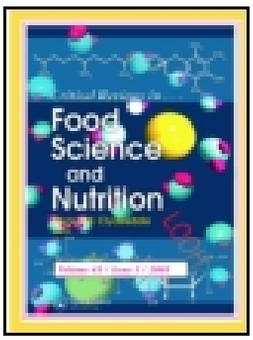

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The effects of food essential oils on cardiovascular diseases: A review

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Short title: Essential oils and cardiovascular diseases

ACCEPTED MANUSCRIPT

ABSTRACT

Essential oils (EO) are complex secondary metabolites, which are produced by aromatic plants and identified by their powerful odors. Present studies on EO and their isolated ingredients have drawn the attention of researchers to screen these natural products and evaluate their effect on the cardiovascular system. Some EO, and their active ingredients, have been reported to improve the cardiovascular system significantly by affecting vaso-relaxation, and decreasing the heart rate and exert a hypotension activity. Several mechanisms have been proposed for the role of EO and their main active components in promoting the health of the cardiovascular system. The objective of this review is to highlight the current state of knowledge on the functional role of EO extracted from plants for reducing the risk of cardiovascular diseases and their mechanisms of action. Research on EO has the potential to identify new bioactive compounds and formulate new functional products for the treatment of cardiovascular diseases such as arterial hypertension, angina pectoris, heart failure, and myocardial infarction.

Keywords Essential oils, Cardiovascular diseases, Vasoconstriction, Vasodilation, Atherosclerosis, Hypertension

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1. INTRODUCTION

There is a wide range of evidence demonstrating a close relation between nutrition and human health. Essential oils (EO) are volatile compounds obtained from various parts of plants such as stems, flower, seeds, leaves and roots (Bastos et al., 2010). Essential oils have been used globally in ethno-, traditional and folklore medicines to treat various health problems. The positive health effects of EO are mostly associated with terpenes, which are considered as the main chemical compounds of these oils. In general, pure essential oils constitute two distinct chemical groups: 1) hydrocarbons (made up exclusively of terpenes), and 2) oxygenated compounds (Bakkali et al., 2008).

Terpenes are a broad group of natural substances that are known to be the primary components of EO. The characteristics and composition of terpenes do not change during extraction and distillation of plant materials. Therefore, different industries have used them for a long time such as foods, pharmaceuticals, perfumes and cosmetics. Terpenes are widespread in nature and they exist in marine organisms as well as in plants. Terpenes can be classified into several groups based on the length of their carbon chains (Table 1). Terpenes are mainly obtained from plants and have been used as markers in plant metabolome analyses due to their unique finger prints in various plants (Hoffmann, 2003).

Essential oils are secondary metabolites of plants consisting of three subgroups, namely acyclic (e.g. geraniol, myrcene, linalool, citronellol, nerol), monocyclic (e.g. menthol, α-terpineol, pulegone, limonene, phellandrene, carvone and terpinolene), and bicyclic (e.g. α-pinene, thujone, camphor, and fenchone) (Santos et al., 2011, Daniel and Daniel, 2006). There are various chemical compounds responsible for the therapeutic effects of essential oils. Among

them, *mono-terpenes* are considered as the main and the most significant group of active compounds in aromatic plants. Recently, research highlighted the medicinal role of plant EO and some of their isolated constituents, especially monoterpenoids, in improving cardiovascular function and reduction of the cardiovascular diseases (CVDs) risk factors (Santos et al., 2011).

Cardiovascular diseases are the most important non-communicable diseases (NCDs). These diseases are becoming increasingly frequent in human and are linked to a high occurrence of disabilities and deaths. In 2012, CVDs were the leading cause of deaths in NCDs and were responsible for more than 17.5 million deaths, 3 out of the 9 global targets were set for reduction in CVDs (Mendis et al., 2015). In 2013, to deal with NCDs, a comprehensive global monitoring framework (GMF) was adopted by the World Health Assembly (WHA) that sets 25 indicators and 9 voluntary global targets to decrease NCDs by 2025. Over the past decades, substantial advances in knowledge have occurred regarding specific health risk factors in vascular dysfunction. Vascular diseases such as cerebrovascular and coronary heart diseases occur for two main reasons; namely atherosclerosis and thromboembolism. The buildup of fat, cholesterol and other compounds in and on artery walls (plaques), referred to atherosclerosis, results in blood flow restriction. Animal experiments and human studies show that the focal increments in the content of lipoproteins (mostly low density lipoprotein (LDL)) within regions of the intima, oxidative changes of LDL, formation of fatty streaks and consequent inflammatory responses are the initial lesions of atherosclerosis. High density lipoprotein (HDL) removes lipid from the atherosclerotic plaque, and deliver it to the liver (hepatocytes). The hepatocytes can metabolize the sterol to bile acids that can be excreted. This export pathway from sclerotic plaque to hepatocytes partially explains the anti-atherogenic action of HDL.

If atherogenesis is not regressed, the pathologic events result in the formation of the necrotic core, fibrous tissue, smooth muscle cells procreation and production of extracellular matrix in the established atherosclerotic lesion. Atherosclerotic plaque physical disruption usually leads to arterial thrombosis, clot formation and arterial occlusion (Longo et al., 2012). Various parts of the body circulation system are affected by atherosclerosis and could have different clinical presentations. A heart attack is commonly happened due to atherosclerosis of the coronary arteries; whereas, atherosclerosis of the arteries supplying the central nervous system causes strokes. It was estimated that among cardiovascular diseases deaths annually reported; heart attacks and strokes causes about 7.4 million and 6.7 million deaths, respectively (Mendis et al., 2015).

Regardless of age, race, and gender, hypertension is the main independent risk factor for CVDs (Rosendorff et al., 2015). In 2010, more than 9.4 million deaths and disease burden about 7% were caused by hypertension (Mendis et al., 2015). The traditional management of hypertension according to the seventh report of the Joint National Committee is about inhibition, identification, and management of high blood pressure of a systolic blood pressure (SBP) ≥140 mmHg and or a diastolic blood pressure (DBP) ≥90 mmHg and/or the current use of antihypertensive medication (Rosendorff et al., 2015). Lack of hypertension control may result in cardiac failure, myocardial infarction, stroke, renal failure, dementia and blindness, leading to individuals suffer physically and imposes serious financial and facility burdens on health care systems (Mendis et al., 2015). Generally, a fatal coronary accident risk is doubled by each increment in SBP of 20 mmHg (or each 10-mmHg elevation in DBP) (Rosendorff et al., 2015). Several health benefits of blood pressure reduction have been indicated through population-wide

and individual studies by behavioral and pharmacological interventions. For example, epidemiological studies have shown that a 10 mmHg reduction in SBP, led to decrease of 22%, 41% and 41-46% in coronary heart disease, stroke and cardio-metabolic mortality, respectively (Mendis et al., 2015).

The key to a good cardiovascular health is the prevention of illness. According to clinical trials, strategies that are intended to detect and modify the risk factors can lead to decelerate hypertension, atherosclerosis development, and also decrease the incidence of cardiovascular events via both primary and secondary prevention methods. Conventional hypotensive medications drug therapies include the use of angiotensin-converting enzyme inhibitors (ACE-I), diuretics, calcium channel blockers, beta blockers, cholesterol lowering drugs, blood-thinning medications (anti-platelet and anti-coagulants to decrease platelet aggregation), and anti-arrhythmic treatments (Blumenthal et al., 2008). Although, these medications have played great therapeutic roles, most of them exert a wide range of side-effects in patients, such as flushing, fatigue, headache, shortness of breath and dizziness are resulted by some anti-hypertensives drugs (Toyoshima et al., 1997). Also, the use of hypolipidemic agents can lead to hepatic diseases and rhabdomyolysis (Sgro and Escousse, 1990). Therefore, research to find new and alternative therapeutic compounds continues.

EO are able to significantly promote the cardiovascular system and can lead to vasorelaxation, hypotension and prevention and improvement of atherosclerosis. Hence, they could be promising agents for CVDs inhibition and/or treatment. Bakkali et al. (2008) reported that the cardiovascular and pharmacological activities of terpenes are influenced by their structure. In general, alcohol monoterpenes are more effective than hydrocarbons; and the site of the hydroxyl

groups on the benzene ring can influence the efficacy of their hypotensive activity. The effects of monoterpenes on the cardiovascular system have been recently targeted in pharmacological studies. In this review, a comprehensive description of the functional role of EO extracted from plant sources for improvement of cardiovascular diseases and their mechanisms of action are reviewed.

2. ESSENTIAL OILS AND HYPERTENSION

Beneficial effects of EO in the cardiovascular system have been demonstrated in animal studies including antithrombotic, endothelial protective, vaso-relaxant, antiplatelet, and hypotensive activities (Lahlou et al., 2000; Ribeiro et al., 2010). Recent studies revealed the important role that vascular endothelium is playing in regulating cardiovascular homeostasis and the endothelial function (Edris, 2007, Guedes et al., 2002). Activation, inactivation and modulation of ion channels, and neural excitability decrement have been demonstrated to occur by different monoterpenes (Lahlou et al., 2000, Gonçalves et al., 2008). Moreover, it has been reported in previous studies that monoterpene induced blood pressure lowering and bradycardic effects in rats (Bastos et al., 2010; Santos et al., 2011). To clarify the effects of EO on the cardiovascular system, a brief discussion of the cellular events mediating vasocontraction and vasorelaxation is provided as follows.

