Coleman R, Dreher M, Reddy MK, Ferreira D, et al. Pomegranate phenolics from the peels, arils, and flowers are antiatherogenic: studies in vivo in atherosclerotic apolipoprotein e-deficient (E 0) mice and in vitro in cultured macrophages and lipoproteins. Journal of agricultural and food chemistry. 2008;56(3):1148-57.

16. Park SH, Kim JL, Lee ES, Han SY, Gong JH, Kang MK, et al. Dietary ellagic acid attenuates oxidized LDL uptake and stimulates cholesterol efflux in murine macrophages. J Nutr. 2011;141(11):1931-7.

17. Mohammadian Haftcheshmeh S, Karimzadeh MR, Azhdari S, Vahedi P, Abdollahi E, Momtazi-Borojeni AA. Modulatory effects of curcumin on the atherogenic activities of inflammatory monocytes: Evidence from in vitro and animal models of human atherosclerosis. BioFactors. 2020;46(3):341-55.

18. Gao S, Zhou J, Liu N, Wang L, Gao Q, Wu Y, et al. Curcumin induces M2 macrophage polarization by secretion IL-4 and/or IL-13. Journal of molecular and cellular cardiology. 2015;85:131-9.

19. Ledda A, Gonzalez M, Gulfo J, Diaz Ludovico I, Ramella N, Toledo J, et al. Decreased OxLDL uptake and cholesterol efflux in

THP1 cells elicited by cortisol and by cortisone through 11beta-hydroxysteroid dehydrogenase type 1. Atherosclerosis. 2016;250:84-94.

20. Singh RB, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: A multifactorial process. Experimental and clinical cardiology. 2002;7(1):40-53.

21. Jian X, Liu Y, Zhao Z, Zhao L, Wang D, Liu Q. The role of traditional Chinese medicine in the treatment of atherosclerosis through the regulation of macrophage activity. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2019;118:109375.

22. Lin HC, Lii CK, Chen HC, Lin AH, Yang YC, Chen HW. Andrographolide Inhibits Oxidized LDL-Induced Cholesterol Accumulation and Foam Cell Formation in Macrophages. The American journal of Chinese medicine. 2018;46(1):87-106.

23. Wu T, Chen X, Wang Y, Xiao H, Peng Y, Lin L, et al. Aortic plaque-targeted andrographolide delivery with oxidation-sensitive micelle effectively treats atherosclerosis via simultaneous ROS capture and anti-inflammation. Nanomedicine : nanotechnology, biology, and medicine. 2018;14(7):2215-26.

24. Li J, Dong JZ, Ren YL, Zhu JJ, Cao JN, Zhang J, et al. Luteolin decreases atherosclerosis in LDL receptor-deficient mice via a mechanism including decreasing AMPK-SIRT1 signaling in macrophages. Experimental and therapeutic medicine. 2018;16(3):2593-9.

25. Zhang BC, Zhang CW, Wang C, Pan DF, Xu TD, Li DY. Luteolin Attenuates Foam Cell Formation and Apoptosis in Ox-LDL-Stimulated Macrophages by Enhancing Autophagy. Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology. 2016;39(5):2065-76.

26. Jia Z, Nallasamy P, Liu D, Shah H, Li JZ, Chitrakar R, et al. Luteolin protects against vascular inflammation in mice and TNF-alpha-induced monocyte adhesion to endothelial cells via suppressing IKappaBalpha/NF-kappaB signaling pathway. The Journal of nutritional biochemistry. 2015;26(3):293-302.

27. Zeng Y, Peng Y, Tang K, Wang YQ, Zhao ZY, Wei XY, et al. Dihydromyricetin ameliorates foam cell formation via LXRalpha-ABCA1/ABCG1-dependent cholesterol efflux in macrophages. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2018;101:543-52.

28. Liu TT, Zeng Y, Tang K, Chen X, Zhang W, Xu XL. Dihydromyricetin ameliorates atherosclerosis in LDL receptor deficient mice. Atherosclerosis. 2017;262:39-50.

29. Williams J, Ensor C, Gardner S, Smith R, Lodder R. BSN723T Prevents Atherosclerosis and Weight Gain in ApoE Knockout Mice Fed a Western Diet. WebmedCentral. 2015;6(12).

30. Park KS, Ahn SH, Lee KP, Park SY, Cheon JH, Choi JY, et al. The Natural Compound Dansameum Reduces foam Cell Formation by Downregulating CD36 and Peroxisome Proliferator-activated Receptor-gamma; Expression. Pharmacognosy magazine. 2018;13(Suppl 4):S868-S74.

