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Medicinal Herbs Effective Against Atherosclerosis: Classification According to Mechanism of Action

Jae-Yong Kim and Sang Hee Shim*

Colleage of Pharmacy, Duksung Woman's University, Seoul 01369, Republic of Korea

Abstract

Atherosclerosis is a widespread and chronic progressive arterial disease that has been regarded as one of the major causes of death worldwide. It is caused by the deposition of cholesterol, fats, and other substances in the tunica intima which leads to narrowing of the blood vessels, loss of elasticity, and arterial wall thickening, thus causing difficulty in blood flow. Natural products have been used as one of the most important strategies for the treatment and prevention of cardiovascular diseases for a long time. In recent decades, as interests in natural products including medicinal herbs have increased, many studies regarding natural compounds that are effective against atherosclerosis have been conducted. The purpose of this review is to provide a brief overview of the natural compounds that have been used for the treatment and prevention of atherosclerosis, and their mechanisms of action based on recent research.

Key Words: Atherosclerosis, Medicinal herb, Mechanism of action, Cholesterol

INTRODUCTION

Atherosclerosis, the underlying cause of cardiac ischemia, heart failure, heart attack, stroke, and peripheral vascular disease, is known to be one of the major causes of death and morbidity worldwide. Endothelial cell injury, damage, and dysfunction in the heart are characteristic properties of atherosclerosis. Endothelial damage leads the build-up of plaque in the damaged area and narrowing of the arteries, as well as cholesterol accumulation on the artery wall and monocytes adhesion to the endothelium. This process leads to chronic inflammation and eventually causes stenosis or thrombosis (Insull, 2009).

Natural products have been regarded as important all over the world since the beginning of human civilization for many purposes including medicinal use. Like in many other diseases, medicinal herbs have been used to treat patients with atherosclerosis. However, elucidation of the mechanisms of action (MOAs) of these herbs has just started, via the use of cellular models for anti-atherogenic natural product screening (Orekhov, 2013; Orekhov *et al*., 2015; Orekhov and Ivanova, 2016) or extensive reviews on specific plants that have been used for the prevention of atherosclerosis (Prasad, 2010; Varshney and Budoff, 2016) However, in this review, recent studies regarding natural products, and more specifically medicinal herbs, were sorted and described according to their MOAs against atherosclerosis to increasing our understanding of these plants.

BLOOD LIPID-LOWERING EFFECTS OF MEDICINAL HERBS

Dyslipidemia is known as one of the main risk factors of atherosclerosis. Numerous studies have demonstrated that hypercholesterolemia and hypertriglyceridemia lead to the increased risk of development and progression of atherosclerosis (Liu *et al*., 2013; Peng *et al*., 2017; Roubille *et al*., 2018). Previous studies have indicated that increased levels of low-density lipoprotein cholesterol (LDL-C) and its major protein, apolipoprotein B-100 (apoB-100), are critical causes of atherosclerosis. Infiltration and retention of apoB-containing lipoproteins in the artery wall can initiate inflammatory responses and promote the development of atherosclerosis (Liu *et al*., 2013). Many studies have therefore focused on the lipid-lowering effect of natural products (Table 1).

Extract of *Tribulus terrestris* decreased serum lipids in New Zealand rabbits fed a high-cholesterol diet. The experimental

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***Corresponding Author**
E-mail: sangheeshim@duksung.ac.kr
Tel: +82-2-901-8774, Fax: +82-2-901-8386

Table 1. Lowering lipids in the blood by medicinal herbs

Compounds/extracts	Herbs	Targets or indicator	References
Tribulus terrestris extract	*Tribulus terrestris*	Serum TC, TG, LDL-C, HDL-C	Tuncer *et al*. (2009)
Aqueous extract of *Ocimum basilicum*	*Ocimum basilicum*	Serum TC, TG, LDL-C, HDL-C	Amrani *et al*. (2006)
Salvianolic acid B	*Salvia miltiorrhiza*	CD36	Bao *et al*. (2012)
Ethanol extract of *Cynanchum wilfordii*	*Cynanchum wilfordii*	TG, LDL-C, HDL-C	Choi *et al*. (2012)
Ethanol extract of *Terminalia arjuna*	*Terminalia arjuna*	TC, TG, LDL-C, HDL-C	Subramaniam *et al*. (2011)
Polysaccharide from *polygonatum sibiricum*	*polygonatum sibiricum*	TC, LDL-C, Lp(a)	Yang *et al*. (2015)
Marrubium extract	*Marrubium vulgare*	TC, TG, LDL-C	Ibrahim *et al*. (2016)
Panax notoginseng saponins	*Panax notoginseng*	TC, TG, LDL-C, HDL-C	Wan *et al*. (2009)
Propolis, thymoquinone	*Nigella Sativa*	TC, TG, LDL-C, HDL-C	Nader *et al*. (2010)
Celastrus orbiculatus extract	*Celastrus orbiculatus*	TC, non-HDL-C, TG, apoB100, apoE, HDL-C, LDL-R, SR-B1, CYP7A1, HMGCR	Zhang *et al*. (2013)
Sweritamarin	*Enicostemma littorale*	TC, TG, LDL-C, HDL-C	Vaidya *et al* (2009)
Pueraria mirifica extract	*Pueraria mirifica*	LDL-C, HDL-C, apoA-1, apoB	Okamura *et al*. (2008)
Hypericum perforatum extract	*Hypericum perforatum*	TC, TG, LDL-C, HDL-C, MDA	Zou *et al*. (2005)
Astragaloside IV	*Astragalus membranaceus*	TC, TG, LDL-C, HDL-C	Qin *et al*. (2015)

group treated with extract of *T. terrestris* showed decreased levels of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), LDL-C, and triglyceride (TG) in serum compared to those in the negative control group (Tuncer *et al*., 2009). Extract of *Ocimum basilicum* reduced lipid profiles in Triton WR-1339-induced hyperlipidemic rats. In rats treated with *O. basilicum* extract, TC, TG, and LDL-C levels decreased, while HDL-C levels were higher than those in rats treated with Triton alone (Amrani *et al*., 2006).

