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Cardioprotective Potential of Plant-Derived Molecules: A Scientific and Medicinal Approach

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Abstract

Since the beginning of human civilization, plants have been used in alleviating the human distress and it was recorded for about thousands of years ago that the plants are being used for medicinal purposes. Natural bioactive compounds called phytochemicals are obtained from medicinal plants, vegetables, and fruits, which functions to combat against various ailments. There is dire need to explore the plant biodiversity for its medicinal and pharmacological potentials. Different databases such as Google scholar, Medline, PubMed, and the Directory of Open Access Journals were searched to find the articles describing the cardioprotective function of medicinal plants. Various substances from a variety of plant species are used for the treatment of cardiovascular abnormalities. The cardioprotective plants contain a variety of bioactive compounds, including diosgenin, isoflavones, sulforaphane, carotinized, catechin, and quercetin, have been proved to enhance cardioprotection, hence reducing the risk of cardiac abnormalities. The present review article provides the data on the use of medicinal plants particularly against cardiac diseases and to explore the molecules/phytoconstituents as plant secondary metabolites for their cardioprotective potential.

Keywords

cardioprotection, phytochemicals, cardiotoxicity, phytotherapeutic

Introduction

Heart attack, also called myocardial infarction (MI), and related complications are the main causes of deaths throughout the world.[1] The use of herbal antioxidants is increasing as defensive agents against number of cardiovascular abnormalities. The bioactive agents from natural sources have gained fundamental importance in modern system of medicines, reducing the risks of cardiac ailments by scavenging the free radicals formation.[2] Herbal medicines play considerable role in health care to a large proportion of world's population and have been regarded as component of cultural heritage of various tribes. Polyphenols perform cardioprotective activity by inhibiting the oxidation of low-density lipoprotein.[3] Most of the pharmacologically important drugs are derived from plants. Plant derivatives as drugs play significant role in health-care systems around the globe for animals and humans. They not only used for the management of disease condition but also to maintain proper health. Since long, medicinal plants have been used for the treatment of ischemic heart diseases. Accumulation of phytochemical, biological, and clinical data during past decade of 20th century revealed that plant-based herbal remedies are the emerging choice for the treatment of various ailments. Medicinal plants such *Daucus carota* Linn, *Nerium oleander (NO)* Linn, *Amaranthus viridis*, *Ginkgo biloba*, *Terminalia arjuna*, *Tinospora cordifolia*, *Hydrocotyle asiatica* Linn, *Mucuna pruriens*, and *Cichorium intybus* are known to have cardioprotective potential. Large number of important phytochemicals has been identified from plant sources by the scientists. This review article provides useful information for

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researchers and clinicians using natural products as therapy for clinical management of cardiovascular abnormalities, leading to the development of more efficient therapeutic drugs. For example, *Digitalis lanata* is one of the oldest medicinal plants widely used for the treatment of cardiac diseases and the most active constituent present in it is a steroid glycoside called digoxin. Digoxin was also found to be used for the treatment of arrhythmia.[4] Another plant *Atropa belladonna* contains atropine, which is being used for slow heart rate (bradycardia).[5] Most of the widely used modern medicines for the treatment of cardiovascular abnormalities have side effects and there is dire need to search for alternative therapies with fewer or no side effects.

Plants are pivotal source of traditional medicines being used in treating different ailments. About 4 22 000 flowering plants have been reported all over the world, out of which above 50 000 plants are of medicinal importance that are being used for pharmaceutical purposes.[6] About 80% of worldwide populations rely on traditional medicines for primary health-care needs.[7] Remedies of medicinal plants are most often being used as an alternative to allopathic medicines. Pakistan is blessed with an exceptional biodiversity expanded along the 9 major ecological zones. The major parts of the country are fairly rich in medicinal herbs because of its healthy atmosphere.[8] So far, in Pakistan about 6000 plant species have been reported with documented ethnomedicinal knowledge of only 600 plant species. There is a tremendous demand to safeguard the precious traditional knowledge of medicinally important plants. Preservation and promotion of indigenous knowledge about medicinally important plants leads to the discovery of new drugs in addition to rescuing the global traditional medicinal systems.[6]

Medicinal Plants With Cardioprotective Potential

Medicinal plants are used to prepare many drugs, but the phytochemical compounds present on original plant material are more efficient with less side effects than their pharmaceutical derivatives. Variety of plants and their bioactive phytoconstituents are well known for their minimal side effects, providing alternative therapeutic potential against cardiac diseases. Some of the plants having cardioprotective molecules/agents are given below, and the plants having cardioprotective potential against cardiotoxicity induced by various agents are given in Table 1.

Daucus carota

Daucus carota is a white-flowering herb belongs to Apiaceae plant family and is generally recognized as wild carrot. This plant is native to temperate regions of Southeast Asia and Europe. Parts used for medicinal preparations are roots and seeds. The phytochemicals present in this plant include daucosol, xanthophylls, carotene, sesquiterpenoids, and daucoside.[45,46] Muralidharan et al[47] studied the cardioprotective potential of *D carota* Linn's aqueous extract in isoproterenol-induced MI in rats. They studied the cardioprotection by determining the activity of cardiac enzymes like transaminases, lipid peroxidases, cardiac protein, and lactate dehydrogenase (LDH).

