

REVIEW

Overview of Phytomedicine for Stable, Incurable Angina Pectoris

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ARTICLE INFO	ABSTRACT
<p>Article History: Received: 18 December 2022 Accepted: 19 July 2023 Published: 7 November 2023</p>	<p>Herbal treatments have been used to treat heart disease, particularly stable angina pectoris, by people of many different ethnic groups since ancient times. Herbs are used in a variety of ways in alternative medicine. Herbal medicine differs significantly from the pharmaceutical method, which attempts to isolate plants' active ingredients. Stable angina pectoris can be treated with a wide range of medicines from Western, Indian and Chinese herbalisms. This review focused on the philosophical theories that describe bodily functioning and pathophysiological biomedicine begins to talk about changes in the body in a totally different way in this unique approach to understanding health and illness. After an introduction to the guiding principles of herbal medicine, the cardiovascular system and ischemia are discussed from a Chinese medical perspective. This study shows that angina pectoris treatment and the creation of Chinese herbal medicinal formulas are based on this fact. Based on scientific confirmation, the effectiveness of several Chinese herbal compositions is discussed.</p>
<p>Keywords: Herbs, Chinese herbal medicine, Herbal medicine, Cardiovascular, Angina pectoris, Medicinal plant.</p>	

INTRODUCTION

Angina pectoris is a kind of cardiac disease that causes ischemic chest discomfort, often known as angina. Ischemia refers to a lack of blood supply to the myocardial muscles [1]. When the heart muscles are deprived of blood, oxygen cannot reach them as quickly as it should. Ischemia is a condition in which cells and tissues begin to die, causing chest pain. When the heart muscles do not get enough blood, angina pectoris develops and the myocardial muscles begin to die. As a result, the oxygen supply to the heart is insufficient. The aorta is a blood vessel that runs through the heart and distributes oxygen and nutrients to the body. A branch of the aorta that provides blood to the heart is known as the coronary artery. Coronary arteries can become constricted or blocked under certain condi-

tions [2]. Atherosclerosis is a disorder in which fat lipids build up in the arterial lining, narrowing the artery's lumen. This causes blood flow to be obstructed. Sometimes lipid deposits form in the center of arteries, forming a blood clot that obstructs the flow of blood. The process is referred to as thrombus formation [3]. Endothelium of the coronary artery, which has been inflamed or injured is unable to produce anticoagulants that prevent the formation of blood clots, this is one of the reasons why maintaining the endothelium's health is critical [4]. Coronary artery disease impairs blood flow to the heart's myocardial layer, resulting in cell and tissue necrosis. Angina pectoris results in pain in the middle of the chest, although it can also affect the arms, neck, jaw, or upper abdomen. In the chest, it feels tight or heavy. Angina pectoris is the initial symptom of myocardial ischemia. If it is not treated in the acute stage, it can progress

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to myocardial infarction, which is the permanent death of tissues that results in a heart attack. Coronary heart disease occurs when the coronary arteries become unable to supply oxygen rich blood to the myocardial muscles. Ischemia will develop when there is an imbalance between demand and supply. The ventricular myocardium, for example, pumps around 70 mL of blood into the aorta per beat. This is known as stroke volume and the normal resting heart rate is around 72 beats per min. As a result, human myocardium is built to work regularly in normal circumstances. When a person is undertaking exercise, the force of contraction and heart rate will increase, but the heart will quickly compensate for the demand by raising the force of contraction and heart rate. The compensation mechanisms will work up to 180 beats/min, so the heart can supply oxygen and nutrition to the myocardium until the heart rate is around 180 beats/min, but once the heart rate is equal to or greater than 180 beats/min, the myocardium requires a large amount of oxygen and glucose to keep the muscles beating continuously. The diastolic time of the cardiac cycle is shortened when the heart rate is around 180 beats/min. The coronary arteries give blood to the myocardium during the diastolic part of the cardiac cycle. If the heart rate is around 180 beats/min, the coronary artery filling is limited, potentially leading to ischemia. The left anterior descending artery, a branch of the left coronary artery, supplies blood to the anterior section of the left ventricle as well as the interventricular septum and the apex of the heart. Apex has the thickest myocardium, hence it requires a lot of blood.

Types of anginas

Chronic stable angina: It is also known as fixed stenosis and demand ischemia. The term “stenosis” refers to a narrowing of the arteries. It is caused by atherosclerosis [4] or due to the deposition of fats and lipids in the artery wall [5], resulting in stenosis, especially with increased oxygen demand such as physical exertion or exercise, digestion of heavy meals, mental discomfort or stress and so on. It lasts fewer than 5 min and is treated with rest or nitroglycerine [6]. For its pharmacological action, nitro-glycerine is placed on the tongue.

Unstable angina: When a thrombus (blood clot) forms in the coronary artery, it causes unstable angina. When fat deposits break through to the center, they act as clot blockers [7]. When the endothelium gets inflamed, it loses its ability to produce nitric oxide and prostacyclin, which can lead to clot formation. Unstable angina has more severe symptoms, like heart pain that lasts longer than 5 min. It usually occurs during resting conditions and isn't eased by nitroglycerin.

Variant angina: Variant angina is also known as Prinzmetal angina and is caused by vasospasm (a narrowing of the artery that lowers coronary blood flow briefly). Variant angina symptoms include emotional stress and a dysfunctional coronary vascular endothelium that occurs at night or during rest [8]. In those with angina pectoris, it frequently happens unexpectedly when they are resting. A lot of factors can trigger Prinzmetal variant angina. It is caused by coronary artery vasospasm at rest, which can occur with or without coronary artery atherosclerosis [9]. This condition responds quickly to vasodilators. However,

in rare circumstances, the vasoconstriction may be induced by a rise in thromboxane A₂, which originates from platelets within a thrombus that covers the atherosclerotic plaque.

Therapy of angina with the use of ayurvedic herbs: Ayurveda and herbalism both describe a group of treatments for angina pectoris [10]. In the past, a variety of homoeopathic remedies and plant-based products were utilized to treat angina pectoris. Specific data lists the necessary plants and their effects on the human body. Herbalists have long used the ancient therapy of guggul to treat angina. Guggul is a mixture of several components extracted from the *Commiphora mukul* plant [11]. This important substance extracted from the *Commiphora* plant is used to treat atherosclerosis or atherosclerotic cardiovascular disease, which is the leading cause of angina. Many flowers with a variety of vegetative chemical histories are utilized to treat or cure various heart diseases [12]. The *Hawthorn foliate* and its plant are used to treat myocardial infarction and heart failure, chive (*Allium sativum*) is used to treat arterial hardening; and the maidenhair tree is used to treat aneurysms and peripheral artery disease. Herbaceous plants such as alfalfa (*Medicago Tina*), amla (*Emblina officials*) and tilpushpi (*digitalis purple*) are utilized to treat coronary artery disease and massive heart disease. Although the previously mentioned characteristics of drugs should not be directly linked to the alleviation of angina symptoms, they will be useful in the subordinate management of heart disease. Cardiovascular diseases (CVDs) are a serious health issue that is becoming more prevalent all the time [13]. They continue to be the world's primary sources of gloom and mortality. For a long time, when it comes to CVDs, the use of therapeutic spices has remained an elective therapy option. Natural arrangements are increasingly being used in modern restorative frameworks, which is a rare trend. This motivation is fuelled by a number of factors, the most important of which are their astutely beneficial guarantee in comparison to regular current therapies and their general sense of security. Regardless, the claimed security of natural arrangements has yet to be adequately tested. As a result, public awareness of medicinal spice safety, poisonousness, potentially life-threatening antagonistic effects and potential spice drug combinations should be raised [14].

