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Review Article

Therapeutic agents for the management of atherosclerosis from herbal sources

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ABSTRACT

Purpose: Cardiovascular diseases (CVDs) arising from atherosclerosis are a foremost cause of death and morbidity worldwide. Atherosclerosis and hypertension are the most common factors responsible for CVDs. Due to the increasing prevalence of CVDs caused by atherosclerosis, there is a vital need for precise investigations to rationalize the use of the potential herbal medicines. This review aims to judge current available knowledge of therapeutic agents from herbal sources for management of atherosclerosis.

Method: Bibliographic investigation was done to retrieve available published literature by scrutinizing traditional textbooks and peer reviewed papers, accessing worldwide-accepted scientific databases (Scopus, PubMed, SciELO, NISCAIR, and Google Scholar). The inclusion criterion for the selection of plants was based upon all medicinal herbs and their active compounds with attributed potentials in relieving atherosclerosis.

Result: Wide varieties of plants have been used in the management of atherosclerosis. Overall, 300 articles were reviewed for plant literature, and out of the reviewed literature, 80 articles from year 2000–2016 were selected for the study. The plants were categorized according to the drug targets involved in the pathogenesis of atherosclerosis i.e. modification of lipoprotein levels and adhesion of molecules, LDL oxidation, endothelial dysfunction, plaque formation etc.

Conclusion: Herbs are enacting a reappearance and herbal rebirth is being experienced all over the world. The herbal products signify safety in comparison to the synthetics that are considered as a risk to human beings and to the environment as well. This article may provide the insights of rationale use of medicinal agents from herbal sources based on their mode of action in management of atherosclerosis.

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1. Introduction

CVDs are considered as the major health care problem that accounts for approximately 30% mortality worldwide (Chapman, 2010). Primarily CVDs include coronary heart disease (CHD), cerebrovascular disease cardiomyopathy, rheumatic heart disease, peripheral arterial diseases, congenital heart disease, deep vein thrombosis, cardiac dysrhythmias, inflammatory heart diseases etc. According to the World Health Organization, CVDs are responsible for about 50% of premature deaths (Amedeo et al., 2000; Mathers and Loncar, 2006). According to the data collected in 2005, the age standardized mortality rate due to CVDs for developing countries like India, China, and Brazil was between 300 and 450 per 100,000 and that for developed countries like the USA and Japan was 100–200 per 100,000.

A statistics indicated that in the USA, more than 900,000 deaths per year are accredited to cardiovascular causes with a cost of around 400 billion US dollars (Thom et al., 2006). Globally, 17.3 million deaths were recorded in 2008 due to CVDs and in 2030 this might reach 23.3 million with expected global cost of 20 trillion US dollars (Mathers and Loncar, 2006).

The etiology of CVDs is very complex but atherosclerosis and hypertension are the most common factors responsible for CVDs (Alain and Karin, 2009). Atherosclerosis or arteriosclerotic vascular disease is a multifaceted disseminated chronic inflammatory disease of the arterial wall that leads to the growth of atherosclerotic plaques in the internal lining (intima) of the arteries (Navab et al., 1996; Stary et al., 1995). Significant genetic components (hypertension, insulin resistance, obesity etc.) and environmental factors (smoking, high fat diet, infectious agents, lack of exercise etc.) are considered as major risk factors responsible for the development of atherosclerosis (Antonio et al., 2003; Goldstein and Brown, 1977). Atherosclerosis and its clinical consequences symbolize a vast and escalating global burden of morbidity and mortality (Murray and Lopez, 1997) in the form of myocardial infarction (MI), peripheral vascular disease, cerebrovascular disease (Ross, 1999) etc.

Over the past few decades, herbal medicines have fascinated a lot of consideration as feasible therapeutic agents in the prevention and treatment of atherosclerosis due to their potential of targeting multiple steps involved in pathogenesis and fewer side effects. Considering this viewpoint, this review is emphasized on plants and parts of plants including the active chemical constituents responsible for attenuation of atherosclerosis via different mechanisms of action.

2. Materials and methods

In the present review, bibliographic investigation was done to retrieve articles for preclinical studies from worldwide scientific databases like Scopus, PubMed, SciELO, NISCAIR and Google Scholar available during 2005–2015. Botanical names of plants were verified from published literature and database (International Plant Names Index, 2015; The Plant List, 2015). The inclusion criteria for the selection of plants include (i) medicinal plants with reported animal studies targeting steps involved in progression of atherosclerosis, (ii) compounds isolated from medicinal plants with attributed potential in relieving atherosclerosis, and (iii) studies published in the English language and those reporting herbal sources for management of atherosclerosis.

3. Pathophysiology

Atherosclerosis is considered as a composite syndrome manifesting in arteries especially in major arteries like carotid, coronary, aortic and iliac arteries (Wang et al., 2012). Atherosclerosis resulting from the pathological etiologies and risk factors like hyperlipidemia, hypertension, diabetes mellitus, obesity, and smoking are of main clinical importance (Antonio et al., 2003). Atherosclerosis of this particular etiology is proficiently understood and is illustrated here (Fig. 1).

Being a multistep process, the preliminary steps of atherosclerosis include adhesion of the monocytes to the activated endothelial monolayer leading to migration of the bound monocytes into the tunica intima followed by maturation of monocytes into macrophages. The uptake of lipid globules by macrophages leads to formation of foam cells. The foam cells, under lesion progression, go through an inflammatory process, which leads to migration of SMCs from the tunica media to the tunica intima followed by proliferation of the occupant intimal SMCs and synthesis of extracellular matrix macromolecules such as elastin, collagen, proteoglycans etc. SMCs and plaque macrophages may die during lesion advancing by apoptosis. Extracellular lipid secretion of dead and dying cells can accumulate in central region of plaque and lead to formation of lipid or necrotic core. The most definitive impediment of atherosclerosis i.e. rupturing of plaque or thrombosis, is the last step of the atherosclerotic process which causes interruption of blood flow and other cardiovascular problems (Christopher and Joseph, 2001; Goran, 2005; Sakaruka et al., 2013; Xiao-Hua et al., 2013).

