Medicinal plants and atherosclerosis: A review on molecular aspects

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Abstract: Atherosclerosis is an inflammatory vascular disease that is characterized by progressive accumulation of cholesterol in the arterial walls and it is a major cause of cardiovascular disease. Issues related to the side effects of synthetic drugs have in recent times, led to the misuse of drugs, a lack of patient consultations, and consequently, a disruption in meticulous disease control. Therefore, a new insight into medicinal plants has recently emerged and much research has been conducted on these herbs in an attempt to prepare novel naturally based drugs. The aim of this review article was to scrutinize the molecular mechanisms of medicinal plants possession effectiveness against atherosclerosis. To conduct the review, electronic searches were performed to retrieve potentially relevant publications, indexed within internet databases and reference textbooks concerning the effects and underlying molecular mechanisms of plants or their constituents used to treat atherosclerosis. Overall, medicinal plants facilitate atherosclerosis treatment through a variety of mechanisms which include the regulation of expression of inflammatory factors, stimulation of peroxisome proliferator-activated receptors (PPARs), inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase), promotion of ATP-binding cassette transporter A1 (ABCA1) as well as ATP-binding cassette transporter G (ABCG), facilitation of adiponectin activity, reduction of sterol regulatory element-binding proteins (SREBPs) and antioxidant activity. An increased perception of these herbal mechanistic links is an important prelude to the design of novel plant based drugs.

Key words: Atherosclerosis, Medicinal plants, Molecular mechanisms.
1. INTRODUCTION

An increased prevalence of hypertension and associated atherosclerosis is one of the most predominant causes of elevated mortality among younger age groups [1]. Atherosclerosis is an inflammatory vascular disease that is characterized by progressive accumulation of cholesterol in the arterial walls and it is a major cause of cardiovascular disease [2]. During atherosclerosis, two key events occur in the arterial walls: stimulation and differentiation of monocytes in the bloodstream, and uptake of low density lipoprotein (LDL) by macrophages to form foam cells that participate in the formation of atherosclerotic plaques. Adhesion molecules also contribute to leukocyte-endothelial interactions and monocyte leakage [3].

Many contributory risk factors to varying degrees either directly or indirectly, play a role in the development of atherosclerotic changes in blood vessels. These include cigarette smoking, hypertension, diabetes, obesity, hypercholesterolemia, and a family history of heart disease [1]. Issues related to the side effects of current synthetic agents have in recent times led to the misuse of drugs, a lack of patient consultations and consequently, a disruption in meticulous disease control. Therefore, a new insight into medicinal plants has recently emerged and considerable research has been conducted on these herbs. The use of medicinal plants to treat diseases has been attracting attention since ancient times. Over recent decades, communities in many countries have been using alternative medicine more and more, especially phytotherapy and dietary supplements to treat diseases such as atherosclerosis. In addition to reducing healthcare costs, medicinal plants have led to some reassuring outcomes and it is expedient to use such plants even as adjuncts especially when current therapies fail to control the disease. In addition, the generally weaker side effects of medicinal plants compared to synthetic drugs warrant extensive research on these plants [2].

Due to the health impact of atherosclerosis, the relative ineffectiveness and high cost of some conventional drugs plus their side effects, the use of medicinal plants with fewer adverse effects may well contribute towards improved treatment of atherosclerosis. Some of the currently used drugs worldwide have been developed from traditional agents with known mechanisms. Amassing knowledge about such drugs can serve as a starting point to screen natural isolated compounds and then to synthesize and develop drugs with similar structures. Research has been conducted on the mechanisms of action of medicinal plants used to treat atherosclerosis. Such studies are essential to develop new pharmaceutical formulations with improved effectiveness in relation to fewer side effects. The aim of the current review was to report the most effective medicinal plants employed to treat atherosclerosis and delineate their associated mechanisms of actions.
2. MATERIALS AND METHODS

To conduct this review, electronic searches were performed to retrieve potentially relevant publications, indexed in different internet databases, and reference textbooks to the molecular mechanisms of action of different plants, used to treat atherosclerosis, including inflammatory factors, agonists at peroxisome proliferator-activated receptors (PPARs), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), ATP-binding cassette transporter A1 (ABCA1), ATP-binding cassette transporter G (ABCG), adiponectin, and sterol regulatory element-binding proteins (SREBPs).

3. RESULTS

To date, a number of studies have been conducted on the molecular mechanisms of atherosclerosis and the medicinal plants that are effective against this disease. Much evidence has indicated that efficacy in treating atherosclerosis is mediated via several mechanisms including inflammation and other factors involved in the metabolism of lipids and glucose. These factors have been summarized in table 1 and are discussed below.

