

Anti-atherosclerotic plants which modulate the phenotype of vascular smooth muscle cells



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ABSTRACT

Background: Cardiovascular disease (CVD) remains the leading cause of global death, with atherosclerosis being a major contributor to this mortality. Several mechanisms are implicated in the pathogenesis of this disease. A key element in the development and progression of atherosclerotic lesions is the phenotype of vascular smooth muscle cells. Under pathophysiologic conditions such as injury, these cells switch from a contractile to a synthetic phenotype that often possesses high proliferative and migratory capacities.

Purpose: Despite major advances made in the management and treatment of atherosclerosis, mortality associated with this disease remains high. This mandates that other approaches be sought. Herbal medicine, especially for the treatment of CVD, has been gaining more attention in recent years. This is in no small part due to the evidence-based values associated with the consumption of many plants as well as the relatively cheaper prices, easier access and conventional folk medicine “inherited” over generations.

Sections: In this review, we provide a brief introduction about the pathogenesis of atherosclerosis then we highlight the role of vascular smooth muscle cells in this disease, especially when a phenotypic switch of these cells arises. We then thoroughly discuss the various plants that show potentially beneficial effects as anti-atherosclerotic, with prime attention given to herbs and plants that inhibit the phenotypic switch of vascular smooth muscle cells.

Conclusion: Accumulating evidence provides the justification for the use of botanicals in the treatment or prevention of atherosclerosis. However, further studies, especially clinical ones, are warranted to better define several pharmacological parameters of these herbs, such as toxicity, tolerability, and efficacy.

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Introduction

Cardiovascular disease (CVD) continues to be the leading cause of worldwide morbidity and mortality (WHO 2013). Globally, about one third of total deaths in 2012 were due to CVD (WHO 2014). In Europe alone, CVD accounts for approximately half of all deaths killing more than 4 million people per year (Nichols et al. 2014). In the United

States, CVD kills more than 787,000 people annually, and consumes about 30% of the total medical expenditure (Mozaffarian et al. 2015b; Trogdon et al. 2007). CVD-related deaths are expected to rise, reaching 23 million deaths by 2030 (WHO 2013). In spite of the many key advances in its management and treatment, CVD claims more lives than all forms of cancer combined (Mozaffarian et al. 2015a).

There are several risk factors that contribute to the CVD-associated mortality. These include high cholesterol levels, smoking, sedentary lifestyle, diet, hypertension and atherosclerosis (Falk 2006). Atherosclerosis, in particular, is responsible for nearly 50% of all deaths in developed countries (Tedgui and Mallat 2006b). The underlying pathological basis for atherosclerosis lies in the prolonged inflammation of the arterial wall and the accompanying endothelial dysfunction.

Endothelium dysfunction allows lipoproteins to leak into the sub-endothelial cell layer (intima) and accumulate there (Wang et al. 2012a). After getting oxidized, these trapped low density lipoproteins (LDL) then recruit monocytes into the intima (Fig. 1).

Abbreviations: CVD, cardiovascular disease; VSMC, vascular smooth muscle cell; NO, nitric oxide; CAM, complementary and alternative medicine; V-CAM-1, vascular cell adhesion molecule-1; I-CAM, intercellular adhesion molecule; ECM, extracellular matrix; MMP, matrix metalloproteinase; ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase.

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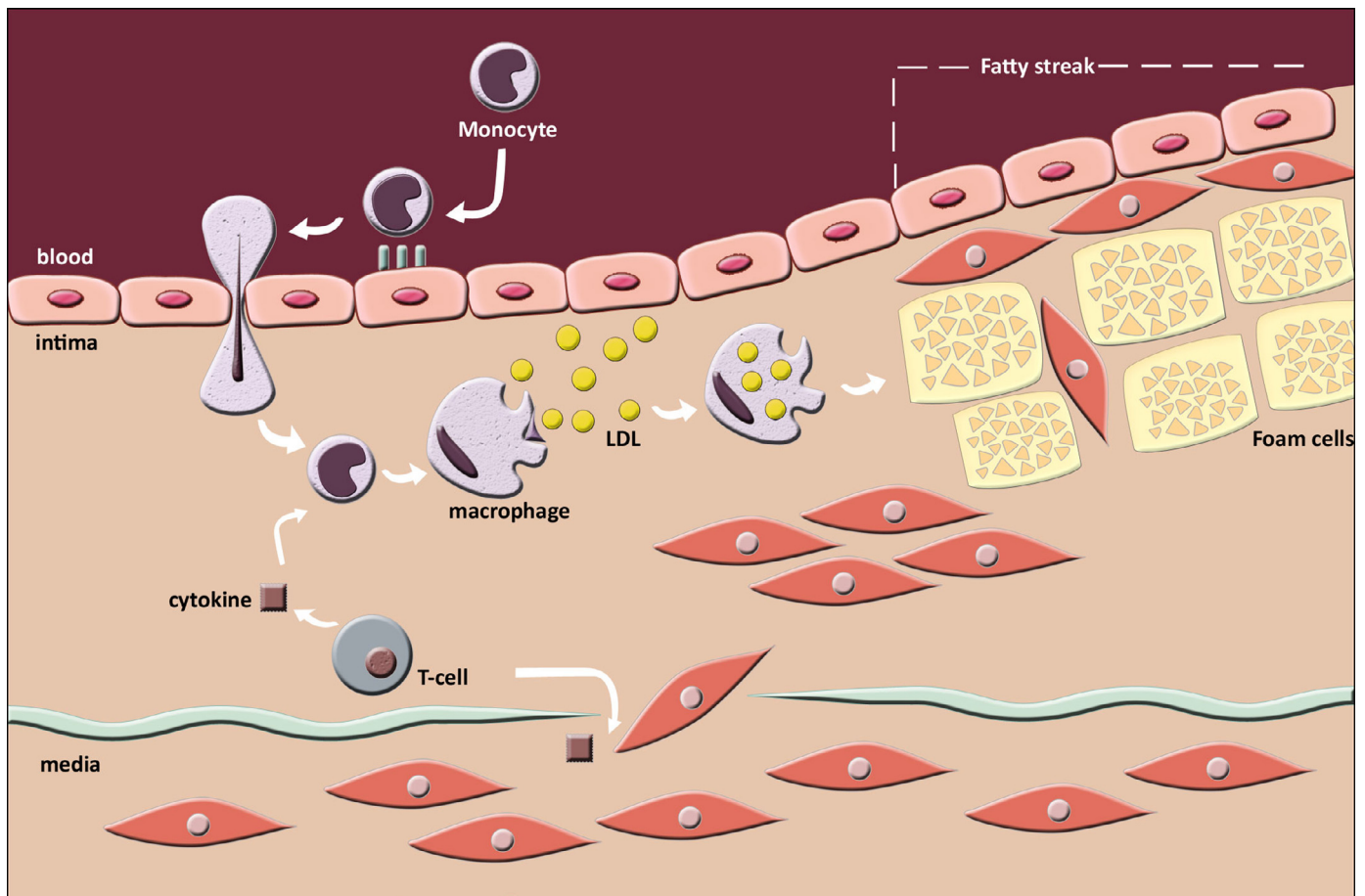


Fig. 1. The interplay between cells and other cues in the onset of atherosclerosis. Monocyte adhesion to the intima is mediated by increased expression of endothelial adhesion molecules. These monocytes then differentiate to macrophages that phagocytose LDL and become “foamy”. The different signaling molecules released in the proximity of the intima (e.g. cytokines) act as chemoattractant for tunica media’s VSMCs. Upon stimulation, these cells then dedifferentiate and migrate to the intima where they form a lesion that may eventually rupture.

