A Review on the Potential Use of Medicinal Plants From Asteraceae and Lamiaceae Plant Family in Cardiovascular Diseases

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Cardiovascular diseases are one of the most prevalent diseases worldwide, and its rate of mortality is rising annually. In accordance with the current condition, studies on medicinal plants upon their activity on cardiovascular diseases are often being encouraged to be used in cardiovascular disease management, due to the availability of medicinal values in certain dedicated plants. This review was conducted based on two plant families, which are Asteraceae and Lamiaceae, to study on their action in cardiovascular disease relieving activities, to review the relationship between the phytochemistry of Asteraceae and Lamiaceae families and their effect on cardiovascular diseases, and to study their toxicology. The medicinal plants from these plant family groups are collected based on their effects on the mechanisms that affect the cardiovascular-related disease which are antioxidant activity, anti-hyperlipidemia, vasorelaxant, antithrombotic, and diuretic effect. In reference to various studies, the journals that conducted in vivo or in vitro experiments, which were used to prove the specific mechanisms, are included in this review. This is to ensure that the scientific value and the phytochemicals of the involved plants can be seen based on their activity. As a result, various plant species from both Asteraceae and Lamiaceae plant family have been identified and collected based on their study that has proven their effectiveness and uses in cardiovascular diseases. Most of the plants have an antioxidant effect, followed by anti-hyperlipidemia, vasorelaxant, antithrombotic, and diuretic effect from the most available to least available studies, respectively. These are the mechanisms that contribute to various cardiovascular diseases, such as heart attack, stroke, coronary heart disease, and hypertension. Further studies can be conducted on these plant species by identifying their ability and capability to be developed into a new drug or to be used as a medicinal plant in treating various cardiovascular diseases.

Keywords: cardiovascular diseases, coronary heart disease, stroke, Asteraceae, Lamiaceae, hypertension, heart failure, medicinal plants
INTRODUCTION

Cardiovascular diseases (CVD) are known as the most frequent and common cause of death worldwide. World Health Organization (WHO) reported that the total number of people who died from CVDs in 2012 was estimated to be around 17.5 million people representing 31% worldwide population. Disorders of heart and blood vessels, including coronary heart disease (CHD), cerebrovascular disease (stroke), increase in blood pressure (hypertension) and myocardial infarction are the precursor that causes CVD (Rastogi et al., 2016). CVD diseases involve the cardiovascular system that comprises of heart and veins. They are the main source of death universally, and its incidence is rising rapidly globally (Gaziano et al., 2010).

CVD diseases that often being suffered by people are heart failure, coronary heart disease (CHD), stroke, myocardial infarction, and hypertension. CHD and stroke, which responsible for 80% of CVD patients’ death, are caused by the lack of oxygen to the brain and heart. The accumulation of fatty deposits within the blood vessel causes the blocking of cerebral and coronary arteries hence narrows their pathway size (Roth et al., 2017). CHD contributes to almost 75% of worldwide death, which occurs both in low- and middle-income countries, due to few factors such as their socio-economy variations and risk factors, due to lifestyle modification (Gaziano et al., 2010).

Heart failure is caused by any functional or structural damage to ventricular filling or in the blood ejection (Klein et al., 2003). It is known as a leading cause of mortality in the western globe and tends to develop when cardiac injury or cardiac insult impairs the heart’s ability to maintain and pump tissue perfusion (Lymperopoulos et al., 2013). Hypertension, which is also known as a common CVD, is a crucial concern in health in diverse parts of the world. When the arterial pressure rises above 140/90 mm Hg, it is known as arterial hypertension (Malik et al., 2018).

Stroke is a heterogeneous disease, which includes the hemorrhage of cerebral and the pathogenic subtypes of ischemic stroke (Sacco et al., 2013). In the contribution of the major cause of death, stroke is one of the lead diseases. Among the stroke cases, 85% of them are ischemic stroke, and the other 15% is the hemorrhage stroke, which is also known as an intracerebral stroke (Woodruff et al., 2011). A clinical study shows that warfarin is being effective in preventing ischemic stroke in patients that are suffering from atrial fibrillation, which has reduced the risk of intracranial hemorrhage (Go et al., 2003). Hemorrhage is the rupture of the blood vessel that causes the blood to escape from its blood vessel. One of the main causes of stroke is due to blood coagulation. When the clotting blood accumulates in the blood vessel, the blood refuses to flow to the brain, and the brain tends to be lack of oxygen that leads to ischemic stroke. In this condition, an anticoagulant will avoid the blood from clotting and allow the ease of blood flow throughout the body and brain from the heart. Based on these regards, plants with anticoagulant activity will help treat cardiovascular diseases of these mechanisms.

Throughout human history, medicinal plants have always been used as medicine to treat various diseases. Almost 80% who live in developed countries are said to be depended on the practice of traditional medicine (Abdala et al., 2012). A report from the World Health Organization (WHO) comes out with a percentage of 80% of the global population tend to rely on traditional medicines. Most of the therapies use extracts and active compounds of the medicinal plant (Craig, 1999). Currently, there is a rise in medicinal plant consumption in the world, due to the proven effectiveness of medicinal plants, in curing certain diseases and claims that shows it is safe to be used (Perez Gutierrez and Baez, 2009). Medicinal plants play a major role in medication since the beginning of human civilization and also contribute to the manufacturing of drugs these days (Rastogi et al., 2016).

Asteraceae plant family is also used to be known as the Compositae plant family, is known as one of the largest plant families with thousands of plant species. Its large production as angiosperm phylogeny is in Asterideae. The Asteraceae plant family consists of 24,000 accepted species. It also has about 1,600 to 1,700 of its genera is distributed around the world, excluding Antarctica. This family is also known as a cosmopolitan family, as it has a great concentration of species in different areas such as temperate, cold-temperate, and subtropical. Asteraceae consists of three subfamilies; Asteroideae, Barnadesioideae, and Cichorioideae (Medeiros-Neves et al., 2018). The Lamiaceae plant family is also called a Labiatae family, which is often uttered as the mint family, and the plant family of flowering plants. They consist of shrubs or herbs which produce and release the aromatic smell, which consists of more than 3,000 species in the Lamiaceae plant family. The largest genera of Lamiaceae plant family are Salvia, Scutellaria, and Stachys (Cantino et al., 1992).

Plant species in Asteraceae and Lamiaceae family are being used to cured various diseases. Satureja species exhibits analgesic, antimicrobial, antiviral, antioxidant, antiproliferative, anti-inflammatory, and vasodilatory activities (Momtaz and Abdollahi, 2008). Meanwhile, Crassocephalum crepidioides (Benth.) S. Moore were used to cure epilepsy, indigestion, hepatotoxicity, swollen lips, tumor, and sleeping sickness (Bahr et al., 2016). Despite their variation in botanical features and traditional values, both Asteraceae and Lamiaceae plant family species exhibits mechanisms of improving cardiovascular disease. The seeds of Gundelia tournefortii L. (Asteraceae) are often used as pickles, and it is an effective diuretic (Çoruh et al., 2007). Achillea millefolium L., which is a plant species from the Asteraceae plant family, also exhibited diuretics effect in a hypertension group (De Souza et al., 2013). It is often found in Brazil and used as the Brazilian folk medicine, usually for kidney and heart diseases. Emilia praeternissa Milne-Redh. reduced hyperlipidemic conditions as an anticoagulant agent through a clinical study (Memariani et al., 2018). Salvia miltiorrhiza Bunge exerts the potential vasodilator effect on the cardiovascular system (Li et al., 1990). S. miltiorrhiza lowered whole blood viscosity, improved the peripheral circulation, and fastened erythropoiesis of erythrocytes (Lei et Chiou, 1986).

Medicinal plants are currently being used in developing a new hypertension drug, and one of them is Marrubium vulgare L.
from Lamiaceae plant family. The crude oil of the plant was examined its hypotensive effect, and due to the presence of diterpenoids in the plant, it has potential cardiovascular activity, which was caused due to relaxation of vessels and reduces systolic blood pressure which are the mechanisms involved in hypertension (Bardai et al., 2001). The second example is Cynara cardunculus L. (syn. Cynara scolymus L.) from the Asteraceae plant family, which is also known as an artichoke. It is one of the oldest medicinal drugs for its cardiovascular effects. It exhibits a lipid-lowering effect and inhibits the biosynthesis of cholesterol (Fintelmaan, 1996). These drugs prove that medicinal plants can be developed into drugs or for as a treatment for therapeutic purposes. New drugs from the available medicinal plant can treat the disease more efficiently, as a safer and more efficient drug can be discovered in the future, which may benefit the patient (Bardai et al., 2001). Based on the traditional uses and the developed drug, it showed that the plant families have a high potential in alleviating cardiovascular diseases. Thus, an in-depth compilation of the activity and mechanism of the plant family on cardiovascular diseases needs to be examined.

A review on phytochemistry and pharmacological of medicinal plants related to cardiovascular diseases specifically on Asteraceae and Lamiaceae family were conducted by using searching engines such as Google Scholar, Scopus, ScienceDirect, ProQuest, Karger, and Molecule. The literature taken range from the year 1979 to 2018 and was evaluated and tabulated in this review. The keywords used during searching includes “cardiovascular diseases,” “coronary heart disease,” “stroke,” “myocardial infarction,” “hypertension,” “heart failure,” “antioxidant,” “anti-hyperlipidemia,” “antithrombotic,” “medicinal plants,” “plants,” “herbs,” “in vivo,” “in vitro” alone and in different combinations. This review specifically focuses on the identification and collection of the information on medicinal plants from the Asteraceae and Lamiaceae family, with proven in vivo or in vitro studies upon cardiovascular diseases. Tables 1 and 2 show the plant species from Asteraceae and Lamiaceae family with their medicinal uses. Tables 3 and 4 are on the mechanisms of the Asteraceae and Lamiaceae family plant species that are involved in cardiovascular diseases. Meanwhile, Figure 1 is composed of chemical compounds derived from the two species that have potential as the lead drug in cardiovascular diseases.

**INHIBITORY ACTIVITY ON CARDIOVASCULAR DISEASES**

**Antioxidant Activity**

The chemical substances that reduce or prevent oxidation are known as antioxidants. Antioxidants can resist the free radicals from causing damaging effects in tissues. They are often used to safeguard cerebrovascular diseases (Bandyopadhyay et al., 2007). The oxidative stress that occurs at the cellular level acts as the prime pathogenic factor for cardiovascular diseases. It occurs due to the free radical’s toxic being released by the vascular smooth muscle cells and endothelial cells (Fearon and Faux, 2009). Apart from that, cardiovascular diseases are caused by oxidative stress by reactive oxygen species (ROS) such as uncoupled nitric oxide synthases, xanthine oxidase, and NADPH oxidases (Taleb et al., 2018). ROS voluntarily attack and cause oxidative damage to various biomolecules such as lipoproteins, lipids, protein, and DNA.

This oxidative harm is an essential etiological figure that ensnared a few endless human sicknesses. Examples are cardiovascular illnesses, rheumatism, diabetes mellitus, cerebrovascular infections, and malignant growth. The damage of DNA and oxidative stress may be caused by oxidized low-density lipoproteins (oxLDL) or by hypercholesterolemia due to individual diet lifestyle (Ceaser et al., 2003). One of the lead causes of atherosclerosis is oxygen-free radicals that reduce the cells’ capacity to inhibit the oxidation. This can leads to fatal inflammation disorder.

