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CHAPTER 5

Natural Products for the Management of Cardiovascular Diseases

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Abstract: Cardiovascular diseases constitute a serious public health problem. It is estimated that they are responsible for nearly 30% of world mortality. Regardless of the developments in the diagnosis and management of cardiovascular diseases, their incidence rate remains increasing. Therefore, newlines of drugs are needed to manage the expanding population of patients with cardiovascular diseases. Even though the most common existing treatments for cardiovascular diseases are synthetic molecules, natural compounds, of different chemical classes, are also being tested. Medicinal plants have been employed in the treatment of some cardiovascular diseases such as congestive heart failure and hypertension many centuries ago. Recently, the traditional remedies application for the treatment of different disorders is gaining revived popularity. In this chapter, we will investigate the efficacy and safety of natural products under preclinical studies and clinical trials with particular emphasis on their

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traditional uses and implementations in the primary health care system. The great potential of medicinal plants and herbs will be discussed in light of the rising prevalence of cardiovascular diseases as one of the most devastating global health problems.

Keywords: Angina, Cardiovascular diseases, Clinical trials, Hypertension, Heart failure, Ischemic heart diseases, Natural products.

1. INTRODUCTION

According to the World Health Organization (WHO) definition, cardiovascular diseases (CVD) are the diseases associated with the heart and/or the blood vessels [1]. Most common Cardiovascular disease (CVD) types include Hypertension, Angina Pectoris, Atherosclerosis, Ischemic Heart Disease and Cerebral and Venous Insufficiency.

There are many cardiovascular risk factors for the development and evolution of CVD. According to "European guidelines on cardiovascular disease prevention in clinical practice" which were published by the European Society of Cardiology, there are two main categories of cardiovascular risk factor: modifiable and non-modifiable factors [2, 3]. As for modifiable cardiovascular risk factors; they include smoking, limited physical activity, inappropriate diet, overweight and obesity or disturbed lipid profile. Non-modifiable individual risk factors include genetic factors, sex, age or family history. Tobacco use is a major risk factor for CVD as well as chronic respiratory diseases and cancer. Several reports showed that proper nutrition, active physical lifestyle and avoiding tobacco are able to decrease CVD risk [4, 5].

The incidence rate of cardiovascular diseases worldwide has increased drastically during the last years. Cardiovascular diseases are considered one of the four main non-communicable diseases (NCDs) accounting for serious threats next to diabetes, cancer and chronic respiratory disease [6]. The WHO estimated that more than 40 million deaths occurred in 2016 due to NCDs, of which 17.9 million deaths were caused by cardiovascular diseases, accounting for 44% of all NCD deaths [6]. Therefore, CVD are ranked as the leading cause of death worldwide.

CVD are presently one of the major causes of death worldwide. The current strategic approaches for the treatment of CVD diseases involve many effective drugs. However, the majority of these drugs have low safety profile and lead to serious side effects. Natural products have constantly been considered a treasured source for innovation of novel drug leads. Growing evidence suggests that numerous natural compounds are invaluable sources of CVD remedies. In this

review, the prevalence and the pathophysiology of CVD disorders are discussed. Additionally, the great impact of medicinal plants and natural compounds for the prevention and treatment of CVD disorders is addressed. Special emphasis is laid on plant-derived products which are in pre-clinical or clinical trials.

2. ISCHEMIC HEART DISEASE AND CONGESTIVE HEART FAILURE

2.1. Pathophysiology of Ischemic Heart Disease

The narrowing of the coronary arteries which provide the cardiac muscle with oxygenated blood is referred to as Ischemic Heart Disease (IHD), Coronary Artery Disease (CAD), or Coronary Heart Disease (CHD). This narrowing leads to ischemic damage of the myocardium. Although CAD can be asymptomatic in some cases, myocardial ischemia usually causes chest pain and/or discomfort known as angina pectoris (Hereafter discussed) due to an imbalance between local oxygen supply to the myocardial tissue and its oxygen demand.

The primary cause of coronary artery narrowing is the process known as atherosclerosis (Hereafter discussed in more detail in section 5). This process involves the pathological deposition of oxidized cholesterol in the arterial wall. In the early course of the disease, coronary endothelial cells become dysfunctional with a reduction in the production of important mediators like nitric oxide and prostacyclin. This can lead to vasospasms and impaired relaxation of the coronaries. As the disease progresses, leukocytes infiltrate the coronary artery wall causing inflammation, plaque formation and eventually thickening and hardening of the vessel wall; as well as narrowing of the lumen which restricts blood flow [7].

Severe and/or prolonged, myocardial ischemia eventually causes regional necrosis of cardiac tissue (myocardial infarction). Depending on the location and size of the necrotic area, disturbance of ventricular contraction happens. Myocardial necrosis with more than 20% trans-mural involvement can cause permanent cardiac wall motion abnormality [8]. Percutaneous Coronary Intervention (PCI) or coronary artery bypass surgery (CABG) may be applied in severe cases [9]. If blood flow is restored in a timely fashion, wall motion abnormalities might recover within a few days [10]. In addition, ventricular remodeling also occurs and can take several forms such as ventricular dilation or even aneurysm. The greater the degree of left ventricular dysfunction, the greater the likelihood of developing heart failure, arrhythmias, and even death may occur [11]. Ischemic Heart Disease (IHD) remains among the major causes of mortality worldwide [12].

Risk factors include hypertension, diabetes mellitus, obesity, lack of exercise, high serum cholesterol levels, family history of a heart attack before the age of 60 years, smoking, depression and alcohol consumption [13, 14]. A healthy lifestyle is the best way to reduce the risk of developing CAD, including healthy dieting, steady exercise, keeping a healthy body mass index and avoiding smoking.

2.2. Pathophysiology of Congestive Heart Failure (CHF)

Heart failure (HF) is a pathophysiological case that occurs when the heart cannot pump enough blood to satisfy the requirements of the metabolizing tissues. With a few exceptions, HF is usually due to defective myocardial contraction. Heart failure, however, should be distinguished from circulatory failure, which is due to decreased blood volume, damage to blood vessels, or decreased concentration of oxygenated hemoglobin [7]. Although heart failure, by definition, results in circulatory failure, the opposite is not necessarily true.

The underlying pathogenesis of the defective myocardium involves ischemic damage, hemodynamic overload, ischemic damage, excessive neuro-humoral stimulation, silent inflammatory responses, bacterial or viral infections, calcium cycling abnormalities, extracellular matrix proliferation as well as ventricular remodeling [15 - 17].

However, uncontrolled diabetes and long-standing hypertension are considered the strongest risk factors of CHF in patients with coronary heart disease [18]. Age is also a major risk factor for developing heart failure due to increased incidence of atherosclerosis, myocardial wall stiffness, and hypertension, which promotes an increased end-diastolic pressure in a rigid ventricle causing pulmonary edema [19, 20]. With increased life expectancy, the incidence of CHF is projected to more than double over the next two decades and its prevalence will rise ten times between the age of 60 and 80 [21, 22].

Decreased myocardial contractility results in reduced ejection fraction (the percent blood pumped out of the ventricle with respect to the end diastolic volume). At the early stages of heart failure, the cardiac output might show normal levels while resting but fails to increase proportionally with exertion. Consequently, one of the most common symptoms and early signs of heart failure is exercise-intolerance and rapid fatigue. As a result of decreased ejection fraction and increased ventricle filling pressure (increased preload), blood accumulates in the systemic venous bed and pulmonary circulation causing pulmonary and/or peripheral edema depending on the type of heart failure being left-sided, right-sided or both [7]. Hence, a major goal of heart failure treatment is to increase myocardial contractility and ejection fraction.

The cardiac output reduction has a number of short-term circulatory and hemodynamic consequences which are triggered by two main compensatory mechanisms. First, a fast-nervous mechanism: Reduced volume of blood delivered into the major arteries results in changes in baroreceptor signaling which will trigger an increase in sympathetic activity [7, 23]. The increase in sympathetic activity results in tachycardia (elevated heart rate) and increased vascular tone. The increase of arterial tone is better causes increased peripheral resistance (afterload), while higher venous tone causes an increase in venous return (preload). Second, a slower renal mechanism: Decreased arterial blood flow causes a reduction in renal perfusion and Renin-Angiotensin-Aldosterone System (RAAS) activation [24]. The increased RAAS activity eventually causes increased vascular tone (increased preload and afterload), retention of sodium and water in the intravascular and interstitial compartments (increased preload), and long-term changes in the myocardium. The excessive retention of fluid is responsible for many of the clinical manifestations of heart failure including pulmonary congestion, dyspnea, and peripheral edema, hence the name *congestive* heart failure. Thus, alleviation of fluid retention and edema is another major goal of treatment [7].

While the increase in sympathetic tone and activation of RAAS help maintain the blood pressure and augment preload to maintain the perfusion to vital organs *e.g.* heart and brain, they also result in maladaptive responses like pulmonary and peripheral congestion, afterload mismatch, decreased energy efficiency, and cardiac dilatation and remodeling. The gradual exacerbation of heart failure symptoms is clinically described as chronic decompensated heart failure [20, 25]. The patients are usually assigned to one of four different stages of CHF based on the severity of the symptoms, with earlier stages having no or mild symptoms and the end-stage involving failure to do daily activities.

Congestive heart failure generally has a poor prognosis with about a year mortality of 33 - 35% [26, 27]. Regardless of the developments in medicine, the treatment of heart failure still represents a challenge to healthcare providers due to the high rate of hospital readmissions besides mortality and morbidity increase. The key targets of heart failure treatment are to alleviate symptoms, improve prognosis and decrease mortality, and prevent organ system damage [28, 29].

2.3. Natural Products for Management of Congestive Heart Failure and Ischemic Heart Disease

Nutraceuticals are getting more popular all over the world as an adjunct to conventional therapy for cardiovascular diseases [30]. Through multiple mechanisms, natural products can provide several benefits to treatment regimens.

First, products with antioxidant activity might delay the onset and slow the progression of CAD by preventing the oxidation of the LDL cholesterol [31]. In addition, antioxidant compounds prevent oxidative damage that occurs due to ischemia / reperfusion in patients with advanced CAD [32]. They also improve vascular and endothelial function through increased levels of nitric oxide [33]. Second, their anti-inflammatory effects help thwart atherosclerosis, vascular plaque formation, myocardial remodeling, and reperfusion damage. Third, some natural products have potent anti-atherogenic effects due to their ability to improve the blood lipid profile. In addition to antioxidant and anti-inflammatory actions, nature may play other beneficial roles such as anti-apoptotic effects, anticoagulant activity, vasodilation, diuretic, and others. Here, we briefly discuss some of the recent advances in using natural products to manage and protect against CAD and CHF.

2.3.1. Flavonoids

A large class of secondary plant metabolites (flavones, flavonols, flavanones, isoflavones and anthocyanidins) found in onions, citrus fruits, berries, tea and cocoa [34, 35]. They are known for their antioxidant activity which can avert the oxidative stress caused by Reactive Oxygen Species (ROS) [36, 37]. This effect protects against low density lipoprotein (LDL) cholesterol oxidation (an early step of atherosclerosis), decreases platelet aggregation, lessens the ischemic damage, and improves blood vessel function [38, 39]. Flavonoids have been also shown to also have anti-inflammatory activity [40, 41].

The role of flavonoids to protect against cardiovascular diseases is, however, controversial [30]. Several studies have shown a reduction in the incidence and mortality of CAD in cases those consuming flavonoid rich diets [42, 43]. Other studies showed no relationship between flavonoid consumption and the incidence of CAD [44 - 46]. Nonetheless, in one of these studies, flavonoids reduced subsequent coronary events in patients diagnosed with CHD [44]. A meta-analysis that included several studies (including ones that showed no benefits), suggested that consumption of flavonoid rich tea reduces the risk of cardiovascular diseases by more than 10% [47].

2.3.2. Resveratrol

Resveratrol is produced by plants due to injury or fungal infection; it is a naturally occurring phytoalexin [48]. High amount of resveratrol is present in the seeds and skin of grapes and in peanuts [49, 50]. It is currently available in the market as a nutritional supplement. There is strong experimental and clinical evidence that

resveratrol exerts cardio protective effects [51].

The cardio protective effects of resveratrol are due to its antioxidant, antithrombotic, antiplatelet, anti-apoptotic and anti-atherosclerotic activities, in addition to improved vascular and endothelial function [52 - 54].

2.3.3. Lycopene

Lycopene is a natural red pigment synthesized by some photosynthetic organisms e.g. plants and algae aiming at absorbing light for photosynthesis and also to protect against sunlight. Lycopene and other carotenoids give the bright orange and red colors to many fruits and vegetables. The major source of lycopene in the diet is tomato-based products.

Dietary intake of tomato and its products has shown a negative correlation with CAD and myocardial infarction [55, 56]. The ideal daily intake of lycopene is not yet defined; however, 8 mg / day has been recommended by some studies [57].

The cardiovascular benefits of lycopene include its antioxidant and free radical scavenging activities [58], improved endothelial functions, and LDL reduction [59].

2.3.4. Omega-3 Fatty Acids

The major dietary sources of omega-3 Fatty acids are fish oil, soya beans, canola oil, and flaxseed oil. Omega-3 Fatty acids are regarded as essential dietary components which belong to the polyunsaturated fatty acids (PUFAs) class. PUFAs are known to possess a multiplicity of beneficial cardio protective actions and play an important role in both prevention and management of cardiovascular diseases [30]. Clinical and epidemiological data suggest that omega-3 fatty acids decrease both the incidence of CAD in healthy humans and complications in cardiovascular patients [60 - 62].

The mechanisms of the cardiovascular benefits of omega-3 fatty acids include thromboxane-A2 reduction, decreasing platelet aggregation, improving vascular and endothelial function through increased nitric oxide production, calcium entry into vascular smooth muscles inhibition and plasma nor-epinephrine levels reduction [63].

2.3.5. Olive Oil

In the Mediterranean diet, olive oil is the major fats source; this diet is related to the lower cardiovascular disease mortality [64, 65].

Although its beneficial cardiovascular effects are usually linked to monounsaturated fatty acids (MUFA) high levels, olive oil contains a long list of natural compounds *e.g*. phenolic compounds, hydrocarbons, tocopherols, fatty alcohols, sterols and polar pigments (chlorophylls and pheophytins). Some of these compounds isolated from olive oil have been shown to improve lipoprotein metabolism and LDL/HDL ratio [66, 67], ameliorate endothelial function and nitric oxide production [68], decrease monocyte adhesion [69 - 71], and decrease oxidative damage and inflammation [72, 73].

2.3.6. Soy

For centuries, soybeans have been employed as food and medicine in Asia [74]. In a number of epidemiological studies, a cardiovascular protective action of soy foods has been reported. Soy products reduce the risk of CAD in both men and women [75 - 77].

The cardio protective actions of soy have been linked to isoflavones, however, soy contains several classes of bioactive compounds [76, 78]. Isoflavones are phytoestrogens that protect against atherosclerosis, 38 clinical studies meta-analysis showed that soy proteins consumption significantly improves the blood lipid profile [79].

2.3.7. Cardiac Glycosides

Cardiac glycosides are produced by several plant species and also found in some animal venoms. Digoxin and digitoxin, the most well-characterized and clinically-used cardiac glycosides, have been used for decades as inotropic agents to treat congestive heart failure.

Digoxin acts by inhibiting the activity of the myocardial Na^+/K^+ ATPase pump which leads to Na^+ accumulation inside the myocardial cells with subsequent inhibition of Ca^{2+} extrusion through the Na^+/Ca^{2+} exchanger [7].

Cardiac glycosides are known for their complex pharmacokinetic profile and low therapeutic index. In fact, some of the plants containing cardiac glycosides have been historically used as poisons. Toxicity manifests as ventricular arrhythmias, heart block, gastrointestinal symptoms [80]. Because these glycosides compete for

the potassium binding site of the Na^+/K^+ pump, plasma levels of K^+ can be a major determinant of toxicity. A specific fab antibody is now available for treatment of digoxin toxicity [81].

3. HYPERTENSION

Hypertension (HTN) is an important risk factor denoting CVD. Globally, about 970 million people are estimated to be suffering from the disease that can significantly result in morbidity, mortality as well as financial burden. Regardless to the current developments in pharmaceutical therapy, 53% only reached the targeted blood pressure [82].

3.1. Pathophysiology of Hypertension

Hypertensive patients are categorized according to the hypertension type whether primary or essential HTN (95%) or secondary HTN (5%) of hypertensive patients [83]. The major cause of essential HTN is not yet known, however commences mostly at the age of 50 - 60 and frequently correlated with high salt consumption and obesity, in addition to family history, underlining the genetic predisposition possibility for the disease [83]. On the other hand, secondary hypertension etiology includes renal artery stenosis, chronic renal disorders and sleep apnea [83]. Both disorders (primary & secondary) are the import of numerous mechanisms which are responsible for maintaining normal blood pressures which are:

3.1.1. Sympathetic Nervous System

Sympathetic nervous system SNS hyperactivity leads to the promotion, maintenance and development of hypertension HTN. Adrenergic hyperactivity has been correlated with numerous forms of HTN; systolic-diastolic and isolated systolic hypertension [84, 85] white- coat hypertension and masked hypertension [86] as well as dipping, extreme dipping, non-dipping and reverse dipping cases [87, 88], in addition to, gestational hypertension [89]. Accordingly, sympathetic nervous system is aggravated in correlation with hypertension conditions [90]. Numerous reports evidenced that hyperactivity of SNS, demonstrated by norepinephrine increase, extends to patients with HTN approving that the overactive SNS is one of the major reasons in the pathophysiology of hypertension. On the other hand, renal sympathetic nervous system is crucial in the progress and preservation of HTN. It has an impact on blood pressure through two pathways; the efferent and afferent pathways [82].

