



# Revisiting *Terminalia arjuna* – An Ancient Cardiovascular Drug

Shridhar Dwivedi<sup>1</sup>, Deepti Chopra<sup>2</sup>

<sup>1</sup>Department of Medicine and Preventive Cardiology, Hamdard Institute of Medical Sciences and Research, Jamia Hamdard, New Delhi, India.

<sup>2</sup>Department of Pharmacology, Hamdard Institute of Medical Sciences and Research, Jamia Hamdard, New Delhi, India.

## ABSTRACT

*Terminalia arjuna*, commonly known as *arjuna*, belongs to the family of Combretaceae. Its bark decoction is being used in the Indian subcontinent for angular pain, hypertension, congestive heart failure, and dyslipidemia, based on the observations of ancient physicians for centuries. The utility of *arjuna* in various cardiovascular diseases needs to be studied further. Therefore, the present review is an effort to give a detailed survey of the literature summarizing the experimental and clinical studies pertinent to *arjuna* in cardiovascular disorders, which were particularly performed during the last decade. Systematic reviews, meta-analyses, and clinical studies of *arjuna* were retrieved through the use of PubMed, Google Scholar, and Cochrane databases. Most of the studies, both experimental and clinical, have suggested that the crude drug possesses anti-ischemic, antioxidant, hypolipidemic, and antiatherogenic activities. Its useful phytoconstituents are: Triterpenoids,  $\beta$ -sitosterol, flavonoids, and glycosides. Triterpenoids and flavonoids are considered to be responsible for its beneficial antioxidant cardiovascular properties. The drug has shown promising effect on ischemic cardiomyopathy. So far, no serious side effects have been reported with *arjuna* therapy. However, its long-term safety still remains to be elucidated. Though it has been found quite useful in angina pectoris, mild hypertension, and dyslipidemia, its exact role in primary/secondary coronary prevention is yet to be explored.

**Key words:** Antioxidant, Cardiovascular disorders, Coronary prevention, Flavonoids, *Terminalia arjuna*, Triterpenoids

## INTRODUCTION

*Arjuna* is a potential cardioprotective agent belonging to the Combretaceae family. It is an ayurvedic remedy that has been mentioned since vedic period in many ancient Indian medicinal texts including Charaka Samhita, Sushruta Samhita, and Astang Hridayam. It was Vagabhatta who, for the first time, advocated the use of stem bark powder in heart ailments.<sup>[1]</sup>

## ETHNOMEDICAL USES

The bark has been described as an astringent, demulcent, expectorant, cardiogenic, styptic, antidiarrheal, urinary astringent,

and has shown to be useful in fracture, ulcers, leukorrhea, diabetes, anemia, cardiopathy, and cirrhosis.<sup>[2]</sup> Chakradatta, the great ancient physician, recommended it to be given as a decoction of bark with milk or as a ghrta (a preparation with ghee or butter).<sup>[3]</sup> Decoction of the bark has been used as ulcer wash, while bark ashes have been prescribed for snakebite and scorpion sting.<sup>[4]</sup> Traditional healers from Kancheepuram district, Tamil Nadu boil the bark powder with water, and inhale it to cure headache and to kill worms in teeth. They also use fruit paste topically on wounds.<sup>[5]</sup> Fresh leaf juice is used for the treatment of earache and bark powder for treating heart ailments by Malabar tribe, Kerala.<sup>[6]</sup> Tribals living in Sundargarh District, Orissa use dried bark powder along with

### Correspondence to:

Dr. Shridhar Dwivedi, Department of Medicine and Preventive Cardiology, Hamdard Institute of Medical Sciences and Research, Jamia Hamdard, New Delhi - 62, India. Tel: +01126059684; Fax: +91-11-2605979; E-mail: [shridhar.dwivedi@gmail.com](mailto:shridhar.dwivedi@gmail.com)

DOI: 10.4103/2225-4110.139103

rice washed water to treat blood in urine, and tribes living in Malkangiri district chew the fresh bark and swallow the juice as an antacid.<sup>[7,8]</sup>

## HABITAT

*Arjuna* tree is about 60-80 ft in height, and is seen along rivers, streams, and dry water bodies throughout the Indo-sub-Himalayan tracts of Uttar Pradesh, southern Bihar, Chota Nagpur, Burma, Madhya Pradesh, Delhi, and Deccan region [Figure 1]. It is also found in the forests of Sri Lanka and Mauritius.<sup>[3,9]</sup> It grows almost in all types of soils, but prefers humid, fertile loam and red lateritic soils. It can tolerate half submergence for a few weeks. *Arjuna* is propagated by seeds; Germination takes 50-70 days with 50-60% germination.<sup>[10]</sup>

## PHARMACOGNOSTIC FEATURES

The outer surface of the bark is smooth, while the inner surface has longitudinal striation and is pinkish in color.<sup>[2]</sup> The bark gets flaked off itself in the month of April–May [Figure 2].<sup>[11]</sup>

