

## Lamiaceae in the treatment of cardiovascular diseases

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### 1. ABSTRACT

Lamiaceae (Labiatae) are an important group of medicinal plants, which have been used for treating heart disease in traditional medicine for centuries. These mainly aromatic plants are used as essential oils, extracts or isolated components (polyphenols, phenolic compounds, terpenes, iridoids etc.). Some Labiatae species (more than 30, such as cornmint, lavender, patchouli, rosemary etc.) are famous for their use in essential oil production worldwide. In this review, cardioprotective effects of Lamiaceae and their active secondary metabolites, as well as mechanism of action against cardiovascular diseases (hypertension, angina pectoris, hyperlipidemia, thromboembolism, coronary heart disease, heart failure, venous insufficiency, arrhythmia) will be discussed. Use of Labiatae as food or food additives (such as spices) may prevent risk of cardiovascular diseases,

diabetes and cancer. This approach is also described as a part of the article. Studies on developing new, effective and safe natural products from Lamiaceae (rich source of flavonoids and other active compounds) are promising and may offer prevention and treatment for patients with coronary disease and other related diseases.

### 2. INTRODUCTION

Cardiovascular diseases (CVDs) are disorders of the heart and blood vessels and include conditions such as hypertension, hyperlipidemia, thromboembolism, coronary heart disease, and heart failure. Among these conditions, hypertension is the most common, and plays a major role in the development of CVDs (1). According to World Health Organization (WHO), over 17 million people die per

year (31% of all global deaths) from CVDs). With the increasing number of diagnoses of CVD, it is projected that mortality will reach 23.3 million before 2030 (2).

Herbs and herbal products have been used for the treatment of several ailments for centuries. More than 2000 plants are known in ethnomedicine, and some of them are traditionally used to prevent or treat people suffering from CVDs and related complications. It is estimated that around 25% of currently commercialized medicines are derived from herbal plants used in traditional medicine. Herbal products are effective against CVD alone or in combination with other drugs, as Mahady *et al.*, (3) noted that hundreds of plant-based products are traditionally used to treat diseases. However, some of the herbs show side effects that sometimes exceed their benefits. Therefore, impact of herbs on biological mechanisms needs to be investigated.

A large number of traditional herbs have been reported, which have efficacy against CVD. Some of the suggested and scientifically proven herbs are *Cynara scolymus* (artichoke), *Allium sativus* (garlic), *Ginkgo biloba*, *Commiphora mukul*, *Crataegus* species, *Vitis vinifera* (grape), *Crocus sativa* (saffron), and *Camellia sinensis* (tea) (3). These herbs exhibit potent antioxidant and anti-inflammatory activities, which makes them effective against CVD and associated complications. Chemical analysis of these plant extracts revealed that they contain large number of bioactive phytochemicals, which provides unlimited opportunities for the development of new drugs against several diseases, including CVD (4).

Numerous studies reported that species from the Lamiaceae family have potent cardioprotective effects among various medicinal and aromatic herbs (5-8). These plants can be used as crude extracts, essential oils (EOs), or active compounds against CVD (Table 1.) (7; 9; 10). It is important to note that the Lamiaceae family of plants contains various classes of bioactive compounds including flavonoids, terpenoids, and alkaloids. This plant family and their active compounds have shown promising cardioprotective activity *in vitro* and *in vivo* (Table 1, Figure 1, Figure 2). One of the most

investigated Lamiaceae species belongs to the *Salvia* genera, known to act as strong cardioprotective agents, which can notably improve myocardial ischemia in patients with CVDs (11). *Salvia*, in combination with other herbs, has a more potent effect. For example, *Salvia* and *Astragalus* show a positive synergistic effect and reduce symptoms of hemorrheology in patients with heart failure (11). However, some studies reported that combination of conventional and alternative medicine may cause herb-drug interactions and result in side effects (2). This review compiles the list of Lamiaceae species with cardioprotective effects, potential mechanisms of their active components, consumption to decrease risks or avoid CVDs, as well as a number of case reports.

### 3. HERBAL PRODUCTS FOR TREATMENT OF CARDIOVASCULAR DISEASES

Natural plant products are widely used to treat various diseases, including CVD. Based on structures, a wide range of bioactive compounds from plants are used for synthesis of some commercial pharmaceutical drugs. For example, ephedrine isolated from *Ephedra sinica*, (2) semi-synthetic aspirin derived from salicin (isolated from *Salix alba*), artemisinin isolated from *Artemisia annua*, alkaloid morphine found in *Papaver somniferum*, and capsaicin from *Capsicum annuum* (12). Besides these, several medicinal plants worldwide are used in traditional medicine in the treatment of cardiovascular disorders. For example, *Allium sativum* (garlic) is well known for its hypotensive and hypocholesteremic effects (13), while *Camellia sinensis* (tea) possess cardioprotective effects, which consists of number of flavonoids: catechin (the major), (–)-epicatechin, (–)-epicatechin-3-gallate, (–)-epigallocatechin, and (–)-epigallocatechin-3-gallate, (–)-epigallocatechin-3-gallate etc. (13). *Crataegus* spp. is famous for its antihypertensive activity probably due to the large flavonoid content (hyperoside, quercetin, rutin, and vitexin). *Nigella sativa* (black cumin), a well-known spice, contains thymoquinone as the major bioactive constituent with cardiovascular healing effects (13). *Coriandrum sativum* is known as a natural antioxidant and has been shown to increase levels of antioxidants in food.

**Table 1.** Lamiaceae species with cardioprotective effects *in vitro* and *in vivo*

Scientific name	Active ingredients	Cardioprotective effects and traditional use	Reference(s)
1. <i>Ajuga iva</i> (L.) Schreber	Aqueous extract	<ul style="list-style-type: none"> <li>NO-mediated and NO-independent vasorelaxing properties <i>in vitro</i> while only the endothelium-independent effect was observed <i>ex vivo</i></li> </ul>	(39)
2. <i>Cedronella canariensis</i> (L.) Webb. & Berth		<ul style="list-style-type: none"> <li>Leaves possess cardiovascular activity</li> </ul>	(153)
3. <i>Clinopodium umbrosum</i> (M.Bieb.) Kuntze		<ul style="list-style-type: none"> <li>Heart tonic</li> </ul>	(154)
4. <i>Dracocephalum moldavica</i> L.	Flavonoids	<ul style="list-style-type: none"> <li>cardioprotective effects against acute ischemia</li> </ul>	(155)
5. <i>Lavandula angustifolia</i> Mill.	Essential oils	<ul style="list-style-type: none"> <li><b>Protects myocardium against isoproterenol induced myocardial infarction that it could be related to its antioxidant properties</b></li> </ul>	(9)
6. <i>Leonotis leonurus</i> (L.) R.Br	Diterpenoid Marrubiin	<ul style="list-style-type: none"> <li>Anticoagulant, antiplatelet, and anti-inflammatory effects</li> </ul>	(33)
7. <i>Leonurus cardiaca</i> L.	Phenolic compounds	<ul style="list-style-type: none"> <li>Strengthening cardiac muscle</li> <li>The healing of heart diseases, Analgesic effect</li> </ul>	(41) (156) (157)
8. <i>Marrubium vulgare</i> L.		<ul style="list-style-type: none"> <li>Protective effect against cardiac complications</li> </ul>	(44)
9. <i>Mentha arvensis</i> L.		<ul style="list-style-type: none"> <li>Beneficial effects of <i>M. arvensis</i> in patients with ischemic heart disease</li> </ul>	(8)
10. <i>Mentha x piperita</i> L.	Aqueous extract	<ul style="list-style-type: none"> <li>Decreases levels of glucose, cholesterol and triglycerides and increase the high-density lipoprotein cholesterol and HDL-ratio without affecting serum insulin levels in fructose-fed rats</li> </ul>	(158)
11. <i>Mentha pulegium</i> L.	Polyphenolic compounds (Salvianolic acid B; Salvianolic acid E; Isosalvianolic acid B; Salvianolic acid I; Salvianolic acid H; Lithospermic acid, luteolin-6,8-C-dihexose; Syringetin; Quercetin	<ul style="list-style-type: none"> <li>Cardioprotective effect</li> </ul>	(158)

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Table 1. Contd...

