



Review Article

**A SYSTEMIC REVIEW ON CHALLENGES WITH CURRENTLY AVAILABLE
CARDIOTONICS AND THEIR SAFER HERBAL ALTERNATES USED IN INDIA**

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ABSTRACT

Cardiac disease is an important cause of premature death in industrialized countries. It is estimated that cardiac disease will emerge as single largest contributor to morbidity in India accounting for nearly one third of total deaths in near future. Cardiotonics are the agents which increase the force of contraction without altering heart rate, which can be used to treat cardiac diseases. Due to life-threatening or severe adverse drug reactions of available cardiotonic, people are seeking alternative therapies that may have maximum beneficial effects with least side effects. The present review focuses on various classes of cardiotonic, their mechanism & major adverse effects as well as better herbal alternate of these available cardiotonics. Many of them were scientifically proved as a cardiotonic. All of the drugs finally increase intra-cellular calcium (Ca^{2+}) level which results into increase in force of contraction. Present review also emphasis on the major challenges associated with current cardiotonics as well as future aspects in research related to cardiotonics.

KEY WORDS: Cardiotonics, arjuna, digitalis, tulsi, *solanum indicum*, Ca^{2+} sensitizer

INTRODUCTION

These are the substances which tend to increase the efficiency of contraction of heart muscle without increasing oxygen

consumption. ¹ These are the agents who increase the force of contraction & thus they are also known as positive inotropic agents.

They stimulate the heart & thus also known as cardio-stimulants².
 Cardiotonics are therapeutically used in regurgitations⁴, coronary artery diseases (CHF)⁵, angina pectoris⁵, persistent pulmonary hypertension (CAD)⁴ pulmonary stenosis⁴, dilated in newborn (PPHN)^{6, 7}, mitral cardiomyopathy⁴.

as cardio-stimulants².
 regurgitations⁴, coronary artery diseases (CAD)⁴ pulmonary stenosis⁴, dilated cardiomyopathy⁴.

CLASSIFICATION OF CARDIOTONICS: 8, 11, 12

Based on origin:

Natural		Synthetics			
Cardenolide	Bufadienolifde	Adrenergic agonist	Dopamine agonist	PDE inhibitors	Other cardiac stimulants
Digoxin, Digitoxin, Lanatoside C, Metidigoxin, Ouabain, Cymarin, Strophanthin	Bufotalin, Arenobufagin, Cinobufagin, Marinobufagin, Proscillaridin, Scilliroside	<p>α – adrenergic:</p> Phenylephrine, Methoxamine	Dopamine, Dopexamine, Ibopamine, Cafedrine, Theodrenaline	Amrinone, Milrinone, Enoximone, Bucladesine	Xamoterol, L- simendan, Angiotensin-amide
		<p>β – adrenergic:</p> Isoprenaline, Prenalterol			
		<p>Mix adrenergic:</p> Adrenaline, NA			

Based on mode of action: 8

Class I	Class II	Class III	Class IV
Agents that increases intracellular cAMP; Ex: β – adrenergic agonists & Phosphodiesterase inhibitors.	Agents that affecting sarcolemmal ion pumps & channels; Ex: Cardiac glycoside, who inhibiting Na^+/K^+ ATPase.	Agents that modulate intracellular Ca^{2+} action or level Ex: no example available...	Agents having multiple mechanisms of actions.

Cardiac glycoside: 9, 10

The following herbs contain cardiotonic glycosides: ^{9, 10} Digitalis (*Digitalis purpurea*; *D. lanata*),

Strophanthus (*Strophanthus gratus*; *S. kombi*),

Urginea species (*Urginea maritime* & *U. indica*);

Oleander, Adonis;

Lily of the valley,

Bufonis venenum, etc.