The dried roots of *Salvia miltiorrhiza*, commonly called Danshen, have long been used in traditional oriental medicine for the prevention and treatment of cardiovascular diseases such as atherosclerosis. Cluster of differentiation 36 (CD36), a class B scavenger receptor, is known to be important in the pathogenesis of vascular inflammatory diseases. Salvianolic acid B, the most abundant bioactive compound from *S. miltiorrhiza*, showed inhibition of CD36-mediated lipid uptake. Using surface plasmon resonance analysis, salvianolic acid B was found to bind directly to CD36 with high affinity, thus confirming its physical interaction with this receptor (Bao *et al*., 2012). Treatment of rats fed with high-fat/-cholesterol diets with *Cynanchum wilfordii* ethanol extract reduced TG and LDL-C levels while increasing HDL-C levels (Choi *et al*., 2012). The ethanolic fraction of *Terminalia arjuna* markedly decreased TC, TG, and LDL levels, increased HDL levels, and furthermore lessened atherosclerotic lesions in the aortas of rabbits fed a high-fat diet (Subramaniam *et al*., 2011). Polysaccharides from *Polygonatum sibiricum* displayed hypolipidemic activities on TC, LDL-C, and lipoprotein(a) (Lp(a)), but not on TG or HDL-C in a high-cholesterol diet-induced atherosclerosis rabbit model (Yang *et al*., 2015). *Marrubium vulgare* extract containing polar products decreased plasma lipid levels. The lipid-lowering effects of petroleum ether-, chloroform-, ethyl acetate-, and methanol-soluble fractions of *M. vulgare* extract were investigated. The solvent-soluble fractions showed lipid-lowering effects in plasma TC, and petroleum ether fractions significantly lowered not only LDL-C levels but also TG levels. Elevated atherogenic indexes (AIs) and LDL-/HDL-C ratios were more influenced by polar fractions (methanol and ethyl acetate), while these atherogenic markers were not significantly inhibited by the chloroform- and petroleum ether-soluble fractions (Ibrahim *et al*., 2016). Saponins from *Panax notoginseng* also showed lipid-lowering properties in apolipoprotein-E (apo-E)-knockout rats. Ginseng saponins significantly reduced serum lipids, including TC, LDL-C, HDL-C, and TG in apo-E-knockout mice (Wan *et al*., 2009). Propolis and thymoquinone, the active constituents of *Nigella sativa* seed oil, inhibited the formation of early atherosclerotic lesions in hypercholesterolemic rabbits. Administration of propolis or thymoquinone together with a cholesterol-rich diet remarkably decreased TC, LDL-C, and TG while increasing HDL-C levels (Nader *et al*., 2010). *Celastrus orbiculatus* decreased TC, non-HDL-C, TG, apoB-100, and apo-E levels, and elevated HDL-C levels. Furthermore, messenger ribonucleic acid (mRNA) levels of the LDL receptor (LDL-R), scavenger receptor class B type 1 (SR-B1), cholesterol 7α-hydroxylase A1 (CYP7A1), and 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase were up-regulated by *C. orbiculatus*. Conversely, *C. orbiculatus* significantly decreased lipid deposition in the arterial wall (Zhang *et al*., 2013). Administration of swertiamarin isolated from *Enicostemma littorale* lowered serum TC, TG, and LDL-C levels while elevating HDL-C levels in poloxamer 407-induced hyperlipidemic rats (Vaidya *et al*., 2009). Lipid metabolism dysfunction leads to consequential health problems in postmenopausal women and can be a risk factor for the progression of atherosclerosis. *Pueraria mirifica* remarkably lowered serum apo-B and LDL-C levels in postmenopausal women, and elevated serum apolipoprotein A-I (apo A-I) and HDL-C levels. Moreover, ratios of LDL-C to HDL-C and apo-B to apo A-I were significantly reduced in the *P. mirifica*-treated group (Okamura *et al*., 2008). Administration of medium-dose (75 mg/kg body weight (BW)/day) and high-dose (150 mg/kg BW/day) flavonoid-rich extract of *Hypericum perforatum* significantly reduced serum levels, including those of TC, LDL-C, and TG, while it increased HDL-C levels in rats fed a cholesterol-rich diet (Zou *et al*., 2005). Astragaloside IV,

the major effective component from *Astragalus membranaceus*, down-regulated TC, TG, and LDL-C levels while elevating HDL-Cs level in the blood of apo-E-knockout mice fed a high-fat diet (Qin *et al*., 2015).

INHIBITORY EFFECTS OF MEDICINAL HERBS AGAINST MONOCYTE RECRUITMENT AND ACTIVATION

Monocyte-endothelial cell interactions are reported to induce the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), endothelial leukocyte adhesion molecule-1 (E-selectin), and intercellular cell adhesion molecule-1 (ICAM-1), which may cause the accumulation and migration of monocytes into the subendothelial space. Very low-density lipoprotein (VLDL), modified LDL, and APs act on monocyte-derived macrophages, which accelerates the transition of monocytes into foam cells. Foam cells are fat-laden macrophages that serve as the hallmark of early stage atherosclerotic lesion formation.