Scientific name	Active ingredients	Cardioprotective effects and traditional use	Reference(s)
12. <i>Melissa officinalis</i> L.	Phenolic compounds	<ul style="list-style-type: none"> <li>Cardioprotective effect</li> </ul>	(159)
13. <i>Ocimum basilicum</i>	Rosmarinic acid	<ul style="list-style-type: none"> <li>Strongly protect the myocardium against isoproterenol induced infarction</li> <li>Anticoagulant effect</li> <li>Cardioprotective effect of rosmarinic acid</li> </ul>	(53) (160) (31)
14. <i>Ocimum gratissimum</i> L.	Cardioprotectin	<ul style="list-style-type: none"> <li>Cardioprotective effect</li> </ul>	(161)
15. <i>Ocimum sanctum</i> L.		<ul style="list-style-type: none"> <li>Hypotensive, cardiac depressant activity</li> </ul>	(162)
16. <i>Origanum vulgare</i> L.		<ul style="list-style-type: none"> <li>Contain cardioprotective flavonoids</li> </ul>	(27)
17. <i>Origanum majorana</i> L.	Flavonoids (Kaempferol-O-glucuronide; Sakuranetin; Salvianolic acid; Luteolin-6,8-C-dihexose; Taxifolin; dihydrokaempferide; Luteolin-O-glycoside; Kaempferol-O-sambubioside; Luteolin glucoside; Syringetin; Quercetin	<ul style="list-style-type: none"> <li>Cardioprotective effect</li> </ul>	(158)
18. <i>Orthosiphon thymiflorus</i> Benth.		<ul style="list-style-type: none"> <li>Anti-inflammatory and hypertensive</li> </ul>	(36)
19. <i>Plectranthus barbatus</i> Andrews	Forskolin (labdane diterpene)	<ul style="list-style-type: none"> <li>Cardioprotective activity</li> </ul>	(7)
20. <i>Pogostemon cablin</i> (Blanco) Benth.	( $\alpha$ -bulnesene) sesquiterpene present in EO	<ul style="list-style-type: none"> <li>Anti-PAF (Platelet-Activating Factor)</li> </ul>	(163)
21. <i>Rosmarinus officinalis</i> L.	Polyphenols and Flavonoids	<ul style="list-style-type: none"> <li>Antineoplastic effects</li> </ul>	(164) (165) (166)
22. <i>Salvia hispanica</i> L.	Seeds $\alpha$ -Linolenic acid	<ul style="list-style-type: none"> <li>Prevent cardiovascular diseases, inflammatory and nervous system disorders, and diabetes</li> <li>precursor of eicosapentaenoic acid and docosahexaenoic acid connected to the antiatherogenic and cardioprotective effects</li> </ul>	(167) (168)
23. <i>Salvia miltiorrhiza</i> Bunge	Extract Lipophilic tanshinones Salvianolic Acid B	<ul style="list-style-type: none"> <li>Antianginal, Hypertension,</li> <li>prevention of LDL-C oxidation</li> <li>cardiovascular effect</li> </ul>	(169) (170) (10) (171)

contd...

Table 1. Contd...

Scientific name	Active ingredients	Cardioprotective effects and traditional use	Reference(s)
24. <i>Salvia columbariae</i> Benth.	Miltionone II, Cryptotanshinone and Tanshinone IIA	<ul style="list-style-type: none"> <li>important in the treatment of stroke and heart attack</li> </ul>	(6)
25. <i>Salvia officinalis</i> L.		<ul style="list-style-type: none"> <li>Tea - relevant to diabetes and associated cardiovascular complications</li> </ul>	(172)
26. <i>Salvia libanotica</i> (Boiss. et Gaill)		<ul style="list-style-type: none"> <li>Traditionally used in Lebanon for curing abdominal pains, headaches, indigestion, and heart disorders</li> </ul>	(173)
27. <i>Satureja hortensis</i> L.	Polyphenolic compounds (Litospermic acid B)	<ul style="list-style-type: none"> <li>Cardioprotective activity</li> </ul>	(174)
28. <i>Satureja montana</i> ssp. <i>kitaibelii</i> Wierzb.	presence of polyphenols (Quinic acid; Dihydroxybenzoic acid glucoside isomer; Caffeoylquinic acid isomer; Luteolin-7-O- $\beta$ -glucopyranoside, Chlorogenic acid; Caffeoylquinic acid methyl ester; Quercetagenin 7- $\beta$ -D-glucoside; Quercetin 3- $\beta$ -D-glucoside Acacetin-rutinoside isomer, Apigenin-6,8-di-C- $\beta$ -D-glucopyranoside;	<ul style="list-style-type: none"> <li>Cardioprotective activity</li> </ul>	(175) (176)
29. <i>Scutellaria baicalensis</i> Georgi.	Flavonoids	<ul style="list-style-type: none"> <li>Cardiac protection against ischemic heart disease</li> </ul>	(176)
30. <i>Thymus atlanticus</i> (Ball) Roussine		<ul style="list-style-type: none"> <li>Anticoagulant activities</li> </ul>	(177)
31. <i>Thymus satureioides</i> Cosson		<ul style="list-style-type: none"> <li>Anticoagulant activities</li> </ul>	(177)
32. <i>Thymus zygis</i> subsp. <i>gracilis</i> Morales		<ul style="list-style-type: none"> <li>Anticoagulant activities</li> <li>Anti-inflammatory</li> </ul>	(177)
33. <i>Thymus vulgaris</i> L.	Cardioprotective flavones (Apigenin, Luteolin, Chrysin)	<ul style="list-style-type: none"> <li>cardioprotective activity</li> </ul>	(178)

contd...

Table 1. Contd...