2.1. Mechanism of vasoconstriction

In general, blood flow in an organ of the body is determined by the balance between vasodilation and vasoconstriction. Vasoconstriction in normal blood vessel is mediated by

receptors, which can lead to the opening of calcium channels on the cell membrane and/or sarcoplasmic reticulum. Bolton (1979) reported that the acetylcholine-induced contraction in smooth muscle is caused by Ca^{+2} which entries through the voltage-dependent channel and released from the sarcoplasmic reticulum into the cytoplasm. When an action potential triggers the sympathetic motor neuron at the synaptic terminal, it causes voltage activation operated calcium channels (VOCC) and induces influx of Ca^{2+} ions inside the cytoplasm (Bolton, 1979)

In the sympathetic terminal, the increase of Ca^{2+} forces the norepinephrine out into the interstitial space. When norepinephrine meets the membrane of smooth muscle it attaches and activates a G protein coupled ligand channel receptor, which in turn induces phospholipase C activation (Figure 1). Then, the activated phospholipase C breaks phospholipids into inositol triphosphates (IP_3s) and diacylglycerols (DAGs). The DAG attaches to the plasma membrane Ca^{2+} receptors opens Ca^{2+} channel and allows Ca^{2+} influx. The IP_3 also bind to the receptors of the sarcoplasmic reticulum and leads to Ca^{2+} outflow from the reticulum into the cytoplasm. As a result, contraction happens as long as high concentration of Ca^{2+} is present (Wynne et al., 2009).

2.2. Mechanism of active vasodilation

Mechanism of vasodilation involves lowering intracellular calcium concentration. Nitric-oxide synthase (NOS) and cyclooxygenase (COX) enzymes are two main enzymes that are found almost in all organs. As shown in Figure 2, endothelial receptors act through cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) pathways to relax the smooth vascular muscles (Huo et al., 2015). In COX, or cAMP pathways, COX and prostacyclin synthase (PGI_2 Syn.) produce prostacyclin (PGI_2) from arachidonic acid (AA), which in turn lead

to an increase in cAMP in the smooth muscle and subsequently to a relaxation of the vascular smooth muscle (Mollace et al., 2005). On the other hand, the enzyme nitric oxide synthase (NOS) synthesizes nitric oxide (NO), an endothelium derived relaxing factor (EDRF), from the amino acid L-arginine (Vallance et al., 1989). NO derived from both endothelium and the terminal of cholinergic nerves can easily diffuse through cell membranes. Stimulation of the endothelial cells with acetylcholine (ACh) can also result in the formation and release of NO, which stimulates guanylyl cyclase to increase cGMP in the vascular smooth muscle to produce relaxation. NO acts through modulation of cGMP path, which reduces intracellular Ca^{2+} and relax and dilate the vascular smooth muscle fibers. These paths can be inhibited using L-arginine analogue, i.e. NG-nitro L-arginine methyl ester (L-NAME).

2.3. Compounds used for investigation of the regulation of heart rate and arterial pressure

Research over the last decades attempted to disclose the effects of EO on average arterial pressure (MAP) and heart rate (HR) and the mechanisms involved. The majority of these studies have been designed *in vivo* and/or *in vitro*. To find the mechanisms and the locations of EOs that influence changes in the cardiovascular system, the following materials have been used (Table 2, Figure 3).

- *High potassium* depolarizes the smooth muscle cell membrane and opens VOCC, leading to an influx of extracellular Ca^{2+} and contractile machinery activation (Karaki et al., 1984, Jackson, 2000).

- *Phenylephrine* is a synthetic compound related to epinephrine that is used as a vasoconstrictor (Van Hove et al., 2009).

- *Acetylcholine* (ACh) is the most abundant neurotransmitter located in the central and peripheral nervous system. *Acetylcholine* is also a main part of the peripheral autonomic nervous system and works as an activator of muscles. As shown in Figure 3 and Table 3**,** acetylcholine is a vasodilator, due to its involvement in the release of NO from vascular endothelial cell (Furchgott and Zawadzki, 1980).

- *Atropine* d is an anticholinergic or anti-parasympathetic drug. It antagonizes the muscarine-like actions of acetylcholine as well as other choline esters, and thus it is labeled as an anti-muscarinic agent.

- *Methylatropine* is also classified as an anticholinergic compound that binds to cholinergic receptors, thereby blocking the actions of acetylcholine or cholinergic agonists.

- *Hexamethonium* is a non-depolarising ganglionic blocker. While there are no reports on the influence of hexamethonium on the muscarinic receptors of acetylcholine that placed on the parasympathetic targeted organs, its action as an antagonist on the nicotinic receptors of acetylcholine, which are located in sympathetic and parasympathetic ganglia, has been documented (Mycek et al., 1997).

- *Atenolol* is a competitor of sympathomimetic neurotransmitters, such as catecholamines, to bind at β_1-adrenergic receptors in the heart and vascular smooth muscle. This leads to inhibition of the sympathetic stimulation.

- *Reserpine* is an anti-psychotic and antihypertensive drug. As a result of reserpine ability to deplete catecholamines from peripheral sympathetic nerve endings, it is labeled as an

antihypertensive drug. Some actions of these substances include heart rate control, cardiac contraction force and peripheral vascular resistance (Buelke-Sam et al., 1984).

- *Verapamil* blocks voltage-dependent calcium channels and hence acts as a calcium antagonist.

- *L-NAME* NG-nitro-L-arginine methyl ester has been widely used to inhibit nitric oxide synthesis (NOS) in different biological systems. The nitric oxide role in modulation of cGMP path and relaxation of the smooth muscles has been commonly involved the use of L-NAME in the experiments as a negative control (Uddman, 2012).

- *Indomethacin* is a non-steroidal anti-inflammatory drug (NSAID) and prevents the production of prostaglandins by inhibition of COX-2 activity. The COX metabolizes polyunsaturated fatty acids to prostaglandin in the first step of a metabolic cascade that leads to the generation of prostacyclines and thromboxanes (Hamberg and Samuelsson, 1973).

2.4. Essential oils and vasodilation

A summary of the reported effects of EO from different plants on the mean arterial pressure (MAP) and heart rate (HR) are shown in Table (3). A discussion of these plants is presented in the following section.

Nigella sativa

Nigella sativa, or black seed (Family Ranunculaceae), is an annual herbaceous plant that is widely cultivated throughout the world, particularly in the Middle East and Southeast Asia. This plant contains a high number of antioxidants including; thymoquinone, *p*-cymene, 4-terpineol, anethole, and carvacrol. The plant has been extensively used to treat different illnesses (Amin

and Hosseinzadeh, 2016, Rahmani and Aly, 2015). It has been reported that black seeds contain 26% protein, 25% carbohydrates, 8.4% crude fiber, 4.8% ash and high level of minerals (e.g. Cu, P, Zn, and Fe) (Ahmad et al., 2013) as well as oil, alkaloids and saponins (36-38%) (Singh et al., 2005). The seeds contain 0.4-2.5 % EO, making it suitable to be used for flavouring or as a spice in wide range of foods such as bread or cheese (Wajs et al., 2008). The influence of *Nigella sativa* EO along with various drugs, such as hexamethonium, atropine, reserpine, and spinal pithing, on heart rate and blood pressure was investigated by El Tahir et al. (1993). The intravenous administration of *Nigella sativa* EO can decrease the arterial blood pressure and the heart rate in anaesthetised rats in a dose-dependent manner. Eventually, it was suggested that these effects were mediated mainly centrally in the brain stem (El Tahir et al., 1993).

Croton nepetaefolius

The effect of *Croton nepetaefolius* EO was studied on hypotensive rats (Lahlou et al., 2000). The nephrectomised rats were divided into two groups: 1) deoxycorticosterone acetate (DOCA)-salt hypertensive group, and 2) normotensive control group. Then, the changes in MAP and HR were determined through both *in vivo* and *in vitro* experiments. The findings of this study showed that intravenous treatment with *Croton nepetaefolius* EO in both groups decreased the MAP and HR in a dose-dependent manner, and the magnitude and duration of decreasing MAP were significantly greater in hypertensive rats. It was observed that when the rats were treated with hexamethanium, the administration of EO was able to produce hypotension, but unable to produce bradycardia. Therefore, it was found that EO was not dependent on central autonomic nervous system to reduce blood pressure. Further evaluation was carried out to investigate the

role of 1,8-cineole, the major component of *Croton nepetaefolius* EO, on cardiovascular system in normotensive rats (Lahlou et al., 2002a). It was found that 1,8-cineole has hypotensive effects and simultaneously induces bradycardia in a dose-dependent manner. Pre-treatment with methylatropine, atenolol, hexamethonium, or vagotomy in rats had no effect on the 1,8-cineole-induced blood pressure-lowering effect, however, the administration of these drugs lowered 1,8-cineole-induced bradycardia (Table 2, figure 3). Thus, it was concluded that the mechanism of hypotension was different from the mechanism of bradycardia and 1,8-cineole could lead to hypotension through an active vascular relaxation, but not via inactivation of sympathetic nervous system. In addition, the authors observed that the time needed for the maximal blood pressure-lowering effect was similar for acetylcholine and 1,8-cineole; so they assumed that the hypotensive effect might be partly mediated by L-arginine-nitric oxide pathway (Lahlou et al., 2002a). In another study, the hypotensive effect of methyleugenol, another bioactive constituent of *Croton nepetaefolius* EO, was investigated (Lahlou et al., 2004a). It was stated that the hypotensive action of methyleugenol was related to the endothelial L-arginine nitric oxide pathway.

Mentha x Villosa

Lahlou et al. (2001) evaluated the dose-effect relationship between piperitenone oxide (PO), the major constituent of *Mentha x villosa* EO, and cardiovascular changes. In that work, the autonomic nervous system role on the cardiovascular effects of EO was also examined. The injection of *Mentha x villosa* EO in rats resulted in hypotension and bradycardia. However, when the rats' central autonomic nervous system was completely eliminated by hexamethonium, it was

found that EO induced hypotension but not bradycardia in the experimental animals. Thus, it was concluded that the bradycardia induced by *Mentha x Villosa* EO was dependant on the autonomic nervous system. Furthermore, pre-treatment with methylatropine had no effect on the EO-induced bradycardia, which suggested that a sympathetic inhibition lowered the HR rather than vagal activation.