3.1.2. Endothelial Function

There is a solid basis of a clear relation between the endothelial dysfunction grade and the hypertension severity. The decrease in the nitric oxide level which results from oxidative stress could be the primary mechanism for endothelial dysfunction recognized in hypertension. This impaired nitric oxide production could be resorted by antihypertensive drugs; however, endothelium dependent vaso-relaxation alteration may last directly after hypertension is established. Therefore, endothelium-derived nitric oxide synthase inhibition leads to hypertension in humans [82]. There are other vaso-relaxing factors alongside with nitric oxide (NO) for instance, ROS, arachidonic acid metabolites, vaso-active peptides and endothelial originated micro-particles that are involved in preservation of vascular tone. The aforementioned factors cause extreme vascular oxidative stress and inflammation leading to endothelial dysfunction [91, 92]. Thus endothelial dysfunction could be recognized as massive modifications in the vascular environment that contributes to structural and functional changes inside the arteries. Improvement of vascular function by treatments those targeting key pathways decrease cardiovascular risk.

3.1.3. Renin-angiotensin-aldosterone System (RAAS):

The RAAS is crucial in maintaining normal blood pressures. There are two mechanisms controlling RAAS; stimulation of the sympathetic nervous system and glomerular under perfusion [93]. The result of these stimulations is the renin release from the juxtaglomerular apparatus that alters angiotensinogen into inactive angiotensin I. Angiotensin I is then converted by endothelium bound angiotensin converting enzyme (ACE) into angiotensin II, the latter is a potent vasoconstrictor [94]. Conversion of angiotensin I into angiotensin II occurs in all tissue and mainly in the lungs. Furthermore, low intake of salt leads to aldosterone release through RAAS from the adrenal glands which results in reabsorption of salt and retention of water leading to elevation in blood pressure. Studies revealed that only 15% of the patients have shown an increase in the plasma renin level, and it remained normal in 60% and reduced in 25%. Therefore, there is an acquiescent for the occurrence of local renin systems that regulates the blood flow that might be correlated to the pathophysiology of HTN [95].

3.1.4. Obesity

Severity of hypertension is extremely conjugated with obesity. Patients recording 30 kg/m2 BMI are liable to uncontrolled systolic blood pressure (SBP) with

increase 1.5 folds as compared with those less than 25 kg/m2. Another report evidenced that obese patients recorded high blood pressure as regards to normal cases. The famous mechanism explaining this phenomenon involved in obesity-induced hypertension is neuro-adrenergic hypothesis in addition to sodium excretion impairment, fluid retention and the RAAS activation [96].

3.1.5. Vascular Smooth Muscles

The vascular smooth muscle cell invades vascular lumen which initiates increase in peripheral vascular resistance and consequently development of hypertension [97]. The whole procedure depends on the interaction between many modulating factors by either stimulating or inhibiting vascular smooth muscle cell (VSMC) progression. The fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), the endothelin-1, the Angiotensin II (Ang II), and the Ca^{2+}- calmodulin interaction are the prominent causes involved in the vascular remodeling. These factors control the cross-bridge cycling actin and myosin (Contractile proteins) [98].

3.1.6. Reactive Oxygen Species

Pathogenesis of hypertension and other vascular complications are clinically evidenced by excessive production of reactive oxygen species ROS through different pathologic states. ROS such as hydrogen peroxide (H_2O_2), superoxide (O_2^-) and hydroxyl (OH^-) anions, normalize many cellular processes [99, 100].

3.2. Natural Products and Hypertension

Nowadays, herbal drugs have drawn attention for treatment of several ailments as cardiovascular disorders including hypertension. Due to their safety and effectiveness herbs and naturals are regarded as an important complement to conventional therapy. Nevertheless, there are some concerns regarding the use of herbs, because of the lack of continuous supervision, serious complications and interactions with other traditional medicines [98].

3.2.1. Nigella sativa (Black Cumin, Black Seed)

Thymoquinone, the key ingredient of the volatile oil of *Nigella sativa* seeds, evidenced a decreasing action on BP in humans, as well as, animals [101] studied the activity of *N. sativa* seeds oil on lowering blood pressure applying controlled clinical trial, in seventy healthy subjects of age ranging from 34 - 63 years. The

protocol was designed that randomized subjects were given 2.5 ml seed oil or placebo twice daily for two months. Results revealed that the oil decreased the SBP. Another similar clinical study dealt with *N. sativa* extract at two dose (100 and 200 ml) levels; two times / day for two months, there was also a reduction in blood pressure [102]. Nigella seed extract exerted also significant reduction in the total and LDL-cholesterol levels. Interestingly, there were no complications due to the chronic administration of nigella seeds. Therefore, it was established that the daily use of nigella seed extract for about two months could lower blood pressure effect in patients suffering from mild hypertension. The suggested mechanism for the antihypertensive effects of *Nigella sativa* was its antioxidant activity by reducing oxidative stress and also by blocking Ca^{2+} channels gate leading to vaso-relaxation.

3.2.2. Beta Vulgaris (Red Beet, Table Beet or Golden Beet)

Beet root is a rich source of dietary NO_3^- [103] several reports have studied its potential for regulating blood pressure in humans which was more prominent in men. A randomized, placebo-controlled study [104], examined the impact of dietary supplementation of beetroot juice on 68 hypertensive subjects, 34 patients were treated as control, and 34 treated with age ranging from 18 - 85 years for one month. Results evidenced that Beetroot intake reduced the blood pressure and enhanced the endothelial function, together with a reduction in arterial stiffness. It was also concluded that beetroot supplements were well tolerated with no tachyphylaxis evidence throughout the treatment. Another crossover study was conducted on fifteen women and fifteen men. The volunteers received 500 g of beetroot juice or placebo juice (PL) randomly. The blood pressure was measured at baseline and each one hour for 24 hours after juice intake using an ambulatory blood pressure monitor (ABPM). The process was repeated two weeks later. Results revealed a decrease in the SBP at the sixth hour by 4 - 5 mmHg after consuming Beetroot juice as compared to placebo juice [105]. The high amount of inorganic nitrates supplement and the endothelial nitric oxide generation account for the antihypertensive actions of beetroot juice.

3.2.3. viz Coptis chinensis (Goldthread)

Bebeerine alkaloid (a quaternary ammonium salt) is the major active ingredient of *Coptis chinensis*. Bebeerine is reported for the treatment of CVD [106]. The antihypertensive effects of berberine was reviewed on 228 hypertensive patients. The hypertensive volunteering patients were randomized to receive bebeerine at a dose 0.6 g/day in addition to their conventional antihypertensive medications (n = 116) or to control groups receiving antihypertensive medications solely (n = 112).

Results evidenced that concomitant treatment of bebeerine along with the antihypertensive medications reduced blood pressure as regards to control group. The proposed mechanism for bebeerine was claimed to be due to the increased generation of nitric oxide *via* NO synthase (eNOS) stimulation and the catecholamine levels reduction causing peripheral vasodilation and consequently decreasing blood pressure [107]. Another hypothetical mechanism for the hypotensive mechanism of bebeerine that the prostaglandin I2 (PGI2) levels are increased, opening the KATP and blocking the iCa^{2+}voltage gated channels, hence blocking the Ca^{2+} cell influx [108].

3.2.4. Hibiscus sabdariffa L.

The blood lowering pressure of *Hibiscus sabdariffa* L. has been previously reported and studied on BP-lowering effects have been anthocyanins (polyphenolic compound) and hibiscus acid is the major constituent in *Hibiscus* calyxes and epicalyces are considered the phyto constituents responsible for the antihypertensive studied in both animals and man [109]. There were no signs of hepatic or renal toxicity associated with the consumption of *Hibiscus* extract, except for probable hepatic side effects at higher doses [110].

A trial [111] was conducted on 65 untreated pre-hypertensive and mildly hypertensive cases of ages that ranged from 30– 70 years. The protocol involved randomizing cases to three consumptions daily of 240 ml of either *Hibiscus* or placebo for one and a half months. Results evidenced that *H. sabdariffa* intake lowered the SBP, however the DBP. Participants recording higher baseline blood pressure showed more reductions in BP. Furthermore, there was no evidence of adverse clinical or metabolic effects. It was concluded that Hibiscus tea consumption may decrease the BP of hypertensive patients due to the NO increased production, Ca^{2+} channels inhibition and the KATP channels opening [112].

3.2.5. Crataegus Monogyna (Hawthorn)

Hawthorn berries are rich in oligomeric procyanidins (leucoanthocyanidins) and flavonoids that have been employed traditionally for the management of CVD. Hawthorn extracts evidenced moderate decrease in blood pressure in hypertensive patients [113]. A cross-over study was performed to investigate Hawthorn extract's impact on lowering blood pressure and in flow-mediated vasodilation. Results showed that there was no significant change from baseline in ABP or in flow-mediated vasodilation by hawthorn extracts [114]. It was suggested that Hawthorn extract constitutes bioactive metabolites; procyanidins and flavonoids

that might increase nitric oxide level and improve endothelial function and hence exert hypotensive action. Moreover, about 90.5% of the participants recommended the use of Hawthorn extract in combination with their conventional antihypertensive drugs.

3.2.6. Allium sativum L. (Garlic)

Garlic is an underground stem (bulb) rich in sulfur compound known as allicin, it is present in several preparations whether powder or extract. It has been employed for the management of hyperlipidemia, the prevention of CVD in addition to its hypotensive effect. A randomized, double-blind, placebo-controlled study [115] the aged garlic action on uncontrolled was established. In that study eighty-eight patients suffering from uncontrolled blood pressure received either aged garlic extract at a dose 1200 mg / day or placebo and Bo was monitored for twelve. Results evidenced that the blood pressure was significantly reduced with garlic compared to placebo. Other parameters (central hemodynamic) were measured indicating an improvement in central BP, central pulse pressure (PP), pulse wave velocity (PWV), and arterial stiffness as regards to placebo. It was concluded that garlic significantly reduced the brachial BP and enhanced central hemodynamics, in addition to its tolerance and acceptance by the patients. Another study comprising 482 hypertensive subjects was accomplished to track the effect of garlic on hypertension [116]. The study was conducted from 12 - 26 weeks where patients consumed garlic preparations at different doses. Results revealed that the average decrease in BP was significantly lower than placebo [117]. examined the impact of garlic administration in eighteen trials involving 799 normotensive and hypertensive subjects. The follow–up was from 3 - 6 months at different dose levels of garlic administration 300 - 2400 mg/day. It was reported that the BP was reduced in the hypertensive but not in the normotensive subjects and was better than that of placebo treatment. The mechanism anticipated for the BP lowering effect of garlic was correlated the sulfur compounds- allicin the most important- which are reputed for modulating endothelium-relaxing factors; stimulation for No production and hydrogen sulfide (H2S), also allicin causes ACE inhibition and hence BP was reduced [115].

3.2.7. Crocus sativus L. (Saffron)

Saffron is rich in interesting bioactive metabolites as safranal, crocetin, crocin and picrocrocin, flavonoids and anthocyanins that exert antihypertensive and vasodilatory effects [118]. A randomized, placebo-controlled study was performed in thirty volunteers to clinically prove the BP-lowering effects of *Crocus sativus* [119]. Study design was achieved by dividing the subjects into

three groups (10 per group) and blood pressure was monitored for one week. Results evidenced significant decrease in SBP 11 mmHg and lowering arterial pressure 5 mmHg at dose level 400-mg of the herb. The mechanism of action for the antihypertensive and vasodilatory action of *C. sativus* suggested in this study was mediated *via* Ca^{2+} channels blockade, K^{+} channels opening and *β*-adrenoceptor antagonism.

3.2.8. Panax ginseng (Ginseng)

Panax ginseng (F. Araliacea) roots have been reputed in folk medicine for different disorders including cardiovascular disorders and hypertension. Triterpenoidal and steroidal saponins are the major bioactive ingredients of ginseng responsible for its CV effects. Clinical trials evidenced a significant decrease in blood pressure. American ginseng (AG) effects on arterial stiffness and BP reduction was revised in a randomized study [120]. The study was pursued in 64 hypertensive diabetic patients aging 63 ± 9.3 years for 12 weeks. Results revealed a reduction in BP, the augmentation index (AIx)and the pulse pressure (PP). Another randomized, double-blind, cross-over [121] investigated the Korean red ginseng effects on BP and arterial stiffness in twenty three normotensive samples aging 25 ± 2 years. The extract exhibited statistically-significant reductions in AIx, central SBP, central DBP and brachial BP, three hours after intervention as compared to the control. The effects of *P. ginseng* extracton BP was further studied in ninety subjects with the age range of 55.2 ± 11.8 years and BP range of 120 - 159/80 - 99 mmHg and the follow-up was for two months [122]. Results showed that the seated SBP (sSBP) and DBP (sDBP) levels were decreased only upon the administration of high dose at the fourth week. Unlikely, at the eighth week, there was a decline in the differences between the groups. Moreover, no significant metabolic or clinical side effects were reported. The effects of *P. ginseng*on BP reduction were mainly accredited to its vascular effects intermediated by a massive eNOS expression increase and NO production increase, in addition to, Ca^{2+} channels blockade [120, 123].

3.2.9. Camelia sinensis L. (Tea Plant, Tea Shrub)

Camellia sinensis L. (Family Theaeceae) (leaves and leaf buds) is the most commonly consumed beverage worldwide and are the most frequently consumed beverages worldwide. Tea leaves have diverse biological activities; anti-inflammatory, antidiabetic, and antihypertensive actions. Many studies have demonstrated significant antihypertensive action. In a trial by [124], where 95 hypertensive patients in the age ranging from 35 to 75 years under took the study. The BP follow-up duration was for six months. Results were in good agreement

where the arterial blood pressure (ABP)measured through 24 hours was reduced in the group receiving tea as compared to the placebo group. Another report on the effect of black and green tea to reduce blood pressure [125]. Eleven trials were revised; 7 consumed green tea and 4 received black tea in 821 subjects for 6 months. It was deduced that the green tea caused more reduction in BP compared to black tea. There were no adverse reactions and was well tolerated treatment as well. On analyzing the mechanism of action of both black and green tea in reducing blood pressure, the major action is supposed to be due to its polyphenolic content mainly catechins. Catechin is a flavan-3-ol with powerful antioxidant activity that stimulates nitric oxide production and reduces endothelin-1concentrations in the plasma. These actions collectively lead to a decrease in vascular tonicity leading to vasodilatation and peripheral vascular resistance reduction and BP reduction.

3.2.10. Cymbopogon citratus (Lemongrass)

Citral the active ingredient of the volatile oil of Lemongrass has been used in the management of hypertension due its vasodilating action. Lemon grass proved in a hypertensive rat model its effect to reduce blood pressure [126]. This was correlated to its vaso-relaxant and antioxidant effect [127].

3.2.10. Peumus boldus (Family Monimiaceae)

is an aromatic and evergreen shrub, where the leaves are the most common part used due to its boldine content. Boldine is an alkaloid of the aporphine class with potent antioxidant activity. The effects of boldine on endothelial dysfunction were evaluated in spontaneously hypertensive rats (SHR). The study used SHR *versus* their age-equivalent normotensive rat for one week. Results revealed that control group of SHR demonstrated SBP elevation, endothelium-dependent aortic relaxation to acetylcholine reduction, endothelium-independent aortic relaxation to sodium nitroprusside attenuation, aortic superoxide increase and peroxynitrite production, and p47 protein expression enhancement as regards to control rats. In conclusion, boldine possesses endothelial protective action in hypertension *via* NADPH-mediated superoxide production inhibition [128, 129].

4. ANGINA PECTORIS

Angina, known as angina pectoris/angina cordis / angor pectoris / Rougnon-Heberden disease, is a well-known cardiovascular disorder which is frequently associated with coronary heart diseases. The term “angina pectoris” was first introduced in 1772 by William Heberden [130]. It occurs due to the failure of the

coronary blood supply to meet the myocardial oxygen demands. Basically, this failure is a result of coronary obstructions in which the atherosclerosis restricts the blood flow to the heart muscle forming a fixed obstruction. Sometimes this obstruction is dynamic due to coronary spasms or even patients with mixed angina may have both kinds of obstruction. Other causes extend to include anemia, arrhythmia and heart failure [131 - 133].

Globally, CAD is the major cause of mortality, accounting for about 7.2 million deaths annually [134]. The prognosis of angina depends predominantly on the quantity of obstructed vessels and the obstruction extent. The risk of vasospasm and thrombosis is significantly increased in cases of 80% or more vessels obstruction. A twelve-year survival rate is estimated to be 88%, 74%, 59%, and 40% for subjects having zero, one, two, and three-vessel disease respectively. This estimated survival rate could be affected by other factors such as congestive heart failure, ejection fraction, previous myocardial infarction, diabetes, age and smoking history. It could be concluded that, patient prognosis remarkably varies by up to 10 folds according to several parameters as clinical, anatomical and functional factors [135, 136].

The diagnostic tools employed for angina are clinical manifestations, laboratory tests and other invasive and non-invasive cardiac investigations. These tools are usually used for both diagnostic and prognostic evaluations which are done randomly. The history of the patient is considered the foundation of angina diagnosis; hence, confident diagnosis could be based solely on it [136].

Angina patients suffer from paroxysmal thoracic pain with a heavy strangulation or pressure-like sensation that radiates to the left arm, jaw, epigastrium, back and shoulder as explained by referred pain. This pain is usually accompanied by suffocation feeling, shortness of breath, tiredness, sweating, dizziness, sometimes nausea, tachycardia and hypertension [137].

The chest pain in angina patients should be described in regards to its location, duration, character and its relation to exertion to prevent any confusion with other cardiovascular diseases [136]. Angina should not be confused with heart attacks, where in case of angina the blood flow restrictions are related to physical exercise, temporary and does not cause damage or destruction to the heart muscles. However, angina patients are at higher risk of having heart attacks and its complications [133].

Laboratory tests for angina includes tests undertaken to (a) Determine the causes of ischemia, such as hemoglobin and thyroid hormones (if susceptible thyroid disorder), also, markers of myocardial injuries as Creatinine Kinase Myocardial Band (CKMB) could be used to exclude myocardial damage if required clinically.

