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Immunosuppression-lipid metabolism interplay and medicinal plants in atherosclerosis: a review

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Abstract:

Atherosclerosis is a chronic arterial disease responsible for the majority of vascular related deaths throughout the world. Immune cells and inflammation in conjunction with hyperlipidemia, play a key role in atherosclerosis development. Regarding the low efficacy of synthetic drugs and also the associated negative side effects which can adversely influence health-related quality of life, looking for natural, affordable and non-toxic substances appears to be necessary. Plant-derived natural products play a critical role in prevention and treatment of atherosclerosis. In this review, we aimed to outline the most important medicinal herbs effective on atherosclerosis through an impact on the immune system.

Keywords: Atherosclerosis, Cardiovascular disease, Medicinal plants, Immune system,

Introduction:

According to WHO estimates, cardiovascular disease (CVD)-related events such as myocardial infarction (MI) and stroke are responsible for one-third of deaths worldwide (1, 2). Due to the increase in obesity and diabetes, CVD is expected to rise to roughly 44% by 2030 so inflicting a great deal of pressure on healthcare services (3, 4).

Atherosclerosis, as the leading cause of CVD, is a chronic inflammatory disorder of the vasculature (5) that is affected by genetic susceptibility and also different lifestyle factors including age, gender, stress, smoking and dietary habits (6, 7). However, in spite of lifestyle modifications and the development of new pharmacological approaches for reducing plasma concentrations of total cholesterol, CVD remains a predominant cause of mortality throughout the world (8, 9).

Not only as a lipid accumulation disorder, but also as a chronic inflammatory process of arterial walls, atherosclerosis is induced by factors including an interaction of lipid metabolism imbalance, abnormal immune response and genetic alterations (10-12). In this regard, components of both innate and adoptive immune systems participate in atherosclerosis pathology (12, 13). Briefly, LDL-cholesterol deposits and accumulates in the arterial wall and then LDL is oxidized (OxLDL). It has been proposed that the formation of OxLDL is a critical incident that exacerbates inflammation in the arterial wall. Due to overexpression of adhesion molecules, different types of leukocyte and also monocytes migrate into the vascular wall and produce chemokines and pro-inflammatory cytokines. The uptake of OxLDL is performed by monocyte-derived macrophages through scavenger receptors transforming the cells into lipid-laden foam cells (13, 14). The differentiation into lipid-laden foam cells is crucial in the development of atherosclerosis (15).

The first visible lesion in the development of atherosclerosis is a fatty streak which contains lipids and various immune cells consisting of T lymphocytes, dendritic cells, and macrophages. Progressed atherosclerotic lesions involve migrated smooth muscle cells (SMCs), debris, apoptotic cells, and extracellular matrix comprising collagen and proteoglycans (13). It is thought that B lymphocytes and their secreted immunoglobulins, including IgG and IgM, are associated with atherogenesis. Unstable atherosclerotic plaques may suddenly break off and give rise to a life-threatening coronary thrombosis. Substantial features of indolent plaque include infiltration of many inflammatory cells, a large lipid core, and a thin fibrous cap (16, 17).

Pro-inflammatory cytokines like interleukin 1 and tumor necrosis factor regulate the expression of adhesion molecules involved in early and late stages of atherogenesis. IL-1 and TNF can stimulate the production of growth factors, including fibroblast growth factors (FGF) and platelet derived growth factor (PDGF). These growth factors attract smooth-muscle cells into the tunica intima resulting in inflammation. However, other cytokines and growth factors may be important in developing a more advanced form of atherosclerosis with a decreased susceptibility of plaque to rupture. For example, interstitial collagen production is stimulated by transforming growth factor- β (TGF- β) while it is neutralized by interferon- γ (IFN- γ) (18, 19).

Altogether, prevention of atherosclerosis might be achieved by intervening at each step or the inflammatory-associated factors involved in the atherogenesis process (14).

Nevertheless, regarding the low efficacy of synthetic drugs and also their associated adverse effects including dry mouth, emotional distress, vertigo and stomach disturbances which can adversely affect health-related quality of life, looking for natural, affordable and non-toxic substances appears to be necessary. Currently, plants are widely used in traditional medicine

to treat a broad spectrum of illnesses and approximately 80% of the emerging world population depends upon traditional medicine for primary health care (20). In this review, we aimed to outline the most important medicinal herbs effective on atherosclerosis through an impact on the immune system.

Medicinal Plants and Atherogenesis

Targeted intervention strategies, including anti-inflammatory and immunomodulatory approaches or lipid metabolism modifier-based procedures have been employed to control atherosclerosis (21, 22). Traditional medicine, which is profoundly ingrained in history, has been widely used to prevent and treat a variety of diseases including atherosclerosis. Medicinal herbs are supposed to suppress immune responses and any consequent inflammation. Having knowledge of medicinal plants employed in atherosclerosis management is very helpful to determine the possible use of these herbs in cytokine or lipid metabolism-based therapies. In the following discourse, the potential clinical predictive value of some medicinal herbs in reducing proinflammatory cytokine expression or modifying lipid metabolism in the management of the progression and complications of atherosclerosis will be explained.