The potential for spices to treat a wide range of medical issues will next be discussed. Data on the ethnopharmacological therapeutic and restorative properties of four commonly used herbs, namely *Ginseng*, *Ginkgo biloba*, *Ganoderma lucidum* and *Gynostemma pentaphyllum*, have also been compiled and researched. These four plants' work on CVDs such as myocardial dead tissue, hypertension, peripheral vascular disorders, coronary disease, cardiomyopathies and dyslipidemia has been extensively researched, analyzed and discussed [15]. Restorative spices may have beneficial effects on CVDs in the long run, according to research centre data, because they can block a few CVD risk factors. There have been numerous attempts to shift restorative spice concentrations from the seat to the bedside in order to successfully use spices in CVD treatments. This survey focuses on CVDs and their risk factors.

Garlic (*Allium sativum*): *Allium sativum* is a well-known herb that is commonly found in the Middle East and is widely

used in the treatment of coronary artery disease, with demonstrated effects on atherogenesis (development of fat in the veins), lipid digestion, fundamental vascular obstruction and thrombolysis. Garlic is the edible bulb of a plant in the *Liliaceae* family [12]. *Allium* genus, it should be stored at temperatures between 60 and 65 °C. Phosphorus, sulphur, zinc, flavonoids, retinol, ascorbic acid and B-complex vitamins are higher, while calcium, magnesium, sodium, iron and saponins are lower [16]. There is considerable evidence that garlic can reduce parameters related to cardiovascular disease that comes from *in vitro* investigations; however, the evidence from clinical trials has been inconsistent. Garlic has been shown in several clinical investigations to reduce the amount of platelet aggregation in patients [17]. The examination is much more precise in demonstrating the effects of cloudy lipids, hypertension and other forms of extreme harm. Thirty four patients were given garlic intravenously at a dose of 60 mg per day, while 21 control patients were given nitroglycerin at an unknown dosage. According to the findings, the overall effective rates of symptomatic improvement and electrocardiographic improvement following therapy with garlic were 82% and 62%, respectively [18]. Garlic is beneficial to one's heart and overall wellness. Since then, studies have shown that garlic lowers cholesterol, blood pressure and improves vascular health, making veins healthier. This adds a lot of proof to the hypothesis and what we've been doing for the past 10 years is confirming its influence on plaque in the heart. Atherosclerosis is being studied to determine whether it can slow or switch coronary disease. Garlic has been shown to have heart-health benefits. It had an unexpected benefit in that it reduced plaque growth by roughly 60% and improved vein health by making vessels more pliable and elastic. Garlic therapy eliminates previous endothelium plaque. Individuals from all around the world have used it for health reasons for a long time [19]. The structure of gracillin is shown in Fig. 1.

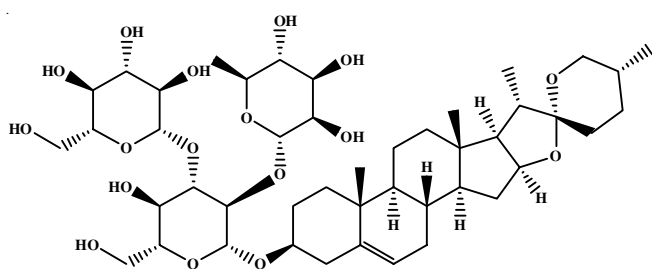


Fig. 1. Gracillin

Hawthorn (*Crataegus monogyna*): Hawthorn berries can be found throughout Europe and Asia. These are nutrient-dense and antioxidant-rich. Quick thorn, thornapple and Hawthorn are common names for this plant. Hawthorn is the traditional name for a variety of plants and trees. *C. pimatifida* and *C. laevigata* are two species native to the Western Hemisphere, Asia and North America [20]. *Crataegus monogyna* has several vitamin C rich plants, florets and beans that are thought to be responsible for its heart activity. The most important components are vitamin C, quercetin, triterpene saponins, coronary artery disease, high blood pressure, atherosclerosis, acute myocardial infarction and burgers sickness were all treated

with *Crataegus monogyna*, a traditional botanical remedy, an important herb in Chinese medicine. Heart failure and cardiovascular illness are treated using the roots of the Hawthorn berry. Polyphenols, which are potent antioxidants that fight harmful free radicals and pollutants in the body. These antioxidants help to prevent chronic diseases including cardiovascular disorders. It also decreases the inflammation caused by diseases. Hawthorn berry extract reduces inflammation to the point where it can aid with asthma symptoms and other inflammatory illnesses including arthritis and joint pain. The hawthorn berry decreases triglycerides and bad cholesterol. According to several research, hawthorn extract improves lipid profile by boosting good cholesterol while lowering bad cholesterol and triglycerides. Atherosclerosis, or plaque build-up in the blood vessels, is caused by bad cholesterol and can lead to heart attack or stroke. Hawthorn berry is well recognized in traditional medicine for its use in the treatment of heart failure. In addition to their medicine, those with heart problems should take a Hawthorn berry supplement.

Many studies show that Hawthorn plucking increases the force of myocardial contraction (cardiotonic effect), which increases the strength of the middle layer of the heart wall constriction, magnifies blockage in the plasma circulation, improves dephlogisticated air application at the myocardium and extends the duration of intractable time, as well as spikes within cardiac coronary and papillate clout [15]. *Crataegus monogyna* has been found to improve myocardial oxygenation, have a mild hypotensive impact, prevent atherosclerosis, have a gloomy parasympatholytic effect and have a positive effect on the force of heart reduction on a constriction volume around heart muscles. Due to cardiac arrest, shortness of breath and biological outcomes, Hawthorn has been awarded as advantageous while an additional treatment [16]. Whitethorn digitalis has an antiquated evident boost in activity when it comes to closing. The efficiency of therapeutic composition of lanolin in patients with mild heart failure chronic heart failure is never lower in commonly used ACE inhibitors due to 15 constants chosen to maximize effectiveness, according to empirically supported study. In a recent randomized controlled trial, it was discovered that a Hawthorn pluck out dose (1000 mg, 1500 mg or 2000 mg) According to research, removing a bean possess hypertension decreasing result [17], it is treated along with nitrogen monoxide. Although, because the placebo treatment included 20 drops of alcohol solution, which is known to increase orthostatic hypotension the results are mixed. Hawthorn is also containing tocopherol, which prevents the production of vasoconstrictor within the glass.

