Atherosclerosis: Process, Indicators, Risk Factors and New Hopes

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ABSTRACT

Background: Atherosclerosis is the major cause of morbidities and mortalities worldwide. In this study we aimed to review the mechanism of atherosclerosis and its risk factors, focusing on new findings in atherosclerosis markers and its risk factors. Furthermore, the role of antioxidants and medicinal herbs in atherosclerosis and endothelial damage has been discussed and a list of important medicinal plants effective in the treatment and prevention of hyperlipidemia and atherosclerosis is presented.

Methods: The recently published papers about atherosclerosis pathogenesis and herbal medicines effective in the treatment and prevention of hyperlipidemia and atherosclerosis were searched.

Results: Inflammation has a crucial role in pathogenesis of atherosclerosis. The disease is accompanied by excessive fibrosis of the intima, fatty plaques formation, proliferation of smooth muscle cells, and migration of a group of cells such as monocytes, T cells, and platelets which are formed in response to inflammation. The oxidation of low density lipoprotein (LDL) to Ox-LDL indicates the first step of atherosclerosis in cardiovascular diseases. Malondialdehyde factor shows the level of lipoperoxidation and is a sign of increased oxidative pressure and cardiovascular diseases. In special pathological conditions such as severe hypercholesterolemia, peroxynitrite concentration increases and atherosclerosis and vascular damage are intensified. Medicinal plants have shown to be capable of interacting these or other pathogenesis factors to prevent atherosclerosis.

Conclusions: The pathogenesis factors involved in atherosclerosis have recently been cleared and the discovery of these factors has brought about new hopes for better prevention and treatment of atherosclerosis.

Keywords: Atherosclerosis, inflammation, lipids

Review Article

INTRODUCTION

Atherosclerosis is the result of hyperlipidemia and lipid oxidation and has always been a major cause of mortality in developed countries. It is a disease of vascular intima, in which all the vascular system from aorta to coronary arteries

can be involved and is characterized by intimal plaques.[1,2]

The term atherosclerosis is of Greek origin, meaning thickening of the intimal layer of arteries and accumulation of fat. Fatty material is located in the central core of the plaque, covered by fibrous cap. The term, atherosclerosis consists of two parts; atherosis (accumulation of fat accompanied by several macrophages) and sclerosis (fibrosis layer comprising smooth muscle cells [SMC], leukocyte, and connective tissue).[3,4]

Currently, atherosclerosis is a common disease in which fatty deposits called atheromatous plaques appear in the inner layers of arteries. Formation of these plaques starts with the deposition of small cholesterol crystals in the intima and its underlying smooth muscle. Then the plaques grow with the proliferation of fibrous tissues and the surrounding smooth muscle and bulge inside the arteries and consequently reduce the blood flow. Connective tissue production by fibroblasts and deposition of calcium in the lesion cause sclerosis or hardening of the arteries. Finally, the uneven surface of the arteries results in clot formation and thrombosis, which leads to the sudden obstruction of blood flow.[5]

Hyperlipidemia and hyperglycemia are related to increased oxidative damage, which affects antioxidant status and lipoprotein levels.[6-8] Studies have shown that lipid lowering medicinal herbs can reduce the blood lipids especially after meals in addition to their antioxidant effects. Therefore, they can prevent atherosclerosis and vascular endothelium damage.[6]

There are a couple of valuable review papers addressing the pathogenesis of atherosclerosis.[7,8] In this study, we aimed to review the mechanism of atherosclerosis and its risk factors, focusing on new findings in atherosclerosis markers and its risk factors. Furthermore, the role of antioxidants and medicinal herbs in atherosclerosis and endothelial damage has been discussed and a list of important medicinal plants effective in the treatment and prevention of hyperlipidemia and atherosclerosis is presented.

METHODS

The recently published papers about atherosclerosis pathogenesis and herbal medicines effective in the treatment and prevention of hyperlipidemia and atherosclerosis were searched in databases such as Web of Science, Medline, PubMed, Scopus, Embase, Cinhal and the Cochrane from 2000 to 2013. The keywords searched included hyperlipidemia, Atherosclerosis, Pathogenesis of atherosclerosis, Atherosclerosis risk factors and biomarkers, Medicinal plants and atherosclerosis as well as herbal medicine and atherosclerosis.

RESULTS

The atherosclerosis process

- Fatty streaks formation
- Atheroma formation
- Atherosclerotic plaques formation.

Fatty streaks formation

Both animal and human studies show that the fatty streaks are the first sign of atherosclerosis. The initial lesions are usually caused by the focal increase in the lipoproteins of the intimal layer of the arteries.[5]

Lipoprotein particles are composed of proteins, phospholipids, and also lipids such as cholesterol and triglyceride. One of the most important atherogenic lipoproteins is the cholesterol-rich low density lipoprotein (LDL). This lipoprotein can be accumulated in the vascular intima due to its ability to infiltrate into the endothelium or to adhere to extracellular matrix components like proteoglycan.

At the site of lesions, the balance between the different components of the matrix may be disturbed. For instance, among the three main groups of proteoglycans, the relative increase in heparin sulfate molecules in comparison with keratan sulfate and chondroitin sulfate may cause the adhesion of lipoproteins, which slows down the process of exiting from the intima leading to their accelerated accumulation.[9]

In the initial steps of atheroma formation, plaques usually grow through the opposite direction of the vessel. Atherosclerotic vessels are willing to grow in diameter. When a plaque covers more than 40% of internal elastic layer of the vessel, the arterial channel is considered to be occupied. At the end of the plaque's lifetime, the restrictive obstruction of the blood flow happens. Studies show that atherosclerosis is a result of

intima damage with some cellular responses that involve monocytes, SMC, and lymphocytes. The initial soft lesion is composed of foam cells and extracellular fat deposits and a small number of platelets. During the progress of the process, SMC proliferate and in the final steps, intensify bleeding into the plaque[5-10] [Figure 1].

The formation of fatty streaks has four steps

- Low density lipoprotein-cholesterol (LDL-C) trapping
- Activation of endothelial cells
- Leukocytes activation
- Formation of foam cells.

Low density lipoprotein-cholesterol trapping

The first step in atherogenesis is trapping the lipoprotein in the lesion site. Although, LDL-C cannot pass through the firm endothelial junctions, it can rapidly enter the endothelial cells through endocytosis.

In normal conditions, there is equilibrium between the plasma LDL and intracellular LDL concentration of arterial walls. Along with an increase in plasma lipids many of these particles become trapped in the intima (because of the increased extracellular proteoglycans, which have a high LDL affinity).[5] Because of the direct correlation between serum LDL concentration and the amount of lipoprotein trapping in the lesion, its blood level can be considered as an indicator of atherogenesis.