Nerium oleander

Nerium oleander (*NO*) from Apocynaceaefamily is an ever green shrub that grows primarily in the Easter Mediterranean regions, northern America, and Anatolia. By boosting antioxidant components against oxidative stress, *NO* concentrate has been experimentally shown to serve as a cardioprotective agent.[48] Parts used for pharmaceutical preparations are leaves, flowers, roots, and root bark. Phytochemicals present in this plant includes tannic acid, oleanolic acid, uzarigenin, neriodorein, oleandrose, karabin, neriodin, nerium D, nerium F, oleanolic acid, digitoxigenin, gitoxigenin, neriantin, odoroside, adyresin, ursolic acid, oleandrin, scopolin, scopoletin, oleandrigenin, 16-acetyl gitoxigenin, deacetyloleandrin, and dambonitol.[49] Gayathri et al[50] studied the cardioprotective potential of *NO* flowers in rats using isoproterenol for the induction of myocardial oxidative stress and found good cardioprotective activity of this plant.

Amaranthus viridis

Amaranthus viridis Linn is commonly known as slender amaranth in English while it was called as never fading flower in Greek. It is an annual herb.[51,52] Various parts such as leaves, roots, and whole plants are used for pharmacological purpose. Active phytoconstituents are quercetin and rutin.[53] This plant also contains variety of amino acids, including leucine, lysine, isoleucine, arginine, cystine, histidine, valine, phenylalanine, methionine, threonine, tryptophan, and tyrosine.[54] Various studies reported the cardioprotective potential of *A viridis* Linn in rats. In a study conducted by Saravanan et al[55] to evaluate the cardioprotective potential of this plant using isoproterenol to induce MI at a dose concentration of 20 mg/kg body weight subcutaneously for 2 consecutive days. They observed significant variation in cardiac enzymes. *Amaranthus viridis* was orally administered at dose concentrations of 100, 200, and 300 mg/kg body weight for 45 days. Lower levels of cardiac enzymes were observed in plant-treated groups of rats, showing its cardioprotective activity. *Amaranthus viridis* was found more effective at a dose of 300 mg/kg body weight.[55]

Ginkgo biloba

Ginkgo biloba L belongs to Ginkgoaceae plant family. This plant is also known as "living fossils" because of its existence among the oldest seed plants. It contains Ginkgolides, flavones glycosides, flavonol, ascorbic acid, diterpen lactones, catechin, sesquiterpenes, and iron-based superoxide dismutase. Variety of biological activities of this plant have been reported, including antioxidants, antimicrobial, anti-inflammatory, memory enhancer, hepatoprotective, antidepressant, anticoagulant, antiulcer, cytotoxic, antiaging, and antistress activities. This plant

Table 1. Reported Cardioprotective Activities of Medicinal Plants Against Cardiotoxicity Produced by Various Agents.

Common Name	Plant Names	Family	Parts Used	Dosage Form	Chemical Constituents	Actions	References
Against isoproterenol-induced cardiotoxity							
Fountain tree, African tulip tree, pichkari or nandi flame	*Spathodea campanulata*	Bignoniaceae	Bark	Ethanol extract	Saponin, flavonoids, steroid, alkaloids, glycoside, tannin, phenol, phlobatanin, terpenoids, and anthraquinone	Antimalarial, anti-HIV, hypoglycemic, cardioprotective	9
Garlic	*Allium sativum*	Liliaceae	Bulb	Garlic oil	Alkaloids, flavonoids, tannins, saponins, and cardiac glycosides	Antimicrobial, antihyperlipidemic, and cardioprotective	10
Hairy fig	*Ficus hispida*	Moraceae	Leaves	Methanol	Alkaloids, terpenes, saponins, glycosides, mucilage, gums, flavonoids, phenols, sterols, amino acids, β-amyrine acetate, protein, carbohydrates, n-triacontanol, lupeol acetate, β-sitosterol, gluanol, and β-amyrin	Cardioprotective, antipyretic, hepatoprotective, anti-inflammatory	11
Kerala ginseng, ginseng of Kani tribes	*Trichopus zeylanicus*	Trichpodaceae	Leaves	Ethanol	Alkaloids, glycosides, flavonoids, steroids, tannins, steroids, terpenoids	Cardioprotective, adoptogenic, aphrodisiac	12
Gokhru, kharkhask, caltrop	*Tribulus terrestris*	Zygophyllaceae	Fruit	Aqueous	Flavonol, flavonoids, alkaloids, glycosides, and steroidal saponins	Cardioprotective, antilithiatic, diuretic, hypouricemic, anti-inflammatory, aphrodisiac	13,14
Baladur, billar, bhilavan	*Semecarpus anacardium*	Anacardiaceae	Dried nuts	Ethanol	Bhilwanols, phenolic compounds, biflavonoids, sterols, glycosides, ursuhenol, anacardoside, semecarpetin, nallaflavanone, jeediflavanone, semecarpuflavanone	Cardioprotective, antioxidant, anticancer, antidiabetic	15
Kalmegh	*Andrographis paniculata*	Acanthaceae	Leaves	Methanol	Andrographolide, diterpenoids, flavonoids, quinic acid, xanthones, noriridoids, and andrographidoids A, B, C, D, and E	Cardioprotective, gastroprotective, antioxidant	16
Zafran, Saffron	*Crocus sativus*	Iridaceae	Flowers	Aqueous	Carotenoid compounds, crocetin, crocin, safranal, glucoside picrocrocin, anthocyanins, delphinidin, petunidin	Cardioprotective, hypnotic, anxiolytic, anticancer	17
Tulsi	*Ocimum sanctum*	Lamiaceae	Seeds	Hydroalcohol	Alkaloids, saponins, tannin, steroid, flavonoids, terpenoid	Cardioprotective, antioxidant, hypolipidemic, hypoglycemic	18
Basil, Saint-Joseph's-wort	*Ocimum basilicum*	Lamiaceae	Aerial parts	Ethanol	Flavonoids, phenolic compounds	Antibacterial, antifungal, antioxidant, and cardioprotective	19
Moringa, drumstick tree	*Moringa oleifera*	Moringaceae	Leaves	Hydroalcohol	Tannins, saponins, alkaloids, terpenes, carbohydrates, flavonoids, and cardiac glycosides	Anticancer, anti-inflammatory, antipyretic, and cardioprotective	20,21
Bottle gourd	*Lagenaria siceraria*	Cucurbitaceae	Fruit	Juice	Sterols, flavonoids, terpenoids, and saponin	Antioxidant, antihyperlipidemic, and cardioprotective	22
Picrorhiza, kutki, katuka	*Picrorhiza kurroa*	Scrofulariaceae	Rhizome	Ethanol	Sterols, glycosides, phenolic compounds, cucurbitacins (triterpenoids), and iridoid glycosides	Antioxidant, anti-inflammatory, and cardioprotective	23