4. Major targets for anti-atherosclerotic activity

4.1. *Modification of lipoprotein levels*

Lipoproteins are composed of lipids (phospholipids and triacylglycerol), proteins and cholesterol. It is well recognized that eminent blood lipid levels amount to the primary risk factor for atherosclerosis. Epidemiological studies have indicated that dyslipidemia and coagulation disturbances are among most considerable risk factors of the development of atherosclerotic conditions (Erqou et al., 2009; Nordestgaard et al., 2010).

In state of hyperlipidemia, excess of LDL infiltrates arteries and is retained in the tunica intima. The retained LDL undergoes oxidative modifications in the sub-endothelial space (Leitinger, 2003; Skalen et al., 2002). The infiltration of LDL can be controlled either by direct lowering of lipoprotein levels of

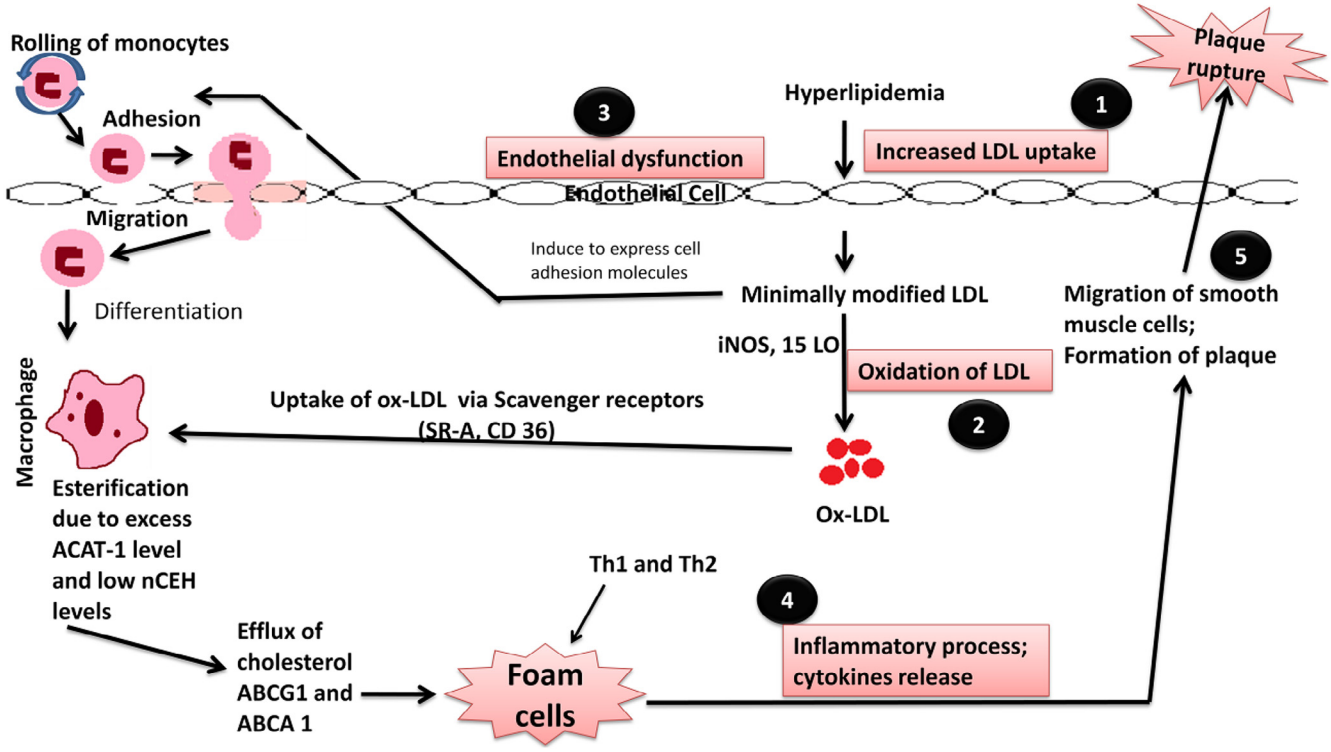

Fig. 1 – Pathophysiology of atherosclerosis: 1, Hyperlipidemia causes an increased LDL uptake in endothelial cells where it changes to minimally modified LDL. 2, mmLDL further acted upon by oxidants lead to formation of ox-LDL. 3, Endothelial dysfunction leads to LDL uptake, oxidation of LDL and adhesion of monocytes (is also triggered by mmLDL) as well. Monocytes adhere to the surface of cells by rolling down and then transmigrate into endothelial cells. The migrated monocytes differentiate and form macrophages. Macrophages uptake the oxLDL through scavenger receptors SR-A and CD-36 by phagocytosis and pinocytosis. The uptaken cholesterol undergoes esterification by imbalanced levels of ACAT1and nCEH. The esterified cholesterol effluxes through ABCG1 and ABCA1, which leads to formation of foam cells. 4, Foam cells undergo inflammatory process, causing migration of smooth muscle cells, and plaque is formed. 5, The final step is rupturing of the plaque, which blocks the artery and blood flow thereof.

the blood or by elevating levels of HDL or by targeting lipid lowering enzyme i.e. HMG CoA reductase enzyme.

Based upon these observations, it was found that ethanolic extract of *Apium graveolens* seeds (Kamal et al., 2009) significantly attenuated atherosclerosis by decreasing serum total cholesterol (TC), triglyceride (TG), phospholipids, LDL, and VLDL. Moreover, the ethanolic extract of *Passiflora foetida* at doses of 100, 250 and 500 mg/kg was found to lower the levels of TC, TG, LDL and VLDL significantly (Ravi et al., 2016).