(b) Evaluate cardiovascular risk factors, for example, fasting blood glucose, glycated hemoglobin, serum creatinine and total lipid profile and furthermore, cholesterol subfractions (Apo A and Apo B), homocysteine, lipoprotein a (Lpa), and hemostatic abnormalities, inflammatory markers (hs-C-reactive protein) and NT-BNP are used as predictors of long-term risk factors. (c) Evaluate the prognosis, such as complete blood count including WBCs count. However, the laboratory tests used for initial diagnosis and routine reassessment are controversial and variable according to the case evaluated [136].

Non-invasive investigations include the regular resting Electrocardiography (ECG); ECG stress testing, stress testing (with imaging), echocardiography (at rest) and ambulatory ECG monitoring. In addition, coronary calcification and coronary anatomy assessments such as computed tomography (CT) scans and Magnetic Resonance (MR) arteriography may be used as non-invasive diagnostic tools for angina. Invasive investigations are used to ascertain the diagnosis or treatment options [136].

There are four major classes of angina;

(a) Stable angina: It is characterized by chest pain and associated symptoms that are precipitated by physical activity, cold weather, heavy metals, excitement or emotional stress. These symptoms subside at rest or upon treatment with nitroglycerin. Hence, this type of angina is the classical type and referred to as effort angina [138]. Stable angina is regarded as the most common manifestation of myocardial infarction [139].

(b) Unstable angina: It is defined as the worsening of angina, in which the chest pain occurs with sudden-onset at rest or minimal exercise and lasts for more than ten minutes, becomes more severe and more frequent. This type of angina is referred to as crescendo angina as it occurs with a crescendo pattern i.e. prolonged, more severe and more frequent [131].

(c) Prinzmetal angina: It is similar to the unstable angina in which the patients suffer from severe pain that usually occurs while resting or sleeping; however, it arises from transient increase in coronary vascular tone (vasospasm). It is also known as variant or vasospastic angina [140].

(d) Microvascular angina: It was historically known as cardiac syndrome X, characterized by angina-like chest pain [141]. Studies consider this type of angina a part of the pathophysiology of ischaemic heart disease that is more common in women [142, 143]. It does not show major arterial blockages however it is suggested to result from endothelial dysfunction and reduced flow in the micro-blood vessels of the heart [144].

The major risk factors of angina are the age factor (men over forty-five years and women over 55 years), smoking, Diabetes mellitus, hypercholesterolemia, hypertension, renal diseases, obesity (body mass index exceeding 30), family history of premature cardiovascular diseases, sedentary lifestyle and emotional stress [145].

The patient age is paramount to the prevalence of angina, as it increases from 0.1 - 1% to 10 - 15% as for 45-54 years old women to 65 - 74 years old women respectively, similarly, it increases form 2 - 5% to 10 - 20% as for 45 - 54 years old men to 65 - 74 years old men respectively. Fortunately, there is a pragmatic decline in the incidence rate of angina in the recent decades [136].

4.1. Pathophysiology of Angina Pectoris

The imbalance between the oxygen supply to the heart and its demand will evoke angina. This imbalance could arise from exercise, for example, in which there is an increase in the demand for oxygen and in cases of atherosclerosis or coronary arteries obstruction there will not be a sufficient oxygen supply. The myocardial oxygen demands vary according to the heart rate, heart muscle contractility and most importantly, the intra-myocardial wall tension. The myocardial oxygen supply is affected by the difference of arteriovenous oxygen pressure and the coronary blood flow [139]. This blood flow may be radically altered by atherosclerotic plaque which will result in an imbalance in case of increased myocardial oxygen demand. In most cases, the pathophysiological substrate of angina is atheromatous, nevertheless, it varies according to the patient's gender, whereas; women usually suffer from non-obstructive coronary disease type of angina [136, 146, 147].

Conventional treatment of angina is primarily aiming to relieve its symptoms, slow its progression and prevent its long-term complications as decreasing the risks of its development to heart attacks or even mortality. Different treatment pathways are depicted in Fig. (**1**). These treatments comprise the use of vasodilators, mainly nitroglycerin (used sublingual for acute cases with short duration, oral for intermediate duration cases and transdermal for longer durations) [148]. Caution should be taken with patients taking a phosphodiesterase (PDE5) inhibitor, as sildenafil, as it is contraindicated with any form of nitrates causing sudden decrease in the blood pressure. Other vasodilators used for treatment of angina include Ca^{2+} channel blockers, β- blockers and ACE inhibitors in which their mechanisms of action involve decreasing the heart work load which will decrease the myocardial oxygen demand or increase the coronary blood flow resulting in myocardial oxygen supply increase. Both mechanisms will in turn reverse the case of imbalance between the oxygen supply and demand

[136, 149]. Cyto-protective medications such as trimetazidine, are usually used as antianginal agents to increase the cell tolerance to ischemia by maintaining cellular homeostasis [150]. Recently, new classes has been used in the treatment of angina, for example If inhibitors (Ivabradine), which act by decreasing the heart rate with major anti-ischaemic and antianginal efficacy [151] and potassium channel openers (Nicorandil).

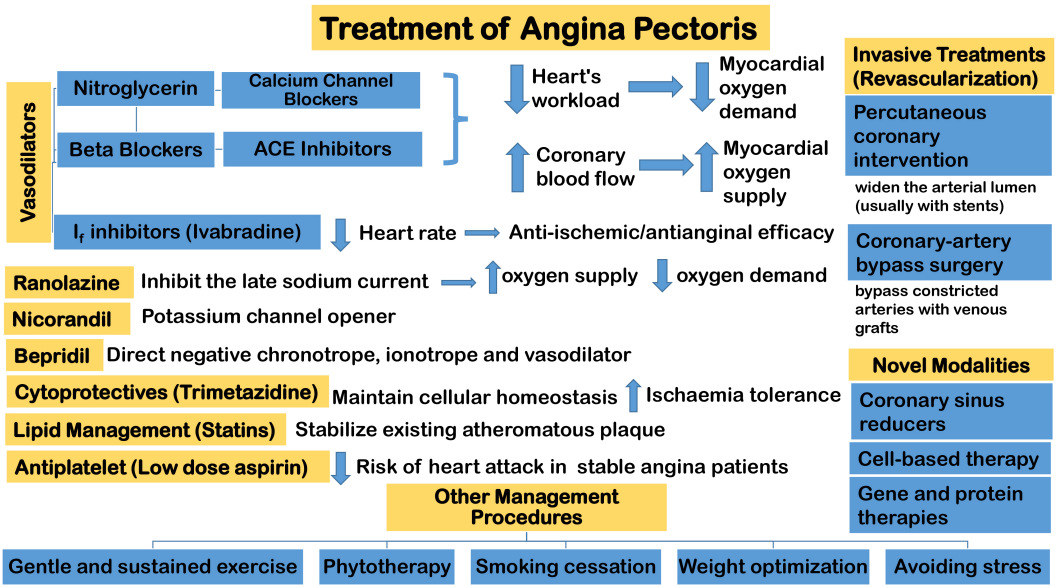

Fig. (1). Different treatments for angina pectoris [136, 148 - 158].

In 1990, the FDA approved bepridil as an antianginal agent having direct negative chronotropic, ionotropic and vasodilator effects. It differs from calcium channel blockers in which it causes the inhibition of receptor-operated, voltage-gated Ca^{2+} channels as well as K^{+} currents and intracellular Ca^{2+}/calmodulin complexes [152]. Also, ranolazine was recently approved as a treatment of angina either as a replacement of beta blockers or as a complementary therapy with them. It acts by inhibiting the late sodium current, therefore reducing intracellular Na^{+} and Ca^{2+} accumulation which in turn increases oxygen supply and reduces oxygen demand [153]. In addition, anti-hypercholesterolimics as statins, could be used to stabilize the atheromatous plaque and reduce the regression of coronary atherosclerosis [154]. Although, classically the administration of antiplatelets such as low doses of aspirin was a standard treatment for angina along with the vasodilators, it is now restricted to cases of high risk of myocardial infarction as it was found to cause hemorrhagic stroke and gastrointestinal bleeding [155].

Invasive treatment of angina (Revascularization) includes Percutaneous Coronary

Intervention (PCI), where a catheter enclosing a balloon enters to the arterial lumen then inflates to cause lumen widening; it is usually accompanied with stents to maintain the widening effect. Also, coronary-artery bypass surgeries (CABG) may be employed where venous grafts are used to bypass the constricted arteries. Revascularization is basically performed to relieve the angina symptoms yet it also has a prognostic benefit for patients who are at high risk [156].

Cell-based therapies for ischemic cardiomyopathy are still in its preclinical phases questioning its efficacy and feasibility. Experimentally, it was found that induced pluripotent stem cells and embryonic stem cells have regenerative abilities and cause cardiac function improvement after ischemia [152]. However, novel treatment modalities, for example coronary sinus reducers, cell-based therapies, gene and protein therapies, are still under evaluation [157].

Other management procedures could be used for the control of angina such as; gentle long-term exercise aiming to improve the blood pressure and promote the collateralization of the coronary arteries. In addition to, the control of lipid profile, blood pressure, diabetes and weight, quitting smoking and avoiding psychological stress [158].

4.2. Natural Products and Angina Pectoris

The evidence-based therapy of cardiovascular diseases by natural products is controversial. In fact, the use of botanicals in the treatment of angina is questionable as it may not cause relieving of the angina symptoms directly, which is the chief goal of the treatment as fore-mentioned. However, these natural products may be employed as secondary treatments for cardiovascular diseases [159]. Table **1** represents the key individual botanicals employed in the management of angina pectoris, it includes parts used, major active ingredients, the designs of different experiments that reported their activity and their mechanisms of action.

Key botanicals used in the treatment of angina includes Hawthorn (*Crataegus oxyacantha, C. monogyna, C. laevigata, and C. pinnatifida*) [159, 160], Danshen (*Salvia miltiorrhizae*) [159], San qi (*Panax notoginseng*) [159], Garlic (*Allium sativum*) [159], *Gingko biloba* [159, 161], Arjuna (*Terminalia arjuna*) [159, 160], Pushkarmoola (*Inula racemose*) [159, 160, 162], Turmeric (*Curcuma longa*) [159], *Ligusticum chuanxiong* Hort [159]. Guggul (*Commiphora mukul*) [160], Gualoupi (*Trichosanthis kirilowii or T. rosthornii*) [163].

Other natural products that could be used as antianginal agents are; grapes, as it has been proposed that resveratrol is an antiaging metabolite and prevents the

decline in cardiovascular function caused by aging through the expression of several longevity genes [164]. Coleus contains the alkaloid forskolin, exhibits hypotensive, positive inotrophic, vasodilator, anti-platelet aggregation activities [165]. Khellin, from khella, was reported to have more potent action than many of the common coronary vasodilators [166]. Also, Alfalfa leaves, sprouts, ginger, green tea, lingzhi and brindle berry were found to possess hypolipidimic activities, through which they have potential antiatherosclerotic effects [167].

A step further was undertaken to evaluate the beneficial effects of single compounds in the treatment of angina. However, most of these compounds were assessed as an approach to avert its long-term complications, with exception to puerarin, a well-established antianginal agent. It is an isoflavone purified from Pueraria genus, which significantly reduces the frequency of angina events and myocardial oxygen consumption, increases the duration of exercise and reverses the abnormal rest ECG in a clinical study involving unstable angina patients [168].

Table 1. Key botanicals used in the treatment of stable angina pectoris.

Plant	**Part Used**	**Main Active Constituents**	**Experimental Design**	**Mechanism of Action**
Hawthorn *(Crataegus oxyacantha), (C. monogyna), (C. laevigata),* and *(C. pinnatifida)*	Leaves, flowers, and berries	Oligomeric proanthocyanidin	Randomized controlled trials, observational cohort study, multicenter, placebo-controlled, double-blind study and In vitro studies	● Increases the force of myocardial contraction ● Enhances coronary blood flow and coronary perfusion ● Improves oxygen utilization by cardiomyocytes ● Prolonges the refractory period and action-potential duration in heart and papillary muscles ● Has a mild hypotensive effect ● Antagonizes atherogenesis with a negative chronotropic effect and a positive inotropic effect on the contraction amplitude of cardiac myocytes ● Inhibits 3′,5′-cyclic adenosine monophosphate phosphodiesterase ● Lowers arrhythmogenic risk as it prolongs the effective refractory period

Plant	**Part Used**	**Main Active Constituents**	**Experimental Design**	**Mechanism of Action**
Danshen *Salvia miltiorrhizae*	Root	Tanshinone (I, IIA, and IIB) and salvianolic acids (A, B)	Animal studies, In vitro studies and randomized controlled trials	● Enhances the recovery of contractile force upon reoxygenation following myocardial ischemia ● Reduces ischemic symptoms and improves the pathological electrocardiogram (ECG) pattern ● Has a negative inotropic effect and increases the coronary flow rate ● Can reduce the infarct size caused by myocardial ischemia ● Reduces the risk of myocardial tissue necrosis. ● Upregulates the expression of vascular endothelial growth factors ● Improves microcirculation, causes endothelium-dependent vasodilation in aortic strips, causes general vasodilation (low dose) and vasoconstriction in noncoronary arteries (high dose) ● Inhibits angiotensin-converting enzyme ● Increases nitric oxide production by endothelial cells. ● Inhibits thrombosis, thromboxane B2 formation, and platelet aggregration ● Antioxidant activity

Plant	Part Used	Main Active Constituents	Experimental Design	Mechanism of Action
San qi *Panax notoginseng*	Root	Saponines (ginsenosides) and notoginsenosides	Animal studies, In vitro studies	● Reduces myocardial oxygen consumption and protects the myocardium ● Increase coronary blood flow ● Enhances blood fibrinolytic parameters ● Dilates coronary arteries (dose dependent) ● Inhibits atherosclerosis by inhibiting the proliferation of aortic smooth muscle cells ● Reduces thrombogenicity and increases erythrocyte deformability. ● Suppresses cardiac arrhythmias during oxygen-deprivation ischemia and reperfusion ● Calcium ion channel antagonist in vascular tissues, resulting in hypotension ● Lipid-lowering effects and antioxidant activity
Garlic *Allium sativum*	Bulbs	Garlicin	Randomized controlled trials, double-blind, crossover study and In vitro studies	● Inhibits platelet aggregation ● Hypolipidemic action ● Enhances the fibrinolytic activity ● Protects the elastic properties of the aorta ● Hypoglycemic action
Maidenhair *Gingko biloba*	Leaves	Ginkgolides, flavonoid glycosides, terpene lactones and ginkgolic acid	Animal models, and clinical trials	● Inhibits the platelet-activating factor ● Antioxidant activity ● Increases the blood flow via release of nitric oxide and prostaglandins
Arjuna *Terminalia arjuna*	Stem bark	Triterpinoids, flavonoids, and minerals	Animal models, double-blind crossover study, open-label studies and randomized controlled trials	● Positive inotropic ● Vasodilator effect on coronary arteries ● Reverses smoking-related endothelial dysfunction ● Lipid-lowering effects and antioxidant activity

Plant	**Part Used**	**Main Active Constituents**	**Experimental Design**	**Mechanism of Action**
Pushkarmoola *Inula racemosa*	Root	Sesquiterpene lactones (alantolactone and isoalantolactone)	Animal studies, preliminary clinical study, open-label clinical study	● Negative ionotropic and negative chronotropic effect ● Blocks the action of adrenaline ● Act as an agonist for propranolol ● Improves hemodynamic function and left-ventricular function ● Antioxidant activity
Turmeric *Curcuma longa*	Rhizome	Curcuminoids demethoxycurcumin (curcumin II), bisdemethoxycurcumin (curcumin III), and cyclocurcumin	Animal studies, randomized controlled trials	● Antioxidant effects that attenuate adriamycin-induced cardiotoxicity ● Prevents cardiovascular complications associated with diabetes ● Inhibit p300-HAT and thus can ameloriate the development of cardiac hypertrophy and heart failure ● Antiinflammatory effects may prevent atrial arrhythmias ● Lipid lowering effects
Ligusticum *chuanxiong Hort* .	Root	Phalides (senkyunolide, Z-ligustilide, ligustiliden, ligustilide dimers, ligustrazine neocnidilide, 3-butylphthalide, Butylidenephthalide, and Tetramethylpyrazine)	*In vitro* studies, controlled and self-crossover clinical trial	● Relaxes the vascular rings and inhibits against contractions induced by phenylephrine; the potentiation of relaxation is postulated to be related to nitric oxide ● Increases coronary blood flow and decreases myocardial contractile force ● Inhibits the TNF-alpha production and TNF-alpha bioactivity in human monocytic cell lines
Guggul *Commiphora mukul*	Oleo-gum-resin	Guggulipid and guggulsterones	Animal studies, double-blind placebo control study	● It is an antagonist ligand for the bile acid receptor (farnesoid X receptor) which causes hypolipidemia ● Increases the plasma fibrinolytic activity

Plant	Part Used	Main Active Constituents	Experimental Design	Mechanism of Action
Gualoupi *Trichosanthis kirilowii* or *T. rosthornii*	Pericarp of ripe fruits	Lignan, trichobenzolignan and trichosanthin	Animal studies, randomized controlled trials	● Regulates lipid metabolism, exerts antiatherosclerotic effects and protects the vascular endothelium. ● Protects against ischemia reperfusion, injury, hypoxia, and calcium antagonism

Its mechanism of action involves the preservation of the mitochondrial structure and decreasing the myocardial lactate production and creatine phosphokinase release following a myocardial injury in a dog model [169]. Another clinical study proved that puerarinis involved in regulating endothelin, rennin, and angiotensin II imbalance in acute myocardial infarction patients [170]. Nevertheless, another clinical study suggested an alternative mechanism of action of puerarin involving platelet activating factors in patients with unstable angia pectoris [171].