31. Zhang BC, Li WM, Guo R, Xu YW. Salidroside decreases atherosclerotic plaque formation in low-density lipoprotein receptor-deficient mice. Evidence-based complementary and alternative medicine : eCAM. 2012;2012:607508.

32. Ni J, Li Y, Li W, Guo R. Salidroside protects against foam cell formation and apoptosis, possibly via the MAPK and AKT signaling pathways. Lipids in health and disease. 2017;16(1):198.

33. Kawai Y, Nishikawa T, Shiba Y, Saito S, Murota K, Shibata N, et al. Macrophage as a target of quercetin glucuronides in human atherosclerotic arteries implication in the anti-atherosclerotic mechanism of dietary flavonoids. Journal of Biological chemistry. 2008;283(14):9424-34.

34. Wu FC, Jiang JG. Effects of diosgenin and its derivatives on atherosclerosis. Food & function. 2019;10(11):7022-36.

35. Lv YC, Yang J, Yao F, Xie W, Tang YY, Ouyang XP, et al.

Diosgenin inhibits atherosclerosis via suppressing the MiR-19b-induced downregulation of ATP-binding cassette transporter A1. Atherosclerosis. 2015;240(1):80-9.

36. Pravst I, Zmitek K, Zmitek J. Coenzyme Q10 contents in foods and fortification strategies. Critical reviews in food science and nutrition. 2010;50(4):269-80.

37. Parmar SS, Jaiwal A, Dhankher OP, Jaiwal PK. Coenzyme Q10 production in plants: current status and future prospects. Critical reviews in biotechnology. 2015;35(2):152-64.

38. Wang D, Xia M, Yan X, Li D, Wang L, Xu Y, et al. Gut microbiota metabolism of anthocyanin promotes reverse cholesterol transport in mice via repressing miRNA-10b. Circulation research. 2012;111(8):967-81.

39. Allen RM, Vickers KC. Coenzyme Q10 increases cholesterol efflux and inhibits atherosclerosis through microRNAs. Arteriosclerosis, thrombosis, and vascular biology. 2014;34(9):1795-7.

40. Moon CY, Ku CR, Cho YH, Lee EJ. Protocatechuic aldehyde inhibits migration and proliferation of vascular smooth muscle cells and intravascular thrombosis. Biochemical and biophysical research communications. 2012;423(1):116-21.

41. Zhao GJ, Tang SL, Lv YC, Ouyang XP, He PP, Yao F, et al. Antagonism of betulinic acid on LPS-mediated inhibition of ABCA1 and cholesterol efflux through inhibiting nuclear factor-kappaB signaling pathway and miR-33 expression. PloS one. 2013;8(9):e74782.

42. Yoon JJ, Lee YJ, Han BH, Choi ES, Kho MC, Park JH, et al. Protective effect of betulinic acid on early atherosclerosis in diabetic apolipoprotein-E gene knockout mice. European journal of pharmacology. 2017;796:224-32.

43. Cai Y, Kurita-Ochiai T, Hashizume T, Yamamoto M. Green tea epigallocatechin-3-gallate attenuates Porphyromonas gingivalis-induced atherosclerosis. Pathogens and disease. 2013;67(1):76-83.

44. Yan X, Li Y, Yu H, Wang W, Wu C, Yang Y, et al. Epigallocatechin-3-gallate inhibits H2O2-induced apoptosis in Mouse Vascular Smooth Muscle Cells via 67kD Laminin Receptor. Scientific reports. 2017;7(1):7774.

45. Wang W, Zhang Z-Z, Wu Y, Wang R-Q, Chen J-W, Chen J, et al. (–)-Epigallocatechin-3-Gallate Ameliorates Atherosclerosis and Modulates Hepatic Lipid Metabolic Gene Expression in Apolipoprotein E Knockout Mice: Involvement of TTC39B. Frontiers in pharmacology. 2018;9:195.

46. Ricciarelli R, Zingg JM, Azzi A. Vitamin E: protective role of a Janus molecule. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2001;15(13):2314-25.

47. Meydani M, Kwan P, Band M, Knight A, Guo W, Goutis J, et al. Long-term vitamin E supplementation reduces atherosclerosis and mortality in Ldlr-/- mice, but not when fed Western style diet. Atherosclerosis. 2014;233(1):196-205.