Most of the plants from the Asteraceae and Lamiaceae plant family were proven to possess the antioxidant effect via in vitro assay such as 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay. The plants from the Asteraceae family that shows antioxidant effect based on this study are Achillea tenuifolia Lam. (syn. Achillea santolina L.), Anthemis melampodina subsp. deserti (Boiss.) Eig (syn. Anthemis deserti Boiss), Artemisia absinthium L., Baccharis trimera (Less.) DC, C. crepidioides (Benth.) S. Moore, Helichrysum leucocephalum Ausfeld, Lagerra decurrens (Vahl) Hepper and J. R. I. Wood, Senecio ovatus subsp. stabianus (Lacaia) Greuter (syn. Senecio stabianus Lacaia), and Silybum marianum (L.) Gaertn. The plants from Lamiaceae that show antioxidant activities are Ajuga ivia (L.) Schreb., Ballota glandulosissima Hub.-Mor. and Patzak, Dracopetalum moldavica L., H. leucocephalum Ausfeld, Lavandula angustifolia Mill., Lavandula stoechas L., Micromeria macrocephalum Coss. (syn. Satureja macrocephalum (Coss.) Maire), Origanum vulgare L., Plecnranthus monostachyus (P. Beauv.) B. J. Pollard (syn. Solenostemon monostachyus (P. Beauv.) Briq), and Salvia officinalis L. These plants had shown the antioxidant effect, with its scientific value. Based on the studies, antioxidant properties were mostly exhibited by phenolic compounds due to their tendency to scavenge the free-radicals. The phenolic compounds act by chelating the metal ions, improving the endogenous antioxidant system, and avoiding the formation of free radicals. Due to this, studies on the search for natural antioxidants from plant origin have become more intense in recent years (Seyoum et al., 2006). Other chemical compounds in these plants that mainly contribute to its antioxidant activity are flavonoids, flavanols, and diterpenes. Achillea tenuifolia Lam. is known for its free radical scavenging activity. The ferric thiocyanate test was conducted to determine the antioxidant activity of A. tenuifolia extract (ATE) by measuring peroxide concentration during the early stage of lipid peroxidation (Ardestani and Yazdanparast, 2007). ATE concentration of 200 and 400 µg/mL suppress the lipid peroxidation by the extension on the lag phase and the reduction of the propagation rate, which reflects the typical chain-breaking...
| Plant Name | Country/Region | Common Name | Medicinal Uses | Part/s Used | Mode of Usage/Preparation | References |
|------------|----------------|-------------|----------------|-------------|--------------------------|------------|
| Achillea arabica Kotschy (syn. Achillea biebersteinii Hub.-Mor.) | Mediterranean | Qaysoum | Hypolipidemic | Aerial parts | – | (Mais et al., 2016) |
| Achillea millefolium | Europe, North America, Australia, and Asia | Mil-folhas | Diuretic and hypotensive actions | Aerial parts (leaves, stalks, and stems) | Aqueous extract | (De Souza et al., 2013) |
| Achillea tenuifolia Lam. (syn. Achillea santolina L.) | Europe | Yarrow | Antioxidant | Aerial parts | – | (Ardestani and Yazdanparast, 2007) |
| Ageratum conyzoides (L.) L. | Brazil | Billygoat-weed | Hypolipidemic | Leaf, stem, and root | Whole plant | Aqueous extract | (Atawodi et al., 2017) |
| Anthemis melampodina subsp. deserti (Boiss.) Eig (syn. Anthemis deserti Boiss) | Saudi Arabia | – | Antioxidant | Whole plant | – | (Shahat et al., 2014) |
| Artemisia absinthium | Europe, North America, and Asia | Wormwood | Antioxidant | Aerial parts (leaves, stalks, and stems) | Methanolic extract | (Bora and Sharma, 2011) |
| Artemisia campestris L. | Eastern Morocco | – | Antihypertensive and vasorelaxant | Aerial parts | – | (Ob et al., 2017) |
| Baccharis trimera (Less.) DC | South America | Carqueja | Vasorelaxant | Whole plants | Infusions, decoctions, and tinctures of its aerial parts | (Sabir et al., 2017) |
| Bidens pilosa L. | South America | Spanish needles, beggar’s ticks, devil’s needles | Antihypertensive, vasodilation | Leaf | Dry powder, decoction, maceration or tincture | (Dimo et al., 2001) |
| Chamaemelum nobile (L.) All. | Roman chamomile | – | Hypotensive and diuretics | Whole plant | – | (Zeggzvgagh et al., 2009) |
| Chromolaena odorata (L.) R. M. King and H. Rob. | South and Central America, India | Ahhia eliza or Siam Weed | Anti-hyperlipidemic | Leaves | Fresh leaves or decoction | (Kewuchi and Ikwuchi, 2011) |
| Chrysanthemum x morifolium Ramat. Hemsli. | Japan | Chrysanthemum | Vasodilation | Flowers | Extract | (Gao et al., 2016) |
| Crossocephalum crepidioides (Benth.) S. Moore | Africa | Okinawa Spinach, Red flower | Antioxidant and anti-hyperlipidemic | Aerial Parts (leaves, stalks, and stems) | Maceration | (Bahar et al., 2016) |
| Cynara cardunculus L. (syn. Cynara scolymus L.) | Mediterranean | Global artichoke | Hypolipidemic | Leaf | Aqueous extract | (Mocelin et al., 2016) |
| Eclipta prostrata (L.) L. | India, Nepal, China, and Brazil | False daisy | Hypolipidemic | Leaves | Herb or plant juice taken orally | (Ohandiapani, 2007) |
| Emilia praetermissa Milne-Redh | Sierra Leone and Nigeria | Kpo or Koyajo or Coastal plain yellowtops | Lipid-lowering effect | Leaves | Orally consumed as fresh salads or cooked. Maceration for improving heart conditions. | (Ngozi et al., 2013) |
| Erigeron canadensis L. | North America and Central America | Coryza and canadensis | Antithrombotic | Flowering parts | Raw material | (Pawlaczyk et al., 2011) |
| Flaveria bidentis (L.) Kuntze | South America | Coastal plains | Anticoagulant | Leaves | – | (Guglielmone et al., 2002) |
| Gundelia tournefortii L. | South America | Kuba | Hypolipidemic | Seeds | Oil extract | (Sharaf and Ali, 2004) |
| Gymnanthemum amygdalinum (Delile) Sch. Bip. (syn. Vernonia amygdalina Delile) | Africa | Bitter leaf | Hypolipidemia and antioxidant | Leaf | Orally consumed | (Audu et al., 2012) |
| Helichrysum leucocephalum Ausfeld | Eurasia, Africa, and Australi | Curry plant or Italian strawflower | Antioxidant | Aerial parts (leaves, stalks, and stems) | Extract | (Goldansaz et al., 2018) |
| Inula racemosa Hook F. | India, Asian | Pushkarmod | Hypotensive, antihyperlipidemic and antioxidant | Roots | Administered orally for rheumatic pains | (Mangathayaru et al., 2009) |
| Lagerra decurrens (Vahl) Hepper and J. R. I. Wood. | Africa | Fwimba | Antioxidant | Aerial parts | Traditional herb | (Mothana et al., 2011) |

(Continued)
antioxidant characteristics. The activity was determined using a linoleic acid system. The peroxidation activity was measured using the thiocyanate method by using the absorbance at 500 nm to determine the peroxide values. The study showed that the ATE contained 55 mg ascorbic acid equivalents per gram of extract with the EC$_{50}$ value of 55 µg/mL (Ardestani and Yazdanparast, 2007). Besides, it consists of gallic acid (2) and catechin (2), this plant also contains phenols and flavonoids, which induce the antioxidant activity in nature (Khafagy et al., 2015).

The methanolic extract of $A. melampodina$ subsp. deserti (Bois.) Eig in the concentration of 25, 50, and 100 µg/mL showed more significant DPPH radical scavenging activity, compared to the positive controls, 1-ascorbic acid, and butylated hydroxytoluene, BHT (Shahat et al., 2014). The DPPH radical scavenging activity and chelating effect of the plant were concentration-dependent. The plant extract at the concentration of 400 µg/mL showed a 100% chelating effect. The activity was determined using a thiocyanate method by using the absorbance at 500 nm. As a whole, it causes inhibitory activity on oxidative stress induced by cerebral ischemia and reperfusion. GSH is known as a central component in the antioxidant and known as the defense cells. It acts by detoxifying ROS directly and as a substrate for various peroxides (Bora and Sharma, 2014). The plant extract consists of quercetin (3), rutin, and vanillic acids (4). It was reported that the plant manages to alleviate stroke disease by reducing SOD activity in the serum (Spranger et al., 1997). Its antioxidant activity has potential in the acute treatment of cerebral ischemia.

$ Artemisia absinthium$ L. methanolic (MAB) extract at the concentration from 25 to 100 µg/mL showed scavenging activity on superoxide anion radicals produced from the PMS-NADH system (Bora and Sharma, 2011). When the MAB was administered orally at doses of 100 or 200 mg/kg, it restored superoxide dismutase (SOD) and glutathione (GSH) levels and decreased the thiobarbituric acid reactive substances (TBARS) level. As a whole, it causes inhibitory activity on oxidative stress induced by cerebral ischemia and reperfusion. GSH is known as a central component in the antioxidant and known as the defense cells. It acts by detoxifying ROS directly and as a substrate for various peroxides (Bora and Sharma, 2014). The plant extract consists of quercetin (3), rutin, and vanillic acids (4). It was reported that the plant manages to alleviate stroke disease by reducing SOD activity in the serum (Spranger et al., 1997). Its antioxidant activity has potential in the acute treatment of cerebral ischemia.

$Ballota glandulosissima$ Hub. -Mor. and Patzak is a Turkish Ballota species, collected from Kumluca. The aerial parts of B. glandulosissima were extracted using ethanolic extract and were determined its antioxidant activity via in vitro (Citoglu et al., 2004). The extract showed remarkable anti-superoxide anion formation by inhibiting the activity with an IC$_{50}$ value of 0.51 mg/mL. In inhibiting lipid peroxidation, the extract exhibited a
| Plant Name                  | Country/Region       | Common Name          | Medicinal Uses                        | Part/s Used     | Mode of Usage/Preparation                  | References                                                                 |
|----------------------------|----------------------|----------------------|---------------------------------------|-----------------|-------------------------------------------|---------------------------------------------------------------------------|
| Agastache mexicana         | Mexico               | Mexican giant hyssop  | Vasorelaxant                           | Aerial parts    | –                                         | (Hernandez-Abreu et al., 2013)                                            |
| Ajuga integrifolia         | Ethiopia             | Armagusa             | Diuretics                             | Leaves          | Methanolic extract                        | (Hailu and Engidawork, 2014)                                              |
| Ajuga iva                  | Mediterranean        | Southern Bugle       | Antioxidant and hypolipidemic         | Whole plant     | Aqueous extract                           | (Taleb-Senouci et al., 2009)                                              |
| Ballota glandulosissima    | Turkey               | Horehound            | Antioxidant                           | Aerial parts    | External use or aerial parts used internally | (Citoglu et al. 2004)                                                     |
| Clerodendrum volubile      | Nigeria              | Marugbo              | Antioxidant and hypolipidemic         | Whole plant     | Leaf extract (dried and blended fresh leaves) | (Akinpelu et al., 2016)                                                  |
| Clinopodium vulgare        | Pakistan             | Wild basil           | Antihypertensive and vasodilation     | Aerial parts    | Crude extract and methanolic extract      | (Khan et al., 2018)                                                       |
| Dracocephalum moldavica    | Central Asia         | Moldavian dragonhead | Antioxidant and cardioprotective      | Aerial parts    | Oral consumption as food or tea           | (Jiang et al., 2014)                                                      |
| Isodon rugosus             | Pakistan             | Wall, ex Benth       | Vasorelaxant and antioxidant          | Aerial parts    | –                                         | (Janbaz et al., 2014)                                                     |
| Lagenaria siceraria        | African              | Long melon, New Guinea bean and Telangui | Cardioprotective, antihyperlipidemic, and diuretic activities | Fruit | Fruit powder | (Mali et al., 2012) |
| Lallemantia royleana       | Iran                 | Balangu              | Anticoagulant and antiplatelet        | Leaves          | Organic extract                           | (Monnobi et al., 2011)                                                   |
| Lavandula angustifolia     | Iran                 | Ostokhoddus          | Antioxidant                           | Aerial parts    | Essential oil                             | (Ziaee et al., 2015)                                                      |
| Lavandula stoechas         | Morocco              | French lavender      | Antioxidant                           | Aerial parts    | –                                         | (Ezzoubi et al., 2014)                                                    |
| Leonotis leonurus          | South Africa         | Lion’s tail/Wild dagga | Anticoagulant and antiplatelet       | Leaves          | Organic extract                           | (Monnobi et al., 2011)                                                   |
| Leonurus cardiaca          | Europe               | Matthiolius          | Antiarrhythmic                        | Aerial parts    | –                                         | (Ritter et al., 2010)                                                     |
| Lepechinia caulescens      | Mexico               | Island pitchergsage  | Antihypertensive and vasorelaxant     | Aerial parts    | Oral beverage or tea                      | (Escudero-Soto et al., 2012)                                              |
| Melissa officinalis        | India                | Thumbai              | Antihyperlipidemia                    | Leaf            | Ethanolic extract                         | (Kumar, 2016)                                                            |
| Micromeria macrocephaloides| Morocco              | Mare                 | Antioxidant                           | Aerial parts    | Extract                                   | (Amiri, 2011)                                                            |
| Origanum vulgare           | Europe, North Africa, America | Oregano | Antioxidant                           | Whole plants    | Traditional medicine                     | (Zhang et al., 2014)                                                      |
| Orthosiphon aristatus      | Asia                 | Kurmis kucing, Misai kusing | Antihypertensive and vasorelaxant | Leaves, whole plant | Water decoction, extract                  | (Matsubara et al., 1999)                                                  |
| Plectranthus barbatus      | India                | Plectranthus barbatus | Antihypertensive and vasodilation     | Whole plant     | Ethanolic extract                         | (Dubey et al., 1981)                                                     |
| Plectranthus hadiensis     | Pakistan             | Jerusalem sage       | Vasoilidation                          | Whole plant     | Methanolic extract                        | (Khan et al., 2012)                                                      |
| Plectranthus monostachyus   | Ivory Coast           | Coleus               | Antioxidant and antihypertensive      | Leaves          | Ethanolic extract                         | (Fidele et al., 2012)                                                    |
| Pogostemon elsholtzioides   | Eastern Himalaya     | Nakhrang shing       | Vasorelaxant and antiplatelet         | Leaves          | Leaf decoction                            | (Shiva Kumar et al., 2017)                                                |