Tetrahydropalmatine, an isoquinoline alkaloid isolated from *Corydalis* genus and *Stephania rotunda*, was reported to treat the increase of creatine kinase and aspartate aminotransferase in a rat model [172]. Magnesium tanshinoate B isolated from *Salvia miltiorrhizae* was found to stimulate NO release, enhance the cellular activities of NO synthase and associated increase the levels of constitutive NO in human endothelial cells *in vitro* [173]. Scutellarin, the major constituent of *Erigeron breviscapus,* decreased the degree of MI induced by isoprenaline in rats as proved recently by Huang *et al.* [174] Similarly, Baicalin from the genus Scutellaria, possesses protective actions on MI in rats. The probable mechanisms may involve its resistance to oxidative stress, and up-regulation of B-cell lymphoma-2 (Bcl-2) protein expression and down-regulation of Bcl-2 associated X (Bax) protein expression in myocardial tissue [175]. Also, the benzylisoquinoline alkaloid, berberine, significantly reduced the release of creatine phosphokinase and reversed the ultrastructural damage in isolated rat hearts [176], berberine's positive inotropic effect and mild vasodilation action helps its amelioration of the impaired left ventricular function and the decreased cardiac output in dogs [177, 178].

In conclusion, the mechanisms of action of most of these natural products need further clarifications and there is insufficient basis of their effectiveness in the treatment of various CVD. Hence, it is a need rather than an interest, to pay more attention to confirm the traditional claims of their use as antianginal agents. Multidisciplinary research is very important to evaluate the therapeutic potential

of these natural plants and point out the active constituent(s) responsible for the activity and its/their effective dose, through biologically guided studies. In addition to, their possible synergistic interactions with each other or other antianginal drugs and their adverse side effects. This will aid in their establishment as antianginal agents and their addition to the mainstream of cardiovascular remedies.

5. ATHEROSCLEROSIS

5.1. Pathophysiology of Atherosclerosis

Atherosclerosis is the key cause for the development of various CVD such as angina, myocardial infarction and ischemic heart failure. Atherosclerosis is characterized by endothelial dysfunction, inflammatory responses, extracellular matrix alteration, Smooth Muscle Cell (SMC) proliferation and thrombosis [179]. Atherosclerosis development may lead to blood supply reduction to the coronary arteries which can cause MI, which is the main pathological factor for coronary heart diseases [180].

Large and middle-sized arteries intima are particularly the sites of arterial bifurcations and they are highly influenced by atherosclerosis. Vascular SMCs, WBCs and modified lipids are accumulated in the intima. The accumulated SMCs at the tunica intima layer of the arteries can then migrate to form atheroma plaque through their proliferation. Pro-inflammatory activation of vascular SMCs causes a change to synthetic from contractile phenotype, leading to cell proliferation and migration. This migration of the activated vascular SMCs from the media to the intima leads to pro-atherosclerotic vascular remodelling [181].

The matrix metalloproteinases (MMPs), are involved in the process of proliferation and migration of vascular SMCs as it has a proteolytic activity that allows it to cause elastic lamina barrier of extracellular matrix degradation leading to various pathological conditions [182, 183].

In addition, these arterial regions suffer a turbulent shear stress that promotes endothelial cells (ECs) pro-inflammatory activation [184]. This activation is stimulated by the modified LDL, especially the oxidized LDL (oxLDL). The activated ECs express intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM-1) which attract monocytes and lymphocytes binding the endothelium and infiltrate the intima. Also accumulation of oxLDL takes place in the sub-endothelial level developing the atheorosclerotic plaque. In the intima, monocytes differentiate to macrophages which engulf oxLDL deposits and transform into foam cells [185]. Other immune cells are present in the lesion

and are involved in the intraplaque inflammation [186]. During the progression of atherosclerosis, immune and non-immune vascular cells release a variety of pro-inflammatory messengers that preserve and improve the local inflammation and atherosclerotic lesions development) Fig. **(2)**. Also, the concomitant up-regulation of pro-inflammatory signalling pathways in both vascular and blood cells stimulates atherogenesis [187].

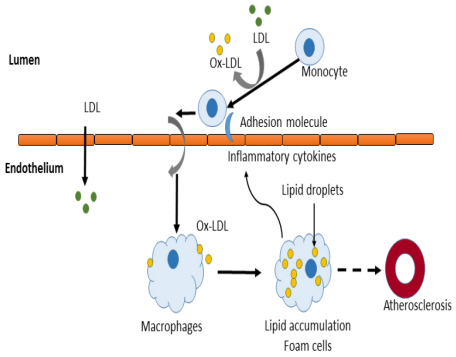

Fig. (2). Schematic representation of the mechanism of atherosclerosis.

There is increasing evidence that NO and NO synthase (NOS) systems in vascular SMCs can regulate the local vascular injury accompanying atherosclerosis. In healthy vessels, endothelial isoform of NOS (eNOS) produces NO in the endothelium and acts as an endothelium-derived relaxing factor essential for maintenance of vascular homeostasis. In atherosclerotic vessels, the endothelium-dependent relaxation impaired and represents the reduced eNOS-derived NO bioavailability that promotes atherosclerosis development [187]. In case of atherosclerosis, the inducible isoform of NOS (iNOS) is unable to recompense for the lost functional endothelium and eNOS [188]. Increased expression of iNOS has been linked to stimulating the pathogenesis of atherosclerosis [189]. In the advanced atherosclerotic plaques, iNOS may constantly indorse a pathogenic environment *via* oxidative and nitrosative stress enhancements [190]. There are much evidences that foresees the NO and NOS system as a potential target for atherosclerosis management.

5.2. Natural Products and Atherosclerosis

5.2.1. Ginkgetin

Medicinal plants have proven great efficacy as therapeutic agents for atherosclerosis. *G. biloba* is a plant of family Ginkgocea whose leaves have high content of acylatedflavonols, bioflavonoids and terpenoids [191]. Among Ginkgo biflavones, ginkgetin **3**) Fig. **(3)** has been shown to possess anti-inflammatory, neuroprotective, and anti-cancer activities [192]. Ginkgetin has been reported to down-regulate the expression of the matrix metalloproteinase (MMP-2 and MMP-9) in thoracic aortas of atherosclerotic rats [193]. As mentioned before, MMPs have a primary role in enhancing vascular remodeling and SMC migration [194]. Various matrix cells and macrophages produce MMP-9 which contributes in the degradation process of active substance in extracellular matrix of various tissues [195]. Thus, reduction in MMPs expression helps the remodeling of vascular extracellular matrices and reduces the migration of SMCs, thus contributes to the improvement of atherosclerotic rats.

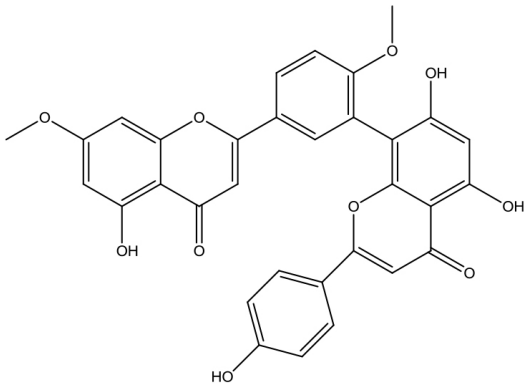

Fig. (3). Structure of Ginkgetin.

NO can suppress the progression of atherosclerosis by decreasing monocyte-endothelial cell interaction, hindering the adherence and aggregation of the platelets, and thus prevent SMC proliferation. Moreover, in the atherosclerotic rats, the expression of eNOS in serum and thoracic aortas was notably reduced, indicating that absence of NO promotes the pathogenesis of atherosclerosis [193]. Ginkgetin could increase the levels of NO in atherosclerotic rats. Ginkgetin was also found to up-regulate the levels of eNOS expression and down-regulate the levels of iNOS expression which were elevated atherosclerotic rats [193]. The increased expression and activity of iNOS was linked to the progression of atherosclerosis that was induced in vascular SMCs by pro-inflammatory cytokines

released from injured cells [190]. Thus that ginkgetin can be said to ameliorate atherosclerosis through modulation of NO/NOS system.

5.2.2. Colchicine

Colchicine as shown in Fig. (**4**) is a tropolone alkaloid isolated from the seeds and corms of genus Colchicum. Now, Colchicine is used for relieving the pain resulting from gout or familial Mediterranean fever, and under research to be used for treatment of pericarditis, and Behçet's disease due to its anti-inflammatory activity but its clinical applications is still limited due to its toxicity [196 - 198]. Anti-inflammatory activity of colchicine through which it inhibits inflammation in patients with acute coronary syndrome (ACS) or after acute MI is mediated by its anti-tubulin action and neutrophil function inhibition [199].

In a clinical trial, administration of oral dose (1 mg) of colchicine daily for 4 weeks has caused reduction in CRP levels in patients suffering from CAD [200]. In another clinical trial conducted on larger sample (532 of CAD patients), a daily dose of colchicine (0.5 mg) for 30 days caused a three-fold reduction of incidence cardiac arrest and non-embolic stroke and this effect last during the median three-year follow-up period [201].

In a prospective non-randomized pilot study conducted on 80 subjects with recent post-acute coronary syndrome (ACS) that last for less than one month, patients received either 0.5 mg/day colchicine plus optimal medical therapy (OMT) or OMT alone and with a followed up over a year. The results of this pilot study showed that colchicine at low dose caused modification of the coronary plaque, independent of high-dose statin combined therapy and significantly reduced the low-density lipoprotein (LDL). Colchicine also improved the plaque morphology through its anti-inflammatory effect which also helped in the reduction of high-sensitivity C-reactive protein (hsCRP), rather than changes in lipoproteins [202].

A review of 4992 patients in thirty nine trials of any clinical setting involving long-term colchicine compared to control showed that colchicine proved no effect on heart failure and stroke, however it showed efficacy in populations suffering Myocardial Infarction (MI) at high-risk [203]. Administration of colchicine for more than 6 months showed potential efficacy in minimizing MI risk and cardiovascular mortality [204].

A study was conducted on 1288 subjects having gout, and at high cardiovascular risk, in which the administration of colchicine caused a fifty four percent reduction in relative risk of MI [205]. Another retrospective cohort study investigated 501 gout patients and similar protective effects of colchicine were

observed [206].

Another trial was performed on 196 patients suffering from diabetes mellitus who had percutaneous coronary intervention with a bare metal stent. Administration of Colchicine for six months exerted a decrease in in-stent restenosis relative to placebo as shown in the follow-up angiography and intravascular ultrasound [207]. However, another double blinded, placebo-controlled study of 145 patients using the same dose of colchicine did not show improvement in the rate of angiographic restenosis in elective coronary angioplasty of 393 lesions without stent placement [208].

Furthermore, the role of colchicine was assessed specifically in a randomized trial conducted on 151 patients with ST-segment elevation MI (STEMI) who received colchicine for five days. Colchicine treated group showed a significant lower infarct size, as evaluated by creatine kinase-muscle/brain (CK-MB) concentration when compared to the placebo group. The cardiac magnetic resonance imaging of 60 of these patients confirmed that colchicine could significantly reduce the infarct size when compared to the left ventricular myocardial volume [209].

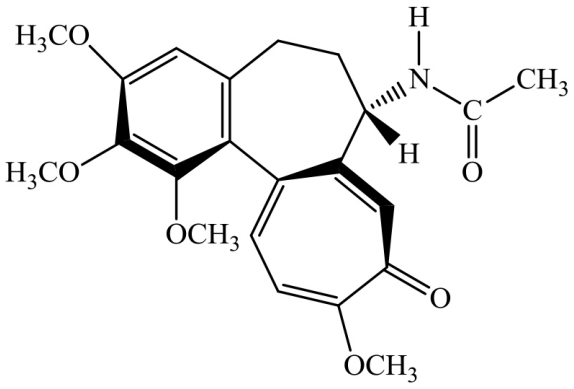

Fig. (4). Structure of Colchicine.

5.2.3. Garlic

Garlic (*Allium sativum*) contains active ingredients which exert prophylactic and treating effects against atherosclerosis [210].

A garlic-based herbal preparation was prepared and named Allicor. This preparation was tested in a pilot study which included 28 healthy men with the age range of 46–58 (52.0 ± 9.0). Anti-atherosclerotic activity of the preparation was indicated by the carotid intima-media thickness (cIMT), the subjects received Allicor daily for total duration of a year, however, ultrasound examination of the

carotid arteries were held every 3 months. The product was well-tolerated that was deduced from the absence of the adverse effects during the follow-up period. Allicor significantly reduced the tendency to cIMT [210].

In a clinical study, the effect of Allicor on the cIMT progression in 211 asymptomatic men aged 40 - 74 was studied. By the end of the first year follow-up period, a significant reduction of cIMT was observed in the Allicor-treated group, when compared to the placebo group [211]. After the 2-years follow-up period, the mean rate of cIMT was significantly reduced in the Allicor-treated group, relative to the placebo group [212, 213]. Consequently, it was recorded that long-term treatment with Allicor possessed an anti-atherosclerotic effect which was attributable to the improvement of serum atherogenicity [212, 213].

5.2.4. Anti-inflammatory Herbs

Inflammation has a crucial role in all the development stages of atherosclerosis [214, 215]. Many anti-inflammatory plants of the Mediterranean region can be used for the protection against atherosclerosis. Therefore, Calendula (*Calendula officinalis*), elder (*Sambucus nigra*) and violet (*Viola tricolor*) have been reported to have both anti-inflammatory and anti-atherogenic effects [216, 217]. Inflaminat is a combination of the three above mentioned plants, its effect was evaluated on cIMT in a pilot phase of a study designed on 67 asymptomatic men for a year [213, 218, 219]. In subclinical atherosclerosis, inflaminat could induce cIMT regression, which was significant relative to the placebo group. Thus, Inflaminat demonstrated anti-inflammatory and anti-atherosclerotic effects on cellular levels and induced regression of subclinical atherosclerosis in asymptomatic men.

5.2.5. Phytoestrogen-rich Herbs

Several natural herbs that are rich in phytoestrogen, showed promising *in vitr*o and *ex vivo* anti-atherogenic activity were incorporated into an herbal preparation named Karinat [220 - 222]. These herbs are garlic powder, extract of grape seeds (*Vitis vinifera*), green tea leaves (*Camellia sinensis*) and hops (*Humulus lupulus*). Additionally, Karinat was rich in biologically active polyphenols including resveratrol, genistein and daidzein, thus it could improve phytoestrogen profile. Karinat was tested for anti-atherosclerotic effect in a pilot clinical study on 157 asymptomatic postmenopausal women for a year [223, 224]. At the end, an increase in the mean cIMT was detected in the placebo group, with a 40% growth in the atherosclerotic plaque in postmenopausal women. Inversely, the mean cIMT remained stable in the Karinat-treated group. The studied phytoestrogen complex suppressed the formation of new atherosclerotic lesions in post-

menopausal women [213, 225].

6. HERBAL TREATMENT OF CEREBROVASCULAR DISORDERS

Cerebrovascular disorders involve different kinds of diseases, such as stroke, cerebral edema, vascular dementia, and transient ischemic attack, in addition to age-associated memory impairment which is experienced by elderly people, as dizziness, depression, and tinnitus [226]. Regrettably, the mortality data conveyed to the WHO by different countries are inconsistent [227]. However, these diseases, especially stroke, represent the third leading cause of death in the United States after heart diseases and cancer [226].

This category of diseases is considered as a type of peripheral vascular diseases. They occur as a consequence of the brain cells dysfunction, which happens due to free radicals including superoxide, hydrogen peroxide and hydroxylation radicals or decreased oxygenation level. This part of the chapter will focus mainly on the second point; major causes of decreased oxygen level supplied to brain neuronal cells and its possible herbal treatment.

Cerebral tissues consume approx. 20% of the total body requirement from oxygen to live and work properly. Deficiency of oxygen supply in cerebral tissues has many reasons, which could be classified into abnormalities of the vessels supplying the blood to the brain due to atherosclerosis or arthritis or abnormalities in the blood flow itself. Diseases in blood vessels provoke secretion of platelet-activating factor (PAF) and thrombus formation. Thrombosis or embolism reduces the oxygen supply to the cerebral tissues significantly and results in tissue hypoxia or ischemia affecting the blood flow and tissue oxygenation as well.

Major developments in treating ischemic stroke have been performed over the last decade. However, stroke is still a serious concern for which effective drug therapy is not yet available [228]. To date, the FDA only approved Recombinant plasminogen activator (rt-PA) for the treatment of stroke. However, thrombolysis lessens stroke morbidity but is only relevant to a small percentage of stroke patients [229].

6.1. Physiology and Pathophysiology of Blood Coagulation

Physiologically, blood coagulation systems or hemostasis functions through extrinsic and intrinsic pathways that are promoted differently *via* tissue injury or abnormal pathological conditions. However, they joined in a common pathway at the conversion step of thrombin from prothrombin.

Coagulation cascades are monitored through a number of clinical laboratory tests, such as APTT for the intrinsic pathway, PT for extrinsic pathway, and TT for common pathway. In addition, International Normalized Ratio (INR) or standardized prothrombin time is sometimes required especially for patients taking anti-clotting medicines, such as warfarin.

6.2. Natural Treatments of Coagulation Abnormalities

Natural herbal antioxidants are out of scope of this part. Therefore, a number of herbal treatments that could be used to alleviate symptoms of thrombosis and resulting cerebrovascular disorders will be covered in the following section.

6.2.1. Ginkolides and Bilobalides

Ginko tree (*Ginko biloba* L., Ginkoaceae) is always described by the "living fossil". Additionally, it has a long history, some 2000 years especially in China, in treating many diseases. *Ginkgo biloba* is amongst the best seller medicinal plants with 4.5 to 5.1 million pounds annual consumption in 2001 of the dried leaves. Currently there are about 142 *G. biloba* products on the market worldwide and its utilization is estimated to grow threefold in the upcoming five years [230].

Standardized leaf extracts of *G. biloba* (SGB extracts) have neuroprotective activities. In addition, it may be useful in preventing and treating CVD, mainly ischemic cardiac syndrome [231, 232].

