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# Traditional herbs: a remedy for cardiovascular disorders

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ABSTRACT

*Background:* Medicinal plants have been used in patients with congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency and arrhythmia since centuries. A recent increase in the popularity of alternative medicine and natural products has revived interest in traditional remedies that have been used for the treatment of cardiovascular diseases.
*Aim:* The purpose of this review is to provide updated, comprehensive and categorized information on the history and traditional uses of some herbal medicines that affect the cardiovascular system in order to explore their therapeutic potential and evaluate future research opportunities.
*Methods:* Systematic literature searches were carried out and the available information on various medicinal plants traditionally used for cardiovascular disorders was collected via electronic search (using Pubmed, SciFinder, Scirus, GoogleScholar, JCCC@INSTIRC and Web of Science) and a library search for articles published in peer-reviewed journals. No restrictions regarding the language of publication were imposed.
*Results:* This article highlights the cardiovascular effects of four potent traditional botanicals viz. Garlic (*Allium sativum*), Guggul (*Commiphora wightii*), Hawthorn (*Crataegus oxyacantha*) and Arjuna (*Terminalia arjuna*). Although these plants have been used in the treatment of heart disease for hundreds of years, current research methods show us they can be utilized effectively in the treatment of cardiovascular diseases including ischemic heart disease, congestive heart failure, arrhythmias and hypertension.
*Conclusion:* Although the mechanisms of action are not very clear, there is enough evidence of their efficacy in various cardiovascular disorders. However, for bringing more objectivity and also to confirm traditional claims, more systematic, well-designed animal and randomized clinical studies with sufficient sample sizes are necessary. Multidisciplinary research is still required to exploit the vast potential of these plants. Potential synergistic and adverse side effects of herb–drug interactions also need to be studied. These approaches will help in establishing them as remedies for cardiovascular diseases and including them in the mainstream of healthcare system.



## Introduction

Cardiovascular diseases (CVDs) are caused by disorders of the heart and blood vessels, and include coronary heart disease (heart attacks), cerebrovascular disease (stroke), raised blood pressure (hypertension), peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure (http://www.who.int/topics/cardiovascular_diseases/en/). Globally, more people die from CVDs than from any other cause annually. An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke. The cause of heart attacks and strokes are usually the presence of a combination of risk factors, such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol, hypertension, diabetes and hyperlipidaemia. Over three quarters of CVD deaths take place in low- and middle-income countries (http://www.who.int/mediacentre/factsheets/fs317/en/).

Herbs have been an integral part of society since the beginning of human civilization. They have been used both because of their culinary as well as medicinal properties. Herbal medicine has made many contributions to commercial drug preparations manufactured today including ephedrine from *Ephedra sinica*, digitoxin from *Digitalis*

*Abbreviations:* AIIMS, All India Institute of Medical Sciences; BAR, bile acid receptor; BNP, brain natriuretic peptide; CAD, coronary artery disease; CAZRI, Central Arid Zone Research Institute; CCRAS, Central Council for Research in Ayurveda & Siddha; CDRI, Central Drug Research Institute; CHF, congestive heart failure; CIMAP, Central Institute of Medicinal and Aromatic Plants; CVDs, cardiovascular diseases; CYP7A1, cholesterol 7- alpha-hydroxylase/cytochrome P450 7A1; FXR, farnesoid X receptor; HDL, high density lipoprotein; KCCQ, Kansas City Cardiomyopathy Questionnaire; LDL, low density lipoprotein; NMPB, National Medicinal Plants Board; NYHA, New York Heart Association; OPC, oligomeric procyanidins; PGE2, prostaglandin E2; PXR, pregnane X receptor; STZ, streptozotocin..

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*purpurea*, salicin (the source of aspirin) from *Salix alba* and reserpine from *Rauwolfia serpentina*. A naturally occurring $\beta$-adrenergic blocking agent with partial agonism has been identified in a herbal remedy (Wu et al. 1998). The recent discovery of the antineoplastic drug paclitaxel from *Taxus brevifolia* (pacific yew tree) stresses the role of plants as a continuing resource for modern medicine.