Low density lipoprotein trapping results in the increased concentration of LDL in the intima as well as increased duration of their stay in the lesion. Both such factors lead to spontaneous oxidation and cell oxidation of the trapped particles.[5]

Activation of endothelial cells

Cytokines and oxidized lipids play important roles in the activation of endothelial cells. During the early steps of atherosclerosis, monocytes and T lymphocytes infiltrate into vascular intima.[11]

Meanwhile the produced adhesion and absorbing molecules are important because of various molecular types during LDL oxidation.[12] Monocyte-to-macrophage differentiation causes them to take oxidized lipids such as oxidized LDL (Ox-LDL) to form foam cells.[13] This process depends on the expression of receptors for cleaning the secretions of enzymes and different cytokines. Ox-LDL plays a role in the activation of T cells and works as an antigen for T cells; hence, secreting cytokines to activate the macrophages and alter the endothelial and SMC.[11]

Leukocytes activation

During the initial steps of atherosclerosis, mononuclear leukocytes, monocytes, and T cells enter the intact endothelium through vascular walls. This process needs the expression of leukocyte and chemokine adhesion molecules in which the transcription is performed by NF-αβ factor. This factor is a transcription factor and becomes

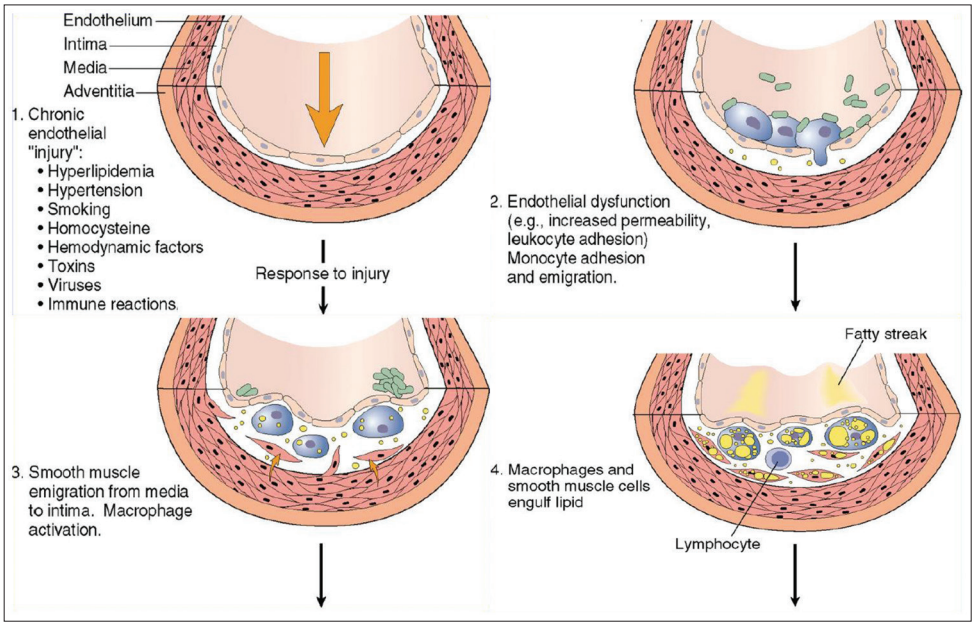

Figure 1: Sages of fatty streaks formation

activated when pro-inflammatory cytokines bind to their receptors on the endothelial surface.

Leukocyte adhesion molecules are involved in the primary stages of atherosclerosis. Endothelial cells are important sources for producing adhesion molecules on leukocytes.

Receptors of adhesion molecules express on the specific leukocytes, SMC, or vascular endothelial cells. It has been shown that adhesion molecules have an important role in production and release of attractant molecules and/or chemokines. Chemokines are proteins or attractant cytokines with a low molecular weight (8-10 kDa), which have a pivotal role in leukocytes activation and migration.[14]

Moreover, specific chemokines cause endothelial and SMC to migrate. Studies have demonstrated that in the first steps of atherosclerosis, inhibitory monocyte chemokine protein (MCP-1) is expressed considerably by macrophages and in a less amount by SMC and endothelium. This enhancement is resulted from the increased dietary cholesterol and causes monocytes to move toward the vascular walls and infiltrates them into the lesion. MCP-1 is expressed in all steps of atherosclerosis.[15]

It has currently been shown that Ox-LDL up regulates the adhesion molecules. It also expresses messenger ribonucleic acid (mRNA) MCP in the endothelial and SMC by means of lysophosphatidylcholine which is resulted from A2 phospholipase function on LDL.[16]

Foam cell formation

Mononuclear phagocytes differentiate to macrophage after insertion in the intima. Phagocytes may participate in preventing atherosclerosis by phagocytosis of lipids from the extracellular space. Some lipid accumulated macrophages may leave the arterial wall and take out the lipids from the artery. If the level of lipid entrance into the artery wall is more than its exiting (by phagocytes or other ways), it will lead to accumulation of lipids and consequently the tendency to form atheroma is increased.

Macrophages perform uptake and accumulation of Ox-LDL by their scavenger receptors, which will be converted to foam cells.[17] The expression of these receptors on the surface of macrophages, endothelial cells, fibroblasts, and SMC has been documented.[18]

Expression of these scavenger receptors increase during differentiation of monocytes to macrophages by cytokines and oxidized lipids. Their expression is also facilitated by macrophage colony-stimulating factor.[17]

The surface Ox-LDL ligand that causes its absorption to scavenger receptors of macrophages, are phospholipids in the structure of Ox-LDL, which will be oxidized in location two, and form aldehydes which are able to attack lysine residues of ApoB.[18,19] Accumulation of these yellow foam cells on the arterial walls lead to the formation of lipid streaks.[20]

Some foam cells in the developing intimal lesion die through apoptosis. This apoptosis makes a lipid rich necrosing nucleus in the center of more developed atherosclerotic plaque. Monocytes, other than producing foam cells, can produce cytotoxic substances such as tumor necrosis factor (TNF), growth factor, precoagulation substances (including tissue factors), and free radicals. These substances can cause more damage to endothelium as well as more LDL oxidation, leading to more metabolic changes.[20]

Atheroma formation

Severe damage to vascular tissue happens when adjacent SMC and endothelial cells secret small peptides such as cytokines and growth factors such as interleukin 1 (IL-1), and TNF (which causes cell growth). These factors cause SMC to migrate into the luminal side of vessel wall. In this condition, smooth muscle cell migration and synthesized extracellular matrix form the fibrous cap. Fibrous cap is composed of collagen-rich fiber tissues, SMC, macrophages and T lymphocytes. All of them form the mature atherosclerosis plaque and bulge into the channel and reduce the blood stream in the vessels.[17]

Macrophages and T lymphocytes are found in the borders of developed plaque. Macrophages secrete meta proteinase, which contribute to the lysis of extracellular matrix. T cells produce TNF-α which prevents the collagen synthesis in the SMC.

