Review Article

Herbal Remedies for Cardiovascular Diseases

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ABSTRACT

Cardiovascular diseases are currently the leading cause of death in industrialized countries and include a broad range of diseases, including hypertension, hyperlipidemia, thromboembolism, coronary heart disease, heart failure, endocarditis, stroke, peripheral vascular disease and many other conditions. CVDs are the leading cause of death globally. The most opted treatment for CVDs remains conventional drug therapies for example diuretics, vasodilators, anticoagulants, anti-platelet agents and β-blockers. But still herbal medication are high in their value and this option is now becoming a world wide procedure in many disease treatments including heart diseases. In this review, few herbal medications with their action on the cardiovascular system has been enlisted and shows their use as a cardiovascular medicine. Compared with conventional medications, herbal medications do not require clinical studies before their marketing or formal approval from regulatory agencies, and for this reason their efficacy and safety are rarely proven

Keywords: Cardiovascular diseases, herbal remedies, cardiac tonic.

INTRODUCTION

The cardiovascular system is made up of the heart and blood vessels. Cardiovascular disease is defined as any serious, abnormal condition of the heart or blood vessels (arteries, veins). Cardiovascular diseases are currently the leading cause of death in industrialized countries and include a broad range of diseases, including hypertension, hyperlipidemia, thromboembolism, coronary heart disease, heart failure, endocarditis, stroke, peripheral vascular disease and many other conditions. CVDs are the leading cause of death globally. A recent research from the World Health Organization estimated that around 18 million people died from CVDs and by 2030 mortality figures may reach 23.3 million[1]. The underlying pathology of CVD is atheromatous vascular disease, leading to other disorders such as CAD, cerebrovascular disease, peripheral vascular disease, and development of heart failure and cardiac arrhythmia's. The most opted treatment for CVDs remains conventional drug therapies for example diuretics, vasodilators, anticoagulants, anti-platelet agents and β-blockers. Most of the risk factors for cardiovascular disease and stroke are modifiable or entirely preventable. By modifying risk factors, we can decrease the chances of getting diseases. Modifiable risk factors include tobacco use, high blood pressure, physical inactivity, high blood cholesterol, obesity, heavy alcohol consumption, and poor nutrition. Non-modifiable risk factors are age and family history.

Congestive heart failure is a chronic progressive condition that affects the pumping power of your heart muscles. While often referred to simply as "heart failure," CHF specifically refers to the stage in which fluid builds up around the heart and causes it to pump inefficiently. In heart failure, the heart may not provide tissues with adequate blood for metabolic needs, and cardiac-related elevation of pulmonary or systemic venous pressures may result in organ congestion. This condition can result from abnormalities of systolic or diastolic function or, both. Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason for this is a build-up of fatty deposits on the inner walls of the blood vessels that supply the heart or brain. Strokes can also be caused by bleeding from a blood vessel in the brain or from blood clots. 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[2] It can be difficult to recognize heart failure in infants and young children. Symptoms may include: poor feeding, excessive sweating, difficulty in breathing. These symptoms can easily be misunderstood as colic or a respiratory infection. Poor growth and low blood pressure can also be signs of heart failure in children. Elderly patients are more prone than are younger ones to develop CVD symptoms in response to the stress of systemic disorders or relatively modest cardiovascular insults.

The herbal medicines can be beneficial for some heart diseases. Along with the increased use of herbal medicines, useful information about the interactions of these supplements and medications should be given to the

patients to prevent the complications resulting from their interactions that are sometimes very critical. There are many plants that have therapeutic effects, may prevent cardiovascular diseases, and influence hypolipidemia, blood pressure and heart failure through antioxidant, anti-clotting, hypotensive, anti-atherosclerosis, heart rate-regulating and vasodilating properties. The plants may also have a negative impact on the performance of the heart and blood vessels, including the development of arrhythmia, blood pressure and similar effects on the sympathetic nervous currents that cause interference in the activity of the heart.[3] A number of herbs contain potent cardioactive glycosides, which have positive inotropic actions on the heart. The drugs digitoxin, derived from either *D purpurea* (foxglove) or *Digitalis lanata*, and digoxin, derived from *D lanata* alone, have been used in the treatment of congestive heart failure for many decades. Cardiac glycosides have a low therapeutic index, and the dose must be adjusted to the needs of each patient. The only way to control dosage is to use standardized powdered digitalis, digitoxin, or digoxin. Thus treating congestive heart failure with nonstandardized herbal drugs would be dangerous.