On microscopic examination of the mature bark, a cork consisting of 9-10 layers of tangentially elongated cells, 2-4 cells thick phellogen, and phelloderm consisting of tangentially elongated cells are seen. The phloem is broad, consisting of ceratenchyma, phloem parenchyma, phloem fibers, and crystal fibers with rosette crystals of calcium oxalate. Periderm and secondary phloem are present in the old bark.<sup>[9,11,12]</sup>

Leaves are sub-opposite, coriaceous, oblong/elliptic, dull green from the upper side and pale brown on the lower side, often unequal sided with 10-15 pairs of nerves [Figure 3]. Flowers are white in color and bisexual, arranged in spikes with linear bracteoles [Figure 4]. Fruits are ovoid/oblong with 5-7 hard angles or wings. The lines on wings are oblique and curving upward [Figure 5].<sup>[2]</sup>

Major chemical constituents of *arjuna* have been shown in Table 1.<sup>[9,13-17]</sup>

Various extracts of the stem bark of *arjuna* have shown to possess many pharmacological properties including inotropic, anti-ischemic, antioxidant, blood pressure lowering, antiplatelet, hypolipidemic, antiatherogenic, and antihypertrophic.<sup>[18]</sup> Thus, in the present article, we have made an attempt to review and give up-to-date information pertinent to the usage of *arjuna* as a potential cardioprotective agent.

## EXPERIMENTAL STUDIES

### Effects on cardiac hemodynamics, coronary flow, and blood pressure

Bark stem of *arjuna* possesses diuretic, inotropic, and chronotropic properties.<sup>[9]</sup> In the Langendorff's rabbit heart preparation, the aqueous extract has demonstrated to cause an increase in the coronary flow.<sup>[19]</sup> Substantiating the earlier findings recently, an experimental study showed that the aqueous extract of *arjuna* increased the force of contraction of cardiac muscle in frog's heart *in situ*, hypodynamic frog's heart *in situ*, and isolated perfused rabbit heart. It increased the coronary flow in isolated perfused

rabbit heart and produced bradycardia.<sup>[20]</sup> The inotropic effect is considered to be mediated through the high concentration of  $\text{Ca}^{++}$  present in the plant.<sup>[21]</sup>

Aqueous and alcoholic bark extract, when given intravenously, intracerebrally, and intravertebrally in dog, resulted in a



Figure 1. *Terminalia arjuna* tree



Figure 2. Bark stem of *Terminalia arjuna*



Figure 3. Leaves of *Terminalia arjuna*

dose-dependent decrease in blood pressure.<sup>[9]</sup> Singh *et al.* reported that an aqueous solution of 70% alcoholic bark extract produced dose-dependent decrease in heart rate and blood pressure in dogs, though the mechanism was not determined.<sup>[22]</sup>

Takahashi *et al.* demonstrated that the hypotensive effect of *arjuna* was observed with a fraction containing tannin-related compounds separated from the aqueous extract, which was not affected by pretreatment of rats with propranolol, but was attenuated by pretreatment with atropine. This suggested that the hypotensive effect may be mediated by cholinergic mechanisms.<sup>[23]</sup> Later on, it was documented that the 70% alcoholic extract produced dose-dependent hypotension of peripheral origin which might be due to adrenergic  $\beta_2$ -receptor agonistic and/or direct action on the heart muscle. It was also suggested that muscarinic

or histaminergic mechanisms are not likely to be involved in the hypotension produced.<sup>[24]</sup>

In a recent study, it has been established that the method of administration and/or selective omission of the hydrophobic components from the bark powder could be crucial to the efficacy and safety of *arjuna* bark in cardiac therapy.<sup>[25]</sup>

#### Antioxidant and cardioprotective effect

Dried, pulverized bark has been shown to augment endogenous antioxidant compounds of rat heart and prevent oxidative stress associated with ischemic–reperfusion injury of the heart.<sup>[26]</sup>

It was suggested that the alcoholic extract of *arjuna* in rabbit induces myocardial heat shock protein 72 and augments myocardial endogenous antioxidants which offer cardioprotection against oxidative stress associated with myocardial ischemic–reperfusion injury.<sup>[27]</sup> The cardioprotective effect of the active phytoconstituents of *arjuna* bark against carbon tetrachloride and sodium fluoride induced oxidative stress, probably via its antioxidant properties, has also been documented. In the above models, ferric



Figure 4. Flower of *Terminalia arjuna*



Figure 5. Fruits of *Terminalia arjuna* (ripe, fresh)