Alpinia zrumbet

In 2002, the effects of terpinen-4-ol, the main compound of the essential oil of *Alpinia zrumbet*, on MAP and HR were studied by Lahlou et al. (2002b). Intravenous treatment with the EO resulted in a prompt and notable hypotension that could be partially associated with terpinen-4-ol. The authors suggested that the *Alpinia zrumbet* EO treatment may result in a direct vasorelaxation that is partially mediated by the L-arginine-nitric oxide pathway.

Ocimum gratissimum

The cardiovascular outcomes of an intravenous intervention with EO of *Ocimum gratissimum* leaves and eugenol (the major constituent of EO) were investigated in anaesthetized and conscious rats as well as the role of the autonomic nervous system in the observed results by Lahlou et al. (2004b). Intravenous bolus injections of *Ocimum gratissimum* EO showed prompt and dose-dependent reductions in MAP and HR. The findings emphasised that the hypotensive activity of EO was related to the eugenol activity, the major constituent of EO. This conclusion was supported by the findings that; 1) hypotension and bradycardia became significant after injection of eugenol and highest level of hypotension was found during the first 20-30 seconds

after the injection, which was similar to findings detected for EO, 2) pre-treatment with hexamethonium partly, but notably, lowered the bradycardia impacts of eugenol but did not change the hypotension effect of EO, which was similar to that observed in EO treatment (Lahlou et al., 2004b).

The authors repeated the same approach for eugenol, a natural ingredient of various plants' EO (Lahlou et al., 2004c). It was confirmed that intravenous treatment with eugenol could dose-dependently induce hypotension and bradycardia. The results showed that the bradycardia and the hypotension activities happened independently, and the bradycardia appeared to rely on the parasympathetic nerve supplied the heart. The authors concluded that the vascular relaxation and hypotension were due to the active induction of parasympathetic rather than removal of sympathetic tone. However, they did not confirm that the endothelial L-arginine/nitric oxide pathway was involved in vasorelaxation effect of eugenol.

Nishijima et al. (1999) had also evaluated the effect of eugenol on segments of the thoracic aorta of rabbits and found that eugenol impacts on contractions were induced by excess K^+ concentrations in association with Ca^{2+}. The authors found that eugenol was able to inhibit the voltage-dependent Ca^{2+} channels and that eugenol might be a metabolic contraction inhibitor through several pathways.

Aniba canelilla

Aniba canelilla is an aromatic plant widely found in the Amazon region. 1-nitro-2-phenylethan and methyleugenol are important volatile constituents of its EO. The effect of the EO of *Aniba canelilla* bark on MAP and HR was investigated in rats (Lahlou et al., 2005). In this

investigation the effects of *Aniba canelilla* EO on the autonomic nervous system and on the endothelium in rats were determined. Pre-treatment of conscious rats with methylatropine, which can cross the blood-brain barrier, reduced the impact of *Aniba canelilla* EO on hypotension. Moreover, when the influence of the central autonomic nervous system was eliminated through pre-treatment with hexamethonium, EO did not cause bradycardia while a hypotensive response due to EO remained unaffected. These findings along with those found in vagotomised rats that suggested *Aniba canelilla* EO could induce hypotension, determined that EO cannot reduce the blood pressure through activation of the central parasympathetic. Thus, it was suggested that the hypotension and the bradycardia activities of *Aniba canelilla* EO occurred independently; i.e. EO-induced bradycardia was dependent on the autonomic nervous system but EO-induced hypotension was not. This contention was supported by the fact that the EO-induced blood pressure lowering activity was more prominent on diastolic arterial blood pressure rather than systolic blood pressure (Lahlou et al., 2005). Pre-treatment of conscious rats with the NO synthase inhibitor, L-NAME, showed that the EO was not able to induce hypotension while created bradycardia. These findings confirmed that *Aniba canelilla* EO-induced hypotension was due to an active vascular relaxation and endothelial L-arginine/nitric oxide pathway was not involved. *In vitro* experiment was designed to further explore the role of endothelium on vaso-relaxant activity of the EO. The endothelium was removed from some aortic segments; then all aortic segments, either with or without endothelium, and was treated with high concentration of KCl. High potassium content can depolarize the membrane of smooth muscle cell, open the voltage dependent Ca^{2+} channels, and results in contraction. It was observed that EO did not inhibit the contraction induced by potassium in aortic segments that lacked endothelium. When

the aortic segments pre-treated with atropine, the segment with-endothelium could not show a vasodilation response. Thus, the authors proposed that the vasorelaxation caused by *Aniba canelilla* EO was partially facilitated via an endothelial L-arginine/nitric oxide pathway, by activation of peripheral muscarinic receptor (endothelial-dependent relaxation); and mainly by inhibition of Ca^{2+} inflow (endothelial-independent relaxation). This demonstrated that EO directly acted on vascular smooth muscle and induced relaxation (Lahlou et al., 2005).

Croton zehntneri

The cardiovascular benefits of *Croton zehntneri* essential oil and its main ingredients (such as anethole and estragole) were investigated in normotensive rats (de Siqueira et al., 2006). Leaves of *Croton zehntneri* have EO mainly including mono- and sesqui-terpenes. In the first phase of the study by de Siqueira et al. (2006), intravenous injections of EO and its main constituents showed dose-dependent hypotension and bradycardia activities. It was concluded that EO cardiovascular effects may be associated with the actions of anethole and in part to the actions of estragole. However, in a second phase of the study, rats pre-treated with methylatropine (a blocking agent that inhibit the actions of acetylcholine or cholinergic agonists), the initial hypotensive and bradycardic responses of EO were remarkably reversed into arterial pressure and tachycardia. Thus, the authors suggested that peripheral a cholinergic mechanism was involved in the both MAP and HR effects of *Croton zehntneri* EO. Additionally, they stated that a pre-treatment with atenolol (a selective β_1-adrenergic antagonist), caused an initial bradycardia that was elicited by EO and determined the bradycardia was independent of the sympathetic nerve reaches the heart. Thus, it was concluded that bradycardic response could result from stimulating cardiac M2-muscarinic receptor, the cardiac ganglia, and/or the brainstem, which in

turn activated vagal cholinergic afferents. The authors proposed that the initial vasodilation and blood pressure lowering evoked by EO, were conducted by activation of peripheral muscarinic receptor and may be involve the endothelial-arginine/NO pathway. *In vitro* findings, however, showed that the blockage of endothelial role through elimination of endothelium or pre-treatment by L-NAME, could preserve the vaso-relaxant effects of EO. Therefore, they claimed that the endothelial-arginine/NO pathway was unlikely to be involved in initial hypotension of *Croton zehntneri EO* (de Siqueira et al., 2006).

Hyptis fruticose

Santos et al. (2007) evaluated the vasodilation effects of EO of *Hyptis fruticose*. The EO contains α-pinene, caryophyllene, and 1,8 cineole. It was determined that the endothelium is essential to regulate the vascular tonicity via releasing mainly NO and COX-derived products, endothelium derived relaxing factors (EDRF). Calcium-potassium channels (KCa) prominently contribute to the vascular tone. *In vitro* experiments were designed, and superior mesenteric arterial rings (with and without endothelial) were pre-treated with either potassium or phenylephrine. The authors observed that EO induced a direct vasodilatation, which was more effective in the rings pre-treated with K^+ rather than in those treated with phenylephrine. Therefore, they suggested that *Hyptis fruticose* EO could possibly inhibit Ca^{2+} entry by means of voltage operated calcium channels (VOCCs). Thu**s,** they hypothesized that *Hyptis fruticose* EO was able to antagonize the $CaCl_2$-induced contractions and it could act as a calcium-blocking agent (Santos et al., 2007).

Cymbopogon winterianus

The cardiovascular effects of *Cymbopogon winterianus* EO in male Wistar normotensive rats were investigated by De Menezes et al. (2010). The main components of EO were the terpenoids geraniol, citronellol, and citronellal. To examine the role of NO and the COX's metabolites, particularly prostacyclin (PGI_2), in the responses induced by EO, the following approach was designed. The endotheliums were removed from mesenteric arteries rings and were pre-contracted with high K^+ and phenylephrine. It was reported that the vaso-relaxation effect of EO in pre-contracted arteries with K^+ was similar to those exposed to phenylephrine. Moreover, an *in vitro* contraction-response curve to $CaCl_2$ was surveyed before and after incubation with EO. EO treatment shifted the contraction-curve to the right and caused a dose-dependent reduction in the maximal influence of $CaCl_2$. Thus, the authors suggested that EO induced hypotension through prevention of Ca^{2+} influx via calcium channels. In addition, because L-NAME (NO synthase inhibitor**)** and indomethacin (an inhibitor of COX) were unable to change the hypotension induced by EO, they concluded that the hypotension induced by the EO was not mediated by main endothelial mediators such as NO and COX. Meanwhile, as *Cymbopogon winterianus* EO induced hypotension associated with a tachycardia, they also suggested that the EO acted like a calcium-blocker such as nifedipine and verapamil. Furthermore, the authors suggested that *Cymbopogon winterianus* EO could temporarily block sinoatrial node, induce junctional rhythm and also a first-degree atrioventricular blockage by means of muscarinic receptor of cardiac muscles (De Menezes et al., 2010).

Other aromatic plants

Ribeiro et al. (2010) explored the cardiovascular influences of α-terpineol, an essential oil monoterpene present widely in aromatic plant species. Their attempt was to explore the direct impact of α-terpineol on arteries, without any neuro-humoral influence. They used superior mesenteric arteries from rats and showed that α-terpineol induced vasorelaxation resulted in notable reduction after removal of the endothelium. The addition of L-NAME or NO scavenger, resulted in a reduction in the vaso-relaxant effect of α-terpineol. The addition of the exogenous L-arginine had no effect on the vasorelaxation, while treatment of the rings with the L-NAME plus L-arginine lowered the vaso-relaxant response of α-terpineol. Treating the tissue ring with 1H-[1,2,4] oxadiazolo[4,3-a]quinoxalin-1-one, which is a soluble guanylate cyclase inhibitor (sGC), reduced the relaxation of α-terpineol. Collectively, these results suggested that the hypotension elicited by α-terpineol may be the result of a release of NO from the vascular endothelium and the activation of the NO-cGMP pathway. To determine the vaso-relaxant effect of α-terpineol on COX pathway, the rings were treated with indomethacin, which is a non-selective COX inhibitor. Under these conditions, the vaso-relaxant effect of α-terpineol was unaffected, which led the authors to conclude that COX products were not involved in the vaso-relaxant effect of α-terpineol.