These processes weaken the formed plaque shaped fibrous cap and can destroy it. Destruction of fibrous cap exposes collagen and lipids to blood stream which contributes to accumulation and adhesion of platelets and blood clot formation which may suddenly block the blood stream[17-20] [Figure 2].

Atherosclerotic plaque formation

Atherosclerotic plaques constituents are as follows:

- Vascular epithelium: Vascular epithelium reacts with macromolecules and blood components to increase the protein transfer in plasma
- Arterial smooth muscle: The maintenance

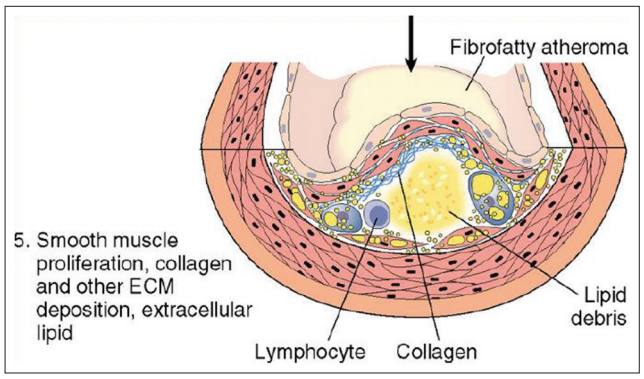

Figure 2: Atheroma formation

of vascular repair and metabolism of blood products including lipids, and the secretion of various cytokines, is essential in the control of vascular wall tonus

- Lymphocytes: They may participate in the immune reactions. The core of plaque is composed of cell lesions, foam cells, calcium, cholesterol esters, and a mass of fatty substances. Lipid nucleus is a pale yellow mass, which its color is caused by carotenoid pigments[2] [Figure 3].

Atherosclerosis risk factors and indicators

The exact causes and risk factors of atherosclerosis are unknown; however, certain conditions, traits, or habits may raise the chance of developing atherosclerosis [Table 1]. Most risk factors including high cholesterol and LDL, low level of high density lipoprotein (HDL) in the blood, hypertension, tobacco smoke, diabetes mellitus, obesity, inactive lifestyle, age can be controlled and atherosclerosis can be delayed or prevented.[7,8,19]

Cholesterol increase

Cholesterol is a hydrophilic lipid that is progenitor of steroid hormones such as corticosteroids, sex hormones, bile acids, and vitamin D. Cholesterol is a major component of cell membrane. It has two synthetic and dietary sources. Half of the body's cholesterol is provided by synthesis, mainly in the liver of mammals while all tissues containing nucleated cells are able to synthesize cholesterol.[20-22]

Cholesterol exists in everyone's diet. It can slowly be absorbed into intestine lymphatic vessels through gastrointestinal (GI) tract. The cholesterol which exists in GI tract is slightly fat soluble and can form esters after reaction with

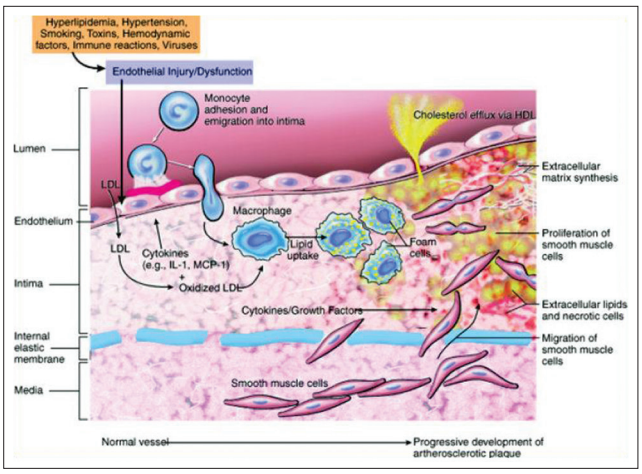

Figure 3: Atherosclerotic plaque formation

fatty acids. In fact 70% of plasma cholesterol is in the form of ester cholesterol. Cholesterol is only found in animals. Egg yolk and animal fat contain the maximum amount of cholesterol. Cholesterol is absorbed in intestine and enters the blood as chylomicrons through the mucosa of digestive system. Cholesterol is synthesized inside the cell and the excess amounts are inhibited by 3-hydroxy-3-methylglutaryl-CoA reductase. Esterification increases cholesterol synthesis and decrease LDL receptors synthesis. All these steps regulate the amount of intracellular cholesterol through feedback control.[23]

Extracted cholesterol from cells can be absorbed by HDL. Some types of HDL contain apoprotein E and bind to other cells along with LDL receptors. They transfer cholesterol from one cell to another. Chylomicrons in intestinal mucosa enter the blood stream through lymphatic vessels along with absorption of fat digested products. Chylomicrons decompose to free fatty acids and glycerol in capillaries by lipase protein function and undergo esterification after entering into fat cells. Chylomicrons contain apoprotein C and remain as chylomicron residue called rich lipoprotein after triglyceride depletion. These residues will be transferred to the liver, bind to their receptors and LDL and then enter cells rapidly. Very low density lipoprotein (VLDL) is also made in the liver and transfer triglycerides, which are formed from lipids and carbohydrates in liver, to extra-hepatic tissues. Subsequently, triglycerides separate from VLDL by lipoprotein lipase and will be converted to LDL. Binding HDL to specific superficial parts, which function as LDL receptors, is another mechanism