Turmeric

Turmeric (*Curcuma longa*) or “Indian saffron” is a spice that has also been used in some medicinal preparations and as a cosmetic for many years in Southeast Asian countries (23). One of the most well-known plant-based natural compounds, called Curcumin, is extracted from the rhizome of the Turmeric plant. Curcumin is a hydrophobic, low molecular weight polyphenol and also a major active component in turmeric. It has been shown to be effective

in the treatment of age-associated diseases like atherosclerosis by exerting anti-inflammatory, anti-oxidative, and anti-atherosclerotic effects (24). Studies have indicated that curcumin significantly represses MCP-1 production and increases cholesterol efflux through inhibition of JNK pathways and it has been concluded that curcumin protects the vascular system against developing atherosclerotic lesions (25).

Cassia occidentalis

Different parts of the annual herb *Cassia occidentalis* Linn. (Caesalpiniaceae) have a variety of medicinal impacts including anti-inflammatory, antihepatotoxic (26), antibacterial (27), antiplasmodial (28) and antidiabetic (29) properties. A leaf aqueous extract of this herb has been used for the treatment of cardiovascular diseases in African traditional medicine. According to studies, treating animal models with a leaf aqueous extract of *Cassia occidentalis* significantly increased the faecal excretion of cholesterol by transformation of cholesterol into biliary acids in rats subjected to a feeding regime high in cholesterol. Furthermore, by increasing LCAT activity, aqueous extract of *Cassia occidentalis* enriched the HDL-C out of cholesterol esters. Taken together, studies have provided evidence of involving the aqueous extract of *C. occidentalis* in lipid metabolism, even though safety has yet to be explored (28).

Cornelian cherry

Cornus mas L. (Cornelian cherry) is a flowering plant in the dogwood family. Due to its high antioxidant and anti-inflammatory properties, Cornelian cherry is considered a medicinal herb and applied in therapeutic approaches against a variety of conditions including inflammatory bowel disease, fever, kidney stones, urinary tract infections as well as bleeding. Moreover, several studies have demonstrated that *Cornus mas* L. has a protective role against atherosclerosis and give rises to a reduction of fat accumulation in the liver (30).

Humulus japonicas

Humulus japonicas (HJ) is a decorative plant in the Cannabaceae family and is a native plant in temperate parts of Asia and the tropical area of Vietnam. According to a study conducted in 2016 by Lim et al, *Humulus japonicas* significantly prevented atherogenesis by repressing inflammation and the development of atherosclerotic lesions *in vitro* and in animal models, respectively. *Humulus japonicas* therefore, appears to be effective against the development of atherosclerosis, so it may have a potential therapeutic application in atherosclerosis treatment (9).

Artemisia judaica L.

Artemisia judaica L. is a medicinal herb which is specifically found in the southern desert of Jordan near to the Jordan-Saudi Arabia borders and in Wadi Araba in Southern Badia. A Study by Abu-Darwish et al., in 2016, revealed that safe concentrations of *Artemisia judaica* essential oil effectively suppress NO production evoked by lipopolysaccharide in macrophages, emphasizing the possible anti-inflammatory properties of *Artemisia judaica* (31).

Salvia miltiorrhiza

Salvia miltiorrhiza var. alba is a perennial plant in the genus *Salvia*. This herb is highly valued in traditional Chinese medicine. It has been used for many years in traditional Chinese medicine to treat cardiovascular diseases associated with inflammation including atherosclerosis. Ma et al., (2016) demonstrated that the root extract of *Salvia miltiorrhiza* effectively suppressed the expression of inflammatory factors including TNF- α , IL-1 β , and IL-8 proposing a potential application of this herb in diseases like atherosclerosis due to its anti-inflammatory properties (32).

Prosopis farcta

Syrian mesquite (*Prosopis farcta*) is a species of the genus *Prosopis* and native to Asia, ranging from India to Iran. In herbal medicine, *Prosopis farcta* root is a suggested treatment for cardiovascular diseases. Saidi et al., (2016) investigated the efficacy of an aqueous extract of *Prosopis farcta* root on the development of experimental atherosclerosis in rabbits. According to their findings, serum lipid parameters including total cholesterol, HDL, TG, LDL, and VLDL levels were substantially increased in hypercholesterolemic animals. However, according to histopathological results, atherosclerotic plaque size was minimally influenced. This outcome may reflect a decline of chest pain or the advantageous impacts of this plant root extract on cardiovascular health (33).

Persimmon (Diospyros kaki L.)

