Potential use for the treatment of cardiovascular diseases from traditional herbs: A mini review

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ABSTRACT
The prevalence of non-communicable diseases (NCDs), which include cancers, chronic respiratory diseases and cardiovascular disease (CVD), has become a leading health threat to various societies, contributing approximately 60% to the global mortality. Among the three diseases, CVD is labeled as the top cause of deaths, accounting for half of mortality due to NCDs. Risk factors are contributing to the acquisition of CVD that may range from family history, lifestyle, diet and medication. This article aims to deliver a brief literature review concerning efficacies of some traditional herbs in CVD treatment and a current background on this research topic.

Keywords: *herbal medicine, cardiovascular diseases, protective effect, hypertension*

1. INTRODUCTION

The term cardiovascular disease generally refers to disorders impairing the normal functions of the heart or blood vessels. The direct cause of CVD could be attributable to accumulation of fats in arteries, which in turn poses high risk of blood clotting, or to damaged arteries in organs such as the brain, heart, kidneys and eyes. According to WHO, in 2019, 32% of the global mortality, which is approximately 17.9 million deaths, could be attributable to CVDs and this figure is forecast to rise to 23 million in 2030. In Europe, there are 1.3 million deaths due to CVDs, accounting for about 33% [1]. The situation is also aggravated in many developing countries where health care is inadequate and public attention to CVD is scant. In Vietnam, CVD also accounts for 33% of all deaths [2].

The exact mechanism of CVD formation has not yet been fully understood. However, the risk of developing CVD can be reduced by mitigating associated factors, which are typically categorized into three main types. The first category mainly involves unhealthy behavioral risk factors including smoking, lack of physical activity and high consumption of salt, fat and calories. The second group of factors are conditions that are related to metabolism-metabolic risk such as high blood pressure (hypertension), raised blood sugar (diabetes), blood lipids, overweight and obesity. The third category are socio-economic characteristics such as educational level, age, and gender, genetic disposition and psychological risks such as stress or depression.

Although CVD is the top cause for death globally, 90% of CVDs can be preventable if established risk factors are avoided [3]. In addition, not only does the practice of measures such as reduced alcohol consumption or regular physical activities could reduce CVD risk, the maintenance of a healthy lifestyle

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also prevents the worsening health state in medicated patients with CVD. Many studies have been performed to find out efficient drugs for treatment of CVD. Recently, herbal medicines have been the subject of focus because of their natural and safe characteristics. Herbal medicine is a long-established way of treatments since the beginning of humankind and is still widely used in many parts of Asia and Africa. To date com-pounds isolated from herbs and plant have become important medicines, such as aspirin, reserpine, and digitalis. This review focuses on some potential herbs on CVD treatment. This review focuses on reports on herbs demon-strated beneficial and positive impact in preventing and treatment of CVD.

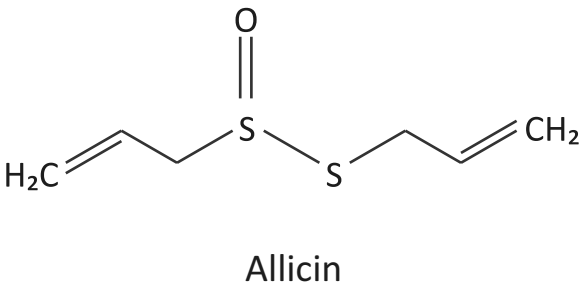
2. SOME HERBAL PLANTS FOR TREATMENT OF CVD

2.1. *Allium sativum* L. (garlic)

Allium sativum L. (garlic), belonging to onion genus, has been used widely for millenniums in both culinary and medicinal applications. In a review article, it was indicated that past evidence agreed on the cardiovascular risk reducing effects of garlic, including reduction in abnormal plasma lipids, oxidized low density lipoproteins (LDL), abnormal platelet aggregation and a high blood pressure [4].