Scientific name	Active ingredients	Cardioprotective effects and traditional use	Reference(s)
34. <i>Teucrium polium</i> L.	aqueous-ethanol extract	<ul style="list-style-type: none"> <li>Positive effect blood pressure, heart rate and intraventricular pressure</li> </ul>	(180) (34)
35. <i>Teucrium cartaginenses</i> L.	Methanol extract	<ul style="list-style-type: none"> <li>Reduces mean arterial blood pressure</li> </ul>	(181)
36. <i>Stachys inflata</i> Benth.		<ul style="list-style-type: none"> <li>Hydroalcoholic extract attenuates the infarct size following ischaemia</li> </ul>	(78)
37. <i>Scutellaria baicalensis</i> Georgi.		<ul style="list-style-type: none"> <li>Inhibits thrombin-induced production of plasminogen activator inhibitor-1 and interleukin-1<math>\beta</math>- and tumor necrosis factor-<math>\alpha</math>-induced adhesion molecule expression in cultured human umbilical vein endothelial cells, anti-thrombotic, anti-proliferative and anti-mitogenic effects of the roots</li> </ul>	(182)

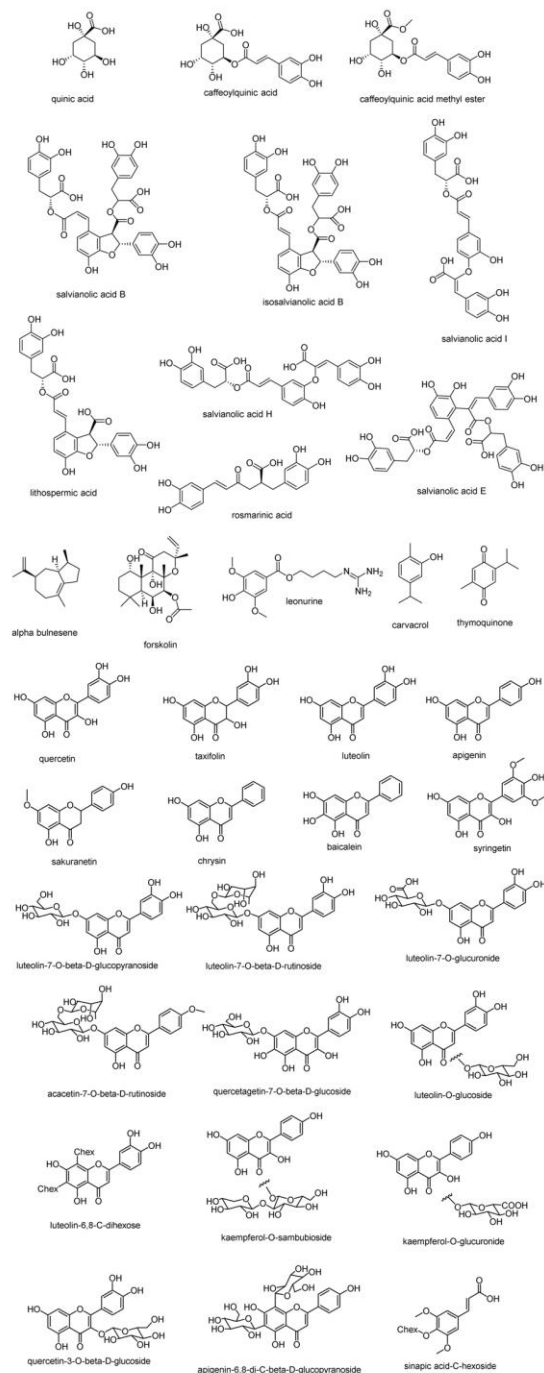
Kousar *et al.*, (14) demonstrated that the leaves of *Coriandrum sativum* show significant cardioprotective ability by increasing levels of superoxide dismutase and decreasing levels of serum marker enzymes and peroxidase. Extracts (ethanol and aqueous) of *Curcuma longa* show cardioprotective effects against doxorubicin (DOX) induced cardiotoxicity in rats. Turmeric is rich source of curcuminoids, terpinolone, *p*-cymene, undecanole, 1,8-cineole,  $\alpha$ -turmerone, and other active secondary metabolites related to its cardioprotective activity (15). Anthocyanins, glucosinolates, isothiocyanates, and phenolic compounds are responsible for the cardioprotective effects of *Raphanus sativus* against myocardial injury induced by isoproterenol (16) in rats.

### 3.1. Lamiaceae family

The Lamiaceae (Labiatae) family contains medicinal and aromatic plants with around 7,200 species distributed in 240 genera. Current literature data suggests Lamiaceae can act as an antioxidant, antimicrobial and anti-inflammatory agent, while

several studies recommend some Lamiaceae species as functional foods (17).

Lamiaceae plants, indigenous to Mediterranean regions and traditionally employed as culinary herbs, also have a long traditional history of use for several medicinal purposes (5, 18, 20). This economically important plant family consists of cultivated and ornamental garden plants (*Salvia splendens*, *Lavandula*, *Teucrium*, *Phlomis*...). Plants of this family are widely used as culinary herbs and spices such as sage (*Salvia*), thyme (*Thymus*), mint (*Mentha*), oregano, and marjoram (*Origanum*), rosemary (*Rosmarinus*), lavender (*Lavandula*), and basil (*Ocimum*). These are also important perfumery ingredients (mint and lavender), flavor additives used in food industries (*Rosmarinus officinalis*, *Ocimum basilicum*, *Origanum majorana*), and as beverages and teas (*Satureja montana*, *Mentha x piperita*, *Salvia officinalis*, *Sideritis scardica* etc.). The medicinal properties of the Lamiaceae species are attributed to their high content of volatile (5) and flavonoid compounds. To date, a number of secondary metabolites from the Lamiaceae family of



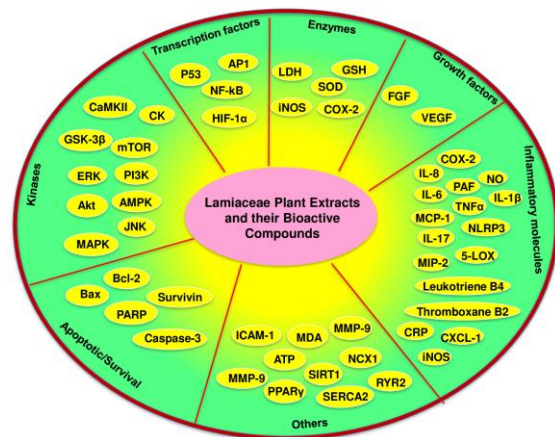
**Figure 1.** Chemical structures of bioactive Lamiaceae secondary metabolites.

plants are isolated (flavonoids, iridoids, terpenoids etc.) and their different biological activities are confirmed (21; 26).

### 3.2. Cardioprotective effects of Lamiaceae species and their active compounds

The Lamiaceae species, which are a rich source of antioxidants (polyphenolic compounds), possess promising benefits to decrease the risk of CVDs through the suppression of inflammation (27). One of the plants of the Lamiaceae family, *Satureja hortensis*, is traditionally well known for the treatment of CVDs and associated complications (28). It has been reported that methanol extract of *S. hortensis* has an inhibitory effect on blood platelet adhesion, aggregation, secretion and also has blood anticoagulant activity (29). Further studies revealed that monoterpenes (such as carvacrol), flavonoids and phenolic acids (like labiatic acid) present in *S. hortensis* are responsible for its anti-platelet properties. Another plant of this family, *Leonurus turkestanicus*, has been shown to be effective against cardiovascular, stomach, and other related diseases (30). In a study, camphor, limonene, tannins, triterpenoids, coumarins, cineole, and flavonoids, present in *Lavandula agustifolia*, showed significant antioxidant properties and decreased cardiac tissue damage and strengthened myocardial membrane (31). *Stachys schimperi* possess cardioprotective effects on DOX-induced cardiotoxicity in rats. Isoscutellarein 7-O- $\beta$ -D-glucopyranoside, found in methanol extract of this species, showed notable free radical scavenging activity, with mild protection against DOX-induced cardiotoxicity as shown by histopathological analysis. *In vivo* experiments in rats with isoproterenol-induced myocardial infarction showed that rosmarinic acid, found in high quantities in the leaves of basil (*Ocimum basilicum*), exhibited cardioprotective effects, which could be related to the antioxidant activities of rosmarinic acid. (31). Another example is *Plectranthus barbatus* (syn. *Coleus forskohlii*), which has been shown to be anti-atherogenic and cardioprotective (32). In that study, rats with myocardial infarction were administered the treatment (obtained from the dry, tuberous roots of the plant) for 20 days-post MI. The authors speculated that forskolin (labdane diterpene), found in the roots, is responsible for these activities (Table 1, Figure 1.)