Corilagin from *Phyllanthus emblica* and its analogue Dgg16 are reported to have anti-atherogenic effects. Human umbilical vein endothelial cells (HUVECs) incubated with oxidized LDL (oxLDL) were treated with corilagin or Dgg16, followed by incubation with monocytes. OxLDL up-regulated adhesion of monocytes to endothelial cells, although co-treatment of oxLDL with corilagin or Dgg16 quickly decreased adhesion at a dose of 0.001 mmol/L or higher (Duan *et al*., 2005). Danshenol A from *Salvia miltiorrhiza* suppressed ICAM-1 expression induced by tumor necrosis factor-α (TNF-α) and relevant monocyte adhesion to endothelial cells through the NADPH oxidase subunit 4 (NOX4)-dependent inhibitor of kappa B (IκB) kinase β (IKKβ)/nuclear factor-kappa B (NF-κB) pathway (Zhao *et al*., 2017). The anti-atherogenic activity of cryptotanshinone, a constituent of *S. miltiorrhiza*, was evaluated using apo-E-deficient mice fed an atherogenic diet as well as oxLDL-stimulated HUVECs. Cryptotanshinone reduced lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) mRNA and protein expression induced by oxLDL, and suppressed subsequent LOX-1-induced adhesion of monocytes to HUVECs by lowering the expression of ICAM-1 and VCAM-1 (Liu *et al*., 2015). In addition, cryptotanshinone attenuated monocyte adhesion to endothelial cells by inhibiting expression of adhesion molecules (Ang *et al*., 2011). The ethanol extract of *Prunella vulgaris* suppressed adhesion of monocyte-/macrophage-like human macrophage cells (THP-1 cell). *P. vulgaris* also decreased expression of ICAM-1, VCAM-1, reactive oxygen species (ROS), E-selectin, and NO production in TNF-α-induced human aortic smooth muscle cells (HASMCs) and decreased NF-κB activation (Park *et al*., 2013). Paeonol, the active compound of *Paeonia lactiflora*, dose-dependently reduced ICAM-1 expression through inhibition of NF-κB p65 translocation into the nucleus and phosphorylation of IκBα. Paeonol also blocked the phosphorylation of p38 and extracellular signal-regulated kinase (ERK) induced by TNF-α, which is involved in regulating ICAM-1 production (Nizamutdinova *et al*., 2007). *P. notoginseng* saponins decreased monocyte adhesion to the endothelium in a concentration-dependent manner and suppressed the expression of TNF-α-induced endothelial adhesion molecules such as ICAM-1 and VCAM-1 (Wan *et al*., 2009). Curcumin, isolated from *Curcuma longa*, showed a sonodynamic effect on THP-1-derived macrophages. Commercial drugs that have sonodynamic effects become cytotoxic upon exposure to ultrasound, which can be useful when treating a localized part of the body, thus reducing the risk of systemic side effects (Wang *et al*., 2013). Fibronectin is one of the most important extracellular matrix proteins as it plays a critical role in leukocyte recruitment to the endothelium and initiates the process of atherosclerosis. The effects of protocatechualdehyde, an aqueous ingredient of *S. miltiorrhiza*, were evaluated on the expression of fibronectin in HUVECs stimulated with TNF-α via enzyme-linked immunosorbent assay (ELISA) and western blot analysis. Protocatechualdehyde treatment remarkably attenuated TNF-α-stimulated fibronectin surface expression and secretion in a dose-dependent manner. TNF-α-induced ROS generation and c-Jun NH_2-terminal kinase (JNK) activation were also inhibited by protocatechualdehyde (Tong *et al*., 2015). Aqueous extract of *Buddleja officinalis* reduced the up-regulation of cellular adhesion molecules. Pretreatment of HUVECs with *B. officinalis* extract (1-10 μg/mL) dose-dependently decreased TNF-α-induced adhesion of U937 monocytic cells. Furthermore, mRNA and protein expression of VCAM-1 and ICAM-1 were suppressed by this extract via inhibition of NF-κB and ROS. In addition, TNF-α-induced degradation of IκBα was inhibited by blocking phosphorylation of IκB-α in HUVEC (Lee *et al*., 2010). *Ziziphus nummularia* extract suppressed TNF-α-induced adhesion of THP-1 monocytes to HASMCs and endothelial cells in a concentration-dependent manner (Fardoun *et al*., 2017). Purple perilla extract and its major compound α-asarone inhibited oxLDL-induced foam cell formation by inhibiting SR-B1 expression. However, purple perilla extract promoted the up-regulation of the adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) and ABCG1, and subsequently promoted cholesterol efflux from macrophages by activating interactions between peroxisome proliferator-activated receptor γ (PPARγ), liver X receptor α (LXRα), and ABC transporters (Park *et al*., 2015). These results are summarized in Table 2.

ANTI-INFLAMMATORY EFFECTS OF MEDICINAL HERBS

Many studies have revealed the association between the initiation and progression of atherosclerosis with the vascular inflammation mechanisms. Inflammation participates in all stages of atherogenesis, from lesion initiation to thrombotic complications of the disease. Arterial endothelial cells begin to express adhesion molecules that bind leukocytes. Leukocytes adhere to the endothelium to penetrate into the intima at the lesion formation site in response to chemoattractants. Next, blood-derived inflammatory cells participate in and trigger inflammatory responses.

Signal transducer and activator of transcription protein 3 (STAT3), a transcription factor involved in inflammatory responses and the cell cycle, is activated by chemokines such as interleukin (IL)-6 and IL-8. Pretreatment of endothelial cells with magnolol isolated from *Magnolia officinalis* suppressed IL-6-induced phosphorylation of Tyr705 and Ser727 on STAT3 in a concentration-dependent manner. However, it did not affect the phosphorylation of Janus kinase 1 (JAK1), JAK2, or ERK1/2. An electrophoretic mobility shift assay (EMSA) revealed that magnolol treatment significantly decreased STAT3

Table 2. Inhibitory effects of medicinal herbs against monocyte recruitment and activation

Compounds/extracts	Herbs	Targets or indicator	References
Corilagin, Dgg16	*Phyllanthus Emblica*	oxLDL, MDA	Duan *et al*. (2005)
Danshenol A	*Salvia miltiorrhiza*	ICAM-1, ROS, NOX4, Nrf-2	Zhao *et al*. (2017)
Cryptotanshinone	*Salvia miltiorrhiza*	LOX-1, ICAM-1, VCAM-1	Liu *et al*. (2015)
Cryptotanshinone	*Salvia miltiorrhiza*	ICAM-1, VCAM-1, NO	Ang *et al*. (2011)
Ethanol extract of *Prunella vulgaris*	*Prunella vulgaris*	ICAM-1, VCAM-1, NF-κB, NO, E-selectin, ROS	Park *et al*. (2013)
Paeonol	*Paeonia lactiflora*	ICAM-1, NF-κB, IκBα, p38, ERK	Nizamutdinova *et al*. (2007)
Panax notoginseong saponins	*Panax notoginseng*	ICAM-1, VCAM-1	Wan *et al*. (2009)
Curcumin	*Curcuma longa*	Macrophages	Wang *et al*. (2013)
Protocatechualdehyde	*Salvia miltiorrhiza*	Fibronectin, NF-κB	Tong *et al*. (2015)
Aqueous extract of *Buddleja officinalis*	*Buddleja officinalis*	VCAM-1, ICAM-1, NF-κB, ROS, IκB-α	Lee *et al*. (2010)
Purple perila extract	Purple perilla	ABCA1, ABCG1, foam cell formation PPARγ, LXRα	Park *et al*. (2015)