Once monocytes reach the lesion, they proliferate and differentiate into macrophages which then give rise to foam cells after attempting to take up oxidized LDL (Douglas and Channon 2010). The repeated incidence of the production and death of foam cells ends up with the development of a necrotic lipid core within the intima (Douglas and Channon 2010). Adhesion of leukocytes and platelets is then potentiated as a result of the upregulated expression of cell adhesion molecules. As platelets aggregate, they start to release platelet – derived growth factor (PDGF) and transforming growth factor β (TGF- β). Both PDGF and TGF- β , among many other physical and biochemical cues, induce a phenotypic switch in VSMCs, which often results in increased proliferative, migratory and invasive capacities of these cells. Eventually, the behavior of these “now-synthetic” cells leads to narrowing of the arterial lumen and dysregulation of vasotone (Douglas and Channon 2010).

There is an intricate relationship between vasotone and atherosclerosis. For example, under normal physiological conditions, nitric oxide (NO), which is a potent vasodilator, plays a major role in regulating vascular tone. Interestingly, NO also inhibits vascular smooth muscle cell (VSMC) proliferation and migration, decreases platelet adhesion and aggregation, as well as represses inflammation (Douglas and Channon 2010). All these NO-modulated parameters are key elements in the pathogenesis of atherosclerosis. Indeed, atherosclerotic lesions could more readily develop when endothelial cells lose the ability to produce NO (Douglas and Channon 2010). This would not be surprising given that atherosclerosis is an inflammatory disease and that NO possesses a potent anti-inflammatory capacity. If left unchecked, increased inflammation can then

modulate the behavior of VSMCs by inducing their dedifferentiation. It is worth mentioning that development of atherosclerosis involves many cell types including endothelial cells, neutrophils, lymphocytes, VSMCs and macrophages (Fig. 1) (Chistiakov et al. 2015; Orekhov et al. 2015). However, in the following sections, we will focus our attention on VSMCs and their phenotypic modulation by plants.

Differentiation of VSMCs

VSMCs originate from at least 5 different progenitors during embryonic development. They are responsible for controlling vessel tone and diameter, both of which are key players in the regulation of blood pressure and flow. Differentiated VSMCs proliferate at a very low rate, display a reduced synthetic activity as well as express a distinctive group of contractile proteins, ion channels, and signaling molecules that are essential for cellular function. However, unlike skeletal or cardiac muscle cells, VSMCs maintain a remarkable plasticity that allows them to undergo a phenotypic switch from the differentiated, quiescent and “contractile” phenotype to the proliferative, less differentiated and synthetic state, especially in response to pathological stimuli (Owens 1995; Wang et al. 2012a) (Fig. 2).

Differentiated or contractile VSMCs express unique markers, such as smooth muscle myosin heavy chain (SM-MHC), smooth muscle α -actin, transgelin, high molecular weight caldesmon (h-caldesmon) and calponin, all of which are crucial for vasoregulation. During development, smooth muscle α -actin is the earliest marker expressed by differentiating cells. About 40% of total cell protein is made up

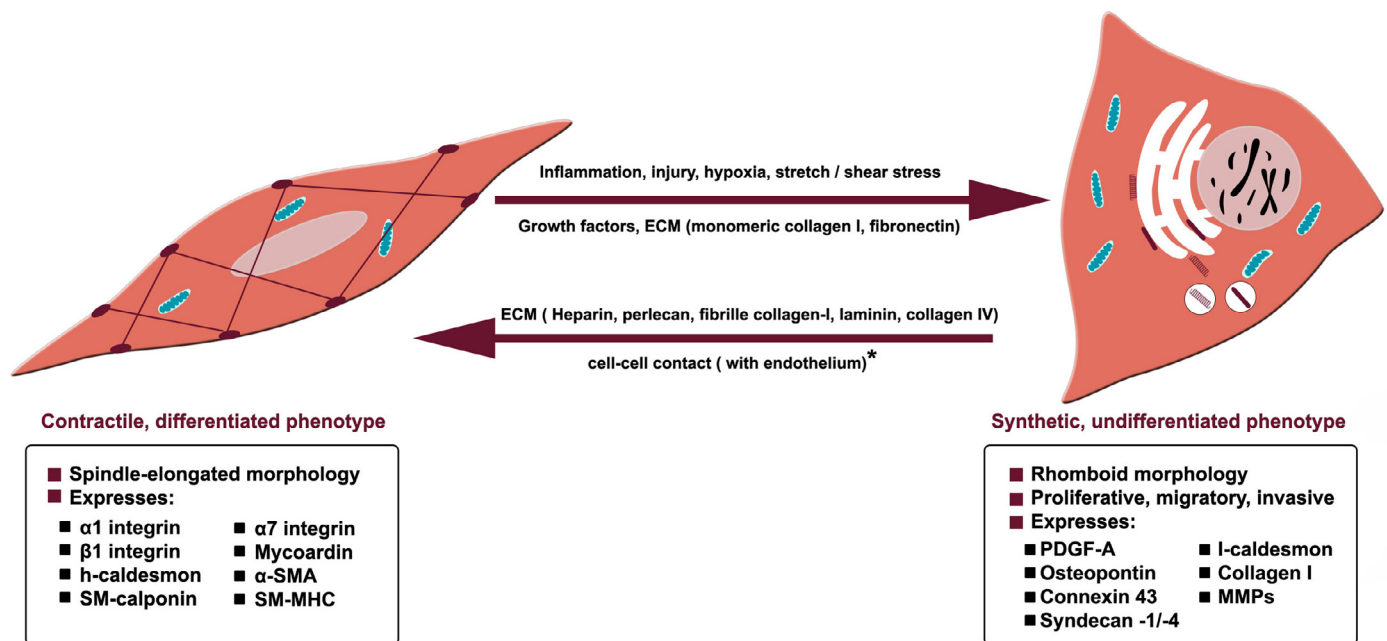


Fig. 2. Different characteristics and expression patterns of contractile versus synthetic VSMCs. Some of the stimuli that promote or inhibit the phenotypic switch are shown. * indicates that in some instances, contact between VSMCs and the endothelium may have the opposite effect i.e. may induce a proliferative phenotype.

of α -actin, making it the most abundant protein in differentiated cells (Fatigati and Murphy 1984). A rather unique marker of differentiated VSMCs is SM-MHC, which is also expressed early during differentiation (Owens 1995). On the other hand, proliferative or synthetic SMCs show altered protein expression including increased expression of low-molecular weight caldesmon (l-caldesmon), c-fos, Egr-1, epiregulin, and SMemb MHC (Sobue et al. 1999).

Other regulatory proteins such as calponin and caldesmon are expressed later during differentiation (Frid et al. 1992). Calponin is involved in the regulation of thin-filament system in SMCs and it binds actin, calmodulin and tropomyosin. While calponin is expressed transiently in the heart during development, its existence is limited to SMCs later in life (Samaha et al. 1996). Caldesmon is another regulatory protein that is expressed concomitantly with calponin (Frid et al. 1992). Interestingly, exposure of cultured smooth muscle cells to oxidized Low density Lipoproteins (oxLDL) is suggested to reduce the expression of several contractile markers including SM-MHC1, α -actin, and calponin (Damiani et al. 1998).

