Origanum majorana spp.

Origanum majorana is one of the most important plant resources of phenolic antioxidants. *Origanum vulgare* has high levels of dietary antioxidants and *O. majorana* has moderate levels of dietary antioxidants. The antioxidant effects of *O. majorana* essential oil are dose-dependent and a little lower than those of ascorbic acid or butylated hydroxytoluene. A study attributed this effect to high concentration of phenolic compounds such as carvacrol and thymol methyl ether in the *O. majorana* essential oil.[57] These compounds cause equilibrium between free radicals-producing systems and scavenging systems, leading to oxidative stress, and prevent development of foam cells in atherosclerotic vessels.

Morus nigra fruit

Morus nigra fruit is a rich source of anthocyanins. Anthocyanins are glycosylated derivatives of polyhydroxy and polymethoxy from cathinone 2 of phenyl benzopyrylium, i.e., cathinone flavylium. Aglycone is the main constituent of anthocyanins which is composed of binary bonds. Many studies have demonstrated antioxidant activities and health benefits of anthocyanins found in different fruits and vegetables. Decreasing angiogenic index and the levels of triglyceride and free fatty acids is another pharmacological property of anthocyanins. Because of exerting anticancer, antioxidant, anti-angiogenic, anti-atherosclerotic, and anti-inflammatory properties, anthocyanins help the body keep healthy, which is a remarkable issue.[58]

Linum usitatissimum

Linum usitatissimum contains phenolic compounds, protein, carotenoid, anthocyanin, flavonoid, estrogen, Vitamin E, Vitamin C, proline, and fiber. *L. usitatissimum* seed is an appropriate source of unsaturated fatty acids, mainly including omega-6 and omega-3, at 0.3/1 ratio, alpha-linolenic acid, lignans, dietary and protein fibers, minerals, and vitamins. Linolenic acid, found in fatty acids of *L. usitatissimum* essential oil, exerts useful effects in decreasing cholesterolemia, LDLT, atherosclerosis and associated heart disease, and atherosclerosis.[59]

Portulaca oleracea Linn

Study of *Portulaca oleracea* effect on hepatocyte oxidation system and nonenzymatic glycosylation of hemoglobin and red blood cells demonstrated that this plant has an acceptable antioxidant property. The antioxidant effects of *P. oleracea* can be due to the presence of omega fatty acids such as alpha-linolenic acid, flavonoids, coumarins, alkaloids, 3-monoterpenes, and betalain. Betalain exerts antioxidant and anti-atherosclerotic effects and prevents different diseases, including cardiovascular and liver diseases, through inhibiting free radicals.[60]

Silybum marianum Linn

Silybum marianum is a medicinal plant with hepatoprotective effects and has several compounds, such as flavonoids, with antioxidant, cell membrane-stabilizing, and blood glutathione-reducing properties, that have exerted optimal *in vitro* effects on several diseases including hypolipidemia, atherosclerosis, and vascular disease.[61]

Ziziphus jujuba

Ziziphus jujuba has antidiabetic effects. *Z. jujube* is likely to have antioxidant properties especially in two systems - hemolysis of red blood cells and nonenzymatic glycosylation. Besides that, red blood cells are exposed to large amounts of oxygen and are appropriate sites for development of free radicals under pathological conditions, which leads to destruction of free radicals. *Z. jujube* can be examined for prevention of this condition.[62]

Bunium persicum Boiss and Zataria multiflora

Bunium persicum and *Zataria multiflora* (at 0.6% and 0.1% concentrations, respectively) can be considered to have antioxidant activity equal to a synthetic antioxidant, butylated hydroxyanisole (BHA), at 0.2% concentration in soybean oil. The antioxidant activity of the studied essential oils was likely to be related to the monoterpene compounds present in them. This study can be an introduction to use of *B. persicum* and *Z. multiflora* in foods and for treatment and prevention of cardiovascular diseases and atherosclerosis.[63]