The role of HDL in removal of excess of cholesterol from cells by reverse cholesterol transport is well renowned. The multistep process of reverse cholesterol transport results in the movement of cholesterol from peripheral tissues back to the liver via plasma. Thus, elevation of HDL would be beneficial for attenuation of LDL infiltration (Olga and Yechezkiel, 1999). Ethanolic extract of bark of *Terminalia arjuna* at a dose of 100 and 200 mg/kg (p.o) significantly elevated HDL and induced partial inhibition of aortic atherosclerosis (Saravanan et al., 2011). Aqueous and ethanolic extracts of leaves of *Cassia auriculata* have also augmented the HDL levels (Shipra et al., 2009). Ethanolic extracts of *Cinnamomum zeylanicum* bark and *Syzygium cumini* seeds at a dose of 200 mg/kg (p.o) have significantly increased the HDL level and decreased TC, TG and LDL levels as well (Khaled and Moattar, 2015).

HMG CoA reductase is known to catalyze the conversion of the HMG CoA to mevalonate. Methanolic extract of fruits of *Emblica officinalis* at a dose of 10 and 20 mg/kg reversed the atheromatous plaques by inhibition of HMG CoA reductase activity (Antony et al., 2006). Ethanolic extract of *Lagenaria siceraria* at a dose of 200 and 400 mg/kg (p.o) ameliorated the atheromatous lesions by modulating HMG-CoA reductase and lipoprotein lipase enzyme activities (Mithun et al., 2014). Methanolic extract of *Ficus virens* bark at a higher dose of 100 mg/kg (p.o) altered the levels of lipoproteins, oxidative stress and inhibition of hepatic HMG-CoA reductase activity as well (Danish et al., 2015). A list of plants acting through the above-mentioned three mechanisms is listed in Table 1.

4.2. *LDL oxidation*

Oxidative damage by free radicals has been concerned as the ground of diverse diseases. Numerous evidence from the conducted studies put forward that oxidation of LDL plays a key role in pathogenesis of atherosclerosis (Anna et al., 2013).

After infiltration of LDL in the artery, LDL is converted to mmLDL in which LDL can still be recognized by the LDL receptors. The monocytes are attached to endothelial cells that have been induced to express cell adhesion molecules by

Table 1 – Modification of lipoprotein levels.

Plant Name	Family	Part of plant	Active Constituents	Dose	Model used	Positive Control	Inference
Aegle marmelos (Linn.) (Vijya et al., 2009)	Rutaceae	Leaves	Skimmianine, Aegeline, Lupeol, Cineol, Citral, Citronella, Cuminaldehyde, Eugenol, Marmesinine	125 and 250 mg/kg (p.o) 50% Ethanolic extract	Triton WR 1339 induced hyperlipidemia in Wistar albino rats	Atorvastatin (1 mg/kg; p.o.) Gemfibrozil (50 mg/kg; p.o)	Attenuated serum TC and TG with an increase in HDL
Apium graveolens Kamal et al., 2009	Apiaceae	Seeds	Flavonoids, coumarins, and terpenoids	213 or 425 mg/kg (p.o) Ethanolic extract	Hypercholesterolemic diet induced dyslipidemia in male albino rats	–	Significant decrease of serum total cholesterol, TG, LDL and significant increase in HDL
Brassica juncea (Avery and Mahua, 2011)	Brassicaceae	Seeds	Erucic acid	20% MCTM and 20% PUFAM	Hypercholesterolemic male albino rats	–	Hypocholesterolemic and hypolipidemic effects with increase in HDL level
Carica papaya L (Iyer et al., 2011)	Caricaceae	Fruit	Papain (proteolytic enzyme), tannins, alkaloids, glycosides	Oral doses of 200 and 400 mg/kg body weight ether and water soluble fractions of ethanolic extract	Olive oil-induced hyperlipidemic rats	–	Inhibited TC,TG, LDL levels, and significantly increased HDL level
Cassia auriculata (Shipra et al., 2009)	Fabaceae	Leaves	Alkaloid, flavonoid, Saponin, tannins, cardiac glycosides, phenols	100, 200, 400, 600 mg/ kg body weight daily for 21 days (p.o) Aqueous and ethanolic extracts	Alloxan induced mild and severe diabetes	Glibenclamide	Increased level of insulin, decreased plasma levels of TG, TC and LDL, increased HDL levels
Cassia tora (Umesh and Patil, 2004)	Fabaceae	Seeds	Anthraquinone, beta-sitosterols	Ethanolic extract	Triton induced hyperlipidemia	–	Reduction in LDL and TC levels
Cinnamomum zeylanicum Blume (Khaled and Moattar, 2015)	Lauraceae	Bark	Monoterpenoids and phenyl propanoids	200 mg/kg (p.o) Ethanolic extract	Streptozotocin induced diabetes mellitus	–	Significant elevation in HDL level and decrease in total cholesterol, triglycerides and LDL levels
Cyamopsis tetragonoloba (Todd et al., 2006)	Fabaceae	Seeds	Gum (polysaccharide)	Seed powder	Pigs fed on Atherogenic diet	–	Reduction in hepatic free cholesterol concentration; increased SREBP2 expression and hepatic LDL receptor abundance
Cynara scolymus, (Lupattelli et al., 2004)	Asteraceae	Leaves	Flavonoids (luteolin)	20 ml/die of frozen artichoke juice (p.o)	Isocaloric-hypolipidic diet induced endothelial dysfunction	–	Significant reduction in total and LDL level
Eclipta prostrate (L.) L. (Dhandapani, 2007)	Asteraceae	Leaves	Beta-amyrin, wedelolactone, triterpenoids, flavonoids, leutiolin-7-o-glucoside, stigmasterol, l-terthenyl methanol	100 and 200 mg/kg (p.o) Aqueous extract	Atherogenic diet induced hyperlipidemia in rats	–	Significant reduction in TC, TG and elevation of HDL level
Embelia ribes Burm (Uma et al., 2002)	Myrsinaceae	Fruit	Embelin, Embeliol	200 mg/kg (p.o) Ethanolic extract	Streptozotocin induced diabetes in Wistar rats	Gliclazide (25 mg/kg, orally)	Decrease in blood glucose, serum TC, TG and increase in HDL levels
Emblica officinalis (Antony et al., 2006)	Euphorbiaceae	Fruit	Flavonoids emblicanin-A- and emblicanin-B-	10 and 20 mg/kg (p.o) Methanolic extract	Cholesterol diet induced hypercholesterolemia in NZ white rabbits	–	Inhibition of HMG CoA reductase activity and elevating HDL level to enhance reverse cholesterol transport