Medicinal plants have been used in patients with congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency, and arrhythmia. Although most herbal medicines have multiple cardiovascular effects that frequently overlap, they can be categorized under the primary conditions they treat (Mashour et al. 1998). A number of herbs contain potent cardioactive glycosides, which have positive inotropic actions on the heart. The drug digitoxin, derived from either *D. purpurea* (foxglove) or *D. lanata*, and digoxin, derived from *D. lanata* alone, has been used in the treatment of congestive heart failure (CHF) for many decades. Some common plant sources of cardiac glycosides include *D. purpurea* (foxglove), *Adonis microcarpa* and *Adonis vernalis* (adonis), *Apocynum cannabinum* (black Indian hemp), *Asclepias curassavica* (redheaded cotton bush), *Asclepias fruticosa* (balloon cotton), *Calotropis procera* (king's crown), *Carissa spectabilis* (wintersweet), *Cerebera manghas* (sea mango), *Cheiranthus cheiri* (wallflower), *Convallaria majalis* (lily of the valley, convallaria), *Cryptostegia grandiflora* (rubber vine), *Helleborus niger* (black hellebore), *Helleborus viridis*, *Nerium oleander* (oleander), *Plumeria rubra* (frangipani), *Selenicereus grandiflorus* (cactus grandiflorus), *Strophanthus hispidus* and *Strophanthus kombe* (strophanus), *Thevetia peruviana* (yellow oleander), and *Urginea maritima* (squill). However, accidental poisonings and even suicide attempts with ingestion of cardiac glycosides are abundant in the medical literature. The root of *Rauwolfia serpentina* (snakeroot), the natural source of the alkaloid reserpine, has been a Hindu Ayurvedic remedy since ancient times. In 1931, Indian literature first described the use of *R. serpentina* root for the treatment of hypertension and psychoses. *Stephania tetrandra* is a herb sometimes used in traditional Chinese medicine to treat hypertension. Tetrandrine, an alkaloid extract of *S. tetrandra*, has been shown to be a calcium ion channel antagonist, paralleling the effects of verapamil. Tetrandrine blocks T and L calcium channels, interferes with the binding of diltiazem and methoxyverapamil at calcium-channel binding sites, and suppresses aldosterone production. The root of *Lingusticum wallichii* is used in traditional Chinese medicine as a circulatory stimulant, hypotensive drug, and sedative. Tetramethylpyrazine is the active constituent extracted from *L. wallichii. Uncaria rhynchophylla* is sometimes used in traditional Chinese medicine to treat hypertension. Its indole alkaloids, rhynchophylline and hirsutine, are thought to be the active principles responsible for *U. rhynchophylla's* vasodilatory effect. *Evodia rutaecarpa* (wu-chu-yu) is a Chinese herbal drug that has been used as a treatment for hypertension. It contains an active vasorelaxant component called rutaecarpine that can cause endothelium-dependent vasodilation in experimental models. *Crataegus hawthorn*, a name encompassing many *Crataegus* species (such as *Crataegus oxyacantha* and *Crataegus monogyna* in the West and *Crataegus pinnatifida* in China), has acquired the reputation in modern herbal literature as an important tonic for the cardiovascular system that is particularly useful for angina. From current studies, *Crataegus* extract appears to have antioxidant properties and can inhibit the formation of thromboxane as well. In traditional Chinese medicine, the root of *Panax notoginseng* is used for analgesia and haemostasis. It is also often used in the treatment of patients with angina and coronary artery disease (CAD). In traditional Chinese medicine, the root of *Salvia miltiorrhiza* is used as a circulatory stimulant, sedative, and cooling drug. *S. miltiorrhiza* may be useful as an antianginal drug because it has been shown to dilate coronary arteries in all concentrations, similar to *P. notoginseng*.

The powdered tree bark of *Terminalia arjuna* has been mentioned to be useful for "hritshool" (angina) and other related cardiac ailments by the ancient Indian physicians. Recently there has been renewed interest in this plant because of its multimode cardioprotective activity. In addition to its use in the culinary arts, garlic (*Allium sativum*) has been valued for centuries for its medicinal properties. Garlic is one of the herbal medicines that have been examined more closely by the scientific community. In recent decades, research has focused on garlic's use in preventing atherosclerosis. The resin of *Commiphora wightii* or *Commiphora mukul* (gugulipid), a small, thorny tree native to India, has long been used in Ayurvedic medicine to treat lipid disorders.

Some herbs that are commonly used for cardiovascular disorders in different parts of the world have been listed in Table 1.

A recent increase in the popularity of alternative medicine and natural products has revived interest in traditional remedies that have been used for the treatment of CVDs through centuries. This review examines four such herbal medicines viz. Garlic (*A. sativum*), Guggul (*C. wightii*), Hawthorn (*C. oxyacantha*) and Arjuna (*T. arjuna*) that affect the cardiovascular system both in terms of efficacy and safety as evidenced from the scientific literature that is available. This review may be useful in increasing our knowledge of their history as well as their therapeutic effects and in improving our future experimental and clinical research plans.

## Methods

Systematic literature searches were carried out and the available information on various medicinal plants traditionally used for cardiovascular disorders was collected via electronic search (using Pubmed, SciFinder, Scirus, GoogleScholar, JCCC@INSTIRC and Web of Science) and a library search for articles published in peer-reviewed journals. No restrictions regarding the language of publication were imposed.

## Results and discussion

### Allium sativum *L*

#### *Plant description and distribution*

Garlic, *A. sativum* L. is a member of the Alliaceae family. It is a bulbous plant; grows up to 1.2 m in height. Cultivated practically throughout the world, garlic appears to have originated in central Asia and then spread to China, the Near East and the Mediterranean region before moving west to Central and Southern Europe, Northern Africa (Egypt) and Mexico (Singh and Singh 2008).

#### *History of use*

It is used universally as a flavouring agent as well as traditional medicine. Garlic has been used for thousands of years for medicinal purposes. Sanskrit records show its medicinal use about 5000 years ago, and it has been used for at least 3000 years in Chinese medicine. The Egyptians, Babylonians, Greeks, and Romans used garlic for healing purposes. It has long been used both for flavouring and for the potential benefits of preventing and curing ailments in many cultures (Londhe et al. 2011). The beneficial effects of garlic consumption in treating a wide variety of human diseases and disorders have been known for centuries; thus, garlic has acquired a special position in the folklore of many cultures as a formidable prophylactic and therapeutic medicinal agent. It is even cited in the Egyptian Codex Ebers, a 3500-year-old document, as useful in the treatment of heart disorders, tumours, worms, bites, and other ailments (Rahman 2001).

Some of the earliest references to this medicinal plant were found in Avesta, a collection of Zoroastrian holy writings that was probably compiled during the sixth century BC (Dannesteter 2003). Garlic has also played as an important medicine to Sumerian and the

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**Table 1**
List of plants used for prevention of cardiac diseases.

