Indian J Physiol Pharmacol 2018; 62(1) : 8–19

Review Article

Role of *Terminalia Arjuna* in Improving Cardiovascular Functions : A Review

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Abstract

Cardiovascular diseases are the most common cause of deaths worldwide and will become even more prevalent with the recent changes in life style, food habits and environmental pollution. Herbal medicines have been used for cardiovascular diseases and some of their derivatives have become mainstay of human pharmacotherapy. Various clinical and pharmacological studies have indicated the cardioprotective role of *Terminalia arjuna* in cardiac ailments. The present review is an effort to give a detailed survey of the literature summarizing the experimental studies of *T. arjuna* on cardiovascular system. It mainly focuses on experimental studies pertaining to various aspects of cardiovascular functions, autonomic control of myocardial functions, molecular mechanisms of its action and Cardiac histopathology.

Introduction

Cardiovascular diseases (CVD) are the number one cause of death worldwide (1). In addition to mortality, poorly managed CVD can lead to significant long-term disability from their complications. In the past quarter century, much progress has been made in understanding the molecular and cellular processes that contribute to CVD, leading to the development of effective therapies.

Natural products due to their chemical diversity are receiving increased attention from scientific and pharmaceutical communities. The newer work on medicinal plants is mostly the rediscovery of traditional effects at cellular and molecular levels (2). *Terminalia arjuna* (*T. arjuna*, -Family: Combretaceae), is an important medicinal plant widely used in medicinal formulations for several ailments. It is used in traditional medicine for treating ulcers, wound healing, and also for antibacterial, antimutagenic/anticarcinogenic, antioxidant and hypocholesterolemic activities (3-8). The use of *T. arjuna* bark in the management of cardiovascular diseases has been widely reported (8-16). This review

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(Received on August 1, 2017)

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Plant profile

Habitat

Terminalia arjuna is a deciduous and evergreen tree, standing 20–30 m above ground level (Fig. 1). It belongs to Combretaceae family (17-19). It is found in abundance throughout Indo-sub-Himalayan tracts of Uttar Pradesh, South Bihar, Madhya Pradesh, Delhi and Deccan region near ponds and rivers. It is also found in forests of Sri Lanka, Burma and Mauritius (20).

Ethnomedical considerations

The bark, leaves and fruits of *T. arjuna* have been used in indigenous system of medicine for different ailments (21). The bark is said to be sweet, acrid, cooling and heating, aphrodisiac, expectorant, tonic, styptic, antidysenteric, purgative and laxative. Its use has been advocated in urinary discharge, strangury, leucoderma, anaemia, hyperhidrosis, asthma and tumours. The use of bark powder as an astringent and diuretic finds mention in the literature (22). The bark powder has been attributed to possess cardioprotective properties (8-15).

Phytochemistry

From medicinal point of view bark of *T. arjuna* was considered to be the most important constituent. Hence most of the early studies were limited to bark stem of the plant. Chemical analysis of the bark showed evidence of sugar, tannins (12%), colouring matter, a glycoside, and carbonates of calcium, sodium and traces of chloride of alkali metals (23). Subsequently presence of an alkaloid as well as a glycoside was confirmed. The major chemical constituents of various parts of *T. arjuna* are shown in Table I. The glycoside was capable of increasing the force of contraction of the frog heart (24). Attempt to isolate the glycoside resulted into finding of an organic acid with a high melting point, a phytosterol, an organic ester easily hydrolysed by mineral acids, 12% tannins consisting largely of pyrocatechol tannins, large quantities of calcium and smaller amounts of aluminium and magnesium salts, colouring matter and sugar (17).

Experimental studies

Studies based on autonomic control of cardiovascular functions

The cardiovascular system is subject to precise reflex regulation so that an appropriate supply of oxygenated

Fig. 1 : *Terminalia arjuna* plant.

TABLE I: Major chemical constituents of various parts of *Terminalia arjuna* (22).