(*continued on next page*)

Table 1 – (*continued*)

Plant Name	Family	Part of plant	Active Constituents	Dose	Model used	Positive Control	Inference
Ficus carica L. (Lorenz et al., 2014)	Moraceae	Leaves	Phytosterols, organic acids, anthocyanin composition, triterpenoids, coumarins	50 mg/kg or 100 mg/kg	High fat diet induced hyperlipidemia in Male Sprague-Dawley rats	Pioglitazone 30 mg/kg (p.o)	Improved the lipid profile and decreased adipogenic risk factors through an increase in HDL levels
Ficus virens Ait (Danish et al., 2015)	Moraceae	Bark	Saponin, alkaloid, tannins, sterols	100 mg/kg (p.o) Methanolic extract	Triton WR-1339-induced hyperlipidemic rats	Atorvastatin 10 mg/kg (p.o)	Altered levels of lipoproteins, and inhibition of hepatic HMG-CoA reductase activity
Lagenaria siceraria (Mol.) Stand. (Mithun et al., 2014)	Cucurbitaceae	Fruit	Flavonoids, triterpenoids, pectins, sterols	200 and 400 mg/kg (p.o) Ethanolic extract	Atherogenic diet induced hypercholesterolemia in albino Wistar rats	Atorvastatin 10 mg/kg (p.o)	Ameliorated the atheromatous lesions by modulating HMG-CoA reductase and lipoprotein lipase enzymes activity
Lagenaria siceraria (Mol.) Stand. (Ghule et al., 2006)	Cucurbitaceae	Fruit	Flavonoids, sterols, cucurbitacin saponins and polyphenolics	200 and 400 mg/kg body weight (p.o) Petroleum ether, alcoholic, aqueous and chloroform extracts	Triton induced hyperlipidemia in rats	–	Antihyperlipidemic activity via lowering of LDL, TC, TG and increased levels of HDL levels
Medicago sativa (Dixit and Prabha, 1990)	Leguminosae	Seeds	TRH and Saponin	Ethanolic extract	High fat diet induced atherosclerosis in rabbits	–	Decrease in the serum total cholesterol, triglyceride, phospholipids, LDL and VLDL
Musa paradisiacal (Chhanda et al., 2006)	Musaceae	Root	Rutin, norepinephrine, lignin	80 mg/0.5 mL olive oil/ 100 g body weight/rat/ day for 14 days Methanolic extract	Streptozotocin-induced diabetes in Wistar strain male albino rats	–	Significant decrease in LDL and increase HDL serum level
Passiflora foetida L. (Ravi et al., 2016)	Passifloraceae	Leaves	Glycosides, flavonoids	100, 250, 500 mg/kg (p.o) Ethanolic extract	Dextrose induced diabetes mellitus	Glipizide, Sitagliptin and Vildagliptin	Significant decrease in total cholesterol, triglycerides, LDL, VLDL levels
Persea Americana (Brai et al., 2007)	Lauraceae	Leaves	Persenone A and B	10 mg/kg of body weight aqueous and methanolic leaf extracts	High fat diet induced hypercholesterolemia in Albino rats	–	Lowers plasma glucose and influence lipid metabolism with consequent lowering of TC, LDL and restoration of HDL levels
Polyalthia longifolia var. pendula, (Koneni et al., 2011)	Annonaceae	Leaves	Diterpenes	500 mg/kg body-wt Ethanolic extract	High fat diet induced dyslipidemia in hamsters	Lovastatin at the dose of 25 mg/kg body-wt	Reversal of dyslipidemia by inhibition of HMG -CoA reductase activity
Symplocos racemosa Roxb. (Durkar et al., 2014)	Symplocaceae	Bark	Flavonoids, phenolic glycosides, alkaloids, triterpenoids, steroids	200 and 400 mg/kg (p.o) Ethanolic extract	Triton WR 1339 and high fat diet induced hyperlipidemia in male Sprague Dawley rats	Simvastatin 10 mg/kg p.o	Exhibited antihyperlipidemic activity via inhibition of HMG-CoA reductase; Antioxidant activity
Terminalia arjuna (Saravanan et al., 2011)	Combretaceae	Bark	Phenolics compounds, tannins, glycosides, saponins, alkaloids and flavonoids	100 and 200 mg/kg (p.o) Ethanolic extract	High fat diet induced atherogenesis in rabbits	Atorvastatin	Hypolipidemic, elevated HDL and induced partial inhibition of aortic atherosclerosis
Viscum album (Oluwatosin et al., 2012)	Santalaceae	Excudate	Alkaloids, cardenolides, anthraquinones, saponins and tannins	50 mg/kg and 100 mg/kg Methanolic extract	Hyperlipidemia in streptozotocin-induced diabetic rats.	Glibenclamide	Decreased levels of serum triglyceride, urea, lactate dehydrogenase, α-amylase and LDL; increased levels of HDL levels
Viscum album (Ben et al., 2006)	Santalaceae	Leaves	Alkaloids	200 mg/kg body weight orally and daily Aqueous extract	Hypercholesterolemic male Wistar rats	–	Increased HDL levels

mmLDL. Further, mmLDL undergoes oxidation, which leads to formation of extensively oxidized LDL (oxLDL) (Fig. 1). Oxidation of LDL involves lipid peroxidation, in which the polyunsaturated fatty acids in LDL core and in phospholipids are swiftly converted to lipid hydroperoxides and aldehydic lipid peroxidation products. The so-formed particles do not bind to LDL receptor but rather bind to scavenger receptors expressed on macrophages and smooth muscle cells (Christopher and Joseph, 2001; Leitinger, 2003; Nakashima et al., 1998; Skalen et al., 2002).