Table 1: The risk factors of atherosclerosis

Category	No.	Risk	Comments
Major	1	Unhealthy blood cholesterol and lipoproteins levels	Broadly, the ideal levels for cholesterol and various lipoproteins are as follows Total cholesterol ≤5mmol/L Cholesterol: HDL ratio ≤4 LDL cholesterol ≤3mmol/L HDL cholesterol ≥1mmol/L
	2	High blood pressure	Blood pressure is considered high if it stays at or above 140/90 mmHg over time. If you have diabetes or chronic kidney disease, high blood pressure is defined as 130/80 mmHg or higher
	3	Smoking	Smoking doesn't allow enough oxygen to reach the body's tissues. Smoking can also damage and tighten blood vessels, raise cholesterol levels, and raise blood pressure
	4	Insulin resistance	This condition occurs if the body can't use its insulin properly. Insulin resistance may lead to diabetes
	5	Diabetes	The body doesn't make enough insulin or doesn't use its insulin properly, hence the blood sugar is high
	6	Overweight or obesity	The terms "overweight" and "obesity" refer to body weight that's greater than what is considered healthy for a certain height
	7	Lack of physical activity	A lack of physical activity can worsen other risk factors for atherosclerosis, such as unhealthy blood cholesterol levels, high blood pressure, diabetes and overweight and obesity
	8	Unhealthy diet	Foods that are high in saturated and trans fats, cholesterol, sodium and sugar can worsen other atherosclerosis risk factors
	9	Older age	Genetic or lifestyle factors cause plaque to build up in the arteries as with age. In men, the risk increases after age 45 and in women, the risk increases after age 55
	10	Family history of early heart disease	Your risk for atherosclerosis increases if your father or a brother was diagnosed with heart disease before 55 years of age, or if your mother or a sister was diagnosed with heart disease before 65 years of age
	11	Inflammation	Inflammation is the body's response to injury or infection. Damage to the arteries inner walls seems to trigger inflammation and help plaque grow
Emerging risk factors*	12	High levels of CRP	High levels of CRP are a sign of inflammation in the body and high level of CRP may develop atherosclerosis at a higher rate. Research is under way to find out whether reducing inflammation and lowering CRP levels also can reduce the risk for atherosclerosis
	13	Triglycerides	High levels of triglycerides in the blood also may raise the risk for atherosclerosis, especially in women
	14	Sleep apnea	Untreated sleep apnea can raise the risk for high blood diabetes, pressure and even a heart attack or stroke
	15	Stress	The most commonly reported "trigger" for a heart attack is an emotionally upsetting event, especially the one involving anger
	16	Alcohol	Heavy drinking can damage the heart muscle and worsen other risk factors for atherosclerosis

*Several other possible risk factors have been Scientists continue to study other for atherosclerosis. CRP=C-reactive protein, HDL=High density lipoprotein, LDL=Low density lipoprotein

that causes cholesterol to exit by HDL. This binding transfers the intracellular cholesterol to plasma membrane. Cholesterol turns into LDL after esterification.[24]

Familial hypercholesterolemia is a heritable disease in which defected genes for LDL receptors formation on the surface of cells are inherited. Liver is not able to absorb LDL in the absence

of these receptors. Without the natural return of cholesterol to the hepatic cells, cholesterol production of hepatic cells is activated and the new cholesterol is formed and the feedback inhibition of high cholesterol levels is no longer responding. Consequently, the liver transfer of VLDL to the plasma will be highly increased.[25]

Hypercholesterolemia increases superoxide free radicals production in the vessels and decreases synthesis and release of endothelium derived vasodilators. It also increases nitric oxide (NO) deactivation after its release from endothelial cells.[3,17]

Apolipoproteins and lipoproteins

High concentrations of some plasma lipoproteins are related to atherogenesis. Atheromagen lipoproteins include VLDL, LDL, and intermediate-density lipoproteins. Cholesterol esters are found in atheroma cells and in the extracellular matrix. They can induce fibroblasts to produce collagen.

Cholesterol levels show total cholesterol including ester cholesterol and unesterified cholesterol. Triglyceride and cholesterol levels give some information about serum lipoproteins. Elevated plasma cholesterol level shows that concentration of chylomicron or VLDL and also LDL have increased. Increased plasma VLDL concentration and decreased HDL cholesterol are seen in people with small but high density LDL particles. Four cell types including endothelial cells, SMC, macrophages, and lymphocytes are able to oxidize LDL. Since unsaturated fatty acids which are located on side-chains of ester cholesterol and LDL's phospholipids are main substrates for LDL lipid oxidation, their amount indicates the LDL oxidation capability.[26]

There are six main categories and various sub-categories for apolipoproteins. Apolipoproteins B or ApoB is responsible in forming LDL, which is also known as bad cholesterol. Most of these proteins' structure is beta-sheet, which irreversibly associate with lipid droplets. Good cholesterol or HDL is another form of apolipoproteins that are composed of alpha-helices. Unlike the LDL, HDL reversibly associates with lipid droplets. Three-dimensional structure of these proteins is changed while binding to lipids.[27]

Apolipoprotein A-1 (ApoA) is a hydrophilic glycoprotein, which resembles plasminogen (a plasmin proenzyme that solves fibrin fiber). It can inhibit fibrinolysis in competition with plasminogen.[28]

Apolipoprotein A-1 is the main protein in HDL, which constitutes about 70-80% of HDL's protein weight. ApoA-I can be synthesized both in liver and in small intestine and functions as an activator for lecithin cholesterol acetyl transferase (LCAT) enzyme which esterifies the free plasma cholesterol. ApoA-II is the second apoprotein in HDL particles which can be synthesized both in liver and small intestine and may have an activating role for LCAT enzyme.[29]

ApoB is a main transporter to carry cholesterol to various body compartments. Its function is being a ligand for LDL receptors. High levels of ApoB may form plaques leading to atherosclerosis and finally to heart disease, mechanism of which is not thoroughly understood. It has been shown that plasma ApoB levels indicate the risk of heart disease more accurately compared with serum LDL or total cholesterol levels, although assessing serum total and LDL cholesterol is still the primary test for determining the risk of atherosclerosis.[27]

Recently, there has been a challenge about the concept that increased HDL cholesterol concentrations will result in improved cardiovascular risk. However, Onat *et al*. indicated that high HDL cholesterol concentrations do not usually protect against future risk of coronary heart disease or diabetes.[30,31]

Along with providing ample evidence that high concentrations of serum ApoA-1 can also lose antioxidant and atheroprotective functions relative to cardiometabolic risk, Onat and Hergenç, developed the concept of dysfunction of ApoA-1 and HDL particles in a milieu of enhanced low-grade inflammation in the population.[32] They also in a large systematic review of randomized trials[33] disclosed a lack of association between treatment-induced change in HDL cholesterol and risk ratios for cardiovascular disease morbidity and mortality, when changes in LDL cholesterol were adjusted. Evidence is further beginning to emerge that the antioxidant and atheroprotective functions of ApoA-1, become impaired in the process of autoimmune activation. Such impairment could be linked to excess circulating lipoprotein(a) and its oxidized phospholipids, and could represent a common denominator underlying various different chronic diseases.[32-34]

Thus, it is time to recognize that the clinical significance of HDL cholesterol concentrations in the general population is markedly heterogeneous, and high concentrations do not necessarily imply reduced cardiometabolic risk. Evidence is presented that enhanced systemic inflammation, or oxidative stress associated with elevated plasma triglyceride rich lipoproteins and their remnants, and excess oxidized lipoA phospholipids underlie this risk. The adverse risk profile is augmented by loss of the anti-inflammatory, antioxidative and atheroprotective properties of HDL and its apoprotein. Common clinical manifestations are atherogenic dyslipidemia and hypertriglyceridia with elevated ApoB or hypertriglyceridemic waste phonotype. Those manifestations are accompanied by such inflammatory mediators/markers as elevated ApoB, C-reactive protein (CRP), complement C3 and uric acid levels. Much research is needed on this topic to further clarify the impact of ApoA-1 dysfunction to elucidate the underlying genetics and mechanisms and to determine preventive measures and optimal managements.[32-35]