binding to the IL-6 response elements region, and ICAM-1 expression was significantly reduced on the endothelial surface (Chen *et al*., 2006). Emodin from rhubarb stabilized the vulnerable atherosclerotic plaque in the aortic root of apo-E-knockout mice by exerting anti-inflammatory effects. It also significantly inhibited the expression of matrix metalloproteinase-9 (MMP-9) and granulocyte-macrophage colony-stimulating factor (GM-CSF), while inducing PPAR-γ expression in plaque (Zhou *et al*., 2008). Astragaloside IV significantly down-regulated CD40 ligand and C-X-C chemokine receptor type 4 (CXCR4) expression of the platelet surface, and also reduced stromal cell-derived factor-1 (SDF-1) and CXCR4 expression in the aorta. Western blotting and real-time polymerase chain reaction (PCR) demonstrated that astragaloside IV significantly down-regulated the mRNA and protein expression of SDF-1 and CXCR4 in apo-E-knockout mice fed a high-fat diet (Qin *et al*., 2015). Cryptotanshinone remarkably suppressed endothelial permeability, monocyte-endothelial cell adhesion, and expression of ICAM-1 and VCAM-1 in HUVECs (Ang *et al*., 2011). Cryptotanshinone significantly suppressed formation of atherosclerotic plaque and increased plaque stability in apo-E-knockout mice by reducing the expression of LOX-1 and MMP-9, and NF-κB activation. In addition, it reduced the expression of serum pro-inflammatory mediators without altering the serum lipid profile (Liu *et al*., 2015). The ethanolic extract of *P. vulgaris* suppressed adhesion of THP-1 cells to HAMCs, and inhibited p38 mitogen-activated protein kinase (MAPK) and ERK phosphorylation by induction of TNF-α (Park *et al*., 2013). Salvianolic acid B decreased the phosphorylation of JAK2 (Tyr 1007/1008) and STAT1 (Tyr701 and Ser727) by inducing interferon-γ (IFN-γ). Monocyte adhesion to IFN-γ-treated endothelial cells was decreased by pretreatment with salvianolic acid B. This compound also increased the expression of protein inhibitor of activated STAT 1 (PIAS1) and suppressor of cytokine signaling 1 (SOCS1) in endothelial cells (Chen *et al*., 2011). Salvianolic acid B pretreatment also reduced adhesion of adenosine diphosphate (ADP)-activated platelets to EA.hy926 cells (a human endothelial cell line) and inhibited activation of NF-κB. In addition, salvianolic acid B significantly inhibited mRNA expression of platelet-induced pro-inflammatory mediators (monocyte chemoattractant protein 1 (MCP-1), ICAM-1, IL-1β, IL-6, and IL-8) and the release of their corresponding proteins in EA.hy926 cells (Xu *et al*., 2014). Honokiol, an active component isolated from *M. officinalis*, markedly suppressed the overexpression of pentraxin 3 in palmitic acid (PA)-induced HUVECs by reducing IκB phosphorylation and expression of NF-κB subunits p50 and p65 in the IKK/IκB/NF-κB signaling pathway. In addition, honokiol markedly inhibited the production of IL-6, IL-8, and MCP-1 in PA-induced HUVECs (Qiu *et al*., 2015). Eleven ingredients of the herb Folium Eriobotryae were shown to possess anti-inflammatory properties. Using systematic network analyses, their targets were determined to be 43 inflammation-associated proteins including cyclooxygenase 1 (COX1), 5-lipoxygenase (5-LO), PPAR-γ, TNF, and transcription factor p65 (RELA), which are mainly involved in the MAPK and NF-κB signaling pathways (Zhang *et al*., 2015). Artesunate, a derivative of artemisinin isolated from sweet wormwood, attenuated the progression of atherosclerotic lesion formation alone or in combination with rosuvastatin in western-type diet-fed apo-E-knockout mice. No differences in food uptake, BW, and plasma lipid levels were observed in any of the groups, but a significant reduction in the expression of pro-inflammatory mediators such as TNF-α and IL-6 was noted in the treated groups. Furthermore, artesunate suppressed expression of pro-inflammatory chemokines such as IL-8 and MCP-1 in the aortas of mice. Rosuvastatin combined with artesunate delayed the progression of atherosclerotic lesions more effectively than artesunate alone (Jiang *et al*., 2016). β-Elemene isolated from *Curcuma wenyujin* reduced the size of atherosclerotic lesions and increased plaque stability in apo-E-knockout mice by inhibiting the production of pro-inflammatory cytokines and cell adhesion molecules such as IL-1β, TNF-α, INF-γ, MCP-1, and ICAM-1 (Liu *et al*., 2017). Because 5-LO is a key enzyme in inflammatory disorders such as atherosclerosis, 5-LO inhibition by *Plectranthus zeylanicus* extract, a medicinal plant extensively used in Sri Lanka and South India to treat inflammatory disorders, was evaluated (Napagoda *et al*., 2014). *P. zeylanicus* extracted with the non-polar solvents n-hexane and dichloromethane significantly inhibited 5-LO activity in stimulated human neutrophils with 50% inhibitory concentrations (IC_{50}) of 6.6 and 12 μg/mL, respectively, and suppressed human recombinant 5-LO with IC_{50} of 0.7 and 1.2 μg/mL, respectively (Napagoda *et al*., 2014). A cell-free assay using isolated human recombinant 5-LO was employed in this study in order to investigate whether the extract directly inhib-

Table 3. Anti-inflammatory effects of medicinal herbs

Compounds/extracts	Herbs	Targets or indicator	References
Magnolol	*Magnolia offinicalis*	STAT3, ICAM-1, Tyr705 and Ser727, cyclin D1, MCP-1, monocyte adhesion	Chen *et al*. (2006)
Emodin	Rhubarb	PPAR-γ, GM-CSF, MMP-9	Zhou *et al*. (2008)
Astragaloside IV	*Astragalus membranaceus*	CD40L, CD40, CXCR4, SDF-1	Qin *et al*. (2015)
Cryptotanshinone	*Salvia miltiorrhiza*	Monocyte adhesion, ICAM-1, VCAM-1	Ang *et al*. (2011)
Cryptotanshinone	*Salvia miltiorrhiza*	LOX-1, MMP-9, ROS, NF-κB, monocyte adhesion, ICAM-1, VCAM-1	Liu *et al*. (2015)
Ethanol extract of *Prunella vulgaris*	*Prunella vulgaris*	VCAM-1, ICAM-1, E-selectin, ROS, ERK, p38 MAPK	Park *et al*. (2013)
Salvianolic acid B	*Salvia miltiorrhiza*	JAK2 (Tyr 1007/1008), STAT1 (Tyr701 and Ser727), CXC chemokines' IP-10, Mig, I-TAC, monocyte adhesion, PIAS1, SOCS1	Chen *et al*. (2011)
Salvianolic acid B	*Salvia miltiorrhiza*	MMP-2, MMP-9, ERK1/2, JNK	Lin *et al*. (2007)
Salvianolic acid B	*Salvia miltiorrhiza*	Soluble P-selectin, NF-κB, ICAM-1, IL-1β, IL-6, IL-8 and MCP-1	Xu *et al*. (2014)
Honokiol	*Magnolia officinalis*	PTX3, IκB, NF-κB subunits (p50 and p65), IL-6, IL-8, MCP-1	Qiu *et al*. (2015)
Eleven compounds of *Folium eriobotryae*	Folium eriobotryae	43 inflammation-associated proteins including especially COX2, ALOX5, PPARG, TNF and RELA	Zhang *et al*. (2015)
Artesunate	Sweet wormwood	TNF-α, IL-6, IL-8, MCP-1	Jiang *et al*. (2016)
β-Elemene	*Curcuma wenyujin*	IL-1β, TNF-α, INF-γ, MCP-1, ICAM-1, NO, eNOS, Akt	Liu *et al*. (2017)
Plectranthus zeylanicus extract	*Plectranthus zeylanicus*	5-LO	Napagoda *et al*. (2014)
Ethanol extract of *Ziziphus nummularia*	*Ziziphus nummularia*	MMP-2, MMP-9, NF-κB, ICAM-1, VCAM-1, adhesion of THP-1 monocytes	Fardoun *et al*. (2017)
Celastrus orbiculatus extract	*Celastrus orbiculatus*	CRP, IL-6, TNF-α, CD68, NF-κB p65	Zhang *et al*. (2013)
Celastrol	*Tripterygium wilfordii*	IκB, iNOS, NO, TNF-α, IL-6	Gu *et al*. (2013)
Bisacurone	*Curcuma longa*	VCAM-1, NF-κB p65, IκB, Akt, PKC, monocyte adhesion	Sun *et al*. (2008)
Patchouli alcohol	*Pogpstemonis herba*	MCP-1, iNOS, IL1β, IL-6, CXCL9, CXCL11	Wang *et al*. (2016)
Tetrahdroxystilbene glucoside	*Polygonum multiflorum*	Calreticulin, vimentin, HSP70, lipocortin 1, Apo A-1	Yao *et al*. (2013)
Do In Seung Gi-Tang	*Rheum undulatum*, *Prunus persica*, *Conyza canadensis*, *Cinnamomum cassia*, and *Glycytthiza uralensis*	Body weight, liver weight, TC, LDL-C, lipoprotein-cholesterol, TG, glucose, ICAM-1, VCAM-1, E-selectin, FAS, AMPK, ACC	Park *et al*. (2016)