Table 1. Major chemical constituents of arjuna

Part of plant	Major chemical constituents	Major chemical constituents
Stem bark	Triterpenoids	Arjunin, arjunic acid, arjunolic acid, arjungenin, terminic acid, arjunglucosides IV and V, arjunasides A-E, 2- $\alpha$ , 3- $\beta$ -dihydroxyurs-12,18-dien-28-oic acid 28-O- $\beta$ -d-glucopyranosyl ester
	Glycosides	Arjunetin, arjunoside I, arjunoside II, arjunaphthanolide, terminoside A
	Flavonoids	Arjunolone, arjunone, baicalein, luteolin, gallic acid, ethyl gallate, quercetin, kempferol, pelargonidin, oligomeric proanthocyanidins
	Tannins	Pyrocatechols, punicallin, punicalagin, terchebulin, terflavin C, castalagin, casuarinin, casuarinin
	$\beta$ -sitosterol	
Roots	Minerals/trace elements	Calcium, aluminum, magnesium, silica, zinc, copper
	Triterpenoids	Arjunic acid, arjunolic acid, oleanolic acid, terminic acid
	Glycosides	Arjunoside I, arjunoside II, arjunoside III, arjunoside IV, 2 $\alpha$ ,19 $\alpha$ -dihydroxy-3-oxo-olean-12-en-28-oic acid 28-O- $\beta$ -d-glucopyranoside
Leaves	$\beta$ -sitosterol	
	Flavonoids	
	Alkaloids	
	Tannins	
	Steroids	
	Phenolic compounds	
	Oxalic acid	
Fruits	Inorganic acid	
	Glycosides	
	Flavonoids	Luteolin
Seeds	Cardenolide	14,16-dianhydrogitoxigenin-3- $\beta$ -d-xylopyranosyl (1-->2)-O- $\beta$ -d-galactopyranoside

reducing/antioxidant power assay revealed that ethanol extract enhanced the cardiac intracellular antioxidant activity.<sup>[28,29]</sup> In a recent study, the methanol extract yielded the highest phenolic and flavonoid content and was found to possess the highest total antioxidant capacity. Thus, it can be inferred that there exists a linear correlation between the antioxidant capacity and the total phenolic content of the extracts.<sup>[30]</sup> In another study, both alcoholic and aqueous extracts of the bark attenuated H<sub>2</sub>O<sub>2</sub>-mediated reactive oxygen species generation in human monocytic cells by promoting catalase and glutathione peroxidase (GPO) activities and by sustaining cellular reducing power. Moreover, the extracts inhibited lipid peroxidation (LPO) and 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, but had no effect on lipoprotein lipase.<sup>[31]</sup>

In isoprenaline-induced myocardial ischemia (MI), *arjuna* has been found to possess prostaglandin E<sub>2</sub>-like activity with coronary vasodilatation and hypotension.<sup>[1]</sup> The bark extract has shown to significantly prevent isoprenaline-induced increase in oxidative stress and decline in endogenous antioxidant level.

Arjunolic acid has been found to prevent the decrease in the levels of superoxide dismutase, catalase, GPO, ceruloplasmin,  $\alpha$ -tocopherol, reduced glutathione, ascorbic acid, lipid peroxide, and myeloperoxidase.<sup>[32]</sup>

Further, the bark extract has also shown protective effects against doxorubicin-induced DNA damage and cardiotoxicity.<sup>[33,34]</sup> Kumar *et al.* demonstrated that *arjuna* protects the heart against myocardial changes induced by chronic  $\beta$ -adrenoceptor stimulation.<sup>[35]</sup> Substantiating this, in a recent experiment, the bark extract significantly attenuated cardiac dysfunction and myocardial injury in rats with congestive heart failure (CHF). Cardioprotective action of *arjuna* was comparable to fluvastatin. *Arjuna* bark extract has a significant prophylactic and therapeutic beneficial effect in protecting heart against catecholamine-induced CHF, possibly through maintaining endogenous antioxidant enzyme activities and inhibiting LPO and cytokine levels.<sup>[36]</sup>

Recently, Mythili *et al.* confirmed the earlier findings that triterpenoids derived from *arjuna* extract containing arjunolic acid show cardioprotective activity by boosting endogenous antioxidant defense system.<sup>[37]</sup>

### Hypolipidemic and antiatherogenic activity

Earlier animal experiments have demonstrated that *arjuna* bark powder/extract reduces the total cholesterol (TC) and triglyceride (TG) levels.<sup>[38-41]</sup> On comparing the hypolipidemic property of the bark in different solvent fractions (petroleum ether, solvent ether, ethanol, and water) in hyperlipidemic rats, it was observed that only the ethanolic fraction exerted significant lipid-lowering effect. Solvent ether and ethanolic fractions caused a decrease in the plasma levels of lipids in triton as well as in high fat diet (HFD) fed models of hyperlipidemia in hamsters. In an *in vitro* experiment with *arjuna* fractions at concentrations of 50-500  $\mu$ g/ml, they were found to inhibit the oxidative degradation of lipids induced by metal ions in human low density lipoprotein (LDL) and rat liver microsomes. When these fractions were tested against the generation of oxygen free radicals, they counteracted the formation of superoxide anions and hydroxyl radicals in nonenzymic

test systems. The efficacy of *arjuna* fractions was found to be in the order: Ethanol fraction > solvent ether fraction > petroleum ether fraction.<sup>[42]</sup>

The ethanolic fraction possesses potent antioxidant and hypolipidemic properties compared to other fractions, and this has been substantiated by other studies also.<sup>[43,44]</sup> Subsequent work done by Sharma *et al.* also substantiated the hypolipidemic and antioxidant effect of *arjuna*. In addition to this, they also found that recipes (Arjuna Omelette and Arjuna En Upma) incorporating *arjuna* bark showed good acceptability, meriting their inclusion in the daily diet of the people needing long-term intervention for elevated lipids and oxidative stress levels.<sup>[45]</sup>