Cardiac glycosides mainly act by inhibiting Na⁺/K⁺ATPase pump, thus increase the intracellular Ca²⁺ level, which results into positive inotropic effect. ¹⁴

Main disadvantages of cardiac glycosides are they have a narrow margin (narrow therapeutic window) of safety especially the digitalis. Poor appetite, vomiting, diarrhea, visual embarrassment, lassitude, amyosthenia occur, reactions in aspects of gastrointestinal tract, CNS and the heart when poisoning occurs. The most serious heart reactions: abnormal heart rate, large dose directly inhibit cardionector to appear brady and partially or completely conduction blockade. ⁵

Phosphodiesterase inhibitors ¹⁵

Enoximone and milrinone are used clinically for short-term treatment of cardiac failure. These drugs mimic sympathetic stimulation and

increase cardiac output. PDE3 is sometimes referred to as cGMP-inhibited phosphodiesterase. The approved PDE3 inhibitors are Enoximone, Amrinone, Cilostazol, and Milrinone. PDE 3 inhibitors mainly act by inhibition of the PDE isoenzyme 3 leads to an increase of intracellular concentrations of the cyclic adenosine monophosphate (cAMP). cAMP mediates the phosphorylation of protein kinases, which in turn activates cardiac calcium channels. ^{15, 16} An increased calcium influx from the sarcoplasmic reticulum (SR) during phase 2 (the plateau phase) of the cardiac action potential leads to a positive inotropic effect of PDE3 inhibitors i.e. they increase the force of cardiac contraction. Increased reflux of calcium into the Sarcoplasmic Reticulum following the plateau phase is responsible for their positive lusitropic effect i.e. they increase relaxation speed. Additionally, PDE3 inhibitors act as vasodilators. Toxicity of PDE 3 inhibitors are Arrhythmias, vomiting, headache, fever, chest pain, hypokalemia, thrombocytopenia (especially with inamrinone), increase in heart rate, increased transaminase levels. ¹⁷

Adrenergic drugs: ^{11, 12}

α – agonists	β – agonists	Mix agonists
Phenylephrine Methoxamine	Isoprenaline Dobutamine	Adrenaline Noradrenaline

The α_1 and β_1 receptor agonist act as cardiostimulant, in which α_1 agonist act via Gq type of GPCR and activate Phospholipase C which further increase IP_3 level which increase cytosolic Ca^{2+} level which increases force of contraction while β_1 act on G_s type of GPCR which further activate adenylyl cyclase which increase cAMP level in myocytes, which gives positive inotropic effect and act as cardiostimulant activity. Thus both α_1 & β_1 agonist increase the force of contractions i.e. contractility & give positive inotropic & positive chronotropic effects. Adverse drug reactions of Adrenergic drugs are tachycardia, dysrhythmia, hypertension, tremor, cold extremities, agitation, cerebral hemorrhage, headache, etc.¹⁸

Dopaminergic drugs:

Dopaminergic drugs possess a unique pharmacologic profile since they add to the adrenergic stimulation their selective action on dopaminergic receptors. The administration of levodopa to patients with heart failure can induce a significant hemodynamic improvement that is maintained during chronic therapy. **Ibopamine** has been widely shown to cause a significant hemodynamic improvement in patients with heart failure. Its effects can be ascribed to a moderate increase of myocardial contractility

accompanied by peripheral and renal vasodilatory actions.²⁰

Example of Dopaminergic drugs used as cardiostimulant¹²

Dopamine, Bromocriptine, Dopexamine, Ibopamine, Cafedrine, Theodrenaline, etc. Dopamine act on both β_1 - adrenoceptors as well as stimulates dopamine and α -adrenoceptors.²¹ Besides multi-receptor activity, they also possess diuretic action, reduce aldosterone & renin secretion as well as promote the atrial natriuretic peptide release. The multi-receptor mechanism of dopamine-like drugs, which accounts for their favorable hemodynamic, neurohumoral, and diuretic effects, represents the most promising approach to inodilator therapy.²² Adverse effects of Dopaminergic drugs (Dopamine) are Chest pain, Atrial tachycardia, irregular heartbeat, skin necrosis, sloughing & even gangrene²⁴; Decrease TSH & thyroxin level in low birth weight newborns²³, Hypo-prolactemia²⁴, "Low T_3 syndrome" or Hypothyroidism; Respiratory depressions;

Miscellaneous: Severe headache, pilo-erection, skin rashes, natriuresis.²⁴

Herbs which can act as a cardiostimulant (Other than cardiac glycosides):

Mimusops elengi

Elettaria cardamomum

Elephantopus scaber

Bacopa monniera

Piper longum

Plumbago zeylanica

Cinnamom camphora

Vitex nergundo

Solanum indicum

Terminalia arjuna

Cocus nucifera (Coconut water)

Hardinia cordifolia

Ocimum sanctum (Tulsi)