Ginkgo (*Ginkgo biloba*): A *Ginkgo biloba* tree is a large tree with fan-shaped leaves. *Ginkgo biloba* leaves and parts of the spice have long been used in medicine. The leaves have been used in Chinese medicine since ancient times to treat respiratory ailments, coughs, alcohol abuse and bladder problems. The green leaves are used to treat heart and lung stress as well as skin sores. In Europe, systematic plucking of the leaves is widely used as a phytomedicine. Ginkgolides and flavonoid glycosides, which are potent inhibitors, are highly dynamic components of *G. biloba* leaves [18]. EGB-761 (an

extract of *Ginkgo biloba*) has been widely used to treat peripheral vascular disease. Solutions for coronary heart disease, angina pectoris, Alzheimer's infection, cerebral infraction and age-related dementias are among the other objective applications. *Ginkgo biloba* is perhaps the most popular restorative plant. It is one of the spices mentioned in the almost 5000 years old Chinese Materia Medica and its seeds and leaves—fresh or dried have been used in traditional natural medicine for millennia. *Ginkgo biloba* leaves are commonly used in ebb and flow research on their beneficial characteristics and many pharmaceutical companies, particularly those in the United States and Europe, produce and market concentrations of the leaves [19]. The leaves can be used to cure asthma and bronchitis in the form of tea, which is commonly consumed by Chinese people. More broadly, the leaves can be used to make a normalized separation containing the most dynamic elements, which can then be administered as a tablet, a fluid structure, or given intravenously. The progression and movement of various CVDs, such as vascular wounds and atherosclerotic plaque arrangement, are accelerated by extreme age. During CVD pathogenesis, the balance between free ageing and cell reinforcement protection is disproportionately shifted. Due to their cell reinforcement activity, *Ginkgo biloba* extract (GBE) re-establishes the disrupted oxidative state balance, which aids in the detection of excessive free radicals and the reduction of free radical ageing [20]. GBE's vasodilatory and antihypertensive characteristics can also have cardioprotective benefits. GBE has demonstrated ACE inhibitory activities, cholinergic pathway activation, endothelial health improvement, endothelium activation and bond inhibition and serum lipid-lowering activities, among other beneficial effects in CVD. The GBE can limit lipopolysaccharide-induced vascular smooth muscle cell expansion (LPS-induced VSMC expansion) and morphological changes by acting as an adversary to atherothrombotic and mitigating specialists. The GBE also reduces the movement of the reactive oxygen species (ROS) *i.e.* the ROS-producing chemical nicotinamide adenine dinucleotide phosphate oxidase and the phosphorylation of mitogen-activated protein kinases, which helps control the fiery reaction in veins. In human aortic smooth muscle cells, MAPKs suppress costo-like receptor-4 articulation [21]. GBE can also reduce the production of MMP-1, a molecule linked to atherosclerotic plaque rupture in human coronary smooth muscle cells, initiated by oxidized LDL and 4-hydroxynonenal. Ginkgolide B (Fig. 2), a GBE component, inhibited monocyte chemotactic protein 1, intercellular bond molecule 1 and vascular cell bond molecule 1 formation in oxidized LDL-induced HUVECs, causing endothelial damage. In oxidized LDL-induced mouse RAW264.7 macrophages, ginkgolide B therapy reduced the expression of a few incendiary cytokines. Ginkgolide C (Fig. 2), another GBE component, can reduce adipogenesis and increase lipolysis, masking lipid buildup. Ginkgolide treatment inhibited the expression of PPAR adipogenesis related transcription factors in 3T3-L1 adipocytes [22]. Supplementing with ginkgolide improved the Sirt1/AMPK pathway, leading to a decrease in acetyl-CoA carboxylase activity and a rise in unsaturated fatty acid combinations. Ginkgolide C also boosted lipolysis by stimulating the synth-

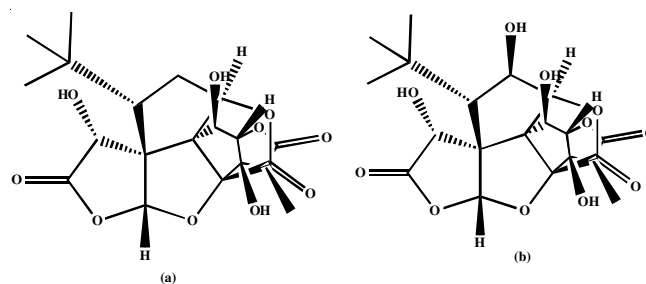


Fig. 2. (a) Ginkgolide B (b) Ginkgolide C

esis of fatty oil lipase and chemically sensitive lipase. To get comparable results, the human HepG2 hepatocyte cell line was employed. *Ginkgo biloba* seed contamination has been reported in Japan and China, with the most common side effects being spasm, heaving and loss of cognition [23]. The primary cause of injury is the neurotoxic chemical 42-O-methylpyridoxine, which interferes with the digestion of pyridoxine (vitamin B₆), resulting in genuine neurological symptoms such as neurotoxicity, seizures and loss of cognition. The ginkgo leaf contains extremely small amounts of ginkgotoxin. Regardless, because ginkgotoxin is regulated to be too low in the concentrate, GBE is unlikely to contain this dangerous component. In several investigations, GBE has been demonstrated to activate cyto-chrome P450 (CYP) in humans, providing insight into potential interactions between GBE and conventional medications. Omeprazole, ritonavir and tolbutamide plasma convergences have all been demonstrated to be reduced by *Ginkgo biloba* [24]. Antiepileptics, acetyl-salicylic corrosive, diuretics, ibuprofen, risperidone, rofecoxib, trazodone and warfarin, an anticoagulant medication, can all communicate with it. As a result, it is recommended that GBE be stopped at least two weeks before surgery [25]. Because of their anti-platelet properties, GBEs (including seeds and leaves) should be used with caution throughout pregnancy, especially around labour and throughout lactation. Leaf extracts of *Ginkgo biloba* have been associated with cardiac events in rats. The Public Toxicology Program hypothesized that GBE could cause toxic and cancerous development in rodents. Among the cancer causing effects described were stomach ulcers, organ alteration remembering cancer-causing action for the liver, liver and thyroid organ hypertrophy, liver hyperplasia and hyperkeratosis [27]. These findings raise concerns regarding GBE's security. Following the PTP study, the International Agency for Research on Cancer stated in 2014 that there is insufficient evidence that GBE causes cancer among the general public. Following this publication, clinical and genomic well-being as measured by a normalized GBE [28] were assessed in elderly patients using a randomized, placebo-controlled clinical trial. The therapy group received 120 mg of IDN 5933 twice a day for six months. In the treat-ment group, there were no adverse clinical effects or increases in liver damage indicators [29]. There is no difference in micro-nucleus recurrence or DNA breakage between the treated and negative control treatment groups. The articulation of characteristics recognized to be modified in right-on-time carcinogenesis was not substantially different among bunches at the beginning and end of the study [30]. These