	(A) Stem bark
1.	Triterpenoids: arjunin, arjunic acid, arjunolic acid, arjungenin, terminic acid (25,26)
2.	Glycosides: arjunetin, arjunoside I, arjunoside II, arjunaphthanoloside, terminoside A (23,24).
3.	Sitosterol (24, 26).
4.	Flavonoids: arjunolone, arjunone, bicalein, luteolin, gallic acid, ethyl gallate, quercetin, kempferol, pelorgonidin, oligomeric proanthocyanidins (27,28).
5.	Tanins: pyrocatechols, punicallin, punicalagin, terchebulin, terflavin C, castalagin, casuariin, casuarinin (17, 23, 29).
6.	Minerals/trace elements: calcium, aluminium, magnesium, silica, zinc, copper (30).
	(B) Roots
1.	Sitosterol (26)
2.	Triterpenoids: arjunic acid, arjunolic acid, oleanolic acid, terminic acid (26).
3.	Glycosides: arjunoside I, arjunoside II, arjunoside III, arjunoside IV, 2,19-dihydroxy-3-oxo-olean-12-en28-oic acid28-*O*-_-d-glucopyranoside (26, 31).
	(C) Leaves and fruits
1.	Glycosides
2.	Flavonoids: luteolin (28).

blood can be reliably provided to different body tissues under a wide range of circumstances. The sensory monitoring for this critical homeostatic process entails primarily mechanical (barosensory) information about pressure in the arterial system and, secondarily, chemical (chemosensory) information about the level of oxygen and carbon dioxide in the blood. The parasympathetic and sympathetic activity relevant to cardiovascular control is determined by the information supplied by these sensors.

The autonomic nervous system modulates beat-to-beat fluctuations in heart rate (HR). It modulates the electrical and contractile activity of the myocardium via the interplay of sympathetic and parasympathetic activity. Cardiovascular autonomic neuropathy, a common form of autonomic dysfunction, causes abnormalities in heart rate control, as well as defects in central and peripheral vascular dynamics (32). Methods to quantify HR and blood pressure variability have been evaluated as indicators of sympathetic and parasympathetic modulation of the cardiovascular system in humans and in experimental models. These methods seemed to detect early autonomic dysfunction at a time when other metabolic dysfunctional changes were not clearly observed. Baroreflex sensitivity and Heart rate variability are the two frequently used parameters to assess autonomic control of cardiovascular functions.

Baroreflex sensitivity

The evaluation of baroreflex sensitivity (BRS) is an established tool for the assessment of autonomic control of the cardiovascular system. Arterial baroreceptors provide the central nervous system with a continuous stream of information on changes in blood pressure (which are sensed by the stretch receptors in the wall of the carotid sinuses and aortic arch), on the basis of which efferent autonomic neural activity is dynamically modulated. Activation of arterial baroreceptors by a rise in systemic arterial pressure leads to an increase of the discharge of vagal cardioinhibitory neurons and a decrease in the discharge of sympathetic neurons both to the heart and peripheral blood vessels. This result in bradycardia decreased cardiac contractility and decreased peripheral vascular resistance (33). Various studies demonstrating the improvement of baroreflex sensitivity with *Terminalia arjuna* are shown in Table II.

Heart rate variability

Heart rate variability (HRV) can detect cardiac autonomic impairment in individuals before traditional cardiovascular autonomic function tests (34). HRV analysis is the ability to assess over all cardiac health and the state of the autonomic nervous system (ANS) responsible for regulating cardiac activity. It

TABLE II: Experimental studies on *Terminalia arjuna* related to autonomic control of cardiovascular functions.

