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Original Article

Effects of Medicinal Plants and Secondary Metabolites on the Most Important Risk Factors of Cardiovascular Diseases: A Review

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ABSTRACT

Although the people's knowledge about cardiovascular diseases (CVDs) has increased, these diseases are still among the main causes of mortality in industrialized and developing countries and communities. For controlling and treating CVDs, both pharmaceutical and non- pharmaceutical methods can be helpful. The high global prevalence of CVDs and associated serious effects on the body organs made them a major health problem in all societies. Concerns about the side effects of synthetic drugs lead to their improper usage and rejection by patients and subsequently a disrupted disease management process. For this reason, today, a new approach is emerging toward medicinal plants, and in fact, they are subjected to extensive research these days. The aim of this review was to introduce medicinal plants and present their action mechanisms, which have been effective in the treatment of CVDs. A literature search was conducted to recruit the articles published in various databases. We also reviewed reference textbooks to elaborate on the mechanisms of action of various plants in the treatment of cardiac diseases and investigate the involved molecular mediators and pathways. Studies have shown that herbal medicines through various mechanisms such as lowering blood pressure, resolving diabetes, improving atherosclerosis, reducing blood fats, inducing nitric oxide, blocking calcium channels, and suppressing the renin-angiotensin pathway can help improve CVDs.

INTRODUCTION

Cardiovascular diseases (CVDs) are the main causes of mortality in industrialized and developing countries and account for approximately 20% of total annual deaths world [1, 2]. Today, CVDs have been considered the first cause of death in industrialized countries. Reports indicated that CVDs killed 950,000 people in the United States in 1998, and the country has spent about $ 118 billion for managing CVDs in 2000. The global prevalence of CVDs has risen from < 3.4% to a maximum rate of 72.5% [3, 4].

Pressure is closely related to obesity, especially central or abdominal obesity. Abdominal obesity is an important cause of coronary artery disease, stroke, and congenital heart failure. The spread of obesity-related hypertension is associated with high blood cholesterol, insulin resistance, diabetes risks, and chronic renal diseases. Many studies have indicated a close relationship between the risk factors of CVDs and obesity or hypertension. Moreover, overweight and obesity, as parts of the metabolic syndrome, have been linked with the development and progression of hypertension [5]. Hypertension is a progressive disease triggering the development of CVDs. Around 25% of the world's population suffer from hypertension, which is a chronic disease with increasing global prevalence. This disease has been associated with several complications, such as cardiac and cerebral strokes [6].

Diabetes is another important risk factor for hypertension and CVDs. Type 2 diabetes has been associated with high blood pressure and an increased risk of CVDs, leading to abnormalities in the structure and function of central and peripheral cardiovascular systems and even death [7, 8]. Patients with long-term diabetes mellitus generally suffer from renal failure, eye problems, and cardiovascular and central nervous system insufficiencies [9].

The nervous system, heart, vessels, and kidneys are the four main targets of antihypertensive drugs [10].

The vascular endothelium also plays a central role in the regulation of vascular tone by releasing various neuro-hormonal modulating factors including vasoactive substances such as nitric oxide, prostaglandin I_2, endothelium-derived hyperpolarizing factor (EDHF), and vasoconstrictors [11].

Hyperlipidemia, especially elevated blood cholesterol, is an important factor exacerbating CVDs. Currently; more than 100 million American adults have high blood cholesterol levels, about 50 million of whom require therapeutic interventions. Statistical data indicates that 50% of those who need treatment receive pharmaceutical drugs. In addition, of the patients who receive drug therapy, only 23% reach adequate treatment [12, 13].

Today, hyperlipidemia and its side effects are recognized as one of the important problems of the health system of most communities. In addition to aggravating metabolic disorders, hyperlipidemia exacerbates CVDs, especially in patients with diabetes and hypertension. Evidence indicates that the compounds available in dietary supplements and medicinal herbs, including dietary fiber, vitamins, flavonoids, sterols, and other antioxidants, can affect fat metabolism in different tissues via modulating various metabolic pathways.