(Continued)
TABLE 2 | Continued

| Plant Name                  | Country/ Region | Common Name                   | Medicinal Uses                                      | Part/s Used                        | Mode of Usage/ Preparation | References                          |
|-----------------------------|-----------------|--------------------------------|-----------------------------------------------------|------------------------------------|----------------------------|-------------------------------------|
| Prunella vulgaris L.        | –               | Self-heal                      | Antihyperlipidemic and antioxidant                  | Rhizome, stem                     | Aqueous extract              | (Zargar et al., 2017)               |
| Rosmarinus officinalis L.   | Mediterranean   | –                              | Anti-hypercholesterolemic                            | Leaves                            | Aqueous extract              | (Belmouchoub et al., 2017)          |
| Salvia miltiorrhiza Bunge   | China and Japan | Danshen                       | Antithrombotic                                       | Root                              | Oral consumption of dried root | (Fan et al., 2010)                  |
| Salvia officinalis L.       | Mediterranean   | Sage                           | Antioxidant                                          | Shoots                            | Raw material, essential oils or extract | (Santos-Gomes et al., 2002)          |
| Salvia scutellariaoides Kunth | Colombia    | Mastranto                      | Antihypertensive and diuretic effects                | Leaves, stem                      | Aqueous extract              | (Ramirez et al., 2006)              |
| Satureja cuneifolia Ten. (syn. Satureja obovata Lag.) | Lanjoran | Thin savory                    | Vasodilatation and vasorelaxant                      | Whole plant                       | Aqueous extract              | (De Rojas et al., 1999)             |
| Sideritis raeseri Boiss. and Heldr. | Mediterranean | Ironwort, mountain tea, and shepherd's tea | Hypotension and vasodilatation                      | Aerial parts                      | –                           | (Kitic et al., 2012)                |
| Teucrium polium Linn.       | South-western Asia and Europe | Felty germander | Hypolipidemic                                       | Aerial parts                      | Aqueous extract              | (Rassel et al., 2001)              |
| Thymus dreatensis Batt. (syn. Thymus atlanticus (Ball) Pau) | Morocco | Thyme, German thyme            | Antihyperlipidemic and anticoagulant                | Whole plant                       | Extract                     | (Ramchoun et al., 2012)             |
| Thymus saturejoides Coss.   | Morocco         | Thyme borneod                   | Antioxidant                                          | –                                 | –                           | (Khoyu et al., 2015)                |
| Thymus serpyllium Linn.     | Europe and North America | Breckland thyme                | Antithrombotic                                       | Whole plant                       | Culinary herb                | (Katalinic et al., 2006)            |
| Thymus zygis L.             | Morocco         | Thyme, sauce thyme             | Anticoagulant                                        | Whole plant                       | Extract                     | (Ocanas and Reglero, 2012; Khoyu et al., 2015) |
| Vitex megapotamica (Spreng.) Moldenke | South America | Forest olve                    | Antihyperlipidemic                                   | Leaves                            | Extract                     | (Pires et al., 2018)               |
| Zizipora clinopodioides Lam. | China           | Blue mint bush                  | Vasodilatation and antihypertensive                  | Whole plant                       | Decoction of whole plant     | (Senejoux et al., 2010)             |

strong inhibitory capacity and potent scavenging property (IC$_{50}$ 15 mg/mL) compared to α-tocopherol (IC$_{50}$ 3 mg/mL) (Citoglu et al., 2004).

The antioxidant activity of methanolic extract of aerial part of C. crepidioides (Benth.) S. Moore was determined by measuring its total phenol and flavonoid content, reducing capacity and radical scavenging activity on DPPH assay (Bahar et al., 2016). The plant consisted of various phytochemicals such as flavonoids, alkaloids, tannins, sapogenins, glycosides, and reducing sugar which, contributed to the extract’s antioxidant activity. The activity reported was lower (IC$_{50}$: 130.32 µg/mL) compared to ascorbic acid (IC$_{50}$ 11.24 µg/mL). The aerial part extract of the plant consists of gallic acid (1) and quercetin (3), which tends to cause the antioxidant effect (Bahar et al., 2016).

_Dracacephalum moldavica_ L. contains antioxidant compounds with cardioprotective effects (Jiang et al., 2014). The total flavonoid extract (5 µg/mL) from _D. moldavica_ pre-treatment had caused improvement in the heart rate and coronary flow by decreasing lactate dehydrogenase levels, creatinine kinase levels, and caused a rise on left ventricular developed pressure. In the concentration of higher than 70 mg/L, the total flavonoid extract exhibited a higher DPPH radical scavenging activity than vitamin E. The study showed that _D. moldavica_ exhibited protection against myocardial ischemia/reperfusion(I/R)-induced injury by enhancing GSH/GSSG ratio and SOD activity and attenuating malondialdehyde (MDA) production (Jiang et al., 2014). The ethanolic extract of _H. leucocephalum_ Ausfeld aerial parts showed an antioxidant effect _via in vitro_ assay. The extract exhibited antioxidant activity with an IC$_{50}$ value of 69.94 ± 0.17 µg/mL. The high amount of phenolic compounds from this plant showed a sufficient antioxidant activity in the DPPH assay (Goldansaz et al., 2018).

_Laggera decurrens_ (Vahl) Hepper and J. R. I. Wood. contains 46.3% of oxygenated monoterpenes and among them are thymol (5.7%) and 3-methoxy-2-methyl-5-(1-methylethyl)-2,5-cyclohexadiene-1,4-dione (28.1%) (Mothana et al., 2011). The oil consisted of 22.7% oxygenated monoterpenes, especially, at a concentration of 5.1% and eudesma-11-en-4a-ol (7.0%) as the main compounds. The essential oil, especially, at a concentration of 69.94 µg/mL exhibited strong antioxidant activity by causing a reduction in DPPH concentration which is comparable to ascorbic acid activity due to the presence of carvacrol, 3-methoxymyrcenone, and thymol (Mothana et al., 2011).

_Lavandula angustifolia_ Mill. from the Lamiaceae family consists of essential oil that can inhibit isoproterenol-induced myocardial infarction in rats (Ezzoubi et al., 2014). It protected the myocardium against isoproterenol-induced myocardial infarction at the concentration of 20 mg/kg of the essential oil. This amount of oil had caused the reduction in the ST-elevation...
### TABLE 3 | Mechanism of action of Asteraceae family plant species.

| Plant Name | Parts Used | Isolated Compound/ Extract | Class | In Vivo/ In Vitro | Mechanism of Action | References |
|------------|------------|-----------------------------|-------|-------------------|---------------------|------------|
| Achillea arabica Kotschy (syn. Achillea biebersteinii Hub.-Mor.) | Aerial parts | Ethanolic extract | Sesquiterpenes lactones, polyphenols, flavonoids, | In vivo | The extract at a dose of 400 mg/kg showed a significant decrease in the levels of serum cholesterol, triglycerides, and LDL. It also significantly decreased hepatic total cholesterol and triglycerides. | (Mais et al., 2016) |
| A. millefolium L. | Aerial parts (leaves, stalks, and stems) | Hydroethanolic extract (HEAM), Dichloromethane (DCM), and armetin | Flavonoid | In vivo | With the dose of 300 mg/kg of HEAM, it increased the diuresis around 30-60% between 4 and 8 h after administration. The diuresis effect decreased systemic vascular resistance. The extract also reduced blood volume and cardiac output. A single dose of HEAM (100 mg/kg), which was administered to the rats 3 h before measurement, showed a lower MAP reading by 13 ± 1 mm Hg. Increasing the dose to 300 mg/kg, decreased MAP by 14 ± 3 mm Hg. | (De Souza et al., 2013) |
| A. tenuifolia Lam. (syn. Achillea santolina L.) | Aerial | Hydroalcoholic extract (ASE) | Phenol and flavonoid | In vitro | At high concentrations (200 and 400 mg/kg), ASE suppressed lipid oxidation, by extending the lag phase and reducing the propagation rate. It reflects a typical characteristic of a chain-breaking antioxidant, similar to that of known antioxidants. | (Ardestani and Yazdanparast, 2007) |
| Ageratum conyoides (L.) L. | Leaf, stem, and root | Methanol extract | Alkaloids, carbohydrate, cardiac glycosides, flavonoids, saponins, tannins, steroids, and triterpenes | In vivo | The leaves and stem extracts (100 mg/kg) lowered total cholesterol, LDL-C, and triglycerides level. | (Atawodi et al., 2017) |
| A. melampodina subsp. deserti (Boiss.) Eig (syn. Anthemis deserti Boiss) | Whole plant | Methanolic extract | Flavonoid | In vitro | The extract exhibited antioxidant capacity at 400 μg/mL. All concentrations of the extract tested possessed radical scavenging activity. Higher concentrations of the extract showed similar activity as standards. | (Shahat et al., 2014) |
| Artemisia absinthium L. | Aerial parts | Quercetin (3), rutin, isoquercitin, quercitin-3-O-β-d-glucoside, glucoside, chlorogenic, syringic, coumaric, salicylic, and vanillic acids (4). | Flavonoids, flavonoid glycosides, phenolic acid | In vitro | The extract showed a significant (p < 0.05) activity at the dose of 100 μg/mL in the scavenging of superoxide radical. Pre-treatment of ischemic brain mouse with the extract significantly (p < 0.05) decreased the elevated TBARS concentration in brain mitochondrial and supernatant fractions as compared to the control group. Reducing power of the extract data suggests that it contributes significantly to the observed antioxidant effect. | (Sora and Sharma, 2011) |
| Artemisia campestris L. | Aerial parts | 3,5-dicaffeoylquinic (isochlorogenic A) acid, 5-cafeoylquinic (chlorogenic) acid, and vicenin-2 (16). | Flavonoids | In vivo | The extract at the dose of 150 mg/kg/day prevented hypertension on hypertensive rats and reduced SBP from 172 mm Hg to 144 mm Hg. At the dose of 40 mg/kg, the extract reduced SBP, DBP, and MAP, without affecting the heart rate. The extract (10−5–2 mg/mL) relaxed the pre-contracted aorta by 95.8 ± 1.3%. | (Db et al., 2017) |
| Baccharis trimera (Less.) DC | Whole plant | Aqueous extracts (rutin and quercetin (3)) | Flavonoids and terpenes | In vitro | The aqueous extract showed higher efficiency in eliminating DPPH radical with an IC50 value of 415 ± 12.1 μg/mL. The extract was capable of reducing deoxyribose damage at all concentrations by its ability to chelate iron by greater than 50% at the extract concentration of 100 μg/mL. | (Sabir et al., 2017) |
| Bidens pilosa L. | Leaf | Aqueous and methylene chloride extracts | Flavonoids, alkaloids, saponins, phenyl acetylenes, and terpenes | In vivo | Aqueous extract (150 or 350 mg/kg) and methylene chloride extract (150 mg/kg or 300 mg/kg) of B. pilosa completely blocked the elevation of blood pressure in fructose-treated rats and provoked a decline toward control values. The extracts reversed the increase in SBP. | (Dino et al., 2001) |
| Chamaemelum nobile (L.) All. | Whole plant | Aqueous extract | – | In vitro and | Single oral administration of the extract (140 mg/kg) produced a significant reduction in SBP. Daily oral administration of the extract (140 mg/kg) during three weeks, produced a significant reduction in SBP in day eight of treatment. | (Zeggwagh et al., 2009) |
### TABLE 3 | Continued