Camellia sinensis

Camellia sinensis seed essential oil has a potent antioxidant property which can help keep sunflower oil more efficiently at 5% concentration. This therapeutic effect of *C. sinensis*, with different concentrations of thymol and carvacrol in sunflower oil, can slow down oxidation and is useful to treat and prevent cardiovascular diseases and atherosclerosis.[64]

Hypericum perforatum Linn

Hypericum perforatum has certain flavonoids such as flavonol, flavones, bioflavonoids, and catechins, phenolic compounds, essential oils, acids, volatile oils, carotenoids, beta-sitosterols, and phytosterols. These compounds can exert efficient antioxidant effects and destroy free radicals. *H. perforatum* is used to treat cardiovascular diseases and atherosclerosis and helps decrease atherosclerotic lesions.[65]

Amaranthus caudatus Linn

Amaranthus caudatus contains high amounts of protein, beta-sterol, phytosterol, minerals, vitamins, and unsaturated fatty acids. Different types of *A. caudatus* have tocotrienol, tocopherol, and scovaline which contribute to cholesterol biosynthesis. Beta-carotene and ascorbic acid have antioxidant activity and cause destruction of free radicals. Flavonols and anthocyanins play a significant role in

regulating and decreasing different risk factors for cardiovascular diseases including decreasing platelets accumulation and increasing antioxidant activity and markers of inflammation. *A. caudatus* is used to treat allergy, liver diseases, and cardiovascular diseases.[66]

Kelussia odoratissima

Kelussia odoratissima is a herbaceous, edible plant with large amounts of polyphenols with antioxidant property. *K. odoratissima* can decrease oxidative stress and protect the body's metabolic tissues such as liver against chemical damage. Oral use of *K. odoratissima* can decrease total cholesterol, cholesterol, LDL, and triglyceride.

Given the oxidative stress-causing role of polysaccharides, flavonoids, glycoproteins, polypeptides, steroids, alkaloids, and pectin, found in medicinal plants, the potential hypoglycemic and hypolipidemic effects of some of the medicinal plants used to treat diabetes, such as aerial parts of *Albizia odoratissima*, can be partly explained in terms of preventing biochemical variations in the blood. Besides that, caffeic acid, present in *A. odoratissima*, has antioxidant properties because of having o-quinol.[67]

Camellia sinensis

There are growing evidence on the significant contribution of dyslipidemia, oxidative stress, and inflammatory factors in pathogenesis of diabetes and development of its complications. In patients with diabetes mellitus, different factors such as increased formation of oxygen-free radicals cause an increase in incidence of atherosclerosis and cardiovascular diseases through increasing glycemia and intensifying lipid peroxidation. In this regard, cardiovascular problems due to diseases, especially metabolic disorders such as diabetes mellitus, hyperlipidemia, and obesity, affect a high proportion of population especially older people.[68]

This imposes a heavy burden on health care system. The main compounds of 20% fraction of *C. sinensis* are caffeine, epicatechin gallate, quercetin, and kaempferol. Administration of *C. sinensis* has optimal effects on incidence and progression of diabetes complications.[69] In addition to exerting antioxidant and cardioprotective properties, this plant can inhibit angiotensin I-converting enzyme and hence decrease arterial blood pressure.[70]

Allium sativum Linn

Allium sativum causes inhibition of cyclooxygenase and lipoxygenase and prevents accumulation of thrombocytes.[71] In addition, large amounts of flavonoids, such as kaempferol with antioxidant, antidiabetic, and cardiac system- and bloodstream-protective properties, have been demonstrated to exist in this plant. Administration of total *A. sativum* extract causes decrease in the levels of lipid peroxidation markers, such as MDA and superoxide and hydroxyl radicals, tissue-protective enzymes with antioxidative property, arterial blood pressure, and atherosclerosis.[72]

Morus nigra

L-butanol of *M. nigra* leaf decreased arteries atherosclerotic plaques in hypercholesterolemic rabbits. L-butanol of *M. nigra* leaf decreased serum lipids concentration and atheromatous thickness of arteries intima in hypercholesterolemic rabbits.[73]