3.1. Inflammatory factors

At the onset of atherosclerosis, mononuclear leukocytes such as monocytes and T cells enter the arterial wall endothelium via a process requiring adhesion molecules. Transcription of these cell surface proteins is regulated by nuclear factor (NF)-κB [4]. NF-κB is a transcription factor that is activated when pro-inflammatory cytokines bind to their receptors at the endothelial surface. Binding molecules such as E-selectin, intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and P-selectin are induced by this method. VCAM-1 is not only induced by stimulation of cytokines but also produced in response to pro-inflammatory macromolecules [5,6]. Hypercholesterolemia also causes the oxidation of lipoproteins and the oxidation of VCAM-1 at the aortic endothelial surface [7,8].

At the surface of endothelial cells, ICAM-1 is induced through cytokine-dependent pathways, and ICAM-1 expression is increased by hemodynamic oxidative stress or hypertension; as a result, hypercholesterolemia and hypertension are two main risk factors for atherosclerosis that cause leukocyte adhesion to arteries. Adhesion is a multistep process that causes leukocytes to attach to artery walls. Adhesion is dependent on the reaction of E-selectin, ICAM-1, and VCAM-1 with the endothelium [9] and inhibition of ICAM-1 and VCAM-1 in particular reduces the development of fatty streaks [10].

It is necessary for leukocytes to migrate prior to binding to the vessel wall. The cell migration is accomplished by chemotactics including monocyte chemotactic protein-1 (MCP-1) [11]. MCP-1
is expressed in all steps of atherosclerosis such that its decreased expression arrests atherosclerotic lesion growth [12].

Macrophages play an important role in inflammation and the immune response which are dependent on the capacity to produce oxygen free radicals, proteases, complement factors, and cytokines, all of which are important in atherosclerosis. In relation to this, the differentiation of monocytes to macrophages is stimulated by macrophage colony-stimulating factor (M-CSF) [13].

Macrophage uptake is aided by oxidatively modified lipoproteins through receptors that are regulated by certain cytokines such as tumor necrosis factor α (TNF-α). TNF-α, TNF-β, interleukin 2 (IL-2), and interferon-γ (IFN-γ) all causing activation of macrophages and inflammation (14). IL-2 is produced by lesion cells and causes differentiation of T helper 1 (Th1) cells [15]. IFN-γ is an active immune cytokine that can activate macrophages for an inflammatory response [16]. Both TNF-α and IL-1 are also present in the lesions [17] and cause proliferation of smooth muscle cells (SMCs) [18]. The pathway of cytokine inflammation is activated by the expression of TNF-α, IL-1, and C-reactive protein (CRP) [19]. These cytokines stimulate macrophages to secrete matrix metalloproteinase 9 (MMP-9). MMP-9 causes migration of the SMCs in atherosclerosis and due to stimulation of inflammatory cytokines, vascular SMCs migrate from media to intima and produce collagen, which induces the formation of a fibrous cap in the lesions [20].

To date, various studies have been conducted on the anti-inflammatory effects of medicinal plants in the treatment of atherosclerosis. Notably, Lee et al., demonstrated in 2001, that treatment with the citrus flavonoids naringin and naringenin caused a significant decrease in VCAM-1 and MCP-1 in hypercholesterolemic rabbits [21]. While Suh et al., reported five years later that cryptotanshinone isolated from Salvia miltiorrhiza decreased the expression of MMP-9 and NF-κB [22]. A 3-month clinical trial, demonstrated that virgin olive oil exerted an anti-inflammatory effect and led to a decrease in CRP, IL-6, and endothelial and monocyte adhesion molecules in addition to chemokines in patients with atherosclerosis [23].

The aqueous, ethanolic, and chloroform extracts of S. miltiorrhiza inhibited MMP-9 and prevented the migration of human aortic smooth muscle cells. In addition, treatment with S. miltiorrhiza decreased the production of adhesion molecules and the fibrosis of atherosclerotic plaques in apolipoprotein E–deficient mice fed with high-fat diet [24]. Wang and coworkers (2013) showed that the use of a Bu-shen-Ning-Xin decoction initiated a decrease in the expression of NF-κB, monocyte chemoattractant protein 1 (MCP-1), ICAM-1, VCAM-1, and E-selectin [25]. Moreover, an ethanolic extract of Gastredia elata displayed an inhibitory action against MMP-2/-9 in human umbilical vein endothelial cells [26].

Furthermore, a Ginkgo biloba extract was found to decrease IL-1β expression and VSMC growth in hypercholesterolemic rabbits. In addition, 8-week treatment with this plant extract also
decreased the expression of IL-1β, TNF-α, and IL-10 in the brains of hypercholesterolemic rats with atherosclerosis [27].

3.2. Peroxisome proliferator-activated receptors (PPARs)

As a chronic inflammatory disease, atherosclerosis develops due to a disruption of lipid metabolism. The accumulation of cholesterol-rich lipoproteins in arterial walls causes monocytes to bind to the endothelium and differentiate to macrophages. These macrophages play an important role in producing chemokines, cytokines, and reactive oxygen species (ROS) that trigger the early stages of lesion formation. PPARs consist of PPAR-α, β, and γ [28] and are expressed in the arterial walls. PPAR agonists are effective in the treatment of atherosclerosis [29] such that the activities of these receptors are beneficial in the arterial walls and in this context PPAR-γ regulates a pathway of cholesterol efflux in macrophages [30]. PPAR-γ also regulates CD36 expression, and both PPAR-γ and PPAR-α induce the expression of liver X receptor α (LXR-α) and ABCA1 [30, 31]. In addition, PPAR activators inhibit the expression of inflammatory genes in the macrophages [32].