Fortification against LDL oxidation is a goal study for prevention of the instigation and progression of atherosclerosis. Antioxidants, which can efficiently hold back the LDL oxidation, may prevent atherosclerosis due to the early diminution of atherosclerotic progression. Methanolic extract of fruits of *E. officinalis* at a dose of 10 and 20 mg/kg (p.o) impede the generation of atheromatous plaques by prevention of LDL oxidation (Antony et al., 2006). Rhizomes of *Zingiber officinale roscoe* attenuated the development of atherosclerotic lesions via reduction in plasma and LDL cholesterol levels and a significant reduction in the LDL basal oxidative state, as well as their susceptibility to oxidation and aggregation (Fuhrman et al., 2000). Hydroalcoholic extract of rhizomes of *Curcuma longa* has reduced the oxidative stress and attenuation of the development of fatty streaks (Quiles et al., 2002). Ethanolic extract of flowers of *C. auriculata* also produced protective effect against atherosclerosis by exhibiting strong antioxidant activity (Vijayaraj et al., 2011). Methanolic extract of *Aframomum melegueta* seeds has elevated the antioxidant enzyme levels at 100, 200 and 400 mg/kg dose in albino Wistar rats (Samuel et al., 2014). Kim et al. (2015) have found the extract of *Scutellariae baicalensis* effective against inhibition of LDL oxidation and thus possessing an anti-atherosclerotic potential. Ethanolic extracts of *C. zeylanicum* bark and *S. cumini* seeds at a dose of 200 mg/kg (p.o) have elevated the levels of antioxidant enzyme, showing inhibitory potential of plants against LDL oxidation (Khaled and Moattar, 2015). Hydro-alcohol extract of *Myrtus communis* was studied for its inhibitory activity against production of ox-LDL, which leads to a decrease in the development and the progression of atherosclerosis (Bahador et al., 2015). The plants acting through the above-mentioned mechanisms are listed in Table 2.

4.3. *Endothelial cell dysfunction and adhesion of molecules*

Endothelial cells are an edge and functional link between circulating blood and the rest of the blood vessel wall. Endothelium produces NO, prostacyclin, endothelin-1 and angiotensin II (Ignarro et al., 1999; Vallance and Chan, 2001). NO which is an important signaling molecule, synthesized by nitric oxide synthase (NOS) enzymes family, has a crucial role in vascular homeostasis. NO exhibits multiple effects on the vessel wall including activation and aggregation inhibition of platelets, inhibition of cell adhesion and migration, relaxation and inhibition of proliferation of vascular smooth muscle cells etc. Any biochemical or physical damage in the phenotype of endothelial cells leads to impaired production of homeostatic mediators of vascular health i.e., NO which results to progression of atherosclerosis (Claudio et al., 2007; Vallance and Chan, 2001). Thus, sound levels of NO and endothelial cell functioning can help in preventing the development and progression of atherosclerosis. Fruits of *Gardenia jasminoides* have shown restoration of endothelium-dependent relaxation increasing the vessel eNOS activity, leading to elevation of NO production (Tang et al., 2006). Leaves of *Camellia sinensis* have shown a decrease in atherosclerosis progression by reversing endothelial dysfunction (Minatti et al., 2012). Plants with this mechanism are listed in Table 3.

4.3.1. *Adhesion of molecules*

The atherogenic conscription of leukocytes comprises tethering and rolling, firm adhesion and transmigration to the endothelial cells. During atherosclerotic progression, the monocytes in the circulation engage to the vascular wall at the sites of lipid accumulation. The migration of monocytes in the subendothelial space is triggered by adhesion of molecules like VCAM-1, ICAM-1, and P-selectin (Cybulsky and Gimbrone, 1991). Monocytes are differentiated in sub-endothelial space and are converted to macrophages. The ox-LDL binds to macrophage scavenger receptors where it is internalized, and then gets accumulated within macrophagic cells. This accumulation results in formation of the foam cell (a macrophage swollen with lipid vacuoles). If the migration of monocytes in the subendothelial space is inhibited, the further process would not take place itself. Migration could be stopped by inhibiting expression of adherent molecules (Xiao-Hua et al., 2013).

Seeds of *Linum usitatissimum* prevented adhesion of monocytes and platelets to endothelial cells and reduced soluble adhesion molecules (sVCAM-1) and endothelial integrity markers (Raluca et al., 2013). *Vitis vinifera* seed extracts have shown a significant lowering in the levels of VCAM-1 and ICAM-1 via inhibition of NF-κB and thus preventing the endothelial dysfunction (Jiang et al., 2015). Dried root extracts of *S. baicalensis* have been found to be significantly inhibiting the NO production and iNOS expression (Kim et al., 2015).

4.4. *Inflammatory process and smooth muscle cell migration and plaque formation*

In atherosclerosis, there is an abnormal activation of inflammatory cells, which are aimed toward the lipid deposited in the vascular wall. The inflammatory process in the atherosclerotic artery leads to increased blood levels of inflammatory cytokines and other acute-phase reactants. Specifically, there is an increase in plasma levels of pro-inflammatory mediators like cytokines, chemokines and migratory potential in macrophages (Croce and Libby, 2007).

T-helper cells (Th) and regulatory T-cells predominate in atherosclerosis. During early atherosclerosis, the Th cells secrete a number of inflammatory pro-atherogenic cytokines like interferon-g. Interactions between macrophage foam cells, Th1 and Th2 cells establish a chronic inflammatory process, which results in attraction and migration of SMCs. SMCs further proliferate and thicken the arterial wall (Mallat et al., 2009). The therapeutic agents with anti-inflammatory response may alter this step and help in attenuating the progression of atherosclerotic plaque formation. Methanolic extract of *Ruta graveolens* L. was investigated for anti-inflammatory effect on murine macrophage cells (J-774). Results revealed that plant extract has

Table 2 – LDL oxidation.