48. Upston JM, Kritharides L, Stocker R. The role of vitamin E in atherosclerosis. Progress in lipid research. 2003;42(5):405-22.

49. Badolati N, Sommella E, Riccio G, Salviati E, Heintz D, Bottone S, et al. Annurca Apple Polyphenols Ignite Keratin Production in Hair Follicles by Inhibiting the Pentose Phosphate Pathway and Amino Acid Oxidation. Nutrients. 2018;10(10).

50. Sommella E, Badolati N, Riccio G, Salviati E, Bottone S, Dentice M, et al. A Boost in Mitochondrial Activity Underpins the Cholesterol-Lowering Effect of Annurca Apple Polyphenols on Hepatic Cells. Nutrients. 2019;11(1).

51. Ishihara A, Kojima K, Fujita T, Yamamoto Y, Nakajima H. New series of avenanthramides in oat seed. Bioscience, biotechnology, and biochemistry. 2014;78(12):1975-83.

52. Thomas M, Kim S, Guo W, Collins FW, Wise ML, Meydani M. High Levels of Avenanthramides in Oat-Based Diet Further Suppress High Fat Diet-Induced Atherosclerosis in Ldlr(-/-) Mice.

Journal of agricultural and food chemistry. 2018;66(2):498-504.

53. Andersson KE, Svedberg KA, Lindholm MW, Oste R, Hellstrand P. Oats (Avena sativa) reduce atherogenesis in LDL-receptor-deficient mice. Atherosclerosis. 2010;212(1):93-9.

54. Liu L, Zubik L, Collins FW, Marko M, Meydani M. The anti-atherogenic potential of oat phenolic compounds. Atherosclerosis. 2004;175(1):39-49.

55. Kovanen PT, Pentikäinen MO. Circulating lipoproteins as proinflammatory and anti-inflammatory particles in atherogenesis. Current opinion in lipidology. 2003;14(5):411-9.

56. Carmena R, Duriez P, Fruchart JC. Atherogenic lipoprotein particles in atherosclerosis. Circulation. 2004;109(23 Suppl 1):III2-7.

57. Nowak WN, Deng J, Ruan XZ, Xu Q. Reactive Oxygen Species Generation and Atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology. 2017;37(5):e41-e52.

58. Marchio P, Guerra-Ojeda S, Vila JM, Aldasoro M, Victor VM, Mauricio MD. Targeting Early Atherosclerosis: A Focus on Oxidative Stress and Inflammation. Oxidative medicine and cellular longevity. 2019;2019:8563845.

59. Ramprasath VR, Jones PJ. Anti-atherogenic effects of resveratrol. European journal of clinical nutrition. 2010;64(7):660-8.

60. Rocha KK, Souza GA, Ebaid GX, Seiva FR, Cataneo AC, Novelli EL. Resveratrol toxicity: effects on risk factors for atherosclerosis and hepatic oxidative stress in standard and high-fat diets. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association. 2009;47(6):1362-7.

61. Brites F, Martin M, Guillas I, Kontush A. Antioxidative activity of high-density lipoprotein (HDL): Mechanistic insights into potential clinical benefit. BBA clinical. 2017;8:66-77.

62. Xu S, Zhong A, Bu X, Ma H, Li W, Xu X, et al. Salvianolic acid B inhibits platelets-mediated inflammatory response in vascular endothelial cells. Thrombosis research. 2015;135(1):137-45.

63. Bao Y, Wang L, Xu Y, Yang Y, Wang L, Si S, et al. Salvianolic acid B inhibits macrophage uptake of modified low density lipoprotein (mLDL) in a scavenger receptor CD36-dependent manner. Atherosclerosis. 2012;223(1):152-9.

64. Yang J, Park KW, Cho S. Inhibition of the CD36 receptor reduces visceral fat accumulation and improves insulin resistance in obese mice carrying the BDNF-Val66Met variant. The Journal of biological chemistry. 2018;293(34):13338-48.

65. Orekhov AN, Ivanova EA. Cellular models of atherosclerosis and their implication for testing natural substances with anti-atherosclerotic potential. Phytomedicine : international journal of phytotherapy and phytopharmacology. 2016;23(11):1190-7.

66. Kim JY, Shim SH. Medicinal Herbs Effective Against Atherosclerosis: Classification According to Mechanism of Action. Biomolecules & therapeutics. 2019;27(3):254-64.

67. Chen Y, Yang W, Guo L, Wu X, Zhang T, Liu J, et al. Atractylodes lactone compounds inhibit platelet activation. Platelets. 2017;28(2):194-202.

