

Natural compounds as antiatherogenic agents

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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 for AS 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

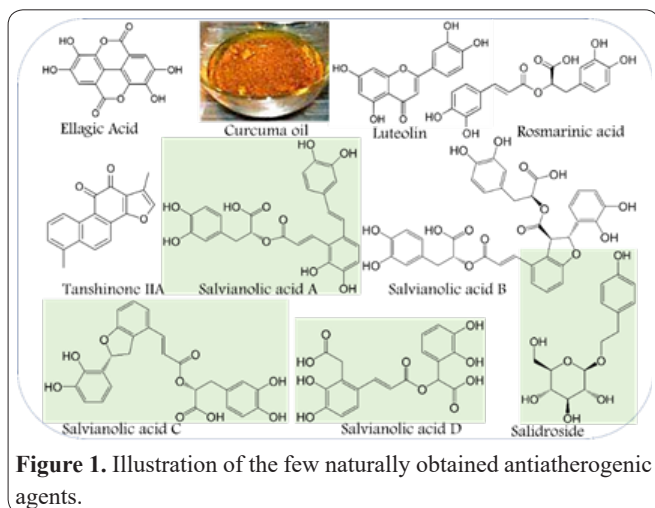
Atherosclerosis (AS) is a disease stemming from the endothelial cell inflammatory signalling of the vessel wall. An estimated 17.9 million deaths occur globally due to cardiovascular diseases (CVDs) owing to the complications associated with AS (1, 2). The hardening and narrowing of arteries due to the 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, includ-

ing 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 allacor (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 alternatives 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 dysfunction by weakening lectin-like oxidized



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 PPAR γ -LXR α -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 PPAR α , ABCA1, ABCG1, and LXR α 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 IKB α /NF- κ B signalling pathway (25, 26).

Ampelopsin/Dihydromyricetin

Dihydromyricetin (DHM) is a flavonoid-rich in *Ampelopsis grossedentata*. It enriches foam cell formation via LXR α -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), *Amomum xanthioides* 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, O₂[•] 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 rich in 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 CD36 was 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)

Anthocyanins are 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 and thus stops 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) is a 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 cholesterologenesis. 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, preincubation of HAEC's with AEM expressively reduced IL-1 β -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 atractylenolides 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 *Atractyloides 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 acid on 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-1 is 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).

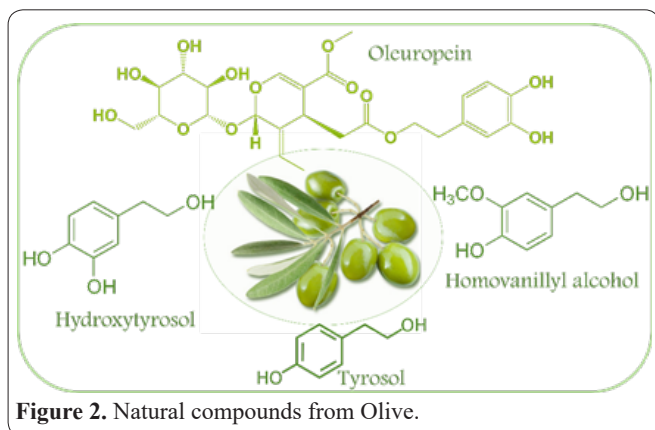


Figure 2. Natural compounds from Olive.

Spiromastixones

Spiromastixones are obtained from deep sea-derived fungus, *Spiromastix sp.* They have been shown to possess 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 PPAR γ -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 effective to inhibit macrophage foam cell formation by inhibiting NF- κ B activation, thereby protecting ApoE $^{-/-}$ mice from a high-fat diet (HFD)-induced AS (72).

Chlorogenic acid

Chlorogenic acid (CGA, 5-caffeoylquinic acid), a rich polyphenol in the human diet, present in tomato, peach, sweet potato, oilseeds, carrot, apple, prune, and coffee (73). It effectively decreases AS progress in ApoE $^{-/-}$ mice. The potential anti-atherosclerotic actions of CGA responsible for the protection against AS comprise a reduction of serum lipid, promotion of cholesterol efflux and suppression of vascular inflammation from macrophages (74). Upregulation of PPAR γ , LXR α , ABCA1, and ABCG1 transcription and PPAR γ 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 PPAR γ -LXR α -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 artery in a rabbit model of AS (78) (Fig.3). Polydatin is one 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-I κ B α /I κ B β dose-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