The hypolipidemic action is thought to be mediated through increased hepatic clearance of cholesterol, down-regulation of lipogenic enzymes, and inhibition of HMG-CoA reductase.<sup>[46]</sup> Further, Parmar *et al.* showed that there is a possibility of involvement of thyroid hormones (suppression of thyroid function) in the amelioration of cardiac and hepatic LPO by the bark extract in albino rats.<sup>[47]</sup>

## CLINICAL USES

### Angina/myocardial infarction

The anti-ischemic effect of bark powder was evaluated in 30 patients of stable angina/post-infarct angina (500 mg tds). The authors observed that the mean anginal frequency decreased significantly, along with a significant decrease in systolic blood pressure (SBP), improvement in ECG changes, and reduction in plasma cortisol and serum cholesterol levels.<sup>[48]</sup>

Later, in a study, 500 mg of bark powder was administered twice daily to 25 coronary artery disease (CAD) patients for 3 months. A reduction in the grade of positivity of treadmill test (TMT) response was observed in six patients, in addition to improvement in exercise tolerance and a reduction in the frequency of anginal attacks and use of sublingual nitrates.<sup>[49]</sup>

Subsequently, in an open-label trial, it was demonstrated that there was a 50% reduction in angina episodes along with a significant delay in the time to the onset of angina on TMT and appearance of ST-T changes in ECG after *arjuna* therapy was administered in stable angina patients. Significant lowering of SBP and body mass index, with a marginal improvement in left ventricular ejection fraction (LVEF) and a slight increase in high density lipoprotein (HDL) levels were also observed. In unstable angina patients, there was an insignificant reduction in anginal frequency. These results suggest that monotherapy with *arjuna* is fairly effective in patients with stable angina, but has a limited role in unstable angina.<sup>[50]</sup>

In yet another study, 500 mg of bark powder was administered 8 hourly to 10 patients of post-myocardial infarction angina and 2 patients of ischemic cardiomyopathy for a period of 3 months. These patients were compared with matched patients of post-myocardial infarction angina receiving only conventional treatment. Significant reduction in anginal frequency, improvement in LVEF (from 42.25  $\pm$  9.96% to 52.57  $\pm$  12.32%), and reduction in left ventricular mass (LVM; from 159.18  $\pm$  51.11 g/m<sup>2</sup> to 140.62  $\pm$  55.65 g/m<sup>2</sup>) was noted.<sup>[51]</sup>

The efficacy of Hartone (an herbal product containing *arjuna*) was studied in 10 stable angina patients. The results were compared with those of 10 patients of stable angina on 20 mg of isosorbide mononitrate (ISMN) administered twice daily. It was observed that Hartone gave symptomatic relief in 80% of patients as compared to 70% in ISMN alone group. In addition, *arjuna* was better tolerated than ISMN.<sup>[52]</sup>

In a randomized, double-blind, cross-over study, 58 male patients with chronic stable angina (class II–III) with evidence of provokable ischaemia on TMT received 500 mg of 90% alcohol extract 8 hourly, ISMN (40 mg/day), or a matching placebo for 1 week each after a washout period of at least 3 days. It was found that *arjuna* therapy was associated with a significant decrease in the frequency of angina and the need for isosorbide dinitrate. Improvements in clinical and TMT parameters were observed with both *arjuna* and ISMN as compared to placebo. No significant differences were observed in the above parameters when *arjuna* and ISMN therapies were compared.<sup>[53]</sup>

### CHF/hypertension

In one of the earliest studies, 10 patients with CHF received 4 g of *arjuna* bark powder twice daily for 1 month. The researchers observed improvement in the functional class, breathlessness, and overall well-being with significant diuresis, and a fall in both systolic and diastolic blood pressure.<sup>[54]</sup>

Subsequently, the effect of bark extract (500 mg 8 hourly) was studied in a double-blind placebo-controlled two-phase trial comprising 12 patients with refractory CHF. In the first phase, *arjuna* was administered for a period of 2 weeks. A decrease in echo-left ventricular end-diastolic and end-systolic volume indices, an increase in left ventricular stroke volume index, and an increase in LVEF were recorded suggesting improvement. On long-term evaluation (20–28 months), in addition to continued improvement in symptoms and signs, they also reported an improvement in quality of life.<sup>[55]</sup>

A study done with abana (herbal formulation containing *arjuna*) in hypertensive individuals revealed an improvement in cardiac function as indicated by an increase in ejection fraction and a significant reduction of the SBP, echocardiographic left ventricular internal diameter, posterior wall thickness, and inter-ventricular septal thickness.<sup>[56]</sup>

Recently, *arjuna* has also been shown useful in improving cardiovascular endurance and in lowering SBP in normal healthy subjects.<sup>[57]</sup>