ited 5-LO activity.

Z. nummularia extract decreased expression of MMP-2, MMP-9, NF-κB, ICAM-1, and VCAM-1 induced by TNF-α in a concentration- and time-dependent manner, as revealed via reverse transcription (RT)-PCR and western blot analysis. *C. orbiculatus* reduced C-reactive protein (CRP), IL-6, and TNF-α levels in plasma. Immunohistochemistry and western blot analysis showed that CD68 up-regulation and NF-κB p65 protein activation in the arterial wall were reduced by *C. orbiculatus* treatment as well (Zhang *et al*., 2013). Celastrol, a triterpenoid isolated from *Tripterygium wilfordii*, inhibited the phosphorylation and degradation of IκB and decreased the production of inducible nitric oxide synthase (iNOS), NO, and pro-inflammatory cytokines including TNF-α and IL-6 (Gu *et al*., 2013). Bisacurone isolated from *C. longa* concentration-dependently suppressed VCAM-1 expression and inhibited NF-κB p65 translocation into the nucleus and phosphorylation of IκBα, protein kinase B (Akt), and protein kinase C (PKC; Sun *et al*., 2008). Patchouli alcohol, a tricyclic sesquiterpene isolated from Pogostemonis Herba, blocked aortic mRNA expression of inflammatory cytokines such as iNOS, MCP-1, IL-1β, IL-6, CXCL9, and CXCL11 (Wang *et al*., 2016). Proteomic analysis of the relationship between atherosclerosis and 2,3,5,4′-tetrahydroxystilbene-2-*O*-β-D-glucoside revealed that five proteins were mainly involved in cholesterol transport, inflammation, cell apoptosis, and cell adhesion. 2,3,5,4′-Tetrahydroxystilbene-2-*O*-β-D-glucoside elevated the expression of heat shock protein 70 (HSP70), lipocortin 1, and apo A-1 but reduced the expression of calreticulin and vimentin (Yao *et al*., 2013). Do In Seung Gi-Tang, a traditional herbal

preparation composed of *Rheum undulatum*, *Prunus persica*, *Conyza canadensis*, *Cinnamomum cassia*, and *Glycyrrhiza uralensis* (ratio, 8:6:4:4:4), shows anti-inflammatory activities by regulating the 5′ AMP-activated protein kinase (AMPK) pathway. Treatment with this herbal preparation reduced the size of atherosclerotic lesions, suppressed ICAM-1, VCAM-1, and E-selectin expression, and reduced lipid accumulation, progression of inflammation, and fatty acid synthase (FAS) levels. Furthermore, Do In Seung Gi-Tang promoted AMPK and inhibited acetyl-CoA carboxylase (ACC) expression in liver tissues (Park *et al*., 2016). These results are summarized in Table 3.

ANTI-OXIDATIVE EFFECTS OF MEDICINAL HERBS

Oxidative stress induced by the excessive generation of ROS and macrophage inflammation has emerged as a crucial mechanism for the initiation and progression of endothelial dysfunction and atherosclerosis (Kattoor *et al*., 2017). OxLDL is a harmful type of cholesterol that is formed when LDL-C is damaged by free radicals. Malondialdehyde (MDA), which is formed during oxidation of LDL, is used as an oxidative stress marker.

