Terminalia arjuna in Cardiovascular Diseases: Making the Transition from Traditional to Modern Medicine in India

S.K. Maulik[1,*] and C.K. Katiyar[2]

[1]*Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India;* [2]*Ayurvedic Research, Dabur Research and Development Centre, Ghaziabad (U.P.), India*

Abstract: The stem bark of *Terminalia arjuna* (Roxb.) is used by the Ayurvedic physicians in India for the treatment of various cardiovascular diseases, collectively referred to as *hritroga*. It has been extensively studied in animal models to demonstrate cardioprotective properties, ranging from positive inotropic- , hypolipdemic-, coronary vasodilatory- and antioxidant effects to induction of stress protein in heart. Various bioactive compounds, like triterpinoids, tannins, flavonoids and minerals have been isolated from the stem bark. A number of clinical studies have also reported its beneficial effects in patients of chronic stable angina, endothelial dysfunction, heart failure and even ischemic mitral regurgitation. However, there are some identified lacunae, like standardisation of the 'drug', toxicity studies along with pharmacological interactions with other drugs and large multicentre randomized clinical trials, before its use by modern medicine is acceptable.

Keyword: Terminalia arjuna, heart failure, cardiovascular disease, clinical trial, preconditioning, ayurveda, medicinal plants.

INTRODUCTION

Plants have been a major source of drugs in modern medicine for the last two centuries [1]. Digoxin (*Digitalis lanata*), reserpine (*Rauvolfia serpentine*), morphine (*Papaver somniferum*), quinine/quinidine (*Cinchona ledgeriana*), physostigmine (*Physostigma venenosum*) are some of the hundreds of such examples. The practitioners of ancient systems of medicine across the world, like Ayurvedic, Unani, Chinese were also aware of this fact and used the plants accordingly in various ailments afflicting mankind.

AYURVEDIC INFORMATION

In Ayurvedic system of medicine, one such medicinal plant is *Terminalia arjuna* (Roxb. Combretaceae family), which is known as arjuna in many Indian languages. Arjuna has been used as a medicinal plant since the period of *Vedas*. In Ayurvedic texts [2], it is addressed with synonyms of *Arjun*, the Hero of the great epic, *Mahabharata*. Other synonyms used for Arjuna are *Kukubha*, *Nadi Sarja*, *Indradru*, *Veera Vrksha*, *Veera*, *Dhavala* etc. It is mainly attributed with *Kashaya Rasa* (Astringent taste), and *Sheeta Veerya* (cooling property) as its inherent property. The stem bark of the plant is mainly used for medicinal purposes. It is mentioned to be a cardiac tonic (*Hrdya*). The bark of Arjuna is indicated for *Kshata* (injury or wound), *Kshaya* (ematiated condition), *Visha* (poison), *Rakta Vikara* (as a styptic), *Meda Roga* (obesity), *Prameha* (urinary disorders), *Vrana* (ulcer/ wound) etc. It pacifies the *Kapha* and *Pitta Dosha* as per *Ayurveda*. It has been used in powder form, decoction and Ksheerpak (boiled in water and milk) as cardioprotective.

*Address correspondence to this author at the Department of Pharmacology, All India Institute of Medical Sciences, New Delhi 110029, India; E-mail:skmaulik@gmail.com

The tree grows throughout the greater part of the Indian subcontinent, Burma and Sri Lanka. It is particularly found in the sub-Himalayan tracts. In India, its use is considerable in view of the fact that Ayurvedic system of medicine has an official recognition in India. Moreover, the bark powder is easily available as an over the counter (OTC) product, without a prescription.

Many important biologically active chemical compounds have been isolated from *T. arjuna.* These include triterpenoids (like, arjunolic acid, arjunic acid, arjungenin, arjunoglucoside), tannins (ellagic acid, gallic acid), flavonoids (leucocyanidin, luteolin) and minerals (magnesium, calcium, zinc and copper) (Table **1**).

Over the last few decades, there has been a resurgence of scientific interest in exploring the pharmacological activities of the plant using modern methodologies.

EXPERIMENTAL STUDIES

Experimental studies have been largely based on the observations made in the Ayurvedic literature. Various extracts and their doses were selected with careful consideration of their traditional use (Table **2**).