### Rheumatic heart disease

Efficacy of *arjuna* in decompensated rheumatic heart disease was studied in a double-blind study in which 30 patients of rheumatic valvular heart disease with CHF were administered 200 mg *arjuna* thrice daily. The results revealed a significant improvement in LVEF, exercise duration, and significant reduction in heart size.<sup>[58]</sup>

### Ischemic mitral regurgitation

In a randomized, double-blind, placebo-controlled study done in patients with ischemic mitral regurgitation (IMR) following acute myocardial infarction, *arjuna* was found to significantly

decrease IMR and anginal frequency. In addition, there was also significant improvement in diastolic dysfunction (E/A ratio; from  $0.93 \pm 0.31$  to  $1.38 \pm 0.40$  at 12 weeks).<sup>[59]</sup>

### Cardiomyopathy

In addition to its anti-ischemic property, *arjuna* was found to reduce LVM and improve LVEF.<sup>[59]</sup> A recent observational study revealed that when patients of dilated cardiomyopathy with reduced LVEF received *arjuna* in addition to their standard therapy, there was a significant improvement in left ventricular parameters as well as functional capacity.<sup>[60]</sup>

### Platelet aggregation

The bark extract has been found to decrease platelet activation and possess antithrombotic properties *in vitro* in 20 patients of angiographically proven CAD and 20 age- and sex-matched controls. The possible mechanism could be by desensitizing platelets by competing with platelet receptor or by interfering with signal transduction.<sup>[61]</sup>

In another recent randomized, double-blind, parallel-group, placebo-controlled study in patients with type 2 diabetes mellitus, 500 mg of *arjuna* administered thrice daily resulted in a significant increase in mean cardiac output from  $4.34 \pm 0.38$  to  $4.86 \pm 0.20$  (l/min). In addition to this, there was a reduction in mean systemic vascular resistance from  $1729 \pm 93.52$  to  $1484 \pm 115.5$  (dyne sec/cm<sup>2</sup>). *Arjuna* also caused significant inhibition of platelet aggregation.<sup>[62]</sup>

### Oxidative stress/dyslipidemia

In a study on 21 patients with coronary heart disease administered 1 g of bark powder twice daily with milk for 4 months, the patients showed improvement in lipid profile. In addition to this, patients got symptomatic relief after 1 month of treatment.<sup>[63]</sup>

Antioxidant effect of bark powder (500 mg) has been demonstrated to be comparable to vitamin E (400 IU) in a randomized, controlled, open trial done in 105 patients with coronary heart disease. The authors also observed a significant decrease in TC, LDL, and lipid peroxide levels. The hypocholesterolemic effect was attributed to the soluble fibers and sitostanol content, while the antioxidant effect was attributed to the flavonoids.<sup>[64]</sup> Further, it was observed in a study that when the bark powder was given along with statin for 3 months, it resulted in 15% reduction in TC, 11% reduction in TG, and 16% reduction in LDL, while there was minimal decline in lipoprotein (a) and nitrite levels.<sup>[65]</sup>

In a prospective cohort study, dyslipidemic patients received *arjuna* powder (5 g, BD) for 3 weeks followed by Arogyavardhini Vati (500 mg, BD) for 4 weeks. A significant reduction in TC, LDL, TG, serum C-reactive protein, blood glucose, and an increase in HDL level were found, which supported the role of *arjuna* in dyslipidemic patients.<sup>[66]</sup>

### Lipoprotein(a)

A significant reduction in lipoprotein(a) levels amounting to 24.71% following the administration of *arjuna* in a patient of  $\beta$ -thalassemia associated with hyperlipoproteinemia and metabolic syndrome has been reported.<sup>[67]</sup>

## Endothelial dysfunction

In a double-blind, placebo-controlled, cross-over study involving 18 healthy male smokers and an equal number of age-matched non-smoker controls, it was observed that the hydroalcoholic extract of bark when given for 2 weeks led to significant regression of the endothelial abnormality amongst smokers.<sup>[68]</sup>

## Thrombotic condition

In a recent study done to investigate the *in vitro* thrombolytic and membrane-stabilizing action of four Bangladeshi medicinal plants including *arjuna*, the methanol extract was found to possess significant thrombolytic activity (30.57%). It also significantly inhibited the hemolysis of RBCs in both hypotonic solution and heat-induced conditions. This showed that it has moderate thrombolytic activity; however, more research is needed to isolate the secondary metabolites responsible for the activity.<sup>[69]</sup>

Not much data is available to comment on the effect of *arjuna* on cytochrome P450 (CYP450) enzyme. Results from a recent *in vitro* study indicate that *arjuna* extracts contain constituents that can potentially inhibit the activity of CYP1A.<sup>[70]</sup>

## TOXICITY AND SIDE EFFECTS

Mild side effects like nausea, gastritis, headache, bodyache, constipation, and insomnia have been reported. No hematological, renal, or metabolic toxicity has been reported even after more than 24 months of its administration.<sup>[48,50,53,55]</sup> However, Parmar *et al.* noticed that administration of *arjuna* resulted in reduction of thyroid hormone concentration in euthyroid animals, whereas the hepatic LPO was increased. Thus, high amounts of the plant extract should not be consumed, as it may induce hepatotoxicity as well as hypothyroidism.<sup>[47]</sup> The results from a recent acute and oral toxicological study done in animals showed that administration of ethanolic extract at a limit dose of 2000 mg/kg orally did not produce any kind of toxicity and death in animals.<sup>[46]</sup>