| Plant Name                        | Parts Used            | Isolated Compound/Extract | Class                  | In Vivo/ In Vitro | Mechanism of Action                                                                 | References                  |
|-----------------------------------|-----------------------|---------------------------|------------------------|------------------|-------------------------------------------------------------------------------------|-----------------------------|
| *Chromolaena odorata* (L.) R. M.  | Leaves                | Aqueous extract           | –                      | In vivo          | The extract produced a significant increase in urinary output and electrolytes excretion. | (Ikegwu and Ikewuchi, 2011) |
| [King and H. Rob. *Chrysanthemum x morifolium* Ramat. Hemsli.](L.) L. | Flower                | C. morifolium extract (CME) | Polyphenols            | In vivo          | PolypHENOL-rich CME alleviated hypertensive cardiac hypertrophy in rats through the reduction of blood pressure. Administration of CME at the dose of 75–150 mg/kg for four weeks lowered the SBP. | (Gao et al., 2016)          |
| *C. crepidioides* (Benth.) S. Moore | Aerial parts Aerial methanolic extract, curcumin, and reducing sugar | Alkaloids, glycosides, cardiac steroids, tannins, flavonoids, saponins, and glycosides | In vitro and in vivo | Increasing concentration of the methanolic extract increased its DPPH radical scavenging activity. The Wistar albino rats were administered with plant extract (150 and 300 mg/kg/day) orally. It significantly reduced the serum total cholesterol, triglycerides, LDL-C, VLDL-C levels, and significantly increased serum HDL-C level compared with a positive control group. The dose of 300 mg/kg showed significant (p < 0.01) anti-hyperlipidemic activity compared with the positive control group. | (Bahar et al., 2016)        |
| *C. cardunculus* L. (syn. *Cynara scolymus* L.) | Leaf                 | Quercetin (3)             | Phenols and flavonoids | In vitro and in vivo | The extract exhibited a free radical scavenging effect. Hyperlipidemic rat administered with the extract of 150 to 600 mg/kg decreased triglyceride and LDL-C levels. It also reduced HMG-CoA reductase enzyme activity, hence reduced the formation of VLDL from the liver. | (Mocelin et al., 2016)      |
| *Eclipta prostrata* (L.) L.     | Leaves                | Leaf extract              | Alkaloids, phytosterols, flavonoids, saponins, tannins, sugar | In vivo          | The extract reduced total cholesterol, triglyceride, protein, and increased HDL-C. The extract (100 and 200 mg/kg) showed a significant hypolipidemic effect. | (Chandrapani, 2007)         |
| *E. praeternissa* Milne-Redh      | Leaves                | Aqueous extract           | Tannins, cardiac glycosides, flavonoids, terpenoids | In vivo          | The aqueous extract significantly reduced the triglyceride level (47.80 ± 4.75 mg/dl to 37.22 ± 2.18 mg/dl) at a dose of 200 mg/kg after 2 h. The level of HDL was significantly increased (48.44%) by 400 mg/kg of the extract. The extract (100 mg/kg) caused significant reductions in LDL level when it was administered concomitantly with 15 and 50 mg/kg atorvastatin, respectively. | (Ngozi et al., 2013)        |
| *E. praeternissa* Milne-Redh      | Flowers              | Plant extract (polysaccharide-polyphenolic) | Flavonoids and tannins | In vitro and In vivo | The extract inhibited thrombin and factor Xa amidolytic activities in the presence of antithrombin. The plant preparation inhibits plasma clot formation in aPTT at the concentration as low as 390 µg/mL of standardized human blood plasma, and in PT test at the concentration of 1.56 mg/mL. The strong anticoagulant effect was observed after 40 min after the administration, with the clotting time almost three times longer than control measurement. | (Pawlaczyk et al., 2011)     |
| *Flaveria bidentis* (L.) Kuntze   | Leaves                | Quercetin 3-acetyl-7,3′,4′-trisulfate (ATS) and quercetin 3,7,3′,4′-tetrasulfate (QTS) | Flavonoids | In vitro       | The oil extract (90 mg/kg) possessed a hypolipidemic effect by reducing plasma total lipid, total cholesterol, VLDL-cholesterol, LDL-cholesterol, and atherogenic indices. It also increased the HDL value and reduced the total cholesterol level in the liver. | (Sharaf and Al, 2004)       |
| *G. tournefortii* L.              | Seeds                 | Tyramine                  | Saponin and alkaloid    | In vivo          | The extract caused a decrease in plasma total cholesterol, LDL, triglycerol, and VLDL and an increase in plasma HDL-C concentration of hyperlipemic animals. | (Audu et al., 2012)         |
| *Gymnanthemum amygdalimum* (Delile) Sch. Bip. (syn. *Vernonia amygdalina* Delile) | Leaf                  | Aqueous extract           | Flavonoids and phenolics | In vivo          | The extract produced a significant increase in urinary output and electrolytes excretion. | (Continued) |
### TABLE 3 | Continued

| Plant Name                          | Parts Used                  | Isolated Compound/Extract                  | Class               | Mechanism of Action                                                                 | References |
|------------------------------------|------------------------------|---------------------------------------------|---------------------|--------------------------------------------------------------------------------------|------------|
| **H. leucocephalum**               | Aerial parts (leaves, stalks, and stems) | Chalcones, phthalides, α-pyron derivatives, essential oils, volatiles, and fatty acids | Phenol, terpenoids, and flavonoids | In vivo - The extracts exhibited scavenging activity towards DPPH radicals.            | (Goldansaz et al., 2018) |
| **Inula racemosa**                 | Roots                        | Alcohol extract (essential oil of the roots), phenyl acetonitrile and phenyl ethanol | Sesquiterpenes and phenolics | In vivo - IA decreased total cholesterol, triglycerides, LDL-C, and the atherogenic index, and increased HDL-C compared with the positive control. It also reduced lipid peroxidation, and reduced lipid uptake, resulting in a reduction of fatty streak formation, via decreased foam cell formation. | (Mangathayaru et al., 2009) |
| **L. decurrens**                   | Aerial parts                 | Essential oil (3-methoxythymoquinone, thymol, and carvacrol) | Monoterpenes, Phenols | In vitro - The extract (500 µg/mL) exhibited high antioxidant activity (91%) by scavenging DPPH. | (Mothana et al., 2011) |
| **Pectis brevipedunculata**        | Aerial parts                 | Essential oil (Citral, geranial (19), limonene, and α-pinene) | Monoterpenes compounds, hydrocarbons, sesquiterpenes, alcohols and aldehydes | In vitro - The essential oil caused vasorelaxation activity. The citral possessed vasodilator activity towards KCl-contracted aorta. Citral attenuated the contracture induced by Ca²⁺ in the depolarized aorta. EOPB and citral elicited vasorelaxation on thoracic aorta by affecting the NO/cyclic GMP pathway and the calcium influx through voltage-dependent L-type Ca²⁺ channels. | (Pereira et al., 2013) |
| **Senecio nutans**                 | Branches and leaves          | Hydroalcoholic extract, dithydropyridinyl-p-hydroxy acetonaphone | Terpenes and flavonoids | In vivo - The plant extract (40 mg/kg) caused a reduction in SBP and DBP by 23% and 35%, respectively. The extract also decreased MAP and heart rate by intravenous (IV) route administration, in addition to prolonged dilatation time. | (Quesantes et al., 2016) |
| **S. ovatus subsp. stabianus**     | Aerial parts                 | Plant extract                               | Phenol and flavonoid | In vitro - Ethyl acetate extract showed the highest activity with IC₅₀ values of 35.5 and 32.7 mg/mL on the DPPH test and ABTS test, respectively. | (Tundis et al., 2012) |
| **Silybum marianum**               | Seeds                        | Silybin (the main component of Silymarin mixture) | Polyphenols | In vivo - Silymarin (12) acts as a free radical scavenger such as OH and O₂⁻ and it enhances the antioxidant enzymes CAT, SOD, and GPx. Thus, it increased the antioxidant cell defense and the activity of the mitochondrial enzyme. It caused activation of Nrf2 and inhibited NF-kB, and expressions of eNOS and MAPK (ERK1, 2, JNK). It activated the ribosome and increased protein synthesis to regenerate cardiovascular tissues. It also scavenged free radicals in the cytoplasm and increased ribosomal RNA synthesis. A dose of 200 mg/kg of silymarin (12) reduced the ROS level of rats when given intraperitoneally. 100 mg/kg of silymarin (12) increased HDL-cholesterol and decreased liver cholesterol of hypercholesterolemic rats. | (Takib et al., 2018) |
| **Solidago chilensis**             | Aerial parts                 | Hydroalcoholic extract                      | Flavonoids | In vitro - The extract exhibited antioxidant properties with an IC₅₀ value of 59.12 ± 3.14 µg/mL. | (Schneider et al., 2015) |
| **Launaea stabeliana**             | Whole plant                  | Ethanolic extract                           | –                   | In vivo - At a dose of 200 mg/kg, the extract reduced the level of plasma total cholesterol, ester cholesterol, free cholesterol, free fatty acid phospholipids, and triglycerides in comparison with AD rat. Whereby at a dose of 400 mg/kg, the extract increased the rats’ HDL-C level. The reduction of the plasma lipid and lipoprotein profile was due to the presence of phenolic and flavonoids compounds. HDL reversing cholesterol transport, inhibiting the oxidation of LDL and neutralizing the atherogenic effects of oxidized LDL. | (Devi and Muthu, 2015) |
TABLE 3 | Continued

| Plant Name | Parts Used | Isolated Compound/Extract | Class | In Vivo/In Vitro | Mechanism of Action | References |
|------------|------------|---------------------------|-------|-----------------|---------------------|------------|
| *Sphaeranthus indicus* L. Flower | Ethanol extract | Tannin | In vitro | The extract at the dose of 125, 250, or 500 mg/kg decreased the total cholesterol of rats. | (Pande and Dubey, 2009) |
| *Tagetes erecta* L. (syn. *Tagetes patula* L.) | Roots | Citric acid (24), dimethyl citrate, and malic acid | Tricarboxylic acid | In vivo | The citric acid (24) reduced the blood pressure of nonmotile rats in a dose-dependent manner. It caused 17–21% and 32–35% fall in MABP at the corresponding doses of 3 and 30 mg/kg, respectively. | (Saleem et al., 2004) |
| *T. vulgare* L. | Leaves | Plant extract | – | In vivo | Administration of 10 mg/kg of the leaf extract caused an increase in urine output. The levels of Na⁺ and K⁺ in the urine increased, but the plasma Na⁺ and K⁺ were not affected in this activity. | (Lahiou et al., 2007) |
| *Tridax procumbens* (L.) L. | Leaves | Extract | Sulfated polysaccharide | In vitro | The sulfated polysaccharides prolonged aPTT (113 s) at a dose of 100 µg/mL, which was approximately 4.0-fold compared with the saline group. | (Naqash and Nazeer, 2011) |
| *Vernonia elaeagnifolia* DC. | Leaf | Ethanol extract | Flavonoids, phenolic compounds, tannins, terpenoids, phyto steroids, alkaloids, and coumarins | In vivo | The extract restored the levels of LDL and HDL cholesterol of albino rabbits. | (Sultana et al., 2017) |

of the myocardial infarction situation, resembled its effectiveness in cardiovascular disease, and indicated its protective effects on cell membrane functions (Ezzoubi et al., 2014). The essential oils and subfractions of *M. macrophon* Coss. methanolic extract were examined their antioxidative properties via in vitro study (Amiri, 2011). In examining the effect of *M. macrophon* on DPPH assay, the polar subfraction of the flowering stage was more potent with an EC₅₀ value of 57.0 ± 0.6 mg/mL. In contrast, the essential oil of the flowering stage was more potent (EC₅₀: 91.7 ± 1.2 mg/mL) in inhibiting a-carotene oxidation with almost similar inhibitory activity compared to the positive control, BHT. The oxidation of a-carotene was determined by observing its a-carotene that generates free radicals.

The phenolic compounds isolated from the ethanolic extract of the whole plant of *O. vulgare* L. were determined their antioxidant activity. From the study, *O. vulgare* consists of phenol compounds such as 2,5-dihydroxybenzoic acid, 3,4-dihydrobenzoic acid, rosmarinic acid (5), oragnoside, maltol, E-caffeic acid (6), apigenin (7), luteolin (8), and didymin (Zhang et al., 2014). Based on the *in vitro* test, the phenolic compounds of *O. vulgare* showed potent antioxidant activity. The SC₅₀ values of the compounds ranged from 16.7 ± 1.1 to 221.8 ± 49.0 µM. The scavenging activity of the compound that consists of 3,4-dihydroxyphenyl and gasterodin moiety was higher than its positive control, the ascorbic acid. The highest radical scavenging activities were exhibited by compounds with danshensu moieties with SC₅₀ values 17.5 ± 1.1 µM and 16.7 ± 1.1 µM. The phenolic structure is responsible for the scavenging activity by donating the hydroxyl group to the free radicals (Graf, 1992). The ferric reduced antioxidant power (FRAP) assay also showed similar antioxidant activity of the phenolic compounds. The FRAP values of the compounds ranged from 143.0 ± 4.0 and 201.0 ± 8.0, with the highest activity exhibited by origanoside and apigenin (7) (Zhang et al., 2014).

*Salvia officinalis* L., which is also known as sage, contains phenolic compounds in its shoot part (Santos-Gomes et al., 2002). The antioxidant extract of the shoots contains phenolic acids such as gallic acid (1), rosmarinic acid (5), caffeic acid (6), 5-O-cafeoylquinic acid, and 3-O caffeoylquinic acid. The identified flavonoids in the extract are hesperetin, genkwanin, hispidulin, cirsimaritin, and apigenin (7). Whereas, the phenolic diterpenes are methyl carnosate, rosmanol (9), epirosmanol, episorosmanol ethyl ether, epirosmanol methyl ether, carnosic acid, rosmedial, and carnosol (10). The rosmarinic acid (5), carnosic acid, and carnosol (10) contributed to *S. officinalis* inhibitory activity on lipid peroxidation (Santos-Gomes et al., 2002). The ethanolic leaves extract of the plant contains a high amount of chlorogenic acid (11) and rosmarinic acid (5). The compounds exhibited strong antioxidant activity due to the ability of their phenols structure to donate hydrogen atoms to free radicals. (Ramu et al., 2012).