68. Yu B, Zhang G, Jin L, Zhang B, Yan D, Yang H, et al. Inhibition of PAI-1 activity by toddalolactone as a mechanism for promoting blood circulation and removing stasis by chinese herb Zanthoxylum nitidum var. tomentosum. Frontiers in pharmacology. 2017;8:489.

69. Fu J, Zhu X, Wang W, Lu H, Zhang Z, Liu T, et al. 1, 6-di-O-caffeoyl-beta-D-glucopyranoside, a natural compound from Callicarpa nudiflora Hook impairs P2Y12 and thromboxane A2 receptor-mediated amplification of platelet activation and aggregation. Phytomedicine : international journal of phytotherapy and phytopharmacology. 2017;36:273-82.

70. Venkadeswaran K, Thomas PA, Geraldine P. An experimental evaluation of the anti-atherogenic potential of the plant, Piper betle, and its active constitutent, eugenol, in rats fed an atherogenic diet. Biomedicine & Pharmacotherapy. 2016;80:276-88.

71. Wu C, Chen R, Liu M, Liu D, Li X, Wang S, et al. Spiromastixones Inhibit Foam Cell Formation via Regulation of Cholesterol Efflux and Uptake in RAW264.7 Macrophages. Marine drugs. 2015;13(10):6352-65.

72. Xia X, Li Y, Su Q, Huang Z, Shen Y, Li W, et al. Inhibitory effects of Mycoepoxydiene on macrophage foam cell formation and atherosclerosis in ApoE-deficient mice. Cell & bioscience. 2015;5:23.

73. Liang N, Kitts DD. Role of Chlorogenic Acids in Controlling Oxidative and Inflammatory Stress Conditions. Nutrients. 2015;8(1).

74. Wu C, Luan H, Zhang X, Wang S, Zhang X, Sun X, et al. Chlorogenic acid protects against atherosclerosis in ApoE−/− mice and promotes cholesterol efflux from RAW264. 7 macrophages. PloS one. 2014;9(9):e95452.

75. Ren K, Li H, Zhou HF, Liang Y, Tong M, Chen L, et al. Mangiferin promotes macrophage cholesterol efflux and protects against atherosclerosis by augmenting the expression of ABCA1 and ABCG1. Aging. 2019;11(23):10992-1009.

76. Satyanarayana K, Sravanthi K, Shaker IA, Ponnulakshmi R, Selvaraj J. Role of chrysin on expression of insulin signaling molecules. Journal of Ayurveda and integrative medicine. 2015;6(4):248-58.

77. Wang S, Zhang X, Liu M, Luan H, Ji Y, Guo P, et al. Chrysin inhibits foam cell formation through promoting cholesterol efflux from RAW264. 7 macrophages. Pharmaceutical Biology. 2015;53(10):1481-7.

78. Campbell JH, Efendy JL, Smith NJ, Campbell GR. Molecular basis by which garlic suppresses atherosclerosis. The Journal of nutrition. 2001;131(3):1006S-9S.

79. Wu M, Liu M, Guo G, Zhang W, Liu L. Polydatin Inhibits Formation of Macrophage-Derived Foam Cells. Evidence-based complementary and alternative medicine : eCAM. 2015;2015:729017.

80. Wan Q, Liu Z, Yang Y, Cui X. Suppressive effects of berberine on atherosclerosis via downregulating visfatin expression and attenuating visfatin-induced endothelial dysfunction. International journal of molecular medicine. 2018;41(4):1939-48.

81. Zhang H, Zhai Z, Zhou H, Li Y, Li X, Lin Y, et al. Puerarin Inhibits oxLDL-Induced Macrophage Activation and Foam Cell Formation in Human THP1 Macrophage. BioMed research international. 2015;2015:403616.

82. Zolberg Relevy N, Bechor S, Harari A, Ben-Amotz A, Kamari Y, Harats D, et al. The inhibition of macrophage foam cell formation by 9-cis beta-carotene is driven by BCMO1 activity. PloS one. 2015;10(1):e0115272.

83. Wang S, Zhang X, Li X, Liu Q, Zhou Y, Guo P, et al. Phenylpropanoid glucosides from Tadehagi triquetrum inhibit oxLDL-evoked foam cell formation through modulating cholesterol homeostasis in RAW264.7 macrophages. Natural product research. 2019;33(6):893-6.