findings demonstrate the security of IDN 5933 at pre-owned dosages for a period of six months. Their beneficial characteristics and many pharmaceutical companies, particularly those in the United States and Europe, produce and market concentrations of the leaves [19]. The leaves can be used to cure asthma and bronchitis in the form of tea, which is commonly consumed by Chinese people. More broadly, the leaves can be used to make a normalized separation containing the most dynamic elements, which can then be administered as a tablet, a fluid structure or given intravenously. The progression and movement of various CVDs, such as vascular wounds and atherosclerotic plaque arrangement, are accelerated by extreme age. During CVD pathogenesis, the balance between free ageing and cell reinforcement protection is disproportionately shifted. Due to their cell reinforcement activity, *Ginkgo biloba* extract (GBE) re-establishes the disrupted oxidative state balance, which aids in the detection of excessive free radicals and the reduction of free radical ageing [20]. GBE's vasodilatory and antihypertensive characteristics can also have cardioprotective benefits. GBE has demonstrated ACE inhibitory activities, cholinergic pathway activation, endothelial health improvement, endothelium activation and bond inhibition and serum lipid-lowering activities, among other beneficial effects in CVD. GBE can limit lipopolysaccharide-induced vascular smooth muscle cell expansion (LPS-induced VSMC expansion) and morphological changes by acting as an adversary to atherothrombotic and mitigating specialists. GBE also reduces the movement of the reactive oxygen species, *i.e.* the ROS producing chemical nicotinamide adenine dinucleotide phosphate oxidase and the phosphorylation of mitogen-activated protein kinases, which helps control the fiery reaction in veins. In human aortic smooth muscle cells, MAPKs suppress costo-like receptor-4 articulation [21]. GBE can also reduce the production of MMP-1, a molecule linked to atherosclerotic plaque rupture in human coronary smooth muscle cells, initiated by oxidized LDL and 4-hydroxynonenal. Ginkgolide B, a GBE component, inhibited monocyte chemotactic protein 1, intercellular bond molecule 1 and vascular cell bond molecule 1 formation in oxidized LDL-induced HUVECs, causing endothelial damage. In oxidized LDL-induced mouse RAW264.7 macrophages, ginkgolide B therapy reduced the expression of a few incendiary cytokines. Ginkgolide C, another GBE component, can reduce adipogenesis and increase lipolysis, masking lipid buildup. Ginkgolide treatment inhibited the expression of PPAR adipogenesis-related transcription factors in 3T3-L1 adipocytes [22]. Supplementing with ginkgolide improved the Sirt1/AMPK pathway, leading to a decrease in acetyl-CoA carboxylase activity and a rise in unsaturated fatty acid combinations. Ginkgolide C also boosted lipolysis by stimulating the synthesis of fatty oil lipase and chemically sensitive lipase. To get comparable results, the human HepG2 hepatocyte cell line was employed. *Ginkgo biloba* seed contamination has been reported in Japan and China, with the most common side effects being spasm, heaving and loss of cognition [23]. The primary cause of injury is the neurotoxic chemical 42-O-methylpyridoxine, which interferes with the digestion of pyridoxine (vitamin B₆), resulting in genuine neurological symptoms

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Arjuna (*Terminalia arjuna*): Arjuna is also known as arjuna plant, which is a widely planted tree in India. It has several healing effects, including soothing, antimicrobial and cancer-prevention capabilities [31]. *T. arjuna* has been found to be extended ionotropically in order to vasodilate coronary artery, triterpenoids, flavonoids and minerals are among the vitally dynamic combinations separated from the stem. *T. arjuna* extract was administered orally at a dose of 500 mg every 8 h in a double sluggish blind study, compared to a placebo treatment for 14 to 18 days [32]. As measured by both endothelium ward and endothelium autonomous, flow contemplated expansion of the brachial vein, *T. arjuna* appeared to decrease smoking-related breakage [33]. During the intercession, there was no smoking obstruction to eliminate any valuable impact from the smoking end that could solidify the review results. *T. arjuna* was given to the beneficiary at a dose of 500 mg every 8 h. Treatments were separated by a three-day cancellation interval.

A more recent RCT included 58 male individuals with chronic stable angina, who had verifiable ischemia on a running activity test. An open review was conducted to assess the efficacy of hartone, a solution comprising *T. arjuna* [34]. 10 subjects with stable angina were given 2 cases of hartones BID every day for a long period, with the container bid changing every day for the next 42 days. The appropriateness of the home grown pluck out was determined by an increase in the number of angina events and an improvement in a pressure test. The effects of isosorbide mononitrate (ISMN) at a dose of 20g given twice a day to 10 elderly people with stable angina pectoris were studied. The study found that hartone relieves adverse effects in 80% of wiped-out people compared to 70% of those using ISMN and that the number of angina episodes reduced from 79 per week to 24 per week in the hartone group compared to 26 per week to 7 per week in the ISMN group. Despite the fact that both groups improved their pressure-test limits, there was a considerable disparity between them.

Pushkar moola (*Inula racemosa*): The small particles of *I. racemosa*, a spice used in Ayurvedic treatment, are used to treat angina and dyspnoea. It is one of the most remarkable ayurvedic spices [35]. Animal research suggests that this spice concentration has a cardioprotective effect in frogs separated into four basic sections: A, B, C and D, with a lower chronotropic impact on the frog heart. Part D was discovered to inhibit the activity of adrenaline and act as an antagonist for propranolol. In an underlying clinical study coordinated almost 30 years

ago, the counter-angina influence (alleviation by decreasing oxygen admittance) of *I. racemosa* was investigated in nine wiped out individuals with ischemic coronary sickness. The primer treatment with *I. racemosa*, 3 g taken orally 1 h and a half before the preliminary was linked to less clear-cut stake practise ST bitterness [36]. It is impractical to confirm if the Nitrocot was taken orally. However, if the Nitrocot was taken late, this could nullify the results. Furthermore, in an open limited examination of 60 parts, 3 were determined to have angina pectoris. *I. racemosa* (n = 30) and *Saussurea lappa* (n = 30) were each taken sublingually, 500 mg threefold every day for 90 days. The structures of the chemical constituents isolated from *I. racemosa* are shown in Fig. 3.

Turmeric (*Curcuma longa*): It belongs to the ginger family and is excellent for wound healing due to its antioxidant and mitigating properties [37]. Temu lawak in turmeric is responsible for the yellow colour. Turmeric contains active ingredients such as cyclocurcumin, bisdemethoxycurcumin and curcumin. Furthermore, there is extensive evidence that it plays a protective role in a variety of cardiovascular infections. According to Phrommintikul & Wongcharoen [38], curcumin (Fig. 4) has cell reinforcement effects that lower adriamycin-convince cardiotoxicity, which may prevent cardiovascular difficulties linked with diabetes mellitus and has antiproliferative and anti-inflammatory effects. They also highlight that a creature model study has shown that curcumin's potential to inhibit p300-HAT can work on the development of cardiac hypertrophy and cardio-