In mice with an LDL receptor deficiency, treatment with PPAR-γ agonists evokes a decrease in inflammatory mediators [32]. Thus, Li et al., reported in 2004 that PPAR-γ and PPAR-α ligands prevented lipid accumulation, and that PPAR-γ ligands decreased cholesterol esterification in macrophages.

LXR-α contributes to the activity of PPAR ligands on atherosclerosis. This receptor is a regulator of the expression of ABCG and ABCA1 and it has been postulated that inhibiting foam cell formation using PPAR-α requires LXR expression. In relation to this, ABCG1 stimulates the removal of cholesterol from macrophages [33]. It has also been reported that soy isoflavones exert not only hypocholesterolemic but also anti-atherosclerotic effects by means of an elevated expression of both PPAR-γ and PPAR-α in rats with type 2 diabetes [34].

It has been demonstrated that oral treatment with a Pandanus tectorius fruit extract augmented mRNA levels of PPAR-α and PPAR-α-regulated genes as well as AMP-activated protein kinase (AMPK) in the liver of hyperlipidemic hamsters. The PPAR-α-related genes in question, included those for acyl-CoA oxidase (ACO), carnitine palmitoyltransferase 1 (CPT1), hormone sensitive lipase (HSL), and lipoprotein lipase (LPL) that serve as markers of upregulation in the PPAR-α-related hypolipidemic pathway. In addition, transcription of PPAR-γ (insulin sensitivity) was shown to be increased [35].
A further study has shown that 8-week oral treatment with an extract of *Rheum undulatum* produced an overexpression of PPAR-α and CPT1 in the liver resulting in a reduction of total and low density lipoprotein-cholesterol blood levels [36].

Park et al., (2005) reported that extracts of mulberry leaf (0.5%), Korean red ginseng (0.5%), and banana leaf (0.5%), decreased blood glucose, insulin, triglyceride (TG), and HbA1c but they also increased gene expression of hepatic PPAR-α and PPAR-γ in the adipose tissue of non-insulin-dependent diabetic mice [37]. It was similarly demonstrated that ethanolic extracts of *Astragalus membranaceus* and *Pueraria thomsonii* generated increased activity of PPAR-α and PPAR-γ [38]. Likewise, an aqueous *Salacia oblonga* root extract administered by oral gavage (≤ 900 mg/kg) for 28 days in rats increased PPAR-α activity and as a consequence, it activated hypolipidemic pathways leading to a decrement in lipids, especially TG [39].

Using reverse transcription polymerase chain reaction (RT-PCR) and microarray technology, it has been disclosed that 150 mg/kg of berberine administered over a nine week period, enhanced the expression of PPAR-α and LXR-α in diabetic hamsters [40]. Correspondingly, it has been reported in hypercholesterolemic rats that oral treatment with 50-200 mg/kg of *Corni fructus* extract on a daily basis for 10 days diminished not only the atherogenic index but also total cholesterol (TC) whilst simultaneously increasing the expression of PPAR-α and LXR-α [41]. Additionally, oral treatment of hypercholesterolemic mice with a methanolic mulberry (*Morus alba*) leaf extract for four weeks raised the hepatic gene expression of PPAR-α and downregulated the expression of genes involved in cholesterol biosynthesis including sterol 14α-demethylase cytochrome P450 (CYP51) [42].

### 3.3. ATP-binding Cassette Transporter G (ABCG) and ATP-binding Cassette Transporter A1 (ABCA1)

An inverse correlation between plasma high density lipoprotein (HDL) levels and the risk of atherosclerosis reflects the role of HDL and its receptors (generally along with Apolipoprotein A1 and A2 [ApoAI and ApoAII]) in receiving and transporting cholesterol. The uptake of additional cholesterol from macrophage foam cells by HDL and ApoAI is considered one of the most important protective mechanisms of HDL against atherosclerosis [43]. Studies of defects in human and animal HDL have indicated that the membrane lipid translocases ABCA1 and ABCG1, are the main markers of plasma HDL levels and they represent important protective factors against atherosclerosis [44-46]. ABCA1 is a prominent member of the ABC transporter family, and it is largely expressed in liver and tissue macrophages [47]. ABCG1, has recently been demonstrated to be one of the important regulators of cholesterol transport in reverse cholesterol transfer (RCT). RCT is an anti-atherosclerotic process and refers to the net movement of additional cholesterol from peripheral tissues, such as arterial wall macrophages, back to the liver alongside HDL formation.
The LXRs regulating ABC transporter genes are key sub-processes involved in RCT. The most important members of this family are ABCA1 and ABCG1 [48,49] being the main regulators of cholesterol and phospholipid efflux from macrophage foam cells. ABCA1 transports these compounds to cholesterol-free lipoproteins stimulating formation of HDL, but ABCG1 is responsible for transporting cholesterol to mature HDL.