Olea europaea

Olea europaea powder has antioxidant property and prevents LDL oxidation. Previous studies found that *O. europaea* leaf contains a compound, referred to as oleuropein, that prevents LDL oxidation, and because LDL oxidation is the main stage of development of atherosclerotic plaques, oleuropein is considered an important agent to treat atherosclerosis.[74]

Punica granatum

Measuring antioxidant property of *Punica granatum* kernel essential oil demonstrated that its antioxidant property is approximately equal to that of a commercial antioxidant agent, BHA. The amount of phenolic compounds in *P. granatum* kernel essential oil was reported to be 0.015%. These potent antioxidant compounds are also useful to treat atherosclerosis and vascular diseases.[75]

Mentha piperita Linn

Mentha piperita extract contains large amounts of phenolic and flavonoid compounds and exhibits acceptable antioxidant activity.[76]

Rosmarinus officinalis

Rosmarinus officinalis has been demonstrated to have high antioxidant activity that is directly associated with phenolic content of this plant.[77]

Trigonella foenum-graecum Linn

Fat-free *Trigonella foenum-graecum* seed, alongside diet, total cholesterol, and triglyceride, decreases insulin-dependent diabetes and LDL considerably.[78]

Coriandrum sativum

Coriandrum sativum has hypocholesterolemic and antioxidant properties that can be due to phenolic and carotenoid compounds present in this plant. Anti-radical property of *C. sativum* has been reported to be 80%. Phenolic compounds serve as iron donators and are likely to neutralize unpleasant reactions induced by free radicals in the body. Antioxidants can, therefore, cause decrease in the risk of acquiring cardiovascular diseases, atherosclerosis, and MI.[79]

Trachyspermum copticum Linn

Diphenyl picryl hydrazyl is a stable and nitrogen-containing free radical that is widely used to test free radicals-scavenging. According to some studies, the antioxidant property of diphenyl picryl hydrazyl of *Trachyspermum copticum* was found to be greater than that of *C. sativum* and to cause decrease in the risk of acquiring cardiovascular diseases, atherosclerosis, and MI.[80]

Nigella sativa

Plant-based extracts, especially *Nigella sativa* seed extract, contains phytosterols consisting of beta-sitosterol, stigmasterol, and campesterol. *N. sativa* compounds cause changes in the levels of lipoproteins appropriate for markers of inflammation and plasma antioxidant properties. The presence of phytosterols in *N. sativa* causes decrease in development of atherosclerotic lesions. Moreover, *N. sativa* causes prevention of LDL oxidation.[81]

Studies demonstrated that thymoquinone and its metabolites, i.e., dihydrothymoquinone, prevent lipids nonenzymatic peroxidation in mice liver. This compound ameliorates free radicals-induced renal injuries in rats and mouse[82] and induces antioxidant and hence antitoxic effects through increasing oxidants-scavenging system.[83]

Vitis sylvestris

Vitis sylvestris is an acidic extract and ancient product which is used as seasoning and has many pharmaceutical uses. *V. sylvestris* contains certain flavonoids such as catechin and anthocyanins.[84] A study on *V. sylvestris* acute effects on some of the risk factors for atherosclerosis demonstrated that acute (daily) use of *V. sylvestris* caused decrease in glucose, fibrinogen, OxLDL, and MDA and ameliorated the severity of atherosclerotic plaque. This is probably due to the effect of flavonoids on inflammatory reactions and arachidonic acid metabolism, decreased production of free radicals and peroxidation of lipids, and increased HDL concentration.

