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HERBAL PHYTOCONSTITUENTS OVERVIEW: A NEW THERAPEUTIC APPROACH IN MANAGEMENT OF CARDIAC DISORDERS

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ABSTRACT: Worldwide, cardiac disorders constitute a leading cause of morbidity and mortality. Cardiac disorders include high blood pressure, atherosclerosis, arrhythmia, congestive heart failure, stroke etc. Increase in incidence of cardiac disorders is a manifestation of lifestyle changes. Although modern drugs are effective in preventing the cardiac disorders, their use is often limited because of their side effects and adverse reactions. Use of herbal drugs is not only cost effective but also has better safety and efficacy. The World health Organisation (WHO) estimates that about 80% of the population living in the developing countries still relies on herbal drugs for their primary healthcare needs. Today, ethno-botanical and ethno-pharmacological studies of medicinal plants continue to attract investigators for research work globally. Aim of this current review to explain herbal phytoconstituents therapy on the basis-"Type of disorder, Mode of action and Pharmacological screening model", which could be an informatics approach in management of cardiac disorders.

INTRODUCTION: Cardiac disorders are the most prevalent cause of death and disability worldwide. The debilitating and often fatal complications of cardiac disorders are usually seen in middle-aged or elderly men and women. Report from the American Heart Association indicates that an estimated 82,600,000 Americans (>1 in 3) have 1 or more types of cardiac disorder. Of these, 40,400,000 are estimated to be ≥60 years of age. It is estimated that >2200 Americans die of cardiac disorder each day, which is equivalent to 1 death every 39 seconds [1].

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The traditional medicine all over the world is nowadays revalued by an extensive activity of research on different plant species and their therapeutic principles. Herbal drugs are often the only medicine available in less developed areas and also becoming a popular alternative treatment in more developed areas. World Health Organization (WHO) estimates that eighty percent of total world's population presently uses medicines of herbal origin for primary health care [2].

The basis of development of modern medicine is rooted in traditional medicine and therapies. The scientific literature is replete with research documenting the link between certain phyto-constituents and inhibition or protection against the cardiac disorder. Many of plants have been investigated to contain active substances that are medically useful in cardiac disorders.

Today, there has been an increasing demand to evaluate cardioprotective activities of phytoconstituents isolated from plant origin and therefore, evaluation of phytoconstituents is done by number of methods on the following basis;

1. Type of disorder (Hypertension, atherosclerosis, heart failure, arrhythmia)
2. Mode of action (ACE inhibitor, antiplatelet, NADPH oxidase inhibitor, lipid lowering, antioxidant)
3. Pharmacological screening model (Isoproterenol, Doxorubicin, Ischemia reperfusion injury, DOCA salt induced hypertension).

1. Phytoconstituents and disorder type (Table 1): Cardiac disorders are the most prevalent cause of death and disability worldwide include hypertension, arrhythmia, atherosclerosis, congestive heart failure etc. Epidemiological studies highlight the potential therapeutical role of phytoconstituents in cardiac disorders and shown a strong inverse relationship between cardiac disorders and phytoconstituents rich diets.

a. **Hypertension:** Hypertension is the most common public health problem in both developed and developing countries and also a risk factor for atherosclerosis, ischemic heart disease (myocardial infarction), cardiac failure and stroke [3, 4]. Hypertension usually produces no noticeable symptoms and therefore, known as a silent killer. Herbal treatments are usually necessary as long term therapy in the management of hypertension. *Rauwolfia serpentina* which contains the alkaloid reserpine, was the first potent drug widely used in long term treatment of hypertension [5]. Flavonoids are widely distributed in plants and present in considerable amounts in fruits and vegetables. Epicatechin seems to be a major bioactive constituent of cocoa and other flavonol-rich foods and beverages which has been shown to improve endothelial function and lowers blood pressure [6]. Antihypertensive activity of quercetin also evaluated in the deoxycorticosterone acetate (DOCA)-salt hypertensive rats [7], Goldblatt hypertensive rats [8] and other models of hypertension.

b. **Atherosclerosis:** Atherosclerotic vascular disease manifests predominantly as heart disease and stroke, which are the most frequent causes of death in the United Kingdom. Atherosclerosis is characterized by accumulation of lipids and fibrous elements in the arteries. Most myocardial infarcts that occur due to imbalance between coronary blood supply and myocardial demands are the results of coronary atherosclerosis. Phytosterols are plant derived sterols that inhibit or reduce intestinal absorption of cholesterol [9] and serum LDL-cholesterol levels [10, 11]. Foods with plant stanol or sterol esters also lower serum cholesterol levels [12].

c. **Heart failure:** Heart failure exists when cellular respiration becomes impaired because the heart cannot pump enough blood to support the metabolic demands of the body. It can be caused by arteriosclerotic, valvular, hypertensive and congenital heart diseases as well as dilated cardiomyopathy. Cardiac glycosides are universally acknowledged to be important agents in the drug therapy of advanced congestive heart failure (CHF).