Corilagin and its analogue Dgg16 decreased the formation of MDA and inhibited the proliferation of vascular smooth muscle cells (VSMC) activated by oxLDL (Duan *et al*., 2005). Danshenol A inhibited ROS generation and NOX4 expression (Zhao *et al*., 2017). The aqueous extract of *O. basilicum* displayed very high antioxidant power, indicating that 1 L of the extract possessed antioxidant capacity equal to that of 32.8 g ascorbic acid (Amrani *et al*., 2006). Cryptotanshinone reduced LOX-1 mRNA and protein expression, and suppressed NOX4-induced ROS production and comparative activation of NF-κB in HUVECs (Liu *et al*., 2015). Tanshinone IIA, which was also isolated from *S. miltiorrhiza*, showed protective effects against H_2O_2-induced apoptosis and protected HUVECs from inflammatory mediators induced by H_2O_2 via pregnane X receptor (PXR) activation (Zhu *et al*., 2017). Pretreatment with tanshinone IIA reduced H_2O_2-induced ROS formation and H_2O_2-triggered cell apoptosis in EA.hy926 cells. RT-PCR and western blotting results indicated that it remarkably suppressed the expression of pro-apoptotic proteins such as B-cell lymphoma (Bcl)-2-associated X protein (Bax) and caspase-3, while increasing the expression of the anti-apoptotic protein Bcl-2 (Jia *et al*., 2012). Tanshinone IIA also increased glutathione peroxidase 1 (GPx-1) mRNA levels and GPx activities, and protected cultured macrophages from H_2O_2-induced cell death (Li *et al*., 2008). *Cymbopogon citratus* extract reduced the formation of ROS by D-glucose, hydrogen peroxide, and oxLDL in HUVECs (Campos *et al*., 2014). The protective effects of Danshen aqueous extract and its active compounds were studied on HUVECs using an *in vitro* tube formation assay. The Danshen extract and its pure compounds showed effectiveness in protecting HUVECs against homocysteine-induced injury, providing evidence of its beneficial effects on cardiovascular disease. Treatment with *B. officinalis* inhibited TNF-α-induced ROS formation in HUVECs (Lee *et al*., 2010). Farrerol, a flavonoid considered to be the major component in the dried leaves of *Rhododendron dauricum*, significantly increased cell viability and enhanced superoxide dismutase (SOD) and GPx activity in H_2O_2-induced EA.hy926 cells. Farrerol also reduced elevation of intracellular MDA, ROS, and apoptosis, and significantly reduced the expression of Bax mRNA and protein, cleaved caspase-3, and phospho-p38 MAPK, while increasing the expression of Bcl-2 mRNA and protein in H_2O_2-induced EA.hy926 cells, as determined via real-time PCR and Western blot analysis (Li *et al*., 2013). Salvianolic acid B reduced oxidative stress, LDL oxidation, and oxLDL-induced cytotoxicity. Salvianolic acid B inhibited cupric ion-mediated LDL oxidation *in vitro* and attenuated human aortic endothelial cell-mediated LDL oxidation as well as ROS elevation (Yang *et al*., 2011). Treatment with β-elemene up-regulated the activities of antioxidant enzymes such as catalase, GPx, and glutathione in the aorta, while lowering oxidative damaging biomarker MDA. β-Elemene also elevated the generation of NO and up-regulated phosphorylation of eNOS (ser1177) and Akt *in vitro* (Liu *et al*., 2017). Low-molecular weight compounds from white ginseng, mostly phenolic compounds, decreased the extent of atherosclerosis by attenuating oxidative stress (Lee *et al*., 2013). Protocatechualdehyde suppressed ROS generation induced by platelet-derived growth factor-BB (PDGF-BB) in VSMCs, and increased the phosphorylation of Akt and ERK 1/2 via PDGF stimulation. These results suggest that protocatechualdehyde inhibits PDGF signaling by acting upstream of Akt and ERK 1/2, which indicates that its antioxidant effect might be related to PDGF signal transduction inhibition (Moon *et al*., 2012). Ethanolic propolis extract or thymoquinone treatment could reverse the oxidative damage resulting from a high-cholesterol diet in rabbits. Ethanolic propolis extract and thymoquinone decreased serum thiobarbituric acid reactive substances (TBARS) levels while enhancing glutathione levels in high-cholesterol diet-fed rabbits (Nadar *et al*., 2010). *C. orbiculatus* decreased MDA levels and increased SOD activity in the plasma of guinea pigs fed a high-fat diet. These results indicate that *C. orbiculatus* inhibited oxidative stress (Zhang *et al*., 2013). Isorhamnetin, a flavonoid isolated from *Hippophae rhamnoides*, significantly inhibited oxLDL-induced THP-1-derived macrophage impairment by decreasing ROS levels, lipid accumulation, and caspase-3 activation. Isorhamnetin also induced phosphatidylinositol 3-kinase (PI3K)/AKT activation and heme oxygenase-1 (HO-1) induction, which inhibited atherosclerotic plaque progression in apo-E-knockout mice (Luo *et al*., 2015). Celastrol significantly suppressed oxLDL-induced excessive expression of LOX-1 and production of ROS in RAW264.7 mouse macrophages. Furthermore, celastrol remarkably reduced the expression of LOX-1 and generation of superoxide in mouse aortas (Gu *et al*., 2013). The aqueous extract of *Chlorophytum borivilianum* showed high antioxidant capacity through powerful NO, superoxide, hydroxyl, 2,2-diphenyl-1-picrylhydrazyl (DPPH), and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical-scavenging activity. Furthermore, this extract showed ferric ion reducing capacity, metal chelating ability, and reduced lipid peroxidation in mitochondrial fractions significantly more than ethanolic extracts. In addition, the extract remarkably inhibited LDL oxidation (Visavadiya *et al*., 2010). The ethanolic extract of *Glossogyne tenuifolia* and its main compound luteolin-7-glucoside were revealed to be scavengers of superoxide, DPPH, and hydroxyl radicals (Wu *et al*., 2005). Copper-mediated LDL oxidation was also reduced by treatment with *G. tenuifolia* extract and luteolin-7-glucoside, and this was evaluated by measuring the formation of conjugated dienes and MDA, as well as electrophoretic mobility. Oral administration of the

Table 4. Anti-oxidative effects of medicinal herbs

Compounds/extracts	Herbs	Targets	References
Corilagin, Dgg16	*Phyllanyhus Emblica*	MDA, oxLDL	Duan *et al*. (2005)
Danshenol A	*Salvia miltiorrhiza*	ROS, NOX4	Zhao *et al*. (2017)
Aqueous extract of *Ocimum basilicum*	*Ocimum basilicum*	Radical anion superoxide	Amrani *et al*. (2006)
Cryptotanshinone	*Salvia miltiorrhiza*	ROS, oxLDL, LOX-1, NOX4, NF-κB	Liu *et al*. (2015)
Tanshinone IIA	*Salvia miltiorrhiza*	PXR, GSH	Zhu *et al*. (2017)
Tanshinone IIA	*Salvia miltiorrhiza*	ROS, Bax, caspase-3, Bcl-2	Jia *et al*. (2012)
Tanshinone IIA	*Salvia miltiorrhiza*	GPx	Li *et al*. (2008)
Cymbopogon citratus extract	*Cymbopogon citratus*	ROS	Campos *et al*. (2014)
Danshen aqueous extract	*Salvia miltiorrhiza*	Hcy	Chan *et al*. (2004)
Aqueous extract of *Buddleja officinalis*	*Buddleja officinalis*	ROS	Lee *et al*. (2010)
Farrerol	*Rhododendron dauricum*	SOD, GSH-Px, MDA, ROS, Bax, caspase-3, phosph-p38 MAPK, Bcl-2	Li *et al*. (2013)
Salvianolic acid B	*Salvia miltiorrhiza*	oxLDL, ROS, MDA	Yang *et al*. (2011)
β-Elemene	*Curcuma wenyujin*	ROS, NO, eNOS, Akt, SOD, MDA, CAT, GPx, GSH, p22phox	Liu *et al*. (2017)
Panax ginseng extract	*Panax ginseng*	SOD, CAT	Lee *et al*. (2013)
Protocatechualdehyde	*Salvia miltiorrhiza*	ROS, Akt, ERK1/2, PDGF	Moon *et al*. (2012)
Propolis, thymoquinone	*Nigella sativa* seed oil	GSH, TBARS	Nadar *et al*. (2010)
Celastrus orbiculatus extract	*Celastrus orbiculatus*	MDA, SOD	Zhang *et al*. (2013)
Isorhamnetin	*Hippophae rhamnoides*	Ox-LDL, ROS, PI3K/AKT, HO-1, caspase-3, TUNEL-positive cells, Bcl-2, Bax, caspase-9	Luo *et al*. (2015)
Celastrol	*Tripterygium wilfordii*	OxLDL, LOX-1, ROS, IκB, iNOS, NO	Gu *et al*. (2013)
Aqueous extract of *Chlorophytum borivilianum*	*Chlorophytum borivilianum*	NO, superoxide, hydroxyl, DPPH and ABTS radicals, LDL oxidation, lipid hydroperoxides	Visavadiya *et al*. (2010)
Ethanol extract of *Glossogyne tenuifolia*, Luteolin-7-glucoside	*Glossogyne tenuifolia*	DPPH, superoxide, hydroxyl radicals, oxLDL, ROS	Wu *et al*. (2005)
Hypericum perforatum extract	*Hypericum perforatum*	MDA, SOD, CAT	Zou *et al*. (2005)