For many years, Persimmon leaves have been used to treat disorders like ischemic stroke, internal hemorrhage and atherosclerosis in traditional Chinese medicine. Xie et al., in a review on traditional uses of persimmon leaves published in 2015, declared that it could potentially be used as a therapeutic agent in cardiovascular disease treatment and prevention including atherosclerosis owing to its immunomodulatory and anti-inflammatory properties. However they proposed more investigation on the safety to use it as a natural drug in medicinal practices (34).

Andrographis paniculata

As an annual plant in the Acanthaceae family, *Andrographis paniculata* is widely found in Southern and Southeastern Asia. For many years, its main bioactive component called Andrographolide (AND) has been used in herbal remedies. According to different studies AND exerts its antiatherogenic properties by reducing VCAM-1 and ICAM-1 as two cell

adhesion molecules which play a key role in migration of vascular smooth muscle cells (SMCs) (35).

Plectranthus zeylanicus Benth

Plectranthus zeylanicus Benth is a perennial herb cultivated in Sri Lanka and South India. People native to these two countries use it as a remedy to treat inflammatory diseases such as asthma and atherosclerosis. Napagoda et al., (2014) in their study revealed that *Plectranthus zeylanicus* Benth inhibited 5-lipoxygenase (5-LO). 5-LO has a key role in initiating the biosynthesis of pro-inflammatory leukotrienes, thus emphasizing the anti-inflammatory impact of this remedy in managing inflammatory associated diseases including atherosclerosis (36).

Prunella vulgaris

As a perennial herbaceous plant, *Prunella vulgaris* is widely distributed throughout the world. This herb belongs to the *Prunella* genus, and for many years it has been used in herbal medicine to treat inflammatory diseases. A study published in 2013 indicated that *Prunella vulgaris* can reduce the expression of adhesion molecules including intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selectin and also the activation of NF- κ B. Molecular analysis revealed that *Prunella vulgaris* exerts its anti-inflammatory effects by inhibiting the p38 MAPK/ERK signaling pathway (37).

Phyllostachys edulis (Bamboo)

For centuries, Bamboo leaves have been used as a food or a natural remedy in Asian countries like Japan and Korea. Owing to its anti-inflammatory and anti-oxidant activity, Bamboo leaves may be beneficial in treating cardiovascular diseases including atherosclerosis. *In vitro* investigation of Bamboo leaf extract effects on human umbilical vein

endothelial cells (HUVECs) has shown that it is able to inhibit monocyte adhesion and vascular cell adhesion molecule-1 expression, reduce oxygen species generation and inhibit interleukin-6 secretion from lipopolysaccharide-stimulated monocytes (38).

Panax notoginseng saponins

Panax notoginseng saponins, also known as Chinese ginseng in English, has been used for many years as a natural remedy for cardiovascular diseases in Asian countries including China, Korea and Japan. Studying *Panax notoginseng* saponins (PNS) effects on atherosclerosis in rats has indicated that PNS upregulates liver X receptor alpha (LXR α) expression and consequent ABCA1 and ABCG1 overexpression and it also inhibits NF- κ B DNA binding activity. LXR α as a receptor, regulates macrophage function which is involved in lipid metabolism and inflammation (39).

PNS not only decreases lipids, serum Ox-LDL level as well as CD40 and MMP-9 expressions in apoE (-/-) mice (40), but also lessens the size of atherosclerotic plaques, enhances endothelialization (41) and suppresses the formation of foam cells (42).

Furthermore, a Ginsenoside derivative known as Ginsenoside Rd blocks voltage dependent Ca²⁺ channels and markedly decreases the size of atherosclerotic plaques and Ox-LDL in the apoE (-/-) rats. Moreover, the formation of foam cells is suppressed by Ginsenoside Rd *in vitro* (42). Conclusively, with regard to the anti-inflammatory effects of PNS and also its role in lipid metabolism regulation, this natural remedy might be introduced as a potential therapeutic agent in atherosclerosis treatment.

Astragalus mongholicus Bunge

In traditional Chinese medicine, *Astragalus mongholicus* Bunge has been used for hundreds of years. Studies using animal models and clinical trials have demonstrated that this medicinal herb may be beneficial in atherosclerosis. Thus, an extract of *Astragalus mongholicus* Bunge lowered total cholesterol and triglyceride in the blood and also the levels of LDL cholesterol and apolipoprotein B. Moreover, *Astragalus mongholicus* Bunge extract reduced fatty streaks and the sclerosing index (43). Total flavonoids of Astragalus (TFA) as the major active ingredient in *Astragalus mongholicus* Bunge is thought to possess the main antioxidant activity of this extract in managing atherosclerosis (44).

