International Research Journal of Pharmaceutical and Applied Sciences
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2012; 2(1):11-23

IRJPAS **ISSN-2277-4149**

Review Article

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

Ganatra Tejas H*, Joshi Umang H, Bhalodia Payal N, Desai Tusharbindu R, Tirgar Pravin R
Department of Pharmacology, R. K. College of Pharmacy, Kasturbadham, Tramba, Rajkot – 360020, India

(Received: 18 Feb, 2012; Accepted: 25 Feb, 2012; Published: 29 Feb, 2012)

**Corresponding author's email:* th.ganatra@yahoo.com

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-stimulants[2.] Cardiotonics are therapeutically used in congestive heart failure (CHF) [5,] angina pectoris[5], persistent pulmonary hypertension in newborn (PPHN) [6, 7], mitral regurgitations[4], coronary artery diseases (CAD)[4] pulmonary stenosis[4], dilated cardiomyopathy [4].

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, Proscillardin, Scilliroside	α – adrenergic: Phenylephrine, Methoxamine β – adrenergic: Isoprenaline, Prenalterol Mix adrenergic: Adrenaline, NA	Dopamine, Dopexamine, Ibopamine, Cafedrine, Theodrenaline	Amrinone, Milrinone, Enoximone, Bucladesine	Xamoterol, L- simendan, Angiotensin-amide

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 Ca^{2+} 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 cardiotonic, in which α1 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 Gs type of GPCR which further activate adenyl cyclase which increase cAMP level in myocytes, which gives positive inotropic effect and act as cardiotonic 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, dysrrhythmia, hypertension, tremor, cold extrimities, 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 vasodilatatory actions. [20]

Example of Dopaminergic drugs used as cardiotonic [12]

Dopamine, Bromocriptine, Dopexamine, Ibopamine, Cafedrine, Theodrenaline, etc.

Dopamine act on both β_1- adrenoreceptors as well as stimulates dopamine and α-adrenoreceptors. [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 gangrene [24]; Decrease TSH & thyroxin level in low birth weight newborns [23], Hypo-prolactemia [24], "Low T_3 syndrome" or Hypothyroidism; Respiratory depressions;

Miscellaneous: Severe headache, pilo-erection, skin rashes, natriueresis. [24]

Herbs which can act as a cardiotonic (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 negundo* belongs to family Verbenaceae. It was proved by Pai PT et al, that leaves of *Vitex negundo* 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*:**

Commonaly it is known as 'Kanatakari'. 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 cardiotonic 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 cardiotonic 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]

***Cocus nucifera*:**

Common name of *Cocus nucifera* is coconut, belongs to family Arecaceae. Pattigadapa et al proved cardiotonic 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 cardiotonic 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 Ca^{2+} ion mediated. [40]

***Hardinia cordifolia*:**

It is commonly known as haridru [41] belongs to family Rubiaceae. Dama GY et al proved cardiotonic activity of plant or heartwood of *Hardinia codifolia* 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 cardiotonic activity compare to digoxin with least adverse drug reaction. Future aspects of that study is to isolate the main responsible chemical constitute for its cardiotonic activity. [41]

Peltophorum pterocarpum:

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

steroidal glycosides (campesterol-3-0-beta-Dglucopyranoside, stigmasterol-3-0-beta-D-glucopyranoside and β-sistosterol-3-0-beta-glucopyranoside) which are responsible for its cardiotonic activity. They found the cardiotonic 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 cardiotonic activity of digoxin-the life saving cardiotonic. The study was done on isolated frog heart assembly, which confirmed the better cardiotonic 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 cardiotonic activity. [46]

***Astragalus membranaceous*:**

It is also known as Astragalus belongs to family Fabaceae. Kathi and Rebecca reported that the roots of *Astragalus membranaceous* show cardiotonic 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 membranaceous* to find out its mechanism of action as cardiotonic. 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 cardiotonic activity. [48]

***Crataegus pinnatifida Bunge*:**

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

***Vitis venifera*:**

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

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

4	Moraceae	Antiaris, Antiaropsis, Castilla,
5	Scrophulariaceae	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 Ca2+ releaser having caffeine-like properties, may provide a promising tool for studying the molecular mechanism of the Ca2+ 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.