The primary and continuous production of nitric oxide by endothelial cells is among the factors participating in maintaining vascular integrity and proper blood flow. Nitric oxide production in endothelial cells is mediated by the eNOS isozyme. It is well established that with atherosclerosis progression and due to endothelial cell dysfunction, the production of nitric oxide by eNOS decreases. On the other side, nitric oxide production in inflammatory conditions is significantly increased by the action of iNOS isoenzyme. The excessive production of nitric oxide in this condition induces nitrative damage and the progression of inflammation and atherosclerosis [14, 15]. Patients with chronic heart failure often develop ventricular arrhythmias, which are associated with high mortality rates characterized with changes in the ventricular myocardium. This change may lead to the direct electrophysiological response of the heart to epinephrine and norepinephrine [16,17]. Hypertension is also one of the most significant risk factors predisposing to atherosclerosis, myocardial infarction, left ventricular hypertrophy, and cerebrovascular events [18]. Despite the advent of multiple chemical antihypertensive drugs, many patients still suffer from the disease. Even in developed countries, arterial hypertension is controlled in only one-third of patients, and today we are facing drug resistant hypertension, indicating the ineffectiveness of available drugs. Treating drug-resistant hypertension requires selecting the therapeutic regimens consisting of several drugs with complementary mechanisms of action [19-21]. Due to the adverse effects of many chemical drugs and their relatively high costs, the tendency toward using medicinal plants has increased in recent decades so that more than 20% of the drugs currently used in the United States are of plant origin [22,23].

In traditional medicine, several therapies, particularly medicinal plants, are used to treat heart diseases. Recent researches on dietary supplements and herbs used in traditional medicine indicate that their constituents including dietary fiber, vitamins, flavonoids, sterols, and other antioxidant compounds can improve CVDs via lowering blood lipids, inhibiting LDL oxidation, scavenging oxygen free radicals, and improving metabolic abnormalities and the immune system function [24-27].

Due to the high prevalence of CVDs and their requirements for intensive care, and because of the side effects of many chemical drugs, researchers today by taking into consideration of the pathological mechanisms of these diseases, suggest using non-pharmaceutical methods and medicinal plants instead of common therapeutic regimens to manage CVDs. This review discusses the mechanisms of various medicinal plants in modulating the risk factors and causes of CVDs with an emphasis on the involved molecular mechanisms.

MATERIALS AND METHODS

For conducting this review, a literature search was performed using relevant keywords to gather the articles published in various scientific databases. We also checked reference text books to review the mechanisms of actions (such as vasodilation, nitric oxide (NO) production, calcium channels blocking, blood pressure lowering, renin-angiotensin pathway inhibition, blood lipid reduction, and diabetes and atherosclerosis improvement) of different plants affecting CVDs. A thorough discussion was also provided on the molecular mechanisms involved in the pathogenesis of these diseases.

RESULTS

Vitamin E: This vitamin can inhibit platelet aggregation and, therefore, the formation of platelet thrombosis by suppressing the activity of platelet enzymes. This vitamin can also prevent the oxidation of low molecular weight fats and the re-formation of atherosclerotic plaques [28,29]. However, it can be said that the decreased oxidase function of platelets leads to a spontaneous reduction in the number of platelets. So, by suppressing the production of free radicals via inhibiting adenosine deaminase and cyclic ADP following stroke, it is amenable to dampen the risk of a second stroke in patients [30].

Vitamin C: Vitamin C reduces the risk of CVDs by trapping and then inactivating free radicals and reactive oxygen molecules. In order to prevent tissue damage, antioxidants also act via preventing the formation of atherosclerotic plaque by reducing LDL level and preventing electron oxidation, which induce changes in platelet morphology [31].

Nettle: Nettle, with the scientific name of *Urtica dioica L*. and a member of Urticaceae family, is a flowering herbaceous perennial plant with high nutritional and medicinal values [32].

The plant contains flavanols, xanthophyll, flavones, and leucoanthocyanidins, and flavonoid compounds are probably involved in the systolic blood pressure lowering effects of nettle [33].