84. Duan J, Xiang D, Luo H, Wang G, Ye Y, Yu C, et al. Tetramethylpyrazine suppresses lipid accumulation in macrophages via upregulation of the ATP-binding cassette transporters and downregulation of scavenger receptors. Oncology reports. 2017;38(4):2267-76.

85. Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL. Oxidative Stress in Atherosclerosis. Current atherosclerosis reports. 2017;19(11):42.

86. Khan MA, Younus H. Thymoquinone shows the diverse therapeutic actions by modulating multiple cell signaling pathways: single drug for multiple targets. Current pharmaceutical biotechnology. 2018;19(12):934-45.

87. Nagi MN, Mansour MA. Protective effect of thymoquinone against doxorubicin–induced cardiotoxicity in rats: A possible mechanism of protection. Pharmacological research. 2000;41(3):283-9.

88. Ojha S, Azimullah S, Mohanraj R, Sharma C, Yasin J, Arya DS, et al. Thymoquinone Protects against Myocardial Ischemic Injury by Mitigating Oxidative Stress and Inflammation. Evidence-based complementary and alternative medicine : eCAM. 2015;2015:143629.

89. Nader MA, el-Agamy DS, Suddek GM. Protective effects of propolis and thymoquinone on development of atherosclerosis in cholesterol-fed rabbits. Archives of pharmacal research. 2010;33(4):637-43.

90. Lee WR, Kim A, Kim KS, Park YY, Park JH, Kim KH, et al. Alpha-lipoic acid attenuates atherosclerotic lesions and inhibits proliferation of vascular smooth muscle cells through targeting of the Ras/MEK/ERK signaling pathway. Molecular biology reports. 2012;39(6):6857-66.

91. Yu J, Vasanthan T, Temelli F. Analysis of phenolic acids in barley by high-performance liquid chromatography. Journal of agricultural and food chemistry. 2001;49(9):4352-8.

92. Vivancos M, Moreno JJ. Effect of resveratrol, tyrosol and β-sitosterol on oxidised low-density lipoprotein-stimulated oxidative stress, arachidonic acid release and prostaglandin E 2 synthesis by RAW 264.7 macrophages. British Journal of Nutrition. 2008;99(6):1199-207.

93. Vinson JA, Teufel K, Wu N. Green and black teas inhibit atherosclerosis by lipid, antioxidant, and fibrinolytic mechanisms. Journal of agricultural and food chemistry. 2004;52(11):3661-5.

94. Murad S, RAZA H, BASHIR A. Atherosclerosis may be prevented by using psyllium husk. Pakistan Journal of Medical & Health Sciences. 2010;4(3):255-8.

95. Kalampogias A, Siasos G, Oikonomou E, Tsalamandris S, Mourouzis K, Tsigkou V, et al. Basic Mechanisms in Atherosclerosis: The Role of Calcium. Medicinal chemistry. 2016;12(2):103-13.

96. Páramo JA. A new favourable effect of cocoa on atherosclerosis? : Oxford University Press; 2008.

97. Weiner BH, Ockene IS, Levine PH, Cuenoud HF, Fisher M, Johnson BF, et al. Inhibition of atherosclerosis by cod-liver oil in a hyperlipidemic swine model. The New England journal of medicine. 1986;315(14):841-6.

98. Johnsen SH, Jacobsen BK, Braekkan SK, Hansen JB, Mathiesen EB. Fish consumption, fish oil supplements and risk of atherosclerosis in the Tromso study. Nutrition journal. 2018;17(1):56.

99. Suarez-Rivero JM, Pastor-Maldonado CJ, de la Mata M, Villanueva-Paz M, Povea-Cabello S, Alvarez-Cordoba M, et al. Atherosclerosis and Coenzyme Q10. International journal of molecular sciences. 2019;20(20).

100. Cui S, Li W, Lv X, Wang P, Gao Y, Huang G. Folic Acid Supplementation Delays Atherosclerotic Lesion Development by Modulating MCP1 and VEGF DNA Methylation Levels In Vivo and In Vitro. International journal of molecular sciences. 2017;18(5).

101. Thomas M, Kim S, Collins FW, Wise ML, Meydani M. In Vivo Suppression of Atherosclerosis by Dietary Oats Avenanthramides. The FASEB Journal. 2016;30(1_supplement):1175.1-.1.

102. Laitinen K, Gylling H. Dose-dependent LDL-cholesterol lowering effect by plant stanol ester consumption: clinical evidence. Lipids in health and disease. 2012;11:140.