Cardiostimulatory Effects

About one hundred years ago, its direct inotropic effect was first reported in isolated hearts of rabbit and frog [3]. Thereafter, various other studies have documented positive cardiac inotropic and chronotropic effects of the bark powder, its water and alcoholic extracts in different *in vitro and vivo* animal models [3-6]. More recent studies have also shown that alcoholic extract of *T. arjuna* had a negative inotropic and chronotropic effects in isolated frog heart, rat atria and isolated perfused frog and rabbit hearts [7], while

1389-2010/10 $55.00+.00

the aqueous extract of the bark in isolated rat atria demonstrated positive inotropic activity [8].

Table 1. Major Chemical Compounds, Isolated from The Stem Bark of *Terminalia arjuna* (Roxb.)

Chemical Compounds
A: Triterpenoids
1. Arjunolic acid 2. Arjungenin 3. Arjunic acid 4. Arjunglycoside 5. Arjunolitin 6. Arjunoside 7. Arjunetoside
B: Tannnins
1. Pentagalloyl glucose 2. Hexadroxdiphenyl galloyl glucose 3. Tetragalloyl glucose 4. Ellagic acid
C: Flavonoids
1. Leucocyanidin 2. Luteolin
D: Minerals
1. Magnesium 2. Calcium 3. Zinc and Copper

Blood Pressuring Lowering Effects

A number of experimental studies have reported its effects on blood pressure. Both water [9] -and alcoholic extracts [10] of the bark caused dose -dependent fall in blood pressure in anesthetized dogs. Interestingly dose-dependent hypotensive effect of the alcoholic extract was blocked by propranolol but not by atropine and mepyramine. It indicates the presence of some active compound(s) possessing ß2- adrenergic receptor agonist effect. In another study, the aqueous extract as well as a fraction of the extract containing tannin-related compounds produced hypotensive effects [11]. This hypotensive effect was not affected by pre-treatment with propranolol, but was blocked by pre-treatment with atropine. This implies an involvement of cholinergic system in its hypotensive effect. Intracerebroventricular administration of both these extracts caused hypotension and bradycardia in anesthetized dogs, suggesting a central effect. The effects were blocked by prior vagotomy [12]. Despite all these experimental supports, it is interesting to note (see below) that there is no reported clinical study on its blood pressure lowering effects.

Direct Cardioprotective Effects

Enhanced oxidative stress has been identified as a novel risk factor for coronary artery disease in addition to traditional risk factors [13]. A number of recent studies have reported antioxidant activities of *T. arjuna*. The antioxidant effect of pulverised bark powder of *T. arjuna* on ischemic perfused rat heart has been reported by us [14]. In this study, oral administration of the bark powder for a long period (12 weeks) in rats caused augmentation of endogenous cardiac antioxidants, like superoxide dismutase (SOD), reduced glutathione (GSH) and catalase (CAT). Significant protection against oxidative stress was observed when hearts from these rats were subjected to *in vitro* ischemic-reperfusion injury. In a subsequent study [15], we have reported that chronic administration of the pulverised bark powder in rabbits not only augmented the cardiac antioxidants but also caused induction of heat shock protein 72 in cardiac muscle. This offered further protection against oxidative stress associated

Table 2. Experimental Studies with the Stem Bark of *T. arjuna*

Pharmacological Effect	Preparation	Model	Ref.
1. Cardioprotective Effects	1. a) Pulverised bark powder fed orally for 12 weeks b) Pulverised bark powder fed orally for 12 weeks c) Polyherbal preparation containing *T.arjuna* d) Arjunolic acid isolated from the stem bark e) Alcoholic extract administered orally f) Butanolic fraction administered g) Ethanol extract h) Water extract	a) *In vitro* ischemic reperfusion injury (IR) in rat b) *In vivo* IR-injury & myocardial hsp 72 expression in rabbits c) Isoproterenol induced myocardial injury in rat d) Isoproterenol induced myocardial injury in rat e) Oxidative stress in isoproterenol induced myocardial injury in rat f) Doxorubicin induced myocardial injury in rat g) Na-fluoride induced myocardial injury in rat h) Isoproterenol induced myocardial hypertrophy, fibrosis and oxidative stress in rat	[14] [15] [18] [19] [21] [22] [24] [25]
2.Antioxidant effects	2. Arjungenin isolated from the stem bark	*In vitro* free radical scavenging activity	[20]
3. Lipid lowering effect	3.a) Crude extract b) Alcoholic extract c) Crude extract	a) High cholesterol diet -induced hyperlipidemia in rabbits b) Hypercholesterolemia in rabbits c) Atherosclerosis in rabbits	[26] [27 29]

