

Research Article

Therapeutic application of herbal essential oil and its bioactive compounds as complementary and alternative medicine in cardiovascular-associated diseases

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Abstract

Background: Herbal essential oil contains pharmacological benefits for intervention treatment of various diseases. Studies have demonstrated its antimicrobial, antioxidant, and anti-inflammatory effect involving in vitro cell culture and preclinical animal models. It has been also traditionally used to reduce anxiety and hypertension in human. However, scientific studies elucidating its mechanism of action and pharmacological targets, as well as its effectiveness and safety as phytotherapeutic compounds are still progressing. Recent studies showed its promising effect in depression-cardiovascular disease intervention. However, comprehensive evaluations to enlighten latest advancement and potential of herbal essential oil are still lacking.

Objective: In this systematic review, the depression-cardiovascular effects of herbal essential oil on lipid profile, biochemical and physiological parameters (e.g haemodynamic) are presented. The route of delivery and mechanism of action as well as main bioactive compounds present in respective essential oil are discussed.

Methods: Article searches are made using NCBI PubMed, PubMed Health, SCOPUS, Wiley Online, tandfonline, ScienceDirect and Espacenet for relevant studies and intellectual properties related to essential oil, depression and cardiovascular disease.

Results: In experimentation involving in vitro, in vivo and clinical trials, herbal essential oil showed its effectiveness in reducing coronary artery disease (narrowing of the arteries), heart attack, abnormal heart rhythms, or arrhythmias, heart failure, heart valve disease, congenital heart disease, heart muscle disease (cardiomyopathy), pericardial disease, aorta disease, Marfan syndrome and vascular (blood vessel) disease.

Conclusion: This review gives a valuable insight on the potential of essential oil in the intervention of depression associated with cardiovascular diseases. Studies showed that herbal essential oil could act as vasodepressor, calcium channel blocker, antihyperlipidemia, anticoagulant, antiatherogenesis and antithrombotic. It can be proposed as an interventional therapy for depression-cardiovascular disease to reduce doses and long-term side-effect of current pharmacological approach.

Introduction

Depression is debilitating health mental disorder, a common and an independent risk factor associated with cardiovascular disease (CVD) and increased mortality. A deprived health condition in conjunction to the heart failure (e.g involving heart's valve, pericardial, muscle) and malfunction of the blood vessels (e.g coronary artery, vascular) can ultimately lead to serious events such as heart

attack or stroke. Increasing trend of morbidity and mortality linked to depression associated with cardiovascular disease has caused a great concern in many countries [1,2]. It also imposed financial burden to the government as well as hundred thousands of patients and their families [2-4]. It has caused considerable losses and reduced the quality of life of many individuals. In the last few years, it was estimated that more than 17 million of people died from CVD in United States

More Information

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Keywords: Bioactive; Cardiovascular; Essential oil; Ischaemic heart; Pharmacologic effect





and more than 1.5 million of people suffered from myocardial infarction [1,3,4]. In 2016, data from the Department of Statistics of Malaysia showed that ischaemic heart disease (e.g coronary heart disease, myocardial infarction) was the highest (15.3%) case of deaths among Malaysian as compared to other type of incidents or diseases [5]. The manifestation of CVD is often coupled with several risk factors such as family history, metabolic syndrome [e.g visceral obesity, glucose intolerance, insulin resistance, high triglyceride (TG), low high density lipoprotein (HDL)], hypertension and dietary composition in relation to atherogenesis and thrombosis [3,6]. Particularly, hypertension has become a prevalent risk factor for CVD morbidity whereby individuals with this risk factor was estimated to increase to about 60% with a total of about 1.6 billion people in 2025 [1-3]. Other risk factor such as coronary atherosclerosis is often pathologized by the accumulation of fats [e.g lipids, cholesterol and TG], within the arterial blood vessels, endothelial dysfunction as well as coagulation (e.g platelet-mediated) [7-9]. Important consequences of coronary atherosclerosis include coronary artery disease (CAD), angina (ischaemic chest pain) and myocardial infarction (MI). Many studies also showed that hyperlipidemia is the root cause of atherosclerosis, stroke and ischaemic heart disease whereby their correlation with single nucleotide polymorphisms of genes for lipid metabolism [e.g lipoprotein lipase (LPL) and apolipoprotein A5 (APOA5)] have been demonstrated [4,7,8]. Modern applications of pharmacological drugs (e.g Aspirin, statins, opioids) have their own limitations related to patient compliance, dose, effectiveness and side-effect mostly due to the differences in individual genetic makeup, foods, diets (e.g lipids ratio/type composition) and lifestyle [2,10]. Several drawbacks from great reliance on modern pharmaceutical drugs has caused long-term problem on financial circumstances and health side-effect. Some CVD drugs have been implicated as causes of depression. Likewise, some antidepressant drugs (e.g Tricyclic antidepressants) are not suitable for CAD patient. Some other side-effects from the interaction between antidepressant and CAD drugs are also a concern in patient suffering depression with CAD. Noteworthy, patient with CVD is at an increased risk of developing depression. As high as 45% of patients with CAD (includes stable CAD), unstable angina or MI had experienced from clinically significant depressive symptoms. Hence, a new strategy to mitigate this disease using compounds of natural resources have been studied and proposed [8,10-14].

Research disclosed that marine fish, cod liver and plant oils with a high amount of polyunsaturated fatty acids (PUFA, e.g omega-3) reduced TG and LDL levels (e.g triglyceridemia), halt thrombosis (e.g platelet aggregation/reactivity, plasma viscosity) as well as alleviate atherosclerotic plaque formation and rupture thus preventing cardiovascular disease (e.g acute coronary syndrome). Hence, oils and lipids from such sources have been widely studied and reviewed [2,4,6,15]. Little attentions have been given to evaluate and

review the beneficial depressive-cardiovascular function of oil of other resources. This is due to the fact that depressive-cardiovascular relevance of plant oils does not only rely on the presence of PUFA or their other functional lipids components (e.g phospholipids) [1,3]. Several analysis indicated that plant oils particularly herbal essential oils contain considerable amount of lipophilic bioactive compounds which are intervening CAD [13-17]. Several known flavonoids and other polyphenolic antioxidants [e.g ubiquinone, (vitamin E; tocopherols: tocotrienol), γ -oryzanol, ferulic acids triterpenyl esters] which were abundantly present in essential oils significantly inhibited oxidation of LDL-cholesterol and reduced thrombotic development [10-12]. These lipophilic antioxidants were capable of reducing thiobarbituric acid reactive substances (TBARS), lipid peroxidation (LPO), glutathione peroxidase (GPx) and superoxide dismutase (SOD) activity *in vitro* [18-20].