Plant Name	Family	Part of plant	Active Constituents	Dose	Model used	Positive Control	Inference
Aframomum melegueta (Samuel et al., 2014)	Zingiberaceae	Seeds	Mono and Sesquiterpenes	100, 200 and 400 mg/kg dose Methanolic extract	In vivo oxidative stress in male albino Wistar rats	–	Elevated the antioxidant enzyme
Allium sativum (Hassan et al., 2010)	Alliaceae	Fruit	Polyphenolic compounds and phytosterols	Homogenate of garlic (100 mg/kg) orally	Cholesterol-containing diet induced atherosclerosis in pregnant rats and their offspring	–	Antihyperlipidemic and antioxidant
Brassica oleracea (Sankhari et al., 2012)	Brassicaceae	Fruit	Anthocyanins, alkaloids, tannins, saponins, phenols, glycosides, steroids, terpenoids and flavonoids	100 mg/kg of body weight	Atherogenic (ATH) diet-induced hypercholesterolemia in rats	–	Prevented elevation in serum and tissue lipids and attenuation of cardiac and hepatic antioxidants and lipid peroxidation
Cassia auriculata (Vijayaraj et al., 2011)	Fabaceae	Flowers	Flavonoids, sitosterol, d-glucoside, polysaccharides, anthracene and myristyl alcohol	150, 300, 450 mg/kg b.w./day Ethanolic extract	Triton WR 1339 induced hyperlipidemia	Lovastatin	Antihyperlipidemic and antioxidant
Curcuma longa (Quiles et al., 2002)	Zingiberaceae	Rhizomes	Bis-demethoxy-curcumin, demethoxy-curcumin, and Curcumin	Hydroalcoholic extract	High cholesterol diet induced atherosclerosis in rabbits	–	Reduction of oxidative stress and attenuation of the development of fatty streaks
Curcuma longa (Jingjing et al., 2012)	Zingiberaceae	Rhizomes	Terpinolene, b-Caryophyllene, Curcumene, Zingiberene, b-Bisabolene, b-Sesquiphellandrene, a-Turmerone, b-Turmerone	100 and 300 mg/kg of body weight (p.o) Turmeric oil	High fat diet induced hyperlipidemia in male Sprague Dawley rats	Xuezhikang	Anti-hyperlipidemic and antioxidant
Cynara scolymus (Küskü-Kiraz et al., 2010)	Asteraceae	Leaves	Caffeoylquinic acid derivatives (cynarine and chlorogenic acid) and flavonoids (luteolin, apigenin)	1.5 g/kg/day (p.o)	High cholesterol diet induced hypercholesterolemia and lipid peroxidation	–	Prevention of hypercholesterolemia-induced pro-oxidant state in LDL + VLDL fraction and the reduction of increased serum cholesterol and triglyceride levels
Emblica officinalis (Antony et al., 2006)	Euphorbiaceae	Fruit	Flavonoids emblicanin-A- and emblicanin-B-	10 and 20 mg/kg (p.o) Methanolic extract	Cholesterol diet induced hypercholesterolemia in NZ white rabbits	–	Reversal of dyslipidemia and atheromatous plaques by prevention of LDL oxidation

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Table 2 – (*continued*)

Plant Name	Family	Part of plant	Active Constituents	Dose	Model used	Positive Control	Inference
Ipomoea batatas L. (Miu et al., 2011)	Convolvulaceae	Leaves	Polyphenols (caffeoylquinic acid)	18 g of raw leaves	Lag time, TBARS products and LDL mobility determination test	–	Inhibition of LDL oxidation
Punica granatum (Michael et al., 2008)	Punicaceae	Peels, Arils, seeds and Flowers	Phenolics (punicalagin, punicalin, gallic acid, and ellagic acid	200 μg of gallic acid equivalents (GAE)/mouse/day	Assessment of atherosclerosis in Apolipoprotein E-Deficient (E^0) Mice and Cultured Macrophages and lipoproteins	–	Attenuation of atherosclerosis by decrement in serum cholesterol level together with a significant inhibition in macrophage uptake of ox-LDL and in cellular cholesterol biosynthesis rate
Punica granatum (Marielle et al., 2001)	Punicaceae	Whole fruit	Polyphenolic flavonoids like anthocyanins, catechins, ellagic, tannins, gallic and ellagic acids	31 mL of fruit juice per day; oral route	Serum cholesterol, lipid peroxidation and paraoxonase (arylesterase) activity	–	Reduction in macrophage lipid peroxidation, cellular cholesterol accumulation and atherosclerotic development
Scutellariae baicalensis (Kim et al., 2015)	Lamiaceae	Roots	Baicalein, wogonin, neobaicalein, and skullcapflavone	Dried root extract	LDL oxidation and inflammation in macrophages	–	Inhibition of LDL oxidation
Sesamum indicum Linn (Nishant et al., 2009)	Pedaliaceae	Seeds	Lignans-sesamol, sesamolinol, pinoresinol, sesaminol, vitamin-E	Aqueous and ethanolic extract	Lipid peroxidation and Copper-mediated LDL oxidation in vitro	–	Protection against LDL oxidation
Vitis vnifera (Bianca et al., 2005)	Vitaceae	Fruit	Flavanols, Anthocyanins, Quercetin, Myricetin, Kaempferol, Resveratrol	150 μg total polyphenols/day in the form of grape powder	Assessment of atherosclerosis in Apolipoprotein E-Deficient (E^0) Mice	–	Anti-atherosclerotic effect by reducing macrophage-mediated oxidation of LDL and cellular uptake of oxidized LDL.
Zingiber officinale Roscoe (Fuhrman et al., 2000)	Zingiberaceae	Rhizomes	Gingerol, zingerone, shogaols	5 mg of ginger extract/d in 1.1% alcohol and water	Atherosclerosis in apolipoprotein E-deficient (E^0) mice	–	Attenuates the development of atherosclerotic lesions via reduction in plasma and LDL cholesterol levels and a significant reduction in the LDL basal oxidative state, as well as their susceptibility to oxidation and aggregation

Table 3 – Endothelial cell dysfunction and adhesion of molecules.