A research has shown that nettle has diuretic and natriuretic, as well as blood pressure lowering effects in rabbits [34]. Taheri *et al*. also confirmed the effects of nettle on the cardiovascular system by reducing blood pressure via influencing renal function and its diuretic and natriuretic effects [35]. Nettle, probably through lowering blood pressure, reduces heart rate, which is one of the signs predicting cardiovascular events [36].

Walnut with the scientific name of *Juglans regia* is among the plants used in Iranian traditional medicine because of its multiple therapeutic benefits, including blood sugar lowering properties. The leaves of this plant contain tannins, essential fatty acids, ascorbic acid, flavonoids, and caffeic acid. In addition, paracoumaric acid Jugolon is the most prominent substance in various organs of the plant, conferring walnut additional features in reducing blood lipids and sugar and preventing vascular plaque formation. Walnut has also been effective in lowering cholesterol and improving CVDs [37].

Lettuce with the scientific name of *Lactuca sativa* has potent antioxidant effects [38-40]. Lettuce can induce the release of histamine from mast cells and subsequently lead to the dilation of blood vessels and a reduction in blood pressure. The opioid-like alkaloids, which are present in lettuce extract, may be involved in the antihypertensive effects mediated by histamine receptors [41, 42]. Moreover, it has been shown that agonists of opioid receptors can alter arterial blood pressure by various mechanisms such as modulating the nervous system [43, 44].

Cumin: Cumin with the scientific name of *Cuminum cyminum* has also high antioxidant capacities. The preventive effects against the oxidation of HDL have been related to the act of paraoxonase (PON1) enzyme. Regarding the antioxidant properties of cumin, it is expected that its consumption will increase PON1 enzymatic activity in plasma and therefore decrease the risk of CVDs [45].

Saffron: The scientific name of saffron is *Crocus sativus*, a plant with various pharmaceutical properties and multiple components including anthocyanins, flavonoids, vitamins (such as riboflavin and thiamine), minerals, fiber, carbohydrates, proteins, and fat, which have major effects on human's health [46].

In addition, the value of *C. sativus*, in part, is attributed to the presence of three important secondary metabolites (i.e. crocin, picrocrocin, and safranal) in the extract of this plant [47].

Saffron has been reported to have antihypertensive and anti-ischemic effects [48]. Saffron-derived crocin causes an increase in the production of vasodilators including nitric oxide [49].

Reports have also shown that crocin can suppress the release of calcium from the sarcoplasmic reticulum of vascular smooth muscle [50]. Also, saffron extract was described to inhibit calcium channels in the isolated heart of guinea pigs [51]. According to these, it has been suggested that the antihypertensive effects of crocin may be mediated by angiotensin via at least one of the above-mentioned pathways [52]. Pharmacological studies also confirm the potent antioxidant properties of crocin [53]. For example, crocin can protect the heart against oxidative damage and prevent myocardial infarction by boosting the activity of superoxide dismutase enzyme and reducing malondialdehyde production in the myocardium [54].

One of the active ingredients of saffron is crocetin. Crostine has protective effects on cardiovascular damage (such as heart hypertrophy and atherosclerosis). Crocetin has also been shown to modulate blood pressure and synthesize inflammatory mediators in the heart after hemorrhagic shock [55,56].

Borago: *Borago officinalis* is a plant belonging to the borage family. The hypolipidemic effect mediated by flavonoids and free radical scavenging ability of borage flower extract have been demonstrated in previous studies. Alkaline compounds such as pyrrolizidine glycoside and beneficial lipids have been isolated from different parts of *B. officinalis*, and their antioxidant activity, gastric mucosa protective effects, as well as hypoglycemic and cardiovascular modulating properties have been investigated. Borage lowers blood pressure via reducing heart rate. The plant is also beneficial to patients with CVDs as it can promote hemodilution [57-60]. So far, several properties such as antioxidant [61], antihypertensive [62], along with biochemical and clinical effects have been reported for the members of the borage plant family [63].