In these present years, several essential oils (EOs) have been demonstrated as alternative intervention therapies for both depression and cardiovascular disease. Recent advance in this new approach shows potential alternative to conventional dietary or pharmacological approach. EOs are unique as compared to vegetable/marine oils which the former contain many other distinctive bioactive compounds that potentially led to new discovery (e.g bioactive drugs or techniques) in the intervention of cardiovascular disease. In this present article, EOs and their bioactive compounds as potent complementary therapy in the intervention of depression associated with CAD are systematically reviewed using reliable sources and databases. Their pharmacological effects on lipid profile, biochemical and physiological (e.g hemodynamic) parameters are illustrated. This present article also elucidates mechanism of action and pharmacological targets of EOs, as well as its effectiveness and safety as phytotherapeutic compounds.

Materials and Methods

Search strategy and screening

Searches were performed using NCBI PubMed, PubMed Health, SCOPUS, Wiley Online, tandfonline, ScienceDirect and Espacenet databases. The records provide coverage of high quality and peer-reviewed articles in the fields of health and medicine. Searches were performed from January 2018 to February 2020 and were selected for review without any limitations. Terms and keywords relating to “essential oil” or “depression” and “cardiovascular” were used in the searches. Titles and abstracts were independently screened in accordance with our predetermined inclusion criteria. The reference lists of included studies were manually searched for potentially relevant studies. Studies that did not meet the inclusion criteria were excluded. Research topics were devised to essential oil and depression-CAD intervention. Review articles were excluded as well as studies examining the use of

oil from non-plant origin. English and other language studies were included.

Data extraction

Data was collected based on author, date, intervention treatment (essential oils and bioactive compounds) and intervention results on depression and CAD. The outcomes were categorized and compared between studies with different essential oils and their bioactive compounds.

Results

Searches in NCBI Pubmed and PubMed Health have retrieved works assessing the effect of essential oils and their bioactive compounds on CAD condition. In this systematic review, total of 1366 articles have been identified and 1269 of them have been excluded after screening of duplication and the titles/abstracts. The full-length research articles were retrieved in details and reviewed. A final total of 23 articles were selected for inclusion in this review. A flow-chart of the process of article selection is illustrated in figure 1.

Several *in vitro* studies

Based on the search criteria, 90 selected articles were evaluated (Tables 1,2). *In vitro* studies indicated that EO of *O. basilicum L.* and *R. A. Tatarinowii*, had cytoprotective effect in cultured cardiomyocytes (e.g depress pulse frequency and increase the viability of cardiomyocytes) [21,22]. Particularly, *R. Acori Tatarinowii* EO ameliorated cell viability of neonate rat cardiac myocytes and reduced its pulse frequency [22]. In comparison, *T. capitata* EO had cytoprotective effect against LPO product (4-hydroxy-2-nonenal, pathophysiologic concentration, less than 10 μM)-induced neonatal rat cardiomyocytes death [23]. This EO at 20-40 parts per million (ppm) and pre-incubation at 12 h also reduced reactive oxygen species (ROS) generation and loss of mitochondrion membrane integrity but resembled cytotoxicity at concentration greater than 40 ppm [23]. The

composition of the *T. capitata* EO revealed that it contained a considerable amount of monoterpenes [23]. In contrast, *S. pinnatifolia* EOs showed notable protective effect (high cell viability) on H₂O₂ induced death in rat myocyte culture *in vitro* [24]. Some other EOs such as *F. A. zerumbet* EO protected human endothelial cells from injury caused by oxidized low-density lipoprotein molecules. Its protective effect was mainly due to an increase of glutathione (GSH) and SOD activities [17,25].

On the other hand, *S. Chinensis Fructus* EO and its bioactive compounds (e.g lignans, volatile oils and polysaccharides) have an ability to intervene several parameters in cardiovascular diseases mostly via antioxidant, apoptosis inhibition mechanism and anti-inflammation activity [26]. Study also showed that magnolol (C₁₈H₁₈O₂), bioactive component from *M. officinalis*, up-regulated lipoprotein lipase (LPL) activity in a concentration-dependent, probably via alleviating LPL mRNA transcription, in mouse 3T3-L1 pre-adipocytes [27].

Similarly, R(+)-pulegone (C₁₀H₁₆O), the main constituent of several EOs had antioxidant activity on isolated cardiac myocytes [28,29]. On the other hand, both *A. melegueta* and *A. danielli* seeds EOs reduced Fe²⁺-induced LPO in rats' heart in a concentration-related manner [18]. They also inhibited angiotensin-converting enzyme (ACE) activity but lower than that of Captopril, a commercial drug for congestive heart failure [18]. GC-MS data identified eugenol (C₁₀H₁₂O₂), 1,8-cineole (C₁₀H₁₈O), α-terpineol (C₁₀H₁₈O), α-caryophyllene (C₁₅H₂₄) and β-caryophyllene (C₁₅H₂₄) as major biocomponents in *A. melegueta* and *A. danielli* seeds EOs [18]. As compared to previously mentioned bioactive compounds, camphene (C₁₀H₁₆) which is abundant in *Chios mastic* gum EOs had anti-hypercholesterolemic and anti-hypertriglyceridemic effects on HepG2 cells with a significant reduction of cellular cholesterol level to a level comparable to that of mevinolin, a known 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor [30]. Unlike mevinolin, the former bioactive compound reduced cholesterol content via mechanism independent from HMG-CoA reductase activity [30]. Likewise, *P. asiatica* EO also modulated mRNA and protein expression of LDL receptor and HMG-CoA reductase in HepG2 cells [31].