with *in vivo* myocardial ischemic-reperfusion injury both in terms of oxidative stress and hemodynamic recovery. In this regard, it is worth mentioning that heat shock protein is known to provide protection against a variety of tissue injury, including ischemia-reperfusion injury by its chaperoning function [16, 17]. In an earlier study, a polyherbal preparation containing *T. arjuna* offered significant protection against isoproterenol-induced myocardial injury in rabbits, while the preparation without *T. arjuna* did not offer protection to a similar extent [18]. Arjunolic acid isolated from the bark of *T. arjuna* also prevented oxidative stress and histopathological changes associated with isoproterenol-induced myocardial injury [19]. Arjungenin an oleanane terpenoid and a glucoside, arjunglucoside II isolated from *T. arjuna* bark have been reported to exert *in vitro* free radical scavenging activities in human polymorphonuclear cells [20]. Alcoholic extract of the bark administered for 4 weeks in rats also prevented isoproterenol-induced myocardial necrosis and oxidative stress (increased TBARS and depleted glutathione levels as well as reduced SOD and catalase activities) [21]. Butanolic fraction of the ethanolic extract of the bark demonstrated protective effects against doxorubicin-induced myocardial oxidative stress, serum CKMB levels and ultrastructural changes (mitochondrial swelling, Z-band disarray, focal dilatation of smooth endoplasmic reticulum and lipid inclusions) in rat [22]. The bark extract prevented adriamycin-induced micronuclei formation in cultured human peripheral blood lymphocytes [23]. An ethanol extract of the bark of *T. arjuna* has been reported to be effective against sodium fluoride -induced oxidative stress in murine heart. The study is important in view of the fact that fluoride is a ubiquitous environmental pollutant [24]. Recently we have reported that a standardised water extract of *T. arjuna* bark was effective in preventing major deleterious events, like increased oxidative stress, collagen content and fibrosis - associated with isoproterenol-induced left ventricular hypertrophy in rat. However, it did not affect the changes in heart weight: body weight and increase in myocytes diameter. As oxidative stress and fibrosis cause progression of hypertrophy to heart failure, attenuation of these factors might be clinically meaningful [25]. We have observed the protective effect of the standardised water extract of *T. arjuna* in an animal model of left ventricular dysfunction (unpublished data). Left ventricular dysfunction was produced in rat with daily low-dose (sub-necrotic; 5mg/kg s.c.) administration of isoproterenol (a β adrenoceptor agonist) for 12 weeks. The rats developed left ventricular hypertrophy, which slowly underwent adverse remodeling to cause ventricular dilatation with reduction in left ventricular ejection fraction in serial echocardiography. The standardised extract along with diuretic and enalapril caused statistically significant improvement in ejection fraction, maintained for a period of 8 weeks. The study supports a possible role of adjunct therapy of *T. arjuna* along with other standard drugs in patients of heart failure.

Lipid Lowering Effects

There are a number of animal studies which have reported beneficial effects of *T. arjuna* on plasma total cholesterol, LDL and HDL levels. Crude extract demonstrated marked reduction in total cholesterol and triglycerides along with rise in high density lipoprotein cholesterol in high cholesterol diet- induced hyperlipidemia in rabbits [26]. However, in a later study [27], alcoholic extract of the bark in hypercholesterolemia rabbits caused significant reduction in total cholesterol and LDL cholesterol levels, with a trend in the decrease in HDL- cholesterol (which was not significant) and no effect on triglycerides. It highlights the presence of different bioactive compounds in the extracts used in these studies. Serum lipids were found to be lowered by *T. arjuna* in triton-induced as well as cholesterol-fed hyperlipidemia in rats [28]. The lipid lowering action of this natural product has been attributed to inhibition of hepatic cholesterol biosynthesis, increased fecal bile acid excretion, enhanced plasma lecithin:cholesterol acyltransferase activity and stimulation of receptor mediated catabolism of low density lipoprotein. *T. arjuna* also inhibited development of atherosclerotic lesions in cholesterol-rich diet induced hyperlipidemic rabbits [29].