In another study, the effect of four mono-terpenes (e.g. (+)-α-pinene, (-)-β-pinene, (±)-citronellol, (±)-linalool) and one sesqui-terpene (e.g. (-)-α-bisabolol) on MAP and HR were studied in rats (Menezes et al., 2010). The authors observed that monoterpenes induced hypotension with tachycardia, which suggested hypotensive effect followed by a baroreflex response. On the other hand, (-)-α-bisabolol induced hypotension with bradycardia, that indicated different mechanism of action. The authors claimed that the (-)-β-pinene, consists the

exocyclic double bond, had more pharmacological effect than (+)-α-pinene, which has an endocyclic double bond. They also suggested that the terpene alcohols were more effective than the hydrocarbon terpenes. In general, it was concluded that all the examined terpenes had hypotensive effects and the structures of the terpenes can influence the efficacy of their hypotensive activity.

3. ESSENTIAL OILS AND ATHEROSCLEROSIS

Several studies reported the impact of plants' EOs and their constituents, especially phenylpropanoids and monoterpenoids, on atherosclerosis (Table 4).

Onion and garlic

In 1975, an evaluation of the effects of garlic and onion EO was conducted in rabbits fed high cholesterol diet and were compared to control treatment group, treated with clofibrate (Bordia et al., 1975). After 3 months of high cholesterol feeding, the serum cholesterol escalation in the Indian albino rabbits was significantly decreased in the experimental rabbits that consumed onion and garlic essential oils compared to those treated with clofibrate. Compared to clofibrate, the EO of onion and garlic demonstrated higher efficacy at a regular clinical dose of 33 mg/kg/day. Although, feeding cholesterol remarkably enhanced lipid level of the aorta (from 5.95 to 13.75 mg/100 mg dry weight), clofibrate, onion or garlic EO treatment decreased this value to 7.79, 6.23 and 5.28 mg/100 ml, respectively. It was reported that garlic EO was even more effective than onion EO. Fibrinolytic activity was also increased in rabbits consumed onion and garlic EO compared to the control groups. The fibrinolytic action was suggested to be caused

by the sulphur-containing compounds in garlic and onion (mainly ally1 propyl disulphide and diallyl disulphide). In that study, the protective effects of onion and garlic were more pronounced than those of clofibrate and it was concluded that they could prohibit atherosclerosis progress in the long term (Bordia et al., 1975).

Another study was conducted to investigate the effects of onion and garlic EO on atherosclerosis in rabbits (Bordia et al., 1977a). Administration of onion and garlic EO decreased serum cholesterol and serum triglycerides during the four months treatment. High cholesterol feeding of the rabbits significantly increased β- and pre-β lipoproteins and decreased the α-fraction. The β/α ratio was increased from 1.3:1 (initial) to 4.5:1 (at the end of 2 months) and to 5.7:1 (at the end of the 4 months treatment period). Adding onion and garlic EO to the rabbits' diet was found to prevent the increase of this ratio. It was also found that the fibrinolytic activity was significantly enhanced with onion and garlic EO consumption while feeding only cholesterol reduced it. A significant reduction, about half, in aortic atheroma was caused by treatment with onion and garlic EO. The protective effect of the EO of onion and garlic against experimental atherosclerosis was reported to be due to the three possible mechanisms; 1) by controlling the increase in the lipids and cholesterol of blood, 2) by preventing the reduction in the α-lipoprotein fraction through keeping the β/α ratio around the normal range, or 3) by enhancing fibrinolytic activity of plasma (Bordia et al., 1977a).

In addition to the animal study, the effects of garlic EO on blood lipids (Bordia, 1981) and serum fibrinolytic activity (Bordia et al., 1977b) were investigated in humans with coronary heart disease (Table 4). Garlic EO resulted in significant reductions in serum cholesterol and triglycerides and increment in the content of high-density lipoproteins (HDL) in healthy

individuals as well as coronary heart disease patients (Bordia, 1981). Garlic EO enhanced the activity of fibrinolysis in chronic infarction cases (Bordia et al., 1977b). Thus, garlic EO was considered to be a significant dietary compound for persons with high possibility of suffering from atherosclerosis and thrombosis.

Satureja khuzestanica

Satureja khuzestanica is a native plant of Iran and is widely spread in the southern part of the country (such as in Lorestan and Khuzestan provinces). The genus *Satureja* belongs to the *Lamiaceae* family, *Nepetoideae* subfamily and the tribe *Mentheae*. The high amount of EO (more than 0.5%) is considered as a particular property of the subfamily *Nepetoideae* (El-Gazzar and Watson, 1970). A remarkable difference in the EO composition between and within the subspecies of *Satureja* was reported (Slavkovska et al., 2001).

Several controversial studies reported the antihyperlipidemic and triglyceride-lowering effects of powder, extracts and EO of *Satureja khuzestanica* leaves. In 2003, the EO of the aerial parts of the *Satureja khuzestanica* was extracted and its antihyperlipidemic effect was investigated in Sprague-Dawley male rats (Abdollahi et al., 2003). *Satureja khuzestanica* EO treatment had significantly decreased the triglycerides levels (201±17.6 vs 166±14.9 (mg/dl)), but no significant effect was observed on blood total cholesterol levels (156±14.1 vs 146±9.6 (mg/dl)). Nazari et al. (2005) studied the effect of *Satureja khuzestanica* EO on triglyceride level in male Wistar rats and found a significant decrease at the dose of 1000 ppm. The effect of *Satureja khuzestanica* supplement (tablets containing 250 mg dried leaves) in hyperlipidemic patients with type 2 diabetes mellitus was studied (Vosough-Ghanbari et al., 2008). Compared to the

baseline values, treatment with the tablets for 60 days could significantly decrease the TC and LDL-C, increased HDL-C, and had no effect on the triglyceride level. In contrast to this study, another study examined the lipidemic influence of *Satureja khuzestanica* EO in type 1 diabetic rats (Alloxan-induced) (Ahmadvand and Tavafi, 2012). It was observed that TC, LDL-C, VLDL and TG were significantly decreased and HDL-C was increased when the rats were treated with *Satureja khuzestanica* EO. There is need to conduct further research to elucidate the antihyperlipidemic effect of *Satureja khuzestanica* EO and its mechasnim of action.

Artemisia species

Artemisia is a large and diverse member of plant family Asteracae (Compositae), which is reputed to have more than 300 species, and is mostly found in Europe, America, North Africa, and Asia arid and semi-arid areas (Negahban et al., 2007, Shekari et al., 2008). Some of Artemisia species were reported to have cardioprotective properties. Wormwood (*Artemisia princeps*), an eastern medicinal plant, considered as a common aromatic herb, widely used as flavoring and aromatic tonic in Korea and China. Wormwood EO have been reported to contain various types of bioactive compounds such as phenolic compounds, vitamins, and different minerals (Canadanovic-Brunet et al., 2005, Geszprych et al., 2010, Khangholil and Rezaeinodehi, 2008, Msaada et al., 2015, Riahi et al., 2013).

Chung and colleagues studied the anti-atherosclerotic properties of EO of wormwood (Chung et al., 2007). To study the mechanisms of action, they evaluated the presence of key genes involving in metabolism of cholesterol such as the LDL receptor, sterol regulatory element binding proteins, and the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a

rate-controlling enzyme of cholesterol pathway. They observed a two-fold increase in LDL receptor, when HepG2 cells were treated at concentration of 0.05 mg/mL of EO for 24 h. Interestingly, when EO was mixed with vitamin E at concentration of 0.2 mg/mL, the LDL receptor was significantly decreased by 5-6 folds. The HMG-CoA reductase activity was not altered, and cytotoxicity was found with treatments at high concentrations. The anti-atherogenic properties of this EO with vitamin E were due to blocking of LDL oxidation and upregulating of the LDL receptor (Chung et al., 2007).

Another study investigated the effects of *Artemisia sieberi* EO on biochemical metabolites in alloxan-induced-diabetic rats (Irshaid et al., 2012). There was a notable decrement in the mean values of TC, TG, and LDL-C by oral intervention of extract and the average values of the HDL-C in diabetic rats were increased. However, the control group in that study had no remarkable changes in these parameters.

Asian plantain (*Plantago asiatica*)

Asian plantain (*Plantago asiatica*) has been used as medicine in Korea, Japan, and China for the treatment of a number of diseases (Liu et al., 2002, Samuelsen, 2000). The polysaccharides of the *Semen plantaginis* (the ripe seed of *Plantago asiatica)* have been reported to have hypocholesterolemic effects (Solà et al., 2010, Xiong et al., 2008). Postprandial oxidative stress can be decreased by the phenolic compounds of Asiatic plantain in overweight hyperlipidemic subjects (Lim et al., 2013). The presence of key genes for metabolism of cholesterol and lipid-lowering capacity of Asian plantain EO was investigated (both *in vitro* and *in vivo*) and the hypolipidemic mechanism of action was evaluated by Chung et al. (2008). Incubation of 0.2 mg

Asian plantain EO with human liver carcinoma cell line (HepG2 cells) for 24 h altered the LDL receptor and HMG-CoA reductase. It was also concluded that the remarkable inhibition of LDL oxidation was due to the prevalence of linalool in Asian plantain EO. There were significant reductions in TC (29%) and TAG (46 %) concentrations after 3 weeks of oral administration of Asian plantain EO in C57BL/6 mice. It was also shown that the mRNA levels of the LDL receptor were considerably higher in the liver of Asian plantain EO-fed mice compared to the control group. In addition, significantly lower mRNA and protein levels of HMG-CoA reductase were found in Asian plantain EO-fed mice compared to the control group. Thus, it was concluded that Asian plantain EO may have hypocholesterolaemic effects by changing the HMG-CoA reductase expression (Chung et al., 2008).