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 friticosa* (balloncotton), *Calotropis precera* (king's crown), *Carissa spectabilis* (wintersweet), *Cerebra manghas* (sea mango), *Cheiranthus cheiri* (wallflower), *Convallaria majalis* (lily of the valley, convallaria), *Cryptostegia grandiflora* (rubber vine), *Helleborus niger* (black hellebore), *Helleborus viridus*, *Nerium oleander* (oleander), *Plumeria rubra* (frangipani), *Selenicerus grandiflorus* (cactus grandiflorus), *Strophanthus hispidus* and *Strophanthus kombe* (strophanus), *Thevetia peruviana* (yellow oleander), and *Urginea maritima* (squill). Even the venom glands of the animal *Bufo marinus* (cane toad) contain cardiac glycosides. Recently, the digitalis like steroid in the venom of the B marinus toad was identified as a previously described steroid, marinobufagenin. Marinobufagenin demonstrated high digoxin like immunoreactivity and was antagonized with an antidigoxin antibody.

HERBAL REMEDIES

I. *Digitalis purpurea*

Digitalis consists of dried leaves of Digitalis purpurea Linn. belonging to family Plantaginaceae; native to and widespread throughout most of temperate Europe.[4] The plants are well known as the original source of the heart medicine digoxin (also called digitalis or digitalin).[5] The Active constituents include Digitoxin, Tigogenin, Digitalin, Gitonin, Gitosine, Allonegitosin, Digipronin, Digiprolactone, Digitoxigenin, Purpogenin, Purnalosides A and B. The main property of cardiac glycosides is their selective action on the heart, the main effect of which is the strengthening of systole, which creates a more economic condition for heart work: strong systolic contractions change into periods of "rest" (diastole), which facilitate restoration of energetic resources of the myocardium.

Digitalis medicines strengthen the force of the heartbeat by increasing the amount of calcium in the heart's cells (Calcium stimulates the heartbeat). When the medicine reaches the heart muscle, it binds to sodium and potassium receptors. These receptors control the amount of calcium in the heart muscle by stopping the calcium from leaving the cells. As calcium builds up in the cells, it causes a stronger heartbeat. Digitalis medicines control irregular heart rhythms (called arrhythmias) by slowing the signals that start in the SA node. This, in turn, reduces the number of signals that travel through the AV node thus reducing arrhythmias.[6] Digoxin also increases the force of contraction of the muscle of the heart by inhibiting the activity of an enzyme (ATPase) that controls movement of calcium, sodium, and potassium into heart muscle. Calcium controls the force of contraction. Inhibiting ATPase increases calcium in heart muscle and therefore increases the force of heart contractions. Digoxin also slows electrical conduction between the atria and the ventricles of the heart and is useful in treating abnormally rapid atrial rhythms such as atrial fibrillation, atrial flutter, and atrial tachycardia. During rapid atrial rhythms, electrical signals from the atria cause rapid contractions of the ventricles which are inefficient in pumping blood containing oxygen and nutrients to the body, causing symptoms of weakness, shortness of breath, dizziness, and even chest pain. Digoxin alleviates these symptoms by blocking the electrical conduction between the atria and ventricles, thus slowing ventricular contractions.[7] Digitalis is used in the treatment of various heart conditions like Atrial fibrillation, Atrial flutter and Heart failure that cannot be controlled by other medication. Despite its wide therapeutic use, compound has a low therapeutic index and toxicity is common. It was found that toxicity can occur within the therapeutic range with old patients being especially at risk of developing digoxin toxicity.