(continued)

Table 1. (continued)

Common Name	Plant Names	Family	Parts Used	Dosage Form	Chemical Constituents	Actions	References
Ban tulasi, raan tulas	*Croton sparsiflorus*	Euphorbiaceae	Leaves	Methanol	Terpenoids, saponins, tannins, phenols, flavonoids, alkaloids	Antinociceptive, anti-inflammatory, and cardioprotective	24
Against isoprenaline hydrochloride–induced cardiotoxicity							
Neem tree, Indian lilac	*Azadirachta indica*	Meliaceae	Aqueous	Leaves	Reducing sugar, tannins, flavonoids, steroids, terpenoids, glycosides, and alkaloids	Cardioprotective, chemopreventive, antiplasmodial, anti-inflammatory	25
Gander	*Coleus forskohlii*	Lamiaceae	Roots	Ethanol	Forskolin hydrochloride, demethylcryptojaponol, α-amyrin, betulic acid, α-cedrol and β-sitosterol, diterpene glycosides, and diterpenoids forskolin	Antihypertensive, antithrombotic, antiobesity, and cardioprotective	26
Kokum, red mango tree	*Garcinia indica*	Clusiaceae	Fruit	Aqueous	Garcinol, isoxanthochymol, xanthochymol, hydroxycitric acid, phenolic acids, flavonoids, benzophenones, isogarcinol, anthocyanins, and tannins	Cardioprotective, antibacterial, hepatoprotective, antioxidant	27
Against ischemia-reperfusion–induced cardiotoxicity							
Hawthorn	*Crataegus oxyacantha*	Rosaceae	Berries	Ethanol	Flavonoids, oligomeric procyanidins, triterpenes, phenolic acids, fatty acids, and sterols	Anti-inflammatory, antiapoptotic, and cardioprotective	28
Lemon guava, Guava	*Psidium guajava*	Myrtaceae	Leaves	Aqueous	Phenolic, carotenoid, flavonoid, terpenoid, and triterpene.	Cardioprotective, antispasmodic, antidiabetic	29
Gotu kola, Brahmi	*Hydrocotyle asiatica*	Umbelliferae	Whole plant	Alcohol	Alkaloids, flavonoids, and glycosides	Cardioprotective, antipsoriatic, neuroprotective	30
Maqui berry	*Aristotelia chilensis*	Elaeocarpaceae	Fruits	Methanol	Phenolic compounds, anthocyanidins, flavonoids, delphinidin, cyanidin, gallate, gallocatechin gallate, quercetin, rutin, myricetin, and catechin action	Cardioprotective, antioxidant, analgesic, anti-inflammatory	31
Arjuna or arjun tree	*Terminalia arjuna*	Combretaceae	Bark	Alcohol	Lactones, phytosterol, flavonoids, phenolic compounds, glycosides, and tannins	Antioxidant, antihyperlipidemic, and cardioprotective	32
Against doxorubicin-induced cardiomyopathy							
Bottle brush	*Callistemon lanceolatus*	Myrtaceae	Leaves	Ethanol	Phenolic compounds, carbohydrates, saponins, alkaloids, flavonoids, glycosides, phytosterols, and tannins	Anti-inflammatory, antioxidant, and cardioprotective	33
Stone breaker, Black katnip	*Phyllanthus niruri*	Phyllanthaceae	Whole plant	Aqueous	Flavonoids, terpenoids, alkaloids, lignans, tannins, polyphenols, coumarins, and saponins	Cardioprotective, anticancer, antimicrobial, hypolipidemic, antihepatotoxic	34
Turmeric	*Curcuma longa*	Zingiberaceae	Rhizome	Ethanol	Curcumin, ar-turmerone, β-sesquiphellandrene, curcumenol, sesquiterpenes, and phenolic constituents	Cardioprotective, anti-inflammatory, antioxidant	35
Shershir	*Tribulus macropterus*	Zygophyllaceae	Aerial parts	Methanol	Flavonoids, saponins, alkaloids, glycosides, and flavonol	Cytotoxic and cardioprotective	36

(continued)

Table 1. (continued)