Peltophorum pterocarpum

***Mimusops elengi* (Bakul)**

It is a glabrous tree, belongs to family Sapotaceae.²⁷ The bark is acrid, sweet, cooling, **cardiotonic**, alexipharmic, stomachic, anthelmintic, astringent, cures biliousness also used in fever, ulcers, diseases of the gums and teeth (ododentopathy).^{29, 30.} It is mentioned in various ayurvedic books that the bark of *Mimusops elengi* contains ester of α -spinasterol, 3β , 6β , 19α , 23-tetrahydroxy-urs-12-ene, 1β -hydroxy- 3β -hexanoyllup-20(29)-ene-23, 28-dioic acid and fewer pentacyclic fernane type tri-terpenoids.²⁸

Elettaria cardamom

Cardamom is the dried ripe seed of *Elettaria cardamom* belongs to family Zingiberaceae. The seeds are stimulant, carminative, stomachic, diuretic, **cardiotonic**, abortifacient and are useful in bronchitis, hemorrhoids, renal and vesical calculi, anorexia, dyspepsia and gastropathy.³¹

***Cinnamomum camphora*:**

According to Dan Kenner, camphor is good cardiotonic, diuretic, respiratory anti-septic, anti-depressant and analgesic. Due to cardiotonic activity, it can be used in

cardiac failure, shock, hypotension and depression. By inhalation it can be used to treat bronchitis, pulmonary tuberculosis, as well as topically it can be used to treat itching and rheumatoid arthritis.³²

***Vitex nergundo*:**

These are the dried ripe leaves of *Vitex nergundo* belongs to family Verbenaceae. It was proved by Pai PT et al, that leaves of *Vitex nergundo* possess potent cardiotonic activity in isolated frog heart perfusion technique (IFHP). They also used ringer solution without Calcium in it, which exactly mimic the condition like heart failure.³³ There is a chance of discovery of potent cardiotonic without severe adverse drug reaction (as seen with digoxin), if anyone isolate the particular chemical constitute which may be responsible for the cardiotonic activity.

***Solanum xanthocarpum*:**

Commonly it is known as 'Kanakari'. Samuel GY et al had proved the cardiotonic activity of infusion of fruits of *Solanum xanthocarpum* at different concentration, using isolated frog heart preparation, which were compared with

digoxin. They mentioned that the isolation of active constitute, responsible for cardiotoxic activity would be done in future.^{34, 35}

Terminalia arjuna:

These are the dried barks of *Terminalia arjuna* belongs to family Combretaceae. Ghosal et al. proved cardiotoxic activity of arjuna on isolated frog heart and isolated rabbit heart which was confirmed by administering isolated glycoside from bark of arjuna, resulted in to rise in blood pressure.^[37] It also possesses diuretic activity which was studied in same study.^[38] Other reported activities of arjuna are hypotensive, anti-oxidant, cardioprotective, anti-mutagenic, anti-hyperlipidemic, etc.³⁶

Cocos nucifera:

Common name of *Cocos nucifera* is coconut, belongs to family Arecaceae. Pattigadapa et al proved cardiotoxic activity of coconut water using isolated frog heart and compare the effect with digoxin. In that study they used both diluted and undiluted coconut water to evaluate cardiotoxic activity.³⁹ Its anti-ulcer (in indomethacin induced ulcer model – coconut milk) and anti-cancer (due to hexane component of water) activity has already proved.

Ocimum sanctum:

It is commonly known as Tulsi, belongs to family Lamiaceae. Pravin et al proved

cardiotonic activity of *Ocimum sanctum* with other herbs using isolated frog heart as well as frog's hypodynamic heart preparation. They found that *Ocimum sanctum* restore cardiac activity of hypodynamic heart, which was characterized by increase in force of contraction (i.e. positive inotropic effect). They also found that Nifedipine didn't block its effect which indicates that its effect is not Ca²⁺ ion mediated.⁴⁰

Hardinia cordifolia:

It is commonly known as haridru^[41] belongs to family Rubiaceae. Dama GY et al proved cardiotoxic activity of plant or heartwood of *Hardinia cordifolia* on isolated frog heart preparation as well as hypodynamic heart preparation, which were compared with standard digoxin solution. They came to know that Haridru shows better cardiotoxic activity compare to digoxin with least adverse drug reaction. Future aspects of that study is to isolate the main responsible chemical constitute for its cardiotoxic activity.⁴¹

Peltophorum pterocarpum:

It belongs to family Fabaceae. Bairi R et al used various extract like petroleum ether and ethanolic extract to evaluate cardiotoxic activity of *peltophorum pterocarpum* in which ethanolic extract was found more effective cardiotoxic. They evaluated cardiotoxic activity by isolated frog heart assembly. It contains

steroidal glycosides (campesterol-3-0-beta-D-glucopyranoside, stigmasterol-3-0-beta-D-glucopyranoside and β -sistosterol-3-0-beta-glucopyranoside) which are responsible for its cardiotoxic activity. They found the cardiotoxic effect was inhibited by Nifedipine as well as heart homogenate show reduced level of Na^+/K^+ ATPase and Mg^{2+} ATPase and an increase in Ca^{2+} ATPase enzyme level. They also studied the effect on membrane bound enzyme of heart (i.e. CPK, LDH, AST, ALT) to confirm that the extract were not producing any cardiac injury.⁴²

Bacopa monniera:

It is also known as Brahmi belongs to family Scrophulariaceae. Preclinical study shown that the extract of whole plant of *Bacopa monniera* increase force of contraction i.e. positive inotropic effect as well as also shown neuromuscular blocking effect on frog.⁴³

Cassia angustifolia:

It is also known as Senna alexandrina belongs to family Fabaceae. From the experiment done on hypodynamic frog heart, the infusion of leaflets of *Cassia angustifolia* restore the hypodynamic frog heart activity which means increase force of contraction i.e. positive inotropic effect on frog. The study also demonstrated that undiluted infusion was better than other diluted infusion.⁴⁴

Nerium oleandrum:

It is also known as Karen or Kaner belongs to family Fabaceae. The crude ethanolic extracts of the dried leaves of *Nerium* were tested for force of contraction, heart rate and cardiac flow on isolated guinea pig hearts. The study demonstrated that extracts brought dose-dependent increase in all the parameters from their baseline readings. Mechanism of action seems similar to digoxin from the data obtained. This finding would tend to provide a strong rationale for the herb's traditional use in cardiovascular illness.⁴⁵

Helicteres isora:

It is also known as Screw nut belongs to family Sterculiaceae. Phytochemical studies had revealed the presence of glycosides, saponins, tannins. Preclinical study was carried out to determine the cardiac stimulant effect by using infusion of fruits with different dilutions & compared with cardiotoxic activity of digoxin-the life saving cardiotoxic. The study was done on isolated frog heart assembly, which confirmed the better cardiotoxic activity of *Helicteres isora* as compared to digoxin. Further studies can confirm the reduced toxicity & this will be the advantage of *Helicteres isora* over digitalis. Thus, in future it will be interesting to isolate the active chemical constituents which are responsible for the cardiotoxic activity.⁴⁶

Astragalus membranaceus:

It is also known as Astragalus belongs to family Fabaceae. Kathi and Rebecca reported that the roots of *Astragalus membranaceus* show cardiotoxic and liver tonic activity. Treatment with astragalus in rats with experimentally induced Chronic Heart Failure, improved left ventricular systolic function and improved renal response to atrial natriuretic peptide. The same response was observed on randomly chosen 19 Chinese patients but there are no control trial evaluating the effectiveness of astragalus in treatment of CHF.⁴⁷

Chen LX et al also do experiments using *Astragalus membranaceus* to find out its mechanism of action as cardiotoxic. In preclinical study, they observe the rise in SOD (Super oxide dismutase) and reduction in lipid peroxidation (LPO). From this study, they found that the anti-oxygen free radical (anti-OFR) activity of Astragalus could be one of mechanism of its cardiotoxic activity.⁴⁸

***Crataegus pinnatifida* Bunge:**

The drugs with cardiac glycosides (listed below) will act similarly to digoxin with same adverse drug reaction.

Herbs with cardiac glycosides:²⁶

Sr. No.	Family	Plants
1	Apocynaceae	Acocanthera, Adenium, Apocynum, Carissa, Nerium, Cerbera, Strophanthus, Thevetia, Tanghinia
2	Asclepiadeceae	Asclepias, Calotropis, Cryptostegia, Menabea, Pachycarpus, Periclopa
3	Liliaceae	Urginea, Rohdae, Ornithogalum, Convalarria, Bowiea

It is also known as Hawthorn belongs to family Rosaceae. In many traditional books, it is reported that extract of Hawthorn fruit is most commonly used cardiotoxic remedy. Jakstas reported that Hawthorn is a well known and widely used medicinal plant due to its cardiotoxic activity.⁴⁹