Phenotypic switch of VSMCs

Phenotypic switch, often considered as dedifferentiation, of VSMCs plays a vital role in atherosclerosis. Whereas differentiated VSMCs are generally restricted to the tunica media in healthy vessels, synthetic VSMCs are capable of migrating from the media to the intima with the subsequent formation of fibrous cap by proliferation and adhesion (Rudijanto 2007) (Fig. 2). Contrary to differentiated VSMCs which typically adhere well to the extracellular matrix (ECM) (Eid 2012), synthetic cells can detach from the matrix owing to their ability to express an altered set of adhesion receptors (Moiseeva 2001). Dedifferentiated VSMCs contribute to plaque growth and stability because of their ability to produce ECM components like proteoglycans, which increase the affinity of vessel wall to LDL (Rudijanto 2007). Importantly, these cells often upregulate the expression of adhesion molecules such as vascular cell adhesion molecule-1 (V-CAM-1), which in turn can recruit monocytes and lymphocytes to the atherosclerotic lesion (Rudijanto 2007).

Modulation of VSMC phenotype is regulated via several mechanisms. Growth factors and cytokines including platelet derived growth factors (PDGF), tumor necrosis factors (TNF- α), and interleukin-6 (IL-6) activate a family of serine/threonine kinases known as mitogen activated protein kinases (MAPKs) (Goetze et al. 1999; Hu et al. 1998; Son et al. 2008). This family encompasses the extracellular signal-regulated kinases (ERKs), c-Jun NH2-terminal protein kinases (JNKs) or stress-activated protein kinases (SAPKs), and p38 MAPKs (Chang and Karin 2001) (Fig. 3). Activation of MAPKs, particularly in these differentiated cells, can often lead to detrimental consequences as cell apoptosis followed by plaque rupture (Wernig et al. 2003).

Signaling molecules such as PDGF, IL-1, TNF- α , and LPS can also stimulate atherosclerotic plaque's cells to produce reactive oxygen species (ROS) (Tedgui and Mallat, 2006a). ROS, in turn, triggers a series of reduction-oxidation (redox) signaling pathways that control the expression of inflammatory genes such as JNK and nuclear factor- κ B (NF- κ B) (Tedgui and Mallat 2006a). Being a major regulator of growth factors and adhesion molecules such as PDGF and VCAM-1 respectively, NF- κ B plays a critical role in the recruitment of leukocytes and the resultant inflammation (Van der Heiden et al 2010).

During atherosclerosis, cytokines stimulate VSMCs to secrete matrix metalloproteinases (MMPs). MMPs mediate the digestion of extracellular matrix (ECM) components, thereby promoting cell migration to the intima (Chistiakov et al. 2013; Cho and Reidy 2002). The main MMPs that are activated in response to vascular injury are the gelatinases MMP-2 and MMP-9 (Khan et al. 2002). These MMPs are regulated by different mechanisms. MMP-2 is constitutively expressed in VSMCs. However, expression of MMP-9 is usually low but can be dramatically increased by cytokines and growth factors, such as those released during vascular injury/inflammation (Khan et al. 2002).

Plants that modulate VSMC phenotype

Most therapy regimens for treating atherosclerosis aim at modulating hypertension and hyperlipidemia or controlling hemostasis in order to avoid thrombotic complications (Weber and Noels 2011).

However, many of these modalities often neglected the role of inflammation in atherosclerosis (Weber and Noels 2011). As these therapies remained insufficient in reducing the burden of atherosclerosis-related mortality, other approaches like complementary and alternative medicine (CAM) have recently started to gain more attention (Frishman et al. 2009; Orekhov et al. 2013; Su and Li 2011). It is, therefore, not surprising that more than half of all small-molecule new chemical entities introduced as drugs during the last three decades are either natural products or inspired by nature (Newman and Cragg 2012). Moreover, visits of American patients to CAM providers far exceed those to primary care physicians (Eisenberg et al. 1998; Tachjian et al. 2010). And in the United States alone, about 72 million adults spend more than 34 billion US Dollars on CAM (Tachjian et al. 2010; Tindle et al. 2005). Relevantly, the most common type of CAM among CVD patients is herbs (Yeh et al. 2006). There are several mechanisms by which different plants/herbs modulate VSMC phenotype (Fig. 3). Here we list the CAM plants in alphabetical order with common name shown in parenthesis.

Akebia quinata (Chocolate vine)

Akebia quinata is commonly known as chocolate vine. The stem of this plant is employed for the treatment of inflammatory and urinary disorders in China, Korea and Japan. *Akebia quinata* is known to have anti-inflammatory capacity, evident by its ability to prevent TNF- α mediated signaling and vascular inflammation (Koo et al. 2013). A.

quinata ethanolic extract (AQEE) can indeed inhibit TNF- α induced expression of I-CAM-1 and E-selectin as well as monocyte adherence to human VSMCs (Koo et al. 2013). Moreover, saponin and sapogenins isolated from this plant's stem show anti-inflammatory effects in rats (Choi et al. 2005). Recently, it was further shown that AQEE regulates adipogenesis and exerts hypolipidemic effects in high-fat diet-fed mice (Sung et al. 2015), clearly highlighting its potential as anti-atherosclerotic.

Allium sativum (Garlic)

Garlic has been used as a remedy for various diseases by many civilizations. About one third of CVD patients use garlic supplements (Yeh et al. 2006). Several clinical studies have demonstrated that garlic has the potential to reduce blood pressure in hypertensive patients (Ashraf et al. 2013; Reinhart et al. 2008; Sobenin et al. 2009). The potent hypotensive properties of garlic were suggested to be due to its ability to scavenge free radicals, inhibit NF- κ B activation, and enhance production of both hydrogen sulfide (H₂S) and nitric oxide (NO) (Al-Qattan et al. 2006; Benavides et al. 2007; Geng et al. 1997; Lee et al. 2011; Maldonado et al. 2003). Allyl methyl sulphide (AMS) and diallyl sulphide (DAS), two organosulphur compounds derived from garlic, have been shown to inhibit Ang II-induced migration in aortic smooth muscle cells. AMS and DAS treatment attenuated Ang II-induced cell cycle progression, ROS production, p27 downregulation, and MAPK activation (Castro et al. 2010). Importantly, in a