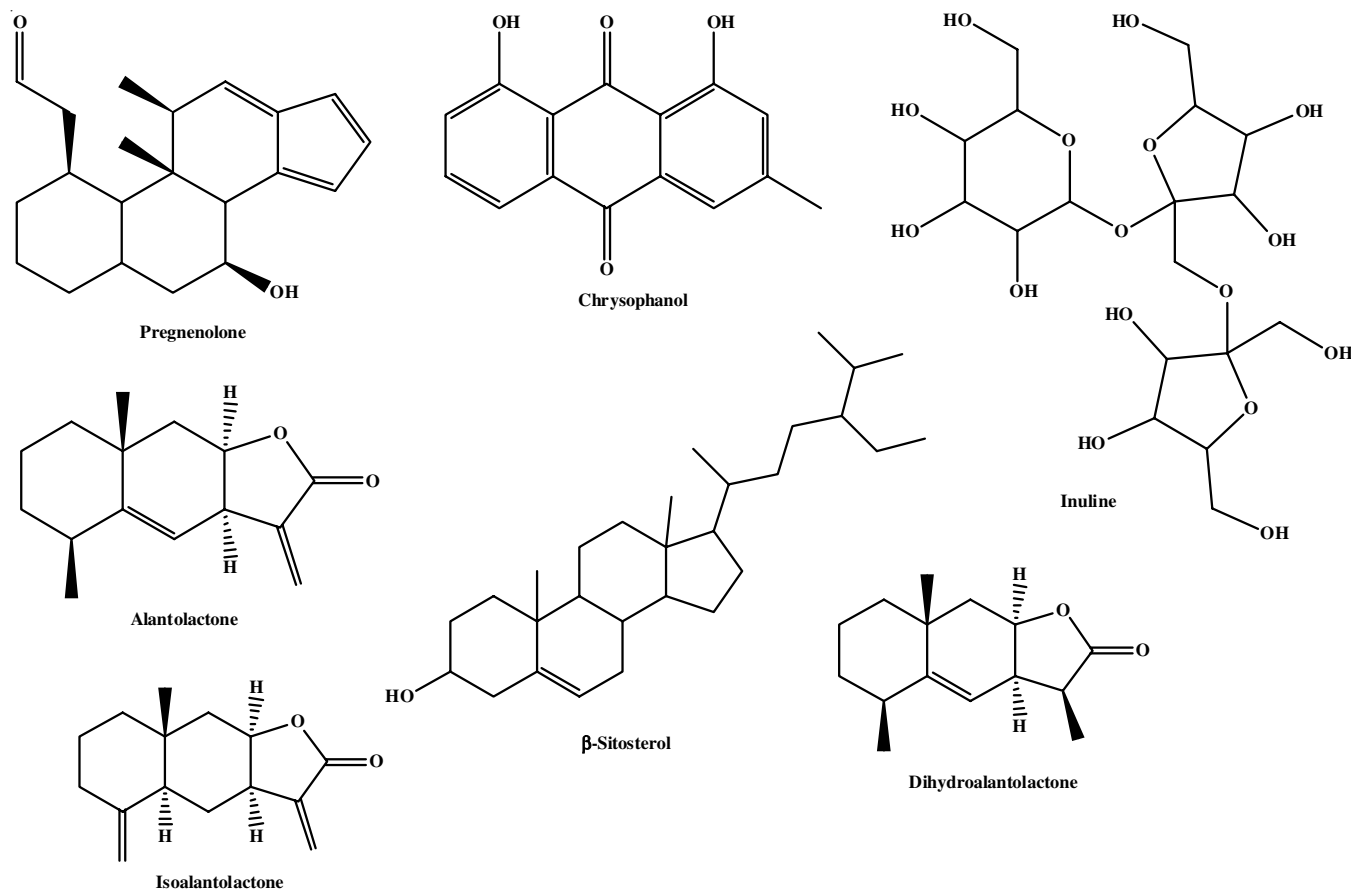


Fig. 3. Chemical constituents of *Inula racemosa*

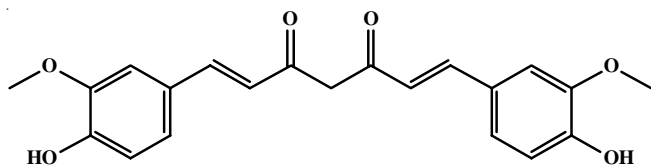
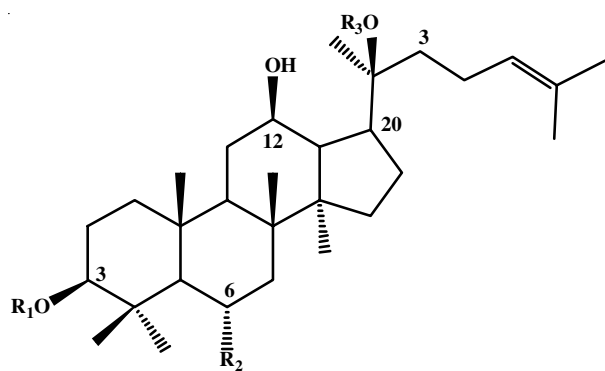


Fig. 4. Chemical structure of curcumin

vascular breakdown [38]. The potency of curcumin was demonstrated in a root waterway therapy designed to examine the effects of curcumin on total cholesterol, low thickness lipoprotein cholesterol, HDL cholesterol and fatty substances in people with basic coronary disease [39]. In individuals with basic coronary disease, consuming a low dose of curcumin (15 mg/day) three times a day was linked to lower total and LDL cholesterol levels, according to the study.

Ginseng (*Pinax ginseng*): Ginseng has also been found to contain 300 bioactive chemicals. Ginseng's major bioactive components are called ginsenosides. The 40 ginsenosides isolated to this point have been investigated the most: Rb1, Rg1, Rg3, Re and Rd. It is found that Rg3, Rg5 and RK1 are ideal for growing Korean ginseng [40]. Later research into filtering particular ginsenosides rather than the entire ginseng root has piqued interest. Ginseng has anticancer, antioxidant and vasorelaxant properties. The chemical structure of different ginsenosides is shown in Fig. 5.



Ginsenosides	R ₁	R ₂	R ₃
Rb ₁	-Glc ₂ -Glc	-H	-Glc ₆ -Glc
Rb ₂	-Glc ₂ -Glc	-H	-Glc ₆ -Ara(pyr)
Rc	-Glc ₂ -Glc	-H	-Glc ₆ -Ara(fur)
Rd	-Glc ₂ -Glc	-H	-Glc
Re	-H	-O-Glc ₂ -Rha	-Glc
Rf	-H	-O-Glc ₂ -Glc	-H
Rg ₁	-H	-O-Glc	-Glc
Rg ₂	-H	-O-Glc ₂ -Rha	-H
Rg ₃	-Glc ₂ -Glc	-H	-H

Fig. 5. Chemical structure of ginsenosides

Ginseng has been used in traditional medicine for almost 2,000 years, but its application in Western medicine stems from the mid-twentieth century, when two researchers explored the Chinese natural therapies [41]. Ginseng can be found in Asian countries including China, Korea, Vietnam and Japan, as well as North American countries like Canada and the United States. Korean red ginseng, Chinese ginseng, American ginseng and Japanese ginseng are the most commonly utilized ginsengs (*Panax japonicas* C.A. Mey). The roots of 5 to 7-year-old plants

are often air-dried or sun-dried to produce white ginseng or steam treated at 98-100 °C for 2-3 h and then sun-dried to produce red ginseng [42]. The elements of ginseng compounds undergo changes while steaming, making red ginseng more pharmacologically viable than white ginseng. Ginseng is currently available in both liquid (oil concentrates or tea) and solid forms (tablets, cases or dried roots). On the other hand, ginseng root, berry and leaf extracts have been shown to have anti-obesity, anti-hyperglycaemic, anti-hypertensive, insulin-refining and anti-hyperlipidaemic properties. Ginseng has hypotensive effects because it increases blood vessel capacity. Surprisingly, ginsenosides act as vasorelaxants in a variety of arteries, including rat aortas, murine coronary veins and monkey cerebral veins. Ginseng stimulates endothelial nitric oxide synthase (eNOS) articulation and NO production, but ginsenoside Rg3 inhibits eNOS. KRG affects vascular tone by inducing NO-dependent vasorelaxation [43]. These effects are mitigated by inhibiting arginase movement, increasing NO generation and increasing eNOS dimer formation. The extract of *Panax ginseng* G115 has also been demonstrated to inhibit ACE movement in human umbilical vein endothelial cells (HUVECs) and angiotensin I-induced compressions of ox-like mesenteric supply pathways. Ginseng's antioxidant and anti-hyperlipidemic properties, as well as its capacity to direct Ca²⁺ channels, are also CVD-related.