REFERENCES

1. http://medical-dictionary.thefreedictionary.com/cardiotonic
2. http://en.wikipedia.org/wiki/Cardiotonic
3. http://www.hrsonline.org/patientinfo/treatments/medications/hfdrugs/
4. Peter MM et al: "How the cardiotonic pill can improve the micro- circulation of the pituitary gland; important in the function of the immunity system"; *Tasly Live Journal*
5. Drugs That Affect the Cardiovascular System; "Cardiotonics and miscellaneous inotropes", page no.: 357 – 366.
6. Drummond WH et al: "Use of cardiotonic therapy in the management of infants with PPHN"; *Clin Perinatol.* **1984**, Oct: 11 (3):715-28.
7. Abman SH. "Recent Advances in the Pathogenesis and Treatment of Persistent Pulmonary Hypertension of the Newborn"; *Neonatology*. **2007**, 91: 283-290.
8. Feldman AM et al: Classification of positive inotropic agents. **1993** Oct; 22 (4):1223-7.
9. Cornell University, Department of Animal Science "Plant poisons to livestock"
10. Desai UR: "Cardiac glycosides", VCU, School of pharmacy, January 5, **2000**.

11. Rang HP, Dale MM: "Pharmacology", Edition: 6th; Page no.: 290 – 292; Churchill Livingston, Elsevier.
12. Brunton LL, Lazo JS, Parker KL; "Goodman and Gilman's The Pharmacological Basics of Therapeutics", Edition: 11th; **2006**; Page No.: 563 - 579; MC Graw Hill, Medical publishing division.
13. Richard EK: "Cardiovascular Pharmacology Concepts": Phosphodiesterase Inhibitors.
14. Chapter: 4; Drugs Used in the Blood Circulatory System.
15. Forth; Henschler; Rummel (in German). *Allgemeine und spezielle Pharmakologie und Toxikologie*. Munich. **2002** p. 457.
16. Mutschler, Ernst; Schäfer-Korting, Monika(inGerman). *Arzneimittelwirkungen*. Stuttgart: Wissenschaftliche Verlagsgesellschaft. **1997** pp. 454–455, 496.
17. http://pharmacology-notes-free.blogspot.com/2011/03/pde-inhibitors.html
18. Cassidy JP: Review - Epinephrine: Systemic Effects and Varying Concentrations In Local Anesthesia; November: **1986**; Page No.: 289 – 297.
19. Lippincott Williams & Wilkines: "Introduction to clinical pharmacy"; Chapter: 24 (Adrenergic drugs); Wolters Kluwer Health.
20. Dei Cas L: "Clinical pharmacology of inodilators"; J Cardiovasc Pharmacol. **1989**; 14 Suppl 8:S60-71.
21. http://edoctormed.com/cardio/cordial/cardiotonic/beta/
22. Cargnelli G et al.: "Present and future trends in research and clinical applications of inodilators." **1989**; 14 Suppl 8: S124-32.
23. Filippi L: Dopamine infusion and hypothyroxinaemia in very low birth weight preterm infants. *Eur J Pediatr*. **2004** Jan;163(1):7-13. Epub 2003 Nov 25.
24. http://www.drugs.com/sfx/dopamine-side-effects.html
25. Tisdale JE: Electrophysiologic and proarrhythmic effects of intravenous inotropic agents. *Prog Cardiovasc Dis*. **1995** Sep-Oct; 38 (2):167-80.
26. A Hollman: Plants and cardiac glycosides; Br Heart 7 **1985**; 54: 258-61
27. Kirtikar KR, Basu BD. Indian Medicinal Plants, 2nd ed: M/s Bishensingh Manendra Palsingh, New Connaught Place, Dehradun; M/s Periodical Experts, Vivek Vihar, Delhi, **1935**,pp 1494-1496.
28. Akhtar N, "Pentacyclic triterpenes from the stem bark of *Mimusops elengi* l."; *Acta Poloniae Pharmaceutical and Drug Research*, Vol. 66 No. 5 pp. 549-552.
29. Shah PJ et al., "Study of *Mimusops elengi* bark in experimental gastric ulcers", *Journal of Ethnopharmacology*, **2003**, 89:2-3, 305-311
30. Katedesmukh RG et al, "Acute toxicity and diuretic activity of *Mimusops elengi* extracts"; International Journal of Pharma and Bio Sciences; Vol.1/Issue-3/Jul-Sep.2010.
31. AC. 1994. In topics in Indian medicinal plants used ayurvedic preparations, Bishen Sing Mahendra Pal, Dehradun.
32. Kenner D and Requena Y: "Botanical medicine – A European Professional Perspective"; Paradigm Publication; Page: 243.