ABCA1 is essential to the transport of cholesterol from inside the plasma membrane and in maintaining equitable levels of HDL. The role of ABCA1 in exporting cell cholesterol was revealed when the ABCA1 gene was found to be defective in patients with Tangier disease [50]. In the absence of ABCA1, these patients had very low levels of HDL, could not transport cholesterol from the cell to ApoA1, and presented with accumulated cholesteryl ester in many tissues, particularly the arteries. Hence, early atherosclerosis is another complication of Tangier disease. Besides that, overexpression of ABCA1 in genetically modified mice leads to a significant decrease in the size and complexity of atherosclerotic lesions and an increased export of cholesterol from the cell promoting HDL biogenesis [51,52]. Thus, an ethanolic extract of Brazilian red propolis has been shown to stimulate the expression of PPAR-γ, LXR, and ApoA1 in addition to the activity of ABCA1 [53].

Chen et al. (2013) studied the anti-atherosclerotic properties of Hibiscus salodariffa leaf extract which is a rich source of flavonoids. This extract increased the expression of the LXR-α/ABCA1 pathway thereby preventing cholesterol uptake by macrophages and delaying the development of atherosclerosis. In addition, administration with Xuemai Ning caused an increase in ABCA1 expression in hypercholesterolemic rabbits [54,55]. What is more, an extract of Crataegus pentaegyna caused a marginal increase in the expression of ABCA1 and PPAR-α in hypercholesterolemic rat hearts [56]. Analogously, an alcoholic extract of Allium sativum boosted the expression of ABCA1 in a macrophage containing culture medium [57].

3.4. 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitors

Hypcholesterolemic drugs slow down atherosclerosis progression, and HMG-CoA reductase inhibitors contribute to this effect [58] such that they inhibit metalloproteinase (MMP) preventing the migration and proliferation of smooth muscle cells, and the accumulation of cholesterol in macrophages. Generally, HMG-CoA reductase inhibitors interfere with the main atherogenic processes that occur in the arterial walls [59]. In 2013, Yang et al. reported that oral treatment with gypenoside (50-200 mg/kg daily for five weeks) caused a 20-50% decrease in HMG-CoA reductase activity with a consequent decline in cholesterol synthesis in the liver, alongside decreased TC, TG, glutathione peroxidase, superoxide dismutase, catalase, and malondialdehyde [60].

It has also been reported that 4-week oral treatment with a methanolic Aconitum heterophyllum root extract (200 and 400 mg/kg) lowered the levels of TC, TG, and ApoB in addition to raising
serum HDL cholesterol (HDL-C) and ApoA levels in obese rats. The A. heterophyllum extract also decreased HMG-CoA reductase activity in the liver and subsequently, the synthesis of endogenous cholesterol whilst stimulating the activity of lecithin–cholesterol acyltransferase to generate elevated HDL-c [61].

Jain et al. reported in 2010, that 30-day treatment of rats with ≤ 600 mg/kg of methanolic moringa extract induced a fall in TC and LDL cholesterol (LDL-C) levels compared to controls. The hypocholesterolemic effect of this plant was ascribed to the inhibition of cholesterol reabsorption from endogenous sources and an increased release into feces as neutral steroids. In addition, HMG-CoA reductase activity decreased in response to treatment with this extract [62]. Likewise, an ethanolic Ananas comusus leaf extract caused a decrease in TG and TC concentrations in hypolipidemic rats. The extract also significantly inhibited HMG-CoA reductase activity [63].

Additionally, it was also shown in a study by Vaidya et al. in 2009, that 7-day treatment with swertiamarine (isolated from Enicostemma littorale) in rats on a high-cholesterol diet decreased cholesterol and TG levels via HMG-CoA reductase inhibition and it also increased the excretion of bile acids and esters [64]. In addition, in hyperlipidemic rats, pulverized Terminalia arjuna bark extract given by oral gavage, initiated a decrease in TC, TG, LDL-C, and very low density lipoprotein cholesterol (VLDL-C) in a dose-dependent manner in [65]. Moreover, oral treatment with 100 and 200 mg/kg of the dried pulp of Aloe vera leaf in hyperlipidemic rats produced a considerable decrease in TC, TG, VLDL-C, and LDL-c levels as well as the atherogenic index in addition to augmenting HDL-c. Besides this, the treatment instigated a substantial decrease in the HMG-CoA reductase activity [66].

Brusq et al. (2006) showed that 15 µg/ml of berberine activated AMPK, a sensor of energy in mammalian cells. HMG-CoA reductase and acetyl-CoA carboxylase are implicated in the synthesis of cholesterol and fatty acids, and because they are inactivated by AMPK-mediated phosphorylation, the overall outcome was an inhibition of cholesterol and TG production [67]. In another study, it was reported that treatment with ≤ 1% of lyophilized green tea powder in rats fed a diet containing 6% fructose, there was a reduction in TG concentration, while fructose produced an increase in serum TG and TC levels. It was notable that green tea also diminished ABCA1 and HMG-CoA reductase gene expression [68].