Ocimum sanctum (Holy Basil or Tulsi)

Ocimum sanctum is an aromatic plant, which is distributed in the Southeast Asian tropical zones. Its main EO constituents consist of phenylpropanoid substances such as eugenol and methyleugenol. Few studies investigated the anti-lipidemic activities of EO isolated from *Ocimum sanctum* L. leaves in male Wistar rats maintained on high cholesterol diets (Suanarunsawat et al., 2009a,b). The oral administration of essential oil significantly reduced TC, LDL-C, TG, atherogenic index, serum lactate dehydrogenase and Muscle-Brain (MB) subunit of creatine kinase, whereas there were no significant changes in alkaline phosphatase, HDL-C, aspartate aminotransferase, and alanine aminotransferase. While, the EO reduced the liver high levels TC and TG, both lipids were not found in faeces. Moreover, it was observed that EO treatment decreased superoxide dismutase (SOD), glutathione peroxidase (GPx) and

thiobarbituric acid reactive substances (TBARS). However, there was no substantial change in catalase (CAT) of the cardiac tissue. TBARS content was reduced without any remarkable difference GPx, SOD and CAT in the liver (Suanarunsawat et al., 2009b). Thus, according to the results, EO obtained from *Ocimum sanctum* leaves could result in lipid reduction in high cholesterol diet rats through suppression of liver lipid synthesis.

Pinus koraiensis

Pinus koraiensis or Korean pine is an evergreen tree species found in Korea, China, Manchuria, Mongolia, far eastern Russia, and central Japan. Few *in vivo* and *in vitro* studies evaluated the antihyperlipidemic activities of EO extracted from the *Pinus koraiensis* leaves. Treatment of HepG2 cells with *Pinus koraiensis* EO up-regulated LDL receptor through an increment in mRNA level and conversely by suppressing the presence of fatty acid synthase, sterol regulatory element-binding protein (SREBP)-1c, SREBP-2, HMG-CoA reductase, and glycerol-3-phosphate acyltransferase (GPAT) involved in lipid metabolism. Moreover, western blot analysis revealed that *Pinus koraiensis* EO activated LDL receptor and decreased the expression of fatty acid synthase at the protein level. *Pinus koraiensis* EO remarkably inhibited acylcoenzyme A in human cholesterol acyltransferase (hACAT) 1 and 2 and decreased the oxidative action of LDL (Kim et al., 2012).

Another study also showed the anti-obesity and hypolipidemic mechanism of *Pinus koraiensis* EO using *in vitro* 3T3-L1 cells and *in vivo* HFD-fed rats (Ko et al., 2013). *Pinus koraiensis* EO significantly suppressed fat accumulation and intracellular triglycerides associated by down-regulating the presence of adipogenic transcription factors such as CCAAT/enhancer binding

protein α (CEBPα) and peroxisome proliferator activated receptor (PPARγ). Moreover, the EO reduced fatty acid-binding proteins (FABP) and Glycerol-3-phosphate dehydrogenase (GPDH) by suppressing the expression of target genes of PPARγ. Confirming the *in vitro* observations, an *in vivo* study was carried out by feeding normal diet, high fat diet, with and without *Pinus koraiensis* EO (at the dose of 100 or 200 mg/kg for 6 weeks) into male Sprague-Dawley rats. Consistently, EO significantly suppressed body weight gain, TG, TC, LDL-C, and atherosclerosis index (AI) value and enhanced HDL-C in a dose-dependent manner. Immunohistochemistry studies revealed that EO treatment repealed the presence of PPARγ in the livers of abrogated-treated rats. It was concluded that *Pinus koraiensis* EO has anti-obesic and hypolipidemic potential through inhibition of PPARγ-related signalling (Ko et al., 2013)

Fenugreek seed

Fenugreek is an annual herb, commonly found in India, Egypt, and Middle Eastern countries and is widely used in medicinal, pharmaceutical and nutraceutical applications (Khosla et al., 1995, El Nasri and El Tinay, 2007, Zandi et al., 2015). Fenugreek seed EO is rich in terpenenes and has been applied in Indian folk medicine due to its ability of curing various health problems including; antipyretic, diuretic, dropsy treatment, heart and cardiovascular diseases, and spleen and liver enlargement (Ranjbar et al., 2009). Terpenes were reported to be absorbed through the gut and have a decisive effect on the control of cholesterol metabolism (Strømgaard and Nakanishi, 2004). A work performed by Hamden et al. (2011), investigated the inhibitory potential of omega-3 fatty and fenugreek EO on key enzymes related to lipid metabolism. Omega-3 formulation incorporated with fenugreek terpenenes significantly decreased TG, TC,

and LDL-C levels in the liver and plasma of diabetic rats. The formulation also caused an increment in the HDL-C content, which helped to maintain the homeostasis of blood lipid.

Melissa officinalis

Melissa officinalis is a perennial herb commonly found in south-central Europe, North Africa, the Mediterranean region, and Central Asia (Jalal et al., 2015). The constituents of the EO of this plant differ according to location, but generally citral (geranial and neral), citronellal, and geraniol have been reported to be the main components of the EO (Moradkhani et al., 2010). Karimi et al. (2010) investigated the antihyperlipidemic properties of *Melissa officinalis* EO included at different percentages (0%, 1%, and 3%) in a high cholesterol diet on the lipid profile of rabbits. In comparison to normal control group, feeding EO (1% and 3%) significantly reduced TC, LDL-C, VLDL-C, TG, and HDL-C, whereas no significant effect on atherogenic index was observed.

Through biomarker and transcriptome approaches, the lipidemic impacts of *Melissa officinalis* EO was also evaluated in human APOE2 transgenic mice and in HepG2 cells (Jun et al., 2012). Compared to the vehicle-treated group, administration of EO (12.5 mg/d) for 2 weeks significantly decreased the TG concentrations in APOE2 mice. Compared to controls, a significant and dose-dependent decrease was observed in TG and cholesterol concentrations in HepG2 cells stimulated with EO. Mouse hepatic transcriptome analysis showed that *Melissa officinalis* EO feeding could alter some lipid pathways such as cholesterol synthesis, bile acid and fatty acid metabolism. *Melissa officinalis* EO possibly decreased the translocation of sterol

receptor element-binding protein-1c (SREBP-1c) and led to a reduction in genes related to fatty acid synthesis, which suppress the synthesis of hepatic fatty acid (Jun et al., 2012).

Nigella sativa

Several studies evaluated the health benefits of *Nigella sativa* and reported that the EO of the black seeds can modulate glutathione redox enzymes (Sultan et al., 2015b) and can improve the activity of antioxidant enzymes and immunity (Sultan et al., 2015a). Recently, a study was conducted to discover the antidiabetic properties of *Nigella sativa* EO through the estimation of serum lipid profile (Sultan et al., 2014). It was reported that administration of *Nigella sativa* EO into Streptozotocin-induced diabetes mellitus for 56 days significantly decreased the TC (8.89%), TG (5.33%), and LDL-C (19.89%) levels. There is need for more research to investigate the hypocholesterolemic properties of black seeds EO and their mechanism of action.

Other plants

Citrus plants are amongst the most important fruit trees that are widely distributed and used extensively in the world. Several studies showed that diets supplemented with citrus EO improved the plasma lipid content and resulted in an increase in the plasma antioxidant activity (Constans et al., 2015, García Mesa, 2014, Gorinstein et al., 2005, Jeon et al., 2002). Recently, *Citrus aurantium L.* EO was fed to adult Swiss male mice and the plasma cholesterol and triglyceride levels were determined (Costa et al., 2013). A 14-day EO treatment did not reduce the TG level, while TC was significantly decreased by a 10 mg/kg EO treatment level.

Salix aegyptiaca L., commonly known as Musk Willow, is a flowering plant belonging to the family of Salicaceae and generally cultivated in some Middle East countries (e.g. Iran, Turkey). The mixture of this plant barks, leaves, and essences are widely used to treat several diseases. The effects of *Salix aegyptiaca* EO in hypercholesterolemic rabbit model was investigated (Karimi et al., 2011). The major compounds isolated from *Salix aegyptiaca* EO were reported as follows: phenylethyl alcohol, carvone, citronellol, methyleugenol, eugenol, *n*-tetradecane and 4´-methoxyacetophenone. Administration of EO at different percentage (1% and 3%) in hypercholesterolemic rabbits did not improve the serum TC, LDL-C, HDL-C and TG levels. Thus, it was concluded that the EO of the *Salix aegyptiaca* leaves cannot prevent dyslipidemia in hypercholesterolemic rabbits.

Pistacia lentiscus L. is an evergreen shrub which originated from the Mediterranean region. Chios mastic gum is a resin, which can be attained from the branches and trunk of *Pistacia lentiscus* L. var. *chia*, is widely used in herbal drugs or functional foods (Dimas et al., 2012, Tsokou et al., 2007). Cheurfa and Allem (2015), Djerrou (2014), and Tounes et al. (2008) investigated the hypocholesterolemic activity of *Pistacia lentiscus* extracts and oils. The hypolipidemic effect of EO from Chios mastic gum (MGO) was studied in naive and vulnerable to detergent-induced hyperlipidemia rats (Vallianou et al., 2011). A dose-dependent effect was found after the administration of MGO in the naive rats that lowered the synthesis of TC and TG levels in serum. It was reported that the hypolipidemic effect of MGO treatment in hyperlipidemic rats could be related to camphene (a bicyclic monoterpene). Administration of camphene (30 μg/gr of body weight) in hyperlipidemic rats, considerably reduced the TC (54.5%), LDL-C (54%), and TG (34.5%) levels. Moreover, camphene treatment of HepG2 cells

reduced cellular cholesterol similar to mevinolin, which is a HMG-CoA reductase inhibitor. Nevertheless, it was claimed that the lipidemic action of camphene is probably independent of the activity of HMG-CoA reductase.