These bioactivities owe to its mixture contents from flavonol and biflavone glycosides, such as quercetin and kaempferol, in addition to sesquiterpene and diterpene lactones, including bilobalide and ginkolides, respectively. Flavonoid contents enhance the capillary integrity in addition to its function as free-radical scavengers as well [233]. While terpene lactones work as platelet-activating factor inhibitors produced by different tissues. This function prevents platelet aggregation and its subsequent thrombus formation.

6.2.2.. Sulphated Polysaccharides

Marine macroalgae produce sulphated and non-sulphated polysaccharides possessing a wide-range of interesting medical applications making them promising pharmaceutical products [234]. Among them are Phaeophytes or brown algae polysaccharides, *e.g*., fucoidan, alginate and laminarin. Several reports investigated the potential anticoagulant activity of the sulphated polysaccharide fucoidan [235 - 237]. They reported that it acts in a heparin-like manner and

interfered mainly with the intrinsic pathway of the coagulation system [238, 239]. In addition, the negative charge distribution of its structure together with its long polysaccharide chain, high molecular weight, and structure comfort ability contributed to inhibition of thrombin and discontinuation of the fibrinogen conversion to fibrin [240].

6.2.3. Garlic Thiosulphinates

Chemistry and biology of garlic (*Allium sativum* L., family Alliaceae) have been intensively investigated as one of the most investigated medicinal plants. More than 3000 research articles were published in the last few decades during 1960 to 2007. Most of these studies focused on the possible indication of garlic in treatment of CVD [241]. Garlic contains over a hundred 100 sulfur-containing metabolites. Allicin represents 70-80% of the total thiosulphinates. The anti-platelet activity of garlic has been attributed to adenosine, allicin and other thiosulfinates [242].

6.2.4. Extract of Antrodia camphora

A. camphorate is a fungal parasite that lives and grows on *Cinnamomum kanehirae* (Bull camphor tree) Hayata (Lauraceae) [243]. Polysaccharides, terpenoids, lignans, benzenoids, benzoquinone derivatives have been identified.

Pharmacologically, it is used in Traditional Chinese Medicine (TCM) for the treatment of viral hepatitis and cancer, yet, it has shown neuroprotective effects in embolic rats, recently [228]. It is useful in reestablishing blood flow to the ischemic brain through the reduction of perfusion deficits following ischemia and without causing any hemorrhagic incidence when used in conjunction with aspirin therapy [244].

6.2.5.. Alpha-lipois Acid

Alpha-lipoic acid or ALA is found in various foods. It shows a significant part in metabolic processes. It functions as a cofactor for several key enzymes. It has been known as the “perfect” antioxidant [245]. It protects against oxidation, thus prevents Ischemia-reperfusion injury [245]. It attenuates middle cerebral artery occlusion-induced cerebral ischemia and reperfusion injury. It acts *via* insulin receptor-dependent and PI3K/Akt-dependent inhibition of NADPH oxidase. Moreover, an interesting study established the effects of Tetra Methyl Pyrazine (TMP) on functional recovery and neuronal dendritic plasticity after experimental

stroke. In that study, the authors have demonstrated that enhanced dendritic plasticity contributes to TMP-elicited functional recovery after ischemic stroke [246].

CONCLUDING REMARKS

The increase in the popularity of the use of natural products has raised the interest in natural remedies that can be beneficial in the treatment of cardiovascular diseases. This chapter highlights the cardiovascular effects of natural products and their metabolites in controlling cardiovascular diseases especially those subjected to sub-clinical or clinical trials. Although most of the mentioned plants have a long history in treating heart diseases, recent research strategies show how efficient they are in the treatment of different cardiovascular diseases including ischemic heart disease, congestive heart failure, and hypertension by unique mechanisms. In addition, we also discussed the chemical constituents of these plant species which provide beneficial effects by various modes of action that can improve the quality of life in patients with heart disease and potentially save their lives.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors confirm that they have no conflict of interest to declare for this publication.

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REFERENCES

[1] W.H.O. Hearts. technical package for cardiovascular disease management in primary health care WHO Press, 20 Avenue Appia, 1211 Geneva 27, Switzerland.

[2] Kulczyński B, Gramza-Michałowska A, Kobus-Cisowska J, Kmiecik D. The role of carotenoids in the prevention and treatment of cardiovascular disease – Current state of knowledge. J Funct Foods 2017; 38: 45-65.
[http://dx.doi.org/10.1016/j.jff.2017.09.001]

[3] Piepoli MF, Hoes AW, Agewall S, *et al.* 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Atherosclerosis 2016; 252: 207-74.
[http://dx.doi.org/10.1016/j.atherosclerosis.2016.05.037] [PMID: 27664503]

[4] Chomistek AK, Manson JE, Stefanick ML, *et al.* Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's Health Initiative. J Am Coll Cardiol 2013; 61(23): 2346-54.

[http://dx.doi.org/10.1016/j.jacc.2013.03.031] [PMID: 23583242]

[5] Chistiakov DA, Orekhov AN, Bobryshev YV. Treatment of cardiovascular pathology with epigenetically active agents: Focus on natural and synthetic inhibitors of DNA methylation and histone deacetylation. Int J Cardiol 2017; 227: 66-82.
[http://dx.doi.org/10.1016/j.ijcard.2016.11.204] [PMID: 27852009]

[6] W.H.O. World health statistics 2018. monitoring health for the SDGs, sustainable development goals Geneva: World Health Organization; Licence. 2018. CC BY-NC-SA 3.0 IGO.

[7] Mann D, Zipes D, Libby P, Bonow R. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Saunders 2014; p. 2040.

[8] Homans DC, Asinger R, Elsperger KJ, *et al.* Regional function and perfusion at the lateral border of ischemic myocardium. Circulation 1985; 71(5): 1038-47.
[http://dx.doi.org/10.1161/01.CIR.71.5.1038] [PMID: 3986974]

[9] Deb S, Wijeysundera HC, Ko DT, Tsubota H, Hill S, Fremes SE. Coronary artery bypass graft surgery vs percutaneous interventions in coronary revascularization: a systematic review. JAMA 2013; 310(19): 2086-95.
[http://dx.doi.org/10.1001/jama.2013.281718] [PMID: 24240936]

[10] Nidorf SM, Siu SC, Galambos G, Weyman AE, Picard MH. Benefit of late coronary reperfusion on ventricular morphology and function after myocardial infarction. J Am Coll Cardiol 1993; 21(3): 683-91.
[http://dx.doi.org/10.1016/0735-1097(93)90101-6] [PMID: 8436750]

[11] Sabia P, Abbott RD, Afrookteh A, Keller MW, Touchstone DA, Kaul S. Importance of two-dimensional echocardiographic assessment of left ventricular systolic function in patients presenting to the emergency room with cardiac-related symptoms. Circulation 1991; 84(4): 1615-24.
[http://dx.doi.org/10.1161/01.CIR.84.4.1615] [PMID: 1914101]

[12] Cassar A, Holmes DR Jr, Rihal CS, Gersh BJ. Chronic coronary artery disease: diagnosis and management. Mayo Clin Proc 2009; 84(12): 1130-46.
[http://dx.doi.org/10.4065/mcp.2009.0391] [PMID: 19955250]

[13] Charlson FJ, Moran AE, Freedman G, *et al.* The contribution of major depression to the global burden of ischemic heart disease: a comparative risk assessment. BMC Med 2013; 11: 250.
[http://dx.doi.org/10.1186/1741-7015-11-250] [PMID: 24274053]

[14] Mehta PK, Wei J, Wenger NK. Ischemic heart disease in women: a focus on risk factors. Trends Cardiovasc Med 2015; 25(2): 140-51.
[http://dx.doi.org/10.1016/j.tcm.2014.10.005] [PMID: 25453985]

[15] Anker SD, von Haehling S. Inflammatory mediators in chronic heart failure: an overview. Heart 2004; 90(4): 464-70.
[http://dx.doi.org/10.1136/hrt.2002.007005] [PMID: 15020532]

[16] Dassanayaka S, Jones SP. Recent Developments in Heart Failure. Circ Res 2015; 117(7): e58-63.
[http://dx.doi.org/10.1161/CIRCRESAHA.115.305765] [PMID: 26358111]

[17] Hofmann U, Frantz S. How can we cure a heart "in flame"? A translational view on inflammation in heart failure. Basic Res Cardiol 2013; 108(4): 356.
[http://dx.doi.org/10.1007/s00395-013-0356-y] [PMID: 23740214]

[18] Bibbins-Domingo K, Lin F, Vittinghoff E, *et al.* Predictors of heart failure among women with coronary disease. Circulation 2004; 110(11): 1424-30.
[http://dx.doi.org/10.1161/01.CIR.0000141726.01302.83] [PMID: 15353499]

[19] Stein GY, Kremer A, Shochat T, *et al.* The diversity of heart failure in a hospitalized population: the role of age. J Card Fail 2012; 18(8): 645-53.
[http://dx.doi.org/10.1016/j.cardfail.2012.05.007] [PMID: 22858081]

[20] Lazzarini V, Mentz RJ, Fiuzat M, Metra M, O'Connor CM. Heart failure in elderly patients: distinctive features and unresolved issues. Eur J Heart Fail 2013; 15(7): 717-23.
[http://dx.doi.org/10.1093/eurjhf/hft028] [PMID: 23429975]

[21] Roger VL, Go AS, Lloyd-Jones DM, *et al.* Heart disease and stroke statistics--2011 update: a report from the American Heart Association. Circulation 2011; 123(4): e18-e209.
[http://dx.doi.org/10.1161/CIR.0b013e3182009701] [PMID: 21160056]

[22] Lloyd-Jones D, Adams RJ, Brown TM, *et al.* Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 2010; 121(7): e46-e215.
[http://dx.doi.org/10.1161/CIRCULATIONAHA.109.192667] [PMID: 20019324]

[23] Floras JS. Sympathetic nervous system activation in human heart failure: clinical implications of an updated model. J Am Coll Cardiol 2009; 54(5): 375-85.
[http://dx.doi.org/10.1016/j.jacc.2009.03.061] [PMID: 19628111]

[24] Zucker IH, Xiao L, Haack KK. The central renin-angiotensin system and sympathetic nerve activity in chronic heart failure. Clin Sci (Lond) 2014; 126(10): 695-706.
[http://dx.doi.org/10.1042/CS20130294] [PMID: 24490814]

[25] Mangini S, Pires PV, Braga FG, Bacal F. Decompensated heart failure. Einstein (Sao Paulo) 2013; 11(3): 383-91.
[http://dx.doi.org/10.1590/S1679-45082013000300022] [PMID: 24136770]

[26] Johansen H, Strauss B, Arnold JM, Moe G, Liu P. On the rise: The current and projected future burden of congestive heart failure hospitalization in Canada. Can J Cardiol 2003; 19(4): 430-5.
[PMID: 12704491]

[27] Azad N, Lemay G. Management of chronic heart failure in the older population. J Geriatr Cardiol 2014; 11(4): 329-37.
[http://dx.doi.org/10.11909/j.issn.1671-5411.2014.04.008] [PMID: 25593582]

[28] Tamargo J, López-Sendón J. Novel therapeutic targets for the treatment of heart failure. Nat Rev Drug Discov 2011; 10(7): 536-55.
[http://dx.doi.org/10.1038/nrd3431] [PMID: 21701502]

[29] Inamdar AA, Inamdar AC. Heart Failure: Diagnosis, Management and Utilization. J Clin Med 2016; 5(7)E62
[http://dx.doi.org/10.3390/jcm5070062] [PMID: 27367736]

[30] Shukla SK, Gupta S, Ojha SK, Sharma SB. Cardiovascular friendly natural products: a promising approach in the management of CVD. Nat Prod Res 2010; 24(9): 873-98.
[http://dx.doi.org/10.1080/14786410903417378] [PMID: 20461632]

[31] Esterbauer H, Waeg G, Puhl H, Dieber-Rotheneder M, Tatzber F. Inhibition of LDL oxidation by antioxidants. EXS 1992; 62: 145-57.
[PMID: 1450582]

[32] Janero DR. Ischemic heart disease and antioxidants: mechanistic aspects of oxidative injury and its prevention. Crit Rev Food Sci Nutr 1995; 35(1-2): 65-81.
[http://dx.doi.org/10.1080/10408399509527688] [PMID: 7748481]

[33] Weseler AR, Bast A. Oxidative stress and vascular function: implications for pharmacologic treatments. Curr Hypertens Rep 2010; 12(3): 154-61.
[http://dx.doi.org/10.1007/s11906-010-0103-9] [PMID: 20424954]

[34] Arai Y, Watanabe S, Kimira M, Shimoi K, Mochizuki R, Kinae N. Dietary intakes of flavonols, flavones and isoflavones by Japanese women and the inverse correlation between quercetin intake and plasma LDL cholesterol concentration. J Nutr 2000; 130(9): 2243-50.
[http://dx.doi.org/10.1093/jn/130.9.2243] [PMID: 10958819]

[35] Arima H, Ashida H, Danno G. Rutin-enhanced antibacterial activities of flavonoids against Bacillus

cereus and Salmonella enteritidis. Biosci Biotechnol Biochem 2002; 66(5): 1009-14.
[http://dx.doi.org/10.1271/bbb.66.1009] [PMID: 12092809]

[36] Binsack R, Boersma BJ, Patel RP, *et al.* Enhanced antioxidant activity after chlorination of quercetin by hypochlorous acid. Alcohol Clin Exp Res 2001; 25(3): 434-43.
[http://dx.doi.org/10.1111/j.1530-0277.2001.tb02232.x] [PMID: 11290856]

[37] Kähkönen MP, Heinonen M. Antioxidant activity of anthocyanins and their aglycons. J Agric Food Chem 2003; 51(3): 628-33.
[http://dx.doi.org/10.1021/jf025551i] [PMID: 12537433]

[38] de Whalley CV, Rankin SM, Hoult JR, Jessup W, Leake DS. Flavonoids inhibit the oxidative modification of low density lipoproteins by macrophages. Biochem Pharmacol 1990; 39(11): 1743-50.
[http://dx.doi.org/10.1016/0006-2952(90)90120-A] [PMID: 2344371]

[39] Duffy SJ, Keaney JF Jr, Holbrook M, *et al.* Short- and long-term black tea consumption reverses endothelial dysfunction in patients with coronary artery disease. Circulation 2001; 104(2): 151-6.
[http://dx.doi.org/10.1161/01.CIR.104.2.151] [PMID: 11447078]

[40] Guardia T, Rotelli AE, Juarez AO, Pelzer LE. Anti-inflammatory properties of plant flavonoids. Effects of rutin, quercetin and hesperidin on adjuvant arthritis in rat. Farmaco 2001; 56(9): 683-7.
[http://dx.doi.org/10.1016/S0014-827X(01)01111-9] [PMID: 11680812]

[41] Choi JH, Chang HW, Rhee SJ. Effect of green tea catechin on arachidonic acid cascade in chronic cadmium-poisoned rats. Asia Pac J Clin Nutr 2002; 11(4): 292-7.
[http://dx.doi.org/10.1046/j.1440-6047.2002.00305.x] [PMID: 12495261]

[42] Hollman PC, Hertog MG, Katan MB. Role of dietary flavonoids in protection against cancer and coronary heart disease. Biochem Soc Trans 1996; 24(3): 785-9.
[http://dx.doi.org/10.1042/bst0240785] [PMID: 8878848]

[43] Hollman PC, Katan MB. Dietary flavonoids: intake, health effects and bioavailability. Food Chem Toxicol 1999; 37(9-10): 937-42.
[http://dx.doi.org/10.1016/S0278-6915(99)00079-4] [PMID: 10541448]

[44] Rimm EB, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Relation between intake of flavonoids and risk for coronary heart disease in male health professionals. Ann Intern Med 1996; 125(5): 384-9.
[http://dx.doi.org/10.7326/0003-4819-125-5-199609010-00005] [PMID: 8702089]

[45] Brown CA, Bolton-Smith C, Woodward M, Tunstall-Pedoe H. Coffee and tea consumption and the prevalence of coronary heart disease in men and women: results from the Scottish Heart Health Study. J Epidemiol Community Health 1993; 47(3): 171-5.
[http://dx.doi.org/10.1136/jech.47.3.171] [PMID: 8350026]

[46] Hertog MG, Sweetnam PM, Fehily AM, Elwood PC, Kromhout D. Antioxidant flavonols and ischemic heart disease in a Welsh population of men: the Caerphilly Study. Am J Clin Nutr 1997; 65(5): 1489-94.
[http://dx.doi.org/10.1093/ajcn/65.5.1489] [PMID: 9129481]

[47] Peters U, Poole C, Arab L. Does tea affect cardiovascular disease? A meta-analysis. Am J Epidemiol 2001; 154(6): 495-503.
[http://dx.doi.org/10.1093/aje/154.6.495] [PMID: 11549554]

[48] Frémont L. Biological effects of resveratrol. Life Sci 2000; 66(8): 663-73.
[http://dx.doi.org/10.1016/S0024-3205(99)00410-5] [PMID: 10680575]

[49] Wang L, Xu M, Liu C, *et al.* Resveratrols in grape berry skins and leaves in vitis germplasm. PLoS One 2013; 8(4)e61642
[http://dx.doi.org/10.1371/journal.pone.0061642] [PMID: 23637874]

[50] Sales JM, Resurreccion AV. Resveratrol in peanuts. Crit Rev Food Sci Nutr 2014; 54(6): 734-70.
[http://dx.doi.org/10.1080/10408398.2011.606928] [PMID: 24345046]

[51] Magyar K, Halmosi R, Palfi A, *et al.* Cardioprotection by resveratrol: A human clinical trial in patients with stable coronary artery disease. Clin Hemorheol Microcirc 2012; 50(3): 179-87.
[http://dx.doi.org/10.3233/CH-2011-1424] [PMID: 22240353]

[52] Frankel EN, Waterhouse AL, Kinsella JE. Inhibition of human LDL oxidation by resveratrol. Lancet 1993; 341(8852): 1103-4.
[http://dx.doi.org/10.1016/0140-6736(93)92472-6] [PMID: 8097009]