*Senecio ovatus* subsp. *stabianus* (Lacaita) Greuter was used an *in vitro* assay to examine its antioxidant activity by conducting azino-bis (3-ethylbenzthiazoline-6-sulphonate) (ABTS) and DPPH assay (Tundis et al., 2012). The study showed that the
### TABLE 4 | Mechanism of action of Lamiaceae family plant species.

| Plant Name                                      | Parts Used | Isolated Compound/ Extract | Class | In Vivo/ In Vitro Mechanism of Action                                                                 | References                                                                 |
|-------------------------------------------------|------------|-----------------------------|-------|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Agastache mexicana (Kunth.) Lint. and Epling. | Aerial parts | Acacetin, oleanolic acid (25), and usnic acid | Flavonoid | In vivo Each hypertensive mouse received an intragastric dose of usnic acid (50 mg/kg). It inhibited vasoconstriction induced by KCl and noradrenaline bitartrate (NA) in endothelium-denuded aortic rings, and also inhibited the concentration-response contraction of NA in a nonparallel manner and depressed its maximal response. The extract at the dose of 112, 200, and 625 µg/mL possessed Ca<sub>2</sub>+ entry blocking activity. | (Hernandez-Abreu et al., 2013)                                           |
| Ajuga integrifolia Buch.-Ham. ex D. Don (syn. Ajuga remota Benth.) | Leaves | phenolic compounds, tannins, saponins, flavonoids, terpenoids, steriods, and cardiac glycosides | Flavonoid | In vivo 80% methanolic extract produced significant diuresis (p < 0.01), while the aqueous extract had shown diuresis both at the middle (p < 0.01) and higher (p < 0.01) doses by the end of the fifth hour of administration. | (Hailu and Engidawork, 2014)                                           |
| Ajuga iva (L.) Schreb. | Whole plant Aqueous extract | Ecdysone, terpenoid, flavonoid | Flavonoid | In vitro The extract (1 mg/mL) reduced plasma cholesterol and triacylglycerol. It also reduced TBARS concentration, the lipid peroxidation product. Product concentration was reduced to 20 mg/mL. | (Taleb-Senouci et al., 2009)                                           |
| Ballota glandulosissima Pub. -Mor. and Patzak Clerodendrum volubile P. Beauv. | Aerial parts 5-hydroxy-7,3',4'-trimethoxyflavone, velutin, corymbosin, retusine | Flavanoid | Flavonoid | In vivo The extract (250 and 500 mg/kg) significantly lowered the total cholesterol, LDL-, VLDL, and triglycerides, and increased HDL level dose-dependently, in both phyto-preventive and curative animals. | (Siver, 2000; Citoglu et al., 2004)                                           |
| C. vulgaris (L.) Druce | Aerial parts Crude extract | Phenolic and flavonoid | Flavonoid | In vivo and in vitro The extract and fractions showed an antihypertensive effect at doses of 10 and 30 mg/kg, respectively, by reducing the MAP of hypertensive rats. | (Khan et al., 2018)                                           |
| Draccocephalum moldavica L. | Aerial parts Plant extract | Flavonoid | Flavonoid | In vitro The flavonoids fraction, at the concentration of more than 70 mg/L, exhibited a higher DPPH radical scavenging activity than vitamin E. The flavonoids fraction also possessed scavenging activity on DPPH, hydroxyl radicals, and superoxide anion radicals. | (Jiang et al., 2014)                                           |
| Isodon rugosus (Wall. ex Benth) Codd | Aerial parts Crude extract | Flavonoid | Flavonoid | In vivo and in vitro The crude extract (0.01–0.3 mg/mL) possessed a relaxant effect on isolated rabbit jejunum, trachea, and aorta preparations. The mechanism of action was assumed to be by the Ca<sup>2+</sup> channel blockade. | (Janbaz et al., 2014)                                           |
| Lagenaria siceraria (Mol.) Standl | Fruit | C-glycosides | Flavone | In vivo L-NAME was used to induce hypertension in rats. Concomitant treatment of L. siceraria fruit powder (LS) and L-NAME for 28 days reduced cholesterol level but did not reduce triglycerides levels. It also reduced SBP, DBP, and MABP significantly. | (Mali et al., 2012)                                           |
| Lallemantia royleana Benth. in Wall. | Seeds | Oleic, linoleic, and linolenic acid content | – | In vivo Administration of the seeds for 12 weeks decreased (p < 0.05) the rabbit’s total serum cholesterol and triglycerides. It also significantly decreased LDL-C and HDL-C of the hypercholesterolemic group (p < 0.05). | (Ghannadi et al., 2015)                                           |
| Lavandula angustifolia Mill. | Aerial parts Essential oil (linalool, linalyl acetate camphor (14), 1,8-cineol, luteolin (8), terpenoids like usnic acid and coumarine) | Mono and sesquiterpenes, flavonoids | Flavone | In vivo The essential oil (10 mg/kg) significantly decreased heart to body weight ratio (p < 0.001). Treatment with 10 and 20 mg/kg of essential oil demonstrated a profound reduction (p < 0.001) in the ST-segment elevation. | (Ziaee et al., 2015)                                           |
| Lavandula stoechas L. | Aerial parts Ethanolic extract | Flavonoid | Flavonoid | In vitro The extract exhibited antioxidant activity by scavenging DPPH with an IC<sub>50</sub> value of 1.2 µg/mL while the IC<sub>50</sub> value of the reference standard, BHT was 0.2 µg/mL. | (Ezzoubi et al., 2014)                                           |
| Leonotis leonurus (L.) R. Br. | Leaves Marrubiin (20) and organic extract | Diterpenoids | – | In vivo The extract (25–2,000 µg/mL) and marrubiin (20) (1.25–100 µg/mL) inhibited platelet aggregation by suppressing the | (Mniong et al., 2011)                                           |

(Continued)
### TABLE 4 | Continued

| Plant Name                  | Parts Used | Isolated Compound/ Extract | Class | In Vivo/ In Vitro | Mechanism of Action                                                                 | References            |
|-----------------------------|------------|----------------------------|-------|-------------------|-------------------------------------------------------------------------------------|-----------------------|
| Leonurus cardiaca L.        | Aerial parts | Leonurus cardiaca refined extract (LCRE) Cardioactive lavandulifolioside and verbascoside | Phenylethanoid glycosides | In vitro | LCRE at the dose of 1.0 to 2.0 mg/mL was infused intracoronary for 10 min before mapping its epicardial potential. It reduced the left ventricular pressure in a dose-dependent manner and elevated the relative coronary flow. | (Ritter et al., 2010) |
| Lepechinia caulescens (Ortega) Epling | Aerial parts | Methanolic extract (ursolic acid, terpinene-4-ol, salvigenin, and spathuleno) | – | In vitro | Methanolic extract L. caulescens (MELc) at 38 and 120 mg/kg induced a significant decrease in heart rate, SBP, and DBP in comparison with control; captopril (30 mg/kg). MELc (120 mg/Kg) induced a long-term antihypertensive and vasorelaxant effect. | (Estrada-Soto et al., 2012) |
| L. aspera (Willd.) Link     | Leaf       | Ethanolic extract of leaf | Phytosterols and alkaloids | In vivo | The ethanolic extract of leaves (200 and 400 mg/kg) showed significant inhibition against dexamethasone-induced hyperlipidemia in rats by maintaining the serum levels of cholesterol and triglycerides near to normal levels. | (Kumar, 2016)         |
| M. officinalis L.           | Leaves     | Hydroxycinnamic acid derivatives (rosmarinic acid (5) and caffic acids (6)) | Phenol | In vitro | The aqueous extract (1–1,000 µg/mL) exhibited concentration-dependent relaxation in phenylephrine-precontracted endothelium intact thoracic rings. Rosmarinic acid (5) possessed a dose-dependent vasorelaxant effect. | (Ensoy et al., 2008)  |
| M. macrosiphon Coss. (syn. S. macrocephalum) (Coss.) Maire | Aerial parts | Methanolic extract (carvacrol, thymol, flavonoids, beta-caryophyllene, gamma-terpinene, and linalool) | Isopropanoids | In vitro | The methanolic extract of its flowering stage possessed higher activity in inhibiting β-carotene oxidation with an EC50 value of 57.0 ± 6.0 mg/mL. | (Aniri, 2011)         |
| O. vulgare L.               | Whole plants | Flavonoids and phenolic acids, rosmarinic acid (5), orangoside | Phenolic compounds | In vitro | The in vitro test of the phenolic compounds exhibited potent DPPH radical scavenging activities with SC50 values ranging from 16.7 ± 1.1 to 221.8 ± 49.0 µM. | (Zhang et al., 2014)   |
| Orthosiphon aristatus (Blume) Miq. (syn. Orthosiphon stamineus Benth.) | Leaves | Methylripiriochromene (MRC) | – | In vivo | MRC (50 and 100 mg/kg) reduced SBP and heart rate of the mice via the subcutaneous route. The MRC reduced BP due to the dilation of the blood vessel decreased in cardiac output. It also has suppressive actions to contractions. | (Matsubara et al., 1999) |
| Phlomoides bracteosa (Royle ex Benth.) Kamelin and Makhm. (syn. Phlomis bracteosa (Royle ex Benth.) Kamelin and Makhm.) | Whole plant | Sinensetin (17), eupatorin (26), flavonoid | – | In vitro | Sinensetin (17) (0.03–2.11 µM) caused concentration-dependent vasorelaxation of phenylephrine-contracted endothelium-intact aortic rings. O. aristatus caused aortic ring that was pre-contracted with phenylephrine in the presence and absence of endothelium to be relaxed. It also caused relaxation to the aortic ring that was pre-contracted with potassium chloride in the endothelium-intact aortic ring. It exhibited a vasodilator effect mediated through dual Ca2+ channel inhibition (endothelium-independent) and nitric oxide (NC) generation (endothelium-dependent) pathways. Marrubiin (20), phlomeic acid, RA, and RB inhibited the K+ and PE-induced contractions in endothelium-denuded rings with different patterns. | (Yam et al., 2016; Yam et al., 2018) |
| Plectranthus hadiensis (Forsk.) Schweinitz, ex Sprenger (syn. Coleus forskohlii Willd.) | Whole plant | Ethanolic extract | Diterpene | In vivo | Coleonol produced well-marked and sustained hypotension in the anesthetized cat in a dose range of 0.1–1.0 mg/kg, given intravenously in the smooth muscle. A close intra-arterial injection of coleonol (0.1 mg) increased the blood flow in the femoral artery. | (Dubey et al., 1981) |
| P. monostachyus (P. Beauv.) B. J. Pollard (syn. S. | Leaves | Ethanolic extract | flavonoids, coumarin, polyphenol | In vivo | The extract (0.6–17.6 mg/kg bw) induced a significant decrease in arterial blood pressure (EC50 = 2.5 ± 0.15 mg/kg b.w) in a dose-dependent manner (p < 0.001). The extract | (Fidiale et al., 2012) |

(Continued)
| Plant Name | Parts Used | Isolated Compound/ Extract | Class | In Vivo/ In Vitro | Mechanism of Action | References |
|------------|------------|-----------------------------|-------|-------------------|---------------------|------------|
| Pogostemon elsholtziioides | Leaves | Essential oil (Curzerene, majority sesquiterpenes) | – | In vitro | (10−2−1 mg/mL) inhibited aorta smooth muscle contraction suggesting calcium channel blocking action with a major inhibitory effect on L-type voltage-operated Ca2+ channels. The essential oil of P. elsholtziioides induced dose-dependent vasodilatation in pre-contracted aortic rings against contraction evoked by Phe (10−6M). Injection of the essential oil at the dose level 20 mg/kg induced a significant decrease in MAP and heart rate. | (Shiva Kumar et al., 2017) |
| P. vulgaris L. | Whole plant | Rosemarinic acid | – | In vivo | The aqueous extract showed a substantial increase in the HDL level. The extract exhibited radical scavenging activity towards superoxide, hydroxyl, and hydrogen peroxide. | (Zargar et al., 2017) |
| R. officinalis L. | Leaves | n-butanol extract | Flavonoids and phenolic | In vivo | The n-butanol extract (400 mg/kg) significantly reduced (p < 0.01) the plasma total cholesterol level of diabetic mice group by 51.85% reduction. | (Belmouhoub et al., 2017) |
| S. miltiorrhiza Bunge | Root | Salvianolic acid (23) | Phenolic acids | In vivo | Salvianolic acid (23) reduced thrombus weight and increased plasma CAMP level. Salvianolic acid (23) (2.5–10 mg/kg) administered inhibited the platelet aggregation in a dose-dependent manner. The acid inhibited various agonists that stimulate platelet aggregation. It also induced CAMP levels in platelets that were activated by ADP. Induce a rise in CAMP level in platelets activated by ADP. | (Fan et al., 2010) |
| S. officinalis L. | Shoots | Phenolic acids, carnosol derivatives, and flavonoids, namely, rosmarinic acid (5), carnosic acid, and carnosol (10) followed by caffeic acid (6), rosmarinal (9), rosmadial, geranikovan, and cinsimartin | Phenolic compound and flavonoids | In vitro | It exhibited scavenging activity towards active oxygen’s such as superoxide anion radicals, hydroxyl radicals, and singlet oxygen, and inhibits lipid peroxidation. | (Masaki et al., 1995; Santos-Gomes et al., 2002) |
| Salvia scutellarioides Kunth | Leaves and stem | Aqueous plant extract | – | In vivo | Intravenous consumption of 1 and 2 g/kg of the extract produced a significant increase in diuresis. It increased the urinary excretion of potassium and chloride. High tubular concentrations of potassium stimulated the activity of the Na+ / K+ ATPase pump in the basolateral membrane of the tubular epithelial cells, decreasing the sodium concentration in the urine. | (Ramirez et al., 2008) |
| Satureja cuneifolia Ten. (syn. Satureja obovata Lag.) | Whole plant | Eriodictyol (21) | Flavonoid | In vitro | Eriodictyol (21) inhibited the KCl and noradrenaline-induced contraction in a concentration-dependent manner. Eriodictyol (21) (105, 5 × 105, 104, and 5 × 104 M) added before the contraction reduced the tonic phase of contraction. | (De Rojas et al., 1999) |
| Sideritis raeseri Boiss. and Heldr. | Aerial parts | Plant extract | Terpenoids, sterols, coumarins, flavonoid aglycones, and glycosides | In vivo | The extract (0.025–7.5 mg/kg) caused a dose dependent decrease of the arterial pressure and heart rate, with an EC50 value of 24.31 ± 3.87 mg/kg and 88.14 ± 7.51 mg/kg, respectively. Extract of S. raeseri (0.005–1.5 mg/mL) elicited a vasodilator action (EC50: 0.11 ± 0.008 mg/mL). | (Kitic et al., 2012) |
| T. polium L. | Aerial parts | Aqueous extract | Diterpenoids, flavonoids, iridoids, sterols, and terpenoids | In vivo | Administration of 50 to 150 mg/kg of the extract for ten days significantly reduced the serum levels of cholesterol and triglycerides in hyperlipidemic rats dose-dependently. | (Rasekh et al., 2001) |
| Thymus satureoides Coss. | Whole plant | Caffeic acid (6) Rosmarinic acid (5) Quercetin (3) | Polyphenolic compound and flavonoids | In vivo | The extract exhibited a hypolipidemic effect. Injection of 0.2 g/100 g of the extract significantly lowered both plasma triglycerides and cholesterol levels after 24 h of treatment. The reduction of plasma total cholesterol was associated with a decrease in the LDL fraction. It suppressed the elevated blood concentrations of triglycerides. | (Ramchoun et al., 2012; Khousa et al., 2015) |
| Thymus serpyllum L. | Whole plant | GAE, and rosmarinic and caffeic acids (6) | Phenols and flavonoids | In vivo | The injection via bolus of 100 mg/kg body weight produced a significant decrease in SBP, DBP, and total peripheral | (Katalinic et al., 2006; |
TABLE 4 | Continued