Common Name	Plant Names	Family	Parts Used	Dosage Form	Chemical Constituents	Actions	References
Olive	*Olea europaea*	Oleaceae	Aerial parts	Methanol	Flavonoids, iridoids, secoiridoids, flavanones, benzoic acid derivatives, and triterpenes	Antidiabetic, anticancer, antimicrobial, and cardioprotective	[36]
Athel tree, Athel pine, and saltceda	*Tamarix aphylla*	Tamaricaceae	Aerial parts	Methanol	Alkaloids, tannins, glycosides, phenolic compounds, and saponins.	Antidiabetic, anticholinsterase, antioxidant, and cardioprotective	[36]
Sorrel	*Hibiscus sabdariffa*	Malvaceae	Petals	Aqueous	Tannins, saponnins, phenols, glycosides, alkaloids, and flavonoids	Antihypertensive, antioxidant, and cardioprotective	[37]
Malta fungus	*Cynomorium coccineum*	Cynomoriaceae	Aerial parts	Methanol	Alkaloids, glycosides, anthraquinones, flavonoids, tannins, saponins, and terpenoids	Antioxidant, antihypertensive, and cardioprotective	[36]
Assyrian plum	*Cordia myxa*	Boraginaceae	Fruit	Methanol	Flavonoids, saponins, and tannin	Anti-inflammatory, analgesic, and cardioprotective	[36]
	Calligonum comosum	Polygonaceae	Aerial parts	Methanol	Flavonoids, anthraquinones, and dehydrodicatechin	Cytotoxic, anticancer, and cardioprotective	[36]
	Camellia sinensis	Theaceae	Leaves	Aqueous	Tannins, flavonoids, steroids, and flavonoids	Antioxidant, antiobesity, and cardioprotective	[38]
	Withania somnifera	Solanaceae	Leaves and roots	Herbal tablet	Alkaloids, steroids, glycosides, hentriacontane, dulcitol, withaniol, withananine, withananinine, pseudo-withanine, tannins, and flavonoids	Anti-inflammaory, analgesic, immunomodulant, antirhematic, and cardioprotective	[39]
	Ficus racemosa	Moraceae	Bark	Acetone	Flavonoids, triterpenoids, alkaloids, tannins, kaempferol and coumarin, glycoside	Antioxidant, hepatoprotective, and cardioprotective	[40]
Onion	*Allium cepa*	Alliaceae	Leaves	Methanol	Flavonoids, triterpenic acids, amino acids, steroids	Cardioprotective, antibacterial, antioxidant, hypouricemic	[41]
Against cigarette smoke–exposed rats							
	Sesbania grandiflora	Fabaceae	Leaves	Aqueous suspension	Alkaloids, flavonoids, glycosides, tannin, anthraquinone, steroid, pholobatannins, and terpenoids	Antibacterial, anxiolytic, and cardioprotective	[42]
Against glucose-induced oxidative stress in H9C2 cardiomyocytes							
	Syzygium cumini	Myrtaceae	Seeds	Methanol	Anthocyanins, ellagic acid, glucoside, kaemferol isoquercetin, alkaloids, myrecetin, glycosides, and jambosine	Antidiabetic, antioxidant, and cardioprotective	[43]
Against *Naja sputatrix* (Javan spitting cobra) venom							
Velvet bean, Cowhage	*Mucuna pruriens*	Fabaceae	Seeds	Aqueous	Alkaloids, sterols, saponins, alkylamines, 6-methoxyharman, mucunain, mucunadine, and mucunine	Cardioprotective, antidepressant, neuroprotective	[44]

is also popular for its medicinal and nutritional potential.[56] *Ginkgo biloba* also contains many other phytoconstituents, including fatty acids, resins, essential oils, tannins, carotenoids, quercetin, and myricetin.[57] *Ginkgo biloba* extract was observed in improving the blood flow, preventing hypoxia, improving blood rheology, causing platelet aggregation, and reducing the capillary permeability due to the release of prostaglandins and *NO*.[58]

Leaves and seeds of *G biloba* have been reported to have cardioprotective effect. Panda[59] in his study administered *Ocimum sanctum* and *G biloba* extract in isoproterenol-induced myocardial necrosis rats. He found an increase in serum enzymes of isoproterenol-induced myocardial necrosis rats compared with serum enzymes of normal rats. The rats were given *O sanctum* (50 and 75 mg/kg body weight) and *G biloba* (100 mg/kg body weight) orally for 1 month. Isoproterenol at a dose of 85 mg/kg body weight was administered through subcutaneous route. Serum enzymes level was reduced significantly on the 29th and 30th days of therapy. *Ocimum sanctum* (100 mg/kg body weight) and *G biloba* (50 mg/kg body weight) showed significant cardioprotection as compared to combined administration of *O sanctum* (50 mg/kg body weight) and *G biloba* (100 mg/kg body weight).[59]

Terminalia arjuna

Terminalia arjuna is a large ever green tree with an average height of about 60 to 80 feet. This plant belongs to family Combretaceae. It is found most abundantly all around the sub-Himalayan tracts in India. It's bark outer covering is gray brown while the inside is red. *Arjuna* plant contains variety of phytoconstituents, including flavonoids, triterpenes, and tannins.[60] Leaves and barks of *Arjuna* plant have cardioprotective activity. Phytoconstituents are arjunetin, polyphenols, β-sitosterol, freidelin, arjunic acid, and triterpenes.[61] Cardioprotective potential of *T arjuna* alcoholic extract was investigated against isoproterenol-induced myocardial injury in Wistar rats by administering extract dose concentrations orally for a period of 28 days. After 4 weeks treatment period, the rats were administered subcutaneously with isoproterenol (85 mg/kg body weight) for 2 consecutive days to all the treated animals, except control group rats (normal untreated rats) to induce myocardial injury. Results of the study showed that *T arjuna* restored the myocardial ischemic–reperfusion injury induced by isoproterenol protecting the myocardium.[31] In another study conducted for investigating the cardioprotective effect of *T arjuna* bark aqueous extract on mice model against DOX-induced cardiotoxicity. The study concluded that *T arjuna* aqueous extract is a relatively safe and promising cardiotonic with cardioprotective potential. The bark extract of this plant is beneficial for healthy heart that can be used as cardioprotective agent in adjuvant chemotherapy for patients with cancer.[62]