**Figure 2.** Molecular targets of Lamiaceae plant extracts and their bioactive compounds.

Marrubiin (labdane diterpenoid), a major compound of *Leonotis leonurus* plant extract, has shown anticoagulant, antiplatelet, and anti-inflammatory properties (33). Further, a study *in vivo* showed that the marrubiin in *L. leonurus* plant extract prolonged activated partial thromboplastin time (APTT). In addition, *in vitro* studies further revealed that the extract of *Leonotis leonurus*, as well as marrubiin, inhibit platelet aggregation through the inhibition of the binding of fibrinogen to glycoprotein IIb/IIIa receptor (33). In a study using human umbilical vein endothelial cells HUVECs, ethanol extract of *Teucrium polium* induced anti-angiogenic effects (34). Moreover, a combination of *T. polium* and tranilast (an analog of a tryptophan metabolite) remarkably increased anti-angiogenic properties.

Thymoquinone (2-Isopropyl-5-methylbenzo-1, 4-quinone), which is the major component of some spices belonging to the Lamiaceae family (mainly from *Thymus* genera), showed healing effects against coronary artery diseases, urinary system failures, hypertension, diabetes, apoptosis, inflammation, and oxidative stress. The cardioprotective effect of Thymoquinone is related to its antioxidant and anti-inflammatory activity (35). Comprehensive investigation on antihypertensive activity of leaf extract and compounds isolated from *Orthosiphon* species have also been studied and showed that isolated components (Methylripariochromene A, Orthochromene A, Neoorthosiphol A and B and

Tetramethylscutell) decreased systolic blood pressure (36). In a study using rats, EO of *Lavandula angustifolia* has shown to protect isoproterenol-induced myocardial infarction. The authors concluded that *Lavandula* EO decreased cardiac tissue damage and provided strength to the myocardial membrane. This remarkable cardioprotective effect of *L. angustifolia* EO was found associated with its antioxidant activity (9) (Table 1).

#### 4. CARDIOVASCULAR DISEASES MITIGATED THROUGH ANTI-INFLAMMATORY EFFECT OF HERBS

Inflammation is one of the common causative factors of several diseases, including CVDs. Although it is not clearly proven that inflammation directly contributes to heart disease, CVD patients are reported to have increased level of inflammation. Various epidemiological and clinical studies have shown that increased inflammation has strong relationships with risk of cardiovascular diseases (37). Several inflammatory markers have been detected in CVD patients, but high-sensitivity C-reactive protein (CRP) is noted as the most clinically reliable and accessible inflammatory marker. A number of agents that can reduce inflammation associated CVD have been discovered, including 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, in the form of statins (38). However, it is not well known whether reduction of CRP really lowers cardiovascular risk. Therefore, there is a dire need of agents that can reduce the risk of CVD effectively and safely.

Because of their biologic properties as shown in Figure 2, Lamiaceae can reduce the risk factors of CVD and decrease the incidence of occurrence. Among several herbs, aqueous extract of *Ajuga iva* has shown to possess vasorelaxing properties *in vitro* (39). Vasorelaxation of *Ajuga iva* extract was found to be influenced by nitric oxide (NO) modulation, as NO regulates the functional activity of inflammatory cell types including macrophages (39). *Lavandula angustifolia* EOs inhibited platelet-activating factor (PAF), an inflammatory phospholipid mediator. Inhibition of PAF leads to protection of myocardium against isoproterenol-induced myocardium infarction in rats



(9). Ethyl acetate extract of *L. angustifolia* also inhibits lipopolysaccharide (LPS)-induced inflammation in RAW264.7 macrophages through suppression of iNOS/NO signaling, IL1 $\beta$ , and cyclooxygenase (COX)-2 genes (40). Thus, modulation of inflammation by these plants contributes to reduction of CVD.

*Leonurus cardiaca* has been studied for its efficacy in strengthening cardiac muscle, which could be the potential factor in reduction of risk of CVD (41). Although the mechanism of strengthening muscle is not known, polyphenol rich extract of this plant is reported to mitigate inflammation by inhibiting the PAF secretion induced by staphylococcal peptidoglycan (42). The methanol extract of *Marrubium vulgare* at doses of 10, 20, and 40 mg/kg has shown to protect isoproterenol-induced acute myocardial infarction (43). Furthermore, 40  $\mu$ g/mL of *M. vulgare* aqueous fraction has shown to decrease ischaemia-reperfusion (I/R) injury in rats (44). These findings suggest that the *M. vulgare* has cardioprotective properties. Although the mechanism of action for their cardioprotective activities is not clear, it can be speculated that this property is mediated through its anti-inflammatory activity, since it inhibits inflammatory molecule COX-2.

*Mentha arvensis*, which is used around the world, has shown cardioprotective effects through the inhibition of inflammation. At 100 $\mu$ g/ml, extract of this plant exhibited strong inhibitory activity against IL-8 secretion in AGS cells, which might be associated with CVD (45). Another species of mentha, *M. piperita*, also possess an anti-inflammatory effect against acute and chronic inflammation (46). The anti-inflammatory effect was mediated through suppression of tumor necrosis factor-alpha (TNF- $\alpha$ ), vascular endothelial growth factor (VEGF), and fibroblast growth factor-2 (FGF-2) (47). This anti-inflammatory activity of *M. piperita* could be associated with suppression of CVD, since CVD patients have increased inflammation. Moreover, *M. modarresi* exhibits cardioprotective effects (48). *M. pulegium* has also shown anti-inflammatory as it strongly reduces IL-6, MCP-1, and TNF- $\alpha$  secretion in murine RAW 264.7 macrophages (49). These studies affirm the use of Lamiaceae is beneficial as cardioprotective and anti-inflammatory agents.

*Melissa officinalis* has been used as traditional medicine in several African countries as calming agent, antispasmodic, and cardioprotective agent. The anti-inflammatory activity of EO obtained from this plant's leaves was observed in carrageenan and experimental trauma-induced hind paw edema in rats (50). *M. officinalis* extract has also exhibited protective effects against reperfusion-induced lethal ventricular arrhythmias in rats. Moreover, lyophilized aqueous extract of *M. officinalis* leaves can be used for the treatment of benign palpitations, as heart palpitation is a common complaint that is associated with a marked distress and makes the condition difficult to treat. A study conducted in healthy volunteers treated with 500 mg lyophilized aqueous extract of *M. officinalis* leaves (or placebo) twice a day for 14 days showed reduced frequency of heart palpitation episodes (51). In another randomized, double-blind clinical trial, *M. officinalis* was found to be cardioprotective, as it is effective in improvement of lipid profile, glycemic control, and reduction of inflammation (52). Extracts of *Ocimum* species also play a significant role in cardiac functions. Ethanol extract of aerial parts of *O. basilicum* and *O. sanctum* have shown protective effect on isoproterenol-induced myocardial infarction in rats (53; 54). This cardioprotective effect of *Ocimum* species may be mediated through suppression of inflammation. The anti-inflammatory activity of *O. basilicum* EO was shown against carrageenan and different other mediator-induced paw edema in rats. It inhibited arachidonate metabolism, a mediator of inflammation, in rats (55). Methanol extract of *O. sanctum* leaves was also shown to inhibit inflammation in isoproterenol-induced myocardial infarction in rats. Pre-treatment of this extract inhibited 5-lipoxygenase, COX-2, levels of leukotriene B4 and, thromboxane B2 induced by isoproterenol in rats (56).