Antioxidative Effects

Various studies have reported antioxidative properties of this plant mostly in relation to different pathological conditions. However, there are no *in vitro* antioxidative studies available which can provide mechanistic insights Ethanolic extract of the stem bark reduced oxidative stress and caused a significant increase in superoxide dismutase, catalase, glutathione peroxidase activities in the liver and kidney tissues of alloxan-induced diabetic rats [30]. Many of the above mentioned animal studies have also reported significant antioxidant effects of the plant.

CLINICAL STUDIES

Based on the observations made from experimental studies and more importantly due to its use in Indian traditional system of medicine, a number of clinical studies have been carried out in various types of cardiovascular diseases.

Ischemic Heart Disease

The effect of bark powder of *T. arjuna* on anginal frequency, blood pressure, body mass index, blood sugar, cholesterol and HDL-cholesterol was studied in 15 stable and 5 unstable angina patients for 3 months [31]. There was 50% reduction in anginal episodes in stable angina patients. The time to the onset of angina and appearance of ST changes on stress test after *T. arjuna* was delayed significantly. However, in patients with unstable angina there was no significant reduction in anginal frequency. These patients also needed other drugs. like diltiazem, beta-blockers and nitroglycerine. There was fall in systolic blood pressure and body mass index to a significant level and marginal increase in HDL-cholesterol along with some improvement in left ventricular ejection fraction in stable angina patients. There were no deleterious effects on liver or kidney functions. The authors of this study concluded that monotherapy with *T. arjuna* may be fairly effective in patients with stable angina pectoris. In another randomized, double-blind, crossover study [32], 48 male patients with chronic stable angina with evidence of ischemia on treadmill test received *T. arjuna* (500 mg 8 hourly), isosorbide mononitrate (40 mg/daily) or a matching placebo for one week. There was a significant decrease in the fre-

quency of angina and need for isosorbide dinitrate in the patients receiving *T. arjuna*. The treadmill exercise test parameters also improved significantly in this group. In an open label non-randomised trial, a proprietary herbal product primarily containing *T. arjuna* in 10 patients of stable angina, reduced anginal episodes significantly over a period of 12 weeks. It did not cause any change in hepatic or renal functions [33]. In a double blind randomised placebo controlled study, stem bark powder of *T. arjuna* (500 mg 8 hourly for one month) reduced ischemic mitral regurgitation in patients of fresh myocardial infarction and improved diastolic dysfunction significantly. The authors have suggested the use of *T. arjuna* in acute MI along with other antiischemic measures [34]. All these studies strongly indicate antiischemic effects of the plant, which can be used concurrently with the modern drugs.

Heart Failure

Treatment of heart failure in modern medicine is far from satisfactory. Until recently, when some beta-blockers (carvedilol) and ACE-inhibitors were found useful, there was hardly any drug which targeted the basic pathphysiology of the disease. Even these drugs are poorly tolerated in many heart failure patients. Therefore, most drugs used in heart failure cause sympotomatic relief without much effect on the overall morbidity and mortality. In fact, the two-century old digoxin is no longer indicated in these patients. In this context, the use of *T. arjuna* might be very promising.

An hydroalcoholic extract of *T. arjuna* (500 mg q8h) demonstrated some beneficial effects in 12 patients of severe refractory heart failure (NYHA class IV) [35]. The study was divided into two 'phases', in 'phase I' the extract was administered to patients in a double blind cross-over design as an adjuvant to maximally tolerable conventional therapy for 2 weeks with a 2 week drug/ placebo free period during cross-over. *T. arjuna*, compared to placebo, caused improvement in symptoms and signs of heart failure, improvement in NYHA Class (Class III vs. Class IV) and increase in left ventricular ejection fractions (35.33 ± 7.85 vs. $30.24 \pm 7.13\%$; $p < 0.005$). Subsequently in an open design ('phase II'), responders of 'phase I' participants continued to receive the same preparation of *T. Arjuna* in the same dose in addition to diuretic, vasodilator and digitalis for 20-28 months (mean 24 months). Patients showed continued improvement in symptoms, signs, effort tolerance, NYHA Class and in quality of life. Although, the study has certain lacunae, it is the only study which reported beneficial effects of *T. arjuna* in heart failure patients. This interesting finding has generated a need for larger randomized placebo controlled trials in this condition.

