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Review

Sources and possible mechanisms of action of important phytoconstituents with cardiovascular properties

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Herbal medicines are being centrally focused since ages for the screening of newer and better treatment of health problems especially cardiac diseases. In the current manuscript, we have reviewed a number of important constituents of different herbs and plants, which belong to a wide range of families that affect the cardiovascular system by acting through one mechanism or the other as *Rauwolfia serpentine, Nigella sativa, Curcuma longa* and *Allium sativum*. However, there is an evidence for a considerable number of plants such as *Phaleria macrocarpa*, *Inula racemosa*, *Panax notoginseng* etc., that contain constituents affecting the cardiovascular system and can be beneficial for cardiac problems, but still need further investigation and pharmacological evaluation.

Key words: Cardiovascular, medicinal plants, hypertension, atherosclerosis, platelet aggregation.

INTRODUCTION

Over many centuries, cardiovascular diseases have appeared to be a great cause of mortality (Houston et al., 2009). Many diseases manifesting themselves in a different way actually underlie the cardiovascular problem. A lot of researches have been done round the world to sort out medication to prevent and cure cardiovascular diseases (Jouad et al., 2001). Of all, as megavitamins, neutraceuticals, minerals etc., the herbs and plants have played a major role in this regard (Frishman et al., 2005; Houston, 2005). Cardiovascular diseases such as hypertension, angina pectoris, myocardial infarction (Goyal et al., 2010), atherosclerosis, stroke, chronic venous insufficiency, coronary artery diseases (CAD) and arrhythmia are one of the leading causes of death (Houston et al., 2009). In this review article, we have reviewed a number of herbs whose constituents individually or in combinations, by acting through different mechanisms are able to combat the hazardous risks of heart diseases. These mechanisms include inhibiting angiotensin converting enzymes (Klaus et al., 1995) or activating cardiac muscarinic receptors, opening potassium channels or blocking calcium channels, scavenging reactive oxygen species (ROS) or inhibiting oxidation of low density lipoproteins (LDL), blocking platelet aggregation or preventing thrombosis formation etc (Valli et al., 2002). There are a number of plants on which the research is being carried out up to the level of elucidating the constituent responsible for its pharmacological actions and the mechanism of actions followed by the constituent, while still a large number of plants are in need of such depth.

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SOURCES OF IMPORTANT CARDIOACTIVE PHYTOCONSTITUENTS

Aesculus hippocastanum

Commonly known as horse chestnut or conker tree, it belongs to family Sapindaceae. The globular brown seeds of horse chestnut are being used traditionally in the treatment of haemorrhoids, malaria, respiratory diseases, varicose veins and chronic venous insufficiency (CVI) (Suter et al., 2006). The preparations available are made up of horse chestnut seed extract (HCSE), being used in different forms as dried seeds (250 to 300 mg b.i.d), fresh seeds (120 to 180 mg q.i.d), tincture (2 to 3

ml t.i.d) (Abascal and Yarnell, 2007), topical gel, enteric coated tablets (20 mg, 50 mg) (Carrasco and Vidrio, 2007). Main constituents of seeds are aesculin and aescin, acylated polyhydroxyoleanene oligoglycosides, aescins IIIb, IV, V**,** VII and isoescins Ia, Ib and V, triterpenoids, protoaescigenin, barringtogenol-C and flavons (Yoshikawa et al., 1998). Of all, the most important saponin and sapogenin are escin and geninescinol, respectively as both are hyaluronidase inhibitors with inhibitory concentration (IC_{50}) values of 149.9 µM for escin and 1.65 µM for geninescinol (Facino et al., 1995). The saponin aescin inhibits enzymes elastase and hyaluronidase thus, preventing enzymatic proteoglycan degradation combating CVI (Dickson et al., 2004).

Allium sativum

Known as garlic, it belongs to family Amaryllidaceae. It is known for its cardioprotective properties for milleniums (Fehri et al., 2011; Nencini et al., 2010; Ried et al., 2010) including vasorelaxant, antithrombotic and antiathe-rosclerotic by inhibiting platelet aggregation and plaque progression and by lowering cholestrol level in arterial cells (Koscielny et al., 1999; Orekhov et al., 1997). Seven dipeptides are found in allium extracts which are angiotensin converting enzyme (ACE)-inhibitors thus making it effective antihypertensive agent (Suetsuna et al., 1998). The compounds responsible for all these pharmacological activities are allicin, diallyl disulfide, alliin, ajoene and arginine. Anti platelet aggregation activity is found to be due to components of garlic oil, diallyl disulphide (DADS) and diallyl trisulphide (DATS).

Asclepias currasavica

Also known as ornamental milkweed, blood flower, Mexican butterfly weed or scarlet milkweed, it belongs to family Asclepiadaceae (Bendre et al., 2010). The cardenolides found in the plant are mostly present in the aerial parts of the plant (Warashina et al., 2008), 30% of which are found in leaves and latex of stems including labriformin, labriformidin, eriocarpin (Seiber et al., 1978) and the most prominent one is asclepain, possessing positive inotropic effect comparable to digitalis and strophanthin (Patnaik et al., 1978).

Burberis vulgaris

Known as European barberry or jaundice barberry or ambarbaris, it is a plant of family Berberidaceae. Different parts of this plant as fruit, bark, roots and leaves are being used as folk medicine since centuries (Imanshahidi and Hosseinzadeh, 2008) almost 2500 years. More or less 22 alkaloids of medical importance have been isolated from its different parts (Arayne et al., 2007) for example, berberine, berbamine, palmatine etc. Berberine is an isoquinone alkaloid isolated from bark and root of *B. vulgaris*. It has been reported for many pharmacological uses as in cardiovascular diseases including congestive heart failure, hypertension, arrythmias (Kang et al., 2002) and tachycardia. The dried fruit of *B. vulgaris* used as an extract of 1 g/day for 5 days can lower blood pressure. It exhibits its vasodilating activity by inhibiting ACE and releasing nitric oxide/cyclic Guanodine monophosphate (NO/cGMP) in vascular tissues (Kang et al., 2002). It opens the potassium channels activated by cell membrane depolarization (Fatehi et al., 2005). Some of its cardiovascular effects are based on its ability to activate cardiac muscarinic cholinergic receptors (M_2) (Salehi et al., 2009; Salehi et al., 2011).

Cinchona ledgeriana

C. *ledgeriana* is also known as quinine tree and belongs to family Rubiaceae. The alkaloids found in the plant material, different transformed roots and tissue culture cells are quinine and quinidine (Abdulrahman et al., 1991). For centuries, the plant has been used as an antimalarial agent remained under observation for its antiarrythmic properties as converting atrial flutter and fibrillation to sinus rhythm, combating supraventricular and ventricular arrythmias, increasing the excitability threshold, prolonging effective refractory period. The initial dose to prolong refractory period was determined to be 200 mg for five oral doses and 200 to 400 mg oral four times daily as maintenance dose (Dreifus and Morganroth, 1980). The use of quinidine as an antiarrhythmic has been limited since the development of new antiarrhythmic drugs (Cooper, 2007).