Lipid oxidation

During oxidation, LDL converts to Ox-LDL. Ox-LDL activates T cells and macrophages, stimulates the expression of adhesion molecules, attracts macrophages to sarcoplasmic reticulum, and produces foam cells. Oxidation of LDL and its containing cholesterol have an important role in formation of atherosclerotic plaques. The starting point of this process is the damage caused by combination of unsaturated lipids of plasma or arterial membrane with oxygen or side products of their oxidation. Macrophages have receptors for LDL, however proxified LDL can be identified by another receptor called acetyl LDL or collecting LDL. These receptors attract them more strongly in the way that cholesterol accumulates in macrophages to form foam cells. Reactions which cause LDL change are associated with changes in amino acids on protein part of LDL.[3]

Low density lipoprotein is composed of an ester cholesterol core surrounded by lipophilic antioxidants and phospholipids. Lipophilic antioxidants initially preserve LDL particle against deformation, however after antioxidants lowering, unsaturated fatty acids will be oxidized. In this step of oxidation that is associated with small amount of oxidized lipid products and unchanged ApoB-100 protein, LDL particle undergoes some slight changes.

If these steps continue and lipid oxidation products accumulate largely in LDL particle, these materials start reacting with amino acids of ApoB-100 protein and change them by covalent bond formation, which results in LDL's negative charge increase and degradation of their protein part. Oxidative changes in ApoB-100 contribute to the loss of the ligand binding to the receptor that shows the inability of Ox-LDL to attach to the LDL receptor. The result is creating new binding sites to the collecting receptor. LDL oxidation is a process with free radicals in which unsaturated lipids convert to lipid peroxides by lipid peroxidation and then change to aldehyde products such as malondialdehyde (MDA), hexanone and other compounds. The produced aldehydes bond with amino groups of ApoB-100.

Malondialdehyde-LDL is attracted to monocyte derived macrophages and produce foam cells. This is one of the compounds that will be formed during lipid peroxidation. Ox-LDL affects NO release and vascular smooth muscles. One of the side-effects of Ox-LDL formation is vascular contraction.[3]

Meanwhile, lipid peroxides accelerate plaque formation by inhibiting prostacyclin synthesis as a strong inhibitor of platelets aggregation. Oxidation also converts phosphatidylcholine to lysophosphatidylcholine and produces sterols from cholesterol esters in lipid core of LDL.

Therefore, oxidative changes of LDL change lipid and protein components of LDL. Ox-LDL has many effects such as monocytes chemotaxis, inhibition of macrophages movement, fat cells formation, more expression of endothelial adhesion molecules, growth factor stimulation, chemokine expression, monocytes proliferation, fatty streaks formation, and thickening of intima that is effective in the initial progress of atherosclerosis.[36]

Malondialdehyde is the final product in lipid (especially LDL) peroxidations. This compound is an active aldehyde as well as an active type of electrophiles, which can cause toxic stress in cells and advanced glycation end-products. This aldehyde's product is a biomarker for measuring stress oxidative level. During LDL oxidation most of MDA is composed of linoleic, arachidonic and

docosahexaenoic acids. In physiological pH, free MDA is anionic type and is able to react with NH_2 groups of amino acids and proteins.[37]

Hypertension

Hypertension is a risk factor in cardiovascular diseases and stroke. These complications are generally caused by high diastolic blood pressure. Hypertension damages endothelium by increasing the hemodynamic pressure on endothelium and may increase the permeability of arterial walls for lipoproteins. Elevated angiotensin II concentration stimulates SMC growth, increases inflammation and finally accelerates LDL oxidation in such patients.[38,39]

Hypertension is correlated with the increased risk of myocardial infarction. Although, the complications of hypertension were formerly attributed to diastolic blood pressure, there is much evidence showing that systolic blood pressure plays a role as well. The mechanism with which hypertension can accelerate atherosclerosis is still unknown; however, in animals fed with high fat, hypertension accumulates the fatty substances inside the arterial walls.[38,40-43]

Defect in nitric oxide production or function

Nitric oxide is produced from the conversion of L-arginine to L-citruline by enzymatic activity of NADH related to nitric oxide synthase (NOS). This process needs flavin mononucleotid, flavin adenine dinucleotide, Ca^{+2}/calmodolin, and tetrahydrobiopterin (BH_4) as cofactors.[44] NO is produced in the vessels by isoform nitric oxide endothelial synthase (eNOS) after stress and stimulation by agonists such as bradykinin and acetylcholine. NO has different functions, but the most important one is its "endothelium derived vasodilating function for homeostasis."[45,46]

There is endothelium related vasodilation in atherosclerotic vessels even before changes in the vascular structure, which shows decreased eNOS. It has been demonstrated that in special pathologic conditions such as severe hypercholesterolemia, malfunctioned eNOS, and peroxynitrite are produced instead of NO.[45,46]

Dysfunction of eNOS causes vascular dysfunctions such as atherosclerosis. All the effective risk factors of atherosclerosis such as hyperlipidemia, diabetes mellitus, hypertension, and cigarette smoking are related to the damaged endothelium. Although, the effective mechanisms on endothelium are multifactorial, the most important one is the dysfunction of eNOS/NO pathway, which include the decrease in activity and expression of eNOS, decrease in NO sensitivity and increase in NO destruction by reaction to superoxide.[45,46]

Because of eNOS expression in the vessel walls, the level of eNOS decreases in advanced atherosclerosis which is probably because of reduced translation or increased mRNA-instability of eNOS.[47,48] Enzymatic activity of eNOS can be inhibited by different mechanisms which are related to atherosclerosis and hyperlipidemia. Proatherogenic lipids such as Ox-LDL and lysophosphatidylcholine prevent signal conduction from the activated receptor to eNOS.[45-49]

There are reports about endothelium regeneration by antioxidants and superoxide dismutase, which shows the importance of superoxide in the damaged endothelium. Antioxidants can heal the damaged endothelium in human and animal models of atherosclerosis.[50] Vitamin C is particularly effective in regeneration of endothelium damaged by the most risk factors of atherosclerosis.[51]

There are some evidence suggesting that eNOS is an anti-atherogenic factor.[52] Endothelial and leukocyte adhesion, vascular SMC migration, and platelets aggregation, which are all important atherogenic stages, can be inhibited by NO and eNOS inhibition leads to the development of atherosclerosis. Furthermore, chronic consumption of L-Arginine (eNOS substrate) can prevent atherosclerosis in animals.[53]

Nitric oxide is produced in the endothelium and rapidly leaks to reach to the molecular targets in the vascular walls and vascular channels. It can react with transcription factors such as protein (I) activator and KB nuclear factor.[54] NO activates guanylate cyclase in vascular SMC and leads to increased cyclic guanosine monophosphate (cGMP), activation of cGMP mediated protein kinase G, and vasodilation.[55] NO has anti-atherogenic effects in addition to vascular tone adjustment capability.[46] NO has antiplatelet effects and inhibits adhesion and migration of platelets. It also inhibits the expression of inducing thrombin of platelet activating factor.[56]

Nitric oxide has also anti-proliferating effect, and can potentially inhibit the proliferation, migration, and extracellular matrix synthesis. It has anti-inflammatory effects, too.[57]

Nitric oxide prevents translocation of KB factor, blocks the cytokine stimulated expression of endothelial adhesion molecules and decreases neutrophils and monocytes activity[58] [Figure 4].