Black chokeberry (Aronia melanocarpa) extract (50 and 100 µg/ml), added to an in vitro culture medium containing human colorectal adenocarcinoma cells (Caco-2) decreased cholesterol synthesis. There was also a drop in the gene expression for ABCA1 and HMG-CoA reductase and it was postulated that the hypolipidemic effects of this medicinal plant might be partly assigned, to increased apical efflux of LDL-derived cholesterol [69].
3.5. Sterol regulatory element binding proteins (SREBPs)

SREBPs are transcription factors that regulate lipid hemostasis by modifying the expression of enzymes necessary for the synthesis of cholesterol, TG, phospholipids, and fatty acids. Accordingly, they contribute to the control of atherosclerosis [70]. SREBP expression leads to increased vascular fatty streaks and fibrous-fatty plaques. In addition, the formation of foam cells in atherosclerotic lesions is associated with decreased gene expression of SREBPs [71]. Thus, a reduced SREBP gene expression has been observed in diabetic hamsters treated with 150 mg/kg of berberine for nine weeks [40] and also in rats treated with lyophilized pulverized green tea (0.5% and 1%) for six weeks [68]. This finding was substantiated by Kim et al. with A. melanocarpa extract in Caco-2 cells [69], and by Kobayashi et al. in hypercholesterolemic mice treated with methanolic M. alba (0.1 and 1 mg/ml) for four weeks [42]. All of these studies reported that lipogenic pathways in the liver were inhibited by decreasing the gene expression of SREBPs and it has also been concluded that the extent of LXR/PPAR/SREBP participation in the function of the vascular intima varies during atherogenesis with respect to the individual [72].

3.6. Adiponectin

Adiponectin firstly suppresses TNF-α-1 which induces the expression of adhesion molecules in vessel endothelial cells by inhibiting the transcription of NF-κB and subsequently, the expression of the pro-inflammatory cytokine IL-8 in endothelial cells [73,74]. Secondly, it represses growth factor causing proliferation of SMCs by inhibiting mitogen activated protein kinase [75]. Thirdly it inhibits foam cell formation, and the release of TNF-α by macrophages [76]. Increased expression of adiponectin in patients with atherosclerosis diminishes the expression of VCAM-1 and TNF-α in the aorta, restricting the progression of atherosclerotic lesions, thereby exerting an anti-atherosclerotic effect [77]. On top of these actions, adiponectin augments the expression of anti-inflammatory cytokines and metalloproteinase inhibitors in macrophages thereby promoting plaque stability [78].

Medicinal plants are effective in facilitating adiponectin activity. Examples include Momordica charantia [79], Allium sativum [80], Irvingia gabonensis, Radix Astragali [81], Astragalus membranaceus [82], Green tea [83] Sasa Borealis [84], Ganoderma Lucidum [85], Brassica rapa, Phaseolus vulgaris, Brassica rapa, Glycine max, Spinacia oleracea, Pisum sativum, Raphanus sativus, Arctium lappa, Momordica Charantia, and Brassica oleracea [86].

3.7. Plants antioxidants and Atherosclerosis

As mentioned earlier, hyperlipidemia is a risk factor that can accelerate the development of atherosclerosis and the progression of atherosclerotic lesions. It has been shown that boosting intracellular reactive oxygen species (ROS) enhances atherosclerosis development. Malondialdehyde (MDA), an oxidant stress marker, is increased during the development of
hyperlipidemia, so that there is a correlation between hyperlipidemia and atherogenic index (AI) which is considered as an important risk factor for atherosclerosis. ROS are generated during physiological and pathophysiological oxidative metabolism in mitochondria. Both ROS and reactive nitrogen species (RNS) may react with various biomolecules, such as nucleic acids, proteins, lipids and carbohydrates to interfere with cell function. In normal physiological conditions, a balance exists between free radical generation and antioxidant defense systems. However, any imbalance in this equilibrium causes oxidative stress and this is considered as a component of tissue damage mechanisms in variety of human disorders including atherosclerosis [98]. Enzymatic and non-enzymatic antioxidants play important roles in alleviating free radical-induced tissue damage. Serum MDA has been shown to be higher in hyperlipidemic subjects and regresses following antioxidant supplementation [87]. Furthermore, recently published work has strongly suggested a crucial role for nutritional and pharmacological approaches towards antioxidants in the prevention and even treatment of atherosclerosis. Antioxidant application has also been suggested as an adjunct to hypolipidemic therapy to improve the impact of these drugs on coronary artery disease. Production of oxidized LDL (Ox-LDL) is a key factor in atherosclerosis. It has also been suggested that antioxidants are able to suppress oxidative modification of LDL. Hence, antioxidant availability in hyperlipidemic subjects has been suggested to help in preventing the course of problem [88]. In this regard, most medicinal plants and functional foods effective on hyperlipidemia, act in part, through antioxidant activity [88].