Commiphora mukul

C. mukul (guggul) an oleogumresin from mukul myrrh tree belongs to family Burseraceae. It has been used as a traditional medicine in India for the last 2000 years (Moore, 2003) to treat variety of diseases including rheumatism, atherosclerosis, hypercholestrolemia and lipid disorders. The soluble ethyl acetate extract of the plant has shown cardioprotective properties due to guggulsterones that increase uptake of LDL-cholestrol from blood by liver thus reducing concentration of LDL (Mahmood et al., 2010). Guggulsterone is an important constituent responsible to combat hyperlipidemia (Ojha et al., 2008) especially its stereoisomers E- and Z-guggulsterone. The two mechanisms responsible for its antihyperlipidemic effect are blocking of a bile acid receptor named farnesoid X receptor which is a regulator of cholesterol hemostasis (Miller et al., 2004) and other one is enhancing bile salt export pump (BSEP), an efflux transport that removes cholesterol metabolites and bile acids from liver (Deng, 2007). Guggulsterone taken 25

mg daily three times along with diet enriched in vegetables and fruits proved to improve heart health (Retzlaff et al., 2006). It has been reported to treat myocardial ischemia when used in combination with root powder of a folk medicine *Inula racemosa* by acting as beta receptor antagonist with negative inotropic and chronotropic properties (Lokhande et al., 2006).

Convallaria majalis

This is also known as lilly of the valley. *C. majalis* belongs to family Liliaceae (Daniel, 2006). It has been used for long as cardiotonic, diuretic and for circulatory insufficiency (Shubov et al., 1951). The cardiac glycol-sides present in it resemble digitalis and strophanthin in their action.

The cardenolides are mainly present in the herbal portion of plant (Berndt, 2005), predominantly in vacuoles (Loffelhardt et al., 1979). Almost 38 cardenolides have been found in it derived from 9 aglycones (Kopp and Kubelka, 1982) including convallatoxin, convallan, desglucocheirotoxol, periguloside, lokundjoside (in leaves, blossoms and seeds), cannogenol-3-o-alpha-L-rhamnoside cannogenol-3-o-beta-D-allomethyloside (Schenk et al., 1980) and sarmentogenin glycosides including rhodexin A and rhodexesid (Kubelka and Eichhorn, 1970).

Cratageus species

Crataegus species, commonly known as hawthorn belongs to family Rosaceae. Many plants of this species are being used since 4000 years to combat cardiovascular diseases. It acts as an antithrombotic by inhibiting thromboxane (TA_2) thus, inhibiting platelet adhesion (Arslan et al., 2011).

The important constituents present in these plants responsible for cardiovascular properties are flavonoids, proanthocyanidins, triterpene acids, procyanidins and organic acid (Miller et al., 2004). These are found mainly in the extracts of leaves and flowers of plants and are used to treat ischemia, congestive heart failure, arrhythmia, constriction and provide cardioprotective effects, (Veveris et al., 2004) especially WS1442 extract and LI132 extract. *Crataegus* special extract WS 1442 prevents angioplasty related restenosis by inhibiting platelet derived growth factor receptor-β (PDGFR) thus, reducing smooth muscle cell migration and proliferation (Furst et al., 2010). Quercitin, hyperoside and isoquercitin present in dried fruit of *Crataegus pinnatifida* are responsible for its vasodilating activity (Kwok et al., 2010). Vasoprotective activity can be achieved by 2% w/v hawthorn for 4 weeks. One of the most famous flavonoid in hawthorn used as an antiischemic is monoacetyl-vitexinrhamnoside (AVR), which is an inodilator (positive inotropic and vasodilator). It inhibits phosphodiesterase (PDE) and TA_2 synthesis while enhances prostacyclin (PGI_2) synthesis and endothelium derived relaxing factor (EDRF) stimulation (Schussler et al., 1995). Like many other plants of the hawthorn specie, the *C. oxyacantha* is found to treat different heart problems as high blood pressure, chest pain, rapid heartbeat and blocked arteries (Elango et al., 2009).

Curcuma longa

Commonly known as haridra or haldi, *C. longa* belongs to family Zingiberaceae. It is a renowned cardioprotective herb of ginger family (Aggarwal and Harikumar, 2009; Dwivedi, 2007). Main constituents are demethoxy curcumin, bisdemethoxy curcumin and most important the curcumin (diferuloylmethane), a yellow pigment present in the rhizome of *C. longa*. Medicinal properties of curcumin include anti-inflammatory, antiinfectious, antioxidant and antiischemic. It acts as an antihyperhomocysteinemic thus, helps combating after effects of increased homocysteine concentration as platelet activation, thrombosis formation and endothelial dysfunction. It acts as an antiatherosclerotic by inhibiting oxidation of LDL and increasing the excretion of cholestrol and bile acids (Wongcharoen and Phrommintikul, 2009) and appears to be a potent vasorelaxant (Xu et al., 2007) by blocking intracellular release of calcium from inositol-1,4,5- triphosphate sensitive stores and interacting with voltage gated channels to block influx of extracellular calcium (Adaramoye et al., 2009).

Cynara scolymus

This is known as artichoke commonly. *C. scolymus* belongs to family Asteraceae. Artichoke leaf extract (ALE) is found to be antihypercholestrolemic thus, acting as antiatherosclerotic (Kucukgergin et al., 2010; Wider et al., 2009). It contains antihyperlipidemic sesquiterpenes as cynaropicrin, aguerin B, grosheimin, cynarascolosides A, B and C (Shimoda et al., 2003). Artichoke juice containing cynarin, leuteolin and ferulic acid can reduce both systolic and diastolic blood pressure thus, preventing stroke and coronary heart disease (Roghani et al., 2009).

Digitalis lanata

D. lanata is known as Grecin foxglove or Wooly foxglove. It belongs to family Scrophulariaceae (Singh et al., 2006). It was used in 1785 for dropsy and other diseases. Recently in Denmark, different preparations were made from leaves of this plant and were used as powder in tinctures, infusions, tablets to test activity of cardiac

glycosides present in it (Norn et al., 2004; Oerther et al., 2011). It provided positive inotropic support by maintaining a balance of sodium and potassium ions inside the cells (Maureen et al., 2009). Methanolic extracts of the leaves contain many cardiac glycosides including primary glycosides as Lanatoside A, B and C (Ikeda et al., 1996) deacetyllanatoside C, secondary glycosides as digitoxin, gitoxin, digoxin, α-acetyl digitoxin, α-acetylgitoxin,α-acetyldigoxin, β-acetyldigitoxin and tertiary glycosides as digoxigenin-bis-digitoxoside and aglycones including digitoxigenin, gitoxigenin and digoxigenin (Pellati et al., 2009). Cardenolides (cardiac glycosides) are present in the vacuoles of mesophyll cells of *D. lanata* leaves as primary glycosides only while the secondary glycosides were biosynthetic intermediates or degradation products (Hoelz et al., 1992). Lanatoside C in the dose of 0.4 to 0.8 mg intravenously improved the condition of patients developing congestive heart failure while they were taking maintenance dose of 0.1 to 0.3 g of folia digitalis (Ray et al., 1945).