Inotropic property of cardiac glycosides drugs increase myocardial contractility and output in hypodynamic heart without a proportionate increase in oxygen consumption. Digoxin and digitoxin isolated from *digitalis*, are pure glycosides and popular drugs for the management of congestive heart failure [13, 14].

d. **Arrhythmia:** Arrhythmia is the most important cause of sudden cardiac death. Abnormal automaticity or impaired conduction or both underlie cardiac arrhythmia. Cardiac arrhythmia is a common problem in clinical practice, occurring in digitalis treated patients up to 25%, anaesthetic patients up to 50% and over 80% in patients with acute myocardial infarction (MI). Herbal plants such as *Harpagophytum procumbens*, *Aconitum carmichaelii*,

Crataegus have known for their anti-arrhythmic activity [15, 16, 17] and therefore, need to isolate active phytoconstituents for better therapeutic efficacy.

TABLE 1: CARDIOPROTECTIVE PHYTOCONSTITUENTS ON THE BASIS OF DISORDER TYPE

Plant	Cardioprotective Phytoconstituents	Disorder	References
Sophora flavescens (Fabaceae)	Oxymatrine	Arrhythmia	18
Cnidium monnieri (Umbelliferae)	Osthol	Hypertension	19
Salvia miltiorrhiza (Lamiaceae)	Danshensu	Arrhythmia	20
Digitalis lanata (Plantaginaceae)	Digoxin	Heart failure	21
Erigeron annuus (L.) Pers. (Asteraceae)	Ergosterol peroxide	Atherosclerosis	22
Uncaria Rhynchophylla (Rubiaceae)	Isorhynchophylline	Arrhythmia	23
Genista tinctoria (Fabaceae)	Genistein	Hypertension	24

2. **Phytoconstituents and mode of action (Table 2):** Currently there has been an increased interest globally to identify compounds that are pharmacologically potent and have low or no side effects for use in preventive medicine. Therefore, cardioprotective effect of phytoconstituents is designed on the basis of their mode of action.

a. **Angiotensin Converting Enzyme (ACE) inhibition:** ACE inhibitors prevent the formation of angiotensin II by ACE and thereby reduce peripheral vascular resistance and blood pressure. Number of plants derived compounds such as hydrolysable tannins [25], terpenoids [26, 27], flavonoids, proanthocyanidins [28], xanthones [29], and peptides/amino acids [28, 30] have been investigated for their ability to inhibit ACE, which could serve as model substances in the development of new ACE inhibitors. Recent study highlights 135 plants screened for their ACE inhibiting activity in which 52 species gave more than 50% ACE inhibition [31].

Plants which are rich source of flavonoids and proanthocyanidins show significant *in vitro* ACE-inhibitory activity [32]. These studies suggest that plants could become a source of ACE inhibitors in management of cardiac disorders.

b. **Platelet Aggregation Inhibitors:** Platelets play a critical role in haemostasis and the development of cardiac disorder [33]. Platelet hyperactivity is responsible for morphologic changes in the platelets and the release of chemical mediators, such as adenosine diphosphate (ADP), thromboxane A_2, serotonin, platelet activation factor (PAF) and thrombin and therefore, plays an important role in arterial thrombosis and atherosclerosis. Rutaecarpine, an alkaloid isolated from *Evodia rutaecarpa* is well known for their antiplatelet mechanism [34]. The allicin derivative of garlic root enhances fibrinolytic activity and inhibits platelet aggregation in patients with coronary artery disease [35, 36, 37].

Antiplatelet activity of tomatoes and kiwi fruits has also been evaluated by inhibition of both ADP and collagen induced platelets aggregation [38, 39]. Red pepper (capsaicin), an herb used to alleviate diabetic neuropathy [40], inhibits platelet aggregation and release [41], as well enhancing fibrinolytic activity [42]. Other herbs may also affect platelet function through inhibition of prostaglandin metabolism and reduce the production of PG-endoperoxides and thromboxane through either inhibition of platelet cyclooxygenase [43].

c. **Hypolipidemic action:** Hyperlipidemia (Elevated cholesterol or triglyceride) is a major cause of atherosclerosis induced coronary heart disease (CHD). About half of all deaths in the United States occur due to coronary heart disease. The incidence of CHD is the result of elevated level of low-density lipoprotein (LDL) and low level of high-density lipoprotein (HDL) cholesterol.