Table1. Mechanisms actions of medicinal plants on atherosclerosis

<table>
<thead>
<tr>
<th>Plants</th>
<th>Administration method</th>
<th>Study design</th>
<th>Main findings</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>PPARs</strong></td>
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<tr>
<td><em>Pandanus tectorius</em></td>
<td>Oral</td>
<td>Hyperlipidemic hamsters</td>
<td>Increased expression of hepatic AMPK, PPARα, LPL, ACO, HSL, PPARγ, and CPT1.</td>
<td>[35]</td>
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<tr>
<td><em>Rheum undulatum</em></td>
<td>Oral</td>
<td>Hyperlipidemic mice</td>
<td>Increased hepatic PPARα</td>
<td>[36]</td>
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<tr>
<td>Plant/Organism</td>
<td>Administration</td>
<td>Animal Model</td>
<td>Biological Effects</td>
<td>References</td>
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<tr>
<td>Mulberry, Korean red ginseng and Banana</td>
<td>Oral</td>
<td>Diabetes in db/db mice</td>
<td>Decreased blood glucose, insulin, TG, and HbA1c and increased expression of PPARα in liver and PPARγ in adipose tissue</td>
<td>[37]</td>
</tr>
<tr>
<td>Astragalus membranaceus and Pueraria thomsonii</td>
<td>Addition to cell culture medium</td>
<td>Culture medium containing cervical carcinoma (Hela) cells and HepG2.</td>
<td>Increased activity of PPARα and PPARγ</td>
<td>[38]</td>
</tr>
<tr>
<td>Salacia oblonga</td>
<td>Oral</td>
<td>Rats</td>
<td>Increased liver weight and hepatic PPARα activity</td>
<td>[39]</td>
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<tr>
<td>Berberine</td>
<td>Oral</td>
<td>Diabetic hamsters</td>
<td>Increased expression of hepatic PPARα and LXRα</td>
<td>[40]</td>
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<tr>
<td>Cornifructus</td>
<td>Oral</td>
<td>Hypercholesterolemic rats</td>
<td>Decreased atherogenic index and TC and increased hepatic PPARα expression and excretion of bile acids</td>
<td>[41]</td>
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<tr>
<td>Mulberry (Morus alba)</td>
<td>Oral</td>
<td>Hypercholesterolemic mice</td>
<td>Increased expression of hepatic PPAR-α and decreased expression of genes for cholesterol</td>
<td>[42]</td>
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<tr>
<td>Supplement</td>
<td>Route</td>
<td>Condition</td>
<td>Effects</td>
<td>Reference</td>
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<td>Gypenoside</td>
<td>Oral</td>
<td>Hypercholesterolemic rats</td>
<td>Decreased TC, TG, GSH-Px, SOD, CAT and MDA in serum and hepatic HMG-CoA reductase activity</td>
<td>[60]</td>
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<tr>
<td><em>Aconitum heterophyllum</em></td>
<td>Oral</td>
<td>Obese rats</td>
<td>Decreased level of TC, TG, and ApoB, and hepatic HMG-CoA reductase activity and increased serum HDL-C and ApoA and LCAT activity</td>
<td>[61]</td>
</tr>
<tr>
<td><em>Ananas Comusus</em></td>
<td>Oral</td>
<td>Hyperlipidemic mice</td>
<td>Decreased activity of HMG-CoA reductase and PL and increased activity of LPL</td>
<td>[63]</td>
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<tr>
<td><em>Enicostemma littorale</em></td>
<td>Oral</td>
<td>Hyperlipidemic rats</td>
<td>Inhibited HMG-CoA reductase and decreased TG and TC and increased excretion of esterol bile acids</td>
<td>[64]</td>
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<tr>
<td><strong>Terminalia arjuna</strong></td>
<td>Oral</td>
<td>Hyperlipidemic rats</td>
<td>Decreased TC, TG, LDL-C, VLDL-C and HMG-CoA reductase activity and increased LCAT and LPL</td>
<td>[65]</td>
</tr>
<tr>
<td><strong>Aloe vera</strong></td>
<td>Oral</td>
<td>Hyperlipidemic rats</td>
<td>Decreased TC, TG, VLDL-C, atherogenic index LDL-C, and HMG-CoA reductase and increased HDL</td>
<td>[66]</td>
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<tr>
<td><strong>Green tea</strong></td>
<td>Oral</td>
<td>Rats fed with the diet containing 6% fructose</td>
<td>Decreased expression of FAS, SCP1, ABCA1, HMG-CoA reductase, and NPC1L1</td>
<td>[68]</td>
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<tr>
<td><strong>Black chokeberry</strong> <em>(Aronia melanocarpa)</em></td>
<td>Addition to cell culture medium</td>
<td>Culture medium containing Caco-2 (Human colorectal adenocarcinoma cell)</td>
<td>Decreased expression of HMG-CoA reductase, FAS, ABCA1, ACOX1</td>
<td>[69]</td>
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</tbody>
</table>