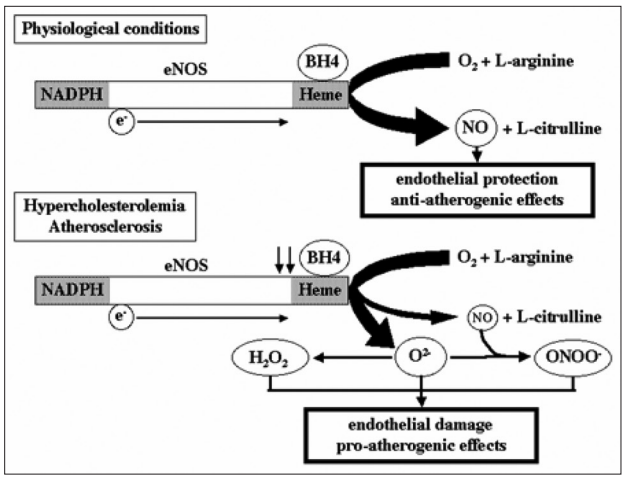

Figure 4: Roles of nitric oxide endothelial synthase in atherosclerosis

Inflammation

Numerous markers such as cytokines (TNF-α, IL-6 and-18), CRP, adhesion molecules (Intercellular Adhesion Molecule-1) are increased in plasma, following chronic inflammation.[59] Matrix metalloproteinase (MMP-9 or gelatinase B) is secreted by macrophages and other inflammatory cells and is identified in various pathological processes such as tumor metastasis, general inflammation, respiratory diseases, vascular aneurysms, myocardial injury, or remodeling. It is also elevated in patients with unstable angina.[60] Independent of IL-18, there is a strong association between baseline MMP-9 levels and future risk of cardiovascular death.[61-63] The presence of IL-18 and MMP-9 identifies patients at very high risk.

Pro-inflammatory cytokines derived from monocytes, macrophages and/or adipose tissues trigger CRP in the liver. CRP, a marker for acute-phase of inflammation, predicts early and late mortality in patients with acute coronary syndromes. CRP itself promotes inflammation[62-64] and atherogenesis through effects on monocytes and endothelial cells and increases the activity and concentration of plasminogen activator inhibitor-1 (PAI-1).[61-64] CRP is a marker for cardiovascular diseases; however, whether or not it should be used in routine screening is still a matter of debate.[61-64]

There is some evidence showing that inflammatory markers are also related to coronary artery disease. For example, CRP shows more predictive information than what other documented risk factors (such as cholesterol) do. Increased levels of acute-phase reactants such as fibrinogen and CRP can reflect the extravascular inflammation, which can intensify the atherosclerosis and its complications. Nevertheless, both factors are effective in increasing the inflammatory markers in patients prone to coronary artery disease.[3]

C-reactive protein is a member of pentraxin proteins family. It is an acute-phase reactant, which releases after infection, acute injury, or other inflammatory stimulations.[65-67] CRP levels increase during the inflammation, because of the increase in plasma IL-6 concentration, which is predominantly produced by macrophages[65-67] and adipocytes.[67]

C-reactive protein can be bound with micro-organism "phosphocholine." In this process, complement system can be bound with damaged foreign cells and reinforce the phagocytosis by macrophages which expresses a receptor for CRP.[65-67] Recent studies show that patients with high baseline CRP levels are more prone to diabetes mellitus,[68] hypertension,[69] and cardiovascular diseases.[70] Cells which have a role in forming atherosclerotic plaques (monocytes, SMC, and T) stimulate production of IL-6, complement factors (C19-C3-C5-C9), cytokines, CRP, and NO.[70-72]

C-reactive protein is a plasma protein which is very similar in both vertebrates and invertebrates.[73] Most of it is produced in liver and is regulated by IL-6.[45] A little amount of CRP is also produced locally on blood lymphocytes.[74] Inflammatory mechanisms have a pivotal role in all steps of atherosclerosis. CRP may have a role in any of these steps through effective direct processes such as complement system activation, absorption, activity, and cellular modulation, lipid accumulation and thrombosis.[45] CRP directly affects arterial endothelial cells by reducing the expression of inhibitory complement factors on the endothelial cells.[75]

Thrombosis is also effective for developing atherosclerotic damage and accelerating the

cardiovascular events. Direct activities of CRP for conducting the pro-thrombotic stage include; reinforcement of precoagulative activity[76] or reduction of fibrinolysis.[77]

C-reactive protein induces platelets binding to endothelial cells[78] and stimulates monocytes and lymphocytes absorption into endothelial walls. CRP intermediates the proliferation and activities of vascular SMC, which leads to accumulation of these cells in the vascular intima that is a key factor in advancing vascular wall damage.

C-reactive protein is a factor related to lipoprotein deposition and complement system activity in atherosclerotic plaques. It amplifies the activity of compliment system, which particularly in the first steps of atherosclerosis may lead to development and advancement of atherosclerotic damage.[79]

Immune and infection mediated atherosclerosis

Mediators of acquired and innate immunity are involved in atherosclerosis, as might be anticipated for a chronic inflammatory process.[80] In the chronic state, atheromata contain activated macrophages, T lymphocytes and mast cells, which are also present in inflammatory infiltrates. Innate immune reactions against viruses and bacteria have been included in the list of pathogenic factors in atherosclerosis.[81]

Acute respiratory infection might be a risk factor for myocardial infarction. An increase in acute coronary diseases during winter infections and flu epidemics has been related to seasonal variations in factor VIIa and fibrinogen, probably induced via activation of the acute-phase response.[82] In these circumstances, an immune response may support an inflammatory process and can be associated with increased trafficking of macrophages into the artery wall causing increase in the incidence of atherosclerosis.[83]

The humoral immune response might be a risk factor for coronary heart disease, inducing inflammation that links immunity with coronary disease.

Immune reaction and infection cause endothelial dysfuction, cell injury and a pro-inflammatory environment.[84] Endotoxins secreted by bacteria are considered as potent activators of various inflammatory reactions, stimulating circulating monocytes, and causing production of several cytokines.[85]

IL-18 gene expression is stimulated by lipopolysaccharides and pro-inflammatory cytokines. Infection is also a trigger of IL-18.