V. sylvestris ameliorates the destructive effects of high-cholesterol diet through decreasing the levels of lipids profile risk factors and increasing antioxidant capacity.[85] Moreover, a study demonstrated antioxidative effects of flavonols and their glycosides such as quercetin, myrcene, and kaempferol on free radicals.[86] Moreover, polyphenols are adequately absorbed and therefore are potentially able to exert their biological effects such as antioxidant capacity-increasing.[87]

Glycyrrhiza glabra

Glycyrrhiza glabra root contains some flavonoids of types of flavone and chalcone for which pharmacological studies have reported antibacterial, antitumor, and antioxidant activities.[88] Glycyrrhizin is considered the sweet substance of *G. glabra* and if pure, it is seen as a crystalized and white powder. Glycyrrhizin concentration is 1%–6% in the dried root and exerts hypolipidemic effects. Glycyrrhizin and its nonsugar constituent, glycyrrhetic acid, are the main compounds of *G. glabra* and are used to treat hyperlipidemia.[89]

The presence of some compounds with potent antioxidant activity in *G. glabra* extract and its hypolipidemic property has caused this plant to be known as an effective agent to prevent progression of atherosclerosis, especially in people at high risk (with hypercholesterolemia). *G. glabra* extract caused a significant decrease in the lesions of vessels wall compared to the control group with hypercholesterolemia. The only lesions were foam cells developed in intima. *G. glabra* extract contains certain flavonoids such as hispaglabridin A, hispaglabridin B, and formononetin that affect the metabolism of arachidonic acid and cause decrease in production of free radicals.

They can also exert antiplatelet, anti-inflammatory, and antioxidant properties.[90] Isoprenyl, chalcone, formononetin, glabridin, and isoliquiritigenin are the antioxidant compounds isolated from *G. glabra* root. Among these compounds, glabridin has the highest concentration in the extract.[91] Through preventing activity of LDL NADPH oxidase, glabridin prevents cholesterol oxidation.[92]

Gundelia tournefortii Linn

Polyphenolic content and consequently antioxidant property of *G. tournefortii* seed is greater than other aerial parts. The effect of *G. tournefortii* is considerable in modulating lipids and apos as the most important risk factors for development and progression of atherosclerosis. Besides that, OxLDL is considered an important factor for atherosclerosis pathogenesis and one of the pioneering agents in development of atherosclerosis. *G. tournefortii* effect is, therefore, considerable in decreasing these factors.[93]

ApoB has been recently known to be a risk factor for cardiovascular disease and its amount represents the particles leading to atherogenic; therefore, decrease in apoB amount leads to decrease in the risk factors for cardiovascular disease.[94]

Glycine max M glycine is considered a protein-rich food in Asia and a cholesterol-free meat in the US traditional cuisine. Several studies have demonstrated that *S. marianum* decreases cholesterolemia by approximately 10%. The use of *S. marianum* decreases cholesterolemia and improves LDL/HDL ratio. Average daily consumption of 47 g *S. marianum* decreases cholesterolemia by

approximately 9%, LDL by approximately 13%, and triglyceride by approximately 10%. The effects of *S. marianum* were less marked on HDL. Evidence indicates that the isoflavones existing in *S. marianum* are the main factors effective in decreasing cholesterolemia.

In addition, the proteins found in *S. marianum* are likely to play a more important role than these flavones. In the USA, the Food and Drug Administration has permitted the producers of *S. marianum*-containing foods to label their products as heart healthy.[95]

The *O. europaea* leaves have been shown to possess hypotensive, hypolipidemic, vasodilator, as well as antioxidant activities.[96] The leaves are the most potent part of the *O. europaea* regarding polyphenolics and Oleuropein which have good effects on cardiovascular disease and atherosclerosis.[97]

Vitis vinifera seeds are used for skin disorders and vomiting. It has high level of polyphenolic compounds with antioxidant activity. Recent studies have revealed that *V. vinifera* seeds possess hypotensive, hypolipidemic, and endothelium protective properties.[98,99]

Theobroma cacao seeds are effective in cardiovascular disease and are potent vasodilator. Hence, they are used as hypotensive remedy. The effects have been attributed to polyphenolics, especially to epigallocatechin. Epigallocatechin causes expression of VCAM-1 and ICAM-1 in apoE gens.[100,101]

A combination of *Hordeum vulgare* and *Avena sativa* extracts have been shown to reduce hyperlipidemia and clotting factors. *H. vulgare* has substantial effect on hyperlipidemia, especially on LDL. It also increases the HDL, hence is a good remedy for hyperlipidemic patients.[102]

Table 1 enlists some of the medicinal plants, their active organs and compounds, and the potential action mechanism on atherosclerosis. As shown in Table 1, we can examine these plants, including those from the same families, for treating atherosclerosis.