Rg3 ginsenoside has the ability to raise NO and cGMP levels, activate Ca²⁺-gated potassium channels, inhibit ACE migration and block Ca²⁺-gated potassium channels. Ginseng has also been proven to have anti-inflammatory properties by blocking the activation of activator protein (AP-1) and nuclear factor kappa B (NFκB), resulting in lower expression of COX-2, IL6, IL1b and growth factor. The saponin component, for example, substantially prevented NO synthesis and diminished the development of incendiary qualities like iNOS, COX-2, TNFα and interferon-β. Surprisingly, all concentrations, including water, saponin and non-saponin components, impede TBK1 function and suppress both atomic and transcriptional movement of its downstream effector interferon administrative element. In rabbits, dietary supplementation of KRG reduces blood cholesterol levels and the organization of atherosclerotic lesions caused by a high cholesterol diet by restricting diacylglycerol freedom [44]. By up-managing the adenosine triphosphate-restricting tape carrier A1, the saponin component of *Panax notoginseng* can constrict cholesterol esters in froth cells. Ginseng has also been shown to have a considerable antithrombotic impact *in vivo*, which may be related to an antiplatelet rather than an anticoagulant action, suggesting that ginseng consumption may be advantageous for people at high risk of apoplexy and CVDs. The dihydro-ginsenoside Rg3 has been reported to reduce platelet aggregation by modulating downstream intracellular signals like cAMP and extracellular signal-controlled kinase in this example.

San Qi (Notoginseng): San qi is prescribed in Chinese medicine as a treatment to replenish the vital fluid. The Chinese drug "san qi is the source of notoginseng" contains ginsenosides, notoginsenosides, dencichine and sugars. San qi has long been used for its astringent effect on inside and outside death,

aggravation of exhaustion and ability to relieve pain from sprains and fissures [45]. It is also used to treat angina and other coronary illnesses, improve myocardial ischemia, lower cholesterol, aid to prevent death, decrease myocardial oxygen use and increase coronary blood flow. Trilinolein is another chemical found in San qi that has been shown to have cancer-prevention agent effects. Trilinolein has been shown to reduce thrombogenicity, arrhythmias and increase RBC deformability. Trilinolein suppresses cardiac arrhythmias during oxygen deficiency ischemia and reperfusion, according to rapid evaluation and treatment. According to animal studies, San qi can broaden the coronary arteries. Although the effect of San qi on essential liquid intimidation is unknown, it may promote vein vasoconstriction. San Qi's triterpene glycosides can lower blood lipids and may disrupt atherosclerosis by impairing the formation of aortic smooth muscle cells [46]. The complete triterpene glycosides of San qi have also been shown to have a moderating effect. Patients with prior diabetic nephropathy treated with tidopidine or San Qi had significantly lower thromboxane B2 and T/K ratios, as well as significantly lower urine albumin and β 2 microglobulin.

Sichuan lovage rhizome (*Chuanxiong rhizoma*): Another medication from the list of spices that revitalise essential liquids in the Chinese medication book "Chuanxiong" is widely used in China for the treatment of coronary diseases [47]. The dried-out wellspring of *Ligustium chuanxiong hort* is known as *Chuanxiong rhizoma*. Senkyunolide, neocinidilide, ligustilide dimers and terpenes are the most active components of *Ligustium chuanxiong hort*. Umbelliferate is frequently used with nitric oxide donors for the treatment of angina and other cardiovascular diseases. The effect of chuanxiong on critical liquids could be due to specific mixes such as senkyunolide A and ligustiliden. Studies on rodent aortas revealed an unwinding of *L. chuanxiong hort* concentrate on vascular circles as well as a super inhibitory effect against phenylephrine-induced shrinking [48]. The increase in self-control is probably related to nitric oxide. The effects of its basic components, senkyunolide An and ligustilide, on vein strain were studied in isolated mouse aortas, with both having the same control potential against reducing the effects caused by a large number of contractile specialists like potassium chloride and phenylephrine. The vasorelaxation findings were not spectacular due to endothelial dissociation. The connectivity between the basic components butylidene phthalide and nitric oxide supplier sodium nitroprusside in constrained rodent aortas tracked down a consolidated interconnection between the two, establishing peace [49]. Another dynamic component, tetramethylpyrazine, has been shown to increase coronary vital liquid flow while decreasing myocardial contractile power in isolated Guinea pig hearts and rodents. During ischemia-resonance, TNF (tumour necrosis factor) can produce myocardial mischief or injury [50]. Another investigation in isolated mouse hearts found that ligustrazine's cardioprotective impact is linked to an elevation in TNF- α concentration due to free radical disruption. The present study investigated the effects of Z-ligustilide and senkyunolide A, two major constituents of *Ligusticum chuanxiong*, on the suppression of TNF- α production and TNF- α biomolecules in

human monocytic cell lines. The findings suggest that Chuanxiong essential oil possesses antipyretic and cancer-preventive capabilities [51].

Angina pectoris therapy herbal medicine: Spices from many parts of the world, including India, the West and traditional Chinese medicine, have all been studied for their potential for improving the symptoms of stable angina pectoris [52]. In traditional medicine, for example and in natural medicine, spices are frequently combined in restorative formulations to treat illnesses such as cardiovascular disease and angina pectoris. On an essential level, given the contention between infection fundamental elements, it is appropriate that the way Chinese medicine is performed is bolstered by a view of how the human body functions differently from the biological model. Angina pectoris can be treated with Chinese herbal medicine under the broadened descriptor "xion bi" (obstructive lung infection), which protects various conditions affecting the respiratory, outer muscle, cardiovascular and gastrointestinal frameworks, all of which realistically share obstructive lung illness [53].

Conclusion

Stable angina pectoris can be treated with a variety of medicines from Western herbalism, Indian herbal medicine and Chinese herbal medicine. In this review, several plants that have been employed for the treatment of stable angina pectoris have been examined. It appears that there are numerous levels of scientific evidence and many of these are quite positive medical systems such as Chinese and Ayurvedic medicines have a long history of using herbs in traditional ways as evidence. In recent years, scientific evidence has surpassed other types of documentation in importance, when it comes to medical practice.

REFERENCES

1. A. Diaz, M.G. Bourassa, M.C. Guertin and J.-C. Tardif, Long-term Prognostic Value of Resting Heart Rate in Patients with Suspected or Proven Coronary Artery Disease, *Eur. Heart J.*, **26**, 974 (2005); <https://doi.org/10.1093/eurheartj/ehi190>
2. W.B. Kannel, C. Kannel, R.S. Paffenbarger Jr. and L.A. Cupples, Heart Rate and Cardiovascular Mortality: The Framingham Study, *Am. Heart J.*, **113**, 1489 (1987); [https://doi.org/10.1016/0002-8703\(87\)90666-1](https://doi.org/10.1016/0002-8703(87)90666-1)
3. M. Böhm, K. Swedberg, M. Komajda, J.S. Borer, I. Ford, A. Dubost-Brama, G. Lerebours and L. Tavazzi, Heart Rate as a Risk Factor in Chronic Heart Failure (Shift): The Association Between Heart Rate and Outcomes in a Randomised Placebo-Controlled Trial, *Lancet*, **376**, 886 (2010); [https://doi.org/10.1016/S0140-6736\(10\)61259-7](https://doi.org/10.1016/S0140-6736(10)61259-7)
4. National Library of Medicine, MedlinePlus: Stable Angina. <https://medlineplus.gov/ency/article/000198.htm>
5. H. Suryapranata, P.W. Serruys, P.J. De Feyter, P.D. Verdouw and P.G. Hugenholtz, Coronary Vasodilatory Action after a Single Dose of Nicorandil, *Am. J. Cardiol.*, **61**, 292 (1988); [https://doi.org/10.1016/0002-9149\(88\)90933-2](https://doi.org/10.1016/0002-9149(88)90933-2)
6. K. Fox, I. Ford, P.G. Steg, J.-C. Tardif, M. Tendera and R. Ferrari, Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure, *N. Engl. J. Med.*, **371**, 1091 (2014); <https://doi.org/10.1056/NEJMoa1406430>
7. A. Fugh-Berman, Herbs and Dietary Supplements in the Prevention and Treatment of Cardiovascular Disease, *Prev. Cardiol.*, **3**, 24 (2000); <https://doi.org/10.1111/j.1520-037X.2000.80355.x>