There is a relationship between the patho-physiology of ischemic heart disease and infection as well as the severity of atherosclerosis.[86] *Chlamydia pneumoniae*, *Helicobacter pylori* and cytomegalovirus are associated with atherosclerotic lesions.

Furthermore, viral and bacterial proteins can induce anti-phospholipid antibody production in humans which might be an additional factor attacking endothelium.[87] *C. pneumoniae* should be more involved in coronary disease through different mechanisms. *C. pneumoniae* might be replicated and maintained in human macrophages and in endothelial cells. It might participate in the acute coronary process through a direct effect on atheroma and initiate the inflammatory process, subsequently being activated during inflammation and acutely exacerbating the response.

C. pneumoniae can colonize atheroma by plaque inflammation, contributing to plaque disruption. The controversial role of *C. pneumoniae* in coronary events was also indicated by the effect of antibiotic treatment. *C. pneumoniae* is sensitive to macrolides (clarithromycin, roxithromycin, and azithromycin),[88] but their anti-infectious activity, an alternative mechanism for macrolides was suggested.[89] They may suppress macrophage activity which means that they may have anti-inflammatory effects, different for each drug. Controversial results could be related to these different anti-inflammatory effects.

Hemostatic factors

Currently, fibrinogen and factor VII (homeostatic factors) are known as confounding risk factors in cardiovascular diseases.

There is a relationship between plasma fibrinogen level or PAI-1 as a fibrinolysis inhibitor and the risk of coronary artery diseases. Fibrinogen is a circulating glycoprotein which has activity in coagulation steps responding to tissue and vascular damage.[90]

In addition to thrombotic role, fibrinogen causes cellular proliferation,[91] contraction of damaged cellular walls, stimulation of platelet aggregation,[92] and regulation of cell adhesion.[93] Fibrinogen is an acute-phase reactant similar to CRP and its synthesis can be increased in response

to inflammations or infections.[94] Epidemiologic information supports the correlation between fibrinogen levels and cardiovascular diseases, infarction, and ischemia. Fibrinogen participates in inflammation and thrombosis. Fibrinogen is probably less affected by inflammatory stimulation compared with CRP and consequently is a specific marker. Fibrinogen increase in patients with atherosclerosis can be a secondary phenomenon, although it participates in lesion formation and thrombosis.[95]

Factor VII is also a coagulative protein, which has an important role in thrombogenesis. Several studies demonstrate the correlation between factor VII and inflammatory factors such as IL-6 and CRP in patients with hypercholesterolemia, which shows their pathophysiologic correlation. There are also some reports showing the correlation between coagulation system constituents (fibrinogen and factor VII) or fibrinolytic factors (tissue plasminogen activator, PAI) and atherosclerosis[96] [Figure 5].

Furthermore, several plant with antioxidant activity have been shown to decrease the fibrinogen and factor VII levels even more than statins.[97-99]

Homocysteine

Although homocysteine does not seem to be a strong predictor of athrosclerosis, Cavalca *et al*.[100] in their study have reported that plasma homocysteine level might be a cardiovascular disease indicator. Impaired homocysteine metabolism may result in oxidative stress,[101] which can play a role in hyperhomocysteinemia-mediated vascular disorders.[102,103] Homocysteine increases TNF-expression, which enhances oxidative stress and induces a pro-inflammatory vascular state that might contribute to the development of coronary atherosclerosis.[104]

Antioxidants and atherosclerosis: New hope for herbal therapy

Trace amounts of antioxidants are able to protect cell membranes and other body compartments against oxidants.[105,106] The equilibrium establishment between per- and anti-oxidants helps cells to regain their normal physiologic function.[107]

Antioxidants are able to prevent diseases such as Alzheimer,[108] seizure, cancer,[109,110] aging,[105] and atherosclerosis[111,112] by reducing the effects of free radicals. Producing reactive oxygen species (ROS)

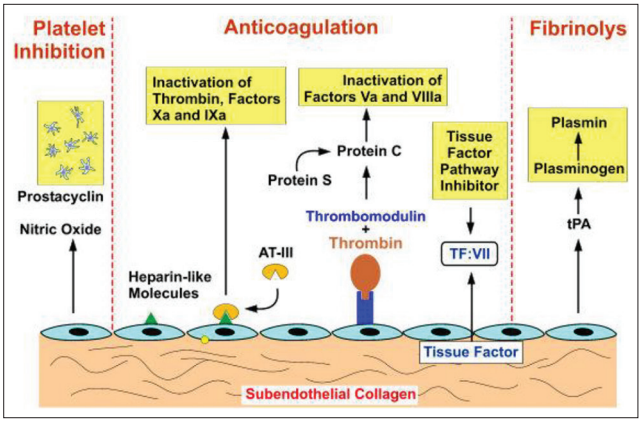

Figure 5: Stages of fibrinolyse, anticoagulation, and platelet inhibition

in cells is a natural process. This production can be amplified in different pathophysiologic conditions such as inflammation, immunologic diseases, drug and alcohol metabolism, ultraviolet ray or radiotherapy, and antioxidant vitamins deficiency. Uncontrolled ROS release usually damages cellular macromolecules such as deoxyribonucleic acid, protein, and lipid.[113]

Antioxidants can function through these mechanisms:

- Reducing reactive oxygen concentration
- Inhibiting lipid chain oxidation by absorption of free radicals
- Inhibiting free radicals production by metal ions chelating agents peroxide decomposition

4. Breaking the reaction chain to inhibit hydrogen absorption by activated radical.[114]

In vitro peroxidation is affected by activity of enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Ions such as Mn^{+2}, Cu^{+2}, Zn^{+2}, Se^{+2}, and Fe^{+2} act as cofactors of antioxidating enzymes. Since lipid peroxidation is considered as the key event in atherosclerosis, antioxidant protection is often related to preventing lipid peroxidation. Therefore, reduction of lipoproteins oxidative change in the body by natural and synthetic antioxidants is an effective way to prevent cardiovascular disorders. Rapid advancements in understanding the molecular mechanisms of atherosclerosis have led to discover and suggest mechanisms to postpone the progress of coronary artery disease.[115]

Antioxidants such as vitamin E, selenium, beta-carotene and chemical compounds such as butyl hydroxytoluene and butyl hydroxyanisol can

prevent cell membrane oxidation.[116,117] However, their widespread use has been limited because of their toxic effect. Therefore, studies on some natural compounds with antioxidant properties without toxic effects to inhibit lipid peroxidation and consequently to prevent related diseases seem necessary.