*Origanum majorana* has been used traditionally against various ailments, including cardiac disease. In isoproterenol-induced myocardial infarcted rats, sweet marjoram leaf powder and marjoram leaf aqueous extract increased the relative heart weight, alleviated myocardial oxidative stress, and the leakage of heart enzymes, such as creatine phosphokinase, lactate dehydrogenase and aminotransferase (57). *In vitro* studies revealed that

EO from oregano leaves exerts an anti-inflammatory effect on LPS-treated murine macrophage RAW264.7 cells. This EO also inhibited the expression and secretion of interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor-alpha (TNF- $\alpha$ ) in RAW264.7 cells treated with LPS (58). Besides its EO, ethanol oregano (*Origanum vulgare*) extract also suppressed propionibacterium acnes-induced inflammation *in vivo* and *in vitro* (59). Thus, the cardioprotective effect of *Origanum* species could be due, in part, to the, anti-inflammatory properties.

*Plectranthus barbatus* extract has shown to reduce the production of pro-inflammatory cytokines, indicating its anti-inflammatory potential (60). Other *Plectranthus* species have also been shown to have inflammation reduction properties. In an LPS-induced rat model, *Plectranthus amboinicus* attenuated the increase in the expression of circulating proinflammatory cytokines TNF- $\alpha$  and IL-8 (61). Extracts of *Plectranthus zeylanicus* prepared with n-hexane or dichloromethane potently suppressed 5-lipoxygenase activity in stimulated human neutrophils (62). Although the cardioprotective effects of *Plectranthus* species are scarcely reported, this anti-inflammatory property may be a causative factor in cardioprotection. Rosemary leaves have shown anti-inflammatory effects in experimental models and are also used against various ailments. Dietary supplementation of rosemary in a rat model attenuated cardiac remodeling by improving energy metabolism. It improved diastolic function, and reduced hypertrophy after myocardial infarction (63).

*Salvia hispanica*, commonly known as salba, was found to reduce postprandial glycemia in healthy subjects. In an acute, randomized, double-blind, controlled study in 11 healthy individuals, bread baked with salba decreased the postprandial glycemia as well as improved blood pressure, coagulation, and decreased markers of inflammation (64). These effects of salba possibly explain its cardioprotective effects. In a rat model, dietary *S. hispanica* seeds normalized blood pressure, improved heart lipotoxicity, and glucose oxidation induced by a sucrose-rich diet (65). This cardioprotective effect of *S. hispanica* may be mediated through suppression of inflammation, since it decreased levels of inflammatory markers such as

IL-6 and TNF- $\alpha$ , as well as xanthine oxidase activity and reactive oxygen species (ROS) contents in rats fed a sucrose-rich diet (66). *S. miltiorrhiza*, another species, also has cardioprotective efficacy. *Salvia miltiorrhiza*, in combination with other extract, attenuated myocardial ischemia/reperfusion (I/R) injury via suppression of NLRP3 inflammasome activation in C57BL6 mice. Moreover, it suppressed serum levels of IL-1 $\beta$ , an indicator of NLRP3 inflammasome activation after I/R injury (67). Thus, it exerts its cardioprotective effects by suppression of NLRP3 inflammasome activation in this I/R injury model.

Plant oils, including thyme, have been shown to mediate anti-inflammatory effects. It has been demonstrated that this oil provides cardioprotective benefits because of the presence of its bioactive components (68). The aqueous methanol extract of aerial parts of *Thymus linearis* benth has shown to decrease heart rate of both normotensive and hypertensive rats (69), thus indicating potential antihypertensive activity. As *Thymus* extract suppresses inflammatory (TNF- $\alpha$ , IL-1 $\beta$ , IL-6) cytokines (70), it can be concluded that cardioprotective activity of this plant extract might be mediated through its anti-inflammatory activities. *Thymus* extract also showed significant anti-inflammatory properties by reducing nuclear factor (NF)- $\kappa$ B transcription factor protein levels, as well as cytokines such as IL-1 $\beta$ , IL-8, and Muc5ac secretion in cell culture model (71). Moreover, in an animal model, *Thymus* extracts produced 34% inhibition against carrageenan and 22% inhibition against egg albumin-induced paw edema (69). Based on these findings, it is concluded that *Thymus* extract could contribute to reduction of inflammatory responses and exhibit cardioprotective effects.

As I/R injury facilitates and accelerates apoptosis in the myocardium, its suppression by safe, natural compounds can prevent incidence of CVD. Hydro-alcoholic extract of *Teucrium polium* has shown to prevent I/R-induced apoptosis in the isolated rat heart (72). This cardioprotective effect of *T. polium* may be mediated through multiple factors including its anti-inflammatory properties. In a study, *T. polium* extract prevented inflammation induced by carrageenan (73) and LPS-induced colon

inflammation (74). It also inhibited inflammatory markers TNF- $\alpha$  and IL-1 $\beta$  in colon tissue of rats (75). Ethyl acetate extract of another species of *Teucrium* has also shown to exhibit an anti-inflammatory effect by blocking both pathways of Arachidonic acid metabolites (COX-2 and lipoxygenase) (76). Extracts obtained from aerial parts of *Stachys inflata* have been used in Iranian folk medicine against rheumatic and other inflammatory disorders. Furthermore, methanol extract of *Stachys inflata* (50-200 mg/kg) inhibited carrageenan-induced paw edema and formalin-induced paw licking in an inflammatory rat model. The hydroalcoholic extract (200 mg/kg) also reduced myeloperoxidase activity, indicating its inflammatory activity (77), and such activity attenuated the infarct size following myocardial I/R (78).

*Scutellaria baicalensis* is a Chinese herb that has been shown to have cardioprotective effects in experimental animal models. In a study, pretreatment with *S. baicalensis* extract (30 mg/kg) for five days showed significant reduction in myocardial infarct size and a marked increase in the activity of catalase in the liver. This cardioprotective effect of *S. baicalensis* is linked to the suppression of CRP. In a study with 79 men and women diagnosed with moderate osteoarthritis, supplementation of *S. baicalensis* blend suppressed CRP along with other inflammatory markers IL-1 $\beta$  and -IL-6, TNF- $\alpha$ , and hyaluronic acid (79). In mice, it also suppressed cigarette smoke extract and LPS-induced production of TNF- $\alpha$ , IL-17A, macrophage inflammatory protein 2 (MIP2), and chemokine (C-X-C motif) ligand 1 (CXCL-1) in lung tissue. These studies indicate that *S. baicalensis* has inflammatory properties that facilitate its cardioprotective activities.