One of the most important compounds responsible for cardio-protective effect of garlic is allicin. Allicin is known to be hydrophobic and can be easily transported through phospholipid bilayer without damaging it and then metabolized to exert pharmacological effects that are important to the cardiovascular system. Such beneficial effect may include induction of vasorelaxation, prevention of hyperlipidemia, and prevention of cardiac hypertrophy. In addition, the beneficial impact of allicin to cardiovascular system is also realized through enhancing the glutathione production and reducing the level of reactive agents [5].

The efficacy of garlic in treatment of cardiovascular disease has been extensively investigated. In rat model fed with cholesterol diets, administration of increasing concentrations of commercial garlic was found to positively and correspondingly influence plasma lipids, antioxidant activity and some indices of blood coagulation. Therefore, it was suggested that commercial garlic could be a valuable atherosclerosis preventing ingredient [6]. In another study, Choudhary et al. tested hypolipidemic property of garlic on cholesterol-fed guinea pigs. Garlic showed significant hypolipidemic activity as it lowered cholesterol, triglyceride and LDL levels [7]. These results showed that garlic can be used in preventing CVD due to atherosclerosis.

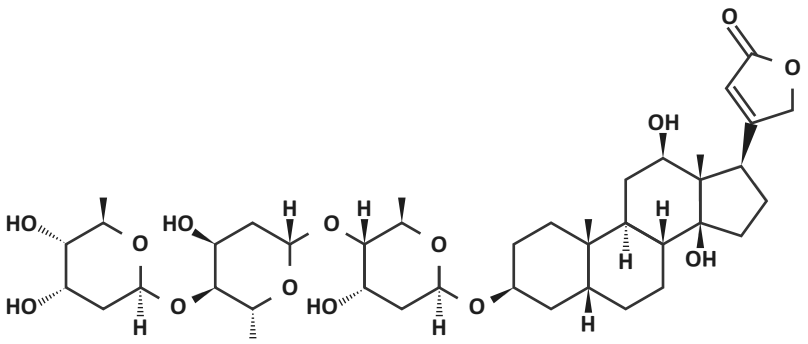


Allicin

Figure 1. *Allium Sativum* L. (garlic) [8] and its major active compound

2.2. *Digitalis purpurea*

Digitalis purpurea, also referred to as Foxglove, is now recognized as *Digitalis mariana* subsp. *Heywoodii (P.Silva & M.Silva) Hinz.* Main compounds obtained from leaves of *Digitalis purpurea* include gitoxin derivatives. In a previous study dealing with various animal subjects, methanolic extract of *Digitalis purpurea* at concentrations of 20 and 40 µg/mL was found to exert dose-dependent contraction force of auricles. In addition, the extract showed the slight diuretic and natriuretic effect and decreased the emesis time within 10 min of injection [9]. Another study demonstrated that two valuable cardiotonic glycosides, namely Digitoxin and Digoxin, could also be harvested from *Digitalis purpurea* biomass[10]. Although the benefit of digoxin in heart failure patients has been questioned, other compounds in the cardiac glycoside class find continual use in treatment of congestive heart failure [11], especially for elderly patients and is ranked as one of the most prescribed medications in United States[12].

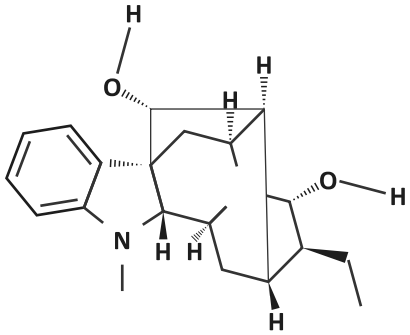


Digoxin

Figure 2. *Digitalis purpurea* [13] and its major compound

2.3. *Rauwolfia serpentina*

Rauwolfia serpentina is medicinal shrub belonging to family Apocynaceae and is usually used as an antihypertensive herb [14]. There were several studies on *Rauwolfia serpentina* that have been reported. On alloxan-induced diabetic rats, hypoglycemic and hypolipidemic activities of the methanolic extract of the plant were confirmed in a previous study. The results showed that total glucose, cholesterol, triglyceride and alanine aminotransferase level of the group of rats treated with plant extract (30 mg/kg) were significantly lower in comparison with those of the control group and group treated with popular anti-diabetic drug chlorpropamide [15]. Similarly, effects of methanolic root extract of *Rauwolfia serpentina* on diabetic mice was also reported, showing reducing effect in level of the extract on total cholesterol, triglycerides, low-density lipoprotein (LDL-c), and very low-density lipoprotein (VLDL-c) cholesterols [16]. These researches confirm the antiatherogenic ability of *Rauwolfia serpentina.* Moreover, antioxidant activity of *Rauwolfia serpentina* makes it a potential cardioprotective agent[17].