| Plant name | Family | Country | Action | References |
|---|---|---|---|---|
| *Agaricus albolutescens* Zeller | Agaricaceae | Bangladesh | Cardioprotection | Azam et al. (2014) |
| *Antiaris toxicaria* Lesch. | Moraceae | India | Circulatory stimulant | Arya and Gupta (2011) |
| *Arnebia benthamii* (Wall. ex G.Don) Johnst. | Boraginaceae | Himachal (India) | Heart ailments | Rana and Samant (2011) |
| *Camellia sinensis* (L.) Kuntze | Theaceae | Bangladesh | Cardioprotection | Azam et al. (2014) |
| *Clinopodium umbrosum* (M.Bieb.) Kuntze | Lamiaceae | India | Heart tonic | Rana and Samant (2011) |
| *Cnidoscolus chayamansa* Mc Vaugh | Euphorbiaceae | Mexico | Cardioprotection | García-Rodríguez et al. (2014) |
| *Convallaria majalis* L. | Asparagaceae | Deliblato Sand, Europe | Against heart disease | Popovic et al. (2014) |
| *Coronilla varia* L. | Fabaceae | Deliblato Sand, Europe | Against heart disease | Popovic et al. (2014) |
| *Crataegus monogyna* Jacq. | Rosaceae | Deliblato Sand, Europe | Regulation of heartbeat | Popovic et al. (2014) |
| *Crataegus monogyna* Jacq. | Rosaceae | Spain | Heart problems; antihypertensive | Blumenthal et al. (1998); WHO (2011) |
| *Crocus sativus* L. | Iridaceae | India | Cardioprotection | Bhargava (2011) |
| *Digitalis purpurea* L. | Scrophulariaceae | India | Cardiotonic | Arya and Gupta (2011) |
| *Digitalis ambigua* Murray | Plantaginaceae | Europe | Against heart disease | Popovic et al. (2014) |
| *Evodia ruticarpa* (A.Juss.) Hook.f. & Thomson | Rutaceae | China | Hypertension | Chiou et al. (1997) |
| *Ginkgo biloba* L. | Ginkgoaceae | Europe, China | Anti-ischemic action | Mouren et al. (1994) |
| *Ipomoea digitata* Linn. | Convolvulaceae | India | Hypertension and heart diseases | Varma (2002) |
| *Juglans regia* L. | Juglandaceae | India | Hypoglycaemic | Arya and Gupta (2011) |
| *Leonurus cardiac* L. | Lamiaceae | Deliblato Sand, Europe | Strengthening cardia muscle | Popovic et al. (2014) |
| *Limonium brasillense* (Boiss.)Kuntz | Plumbaginaceae | South America | Cardioprotective | Anonymous (2012) |
| *Limonium wrightii* (Hance) Kuntze | Plumbaginaceae | China, Japan | Cardioprotective | Anonymous (2012) |
| *Ligusticum wallichii* Franch. | Apiaceae | Traditional Chinese medicine | Hypotensive drug, sedative | Ody (1993) |
| *Malus sylvestris* (L.) Mill | Rosaceae | Spain | Strengthen arteries and heart problems | Calvo and Cavero (2014) |
| *Malus sylvestris* (L.) Mill. | Rosaceae | Spain | Heart Problem | Blumenthal et al. (1998) |
| *Morus alba* L. | Moraceae | India | Hypoglycaemic | Arya and Gupta (2011) |
| *Ocimum gratissimum* L. | Lamiaceae | Bangladesh | Cardioprotection | Azam et al. (2014) |
| *Ocimum sanctum* L. | Lamiaceae | India | Hypotensive, cardiac depressant activity | Singh et al. (1970) |
| *Oroxylum indicum* (L.) Vent | Bignoniaceae | Bangladesh | Cardioprotection | Azam et al. (2014) |
| *Panax notoginseng* (Burkill). H. Chen | Araliaceae | China | Atherogenesis | Ody (1993); Lin et al. (1993) |
| *Portulaca oleraceae* L. | Portulacaceae | Spain | Strengthen arteries and heart problems | Calvo and Cavero (2014) |
| *Rauvolfia serpentina (L.) Benth. ex Kurz* | Apocynaceae | India | Hypertension | Oates (1996) |
| *Rorippa nasturtium-aquaticum* (L.) | Brassicaceae | Spain | Heart palpitations | Blumenthal et al. (1998) |
| *Rosmarinus officinalis* L. | Lamiaceae | Europe, China | Antineoplastic effects | Offord et al. (1995); Haraguchi et al. (1995) |
| *Salvia miltiorrhiza* Bunge | Lamiaceae | China | Antianginal, Hypertension | Lei and Chiou (1986) |
| *Solanum nigrum* L. | Solanaceae | India | Heart ailments | Rana and Samant (2011) |
| *Stephania tetrandra* S. Moore | Menispermaceae | Traditional Chinese medicine | Hypertension | Sutter and Wang (1993) |
| *Tinospora cordifolia Willd.* | Menispermaceae | Bangladesh | Cardioprotection | Azam et al. (2014) |
| *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. | Rubiaceae | Traditional Chinese medicine | Hypertension | Sutter and Wang (1993) |
| *Urtica dioica* L. | Urticaceae | Spain | Antihypertensive | WHO (2011); European Medicines Agency (EMA) (2008–2009) |
| *Valeriana officinalis* L. | Valarianaceae | Deliblato Sand, Europe | Against heart disease and hypertension | Popovic et al. (2014) |
| *Viscum album* L. ssp. *album* | Viscaceae | Spain | Antihypertensive, Heart problem | European Medicines Agency (EMA) (2008–2009) |
| *Weldheimia glabra* (Decne.) Regel. | Asteraceae | Tibet | Heart ailments | Rana and Samant (2011) |

ancient Egyptians. There is some evidence that during the earliest Olympics in Greece, garlic was fed to the athletes for increasing stamina (Lawson and Bauer 1998). Ancient Chinese and Indian medicine recommended garlic to aid respiration and digestion and to treat leprosy and parasitic infestation (Rivlrn 1998). In the medieval period, garlic also played an important role in the treatment of different diseases. Avicenna (1988), in his well-known book, Al Qanoon Fil Tib (The Canon of Medicine), recommended garlic to be useful in the treatment of arthritis, toothache, chronic cough, constipation, parasitic infestation, snake and insect bites, gynaecologic diseases, as well as in infectious diseases.