Common mallow: This is a plant (known in Iran as panirak) with the scientific name of *Malva Sylvestris.* The plant has antioxidant properties because of a relatively high content of antioxidant compounds. It has four major fatty acids including linoleic acid, linolenic acid, palmitic acid, and oleic acid. The methanolic extract of this plant has been shown to contain a variety of phenolic compounds [64]. Such as anthocyanins, carotenoids, and tocopherol [65]. The antioxidant properties of this plant can reduce cholesterol level and lipid peroxidation. *M. Sylvestris* has also been demonstrated to prevent arterial thrombosis and reduce the risk of CVDs [66].

Poales: *Cynodon dactylon* has been recognized as a medicinal plant in some regions of Iran, especially Azerbaijan. Among the essential compounds of this plant are beta carotene, beta-systole, vitamin C, palmitic acid, flavonoids, saponins, and alkaloids [67]. *C. dactylon* has been demonstrated to have antioxidant, lipid-lowering, and anti-inflammatory effects [68]. Hypercholesterolemia induces the local activation of endothelial cells in large and medium arteries, and subsequently LDL retention in the inner layer of blood vessels leads to the initiation of atheroma formation and the recruitment of immune cells such as T lymphocytes and monocytes to this layer. The activation of scavenger receptors on the surface of macrophages and lipoproteins leads to the secretion of proinflammatory cytokines [14].

C. dactylon extract increases antibody production through the induction of humoral immunity reactions while decreases T lymphocyte cellular immune responses [69]. In previous studies, the role of T lymphocytes in the development and spread of atherosclerotic lesions has been suggested [14]. Therefore, *C. dactylon* extract has been effective in lowering triglycerides and cholesterol levels, as well as managing atherogenic factor and atherosclerosis, and finally reducing the risk of CVDs [70].

Felty Germander: The scientific name of this plant is *Teucrium polium*. The plant belongs to the genus of teucrium (Golpureh in Persian). In studies on *T. polium* extract, it was shown that the plant contains tannins, terpenoids, saponins, sterols, and flavonoids [71,72]. The plant shows antibacterial and cholesterol-lowering effects. It also reduces cardiac pain and the risk of CVDs [73]. The plant extract has been effective on blood pressure in hypertensive condition. *T. polium* has positive inotropic effects on myocardium, as shown by a study on the heart isolated from guinea pig. Previous studies have shown muscular relaxing effects of *T. polium* extract on the smooth muscles of vessel wall, ileum, and uterus [74-76].

Hawthorn: The scientific name of this plant is *Crataegus azarolus*. It is an herbal medicine used for the treatment of asthma, kidney stone, and CVDs [77]. The chemical compounds of this plant include vitamin C, flavonoids, tannins, acetylcholine, purine derivatives, and adenosine. The leaves and flowers of *C. azarolus* are used in traditional medicine to treat heart failure and atherosclerosis [78]. The extracts of hawthorn leave and flowers have several pharmacological effects including anti-ischemia/reperfusion, antiarrhythmic, hypolipidemic, and antihypertensive effects [79]. These extracts also reduce plasma VLDL and LDL levels, as well as other blood lipids. These effects have been attributed to the presence of compounds such as oleanolic and ursolic acids, which reduce the intestinal absorption of cholesterol [80]. The antioxidant effects of this plant can be attributed to its polyphenolic nature, which prevents the release of free radicals by maintaining the membrane structure [81, 82].

Feverfew: This plant, which is known with the scientific name of *Tanacetum parthenium*, consists of compounds such as tannin, saponin, and kaempferol, which all have antioxidant properties [83]. The other most important antioxidants of the plant include flavanols, apigenin, and luteolin [84]. These substances prevent enzyme leakage and cell destruction by preventing lipid peroxidation and stabilizing cell membranes. The cardiovascular protective effects of *T. parthenium* are related to its role in reducing cholesterol and fatty acids and preventing the oxidation of cell membranes via protecting against the detrimental effects of free radicals and LDL-cholesterol. The antioxidant properties of this plant can be also attributed to its capacity in inducing antioxidant enzymes such as SOD and GPX, evidenced by a reduction in MDA level [85].