[53] Pendurthi UR, Williams JT, Rao LV. Resveratrol, a polyphenolic compound found in wine, inhibits tissue factor expression in vascular cells : A possible mechanism for the cardiovascular benefits associated with moderate consumption of wine. Arterioscler Thromb Vasc Biol 1999; 19(2): 419-26.
[http://dx.doi.org/10.1161/01.ATV.19.2.419] [PMID: 9974427]

[54] Rotondo S, Rajtar G, Manarini S, *et al.* Effect of trans-resveratrol, a natural polyphenolic compound, on human polymorphonuclear leukocyte function. Br J Pharmacol 1998; 123(8): 1691-9.
[http://dx.doi.org/10.1038/sj.bjp.0701784] [PMID: 9605577]

[55] Kohlmeier L, Kark JD, Gomez-Gracia E, *et al.* Lycopene and myocardial infarction risk in the EURAMIC Study. Am J Epidemiol 1997; 146(8): 618-26.
[http://dx.doi.org/10.1093/oxfordjournals.aje.a009327] [PMID: 9345115]

[56] Sesso HD, Buring JE, Norkus EP, Gaziano JM. Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in women. Am J Clin Nutr 2004; 79(1): 47-53.
[http://dx.doi.org/10.1093/ajcn/79.1.47] [PMID: 14684396]

[57] Matulka RA, Hood AM, Griffiths JC. Safety evaluation of a natural tomato oleoresin extract derived from food-processing tomatoes. Regul Toxicol Pharmacol 2004; 39(3): 390-402.
[http://dx.doi.org/10.1016/j.yrtph.2004.03.005] [PMID: 15135216]

[58] Miller NJ, Sampson J, Candeias LP, Bramley PM, Rice-Evans CA. Antioxidant activities of carotenes and xanthophylls. FEBS Lett 1996; 384(3): 240-2.
[http://dx.doi.org/10.1016/0014-5793(96)00323-7] [PMID: 8617362]

[59] Iribarren C, Folsom AR, Jacobs DR Jr, Gross MD, Belcher JD, Eckfeldt JH. Association of serum vitamin levels, LDL susceptibility to oxidation, and autoantibodies against MDA-LDL with carotid atherosclerosis. A case-control study. The ARIC Study Investigators. Atherosclerosis Risk in Communities. Arterioscler Thromb Vasc Biol 1997; 17(6): 1171-7.
[http://dx.doi.org/10.1161/01.ATV.17.6.1171] [PMID: 9194770]

[60] Djoussé L, Folsom AR, Province MA, Hunt SC, Ellison RC. Dietary linolenic acid and carotid atherosclerosis: the National Heart, Lung, and Blood Institute Family Heart Study. Am J Clin Nutr 2003; 77(4): 819-25.
[http://dx.doi.org/10.1093/ajcn/77.4.819] [PMID: 12663278]

[61] Albert CM, Campos H, Stampfer MJ, *et al.* Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med 2002; 346(15): 1113-8.
[http://dx.doi.org/10.1056/NEJMoa012918] [PMID: 11948270]

[62] Salen P, de Lorgeril M. GISSI-Prevenzione trial. Lancet 1999; 354(9189): 1555.
[http://dx.doi.org/10.1016/S0140-6736(05)76583-1] [PMID: 10551520]

[63] Carroll DN, Roth MT. Evidence for the cardioprotective effects of omega-3 Fatty acids. Ann Pharmacother 2002; 36(12): 1950-6.
[http://dx.doi.org/10.1345/aph.1A314] [PMID: 12452760]

[64] Knoops KT, de Groot LC, Kromhout D, *et al.* Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. JAMA 2004; 292(12): 1433-9.
[http://dx.doi.org/10.1001/jama.292.12.1433] [PMID: 15383513]

[65] Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003; 348(26): 2599-608.
[http://dx.doi.org/10.1056/NEJMoa025039] [PMID: 12826634]

[66] Covas MI, Nyyssönen K, Poulsen HE, *et al.* The effect of polyphenols in olive oil on heart disease risk factors: a randomized trial. Ann Intern Med 2006; 145(5): 333-41.
[http://dx.doi.org/10.7326/0003-4819-145-5-200609050-00006] [PMID: 16954359]

[67] Fitó M, Cladellas M, de la Torre R, *et al.* Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: a randomized, crossover, controlled, clinical trial. Atherosclerosis 2005; 181(1): 149-58.
[http://dx.doi.org/10.1016/j.atherosclerosis.2004.12.036] [PMID: 15939067]

[68] Rodríguez-Rodríguez R, Herrera MD, Perona JS, Ruiz-Gutiérrez V. Potential vasorelaxant effects of oleanolic acid and erythrodiol, two triterpenoids contained in 'orujo' olive oil, on rat aorta. Br J Nutr 2004; 92(4): 635-42.
[http://dx.doi.org/10.1079/BJN20041231] [PMID: 15522132]

[69] Carluccio MA, Massaro M, Bonfrate C, *et al.* Oleic acid inhibits endothelial activation : A direct vascular antiatherogenic mechanism of a nutritional component in the mediterranean diet. Arterioscler Thromb Vasc Biol 1999; 19(2): 220-8.
[http://dx.doi.org/10.1161/01.ATV.19.2.220] [PMID: 9974401]

[70] Yaqoob P, Knapper JA, Webb DH, Williams CM, Newsholme EA, Calder PC. Effect of olive oil on immune function in middle-aged men. Am J Clin Nutr 1998; 67(1): 129-35.
[http://dx.doi.org/10.1093/ajcn/67.1.129] [PMID: 9440387]

[71] Karantonis HC, Antonopoulou S, Demopoulos CA. Antithrombotic lipid minor constituents from vegetable oils. Comparison between olive oils and others. J Agric Food Chem 2002; 50(5): 1150-60.
[http://dx.doi.org/10.1021/jf010923t] [PMID: 11853496]

[72] Hillestrøm PR, Covas MI, Poulsen HE. Effect of dietary virgin olive oil on urinary excretion of etheno-DNA adducts. Free Radic Biol Med 2006; 41(7): 1133-8.
[http://dx.doi.org/10.1016/j.freeradbiomed.2006.06.013] [PMID: 16962938]

[73] Fitó M, Cladellas M, de la Torre R, *et al.* Anti-inflammatory effect of virgin olive oil in stable coronary disease patients: a randomized, crossover, controlled trial. Eur J Clin Nutr 2008; 62(4): 570-4.
[http://dx.doi.org/10.1038/sj.ejcn.1602724] [PMID: 17375118]

[74] Shurtleff W, Aoyagi A. History of Soybeans and Soyfoods in Southeast Asia (13th Century to 2010). 2010.

[75] Zhang X, Shu XO, Gao YT, *et al.* Soy food consumption is associated with lower risk of coronary heart disease in Chinese women. J Nutr 2003; 133(9): 2874-8.
[http://dx.doi.org/10.1093/jn/133.9.2874] [PMID: 12949380]

[76] Jenkins DJ, Kendall CW, Garsetti M, *et al.* Effect of soy protein foods on low-density lipoprotein oxidation and ex vivo sex hormone receptor activity--a controlled crossover trial. Metabolism 2000; 49(4): 537-43.
[http://dx.doi.org/10.1016/S0026-0495(00)80022-0] [PMID: 10778882]

[77] Cavallini DC, Abdalla DS, Vendramini RC, *et al.* Effects of isoflavone-supplemented soy yogurt on lipid parameters and atherosclerosis development in hypercholesterolemic rabbits: a randomized double-blind study. Lipids Health Dis 2009; 8: 40.
[http://dx.doi.org/10.1186/1476-511X-8-40] [PMID: 19814806]

[78] Anthony MS, Clarkson TB, Williams JK. Effects of soy isoflavones on atherosclerosis: potential mechanisms. Am J Clin Nutr 1998; 68(6) (Suppl.): 1390S-3S.
[http://dx.doi.org/10.1093/ajcn/68.6.1390S] [PMID: 9848505]

[79] Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. N Engl J Med 1995; 333(5): 276-82.
[http://dx.doi.org/10.1056/NEJM199508033330502] [PMID: 7596371]

[80] Felicilda-Reynaldo RF. Cardiac glycosides, digoxin toxicity, and the antidote. Medsurg Nurs 2013;

22(4): 258-61.
[PMID: 24147325]

[81] Pincus M. Management of digoxin toxicity. Aust Prescr 2016; 39(1): 18-20.
[http://dx.doi.org/10.18773/austprescr.2016.006] [PMID: 27041802]

[82] Delacroix S, Chokka R, Worthley S. Hypertension: pathophysiology and treatment. J Neurol Neurophysiol 2014; 5: 2.
[http://dx.doi.org/10.4172/2155-9562.1000250]

[83] Weber MA, Schiffrin EL, White WB, *et al.* Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens (Greenwich) 2014; 16(1): 14-26.
[http://dx.doi.org/10.1111/jch.12237] [PMID: 24341872]

[84] Grassi G, Seravalle G, Bertinieri G, *et al.* Sympathetic and reflex alterations in systo-diastolic and systolic hypertension of the elderly. J Hypertens 2000; 18(5): 587-93.
[http://dx.doi.org/10.1097/00004872-200018050-00012] [PMID: 10826562]

[85] Bavishi C, Goel S, Messerli FH. Isolated systolic hypertension: an update after SPRINT. Am J Med 2016; 129(12): 1251-8.
[http://dx.doi.org/10.1016/j.amjmed.2016.08.032] [PMID: 27639873]

[86] Artom N, Salvo F, Camardella F. White-coat hypertension and masked hypertension: an update. Ital J Med 2015; 10: 96-102.
[http://dx.doi.org/10.4081/itjm.2015.662]

[87] Yan B, Peng L, Han D, *et al.* Blood pressure reverse-dipping is associated with early formation of carotid plaque in senior hypertensive patients. Medicine (Baltimore) 2015; 94(10)e604
[http://dx.doi.org/10.1097/MD.0000000000000604] [PMID: 25761180]

[88] Grassi G, Seravalle G, Quarti-Trevano F, *et al.* Adrenergic, metabolic, and reflex abnormalities in reverse and extreme dipper hypertensives. Hypertension 2008; 52(5): 925-31.
[http://dx.doi.org/10.1161/HYPERTENSIONAHA.108.116368] [PMID: 18779438]

[89] Garovic VD, August P. Preeclampsia and the future risk of hypertension: the pregnant evidence. Curr Hypertens Rep 2013; 15(2): 114-21.
[http://dx.doi.org/10.1007/s11906-013-0329-4] [PMID: 23397213]

[90] Grassi G. Assessment of sympathetic cardiovascular drive in human hypertension: achievements and perspectives. Hypertension 2009; 54(4): 690-7.
[http://dx.doi.org/10.1161/HYPERTENSIONAHA.108.119883] [PMID: 19720958]

[91] Coca-Robinot D, Fabregate R, Sanchez-Largo E, *et al.* P-470: Clinical, biochemical and cardiovascular implications of endothelial dysfunction in the dermal microcirculation. Am J Hypertens 2005; 18: 177A.
[http://dx.doi.org/10.1016/j.amjhyper.2005.03.487]

[92] Widlansky ME, Gokce N, Keaney JF Jr, Vita JA. The clinical implications of endothelial dysfunction. J Am Coll Cardiol 2003; 42(7): 1149-60.
[http://dx.doi.org/10.1016/S0735-1097(03)00994-X] [PMID: 14522472]

[93] Sarzani R, Salvi F, Dessì-Fulgheri P, Rappelli A. Renin-angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: an integrated view in humans. J Hypertens 2008; 26(5): 831-43.
[http://dx.doi.org/10.1097/HJH.0b013e3282f624a0] [PMID: 18398321]

[94] Simões E Silva AC, Flynn JT. The renin-angiotensin-aldosterone system in 2011: role in hypertension and chronic kidney disease. Pediatr Nephrol 2012; 27(10): 1835-45.
[http://dx.doi.org/10.1007/s00467-011-2002-y] [PMID: 21947887]

[95] Atlas SA. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. J Manag Care Pharm 2007; 13(8) (Suppl. B): 9-20.

[http://dx.doi.org/10.18553/jmcp.2007.13.s8-b.9] [PMID: 17970613]

[96] Tsioufis C, Kordalis A, Flessas D, *et al.* Pathophysiology of resistant hypertension: the role of sympathetic nervous system. International journal of hypertension 2011.
[http://dx.doi.org/10.4061/2011/642416]

[97] Dzeufiet PDD, Mogueo A, Bilanda DC, *et al.* Antihypertensive potential of the aqueous extract which combine leaf of Persea americana Mill. (Lauraceae), stems and leaf of Cymbopogon citratus (D.C) Stapf. (Poaceae), fruits of Citrus medical L. (Rutaceae) as well as honey in ethanol and sucrose experimental model. BMC Complement Altern Med 2014; 14: 507.
[http://dx.doi.org/10.1186/1472-6882-14-507] [PMID: 25519078]

[98] Chrysant SG, Chrysant GS. Herbs Used for the Treatment of Hypertension and their Mechanism of Action. Curr Hypertens Rep 2017; 19(9): 77.
[http://dx.doi.org/10.1007/s11906-017-0775-5] [PMID: 28921053]

[99] Virdis A, Duranti E, Taddei S. Oxidative stress and vascular damage in hypertension: role of angiotensin II. International journal of hypertension 2011.
[http://dx.doi.org/10.4061/2011/916310]

[100] Montezano AC, Tsiropoulou S, Dulak-Lis M, Harvey A, Camargo LdeL, Touyz RM. Redox signaling, Nox5 and vascular remodeling in hypertension. Curr Opin Nephrol Hypertens 2015; 24(5): 425-33.
[http://dx.doi.org/10.1097/MNH.0000000000000153] [PMID: 26197203]

[101] Fallah Huseini H, Amini M, Mohtashami R, *et al.* Blood pressure lowering effect of Nigella sativa L. seed oil in healthy volunteers: a randomized, double-blind, placebo-controlled clinical trial. Phytother Res 2013; 27(12): 1849-53.
[http://dx.doi.org/10.1002/ptr.4944] [PMID: 23436437]

[102] Dehkordi FR, Kamkhah AF. Antihypertensive effect of Nigella sativa seed extract in patients with mild hypertension. Fundam Clin Pharmacol 2008; 22(4): 447-52.
[http://dx.doi.org/10.1111/j.1472-8206.2008.00607.x] [PMID: 18705755]

[103] Webb AJ, Patel N, Loukogeorgakis S, *et al.* Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate *via* bioconversion to nitrite. Hypertension 2008; 51(3): 784-90.
[http://dx.doi.org/10.1161/HYPERTENSIONAHA.107.103523] [PMID: 18250365]

[104] Kapil V, Khambata RS, Robertson A, Caulfield MJ, Ahluwalia A. Dietary nitrate provides sustained blood pressure lowering in hypertensive patients: a randomized, phase 2, double-blind, placebo-controlled study HYPERTENSIONAHA 2014; 65(2): 320-7.
[http://dx.doi.org/https://dx.doi.org/10.1161%2FHYPERTENSIONAHA.114.04675] [PMID: 25421976]

[105] Coles LT, Clifton PM. Effect of beetroot juice on lowering blood pressure in free-living, disease-free adults: a randomized, placebo-controlled trial. Nutr J 2012; 11: 106.
[http://dx.doi.org/10.1186/1475-2891-11-106] [PMID: 23231777]

[106] Affuso F, Mercurio V, Fazio V, Fazio S. Cardiovascular and metabolic effects of Berberine. World J Cardiol 2010; 2(4): 71-7.
[http://dx.doi.org/10.4330/wjc.v2.i4.71] [PMID: 21160701]

[107] Lan J, Zhao Y, Dong F, *et al.* Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. J Ethnopharmacol 2015; 161: 69-81.
[http://dx.doi.org/10.1016/j.jep.2014.09.049] [PMID: 25498346]

[108] Al Disi SS, Anwar MA, Eid AH. Anti-hypertensive herbs and their mechanisms of action: part I. Front Pharmacol 2016; 6: 323.
[http://dx.doi.org/10.3389/fphar.2015.00323] [PMID: 26834637]

[109] Inuwa I, Ali BH, Al-Lawati I, Beegam S, Ziada A, Blunden G. Long-term ingestion of Hibiscus sabdariffa calyx extract enhances myocardial capillarization in the spontaneously hypertensive rat. Exp Biol Med (Maywood) 2012; 237(5): 563-9.