Cigarette smoking, hypertension, obesity, diabetes, physical inactivity, age and genetic defects known as risk factors for the disturbance of cholesterol levels in the blood.

There are several antihyperlipidemic drugs available in market but today, attention has been shifted towards the use of medicinal plants for chronic therapy. Polyphenols presence in the diet has been shown to reduce the morbidity and mortality from coronary heart disease [44]. Polyphenols found in different plants, fruits, vegetables and beverages like red wine and tea are now available in market as over-the counter (OTC) preparations.

d. **NADPH oxidase inhibitors:** Majority of intracellular reactive oxygen species (ROS) production is derived from the mitochondria and production of mitochondrial superoxide radicals occurs primarily through an enzyme NADPH oxidase. NADPH oxidase family enzymes are the major source of reactive oxygen species that are implicated in the pathophysiology of cardiac disorders. Number of plants show cardioprotective activity by inhibiting NADPH oxidase. Activation of NADPH oxidase by peroxidases or ROS under mild reaction conditions has been found to be inhibited by naturally occurring methoxyphenol apocynin [45]. Apocynin isolated from the traditional medicinal plant *Picrorhiza kurroa* potentially act by blocking the assembly and activation of a functional NADPH oxidase complex [46]. High efficacy and low toxicity of apocynin makes it a promising lead compound in the development of new therapeutic agents for cardiac disorders.

e. **Antioxidant:** The free radical theory posits that oxidative stress is among the major mechanisms in aging and age-related disease, including cardiac disorders. This has led to the hypothesis that antioxidants could be used as an inexpensive means of prevention and possibly, treatment of cardiac disorders. Now a day, substantial interest has been focused on antioxidant therapeutic strategies to cope up with oxidative stress and help in converting the radicals to less reactive species. Recent works highlighted the role of polyphenolic compounds such as flavonols, anthraquinones, anthocyanidins and xanthones, possess remarkable cardio-protective effects by antioxidant mechanism. Epidemiological studies have shown a strong inverse relationship between cardiac disorder and vegetable/fruit rich diets [47] and evidences also reveal that diets rich in polyphenolic compounds are associated with longer life expectancy [48].

TABLE 2: CARDIOPROTECTIVE PHYTOCONSTITUENTS ON THE BASIS OF MODE OF ACTION

Plants	Phytoconstituents	Mode of action	References
Salvia miltiorrhiza (Lamiaceae)	Danshensu	Antioxidant	49
Curcuma amada (Zingiberaceae)	Amadaldehyde	Antiplatelet	50
Daphne giraldii Nitsche Thymelaeaceae)	Daphnetoxin, Gniditrin	Reduce cholesterol level	51
Leonotis leonurus (Lamiaceae)	Marrubiin	Antiplatelet	52
Curcuma longa (Zingeberaceae)	Curcumin	Antioxidant	53
Bacopa monnieri (Scrophulariaceae)	Bacosides A and B	Antioxidant	54
Cinnamomum tamala (Lauraceae)	Cinnamaldehyde	Reduce cholesterol level	55
Ficus racemosa (Moraceae)	Kaempferol	ACE inhibitor	56
Rosa damascene (Rosaceae)	Cyanidin-3-O-beta-glucoside	ACE inhibitor	57
Hibiscus sabdariffa (Malvaceae)	Delphinidin-3-*O*-sambubiosides and cyanidin-3-*O*-sambubiosides	ACE inhibitor	58
Grape fruit/ *Citrus paradise* (Rutaceae)	Naringin	Antioxidant	59
Pinus maritime (Pinaceae)	Pycnogenol	ACE inhibitor	60
Aralia elata (Araliaceae)	Polysaccharide (AEP-w1)	Antioxidant	61
Allium sativum (Liliaceae)	Allicin	Reduce cholesterol level	62
Vaccinium myrtillus (Ericaceae)	Cyanidin, delphinidin and malvidin	ACE inhibitor	63
Crataeva nurvala (Capparidaceae)	Lupeol	Reduce cholesterol level	64

3. **Phytoconstituents and Pharmacological Screening Model (Table 3):** A variety of *in vivo* animal models used in the development of current drug therapies for cardiac disorders via experimental studies. After the isolation and chemical characterization, phytoconstituents have to be tested in animal models which can help us to understand and establishment of new therapies.