Mountain Celery (*Cryptotaenia japonica Hassk*) is a perennial aromatic herb, which is grown in some countries such as Iran, Japan and Taiwan. This plant has been used in Asian countries folklore medicine for long time due to its hypotensive, hypolipidemic, and antiobese properties. A few studies investigated the hypolipidemic effect of Mountain Celery seeds EO. For instance, Cheng et al. (2008) studied the antioxidative and hypolipidemic bioactivities of Mountain Celery seed EO using serial isolation and fractionation processes. It was found that the EO contained 109 substances, including 9 types of monoterpenoids, 31 types of sesquiterpenoids, and 22 types of alcohols. Four different fractions were obtained using *n*-pentane, diethyl ether, acetone, and methanol. The serum TG, TC, and LDL-C contents in serum were notably decreased in male Syrian hamsters receiving native EO, pentane fraction, and diethyl ether fraction. Pentane fraction was found to have more potent hypolipidemic activity. Although, there was notable increase in HDL-C levels in the hamster groups received pentane and ether fractionates, it was totally unaffected in groups consuming native EO. Moreover, the methanol fraction had a high content of2-methylpropanal, γ-selinene, and Z-9-octadecenamide, and showed very powerful superoxide anion scavenging capability. Possibly, γ-selinene, the second highest compound in Mountain Celery seed EO methanolic fraction, contributed to the elevation of HDL-C. In another study, Cheng et al. (2010) studied the hypolipidemic bioactivity of chemically synthesized oleamide. Oleamide was found to have hypolipidemic activity and reduced serum TG, TC, LDL-C, LDL-C/HDL-C, and hepatic TG, but did not affect serum HDL-C and hepatic TC contents.

Dill (*Anethum graveolens*) is a small annual plant, which is cultivated globally. Reduction in TG and TC content in rats' serum with diet-induced hyperlipidemia was reported for water extract of *Anethum graveolens* (Yazdanparast and Alavi, 2001). In another research, the hypolipidemic activity of dill powder and its EO in male Wistar rats fed a rich cholesterol diet was evaluated by Hajhashemi and Abbasi (2008). Dose-dependent administration of *Anethum graveolens* EO to rats for 2 weeks noticeably improved the HDL-C level and significantly reduced TC, TG, and LDL-C levels. Thus, dill EO is considered to be a promising cardioprotective agent.

Korean mint (*Agastache rugosa*) is a member of the Lamiaceae family and is widely cultivated in Korea, China, and Japan. The nutrigenomic analysis of hypolipidemic effects of *agastache rugose* EO was studied in HepG2 Cells and C57BL/6 Mice by Jun et al. (2010). Administration of *agastache rugose* EO (1 mg/mL) significantly decreased LDL oxidation (-93%) in HepG2 Cells. Three weeks feeding of EO into the C57BL/6J mice significantly reduced the TC (-28%) and TG (-26%) levels. Mouse hepatic transcriptome profiling with oligonucleotide microarray showed that *agastache rugose* EO decreased the presence of sterol regulatory element binding factor (SREBF)-1, and SREBF- 2 mRNA as well as the HMG-CoA reductase in both HepG2 cells and in the liver of the mouse. Also, EO enhanced mRNA and protein expression of the LDL receptor in HepG2 cells and the liver of the mouse. Thus, it was concluded that *agastache rugose* EO could inhibit atherosclerosis through 1) prevention of LDL oxidation, 2) the down-regulation of HMG-CoA reductase and SREBF-2 existence, and 3) the up-regulation of LDL receptor.

Lavandula angustifolia (Lamiaceae) is a powerful aromatic and medicinal herb. This plant is native to the Mediterranean region and is commercially cultured in some countries such as the USA, UK, Australia, France, Spain, Portugal, Bulgaria, and China (Djenane et al., 2012). Recently, the cardioprotective effects of *Lavandula angustifolia* EO on isoproterenol-induced acute myocardial infarction in male Wistar rats was investigated (Ziaee et al., 2015). Myocardial infarction is a main feature of the ischemic heart disease and it can be induced by isoproterenol injection for 3 continuous days at an interval of 24 h. Administration of *Lavandula angustifolia* EO protected the myocardium against isoproterenol-induced myocardial infarction by normalizing electrocardiogram (ECG), improved the hemodynamic impairment, reduced lipid peroxidation, suppressed proinflammatory responses, and improved the antioxidant capacity of the systems. Moreover, *Lavandula angustifolia* EO decreased cardiac tissue damage, enhanced the myocardial membrane strength and maintained the architecture of cardiac cells. Thus, it was concluded that *Lavandula angustifolia* EO can protect myocardium against isoproterenol-induced myocardial infarction and this effect may be associated with its antioxidant properties.

4. CONCLUSIONS

A large number of studies highlight the medicinal role of plant EO and some of their isolated constituents to support improvement of cardiovascular diseases. It has been observed that some of the EOs are able to significantly promote the cardiovascular system and can lead to vaso-relaxation, hypotension and regression of atherosclerosis process. Many studies have been conducted to evaluate the role of essential oils on the vasodilation and the heart rate. These studies showed that the hypotension effect induced by EOs was independent to bradycardia and

suggested that changes induced in heart rate were mostly mediated by the autonomic nervous system either parasympathetic or sympathetic. On the other hand, the mechanisms of essential oils to induce vasodilation have often been considered active vasodilation. Active vasodilation may be related to endothelium-dependent pathways such as endothelial L-arginine/NO pathway (NO-cGMP pathway) or endothelial COX pathway (COX-cAMP pathway). Vasorelaxation could be independent from endothelium pathways, and other mechanisms may explain this effect, for instance via blocking VOCC (Voltage Operated Calcium Channel) on vascular smooth muscles' membranes. The anti-atherogenic effects of EOs are mostly related to decreasing the serum level of TC, LDL-C and TG levels, along with increasing the serum level of HDL-C. The anti-atherosclerosis effect of EO was found to be due to their inhibition of LDL oxidation, down-regulation of SREBFs and up-regulation of the LDL receptor. Fibrinolytic activity is another positive effect of these natural remedies during long term use in chronic infarction cases. Some other cardioprotective actions of essential oils have been proposed to be due to altering the expression of hydroxy-methylglutaryl coenzyme A reductase.

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FIGURE CAPTIONS

Figure 1. A schematic of the vasoconstriction mechanism

G: G protein; R: receptor; DAGs: diacylglycerols; IP3s: inositol triphosphates.

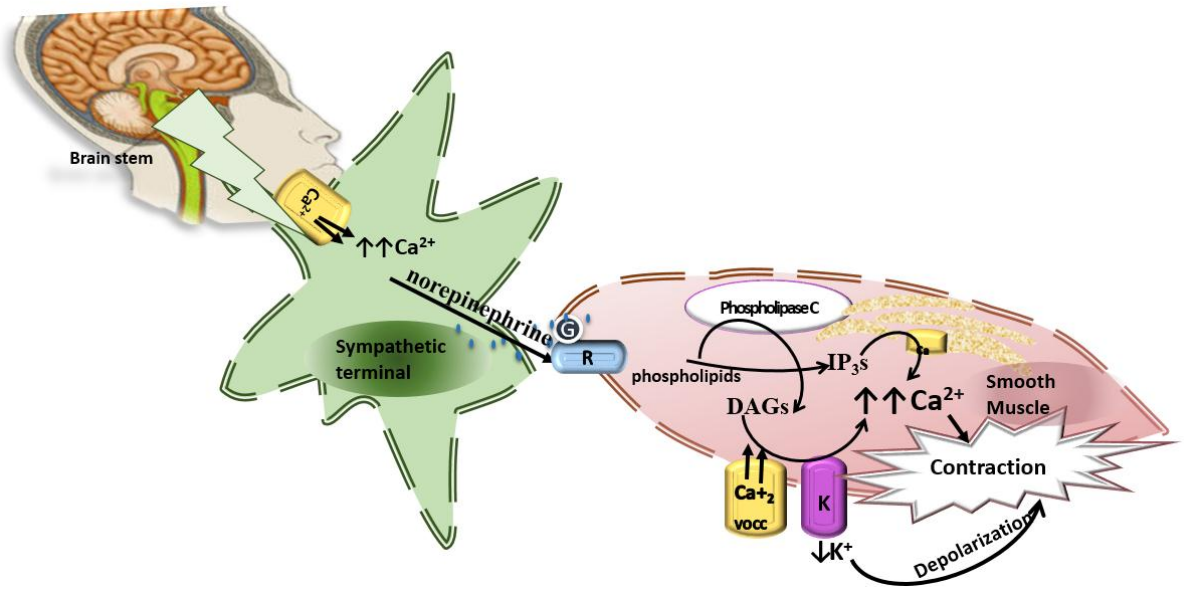

Figure 2. A schematic of the vasodilation mechanism

n- NOS: neuron-nitric-oxide synthase; e -NOS: endotheial-nitric-oxide synthase; NO: nitric-oxide; PGI2: prostacyclin; nitric oxide: COX cyclooxygenase; cAMP: cyclic adenosine monophosphate; cGMP: cyclic guanosine monophosphate; PGI2: prostacyclin; ATP: adenosine triphosphate; GTP: guanosine triphosphate; Ach; acetylcholine