Herbal compounds such as some plants' essence and flavonoid extracts mainly have antioxidant properties.[118,119] They also have less toxicity and side-effects compared with uncontrolled amounts of chemical compounds.[120]

Several studies have demonstrated that receiving a mixture of specific antioxidants as food supplements decrease the production of MDA and protein carbonyl, decrease erythrocyte hemolysis, and increase the total amount of antioxidants.[121,122] The effect of such food supplements as a modulator in ester proteins synthesis has been approved.

Medicinal herbs, as a source of different antioxidants, can be very effective in modulating oxidative stress derived cardiovascular or renal damages.[123,124] Although different components of plants can have antioxidant effect, the main part of such effects is attributed to phenol compounds.

Flavonoids are a group of phenolic compounds with low molecular weights. Their basic structure is similar and found in fruits and vegetables. The amount and type of flavonoids in different plants depend on the species, growth, and maturity of the plants. More than 8000 phenolic structures are known which are composed of various molecules

Table 2: Important medicinal plants with antioxidant and hypolipidimic activities

Row	Plant name	Family	Region	Subject	Reference
1	Verjuice*	*Vitis vinifera*	Iran	Rabbit	[130]
2	Cornelian cherry	*Cornaceae*	Black Sea region	Rabbit	[131]
3	*Allium hirtifolium*	*Amaryllidaceae*	Turkey to Tien Shan	Rabbit	[132]
4	*Kelussia odoratissima Mozaffarian*	*Umbelliferae*	Iran	Mice	[133]
5	*Hypericum perforatum*	*Hypericaceae*	Europe, Turkey	Rat	[134]
6	*Capparis dedicua*	*Capparidaceae*	India, Pakistan	Rat	[135,136]
7	*Aconitum heterophyllum*	*Rununculaceae*	Mountainous parts of the Northern hemisphere	Rat	[137]
8	*Dalbergia latifolia*	*Fabaceae*	India	Rat	[138]
9	*Aloe vera gel*	*Xanthorrhoeaceace*	Northern Africa	Mouse	[139]
10	*Hibiscus cannabinus L*	*Malvaceae*	India and Western world	Rat	[140]
11	*Eclipta prostrata*	*Asteraceae*	India, China	Rat	[141]
12	*Moringa oleifera Lam*	*Moringaceae*	Northwestern India	Rat	[142]
13	*Terminalia chebula*	*Combretaceae*	Southern Asia	Rat	[143,144]
14	*Pithecellobium Dulce*	*Leguminosae*	Tropical regions, America	Rat	[145]
15	*Ougeinia Oojeinensis*	*Fabaceae*	India	Rat	[146]
16	*Randia dumetorum* and *Paederia foetida*	*Rubiaceae* and *Paederia foetida*	Tropical regions, Asia	Rat	[147]
17	*Sesbania grandiflora*	*Fabaceae*	India, Malaysia	Rat	[148]
18	*Luffa aegyptiaca*	*Cucurbitaceae*		Rabbit	[149]
19	*Lycium barbarum*	*Solanaceae*	China	Rabbit	[150]
20	*Tinospora cardifolia*	*Menispermaceae*	India, Myanmar	Rat	[151,152]
21	*Bauhinia purpurea*	*Fabaceae*	South China	Rat	[153]
22	*Piper longum*	*Piperaceae*	Java, Indonesia	Rat	[154]
23	*Urtica dioica*	*Urticaceal*	Europe, Asia	Rat	[155]
24	*Psidium guajava Linn*	*Myrtaceae*	Tropical regions	Rat	[156]
25	*Piliostigma thonningii*	*Fabaceae*	Asia, America	Rat	[157]
26	*Aloe vera leaf gel*	*Xanthorrhoeaceace*	Northern Africa	Rabbit	[158]
27	*Hypericum perforatum*	*Hypericaceae*	India, and China	Rabbit	[159]
28	*Allium hirtifolium Boisson*	*Amaryllidaceae*	Asia, Turkey to Tien Shan	Rabbit	[97]

*Verjuice is a highly acidic juice made mostly from viniferacea family or by pressing unripe grapes, crab-apples or other sour fruit

such as phenolic acids to fully polymerized compounds such as tannins. They are classified in flavonoid main groups comprising anthocyanins, flavonols, flavones, neoflavones, isoflavones, and dihydroflavones.[125]

Flavonoids are among potent antioxidants, free radical scavengers, metal excreters, ROS-family compounds collector, and lipid peroxidation inhibitors. Studies show that flavonoids inhibit LDL oxidation in macrophage culture media and also reduce Ox-LDL absorption by macrophage sweeping receptors.[126,127]

Considering the therapeutic effect of flavonoids for cardiovascular diseases, using plants with such effects seems necessary. Various studies with promising results have been done on plants with such properties.[128,129]

The most important medicinal herbs with documented antioxidant activity and hypolipidemic effects are as follows.[130-135] Some of the most important plants with antioxidant activities and hypolipidemic properties are listed in Table 2.

Rhus coriaria, Juglans regia, Carum carvi, Cornus mas, Ocimum basilioum, Apium graveolens, Silybum marianum, Artemisia dracunculus, Plantago psyllium, S. marianum, Carduus marianus, Anethum graveolens, Rheum ribes, Lepidium sativum, Boswellia carterii, J. regia, Trigonella foenum-graecum, Allium sativum, Trifolium pretense, Artemisia sp., Pistaciam atlantica, Pisacia mutca, Nigella sative, Berberis vulgaris, Berberis thunbergii, Phoenix dactylifeva, Sesamum indicum, Olea europaea, Croucus stivus. Arachis hypogaea, Citrus limon, Linum usitatissimum, Aloe littoralis, Aloe vera, Ziziphus jujube, Zingiber officinale, Onopordon acanthium, Celosia cristata, Mukul comiphora.

CONCLUSIONS

Atherosclerosis starts with fatty streaks formation and progresses with atheroma and atherosclerotic plaque formation.[159-161] Hypercholesterolemia, LDL increase, HDL decrease, lipid oxidation, hypertension, malproduction and dysfunction of NO, and inflammation are the most facilitating factors for atherosclerosis.

Lipid oxidation, in the form of Ox-LDL, demonstrates the first step of atherosclerosis. MDA shows lipid peroxidation level and is a marker of increased oxidative stress. CRP is an indicative marker of body's response to inflammatory processes. It is one of the most important pathogenesis factors along with fibrinogen in atherogenic processes. Nitric oxide is known as a vasodilator and endothelial survival factor which enhances the endothelial cell proliferation and migration. In special pathologic conditions such as severe hypercholesterolemia, peroxynitrate concentration increases, which leads to severe atherosclerotic damage. Considering the role of oxidative stress and lipid oxidation in formation and progress of atherosclerosis and endothelial damage, using antioxidants, especially herbal types can be beneficial.

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