II. *Convallaria majalis*

Lily of the valley, Convallaria majalis is a highly poisonous woodland flowering plant with sweetly scented, pendent, bell-shaped white flowers borne in sprays in spring. It is native throughout the cool temperate Northern Hemisphere in Asia and Europe[8]. It is highly poisonous but exhibit cardioactivity due to presence of active constituent convallarin. Around 38 different cardiac glycosides (cardenolides) have been found in the plant, including : convallarin convallamarin, Convallatoxin. *Convallaria majallus* was considered to be safer than Digitalis. The roots of the Convallaria plant was used in treatment for a weak heart, shortness of breath tachycardia and arrythmia.

The Convallaria plant transforms convalloside (the basic metabolic glycoside) into convallatoxin and other cardiac glycosides. Convallatoxin affects vasoconstriction and

vasodilation, and cardiac stroke volume, pulse pressure and cAMP activity are enhanced by Convallaria. *Convalla maroside* may reduce angiogenesis and have anti-tumor effects. Positive ionotropic effects may also be accomplished with Convallarin and some other herbs. In these plants, the primary mechanism involves cyclic AMP. When stimulated, receptors on the outsides of muscle cell membrane enable the synthesis of adenylyl cyclase, the enzyme that catalyzes the production of intracellular cAMP. The presence of cAMP activates the calcium channels in the muscle cell membranes. In heart muscle cells, calcium influx promotes increased heart contractility. When epinephrine and norepinephrine bind to membrane receptors, a chain reaction is initiated; the increased calcium level results in increased ionotropic capacity.[9] Convallaria have been used for centuries by herbalists in the treatment of certain cardiac dysfunctions like congestive heart failure and cardiomyopathy. Convallarin is effectively used as a cardiotonic and diuretic. It is less powerful than digitalis but is recommended for CHF. It also functions in strengthening the weak heart.

III. ***Strophanthus gratus***

Ouabain also known as g-strophanthin, is a plant derived toxic substance that was traditionally used as an arrow poison in eastern Africa for both hunting and warfare. Ouabain is a cardiac glycoside and in lower doses, can be used medically to treat hypotension and some arrhythmias[10]. *Strophanthus gratus* belongs to the family Apocynaceae. Ouabain can be found in the roots, stems, leaves, and seeds of the *Acokanthera schimperi* and *Strophanthus gratus* plants, both of which are native to eastern Africa. Plants from the genus Strophanthus produce toxic alkaloids and cardiac glycosides g-strophanthin (ouabain), k-strophanthin, and e-strophanthin. The drug acts on the heart before influencing any other organ or tissue.

Cardiac glycosides such as ouabain have a direct cardiotonic action on the myocardium, resulting in an increase in the force of contraction. The increased contractility is caused by inhibition of the membrane-bound enzyme Na+K+ATPase, leading to an increase in the intracellular stores of calcium. When the cardiac glycoside is given to a patient suffering from congestive heart failure, the stroke volume of the heart is increased, causing a more effective emptying of the ventricles, and a lowering of the diastolic pressure[11]. Ouabain is used to treat congestive heart failure and supraventricular arrhythmias due to re-entry mechanisms, and to control ventricular rate in the treatment of chronic atrial fibrillation.

IV. ***Thevetia peruviana***

Thevetia peruviana, 'the yellow oleander', one among the Indian indigenous plants, contain a mixture of several cardiac glycosides. Different plant parts are used in various folk medicines and other clinical applications, and plant material are the only industrial source for cardiac glycoside availability[12]. *Thevetia peruviana* contains a cardiac glycoside called digitoxigenin, thevetin A and B, the veridoside, cerberin, galacturonic acid, rhamnose, aucubin, ursolic acid, cardenolides, quercetin, alpha and beta-amyrin, and phenyl acetate, as prime phytoconstituents.