Digitalis purpurea

This commonly known as lady's glove, purple foxglove or common foxglove, it belongs to family Scrophulariaceae (Singh et al., 2006) and possess significant cardenolides. The amount of cardenolides digitoxigenin and gitoxigenin was found to be 11.34 and 240.59 mg/kg, respectively in 2 years old plant (Oerther et al., 2011; Usai et al., 2007) and gitoxin and digitoxin were estimated to be 0.1453 and 0.0820 mg, respectively per 100 g of dry leaf powder by micro-high performance liquid chromatography (MHPLC) analysis (Fujii et al., 1983). The extracts of gitoxin and its derivatives (digitalinum verum and stropeside) from its leaves showed positive inotropic and chronotropic effects at the dose range of 20 to 40 µg/ml. For clinical practice, the dose of digoxin was found to be very crucial as even the generally recognized therapeutic range of 0.5 to 2 ng/ml in blood increased the risk of death in patients so it needs great optimization as per year almost four million prescriptions are dispensed in UK (Po et al., 2003).

Gingko biloba

This is also known as maidenhair tree and it belongs to family Ginkgoaceae. The leaves of the plant is composed of terpenoids and flavonoids as ginkgolide-A and-B, bilobalide, quercetin, kaempferol, rutin and quercitrin (Trumbeckaite et al., 2007). Pharmacological effects of these components make the plant to act as an antioxidant, antiatherosclerotic by decreasing atherosclerotic non-plaque formation and size (Rodríguez et al., 2007), antiatherogenic by inducing endothelial hemeoxygeanase (HO)-1 expression and scavenging ROS (Chen et al., 2011), cardioprotective, vasorelaxant by inhibiting calcium influx through calcium channels and activating nitric oxide release in endothelium and aortic vessels (Mansour et al., 2011), anti platelet adhesive and anti thrombotic by acting as an antagonist of platelet activating factor (PAF) (Kim et al., 1998). *G. biloba* supplement should be taken with caution in elderly patients as it may cause bradycardia (Kubota et al., 2007).

Kaempferia galanga

K. galanga, commonly known as cekor (Chekor) belongs to family Zingiberaceae (Umar et al., 2011). Most vital constituents present in it are ethyl cinnamate, ethyl-p-methoxycinnamate and propanoic acid (Othman et al., 2006). Ethyl cinnamate isolated from its rhizomes exhibits profound vasorelaxant activity by inhibiting calcium influx into vasculare cells and releasing nitric oxide and prostaglandins from endothelial cells (Zakaria, 1994; Othman et al., 2002).

Monascus purpureus

A species of mold, *M. purpureus* also known as ang-khak rice mold, corn-silage mold, maize-silage mold, red yeast and rice-kernel discoloration belongs to family Monasaceae.

The main risk factor for CAD and peripheral artery disease is increased plasma cholestrol level (Cicero et al., 2005). Cholestin (red yeast rice) used in China and many other countries to treat hypercholesterolemia is prepared from *M. purpureus* fermented on rice (Wei et al., 2003). Cholestin is composed of starch (73.4%), protein (5.8%), fats (less than 2%), fatty acids (2 to 6%), palmitic acid, linoleic acid, oleic acid, stearic acid and monacolins, the most prominent of which is monacolin-K, used by name of mevinolin or lovastatin to inhibit atherosclerosis and hypercholesterolemia by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)-reductase (Li et al., 1998). Red mold rice extracts of this plant contains antihypertensive substances, gamma-amino butyric acid (GABA) and four ACE-inhibitory peptides.

These are Ile-Tyr, Val-Val-Tyr, Val-Phe and Val-Trp (Kuba et al., 2009). Four ACE-inhibitory peptides were isolated from soyabein protein hydrolysates, hydrolysed *by M. purpureus* acid proteinase, LAIPVNKP (IC50= 70 µM) and LPHF (670 µM) from β-conglysinin hydrolysate and SPYP (850 µM) and WL (65 µM) from glycinin hydrolysate (Kuba et al., 2005). *M. purpureus* titrated extract along with octacosanols and niacin have also been proved to lower total cholesterol (TC), LDL-cholesterol and triglycerides (TG) ultimately lowering the risk of cardiovascular diseases.

Nerium oleander

This is known as white oleander simply and it belongs to family Apocynaceae. The leaves of the plant are well known for its actions as cardiotonic especially in angina pectoris (Gayathri et al., 2011). Cardiotonic steroids, cardiac aglycones and glycosides are present in oleanders in many parts of the plant as roots, leaves, stems, twigs, formed from cardenolides and bufodienolides. They increase the intracellular calcium level via adenosine triphosphate (Na-K-ATPase) inhibition. Hydroalcoholic extract of *N. oleander* flowers and its fractions (glycosidic, nonglycosidic) have been proven to aid in cardioprotection. Crude ethanolic extract of dried uncrushed leaves containing glycosides as neriine and oleandrin are used to increase cardiac flow, heart rate, force of contraction in a way similar to digoxin. Roots of *N. oleander* have cardenolides procerragenin and neridienone with digitalis like activity. Methanolic extracts of stems and twigs contain cardenolides B-1,B-2 and oleagenin (Bai et al., 2010) and cardenolide monoglycosides as N-1,N-2,N-3 and N-4 (Zhao et al., 2007). Methanolic extracts of fresh leaves of plant contain central nervous system-depressant cardenolides as neridiginoside, nerizoside, nertaloside and odoroside-H (Siddiqui et al., 1997).