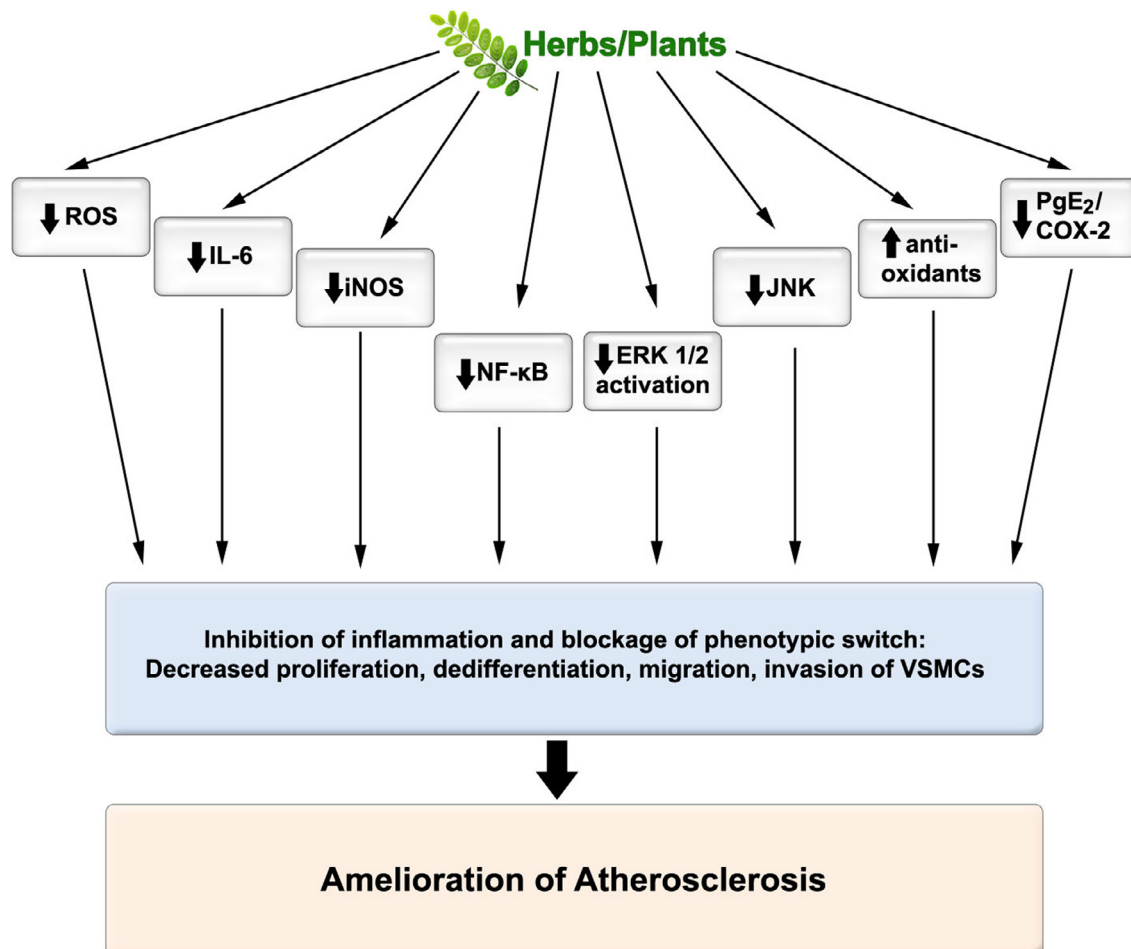


Fig. 3. A summary of the different pathways that are modulated by herbs/plants that inhibit phenotypic switch of VSMCs.

double-blinded placebo-controlled study, garlic was shown to have a lipid-lowering effect (Sobenin et al. 2008), and was proposed as a potential remedy for the secondary prevention of atherosclerotic disease (Sobenin et al. 2010).

Aralia cordata (Mountain asparagus)

Aralia cordata, also referred to as mountain asparagus, is a commonly used herb in oriental medicine, particularly due to its anti-cancer, anti-inflammatory and anti-nociceptive effects. One of its components, pimaric acid (PiMA), has been shown to suppress LPS-stimulated production of key inflammatory markers such as NO, PGE₂, IL-6 as well as the expression of iNOS and COX-2 (Kang et al. 2008). Apparently, PiMA elicits these effects by virtue of its ability to inhibit the activities of NF- κ B, ERK1/2 and p38 (Kang et al. 2008). Furthermore, PiMA can significantly diminish TNF- α -induced migration and invasion of human VSMCs by blocking MAPK and MMP-9 activities (Suh et al. 2012).

Camellia sinenses (Green tea)

Green tea (*Camellia sinenses*) is one of the most commonly consumed beverages worldwide. The health benefits of green tea are attributed to its high polyphenolic contents, which comprise about 36% of green tea dry weight (Balentine et al. 1997). The major polyphenols in green tea are catechins, which can elicit anti-inflammatory, anti-carcinogenic, anti-tumorigenic, anti-mutagenic and anti-diabetic effects (Isozaki and Tamura 2001; Rizvi and Zaid 2001; Valcic et al. 1996; Yang et al. 2013).

Consumption of green tea is reported to result in a lower mortality rate among CVD patients as well as a reduced risk for developing coronary artery diseases (Mineharu et al. 2011; Wang et al. 2011). Epigallocatechin-3-gallate (EGCG) is the principal catechin that has been studied as an anti-atherosclerotic agent. It was found that intraperitoneal injection of EGCG attenuates intimal hyperplasia in the carotid artery injury model (Orozco-Sevilla et al., 2013). Furthermore, EGCG inhibits serum-, Ang II-, PDGF-BB-, TNF- α -, and high glucose-induced proliferation of VSMCs (Han et al. 2006; Kim and Moon 2005; Lee et al. 2013; Lin et al. 2014a; Yang et al. 2011b). Added to that, EGCG can reduce Ang II- and IL-6- induced production of c-reactive protein and ROS in VSMCs (Li et al. 2012). It can also significantly inhibit migration and invasion of VSMCs (Hofmann and Sonenshein 2003; Maeda et al. 2003; Tachjian et al. 2010) as well as suppress TNF- α -induced expression of VCAM-1 and adhesion of macrophages to endothelial cells (Ludwig et al. 2004).

Cinnamomum spp. (Cinnamon)

Cinnamon is a widely known herb that has been used in folk medicine throughout Asia, Africa and Europe. Cinnamon bark has been used in the treatment of cold, diarrhea, nausea and pain. Cinnamon and its components exhibit anti-cancer, anti-diabetic, anti-oxidant, anti-microbial and anti-inflammatory effects (Kim et al. 2006; Kwon et al. 2010; Lee et al. 2003; Matan et al. 2006). Cinnamon water extract (CWE) reduces the *in vivo* LPS-induced production of inflammatory markers including TNF- α and IL-6. Evidence from *in vitro* studies suggests that the anti-inflammatory activities of cinnamon are due to inhibition of both I κ B α degradation and MAPK activation (Hong et al. 2012). With regard to its cardiovascular effects, cinnamon shows potent hypotensive, hypolipidemic, and vasodilatory activities (Jin and Cho 2011a; Nyadjeu et al. 2013; Raffai et al. 2014). It appears that cinnamon's ability to ameliorate high blood pressure occurs by virtue of its ability to enhance NO production (Nyadjeu et al. 2013). Importantly, cinnamon's extract can suppress PDGF-BB-induced proliferation of VSMCs through modulating the expression of p21 and

p27, two cell cycle regulatory proteins (Kwon et al. 2015). The athero-protective properties of cinnamon were also supported by its ability to suppress monocyte differentiation and macrophage scavenger activity (Kang et al. 2014). Furthermore, water extracts of cinnamon show a hypolipidemic effect as well as inhibit protein-glycation, LDL phagocytosis, and atherosclerosis (Jin and Cho 2011b).

Citrus spp.

A lower risk of CVD is linked with a diet rich in citrus fruits. Indeed, citrus fruits are proposed as anti-atherosclerotic agents because they are rich in flavonoids such as nobiletin, naringin, tangeretin and hesperetin. For example, nobiletin inhibits PDGF-BB and Ang-II stimulated proliferation and migration of VSMCs, as well as reduces ROS production, ERK1/2 phosphorylation and NF- κ B expression (Guan et al. 2014; Xu et al. 2013). Nobiletin can also attenuate neointimal hyperplasia and production of IL-6 and TNF- α in balloon-injured rats (Guan et al. 2014). Naringin, another citrus flavone, suppresses MMP-9 expression and AKT phosphorylation leading to reduced migration of TNF- α -treated VSMCs (Lee et al. 2009). Furthermore, naringin can reduce plaque progression and ameliorate endothelial dysfunction in high cholesterol-fed mice (Chanet et al. 2012). On the other hand, tangeretin and hesperetin block VSMCs in the G₀/G₁ phase by upregulating the expression of p27^{Kip1} (Jin et al. 2008; Seo et al. 2011b). Hesperetin can also inhibit PDGF-induced migration of these cells (Seo et al. 2011a).