**inflammatory biomarkers**

<p>| <strong>Citrus flavonoids</strong> <em>(naringin and naringenin)</em> | Oral | Hypercholesteremic rabbits | Decreased expression of VCAM-1 and MCP-1 | [21] |
| <strong>Virgin olive oil</strong> | Oral | Patient with atherosclerosis | Decreased expression of CRP, IL-6 and endothelial and | [23] |</p>
<table>
<thead>
<tr>
<th><strong>Salvia miltiorrhiza</strong></th>
<th>Addition to cell culture medium</th>
<th>Cell cultures of human aortic smooth muscle cells</th>
<th>Decreased expression of MMP-9, NF-κB</th>
<th>[22]</th>
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<tr>
<td>Salvia miltiorrhiza</td>
<td>Addition to cell culture medium</td>
<td>ApoE−/−-mice and cell culture of human aortic smooth muscle cells</td>
<td>Inhibition of MMP-9</td>
<td>[24]</td>
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<td><strong>Bu-shen- Ning-Xin Decoction</strong></td>
<td>Addition to cell culture medium</td>
<td>Culture medium containing human umbilical vein endothelial cells</td>
<td>Decreased expression of NF-κB, MCP-1, VCAM-1 and E-selectin</td>
<td>[25]</td>
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<tr>
<td><strong>Gastredia elata</strong></td>
<td>Addition to cell culture medium</td>
<td>Culture medium containing human umbilical vein endothelial cells</td>
<td>Inhibition of MMP-2/−9 activity</td>
<td>[26]</td>
</tr>
<tr>
<td><strong>Ginkgo biloba</strong></td>
<td>Oral</td>
<td>Hypercholesteremic rabbits and Hypercholesteremic rats</td>
<td>Decreased expression of IL-1β and decreased growth of VSMC and decreased expression of IL-1β, TNF-α and IL-10</td>
<td>[27]</td>
</tr>
</tbody>
</table>

**ABCA and ABCG**
<table>
<thead>
<tr>
<th><strong>Brazilian red propolis</strong></th>
<th><strong>Hibiscus saloddariffa</strong></th>
<th><strong>Xuemai ning</strong></th>
<th><strong>Crataegus pentaegyna</strong></th>
<th><strong>Allium sativum</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition to cell culture medium</td>
<td>Addition to cell culture medium</td>
<td>Oral</td>
<td>Oral</td>
<td>Addition to cell culture medium</td>
</tr>
<tr>
<td>Cell culture medium</td>
<td>Culture medium containing murine macrophage cell line</td>
<td>Hypercholesterolemic rabbits</td>
<td>Hypercholesterolemic rats</td>
<td>Culture medium containing macrophage cells</td>
</tr>
<tr>
<td>Increased expression of PPARγ, LXR ApoA-1 and activity of ABCA1</td>
<td>Increased expression of LXRα/ABCA1</td>
<td>Increased expression of ABCA1</td>
<td>Increased expression ABCA1, LXRα, PPARα</td>
<td>Increased expression of ABCA1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[53]</td>
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</tbody>
</table>

**SREBPs**

<table>
<thead>
<tr>
<th>Berberine</th>
<th>Green tea</th>
<th>Black chokeberry (Aronia melanocarpa)</th>
<th>Mulberry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Oral</td>
<td>Addition to cell culture medium</td>
<td>Oral</td>
</tr>
<tr>
<td>Diabetic hamsters</td>
<td>Rats fed with diet containing 6% fructose</td>
<td>Culture medium containing Caco-2 (Human colorectal adenocarcinoma cell)</td>
<td>Hyperlipidemic mice</td>
</tr>
<tr>
<td>Decreased expression of SREBPs</td>
<td>Decreased expression of SREBP-1c</td>
<td>Decreased expression of SREBP-2</td>
<td>Decreased expression of</td>
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<td></td>
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</tr>
</tbody>
</table>