Nigella sativa

This is commonly known as black cumin, black caraway and kalonji. *N. sativa* belongs to family Ranunculaceae. It has been used traditionally as a medicinal plant since 2000 years (Salem et al., 2005). Its seeds consist of eight essential amino acids and bioactive alkaloids as nigellamine and nigelline (Mehta et al., 2009) while its volatile oil is composed of thymoquinone (2.1%) (Tahraoui et al., 2007), cymene P (4.5%), thujene α (7.8%), pinene β (2.9%), carvacrol (2.2%), terpinene α (1.7%), limonene (2.9%), campholenol α (9.8%) and terpinene G (13%). It is being used to cure a number of diseases including asthma, obesity, dyslipidemia, hypertension (Qidwai et al., 2009), cough, bronchitis, headache, eczema, dizziness, gastrointestinal disturbances, atherosclerosis, fever and influenza. Thymoquinone has been found to be effective as antibacterial, diuretic, immunopotentiator, antiparasitic, antitumor, antibiotic, antifungal, anti-inflammatory, hypoglycemic, hypocholestrolemic, antioxidant (Ebru and Burak, 2008), carminative, lactagogue and antinematode. It is an eicosanoid inhibitor that contributes to its cardioprotective effects (Tousson et al., 2011). It relaxes pulmonary artery by activating potassium channels of the heart (Shafei et al., 2005). It decreases both systolic and diastolic blood pressure in a dose dependent manner (Dehkordi and Kamkhah, 2008) by blocking serotonin, alpha-1 and endothelin receptors (Suddek et al., 2010). It has positive inotropic effect and can cause beneficial cardiac hypertrophy (El-Bahai et al., 2009).

Olea europeae

This is also known as olive. It belongs to family Oleaceae. The olive oil, olive extract and most of all olive leaf extract (OLE) is known for its cardiovascular effects since long. The bitter component of leaf, oleuropein, which gets metabolized to calcium elenolate in the body, is found to be responsible for its pharmacological actions as antiarrhythmic, coronary vasodilator and antihypertensive by involving a number of mechanisms as inhibiting ACE, blocking calcium channels and acting as an antioxidant (Khayyal et al., 2002; Susalit et al., 2011). Its antioxidant, anti-inflammatory (inhibiting transcription of proinflammatory genes) as well as antihyperlipidemic properties (Jemai et al., 2008; Singh et al., 2008) make it worthy to be used as an antiatherosclerotic (Wang et al., 2008) as it decreases the blood lipid content and scavenges ROS and thus prevents free radical generation and oxidation of LDL.

Panax ginseng

This belongs to family Araliaceae. It has been used as a tonic in oriental medicine since 2000 years (Jeon et al., 2000). So far, more than 200 substances have been isolated from it including ginesosides, polyacetylenes, flavonoids, lipids and saponins (Rf) (Persson et al., 2006). Almost 30 ginesosides have been isolated from roots and leaves of *P. ginseng* which are the most active substances biologically for example, Rb1 (Jin-Young et al., 2010), Rg3 and Rh2. Pharmacological activities of *P. ginseng* include antiplatelet adhesion, anticoagulant (Jin et al., 2007; Yun et al., 2001), antihypertensive by inhibiting ACE-activity (Persson et al. 2006), antidiabetic, anticancer, antihyperlipidemic (Ji and Gong, 2007), relieves congestive heart failure (Ding et al. 1995), antioxidant and anti-inflammatory (Kim and Lee, 2010). Rb1 is a potent antihomocysteine thus, acting as an antiatherosclerotic and alleviates cardiac hypertrophy (Ahn et al., 2011). Korean red ginseng (KRG), a steamed variety of *P. ginseng* improves arterial stiffness. Rg and Re ginesosides from protopanaxatriol group enhance nitric oxide (NO)-release from endothelial cells.

Phyllanthus emblica

This is known as amla or Indian gooseberry, (syn. *Emblica officinalis gaertn*.) and belongs to family Euphorbiaceae (Asouti and Fuller, 2008). Fresh juice of fruit of amla containing emblicanin A, B, punigluconin, pedunculagin is found to be cardioprotective by acting as an antioxidant (Bhattacharya et al., 2002). It can also reduce total LDL-cholestrol level thus, preventing

atherosclerosis (Kim et al., 2005).

Rauwolfia serpentina

It is an Indian plant with common name Indian snakeroot or sarpagandha of family Apocynaceae, known for many pharmacological properties, the most prominent being an antihypertensive. It contains as many as 20 alkaloids divided into two classes further as (1) ajmaline group and (2) reserpine group. Ajmalin group alkaloids proved effective for the treatment of cardiac arrythmias secondary to acute ischemia due to digitalis toxicity (Bazika et al., 1966) and Wolf-Parkinson –White Syndrome (Obayashi et al., 1976). Roxinil is an extract of *R. serpentina* that contains multiple alkaloids and has been proven to be an effective agent to treat hypertensive patients (Moyer et al., 1955).

Ruscus aculeatus

R. aculeatus also known as butcher's broom, sweet broom, box holly and Jew's myrtle, belongs to family Liliaceae (Singh et al., 2006). Its constituents include glycolic acid, ruscogenin, non-ruscogenin, flavonoids (Redman et al., 2000), euparone and chrysophanic acid. It is being used medicinally since 2000 years as an anti-inflammatory, vasoconstrictor and tonicizer. Dried rhizome is the part of plant mostly used as laxative, diuretic, for jaundice, headache, edema of ankles, itching and tension.

Roasted root has been used for prostate cancer in South America (Abascal and Yarnell, 2007). It is considered to be the treatment of choice for CVI by activating postsynaptically the (alpha) α_1 and α_2 receptors of vein wall producing venous constriction and increasing activity of presynaptic norepinephrine (NE) released at nerve endings resulting in enhanced venous tone (Parrado et al., 1999) mostly in combination with hesperidin, methylchalcone and ascorbic acid (Cappelli et al., 1988). Dose of the tincture recommended is in the range of 2 to 3 ml t.i.d.

It combats orthostatic hypotension by acting as a direct alpha adrenergic vasoconstrictor. Flavonoids in *R. aculeatus* maintain healthy circulation by reducing capillary fragility (Redman et al., 2000). The anti elastase activity of ruscogenis is found to be IC_{50}=119.9 µM (Facino et al., 1995).

Salvia miltiorrhiza

This is commonly known as danshen, tanshen or red rage. It belongs to family Lamiaceae (Wu et al., 2005). Medicinally, it covers a wide range of diseases as liver fibrosis, cirrhosis, central nervous system diseases (Yuan et al., 2008), hypertension, angina pectoris, myocardial infarction, stroke, ischemia, hyperlipidemia, hepatitis, miscarriage, diabetes, arrhythmia and myocardial ischemic injury (Wang et al., 2003). Almost 50 compounds have been isolated from danshen and divided into two categories as water insoluble and water soluble (Bi and Zuo, 2008). Water insoluble 30 diterpene quinine analogues include tanshinone-1, isotanshinone-2, dihydrotanshinone, tanshinone-2A, tanshinone-2B, methyltanshinone, cryptotanshinone, isocryptotanshinones-1 and -2, while 15 water soluble phenolic acid derivatives include danshensu (salvianic acid A), protocatechuic acid, protocatechuic aldehyde, rosmarinic acid and salvianolic acids A, B and C. The most important is triterpenoid tanshinone 2A, which is effective as cardioprotective, anticancer, antiosteoporotic, cytotoxic, antiatherosclerotic and antioxidant. Danshen in combination with *Pueraria lobata* (gegen), D&G, treats high blood pressure, underlying atherogenic processes thus, preventing atherosclerotic related disorders and inhibits macrophage/foam cell transformation in fat fed monocytes.