Persian Koma: The plant, which is also known as *Ferula persica*, belongs to the apiaceae family. In gas chromatography, 61 different compounds have been identified in this plant, comprising 93.7% of its total essential oil. The main components of the oil include opiul and safranal [86].

Studies on safranal have shown that this compound effectively reduces blood pressure in both healthy and hypertensive mice [87]. The biological effects of *F. persica* are probably due to its impacts on vessels and endothelium. Angiotensin-converting enzyme is a key component of the renin-angiotensin-aldosterone system and an important contributor to the blood pressure regulation process. Abnormal increase in the activity of this system causes hypertension, and angiotensin inhibitors are major targets for controlling blood pressure. Flavonoids, coumarins, and sulfur derivatives of *F. persica*, have been reported to inhibit angiotensin-converting enzyme and reduce blood pressure [88, 89].

Jujube: The scientific name of jujube is *Zizyphus jujubemill*, and it has been used as a medicinal plant since ancient times [90,91]. It contains carbohydrates, proteins, fiber, fats, essential vitamins, and minerals [92]. It has been shown that the plant also contains fatty acids, beta-carotene, α-tocopherol, caffeic acid, and epicatechin [93]. Jujube reduces blood pressure, prevents CVDs, and inhibits inflammation. In the inflamed heart, jujube was described to reduce inflammation and improve myocardial histological structure by inducing hyperemia [91, 94, 95]. In another study, *Z. jujubemill* extract completely improved necrosis in the heart and reduced histological changes and inflammation of the tissue and muscle cells [95].

Green tea: Green tea is known with the scientific name of *Camellia sinensis*. Green tea extract contains polyphenols such as catechins, epicatechins, and epigallocatechin. In the fresh leaves of green tea, there are phenolic acids such as gallic acid and tinine amino acid, as well as flavanols and phenolic acids. Most green tea polyphenols (either soluble or powder) contain from 10% to 45% caffeine. In studies, green tea has been shown to significantly reduce systolic blood pressure and LDL cholesterol. Although the effect on systolic blood pressure has been small, that on total and LDL cholesterol was reported to be moderate.

Most studies suggest that the inhibition of the activity of catecholamine transferase (by polyphenols) and phosphodiesterase (by caffeine), which both present in green tea, results in a synergistic effect in stimulating the sympathetic nervous system and subsequently increasing in cellular energy expenditure, heat production, fat oxidation, as well as reduction in fat cell proliferation and lipogenesis [96, 97]. As green tea contains epigallocatechin gallate, its consumption can lead to the release of nitric oxide and prostaglandins and thus cause vasodilation. The catechins available in green tea have also been reported to reduce systolic blood pressure [98, 99].

Garlic: The plant with the scientific name of *Allium sativum* has significant antioxidant capacity and includes disulfide, propyl sulfide, allyl propyl disulfide compounds, as well as allicin. Studies show that garlic, by exerting a direct impact on vascular wall smooth muscles, induces the vasodilation of peripheral arteries. It seems that this drug via opening potassium channels causes the hyperpolarization of membrane potential and vasodilation. Garlic also increases nitric oxide production by activating nitric oxide synthase, thereby lowering blood pressure. The effects of garlic on lowering cholesterol and triglycerides are probably promoted by suppressing the key enzymes (such as hydroxy methyl glutaryl coenzyme A and acetyl CoA carboxylase) involved in cholesterol and fatty acid synthesis [100].