103. Lynch SM, Gaziano JM, Frei B. Ascorbic acid and atherosclerotic cardiovascular disease. Sub-cellular biochemistry. 1996;25:331-67.

104. Weber C, Erl W, Weber K, Weber PC. Increased adhesiveness of isolated monocytes to endothelium is prevented by vitamin C intake in smokers. Circulation. 1996;93(8):1488-92.

105. Mirhosseini M, Baradaran A, Rafieian-Kopaei M. Anethum graveolens and hyperlipidemia: A randomized clinical trial. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences. 2014;19(8):758-61.

106. Rafieian-Kopaei M, Shahinfard N, Rouhi-Boroujeni H, Gharipour M, Darvishzadeh-Boroujeni P. Effects of Ferulago angulata Ex-

tract on Serum Lipids and Lipid Peroxidation. Evidence-based complementary and alternative medicine : eCAM. 2014;2014:680856.

107.Singh V, Rana M, Jain M, Singh N, Naqvi A, Malasoni R, et al. Curcuma oil attenuates accelerated atherosclerosis and macrophage foam-cell formation by modulating genes involved in plaque stability, lipid homeostasis and inflammation. The British journal of nutrition. 2015;113(1):100-13.

108.Yu CC, Chen CA, Fu SL, Lin HY, Lee MS, Chiou WY, et al. Andrographolide enhances the anti-metastatic effect of radiation in Ras-transformed cells via suppression of ERK-mediated MMP-2 activity. PloS one. 2018;13(10):e0205666.

109.Islam MT. Andrographolide, a New Hope in the Prevention and Treatment of Metabolic Syndrome. Frontiers in pharmacology. 2017;8:571.

110.Wang D, Wei X, Yan X, Jin T, Ling W. Protocatechuic acid, a metabolite of anthocyanins, inhibits monocyte adhesion and reduces atherosclerosis in apolipoprotein E-deficient mice. Journal of agricultural and food chemistry. 2010;58(24):12722-8.

111.Li W, Zhi W, Liu F, He Z, Wang X, Niu X. Atractylenolide I restores HO-1 expression and inhibits Ox-LDL-induced VSMCs proliferation, migration and inflammatory responses in vitro. Experimental cell research. 2017;353(1):26-34.

112.Yang TL, Lin FY, Chen YH, Chiu JJ, Shiao MS, Tsai CS, et al. Salvianolic acid B inhibits low-density lipoprotein oxidation and neointimal hyperplasia in endothelium-denuded hypercholesterolaemic rabbits. Journal of the science of food and agriculture. 2011;91(1):134-41.

113.Ran X, Zhao W, Li W, Shi J, Chen X. Cryptotanshinone inhi-

bits TNF-alpha-induced LOX-1 expression by suppressing reactive oxygen species (ROS) formation in endothelial cells. The Korean journal of physiology & pharmacology : official journal of the Korean Physiological Society and the Korean Society of Pharmacology. 2016;20(4):347-55.

114.Liu Z, Xu S, Huang X, Wang J, Gao S, Li H, et al. Cryptotanshinone, an orally bioactive herbal compound from Danshen, attenuates atherosclerosis in apolipoprotein E-deficient mice: role of lectin-like oxidized LDL receptor-1 (LOX-1). British journal of pharmacology. 2015;172(23):5661-75.

115.Ding Y, Zhang B, Zhou K, Chen M, Wang M, Jia Y, et al. Dietary ellagic acid improves oxidant-induced endothelial dysfunction and atherosclerosis: role of Nrf2 activation. International journal of cardiology. 2014;175(3):508-14.

116.Tang B, Chen GX, Liang MY, Yao JP, Wu ZK. Ellagic acid prevents monocrotaline-induced pulmonary artery hypertension via inhibiting NLRP3 inflammasome activation in rats. International journal of cardiology. 2015;180:134-41.

117.Zeb A, Akbar A. Ellagic Acid Suppresses the Oxidative Stress Induced by Dietary-Oxidized Tallow. Oxidative medicine and cellular longevity. 2018;2018:7408370.

118.Xu J, Zhu L, Liu H, Li M, Liu Y, Yang F, et al. Thymoquinone reduces cardiac damage caused by hypercholesterolemia in apolipoprotein E-deficient mice. Lipids in health and disease. 2018;17(1):173.

119. Gensini GF, Comeglio M, Colcila A. Hemostatic factors, atherogenesis and atherosclerosis. Biomedicine & Pharmacotherapy. 1996;8(50):395.