*Chemistry*

Garlic contains at least 33 sulphur compounds, several enzymes, 17 amino acids, and minerals such as selenium. It contains a higher concentration of sulphur compounds than any other *Allium* species. The sulphur compounds are responsible both for garlic's pungent odour and many of its medicinal effects. Dried, powdered garlic contains approximately 1% alliin (S-allyl cysteine sulphoxide). One of the most biologically active compounds, allicin (diallyl thiosulphinate or diallyl disulphide) does not exist in garlic until it is crushed or cut; injury to the garlic bulb activates the enzyme alliinase, which metabolizes alliin to allicin (Fig. 1.). Allicin is further metabolized to vinyldithiins. This transformation of alliin into allicin molecule upon crushing of a garlic clove is extremely rapid, being complete in seconds. The enzyme responsible for this conversion is alliinase, which is present in unusually large amounts in garlic cloves: at least 10% of the total protein content (10 mg/g fresh weight) (https://allicincenter.com/pdf/Allicin.pdf). Garlic oil, aged garlic and steam-distilled garlic do not contain significant amounts of alliin or allicin, but instead contain various products of allicin transformation (Londhe et al. 2011).

*Pharmacology*

Garlic has been investigated extensively for health benefits, resulting in more than 1000 publications over the last decade alone,

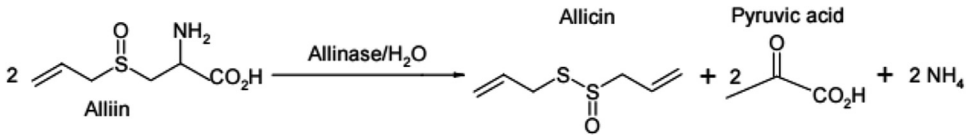



**Fig. 1.** Transformation of Allinin to Allicin in garlic.

and it is considered one of the best disease-preventive foods, based on its potent and varied effects.

Garlic is reported to inhibit the pathogenesis of cardiovascular disease and to prevent cancer and other chronic diseases associated with aging (Rahman 2003). Over the last one-quarter century the role of garlic in treating cardiovascular disease has received much attention. Scientific literature supports the proposal that garlic consumption has significant effects on lowering blood pressure, prevention of atherosclerosis, reduction of serum cholesterol and triglyceride, inhibition of platelet aggregation, and increasing fibrinolytic activity (Chan et al. 2013). Both experimental and clinical studies on different garlic preparations demonstrate these favourable cardiovascular effects.

Epidemiologic studies show an inverse correlation between garlic consumption and progression of cardiovascular disease. Cardiovascular disease is associated with multiple factors such as raised serum total cholesterol, raised low density lipoprotein (LDL) and an increase in LDL oxidation, increased platelet aggregation, hypertension, and smoking. Numerous *in vitro* studies have confirmed the ability of garlic to reduce these parameters. Thus, garlic has been shown to inhibit enzymes involved in lipid synthesis, decrease platelet aggregation, prevent lipid peroxidation of oxidized erythrocytes and LDL, increase antioxidant status, and inhibit angiotensin-converting enzyme. These findings have also been addressed in clinical trials. The studies point to the fact that garlic reduces cholesterol, inhibits platelet aggregation, reduces blood pressure, and increases antioxidant status. Since 1993, 44% of clinical trials have indicated a reduction in total cholesterol, and the most profound effect has been observed in garlic's ability to reduce the ability of platelets to aggregate. Mixed results have been obtained in the area of blood pressure and oxidative-stress reduction. The findings are limited because very few trials have addressed these issues (Rahman and Low 2006).

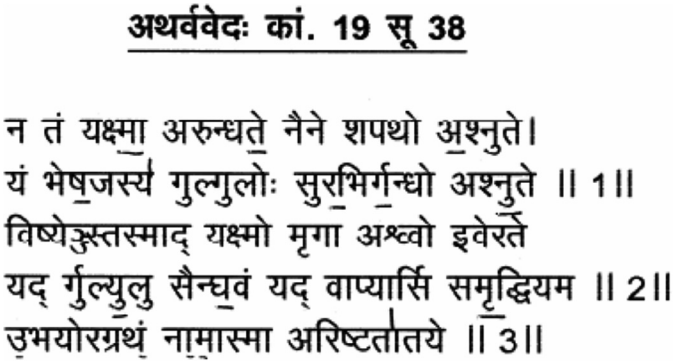
Pooled data from numerous randomized trials suggest that garlic lowers total cholesterol concentrations by approximately 10% and favourably alters high density lipoprotein/low density lipoprotein (HDL/LDL) ratios. Randomized trials also support garlic's effectiveness as a mild antihypertensive which lowers blood pressure by 5–7%. Garlic also inhibits platelet aggregation and enhances fibrinolytic activity, reducing clots on damaged endothelium. *In vitro* data suggest antibacterial effects, but these have not been evaluated in controlled trials in humans (Tattelman, 2005).

Allicin (allyl 2-propenethiosulfinate or diallyl thiosulphinate) is the principal bioactive compound present in the aqueous extract of garlic or raw garlic homogenate. Alliin was found to be the stable precursor that is converted to allicin by the action of an enzyme alliinase.

## Commiphora wightii *(Arn.) Bhandari or* C. mukul *(Hook. ex Stocks) Engl*

### *Plant description and distribution*

Myrrh genus *Commiphora* (Family: Burseraceae) is widely distributed in tropical regions of Africa, Madagascar, Asia, Australia and Pacific Islands (Lal and Kasera 2010). *C. wightii* or *C. mukul* Engl. (Burseraceae) is an important ancient medicinal plant. *C. wightii* is distributed in pockets in India (Rajasthan, Gujarat, Maharashtra and Karnataka, Madhya Pradesh) and adjoining countries of Sind, Baluchistan and Afghanistan (Atal et al. 1975). In India, Rajasthan and Gujarat have been identified as the main commercial centres. *C. wightii* is commonly known as guggul in Hindi and Indian myrrh or Indian bdellium in English. It is shrubby, 1.2–1.8 m high perennial, highly branched, thorny and woody shrub. It thrives well in arid, semi-arid and rocky regions with scanty rainfall.