DISCUSSION

Atherosclerosis is an important cause of mortality. The drugs that are considered to be effective to prevent and treat atherosclerosis are still being challenged. Moreover, many efforts are being made by pharmaceutical industries to develop more efficient drugs. The use of medicinal plants is still being welcome across the world.[1] The following factors have been demonstrated to contribute to development of atherosclerosis: coagulation system, inflammation, hyperlipidemia, and environmental factors. Besides that, the conducted studies on atherosclerosis have demonstrated the active effects of medicinal plants and plant-based compounds in decreasing and ameliorating atherosclerosis with remarkable therapeutic effects in decreasing glucose, fibrinogen, OxLDL, and MDA, decreasing 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.[103-110]

Studying and introducing these food ingredients and plant-based compounds with potential antioxidant properties can contribute to preventing 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.[111]

Coagulation system

Studies have confirmed an association of the constituents of coagulation system (fibrinogen and factor 7) and fibrinolytic factors including tissue plasminogen activator and tissue plasminogen inhibitor with atherosclerosis.[38]

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Throughout inflammation, macrophages produce some cytokines such as interleukin 1 and tumor necrosis factor which cause increase in leukocytes adhesion and platelet accumulation, and monocytic chemotactic proteins cause increase in leukocytes function inside atheromatous plaques. The free radicals produced from macrophages cause proliferation of smooth muscle cells through oxidizing LDL and hence atherosclerosis becomes symptomatic. This condition is the main complication due to heart attack and stroke. NADPH oxidase, NOS, myeloperoxidase, xanthine oxidase, lipoxygenase, cyclo-oxygenase, and the weakened antioxidant defense system contribute to development of atherosclerosis.[112]

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Coronary arteries involved in atherosclerosis are one of the risk factors for atherosclerosis. Smoking causes vascular atherosclerosis more often than other environmental factors.[113]

Hyperlipidemia

Hyperlipidemia is one of the risk factors for atherosclerosis, diabetes-induced complications, and especially cardiovascular disease. Diabetes is a long-term complication of hyperlipidemia that involves many of the body's organs and is responsible for diabetes-associated

Table 1: Important medicinal plants and their compounds with potential mechanism actions on atherosclerosis