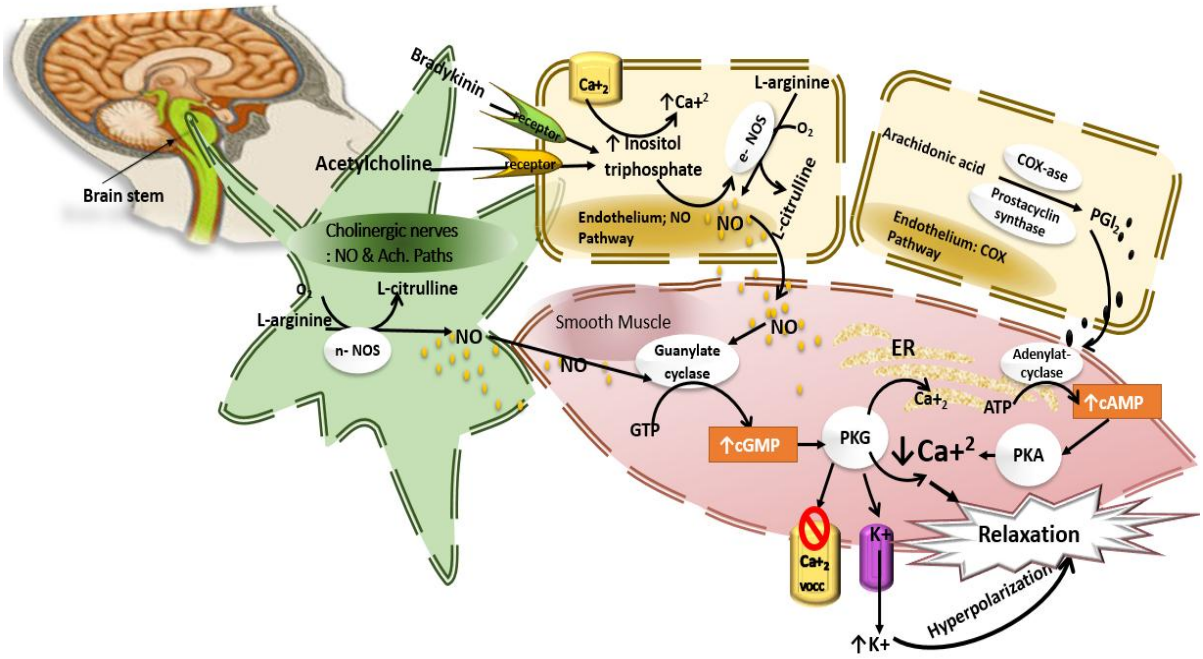

Figure 3. Schematic representing of the vasoregulatory pathways

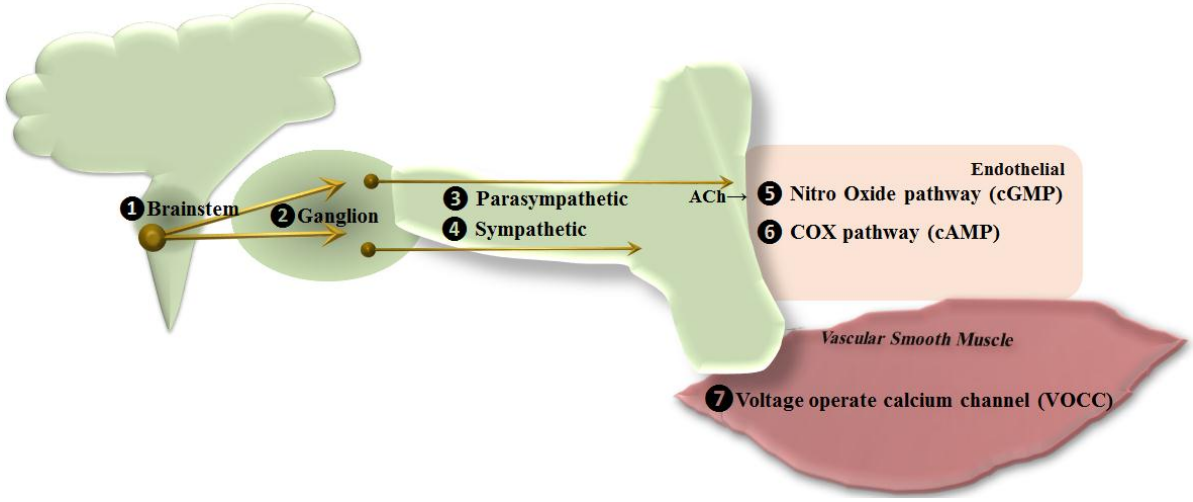

Table 1. Classification of terpenes

Terpenes	Number of Carbons	Examples
Hemi-terpenes	5	Isoprene
Mono-terpenes	10	menthol, geraniol, 1,8-cineole, eugenol, estragole, food additives
Sesqui-terpenes	15	artemisinin: antimalarial drug, α-bisaborol: flavour, cosmetic ingredients
Di-terpenes	20	paclitaxel: antitumor agent, gibberellins: plant hormones
Tri-terpenes	30	lanosterol: precursor of steroid biosynthesis
Tetra-terpenes	40	β-carotene

Table 2. The sites and the actions of pre-treated drugs

Preparation of conscious or unconscious rats		
Drugs	**Actions**	**Sites**
Hexamethonium	Complete ganglionic blockade	Block 2
Methyl atropine	Anti-parasympathetic, Anti-cholinergic, or Acetylcholine inhibitor	Block 3
Atropine	Anti-parasympathetic	Block 3
Atenolol	Anti- sympathetic	Block 4
Reserpine	Anti- sympathetic	Block 4
Acetylcholine	Common neurotransmitter, mostly peripheral nervous system	Active 5
L-NAME	Inhibit nitric oxide synthesis (NOS)	Block 5
Indomethacin	Inhibit COX-2 activity	Block 6
Bi-vagotomised	Block central nervous system	Block 3 and 4
Preparation of aortic or mesenteric arteries' segments		
High Potassium	Opens VOCC (vasoconstriction)	Active 7
Verapamil	Block VOCC	Block 7
Phenylephrine	Sympathomimetic (vasoconstriction)	Active 4
De-endothelialised		Block 5 and 6

Table 3. Vasodilation and heart rate approaches of plants essential oils

Plants	Major monoterpenes	In vivo	Iv vitro	MRP*	Suspected Mechanisms of MRP	HR†	Suspected mechanisms of HR	References
Nigella Sativa	Thymoquinone	+		↓	Centrally (brain stem)	↓	Centrally (brain stem)	Tahir et al. (1993)
Croton nepetaefolius	1,8-cineole	+	+	↓	Not removal of sympathetic, direct vaso-relaxant (partially NO pathway)	↓	Vagal activation	Lahlou et al. (2000, 2002, 2004)
Mentha x Villosa	piperitenone oxide	+		↓	Active vascular relaxation	↓	Sympathetic in-activation	Lahlou et al. (2001)
Alpinia zrumbet	Terpinen-4-ol	+		↓	Direct vaso-relaxant (partially NO pathway)	↓	Sympathetic in-activation	Lahlou et al. (2002)
Ocimum gratissimum	Eugenol & Methyl-eugenol	+		↓	Not removal of sympathetic. Active vascular relaxation, (inhibition VOCC, and maybe NO	↓	Parasympathetic nerve drive to the heart	Lahlou et al. (2004); Hiroaki Nishijima et al. (1998)

					pathway)			
Aniba canelilla	1 -nitro-2-phenylethan & Methyleugenol	+	+	↓	Predominantly by an endothelium-in-dependent relaxation (an inhibition of Ca^{2+} inward current). Directly on vascular smooth muscles.	↓	Activation of vagal cholinergic afferents	Lahlou et al. (2005)
Leaves of *Croton zehntneri*	anethole & estragole	+	+	↓	Unlikely mediated by an endothelial l-arginine/NO pathway	↓	-	Lahlou et al. (2006)
Hyptis fruticose	α-pinene, caryophyllene, 1,8 cineole		+	↓	Blocking VOCC	-	-	Santos et al. (2007)
Cymbopogon winterianus	geraniol, citronellol, citronellal	+	+	↓	Not mediated by main endothelial mediators. Inhibition of the Ca^{2+} influx	↑	Muscarinic receptor within cardiac muscles	Menezes et al. (2010)
Other aromatic	α-Terpineol		+	↓	Strong participation of	-	-	Ribeiro et al. (2010)

plants				the NO-cGMP pathway, Not the COX pathway			
	β-pinene, α-pinene citronellol	+	↓	Tachycardia followed by baroreflex response. The terpene structures influenced the efficacy of their hypotensive action.	↑	-	Menezes et al. (2010)
	Linalool						
	Bisabolol (sesqui-terpene)		↓		↓		

* Mean arterial pressure; † Heart rate

Table 4. Lipidomic approaches of plants essential oils

Plant name	Study type	Biochemical parameters/activities	Type of effect	References
Onion and garlic	In vivo (Indian albino rabbit)	TC, TG, Serum fibrinogen, Whole blood coagulation time, Fibrinolytic Activity, Lipid content of aorta	- The increase of TC, serum TG, blood fibrinogen level, whole blood coagulation time and lipid content of the rabbit aorta was reduced. - Feeding onion and garlic essential oils increased the fibrinolytic activity even above the normal control levels. - The increase of β- and pre-β lipoproteins and decrease of α-fraction caused by cholesterol feeding were prevented. - The β/α ratio, did not increase when onion and garlic were fed.	(Bordia et al., 1975, Bordia et al., 1977a)
	In vivo (Human study)	TC, TG, Fibrinolytic activity, LDL-C, HDL-C	- Garlic essential oils administration significantly lowered the TC, TG, and LDL-C, while increased the HDL-C. - The essential oil of garlic has shown a distinct hypolipidemic action in both healthy individuals and patients of coronary heart disease.	(Bordia, 1981, Bordia et al., 1977b)