Curcuma longa (Turmeric)

Curcuma longa, the source of the turmeric spice heavily used in Indian curries dishes, has been used in traditional medicine to treat many diseases. Recent studies show that turmeric's curcuminoids (curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC)) are useful in the treatment of chronic diseases such as cancer, Alzheimer's disease and cardiovascular diseases (Julie and Jurénka 2009). For instance, DMC attenuates LPS-induced inflammation in N9 microglial cells by inhibiting both MAPK and NF- κ B phosphorylation (Zhang et al. 2010). *In vivo*, administration of DMC significantly reduces neointimal hyperplasia as well as inhibited FAK, PI3K, ERK1/2, and MMP-9 following balloon injury. DMA appears to also inhibit the *in vitro* migratory activities of serum-induced VSMCs. This inhibitory effect was coupled with a decreased activity of MMP-2/9, FAK, ERK1/2, and AKT (Sheu et al. 2013).

Overwhelming evidence now supports the notion that curcumin, another key component of turmeric, exhibits anti-oxidant, anti-proliferative, and pro-apoptotic properties (Chen and Huang 1998; Maheshwari et al. 2006). Indeed, curcumin can inhibit TNF- α -induced migration of human VSMCs by suppressing the expression of both MMP-9 and NF- κ B (Yu and Lin 2010). Furthermore, curcumin prevents lipid modification, LDL oxidation and prostacyclin production *in vitro* (Mahfouz et al. 2009). Standardized curcuminoid extract (SCE) has the ability to protect HUVECs from vascular inflammation by suppressing LPS-induced expression of NF- κ B, toll like receptor-4 (TLR-4), ICAM-1 and VCAM-1 (Angel-Morales et al. 2012).

Dioscorea batatas Decne. (Chinese yam)

Chinese Yam is a herbal plant that has shown efficacy in the treatment of inflammatory diseases like arthritis and bronchitis (Araghiniknam et al. 1996). The anti-inflammatory properties of this plant appear due to its ability to suppress both production of ROS as well as activation of MAPK, Akt and NF- κ B (Choi et al. 2012).

Phytochemical analysis reveals that 6, 7-dihydroxy-2, 4-dimethoxyphenanthrene and batatasin I are the major components of aerial tubil extract of *D. batatas* (Choi et al. 2012). The methanolic extract of *D. Batatas* can inhibit TNF- α induced expression of ICAM-1

and VCAM-1 and the subsequent adherence to monocytes (Choi et al. 2012). Recently, it was shown that extracts of Chinese yam can also protect ApoE deficient mice against atherosclerosis (Koo et al. 2014).

Emblica officinalis Gaertn. (Gooseberry or Amla)

Amla (*Emblica officinalis* Gaertn.), a fruit known for its anti-inflammatory properties, is used in traditional Indian medicine. *In vitro* studies of Amla fruit extract show that it possesses anticoagulant properties (Rao et al. 2013). Indeed, treatment of HUVECs with this extract significantly suppresses LPS-induced E-selectin expression and adherence to monocytes (Rao et al. 2013). It was previously found that this plant reduces cholesterol levels in the serum, aorta and liver of rabbits (Thakur 1985), as well as inhibit cholesterol-induced atherosclerosis (Thakur et al. 1988). Flavonoids of this plant exhibit highly potent hypolipidemic activities in rats (Anila and Vijayalakshmi 2000).

Gastrodia elata (Japanese orchid, Tall gastrodia, etc.)

Gastrodia elata Bl. is a perennial herb that has been used in Chinese and Japanese traditional medicine for the treatment of convulsion, hypertension and stroke (Bulpitt et al. 2007). It can work as a vasodilator by increasing asparagine and glutamine as well as reducing gamma amino butyric acid (Zhang et al. 1989). The major active component of *Gastrodia elata* Bl, gastrodin, has been effective in the treatment of neurasthenia, dizziness, epilepsy, migraine, headache and dementia. Gastrodin can inhibit phenotypic switch (dedifferentiation) of VSMCs by reversing PDGF-BB effects on the expression of SM- α -actin, smoothelin and desmin (Zhu et al. 2012). It can also cause a G1/S cell cycle block by stabilizing the expression of p27^{Kip1} (Zhu et al. 2012). Importantly, mice fed with gastrodin show 50% reduction in neointimal thickening following injury (Zhu et al. 2012). Apparently, the effects of gastrodin are due to its ability to inhibit PDGF-induced ERK1/2, p38 and Akt/GSK3 β activities (Zhu et al. 2012).

This plant also exhibits anti-inflammatory effects, evident by its ability to abrogate TNF- α -induced expression of I-CAM, V-CAM and E-selectin in primary cultures of human umbilical vein endothelial cells (Hwang et al. 2009). Furthermore, extracts from this plants' rhizome favorably modulate atherogenic index by lowering levels of total cholesterol and LDL (Kim et al. 2012).

Gentiana lutea (Gentian or bitter root)

Gentiana lutea is a flowering plant that is widely used for the treatment of gastro-intestinal and inflammatory diseases. Chemical analysis of *G. lutea* reveals that it contains gentiopicroside, a compound that has smooth muscle relaxing effects (Aberham et al. 2007). The aqueous extract of *G. lutea* roots can inhibit proliferation of rat aortic smooth muscle cells. Moreover, *G. lutea* extract inhibits PDGF-BB-induced proliferation by blocking ERK1/2 and iNOS signaling (Kesavan et al. 2013).

Ginkgo biloba (Ginkgo; maidenhair tree)

Ginkgo biloba is a popular anti-atherosclerotic herb in Chinese traditional medicine. Its extract inhibits LPS-induced proliferation of human aortic smooth muscle cells, and suppresses TLR-4 expression, NADPH oxidase activation and ERK1/2 phosphorylation (Lin et al. 2007). This extract can also decrease MMP-1 expression in OxLDL-stimulated coronary artery smooth muscle cells (Akiba et al. 2007). Furthermore, the extract can inhibit platelet aggregation, ameliorate endothelial dysfunction, reduce pro-inflammatory cytokines, as well as increase anti-inflammatory markers (Cho and Nam 2007; Jiao et al. 2005; Ou et al. 2013). As such, it is not surprising that *Ginkgo biloba* extract suppresses atherosclerotic lesion development in different animal models (Lim et al. 2011; Wei et al. 2013).

Gleditsia sinensis (Chinese honey locust, locust)

Fruits and thorns of *Gleditsia sinensis* have been traditionally used in Asian countries for the treatment of epilepsy and helminthic diseases. Various extracts of this plant appear to exert anti-inflammatory, anti-mutagenic, anti-microbial, anti-allergic, or cardioprotective actions (Ha et al. 2008; Lim et al. 2005; Shin and Kim 2000; Wu et al. 2010; Zhou et al. 2007). Of particular interest is the anti-atherosclerotic activity of *Gleditsia sinensis* shown by its ability to attenuate atherogenesis and improve lipid profile in rabbits fed a high-fat diet (Lai et al. 2011). The thorn extract can also inhibit TNF- α -induced proliferation and MMP-9 expression as well as PDGF-stimulated proliferation and migration in VSMCs (Lee et al. 2012; Park et al. 2014). Furthermore, echinocystic acid, an isolate from *Gleditsia sinensis*, protects endothelial progenitor cells from OxLDL-induced damage by increasing Akt/eNOS phosphorylation (Lai and Liu 2014).