Plant Name	Family	Part of plant	Active constituents	Dose	Model used	Positive Control	Inference
Andrographis paniculata (Shen et al., 2013)	Acanthaceae	Leaves	Diterpenoids (andrographolide and neoandrographolide)	100 mg/kg dosage	Hyperlipidemic mice induced by 75% yolk emulsion and in hyperlipidemic rats induced by high fat emulsion	–	Hypolipidemic effects and cardiovascular protection via down-regulation of iNOS expression and up-regulation of eNOS expression
Camellia sinensis (Minatti et al., 2012)	Theaceae	Leaves	Xanthine derivatives	50, 100, or 300 mg/kg once a day by gavage (100 μL/10 g weight)	Hypercholesterolemic diet for atherosclerosis progression in homozygous knockout low-density lipoprotein receptor mice	–	Decrease in atherosclerosis progression by reversing endothelial dysfunction
Cynara scolymus (Graziana et al., 2004)	Asteraceae	Leaves	Flavonoids (luteolin)	20 mL/die of frozen artichoke juice (p.o)	Isocaloric-hypolipidic diet induced endothelial dysfunction	–	Reduction of VCAM-1 and ICAM-1
Gardenia jasminoides (Tang et al., 2006)	Rubiaceae	Fruits	Crocetin	(15, 30 mg/kg) p.o	Hypercholesterolemic rabbit	–	Restoration of EDR (Endothelium-dependent relaxation) of thoracic by increasing the vessel eNOS activity, leading to elevation of NO production.
Linum usitatissimum (Raluca et al., 2013)	Linaceae	Seeds	α-linolenic acid, lignan	15 g/100 g of food	Rats fed on a high-fat diet	–	Prevent leukocytes and platelets adhesion to endothelial cells and to reduce soluble adhesion molecules (sVCAM-1) and endothelial integrity markers (vWF)
Linum usitatissimum (Dupasquier et al., 2006)	Linaceae	Seeds	α-linolenic acid, lignin, PUFA	10% flaxseed-supplemented diet	Hypercholesterolemic conditions in New Zealand White rabbits	–	Attenuation of cholesterol-induced atherogenesis as well as abnormalities in endothelial-dependent vaso-relaxation
Punica granatum (Filomena et al., 2007)	Punicaceae	Whole fruit	Polyphones (punicalagin)	30–50 μL/day Extract diluted with water	Determination of cGMP and NOSIII bioactivity	–	Increased eNOS expression in endothelial cells
Scutellariae baicalensis (Kim et al., 2015)	Lamiaceae	Roots	Baicalein, wogonin, neobaicalein, and skullcapflavone	Dried root extract	LPS-induced RAW264.7 cells	–	Significant inhibition of NO production and iNOS expression
Vitis venifera (Jiang et al., 2015).	Vitaceae	Seeds	Proanthocyanidin	Proanthocyanidin extract	High glucose-induced increased levels of ICAM-1 and VCAM-1	–	Significant lowering of VCAM-1 and ICAM-1 levels via inhibition of NF-κB

shown significant inhibitory effects on upregulation iNOS and COX-2 enzymes which leads to production of pro-inflammatory mediators (Raghav et al., 2006) (Table 4).

The primary function of SMCs is to create vessel contraction in the presence of an external stimulus. During atherosclerosis, SMCs are activated, which leads to their migration from the medial portion of the arterial wall, proliferate and secrete extracellular matrix proteins that form a fibrous plaque. The migration of SMCs is influenced by low levels of NO, inflammatory response, physical factors like blood flow, matrix stiffness and sheer stress etc.

Curcumin, the active constituent of *C. longa*, has been reported to prevent SMCs migration by inhibiting MMP-9 expression (Yu and Lin, 2010). Sulforaphane, an active constituent from *Brassica oleracea* var *italica*, has been found to inhibit smooth muscle cell proliferation and migration by reducing MMP-9 activity via the Ras and RhoA/ROCK pathways (Hung et al., 2013).

5. Miscellaneous

5.1. *Inhibition of ACAT(Acyl CoA: Cholesterol Acyltransferase) activity*

ACAT enzyme esterifies the free cholesterol to cholesterol ester which aids in conversion of macrophage to foam cells (Dove et al., 2006). ACAT-1 plays a significant role in foam cell formation in macrophages. ACAT-1 is highly expressed by macrophage-derived foam cells in atherosclerotic lesions and upregulated during monocytic differentiation into macrophages. ACAT-2 is responsible for the cholesterol absorption process in intestinal mucosal cells. The progression of foam cells by these mechanisms is assumed to engage in succession of early atherosclerotic lesions. Thus, inhibition of ACAT enzyme serves as a target for the treatment of atherosclerosis (Xiao-Hua et al., 2013).

The ethanolic extract of *Glycyrrhiza glabra* has been reported to inhibit rat liver microsomal ACAT activity and to decrease cholesteryl ester formation in HepG2 cells along with a non-competitive type of inhibition against ACAT enzyme (Choi et al., 2007) (Table 5).

5.2. *Attenuation of CETP (Cholesteryl Ester Transfer Protein) activity*

CETP (Cholesteryl Ester Transfer Protein) is a hydrophobic glycoprotein that raises LDL and lowers the level of HDL. As described earlier, the higher amount of LDL leads to progression of atherosclerosis (Li et al., 2013; Norman, 2014). Thus by inhibiting CETP, development of atherosclerosis could be reduced. Kwon et al. (2003) have studied the effect of *Capsicum annum* powder in atherosclerotic rabbits and reported that *C. annum* attenuated atherosclerosis and plasma CETP enzyme activity (Kwon et al., 2003).

6. Conclusion

Pathophysiology of atherosclerosis is very intricate, which is known to involve several mechanisms such as oxidation of LDL,

Table 4 – Inflammatory process and smooth muscle cells migration and plaque formation.