8. J.M. Zapatero, Selections from Current Literature: Effects of Hawthorn on the Cardiovascular System, *Fam. Pract.*, **16**, 534 (1999); <https://doi.org/10.1093/fampra/16.5.534>
9. M. Tauchert, Efficacy and Safety of Crataegus Extract WS 1442 in Comparison with Placebo in Patients with Chronic Stable New York Heart Association Class-III Heart Failure, *Am. Heart J.*, **143**, 910 (2002); <https://doi.org/10.1067/mhj.2002.121463>
10. V.E. Tyler, Herbs of Choice: The Therapeutic Use of Phytomedicinals, Pharmaceutical Product Press: New York (1994).
11. T. Bahorun, F. Trotin, J. Pommery, J. Vasseur and M. Pinkas, Antioxidant Activities of *Crataegus monogyna* Extracts, *Planta Med.*, **60**, 328 (1994); <https://doi.org/10.1055/s-2006-959493>
12. K. Ried, O.R. Frank, N.P. Stocks, P. Fakler and T. Sullivan, Effect of Garlic on Blood Pressure: A Systematic Review and Meta-Analysis, *BMC Cardiovasc. Disord.*, **8**, 13 (2008); <https://doi.org/10.1186/1471-2261-8-13>
13. W. Wongcharoen and A. Phrommintikul, The Protective Role of Curcumin in Cardiovascular Diseases, *Int. J. Cardiol.*, **133**, 145 (2009); <https://doi.org/10.1016/j.ijcard.2009.01.073>
14. S.G. Lin, X.L. Zheng, O.Y. Chen and J.-J. Sun, Effect of *Panax notoginseng* Saponins on Increased Proliferation of Cultured Aortic Smooth Muscle Cells Stimulated by Hypercholesterolemic Serum, *Acta Pharmacol. Sin.*, **14**, 314 (1993).
15. M. Ni, The Yellow Emperor's Classic of Medicine, A New Translation of the Neijing Su Wen with Commentary, Shambala Publications: Boston, USA (1995).
16. K. Chen, *Zhonghua Xinxueguanbing Zazhi*, 81 (1982).
17. A.C. Wang, *Modern J. Integr. Chinese Tradit. Western Med.*, **8**, 1412 (1999).
18. B.M. Scirica, Chronic Angina: Definition, Prevalence, and Implications for Quality of Life, *Rev. Cardiovasc. Med.*, **10**, 3 (2009); <https://doi.org/10.3909/ricm10S10002>
19. N.-E. Tabassum, R. Das, M.S. Lami, A.J. Chakraborty, S. Mitra, T.E. Tallei, R. Idroes, A.A.-R. Mohamed, M.J. Hossain, K. Dhama, G. Mostafa-Hedeab and T.B. Emran, *Ginkgo biloba*: A Treasure of Functional Phytochemicals with Multimedicinal Applications, *Evid. Based Complement. Alternat. Med.*, **2022**, 8288818 (2022); <https://doi.org/10.1155/2022/8288818>
20. C.E. Garber, R.A. Carleton, D.N. Camaione and G.V. Heller, The Threshold for Myocardial ischemia Varies in Patients with Coronary Artery Disease Depending on the Exercise Protocol, *J. Am. Coll. Cardiol.*, **17**, 1256 (1991); [https://doi.org/10.1016/S0735-1097\(10\)80132-9](https://doi.org/10.1016/S0735-1097(10)80132-9)
21. T.J. Ford, P. Rocchiccioli, R. Good, M. McEntegart, H. Eteiba, S. Watkins, A. Shaukat, M. Lindsay, K. Robertson, S. Hood, E. Yui, N. Sidik, A. Harvey, A.C. Montezano, E. Beattie, L. Haddow, K.G. Oldroyd, R.M. Touyz and C. Berry, Systemic Microvascular Dysfunction in Microvascular and Vasospastic Angina, *Eur. Heart J.*, **39**, 4086 (2018); <https://doi.org/10.1093/eurheartj/ehy529>
22. K.L. Gould and N.P. Johnson, Imaging Coronary Blood Flow in AS: Let the Data Talk, Again, *J. Am. Coll. Cardiol.*, **67**, 1423 (2016); <https://doi.org/10.1016/j.jacc.2016.01.053>
23. C. Cianfrocca, F. Pelliccia and A. Auriti, Ginkgo Biloba-induced Frequent Ventricular Arrhythmia, *Italian Heart J.*, **3**, 689 (2009).
24. G.A. Diamond and J.S. Forrester, Analysis of Probability as an Aid in the Clinical Diagnosis of Coronary-Artery Disease, *N. Engl. J. Med.*, **300**, 1350 (1979); <https://doi.org/10.1056/NEJM197906143002402>
25. C. De La Chapelle, The Recognition of Angina Pectoris, *Circulation*, **21**, 1061 (1960); <https://doi.org/10.1161/01.CIR.21.6.1061>
26. R. Mehra, R.H. Zeiler, W.B. Gough and N. El-Sherif, Reentrant Ventricular Arrhythmias in the Late Myocardial Infarction Period. 9. Electrophysiologic-Anatomic Correlation of Reentrant Circuits, *Circulation*, **67**, 11 (1983); <https://doi.org/10.1161/01.CIR.67.1.11>
27. D.E. Winchester, J. Brandt, C. Schmidt, B. Allen, T. Payton and E.A. Amsterdam, Diagnostic Yield of Routine Noninvasive Cardiovascular Testing in Low-Risk Acute Chest Pain Patients, **116**, 204 (2015); <https://doi.org/10.1016/j.amjcard.2015.03.058>
28. R. Koster, J. Kaehler and T. Meinertz, Treatment of Stable Angina Pectoris by Ivabradine in Every Day Practice: The REDUCTION Study, *Am. Heart J.*, **158**, 51 (2009); <https://doi.org/10.1016/j.ahj.2009.06.008>
29. W.D. Finkle, S. Greenland, G.K. Ridgeway, J.L. Adams, M.A. Frasco, M.B. Cook, J.F. Fraumeni and R.N. Hoover, Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men, *PLoS One*, **9**, e85805 (2014); <https://doi.org/10.1371/journal.pone.0085805>
30. G.A. Lanza, L. Barone and A. Di Monaco, Effect of Spinal Cord Stimulation in Patients with Refractory Angina: Evidence From Observational Studies, *Neuromodulation*, **15**, 542 (2012); <https://doi.org/10.1111/j.1525-1403.2012.00430.x>
31. L. Liao, A. Sarria-Santamera, D.B. Matchar, A. Huntington, A.B.S. Lin, D.J. Whellan and D.F. Kong, Meta Analysis of Survival and Relief of Angina Pectoris After Transmyocardial Revascularization, *Am. J. Cardiol.*, **95**, 1243 (2005); <https://doi.org/10.1016/j.amjcard.2005.01.057>
32. G.M. Rosano, I. Sheiban, R. Massaro, P. Pagnotta, G. Marazzi, C. Vitale, G. Mercurio, M. Volterrani, A. Aversa and M. Fini, Low Testosterone Levels are Associated with Coronary Artery Disease in Male Patients with Angina, *Int. J. Impot. Res.*, **19**, 176 (2007); <https://doi.org/10.1038/sj.ijir.3901504>
33. S.E. Miner, A. Al-Hesayen, S. Kelly, T. Benson, J.J. Thiessen, V.R. Young and J.D. Parker, L-Arginine Transport in the Human Coronary and Peripheral Circulation, *Circulation*, **109**, 1278 (2004); <https://doi.org/10.1161/01.CIR.0000118469.77718.3E>
34. S.M. Killalea and H. Krum, Systematic Review of the Efficacy and Safety of Perhexiline in the Treatment of Ischemic Heart Disease, *Am. J. Cardiovasc. Drugs*, **1**, 193 (2001); <https://doi.org/10.2165/00129784-200101030-00005>
35. C.J. Pepine, S.J. Schang and C.R. Bemiller, Effects of Perhexiline on Coronary Hemodynamic and Myocardial Metabolic Responses to Tachycardia, *Circulation*, **49**, 887 (1974); <https://doi.org/10.1161/01.CIR.49.5.887>
36. A. Ciapponi, R. Pizarro and J. Harrison, Trimetazidine for Stable Angina, *Cochrane Database Syst. Rev.*, **4**, CD003614 (2005); <https://doi.org/10.1002/14651858.CD003614.pub2>
37. B.R. Chaitman, C.J. Pepine and J.O. Parker, Effects of Ranolazine With Atenolol, Amlodipine, or Diltiazem on Exercise Tolerance and Angina Frequency in Patients With Severe Chronic Angina-A Randomized Controlled Trial, *JAMA*, **291**, 309 (2004); <https://doi.org/10.1001/jama.291.3.309>
38. P.A. Heidenreich, K.M. McDonald and T. Hastie, Meta-analysis of Trials Comparing β -Blockers, Calcium Antagonists and Nitrates for Stable Angina, *JAMA*, **281**, 1927 (1999); <https://doi.org/10.1001/jama.281.20.1927>
39. S. Bangalore, S. Parkar and F.H. Messerli, Long-Acting Calcium Antagonists in Patients with Coronary Artery Disease: A Meta-Analysis, *Am. J. Med.*, **122**, 356 (2009); <https://doi.org/10.1016/j.amjmed.2008.09.043>
40. H.A. Ghofrani, I.H. Osterloh and F. Grimminger, Sildenafil: From Angina to Erectile Dysfunction to Pulmonary Hypertension and Beyond, *Nat. Rev. Drug Discov.*, **5**, 689 (2006); <https://doi.org/10.1038/nrd2030>
41. R. Pisters, S.H. Hohnloser, S.P. Connolly, C. Torp-Pedersen, L. Naditch-Brulle, R.L. Page and H.J. Crijns, Effect of Dronedarone on Clinical End Points in Patients with Atrial Fibrillation and Coronary Heart Disease: Insights from the ATHENA Trial, *Europace*, **16**, 174 (2014); <https://doi.org/10.1093/europace/eut293>
42. J. Wei, T. Wu, Q. Yang, M. Chen, J. Ni and D. Huang, Nitrates for Stable Angina: A Systematic Review and Meta-Analysis of Randomized Clinical Trials, *Int. J. Cardiol.*, **146**, 4 (2011); <https://doi.org/10.1016/j.ijcard.2010.05.019>
43. J.C. Tardif, I. Ford, M. Tendera, M.G. Bourassa and K. Fox, Efficacy of Ivabradine, A New Selective if Inhibitor, Compared with Atenolol in Patients with Chronic Stable Angina, *Eur. Heart J.*, **26**, 2529 (2005); <https://doi.org/10.1093/eurheartj/ehi586>
44. P. Constantinides, Plaque Fissures in Human Coronary Thrombosis, *J. Atheroscler. Res.*, **6**, 1 (1966); [https://doi.org/10.1016/S0368-1319\(66\)80056-X](https://doi.org/10.1016/S0368-1319(66)80056-X)