Picrorhiza kurroa

Picrorhiza kurroa from Scrophulariaceae plant family is a high-value medicinal plant commonly known as "Kutki." This plant grows mainly in Kashmir to Kum in the northern western Himalayan region while in India's Garhwal and Sikkim regions; it grows above mean sea level at an altitude of 3000 to 4500 miles. The genus *Picrorhiza* in recent past has attracted the great interest and the promising role of *P kurroa* formulations has been revealed in many chemical and pharmacological investigations.[63,64] *Picrorhiza kurroa* is considered a bitter drug that is rich in iridoid glycosides with many biological activities such as antioxidant, anticholestatic, anti-inflammatory, immunomodulatory, and hepatoprotective activities.[64] Chemical constituents found in this plant are berberine, kurrin, picrorhizetin, kutkisterol, sesquiterpene, apocynin, cathartic acid, and kutkin.[65] Cardioprotective activity of *P kurroa* ethanolic extract was investigated in isoproterenol-induced MI using rats model. Significant cardioprotective activity of *P kurroa* extract was observed at dose concentration of 80 mg/kg body weight.[23]

Salvia miltiorrhiza

Salvia miltiorrhiza belongs to Labiatae plant family that is widely used against cardiovascular abnormalities for disease prevention and treatment.[66] This plant has a long history of its medicinal use as well as healthy food and is considered as an essential herbal plant widely used in Chinese traditional medicinal system. In Asia, Europe, and the United States, the rhizome and roots of this plant are extensively used in treating cerebrovascular and cardiovascular diseases in the form of tablets, injection solutions, oral liquid, capsule, and slow-release formulation.[67]

The active ingredients of this plant include both the lipid-soluble and water-soluble substances. The lipophilic substances are tanshinones, which includes tanshinone I, dihydrotanshinone I, tanshinone IIA, cryptotanshinone, and tanshinone IIB.[67,68] While the water-soluble constituents are phenolic acids such as caffeic acid, danshenu, salvianolic acid A, salvianolic acid B, and rosmarinic acid. *Salvia miltiorrhiza* phenolic acids showed many biological actions including antithrombotic, antioxidant, antitumor, anticoagulant, anti-HIV, and anti-blood coagulation activities.[67] Cardioprotective potential of *S miltiorrhiza* extract was investigated in experimental rats against isoproterenol-induced MI. Isoproterenol-treated rats showed reduction in left ventricular systolic pressure with increased serum glutamic oxaloacetic transaminase (SGOT) level and elevated ST-segment. Antioxidant enzymes such as superoxide dismutase and glutathione peroxidase activity were reduced in isoproterenol-treated rats. *Salvia miltiorrhiza* extract was administered orally at dose of 29.76 or 59.52 mg/kg body weight. *Salvia miltiorrhiza* extract reversed the isoproterenol-induced hemodynamic and biochemical changes, indicating cardioprotection against isoproterenol-induced MI.[69]

Tinospora cordifolia

Tinospora cordifolia (Wild) from genus *Tinospora* is a climbing shrub and is well known as "amrita" in Sanskrit and Hindi while "amudamor chindle" in Tamil. It is found throughout the tropical India. The roots and stem of this plant are extremely important in Ayurvedic and tribal medicinal systems. Its preparations are useful for the cure of jaundice, fever, diabetes, respiratory disorders, rheumatism, and neurological abnormalities.[70] The leaves, fruits, roots, and stem of *T cordifolia* possess cardioprotective activity. Phytoconstituents are tinosporin, tinosporic acid, tinosporol, giloin, giloinin, gilosterol, columbin, chasmanthin, palmarin, steroids, glycosides, sesquiterpenoids, diterpenoid lactones, and berberine.[70,71] Cardioprotective activity of *T cordifolia* alcoholic extract was investigated in a study using rat models. Surgical occlusion of coronary artery was performed to induce myocardial ischemia and then reperfusion for 4 hours. Results showed that *T cordifolia* treatment reduces the infarct size and decreased the lipid peroxide level compared to control group, indicating the cardioprotective activity of this plant.[72]

Hydrocotyle asiatica

Phytochemicals found in *H asiatica* whole plant are asiaticoside, tannic acid, and vallarin. Cardioprotective activity of *H asiatica* alcoholic extract (100-1000 mg/kg body weight) has been investigated against ischemia-reperfusion–induced MI in rats by oral administration of plant extract for 1 week. Dose-dependent response was observed. Results showed considerable decrease in infarct size in extract treated rats as compared to normal untreated rats.[30]

Bombax ceiba

Bombax ceiba L belongs to Bombacaceae plant family generally known as kapok tree or red silk cotton that grows in India and other countries such as Sri Lanka, Myanmar, and Indonesia.[73] Pharmacologically active parts are leaves, flowers, fruits, buds, barks, gums, seeds, and roots. This plant contains tannins, flavonoids, β-sitosterol, lupeol, glycosides naphthoquinone, n-triacontanol, and sesquiterpenoids.[74] Patel et al[75] reported the cardioprotective potential of *B ceiba* flowers aqueous extract against cardiotoxicity induced by adriamycin as compared to vitamin E.

Centella asiatica

Centella asiatica (L) belongs to Apiaceae plant family generally known as Asiatic pennywort. It is regularly used as medicinal herb or a culinary vegetable in many Asian countries, including Sri Lanka, India, China, and Thailand.[76] Phytoconstituents found in this plant includes tannins, phenols, vallarine, sitosterol, hersaponin, hydrocotylin, bacogenin, triterpenes, asiaticoside, and asiatic acid.[77] Gnanapragasam et al.[78] investigated the effect of *C asiatica* on cardiac and antioxidant enzymes of experimental animals with adriamycin-induced cardiomyopathy. Induction of myocardial damage due to adriamycin (2.5 mg/kg body weight intraperitoneal) was evident from elevated levels of serum enzymes, including aspartate aminotransferase, alanine aminotransferase, LDH, and creatine phosphokinase. *Centella asiatica* (200 mg/kg body weight) treatment prevented these alterations and restored the enzyme activities to normal, indicating cardioprotective activity of this plant.