a. **Isoproterenol induced myocardial infarction:** Isoproterenol (ISO), a synthetic beta-adrenergic agonist induces myocardial infarction as a result of disturbance in physiological balance between production of free radicals and anti-oxidative defence system [65]. ISO promotes lipolysis in the myocardium which results in elevated concentration of myocardium lipids. Cardioprotective activity of phytoconstituents such as naringin [59] and mangiferin [66] has been evaluated against isoproterenol induced myocardial infarction and therefore, ISO is a well-established model to study the cardioprotective role of various herbal phytoconstituents in animals [67, 68], because pathophysiological changes following ISO administration in rats are comparable to those taking place during MI in humans [69].

b. **Ischemia-reperfusion (I-R) injury:** Myocardial ischemic reperfusion injury is a common cause of morbidity in ischemic heart disease (IHD), where oxidative stress plays an important role [70]. Ischemia-reperfusion (I-R) injury is the result of a tissue been deprived of its blood supply for a period of time and cellular damage occurring as a consequence of restoration of blood flow once the cause of the reduced blood supply is removed [71, 72].

In vivo small rodent models of cardiac ischemia (surgical occlusion of coronary artery) followed by reperfusion have been developed to mimic more closely the real clinical setting and also to study reperfusion-induced cardiac injury [73]. Myocardial I-R injury represents a clinical relevant problem associated with thrombolysis, angioplasty, coronary bypass surgery and heart transplantation which may result in hemodynamic impairment, contractile dysfunction, arrhythmias, depletion of endogenous antioxidant network, membrane permeability changes consequent to increased myocardial lipid peroxidation [74] and therefore, myocardial I-R injury is the suitable experimental model for evaluating cardioprotective phytoconstituents in animals. Phytoconstituents presence in *Desmodium gangeticum* [75] and *Hydrocotyle asiatica* [76] has showed their potential cardioprotective effect against ischemia-reperfusion myocardial injury. Phytoconstituents such as flavonoids have long been known for their potential antioxidant properties and also show reduction in oxidative stress during ischemia–reperfusion condition.

c. **Deoxycorticosterone acetate (DOCA) salt induced hypertension:** In animal models, hypertension can be achieved in uninephrectomised rats by mineralocorticoid administration, for example by weekly subcutaneous injections of deoxycorticosterone acetate (DOCA), and salt loading as 1% NaCl in the drinking water cause increased concentrations of aldosterone leading to increased reabsorption of sodium ions and water in distal the nephron of kidney, thereby influencing blood pressure levels [77]. Therefore, DOCA–salt induced hypertension in animals is well established model to evaluate new antihypertensive compounds. Recently, flavonoids such as diosmin and morin have been evaluated for their antihypertensive activity in DOCA-salt induced hypertensive rats [78, 79].

d. **Doxorubicin induced myocardial injury:** Doxorubicin (DOX), an anthracycline with potent antitumor activity, is most widely used and successful chemotherapeutic drug. However, the clinical usefulness of doxorubicin has been limited by the risk of irreversible cardiotoxicity. Cardiomyopathy, congestive heart failure, electrocardiographic changes are life threatening outcomes after cumulative doxorubicin administration [80, 81]. Doxorubicin- induced myocardial infarction serves as a well standardized model to study the beneficial effects of many herbal phytoconstituents.

TABLE 3: CARDIOPROTECTIVE PHYTOCONSTITUENTS ON THE BASIS OF PHARMACOLOGICAL SCREENING MODEL

Plant	Cardioprotective Phytoconstituents	Pharmacological Screening Model	References
Crocus sativus (Iridaceae)	Crocin	Isoproterenol induced cardiotoxicity	82
Cornus officinalis Cornaceae)	Cornuside	Myocardial ischemia-reperfusion injury	83
Vitis vinifera (Vitaceae), Theobroma cacao (Malvaceae)	Epicatechin	DOCA-salt hypertension	84
Silybum marianum (Compositae)	Silymarin	Ischemia-reperfusion induced myocardial infarction	85
Coptis chinensis (Ranunculaceae)	Berberine	Doxorubicin induced cardiotoxicity	86
Sida rhomboidea (Malvaceae)	Cryptolepine, ephedrine, vasicine	Isoproterenol induced myocardial necrosis	87
Tinospora cordifolia (Menispermaceae)	Berberine and columbin	Ischemia reperfusion induced myocardial infarction	88

CONCLUSION: Summarization of cardio-protective effects of various herbal phyto-constituents provides strong evidence for the potential use of herbal drugs in cardiac disorders. Cardiac disorder is a chronic condition need long term therapy for their management. In this context, herbal phytoconstituents could become a new approach for chronic treatment of cardiac disorders with better safety and efficacy. This compiled data also helpful for the researchers to focus on the isolation of new compounds for future drug development with potential therapeutical efficacy.

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