REVIEW ARTICLE

A review of plant-based compounds and medicinal plants effective on atherosclerosis

Mehrnoosh Sedighi[1], Mahmoud Bahmani[1,2], Sedigheh Asgary[3], Fatemeh Beyranvand[1], Mahmoud Rafieian-Kopaei[4]

[1]Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, [2]Biotechnology and Medicinal Plants Research Center, Ilam University of Medical Sciences, Ilam, [3]Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, [4]Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

Atherosclerosis is one of the most important cardiovascular diseases that involve vessels through the development of fatty streaks and plaques. Plant-based compounds can help treat or prevent atherosclerosis through affecting the involved factors. The main purpose of this review article is to investigate and introduce medicinal plants and their potential activities regarding antioxidant properties, effective on lipids level and development of plaque, atherosclerosis, and progression of atherosclerosis as well as the development of cardiovascular disease and ischemia. To search for the relevant articles indexed in Information Sciences Institute, PubMed, Scientific Information Database, IranMedex, and Scopus between 1980 and 2013, with further emphasis on those indexed from 2004 to 2015, we used these search terms: atherosclerosis, antioxidant, cholesterol, inflammation, and the medicinal plants below. Then, the articles with inclusion criteria were used in the final analysis of the findings. Plant-based active compounds, including phenols, flavonoids, and antioxidants, can be effective on atherosclerosis predisposing factors and hence in preventing this disease and associated harmful complications, especially through reducing cholesterol, preventing increase in free radicals, and ultimately decreasing vascular plaque and vascular resistance. Hence, medicinal plants can contribute to treating atherosclerosis and preventing its progression through reducing cholesterolemia, free radicals, inflammation, vascular resistance, and certain enzymes. They, alone or in combination with hypocholesterolemic drugs, can therefore be useful for patients with hyperlipidemia and its complications.

Key words: Antioxidant, atherosclerosis, hypercholesterolemia

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INTRODUCTION

Atherosclerosis is the most prevalent and important cardiac disease which involves heart and brain. This disease progresses slowly and is the most important cause of mortality that begins from childhood and leads to clinical manifestations in adulthood.[1]

Epidemiological studies have demonstrated a marked association between certain factors and development of atherosclerosis. These factors are referred as coronary artery disease (CAD) risk factors and include hypercholesterolemia, oxidative stress associated with increased free radicals in the blood, smoking, hypertension, diabetes, age, male gender, hyperhomocysteinemia, inflammatory factors, family history, previous cardiac ischemia in the first degree relatives (in men under 55 years and in women under 65 years), atherogenic diet, increased lipoprotein A, and CAD[2] as well as physical inactivity, obesity, increased blood clotting, alcohol, and psychiatric factors (aggression, hostility, and anger).[3] A prospective study demonstrated that atherosclerotic plaque is more prevalent in thoracic aorta artery, carotid artery, and femoral artery compared to people without CAD. Accordingly, the obstruction rate of thoracic aorta artery, carotid artery, and femoral artery is considered a determinative factor in people with

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Address for correspondence: Dr. Mahmoud Rafieian-Kopaei, Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran. E-mail: rafieian@yahoo.com

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atherosclerosis (noncoronary arteries). In that study, the sensitivity and specificity of carotid atherosclerosis were reported 72% and 53%, respectively, for coronary artery obstruction.[4,5]

In the recent decades, in most countries, alternative therapies, particularly phytotherapy and dietary supplements, have been increasingly investigated for the treatment of diseases. In this article, medicinal plants and their potential activities are investigated and introduced regarding antioxidant properties, effects on lipids level and development of plaque, atherosclerosis, and progression of atherosclerosis as well as the development of cardiovascular disease and ischemia.

MATERIALS AND METHODS

To search for relevant articles indexed in Information Sciences Institute, PubMed, Scientific Information Database, IranMedex, and Scopus from 1980 to 2015, with further emphasis on those indexed between 2004 and 2015, these search terms were used: atherosclerosis, antioxidant, cholesterol, inflammation, and the following medicinal plants. After the retrieved articles had been examined, eligible and relevant articles were included in the analysis.