[http://dx.doi.org/10.1258/ebm.2012.011357] [PMID: 22678012]

[110] Hopkins AL, Lamm MG, Funk JL, Ritenbaugh C. Hibiscus sabdariffa L. in the treatment of hypertension and hyperlipidemia: a comprehensive review of animal and human studies. Fitoterapia 2013; 85: 84-94.
[http://dx.doi.org/10.1016/j.fitote.2013.01.003] [PMID: 23333908]

[111] McKay DL, Chen CY, Saltzman E, Blumberg JB. Hibiscus sabdariffa L. tea (tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults. J Nutr 2010; 140(2): 298-303.
[http://dx.doi.org/10.3945/jn.109.115097] [PMID: 20018807]

[112] Alarcón-Alonso J, Zamilpa A, Aguilar FA, Herrera-Ruiz M, Tortoriello J, Jimenez-Ferrer E. Pharmacological characterization of the diuretic effect of Hibiscus sabdariffa Linn (Malvaceae) extract. J Ethnopharmacol 2012; 139(3): 751-6.
[http://dx.doi.org/10.1016/j.jep.2011.12.005] [PMID: 22178178]

[113] Tassell MC, Kingston R, Gilroy D, Lehane M, Furey A. Hawthorn (Crataegus spp.) in the treatment of cardiovascular disease. Pharmacogn Rev 2010; 4(7): 32-41.
[http://dx.doi.org/10.4103/0973-7847.65324] [PMID: 22228939]

[114] Asher GN, Viera AJ, Weaver MA, Dominik R, Caughey M, Hinderliter AL. Effect of hawthorn standardized extract on flow mediated dilation in prehypertensive and mildly hypertensive adults: a randomized, controlled cross-over trial. BMC Complement Altern Med 2012; 12: 26.
[http://dx.doi.org/10.1186/1472-6882-12-26] [PMID: 22458601]

[115] Ried K, Travica N, Sali A. The effect of aged garlic extract on blood pressure and other cardiovascular risk factors in uncontrolled hypertensives: the AGE at Heart trial. Integr Blood Press Control 2016; 9: 9-21.
[http://dx.doi.org/10.2147/IBPC.S93335] [PMID: 26869811]

[116] Rohner A, Ried K, Sobenin IA, Bucher HC, Nordmann AJ. A systematic review and metaanalysis on the effects of garlic preparations on blood pressure in individuals with hypertension. Am J Hypertens 2015; 28(3): 414-23.
[http://dx.doi.org/10.1093/ajh/hpu165] [PMID: 25239480]

[117] Wang HP, Yang J, Qin LQ, Yang XJ. Effect of garlic on blood pressure: a meta-analysis. J Clin Hypertens (Greenwich) 2015; 17(3): 223-31.
[http://dx.doi.org/10.1111/jch.12473] [PMID: 25557383]

[118] Srivastava R, Ahmed H, Dixit RK, Dharamveer , Saraf SA. Crocus sativus L.: A comprehensive review. Pharmacogn Rev 2010; 4(8): 200-8.
[http://dx.doi.org/10.4103/0973-7847.70919] [PMID: 22228962]

[119] Modaghegh M-H, Shahabian M, Esmaeili H-A, Rajbai O, Hosseinzadeh H. Safety evaluation of saffron (Crocus sativus) tablets in healthy volunteers. Phytomedicine 2008; 15(12): 1032-7.
[http://dx.doi.org/10.1016/j.phymed.2008.06.003] [PMID: 18693099]

[120] Mucalo I, Jovanovski E, Rahelić D, Božikov V, Romić Z, Vuksan V. Effect of American ginseng (Panax quinquefolius L.) on arterial stiffness in subjects with type-2 diabetes and concomitant hypertension. J Ethnopharmacol 2013; 150(1): 148-53.
[http://dx.doi.org/10.1016/j.jep.2013.08.015] [PMID: 23973636]

[121] Jovanovski E, Bateman EA, Bhardwaj J, *et al.* Effect of Rg3-enriched Korean red ginseng (Panax ginseng) on arterial stiffness and blood pressure in healthy individuals: a randomized controlled trial. J Am Soc Hypertens 2014; 8(8): 537-41.
[http://dx.doi.org/10.1016/j.jash.2014.04.004] [PMID: 24997863]

[122] Rhee M-Y, Cho B, Kim K-I, *et al.* Blood pressure lowering effect of Korea ginseng derived ginseol K-g1. Am J Chin Med 2014; 42(3): 605-18.
[http://dx.doi.org/10.1142/S0192415X14500396] [PMID: 24871654]

[123] Kim J-H. Cardiovascular diseases and Panax ginseng: a review on molecular mechanisms and medical

applications. J Ginseng Res 2012; 36(1): 16-26.
[http://dx.doi.org/10.5142/jgr.2012.36.1.16] [PMID: 23717100]

[124] Hodgson JM, Puddey IB, Woodman RJ, *et al.* Effects of black tea on blood pressure: a randomized controlled trial. Arch Intern Med 2012; 172(2): 186-8.
[http://dx.doi.org/10.1001/archinte.172.2.186] [PMID: 22271130]

[125] Hartley L, Flowers N, Holmes J, *et al.* Green and black tea for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; 6(6)CD009934
[http://dx.doi.org/10.1002/14651858.CD009934.pub2] [PMID: 23780706]

[126] Devi RC, Sim S, Ismail R. Effect of Cymbopogon citratus and citral on vascular smooth muscle of the isolated thoracic rat aorta. Evidence-Based Complementary and Alternative Medicine 2012; 2012: 8.
[http://dx.doi.org/https://doi.org/10.1155/2012/539475] [PMID: 539475]

[127] Hao P, Jiang F, Cheng J, Ma L, Zhang Y, Zhao Y. Traditional Chinese medicine for cardiovascular disease: evidence and potential mechanisms. J Am Coll Cardiol 2017; 69(24): 2952-66.
[http://dx.doi.org/10.1016/j.jacc.2017.04.041] [PMID: 28619197]

[128] Lau Y-S, Machha A, Achike FI, Murugan D, Mustafa MR. The aporphine alkaloid boldine improves endothelial function in spontaneously hypertensive rats. Exp Biol Med (Maywood) 2012; 237(1): 93-8.
[http://dx.doi.org/10.1258/ebm.2011.011145] [PMID: 22156043]

[129] Lau YS, Ling WC, Murugan D, Mustafa MR. Boldine ameliorates vascular oxidative stress and endothelial dysfunction: Therapeutic implication for hypertension and diabetes. J Cardiovasc Pharmacol 2015; 65(6): 522-31.
[http://dx.doi.org/10.1097/FJC.0000000000000185] [PMID: 25469805]

[130] Heberden W. Some Account of a Disorder of the Breast. Med Transact R Coll Phys Lond 1772; 2: 59.

[131] Dorland D. Dorland's Illustrated Medical Dictionary. 32nd ed., Saunders 2017.

[132] Mosby Mosby's Dictionary of Medicine, Nursing & Health Professions. 10th ed., Elsevier 2017.

[133] Arrebola-Moreno A, Dungu J, Kaski JC. Treatment strategies for chronic stable angina. Expert Opin Pharmacother 2011; 12(18): 2833-44.
[http://dx.doi.org/10.1517/14656566.2011.634799] [PMID: 22098227]

[134] Organization WH. 2004.www.who.int/whr/2004/en/report04_en.pdf

[135] Emond M, Mock MB, Davis KB, *et al.* Long-term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. Circulation 1994; 90(6): 2645-57.
[http://dx.doi.org/10.1161/01.CIR.90.6.2645] [PMID: 7994804]

[136] Fox K, Garcia MA, Ardissino D, *et al.* Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006; 27(11): 1341-81.
[http://dx.doi.org/10.1093/eurheartj/ehl001] [PMID: 16735367]

[137] Sun H, Mohri M, Shimokawa H, Usui M, Urakami L, Takeshita A. Coronary microvascular spasm causes myocardial ischemia in patients with vasospastic angina. J Am Coll Cardiol 2002; 39(5): 847-51.
[http://dx.doi.org/10.1016/S0735-1097(02)01690-X] [PMID: 11869851]

[138] Tobin KJ. Stable angina pectoris: what does the current clinical evidence tell us? J Am Osteopath Assoc 2010; 110(7): 364-70.
[PMID: 20693568]

[139] Talbert RL. Ischemic heart disease.Pharmacotherapy: A Pathophysiologic Approach. 8th ed., New York: McGraw-Hill 2011.

[140] Keller KB, Lemberg L. Prinzmetal's angina. *American journal of critical care: an official publication*. American Association of Critical-Care Nurses 2004; 13: 350-4.

[141] Kaski JC. Chest pain with normal coronary angiograms: pathogenesis, diagnosis and management. Boston: Kluwer 1999; pp. 5-6.
[http://dx.doi.org/10.1007/978-1-4615-5181-2]

[142] Gulati M, Shaw LJ, Bairey Merz CN. Myocardial ischemia in women: lessons from the NHLBI WISE study. Clin Cardiol 2012; 35(3): 141-8.
[http://dx.doi.org/10.1002/clc.21966] [PMID: 22389117]

[143] Shaw LJ, Merz CN, Pepine CJ, *et al.* The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health--National Heart, Lung, and Blood Institute--sponsored Women's Ischemia Syndrome Evaluation. Circulation 2006; 114(9): 894-904.
[http://dx.doi.org/10.1161/CIRCULATIONAHA.105.609990] [PMID: 16923752]

[144] Guyton A. Textbook of Medical Physiology. 11th ed., Philadelphia: Elsevier 2006.

[145] Linden W, Stossel C, Maurice J. Psychosocial interventions for patients with coronary artery disease: a meta-analysis. Arch Intern Med 1996; 156(7): 745-52.
[http://dx.doi.org/10.1001/archinte.1996.00440070065008] [PMID: 8615707]

[146] Vaccarino V. Ischemic heart disease in women: many questions, few facts. Circ Cardiovasc Qual Outcomes 2010; 3(2): 111-5.
[http://dx.doi.org/10.1161/CIRCOUTCOMES.109.925313] [PMID: 20160161]

[147] Banks K, Lo M, Khera A. Angina in Women without Obstructive Coronary Artery Disease. Curr Cardiol Rev 2010; 6(1): 71-81.
[http://dx.doi.org/10.2174/157340310790231608] [PMID: 21286281]

[148] Anthony J. Trevor, BGK, Marieke Knuidering-Hall Katzung & Trevor's Pharmacology Examination and Board Review. 11th ed., McGraw-Hill Education 2015.

[149] Sneader W. Drug discovery: a history. 1st ed., 2005.
[http://dx.doi.org/10.1002/0470015535]

[150] McClellan KJ, Plosker GL. Trimetazidine. A review of its use in stable angina pectoris and other coronary conditions. Drugs 1999; 58(1): 143-57.
[http://dx.doi.org/10.2165/00003495-199958010-00016] [PMID: 10439934]

[151] Sulfi S, Timmis AD. Ivabradine -- the first selective sinus node I(f) channel inhibitor in the treatment of stable angina. Int J Clin Pract 2006; 60(2): 222-8.
[http://dx.doi.org/10.1111/j.1742-1241.2006.00817.x] [PMID: 16451297]

[152] Gupta AK, Winchester D, Pepine CJ. Antagonist molecules in the treatment of angina. Expert Opin Pharmacother 2013; 14(17): 2323-42.
[http://dx.doi.org/10.1517/14656566.2013.834329] [PMID: 24047238]

[153] Fihn SD, Gardin JM, Abrams J, *et al.* 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2012; 126(25): 3097-137.
[http://dx.doi.org/10.1161/CIR.0b013e3182776f83] [PMID: 23166210]

[154] Nissen SE, Nicholls SJ, Sipahi I, *et al.* Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006; 295(13): 1556-65.
[http://dx.doi.org/10.1001/jama.295.13.jpc60002] [PMID: 16533939]

[155] Barnett H, Burrill P, Iheanacho I. Don't use aspirin for primary prevention of cardiovascular disease. BMJ 2010; 340: c1805.
[http://dx.doi.org/10.1136/bmj.c1805] [PMID: 20410163]

[156] Pfisterer ME, Zellweger MJ, Gersh BJ. Management of stable coronary artery disease. Lancet 2010;

375(9716): 763-72.
[http://dx.doi.org/10.1016/S0140-6736(10)60168-7] [PMID: 20189028]

[157] Kocyigit D, Gurses KM, Yalcin MU, Tokgozoglu L. Traditional and Alternative Therapies for Refractory Angina. Curr Pharm Des 2017; 23(7): 1098-111.
[http://dx.doi.org/10.2174/1381612823666161123145148] [PMID: 27881061]

[158] Ades PA, Waldmann ML, Poehlman ET, *et al.* Exercise conditioning in older coronary patients. Submaximal lactate response and endurance capacity. Circulation 1993; 88(2): 572-7.
[http://dx.doi.org/10.1161/01.CIR.88.2.572] [PMID: 8339420]

[159] O'Brien K, Vitetta L. The potential role of herbal medicines in the treatment of chronic stable angina pectoris: A review of key herbs, and as illustration, exploration of the Chinese herbal medicine approach. Botanics 2012; 3: 1.
[http://dx.doi.org/10.2147/BTAT.S28866]

[160] Mahmood ZA, Sualeh M, Mahmood SB, Karim MA. Herbal treatment for cardiovascular disease the evidence based therapy. Pak J Pharm Sci 2010; 23(1): 119-24.
[PMID: 20067878]

[161] Koch E. Inhibition of platelet activating factor (PAF)-induced aggregation of human thrombocytes by ginkgolides: considerations on possible bleeding complications after oral intake of Ginkgo biloba extracts Phytomedicine : international journal of phytotherapy and phytopharmacology 2005; 12: 10-16.
[http://dx.doi.org/10.1016/j.phymed.2004.02.002.]

[162] Singh J, Pandey A A. Pandey, A. A REVIEW: AN IMPACT OF INULA RACEMOSA (PUSKARMULA) ON DYSLIPIDEMIA AND OBESITY. World journal of scientific research 2016; 5: 528-38.

[163] Zhu Y, Xia W, Liu W, Xu C, Gu N. Gualoupi (Pericarpium Trichosanthis) injection in combination with convention therapy for the treatment of angina pectoris: a Meta- analysis. Journal of traditional Chinese medicine = Chung i tsa chih ying wen pan 2017; 37: 1- 11.

[164] Das DK, Mukherjee S, Ray D. Resveratrol and red wine, healthy heart and longevity. Heart Fail Rev 2010; 15(5): 467-77.
[http://dx.doi.org/10.1007/s10741-010-9163-9] [PMID: 20238161]

[165] Jagtap M, Chandola HM, Ravishankar B. Clinical efficacy of Coleus forskohlii (Willd.) Briq. (Makandi) in hypertension of geriatric population. Ayu 2011; 32(1): 59-65.
[http://dx.doi.org/10.4103/0974-8520.85729] [PMID: 22131759]

[166] Conn JJ, Kissane RW, Koons RA, Clark TE. The treatment of angina pectoris with khellin. Ann Intern Med 1952; 36(5): 1173-8.
[http://dx.doi.org/10.7326/0003-4819-36-5-1173] [PMID: 14924454]

[167] Lokhande D, Jagdale S, Chabuksawar AR. Natural remedies for heart diseases. Indian J Tradit Knowl 2006; 5: 420-7.

[168] Zhao Z, Yang X, Zhang Y. Clinical study of puerarin in treatment of patients with unstable angina Chinese journal of integrated traditional and Western medicine 1998; 18: 282-284.

[169] Fan LL, Sun LH, Li J, *et al.* Protective effect of puerarin against myocardial reperfusion injury. Myocardial metabolism and ultrastructure. Chin Med J (Engl) 1992; 105(6): 451-6.
[PMID: 1451545]

[170] Li SM, Liu B, Chen HF. Beneficial effects of berberine on hemodynamics during acute ischemic left ventricular failure in dogs Chinese medical journal 1992; 105: 1014-9.

[171] Luo ZR, Zheng B. Effect of Puerarin on platelet activating factors CD63 and CD62P, plasminogen activator inhibitor and C-reactive protein in patients with unstable angia pectoris. Chinese journal of integrated traditional and Western medicine 2001; 21: 31-33.

[172] Xuan B, Li DX, Wang W. [Protective effects of tetrahydroprotoberberines on experimental myocardial infarction in rats]. Zhongguo Yao Li Xue Bao 1992; 13(2): 167-71.
[PMID: 1598835]

[173] O K, Cheung F, Sung FL, Zhu DY, Siow YL. Effect of magnesium tanshinoate B on the production of nitric oxide in endothelial cells. Mol Cell Biochem 2000; 207(1-2): 35-9.
[http://dx.doi.org/10.1023/A:1007081911734] [PMID: 10888224]

[174] Huang H, Geng Q, Yao H, *et al.* Protective effect of scutellarin on myocardial infarction induced by isoprenaline in rats. Iran J Basic Med Sci 2018; 21(3): 267-76.
[http://dx.doi.org/10.22038/ijbms.2018.26110.6415] [PMID: 29511493]

[175] Wang L, Li Y, Lin S, Pu Z, Li H, Tang Z. Protective Effects of Baicalin on Experimental Myocardial Infarction in Rats. Rev Bras Cir Cardiovasc 2018; 33(4): 384-90.
[http://dx.doi.org/10.21470/1678-9741-2018-0059] [PMID: 30184036]

[176] Huang Z, Chen S, Zhang G, *et al.* Protective effects of berberine and phentolamine on myocardial reoxygenation damage. Chinese medical sciences journal 1992; 7: 221-225.

[177] Huang WM, Wu ZD, Gan YQ. [Effects of berberine on ischemic ventricular arrhythmia]. Zhonghua Xin Xue Guan Bing Za Zhi 1989; 17(5): 300-301, 319. [Effects of berberine on ischemic ventricular arrhythmia].
[PMID: 2483987]

[178] Huang WM, Yan H, Jin JM, Yu C, Zhang H. Beneficial effects of berberine on hemodynamics during acute ischemic left ventricular failure in dogs. Chin Med J (Engl) 1992; 105(12): 1014-9.
[PMID: 1299549]

[179] Bennett MR, Sinha S, Owens GK. Vascular Smooth Muscle Cells in Atherosclerosis. Circ Res 2016; 118(4): 692-702.
[http://dx.doi.org/10.1161/CIRCRESAHA.115.306361] [PMID: 26892967]

[180] Yurdagul A Jr, Finney AC, Woolard MD, Orr AW. The arterial microenvironment: the where and why of atherosclerosis. Biochem J 2016; 473(10): 1281-95.
[http://dx.doi.org/10.1042/BJ20150844] [PMID: 27208212]

[181] Lim S, Park S. Role of vascular smooth muscle cell in the inflammation of atherosclerosis. BMB Rep 2014; 47(1): 1-7.
[http://dx.doi.org/10.5483/BMBRep.2014.47.1.285] [PMID: 24388105]

[182] George SJ. Therapeutic potential of matrix metalloproteinase inhibitors in atherosclerosis. Expert Opin Investig Drugs 2000; 9(5): 993-1007.
[http://dx.doi.org/10.1517/13543784.9.5.993] [PMID: 11060722]

[183] Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res 2003; 92(8): 827-39.
[http://dx.doi.org/10.1161/01.RES.0000070112.80711.3D] [PMID: 12730128]

[184] Koch M, Zernecke A. The hemostatic system as a regulator of inflammation in atherosclerosis. IUBMB Life 2014; 66(11): 735-44.
[http://dx.doi.org/10.1002/iub.1333] [PMID: 25491152]

[185] Pirillo A, Norata GD, Catapano AL. LOX-1, OxLDL, and atherosclerosis Mediators of inflammation 2013.
[http://dx.doi.org/https://doi.org/10.1155/2013/152786]

[186] Tabas I, Lichtman AH. Monocyte-macrophages and T cells in atherosclerosis. Immunity 2017; 47(4): 621-34.
[http://dx.doi.org/10.1016/j.immuni.2017.09.008] [PMID: 29045897]

[187] Chistiakov DA, Melnichenko AA, Grechko AV, Myasoedova VA, Orekhov AN. Potential of anti-inflammatory agents for treatment of atherosclerosis. Exp Mol Pathol 2018; 104(2): 114-24.