Perilla frutescens

Perilla frutescens is a leafy vegetable cultivated widely in some Asian countries, including Japan, and China. This herb exists in two varieties: red and green. Exhibiting its antioxidant effect, *Perilla frutescens* reduces LDL oxidizability. As mentioned earlier, oxidative modification of LDL plays a crucial role in the pathogenesis of atherosclerosis and antioxidant activity can be induced by polyphenol compounds contained in the leaves of *Perilla frutescens*. Oral consumption of the red variety of *Perilla frutescens* results in a longer oxidation lag time and also a significant reduction in lipid peroxide formation as well as the electrophoretic mobility of LDL. Taken together, *Perilla frutescens* consumption can be beneficial for medicinal purposes against the development of atherosclerosis (45).

Dachaihutang

A study performed in 2009 by et al., in rabbits revealed that early treatment of arterial lesions led to a reduction of atherosclerosis size. Dachaihutang resulted in the regression of lesions and also prevented atherosclerosis development by upregulation of carnitine patmitoyl

transferase-1(CPT-1) expression in vascular smooth muscle layers. The treated animal group also displayed a reduction in total cholesterol, triglyceride and LDL serum levels (46).

Cortex moutan

Cortex Moutan (CM, root bark of *Paeonia suffruticosa* Andrews) is widely used in traditional Chinese medicine due to its analgesic, antipyretic, and anti-inflammatory properties and also its ability to prevent thromboembolic diseases. Paeonol is one of the major active ingredients in *Cortex Moutan* which is thought to contribute to the anti-atherosclerotic effect of this remedy. *Cortex Moutan* exerts its anti-atherosclerotic activity by reducing atherosclerosis plaque formation and also by suppressing TNF- alpha, IL-1 beta, and CRP and the translocation of NF- kappaB to the nucleus (47).

Ginkgo biloba

Ginkgo biloba is largely cultivated and is native to China. To assess the effect of this popular traditional medicine, Pierre et al., (2008) conducted an in vitro study using an extract from *Ginkgo biloba* with well-known antioxidant properties. *Ginkgo biloba* extract Egb-761, a standardized formulation of *Ginkgo* leaf extract, protected adhesive properties so preventing endothelial dysfunction as a key event in atherosclerosis development. EGb-761 mediates an inhibition of increased lipoperoxide level by limiting the reduction of Na⁺/K⁺-ATPase activity induced by Ox-LDL in endothelial cells, thereby exerting its protective effect against atherosclerosis (48).

Lycopus lucidus

Lycopus lucidus is widely used in oriental traditional medicine. Pretreatment of exposed- to- high- glucose primary cultured human umbilical vein endothelial cells (HUVEC) with aqueous extract of the leaves of *L. lucidus* Turcz. (ALT) demonstrated that CAMs expression was significantly attenuated and the enhanced cell adhesion between monocyte and HUVEC was blocked. In addition, translocation and promoter transcriptional activity of NF-kappaB was suppressed. All of these consequences can contribute to prevention and treatment of atherosclerosis as a major complication of diabetes mellitus (49).

***Zingiber Officinale* Rosc (ginger)**

Zingiber officinale Rosc is widely used as a spice and also in Chinese traditional medicine and other traditional medicinal systems as a herbal medication. Surveys have indicated that ginger in atherosclerosis exerts its effect by decreasing plasma lipid levels and the size of atherosclerotic lesions and these properties are due to antioxidative activity. This plant could have an inhibitory or scavenging effect on radicals by increasing GSH-Px and reducing LPO (50).

Garlic

Garlic has been widely used to prevent and treat cardiovascular diseases for many years. S-allyl cysteine (SAC) is the main constituent of garlic that inhibits NO production by suppression of iNOS mRNA and protein expression. Moreover, by suppressing the production of hydroxyl radicals, garlic extract demonstrates antioxidant activity. These properties make garlic an effective natural medication against inflammatory based diseases including atherosclerosis (51).

Quercus infectoria

Quercus infectoria is native to southern Europe and the Middle East. This plant has high antioxidant activity by inhibiting Ox-LDL production thereby preventing atherosclerosis development.

Furthermore, *Quercus infectoria* extract reduces the level of total cholesterol, triglyceride and LDL in plasma, emphasizing its contribution in atherosclerosis prevention and treatment (52).

Conclusion:

Although, using synthetic compounds to treat and prevent diseases is attractive, these types of medications can cause side effects. According to preclinical and clinical studies, natural herbs represent potential therapeutic agents in the prevention and treatment of atherosclerosis. Atherosclerosis is the crosstalk of lipid metabolism and inflammation. Medicinal plants may have various properties extended from antioxidant and antihyperlipidemic properties to anti-endothelial dysfunction activity. These features introduce them as potential medications against atherosclerosis. However, sometimes the exact underlying mechanisms have not been precisely determined or understood. These herbs bear promising therapeutic potential to develop safer and less expensive medications to prevent and treat various conditions including atherosclerosis. However, their safety needs to be explored in more detail.

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