RESULTS

Pathogenesis of atherosclerosis

Pathogenesis of atherosclerosis starts with epicardial coronary arteries and damage to vascular endothelium. Endothelium is responsible for muscle tone and intravenous thrombosis and may be damaged by some conditions such as hypertension, hypercholesterolemia, and smoking. The symptoms of atherosclerosis increase with increase in low-density lipoprotein (LDL) reserves (LDL, high cholesterol) in the blood and its accumulation and reserve start in the inner lining of vessels. LDL accumulation causes stimulation and adhesion of monocytes to endothelium and finally facilitates their differentiation to macrophages. Then, the macrophages are activated to digest fats which lead alongside lipids phagocytosis, to the development of fatty streak in coronary lining.

Then, macrophages lead to increased oxidation of LDL and development of plaques. Development of plaques and proliferation of fibroblasts and smooth muscle cells are associated with the development of fibrinolytic lesion or fat-rich fibrous cap that cause a 90% decrease in vessels, stenosis and hence decrease in blood flow.[6,7] Evolution and progression of atherosclerosis are associated with the involvement of T-lymphocytes and development of acute coronary syndrome.[6] With increased accumulation of lipoproteins in macrophages and addition of necrosis process, lipid core forms a connective tissue, composed of collagen fibers, elastic fibers, proteoglycans, and fibrous capsule, around plaques.[8] A sensitive plaque with a nucleus full of lipid and fibrous cap causes pressure to and rupture of the vessel and plaque, collagen and lipid enter bloodstream thrombogenically and develop venous thrombosis. Calcification of the vessels wall due to atherosclerosis has been consistently considered a risk factor for rupture of atheromatous plaques.[9,10] The severity of plaque rupture and the extent of thrombosis are clinically associated with a wide spectrum of acute coronary syndromes consisting of unstable angina, non-Q-wave myocardial infarction (MI), and Q-wave MI. The risk factors for this disease may be inherited, nutritional, metabolic, hemodynamic, inflammatory, and infectious. Besides that, other potential risk factors are under investigation.[11]

In the recent studies, the role of new factors such as apolipoprotein B (apoB), nitrate, nitrite, fibrinogen, and factor 7, alongside conventional factors, has been addressed in the development of atherosclerosis.[12]

Güldiken *et al*.'s study demonstrated that increase in apoB and certain lipoproteins such as LDL, very LDL, and lipoprotein A plays a significant role in stimulating inflammatory cycle.[13] Increased oxidative stress leads to increased production of reactive oxygen species (ROS) and hence inflammation and atherosclerosis. Oxidized LDL (OxLDL) causes absorption of monocytes and T-cells, change in macrophages, and migration to endothelial inner lining. OxLDL is then absorbed by collecting receptors and results in the development of foam cells and fatty streaks and hence arterial stiffness.[14]

ApoA serves as an antiatherogenic component through increasing antioxidant activity, prevents oxidation, and exerts anti-inflammatory activity, which inhibits variations in LDL and prevents function of lipoxygenase. A study indicated that apoA causes decrease in vascular lipids and macrophages and prevents atherosclerosis.[15]

Fibrinogen is a circulating glycoprotein that acts in the steps of coagulation response to tissue and vascular injury. The amount of plasma fibrinogen is associated with the risk of acquiring CAD.[15] In addition to playing thrombotic role, fibrinogen causes proliferation, vasoconstriction in the damaged sites of vessels wall, stimulation of platelets accumulation, and regulation of cell adhesion.[16]

Factor 7 is a coagulation protein that contributes greatly to thrombosis. Studies have demonstrated that factor 7 is associated with inflammatory parameters such as interleukin 6 and C-reactive protein in patients with hypercholesterolemia which represents a pathophysiological association between them in patients with atherosclerosis. Moreover, the components of

coagulation system (fibrinogen and factor 7) and fibrinolytic factors (t-PA and PAI-1) have been reported to be associated with atherosclerosis.[17]

Because of the expression of endothelial nitric oxide synthase (eNOS) in vessels wall, the amount of eNOS decreases in advanced atherosclerosis, which may be explained by decreased translation or increased instability of eNOS mRNA. Endothelium-dependent dilation occurs in atherosclerotic vessels even before changes occur in vessels structure, and represents decreased eNOS. The eNOS has been demonstrated to become disturbed under certain pathological conditions such as severe hypercholesterolemia, and peroxynitrite is produced instead of nitric oxide.[18]

The use of high-fat foods can affect other risk factors such as homeostasis, markers of inflammation, and endothelial functions. A study demonstrated that following consumption of high-fat food, the plasma concentrations of inflammatory cytokines, and adhesion molecules increased.[19] Endothelial function is disturbed, and atherosclerosis and inflammation progress further.[20]

Atherosclerosis, acute coronary syndromes, and brain ischemia or ischemia can be prevented by inhibiting coagulation and inflammatory activities and plaques.