Sonchus asper

Sonchus species are herbaceous plants extensively distributed in Asia, Europe, and Africa. *Sonchus* species aerial parts are rich in essential amino acids, minerals, vitamins, and protein that help reduce hypoalimentation-associated abnormalities. These plant species are generally used in decoctions or infusions administered externally or orally in treating cancer, acute icterohepatitis, inflammation, diarrhea, snake venom poisoning, and rheumatism.[79] This plant contains phenols, flavonoids, flavonols, alkaloids, riboflavins, thiamine, niacin, tannins, sesquiterpenes, and proanthocyanidin.[80] Khan et al[81] studied the cardioprotective effect of *Sonchus asper* methanolic extract against oxidative damage induced by $KBrO_3$ in cardiac tissues of Sprague-Dawley male rats. They found significant cardioprotective activity of *S asper* methanolic extract (100 and 200 mg/kg body weight) against $KBrO_3$-induced oxidative stress.

Mucuna pruriens

Mucuna pruriens (L) DC Is commonly called as velvet bean and is native to the East India and China.[82] Chemical constituents are tannins, iron, zinc, calcium, aluminum, steroids, tetrahydroisoquoline, and glycosides.[83] *Mucuna pruriens* seeds are rich in L-3,4-dihydroxy phenylalanine (L-dopa). This L-DOPA is the precursor of a neurotransmitter dopamine most often used in treating Parkinson disease.[82] Fung et al.[84] studied the cardioprotective potential of *M pruriens* against *Naja sputatrix* (Javan spitting cobra) venom in experimental rats. Cardiorespiratory and neuromuscular depressant activity of *N sputatrix* was attenuated through pretreatment with *Mucuna* extract, which might be due to cobra venom toxins neutralization by antibodies elicited with *M pruriens* extract.

Andrographis paniculata

Andrographis paniculata (*AP*) belongs to Acanthaceae family and is well known due to its medicinal importance. It is widely used for medicinal purposes throughout the world, including China, India, Bangladesh, Pakistan, Thailand, Hong Kong, Malaysia, Philippines, and Indonesia as traditional herbal medicine. It is one of the most commonly used medicinal plant in Ayurvedic and Unani medicines.[85] Chemical constituents found in this plant are sodium, potassium, glycosides, flavonoids, tannic acid, diterpene lactone andrographolide, kalmeghin, 14-deoxy andrographolide, and 14-deoxy-11,12-didehydro andrographolide.[85,86] Woo et al[87] reported

Table 2. Phytochemicals Responsible for Cardioprotective Activity.

Botanical Name	Family	Part Used	Phytoconstituents	References
Allium sativum	Liliaceae	Bulb	Allicin, sulfur compounds	93
Anacardium occidentale	Anacardiaceae	Stem bark	Flavonoids, carotenoids	94
Buxus microphylla	Buxaceae	Leaves	Cyclovirobuxine D	95
Antiaris toxicaria	Moraceae	Bark	Cardiac glycosides	96
Asparagus racemosus	Asparagaceae	Roots	Saponin-shatavarins I-IV	97
Ganoderma lucidum	Ganodermataceae	Fruit	Triterpenes	98
Leptadenia pyrotechnica	Asclepiadaceae	Aerial parts	Triterpenoids	98,99
Digitalis purpurea	Scrophulariaceae	Leaves	Cardiac glycosides	100
Tinospora cordifolia	Menispermaceae	Whole plant	Bitter constituents including tinosporon, tinosporol, tinosporic acid, palmarin, chasmanthin, and columbin; alkaloidal constituents including berberine	101
Crataeva nurvala	Capparidaceae	Stem bark	Pentacyclic triterpene, lupeol and its ester	102
Raphanus sativus	Cruciferae	Fruit	Caffeic acid	103
Crocus sativus	Iridaceae	Flowers	Crocin	104
Glycyrrhiza glabra	Leguminaceae	Roots	Glycyrrhizic acid	105
Garcinia kola	Guttiferae	Seeds	Kolaviron	106
Garcinia mangostana	Guttiferae	Fruit	α Mangostin	107
Morus alba	Moraceae	Leaves	Morin	108
Aegle marmelos	Rutaceae	Fruit	Marmesin	109
Catharanthus roseus	Apocynaceae	Leaves	Vincristine	110
Moringa oleifera	Moringaceae	Leaves	Vincosamide	111
Zingiber officinale	Zingiberaceae	Rhizome	Zingerone	112

cardioprotective activity of *AP* against reoxygenation/hypoxic injury in neonatal rat cardiomyocytes, upregulating the antioxidant enzyme activities and reduced cellular glutathione level.

Cichorium intybus

Cichorium intybus from genus *Cichorium* belongs to Asteraceae plant family. The genus consists of 6 species mainly distributed in Asia and Europe. Cichory plant contains a number of phytocompounds of medicinal importance, such as flavonoids, coumarins, vitamins, inulin, volatile compounds, esculin, and lactones.[88] Cichory contains volatile oils, phenolics, flavonoids, alkaloids, glycosides, saponins, tannins, fatty acids, emodine, triterpenoids, and anthracene.[89] Nayeemunnisa et al[90] studied the *C intybus* for its cardioprotective potential against aging myocardium in albino rats by administering the plant powder for 30 days. They concluded that aging caused an increase in taurine and glutathione level while decreasing the catalase activity in heart. Treatment with cichory plant ameliorated the oxidative damage and aging-induced injury of the heart.