Study pertaining	*Plant preparation, dosage and route*	*Animal model*	*Observations*	*Interpretation*
Baroreflex sensitivity	50% aqueous ethanol extract (500 mg/kg, orally)	Anesthetized rat having diabetic cardiomyopathy. *T. arjuna* therapy started after 8 weeks of STZ and given for 30 days.	(a) Reflex bradycardia elicited by rise in arterial pressure was significantly reduced after diabetes but regained after *T. arjuna* therapy. (b) Reflex tachycardiaduring hypotension did notshow significant recovery after *T. arjuna* therapy due to depressed sympathetic activity (10).	Improved cardiovascular autonomic neuropathy in rats having uncontrolled diabetes.
	50% aqueous ethanol extract (500 mg/kg, orally)	Isoproterenol induced chronic heart failure in rats	Baroreflex sensitivityto both phenyephrine and sodium nitroprusside was significantly improved in rats with prophylactic and therapeutic treatment with *T arjuna* (13)	Improved sympathovagal balance and neurohormonal activationin CHF animals.
Heart rate variability	50% aqueous ethanol extract (500 mg/kg, orally)	Anesthetized rat having diabetic cardiomyopathy. *T. arjuna* therapy started after 8 weeks of STZ and given for 30 days.	Heart rate variability parameters i.e. SDNN, RMSSD, power in LF range, HF range, LF: HF ratio and total power was improved after *T. arjuna* treatment (36).	Improved sympathovagal balance thus improving the autonomic control of cardiovascular functions in diabetic rats.

Note: All experiments were carried out with bark constituents of *Terminalia arjuna*.

Abbreviations: Standard deviation of normal R-R intervals (SDNN), square root of mean- squared difference of successive R-R intervals (RMSSD), power in low frequency range (LF), high frequency range (HF), ISO- Isoproterenol, BRS Baroreflex sensitivity, STZ streptozotocin; CHF congestive heart failure.

reflects the heart's ability to adapt to changing circumstances by detecting and quickly responding to unpredictable stimuli (35). *Terminalia arjuna therapy* is reported to improve the altered HRV in diabetic rats (36, Table II).

Cardiovascular functions

Cardiomyopathy refers to a disease process which affects the myocardium in patients causing a wide range of structural abnormalities eventually leading to LVH (left ventricular (LV) hypertrophy) diastolic and systolic dysfunction or a combination of these (37). The systolic dysfunction is impairment in the ability of the heart to eject blood. The principle hallmark of systolic dysfunction is a depressed LV ejection fraction dysfunction. Diastole is the time period where the myocardium is no longer generating force and subsequently returns to an unstressed length and force. Diastolic dysfunction occurs when there is prolongation and slowing of this process. Experimental studies have revealed *T. arjuna* bark exerting significant inotropic and hypotensive effect, increasing myocardial contractility, coronary artery flow and protecting myocardium against ischemic damage. Table III compiles the various experimental studies on *Terminalia arjuna* related to cardiovascular system.

Molecular mechanisms affecting cardiovascular functions

Cardiovascular disease is a complex and multifactorial disease and is characterized by multiple factors. Epidemiologic studies have identified these as hyperlipidemia, hyperglycemia, inflammatory responses, coagulation factors, increased platelet activation and smoking. However, the pivotal mediator for the pathogenesis of diabetes and its cardiovascular complications is oxidative stress. Oxidative stress is the imbalance between the production of reactive oxygen and nitrogen species

TABLE III: Experimental studies on *Terminalia arjuna* related to cardiovascular system.