## 5. POTENTIAL MECHANISMS OF ACTIVE COMPONENTS WITH CARDIOVASCULAR EFFECT

The extracts of different parts of this Lamiaceae plant family contain varieties of bioactive compounds with cardioprotective and therapeutic properties. Some of these include Leonurine, Rosmarinic acid, Quercetin, Apigenin, Carvacrol, Thymoquinone, Baicalein, and many others (Table 1, Figure 1). These compounds exhibit cardioprotective

effects through regulation of multiple molecules including transcription factors, growth factors, inflammatory molecules, enzymes, kinases, apoptotic, survival, and other molecules (Figure 2.). How bioactive phytochemicals exert cardioprotection by regulating these molecules will be discussed.

Leonurine, a natural active compound of *Leonurus cardiaca*, has been shown to possess various biological activities, including against CVDs. Leonurine has shown to attenuate myocardium injury through its antioxidative and anti-apoptotic properties and acts as an adjuvant cardioprotective agent. This compound also suppresses apoptotic protein Bax and increases anti-apoptotic gene Bcl-2 to prevent acute myocardial ischemia (80; 81). Apigenin (found in *Apium graveolens* and *L. cardiaca*) has shown similar mechanisms in cardioprotection. It reduces apoptosis of cardiomyocytes by reducing caspase-3 activity, Bax protein expression, and increasing Bcl-2 protein expression. Apigenin also inhibits the phosphorylation of p38 MAPKS during myocardial I/R (82; 83). In H9c2 cardiac myocytes, leonurine increases Akt phosphorylation, expression of hypoxia inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), survivin, and VEGF (80), which leads to suppression of cardiac cell death. It has been also reported that leonurine also alleviates collagen deposition and myocardial infarction size, inhibits cell apoptosis, and improves myocardial function. These effects of Leonurine were shown to be mediated by increased levels of phosphorylated (p)-PI3K, p-AKT, p-GSK3 $\beta$  and Bcl-2, as well as, decreased levels of caspase3, cleaved-caspase3 and Bax. Thus, Leonurine exerts potent cardioprotective effects by inducing anti-apoptotic effects by activating the PI3K/AKT/GSK3 $\beta$  signaling pathway (84).

Rosmarinic acid displays potent cardioprotective effects due to its ability to increase antioxidant enzymes and gene expression of sarcoplasmic reticulum Ca<sup>2+</sup> ATPase 2 (SERCA<sub>2</sub>) and ryanodine receptor-2 (RyR<sub>2</sub>), which are involved in Ca<sup>2+</sup> homeostasis (85). A recent study showed that Rosmarinic acid protects against cardiac fibrosis by activation of AMPK $\alpha$ , inhibition of phosphorylation, and nuclear translocation of Smad3. This compound also induces peroxisome proliferator-activated receptors (PPAR- $\gamma$ ) to

attenuate cardiac fibrosis (86). Cardioprotection by Apigenin is also mediated by induction of PPAR- $\gamma$  as its antagonist reversed the myocardial protection conferred by Apigenin (87). Further study showed that apigenin promoted PI3K/Akt/mTOR pathway and prevented adriamycin-induced cardiotoxicity in the mice (88). Quercetin, which is the component of several plants of *Lamiaceae* family, has potent cardioprotective efficacy *in vitro* and *in vivo*. It downregulates inflammatory molecules NF- $\kappa$ B, AP-1, and MMP-9 (89). Quercetin also inhibits MAPK, JNK, and focal adhesion kinase activities induced by thrombin in endothelial cells, and thus exhibits cardioprotective effects (90). It has also shown to act as cardioprotective agent by inducing antioxidant enzymes GSH, improving ATP, as well as reducing the elevated plasma creatine kinase, cardiac TBARS, and NO(x) contents (91 - 92).

Carvacrol, a natural bioactive compound, possess cardioprotective activities through multiple mechanisms. It has been shown to suppress myocardial ischemic damage in a rat model of acute myocardial infarction by diminishing the infarct size and myocardial enzymes including creatine kinase, lactate dehydrogenase, and cardiac troponin T. Carvacrol also reduced malondialdehyde and elevated activities of the antioxidant enzymes superoxide dismutase, glutathione, and glutathione peroxidase. Besides these, carvacrol was also shown to inhibit caspase-3 activation and Bax expression but upregulated Bcl-2 protein expression (93). Another study showed that Carvacrol upregulated phosphorylated ERK and exhibited anti-apoptotic mechanisms against myocardial I/R injury in rats. Carvacrol also increased the activation of Akt/eNOS pathway in cardiomyocytes leading to cardioprotection (82). Thus, the cardioprotective effects of carvacrol, linked to its antioxidant and antiapoptotic activities, is mediated through MAPK/ERK and Akt/eNOS signaling pathways.

Thymoquinone, the active constituent of *Thymus* species of plants, has been reported to have potential protective effects on the cardiovascular system. In a recent experiment, Thymoquinone has shown to improve cardiac function and reduce infarct size. The mechanism of the cardioprotective effect of Thymoquinone was mediated by a decrease in

cardiac lactate dehydrogenase and creatine kinase levels, as well as suppression of apoptosis in myocardial I/R injury in rats (94). It has also been shown that it elevates superoxide dismutase activity and reduces production of hydrogen peroxide and malonaldehyde, thus exhibiting an antioxidative effect. In addition, Thymoquinone up-regulated expression of SIRT1 and inhibited p53 acetylation to protect from cardiac injury (86). Baicalein, an active component from *Scutellaria baicalensis* and *S. lateriflora* plants as well as other Lamiaceae family plants, exhibits cardioprotective effects via multiple molecular mechanisms. Besides its anti-inflammatory effect, it also acts as an antioxidant. It was shown to decrease MDA level and increase SOD and GSH-Px activity, as well as inhibit activation of the MAPK and NF- $\kappa$ B pathways in rats (95 - 96). This compound also exhibited the ability to protect cardiomyocytes against oxidative stress-induced cell injury through the Nrf2/Keap1 pathway (97). Besides these, baicalein downregulates phosphorylation of Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CaMKII) and expression of Na<sup>+</sup>/Ca<sup>2+</sup>-exchangers (NCX1) and upregulates SERCA2 and RYR2 (98). There are several other bioactive compounds from the Lamiaceae family of plants that have cardioprotective activities. We attempted to summarize all of the cardioprotective activities of the bioactive compounds from the Lamiaceae family of plants with their mechanisms; however there are still several other components that are not covered that have similar cardioprotective properties.

## **6. CARDIOPROTECTIVE PROPERTIES OF LAMIACEAE FAMILY AND FOOD**

Aromatic plants appear “fashionable,” since their use is able to positively affect health by reducing the amount of salt in the diet, or by presenting benefits related with their antioxidant properties (99). In fact, in addition to being recognized as a source of proteins, fibers, vitamins, and minerals, they can be considered suppliers of phytochemicals, which take action as antioxidants, antimicrobials, and/or antivirals, for example (100). Generally, the phytochemical function in the plants is to satisfy several biological activities such as seed dispersal and pollination, to serve a structural role, and act in the defense strategies of plant stress conditions such

as wounding, infection, and so on (101). Some authors have also underlined their role as phytoalexins or antifeedants (102). Epidemiological studies have demonstrated that among phytochemicals, natural phenolic antioxidants such as antimicrobial, antiviral, antioxidant, anticancer, anti-inflammatory, and antiulcer factors act in preventing cardiovascular diseases. They further demonstrated that their regular intake is associated with a reduced incidence of coronary heart disease (103). It is well established that oxidative stress influences the pathogenesis of heart diseases, such as hypertension, atrial fibrillation, and atherosclerosis (104). In this perspective, phenolic action is related to reactive oxygen species by acting as reducing agents, hydrogen donors, and singlet oxygen quenchers (105).