अथर्ववेदः कां. 19 सू 38

न तं यक्ष्मा अरुन्धते नैने शपथो अश्नुते।
यं भेषजस्य गुल्गुलोः सुरभिर्गन्धो अश्नुते ॥ 1॥
विष्वेञ्चस्तस्माद् यक्ष्मो मृगा अश्वो इवेरते
यद् गुल्गुलु सैन्धवं यद् वाप्यार्सि समूद्धियम ॥ 2॥
उभयोरग्रथं नामास्मा अरिष्टतातये ॥ 3॥

**Fig. 2.** Sanskrit 'Shloka' in 'Atharva Veda' describing the medicinal properties of *C. wightii.*

### *History of use*

The oleo gum-resin, exudates of the *C. wightii* or guggul known as 'myrth' is used in traditional medicine of ancient India i.e. Ayurveda. It finds mention in the 'Atharva Veda' (Fig. 2) wherein its medicinal properties have been described.

Guggul was first introduced to the scientific world by an Indian Medical Researcher, G. V. Satyavati, in 1966 (Deng 2007). Guggul-gum is known to be hypolipidaemic, hypocholesterolaemic and anti-obesity, astringent and antiseptic, anti-arthritic, antimicrobial, anti-inflammatory, and anti-cancerous (Satyavati et al. 1969). It is also reported for the treatment of thrombosis and chronic bronchitis, nodulocystic acne, spongy gums, chronic tonsillitis and teeth caries. It has wide ethnobotanical usage by Garsarias, Saharia and Kalbelia tribes (Singh and Pandey 2006). Several Ayurvedic formulations containing guggul, e.g. Maha Yogaraja Guggulu, Chandraprabha Vati and Triphala guggulu are available in Indian market.

In 1986, guggul was approved for marketing in India as a hypolipidaemic drug. In the middle 1990s, guggul was introduced into the Western world. Guggul is available in the United States and other Western countries as an over-the-counter dietary supplement (Deng 2007).

### *Chemistry*

Guggul gum is a mixture of 61% resin, 29.3% gum, 6.1% water, 0.6% volatile oil and 3.2% foreign matter. Guggul, the gum-resin exudate from the tree *C. wightii*, is a complex mixture of steroids, diterpenoids, aliphatic esters, carbohydrates and a variety of inorganic ions, besides minor amounts of sesamin and other unidentified constituents. Guggul contains more than 150 compounds and new compounds continue to be reported. Guggulsterones E and Z (Fig. 3) are believed to be hypolipidaemic and the most important components of the guggul gum resin. These two compounds and several others have been reported from time to time by various workers. Guggul gum-resin essentially consists of an ethyl acetate-soluble fraction (45%) and insoluble carbohydrate gum (55%). The desired biological activity lies

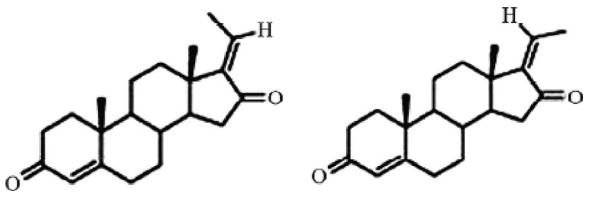


**Fig. 3.** *E*- and *Z*- isomers of guggulsterone.

entirely in the soluble portion and insoluble fraction is toxic to rats and devoid of any hypolipidaemic activity. The crude gum guggul was found to contain 2% guggulsterone and ethyl acetate extract contains 4–4.5% guggulsterones. E and Z guggulsterones have been reported to be 10% (Jain and Nadgauda 2013).

*Pharmacology*

Guggulipid, an extract isolated from the guggul, reduced the low density cholesterol, triglyceride level and total serum cholesterol and increases HDL (Dave and Chopda 2013). Guggulsterone isolated from the *C. mukul* inhibited LDL oxidation. Guggulipid (50 mg twice in a day for 24 weeks) decreased total cholesterol by 11.7%, LDL by 12.5%, triglyceride level by 12%, and the total cholesterol/HDL ratio by 11.1%. Gugulipid, an ethyl acetate extract isolated from *C. wightii,* showed lipid lowering property against streptozotocin (STZ) induced memory deficits in mice. E- and Z guggulsterones of guggul gum are responsible for the hypolipidaemic activity and they act as the FXR antagonist a nuclear hormone receptor, a bile acid receptor (BAR) antagonist a member of the intracellular receptor superfamily and also inhibit human gene cholesterol 7-alpha-hydroxylase (CYP7A1) gene via activation of pregnane X receptor (PXR). The active ingredients in guggulipid are the ketosteroids cis- and trans-4,17 (20)-pregnadiene-3,16-dione, also known as the E- and Z-guggulsterones (Ding and Staudinger 2005)

Presently a few institutes in India viz., CIMAP (Central Institute of Medicinal and Aromatic Plants, Lucknow), CDRI (Central Drug Research Institute, Lucknow) and CAZRI (Central Arid Zone Research Institute, Jodhpur), are carrying out research on this species mostly related to the conservation of genetic resources and development of superior oleo-gum resin. In the year 1972, the Central Council for Research in Ayurveda & Siddha (CCRAS, Govt. of India), initiated a project at Mangliawas (Ajmer). In 2008, India's National Medicinal Plants Board (NMPB) launched a big project in Kutch District (Gujarat) to cultivate 500–700 hectares (1200–2000 acres) of guggul for 3 years as an initiative for conservation and cultivation of this highly traded medicinal plant in this border district (Jain and Nadgauda 2013).

In case of an over-exploited species like *C. wightii*, there is always a limitation of plant in nature for micro- and macro-propagation and also for its product to meet the demand supply gap. An alternative approach to over-coming this limitation is production of active compound in cell culture. Several efforts have been made for the production and its enhancement in cell culture. From among all the species of *Commiphora, C. wightii* is the guggulsterone producing species, therefore, it becomes essential to develop a high throughput method for production of guggulsterone *in vitro* (Jain and Nadgauda 2013).