It reduces high blood pressure by inhibiting angiotensin converting enzyme (Kang et al., 2002). It inhibits angiotensin-II induced plasminogen activator inhibitor (PAI)-1 mRNA, protein expression and cellular ROS and inhibits transformation growth factor (TGF)-β_1 secretion. It has biphasic effect on low concentration acting as vasoconstrictor but in high concentration, it acts as a vasodilator by inhibiting extracellular calcium influx and activating non-selective potassium channels in messengial cells (Zhang et al., 2010). Lyophilized salvia salt of lithospermic acid (SSLA) powder for injection extracted from *S. miltiorrhiza* is effective to treat angina pectoris.

Stephania tetrandra

S. tetrandra belongs to family Menispermaceae. It has many pharmacological actions including antithrombotic, antifibrogenic, antiallergic, antiinflammatory (Xue et al., 2008), antihypertensive, anticoagulant, antioxidant (Pinelli et al., 2010), antiinfarction, antiarthritis and antisilicosis. Components of *S. tetrandra* include fangchinoline, cyclanoline and the most bioactive component is tetrandrine, a bis-benzylisoquinoline alkaloid (Kwan et al., 1999). Its actions are dual in nature as acting directly on smooth muscles as a vasodilator and indirectly as vasoconstrictor by inhibiting NO production by endothelial cells and thus, blocking calcium release activated calcium channels as a Ca^{2+} antagonist (Wong et al., 2000).

Stevia rebaudiana

This is commonly known as sweet leaf, sugar leaf or stevia. It belongs to family Compositae (asteraceae) (Deshpande, 2010). Isosteviol is a derivative of stevioside (sweet glycoside) which is the main component of stevia

leaves responsible for its cardioprotective properties (Xu et al., 2007), especially vasodilating effect (Chan et al., 1998; Melis, 1992) exerted by inhibiting calcium influx and opening adenosine triphosphate-sensitive potassium channels (K_{ATP}) and calcium-sensitive-small conductance potassium channels (SK_{Ca}) (Wong et al., 2004). It acts as an antiproliferative by combating proliferation of vascular smooth muscles by attenuating angiotensin-II-induced ROS synthesis and suppressing extracellular-signal regulated kinase (ERK) (Kar-Lok et al., 2006).

Strophanthus gratus

Strophanthus of family Apocynaceae is a genus of 35 to 40 species of plants known for possessing cardenolides with varying morphology (Kawaguchi et al., 1993; Oerther et al., 2011). Cardenolides have been identified from many of its species. These species include *S. eminii, S. hypoleucus, S. nicholsonii, S. hispidus, S. kombe, S. preussii, S. gerrardii, S. courmontii, S. intermedius, S. amboensis, S. gratus, S. speciosus, S. walwitschii, S. petersianus, S. grandiflorus, S. sarmentosus, S. scu-chardtii* and the glycosides discovered include strophanthidin, strophanthidol, periplogenin, cymarin, emicymarin, sarmentogenin, cymarol, panstroside, pastroside, sarverogenin, intermedioside and ouabain. Pollens of *S. gratus* are the source of cardenolides (Berndt, 2005).

Terminalia arjuna

T. arjuna belongs to family Combretaceae and is commonly known as hridya or neer maruthu. Tree bark powder is composed of flavonoids, tannins (Dwivedi, 2007), minerals, oleanane triterpenoids (arjunolic acid), arjunic acid, glycosides (arjunetin arjunosides I,II,III,IV), gallic acid, ellagic acid, oligomeric proanthocyanidins and phytosterols (Oberoi et al., 2011). Flavonoids possess pharmacologic actions as antioxidant, anti-inflammatory, antihyperlipidemic and antihypercholestrolemic while glycosides especially butanolic fractions of bark are cardioprotective by acting as antioxidant against ischemic reperfusion injury.

It is a known cardiotonic. It shows positive inotropic effects by causing increased release of noradrenaline from sympathetic nerve endings in arterial muscles. It acts as a hypotensive by stimulating adrenergic β_2 receptors or directly acting on heart muscles. It is proved to be beneficial in congestive heart failure. It increases coronary flow by increasing prostaglandin E_2 (PGE_2) and thus, is beneficial in CAD patients (Dwivedi and Agarwal, 1994; Dwivedi and Jauhari, 1997). It acts as an antithrombotic especially in CAD patients by inhibiting phosphoinositol-phospholipase-C and thus, inhibiting diacylglycerol and inositol triphosphate formation thus, inhibiting aggregation of platelets.

Undaria pinnatifida

This is edible brown seaweed commonly known as wakame belonging to family Alariaceae and is considered to be effective as an antihypertensive since ancient times. Alginate, a water soluble fibre of wakame, 10 dipeptides (Suetsuna et al., 2004), hydrolysates with IC_{50}= 86 µg protein/ml (Sato et al., 2002) and four tetrapeptides containing tyrosine have been reported to possess potent ACE-inhibitory activities contributing to its antihypertensive properties.

Veratrum album

This is commonly known as white hellebore. *V. album* belongs to family Melanthiaceae. All veratrum alkaloids are known to be effective as hypotensive agents (Aguado, 1957; Atta et al., 1993; Brunner et al., 1955) especially protoveratrine causing vasodilation (Currens et al., 1953).

Miscellaneous

There are some plants and herbs for which some work has been done to identify their pharmacological properties regarding cardiovascular system but they still need a lot. These plants include *Aloe vera* (Kumar et al., 2011), *Appocyanum cannabinum* (Desruelles et al., 1973), *Prunus armeniaca* (Parlakpinar et al., 2009), *Asclepias fruticosa* (Warashina et al., 1994), *Calotropis precera* (Frishman et al., 2005), *Cryptostegia grandiflora* (Kamel et al., 2001), *Mistletoe*, (Ye et al., 2009) *parsley* (Gadi et al., 2009), *Rosmarinus officinalis* (Tahraoui et al., 2007), *Selenicereus grandiflorus* and *Urgenia maritime* (Frishman et al., 2005), *Adonis microcarpa* (Frishman et al., 2009), *Commiphora oppobalsamum* (Abdul-Ghani and Amin, 1997), *Helleborus viridus* (Frishman et al., 2009), *Inula racemosa* (Lokhande et al., 2006), *Monascus ruber* (Rhyu et al., 2000), *Mahkota dewa* (Kim et al., 2010; Kurnia et al., 2008; Tjandrawinata et al,. 2010; Yan et al., 2006), *Bufo marinus* (Frishman et al., 2004), *Uncaria rhynchophylla* and *Panax notoginseng* (Frishman et al., 2004), *Banaba* leaves (Yamaguchi et al., 2006), *Capsicum annum* (Wu et al., 1996) and *Chrysanthemum* (Hui et al., 2005).