flavonoid-rich extract of *H. perforatum* reduced MDA levels in the sera and livers of rats. It also elevated SOD activity in the serum and liver, although catalase activity was significantly increased only in the liver (Zou *et al*., 2005). These results are summarized in Table 4.

INHIBITORY EFFECTS OF MEDICINAL HERBS AGAINST THE INFILTRATION AND PROLIFERATION OF VASCULAR SMOOTH MUSCLE CELLS

VSMC proliferation and migration, which contribute to the pathogenesis of atherosclerosis, are known to be associated with other cellular processes such as apoptosis, senescence, inflammation, and matrix alterations. Therefore, understanding VSMC behavior in atherosclerosis is critical in identifying therapeutic targets to both prevent and treat atherosclerosis.

Pre-treatment with corynoxeine (5-50 μM) significantly reduced VSMC numbers and inhibited PDGF-BB-induced DNA synthesis and ERK1/2 activation by VSMCs without inducing cytotoxicity (Kim *et al*., 2008). Corilagin and its analogue Dgg16 inhibited oxLDL-induced proliferation of VSMCs (Duan *et al*., 2005). Sparstolonin B, isolated from *Sparganium stoloniferum*, suppressed endothelial cell tube formation and cell migration in a concentration-dependent manner. Treatment of HUVECs with sparstolonin B caused an increase of cells in the G1 phase and decreased the number of cells in the S phase. Cyclin E2 (CCNE2) and cell division cycle 6 (CDC6), cell division regulatory proteins, were down-regulated after sparstolonin B exposure. In addition, sparstolonin B significantly reduced capillary length and branching number (Bateman *et al*., 2013). *Hibiscus sabdariffa* is also known to show hypolipidemic activity in cholesterol-fed rabbits. In addition, it suppressed the formation of foam cells and inhibited the migration of smooth muscle cells and calcification in blood vessels (Chen *et al*., 2003). *Nelumbo nucifera* leaf extract treatment induced apoptosis and altered the JNK and p38 MAPK pathways in VSMCs. Non-cytotoxic doses of this extract also inhibited the secretion of MMP-2/9 and cell migration by suppressing the focal adhesion kinase (FAK)/PI3K/small G protein pathway. Histopathological results revealed that 1.0% of the extract reduced formation of neointima, restrained the proliferation of smooth muscle cells, and reduced MMP-2 secretion in the blood vessels of rabbits (Ho *et al*., 2010). The ethanolic extract of *Gleditsia sinensis* up-regulated p21WAF1 levels and suppressed cyclinB1, cyclin-dependent kinase 1 (Cdc2), cell

Table 5. Inhibitory effects of medicinal herbs against infiltration and proliferation of vascular smooth muscle cells

Compounds/extracts	Herbs	Targets	References
Corynoxeine	*Uncaria rhynchophylla*	DNA synthesis of VSMCs, ERK1/2,	Kim *et al*. (2008)
Corilagin, Dgg16	*Phyllanthus Emblica*	OxLDL	Duan *et al*. (2005)
Sparstolonin B	*Sparganium stoloniferum*	CCNE2, CDC6, capillary length, branching number	Bateman *et al*. (2013)
Hibiscus sabdariffa extract	*Hibiscus sabdariffa*	Foam cell formation, VSMC	Chen *et al*. (2003)
Nucifera leaf extract	*Nelumbo nucifera*	JNK, p38 MAPK, MMP-2/9, FAK/PI 3-kinase/ small G protein	Ho *et al*. (2010)
Ethanol extract of *Gleditsia sinensis*	*Gleditsia sinensis*	P21WAF1, cyclinB1, Cdc2, Cdc25c, ERK1/2, p38 MAPK, JNK, MMP-9, NF-κB, AP-1	Lee *et al*. (2012)
Salvianolic acid B	*Salvia miltiorrhiza*	MMP-2, MMP-9, ERK1/2, JNK	Lin *et al*. (2007)
Protocatechualdehyde	*Salvia miltiorrihza*	PDGF, PI3K/Akt, MAPK, cyclin D2, ROS	Moon *et al*. (2012)
Ethanolic extract of *Ziziphus nummularia*	*Ziziphus nummularia*	MMP-2, MMP-9, NF-κB, ICAM-1, VCAM-1, monocyte adhesion	Fardoun *et al*. (2017)
Esculetin	*Artemisia scoparia*	p42/44 MAPK, c-fos and c-jun, NF-κB, AP-1, PI 3-kinase, Ras	Pan *et al*. (2003)
Honokiol	*Magnolia officinalis*	MMP-2, MMP-9, NF-κB, ERK1/2	Zhu *et al*. (2014)

