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

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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...
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. (2008) |
| Salvianolic acid B | Salvia millifolia | 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, HMGR | Zhang et al. (2013) |
| Swertiamarin | 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) |

The dried roots of *Salvia millifolia*, 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 *Salvia millifolia*, 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 TG, and apo-B100, apoE, HDL-C, LDL-R, SR-B1, CYP7A1, HMGR. 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 transi-118 tion 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 (HUCECs) 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 (IkB) 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 HUCECs. 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 HUCECs 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 IkBα. 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 (Nizamuddinova 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). Fibrotenclin 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 protocatechualedehyde, an aqueous ingredient of S. miltiorrhiza, were evaluated on the expression of fibrotenclin in HUCECs stimulated with TNF-α via enzyme-linked immunosorbent assay (ELISA) and western blot analysis. Protocatechualedehyde treatment remarkably attenuated TNF-α-stimulated fibrotenclin surface expression and secretion in a dose-dependent manner. TNF-α-induced ROS generation and c-Jun NH2-terminal kinase (JNK) activation were also inhibited by protocatechualedehyde (Tong et al., 2015). Aqueous extract of Buddleja officinalis reduced the up-regulation of cellular adhesion molecules. Pretreatment of HUCECs with B. officinalis extract (1-10 μg/mL) dose-dependently decreased TNF-α-induced adhesion of U937 monocyctic 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 IκBα 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 pexosome 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 inflammatory 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

https://doi.org/10.4062/biomolther.2018.231

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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 apoE-/-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-C/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 apoE-/-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 inhibiting the production of pro-inflammatory mediators such as TNF-α, IL-6, and MCP-1 in PA-induced HUVECs. Furthermore, cryptotanshinone significantly inhibited 5-LO expression in platelets and increased plaque stability in apo-E-/-knockout mice by exerting anti-inflammatory effects. 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. 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.
Biomol Ther 27(3), 254-264 (2019)

Table 3. Anti-inflammatory effects of medicinal herbs

| Compounds/extracts           | Herbs                        | Targets or indicator                                                                 | References          |
|------------------------------|------------------------------|--------------------------------------------------------------------------------------|---------------------|
| Magnolol                     | Magnolia officinalis         | 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   | Prunella vulgaris            | VCAM-1, ICAM-1, E-selectin, ROS, ERK, p38 MAPK                                     | Park et al. (2013)  |
| vulgaris                     | 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    | Folium eriobotryae          | 43 inflammation-associated proteins including especially COX2, ALOX5, PPARG, TNF and RELA | Zhang et al. (2015) |
| eriobotryae                  |                              |                                                                                      |                     |
| β-Elemene                    | Curcuma wenyujin             | TNF-α, IL-6, IL-8, MCP-1                                                            | Jiang et al. (2016) |
| Plectranthus zeylanicus extract| Plectranthus zeylanicus      | IL-1β, TNF-α, INF-γ, MCP-1, ICAM-1, NO, eNOS, Akt                                  | Liu et al. (2017)   |
| Ethanol extract of Ziziphus   | Ziziphus nummularia          | 5-LO                                                                                 | Napagoda et al. (2014) |
| nummularia                   |                              |                                                                                      |                     |
| 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            | Pogostemonis herba           | MCP-1, INOS, IL-1β, IL-6, CXCL9, CXCL11                                            | Wang et al. (2016)  |
| Tetrahydroxystilbene glucose | Polygonum multiflorum        | Calreticulin, vimentin, HSP70, lipocortin 1, Apo A-1                               | Yao et al. (2013)   |
| Do In Seung Gi-Tang          | Rheum undulatum, Prunus      | Body weight, liver weight, TC, LDL-C, lipoprotein-cholesterol, TG, glucose,        | Park et al. (2016)  |
| persica, Conyza canadensis,  | persica, Cinnamomum cassia,  | ICAM-1, VCAM-1, E-selectin, FAS, AMPK, ACC                                         |                     |
| Glycyrrhiza uralensis        |                              |                                                                                      |                     |

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 possesses 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 H2O2-induced apoptosis and protected HUVECs from inflammatory mediators induced by H2O2 via pregnane X receptor (PXR) activation (Zhu et al., 2017). Pretreatment with tanshinone IIA reduced H2O2-induced ROS formation and H2O2-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 H2O2-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). Ferrerol, 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 H2O2-induced EA.hy926 cells. Ferrerol 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 H2O2-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). Procatechualdehyde 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 procatechualdehyde 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 polyspor 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). Celastrin significantly suppressed oxLDL-induced excessive expression of LOX-1 and production of ROS in RAW264.7 mouse macrophages. Furthermore, celastrin remarkably reduced the expression of LOX-1 and generation of superoxide in mouse aortas (Gu et al., 2013). The aqueous extract of *Chlorophyllum borivilianum* showed high antioxidant capacity through powerful NO, superoxide, hydroxyl, 2,2-di-phenyl-1-picrylhydrazyl (DPPH), and 2,2’-azino-bis(3-ethylbenzothiazoline-6-sulfonic 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
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 corynoline (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 pretreatment with corynoline (5-50 µM) significantly reduced capillary length and branching number (Bate *et al.*, 2013). Moreover, corynoline suppressed endothelial cell tube formation and cell migration in a concentration-dependent manner.