CONCLUSION

Medication for cardiovascular diseases still needs exploration and research at a larger level. Structures of important phytoconstituents with their specific pharmacological effect are shown in Table 1. A number of medicines originated from different medicinal herbs are already being utilized in the market to cure and alleviate certain cardiovascular problems. These include *Digitalis, B. vulgaris, S. miltiorrhiza, C. mukul, A. hippocastanum,*

Table 1. Important phytoconstituents with cardiovascular activity.

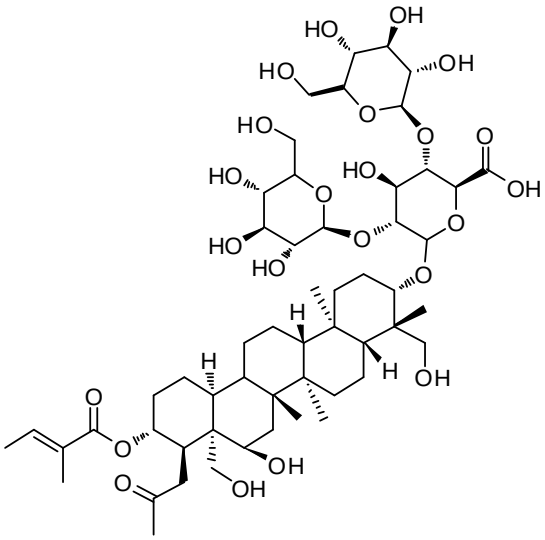
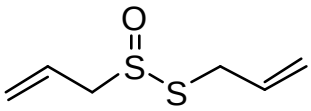
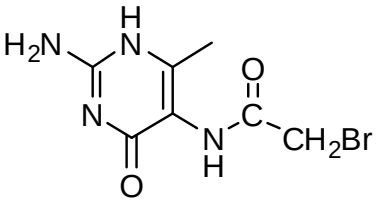
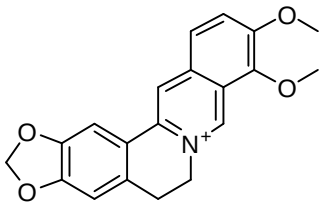
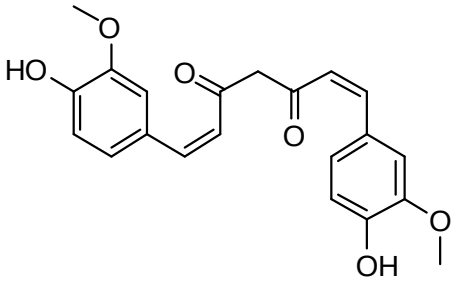
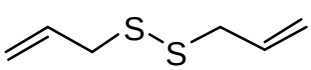
Name	Structure	Cardioavascular activity
Aescin		Inhibits enzymes elastase and hyaluronidase thus prevents enzymatic proteoglycan degradation combating CVI (Dickson et al., 2004).
Allicin		Vasorelaxant, antithrombotic and antiatherosclerotic (Suetsuna et al., 1998).
Asclepain		Positive inotropic (Patnaik etal., 1978).
Berberine		Vasodilator,activates potassium channels, activates scardiac (M_2) muscarinic receptors (Fatehi et al., 2005; Kang et al., 2002; Salehi et al., 2009).
Curcumin		Antihyperhomocysteinemic, a potent vasorelaxant (Wongch et al., 2009; Xu et al. 2007)
Diallyl disulphide		Anti platelet aggregator (Koscielny et al., 1999; Orekhov et al., 1997).

Table 1. Contd.

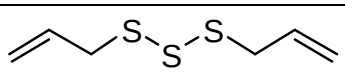
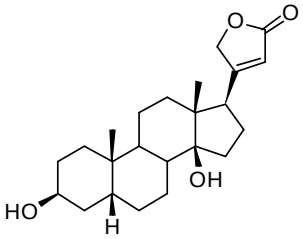
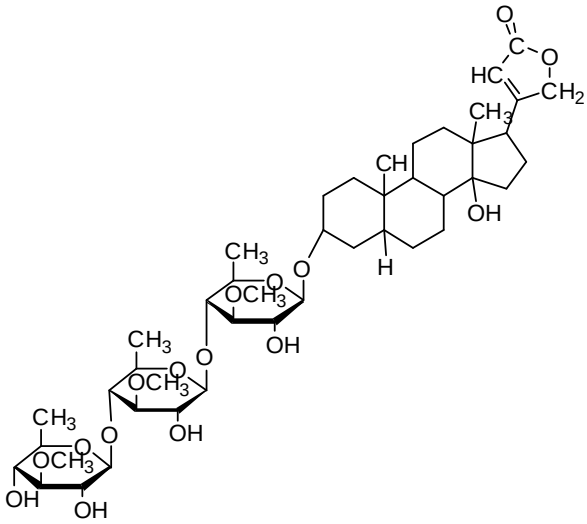
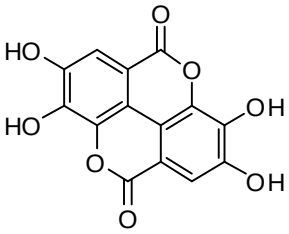
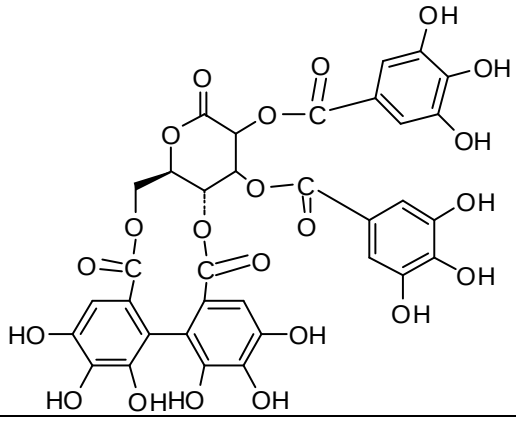
Diallyl trisulphide		Anti platelet aggregator (Koscielny et al., 1999; Orekhov et al).
Digitoxigenin		Positive inotropic support by maintaining a balance of sodium and potassium ions inside the cells (Maureen et al., 2009).
Digitoxin		Positive inotropic support by maintaining a balance of sodium and potassium ions inside the cells (Maureen et al., 2009).
Ellagic acid		ACE-inhibitor, thus antihypertensive (Dwivedi and Agarwal, 1994; Dwivedi and Jauhari, 1997).
Emblicanin A		Cardioprotective by acting as an antioxidant, anti atherosclerotic (Bhattacharya et al, 2002; Kim et al., 2005).

Table 1. Contd.