Hyperlipidemia

In a randomised placebo-controlled trial, 105 patients with coronary heart disease received pulverized *T. arjuna* bark-powder (500 mg daily) for 30 days [36]. All patients followed American Heart Association Step II dietary advice and were not prescribed any other lipid lowering drugs. There was a significant decrease in total cholesterol and LDL cholesterol in the *T. arjuna* treated patients.

Endothelial Dysfunction

Endothelial dysfunction is characterized by reduced vasodilatation, a proinflammatory and prothrombic state. It has been documented in hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, and diabetes mellitus. Therapeutic strategies directed to prevent endothelial dysfunction is associated with reduced cardiovascular risk [37, 38]. In a double blind cross-over study, *T. arjuna* extract (500 mg q8h orally) or placebo were administered for two weeks in eighteen healthy, normotensive, non-diabetic, normo-lipidemic, chronic cigarettes smokers with no family history of cardiovascular disease [39]. *T. arjuna* reversed smoking-related endothelial dysfunction (as measured by both endothelium-dependent and endothelium-independent, flow-mediated dilation of brachial artery). The study participants continued smoking during the intervention to remove any beneficial effect of smoking cessation confounding the study results. The authors claimed that this benefit was similar to the reported reversal of endothelial dysfunction in smokers with the use of vitamins C and E.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) occurs in response to chronic systemic hypertension and many other cardiovascular disorders. It is an independent risk factor for heart failure, stroke, arrhythmias and sudden cardiac death [40]. In the short term, increase in LV mass (LVM) may be beneficial; however, in the long term, it can deteriorate to maladaptive hypertrophy and to increased cardiovascular risk [41]. Both animal and human studies have revealed that appropriate therapy can cause regression of LVH and is associated with lower CV risk [42]. As a result, prevention or reversal of LVH is widely accepted as a desirable treatment strategy. In this regard, *T. arjuna* has been reported to reduce LVM (159.18 ± 51.11 g/m^2 to 140.62 ± 55.65 g/m^2) along with improvement in LV ejection fraction in patients of angina [43].

LACUNAE AND FUTURE

The major lacunae of the studies reported on *T. arjuna* are mainly: i) absence of information on quality standards of the preparations used, ii) safety data of the preparation, iii) clinically meaningful drug interaction/s reports with the preparation and iv) large randomised placebo controlled clinical trials.

Very few or no reported study with *T. arjuna* has mentioned about the standardisation process of the plant part used. Botanical identification (herbarium reference number) and source are missing in many study reports. In many cases, authors might not have been aware of such necessities.

In future all experimental and clinical trials should use standardised preparations of *T. arjuna*. The standardisation process should include a) mention of the plant part used, b) botanical identification (both macroscopic and microscopic), c) identified phytoconstituents present; their chemistry and thin layer chromatography and d) adulterants. This is very useful in comparing data from various studies.

There is a widely held belief that medicinal plants are safe. However, this has been refuted many a time. Many countries have adopted certain guidelines in handling this issue

[44]. Indian Council of Medical Research has drafted a guideline on safety issues of herbal products which have three categories; category 1; a lot is known about the use of a plant or its extract in ancient literature or the plant may actually be regularly used by physicians of the traditional systems of medicine for a number of years and the substance is to be clinically evaluated for same indication for which it is being used or as has been described in the texts, category 2; when an extract of a plant has to be clinically evaluated for a therapeutic effect not originally described in the texts of traditional systems or, the method of preparation is different, it has to be treated as a new substance or new chemical entity (NCE) and the same type of acute, subacute and chronic toxicity data will have to be generated as required by the regulatory authority for synthetic products before it is cleared for clinical evaluation and category 3; an extract or a compound isolated from a plant which has never been in use before and has not ever been mentioned in ancient literature, should be treated as a new drug, and therefore, should undergo all regulatory requirements before being evaluated clinically [45].

Treatment of cardiovascular diseases requires more than one drug and is usually life-long. If *T. arjuna* has to be established in the treatment of any of these conditions, it has to be as an adjunct therapy. In recent years, there have been many reports of many herbs altering the pharmacokinetic and pharmacodynamic profiles of co-administered drugs. There has been a great concern about drug-herb interactions during the last few years and many studies have reported how concurrent administration of herbs can alter the effectiveness of other drugs [46, 47]. In this context, it is important to understand what kind of interactions are possible with *T. arjuna* with other most commonly prescribed drugs for heart ailments. It will help in mitigating negative interactions and may also help enable synergistic interactions.