***Vitis venifera*:**

It is also known as Grapes or Draksh belongs to family Vitaceae. Hadaginhil RV et al had reported that the dried fruits of Grapes are intellect promoting, cardiotoxic, cough remover, anti-diabetic, antioxidant and they possess nootropic effect, adaptogenic, hepatoprotective, bronchodialtory and anti-microbial activity.⁵⁰ Kirtikar Basu has also reported cardiotoxic activity of *Vitis venifera*⁵¹. According to Basavaraju SR et al and review published by Agrawal BB, Resveratrol, a natural phenol, is responsible for cardiotoxic activity of vitis venifera and use of dried fruits of grapes as a cardiotoxic is well documented.^{52, 53}

4	Moraceae	Antiaris, Antiaropsis, Castilla,
5	Scrophularaceae	Digitalis, Isoplexis
6	Cruciferae	Erysimum, Cheiranthus
7	Celastraceae	Euonyms
8	Leguminosae	Coronilla
9	Ranunculaceae	Adonis, Helleborus
10	Sterculaceae	Mansonia
11	Tiliaceae	Corchorus

FUTURE ASPECTS RELATED TO CARDIOTONICS

The narrow therapeutic window or safety level of cardiac glycosides has led to deep & extensive studies for newer cardiotonic which have least side effect compare to cardiac glycosides.⁵⁴ Cardiotonic drugs acting on beta-adrenoceptors and inhibitors of cAMP phosphodiesterase have been extensively studied and used for the treatment of heart failure. Ca^{2+} sensitizers are of interest, since such a mechanism of action may be beneficial for the failing heart.⁵⁴ Certain novel agents with Ca^{2+} sensitizing action have been shown to be more beneficial than Ca^{2+} mobilizers in CHF models of experimental animals and small and/or middle scale clinical trials, which indicates that the development of novel Ca^{2+} sensitizers for the treatment of the cardiac pump dysfunction could provide a breakthrough of the pharmacological therapy of the chronic CHF patients.⁵⁵ Recently, cardiotonic substances with a novel mechanism of action such as gingerol and

xestoquinone have been isolated from natural sources.⁵⁴ Furthermore, 9-methyl-7-bromoeudistomin D, a powerful radiolabeled Ca^{2+} releaser having caffeine-like properties, may provide a promising tool for studying the molecular mechanism of the Ca^{2+} release process.⁵⁴

POTENTIAL FUTURE RESEARCH CHALLENGES

Identification of possible mechanism which is directly associated with cardiotonic activity of selected plant species; Clinical trials on large population for selected species; Determination of the long-term side-effects of natural herbal product formulations; To determine combination therapy of above discussed herbs; Identify the particular chemical constitute responsible for cardiotonic activity; Investigation of the production potential of plant species with clinically proven cardiotonic properties in diverse environments; Development of cardiotonic formulation which is easily to available to public domain, with least side effect and better availability.

SUMMARY

Cardiotonics are the agents which tend to increase in force of contraction of myocardial muscles without increase oxygen demand. The currently available cardiotonics have many severe adverse drug effects. Digoxin shows arrhythmia, heart block, tachycardia and serious heart consequences and due to its very narrow therapeutic window it needs constant therapeutic drug monitoring. Other cardiotonic like PDEIII inhibitors also possess side effects like arrhythmia, thrombocytopenia, etc. Thus, this review mainly focuses on the safer, better as well as experimentally and therapeutically proved cardiotonic herbs. These include herbs like *Mimusops elengi*, *Elettaria*

cardamomum, *Elephantopus scaber*, *Bacopa monniera*, *Piper longum*, *Plumbago zeylanica*, *Cinnamom camphora*, *Vitex nergundo*, *Solanum indicum*, *Terminalia arjuna*, *Cocus nucifera* (Coconut water), *Hardinia cordifolia*, *Ocimum sanctum* (Tulsi), *Peltophorum pterocarpum*. This review also focuses on other cardiotonic herbs which contain cardiac glycosides like *Acocanthera*, *Urginea*, *Nerium*, *Strophanthus*, *Thevetia*, *Adonis*, *Corchorus*, etc. This review also suggests the future aspects in case of cardiotonic like Ca^{2+} channel sensitizer. Thus this review may aid into development of newer, safer, better and economic cardiotonic.

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