| Plant Name          | Parts Used | Isolated Compound/ Extract | Class         | In Vivo/ In Vitro | Mechanism of Action                                                                 | References                  |
|---------------------|------------|----------------------------|---------------|------------------|--------------------------------------------------------------------------------------|----------------------------|
| *Thymus zygis* L.   | Whole plant| Caffeic acid (6) and rosmarinic acid (5) | –             | in vitro         | Rosmarinic acid (5) portrayed a dose-dependent antioxidant activity against in vitro LDL oxidation. It inhibited the formation of conjugated dienes and TBARS. The thyme extract (1 mg/mL) exhibited nitric oxide (NO) scavenging activity of 63.43%, with the IC50 value of 122.36 µg/mL. | Mihalovic-Stanojevic et al., 2013 |
| *Vitex megapotamica* (Spreng.) Moldenke | Leaves | Crude extract | Flavonoid | in vivo | The hydroethanolic extract (500 or 1,000 mg/kg/day) significantly reduced the levels of total cholesterol, triglycerides, LDL-C, and the atherogenic index. The atherosclerotic plaque formation was impaired only by the lower dose of the hydroethanolic extract. | Khouya et al., 2015 |
| *Ziziphora clinopodioides* Lam. | Whole plant | Caffeic acid (6), luteolin (8), 7-methylsudachitin, thymonin | Phenolic and flavonoid | in vitro | The extract exhibited relaxation on the vascular smooth muscle cells through intracellular and extracellular Ca2+ mobilization. It acts on voltage-dependent K+ channels. | Stanojevic et al., 2010 |

ethyl acetate extract of the plant exhibited the strongest activity on ABTS (IC50 value: 32.7 mg/mL) and DPPH (IC50 value: 35.5 mg/mL) assay. Based on the Folin-Ciocalteu method, the plant contains total phenol of 76.3 mg chlorogenic acid (11) equivalent per gram of the plant. Whereas, based on the formation of the flavonoid-aluminum complex method, the plant contains a total flavonoid of 11.8 mg quercetin (3) equivalent per gram of the plant. Thus, it was assumed that the antioxidant activity of the plant due to its flavonoids content (Tundis et al., 2012).

*Silybum marianum* (L.) Gaertn. contains silymarin (12), which is one of the polyphenolic antioxidants. Administration of 200 mg/kg silymarin (12) by intraperitoneal on rats reduced ROS level and protected the rats from supra celiac abdominal aorta ischemia or reperfusion injury. (Kocarslan et al., 2016). Administration of 100 mg/kg silymarin (12) on the rats reduced iron and oxidative stress level of the rats’ blood. Besides, the phenolic structure of silymarin (12) caused the compound to has a strong scavenger activity towards hypochlorous acid (HOCI). It inhibited hydroxyl radical formation, which is essential for the inhibition of xanthine oxidase activity (Varga et al., 2006). A low concentration of silymarin (12) caused inhibition of the NF-κB pathway by treating and attenuating the inflammatory reaction that stimulates atherosclerosis.

**Antihyperlipidemia, Hypolipidemia, and Hypocholesterolemia Activity**

The rise in both blood cholesterol and triglyceride that may be due to hereditary factors is known as hyperlipidemia. One of the CVD that is caused by hyperlipidemia is atherosclerosis. It is the condition where the lipids or fat substances which are denoted as plagues hardened the arteries. These plagues will be built up in the walls of arteries and lead to the narrowing of the arteries. It will diminish the ability of blood flow in the artery that usually associated with vascular diseases, heart disease, and stroke (Akinpelu et al., 2016). The role of substance that possesses the antihyperlipidemic effect is to reduce the total cholesterol level in the body by reducing triglycerides, very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL). The antihyperlipidemic possessing substance also has a role in increasing the high-density lipoprotein (HDL) level in the body, which is known as the good cholesterol in the body that alleviates the risk of CVD.

A few plants from the plant family of Asteraceae and Lamiaceae plant family possess an antihyperlipidemic effect. Of such, the plants from *Asteraceae* are *Achillea arabica* Kotschy (syn. *Achillea biebersteinii* Hub.-Mor.), *Ageratum conyzae* L., *Chromolaena odorata* (L.) R. M. King and H.Rob., *C. crepidoideas* (Benth). S. Moore, *C. cardunculus* L. (syn. *Cynara scolymus* L.), *Eclipta prostrata* (L.) E. praetermissa Milne-Redh, *Gundelia tournefortii* L., *Gymnanthemum amygdalinum* (Delile) Sch. Bip. (syn. *Vernonia amygdalina* Delile), *Inula racemosa* Hook F., *Launaea intybacea* (Jacq.) Beauverd (syn. *Lactuca runcinata* DC.), *Solidago chilensis* Meyen, *Sphaeranthus indicus* L., and *Vernonia elaeagnifolia* DC. The plants from the Lamiaceae family are *Clerodendrum volubile* P. Beauv., *Lagenaria siceraria* (Mo) Standl., *Lallementia royleana* Benth., *Leucas aspera* (Willd.) Link, *Prunella vulgaris* L., *Rosmarinus officinalis* L., *Teucrium polium* L., *Thymus dreanensis* Batt. (syn. *Thymus atlanticus* (Ball) Pau), and *Vitex megapotamica* (Spreng.) Moldenke. These plants’ extracts from different solvents, such as ethanol, methanol, and water lower the lipid markers concentration in the body either *via in vivo* or *in vitro* assays.

*Achillea arabica* Kotschy ethanolic extract was used to test its antihyperlipidemic effect in animals (Mais et al., 2016). The extract was from the aerial parts of the plant taken during its flowering
phase. The high-fat diet was fed to adult male Golden-Syrian hamsters for ten days to cause hyperlipidemia. The dose of 400 mg/kg of the *A. arabica* ethanolic extract had reduced VLDL, cholesterol, LDL, and triglycerides level in the hamsters' serum. It had no significant effect on HDL. Total cholesterol and triglycerides in the hepatic were also reduced. The plant extract contains flavonoids, sesquiterpene lactones, and polyphenols. Whereas, its essential oil contains a high amount of eucalyptol (13) (10.98%), camphor (14) (12.46%) and piperitone (15) (31.06%). These may act as an inducer for the hypolipidemic effect of *A. arabica* upon the experimental hyperlipidemic hamster (Mais et al., 2016). Few reports had documented that flavonoids and phenolic compounds have antioxidant, antihyperlipidemic, and antihypertensive activity as their pharmacological effect (Rouhi-Boroujeni et al., 2015).

*In vivo* study of methanolic extracts of *Ageratum conyzoides* L. root, leaf, and stem were carried out on rats to examine its hypolipidemic activity (Atawodi et al., 2017). The extracts contain flavonoids, alkaloids, cardiac glycosides, triterpenes, saponins, carbohydrates, and tannins. Meanwhile, the leaf also consists of steroids. Fiber, saponins, and flavonoids have an underlying antihyperlipidemic effect. The methanolic extract in a concentration of 100 mg/kg was treated on rats. The extract reduced serum lipids, which is one of the insulin-releasing factors. Insulin inhibits lipolysis, thus causing a rise in uptake of fatty acids into adipose tissue and triglyceride synthesis. The diabetic rat had shown a significant reduction in total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C) levels, and increased high-density lipoprotein cholesterol (HDL-C) (cardioprotective lipid) levels (Atawodi et al., 2017).

![FIGURE 1](continued)
Chromolaena odorata (L.) R. M. King and H.Rob. leaves aqueous extract was examined its atherogenic indices and plasma lipid profiles on rats that have fed loaded with cholesterol (Ikewuchi and Ikewuchi, 2011). The intra-gastric gavages of the plant extract (100 mg/kg body weight) was administered to the rats. As a result, there was a significant reduction in total cholesterol, LDL, non-HDL, VLDL, and plasma’s triglyceride levels. The HDL-C level in the plasma was high once being treated with the extract. The extract contains saponin, which was reported to have a hypercholesterolemic activity (Soetan, 2008). The extract significantly reduced (p < 0.05) the atherogenic index of plasma, cardiac risk ration, and atherogenic coefficient compared to the control group. Thus, the study showed that C. odorata could reduce the risk of heart diseases (Ikewuchi and Ikewuchi, 2011).

Ethanol leaf extract of C. volubile P. Beauv. was evaluated by its anti-hyperlipidemic activity (Akinpelu et al., 2016). Clerodendrum volubile ethanolic leaf extract contains cardiac glycosides, saponins, flavonoids, alkaloids, tannins, and steroids. The extract contains phenolic compounds as the major constituents, followed by flavonoids and alkaloids. The lowest constituent of the extract was tannin, followed by saponin. The extract with a concentration of 250 and 500 mg/kg was administered to the hyperlipidemic animal. The extract significantly reduced the triglycerides, VLDL, total cholesterol, and LDL level in curative and phyto-preventive animals in addition to increased their HDL level (Akinpelu et al., 2016).

The methanolic extract of the aerial parts of C. crepidioides (Benth.) S. Moore had shown an antihyperlipidemic activity (Bahar et al., 2016). The albino rats were induced with a high-fat

**FIGURE 1 |** Chemical structures of phytochemicals with inhibitory activity on cardiovascular diseases from Asteraceae and Lamiaceae species.
diet to mimic hyperlipidemia model. The methanolic extract in a concentration of 150 and 300 mg/kg were administered orally to the rats. As a result, the extract increased HDL-C level while reduced VLDL-C, LDL-C, total cholesterol, and triglycerides levels compared to the positive group. The extract in a concentration of 300 mg/kg showed potent antihyperlipidemic activity compared to the positive control group (Bahar et al., 2016).

*Cynara cardunculus* L. is known for its antiatherogenic and hypolipidemic effects. Hypercholesterolemic rats were fed with *C. cardunculus* leaves aqueous extract at the amount of 150, 300, and 60 mg/kg (Mocelin et al., 2016). The extracts exhibited DPPH scavenging activity with an IC_{50} value of 57.40 ± 2.05 µg/mL. After four weeks of treatment, the serum lipid profile showed that there was a decrease in total cholesterol and LDL-C levels. The flavonoids and phenols content decreased the activities of acetyl-CoA acetyltransferase and HMG-CoA reductase in the hypercholesterolemic rats. It decreased the availability of cholesterol esters to form VLDL, which caused a reduction in the secretion of VLDL from the liver (Mocelin et al., 2016).

*Eclipta prostrata* (L.) L. leaf extract was measured its hypolipidemic activity (Dhandapani, 2007). The phytochemical screening had shown the presence of saponins, alkaloids, flavonoids, phytosterols, and tannins in the leaf extract. Atherogenic diet caused an increase in total cholesterol and total protein and decreased serum HDL-cholesterol level in rats. Daily administration of the aqueous extract in the dose 100 and 200 mg/kg increased the rats’ HDL level and reduced protein level, triglycerides, and total cholesterol significantly. It had also shown an increase in the atherogenic index. The saponins may contribute to the hypolipidemic effect of the plant extract (Dhandapani, 2007).

*Emilia praetermissa* Milne-Redh had shown its antihyperlipidemic effect via its aqueous leaf extract. The extract at doses of 100 mg/kg, 200 mg/kg, and 400 mg/kg were fed to male albino rats. As a result, the extract reduced the levels of plasma atherogenic index, total cholesterol, LDL, and triglycerides, and raised the level of HDL significantly when compared with the hyperlipidemic group. The hypolipidemic activity might due to the cholesterol-lowering effect of the extract, which may be portrayed by tannins, terpenoids, and flavonoids content. Terpenoid acts as an intermediate in cholesterol synthesis. It regulates the degradation of HMG-CoA reductase activity, which is the main enzyme in cholesterol synthesis (Ngozi et al., 2013).