Finally, a standardized extract which has passed the preclinical safety and efficacy studies as per regulatory guidelines, should be subjected to randomised placebo-controlled add-on studies in selected groups of patients.

REFERENCES

[1] Alviano, D.S.; Alviano, C.S. Plant extracts: search for new alternatives to treat microbial diseases. *Curr. Pharm. Biotechnol.*, **2009**, *10* (1), 106-21.

[2] Mishra, B.; Chunekar, K.C.; Bhava Prakasha Nighantu, Chaukhamaba Bharati Academy, Varanasi, **2002**; pp. 523-524.

[3] Ghoshal, L.M. *Terminalia arjuna*. Ph.D. thesis, Calcutta University, Calcutta, India, **1909**.

[4] Caius, J.S.; Mhaskar, K.S.; Isaacs, M. A comparative study of the dried barks of the commoner Indian species of genus Terminalia. *Indian Med. Res. Memoirs,* **1930**, *16*, 51-75.

[5] Chopra, R.N.; Chopra, I.C.; Handa, K.L.; Kapur, L.D. *Terminalia arjuna* W&A (Combretaceae). Chopra, R.N.; Chopra, I.C.; Handa, K.L.; Kapur, L.D. Eds.; *Chopra's Indigenous Drugs of India,* 1st ed.; UN Dhur & Sons: Calcutta, India, **1958**, pp. 421-424.

[6] Gupta, L.P.; Sen, S.P.; Udupa, K.N. Pharmacological studies on Terminalia arjuna. *J. Res. Indian Med.,* Yoga and Homeopath., **1976**, *11*, 16-24.

[7] Srivastava, R.D.; Dwivedi, S.; Sreenivasan, K.K.; Chandrashekhar, C.N. Cardiovascular effects of Terminalia species of plants. *Indian Drugs*, **1992**, *29*, 144-149.

[8] Radhakrishnan, R.; Wadsworth, R.M.; Gray, A.I. *Terminalia arjuna*, an Ayurvedic cardiotonic, increases contractile force of rat isolated atria. *Phytother. Res.,* **1993**, *7,* 266-268.

[9] Vaidya, A.B. Terminalia arjuna is cardiovascular therapy. *J. Assoc. Phys. India,* **1994**, *42,* 281-282.

[10] Nammi, S.; Gudavalli, R.; Babu, B.S.; Lodagala, D.S.; Boini, K.M. Possible mechanism of hypotension produced by 70% alcoholic extract of *Terminalia arjuna* (L.) in anaesthetised dogs. *BMC Complement. Altern. Med.,* **2003**, *3,5.*

[11] Takahashi, S.; Tanaka, H.; Hano, Y.; Ito, K.; Nomura, T.; Shigenobu, K. Hypotensive effects in rats of hydrophilic extract from *Terminalia arjuna* containing tannin-related compounds. *Phytother. Res.,* **1997**, *1*, 424-427.

[12] Singh, N.; Kapur, K.K.; Singh, S.P.; Shankar, K.; Sinha, J.N.; Kohli, R.P. Mechanism of cardiovascular action of *Terminalia arjuna*. *Planta Med.*, **1982**, *45*, 102-104.

[13] Kotur-Stevuljevic, J.; Memon, L.; Stefanovic, A.; Spasic, S.; Spasojevic-Kalimanovska, V.; Bogavac-Stanojevic, N.; Kalimanovska-Ostric, D.; Jelić-Ivanovic, Z.; Zunic, G. Correlation of oxidative stress parameters and inflammatory markers in coronary artery disease patients. *Clin. Biochem*., **2007**, *40*(3-4), 181-187.

[14] Gauthaman, K.; Maulik, M.; Kumari, R.; Manchanda, S.C.; Dinda, A.K.; Maulik, S.K. Effect of chronic treatment with bark of Terminalia arjuna: a study on the isolated ischemic-reperfused rat heart. *J. Ethnopharmacol.,* **2001**, *75*, 197-201.