Study using aortic ring preparations

Vasorelaxant effect in phenylephrine-induced contraction: Evaluations of cardiovascular disease intervention of EOs have also been conducted using isolated endothelium-containing aortic ring preparations pre-contracted with vasopressor drugs (e.g phenylephrine, prostaglandin F₂α). In phenylephrine-induced contracted aortic rings, *C. zehntneri* EO, *A. zerumbet* EO, *C. argyrophyloides* EO and *P. elsholtzioides* EO exhibited vasorelaxant effect as observed in the presence or absence of 100 μM nitric oxide (NO) synthase blocker [Nitro-L-arginine methyl ester (L-NAME)]

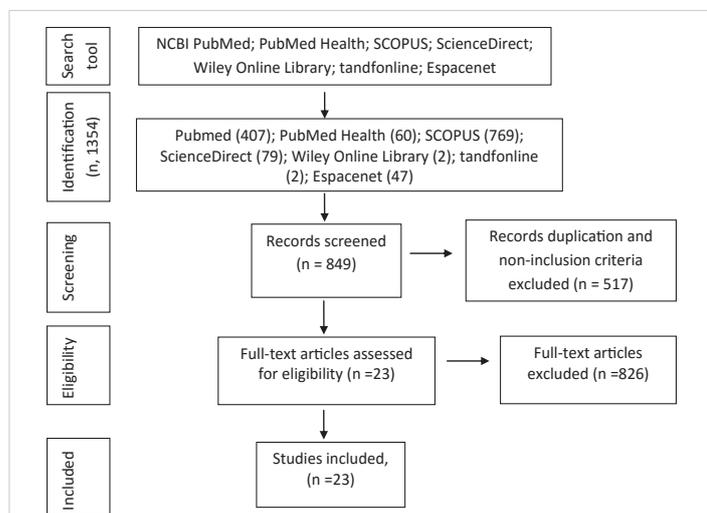


Figure 1: Flow chart showing the process of selecting the relevant studies for the systematic review.

Table 1: Characteristics of the eligible studies.

Author	Intervention herbs	Dose/duration	Route	Study sample	Result
Alves-Santos, et al. [36]	<i>C. argyrophyloides</i>	-	i.v	normotensive rats	↓ Blood pressure
Ziaee, et al. [81]	<i>L. angustifolia</i>	5-20 mg/Kg	i.v	isoproterenol-induced Myocardial infarction male rats	↓ ST-segment elevation (ECG pattern) ↑ R-amplitude
Yan, et al. [24]	<i>Syringa pinnatifolia</i> Hems1. var. <i>alashanensis</i>	8-32 mg/kg	i.v	Wistar rats, Kunming mice	↓ ADP-induced platelet aggregation ↓ Deviation of ST-segment, ↓ Creatine kinase, TnT, LDH, ↑ SOD
Bigliani, et al. [64]	<i>S. areira</i>	-	i.v	isolated mice hearts rabbits	↓ systolic blood pressure
Ram, et al.[7]	Acacia senegal Seeds	500 mg/kg/day	Oral	diet-induced atherosclerosis rabbits	↓ atherosclerotic plaques in aorta ↑ lumen volume
Khan, et al. [59]	<i>C. jwarancusa</i>	-	i.v		↓ body weight, lipid parameters ↓ blood sugar levels
Suanarunsawat, et al. [19]	<i>O. sanctum</i> L. Leaves	2% fed	i.v	Male Wistar rats	↓ high serum lipid profile ↓ atherogenic index
Kumar et al. [37]	<i>P. elsholtzioides</i>		In vitro	endothelium intact aortic prep	↓ BP
Rasheed, et al [50]	<i>Rosa indica</i> L. Petals	0.01-3 ug/mL	i.v	Rabbit aorta rings prep	Calcium Channel Blocking Activity
Hosseini, et al. [68]	Lavender	2%, 10 min	Olfactory	40 open-heart surgery patients	↓ blood pressure ↓ heart rate
Kim, et al. [66]	<i>C. indicum</i> Linné	-	Olfactory	subjects'	↓ systolic blood pressure/ heart rate
Tahir, et al. [63]	<i>Nigella sativa</i>	4-32 µL/kg	i.v	Rats	↓ arterial blood pressure ↓ heart rate
Lahlou, et al. [63]	<i>O. gratissimum</i>	1-20 mg/kg	i.v	anaesthetized and conscious rats	↓ mean aortic pressure ↓ heart rate
Shen, et al. [17]	<i>A. zerumbet</i>	1-20 mg/kg	i.v	DOCA-salt hypertensive rats	↓ mean aortic pressure
Santos, et al. [54]	<i>H. fruticosa</i>	5-40 mg/kg	i.v	normotensive rats	↑ hypotension
de Siqueira, et al. [32]	<i>C. zehntneri</i>	10- 20 mg/kg	i.v	deoxycorticosterone-acetate (DOCA)-salt hypertensive rats	↑ a vago-vagal reflex ↓ heart rate and blood pressure
de Siqueira, et al. [38]	Bark of <i>A. canelilla</i>	1-20 mg/kg	i.v	normotensive rats	↑ hypotension and bradycardia
de Menezes, [53]	<i>C. winterianus</i> EO	1-20 mg/kg	i.v	Rats male Wistar	↑ hypotension and vasorelaxation
Lahlou, et al. [42]	<i>Mentha x villosa</i> EO	1-30 mg/kg	i.v	normotensive rats DOCA-salt-hypertensive rats	Cardiodepressant peripheral vasodilation ↓ blood pressure