The anti-oxidative effects of medicinal herbs are summarized in Table 4.

### Table 4. Anti-oxidative effects of medicinal herbs

| Compounds/extracts | Herbs | Targets | References |
|--------------------|-------|---------|------------|
| Corilagin, Dgg16   | Phyllanthus Emblica | MDA, oxLDL | Duan *et al.* (2005) |
| Danshenol A        | Salvia miltiorrhiza | ROS, NOX4 | Zhao *et al.* (2017) |
| Aqueous extract of *Ocimum basilicum* | Radical anion superoxide | | Amrani *et al.* (2006) |
| Cryptotanshinone    | Salvia miltiorrhiza | ROS, oxLDL, LOX-1, NOX4, NF-κB | Liu *et al.* (2015) |
| Tanshinone IA      | Salvia miltiorrhiza | PXR, GSH | Zhu *et al.* (2017) |
| Tanshinone IA      | Salvia miltiorrhiza | ROS, Bax, caspase-3, Bcl-2 | Jia *et al.* (2012) |
| Tanshinone IA      | 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* | ROS | | Lee *et al.* (2010) |
| Farrerol | Rhododendron dauricum | SOD, GSH-Px, MDA, 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 | Ox-LDL, LOX-1, ROS, IκB, iNOS, NO | Gu *et al.* (2013) |
| Aqueous extract of *Chlorophytum borivillanum* | Chlorophytum borivillanum | NO, superoxide, hydroxyl, DPPH and ABTS radicals, LDL oxidation, lipid hydroperoxides | Visavadiya *et al.* (2010) |
| Ethanolic extract of *Glossogyne tenuifolia* | *Glossogyne tenuifolia* | DPPH, superoxide, hydroxyl radicals, oxLDL, ROS | Wu *et al.* (2005) |
| Hypericum perforatum extract | Hypericum perforatum | MDA, SOD, CAT | Zou *et al.* (2005) |

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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). Salvi-anolic 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 receptor. 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). Cryptotan-shinone, 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). Atractylolides II and III showed suppressive effects on platelet aggregation induced by ADP, U45519, and arachidonate. Atractylolides I, II, and III are the major components of the medicinal plant Atractylodes macrocephala. Atractylolides II and III attenuated agonist-induced platelet aggregation and ATP release from dense granules, whereas atractylolide I did not show such effects. Atractylolides II and III showed suppressive effects similar to those of acetyl-salicylic 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 rudiflora, including 1,6-di-O-caffeyl-β-D-glucopyranoside, suppressed platelet aggregation induced by ADP, U45519, and arachidonate. 1,6-Di-O-caffeyl-β-D-glucopyranoside also revealed obvious competitive effects on thromboxane prostanoid (TP) and P2Y12 receptors, and inhibited RhoA and PI3K/Akt/glycogen synthase kinase 3 beta (GSK3β) signal transduction (Fu et al., 2017). Using an aggregometer, protocatechualdehyde

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

| Compounds/extracts                  | Herbs                           | Targets                                      | References   |
|-------------------------------------|---------------------------------|----------------------------------------------|--------------|
| Corynoline                           | Uncaria rhynchophylla           | DNA synthesis of VSMCs, ERK1/2               | Kim et al. (2008) |
| Corilagin, Dgg16                    | Phyllanthus Emblica             | OxLDL                                        | Duan et al. (2008) |
| Sparstolonin B                       | Sparganium stoloniferum         | CCNE2, CDC6, capillary length, branching     | 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/Pi3-kinase        | Ho et al. (2010) |
| Ethanol extract of Gleditsia sinensis| Gleditsia sinensis              | P21WAF1, cyclinB1, Cdc2, Cdc25c, ERK1/2      | Lee et al. (2012) |
| Salvinolic acid B                    | Salvia miltiorrhiza             | MMP-2, MMP-9, ERK1/2, JNK                    | Lin et al. (2007) |
| Protocatechualdehyde                 | Salvia miltiorrhiza             | PDGF, PI3K/Akt, MAPK, cyclin D2, ROS         | Moon et al. (2012) |
| Ethanol extract of Ziziphus nummularia| Ziziphus nummularia             | MMP-2, MMP-9, NF-κB, ICAM-1, VCAM-1,         | Fardoun et al. (2017) |
| Esculetin                            | Artemisia scoparia              | p42/44 MAPK, c-fos and c-jun, NF-κB, AP-1    | Pan et al. (2003) |
| Honokiol                            | Magnolia officinalis            | PI 3-kinase, Ras                             | Zhu et al. (2014) |
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,| Liu et al. (2015) |
| Atractylonolides           | Atractylodes macrocephala | ATP release, Ser473, phospho-p38 | 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 | αβ3 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.

ACKNOWLEDGMENTS

We thank undergraduate student, Yerin Choi for her dedicated assistance. Supports for this work from National Research Foundation (NRF) of Korea (NRF-2016R1A6A1A03007648 and NRF-2018R1A2B6001733) are greatfully acknowledged, and the fellowship (to J. Y. Kim) from NRF (NRF-2017R1A6A3 A11033480) is also appreciated.

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