Alcohol extract (IrA) and hexane extract (IrH) of *Inula racemosa* Hook F. roots at the dose of 100 mg/kg was administered to guinea pigs to observe the extracts’ hypolipidemic effect (Mangathayaru et al., 2009). IrA showed antihyperlipidemic activity by reducing lipid peroxidation and lipid uptake. It decreased foam cell formation and led to a reduction of fatty streak formation. Meanwhile, IrH exhibited more significant activity in enhancing HDL-C (p < 0.001) than in reducing LDL levels. Based on the effects of the extracts on coronary artery histopathology, IrA and IrH had shown a replacement in a muscular pattern which is the type of primary medial destruction in early atherosclerosis. It also caused the cardiac tissue to be devoid of fatty degeneration. The presence of the phenolic compounds contributes to the inhibition of LDL oxidation and prevent the degradation and uptake of oxidized LDL by macrophages (Mangathayaru et al., 2009).

*Launaea intybacea* (Jacq.) Beauverd exhibited curative and preventive activity against hyperlipidemia (Devi and Muthu, 2015). Its ethanolic extract of the whole plant reduced cardiac risk ration, plasma lipid, and lipoprotein profile. It increased the HDL level, which responsible for neutralizing atherogenic effects of oxidized LDL, in addition to inhibiting LDL oxidation and reversing cholesterol transport. It also reduced free cholesterol and ester levels. Its lipid-lowering activity was due to its inhibition of hepatic cholesterologenesis or due to its ability to increase fecal sterol excretion (Devi and Muthu, 2015).

**Vasorelaxant and Vasodilation Action**

Excessive contraction of vessels can cause increases in pressure that may lead to hypertension. Vasorelaxant facilitates the vasodilation of the contracted vessel to ensure the ease of blood flow through the blood vessels. Vascular smooth muscle relaxation is one of the mechanisms for treatment and prevention of hypertension, with most of the treatments were focusing on impeding vascular smooth muscle contraction (Goodman, 1996). A few plant species from Asteraceae and Lamiaceae exhibited vasorelaxant activity. The plants from the Asteraceae family are *Artemisia campestris* L., *Bidens pilosa* L., *Chrysanthemum x morifolium* Ramat. Hemsl., and *Pectis brevipedunculata* Sch. Bip. The plants from the Lamiaceae family are *Agastache mexicana* (Kunth.) Lint. and Epling. *C. vulgare* L. (syn. *Calamintha vulgaris* (L.) Druce), *Isodon rugosus* (Wall. Ex Benth.) Codd, *Lepechinia caulescens* (Ortega) Epling, *Melissa officinalis* L., *Ortusphon aristatus* (Blume) Miq. (syn. *Ortusphon stamineus* Benth.), *Phlomoides bracteosa* (Royle ex Benth.) Kamelin and Makhm. (syn. *Phlomis bracteosa* (Royle ex Benth.) Kamelin and Makhm.), *Plectranthus hadiensis* (Forssk.) Schweinf. ex Sprenger (syn. *Colesus forskohlii* Willd.), *Pogostemon elsholtziioides* Bentham, *Satureja cuneifolia* Ten. (syn. *Satureja obovata* Lag.), *Sideritis raeseri* Boiss. and Heldr., and *Ziziphus clinopodioides* Lam.

*Agastache mexicana* (Kunth.) Lint. and Epling is a medicinal plant species from the Lamiaceae family that can treat hypertension and anxiety conditions. The antihypertensive activity of the dichloromethane extract of *A. mexicana* (DEAm) and its isolated compound, ursolic acid were determined in the male rat (Flores-Flores et al., 2016). The extract exhibited relaxant activity on noradrenaline bitartrate 0.1 µM and potassium chloride (KCl) 80 mM pre-contracted aortic rings which suggest that the extract exhibited vasodilation effect through several receptors, such as the augment of free cytosolic Ca^{2+} levels. The extract inhibited the vasoconstriction caused by noradrenaline bitartrate and potassium chloride (Hernandez-Abreu et al., 2013). Ursolic acid evoked a significant decrease in systolic blood pressure (SBP) and...
diastolic blood pressure (DBP) with no change in the hypertensive rat. This action was due to its diuretic effect in relieving the hypertension condition (Somova et al., 2003).

The aqueous extract of Artemisia campestris L. aerial parts (AcAE) has a hypertensive and antihypertensive effect due to its vasodilatory effect (Dib et al., 2017). The extract contains a high amount of polyphenols such as mono-and di-cinnamoyl compounds with the highest concentration of 3,5-dicaffeoylquinic (isochlorogenic A) as its constituent. Meanwhile, the major flavonoids in the extract were (5-caffeoylquinic) chlorogenic acid (11) and vicenin-2 (apigenin 6,8-di-C-glucoside) (16). Daily administration of 150 mg/kg of AcAE on L-NAME hypertensive rats prevented hypertension by reducing SBP from 170 to 114 mm Hg. The extract at the dose of 40 mg/kg reduced SBP and DBP without affecting heart rate. The extract caused vasorelaxation via inhibition of calcium influx through voltage-operated calcium channels and the calmodulin-NO-sGC-PKG pathway. Besides, the extract also activated intracellular calcium mobilization into the sarcoplasmic reticulum (Dib et al., 2017).

Based on one of the studies on Bidens pilosa L., the plant exhibited a vasorelaxant effect on precontracted rat aorta induced by the KCl (Nguleleffack et al., 2005). Besides, it also exhibited vasodilating activity on noradrenaline-induced tonic contraction. The endothelium of the vascular managed to secrete contractile factors and relaxant that caused regulation of vascular tone. The chemical and physical stimulations are responded by the endothelial cells, by producing prostacyclin, nitric oxide, and bradykinin which are the relaxant factors (Corvol et al., 1993; Dimo et al., 2001).

Clinopodium vulgare L. was used in in vivo and in vitro studies to understand its antihypertensive activity (Khan et al., 2018). The administration of C. vulgaris crude extract and fractions on normotensive and high salt-induced hypertensive rats reduced the rats’ mean arterial pressure (MAP). It has a distinct effect on hypertensive rats compared to the normotensive rats. At the dose of 1, 3, 10, and 30 mg/kg, the extract had shown an antihypertensive effect in hypertensive rats with the most significant activity exhibited by the extract at the dose of 10 and 30 mg/kg. The vasodilatory effect of the extract (EC50:0.27 mg/mL) in the extracted rat aorta was endothelium-dependently. The extracts worked by inhibiting the high K+ precontraction and rightward shifted Ca2+ concentration-response curves which have an identical mechanism to verapamil. The antihypertensive effect that was showed by C. vulgaris is due to the vasodilation effect that involves muscarinic receptor-linked NO and activation of tetroethylammonium (TEA)-sensitive K+ channels, Ca2+-antagonism, and prostacyclin. The methanolic extract of the plant consists of quercetin (3) and rutin, which may act as the substance that possesses the vasodilatory effect (Khan et al., 2018).

Flower extract of Chrysanthemum x morifolium Ramat. Hemsl. exhibited a vasodilatory effect by reducing the blood pressure of cardiac hypertrophy rats (Gao et al., 2016). The major phytochemicals in this extract are 4,5-di-cafeoylquinic acid, 3,5-dicaffeoylquinic acid, luteolin-7-β-glucoside, 3-chlorogenic acid (11), and apigenin-7-O-glucoside. A range of 75 to 150 mg/kg extract was fed to the rats for four weeks to study the effect of the extract on the rats’ SBP. The dose of 150 mg/kg showed a reduction in the SBP, which was about 4% by the second week. One month administration of the extract caused a reduction in the serum-free fatty acid (FFA) by 18.9% to 29.8%, and myocardial FFA level by 5.4% to 16.0%. In addition to the extract activity in inhibiting myocardial hypoxia-inducible factor-1α (HIF-1α) expression, the extract also caused subsequent modulation of some peroxisome proliferator-activated receptor α (PPARα)-mediated gene expression; a decreased in the glucose transporter-4 (GLUT-4) protein expression and an increased in the pyruvate dehydrogenase kinase-4 (PDK-4) and carnitine palmityltransferase-1a (CPT-1a) protein expression. (Gao et al., 2016).

Orthosiphon aristatus (Blume) Miq. contains sinensetin (17), which is essential for vasorelaxation activity (Yam et al., 2016; Yam et al., 2018). The studies measured the vasorelaxant effect of the compound by conducting a pre-contraction aortic ring assay. The presence of antagonists has shown the mechanism of the vasorelaxant effect of sinensetin (17). Sinensetin (17) had exhibited a relaxation effect of potassium chloride-induced endothelium-intact aortic rings and phenylephrine-induced aortic ring with or without the endothelium. The study showed that sinensetin (17) exhibited a vasorelaxant effect via antagonization of aortic ring contraction through direct and indirect vasorelaxation. The pathways that were involved in this vasorelaxation activity were NO/sGC/cGMP pathways. Sinensetin (17) at a dose of 0.262 µg/mL caused the vasodilatory effect (Yam et al., 2016; Yam et al., 2018).

The vasodilatory effect of essential oil of the Pectis brevipedunculata Sch. Bip aerial parts (EOPB) was identified (Pereira et al., 2013). The essential oil is rich with citral content, which consists of neral (18) and geranial (19), followed by limonene and α-pinene. The vasodilator activity of EOPB and citral was measured using aortic rings obtained from Wistar Kyoto (WKY) rats. EOPB and citral exhibited relaxation to the phenylephrine-induced endothelium-intact aortic rings with an IC50 value of 0.044 ± 0.006% and 0.024 ± 0.004%, respectively. Meanwhile, EOPB and citral exhibited relaxation to the phenylephrine-induced denuded aortic rings with an IC50 value of 0.093 ± 0.015% and 0.021 ± 0.004%, respectively. The high concentrations of EOPB caused vasorelaxation of endothelium-independent which predominated the endothelium-dependent pathway (Pereira et al., 2013).

Phlomoides bracteosa (Royle ex Benth) Kamelin and Makhm. has few phytochemicals which had the vasorelaxant effects, which are marrubiin (20), phlomoeic acid, and new components (RA and RB) (Khan et al., 2012). The whole plant was powdered and extracted using methanol to produce its extract and examined its activity using rat thoracic aorta. The EC50 values of 23.4 and 36.7 µg/mL of marrubiin (20) had shown a relaxant effect upon the phenylephrine-induced contraction.
and inhibited the K⁺. Marrubiin (20) in the concentration of 3.0 to 10 µg/mL induced rightward shift of the Ca²⁺ channels. Marrubiin (20), phlomeoic acid, and RA exhibited a more potent effect against K⁺-induced contractions, compared with phenylephrine, which indicated that it had a greater efficacy in blocking the voltage-sensitive Ca²⁺ channels. Among all four phytochemicals studied, the marrubiin (20) was most potent for its vasodilator activity. It can be used in further studies to test its extent of vasodilation activity in the future (Khan et al., 2012).

Satureja cuneifolia Ten. is a plant species from the Satureja genus. Its constituent, eriodictyol (21), possessed a vasodilatory effect in the rat aorta (De Rojas et al., 1999). The concentration of eriodictyol (21) 10⁻⁵ M and 5 × 10⁻⁵ M showed the inhibitory effect of calcium chloride, CaCl₂ in the concentration-response curve. It possessed a weak inhibition in the calcium from the sarcoplasmic reticulum whereby showing off a light relaxant effect. The final results of the study indicated that the partial mechanism of the vasodilatory effect was due to its inhibition of enzyme protein such as myosin light chain kinase that related to protein kinase C or inhibition of calcium influx (De Rojas et al., 1999).

The dichloromethane extract of Ziziphora clinopodioides Lam. (ZDCE) had shown a significant effect on the inhibition of extracellular Ca²⁺ induced contraction in the pre-contracted rings by high KCl and phenylephrine. It also caused an inhibition of intracellular Ca²⁺ release to the phenylephrine. Among the hexane, dichloromethane, and aqueous extracts, ZDCE had shown the endothelium-independent vasodilation properties that occurs due to the extracellular Ca²⁺ influx via the voltage and receptor-operated Ca²⁺ channels, causing Ca²⁺ inhibition from the stores of the intracellular and lastly via opening the K⁺ channels which are voltage-dependent (Senejoux et al., 2010).

**Anticoagulation and Anti-Thrombosis Activity**

A series of zymogens are involved in the blood coagulation process. Proteolysis caused the conversion of zymogens into active enzymes that caused the production of thrombin, which can lead to the conversion of fibrinogen into fibrin (Rand et al., 1996). Enzymes are involved in mediating the blood coagulation of damaged tissues. Factor VII (FVII) binds to uncoupled tissue factor (TF), which triggers the development of thrombin that causes coagulation of blood. Anticoagulant inhibits thrombin generation and fibrin formation. An ideal clinical anticoagulant should inhibit thrombin activity without induced bleeding. Platelets and other mediators play an important role in thrombosis and cardiovascular diseases. Based on reported studies, few plants from the plant family of Asteraceae and Lamiaceae plant family possess an anticoagulant effect. The plants’ species from the family of Asteraceae are *Erigeron canadensis* L., *Flaveria bidentis* (L.) Kuntze, *Leuzea carthamoides* Willd. DC., and *Tridax procumbens* (L.) L. The plants’ species from the Lamiaceae family are *Leonotis leonurus* (L.) R. Br., *S. miltiorrhiza* Bunge, and *Thymus zygis* L.