Note: TnT: Troponin-T; LDH: Lactate Dehydrogenase; SOD: Superoxide Dismutase

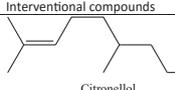
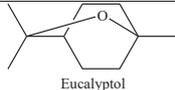
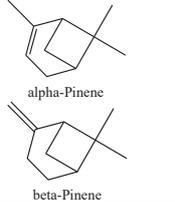
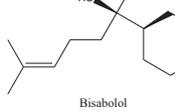
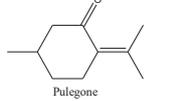
Author	Interventional compounds	Dose/duration	Route	Study sample	Result
Ribeiro-Filho et al [55]	 Citronellol	-	intravenous injection	anesthetized rats	• biphasic hypotension, bradycardia • apnea
Soares et al [72]	 Eucalyptol	(0.003-0.3 mM)	In vitro	Isolated myocardium from male Wistar rats	• reduced isometric tension • reduces contractile activity in rat cardiac muscle
Vallianou et al [30]	 Camphene	30 µg/g	intravenous injection	hyperlipidemic rats	• reduction of total cholesterol • 54% (LDL)-cholesterol, 34.5% of TG
Cardoso Lima et al [29]	 alpha-Pinene beta-Pinene	1-20 mg/kg	intravenous injection	Non-anaesthetized normotensive rats	• induced hypotension and tachycardia
	 Linalool				
Cardoso Lima et al [29]	 Bisabolol	1- 20 mg/kg	intravenous injection	non-anaesthetized normotensive rats	• induced hypotension and bradycardia
Santos-Miranda et al [28]	 Pulegone	infusion of 100 mg/kg	intravenous injection	rat	• inhibit several cardiomyocyte K(+) current components • reducing the heart rate by 26%

Table 2: Bioactive compounds in essential oils and their cardiovascular effects.

[32-37]. Particularly, *C. argyrophyloides* EO induced a dose-dependent aortic relaxation (IC_{50} , ~ 25 $\mu\text{g/mL}$) that was associated with muscarinic receptor stimulation as well as liberation of the endothelium-derived prostacyclin whereby in experimented condition, its activity was greatly lowered by pre-treatment with anti-muscarinic agent (e.g 1 μM atropine, IC_{50} increase to ~ 197 $\mu\text{g/mL}$) [36]. Its action was also affected by cyclooxygenase blocker (e.g at 10 μM indomethacin, IC_{50} increase to ~ 91 $\mu\text{g/mL}$), vascular endothelium removal (at IC_{50} increase to ~ 76 $\mu\text{g/mL}$) and anti-diabetic agent (e.g at 100 μM glibenclamide, IC_{50} increase to ~ 64 $\mu\text{g/mL}$) [36]. Similarly, vasorelaxant effect of *A. zerumbet* EO was also dependent on endothelium and reduced in the presence of indomethacin and tetraethylammonium chloride [34,35]. It has also been reported that 1-Nitro-2-phenylethane, main constituent of *A. Canelilla* EO exerted vasorelaxant effect in endothelium-intact aorta preparations [38]. Nevertheless, as compared to *C. argyrophyloides* EO, some other EO was not antagonized by the presence of atropine. For instance, the vasorelaxant effect (IC_{50} , 189 $\mu\text{g/mL}$) of *C. zehntneri* EO was not significantly altered by either removal of functional vascular endothelium or the treatment of 1 μM atropine [32]. *C. zehntneri* EO may induce a second and delayed hypotension due to its direct endothelium-independent vasorelaxant effects [33]. Likewise, vasorelaxant effect of eucalyptol was not dependent on endothelium [39]. On the other hand, in hypertensive rats-isolated thoracic aorta preparations, *C. nepetaefolius* EO (1-300 $\mu\text{g/ml}$) induced a dose-related reduction of phenylephrine-stimulated contraction [40]. Arteries from hypertensive rats had greater sensitivity to *C. nepetaefolius* EO, as noted by substantial reduction in its inhibition concentration [41].

Vasorelaxant effect in prostaglandin $F_2\alpha$ -induced contraction: Meanwhile, in ~ 10 μM prostaglandin $F_2\alpha$ -induced contracted aortic rings, both *Mentha x villosa* EO and *Citrus aurantium* EO induced vasodilatory effect (IC_{50} , ~ 174) [42-48]. Comparatively, the vasorelaxant and hypotensive activity stimulated by *Mentha x villosa* EO and *C. aurantium* EO was also affected by endothelium removal while the former EO was also affected by the presence of 10 μM indomethacin (IC_{50} , 334 $\mu\text{g/mL}$) [45,47]. Nevertheless, the vasorelaxant effect (IC_{50} , 247 $\mu\text{g/ml}$) of latter EO was not affected by ~ 1 μM atropine but significantly reduced in the presence of nitric oxide (NO) synthase blocker (L-NAME) [47]. On the contrary, *Mentha x villosa* EO (255 $\mu\text{g/ml}$) exhibited vasorelaxant effect regardless in the presence or absence of L-NAME [45].

Vasorelaxant effect in potassium-induced contraction: In rat endothelium intact aorta preparations, *A. canelilla* bark EOs (1-600 $\mu\text{g/mL}$) and *C. zehntneri* EO (1-1000 $\mu\text{g/mL}$) induced a dose-related reduction of K^+ (60 mM)-stimulated contraction [IC_{50} , ~ 65 and 202 $\mu\text{g/mL}$ respectively], an effect that was substantially reduced by treatment of high dose of atropine (10 μM) in the perfusion medium [IC_{50} , 109.5 (72.5-165.4) $\mu\text{g/mL}$] [32,38,49]. In addition, *C. argyrophyloides*

EOs -induced relaxation was also partly linked to the opening of potassium (K^+) adenosine triphosphate (K-ATP)-channel which resulted in its hypotensive effect [36]. *Mentha x villosa* EO (10-500 $\mu\text{g/mL}$) and 1,8-cineole ($C_{10}H_{18}O$) (0.006-2.6 mM) also antagonize the effect of potassium ions (60-80 mM) stimulated contractions (IC_{50} , ~ 165 $\mu\text{g/ml}$) [39,42,45]. Cardiovascular effect of the *Rosa indica L* EO has been shown using isolated rabbit aorta preparations [50].

Electrophysiological evaluation elucidated that *R. indica* EO had greater potency against K^+ (80 mM) as compared to phenylephrine precontractions [50]. Some major bioactive components were artemiseole ($C_{10}H_{16}O$), isosteviol ($C_{20}H_{30}O_3$), caryophyllene oxide ($C_{15}H_{24}O$), dihydromyrcene ($C_{10}H_{18}$), 5-octadecadien ($C_{18}H_{35}NO$), santolina epoxide ($C_{10}H_{16}O$), and 9-farnesene ($C_{15}H_{24}$) as determined using GC-MS analysis [50].