[15] Gauthaman, K.; Banerjee, S. K.; Dinda, A.K.; Ghosh, C.C.; Maulik, S.K. Terminalia arjuna (Roxb.) protects rabbit heart against ischemic-reperfusion injury: role of antioxidant enzymes and heat shock protein. *J. Ethnopharmacol.,* **2005**, *96* 403-409.

[16] Dancsó, B.; Spiró, Z.; Arslan, M.A.; Nguyen, M.T.; Papp, D.; Csermely, P.; Sőti, C. The heat shock connection of metabolic stress and dietary restriction. *Curr. Pharm. Biotechnol.,* **2010**, *7*, 139-145.

[17] Gray, C.C.; Amrani, M.; Yacoub, M.H. Heat stress proteins and myocardial protection: experimental model or potential clinical tool? *Int. J. Biochem. Cell Biol*., **1999**, *31*, 559-73.

[18] Dwivedi, S.; Somani, P.N.; Chansouria, J.P.N.; Udupa, K.N. Cardioprotective effects of certain indigenous drugs in myocardial ischemia in rabbits. *Indian J. Exp. Biol.,* **1988**, *26*, 969-975.

[19] Sumitra, M.; Manikandan, P.; Kumar, D.A.; Arutselvan, N.; Balakrishna, K.; Manohar, B.M.; Puvanakrishnan, R. Experimental myocardial necrosis in rats: role of arjunolic acid on platelet aggregation, coagulation and antioxidant status. *Mol. Cell. Biochem.,* **2001**, *224*, 135-142.

[20] Pawar, R.S.; Bhutani, K.K. Effect of oleanane triterpenoids from Terminalia arjuna—a cardioprotective drug on the process of respiratory oxyburst. *Int. J. Phytomed. Phytopharmacol.,* **2005**, *12,* 391-393.

[21] Karthikeyan, K.; Bai, B.R.; Gauthaman, K.; Sathish, K.S.; Devaraj, S.N. Cardioprotective effect of the alcoholic extract of Terminalia arjuna bark in an *in vivo* model of myocardial ischemic reperfusion injury. *Life Sci.,* **2003**, *73*, 2727-2739.

[22] Singh, G.; Singh, A.T.; Abraham, A.; Bhat, B.; Mukherjee, A.; Verma, R.; Agarwal, S.K.; Jha, S.; Mukherjee, R.; Burman, A.C. Protective effects of Terminalia arjuna against doxorubicin-induced cardiotoxicity. *J. Ethnopharmacol*., **2008**, *117*, 123-129.

[23] Reddy, T.K.; Seshadri, P.; Reddy, K.K.; Jagetia, G.C.; Reddy, C.D. Effect of Terminalia arjuna extract on adriamycin-induced DNA damage. *Phytother. Res*., **2008**, *22*, 1188-1194.

[24] Sinha, M.; Manna, P.; Sil, P.C. Terminalia arjuna protects mouse hearts against sodium fluoride-induced oxidative stress. *J. Med. Food,* **2008**, *11*, 733-740.

[25] Kumar, S.; Enjamoori, R.; Jaiswal, A.; Ray, R.; Seth, S.; Maulik, S.K. Catecholamine-induced myocardial fibrosis and oxidative stress is attenuated by Terminalia arjuna (Roxb.). *J. Pharm. Pharmacol.,* **2009**, *61*,1529-1536.

[26] Tiwari, A.K.; Gode, J.D.; Dubey, G.P. Effect of Terminalia arjuna on lipid profiles of rabbit fed hypercholesterolemic diet. *Pharm. Biol.,* **1990**,*28*, 43-47.

[27] Ram, A.; Lauria, P.; Gupta, R.; Kumar, R.; Sharma, V.S. Hypocholesterolemic effects of Terminalia arjuna tree bark. *J. Ethnopharmacol.,* **1997**, *55,* 165-169.

[28] Khanna, A.K.; Chander, C.; Kapoor, N.K. Terminalia arjuna: an Ayurvedic cardiotonic regulates lipid metabolism in hyperlipidemic rats. *Phytother. Res.,* **1996**, *10*, 663-666.

[29] Shaila, H.P.; Udupa, S.L.; Udupa, A.L. Hypolipidemic activity of three indigenous drugs in experimentally induced atherosclerosis. *Int. J. Cardiol.,* **1998**, *67*, 119-124.