Table 1 important medicinal plants with possible mechanism actions on hypertension

Name	Scientific name	Family	Active organs(s)	Potential anti-atherosclerosis action mechanisms	Active compound(s)
Urtica	*Urtica dioica* L	Urticaceae	Leaves	Slowing of the heart and lowering blood pressure along with diuretic effects	Flavanols, xanthophylls, flavonoids, and leucoanthocyanides
Persian walnut	*Juglans regia*	Juglans regia L	Fruit	Lowering blood lipids and glucose, preventing the formation of vascular plaques	Tannins, essential fatty acids, ascorbic acid, flavonoids, caffeic acid
Lettuce	*Lactuca sativa*	Cichorieae	Leaves	Inducing the release of histamine from mast cells, vasodilation, and lowering blood pressure	Opioid-like alkaloids
Cumin	*Cuminum cyminum*	Apiaceae	Fruit	Preventing the oxidation of HDL via paraoxonase enzyme	Antioxidants
Crocus	*Crocus sativus*	Iridaceae	Stigma	Preventing the release of Ca^{2+} the sarcoplasmic reticulum of vascular smooth muscles, inducing nitric oxide production	Crocin, anthocyanins, flavonoids, mineral vitamins, fiber, carbohydrates, proteins, and fats
Bugloss	*Borago officinalis*	Boraginaceae	Flower	Reducing blood pressure via lowering the heart rate	Alkaline compounds, glycoside, pyrrolizidine, and useful lipids
Common mallow	*Malva* Sylvestris	Malvaceae	Leaves and flower	Reducing cholesterol and lipid peroxidation and preventing thrombosis	Linoleic acid, linolenic acid, palmitic acid and oleic acid
Poales	*Cynodon dactylon*	Poaceae	Leaves	Lowering triglycerides, cholesterol factor and preventing hypercholesterolemia, and atherosclerosis	Beta-carotene, beta-sitosterol, vitamin C, palmitic acid, flavonoids, saponins and alkaloids
Felty Germander	*Teucrium polium*	Labiatae	Flower	Relaxing vascular wall smooth muscles	Tannins, terpenoids, saponins, sterols, and flavonoids
Azarole	*Crataegus* Azarolus	Rosaceae	Fruit and leaves	Anti- ischemia-reperfusion, antiarrhythmic, hypolipidemic, and antihypertensive effects	Flavonoids, tannins, acetylcholine, purine derivatives, and adenosine
Feverfew	*Tanacetum parthenium*	*Compositea*	Leaves	Cardiovascular protective effects via reducing cholesterol and fatty acids	Tannin, saponin, kaempferol
Coma	*Ferula persica*	Umbelliferae	Seeds	Suppressing angiotensin converting enzyme and controlling blood pressure	opiol, safranal
Jujube	*Jujubemill Zizyphus*	Rhamnaceae	Fruit	Anti-inflammatory and antihypertensive effects	Fatty acids, beta-carotene, alpha tocopherol, caffeic acid, epicatechin
Green tea	*Camellia sinensis*	Theaceae	Leaves	Reducing systolic blood pressure and LDL cholesterol	Polyphenols including catechins, epicatechins, epigallocatechins
Garlic	*Allium sativum*	Alliaceae	Seeds	Inhibiting the key enzymes involved in the synthesis of cholesterol and fatty acids (such as hydroxymethylglutaryl coenzyme A and acetyl carboxylase), inducing vasodilation	Disulfide, propyl sulfide, allyl propyl disulfide, and allicin

Chicory	*Cichorium intybus*	Compositae	Leaves	Preventing apoptosis in ischemic myocardium, reducing cardiac infarction, lowering systolic blood pressure	Flavonoids, sesquiterpene, and cinnamic acid
Cinnamon	*Cinnamomum verum*	Lauraceae	Stem	Scavenging free radicals, reducing arrhythmia and cardiac infarction area	Phenolic and flavonoid compounds

Most of the research on garlic has indicated that garlic and its active compounds are effective in reducing cardiovascular and metabolic risk by normalizing abnormal plasma lipids, oxidized low-density lipoproteins, abnormal platelet aggregation, high blood pressure, and cardiac injury. Garlic has the potential to protect the heart against myocardial infarction, doxorubicin-induced cardiotoxicity, arrhythmia, hypertrophy, and ischemia-reperfusion injury. Other mechanisms, such as cytochrome P450 inhibition, histone deacetylase inhibition, regulating ion channels, and modulating Akt signaling pathways, could be responsible for the cardio protective effect of garlic [101].