Crataegus oxyacantha *L.*

*Plant description and distribution*

*Crataegus* is a large genus of trees and shrubs in the rose family, Rosaceae. Hawthorn (*C. oxyacantha*), also known as May thorn, May blossom, is small to medium sized deciduous tree with umbrella shaped clusters of white or pink flowers, glossy green toothed leaves and bright shiny red berries. These small to medium sized trees (5–15 ft tall) are grown as a hedge plant in Europe, and found mostly in temperate areas like North America, Western Asia, India, China and North Africa. In the 1800's, British settlers introduced it into Tasmania and other parts of Australia as a hedge plant, and it now runs wild in Victoria, Tasmania, the Adelaide Hills and the tablelands of New South Wales. *Crataegus* is an aggressive settler that is tenacious and difficult to remove; it has been declared a baneful weed in many Australian states. In India, it is found in the temperate Himalayas, Kashmir and Himachal Pradesh, at an altitude of 1800–3000 m (Kashyap et al. 2012).

*History of use*

*C. oxyacantha* has a long history as a pharmacological active therapeutic substance. It has been used traditionally as a cardiac tonic and current uses include treatment for angina, hypertension, arrhythmias, CHF, etc. (Miller, 1998). Popular Chinese drink Shan Zha containing active therapeutic principles of Hawthorn has been used in lowering blood lipid levels in humans and rats (Chen et al. 1995). *C. oxyacantha* (Aubepine, Hawthorn), was used by European herbalist in the first century A.D (Ju 2005). Hawthorn has an engrossing history of use and it also was considered as sacred by many traditions. The flowering branches of hawthorn tree heralded the beginning of ancient Celtic festival of Beltane and for this reason it was also called the May-flower. In Celtic tradition, Hawthorn tree represented the Goddess and was surrounded by fairies and elemental spirits (Kashyap et al. 2012).

Hawthorn has been used in folk medicine for the treatment of diarrhoea, gall bladder disease, insomnia, and as an antispasmodic agent in the treatment of asthma. In Chinese medicine, hawthorn has also been used for a variety of conditions including digestive problems, hyperlipidaemia, poor circulation, and dyspnoea (Rigelsky and Sweet 2002). The use of hawthorn for the treatment of cardiovascular heart disease dates back to the late 1800s (Hobbs and Foster 1990).

Globally more than twenty species of hawthorn are used as herbal drugs or drug materials. Kumar et al. (2012) have enumerated the various traditional uses of *Crataegus* species worldwide. A decoction of leaves and unripe fruits from *Crataegus aronia* is used to treat cardiovascular diseases, cancer, diabetes and sexual weakness in Arabian traditional medicine system. In Mexico, diabetes is treated with hawthorn extracts. Such treatment may be of considerable benefit especially during the early stages of the illness. In folk medicine, several hawthorn species are mainly used for treating CVDs including *C. pinnatifida* (Chinese hawthorn), *C. pubescens* (Mexican hawthorn), *C. cuneata* (Japanese hawthorn), *C. laevigata* and *C. monogyna* (Europe), *C. oxycantha* and *Crataegus aronica* (Middle East), *C. phaenopyrum* (American hawthorn) and *C. ambigua* (Russian hawthorn). Hawthorn (*C. pinnatifida*) is an edible fruit used in traditional Chinese medicine to lower plasma lipids. Dried fruits of *C. pinnatifida* have been used traditionally as oriental medicine and local soft drink material in Taiwan.

*C. oxyacantha* Linn is an official plant in homeopathic system of medicine, traditionally employed as a cardioprotective. On account of its efficacy and safety hawthorn has made its place in pharmacopoeias of many countries. China, Germany, France and England have officially accepted some of these species (Table 2) (Chang et al. 2002).

*Chemistry*

*C. oxyacantha* contains heptahydroxy flavan glycoside, flavan polymers. The flavonoid components and oligomeric procyanidins, as the key constituents of *C. oxyacantha*, are responsible for its therapeutic potential. The leaves, flowers and berries of hawthorn contain a variety of bioflavonoid-like complexes that appear to be primarily responsible for the cardiac actions of the plant. Biflavonoids found in hawthorn plant include oligomeric procyanidins (OPC), vitexin, quercetin, and hyperoside. The action of these compounds on the cardiovascular system has led to the development of leaf and flower extracts, which are widely used in

**Table 2**
List of *Crataegus* species accepted in different pharmacopoeias.

| Name of pharmacopoeia | *Crataegus* species | Parts used |
|---|---|---|
| British pharmacopoeia (2000) | *C. oxyacantha* L., *C. monogyna Jacq.* | Fruits, leaves, and flowers |
| Chinese pharmacopoeia (English ed., 1997) | *C. pinnatifida Bge., C. pinnatifida Bge. var. major N.E. Br.* | Fruits |
| European pharmacopoeia (1998) | *C. oxyacantha L., C. monogyna Jacq.* | Fruits, flowers |
| France pharmacopoeia (1998) - | *C. oxyacantha* L., *C. monogyna Jacq.* | Fruits |
| German pharmacopoeia (DAB, 1997) and Swiss pharmacopoeia (1997) | *C. oxyacantha L., C. monogyna Jacq., C. pentagyna Waldst. C. nigra Waldst., C. azarolus* L. | Leaves with flower |

Europe. Other chemical constituents include vitamin C, saponins, tannins, cardiotonic amines (phenylethylamine, tyramine, isobutylamine, *O*-methoxy phenylethylamine, choline and acetylcholine), purine derivatives (adenosine, adenine, guanine, caffeic acid, amygdalin), triterpene acids ursolic acid (Verma et al. 2007). Edwards et al. (2012) have discussed in detail the phytochemicals that have been reported in *Crataegus* species