Etiology

According to some studies, increased antioxidant compounds, decreased blood pressure, decreased cholesterol, and CAD can cause decrease in arterial stiffness and also decrease in the development of atherosclerotic plaques in laboratory animals.[21,22] For example, a study demonstrated that inhibited oxidative stress and decreased lipid peroxidation due to consumption of cranberry was an important cause of decrease in the risk of acquiring atherosclerosis.[23]

Inhibition of oxidative stress and decrease in lipid peroxidation due to use of *Anethum graveolens* extract were important causes of decreased incidence and treatment of atherosclerosis. Moreover, the antiglycemic property of *A. graveolens* was demonstrated in this study. Since glycemia is associated with elevated oxidative stress, the antiglycemic property of *A. graveolens* can represent the supportive effect of this plant.[24]

Diagnosis

The diagnosis of atherosclerosis is made by measuring total cholesterol, LDL, high-density lipoprotein (HDL), triglyceride, blood pressure, and body mass index (BMI), history of smoking, MI, severity of angina, and measuring stenosis by coronary angiography.[25]

Treatment

In the light of the growing prevalence of cardiovascular diseases and reduction in age at development of these diseases, it is necessary to find the drugs and medicinal plants that are routinely used in diet, are capable of controlling and preventing the development of atherosclerotic plaques, and can decrease risk factors for cardiovascular diseases. Regarding cardiovascular diseases, there are many medicinal plants that have a high potential to exert antioxidant effect, and these antioxidant agents play a significant role in fighting free radicals.[26]

The positive effect of vegetarian diet has been shown in slowing down the growth of coronary atherosclerotic lesions and preventing and recovering them as well as the clinically useful effects of this diet in reducing angina, total cholesterol, LDL, and BMI in the patients. The main purpose of this study was to study and introduce these food ingredients and plant-based compounds, with potential antioxidant properties, that are able to prevent formation of free radicals and to reduce lipids level, plaques, atherosclerosis, cardiovascular diseases, and ischemia.

Effective factors on atherosclerosis

A wide variety of factors are effective on atherosclerosis, the most important of them are food fibers, exercise, vitamins, acids, and herbal remedies.

Food fibers are complex carbohydrate, plant-based polymers that are composed of simple sugars and generally classified according to their water solubility. Soluble fibers are composed of gel-forming materials, including pectin, gum, and mucilage, that are easily decomposed by bacteria in the colon. Insoluble fibers include structural fibers or certain networks such as lignin, cellulose, and hemicellulose which are excreted without change. Several *in vitro* and clinical studies have found the effect of food fibers in decreasing cholesterolemia and in treating cardiovascular disease and atherosclerosis.[27,28]

Exercise

Moderate and cumulative exercise can reduce the atherosclerotic lesions caused by atherogenic diet in thoracic aorta which is associated with decreased plasma and aortic concentrations of F2a, homocysteine, and 8-iso prostaglandin in the animals fed with standard diet. Exercise can exert reinforcing and antioxidant defense activities and has biological activity of nitric oxide.

The restricted effect of exercise on plasma and aortic concentrations of F2a, homocysteine, and F2a 8-isoprostaglandin in the animals on an atherogenic diet, which was associated with nonsignificant decrease in them, can be partly due to variations in the animals' ability to

adapt to cumulative oxidative stress induced by exercise and cholesterol. Total F2a can be considered a more reliable indicator of oxidative stress and lipids oxidation than malondialdehyde (MDA).[29]

Iron, ferritin

The association between plasma ferritin level and CAD is under investigation. Iron overload in cardiac muscle cells starts the first cardiac damage due to iron. Production of hydroxyl radicals is another adverse effect of iron which causes cardiac cells damage. This adverse effect is intensified considerably in case of iron overload. These changes lead to different clinical manifestations such as restrictive cardiomyopathy, pericarditis, and sometimes thoracic angina in the presence of normal coronary arteries. Besides that, conduction disorders and different arrhythmias are seen in these patients. Iron reserves are practically associated with atherosclerosis.[30]