## CONCLUSION

The eternal interest in medicinal plants has led to the discovery of new chemical constituents and pharmacological actions of *arjuna*. Its efficacy as an anti-ischemic agent, a potent antioxidant, and an antiatherogenic agent has been amply demonstrated in various experimental and clinical studies. However, major lacunae of these studies include the lack of phytochemical standardization of the extract, bioavailability studies, and well-designed studies to evaluate its long-term toxicity effects. Its exact role in primary/secondary coronary prevention needs to be investigated. In addition to this, studies to look for the effect of *arjuna* on CYP450 enzymes and its interactions with other drugs like statin, aspirin, angiotensin-converting enzyme (ACE) inhibitors, and  $\beta$ -blocker need to be designed. Increasing the awareness regarding its medicinal usage can give a direction to the physicians to respond to the challenges in treating cardiovascular diseases.

## REFERENCES

1. Tyler VM, Premila MS. Ayurvedic Herbs: A Clinical Guide to the Healing Plants of Traditional Indian Medicine. Available from: <http://books.google.co.in/books?id=r7JmIeAw9JAC> and [printsec=frontcover#v=onepage](http://books.google.co.in/books?id=X2yNfIOPbrc) and [q](http://books.google.co.in/books?id=X2yNfIOPbrc) and [f=false](http://books.google.co.in/books?id=X2yNfIOPbrc). [Last accessed on 2014 Jan 25].
2. Warriar PK, Nambiar VP, Ramankutty C. Indian Medicinal Plants: A Compendium of 500 Species, Vol. 5. Available from: <http://books.google.co.in/books?id=X2yNfIOPbrc> and [q=terminalia+arjuna#v=snippet](http://books.google.co.in/books?id=X2yNfIOPbrc) and [q=terminalia%20arjuna](http://books.google.co.in/books?id=X2yNfIOPbrc) and [f=false](http://books.google.co.in/books?id=X2yNfIOPbrc). [Last accessed on 2014 Jan 25].
3. Chopra RN, Chopra IC, Handa KL, Kapur LD. Terminalia arjuna W and A (Combretaceae). In: Chopra RN, Chopra IC, Handa KL, Kapur LD, editors. Chopra's Indigenous Drugs of India, 1<sup>st</sup> ed. Calcutta, India: UN Dhur and Sons; 1958. p. 421-4.
4. Jain S, Yadav PP, Gill V, Vasudeva N, Singla N. Terminalia arjuna a sacred medicinal plant: Phytochemical and pharmacological profile. *Phytochem Rev* 2009;8:491-502.
5. Muthu C, Ayyanar M, Raja N, Ignacimuthu S. Medicinal plants used by traditional healers in Kancheepuram District of Tamil Nadu, India. *J Ethnobiol Ethnomed* 2006;2:43.
6. Yesodharan K, Sujana KA. Ethnomedicinal knowledge among Malamalasar tribe of Parambikulam Wildlife Sanctuary, Kerala. *Indian J Tradit Knowledge* 2007;6:481-5.
7. Prusti AB, Behera KK. Ethnobotanical exploration of Malkangiri district of Orissa, India. *Ethnobot Leaflet* 2007;11:122-40.
8. Prusti AB, Behera KK. Ethno-Medico Botanical Study of Sundargarh district, Orissa, India. *Ethnobot Leaflet* 2007;11:148-63.
9. Dwivedi S. Terminalia arjuna Wight and Arn.—A useful drug for cardiovascular disorders. *J Ethnopharmacol* 2007;1:114-29.
10. Arjuna. In hand book on medicinal and aromatic plants. Available from: <http://assamagribusiness.nic.in/nedfi/map17.pdf>. [Last accessed on 2014 Jan 26].
11. Dhingra V, Dhingra S, Singla A. Forensic and pharmacognostic studies of the Terminalia Arjuna Bark. *Egypt J Forensic Sci* 2013;3:15-9.
12. Paarakh PM. Terminalia arjuna (Roxb.) Wt. and Arn.: A review. *Int J Pharmacol* 2010;6:515-34.
13. Wang W, Ali Z, Li XC, Shen Y, Khan IA. Triterpenoids from two Terminalia species. *Planta Med* 2010;76:1751-4.
14. Wang W, Ali Z, Li XC, Shen Y, Khan IA. 18,19-secooleanane type triterpene glycosyl esters from the bark of Terminalia arjuna. *Planta Med* 2010;76:903-8.
15. Wang W, Ali Z, Shen Y, Li XC, Khan IA. Ursane triterpenoids from the bark of Terminalia arjuna. *Fitoterapia* 2010;81:480-4.
16. Nema R, Jain P, Khare S, Pradhan A, Gupta A, Singh D. Preliminary phytochemical evaluation and flavanoids quantification of Terminalia arjuna leaves extract. *Int J Pharm Phytopharmacol Res* 2012;1:283-6.
17. Yadava RN, Rathore K. A new cardenolide from the seeds of Terminalia arjuna (W and A). *J Asian Nat Prod Res* 2000;2:97-101.
18. Maulik SK, Talwar KK. Therapeutic potential of Terminalia arjuna in cardiovascular disorders. *Am J Cardiovasc Drugs* 2012;12:157-63.
19. Bhatia J, Bhattacharya SK, Mahajan P, Dwivedi S. Effect of Terminalia arjuna on coronary flow—an experimental study (Abstract). *Indian J Pharmacol* 1998;30:118.
20. Verma P, Muneesh, Rani S, Bhutani G. Experimental Evaluation of Terminalia arjuna (Aqueous Extract) on cardiovascular system in comparison to digoxin. *J Dent Med Sci* 2013;7:48-51.
21. Haq AM, Huque MM, Chaudhury SA, Haque MN. Cardiogenic effects of Terminalia arjuna extracts on guinea pig heart *in vitro*. *Bangladesh J Pharmacol* 2012;7:164-8.
22. Singh N, Kapur KK, Singh SP, Shankar K, Sinha JN, Kohli RD. Mechanism of cardiovascular action of Terminalia arjuna. *Planta Med* 1982;45:102-4.
23. Takahashi S, Tanaka H, Hano Y, Ito K, Nomura T, Shigenobu K. Hypotensive effect in rats of hydrophilic extract from Terminalia arjuna containing tannin-related compounds. *Phytother Res* 1997;11:424-7.
24. Nammi S, Gudavalli R, Babu BS, Lodagala DS, Boini KM. Possible mechanisms of hypotension produced 70% alcoholic extract of Terminalia