Study pertaining	*Plant preparation, dosage and route*	*Animal model*	*Observations*	*Interpretation*
Hypotensive actions	Aqueous and alcoholic bark extract, i.v., intra cerebral andIntravertebra	Dog, in vivo	Dose-dependent decrease in blood pressure (38).	Dose-dependent hypotension and decrease in heart rate were attributed to principlesof the extract acting centrally.
	Aqueous extract of the bark, intravenously	Dog, in vivo	Dose-dependent fall in blood pressure (39).	The vasorelaxant effect of *T. arjuna* extract could contribute to the fall in BP.
	Aqueous and tannin containing fractions 10–20 mg/kg	Rat	Lowering of blood pressure and heart rate (40).	The blockade by propranolol of the hypotension produced by *T. arjuna* indicates that the extract might contain active compound(s) possessing adrenergic β2-receptor agonist action and/or that act directly on the heart muscle.
	Aqueous extract of bark, 40 mg/kg, i.v.	Dog, in vivo study	Sustained fall in blood pressure (41).	The vasorelaxant effect of *T. arjuna* extract could contribute to the fall in BP.
	Intravenous administration of 70% alcoholic extract (5-15 mg/kg)	Anaesthetized dogs.	Dose-dependent hypotension (42).	
	50% aqueous ethanol extract (500 mg/kg). Therapy started after 8 weeks of STZ and given for 30 days.	Anesthetized rat having diabetic cardiomyopathy.	Did not improve the fall in systolic, diastolic and mean BP observed in diabetic rats (10).	50% aqueous ethanol extract has no effecton BP.
	50% aqueous ethanol extract	Isoproterenol induced chronic heart failure in rats	No effect (12).	
Effect on heart rate	50% aqueous ethanol extract (500 mg/kg, orally)	Anesthetized rat having diabetic cardiomyopathy. *T. arjuna* therapy started after 8 weeks of STZ and given for 30 days.	Did not improve the fall in heart rate observed in diabetic rats (10).	50% aqueous ethanol extract has no effecton heart rate.
	50% aqueous ethanol extract (500 mg/kg, orally)	Isoproterenol induced chronic heart failure in rats	No effect (12).	
	Aqueous and alcoholic bark extract, i.v., intra cerebral and Intravertebral	Dog, in vivo	Dose-dependent decrease in heart rate (38).	Decreased heart rate attributed to principles of the extract acting centrally.
	Aqueous as well as alcoholic bark extract	(a) Isolated frog atria; (b) isolated rat atrium; (c) isolated perfused rabbit heart/both *in vivo* and *in vitro*	Reduction in heart rate (39).	
Cardiac index	50% aqueous ethanol extract (500 mg/kg, orally)	Isoproterenol induced chronic heart failure in rats	Therapeutic and prophylactic treatment with *T. arjuna* showed significant improvement in cardiac index (12).	Improved cardiac performance reflecting cardiop rotective effect.
Cardiac haemo-dynamics	Aqueous bark extract	Isolated frog heart	Rate and force of heart contraction increased in both experiments (23).	The positive inotropic effect of the aqueous extract was proposed to be mediated via

	Aqueous bark extract	Isolated rabbit heart, isolated frog heart	Increased heart rate and force of contraction and finally stoppage of heart (20).	an action on β_1-adrenoceptors and was likely to be due to the release of noradrenaline from the sympathetic nerve endings.
	Water soluble portion of total alcoholic extract of the bark	Isolated frog heart	Increase in heart rate, amplitude and cardiac output (43).	Increased cardiac performance due to positive ionotropic and chronotropic effects.
	Aqueous extract of bark powder in doses of 30 mg/kg	Isolated rat atria	Substantial inotropic effect (45).	
	Aqueous extract of bark powder in doses of 30 mg/kg	Isolated rat atria	Positive inotropic effect which is abolished by propanolol and cocaine (46).	
	Aqueous extract, 150 mg/kg orally 10 days	Rats treated with aqueous extract and then subjectedto isoproterenol necrosis.	Reduction in heart rate and myocardial necrosis (47).	
	Aqueous and organic extracts of *T. arjuna*	Adult rat ventricular myocytes	The aqueous extract, not organic extracts, of *T. arjuna* exerted positive inotropy, accelerated myocyte relaxation and increased caffeine-induced contraction concentration-dependently (48).	Induced cardiotonic action via enhancing sarcoplasmic reticulum function, a unique action minimizing the occurrence of arrhythmias, making it a promising and relatively safe cardiotonic.
	Aqueous extract	Frogs heart in situ, hypodynamic frogs heart in situ and isolated perfused rabbits heart	Increased force of contraction (49).	
	Alcoholic extract of the bark	Dog	Enhances auricular and ventricular contraction (44).	Help in strengthening the heart muscles.
	50% aqueous ethanol extract (500 mg/kg,orally)	Isoproterenol induced chronic heart failure in rats.	Restoration of LV (dP/dt) max, LV (dP/dt) max/P LV(dP/dt) min and restoration of elevated LVEDP due to ISO challenge (12).	Both therapeutic and prophylactic treatments with *T. arjuna* caused overall enhancement of myocardial contractility and relaxation suggesting improvement in left ventricular dysfunction caused by ISO in CHF rats. Reduction in LVEDP implies that there is an increase in blood flow through the subendocardial region of the heart that bears the maximum brunt of the ischaemic insult due to ISO challenge.
	50% aqueous ethanol extract (500 mg/kg, orally)	Anesthetized rat having diabetic cardiomyopathy. *T. arjuna* therapy started after 8 weeks of STZ and given for 30 days.	Improved LVP, LV dP/dt max, LV dP/dt max, ratio of LV dP/dt max and LVP. LVEDP restored to normal (11).	An overall enhancement of myocardial contractility and relaxation, suggesting improvement in left ventricular dysfunction caused by STZ.
Effect on coronary flow	Aqueous extract 1–1024_g injected in the tube	Isolated rabbit heart, Langendorff's preparation	Increase in coronary flow (50).	Increased coronary flow makes it a good choice for CHF patients
	Aqueous extract	Isolated perfused rabbits heart	Increased coronary flow 3.4% at 400 µg only. (49).	