division cycle 25c (Cdc25c), and G2/M cell cycle regulators. In addition, treatment with this extract activated ERK1/2, p38 MAPK, and JNK, and inhibited expression of MMP-9 induced by TNF-α in VSMCs. This extract also reduced the expression of NF-κB and activator protein 1 (AP-1), which are essential *cis*-elements for the MMP-9 promoter (Lee *et al*., 2012). Salvianolic acid B remarkably suppressed LPS-induced cell migration via the inhibition of MMP-2 and MMP-9 synthesis and the reduction of JNK and ERK1/2 (Lin *et al*., 2007). Protocatechualdehyde especially inhibited PDGF-induced migration and proliferation of VSMCs. It also down-regulated the PI3K/Akt and MAPK pathways, both of which regulated major enzymes associated with proliferation and migration. In addition, it promoted S-phase arrest of the VSMC cell cycle and inhibited cyclin D2 expression (Moon *et al*., 2012). The ethanolic extract of *Z. nummularia* decreased HASMC proliferation, adhesion to fibronectin, migration, and invasion (Fardoun *et al*., 2017). Esculetin significantly suppressed the proliferation of VSMCs through a lipoxygenase-dependent pathway. Three predominant signaling pathways are inhibited by esculetin. The first pathway is the activation of p42/44 MAPK and the immediate early genes of the downstream effectors of c-fos and c-jun, the second is the activation of NF-κB and AP-1, and the third is PI 3-kinase activation and cell cycle progression. Furthermore, esculetin also reduced activation of RAS, a shared upstream event of the above signaling cascades (Pan *et al*., 2003). Honokiol inhibited the TNF-α-induced proliferation and migration of rat aortic smooth muscle cells in a dose-dependent manner. Pretreatment with honokiol blocked expression of MMP-2 and MMP-9, activation of NF-κB, and phosphorylation of ERK1/2 induced by TNF-α (Zhu *et al*., 2014). These results are summarized in Table 5.

INHIBITORY EFFECTS OF MEDICINAL HERBS ON PLAQUE FORMATION

Atherosclerosis is characterized by the narrowing and hardening of arteries following the buildup of plaque, which is composed of substances found in the blood, such as fat, cholesterol, and calcium. Plaque blocks the artery and disrupts blood flow around body, leading to life-threatening conditions.

The modulatory effects of salvianolic acid B, the most abundant bioactive compound from *S. miltiorrhiza*, were evaluated on activated platelet-induced inflammation in endothelial cells (Xu *et al*., 2014). This compound inhibited ADP or α-thrombin-induced human platelets aggregation in platelet-rich plasma samples in a dose-dependent manner in a platelet aggregation assay, and significantly reduced the release of soluble P-selectin release. In addition, adhesion of ADP-activated platelets to EA.hy926 cells and NF-κB activation were reduced by pre-treatment with this compound (Xu *et al*., 2014). Cryptotanshinone, another bioactive compound from *S. miltiorrhiza*, significantly suppressed the formation of atherosclerotic plaque and increased plaque stability in apo-E-knockout mice by suppressing the expression of LOX-1 and MMP-9 (Liu *et al*., 2015). The effects of atractylenolides on platelet function were investigated *in vitro* and *in vivo* (Chen *et al*., 2017). Atractylenolides I, II, and III are the major components of the medicinal plant *Atractylodes macrocephala*. Atractylenolides II and III attenuated agonist-induced platelet aggregation and ATP release from dense granules, whereas atractylenolide I did not show such effects. Atractylenolides II and III showed suppressive effects similar to those of acetylsalicylic acid on platelet activation in response to agonists (Chen *et al*., 2017). Plasminogen activator inhibitor-1 (PAI-1) is associated with fibrin deposition, which develops into organ fibrosis and atherosclerosis. The ethanolic extract of *Zanthoxylum nitidum* var. *tomentosum* and its main compound, toddalolactone, showed PAI-1 inhibitory effects. Toddalolactone suppressed binding of PAI-1 with urokinase-type plasminogen activators (uPA), and therefore attenuated formation of the PAI-1/uPA complex (Yu *et al*., 2017). Compounds isolated from *Callicarpa nudiflora*, including 1,6-di-*O*-caffeoyl-β-D-glucopyranoside, suppressed platelet aggregation induced by ADP, U45519, and arachidonic acid. 1,6-Di-*O*-caffeoyl-β-D-glucopyranoside also revealed obvious competitive effects on thromboxane prostanoid (TP) and $P2Y_{12}$ receptors, and inhibited RhoA and PI3K/Akt/glycogen synthase kinase 3 beta (GSK3β) signal transduction (Fu *et al*., 2017). Using an aggregometer, protocatechualdehyde

Table 6. Effects of medicinal herbs on plaque formation

Compounds	Herbs	Targets	References
Salvianolic acid B	*Salvia miltiorrhiza*	P-selectin, NF-κB	Xu *et al*. (2014)
Cryptotanshinone	Danshen	LOX-1, MMP-9, ROS, NF-κB, ICAM-1, VCAM-1	Liu *et al*. (2015)
Atractylenolides	*Atractylodes macrocephala*	ATP release, Ser473, phospho-p38 MAPK	Chen *et al*. (2017)
Toddalolactone	*Zanthoxylum nitidum* var. *tomentosum*	PAI-1, uPA, hydroxyproline	Yu *et al*. (2017)
1,6-Di-*O*-caffeoyl-β-D-glucopyranoside	*Zanthoxylum nitidum* var. *tomentosum*	αIIbβ3 integrin, 5-HT, TXA2, RhoA, PI3K/Akt/GSK3β, TP, P2Y12	Fu *et al*. (2017)
Protocatechualdehyde	*Salvia miltiorrhiza*	PDGF, PI3K/Akt, MAPK, cyclin D2, ROS	Moon *et al*. (2012)

was found to show anti-thrombotic effects associated with inhibition of platelet aggregation (Moon *et al*., 2012). These results are summarized in Table 6.

CONCLUSION

This review highlighted recent studies of effective herbs in the treatment and prevention of atherosclerosis. Herbs have long been used for medicinal purposes and are still widely used today, although elucidation of their therapeutic efficacies and mechanisms has only recently begun. We reviewed most articles concerning herbs that are effective for the treatment of atherosclerosis and classified them into six categories according to their MOAs. The experiments reviewed in this article were conducted with either herbal extracts or pure compounds isolated from herbs. The mechanisms of herbal compounds were diverse, such as blood lipid-lowering activities, inhibition of monocyte recruitment and activation, anti-inflammatory effects, anti-oxidative effects, inhibition of the infiltration and proliferation of vascular smooth muscle cells, and inhibition of plaque formation. Certain medicinal herb-derived compounds such as salvianolic acid B, cryptotanshinone, and protocatechualdehyde did not show not specific MOAs, suggesting that they exhibited anti-atherosclerotic activities via multiple mechanisms. In addition to this, there may be more specific and detailed mechanisms. Moreover, most of the compounds act not just via one mechanism, but in several ways. In conclusion, many reports suggest that herbal compounds are effective in the treatment of atherosclerosis. However, one should note that because *in vivo* studies have been conducted using laboratory animals such as rabbits and rats in most cases, the results and efficacies may not be the same in humans. Moreover, in the studies using plant extracts rather than pure compounds, the proportion of active compounds may differ even in the same kind of herbs as the production environment affects the contents of herbal compounds. Further studies including more subjects are needed for better understanding of herbal compounds, and we hope that this review will be helpful for future studies.

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