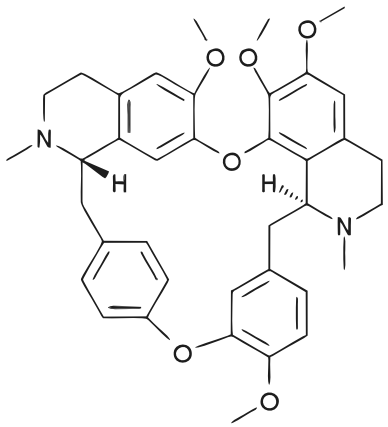


Ajmaline

Figure 3. *Rauwolfia serpentine* [18] and its major compound

2.4. *Stephania tetrandra*

Stephania tetrandra is an herbaceous perennial vine of the Menispermaceae family (*Stephania tetrandra* is a creeping, woody, perennial vine). It is a traditional Chinese medicine containing tetrandrine as the main component. Tetrandrine isolated from *Stephania tetrandra* exhibits antihypertensive and antiarrhythmic effects, demonstrated in experiments involving hypertensive animals and patients. In addition, the extract of *Stephania tetrandra* can suppress elevation of arterial blood vessels [19]. To be specific, in hypertensive rat mode, administration of tetrandrine extracted from *Stephania tetrandra* was showed to reduce blood pressure when comparing with control group (192 vs 210) [20]. Recent researches proposed that the pharmacological mechanisms underlying calcium antagonistic effect of tetrandrine and the interaction of tetrandrine with M receptor involve the blocking the cardiac transmembrane Na^+, K^+, Ca^{2+} ion current [21]. These results suggest that S*tephania tetrandra* can be a potential drug to treat hypertension.



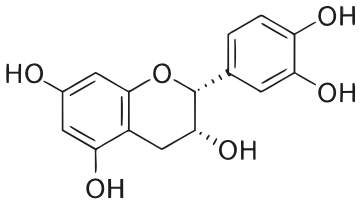
Tetrandrine

Figure 4. *Stephania tetrandra* [22] and its major compound

2.5. *Crataegus species* (Hawthorn)

Crataegus has been used widely because of its preventive effects on heart failure and cardiovascular disease. These pharmacological effects are attributed to content of flavonoids, procyanidin, aromatic acid and cardiotonic amines [23]. A previous study investigating the blood pressure and structure of coronary

arterial wall of L-NAME-induced hypertensive rats showed that aqueous leaf extract of *C. tanacetifolia* (100 mg/kg) contributed to the prevention of the hypertension and conferred beneficial effects on cardiovascular system in examined animal subjects [23]. In another research, Wang et al. examined the effect of the ratio of proanthocyanidins and total flavonoides isolated from *Crataegus pinnatifida* on cardiovascular hemodynamics of anaesthetic dogs. The observation results showed that blood output and blood output/pulse increased, total peripheral resistance decreased [24] with the injection of total flavonoides and proanthocyanidins at 3:1 ratio. In rat model fed with high-cholesterol diet, Hawthorn powder was also found to suppress hypercholesterolemia. This was demonstrated by significant reduction in symptoms associated with high-fat diet such as fatty liver, increased nitric oxide and elevated oxidative stress in the treatment group in comparison with the control group[25].