<p>| | | | | [69] | [42] |</p>
<table>
<thead>
<tr>
<th>Plant/Materia Medica</th>
<th>Administration</th>
<th>Animal Model</th>
<th>Effect on Adiponectin</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morus alba</strong></td>
<td>Oral</td>
<td>C57BL/6J mice</td>
<td>Decreased expression of FAS, SREBP-1a, and GPAT</td>
<td>[72]</td>
</tr>
<tr>
<td><strong>Aloe vera</strong></td>
<td>Oral</td>
<td>C57BL/6J mice</td>
<td>Decreased expression of FAS, SREBP-1a, and GPAT</td>
<td>[72]</td>
</tr>
<tr>
<td><strong>Adiponectin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Momordica charantia</strong></td>
<td>Addition to cell culture medium</td>
<td>Culture medium containing 3T3-L1 cells</td>
<td>Increased expression of adiponectin</td>
<td>[79]</td>
</tr>
<tr>
<td><strong>Allium sativum</strong></td>
<td>Oral</td>
<td>Patient with Atherosclerosis</td>
<td>Increased levels of adiponectin</td>
<td>[80]</td>
</tr>
<tr>
<td><strong>Irvingia gabonensis</strong></td>
<td>Addition to cell culture medium</td>
<td>Culture medium containing 3T3-L1 cells</td>
<td>Increased expression of adiponectin</td>
<td>[81]</td>
</tr>
<tr>
<td><strong>Radix astragali and Astragalus membranaceous</strong></td>
<td>Oral</td>
<td>Obese mice</td>
<td>Increased levels of adiponectin</td>
<td>[81, 82]</td>
</tr>
<tr>
<td><strong>Green tea</strong></td>
<td>Oral</td>
<td>Hyperlipidemic mice</td>
<td>Increased concentration of adiponectin</td>
<td>[83]</td>
</tr>
<tr>
<td><strong>Sasa borealis</strong></td>
<td>Oral</td>
<td>Obese C57/BL6J mice</td>
<td>Increased levels of adiponectin</td>
<td>[84]</td>
</tr>
</tbody>
</table>
**Ganoderma lucidum**  
Addition to cell culture medium  
Murine Pre-adipocyte Cell Line, 3T3-L1 ptr_3242 202..207  
Increased expression of adiponectin  
[85]

**Brassica rapa, Phaseolus vulgaris, Brassica rapa, Glycine max, Spinacia oleracea, Pisum sativum, Raphanus sativus, Arctium lappa, Momordica charantia and Brassica oleracea**  
Addition to cell culture medium  
3T3-L1 Adipocyte s  
Increased activity of adiponectin  
[86]

ABCA1: ATP-binding cassette transporter A1; ABCG: ATP-binding cassette transporter G; ACOX1: acyl-CoA oxidases1; CRP: C-reactive protein; AMPK: 5' Adenosine monophosphate-activated protein kinase; ACO: Acyl-CoA oxidase; CPT1: Carnitine palmitoyltransferase 1; HSL: Hormone sensitive lipase; LPL: Lipoprotein lipase; LXRα: Liver X receptor α; TC: Total cholesterol; CYP51: Cytochrome P450, family 51; GSH-Px: Glutathion peroxidase, SOD: Superoxide dismutase, MDA: Malondialdehyde; ApoB: Apolipoprotein B; HMG-CoA Reductase: 3-Hydroxy-3-methyl-glutaryl-coenzyme A reductase; HDL-C: High-density lipoprotein cholesterol; LCAT: Lecithin cholesterol acyltransferase; VLDL-C: Very low-density lipoprotein cholesterol; FAS: Fatty acid synthase; SCP1: Sterol carrier and lipid transfer proteins; NPC1L1: Niemann-Pick C1-Like 1; TG: Triglyceride; VCAM-1: Vascular cell adhesion molecule-1; MCP-1: Monocyte chemoattractant protein-1; SREBP: Sterol regulatory element-binding proteins; PPARs: Peroxisome proliferator-activated receptor; IL-6: Interloukin 6; MMP-9: Matrix metalloproteinase; VSMC: Vascular smooth muscle cells; SREBP: sterol regulatory element binding protein ; GPAT: Glycerol phosphate acyltransferase

**4. CONCLUSION**

Currently, atherosclerosis is a major health issue in most communities. Due to the convenience of access, relatively fewer side effects, and lower costs, medicinal plants can serve as alternatives or adjuncts to synthetic drugs. Overall, medicinal plants have been reported to benefit the treatment of atherosclerosis through different mechanisms including the regulation of expression
and levels of inflammatory factors, stimulation of PPARs, inhibition of HMG-CoA reductase, promotion of ABCA1 and ABCG, facilitation of adiponectin, reduction of SREBPs and antioxidant activity. The majority of studies have investigated the effects of these plants in treating atherosclerosis but fewer studies have been conducted to investigate the mechanisms of their action on this disease. Gathering knowledge concerning such mechanisms can only assist in the development of novel drugs. Further research is therefore warranted to investigate the effects of medicinal plants and their chemical constituents in treating atherosclerosis.

REFERENCES


[56] Ghanbari-Niaki A, Ghanbari-Abarghooi S, Rahbarizadeh F, Zare-Kookandeh N, Gholizadeh M, Roudbari F, Zare-Kookandeh A. Heart ABCA1 and PPAR-α genes expression responses in
male rats: effects of high intensity treadmill running training and aqueous extraction of Black *Crataegus-Pentaegyna*. Res Cardiovasc Med 2013;2:153-159


[81] Oben JE, Ngondi JL, Blum K. Inhibition of Irvingiagabonensis seed extract (OB131) on adipogenesis as mediated via down regulation of the PPARgamma and leptin genes and up-regulation of the adiponectin gene. Lipids in Health and Disease 2008; 7(1): 1-6.