			- Fibrinolytic activity was increased, during long term use in chronic infarction cases and during the critical acute post-infarction period.	
Satureja khuzestanica	In vivo (Sprague-Dawley rat)	Plasma lipid peroxidation, TC, TG	- Normal blood lipid peroxidation level was decreased - Significant decreases in TG level was observed - Blood TC levels were not affected	(Abdollahi et al., 2003)
		Blood glucose, TC, TG, LDL, VLDL, HDL, Atherogenic index, Activities of ALT, AST and ALP	- Administration of EO inhibited the activities of ALT and ALP, decreased FBG, TG, TC, LDL, VLDL and increased HDL level, while the activities of AST stayed unaltered. - Beneficial effects on the lipid profile, atherogenic index and liver enzymes activity in Alloxan-induced Type 1 diabetic rats were observed.	(Ahmadvand and Tavafi, 2012)
	In vivo (Wister rats)	Blood glucose, TG	TG level was significantly decreased at the dose of 1000 ppm.	(Nazari et al., 2005)

Table 4. Continue

Plant name	Study type	Biochemical parameters/activities	Type of effect/mechanism of action	References
Wormwood (*Artemisia princeps*)	In vitro (HepG2 cells)	Expression of key genes in cholesterol metabolism such as the LDL receptor, The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, Sterol regulatory element binding proteins	- Administration of wormwood essential oils with vitamin E was found to be anti-atherogenic due to their inhibition of LDL oxidation and upregulation of the LDL receptor.	(Chung et al., 2007)
Artemisia sieberi (aerial parts)	In vivo (Wister rats)	Blood glucose, Glucagon, Cholesterol, TG, LDL-C, ESR, Urea, Uric acid, Creatinine, Total protein, Albumin, insulin, HDL-C, Neutrophile count and PCV	- A significant reduction in the mean values of blood glucose, glucagon, cholesterol, TG, LDL-C, ESR, urea, uric acid and creatinine were observed. - An increase in the mean values of the total protein, albumin, insulin, HDL-C, neutrophile count and PCV were observed.	(Irshaid et al., 2012)
Asian plantain	- In vitro (HepG2	TC, TAG	- Oral administration of EO for 3 weeks significantly reduced plasma	(Chung et al., 2008)

(*Plantago asiatica*)	cells) - In vivo (C57BL/6 mice)		TC and TAG concentrations by 29 and 46 %, respectively. - The hypocholesterolaemic effects might be due to the altering the expression of HMG-CoA reductase.	
Ocimum tenuiflorum (*Ocimum sanctum)* Leaves	In vivo (Male Wistar rats)	TC, TG, HDL-C, LDL-C, TBARS, GPx, SOD, CAT, Atherogenic index, Serum lactate dehydrogenase, Creatine kinase MB	- TC, LDL-C, TG, atherogenic index, serum lactate dehydrogenase and creatine kinase MB subunit were reduced, whereas no changes on HDL-C, serum levels of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase was observed. - EO administration decreased the high level of TBARS but didn't affect GPx, SOD and CAT in the liver. - Antihyperlipidemic action was found to be due to the suppression of liver lipid synthesis. - Phenylpropanoid compounds (eugenol and methyl eugenol), might be responsible for the lipid-lowering effect.	(Suanarunsawat et al., 2009a,b)

Plant name	Study type	Biochemical parameters/activities	Type of effect/mechanism of action	References

Table 4. Continue

Pinus koraiensis Leaves	In vitro (HepG2 cells)	Activities of hACAT1 and hACAT2, LDL, LDLR, Specific amino acid sequences	Antihyperlipidemic effect of *Pinus koraiensis* EOs was found to be due to the upregulation of LDLR and inhibition of acyl-coenzyme A.	(Kim et al., 2012)
	- In vitro (3T3-L1 cells) - In vivo (HFD-fed rats)	Serum TG, TC, LDL-C, AI value, HDL-C	- EO suppressed body weight gain, serum TG, TC, LDL-C, and AI value and increased HDL-C in a dose-dependent manner. - EOs had antiobesic and hypolipidemic potential via inhibition of PPARγ-related signaling.	(Ko et al., 2013)
Fenugreek seeds	In vivo (Adult male Wistar rats)	Plasma and kidney serum ACE activity, Glucose, TG, TC, LDL-C, HDL-C	Administration of formulation omega-3 with fenugreek terpenenes decreased the glucose, TG, TC, LDL-C in the plasma and liver of diabetic rats and increased the HDL-C level, which helped maintain the homeostasis of blood lipid.	(Hamden et al., 2011)
Melissa officinalis	In vivo (Adult weight- and age-matched healthy rabbits)	TC, HDL-C, LDL-C, VLDL-C, TG, Atherogenic index	Essential oil administration significantly decreased TC LDL-C, VLDL-C, TG, and HDL-C, whereas no significant effect on atherogenic index was observed.	(Karimi et al., 2010)

	In vitro HepG2 cells In vivo Male human APOE2 (R158C) transgenic mice	TC, TG, LDL-C	- TG and TC were decreased while no significant changes were observed in LDL-C level. - The essential oil was decreased TG by inhibiting sterol regulatory element-binding protein-1c-dependent fatty acid synthesis (SREBP-1c).	(Jun et al., 2012)
Nigella sativa	In vivo (Sprague Dawley rats)	TC, LDL-C, TG, HDL-C	TC, LDL-C, TG were significantly decreased, whereas no significant changes was observed on HDL-C level.	(Sultan et al., 2014)
Citrus aurantium	In vivo (Adult Swiss male mice)	TC, TG	TC was significantly decreased, while no significant changes was observed in TG level.	(Costa et al., 2013)
Salix aegyptiaca (musk willow)	In vivo (Male Albino rabbits)	TC, LDL-C, VLDL-C, HDL-C, TG, AI	- 1,4-Dimethoxybenzene was the main EO isolated compound - Administration of *Salix aegyptiaca* leaves EO didn't prevent dyslipidemia	(Karimi et al., 2011)

Plant name	Study type	Biochemical parameters/activities	Type of effect/mechanism of action	References
			in both dose-and time-dependent manners.	

Table 4. Continue

Pistacia lentiscus	In vitro (HepG2 cells) In vivo (Female Fisher-344 rats)	TC, LDL-C, TG, HMGCoA, Cellular cholesterol, Cholesterol esters	- MGO administration showed a strong hypolipidemic effect. - The hypolipidemic action was associated with camphene. - Administration of camphene (30 mg/g of body weight) reduced TC (54.5%), LDL-C (54%), and TG (34.5%). - Treatment of cells with camphene decreased the cellular cholesterol. - The hypolipidemic mechanism of action of camphene was found to be different from statins.	(Vallianou et al., 2011)
Mountain Celery seed (*Cryptotaenia japonica* Hassk)	In vivo (Male Syrian hamsters)	TC, LDL-C, HDL-C, TG	- TC, TG, and LDL-C levels were suppressed in groups taken native essential oils, groups taken pentane fractionate, and in groups consumed ether fractionate. - EO fractionated with pentane was more potent in reducing the TC, TG, and LDL-C levels.	(Cheng et al., 2008)
			- Oleamide (speculated to be responsible for hypolipidemic	(Cheng et al., 2010)

			action) reduced serum TG, TC, LDL-C, LDL-C/HDL-C, and hepatic TG, but didn't affect serum HDL-C and hepatic TC. - Another coexisting constituent, probably γ-selinene, the second enriched principle in the methanolic fraction of Mountain Celery seed EO, was suggested to contribute to the elevation of HDL-C.	
Dillweed (*Anethum graveolens)* aerial parts	In vivo (Male Wistar rats)	TC, LDL-C, HDL-C, TG	- Alpha-phellandrene (32%), limonene (28%) and carvone (28%) were the major components. - Daily oral administration of EO significantly and in a dose-dependent manner reduced TC, TG, and LDL-C, whereas increased the HDL-C level.	(Hajhashemi and Abbasi, 2008)

Plant name	Study type	Biochemical parameters/activities	Type of effect/mechanism of action	References

Table 4. Continue

Agastache rugosa	In vitro (HepG2 cells) In vivo (Male C57BL/6 mice)	LDL oxidation, TC, TG	- Limonene was found as the major compound of EO. - EO administration reduced LDL oxidation (-93%), TC (-28%) and TG levels (-26%). - EO was suggested to inhibit atherosclerosis through the prevention of LDL oxidation, down-regulation of SREBF-2 and HMG-CoA reductase expression, and up-regulation of LDL receptor expression.	(Jun et al., 2010)
Lavandula angustifolia	In vivo (Male Wistar rats)	MPO, MDA	- EO administration protected the myocardium against isoproterenol-induced MI by normalizing ECG, improvement the hemodynamic impairment, reducing lipid peroxidation, suppressing proinflammatory responses, and improving antioxidant systems. - Cardiac cells structure and architecture were maintained through reducing cardiac tissue damage and strengthening	(Ziaee et al., 2015)

myocardial membrane.

EO: Essential oil; HepG2 cells: Human hepatocarcinoma cells; TC: Total cholesterol; LDL-C: Low density lipoprotein cholesterol; VLDL: Very low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TG: Triglycerides; TAG: Triacylglycerol; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; FBG: Fasting blood glucose; ESR: Erythrocyte sedimentation rate; PCV: Packed cell volume; HMG-CoA reductase: 3-hydroxy-3-methyl-glutaryl-CoA reductase; LDLR: Low density lipoprotein receptor; hACAT: Human acylcoenzyme A: cholesterol acyltransferase; HFD: High fat diet; AI: Atherosclerosis index; SOD: Superoxide dismutase; hACAT1: Human acyl-coenzyme A:cholesterol acyltransferase 1; hACAT2: Human acyl-coenzyme A:cholesterol acyltransferase 2; ACE: angiotensin-converting enzyme; TBARS: thiobarbituric acid reactive substances; GPx: Glutathione peroxidase; CAT: Catalase; HMGCoA: 3-hydroxy-3-methylglutaryl coenzyme A; MGO: mastic gum essential oil, MPO: Myeloperoxidase; MDA: Malondialdehyde; ECG: Electrocardiogram; MI: Myocardial infarction