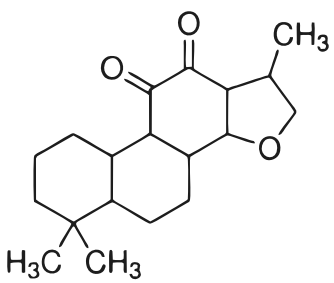


Procyanidin

Figure 5. *Crataegus* species [26]

2.6. *Salvia Miltiorrhiza* (Danshen)

Danshen is an important herb traditionally used to cure blood-related disorders in Chinese medicine [27] and has been experimentally tested against angiotensin II-induced responses in rat model studies in the research of Ouyang and co-workers, danshen root extract was demonstrated to be capable of inhibiting angiotensin II in hypertrophic cardiac cells and preventing hypertrophic reaction of rat cardiac cells [27]. Another similar study also articulated that danshen extract's derivatives produced protective effects on the myocardium against hypertrophy[28].



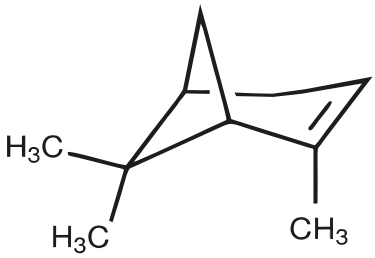
Tansinon IIA

Figure 6. *Salvia Miltiorrhiza* [29] and its main compound

2.7. *Rosmarinus officinalis* (Rosemary)

Rosemary is a widely commercialized plant that figures prominently for antioxidant activity. The antioxidant compounds have demonstrated the benefits in reducing cardiovascular risks.

The antioxidant activity of rosemary extracts have been confirmed in several studies. To be specific, in hypercholesterolemia rats, the treatment of aqueous extract and non-esterified phenolic fraction from rosemary lowered serum total cholesterol (-39.8%), non-HDL-c (-44.4%) and thiobarbituric acid reactive substance (TBARS) levels (-37.7%) in comparison with those of the high-cholesterol diet group[30]. The 2,2-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$) assay also indicated that extracts demonstrated significant antioxidant activity. In another research, Wang and collaborators investigated the antioxidant activity of rosemary extract. In the β-carotene bleaching test system, rosemary extract was demonstrated to exhibit stronger antioxidant activity compared to a synthetic antioxidant, butylated hydroxytoluene[31].

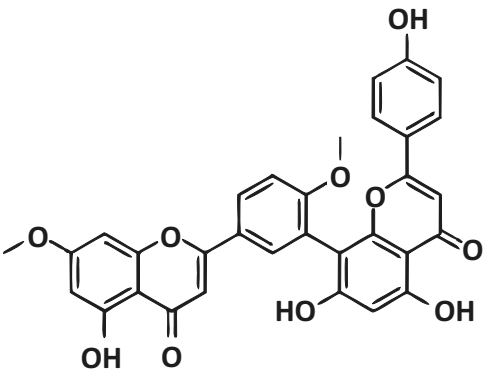


α-pinen

Figure 7. *Rosmarinus officinalis* [32] and its major compound

2.8. *Ginkgo biloba*

Ginkgo biloba is known as ginkgo or gingko, which belongs to Ginkgoaceae family. The plant catches scientific interest thanks to the presence of two pharmacologically valuable groups of substances, namely flavonoids and terpenes. While the former could act as an enhancer for circulatory flow in the absence of blood pressure influences, an inhibitor for formation of platelets and a reductant for vascular resistance, the latter lessens capillary permeability, fragility and acts as free radical scavengers[33, 34]. There are many researches and clinical trials to illustrate the effect of *Ginkgo biloba* on cardiovascular health. In a clinical trial with eight patients under going aortocoronary bypass operation, administration of *Ginkgo biloba* extracts had shown reducing effects on the formation of atherosclerotic nanoplaque and size of nanoplaque by 11.9% and 24.4%, respectively after two months. In addition, the amount of oxLDL/LDL and lipoprotein(a) concentration were respectively lowered by 17% and 23.4% [35]. Some reports have demonstrated the vasodilatory effect of *Ginkgo biloba* extract. In a study, bovine aortic endothelial cells were protected from cell damage caused by hydrogen peroxide when treated with *Ginkgo biloba* extract for 10 min [36]. Additionally, treatment with *Ginkgo biloba* extract decreased the restenosis in obese rats with Type 2 Diabetes after balloon injury to the carotid artery[37].