Homocysteine

Homocysteine is a sulfur-containing amino acid which is produced by intracellular demethylation of methionine. Homocysteine has been addressed as an independent and adjustable risk factor for atherosclerosis. Homocysteine, as one of the glutathione precursors, may be released into the blood to fight exercise-induced oxidative stress and hence serve as a useful antioxidant in vascular diseases and atherosclerosis.[31]

Vitamin C (ascorbic acid)

Vitamin C or ascorbic acid is a water-soluble antioxidant which causes other antioxidants, such as Vitamin E and urate, to enter cycle again in addition to scavenging ROS free radicals. It is therefore likely that the use of these two antioxidants prevent the complications of vascular disease and atherosclerosis.[32]

Vitamin E (tocopherol)

A study on seminiferous tubules demonstrated that because of being fat-soluble, Vitamin E or alpha-tocopherol can prevent destructive effects of ROS on sperm parameters.[33] Because tocopherol molecule, as a volatile antioxidant of the chain, can inhibit two lipid peroxyl radicals and hence two potential reactions of peroxidation chain.[34] It can prevent the complications of cardiovascular disease and atherosclerosis.

Acids

Reducing acids can have anti-food effects through binding to the minerals in foods, such as iron and zinc, and preventing gastrointestinal absorption of these minerals. These acids include oxalic acid found in cocoa, spinach, turnip, and rhubarb; phytic acid in barley, grains, corn, and vegetables; and tannins in tea, bean, and cabbage.[35]

In the light of many benefits of the foods containing these acids, as rich sources of antioxidants, it is necessary to use them to treat and prevent cardiovascular disease. However, these acids should be used alongside meat and zinc- and iron-containing diets less often. Calcium deficiency and iron deficiency in diet is due to using meat and high absorption of phytic acid which is because of using grains.

Uric acid

Uric acid can be considered a supportive agent against oxidative stress. Serum uric acid exerts antioxidant properties and serves to scavenge and trap free radicals in human serum. Uric acid is involved with peroxynitrite to develop stable nitric oxide and hence vascular dilation increases and peroxynitrite-induced oxidative stress decreases.[36]

Bacteria

Certain bacteria such as *Helicobacter pylori* and *Chlamydia pneumonia* and certain viruses such as cytomegalovirus and herpes virus contribute to the development of atherosclerosis and atherosclerosis through involvement in the cell membrane, oxidation of the host cell membrane, production of oxygen free radicals and damage to the cell membrane, and occasionally induction of apoptosis and increase in oxidation of lipids and cholesterol in the atherosclerotic plaque.[37]

Medicinal plants

Quercus

The antioxidant activity and cardiovascular effects of *Quercus robur* have been revealed previously. The plants like *Q. robur* which have high antioxidant activity prevent LDL oxidation, hence preventing atherosclerosis.[38]

Tannins (50%–70%), and in less amounts, gallic acid and ellagic acid are the main constituents of *Quercus infectoria*.[39] This plant is used for its Mann which is a sweat substance which is released from its leaves. D-mannose is one of these which is used against bladder infections.[40]

Medicago sativa Linn

Medicago sativa contains flavonoids, various amino acids such as proline, hydrocarbons such as sucrose and fructose, polyols such as mannitol, ions such as sodium, potassium, and calcium, and organic acids such as malate and citrate.[41] Studies have indicated that *M. sativa* seeds have hypocholesterolemic effects and can prevent associated diseases.[42]

Gundelia tournefortii

Gundelia tournefortii has anti-atherosclerotic effects because of having antioxidant properties, decreasing cholesterol through inhibiting its synthesis, and inhibiting cholesterol

oxidation. Through modulation of LDL, lipids, and apos, which is the main property of *G. tournefortii*, this plant can fight risk factors for development and progression of atherosclerosis. This is directly associated with the presence of coumarins, alkaloids, flavonoids, and terpenoids, repeatedly reported by previous studies. For example, a study found that the protective and antioxidant properties of *G. tournefortii* are due mainly to Vitamin E and alpha-tocopherol.[43]

Through its antioxidant effects, *G. tournefortii* can inhibit oxidation. It is an appropriate plant to modulate and improve diet. The compounds found in *G. tournefortii* leaf, such as cinarin and luteolin, may contribute to decreasing synthesis and levels of cholesterolemia.[44]