Plant Name	Family	Part of plant	Active constituents	Dose	Model used	Positive Control	Inference
Cudrania tricuspidata (Carr.) (Ki Hun et al., 2006)	Moraceae	Root bark	Catecholic xanthones and flavonoids	–	LDL oxidation in TBARS assay	–	Anti-atherosclerotic and anti-inflammatory
Ruta graveolens L. (Raghav et al., 2006)	Rutaceae	Whole plant	Rutin	100–500 µg/mL methanol extract and rutin (20, 40 and 80 µM) for 2 hours	Murine macrophage cells (J-774) challenged with lipopolysaccharide (LPS)	–	Inhibitory effect on upregulation of iNOS and COX-2 enzymes
Xylopia aromatica (Lam.) Mart (Verena et al., 2014)	Annonaceae	Fruit	Alkaloids, flavonoids	Ethanolic extract	Inflammatory dysfunction induced by high refined carbohydrate-containing-diet in mice	Rutin (5, 10, 20, 30 and 40 µg/mL)	Attenuated glucose resistance and liver inflammation

Table 5 – Miscellaneous.

Plant Name	Family	Part of plant	Active constituents	Dose	Model used	Positive Control	Inference
Cajanus cajan (Luo et al., 2008)	Fabaceae	Seeds	Pinostrobin, quercetin, vitexin and cajanin stilbene acid	200 or 100 mg/kg Stilbene extract	Diet-induced hyperlipidemia in Kunming mice	Simvastatin	Hypocholesterolemic activity by enhancement of mRNA expressions of hepatic CYP7A1 and LDL-receptor.
Capsicum annum L. (Kwon et al., 2003)	Solanaceae	Fruit	Capsaicin	1% red pepper powder	Atherosclerosis in cholesterol-fed rabbits	–	Attenuated atherosclerosis and plasma CETP activity
Capsicum annum L. (Gupta et al., 2002)	Solanaceae	Fruit	Oleoresin	75 mg/kg body weight/day Methanolic extract	Atherogenic diet induced hypercholesterolemia in male gerbils	–	Reduced progression of hypercholesterolemia by increasing lipid excretion in fecal matter
Emblica officinalis (Antony et al., 2006)	Euphorbiaceae	Fruit	Flavonoids emblicanin-A- and emblicanin-B-	10 and 20 mg/kg (p.o) Methanolic extract	Cholesterol diet induced hypercholesterolemia in NZ white rabbits	–	Reversal of dyslipidemia and atheromatous plaques by prevention of LDL oxidation, by inhibition of HMG CoA reductase activity and elevating HDL level to enhance reverse cholesterol transport
Glycyrrhiza glabra (Choi et al., 2007)	Fabaceae	Root	Glabrol, isoprenyl flavonoid	Ethanolic extract	Rat liver microsomal ACAT activity	–	Inhibited rat liver microsomal ACAT activity and decreased cholesteryl ester formation in HepG2 cells along with a non-competitive type of inhibition against ACAT
Musa paradisiaca (Hamendra and Anand, 2007)	Musaceae	Fruit peel	Dopamine	100 mg/kg (p.o) Aqueous extract	Hypercholesterolemic diet-induced atherosclerosis	–	Hypolipidemic and anti-atherosclerotic with an alleviative role on thyroid dysfunctions and glucose homeostasis
Punica granatum (Hamendra and Anand, 2007)	Punicaceae	Fruit peel	Flavonoids, polyphenols	200 mg/kg (p.o) Methanolic extract	Hypercholesterolemic diet-induced atherosclerosis	–	Hypolipidemic and anti-atherosclerotic with an alleviative role on thyroid dysfunctions and glucose homeostasis
Scutellaria baicalensis Gerogi (Bak et al., 2014)	Lamiaceae	Root	Wogonin (Flavonoid)	Oral dose of Wogonin	db/db mice	–	Glucose and lipid metabolism related to enhanced PPARα and adiponectin expression via AMPK activation
Solanum lycopersicum (Fuiwara et al., 2012)	Solanaceae	Fruit	Tomatidine		Assessment of atherosclerosis in Apolipoprotein E-Deficient (E^0) Mice	–	Reduction of atherogenesis via suppression of ACAT-1 and ACAT-2
Solanum lycopersicum (Fujiwara et al., 2007)	Solanaceae	Fruit	Esculeoside A, Esculeogenin A	50 and 100 mg/kg/d	Assessment of atherosclerosis in Apolipoprotein E-Deficient (E^0) Mice	–	Reduction of atherogenesis via suppression of ACAT-1 and ACAT-2

endothelial cell dysfunctioning, lipoprotein level modification, adhesion of molecules, SMCs migration, plaque formation etc. Therapeutic agents available for the treatment of atherosclerosis produce their effect through one or more mechanisms. In case of plants, a number of chemical constituents are present and these chemical constituents work through different mechanisms. Although herbal medicines and phytochemicals provide an excellent option to the menace of atherosclerosis, still their utilization in treatment of atherosclerosis is very limited. Present curiosity in traditional medicine has led to the exploration and development of many herbal drugs for the management of atherosclerosis. Moreover, comparing the risk and benefit ratio of synthetic agents with therapeutic agents from herbal sources, we found that herbal sources have upper edge in benefit due to less side effects. Judicious use of herbal drugs (based on their mechanism of action) in management of atherosclerosis can provide an alternative platform.

Abbreviations

CVDs	cardiovascular diseases
CHD	coronary heart disease
SMCs	smooth muscle cells
VLDLs	very low-density lipoproteins
IDLs	intermediate-density lipoproteins
LDLs	low density lipoproteins
TG	triglyceride
TC	total cholesterol
HDLs	high-density lipoproteins
HMG CoA reductase	3-hydroxy-3-methylglutaryl co-enzyme A reductase
mmLDL	minimally modified LDL
ox-LDL	oxidized LDL
SR-A	scavenger receptor
CD36	cluster of differentiation
ACAT-1	Acyl-coenzyme A: cholesterol acyltransferase
ABCG1	ATP binding cassette
nCEH	neutral cholesterol ester hydrolase 1
ABCA1	ATP binding cassette transporter
MI	myocardial infarction
NO	nitric oxide
NOS	nitric oxide synthase
eNOS	endothelial nitric oxide synthase
iNOS	inducible nitric oxide synthase
SERBP-2	sterol regulatory binding protein

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