Due to the importance of phenolic compounds in disease prevention, they were a topic of several reviews (102, 106-111). Plant phenolics include phenolic acids, flavonoids, tannins, and the less common stilbenes and lignans. Flavonoids are the most abundant polyphenols in our diets ((106). Phenolics have been considered powerful antioxidants *in vitro* and proved to be more potent than Vitamin C, Vitamin E, and carotenoids. The inverse relationship between fruit and vegetable intake and the risk of oxidative stress associated diseases such as CVDs, cancer, and osteoporosis has been partially ascribed to phenolics. Polyphenols display antioxidant effects (112 - 113), as well as immunomodulatory and vasodilatory properties that may account for their effects on cardiovascular risk reduction. Indeed, dietary intakes of flavanones, anthocyanidins, and other foods rich in flavonoids were associated with reduced risk of death due to coronary heart disease and cardiovascular disease (113).

In addition, various essential oils, rich in carvacrol and a monoterpenic phenol isomeric with thymol, are recognized to be active against CVDs (114). Since these are the most representative part of EOs deriving from medical and aromatic plants, several pharmacological studies have focused on efforts to investigate the effects of this group of substances on the cardiovascular system (115). Several studies have demonstrated effects on rats.

For example, in Carvacrol, approximately 65% of its composition is made up of a phenolic monoterpene cyclic isomer of the monoterpene (present in the EO of oregano), which has been reported to reduce blood pressure and heart rate, inhibit hypertension induced by L-NAME, and induce vasorelaxation (116-117). Citronellol, a monoterpene found in some plants, is used in combination with antihypertensive agents, and was found to produce hypotension and was shown to act as a vasorelaxant molecule. Limonene, one of the most common terpenes in nature and a major constituent of several citrus oils (orange, lemon, mandarin, lime, and grapefruit), is reported to contribute to the reduction and prevention of cardiovascular injuries caused by pulmonary hypertension. Furthermore, (+)-linalool and (-)-linalool can act as both a cardiovascular system stimulant and depressant (118-119). Also, thymol is reported to have a vasorelaxation effect (114).

Most of the aromatic plants belonging to the Lamiaceae family have different biological activities, which are mainly related to both the phenolic and the volatile constituents (121-123). For example, the activity of rosemary is largely due to Carnosol, Carnosic acid, and Rosmarinic acid present in the extract of rosemary; however,  $\alpha$ -Pinene, (-)-Bornyl acetate, Camphor, and Eucalyptol present in the EO of this plant also contribute to its activity (120-122). Also, minor components can have a potential influence on the biological activity due to the possibility of synergistic effect among their components (123). This aromatic plant can be added directly to the food or incorporated into the food packaging, performing as antimicrobial and antioxidant agent. In addition, rosemary EO and extract has been classified as generally recognized as safe for their intended use, within the meaning of section 409 of the Act Food and Drugs Administration (125 - 126) and according to the Commission Directive 2010/67/EU and Commission Directive 2010/69/EU, respectively. According to the folk medicine, the uses of rosemary have been described in two monographs, one for rosemary leaf (*Rosmarini folium*) and other for rosemary oil (*Rosmarini aetheroleum*) (126, 99). Since aromatic plants, their extracts, and their EOs are gifted of such health promoting features, their 'wise' use in



food formulation could be considered as dietary strategies for disease prevention, with a particular focus on cardiovascular diseases. In fact, “nutritional therapy”, using functional foods and nutraceuticals as therapeutics, is based on the assumption that food is not only a source of nutrients and energy, but can also provide health benefits. In this view, plant-based food and beverages, consumed as part of a normal diet, can offer additional health benefits beyond basic nutritional functions (127). In general, the exploitation of phenolics or EOs extracted from aromatic plants is important in food against product oxidation, color and odor stabilization, and astringency. Also, EFSA (European Food Safety Agency) has recognized most of them for use as food additives, such as flavorings or antioxidants, but claims regarding health-promoting effects for cardiovascular disease are recognized (100). On the other hand, awareness about the health benefits of nutraceuticals and plant-derived bioactive molecules for reducing the risk and incidence of CVDs is increasing among men and women. Consequently, the demand of herbal preparations rich in antioxidants and anti-inflammatory products is trending (128). Moreover, the demand for medicinal herbal products, nutraceuticals, functional foods, probiotics, and alternative therapies have increased during the past few decades (129) for the replacement of synthetic medicines for treating hypertension, hypercholesterolemia, CVD). However, Hippocrates himself, regarded as the father of medicine (ca.460-370 B.C.), advocated the healing effects of foods. He said: “Leave your drugs in the chemist’s pot if you can heal the patient with food”. On the other hand, Labiatae are included in the Mediterranean diet recognized in the prevention of cardiovascular diseases, including reduced mortality rate and lower weight gain (130). Thus, a holistic approach is needed for the prevention of CVDs, diabetes, and cancer. Furthermore, re-thinking food formulation (131) and food processes, and the ability to preserve the biological functions of raw ingredients, is necessary. Recently, some researchers have pointed out the necessity towards biomimetics defined as “science which takes inspirations from nature to solve problems”. In this contest,

biomimetic plant foods (BPFs) can offer solutions for the future with the design of nature-inspired food structures for improved health and well-being (132). In the case of tailor-made foods, designed for preventing CVDs, is very important that the bioactive compounds remain stable during product processing and shelf-life. For this, in the last decade, the use of new, emerging technologies such as high-pressure homogenization, pulsed electric fields, gas-plasma, and other non-thermal technologies were proposed to overcome the nutritional content loss due to the use of severe thermal treatments (132-134).

## **7. POTENTIAL USE OF LAMIACEAE PRODUCT IN THERAPY**

The World Health Organization (WHO) suggests that plants belonging to *Lamiaceae* family, (134) characterized by a long history of use and having therapeutic effects, should also be evaluated for new activities and properties that could be useful in treatment and prevention of different diseases (134). Plants from this family are well known for their antibacterial, antifungal, antioxidant, anticancer (135), and antiviral properties (134). Their exploitation in therapy may be due to the presence of a wide range of bioactive compounds, such as antioxidants and especially, polyphenols (27). According to Bekut *et al.*, (134), the antiviral effects of *Lamiaceae* plants have mainly been shown *in vitro*; however, some effects also have been observed in some trials in healthy volunteers, or inpatients. The EOs, extracts, or other parts of *Lamiaceae* plants have been tested also against CVDs such as hypertension, which is one of the major health concerns in various parts of the world. Arterial hypertension is a chronic medical condition in which the pressure in the arteries exceeds 140/90 mmHg. The incidences of uncontrolled hypertension occur mainly among individuals above 50 years of age (136). High blood pressure can also be affected indirectly by other conditions such as insulin resistance, obesity, kidney failure, nervous system, concomitance, and atherosclerosis (138; 139). Hypertension is estimated to cause 4.5% of the disease burden globally (140 - 141). Generally, biofeedback, relaxation, weight reduction,