Note: All experiments were carried out with bark constituents of *Terminalia arjuna*.
Abbreviations: CHF – Congestive heart failure; LVP - Left ventricular functions; LVEDP- Left ventricular end diastolic pressure; LV (dP/dt) max- maximal rate of rise of left ventricular pressure; LV (dP/dt) min- maximal rate of fall of LVP (D); LV (dP/dt) max/LVP- maximal rate of rise of LVP divided by LVP; ISO- Isoproterenol; STZ streptozotocin.

(ROS and RNS) and antioxidant capacity (51). Proinflammatory cytokines specially, interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α), are capable of modulating cardiovascular function (52). TNFa has been implicated in the development of left ventricular dysfunction, left ventricular remodelling, increased cardiac myocyte apoptosis, the development of anorexia and cachexia, reduced skeletal muscle blood flow and endothelial dysfunction, activation of the inducible form of nitric oxide synthase (iNOS), b receptor uncoupling from adenylate cyclase, and other effects (53). Emerging evidence confirms the pivotal role of hyperlipemia, mainly elevated blood cholesterol, particularly LDL cholesterol and VLDL cholesterol in the development of atherosclerosis-related disease (54).

Dysfunction of the vascular endothelium is an early finding in the development of cardiovascular disease. Endothelin 1 has also been demonstrated to be associated with increased oxidative stress and endothelial dysfunction in humans (55). Apart from its direct vasomotor activity, ET-1 has been implicated in inflammatory processes within the vascular wall. Specifically, ET-1 in subnanomolar concentrations has been demonstrated to activate macrophages, resulting in the release of proinflammatory and chemotactic mediators, including TNF-a, IL-1, IL-6, and IL-8 which are of importance in the atherosclerotic process. Table IV compiles the various biochemical studies on *T. arjuna* related to molecular mechanisms affecting the cardiovascular system.

Cardiac histopathology

Histopathological examination of normal cardiac

TABLE IV : Experimental studies on *Terminalia arjuna* related to molecular mechanisms affecting cardiovascular functions.