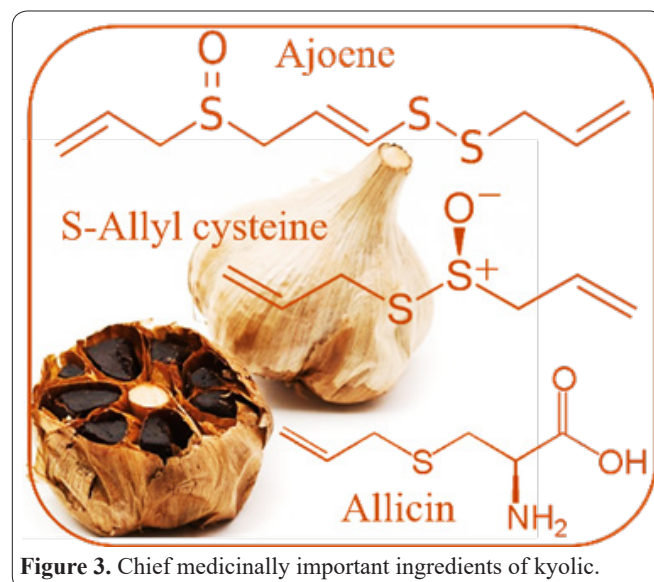


Figure 3. Chief medicinally important ingredients of kyolic.

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 scavenger 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 of upsetting 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-1 β , 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	<i>Curcuma longa</i>	CD36, PPAR α , ABCA1, ABCG1 and LXR α	(107)
2	Andrographolide	<i>Andrographis paniculate</i>	Transcription factor liver X receptor (LXR) depended on ABCA1 & ABCG1	(108, 109)
3	Luteolin	<i>Reseda luteola</i>	IKB α /NF- κ B signalling pathway	(24)
4	Ampelopsin/ Dihydromyricetin	<i>Ampelopsis grossedentata</i>	LXR α -ABCA1/ABCG1	(27)
5	Dansameum Extract (DSE)	A mixture of <i>Salvia miltiorrhiza</i> root, <i>Santalum album</i> lignum, and <i>Amomum xanthioides</i> fruit	CD36 and PARP- γ	(30)
6	Salidroside	<i>Rhodiola rosea</i>	MCP1, ICAM-1, VCAM-1, ABCA1 LOX1, MAPK and Akt pathways	(31)
7	Diosgenin	<i>Dioscorea wild yam</i>	ATP-binding cassette transporter A1 (ABCA1) protein	(34, 35)
8	(-)-Epigallocatechin-3-gallate (EGCG)	<i>Camellia Sinensis</i>	Lxr β , Abcg5, Abcg8, Abca1, Srebf1, Scd1, Scd2, Fas, Elovl5, Mylip; 67kD laminin receptor (67LR)	(43, 44)
9	Protocatechuic acid (PCA)	<i>Hibiscus sabdariffa</i>	miR-10b, ABCA1 and ABCG1	(110)
10	Avenanthramides	<i>Avena sativa</i>	Avenanthramides ICAM-1, VCAM-1	(52)
11	Atractylenolide	<i>Rhizoma atractylodes</i>	Monocyte chemoattractant protein-1 (MCP-1)	(111)
12	Toddalolactone	<i>Zanthoxylum nitidum</i>	Plasminogen activator inhibitor-1 (PAI-1)	(68)
13	Salvianolic acid B	<i>Salvia miltiorrhiza</i>	P-selectin, NF- κ B	(62, 112)
14	Cryptotanshinone	Danshen	LOX-1, MMP-9, ROS, NF- κ B, ICAM-1, VCAM-1	(113, 114)
15	Atractylodes lactone	<i>Atractylodes macrocephala</i>	ATP release, Ser473, phospho-p38 MAPK	(67)
16	1,6-Di-O-caffeoyl- β -D-glucopyranoside	<i>Callicarpa nudiflora</i> Hook	α IIb β 3 integrin, 5-HT, TXA2, RhoA, P2Y12, PI3K/Akt/GSK3 β ,	(69)
17	Protocatechualdehyde	<i>Salvia miltiorrhiza</i>	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 & PPAR γ -LXR α ABCA1 pathway	(115-117)
19	Thymoquinone	<i>Nigella sativa</i> seed or black seed or black cumin	LOX1, IL-1 β , 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.

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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.

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