Hibiscus sabdariffa (Roselle)

Hibiscus sabdariffa or sour tea is an important medicinal herb that is traditionally used for the treatment of hypertension, pyrexia and liver disorders. *Hibiscus sabdariffa* extract (HSE) exhibits cardioprotective properties evident by its ability to prevent development of atherosclerosis in animal models. Indeed, HSE reduces the formation of foam cells and inhibits VSMC migration and calcification in cholesterol-fed rabbits (Chen et al. 2003). Moreover, HSE exerts hypolipidemic, hypotensive, anti-inflammatory, and antioxidant effects both *in vitro* and *in vivo* (Chen et al. 2003; Joven et al. 2014; Perez-Torres et al. 2013; Serban et al. 2015). By attenuating the expression of PCNA and MMP-2, *Hibiscus sabdariffa* polyphenolic isolate can also potentially inhibit high glucose-induced proliferation and migration of VSMCs (Huang et al. 2009). Roselle is also rich in water-soluble pigments called anthocyanins, which themselves can significantly inhibit serum-stimulated proliferation of SMCs, and induce apoptosis via MAPK activation (Lo et al. 2007).

Ipomoea batatas (Purple sweet potato)

Purple sweet potato leaves (PSPL) possesses extremely high polyphenolic content (33.4 \pm 0.5 mg gallic acid/g dry weight) and a free radical scavenging capability (Lin et al. 2006). The methanolic extract of purple-leaved sweet potato reduces LDL and linoleic acid peroxidation (Chao et al. 2014). Further, PSPL extract (PSPLE) and its major components, quercetin and cyanidin, significantly inhibit TNF- α stimulated VCAM-1 expression and monocyte adherence onto human aortic endothelial cells (HAECs). Whereas both cyanidin and quercetin attenuate CD40 surface expression, only quercetin can significantly reduce ICAM-1 and E-Selectin expression (Chao et al. 2013). It is suggested that PSPLE and its components elicit their effects by modulating the NF- κ B and MAPK signaling pathways (Chao et al. 2013).

Litsea cubeba (Exotic verbena; May Chang)

Litsea cubeba is an evergreen tree that belongs to the Lauraceae family and is native to Southeast Asia. Its antioxidant and anti-inflammatory potential are well known (Choi and Hwang 2004; Hwang et al. 2005), and its active principles are beneficial in the treatment of coronary heart disease (Wang 1985). Two alkaloids isolated from this plant, namely laurotetanine and litebamine, are suggested to have cardiovascular protective effects. Laurotetanine causes relaxation of rat thoracic aorta, while litebamine inhibits platelet aggregation, thromboxane B₂ formation and ATP release from rabbit platelets (Chen et al. 1994; Teng et al. 1997). Moreover, litebamine appears to inhibit adhesion of VSMCs onto collagen by modulating FAK activity and cytoskeletal organization (Huang et al. 2008). Added to that,

litebamine inhibits migration of VSMCs by attenuating PDGF-induced PI-3 K phosphorylation (Huang et al. 2008).

Magnolia officinalis (*Magnolia*)

For thousands of years, *Magnolia cortex*, the dried stem bark of *Magnolia officinalis*, has been used in the treatment of several diseases. Studies indicate that the ethanolic extract of *Magnolia cortex* can inhibit both proliferation and migration of VSMCs via different mechanisms such as changing the cytoskeleton superstructure, reducing MMP-2 and MMP-9 activity, decreasing ROS levels, as well as downregulating PCNA, a marker of cell proliferation (Karki et al. 2012, 2013; Wu et al. 2005, 2015). These results are further supported by *in vivo* studies which show that the extract can inhibit intimal thickening in a rat carotid artery model (Karki et al. 2012, 2013). Evidence also indicates that honokiol, a polyphenol derived from *Magnolia officinalis*, can potentially inhibit ERK and NF- κ B activation as well as suppress TNF- α -induced migration and MMP expression in rat VSMCs (Zhu et al. 2014). In addition, honokiol can cause a p21-mediated cell cycle arrest of VSMCs by blocking p38 MAP kinase activity (Lee et al. 2006).

Morus alba L. (*Mulberry*)

In China, Korea, and Japan, leaves of *Morus alba* are traditionally used in preparing tea as well as in relieving pain and edema. Recently, mulberry is reported to possess anti-atherosclerotic, anti-hypertensive, anti-viral, anti-microbial and anti-diabetic properties (Du et al. 2003; Park et al. 2009; Wang et al. 2012b; Yang et al., 2011c, 2012). Indeed, administration of *Morus alba* extract appears to attenuate atherogenesis, improve endothelial function, as well as inhibit migration and proliferation of VSMCs (Chan et al. 2013; Harauma et al. 2007). The anti-proliferative activity of mulberry is likely due to its ability to block the G1 to S phase transition (Chan et al., 2010). Additionally, mulberry leaf extracts can suppress the expression of NF- κ B, MMP-2 and MMP-9, phosphorylation of Akt and FAK, as well as activation of small guanosine triphosphatases (GTPases: c-Raf, Ras, Rac1, Cdc42, and RhoA) in VSMCs (Chan et al. 2009). Moreover, this extract can inhibit inflammation-induced expression of both NF- κ B and lectin-like oxLDL receptor-1 in VSMCs (Shibata et al. 2007). The anti-atherosclerotic properties of mulberry are further demonstrated by its ability to induce VSMCs apoptosis while also inhibiting platelet activation, lipid oxidation, and foam cell formation (Chan et al. 2015; Lee et al. 2014; Yang et al. 2011c).

Olea europaea (*Olive*)

Being a major component of the Mediterranean diet, olive oil consumption has been linked to the lower risk of coronary artery disease that is typically observed in this region's populations (Dimitriou et al. 2015). Olive leaves indeed possess anti-hypertensive, anti-oxidant, hypolipidemic and vasodilatory properties (Andreadou et al. 2006; Khayyal et al. 2002; Le Tutour and Guedon 1992; Zarzuelo et al. 1991). Olive oil polyphenols, in particular, can reduce the concentration and atherogenicity of LDL in healthy young men (Hernaes et al. 2015). By suppressing ERK1/2 activation, these polyphenols induce a G1 to S cell cycle block leading to an inhibition in VSMC proliferation (Abe et al. 2012). Furthermore, olive oil constituents can inhibit neutrophil activity as well as protect the endothelium (Czerwinska et al. 2014; Rodriguez-Rodriguez et al. 2008; Sindona et al. 2012).

Panax ginseng (*Ginseng*)

Ginseng is a well-known herb that has been used to treat various medical conditions (Jang et al. 2011; Kim 2012). The four most common species of ginseng are *P. ginseng* (Asian or Korean ginseng)

(Kim 2012; Valli and Giardina 2002), *P. quinquefolius* (American ginseng) (Kim 2012; Valli and Giardina 2002), *P. japonicas* (Japanese ginseng) (Valli and Giardina 2002) and *P. notoginseng* (Chinese ginseng) (Kim 2012).

Ginseng is known to modulate proliferation of VSMCs. For instance, Chinese ginseng inhibits PDGF-induced VSMCs proliferation by blocking the ERK pathway (Zhang et al. 2012). Moreover, Chinese and other ginsengs can reduce vascular aging in hypertensive compared to normal Wistar-Kyoto (WKY) rats (Tao and Lei 2012). Red ginseng can attenuate the Ang II-induced VSMC growth (Kim 2012). And patients with congestive heart failure showed improvement when treated with red ginseng alone, or in combination with digoxin (Ding et al. 1995). American ginseng, on the other hands, inhibits basal, FBS-, PDGF-, insulin-, and AngII-induced proliferation of VSMCs by suppressing the Jak/Stat pathway (Wu et al. 2012).