45. J.A. Ambrose, Prognostic Implications of Lesion Irregularity on Coronary Angiography, *J. Am. Coll. Cardiol.*, **18**, 675 (1991); [https://doi.org/10.1016/0735-1097\(91\)90788-B](https://doi.org/10.1016/0735-1097(91)90788-B)
46. J.R. Kramer, Y. Matsuda, J.C. Mulligan, M. Aronow and W.L. Proudfit, Progression of Coronary Atherosclerosis., *Circulation*, **63**, 519 (1981); <https://doi.org/10.1161/01.CIR.63.3.519>
47. W.A. Neill, T.P. Wharton Jr., J. Fluri-Lundeen and I.S. Cohen, Acute Coronary Insufficiency—Coronary Occlusion After Intermittent Ischemic Attacks, *N. Engl. J. Med.*, **302**, 1157 (1980); <https://doi.org/10.1056/NEJM198005223022101>
48. C.P. Cannon, W.S. Weintraub, L.A. Demopoulos, R. Vicari, M.J. Frey, N. Lakkis, F.-J. Neumann, D.H. Robertson, P.T. DeLucca, P.M. DiBattiste, C.M. Gibson and E. Braunwald, Comparison of Early Invasive and Conservative Strategies in Patients with Unstable Coronary Syndromes Treated with the Glycoprotein IIb/IIIa Inhibitor Tirofiban, *N. Engl. J. Med.*, **344**, 1879 (2001); <https://doi.org/10.1056/NEJM200106213442501>
49. S.R. Mehta, S. Yusuf, R.J.S. Peters, M.E. Bertrand, B.S. Lewis, M.K. Natarajan, K. Malmberg, H.-J. Rupprecht, F. Zhao, S. Chrolavicius, I. Copland and K.A.A. Fox, Effects of Pretreatment with Clopidogrel and Aspirin followed by Long-Term Therapy in Patients undergoing Percutaneous Coronary Intervention: The PCI-CURE study, *Lancet*, **358**, 527 (2001); [https://doi.org/10.1016/S0140-6736\(01\)05701-4](https://doi.org/10.1016/S0140-6736(01)05701-4)
50. H.D. Aronow, E.J. Topol, M.T. Roe, P.L. Houghtaling, K.E. Wolski, A.M. Lincoff, R.A. Harrington, R.M. Califf, E.M. Ohman, N.S. Kleiman, M. Keltai, R.G. Wilcox, A. Vahanian, P.W. Armstrong and M.S. Lauer, Effect of Lipid-lowering Therapy on Early Mortality After Acute Coronary Syndromes: An Observational Study, *Lancet*, **357**, 1063 (2001); [https://doi.org/10.1016/S0140-6736\(00\)04257-4](https://doi.org/10.1016/S0140-6736(00)04257-4)
51. J.S. Alpert, K. Thygesen and E. Antman, Myocardial Infarction Redefined—A Consensus Document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction, *J. Am. Coll. Cardiol.*, **36**, 959 (2000); [https://doi.org/10.1016/s0735-1097\(00\)00804-4](https://doi.org/10.1016/s0735-1097(00)00804-4)
52. S. Woodworth, D. Nayak, W.S. Aronow, A.L. Pucillo and S. Koneru, Comparison of Acute Coronary Syndromes in Men versus Women =70 Years of Age, *Am. J. Cardiol.*, **90**, 1145 (2002); [https://doi.org/10.1016/S0002-9149\(02\)02785-6](https://doi.org/10.1016/S0002-9149(02)02785-6)
53. J.H. Chesebro and V. Fuster, Thrombosis in Unstable Angina, *N. Engl. J. Med.*, **327**, 192 (1992); <https://doi.org/10.1056/NEJM199207163270310>