Study using mesenteric artery preparations

On the other hand, *Cymbopogon citratus*, *C. winterianus*, *H. fruticosa* EOs and β -citronellol antagonize the effects of contractions induced by both or either phenylephrine or potassium in mesenteric artery rings [51-56]. Several bioactive compounds such as α -pinene ($C_{10}H_{16}$) and caryophyllene ($C_{15}H_{24}$), and 1,8 cineole ($C_{10}H_{18}O$) in *H. fruticosa* EO were suggested to promote its hypotensive effect [54]. Comparatively, vasorelaxant activity of *C. citratus*, *C. winterianus* and *H. fruticosa* EOs was not affected in denuded endothelium [52,54]. It was also suggested that hypotensive effect of *C. citratus* was not linked to K^+ channels where no effect was observed in the presence of tetraethylammonium or potassium ions [52]. Meanwhile, β -citronellol ($C_{10}H_{20}O$) also suppressed spontaneous or electrical-evoked contractions of isolated left or right atrium of an adult rat [55]. *A. speciosa* EO reduced rat left atrial force of contraction with an IC_{50} of 292 $\mu\text{g/ml}$ [57]. Compounds screening and identification via GC-MS analysis revealed that terpinen-4-ol ($C_{10}H_{18}O$, $\sim 38\%$) and eucalyptol ($C_{10}H_{18}O$, $\sim 18\%$) were high among 18 identified bioactive compounds in *A. speciosa* EO [57]. In another study, some bioactive compounds in EO such as carvone epoxide had higher relaxation effect on phenylephrine-induced contraction in mesenteric artery rings as compared to several other EO bioactive components such as limonene ($C_{10}H_{16}$), rotundifolone ($C_{10}H_{14}O_2$), pulegone epoxide ($C_{10}H_{16}O_2$), limonene epoxide ($C_{10}H_{16}O$) and pulegone ($C_{10}H_{16}O$) [29]. Apparently, molecular structures of previously mentioned bioactive compounds are functionally important in artery relaxation [29]. *In vitro* study will assist further analysis in vivo models to attain a deeper understanding and evaluation of EOs in cardiovascular disease.

Study using preclinical model

Cardioprotective effects against myocardial infarction: Several EOs have been used as a therapy for chest pain as well as in myocardial ischemia and myocardial infarction. Intraperitoneally administration of

L. angustifolia EO (5-20 mg/Kg) with antioxidative property had cardioprotective effects in male Wistar rats with isoproterenol-induced myocardium infarction [81]. The previously mentioned EO ameliorated electrocardiogram (ECG) pattern by preventing ST-segment elevation and amplifying R-wave amplitude [81]. This is supported by the fact that *L. angustifolia* EO (1020 mg/Kg) notably reduced heart-body weight ratio and the increase of Malondialdehyde (MDA)-LPO and Myeloperoxidase (MPO)-neutrophils in myocardium and considerably lowered left ventricular end-diastolic pressure [81]. In experimental acute myocardium infarction (anterior interventricular branch of left coronary artery ligated with a 4/0 silk thread), administration of *S. pinnatifolia* EOs diminished deviation of ST-segment [24]. In biochemical parameters and serum marker enzymes analysis, it reduced level of related myocardial enzymes such as LDH, CK and Troponin-T with an increased in SOD activity as compared to myocardium infarction Male Wistar rats control [24]. Histopathological analysis showed that *S. pinnatifolia* EO had protective effect on myocardium infarction with lessen degree of necrosis and infiltration of inflammatory cells in rats [24]. Under hypoxia condition, *S. pinnatifolia* EOs (8-32 mg/kg) can prolong survival time of Kunming mice, suggesting its activity against hypoxia in experimental myocardium infarction [24]. Similarly, *Nardostachyos Radix* and *S. pinnatifolia* EOs exerted protective effect, thus preventing cell death- in chemical (e.g tert-Butyl hydroperoxide, H₂O₂)-induced injury in cardiomyocyte cultures (e.g H9c2, neonatal rat cardiac ventricular myocyte) [24,82]. The cell survival was higher with higher EO concentration due to significant reduction of ROS. EOs reduced the degree of myocardial infarction and the release of LDH and creatine kinase (CK), ameliorated the hemorheology index, increased SOD and glutathione peroxide activity in the myocardium and decreased MDA level [82]. Hesperetin had anti-apoptotic action on cardiomyoblasts via mitochondrion JNK/Bax pathway. Nobiletin activated the PI3K-Akt pathway, reduced cell apoptosis, and reduced myocardium infarct size, hence lowered the risk for myocardium ischemia and reperfusion injury [83,84]. These studies showed the effect of EOs as potent antimyocardial ischemia/infarction, and antimyocardial injury.

Hypolipidemic effect in rats and rabbits: In preclinical trial, Vallianou, et al. [30], and Abass, et al. [56], showed that EOs from *Chios mastic* gum had hypolipidemic effect in young and hyperlipidemic rats. Further evaluation indicated that camphene in this particular EO plays an important role in reducing the constitutive biosynthesis of serum cholesterol and TG [30]. Administration of its bioactive compound, camphene at a concentration of 30 µg/g into hyperlipidemic rat resulted in diminished of total cholesterol (TC), LDL-cholesterol and TG to about 33% - 55% [30]. Similarly, administration of *C. jwarancusa* EO in experimental high-fat-carbohydrate diet rats reduced hyperlipidemic effect (e.g reduction in body weight, fats and blood sugar levels), thus potentially

alleviate the risk of cardiovascular disease [59]. In a study, the administration of magnolol, reduced the serum lipid TG level (up to 50%) in hyperglyceridemic heterozygous transgenic mice (knock-in mice carrying APOA5 c.553G>T variant) [27]. On the other hand, *O. sanctum* EO reduced serum lipid profile (e.g TG, cholesterol) in normal and hypercholesterolemic Male Wistar rats [19]. Other EOs such as *P. asiatica* EO also exerted hypocholesterolaemic effect in C57BL/6 mice with significant reduction of plasma total cholesterol and TG (29% - 46%) as compared to untreated control [31].