exercise, drug treatment, smoking cessation, and dietary modifications, (e.g., reduced salt intake and avoidance of excessive alcohol use) are the non-pharmacological methods used, for mid-hypertension (141 - 142). However, alternative herbal medicines are often preferred over modern medicines. A study showed that 25% of modern drugs and 75% of new medicines against virulent diseases are obtained from natural plant resources (143). According to the WHO, about 80% of people rely on traditional medicines (144). A recent study performed by Yang *et al.*, (145) investigated the therapeutic efficacy of *Salvia przewalskii* total phenolic acid extract (SPE) on immune complex glomerulonephritis (ICG) in rats, concluding that SPE could reduce whole blood viscosity and increase the urine excretion of water. Moreover, they demonstrated that SPE could reduce proteinuria, regulate protein and lipid metabolisms, attenuate renal inflammatory cell infiltration, and delay the progression of glomerular lesions in a rat ICG model, providing evidence that SPE has the potential to become a therapeutic drug for glomerulonephritis.

Also, *Rosmarinus officinalis*, a rich source of phenolic phytochemicals exhibiting significant antioxidant, anti-inflammatory, hypoglycemic, hypolipidemic, hypotensive, anti-atherosclerotic, anti-thrombotic, hepatoprotective, and hypocholesterolemic effects, was proposed, due to the interesting pharmacological effects, in the management of metabolic syndrome, defined by a constellation of complex coexisting cardiometabolic risk factors (146).

A study performed by Mihailovic-Stanojevic *et al.* (147) evaluated total phenol and flavonoid contents, antioxidant capacity, free radical scavenging activity, and potential antihypertensive effects of aqueous extract obtained from *Thymus serpyllum* (wild thyme, TE, highly present in Mediterranean diet), in spontaneously hypertensive rats (SHR) and in normotensive Wistar rats. The TE extract, having total phenol content of  $2008.33 \pm 10.6$  mg/L GAE, rosmarinic, and caffeic acids as predominant phenolic compounds, was able to protect against hypertension in experimental model.

A recent study gave an overview about traditional medicinal knowledge of plants as antihypertensive drugs (148). One hundred eighty-two medicinal plant species, belonging to 77 families, were reported to treat hypertension. It was first attempted to document ethno-botanical information using quantitative approaches on hypertension in the study area. The leaves were reported to be the most used plant part (55.1%) while herbs were the most used form (54%). Decoction was reported to be the most common mode of administration (72 reports). The quantitative approaches, such as Family Importance Value (FIV), Relative Frequency of Citation (RFC), and Disease Consensus index (DCI) were used to assess the importance of traditional knowledge obtained in the study. Highest DCI and FIV values were reported for Rutaceae and Lamiaceae. Meanwhile, there are so many of these naturally occurring plant substances covering a wide range that offer a good opportunity of delivering useful medicinal complexes for the management of hypertension. According to this study, *Ficus palmata*, *Senna tora*, *Teucrium polium*, *Valeriana officinalis*, and *Ziziphus mauritiana* were recorded for the first time as anti-hypertensive medicinal drugs. The study performed by Malik *et al.*, (148), provides basic leads for future pharmacological and phytochemical investigation to explore the potential of such plants in herbal drug discovery. Of course, it is thus recommended that strategies for cultivation and conservation of important species be designed. However, some researchers have pointed out the need to build a database platform to discuss the risks and benefits of herbal medicine use with the aim of enhancing their patients' health outcome (149). In fact, according to a study performed in Sierra Leone by James *et al.*, (149), garlic and lemon grass are the most common herbal medicines used among users against hypertension and cardiovascular disease. However, their use, not dependent to the patient's socio-demographic and health factors, is still related to popular traditions. In this perspective, a recent study tried to predict several plant utilities for cardiovascular disease relating the plant phylogeny and its potential as sources of new cardiovascular drugs. In particular, analyzing 139 plant species in 71 plant families, they found 7 plant families (Apiaceae, Brassicaceae, Fabaceae, Lamiaceae, Malvaceae, Rosaceae, and Zingiberaceae) with 45 species which

emerged as phylogenetically important exhibiting common cardiovascular mechanisms of action within the family. Particularly, Lamiaceae (*Lavandula stoechas*, *Mentha suaveolens*, *Rosmarinus officinalis*, *Scutellaria baicalensis*, *Salvia miltiorrhiza*) had anticoagulant/thrombolytic effects and they were found to possess anti-atherosclerotic properties.

In other studies, Ferreira *et al.* (151), reported cases on *Salvia hispanica*, commonly known as Chia and belonging to the Lamiaceae family, outlined the need for randomized, double-blind, placebo-controlled clinical trials in order to obtain reliable results to compare with traditional medicine.

According to the recent literature, complementary medicine is higher in women than in men (152). Although a majority of herbal medicines have been traditionally considered beneficial, their use deserves more attention, not only for the increasing trend of their use and the imposed expense on patients, but also for their potential harmful and unknown effects. Some risks, such as herbal medicines interference with other drugs and their incongruity with physiologic status, require physicians to ask their patients about consuming these products, and they should also increase their knowledge of herbal medicines. So, the literature reports emphasize on the necessity of implementing effective training programs to improve knowledge of health providers regarding the consumption, adverse effects, and drug interferences of common herbal medicines and also consider the history of taking herbal medicines at the time of patient visits. In fact, although the plants generally have many potential beneficial effects, they also have potential to cause interactions with antiretroviral and other drugs, resulting in a drastic increase or decrease of drug concentrations.

## 8. CONCLUSION

Therapeutic effects of Lamiaceae on prevention and regulation of blood pressure and heart failure through antioxidant, anti-inflammatory, hypotensive, anti-atherosclerosis, heart rate-regulating, and vasodilating properties

are known in ethnomedicine and nowadays in conventional medicine as well. With increasing interest in herbs as anti-inflammatory agents in the management of chronic inflammation connected to CVDs, research is emerging on the use herbs in foods. Therefore, the use of Lamiaceae as modulators of physiological responses and biological pathways should be extensively studied both *in vitro* studies and in animal trials. Moreover, additional studies regarding the improvement of the delivery of proven active compounds need to be performed. The study of Lamiaceae natural compounds can be a source of inspiration for developing novel or enhanced molecules acting against CVDs. Wide compound diversity present in Lamiaceae species are precious natural resources for inexpensive and safe approaches for cardioprotection. However, synergistic effects of herbs and interaction with commercial drugs need to be thoroughly investigated for future pharmaceutical development of herbal drugs. In addition, it is important to highlight that legal surveillance of herbal-drug interactions should be instituted at a global level.

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**Abbreviations:** CVDs-Cardiovascular diseases; EOs-essential oils; DOX -doxorubicin; CRP-C-reactive protein; PAF-platelet-activating factor; TNF- $\alpha$ -tumor necrosis factor-alpha; ROS - reactive oxygen species; MIP2 -macrophage inflammatory protein 2; ICG-complex glomerulonephritis; DCI-Disease Consensus index

**Key Words:** Cardiovascular Diseases, Lamiaceae Family, Active Compounds, Mechanisms, Review

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