*Pharmacology*

Current claims suggested that hawthorn could be used as an alternative therapy for various cardiovascular diseases, such as angina, hypertension, hyperlipidaemia, arrhythmia, and New York Heart Association (NYHA) functional class II CHF (Chang et al. 2005). Nowadays, it is gaining attention for its potential cardiovascular enhancing and protective properties and numerous laboratory tests and clinical trials have demonstrated hawthorn's efficacy in the treatment or prevention of CVDs and the most substantial evidence for clinical benefits of hawthorn is its use in chronic CHF (Long et al. 2006). A meta-analysis of randomized, placebo-controlled trials of hawthorn extract in combination with standard CHF therapy suggested several beneficial cardiovascular effects of hawthorn as compared to placebo. Similarly, a 2008 Cochrane review, wherein all primary literature pertaining to the health effects of hawthorn on humans was assessed, found a significant benefit in symptom control and physiologic outcomes from hawthorn extract as an adjunctive treatment for chronic heart failure. Besides, the antioxidant, positive inotropic, anti-inflammatory, and anti-cardiac remodelling effects and other cardiovascular protective effect of the hawthorn active ingredients were demonstrated in various *in vivo* and *in vitro* experiments. *Crataegus* has a number of pharmacological properties, but the specific mechanism is not clear. The previous described animal studies have suggested that hawthorn extracts exert a wide range of cardiovascular pharmacological properties, including antioxidant activity, positive inotropic effect, anti-inflammatory effect, anti-cardiac remodelling effect, antiplatelet aggregation effect, vasodilating effect, endothelial protective effect, reduction of smooth muscle cell migration and proliferation, protective effect against ischemia/reperfusion injury, antiarrhythmic effect, lipid-lowering effect, and decrease of arterial blood pressure effect. Moreover, numerous clinical studies have demonstrated that hawthorn preparations are very effective in early stages of congestive heart failure. A few researches were also reported on therapy of hypertension and hyperlipidaemia (Wang et al. 2013).

## Terminalia arjuna *(Roxb.) Wight & Arn*

*Plant description and distribution*

*T. arjuna* (Roxb.) Wight & Arn. is a deciduous and evergreen tree, standing 20–30 m above ground level. It belongs to Combretaceae family (Nadkarni and Nadkarni 1954). Commonly known as *Arjuna,* it is native to Indian soil. It is found in abundance throughout Indo-sub-Himalayan tracts of Uttar Pradesh, South Bihar, Madhya Pradesh, Delhi and Deccan region near ponds and rivers. It is also found in forests of Sri Lanka, Burma and Mauritius (Chopra et al. 1958). Remarkably the tree is pest and disease free.

"धृतेन दुग्धेन गुडाम्भसा वा पबिन्तचिुर्णम् कुकुभत्वचो ये
हृद्रोगजर्िणज्वररक्तपत्तिं हत्वा भवेयुश्चरिजीवनिस्ते //"
(BH.PR. 34/11)

**Fig. 4.** Sanskrit 'Shloka' in 'Bhav Prakash' describing the use of *T. arjuna* in heart disorders and other conditions.

*History of use*

The bark leaves and fruits of *T. arjuna* have been used in indigenous system of medicine for different ailments (Warrier et al. 1996). The bark is said to be sweet, acrid, cooling and heating, aphrodisiac, expectorant, tonic, styptic, anti-dysenteric, purgative and laxative. Its use has been advocated in urinary discharge, strangury, leukoderma, anaemia, hyperhidrosis, asthma and tumours.

In the Rigveda, the word *Arjuna* is used (R.V.1/122/5) for the first time (Anonymous 2011). Both Charaka and Sushruta have mentioned this plant in their Samhitas (Seth et al. 2013). The use of bark powder as an astringent and diuretic finds mention in the works of Charaka. The bark powder has been attributed to possess cardioprotective properties. Vagbhata was the first to cite the use of *T. arjuna* bark powder mixed with milk for the relief of chest pain caused by heart in his book 'Ashtanga Hridayam' written some 1200 years ago (Lal Chandra 1963). Subsequently, Chakradutta and also Bhawa Mishra, described its use in chest pain (Dwivedi 2007). Ayurveda recommends different formulations of the bark powder of arjuna. Traditional method of its administration was to prepare an alcoholic decoction of its bark stem (asava) or give it along with clarified butter (ghrita) or along with boiled milk (kshirpak) (Nadkarni and Nadkarni 1954; Warrier et al. 1996; Agera et al., 2015). 'Bhav Prakash', the ancient Ayurvedic text, also describes the use of *T. arjuna* in heart disorders and other related conditions (Fig. 4).

Fresh juice of leaves of Arjuna is used for the treatment of earache in South India and root paste is applied on headache. Paste of leaf made with sugar and milk given once a day for 20 days for the treatment of spermatorrhoea. Traditional healers from South India uses fruit paste topically on wounds. Tribals living in Orissa use dried bark of Arjuna powder along with rice washed water to treat blood in urine, and chew the fresh bark and swallow the juice as an antacid. In Tamil Nadu, people boiled the bark powder with water, and inhale it to cure headache and to kill worms in teeth. Decoction of the bark has been used as ulcer wash, while bark ash is prescribed for snakebite and scorpion sting (Agera et al. 2015). It acts as astringent, cooling, aphrodisiac, cardiotonic, demulcent, styptic, anti-dysenteric, urinary astringent, expectorant, alexiteric, lithontriptic tonic. It is also used in some clinical conditions like fractures, ulcers, urethrorrhoea, spermatorrhoea, leucorrhoea, diabetes, anaemia, cardiac disorders, cough, tumour, excessive perspiration, fatigue, asthma, bronchitis, intrinsic haemorrhage, otalgia, diarrhoea associated with blood, cirrhosis of

liver, hypertension, inflammation and skin disorders (Warrier et al. 1996; Dwivedi and Udupa 1989).