Row	Scientific name	Family	Persian name	Active organ(s)	Active compound(s)	Potential action mechanism of atherosclerosis amelioration	References
1	*Quercus*	Fagaceae	Baloot	Bark, leaves	Gallic acid, malic acid, quercetin	Antioxidant	[38]
2	*M. sativa*	Papilionaceae	Yonjeh	Seeds and aerial parts	Beta-carotene, saponin, and Vitamins B and E	Hypocholesterolemic and LDL-reducing	[41]
3	*G. tournefortii*	Asteraceae	Kangar-farangi	Leaves	Terpenoid, alkaloid, coumarin, and Vitamin E	Hypocholesterolemic and LDL-reducing	[43]
4	*P. gnaphalodes*	Compositae	Alaf-hyzh	Leaves	Tannin, anthocyanin	Antiradical	[45]
5	*V. officinalis*	Valerianaceae	Sonbiletib	Root	Flavonoid	L-name-activating and vasodilatory	[46]
6	*B. vulgaris*	Berberidaceae	Zereshk	Fruit	Berberine	Lipid peroxidation-inhibiting and antioxidant enzymes-increasing	[47,48]
7	*S. indicum*	Pedaliaceae	Konjed	Fruit	Sesamolinol, sesamol	Inhibiting lipid, microsomal, and ADP-Fe+/NADH-induced peroxidation and LDL oxidation	[50,51]
8	*A. ampeloprasum*	Liliaceae	Sie-Vahshi	Leaves	Allicin, ajuin, diallyl disulfide	Producing prostaglandin I2, dilating vessels and aorta, antioxidant	[54]
9	*A. latifolium*	Liliaceae	Valak	Leaves	Cysteine sulfoxide	Inhibiting lipid peroxidation	[56]
10	*O. majorana* spp.	Lamiaceae	Marzanjoosh	Leaves	Thymol, carvacrol	Decreasing vascular foam cells, scavenging oxidative stress	[57]
11	*M. nigra*	Moraceae	Shahtoot	Fruit	Anthocyanins	Hypocholesterolemic, increasing antioxidant enzymes	[58]
12	*L. usitatissimum*	Umbelliferae	Katan	Flower	Vitamins C and E, sterol, proline, carotenoid, anthocyanins	Hypocholesterolemic and LDL-reducing	[59]
13	*P. oleracea*	Portulacaceae	Khorfeh	Leaves	Coumarin, alpha-linolenic acid, monoterpene, betalain	Free radicals-inhibiting and antioxidant	[60]
14	*S. marianum*	Asteraceae	Khar-Maryam	Seed	Flavonoid	Membrane-stabilizing and glutathione-increasing	[61]
15	*Z. jujuba*	Rhamnaceae	Annab	Fruit	Flavonoid	Antioxidant activity-increasing	[62]
16	*B. persicum* Boiss.	Umbelliferae	Zireh-Kohi	Fruit, leaves	Monoterpene	Antioxidant activity	[63]
17	*Z. multiflora*	Labiatae	Avishan-Shirazi	Leaves	Monoterpene	Antioxidant activity	[63]
18	*C. sinensis*	Theaceae	Chay	Leaves	Catechin, beta-sitosterol, phytosterol, carotenoid	Oxidation-reducing	[64]
19	*H. perforatum*	Hypericaceae	Golraei	Flower	Catechin, beta-sitosterol, phytosterol, carotenoid Tocopherol, ascorbic acid, beta-carotene, scovaline, flavonols, anthocyanins	Antioxidant activity, scavenging oxidative stress	[65]
20	*A. caudatus*	Amaranthaceae	Tajkhoroos	Leaves, flower	Tocopherol, ascorbic acid, beta-carotene, scovaline, flavonols, anthocyanins	Antioxidant activity, scavenging oxidative stress, platelet	[66]
21	*K. odoratissima*	Umbelliferae	Karafs-Koohi	Leaves	Caffeic acid	O-quinol-induced decrease in cholesterol and antioxidant activity	[67]

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Table 1: Contd...