33. Pai PT et al., "Evaluation of cardiotonic activity of leaves of *Vitex negundo* Linn"; International Journal of Green Pharmacy, Year: **2009**, Volume : 3, Issue : 4, Page : 306-309.
34. Samuel GY and Henry W, "Comparative cardiotonic activity of *solanum xanthocarpum* with digoxin on isolated frog heart"; International Journal of Institutional Pharmacy and Life Sciences.
35. Kapoor LD, *CRC Handbook of Medicinal Plants*, CRC Press, Inc., **2000** Corporate Blvd, N.W., Boca Raton, FL 33431, **1990**, 484 pp.
36. Dwivedi S., "*Terminalia arjuna* Wight & Arn.—A useful drug for cardiovascular disorders"; Preventive Cardiology Group, University College of Medical Sciences, University of Delhi, Delhi 110095, India.
37. Ghoshal, L.M., **1909**. Terminalia arjuna. Ph.D. thesis, Calcutta University, Calcutta, India.
38. Caius JS et al., "A comparative study of the dried barks of the commoner Indian species of genus Terminalia." Indian Medical Research Memoirs 16, 51–75.
39. Pattigadapa HS, "Pharmacy Cardiotonic activity of coconut water (*cocos nucifera*)" *Recent Research in Science and Technology* **2011**, 3(4): 155-157.
40. Pravin kumar P. "Evaluation of cardiac activity of some traditionally used backyard Indian medicinal plants", Research Journal of Pharmaceutical, Biological and Chemical Sciences.
41. Dama GY "Comparative Cardiotonic Activity of *Haldinia Cordifolia* With Digoxin On Isolated Frog Heart" *International Journal of Current Pharmaceutical Research*. **2011**, 3:1.
42. Bairi R et al.; "Evalution of cardiotonic activity of *Peltophorum pterocarpum" International Journal of Phytopharmacology*. **2011**, 2(1), 1-6.
43. Sabinsa cooperation, 2001 (http://www.bacopin.com/pharma.htm) .
44. Tare HL and Thube BB, "Comparative cardiotonic activity of *Cassia angustifolia* with digoxin on perfused frog heart" International Journal of Pharmaceutical Research and Development, March – **2009**, Volume I, Issue I, Article 3.
45. Adome RO et al., "The cardiotonic effect of the crude ethanolic extract of *Nerium oleander* in the isolated guinea pig hearts", *African Health Sciences*, **2003**, 3: 2; 77 – 82.
46. Dama GY et al., "Comparative cardiotonic activity of *Helicteres isora* with digoxin on isolated frog heart", *International Journal of Preclinical Research*, **2011**, 2(2): 81-86.
47. Kemper KJ and Small R., "Astragalus (Astragalus membranaceous)", The Longwood Herbal Task Force (http://www.mcp.edu/herbal/default.htm) and The Center for Holistic Pediatric Education and Research, September 3, **1999**.
48. Chen L, Liao J, Guo W. Effects of Astragalus membranaceous on left ventricular function and oxygen free radical in acute myocardial infarction patients and mechanism of its cardiotonic action. Chung Kuo Chung; **1995**; 15:141-3.
49. Jakstas V et al., "Capillary electrophoretic analysis of flavonoids in single-styled hawthorn (Crataegus monogyna Jacq) ethanolic extracts", *J*

Chromatogr A. **2006**; 1112(1-2) : 339-44.

50. Hadginhal RV et al., "Evaluation of cognitive enhancing activity of Vitis venifera Linn. on albino rats", *International Research Journal of Pharmacy*,**2008**; 2(4): 154 – 160.
51. Kirtikar KR and Basu BD, "Indian Medicinal Plants", International Book Distributors, Allahabad, edition 2nd, Volume 1, **1996**, P: 616, 634.
52. Basavaraju SR and Wagner WD, "Natural Sources of Resveratrol and Mechanisms of Action with Emphasis on Cardiovascular Disease: A Brief Review".
53. Agrawal BB et al., a review on "From traditional Ayurvedic medicine to modern medicine: identification of therapeutic targets for suppression of inflammation and cancer", Ashley Publications, Page no.: 95.
54. Ohizumi Y., "Novel types of cardiotonic drugs", Nippon yakurigaku zasshi Folia *pharmacologica Japonica* **1992**; 100(3): 259-269.
55. Endoh M., "Mechanisms and Pharmacological Classification of Ca^{2+} Sensitizers"; *Recent Researches in Modern Medicine.* **2011.**