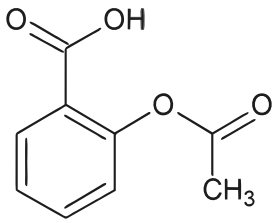


Ginkgetin

Figure 8. *Ginkgo biloba* [38] and its major compound

2.9. *Salix alba*

Salix alba is commonly named white willow bark. The plant has a long history of use in treatment of pain and fever since the ancient period. A previous analysis has identified a minimum of 11 salicylate compounds in the aqueous extract of Salix alba by HPLC mass spectrometry [39]. Among them, acetylsalicylic acid (ASA) has been regarded as an effective agent for primary and secondary prevention of myocardial infarction, ischemic stroke and vascular mortality and has been included in antiplatelet as an important ingredient due to economic and safety reasons[40].



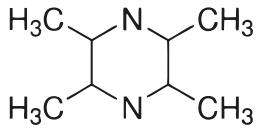
Acetylsalicylic

Figure 9. *Salix alba* [41] and its major compound

2.10. *Lingusticum wallichii*

Lingusticum wallichii, also known as Chuan-xiong in Chinese, has been used in folk remedies in traditional Chinese medicine and in food preparation. Composition of the plant includes essential oil, phenolic acids, alkaloids, phthalide lactones as major constituents. The benefit of *Lingusticum wallichii* was first demonstrated in a past study where rabbits fed with cholesterol containing diets were administered with Chuanxiong pills [42]. The results showed that the level of cholesterol and the red cell deformability in rabbits were reduced in treated rabbits. In another study,

tetramethylpyrazine (TMP) isolated from *Lingusticum wallichii* was found to inhibit platelet thrombus formation. Besides that, TMP was also found to inhibit platelet thrombus formation in another study. To be specific, TMP was suggested to suppress the process of rapid thromboembolism, which is mediated by von Willebrand factor (vWF), producing antiplatelet effect [43, 44]. Moreover, *Lingusticum wallichii* is also widely used China traditional medicine for the treatment and prevention of stroke. This is due to the presence of ferulic acid in the plant which can diminish cerebral infarctions and neuroma. By experimenting on rat models, the mechanisms of the effect were partially explained by the antioxidation of superoxide radicals (ICAM-1 and NF - kB) by ferulic acid[45].



Tetramethylpyrazine

Figure 10. *Lingusticum wallichii* [46] and its major compound

3. CONCLUSION

Utilization of herbs has been a widespread way for treatment of various cardiovascular diseases. Even though there are currently many ongoing studies about the efficacy such herbs, a large number of local plants possessing compounds with cardioprotective activities has not been thoroughly explored. In addition, the topic of safety in use of medicinal plants is also of great importance as it could complement the clinical applications and extend their use into commercial fields.

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Tổng quan về tiềm năng điều trị các bệnh lý tim mạch của thảo dược

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TÓM TẮT

Tỷ lệ mắc các bệnh không lây nhiễm (NCD), bao gồm ung thư, bệnh hô hấp mãn tính và bệnh tim mạch (CVD), đã trở thành mối đe dọa sức khỏe hàng đầu cho xã hội, chiếm khoảng 60% tỷ lệ tử vong trên toàn cầu. Trong số ba bệnh lý, CVD được coi là nguyên nhân gây tử vong hàng đầu, chiếm một nửa tỷ lệ tử vong ở các bệnh không lây nhiễm. Các yếu tố nguy cơ góp phần vào việc mắc bệnh CVD có thể bao gồm từ tiền sử gia đình, lối sống, chế độ ăn uống và thuốc men. Bài viết này nhằm mục

đích tổng quan sơ lược về hiệu quả của một số loại thảo dược truyền thống trong điều trị CVD và cung cấp nền tảng cho hướng nghiên cứu về chủ đề này.

***Từ khóa**: thuốc thảo dược, các bệnh lý tim mạch, tác dụng bảo vệ, tăng huyết áp*

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