Row	Scientific name	Family	Persian name	Active organ(s)	Active compound(s)	Potential action mechanism of atherosclerosis amelioration	References
22	*C. sinensis*	Theaceae	Chay-Siah	Leaves	Epicatechin, quercetin, kaempferol, caffeine	Reducing lipid peroxidation and oxidative stress, antioxidant	[69]
23	*A. sativum*	Liliaceae	Sir	Bulbs	Flavonoid, kaempferol	Reducing lipid peroxidation, superoxide and hydroxyl radicals and increasing antioxidative enzymes	[71,72]
24	*M. nigra*	Moraceae	Shahtoot	Leaves	L-butanolic	Reducing serum lipids concentrations and thickening atheromatous arterial intima	[73]
25	*O. europaea*	Oleaceae	Zeitoon	Seed, fruit	Oleuropein	LDL oxidation-reducing	[74]
26	*P. granatum*	Punicaceae	Anar	Kernel essential oil	Phenol	Antioxidant activity	[75]
27	*M. piperita* Linn.	Lamiaceae	Nana	Leaves	Phenol, flavonoid	High antioxidant activity	[76]
28	*R. officinalis*	Lamiaceae	Rozmari	Leaves	Phenol	High antioxidant activity	[77]
29	*T. foenum*-graecum	Leguminosae	Shanbalileh	Seed	Phenol, flavonoid	Total cholesterol, triglyceride, and LDL	[78]
30	*C. sativum*	Umbelliferae	Geshniz	Leaves, seeds	Phenol, carotenoid	Cholesterol-reducing and antioxidant activity	[79]
31	*T. copticum*	Umbelliferae	Zenian	Leaves	Diphenyl picryl hydrazyl	Free radicals-scavenging activity	[80]
32	*N. sativa*	Ranunculaceae	Siahdaneh	Seed	Phytosterols consisting of beta-sitosterol, stigmasterol, campesterol, thymoquinone	Free radicals-scavenging, cholesterol and LDL-reducing, and antioxidant activity	[81,82]
33	*V. silvestrii*	Vitaceae	Anggor	Fruit	Catechin, anthocyanins, quercetin, myrcene, kaempferol	Ameliorating lesions severity in aorta wall, increasing HDL concentration and antioxidant capacity, hypoglycemic, decreasing fibrinogen, OxLDL, and MDA	[86,87]
34	*G. glabra*	Papilionaceae	Shirinbayan	Root	Flavonoids, glycyrrhizin, and antioxidant compounds such as isoprenyl, chalcone isoliquiritigenin formononetin, glabridin	Reducing production of free radicals, inhibiting activity of LDL NADPH oxidase, and preventing cholesterol oxidation and hypolipidemia	[88,89]
35	*G. tournefortii*	Asteraceae	Kangar	Aerial organs and seed	Polyphenolic	Reducing cholesterol, triglyceride, LDL, oxide apolipoprotein B and factor 7, and increasing cholesterol HDL and apolipoprotein A	[93,94]
36	*G. max*	Papilionaceae	Soya	Seed	Protein isoflavones	Reducing LDL and triglyceride in the blood	[95]
37	*O. europaea*	Oleaceae	Zaitun	Leaves	Phenolicc and Oleoresin	Reducing LDL, having antioxidant activity	[96,97]
38	*V. vinifera*	Vitaceae	Angour	Seed	Polyphenols	Hypolipidemic activity. Especially reducing LDL	[98,99]
39	*T. cacao*	Sterculiaceae	Cacao	Seed	Epicatechin	Polyphenolics, especially epicatechin and epigallocatechin. epigallocatechin cause expression of VCAM-1 and ICAM-1 in apolipoproteins E gens	[100,101]

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Table 1: Contd...

Row	Scientific name	Family	Persian name	Active organ(s)	Active compound(s)	Potential action mechanism of atherosclerosis amelioration	References
40	*H. vulgare*	Poaceae	Joo	Seed	Hordens alkaloid	Reduces hyperlipidemia especially LDL and clotting factors. Increases HDL	[102]
41	*A. sativa*	Poaceae	Youlaf	Seed	Flavonoids, alkaloids, Vitamins B, D, E	Reduces hyperlipidemia and clotting factors	[102]

G. tournefortii = Gundelia tournefortii; *V. officinalis = Valeriana officinalis*; *M. sativa = Medicago sativa*; *P. gnaphalodes = Pulicaria gnaphalodes*; *B. vulgaris = Berberis vulgaris*; *S. indicum = Sesamum indicum*; *A. ampeloprasum = Allium ampeloprasum*; *A. Latifolium = Allium latifolium*; *O. majorana = Origanum majorana*; *M. nigra = Morus nigra*; *L. usitatissimum = Linum usitatissimum*; *P. oleracea = Portulaca oleracea*; *S. marianum = Silybum marianum*; *Z. jujube = Ziziphus jujube*; *B. persicum = Bunium persicum*; *Z. multiflora = Zataria multiflora*; *C. sinensis = Camellia sinensis*; *H. perforatum = Hypericum perforatum*; *A. caudatus = Amaranthus caudatus*; *K. odoratissima = Kelussia odoratissima*; *A. sativum = Allium sativum*; *O. europaea = Olea europaea*; *P. granatum = Punica granatum*; *M. piperita = Mentha piperita*; *R. officinalis = Rosmarinus officinalis*; *C. sativum = Coriandrum sativum*; *N. sativa = Nigella sativa*; *V. silvestrii = Vitis silvestrii*; *G. glabra = Glycyrrhiza glabra*; *G. max = Glycine max*; *V. vinifera = Vitis vinifera*; *T. cacao = Theobroma cacao*; *H. vulgare = Hordeum vulgare*; *A. sativa = Avena sativa*; LDL = Low-density lipoprotein; OxLDL = Oxidized LDL; MDA = Malondialdehyde; HDL = High-density lipoprotein; NADPH = Nicotinamide adenine dinucleotide phosphate; ICAM = Intercellular adhesion molecule; VCAM = Vascular cell adhesion molecule; *T. foenum-graecum = Trigonella foenum-graecum*; *T. copticum = Trachyspermum copticum*