Study pertaining	*Plant preparation, dosage and route*	*Animal model*	*Observations*	*Interpretation*
Antioxidant activities	*Terminalia arjuna* in the doses of 30 mg per tablet in amultimineral herbal formulation, abana, administered orally as a suspension.	Rats subjected to myocardial ischemia induced byisoproterenol and treated with abana.	The reversal of cardiac injury enzyme and improved heart mitochondrial uptake (56).	Enhanced the antioxidant defense against ISO-induced myocardial infarction in rats and exhibited cardioprotective property.
	Terminalia arjuna extract in doses of 5 mg/kg	In vitro study	Ameliorate glycation of Hb and exerts antioxidant effects (57).	Antioxidant effect leading to cardioprotection.
	Arjunolic acid derived from *Terminalia arjuna* bark extract 15 mg/kg, given intraperitoneally.	Rats subjected to isoproterenol induced myocardial necrosis	Arjunolic acid treated rats had significant diminished levels of cardiac injury enzymes and raised SOD, CAT, GPx and myeloperoxidase (58).	Cardioprotection of arjunolic acid pre and post treatment could possibly be due to the protective effect against the damage caused by myocardial necrosis.
	Alcoholic extract of *T. arjuna* (6.75 mg/kg)	Isoproterenol induced myocardial injury in rats	Increase in endogenous anti oxidants (GSH, SOD and Catalase) (59).	Prevents the myocardium rom isoproterenol induced of myocardial ischemic reperfusion injury by augmenting endogenous antioxidant compounds of the rat heart.
	Oral administration of *T. arjuna* for 12 weeks	Rabbit heart	In vivo ischemic reperfusion injury induced oxidative stress, tissue injury of heart and hemodynamic effects were prevented (60).	One or more of the constituents have cardiotonic (glycosides) or free radicle scavenger (tannins, flavones) properties.
	T. arjuna 90 mg/kg single dose	Male Wistar rats	Cardiac lipid peroxidation was reduced (61).	Detoxification of reactive oxygen species.
	Dried pulverized bark of *T. arjuna* (500 mg/kg)	Wistar Albino rat	Increase in baseline contents of thiobarbituric acid reactive substance (TBARS), SOD, GSH and CAT levels (62).	Better cardioprotection against oxidative stress associated with myocardial ischemic reperfusion injury.

	Aqueous extract of *Terminalia arjuna* bark 50 mg/kg orallyfor 1 week	Mice challenged with carbon tetrachloride, 1 ml/kg body weight liver and renal enzyme markers assessed	*T. arjuna* prevented the rise in liver injury enzymes, i.e., SGPT, ALP and TBARS and increased the levels of SOD, CAT, and GSH. Results were comparable to vitamin C group mice (63).	Protect the oxidant damage to the liver and kidney following carbon tetrachloride challenge in mice, indicating its endogenous antioxidant activity.
	Ethanolic extract of *Terminalia arjuna* bark in 400 mg/kg, post orally for 28 days	Single injection of *N*-nitrosodiethylamine-induced liver cancer in male rats treated with *Terminalia Arjuna.*	Decreased levels of lipid peroxidase and near normal levels of antioxidant enzymes-SOD, CAT and glutathione peroxidase (64).	Improved the antioxidant defenses thus preventing the free radical-mediated damage.
	Treatment with arjunolic acid (20 mg/kg) four days prior to Sodium arsenite intoxication	Experimental Mice	Decreased oxidative stress (65).	
	Ethanol extract of *T. arjuna*	Sodium floride induced oxidative stress in murine heart	Treatment prior to Sodium floride administration decreased oxidative stress (66).	
	Butanolic fraction of *T. arjuna*	Doxorubicin induced cardiotoxicity in male Wistar rats	Reduced oxidative stress (67).	Cardioprotection against oxidative stress
	Aqueous extract of *T. arjuna* (5 mg/kg)	Rats on Isoprenaline	Prevented isoprenaline induced oxidative stress and decline in antioxidant levels (68).	
	50% aqueous ethanol extract (500 mg/kg, orally)	Isoproterenol induced chronic heart failure in rats	Reduction in MDA level and significant improvement in GSH and SOD activity, thus maintained the rats at near normal status (12).	Reduces oxidative stress there by preventing the generation of free radicals.
	50% aqueous ethanol extract (500 mg/kg, orally)	Rats having diabetic cardiomyopathy. *T. arjuna* therapy started after 8 weeks of STZ and given for 30 days.	Markedly prevented all the STZ-induced alterations in the levels of MDA, SOD, CAT & GSH and maintained the rats at near normal status (10).	Improved the antioxidant defenses thus preventing the free radical-mediated damage.
Lipid lowering effects	*Terminalia arjuna* bark powder 250 mg/kg administered orally twice daily	Rabbits rendered hypercholesterolaemic by diet richin cholesterol	(a) Reduction in total cholesterol and triglycerides; (b) increase in HDL-cholesterol (4).	Lipid lowering effect leading to decreased risk of cardiovascular disease.
	T. arjuna (100 mg/kg, b.w.)	Triton and cholesterol fed rats	Lowering in lipids and protein levels of β-lipoproteins followed by an increase in high density lipoprotein-cholesterol (69).	
	Ethanolic extract of bark in 100–500 mg/kg dose orally	Rabbit fed high fat diet, in vivo study	(a) Reduces hyperlipidemia; (b) no change in HDL-chol (5).	
	Ethanolic extract of the *Terminalia arjuna* Wight & Arn., *Terminalia bellerica* Roxb. and *Terminalia chebula* Willd. administered orally	Rabbits fed hypercholesterolaemic diet and treated with respective *Terminalias* separately/ concurrently and sacrificed at the end of the experiment	*Terminalia arjuna* proved to be most potent hypolipidaemic agent, raised HDL-chol. and inhibited aortic atherosclerosis (70).	
	Treatment with arjunolic acid (20 mg/kg) four days prior to Sodium arsenite intoxication	Experimental Mice	(a) fall in the level of total cholesterol, triglycerides, and LDL-C (b) increased the level of HDL-C (65).	