Hypotensive effect on hemodynamic parameters in conscious rat and rabbit: In stark contrast, intravenous injection of *A. zerumbet* EO [includes its terpinen-4-ol and Eucalyptol], *Croton zehntneri* EO [includes its anethole and estragole], *Ocimum gratissimum* EO [includes its eugenol], *Hyptis fruticosa* EO, *Mentha x villosa* EO, *S. areira* EO, and *Crocus sativus* EO [includes its Safran], *A. canelilla* bark EO [includes its 1-Nitro-2-phenylethane] showed anti-hypertensive effect in rats [32-35,60,61]. However, hypotensive effect of *A. zerumbet* EOs was much lower than that of its pure bioactive terpinen-4-ol at same doses (1-10 mg/kg) [34,35]. In either experimented deoxycorticosterone-acetate (DOCA)-salt hypertensive or normotensive conscious rat, the effect of *A. zerumbet* EO, *C. zehntneri* EO, *C. argyrophyloides* EO, *C. nepetaefolius* EO (1 to 50 mg/kg), *O. gratissimum* EO, *N. sativa* oil, terpinen-4-ol and 1,8-cineole on hemodynamic parameters can be seen with reduction of mean aortic pressure, heart rate and arterial blood pressure [34,36,40,41,61-63]. These hypotension evidences on hemodynamic parameters of such EOs (e.g *A. canelilla*, *A. zerumbet*, *C. argyrophyloides* and terpinen-4-ol) were mainly caused by active vascular relaxation in lieu to the withdrawal of nervous system sympathetic activity [34,36]. Similarly, the cardiovascular-hypotensive effect of *O. gratissimum* EO was most probably mediated independent of operational autonomic nervous system whereby its vasodilatory activity may have direct interaction with vascular smooth muscle [62]. In conscious rabbit, administration of *S. areira* EO reduced its systolic blood pressure, diastolic blood pressure, and mean arterial pressure in a pattern comparatively similar to nifedipine [64]. In hypertensive rats, pre-treatment with hexamethonium (30 mg/kg) decreased the bradycardia elicited by *C. nepetaefolius* EO (50 mg/kg) exclusively affecting the increment of *C. nepetaefolius* EO-stimulated hypotension [40,41]. This increment was linked to an increase in *C. nepetaefolius* EO-stimulated vascular smooth muscle relaxation with little evidence linked to the enhancement of sympathetic nervous system action in this hypertensive model (e.g its vasodilatory effects directly act upon vascular smooth muscle) [41]. Meanwhile, 1,8-cineole substantially reduced heart rate when only administrated at the highest dose (10 mg/kg) [35]. On the other hand, *N. sativa* and its thymoquinone (C₁₀H₁₂O₂) had cardiovascular depressant effects, mediated primarily via indirect and direct mechanisms involving both 5-hydroxytryptaminergic and muscarinic mechanisms [63].

Likewise, intravenous administration of EOs bioactive compounds (e.g pinenes, citronellol, bisabolol and linalool) also produced hypotensive effect in conscious normotensive rats. Particularly, very high hypotension effect was noted by induction of β -pinene, citronellol and bisabolol at concentration of 20 mg/kg as calculated from its haemodynamics parameters (e.g mean arterial pressure and heart rate) [65]. Intravenous pre-treatment of conscious rats with hexamethonium (30 mg/kg) considerably reduced the resulted bradycardia produced from EOs administration (e.g *A. canelilla* bark, *O. gratissimum*) without affecting their hypotensive effect [49,62]. Unlike *O. gratissimum* EO, the hypotension and bradycardia created by *A. canelilla* bark EO were substantially decreased by pre-treatment with methylatropine (1 mg/kg) [62]. Similarly, cardiovascular depressant effect of *N. sativa* oil (4-32 μ L/kg) or thymoquinone (0.2-1.6 mg/kg) on rats was substantially antagonized by certain concentration of cyproheptadine, atropine and hexamethonium [63]. Likewise, hypotensive and bradycardic responses evoked by *Mentha* EO in rats were blocked by pre-treatment with atropine (2 mg/kg) [42]. On the other hand, pretreatment with methylatropine (1 mg/kg) reduced bradycardic response without affecting hypotensive response [42]. In conscious rats, pre-treatment with hexamethonium (30 mg/kg), methylatropine (1 mg/kg) or atenolol (1.5 mg/kg) had no considerable effects on the 1,8-cineole-stimulated hypotension, whereby bradycardic response to 1,8-cineole (10 mg/kg) was notably decreased by methylatropine [35]. These EOs possess the prospective of being an effective antihypertensive agent. Comparatively, *P. elsholtzioides* EOs contained high amount of bioactive compounds of sesquiterpenes and curzerene, benzophenone, α -cadinol and germacrone as analyzed by GC-FID and GC-MS [37]. These major compounds in this EO were suggested to play an important role in vasorelaxant and cardiovascular effects in Wistar rats whereby physiological and hemodynamic parameters indicated that this EO improved systolic and diastolic blood pressure, mean arterial pressure and heart beats after carotid artery cannulation [37].

Hypotensive effect on hemodynamic parameters in anesthetized rat: Concomitantly, EOs-derived β -Citronellol also had antihypertensive action with vasodilator effect [55]. In anesthetized rats, intravenous administration of β -citronellol led to biphasic hypotension, bradycardia and apnea [55]. In normotensive anaesthetized rat (e.g with pentobarbitone, urethane), the administration of 1,8-cineole (0.3-10 mg/kg), 1-nitro-2-phenylethane (1-10 mg/kg) *N. sativa* (4-32 μ L/kg) and *O. gratissimum* (1-20 mg/kg) elicited similar and concentration-dependent reduction in mean aortic pressure [35,38]. In anesthetized rats, injections of *A. canelilla* bark EOs (1-20 mg/kg) generated concentration-related hypotension [38]. Pre-treatment of anaesthetized rats with bilateral vagotomy did not notably modify the *O. gratissimum* EO-stimulated concentration-related hypotension, while it considerably decreased the bradycardia at the highest

concentration tested [62]. *Mentha x villosa* EO (1-500 μ g/ml) and *S. areira* EO gave negative chronotropic (IC_{50} : 229 μ g/ml) and negative inotropic (IC_{50} : 120 μ g/ml) effects [64].