The drug was found to have an immediate and powerful positive inotropic and negative chronotropic effect, like ouabain, on the failing human heart. Oral peruvoside was also effective in the treatment of congestive heart failure when used on a short-term as well as a long-term basis26. Thus peruvoside is a useful cardiac glycoside in the management of congestive heart failure in man as a quick-acting intravenous preparation. It is equally effective when used orally. Major advantage of peruvoside over digitalis is that it has good absorbability from the gastrointestinal tract and a much wider margin of safety. Cardiac glycosides exert a digoxin-like effect by inhibiting the sodium-potassium-ATP enzyme systems. The increased intracellular sodium concentration and the increased serum potassium concentration produce negative chronotropic and positive inotropic effect[13] . The medicinal use of this plant ranges from the being an extreme cardiotonic agent , antineoplastic agent, cardioactive glycoside, feeding deterrent, showing cytotoxic as well as antimicrobacterial properties, antifungal, anti-diarrhoeal; HIV-1 reverse transcriptase and HIV-1 integerase inhibitory agents.

V. ***Antiaris toxicaria***

Antiarin is a cardiac glycoside, much like digoxin, oleandrin, and cerberin. Like the others, it has a steroid backbone, a cardenolide, conjugated with a sugar moiety (the glycoside part). Like the other glycosides, antiarin also has potential medical use as a treatment for heart failure. It is also used as an arrow and dart poison. *Antiaris toxicaria* is a tree in the mulberry and fig family, Moraceae. The trunk bark of *A. toxicaria* was found to have a strong cardiotonic effect. About twenty-eight cardiac glycosides/aglycones, including Antiarin and some new compounds 1–10, designated as antiarosides A (1), B (2), C (3), D (4), E (5), F (6), G (7), H (8), and I (9) and antiarotoxinin A (10) is found to have effect on human heart. β-Antiarin is administered to the body through injection. Once inside the body, the chemical will affect muscular and cardiac tissues[14].

Beta-antiarin affects Na+K+- ATPase cardiac-muscle membrane activity and over dose may lead to heart attack. The latex of *Antiaris toxicaria* contains intensely toxic cardenolides, cardiac glycoside named antiarin and is used in treatment of CHF. Its use ranges from medical use, such as hypertension treatment, to arrow poison application. It also proves to be more poisonous than curare, sporting a low LD50 of 0.1 mg/kg in most mammals. If the dosage of cardiac glycoside (i.e. beta-antiarin) doubles, then the substance becomes a poison[15]. It is also reported to be used as a fish poison and birdlime. Seeds, leaves and bark are used as a febrifuge and the seeds also as an antidysenteric. The bark is used as an anodyne and

vermifuge, and to treat hepatitis. It has also been used for dyeing.

VI. *Terminalia arjuna*

In traditional Ayurvedic medicine, Terminalia arjuna has been used to balance the three humors: kapha, pitta, and vata. It has also been used for asthma, bile duct disorders, scorpion stings, and poisonings. The bark of Terminalia arjuna has been used in India for more than 3000 years, primarily as a heart remedy[16].Terminalia arjuna is a tree of the genus Terminalia. It is commonly known as arjuna or arjun tree. Three species of terminalia are used for medicine, especially as part of Ayurvedic medicine. These species include Terminalia arjuna, Terminalia bellerica, and *Terminalia chebula*. Arjuna, the ayurvedic heart protector herb is full of bio-chemical constituents. Some of the important phyto-chemicals include Triterpenoids: arjunin, arjunic acid, arjunolic acid, arjungenin, terminic acid; Glycosides: arjunetin, arjunoside I, arjunoside II, arjunaphthanoloside, terminoside A Sitosterol; Flavonoids: arjunolone, arjunone, bicalein, luteolin, gallic acid, ethyl gallate, quercetin, kempferol, pelorgonidin, oligomeric proanthocyanidins; Tanins: pyrocatechols, punicallin, punicalagin, terchebulin, terflavin C, castalagin, casuariin, casuarinin; Minerals/trace elements: calcium, aluminium, magnesium, silica, zinc, copper.