[http://dx.doi.org/10.1016/j.yexmp.2018.01.008] [PMID: 29378168]

[188] Ginnan R, Guikema BJ, Halligan KE, Singer HA, Jourd'heuil D. Regulation of smooth muscle by inducible nitric oxide synthase and NADPH oxidase in vascular proliferative diseases. Free Radic Biol Med 2008; 44(7): 1232-45.
[http://dx.doi.org/10.1016/j.freeradbiomed.2007.12.025] [PMID: 18211830]

[189] Luoma JS, Ylä-Herttuala S. Expression of inducible nitric oxide synthase in macrophages and smooth muscle cells in various types of human atherosclerotic lesions. Virchows Arch 1999; 434(6): 561-8.
[http://dx.doi.org/10.1007/s004280050384] [PMID: 10394893]

[190] Ikeda U, Maeda Y, Shimada K. Inducible nitric oxide synthase and atherosclerosis. Clin Cardiol 1998; 21(7): 473-6.
[http://dx.doi.org/10.1002/clc.4960210705] [PMID: 9669055]

[191] Ahmed HH, Shousha WG, El-Mezayen HA, El-Toumy SA, Sayed AH, Ramadan AR. Biochemical and molecular evidences for the antitumor potential of Ginkgo biloba leaves extract in rodents. Acta Biochim Pol 2017; 64(1): 25-33.
[PMID: 27741326]

[192] Baek SH, Lee JH, Ko JH, *et al.* Ginkgetin Blocks Constitutive STAT3 Activation and Induces Apoptosis through Induction of SHP-1 and PTEN Tyrosine Phosphatases. Phytother Res 2016; 30(4): 567-76.
[http://dx.doi.org/10.1002/ptr.5557] [PMID: 27059688]

[193] Lian N, Tong J, Li W, Wu J, Li Y. Ginkgetin ameliorates experimental atherosclerosis in rats. Biomed Pharmacother 2018; 102: 510-6.
[http://dx.doi.org/10.1016/j.biopha.2018.03.107] [PMID: 29579712]

[194] Fan W-H, Karnovsky MJ. Increased MMP-2 expression in connective tissue growth factor over-expression vascular smooth muscle cells. J Biol Chem 2002; 277(12): 9800-5.
[http://dx.doi.org/10.1074/jbc.M111213200] [PMID: 11773059]

[195] Gliesche DG, Hussner J, Witzigmann D, *et al.* Secreted matrix metalloproteinase-9 of proliferating smooth muscle cells as a trigger for drug release from stent surface polymers in coronary arteries. Mol Pharm 2016; 13(7): 2290-300.
[http://dx.doi.org/10.1021/acs.molpharmaceut.6b00033] [PMID: 27241028]

[196] Ozen S, Kone-Paut I, Gül A. Colchicine resistance and intolerance in familial Mediterranean fever: definition, causes, and alternative treatments. Proceedings of Seminars in arthritis and rheumatism. 115-20.
[http://dx.doi.org/10.1016/j.semarthrit.2017.03.006]

[197] Nava F, Ghilotti F, Maggi L, *et al.* Biologics, colchicine, corticosteroids, immunosuppressants and interferon-alpha for Neuro-Behçet's Syndrome. Cochrane Database Syst Rev 2014; (12): CD010729
[http://dx.doi.org/10.1002/14651858.CD010729.pub2] [PMID: 25521793]

[198] Raval J, Nagaraja V, Eslick GD, Denniss AR. The role of colchicine in pericarditis–a systematic review and meta-analysis of randomised trials. Heart Lung Circ 2015; 24(7): 660-6.
[http://dx.doi.org/10.1016/j.hlc.2015.01.010] [PMID: 25766664]

[199] Dziezanowski MA, DeStefano MJ, Rabinovitch M. Effect of antitubulins on spontaneous and chemotactic migration of neutrophils under agarose. J Cell Sci 1980; 42: 379-88.
[PMID: 7400242]

[200] Nidorf M, Thompson PL. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. Am J Cardiol 2007; 99(6): 805-7.
[http://dx.doi.org/10.1016/j.amjcard.2006.10.039] [PMID: 17350370]

[201] Nidorf SM, Eikelboom JW, Budgeon CA, Thompson PL. Low-dose colchicine for secondary prevention of cardiovascular disease. J Am Coll Cardiol 2013; 61(4): 404-10.

[http://dx.doi.org/10.1016/j.jacc.2012.10.027] [PMID: 23265346]

[202] Vaidya K, Arnott C, Martínez GJ, *et al.* Colchicine therapy and plaque stabilization in patients with acute coronary syndrome: A CT coronary angiography study. JACC Cardiovasc Imaging 2018; 11(2 Pt 2): 305-16.
[http://dx.doi.org/10.1016/j.jcmg.2017.08.013] [PMID: 29055633]

[203] Hemkens LG, Ewald H, Gloy VL, *et al.* Colchicine for prevention of cardiovascular events. Cochrane Database Syst Rev 2016; (1): CD011047
[PMID: 26816301]

[204] Hemkens LG, Ewald H, Gloy VL, *et al.* M. Cardiovascular effects and safety of long-term colchicine treatment: Cochrane review and meta-analysis. Heart , heartjnl-2015-308542 Natural Products and Metabolic Syndrome 2016.

[205] Crittenden DB, Lehmann RA, Schneck L, *et al.* Colchicine use is associated with decreased prevalence of myocardial infarction in patients with gout 2012.
[http://dx.doi.org/10.3899/jrheum.111533]

[206] Solomon DH, Liu C-C, Kuo I-H, Zak A, Kim SC. Effects of colchicine on risk of cardiovascular events and mortality among patients with gout: a cohort study using electronic medical records linked with Medicare claims. Ann Rheum Dis 2016; 75(9): 1674-9.
[http://dx.doi.org/10.1136/annrheumdis-2015-207984] [PMID: 26582823]

[207] Deftereos S, Giannopoulos G, Raisakis K, *et al.* Colchicine treatment for the prevention of bare-metal stent restenosis in diabetic patients. J Am Coll Cardiol 2013; 61(16): 1679-85.
[http://dx.doi.org/10.1016/j.jacc.2013.01.055] [PMID: 23500260]

[208] O'Keefe JH Jr, McCallister BD, Bateman TM, Kuhnlein DL, Ligon RW, Hartzler GO. Ineffectiveness of colchicine for the prevention of restenosis after coronary angioplasty. J Am Coll Cardiol 1992; 19(7): 1597-600.
[http://dx.doi.org/10.1016/0735-1097(92)90624-V] [PMID: 1593057]

[209] Deftereos S, Giannopoulos G, Angelidis C, *et al.* Anti-inflammatory treatment with colchicine in acute myocardial infarction: a pilot study. Circulation 2015; 132(15): 1395-403.
[http://dx.doi.org/10.1161/CIRCULATIONAHA.115.017611] [PMID: 26265659]

[210] Koscielny J, Klüssendorf D, Latza R, *et al.* The antiatherosclerotic effect of Allium sativum. Atherosclerosis 1999; 144(1): 237-49.
[http://dx.doi.org/10.1016/S0021-9150(99)00060-X] [PMID: 10381297]

[211] Sobenin IA, Salonen JT, Zhelankin AV, *et al.* Low density lipoprotein-containing circulating immune complexes: role in atherosclerosis and diagnostic value. BioMed Res Int 2014; 2014205697
[http://dx.doi.org/10.1155/2014/205697] [PMID: 25054132]

[212] Sobenin IA, Chistiakov DA, Bobryshev YV, Orekhov AN. Blood atherogenicity as a target for anti-atherosclerotic therapy. Curr Pharm Des 2013; 19(33): 5954-62.
[http://dx.doi.org/10.2174/1381612811319330014] [PMID: 23438956]

[213] Orekhov AN, Sobenin IA, Korneev NV, *et al.* Anti-atherosclerotic therapy based on botanicals. Recent Pat Cardiovasc Drug Discov 2013; 8(1): 56-66.
[http://dx.doi.org/10.2174/18722083113079990008] [PMID: 23176379]

[214] Libby P, Okamoto Y, Rocha VZ, Folco E. Inflammation in atherosclerosis: transition from theory to practice. Circ J 2010; 74(2): 213-20.
[http://dx.doi.org/10.1253/circj.CJ-09-0706] [PMID: 20065609]

[215] Wolf D, Stachon P, Bode C, Zirlik A. Inflammatory mechanisms in atherosclerosis. Hamostaseologie 2014; 34(1): 63-71.
[http://dx.doi.org/10.5482/HAMO-13-09-0050] [PMID: 24343521]

[216] Gorchakova TV, Suprun IV, Sobenin IA, Orekhov AN. Use of natural products in anticytokine therapy. Bull Exp Biol Med 2007; 143(3): 316-9.

[http://dx.doi.org/10.1007/s10517-007-0099-6] [PMID: 18225751]

[217] Gorchakova T, Sobenin I, Orekhov A. The reduction of proinflammatory cytokine expression by natural components: a new approach to the prevention and treatment of atherosclerosis at the cellular level. J Clin Lipidol 2007; 1: 492.

[218] Gorchakova T, Suprun I, Sobenin I, Orekhov A. YI-844 COMBINED ANTI-INFLAMMATORY AND ANTI-ATHEROGENIC ACTIVITY OF NATURAL DRUG INFLAMINAT—A PERSPECTIVE FOR LONG-TERM ATHEROSCLEROSIS PREVENTION AND TREATMENT. Atheroscler Suppl 2007; 8: 224.
[http://dx.doi.org/10.1016/S1567-5688(07)71854-8]

[219] Gorchakova T, Myasoedova V, Sobenin I, Orekhov A. P387 atherosclerosis prevention with the anti-inflammatory dietary supplement Inflaminat. Atheroscler Suppl 2009; 10e697
[http://dx.doi.org/10.1016/S1567-5688(09)70682-8]

[220] Sobenin L, Nikitina N, Myasoedova V, Korenmaya V, Khalilov E, Orekhov A. 4P-1202 Antiatherogenic properties of isoflavones from phytoesrogen-rich botanicals. Atheroscler Suppl 2003; 4: 339.
[http://dx.doi.org/10.1016/S1567-5688(03)91458-9]

[221] Korennaya V, Mysoedova V, Nikitina N, Sobenin I, Orekhov A. We-P14: 442 Bioflavonoid-rich botanicals reduce blood serum atherogenicity in perimenopausal women. Atheroscler Suppl 2006; 7: 444.
[http://dx.doi.org/10.1016/S1567-5688(06)81795-2]

[222] Nikitina NA, Sobenin IA, Myasoedova VA, *et al.* Antiatherogenic effect of grape flavonoids in an *ex vivo* model. Bull Exp Biol Med 2006; 141(6): 712-5.
[http://dx.doi.org/10.1007/s10517-006-0260-7] [PMID: 17364057]

[223] Sobenin I, Myasoedova V, Orekhov A. Antiatherogenic action of isoflavonoid-rich botanicals: an implementation for atherosclerosis prevention in postmenopausal women. J Clin Lipidol 2007; 1: 491-1.

[224] Myasoedova V, Sobenin I. Background, rationale and design of clinical study of the effect of isoflavonoid-rich botanicals on natural history of atherosclerosis in women. Atheroscler Suppl 2008; 9: 171.
[http://dx.doi.org/10.1016/S1567-5688(08)70689-5]

[225] Sobenin I, Myasoedova V, Orekhov A. Atherosclerosis prevention in postmenopausal women with the isoflavonoid-rich dietary supplement Karinat. J Clin Lipidol 2008; 2: S26-7.
[http://dx.doi.org/10.1016/j.jacl.2008.08.059]

[226] Awang DVC. Tyler's Herbs of Choice: The Therapeutic Use of Phytomedicinals In Cardiovascular system problems. 3rd ed., Boca Raton: CRC Taylor & Francis Group, LLC 2009.
[http://dx.doi.org/10.1136/aim.18.1.84-bpp 91-114]

[227] Thrift AG, Howard G, Cadilhac DA, *et al.* Global stroke statistics: An update of mortality data from countries using a broad code of "cerebrovascular diseases". Int J Stroke 2017; 12(8): 796-801.
[http://dx.doi.org/10.1177/1747493017730782] [PMID: 28895807]

[228] Sheu J-R, Geraldine P, Yen M-H. Bioactives and Traditional Herbal Medicine for the Treatment of Cardiovascular/Cerebrovascular Diseases 2015. Evid Based Complement Alternat Med 2015; 2015320545
[http://dx.doi.org/10.1155/2015/320545] [PMID: 26379742]

[229] Gupta YK, Briyal S, Gulati A. Therapeutic potential of herbal drugs in cerebral ischemia. Indian J Physiol Pharmacol 2010; 54(2): 99-122.
[PMID: 21090528]

[230] Singh B, Kaur P, Gopichand , Singh RD, Ahuja PS. Biology and chemistry of Ginkgo biloba. Fitoterapia 2008; 79(6): 401-18.

[http://dx.doi.org/10.1016/j.fitote.2008.05.007] [PMID: 18639617]

[231] Le Bars PL, Kastelan J. Efficacy and safety of a Ginkgo biloba extract. Public Health Nutr 2000; 3(4A): 495-9.
[http://dx.doi.org/10.1017/S1368980000000574] [PMID: 11276297]

[232] Mahady GB. Ginkgo biloba for the prevention and treatment of cardiovascular disease: a review of the literature. J Cardiovasc Nurs 2002; 16(4): 21-32.
[http://dx.doi.org/10.1097/00005082-200207000-00004] [PMID: 12597260]

[233] Gattuso G, Barreca D, Gargiulli C, *et al.* Flavonoid composition of Citrus juices. Molecules 2007; 12(8): 1641-73.
[http://dx.doi.org/10.3390/12081641] [PMID: 17960080]

[234] de Jesus Raposo MF, de Morais AMB, de Morais RMSC. Marine polysaccharides from algae with potential biomedical applications. Mar Drugs 2015; 13(5): 2967-3028.
[http://dx.doi.org/10.3390/md13052967] [PMID: 25988519]

[235] Chandía NP, Matsuhiro B. Characterization of a fucoidan from Lessonia vadosa (Phaeophyta) and its anticoagulant and elicitor properties. Int J Biol Macromol 2008; 42(3): 235-40.
[http://dx.doi.org/10.1016/j.ijbiomac.2007.10.023] [PMID: 18054382]

[236] Dürig J, Bruhn T, Zurborn KH, Gutensohn K, Bruhn HD, Béress L. Anticoagulant fucoidan fractions from Fucus vesiculosus induce platelet activation in vitro. Thromb Res 1997; 85(6): 479-91.
[http://dx.doi.org/10.1016/S0049-3848(97)00037-6] [PMID: 9101640]

[237] Irhimeh MR, Fitton JH, Lowenthal RM. Pilot clinical study to evaluate the anticoagulant activity of fucoidan. Blood Coagul Fibrinolysis 2009; 20(7): 607-10.
[http://dx.doi.org/10.1097/MBC.0b013e32833135fe] [PMID: 19696660]

[238] Zayed A, Dienemann C, Giese C, Krämer R, Ulber R. An immobilized perylene diimide derivative for fucoidan purification from a crude brown algae extract. Process Biochem 2018; 65: 233-8.
[http://dx.doi.org/10.1016/j.procbio.2017.10.012]

[239] Zayed A, Muffler K, Hahn T, *et al.* Physicochemical and biological characterization of fucoidan from fucus vesiculosus purified by dye affinity chromatography. Mar Drugs 2016; 14(4): 1-15.
[http://dx.doi.org/10.3390/md14040079] [PMID: 27092514]

[240] Li B, Lu F, Wei X, Zhao R. Fucoidan: structure and bioactivity. Molecules 2008; 13(8): 1671-95.
[http://dx.doi.org/10.3390/molecules13081671] [PMID: 18794778]

[241] Singh VK, Singh DK. Pharmacological effects of garlic (Allium sativum L.). Annual Review of Biomedical Sciences 2008; 10: 6-26.
[http://dx.doi.org/10.5016/1806-8774.2008.v10p6]

[242] Srivastava K, Mustafa T. Pharmacological Effects of Spices : Eicosanoid Modula- Ting Activities and Their Significance in Human Health. Biomedical Reviews 2 1993; 29: 15-29.

[243] Levin RM, Juan Y-S, Schuler C, Leggett RE, Lin AD. Medicinal Properties of Antrodia Camphorata - A Review. Curr Top Nutraceutical Res 2012; 10: 53-60.
[http://dx.doi.org/10.5455/spatula.20160413015353]

[244] Lee YM, Chang CY, Yen TL, *et al.* Extract of Antrodia camphorata exerts neuroprotection against embolic stroke in rats without causing the risk of hemorrhagic incidence. ScientificWorldJournal 2014; 2014686109
[http://dx.doi.org/10.1155/2014/686109] [PMID: 25140341]

[245] Majeed M, Praksh L. Alpha-Lipoic Acid : An Efficient Antioxidant Sabinsa corporation 2014.

[246] Dong Y, Wang H, Chen Z. Alpha-lipoic acid attenuates cerebral ischemia and reperfusion injury *via* insulin receptor and PI3K/Akt-Dependent inhibition of NADPH oxidase. Int J Endocrinol 2015; 2015903186
[http://dx.doi.org/10.1155/2015/903186] [PMID: 26294909]