*Erigeron canadensis* L. consists of different types of flavonoids and tannins on top of the essential oil that is present. Its polyphenolic-polysaccharide preparation was isolated from its flowering part and was determined its anticoagulant activity via *in vivo* assay (Pawlaczyk et al., 2011). The plant preparation had shown its anti-platelet activity specifically towards the cyclooxygenase pathway that was induced by the arachidonic acid (AA), which is similar to acetylsalicylic acid activity. The assay was conducted on standardized human plasma by measuring prothrombin time (PT) and partial thromboplastin time (aPTT). The plant preparation inhibited plasma clot formation in aPTT and PT at the concentration of 390 µg/mL and 1.56 mg/mL, respectively. The plant preparation also exhibited significant anti-IIa activity mediated by the cofactor II of heparin. Further fractionation of the plant preparation at the concentration of 50 µg/mL, showed higher anticoagulation activity in aPTT test corresponded to 7 to 9 IU/mg of 5th International Standard for Unfractionated Heparin (ISUH). *In vivo* studies also showed that the dose of 50 mg/mL of the plant preparation has the anticoagulant effect in the rat. These anticoagulant activities are essential in patients suffering from deep vein thrombosis, and those had already been resistant to the acetylsalicylic derivatives drugs (Pawlaczyk et al., 2011).

From the plant *Flaveria bidentis* (L.) Kuntze, the anticoagulant activity of its sulfated flavonoids, quercetin 3,7,3’,4’-tetrasulfate (QTS) and quercetin 3-acetyl-7,7,3’,4’-trisulfate (ATS) was investigated (Guglielmone et al., 2002). Thrombin time (TT), aPTT, antithrombin III (ATIII), PT, and heparin cofactor II (HCII) activation were measured. The flavonoids exhibited HCII activation by acting as agonists with higher activation observed exhibited by QTS than ATS (Guglielmone et al., 2002).

Marrubiin (20) was isolated from *Leonotis leonurus* (L.) R. Br., and both were tested via *in vivo* and *in vitro* studies to determine their anticoagulation reaction (Mnonopi et al., 2011). The marrubiin (20) and the plant extract suppressed the inflammatory markers, platelet aggregation, and coagulation marker while prolonged aPTT. The extract and marrubiin (20) in the concentration of 100 µg/mL were administered on rats. It was observed that the platelet adhesion was reduced in a dose-dependent manner, together with a depletion in protein secretion, fibrin formation, and d-dimer. The intracellular levels of Ca²⁺ were also reduced in a concentration-dependent manner and inhibited the calcium mobilization that was induced by thrombin by 50 to 200 µg/mL. This study shows that marrubiin (20) and the extract may have a direct inhibitory effect upon the synthase activity of cyclooxygenase or thromboxane due to the suppression of thromboxane B2 production (Mnonopi et al., 2011).

*Leuzea carthamoides* Willd. DC. consists of eriodictyol (21) and patuletin (22), which have similar antiplatelet activity (Koleckar et al., 2008). The leaf parts of the plant exhibited antiplatelet activity by inhibiting arachidonic acid and collagen-induced platelet aggregation. It showed a more potent antiplatelet activity in the collagen-induced aggregation compared to the arachidonic acid-induced aggregation. The mechanism that was exhibited by eriodictyol (21) is the decrease in antiplatelet potency that was caused by glycosylation process. Based on the study, apigenin and
quercetin formed from the glycosylation process exhibited a lesser activity compared to their aglycons (Guerrero et al., 2005). Based on the study, the extract of the *L. carthamoides* has a potent antithrombotic effect due to the presence of the antithrombotic agents, not due to the effect of the specific flavonoids that are present in the extract. The plant had shown a strong inhibition activity upon the platelet aggregation that was induced by adenosine diphosphate (ADP) (Kolecak et al., 2008).

Salvia miltiorrhiza Bunge consists of phenolic acid that is water-soluble, which is the salvianolic acid (23) (SAA). The study examined the effect of SAA in the antiplatelet and antithrombotic effect (Fan et al., 2010). In the *in vitro* assay, Tyrode’s solution was used to study the antiplatelet properties using a platelet aggregometer. The maximum height reached via the aggregation curves determines the extent of platelet aggregation of SAA. All tests showed that SAA had an inhibitory effect on ADP, thrombin, and platelet aggregation that was induced by AA. The compound inhibited ADP-induced platelet aggregation of rats with an *IC*$_{50}$ value of 390 µg/mL, whereby it inhibited the thrombin-induced platelet aggregation with an *IC*$_{50}$ value of 912 µg/mL. SAA (1,000 µg/mL) exhibited mild inhibitory activity on AA-induced platelet aggregation. In the *in vivo* study, the administration of SAA at dose 2.5, 5, and 10 mg/kg *via* intravenous caused dose-dependent inhibition upon the platelet aggregation in the rats. A similar observation with the *in vitro* study was observed. This study claimed that the SAA antiplatelet activity was due to the interference to a common signaling pathway, then directly binding to thrombin, ADP or AA to their respective receptors. The inhibition of ADP from dense granules of activated platelet might be one of the factors of the anti-aggregating properties of SAA (Fan et al., 2010).

The anticoagulant activity of *Tridax procumbens* (L.) L. was examined (Naqash and Nazeer, 2011). Sulfated polysaccharide isolated from the leaf extract of *T. procumbens* acts as an anticoagulant on heparin and chondroitin sulfate. Based on the *in vivo* assay, the activated aPTT had been prolonged to 113 s at 100 µg/mL by the sulfated polysaccharides from *T. procumbens*, which is almost 4-fold higher than the standard group. The sulfate group causes the anticoagulant activity but it is dependent on the sulfate group position in the chemical structure (Naqash and Nazeer, 2011).

**Diuresis Action**

Diuresis is an important mode of treatment for cardiovascular diseases, such as hypertension. It can increase the urinary volume and has a fewer side effect compared to others. Diuretics usually used as an independent drug or a combination with other drugs of the same mechanism of action in easing various conditions such as congestive heart failure, ascites, and pulmonary edema as well. Thus, few of the available diuretics cause adverse effects such as an imbalance of electrolytes, alterations in metabolic status, and some may impair the sexual function (Gupta and Neyses, 2005; Morganti, 2005).

Based on the previous studies of Asteraceae and Lamiaceae plant species, the number of plant species that exhibits diuretic effects is lesser than those other mechanisms, such as antioxidants, antihyperlipidemic, and vasorelaxant. The plant species that possess diuretic effect from the Asteraceae family are *Chamaemelum nobile* (L.) All., *Chrysanthemum x morifolium* Ramat. Hems., and *Tanacetum vulgare* L. and the plant species from Lamiaceae family are *Ajuga integrifolia* Buch.-Ham. ex D. Don (syn. *Ajuga remota* Benth.), *Anisomeles indica* (L.) Kuntze, and *Plectranthus amboinicus* (Lour) Spreng. The diuretic effect of *C. nobile* was assessed by examining the rats’ urine after fasted overnight (Zeggwagh et al., 2009). After repeated oral administration of 140 mg/kg aqueous plant extract for three weeks, the extract showed a diuretic and hypotensive effect.

*Plectranthus amboinicus* (Lour) Spreng is a plant species from the Lamiaceae family. Its leaf aqueous, alcoholic, and ethyl acetate extracts increased urine volume and decreased serum sodium level of albino rats after 24 h compared to the moduretic drug (El-Hawy et al., 2012). Meanwhile, the extracts did not show any significant effect on the rats’ potassium level. Based on the study, the ethyl acetate fraction was more potent as a diuretic group with better electrolyte balance (El-Hawy et al., 2012).

*Tanacetum vulgare* L. leaf extract was studied on its ability to act as a diuretic on rats (Lahlou et al., 2007). Water extract of the plant at a dose of 100 mg/kg was administered orally to the male Wistar rats. An increase in urine output was identified after 24 h of administration of the extract with a similar amount compared to furosemide administration. The extract had caused an increased level of Na$^+$ and K$^+$ in the urine, compared to furosemide, which has only an increase in Na$^+$. In contrast, the extract does not affect Na$^+$ and K$^+$ levels of the plasma. The diuretic effect occurs due to the renal tubular suppression upon its tendency for reabsorption of electrolytes and water into the bloodstream. The plant extract does not cause any renal toxicity as repeated dosing upon the rat for nine consecutive days. Thus, it requires a clinical study to ensure that its safety profile matches up with the physiology of humans and the long duration that patients usually take on diuretics. Different studies have shown that *T. vulgare* consists of flavonoids, tri- and sesquiterpene lactones and isoprenoids, polysaccharides, saponins, and polyphenols. Thus, it is unsure of which compound contributes to the diuretic effect of this extract (Lahlou et al., 2007).

**TOXICOLOGICAL STUDIES**

There are plenty of pharmacological studies on the Asteraceae and Lamiaceae plant species on its cardiovascular effects, while the toxicological aspects of these species have yet to be explored. Most of the people believe that medicines that are from medicinal plants or herbal medicines are always safe, simply due to the belief that all plants are safe to be consumed. This does not apply to all the medicinal plants. Medicinal plants have their toxicity nature depending on their dosage and method of extraction (Chanda et al., 2015).

Based on the studies in this review, few had included its toxicology test results and had herbal drug interaction during the administration of the medicinal plant extract in specific conditions. Traditional preparation methods of the medicinal plants into a consumable substance take different toxicity levels. The level of toxicity differs according to the solvents used. Thus it
is important to choose the appropriate solvent either for \textit{in vivo} or \textit{in vitro} experiments.

Acute toxicity test of \textit{Artemisia campestris} L. showed no symptoms of toxicity upon its aqueous extract administration of doses 1, 2, 4, and 6 g/kg (Dib et al., 2017). Based on the acute toxicological studies on \textit{C. crepidioides} (Benth.) S. Moore, it showed that consumption of the plant extract at a dose of 2500 mg/kg was safe. During the observation on the first 8 h, within the interval of every 8 h and upon the next 72 h, no significant change in the animal behavior or mortality was observed (Bahar et al., 2016). It showed that the dose is safe in the \textit{in vivo} testing.

Acute toxicity study was conducted on the ethanolic extract of \textit{Launaea intybacea} (Jacq.) Beauverd (syn. \textit{Lactuca runcinata} DC.) in 1% gum acacia upon rats (Devi and Muthu, 2015). Subsequent administration of the extract at dose 2,000 mg/kg body weight of rats for 14 days showed no toxicity effect, and this dose had helped in the reduction of total cholesterol and elevated the HDL level.

The plant in this study that showed toxicity is \textit{Leonurus cardiaca} L. Lavandulifolioside, the active component of \textit{L. cardiaca}, showed moderate toxicity at the amount of 1,000 mg/kg on the LD$_{50}$ when given intravenously (Wojtyniak et al., 2013). The butanol extract of the plant showed higher toxicity with LD$_{50}$ of 400 mg/kg when administered intravenously compared to LD$_{50}$ of 2,000 mg/kg when administered orally. This showed that the intake of this drug \textit{via} intravenous possess a higher toxicity possibility than \textit{via} oral intake (Wojtyniak et al., 2013).

Aqueous extract of \textit{Salvia scutellarioides} Kunth was administered in mice in two doses of 1 or 2 g/kg for 28 days (Ramirez et al., 2007). The administration showed no mortality. The study also claimed that if \textit{S. scutellarioides} is taken together with other diuretics drug, it might worsen hypokalemia symptoms or increase in digoxin related arrhythmias in patients because of the herb-drug interactions. (Ramirez et al., 2007). \textit{Teucrium polium} L. is known for its risk of hepatotoxicity due to hepatocyte necrosis occurs massively in the central lobular area such as lymphocyte inflammatory infiltrate, bile duct proliferation, and bile retention. Clinical signs are often seen in the usage of this plant; thus, proper usage of this plant on the therapeutic range would resolve the problem.

However, some of the traditional use of the medicinal plant is undocumented that results in the decline of knowledge and making it unreliable. Therefore, it has become necessary to document the knowledge and shared them entirely to ensure their quality and preservation. Based on this review, medicinal plants were widely consumed using decoction or taken orally as a raw product of fruits, leaves, and roots. Most of the plants from Asteraceae and Lamiaceae family are rich in flavonoids and terpenoids, together with other phytochemicals that act as the inducer of the mechanism in alleviating cardiovascular diseases. The plants have a strong antioxidant effect, followed by anti-hyperlipidemic, vasodilation, antithrombotic, and diuretic effects which are mechanisms that are closely related in resolving cardiovascular diseases such as coronary heart diseases (CHD), atherosclerosis, hypertension, and others. As the medicinal plant being beneficial for treating human ailments, we should not waste these resources by leaving them to grow wild and perish, without utilizing them for better pharmaceutical development in the future.

**FUTURE STUDIES**

Based on the evidence-based review on the use of medicinal plant from the plant family of Asteraceae and Lamiaceae in cardiovascular diseases, we hope that information from this review will facilitate future research initiatives to develop new medicinal plant-based medication for cardiovascular disease treatment or continue with any clinical studies to prove the effectiveness of this medicinal plant upon humans. The clinical trial needs to be performed to have a better knowledge of their safety and efficacy to ensure that it can be beneficial to the human race.

**AUTHOR CONTRIBUTIONS**

JM obtained the pieces of literature and wrote the manuscript while NA and KH edited the manuscript.

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**CONCLUSION**

The last few decades have witnessed several rapid changes in the traditional use of the medicinal plant in developing countries.
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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