morbidity and mortality and is effective in acquiring atherosclerosis.[114]

Studies on atherosclerosis have demonstrated that flavonoids and phenolic compounds present in plants exert several biological effects including antioxidant, free radicals-scavenging, anti-inflammatory, and anticancer. Free radicals-induced oxidization of flavonoids leads to development of less active and more stable radicals and exacerbation of the disease.[115]

According to Grenett *et al.* study, the polyphenols of catechin, quercetin, and ethanol exert supportive effects against vascular disease, which can be explained by increased fibrinolytic activity and expression of the proteins involved in fibrinolytic system.[116]

Prasad and Kalra study demonstrated the presence of MDA as the final product of peroxidation and the association of oxygen free radicals amount with the risk of atherosclerosis. MDA decreases with antioxidants-induced decrease in atherosclerosis. This is due to the presence of flavonoid compounds in these plants that cause peroxidation of lipids and reinforcement of antioxidant enzymes.[117]

Postprandial hyperlipidemia has been also known to be a risk factor for atherosclerosis. Flavonoid compounds existing in plants cause decrease in free radicals and support against tocopherol, isolation of LDL-α or production of OxLDL-α, isolation of metal ions involved in oxidation reactions, and decrease in the risk of acquiring atherosclerosis.[118]

Natella *et al.* study demonstrated that LDL oxidation decreases after consumption of procyanidins (grapes kernel) antioxidant in food, and causes decrease in atherosclerosis.[119]

Some plant-based essential oils and extracts can cause increase in the natural and OxLDL tendency to the respective receptors through their antioxidant properties. This can cause optimal effects in treating atherosclerosis and decreasing plasma cholesterol.[120]

Studies have shown an inverse association between consumption of polyphenols-rich foods and cardio-arterial diseases. This finding is due to polyphenols ability to inhibit LDL-C oxidation. Interacting directly with lipoproteins and exerting indirect effects through accumulating in arterial microphages, polyphenols inhibit LDL-C oxidation. This effect is exerted by *P. granatum* polyphenols, as well. These polyphenols increase the activity of serum paraoxonase, which leads to hydrolysis of lipid peroxides in oxidized lipoproteins and atherosclerotic plaques. Much evidence exists on anti-atherosclerotic activity of paraoxonase.[121]

Aviram *et al.* demonstrated the effects of *P. granatum* polyphenols in humans and mice with atherosclerosis and defective production of aposE. According to Aviram *et al.* study, feeding atherosclerotic mice with polyphenols-rich *P. granatum* juice caused a significant inhibition of atherosclerosis progression, which was attributed to the protective role of *P. granatum* polyphenols in LDL-C oxidation.[122]

Studies have demonstrated that internal anger was associated with carotid intima-media thickening and development of atherosclerotic plaques. The association of hostility and anger with CAD can be largely explained by releasing catecholamine and increasing cardiovascular reactivity.[123]

CONCLUSION

The active effects of medicinal plants and synthetic compounds can indicate that medicinal plants and their effects and uses have never been disregarded. The active ingredients of medicinal plants including flavonoids and other phenolic compounds with antioxidant

activity can scavenge free radicals and 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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AUTHORS' CONTRIBUTION

MS prepared the first draft; MRK, MB and SA completed it. MRK and SA edited the last version. All read and confirmed it.

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