- arjuna (L.) in anaesthetized dogs. *BMC Complement Altern Med* 2003;3:5.
25. Oberoi L, Akiyama T, Lee KH, Liu SJ. The aqueous extract, not organic extracts, of Terminalia arjuna bark exerts cardiostimulant effect on adult ventricular myocytes. *Phytomedicine* 2011;18:259-65.
  26. Gauthaman K, Maulik M, Kumari R, Manchanda SC, Dinda AK, Maulik SK. Effect of chronic treatment with bark of Terminalia arjuna: A study on the isolated ischemic-reperfused rat heart. *J Ethnopharmacol* 2001;75:197-201.
  27. Gauthaman K, Mohamed Saleem TS, Ravi V, Patel S S, Niranjali S, Devaraj R. Alcoholic extract of terminalia arjuna protects rabbit heart against ischemic-reperfusion injury: Role of antioxidant enzymes and heat shock protein. *World Acad Sci Eng Technol* 2008;18:488-98.
  28. Manna P, Sinha M, Sil PC. Phytomedicinal activity of Terminalia arjuna against carbon tetrachloride induced cardiac oxidative stress. *Pathophysiology* 2007;14:71-8.
  29. Sinha M, Manna P, Sil PC. Terminalia arjuna protects mouse hearts against sodium fluoride-induced oxidative stress. *J Med Food* 2008;4:733-40.
  30. Shahriar M, Akhter S, Hossain MI, Haque MA, Bhuiyan MA. Evaluation of *in vitro* antioxidant activity of bark extracts of Terminalia arjuna. *J Med Plants Res* 2012;6:5286-98.
  31. Kokkiripati PK, Kamsala RV, Bashyam L, Manthapuram N, Bitla P, Peddada V, et al. Stem-bark of Terminalia arjuna attenuates human monocytic (THP-1) and aortic endothelial cell activation. *J Ethnopharmacol* 2013;146:456-64.
  32. Sumitra M, Manikandan P, Kumar DA, Arutselvan N, Balakrishna K, Manohar BM, et al. Experimental myocardial necrosis in rats: Role of arjunolic acid on platelet aggregation, coagulation and antioxidant status. *Mol Cell Biochem* 2001;224:135-42.
  33. Reddy TK, Seshadri P, Reddy KK, Jagetia GC, Reddy CD. Effect of Terminalia arjuna extract on adriamycin-induced DNA damage. *Phytother Res* 2008;22:1188-94.
  34. Singh G, Singh AT, Abraham A, Bhat B, Mukherjee A, Verma R, et al. Protective effects of Terminalia arjuna against Doxorubicin-induced cardiotoxicity. *J Ethnopharmacol* 2008;117:123-9.
  35. Kumar S, Enjamoori R, Jaiswal A, Ray R, Seth S, Maulik SK. Catecholamine-induced myocardial fibrosis and oxidative stress is attenuated by Terminalia arjuna (Roxb.). *J Pharm Pharmacol* 2009;61:1529-36.
  36. Parveen A, Babbar R, Agarwal S, Kotwani A, Fahim M. Mechanistic clues in the cardioprotective effect of Terminalia arjuna bark extract in isoproterenol-induced chronic heart failure in rats. *Cardiovasc Toxicol* 2011;11:48-57.
  37. Mythili P, Parameswari CS, Dayana J. Phytochemical analysis of the bark extract of Terminalia arjuna and its cardioprotective effect. *Indian J Innov Dev* 2012;1:40-2.
  38. Tiwari AK, Gode JD, Dubey GP. Effect of Terminalia arjuna on lipid profiles of rabbit fed hypercholesterolemic diet. *Int J Crude Drug Res* 1990;28:43-7.
  39. Pathak S R, Upadhyaya L, Singh RN. Effect of Terminalia arjuna on lipid profile of rabbit fed hypercholesterolemic diet. *Int J Crude Drug Res* 1990;28:48-51.
  40. Khanna AK, Chander C, Kapoor NK. Terminalia arjuna: An Ayurvedic cardiostimulant regulates lipid metabolism in hyperlipidemic rats. *Phytother Res* 1996;10:663-5.