About 40 purified compounds, known as ginsenosides, have been identified from ginsengs. (Fuzzati 2004). In addition to promoting vasodilation via NO- dependent activation of K(Ca) channels in VSMCs (Qin et al. 2015), ginsenosides can also suppress neointimal hyperplasia in balloon-injury rat carotid artery model (Yu et al. 2011). Ginsenoside Rb3, for example, inhibits Ang-II- induced proliferation of VSMCs by interfering with G(0)/G(1) to S phase transition and suppressing the expression of c-fos, c-jun and c-myc (Wang et al. 2010). Importantly, ginsenoside Rg1 can rescue the injury-diminished mRNA levels of SM α -actin, clearly indicating its role in promoting a differentiated, rather than a proliferative, phenotype (Gao et al. 2011). Rg1 can also inhibit TNF- α induced proliferation of human VSMCs (Zhang and Wang 2006). Despite these beneficial effects of ginsenosides, it is important to note that vascular dysfunction and remodeling can sometimes be induced by some of these compounds (Lee et al. 2010).

Prunella vulgaris (*Selfheal or Heal-all*)

Prunella vulgaris is a traditional herbal medicine used in the treatment of inflammatory diseases. It is commonly known as Self-heal or Heal-all. In addition to being able to increase eNOS production in human endothelial cells (Xia et al. 2010), *P. vulgaris* provides protection against vascular inflammation by being able to suppress the adherence of monocytes and macrophages onto human VSMCs (Hwang et al. 2012b; Park et al., 2013). Pretreatment with *P. vulgaris* extract abrogates LPS-induced expression of adhesion molecules such as VCAM-1, I-CAM-1, and E-selectin. This decrease in adhesion molecules appears to be due to a suppression in the activity of p38 and ERK (Park et al. 2013). Recently, it was also reported that *P. vulgaris* abrogates high glucose-induced proliferation, migration and invasion of human VSMCs (Hwang et al., 2013). Importantly, these effects are mirrored in an *in vivo* setting where this plant does indeed inhibit diabetes-induced atherosclerosis in db/db mice (Hwang et al. 2012a).

Punica granatum L. (*Pomegranate*)

Pomegranate (*Punica granatum* L.) juice is considered an anti-atherosclerotic and cardioprotective beverage. It is believed that the high polyphenolic contents of pomegranate potentiate its anti-oxidant and anti-inflammatory capabilities. Clinical trials have revealed that consumption of pomegranate juice (PJ) reduces intima media thickness, blood pressure, oxidative stress, and inflammation in human subjects (Asgary et al. 2014; Shema-Didi et al. 2012; Sumner et al. 2005). PJ appears to potentiate the anti-proliferative action of NO on VSMCs as well as improve endothelial function by enhancing NO bioavailability, preventing oxidative destruction and decreasing serum concentration of VCAM-1 (Asgary et al. 2014; Ignarro et al. 2006). Contextually, punicalagin, a bioactive component of pomegranate, suppresses LPS-induced production of inflammatory markers like IL-1 β , IL-6, and TNF- α and prostaglandin E₂ in

macrophages (Xu et al. 2014). It is of clinical relevance to note that a combination of PJ and its bioactive derivatives with statins can significantly reduce foam cell formation (Rosenblat et al. 2013).

Rheum palmatum (Rhubarb)

Rheum palmatum L. possesses anti-inflammatory properties and one of its components, Rhein, can reduce LPS-induced expression of VCAM-1 in HUVECs by blocking the p38 MAPK signaling pathway (Hu et al. 2013). Indeed, Rhein was proposed as a potential prophylactic drug for atherosclerosis because of its ability to prevent monocyte adhesion to HUVECs (Lin et al. 2013).

Rosmarinus officinalis Linn. (Rosemary)

Rosemary (*Rosmarinus officinalis* Linn.) is a widely grown household plant that has been used for centuries in cooking, healing and religious rituals. In folk medicine, rosemary has been employed as a cure for respiratory disorders, poor digestion, migraine and muscle aches (al-Sereiti et al. 1999). Regarding cardiovascular health potential, *Rosmarinus officinalis* extract exhibits an anti-atherogenic property by virtue of its ability to suppress LPS-induced expression of monocyte chemoattractant protein-1 in macrophages (Chae et al. 2012). Carnosic acid, a major polyphenol derived from rosemary, inhibits TNF- α -induced migration of human VSMCs by inhibiting ROS production, MMP-9 expression and NF- κ B activation (Yu et al. 2008). Rosmarinic acid, another bioactive component of rosemary, has demonstrated hypotensive, cardioprotective and anti-inflammatory effects in fructose-fed hypertensive rats (Karthik et al. 2011).

Salvia miltiorrhiza (Danshen)

In Chinese traditional medicine, *Salvia miltiorrhiza*, known as Danshen, is a commonly used herb for the treatment of vascular diseases. *Salvia miltiorrhiza* inhibits TNF- α -induced human aortic smooth muscle cell migration by diminishing MMP-9 activity (Jin et al. 2006). One of this plant's components namely, Tanshinone II A (Tan IIA), can also protect cultured myocytes from oxidative stress-induced apoptosis *in vitro* and *in vivo* (Fu et al. 2007). Moreover, Tan IIA could significantly inhibit atherosclerotic plaque formation in high-fat fed rabbits by downregulating MMP-2 and MMP-9 activities (Fang et al. 2007). Tan II 2 can also prevent *in vivo* atherosclerotic calcification by virtue of its ability to inhibit the production of oxidized LDL (Tang et al. 2007). Randomized clinical trials further demonstrate that Danshen dripping pill is more efficient than isosorbide dinitrate in treating angina pectoris (Jia et al. 2012). Added to that, Danshen treatment can significantly improve the symptoms and electrocardiographs of 80% of ischemic coronary heart disease patients (Cheng 2007). Recently, it was also shown that Danshen pills contribute to LDL reduction in postmenopausal women with borderline hypercholesterolemia (Kwok et al. 2014).

Theobroma cacao (Cacao)

A negative relationship exists between cacao consumption and cardiovascular disease (Buijse et al. 2006). Cacao polyphenols are suggested to lower cardiovascular risk due to their hypotensive and vasodilatory properties (Galleano et al. 2013; Novakovic et al. 2015). Cacao seeds are rich with (–)-Epicatechin which have exhibited high anti-oxidant activities *in vitro* (Luo et al. 2009). (–)-Epicatechin reduced plaque progression and expression of cell adhesion molecules including VCAM-1 and ICAM-1 in apoE (–/–) mice (Natsume and Baba 2014). Cacao polyphenols inhibited LDL oxidation *in vitro* and reduced OxLDL and CRP levels in human subjects after chronic consumption (di Giuseppe et al. 2008; Khan et al. 2012; Richelle et al. 2001).