Clinical studies

In clinical trial, it has been demonstrated that olfactory stimulation of the *C. indicum* Linné EO reduced systolic blood pressure and heart rate of the patients [66]. GCMS evaluation showed that 1,8-cineole and camphor as main biocompounds in this EO [66]. In a singleblinded randomized controlled trial, inhalation of EOs (e.g lavender and grapefruit) via olfactory stimulation (2% EOs for 10-20min) showed some repression on the inflated change values of diastolic blood pressure response in patients with stroke (with anxiety) and patients following coronary artery bypass and open-heart surgery [66-70]. While EOs alleviating stress and improved sleep quality in stroke patients, they had no noteworthy effects on mental stress and respiratory rate and other vital signs in patients underwent coronary artery bypass and open-heart surgery [69,70]. On the other hand, administration of *A. calamus* had significantly reduced chest pain, dyspnea, body weight index as well as improving ECG and lipid profile (serum cholesterol, LDL, HDL) in patients with ischemic heart disease [13]. Based on several studies, EO could be delivered via four different routes (Figure 2).

Mechanism of action

Calcium (Ca^{2+}) channel blocker: Cardiac Ca^{2+} channels (e.g T-type, L-type) in cardiac myocytes play functional role in heart, such as the resource of Ca^{2+} -induced excitation-contraction and facilitate pacemaker depolarization of sinoatrial node in heart [8]. In particular, blockade of these channels has been used in the treatment of cardiovascular disease (e.g reduce contraction). Studies demonstrated that cardiodepressive effect of several EOs (e.g *F. asafoetida*, *Citrus aurantium*) and their bioactive components (e.g eucalyptol) rely onto their potential as Ca^{2+} channel blocker [47,48,71]. Particularly, eucalyptol depressed rate of force development by steady-state contractions, postrest potentiation, force development isometric force as well as positive inotropic effect created by Ca^{2+} [72]. *F. asafoetida* EO, *A. speciosa*

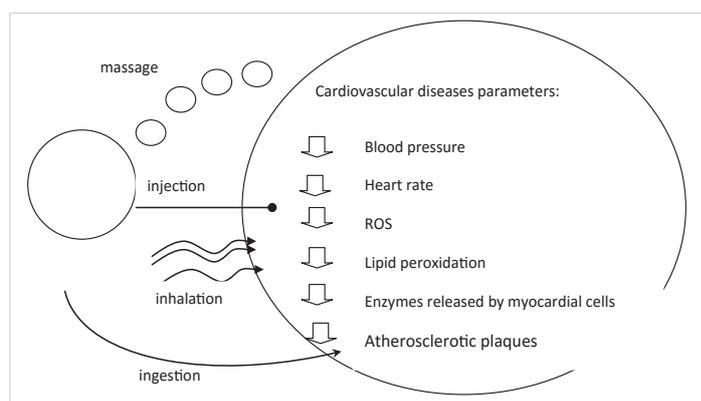


Figure 2: Essential oil route of delivery.

EO, *C. winterianus* EO and *Mentha x villosa* EO had potent cardiodepressive and vasodilatory effect that mediated via endothelium-dependent (e.g EDRFs, NO and prostacyclin) and/or endothelium-independent mechanisms (e.g Ca^{2+} channel blockade) [57,71]. The previously mentioned EOs decreased the influx of Ca^{2+} into the cell via plasma membrane Ca^{2+} channels hence reduced the Ca^{2+} -stimulated contractions [57]. Among EOs, *A. speciosa* EO probably have specific inhibition effect on L-type Ca^{2+} channels in rat heart [57]. The vasodilatory effect of *F. asafoetida* EO was decreased, but not fully inhibited, by either L-NAME or indomethacin [71]. *H. fruticosum* EO was also capable of antagonizing the dose-response curves to Ca^{2+} (3 μ M-30 mM) in a concentration-related manner [54]. Concomitantly, the *C. winterianus* EO also antagonized the effect of Ca^{2+} -induced contractions in depolarizing potassium chloride solution which resulted in hypotension and vasorelaxation [53]. On the other hand, *A. speciosa* EO at 25 μ g/ml and 250 μ g/ml also inhibited left atrial force of contraction by up to ~33% and 89% respectively which was lower as compared to Nifedipine (a L-type Ca^{2+} -blocker) with an IC_{50} of 12 μ g/mL [71].

Anti-atherogenic effect: The effects of anti-atherogenicity of several EOs have also been demonstrated. The *O. sanctum* EO reduced atherogenic index as well as several enzyme/protein released by dying myocardial cells such as serum lactate dehydrogenase (LDH) and creatine-kinase (CK) activity with no adverse effect on high serum levels of aspartate/alanine aminotransferase and alkaline phosphatase in hypercholesterolemic rats [8,19]. EO also reduced elevated levels of TBARS, GPx and SOD with no adverse effect on catalase activity in the myocytes [19]. Histopathological evaluation indicated that EO was capable in preserving myocytes in experimental condition [19]. The compounds screening, identification and matching using GCMS revealed that eugenol and methyl eugenol as the major bioactive compounds in *O. sanctum* EO, thus suggested as being responsible for such pharmacological antihyperlipidemic effects [19]. In atherosclerotic rabbit model, treatment of *A. senegal* seeds (500 mg/kg/day) by 'Per os' for 45 d noticeably reduced serum level of TC, LDL-C, TG, and VLDL-C and atherogenic index (e.g with decreased atherosclerotic plaques in aorta, enlarged lumen volume) as compared to that of control [7]. The improvement on lipid profile and atherogenic index was noted almost comparatively similar to atorvastatin. Histopathological abnormality in aorta wall and other organs (e.g heart, kidney, liver) were reverted to normal condition with *A. senegal* seed supplementation, proven its antiatherosclerotic and cardioprotective effect.

Natural oil occurring lipophilic antioxidants (e.g. vitamin E, beta-carotene, flavonoids, monoterpene, terpenoids) inhibited the oxidative modification of low-density lipoproteins [73-80]. Studies showed that they could possibly prevent atherogenesis and coronary heart diseases. For instance, terpinolene which is the major compound in *Pinus mugo*

EO as well as γ -terpinene from lemon oil effectively retard plasma low-density lipoprotein (LDL)-oxidation [78]. Upon treatment with terpinolene, it was found that the LDL (e.g lipid and protein part) was protected against copper-stimulated oxidation as indicated by conjugated dienes formation and delayed of loss of tryptophan peptide fluorescence [78-80].