	Ethanolic fraction of *T. arjuna* (100 and 200 mg/kg body weight)	Rabbits fed with high fat diet	(a) Decreased TC, LDL and TG levels and increases HDL (b) Lessens atherosclerotic lesion in aorta (71).	
	50% aqueous ethanol extract (500 mg/kg, orally) level of HDL-C (12).	Isoproterenol induced chronic heart failure in rats	(a) Fall in the level of total cholesterol, triglycerides, LDL-C, VLDL-C (b) Increased level of HDL-C [12].	
	50% aqueous ethanol extract (500 mg/kg, orally)	Rats having diabetic cardiomyopathy. *T. arjuna* therapy started after 8 weeks of STZ and given for 30 days.	(a) fall in the level of total cholesterol, triglycerides, and LDL-C (b) increased the level of HDL-C (10).	
Effects on inflammatory markers	50% aqueous ethanol extract (500 mg/kg, orally)	Rats having diabetic cardiomyopathy *T. arjuna* therapy started after 8 weeks of STZ and given for 30 days.	Metabolic changes induced by hyperglycemia lead to dysregulation of cytokine control, increasing their levels by an oxidative mechanism. *T. arjuna* reduced the raised serum TNF-α and IL6 to near normal levels in STZ-treated rats (10).	Anti-inflammatory activity of the bark extract
	50% aqueous ethanol extract (500 mg/kg orally)	Isoproterenol induced chronic heart failure in rats	Prophylactic and therapeutic treatment with *T. arjuna* reduced the elevated serum TNF-α to near normal levels in CHF rats (12).	Anti-inflammatory activity of the bark extract correlated with reduced myocardium Injury.
	Terminalia arjuna back powder (400 mg/kg, orally)	Albino rats	Reduced Formalin induced paw edema (72).	Anti-inflammatory activity.
Effects on Endothelin 1 levels	50% aqueous ethanol extract (500 mg/kg, orally)	Rats having diabetic cardiomyopathy. *T. arjuna* therapy started after 8 weeks of STZ and given for 30 days.	*T. arjuna* reduced the serum ET-1 to near normal levels in STZ-treated rats (11).	Improved the function of vascular endothelium thereby decreasing the pro inflammatory mediators adding to cardioprotective effect.
Effect on aortic prostaglandins	Bark powder 500 mg twice daily, orally in suspension form for 90 days.	Rabbit, in vivo study	Aortic ring PGE2 levels increased in rabbits receiving *Terminalia arjuna* (73).	Increased blood flow leading to improvement in cardiac functions.
Myocardial injury marker CK-MB	50% aqueous ethanol extract (500 mg/kg, orally)	Isoproterenol induced chronic heart failure in rats	Prophylactic and therapeutic treatment with *T. arjuna* almost restored the ISO-induced alterations of serum CK-MB to normal levels (11).	Indicates its action on maintaining membrane integrity thereby restricting the leakage of enzymes.
	Butanolic fraction of *T. arjuna*	Doxorubicin induced cardiotoxicity in male Wistar rats	Cotreatment with Doxorubicin reduced serum CK-MB levels (67).	