[30] Dwivedi, S.; Agarwal, M.P. Antianginal and cardioprotective effects of Terminalia arjuna, an indigenous drug, in coronary artery disease. *J. Assoc. Phys. India*, **1994**, *42*(4), 287-289.

[31] Bharani, A.; Ganguli, A.; Mathur, L.K.; Jamra, Y.; Raman, P.G. Efficacy of Terminalia arjuna in chronic stable angina: a double-blind, placebo-controlled, crossover study comparing Terminalia arjuna with isosorbide mononitrate. *Indian Heart J*., **2002**, *54*(2),170-175.

[32] Kumar, P.U.; Adhikari, P.; Pereira, P.; Bhat, P. Safety and efficacy of Hartone in stable angina pectoris--an open comparative trial. *J. Assoc. Physicians India,* **1999**, *47*, 685-689.

[33] Dwivedi, S.; Aggarwal, A.; Agarwal, M.P.; Rajpal, S. Role of Terminalia arjuna in ischaemic mitral regurgitation. *Int. J. Cardiol*., **2005**, *100*, 507-508.

[34] Bharani, A.; Ganguly, A.; Bhargava, K.D. Salutary effect of Terminalia Arjuna in patients with severe refractory heart failure. *Int. J. Cardiol*., **1995**, *49*, 191-199.

[35] Gupta, R.; Singhal, S.; Goyle, A.; Sharma, V.N. Antioxidant and hypocholesterolaemic effects of Terminalia arjuna tree-bark powder: a randomised placebo-controlled trial. *J. Assoc. Physicians India,* **2001**, *49*, 231-235.

[36] Davignon, J.; Ganz, P. Role of endothelial dysfunction in atherosclerosis. *Circulation*, **2004**, *109*, 327-332.

[37] Endemann, D.H.; Schiffrin, E.L. Endothelial dysfunction. *J. Am. Soc. Nephrol.,* **2004**, *15*, 1983-1992.

[38] Bharani, A.; Ahirwar, L.K.; Jain, N. Terminalia arjuna reverses impaired endothelial function in chronic smokers. *Indian Heart J.*, **2004**, *56*(2),123-128.

[39] Artham, S.M.; Lavie, C.J.; Milani, R.V.; Patel, D.A.; Verma, A.; Ventura, H.O. Clinical impact of left ventricular hypertrophy and implications for regression. *Prog. Cardiovasc. Dis*., **2009**, *52*(2),153-167.

[40] Katz, A.M. Cardiomyopathy of overload: a major determinant of prognosis in congestive heart failure. *N. Engl. J. Med.,* **1990**, *322*, 100-110.

[41] Prineas, R.J.; Rautaharju, P.M.; Grandits, G. MRFIT Research Group. Independent risk for cardiovascular disease predicted by modified continuous score ectrocardiographic criteria for 6-year incidence and regression of left ventricular hypertrophy among clinically disease free men: 16-year follow-up for the multiple risk-factor intervention trial, *J. Electrocardiol.,* **2001**, *34,* 91-101.

[42] Dwivedi, S.; Jauhari, R. Beneficial effects of Terminalia arjuna in coronary artery disease. *Indian Heart J.,* **1997**, *49*, 507-510.

[43] Wu, K.M.; Ghantous, H.; Birnkrant, D.B. Current regulatory toxicology perspectives on the development of herbal medicines to prescription drug products in the United States. *Food Chem. Toxicol.*, **2008**,*46,* 2606-2610

[44] Ethical Guidelines for Biomedical Research on Human Subjects. *Indian Council of Medical Research,* New Delhi, India, **2000**; pp. 51-52.

[45] Chavez, M.L.; Jordan, M.A.; Chavez, P.I. Evidence-based drug--herbal interactions. *Life Sci.,* **2006**, *78*, 2146-2157.

[46] Tachjian, A.; Maria, V.; Jahangir, A. Use of herbal products and potential interactions in patients with cardiovascular diseases. *J. Am. Coll. Cardiol.,* **2010**, *55*, 515-525.

[47] Buijsse, B.; Freskens, E. J.; Kok, F.J.; Kromhout, D. Cocoa intake, blood pressure, and cardiovascular mortality: the Zutphen Elderly Study. *Arch. Intern. Med.*, **2006**, *166*, 411-417.

Received: ????????????????? Revised: ????????????????? Accepted: ?????????????????