Chicory: Chicory, scientifically known as *Cichorium intybus*, contains flavonoids, sesquiterpene, and cinnamic acid. In a study, chicory extract reduced the infarct area time and the infarct tissue mass via filtering and suppressing macrophages compared to the control group. Another reaction involved in the shrinkage of infarct size is the modulation of the chemokine pathway mediated by CXCR4 receptor and SDF-1α, which protects the myocardium against apoptosis and cell death during ischemia [102]. Prolonged inflammation is detrimental for the infarct tissue, causes vasodilation, reduces systolic function, and disrupts tissue structure Chicory extract with reducing inflammation can lead to better tissue repair and reduce the remodeling of the injured area. A recent study shows that the SDF-1α receptor by binding to the CXCR4 receptor induces multiple protective effects such as prolonging cardiac muscles' survival, improving the infarct area's remodeling, and activating endothelial cells and angiogenesis, which improve heart function. Therefore, chicory extract has a beneficial role in improving tissue remodeling by inducing the expression of CXCR4 gene [103-105].

Cinnamon: The scientific name of this plant is *Cinnamomum verum*, and it contains phenolic and flavonoid compounds. A research has shown that these compounds have strong antioxidant properties. Flavonoids have been shown to prevent the development of coronary artery diseases and reduce mortality due to heart diseases [106]. The most important role of flavonoids may be their contribution in scavenging free radicals. In fact, flavonoids and other antioxidants are involved in the improvement of tissue injuries following arrhythmia and infarction. In addition to antioxidative properties, flavonoids have anti-mutation and anti-cancer features [107]. The skin protective activity of cinnamon is related to its antioxidant activity. This activity is characterized by an increase in serum antioxidant enzymes such as GPX and SOD, which decrease in lipid peroxidation (evidenced by a reduction in MDA level) as compared to the control group [108]. Ventricular arrhythmias are important risk factors predicting mortality following surgery and a larger size of myocardial infarction.

The role of potassium channels has been suggested in the pathogenesis of heart diseases and are usually targeted for treating arrhythmias [109]. QT interval and arrhythmias are risk factors of heart diseases, and they need to be managed by therapeutic interventions [110]. In a study, cinnamon extract reduced arrhythmia, QT interval, R wave, and the contractile strength of the heart [111], indicating a negative inotropism effect for this plant on the heart's contractile strength. In another study, cinnamon extract was reported to reduce cTnI and LDH (as cardiac damage markers), the size of myocardial infarction, and blood pressure [107].

Important medicinal plants with possible mechanism actions on hypertension has been summarized in Table 1.

DISCUSSION

The prevalence of CVDs in today's communities is very high and preventing and treating these diseases are among the health priorities in most countries. In recent years, the tendency toward the consumption of herbal medicines and their utilization for the treatment and prevention of diseases has significantly increased. Medicinal plants due to ease of access, low side effects, and affordable price have always been considered as alternatives to chemical drugs, and given special attention in the treatment and prevention of diseases.

A well-known mechanism of the development of CVDs is the formation of arterial atherosclerotic plaques. The atherosclerotic lesion is characterized with a surface fibrotic cap containing smooth muscle cells, white blood cells, and macrophages. According to the available knowledge, atherosclerosis is an inflammatory disease. Besides, among the factors affecting the onset and progression of inflammation are free radicals, hypertension, diabetes mellitus, genetic changes, hypercholesterolemia, and even some microorganisms such as herpes viruses and chlamydia [112, 113].

Therefore, compounds that can affect any of the above-mentioned mediators may be beneficial as therapeutic agents for treating atherosclerosis and cardiac diseases [112-114].