Pulicaria gnaphalodes

Pulicaria gnaphalodes can play a significant role in keeping foods and maintaining humans' health because of containing phenolic compounds and exerting antioxidant and antiradical compounds. *P. gnaphalodes* leaf has such properties and contains many types of flavonoid compounds, tannins, and anthocyanins. These compounds exert antioxidant properties against risk factors for development and progression of atherosclerosis.[45]

Valeriana officinalis

Hydroalcoholic *Valeriana officinalis* root extract mitigates physiological responses to anxiety such as blood pressure and pulse rate. Vascular endothelium is the biggest organ of the body's endocrine system and plays an active role in controlling vascular tone. Nitric oxide is the main cause of endothelium-dependent vascular dilation of L-arginine pathway. Given the significance of disturbed levels of nitric oxide during atherosclerosis, the most prevalent cardiovascular disease, L-NAME which is the inhibitor of this pathway was used.

This extract has been reported to exert relaxant effects in the presence of L-NAME, which are not exerted through endothelial cells but are exerted directly on smooth muscles of the vessels wall. They can, therefore, serve to treat the diseases causing endothelial dysfunction such as atherosclerosis, hypercholesterolemia, diabetes, and hypertension. Accordingly, hypotension, following administration of these extracts, is due to decreased resistance of peripheral arteries. In other words, this extract's effect is exerted through relaxing smooth muscle cells of vessels wall.[46]

Eremurus persicus

Berberine, present in *Eremurus persicus*, can reduce lipogenesis and exert inhibitory effects on lipid and oxidation. *E. persicus* can be used as a supplementary antioxidant to prevent or treat certain diseases such as diabetes, liver diseases, and atherosclerosis.[47] A study demonstrated that the activity of antioxidant enzymes such as catalase and superoxide dismutase was higher in the livers of the rats on an *E. persicus*-containing diet than the control group, representative of the inhibitory effect of *E. persicus* on lipids peroxidation through increasing antioxidant enzymes. *E. persicus* causes regulation of sugar hemostasis through decreasing production of sugar, oxidative stress, and vascular diseases.[48]

Sesamum indicum Linn

The compounds of *Sesamum indicum* decrease development of atherosclerotic lesions, the levels of plasma triglyceride and cholesterol, and LDL-cholesterol (LDL-C).[49] Antioxidant and anti-inflammatory properties of *S. indicum* and the positive effect of this medicinal plant on lipoprotein can potentially contribute to the process of development of atherosclerotic plaques.[50] Lignan, sesamolinol, and sesamol found in *S. indicum* essential oil, exert inhibitory effects on membrane lipid peroxidation, microsomal peroxidation, ADP-$Fe3^{+}$/NADH-induced peroxidation, and Cu ions-induced LDL oxidation.[51] Sesamolinol and sesamin are the most abundantly found lignans in *S. indicum* with antioxidant effects. Sesamin with antioxidant effect, present in *S. indicum* lignan, is hydrophilic and exerts a highly potent antioxidant effect.[52]

Allium ampeloprasum

Allium ampeloprasum increases some enzymes such as superoxide dismutase, catalase, peroxidase, and glutathione peroxidase. The plants from family Alliaceae can prevent development and progression of neurological and cardiovascular complications of diabetes because of containing a potent inhibitor of aldose reductase, i.e., isoliquiritigenin. This compound can produce prostaglandin I2 which exerts dilatory effects on the vessels and aorta in diabetes conditions.[53]

A. ampeloprasum has considerable antioxidant effects because of containing several flavonoids with antioxidant and protective properties including sulfur-containing compounds such as diallyl disulfide, ajuin, and allicin. The antioxidant properties of *A. ampeloprasum* have been reported to be even greater than other plants from the family Alliaceae.[54]

Allium latifolium

Cysteine sulfoxides and sulfoxide acids of *Allium latifolium* have antidiabetic and antioxidant effects.[55] Antioxidant agents with lipid peroxidation-reducing property are abundantly found in *A. latifolium*. As well, the flavonoids of this plant cause decrease in oxidative stress and prevent hypertension and atherosclerosis.[56]

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]

Inflammation

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]

Environmental factors

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]

Contd...

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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Conflicts of interest

There are no conflicts of interest.

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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