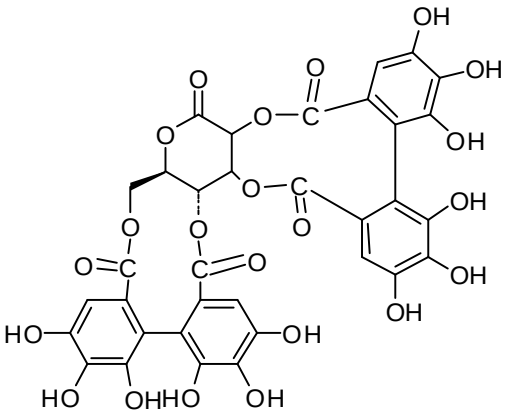
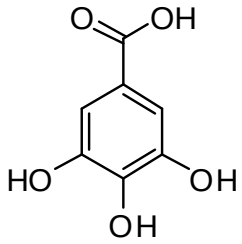
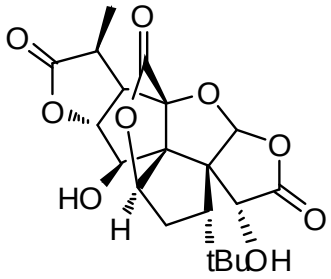
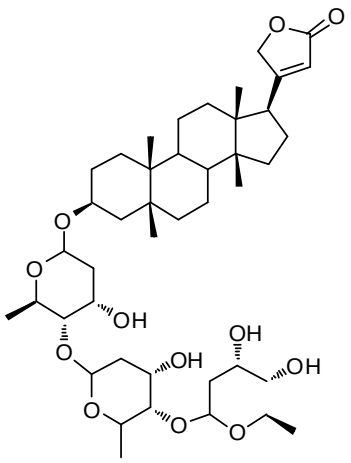
Emblicanin B		Cardioprotective by acting as an antioxidant, anti atherosclerotic (Bhattacharya et al., 2002; Kim et al., 2005).
Gallic acid		Positive inotropic, hypotensive,antithrombotic, inhibits aggregation of platelets (Dwivedi and Agarwal,1994; Dwivedi and Jauhari,1997).
Ginkgolide B		Antiatherosclerotic, antiatherogenic, vasorelaxant, anti platelet adhesive and anti thrombotic (Chen et al., 2011; Kim et al., 1998; Mansour et al., 2011).
Gitoxin		positive inotropic and chronotropic (Usai et al., 2007).

Table 1. Contd.

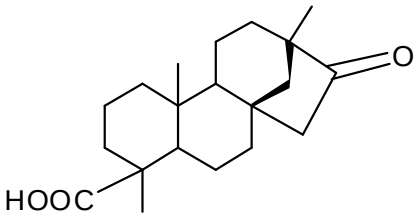
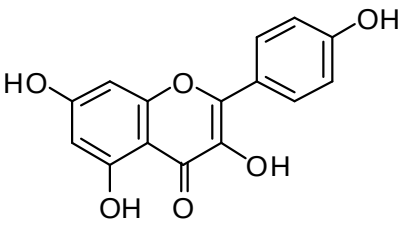
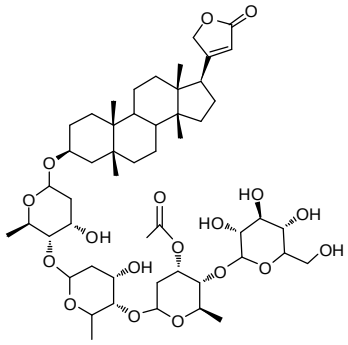
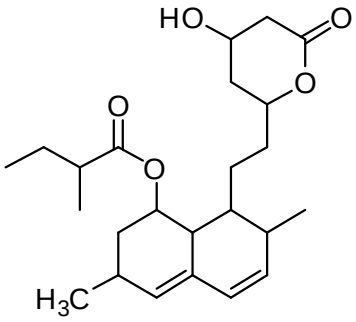
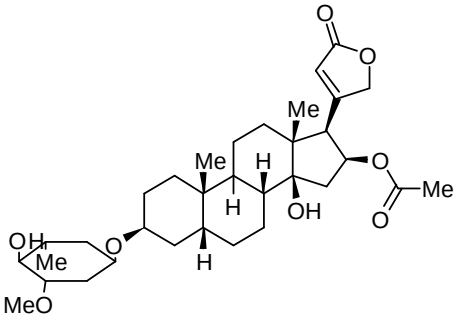
Isosteviol		Vasodilator, antiproliferative (Chan et al., 1998; Kar-Lok et al., 2006; Melis, 1992).
Kaempferol		Antiatherosclerotic, antiatherogenic, vasorelaxant, anti platelet adhesive and anti thrombotic (Chen et al., 2011; Kim et al., 1998; Mansour et al., 2011).
Lanatoside A		Positive inotropic support by maintaining a balance of sodium and potassium ions inside the cells (Maureen et al., 2009 ; Ray et al., 1945).
Monacolin-K		Inhibit atherosclerosis and hypercholesterolemia (Li et al., 1998).
Oleandrin		Increases cardiac flow, heart rate, force of contraction of heart (Gayathri et al., 2011).

Table 1. Contd.

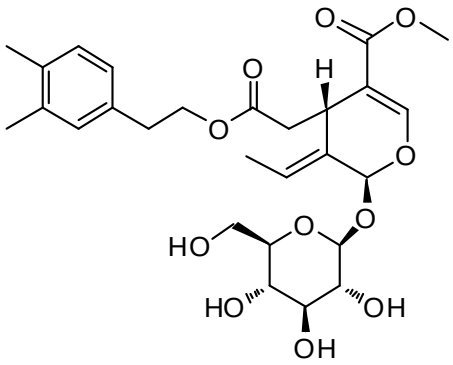
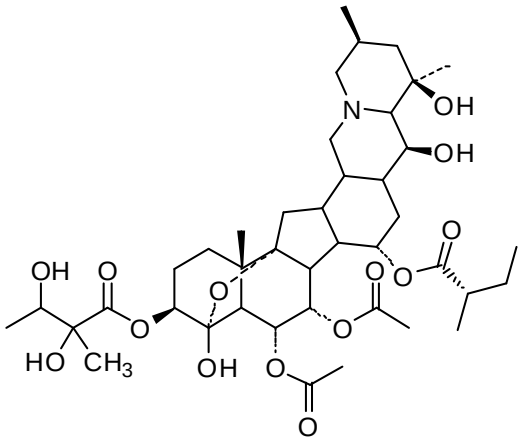
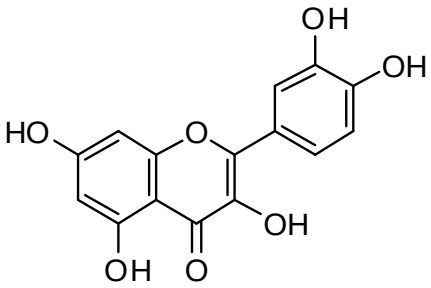
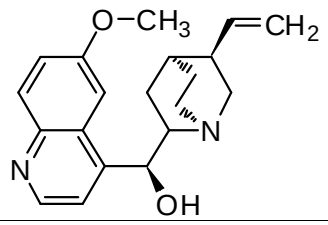
Oleuropein		ACE-inhibitor, antioxidant, antiatherosclerotic (Jemai et al., 2008; Khayyal et al. 2002, Susalit et al., 2011; Wang et al., 2008).
Protoveratrine A and B		Vasodilator (Currens et al., 1953).
Quercetin		Antiatherosclerotic, antiatherogenic, vasorelaxant, anti platelet adhesive and anti thrombotic (Chen et al., 2011; Kim et al., 1998; Mansour et al., 2011).
Quinidine		antiarrythmic , increasing the excitability threshold, prolongs effective refractory period (Dreifus and Morganroth, 1980).