Acute myocardial infarction (AMI) is a disease commonly known as the heart attack. The disruption of blood supply to a part of the heart causes the death of cardiac cells. The obstruction of coronary arteries may occur due to various causes, including the presence of atherosclerotic plaques, which leads to a reduction in the diameter of vessels. In fact, the rupture of atherosclerotic plaques can result in either a decrease in vessel diameter or tissue damage following the formation of a thrombotic mass. Subsequently, shortages in blood supply and oxygen lead to tissue ischemia, which if remains untreated, can progress to cardiac damage or death [115]. Regarding the role of blood platelets in the pathogenesis of CVDs and atherosclerosis, damage to vascular epithelium, the action of sub endothelial adhesive proteins, and platelet activation have been reported as important contributors [116]. The function of GPIIb/IIIa receptor is essential for the development of platelet thrombosis. Therefore, inhibiting platelet activity represents an important approach to treat and manage many vascular pathologies. It has been reported that a number of nutrients, especially antioxidants, can affect platelet function [117]. Platelets, either directly or indirectly, can contribute to either the improvement or deterioration of cardiac blood supply even after a heart attack. The oxidation of platelet enzymes (such as xanthine oxidase) and lipid peroxidation usually increase following a heart attack [118].

On the other hand, free radicals play important roles in pathogenic histological events including LDL oxidation, atherosclerotic plaque formation, and vascular disease development. These determinants, namely the oxidation of platelet enzymes and lipids, are particularly important in the recurrence of CVDs [28]. Reactive oxygen species (ROS) through triggering processes such as inducing the expression of adhesive molecules, promoting the proliferation, migration of vascular smooth muscle cells, disrupting antioxidant/oxidant balance, activating matrix metalloproteinase, as well as modulating endothelial cell apoptosis, lipid, oxidation, and vasomotor function, contribute to the development of cardiac diseases. The effects of ROS on lipids, proteins, and DNA in the body are controlled via the action of a variety of antioxidants including vitamins A, E, C, glutathione, uric acid, etc. [119]. CVDs are multifactorial disorders, and many risk factors such as dyslipidemia have been known to contribute to their pathogenesis [120, 121]. There is a direct relationship between lipids, especially total serum cholesterol, and heart diseases. Individuals who consume higher amounts of saturated fat have higher total serum cholesterol, resulting in higher risks of heart diseases and mortality [122]. The associations among cholesterol level, atherosclerosis, and mortality due to coronary heart disease were assessed in a clinical trial, showing that keeping lower levels of blood lipids could reduce the incidence of cardiovascular complications and increase life expectancy in humans [123].

Antioxidants can be suitable protective agents against free radicals; thereby, they can improve cardiac perfusion and prevent lipid peroxidation, thrombosis, cardiac damage, arrhythmias, and heart attack [20]. In addition, oxidative stress and the excessive production of free radicals are among the most important factors involved in the pathogenesis of CVDs [52]. According to the literature, CVDs can be associated with the overproduction of ROS and decreased activity of endogenous antioxidant systems [124]. Researchers have shown that antioxidant enzymes, as the first defense line against oxidative injuries, are major players in neutralizing ROS [125]. Pharmacological studies have also indicated that compounds with high antioxidant capacity [53], such as crocin can induce superoxide dismutase and reduce malondialdehyde and, therefore, protect the heart against oxidative damage and prevent cardiac infarction. On the other hand, inflammatory responses also play a role in the pathogenesis of vascular dysfunction [126].

CONCLUSION

CVDs are among the most common and important diseases in today's world. Medicinal plants, due to their ease of access, low side effects, and suitable price, are considered as alternatives to chemical drugs. Medicinal herbs with various mechanisms including triggering vasodilation, inducing nitric oxide (NO) production, blocking calcium channels, reducing blood pressure, preventing diabetes, decreasing blood lipids, and suppressing renin-angiotensin system can help to treat CVDs. Most studies have reported the beneficial effects of medicinal plants in the treatment of CVDs; however, less attention has been dedicated to their mechanisms of action. Knowing these mechanisms can assist to synthesize novel drugs in this area. Further studies are required to investigate the effects of medicinal plants and their derivatives on the treatment of CVDs.

Conflict of Interest

The authors declare no conflict of interest among them.

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