Arjuna is a well-known heart tonic and cardio-protective herb. It strengthens the heart muscles and treats the cardiac debility. It also increases the coronary artery flow and protects the heart muscles from ischemic damage. The systolic dysfunction is impairment in the ability of the heart to eject blood. Experimental studies have revealed T. arjuna bark exerting significant inotropic and hypotensive effect, increasing myocardial contractility, coronary artery flow and protecting myocardium against ischemic damage.

VII. *Asclepias currasavica*

Asclepias curassavica contains several cardiac glycosides which include asclepin, calotropin, uzarin and their free genins, calactin, coroglucigenin and uzarigenin. It also contains oleanolic acid, ß- sitosterol, and glycosides of asclepin[17]. *Asclepias curassavica*, commonly known as tropical milkweed, is a flowering plant species of the milkweed genus, Asclepias. *Asclepias curassavica* contains several cardiac glycosides which include Asclepin, Calotropin, Uzarin and their free genins, Calactin, Coroglucigenin and Uzarigenin. It also contains Oleanolic acid, ß- sitosterol, and glycosides of Asclepin.

Asclepin showed a marked positive inotropic effect as evidenced by the increase in the force of contraction. It was found to be more active than the other glycosides. A positive inotropic activity for asclepin extracted from *Asclepias curassavica* has been proved and it was more potent and safer than other cardiac glycosides (including digoxin). It showed longer duration of action than digoxin in many animal studies. [96 h in cat, as opposed to the 72 h of digoxin). *Asclepias curassavica* is a promising medicinal plant with a wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety. Entire plant is dried and decocted as a cardiac tonic, for tonsillitis, pneumonia, bronchitis, urethritis and external and internal bleeding .

VIII. *Adonis vernalis*

Early spring weed, scanty, growing on cultivated lands (near corn-fields, field boundaries, in crops), in plains. Only 4, very fragmented populations have been confirmed. Individuals usually are in groups of 1–1041. *Adonis vernalis*, commonly known as pheasant's eye is a perennial flowering plant in the buttercup family Ranunculaceae. Active constituents in the plant includes glycosides (cardenolides) related to digitalis: adonidoside, adonivernoside, zimarin and adonitoxin and other substances as strophantogenins and vernadigin (adonitoxigenin 3-O-beta-D-diginoside). The rhizome, much more active than the leaves, contains vernadine. Useful for cardiac muscles suffering from fatty degeneration. It is known for regulating pulse and increasing the power of contraction of the heart[18].

Adonis contains cardiac glycosides similar to those found in digitalis purpurea. These substances improve the heart's efficiency, increasing its output while at the same time normalising its rate. Unlike Digitalis, its effect on the heart is slightly sedative and it is generally prescribed for patients with hearts that are beating too fast or irregularly. It is also recommended for certain cases of low blood pressure. It is strongly diuretic and can be used to counter water retention, particularly in cases of poor circulatory function. It is used in homoeopathic medicine as a treatment for angina. Glycosides contained in the plant have effects similar to those of the digitalis. *Adonis vernalis* have heart tonic effects, exerting, at therapeutic doses, diuretic and maybe sedative actions. The Species is used for the treatments of the several kinds of the diseases. The active principles are the bitter glycosides, called as the Adonidin, Arcitrin, Adonidic acid, Aconotin acid, Adonidin Quercitin and Sugars.

IX. *Apocynum cannabinum*

Apocynum means "poisonous to dogs". All parts of the plant are poisonous and can cause cardiac arrest if ingested. The specific epithet cannabinum and the common names hemp, dogbane and Indian hemp refer to its similarity to Cannabis as a fiber plant rather than as a source of a psychoactive drug. *Apocynum cannabinum* (dogbane) is a perennial herbaceous plant belonging to the family apocyanaceae that grows throughout much of North America - in the southern half of Canada and throughout the United States. It is a poisonous plant but exhibit cardiotonic actions. The active Constituents of *Apocynum cannabinum* are the pharmacologically active cardenolides (cardiac glycosides). A total cardenolide content of 0.29% was determined in the fresh roots (water content 59%)[19].