Sesbania grandiflora

Sesbania grandiflora belongs to Fabaceae family. This plant is native to Southeast Asia.[91] Phytoconstituents are vitamin A, C, riboflavin, nicotinic acid, amino acids, and minerals.[92] Ramesh et al[42] conducted a study to investigate the *S grandiflora* cardioprotective effect in adult male Wistar-Kyoto rats exposed to cigarette smoke for 90 days to induce oxidative damage. The rats were given *S grandiflora* (1000 mg/kg body weight) aqueous suspension orally for 3 weeks and an increase in LDH activity with reduction in catalase, glutathione peroxidase, glucose-6-phosphate dehydrogenase, glutathione-S-transferase, glutathione reductase, and cardiac superoxide dismutase activities in cigarette smoke–exposed rats. The study concluded that *S grandiflora* reduces the oxidative stress protecting the heart from cigarette smoke–induced oxidative damage.

Phytoconstituents

Various phytoconstituents found in plants having cardioprotective potential are given below and listed in Table 2.

Cyclovirobuxine D

It contains cyclovirobuxine-D, steroidal alkaloid, artemetin, 4′,5-dihydroxy-3,3′,7-tetra methoxy flavones, (−)-(Z)-buxenone, (−)-(E)-buxenone.[113] Yu et al[114] studied the *Buxus microphylla* to investigate its cardioprotective potential in experimental rats against left coronary artery occlusion-induced heart failure. The rats were given cyclovirobuxine D, derivative of *B microphylla* for a period of 4 weeks. Cardiac functions, hemodynamics, microcirculation, histology, and mortality assessments of experimental rats were recorded. They found that cyclovirobuxine D is useful for the management of cardiac failure due to occlusion of left coronary artery,

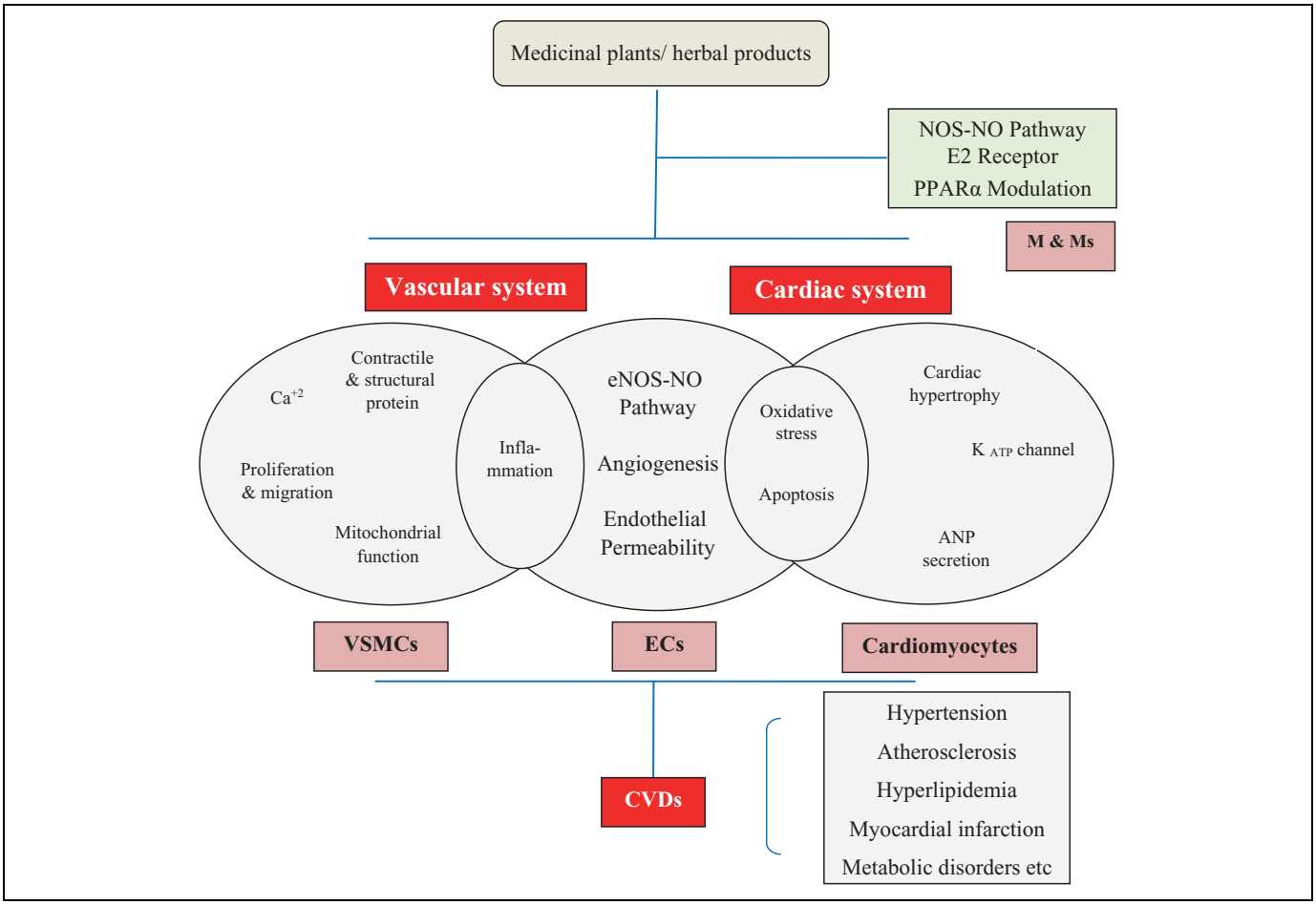

Figure 1. Cardioprotective mechanism of medicinal plants/herbal products on target sites during pathogenesis of cardiovascular abnormalities. ANP indicates atrial natriuretic peptide; CVDs, cardiovascular disorders; E2, estrogen; ECs, endothelial cells; M&Ms, macrophages and monocytes; NOS-NO, nitric oxide synthase-nitric oxide; PPARα, peroxisome proliferator activated receptor α; VSMCs, vascular smooth muscle cells.

leading to the development of new therapeutic agents for the treatment of cardiac failure.