Note: All experiments were carried out with bark constituents of *Terminalia arjuna*.

Abbreviations: ALP, alkaline phosphatase; CAT, catalase; chol, cholesterol; CK-MB creatinine kinase- MB; ET1 – Endothelin 1; GPx, glutathione peroxidase; GSH, Glutathione reductase; Hb, haemoglobin; HDL, high density lipoprotein; IL6, interleukin 6; iNOS Inducible nitric oxide synthase; ISO Isoproterenol; LDL, low density lipoprotein; LPS, liposacharide; MDA malondialdehyde; MPO, myeloperoxidase; NO nitric oxide; PGE2, prostaglandin E2; SGPT, serum glutamic pyruvic transaminase; SOD, superoxide dismutase; STZ streptozotocin; TBARS, thiobarbituric acid reactive substances, TC, - total cholesterol; TG, triglyceride; TNF-á, tumour necrosis factor-á; VLDL, Very low density lipoprotein.

tissue demonstrates normal myofibrillar structure with striations, branched appearance and continuity with adjacent myofibrils. Cardiac tissues having cardiomyopathy shows widespread alterations in myocardial structure with subendocardial necrosis and myovacuolations. Treatment with *T. arjuna*, is seen to preserve myocardium and demonstrated marked improvement in various myocardial injuries (Table V).

Conclusion

The efficacy of *Terminalia arjuna* as a cardioprotective agent, a potent anti inflammatory and antioxidant preventing LDL cholesterol oxidation and its potential to reduce atherogenic lipid levels have been amply demonstrated in various experimental studies. Its molecular actions in different cells of the cardiovascular system are also reported. Its role in improving the autonomic control plays an important part in improving cardiovascular functions. This herbal drug with multiple beneficial effects without causing side effects can modulate the existing treatment strategies. However, there are some identified lacunae, like standardization 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 (14).

TABLE V : Histopathological studies of cardiac tissue on *Terminalia arjuna* therapy.

Study pertaining	*Plant preparation, dosage and route*	*Animal model*	*Observations and Interpretation*
Cardiac histopathology	Arjunolic acid derived from *Terminalia arjuna* bark extract 15 mg/kg, given intraperitoneally	Rats subjected to isoproterenol-induced myocardial ischemia and administered arjunolic acid both pre and post isoproterenol administration	Preserved myocardium thus confirming cardioprotection (58).
	Alcoholic extract of *T. arjuna*	Isoproterenol induced myocardial ischemic reperfusion injury in rats	Preserved myocardium (59).
	Treatment with arjunolic acid (20 mg/kg) four days prior to Sodium arsenite intoxication	Experimental Mice	Reduces injury due to arsenic administration and helps to maintain normal cardiac architecture (63).
	Butanolic fraction of *T. arjuna*	Doxorubicin induced cardiotoxicity in male Wistar rats	Cotreatment with Doxorubicin reduced histological alterations due to Doxorubicin (67).
	50% aqueous ethanol extract (500 mg/kg, orally)	Isoproterenol induced chronic heart failure in rats	Marked improvement in ISO-induced subendocardial necrosis, capillary dilatation and leucocyte infiltration confirming its cardioprotective actions (12).
	50% aqueous ethanol extract (500 mg/kg, orally)	Rats having diabetic cardiomyopathy. *T. arjuna* therapy started after 8 weeks of STZ and given for 30 days (11).	Marked improvement in STZ-induced subendocardial necrosis and vacuolation of the myocytes. Thus alleviated the STZ-induced cardiac injury, confirming its cardioprotective actions.

Note: All experiments were carried out with bark constituents of *Terminalia arjuna*.
Abbreviations: ISO- Isoproterenol, STZ streptozotocin.

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