The principle pharmacodynamic activity of *Apocynum cannabinum* constituents is associated with the cardenolides exerting their action mainly by inhibition of the membranous adenosine triphosphatase in the cardiomuscular tissue. The inhibition causes the ceasation of all energy dependent functions and reduces the cardiac work load. This herb is recommended for simple arrhythmias, with or without cardiac hypertrophy. *Apocynum cannabinum* was also used it to treat a wide variety of complaints including rheumatism, coughs, pox, whooping cough, asthma, internal parasites, diarrhoea and also to increase milk flow in lactating mothers. The root has been used as a tonic, cardiotonic, diaphoretic, diuretic, emetic and expectorant. The fresh root is the most active part medicinally.

X. *Urginea maritima*

Red squill or the sea onion, *Urginea maritima* (Liliaceae), is a large onion like plant that grows wild in the coastal areas around the Mediterranean and is cultivated in the United States. Its major bioactive principle, found in all parts of the plant but concentrated in the bulbs, is a bitter and emetic bufadienolide glycoside, scilliroside[20]. *Drimia maritima* (syn. *Urginea maritima*) is a species of flowering plant in the family Asparagaceae, subfamily Scilloideae. This species is known by several common names, including squill, sea squill, sea onion, and maritime squill. The plant has been used as a poison and as a medicinal remedy. The main active compounds are cardiac glycosides, including unique bufadienolides such as glucoscillaren A, proscillaridine A, scillaren A, scilliglaucoside and scilliphaeoside. The plant can have a cardiac glycoside content of up to 3%. Scilliroside, the most important of the toxic compounds, is present in all parts of the plant. Sea squill contains cardiac glycosides which are strongly diuretic and relatively quick-acting. They do not have the same cumulative effect as those present in foxglove.

The bulb has been widely used by herbalists, mainly for its effect upon the heart and for its stimulating, expectorant and diuretic properties[21]. The fresh bulb is slightly more active medicinally than the dried bulb, but it also contains a viscid acrid juice that can cause skin inflammations. This is a very poisonous plant and it should only be used under the supervision of a qualified practitioner. The dried bulb is cardiotonic, strongly diuretic, emetic when taken in large doses and expectorant.

CONCLUSION

Traditional medicine is “the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, used in the maintenance of health and in the prevention, diagnosis, improvement or treatment of physical and mental illness” (WHO). Among the various medicine specialties, herbal medications have become more prominent in cardiovascular medicine. The effects of the most promising compounds have undergone systematic evaluations, in some cases becoming historic cornerstones in the treatment of cardiovascular diseases. This is, for example, the case for digoxin and digitoxin, derived from *Digitalis lanata* and *Digitalis purpurea*. Although use of herbal medications for the treatment of cardiovascular diseases is not supported by scientific evidence, most of the herbs demonstrate an effect on biological mechanisms associated with cardiovascular diseases and hence is an effective way of treatment[22].

All the plants referred here consist of cardiac glycosides which when converted to a form of herbal formulation can effectively effect the functioning of heart. Since clinical studies on such drugs are limited the actual potential of various cardiac glycosides are to be found out. Physicians should improve their knowledge of herbal medications to adequately weigh the clinical implications related to their use, and be able to discuss with patients their possible benefits and side effects, and explain that natural does not always mean safe. Although medicinal plants are widely used and assumed to be safe, however, they can potentially be toxic. Where poisoning from medicinal plants has been reported, it usually has been due to misidentification of the plants in the form, in which they are sold, or incorrectly preparation and administration by inadequately trained personnel. There is a belief that herbs, as natural products, are inherently safe without side effects and that efficacy can be obtained over a wide range of doses. Although herbs may well have undesirable side effects, and since there are no set doses, herb–drug or herb–herb interactions are possible[23]. As both water and oxygen can kill in excessive amounts, the quantity is also an important consideration.

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