Anti-coagulative, Anti-thrombotic and fibrinolysis effect: Heparin and coumarin derivatives are few of known anticoagulant compounds which help to reduce erythrocyte aggregation, platelet hyperactivity, arterial thrombosis and atherosclerosis, which were potentially useful to minimise the incidence of cardiovascular diseases (e.g coronary heart diseases myocardial infarction and cerebral arterial thrombosis) in human [85-92]. Particularly, *Artemisia dracunculifolia* leaves EO and *F. Aurantii* had a significant anti-coagulative effect [87, 88]. The former had considerable amount of coumarin derivatives while the latter had significant amount of flavonoids which could regulate several coagulation parameters such as lengthening prothrombin time as well as reducing fractional shortening and left ventricular outflow, decreasing blood-clotting time in mice (e.g hematocrit and fibrinogen), and ameliorating the pathological alteration of myocytes in blood stasis model [87]. Some coumarins suppressed vitamin K-dependent γ -carboxylase action involved in the activation of coagulation factors [87]. Some citrus EO and its flavonoids (e.g hesperidin and hesperetin) inhibited the aggregation of erythrocytes and platelets. Hesperidin also inhibited ADP and thrombin-induced rat platelet aggregation [87]. Coumarins inhibited platelet functions via multiple mechanisms including scavenging of ROS and suppressing cyclic nucleotide phosphodiesterase and prostaglandin syntheses [87]. In addition, *S. pinnatifolia* EO at concentration of 1 to 5 μ g/mL also reduced adenosine 5'-diphosphate (ADP)-induced rat platelet aggregation *in vitro* to about 33% - 47% [88]. In the anaesthetized Guinea-pigs, the *C. bergamia* Risso (bergamot) EO demonstrated a protective action against both pitressin-induced coronary arrhythmias and ouabain-induced ventricular arrhythmias [89]. In isolated heart of an adult rat, it also exerted a coronary-dilator action, reduced the hyperkinetic ventricular arrhythmias due to post-ischaemic reperfusion. The bergamot EO possesses significant cardiovascular effect comparable to that of an antidysrhythmic drug verapamil [89]. However, it is unknown whether it had similar action as verapamil by blocking voltage-sensitive Ca^{2+} L-type channels. It is well-understood that Ca^{2+} reduces after-depolarization and suppresses premature ectopic beats.

Anti-hyperlipidemia: Antihyperlipidemic activity of *Pinus koraiensis* leaves EO on several enzymes involved in lipid metabolism has been demonstrated using reverse transcription polymerase chain reaction (RT-PCR) and western blotting [90]. Molecular studies showed that *P. koraiensis* EO upregulated LDL receptor at the mRNA level and negatively inhibited the expression of several sterol regulatory element-binding proteins as well as HMG-CoA reductase, fatty acid

synthase and G3P-acyltransferase in HepG2 cells [90]. It may binds to the active site of HMG-CoA reductase to reduce its activity. Consistently, *P. koraiensis* EO substantially reduced human acylcoenzyme A and cholesterol acyltransferases activity and suppressed the LDL oxidation. GC-MS analysis revealed that *P. koraiensis* EO consisted of camphene (~21%), d-limonene (~21%), α -pinene (~17%) and borneol (~12%) [90]. On the other hand, total blood cholesterol was reduced after *C. citratus* (lemongrass) EO-administration at the highest concentration tested [51].

Safety and limitation

Safe applications and doses of several EOs have been demonstrated [90-95]. For instance, clinical status (morbidity or mortality), morphology and lung:body weight ratio were unaffected by the administration of the EO *S. areira* [64]. On the other hand, LD₅₀ of lemongrass EO based on a 24 h acute oral toxicity study in male Swiss mice was about ~3500 mg/kg with no significant changes in organs [51]. On the other hand, tachycardia was significantly observed in mice/rat administrated with pinenes at 20 μ g/mL, citronellol at 5 μ g/mL, and linalool at 20 μ g/mL at increasing concentration while bisabolol at similar dose causes bradycardia (significant even at 5 μ g/mL) [29,93-95]. On the other hand, high dose of *C. winterianus* EO stimulated transient bradycardia as well as arrhythmias due to a cardiac muscarinic activation secondary to a vagal discharge [53]. Meanwhile, administration of *A. canelilla* bark EO elicited concentration-dependent bradycardia in rats. The bradycardia mostly depended in the presence of an operation-functional parasympathetic drive to the heart [38]. In conscious hypertensive rats, intravenous administration of *C. zehntneri* EO (1-20 mg/kg) stimulated rapid (2-4s) and concentration-dependent bradycardia [32]. The effect of bradycardia of *C. zehntneri* EO was reversed into tachycardiac effects by methylatropine (1 mg/kg) pre-treatment [32]. In contrast, administration of *C. argyrophyloides* EOs via intravenous administration in conscious rats created dose-dependent tachycardia [36]. In non-anesthetized normotensive rats, *Hyptis fruticosa* EO (5-40 mg/kg) also induced tachycardia [54]. In rats, pre-treatment of atropine, but not with atenolol or L-NAME, decreased tachycardiac responses by *C. argyrophyloides* EO [36]. However, hexamethonium pre-treatment converted the effect of the *C. argyrophyloides* EO-stimulated tachycardia into prevailing bradycardia [36]. Moreover, *C. argyrophyloides* EO-stimulated tachycardia in conscious rats may mediated via inhibition of vagal drive to the heart [36].

Conclusion

This systematic review demonstrated the therapeutic application of several EOs as complementary and alternative medicine in cardiovascular diseases. Terpenes are the most active components in EOs gave direct vasorelaxant effect as supported by the results of the present study. Other EOs

lowered blood pressure, reduced risk for myocardial infarction, stroke and heart failure. This study provides a reference for the clinical research and utilization of EOs, as well as the application basis for co-treatment of cardiovascular diseases. This will also pave further evaluation of EOs for potential new application for cardiovascular diseases.

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