Table 1. Contd.

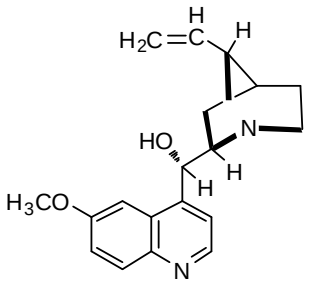
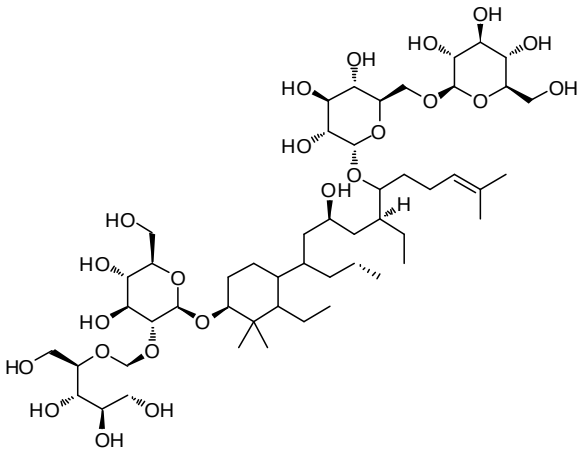
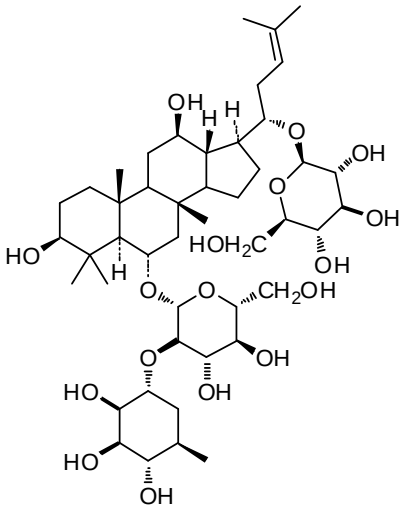
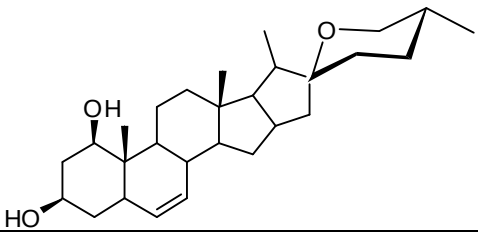
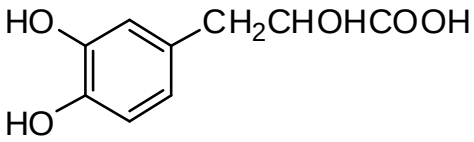
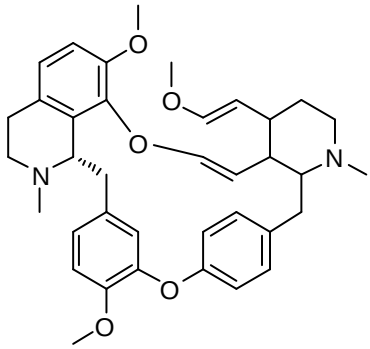
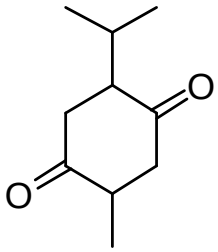
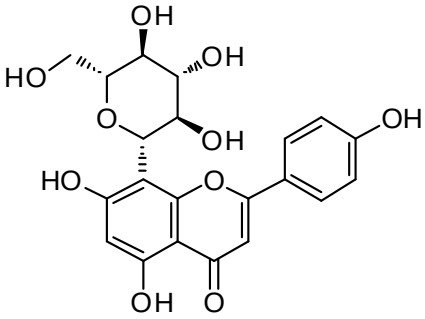
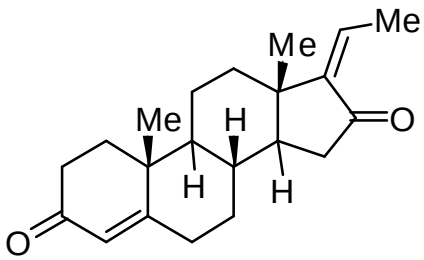
Quinine		antiarrythmic , increasing the excitability threshold, prolongs effective refractory period (Dreifus and Morganroth, 1980).
Rb1 ginesosides		A potent antihomocysteine thus an antiatherosclerotic and alleviates cardiac hypertrophy (Ahn et al., 2011).
Re ginesosides		Enhances nitric oxide (NO)-release from endothelial cells (Persson et al., 2006).
Ruscogenin		Enhances venous tone. direct alpha adrenergic vasoconstrictor (Parrado et al., 1999).

Table 1. Contd.

Salvianic acid A		Prevents atherosclerotic related disorders. biphasic effect, on low concentration as vasoconstrictor, in high concentration as vasodilator (Kang et al., 2002; Zhang et al., 2010)
Tetrandrine		Acts directly on smooth muscles as a vasodilator and indirectly as vasoconstrictor as a Ca^{2+} antagonist (Wong et al., 2000).
Thymoquinone		An eicosanoid inhibitor, cardioprotective. activates potassium channels of the heart. decreases both systolic and diastolic blood pressure , positive inotropic (Dehkordi and Kamkhah, 2008; El-Bahai et al., 2009; Shafei et al., 2005; Tousson et al., 2011).
Vitexin rhamnoside		Antiischemic, an inodilator (positive inotropic and vasodilator) (Kwok et al., 2010; Schussler et al., 1995).
Z-guggulsterone		Antihyperlipidemic (Ojha et al., 2008).

The structural drawings are based on ChemBioDraw version 12.0.

N. sativa, *R. aculeatus* and *M. purpureus* whose specific doses are being determined to combat different heart problems, but huge number of plants are spread worldwide which have been recognized to be beneficial for cardiovascular diseases but their doses and mechanisms of action need attention of researchers for example, *P.*

macrocarpa, I. racemosa, Banaba leaves*, C. precera* etc.

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