Withanolides

Cardioprotective potential of *Withania somnifera* (300 mg/kg body weight) purified extract (withanolide 1.5%) was investigated using male Wistar rats. Rats were given doxorubicin (10 mg/kg body weight) to induce necrosis and apoptosis in cardiac tissues. Doxorubicin administration in rats causes elevation in protein carbonyl levels, catalase activity, and malondialdehyde due to oxidative stress. Total antioxidant capacity and superoxide dismutase activity were exhausted in heart tissues. The study concluded that *W somnifera* possess efficient cardioprotective potential against doxorubicin-induced cardiotoxicity.[39]

Silymarin

Cardioprotective efficacy of silymarin was carried out in experimental rats against ischemia-reperfusion–induced MI. Rats were given 2 different doses (100, 250, and 500 mg/kg body weight) of silymarin for 7 days. Occlusion of left anterior descending coronary artery was performed after 1 week of silymarin treatment for 30 minutes in control (ischemia–reperfusion) and test (silymarin-treated) group rats and then reperfused for 4 hours. Control group rats showed significant cardiac necrosis as evident from elevated serum enzyme levels (SGPT, SGOT, and LDH). Silylmarin administration resulted in the restoration of endogenous antioxidant enzyme activities, suppressed neutrophil infiltration, and reduced infarct area in test group rats as compared to control group rats.[30]

Flax lignin

Linum usitatissimum seeds extract (flax lignan concentrate) was studied for cardioprotective activity against isoprenaline-induced myocardial necrosis in rats.[115] Male Wistar rats (200-230 g) were divided into 3 groups as control group, isoprenaline group, and test (flax lignin treated) group. Test group rats were administered with flax lignin concentrate (500 mg/kg body weight) for 8 days, while isoprenaline was given to rats except control rats at a dose of 5.25 and 8.5 mg/kg body weight subcutaneously during 9th and 10th day of therapy, respectively. Isoprenaline-induced cardiotoxicity was evident from

the elevated cardiac enzymes level, while flax lignin concentrate restored the activities of cardiac enzymes by lowering the serum enzymes level in cardiotoxicity-induced rats. This study concluded that flax lignin concentrate has cardioprotective effect on isoprenaline-induced cardiotoxicity.

Cardioprotective Mechanism of Medicinal Plants

Since ancient times, numerous medicinal plants/herbal remedies have been used for the treatment of cardiovascular ailments. However, no scientific basis have been studied and reported the molecular mechanism of cardioprotective potential of medicinal plant remedies using cellular and molecular techniques. Medicinal plants discussed in this review article appear to show pharmacotherapeutic potential in vitro and in animal studies that may influence the cardiovascular ailments. These natural medicinal plants exert protective therapeutic effect through a series of processes, including the inhibiting, modulating, and regulating the expression of various proteins such as contractile and structural proteins, and glycoproteins, regulating the calcium levels and improvement in the functioning of mitochondria. The schematic mechanisms of cardioprotection of medicinal plants are presented in Figure 1.

The cardioprotective effect of medicinal plants/herbal products during cardiovascular ailments has been demonstrated by attenuating the damage in cardiac muscle cells, vascular smooth muscle cells (VSMCs), endothelial cells (ECs), and macrophages and monocytes. In cardiomyocytes, the protective effect of medicinal plants/herbal products has been shown by opening of K_{ATP} channel, increased secretion of atrial natriuretic peptide, cardiac hypertrophy, oxidative stress, and apoptosis. In ECs, beneficial effects of medicinal plants/herbal products have been shown by inflammation inhibition, oxidative stress & apoptosis, endothelial nitric oxide synthase-nitric oxide (NOS-NO) signaling pathway activation, angiogenesis induction, and endothelial permeability suppression. In VSMCs, medicinal plants/herbal products beneficial effects have been shown through expression inhibition, or inhibition of structural and contractile proteins activities, modulating the extracellular matrix proteins/glycoproteins expression, regulation of calcium levels, alleviating inflammation, attenuating proliferation and migrations, and mitochondrial functional improvements. In macrophages and monocytes, protective effect of medicinal plants/herbal products has been shown through estrogen receptor activation, NOS-NO signaling pathway inhibition, and the activation of nuclear receptor peroxisome proliferator activated receptor α.[116]

Conclusion

The current review concluded that therapeutic and prophylactic potential of plant phytoconstituents for the management of cardiovascular disorders have explored several ways in chemoprevention, although exact molecular mechanisms are still unclear. Apparently, phytoconstituents exert cardioprotective function by suppressing specific factors, inhibiting the key enzymes, and scavenging the oxygen-free radicals. It is described in this review that phytochemicals possess versatile cardioprotective functions. The nutraceutical and pharmaceutical industries can play a promising lead in drug designing and nutraceutical supplementations using medicinal plants. It could not be possible to include all the studies describing cardioprotective effect of medicinal plants or herbal agents in this review because of limited access to research articles and our search strategy. But the evidences presented in this review are strongly indicative of the notion that medicinal plants/herbal products are the source of emerging medicines for the prevention and treatment of cardiovascular ailments. One may predict the increasing attention of the use of herbal products as alternative medicine in coming years. Therefore, to develop more effective and safe agents from natural herbs is a promising way in preventing and treating cardiovascular abnormalities. However, documentation of criteria for clinical studies is essential for standardizing the evaluation of medicinal plants/herbal agents.

Future Prospects

Screening of indigenous medicinal plants from local flora should be carried out to explore specific plant constituents with therapeutic potential against cardiovascular ailments as an alternative to allopathic treatment regimens. Furthermore, characterization of specific isolated compounds from potent indigenous medicinal plants may be considerably helpful in novel drug designing and drug development for the therapy of cardiovascular disorders. International collaboration may be encouraged by the government through financial support for improving the quality of research.

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