*Chemistry*

Phytochemical analysis reveals that *T. arjuna* contains triterpenes (like arjunic acid), arjunolic acid, arjunolitin, and arjungenin, tannins like arjunin, catechin, gallocatechin, epicatechin, epigallocatechin, glycosides like arjunglucoside-I, arjunetoside, terminolitin (23- deoxyarjunolitin oleane derivatives), arjunetoside, arjunaphthanoloside-1 and very high amounts of flavonoids (quercetin, kaempferol, luteolin and pelargonidin), ellagic acids and phytosterols as well as minerals such as calcium, magnesium, zinc, and copper. Some other compounds in *T. arjuna* are terminic acid, arjunin, Casuarinin, sapogenins, serine, valine, etc. (Seth et al. 2013).

*Pharmacology*

The bark of *T. arjuna* has been used in Indian medicine for cardiovascular ailments for a long time. Dwivedi (2007) in his review on *T. arjuna* has extensively discussed its physiological and pharmacological actions and critically evaluated its cardioprotective effects. Sequels of studies were performed that strongly supported its usefulness in several cardiac complications like cardiac failure, hypertension and other digitalis unresponsive cardiac diseases. Current scientific literature suggests that the benefit of arjuna could be in patients with ischaemic heart disease and heart failure. The aqueous extract of *T. arjuna* bark has been reported to have positive ionotropic and antianginal effects in heart patients. *T. arjuna* therapy was associated with significant decrease in anginal episodes in patients. The alcoholic extract of *T. arjuna* has also shown to be effective in decreasing blood pressure and heart rate in cats and dogs. The beneficial effects of *T. arjuna* bark powder and its extract were also established in ischaemic heart diseases and congestive heart failure. The usefulness of *T. arjuna* is also recognized in other indications like obesity, hypertension and hyperglycaemia (Dwivedi and Udupa 1989)

The efficacy of *T. arjuna* as an anti-ischaemic agent and as a potent antioxidant preventing LDL cholesterol oxidation and reperfusion ischemic injury to heart, and its potential to reduce atherogenic lipid levels have been amply demonstrated in various experimental and clinical studies. It can be considered as a useful drug for coronary artery disease, hypertension and ischaemic cardiomyopathy (Dwivedi 2007). Experimental studies have revealed its bark exerting significant inotropic and hypotensive effect, increasing coronary artery flow and protecting myocardium against ischemic damage. It has also been detected to have mild diuretic, antithrombotic, prostaglandin E2 (PGE2) enhancing and hypolipidaemic activity. There is ample clinical evidence of its beneficial effect in coronary artery disease alone and along with statin. Considering its anti-ischaemic activity and its potential to correct dyslipidaemia, reduce left ventricular mass and increase left ventricular ejection fraction, it is essential to examine the molecular mechanism of its action and its core constituents. There is enough convincing evidence that bioflavonoids, by virtue of their free radical scavenging action, prevent oxidation of LDL cholesterol, enhance endothelial derived nitric oxide activity, inhibit endothelial activation and inhibit platelet aggregation (Fuhrman and Aviram 2001). They possibly also inhibit cyclooxygenases and reduce the risk of thrombosis. High intake of dietary flavonoids is considered to be inversely related to the risk of CAD. The high flavonoid content of *T. arjuna* may possibly account for its beneficial effects in CAD (Dwivedi 2007).

Currently in the All India Institute of Medical Sciences (AIIMS), New Delhi, India, a clinical trial on *Arjuna* is going on (Seth et al. 2013). It is a double-blind, randomized placebo controlled clinical trial to study the add-on efficacy of a standardized preparation of the water extract of *T. arjuna* in 100 patients with left ventricular dysfunction, already receiving a standard drug regimen. Patients are getting a dose of 750 mg twice a day of water extract of bark of *T. arjuna* for a period of 3 months. Left ventricular function (by echocardiography), and functional capacity by (NYHA) Class, Kansas City Cardiomyopathy Questionnaire-KCCQ (for quality of life), Six Minute Walk test and Brain Natriuretic Peptide (BNP) are the end points being assessed. They are also being assessed by Dashvidh Pariksha (an Ayurvedic method of assessment of the patient) before and after therapy. All safety end points are being assessed. This trial is expected to give conclusive evidence regarding the effects of *T. arjuna* when administered as an add-on therapy in the patients of heart failure.

## Conclusions

A recent increase in the popularity of alternative medicine and natural products has revived interest in traditional remedies that have been used for the treatment of cardiovascular diseases. This article highlights the cardiovascular effects of four potent traditional botanicals viz. Garlic (*A. sativum*), Guggul (*C. wightii*), Hawthorn (*C. oxyacantha*) and *Arjuna* (*T. arjuna*). Although these plants have been used in the treatment of heart disease for hundreds of years, current research methods show us they can be utilized effectively in the treatment of CVDs including ischaemic heart disease, congestive heart failure, arrhythmias and hypertension. The unique chemical constituents present in these species provide beneficial effects by varied modes of action, can improve the quality of life in individuals with heart disease and potentially save thousands of lives.

However, for bringing more objectivity and also to confirm traditional claims, systematic clinical trials are necessary. More systematic, well-designed animal and randomized clinical studies with sufficient sample sizes are essential to investigate their exact mechanisms of action, safety and pharmacokinetics so as to include them in the mainstream of healthcare system. Multidisciplinary research that combines the forces of natural products chemistry, molecular and cellular biology, synthetic and analytical chemistry, biochemistry, and pharmacology are still required to exploit the vast potential of these plants. As more and more people tend to use traditional remedies as an alternative medicine, more extensive, well-designed preclinical and clinical trials on the potential synergistic and adverse side effects of herb-drug interactions, as well as their mechanisms, are required.

Although such extensive and multidirectional approach to the herbal research is not easy to pursue, it is essential to consider the totality of the materials and approaches so that remedies that are developed from traditional herbs for cardiovascular disorders are grounded in solid scientific evidence.

## Conflict of interest

None

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