Toona sinensis (Chinese cedar, Chinese toon, red toon)

Toona sinensis (TS) is a type of Asian arbor that is widely used in Chinese and Taiwanese cuisines. TS has been used for the treatment of rheumatoid arthritis, gastric ulcers, enteritis, dysentery, and cancer (Hseu et al. 2011). Indeed, TS extract shows antioxidant, anti-cancer, anti-inflammation, and anti-angiogenic effects (Hsiang et al. 2013; Liu et al. 2012). TS can also protect the endothelium by suppressing ROS production and oxidative-stress induced damage (Yang et al. 2011a). When used in combination with gallic acid (GA), TS can inhibit LPS-induced inflammation as well as migration of VSMCs via suppressing MMPs, t-PA, growth factors and adhesion molecules (Yang et al. 2014). Moreover, TS can suppress the activation of NF- κ B and many MAPKs (ERK1/2, JNK1/2, and p38) that are key inducers of VSMC proliferation and migration (Yang et al. 2014).

Tripterygium wilfordii Hook.f. (Thunder god vine)

Tripterygium wilfordii Hook is Chinese herb that has been used in folk medicine to treat arthritis, nephritis and asthma. It has the ability to suppress LPS-induced production of TNF- α and IL-1 β in cultured macrophages possibly by downregulating NF- κ B and TLR-4 expression (Qin et al. 2015). Pretreatment of VSMCs with triptolide, a purified extract from this plant, inhibits FBS-induced proliferation via suppressing ERK1/2 activity (Tao et al. 2011). Celastrol, another compound isolated from this plant, can also inhibit proliferation and migration of VSMCs (Kang et al. 2013). These effects appear to be due to celastrol's anti-inflammatory effects evident by the decreased expression of TLR-4 expression (Kang et al. 2013).

Vitis vinifera (Grapevine)

Grapevine (*Vitis vinifera*) has been used in traditional medicine to treat nausea, cholera, constipation and skin disorders. The beneficial health effects of grapes are attributed to its rich polyphenol content. Clinical trials have confirmed the ability of grape extracts to lower blood pressure, as well as improve endothelial function and vascular elastic properties in human subjects (Draijer et al. 2015; Siasos et al. 2014). It is also reported that treatment of hypertensive rats with whole grape powder markedly reduces blood pressure, improves arterial relaxation and attenuates cardiac hypertrophy (Thandapilly et al. 2012). Grape powder also attenuates oxidation and cellular uptake of LDL, thereby diminishing the atherosclerotic area in ApoE-deficient mice (Fuhrman et al. 2005).

These beneficial effects of grapes can also be found in some of its different formulations or purified compounds. For example, resveratrol, a grape-derived polyphenol, inhibits VSMC proliferation and migration of VSMCs via different mechanisms (Ekshyyan et al. 2007; Kumerz et al. 2011; Lee et al. 2014; Lin et al. 2014b; Shi et al. 2013; Zhang et al. 2013, 2014). Balsamic vinegar, which is made of grapes, has also demonstrated an ability to inhibit LDL oxidation and foam cell formation by decreasing the expression of scavenger receptors in macrophages (Iizuka et al. 2010). Procyanidins of grapes have been shown to inhibit NADPH oxidase in human endothelial cells (Alvarez et al. 2012). The grape seed proanthocyanidin can enhance NO production in endothelial cells (Cui et al. 2012) and in rabbits fed with 1% (w/v) grape seed proanthocyanidins, the atherosclerotic activity of LDL in the aorta was significantly inhibited (Yamakoshi et al. 1999). Similarly, treatment with grape seed proanthocyanidins reduces plasma cholesterol and triglyceride levels as well as diminishes the aortic area covered with foam cells (Vinson et al. 2002).

Zingiber officinale (Ginger)

Ginger (*Zingiber officinale*) is a commonly consumed spice and has been used in traditional medicine for treating gastrointestinal,

respiratory and inflammatory disorders (Pakrashi et al. 1975). The main bioactive components of ginger exhibit many biological effects. For example, (S)-[6]-Gingerol, possesses anti-metastatic, anti-angiogenic, anti-hyperlipidaemic, and anti-platelet activities (Kim et al. 2005; Lee et al. 2008; Nammi et al. 2010; Nurtjahja-Tjendraputra et al. 2003). In addition, (S)-[6]-Gingerol is proposed as an anti-atherosclerotic agent due to its ability to inhibit biglycan synthesis, which is an early mediator of lipid binding in atherosclerosis (Kamoto et al. 2013). Moreover, [6]-Shogaol, the main active component of ginger, inhibits PDGF-BB-stimulated proliferation of VSMCs by blocking cell-cycle transition to G2/M phase (Liu et al. 2015). Importantly, the ethanolic extract of ginger has been found to attenuate atherogenesis and reduce LDL levels in cholesterol-fed rabbits (Bhandari et al. 1998).

In addition to the above mentioned plants, there are some instances in folk medicine where a combination of, rather than individual, plants is used. For example, HMC05 is a traditional medical formula composed of eight herbal drugs that possess anti-atherosclerotic properties. The herbal mixture is composed of *Pinelliae Rhizoma*, *Atractylodis Macrocephalae Rhizoma*, *Gastrodiae Rhizoma*, *Citri Pericarpium*, *Poria*, *Crataegi Fructus*, *Siegesbeckiae herba* and *Coptidis Rhizoma*. In addition to being able to favorably modulate the expression of iNOS, COX-2, TNF- α , IL-1 β and NF- κ B, HMC05 can also attenuate the formation of atherosclerotic lesions in apoE (–/–) mice (Kim et al. 2007). HMC05 appears to potentially inhibit TNF- α -induced VSMC migration and proliferation through inhibiting MAPK and ERK activation (Kang et al. 2012).

Cho-Deung-San (CDS), a Korean medical formulation composed of 11 herbal ingredients, is also used for the treatment of many vascular diseases (Yang et al. 2002). CDS can indeed inhibit TNF- α induced migration of VSMCs by inhibiting MMP-2 and -9 activity (Yang et al. 2002).

Similarly, there are some plant-derived resins that can have an anti-atherosclerotic effect. For instance, olibanum, a resin obtained from the Indian herb *Boswellia serrata*, is used to treat inflammatory diseases such as arthritis, asthma and inflammatory bowel disease (Kimmatkar et al. 2003). *In vitro* studies of olibanum extracts showed that it can inhibit proliferation and migration of rat VSMCs (Choi et al. 2009) (Kim et al. 2004).

Draconis Resina (DR) resin, which is secreted by *Daemonorops draco* BL. (Palmae), has been used in traditional Korean medicine to treat wounds, insect bites and diarrhea (Gupta et al. 2008). Not only can DR suppress reactive oxygen production, but it can also inhibit LPS-induced proliferation of VSMCs (Heo et al. 2010).

Conclusion

Phenotypic switch of VSMCs represents a crucial event in the pathogenesis of atherosclerosis. Therefore, favorable modulation of cell phenotype would represent an attractive approach to attenuate lesion formation, and optimistically, reduce the death burden associated with CVD, particularly atherosclerosis. Herbs and plants are being absorbed into evidence-based medicine for the prevention and/or treatment of atherosclerosis. In fact, herbal extracts and their isolates can favorably modulate VSMC phenotype and they ultimately ameliorate the pro-atherosclerotic milieu. The potential pharmacological actions of herbs or isolates are not limited to inhibiting SMC phenotypic switch, but they can also improve other pro-atherogenic parameters such as endothelial dysfunction, platelet activation, lipid peroxidation, pro-inflammatory signaling, ROS production and macrophage atherogenicity. These actions propose a multi-cellular mechanism of herbal remedy in attenuating atherogenesis, and highlight the need for further clinical trials to hopefully arrive at “prescribing” these herbs in safer and more effective doses as well as at cheaper costs.

Conflict of interest

The authors declare that they have no conflict of interests to report.

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