  41. Ram A, Lauria P, Gupta R, Kumar P, Sharma VN. Hypocholesterolaemic effects of Terminalia arjuna tree bark. *J Ethnopharmacol* 1997;55:165-9.
  42. Chander R, Singh K, Khanna AK, Kaul SM, Puri A, Saxena R, et al. Antidyslipidemic and antioxidant activities of different fractions of terminalia arjuna stem bark. *Indian J Clin Biochem* 2004;19:141-8.
  43. Subramaniam S, Subramaniam R, Rajapandian S, Uthrapathi S, Gnanamanickam VR, Dubey GP. Anti-atherogenic activity of ethanolic fraction of terminalia arjuna bark on hypercholesterolemic rabbits. *Evid Based Complement Alternat Med* 2011;2011:487916.
  44. Subramaniam S, Ramachandran S, Uthrapathi S, Gnanamanickam VR, Dubey GP. Anti-hyperlipidemic and antioxidant potential of different fractions of Terminalia arjuna Roxb. bark against PX- 407 induced hyperlipidemia. *Indian J Exp Biol* 2011;49:282-8.
  45. Sharma S, Sharma D, Agarwal N. Diminishing effect of arjuna tree (Terminalia arjuna) bark on the lipid and oxidative stress status of high fat high cholesterol fed rats and development of certain dietary recipes containing the tree bark for human consumption. *Res Pharm* 2012;2:22-30.
  46. Patil RH, Prakash K, Maheshwari VL. Hypolipidemic effect of Terminalia arjuna (L.) in experimentally induced hypercholesteremic rats. *Acta Biol Szeged* 2011;55:289-93.
  47. Parmar HS, Panda S, Jatwa R, Kar A. Cardio-protective role of Terminalia arjuna bark extract is possibly mediated through alterations in thyroid hormones. *Pharmazie* 2006;61:793-5.
  48. Dwivedi S, Chansouria JP, Somani PN, Udupa KN. Effect of Terminalia arjuna on ischaemic heart disease. *Altern Med* 1989;3:115-22.
  49. Jain V, Poonia A, Agarwal RP, Panwar RB, Kochar DK, Mishra SN. Effect of Terminalia arjuna in patients of angina pectoris (A clinical trial). *Indian Med Gaz* 1992;36:56-9.
  50. Dwivedi S, Agarwal MP. Antianginal and cardioprotective effects of Terminalia arjuna, an indigenous drug, in coronary artery disease. *J Assoc Physicians India* 1994;42:287-9.
  51. Dwivedi S, Jauhari R. Beneficial effects of Terminalia arjuna in coronary artery disease. *Indian Heart J* 1997;49:507-10.
  52. Kumar PU, Adhikari P, Pereira P, Bhat P. Safety and efficacy of Hartone in stable angina pectoris—an open comparative trial. *J Assoc Physicians India* 1999;47:685-9.
  53. Bharani A, Ganguli A, Mathur LK, Jamra Y, Raman PG. Efficacy of Terminalia arjuna in chronic stable angina: A double-blind, placebo-controlled, crossover study comparing Terminalia arjuna with isosorbidedimonitrate. *Indian Heart J* 2002;54:170-5.
  54. Verma SK, Bordia A. Effect of Terminalia arjuna bark (arjunchhal) in patients of congestive heart failure and hypertension. *J Res Educ Indian Med* 1988;7:31-6.
  55. Bharani A, Ganguly A, Bhargava KD. Salutary effect of Terminalia Arjuna in patients with severe refractory heart failure. *Int J Cardiol* 1995;49:191-9.
  56. Ygnanarayan R, Sangle SA, Sirsakar SS, Mitra DK. Regression of cardiac hypertrophy in hypertensive patients—comparison of abana with propranolol. *Phytother Res* 1997;11:257-9.
  57. Sandhu JS, Shah B, Shenoy S, Chauhan S, Lavekar GS, Padhi MM. Effects of Withania somnifera (Ashwagandha) and Terminalia arjuna (Arjuna) on physical performance and cardiorespiratory endurance in healthy young adults. *Int J Ayurveda Res* 2010;1:144-9.
  58. Antani JA, Gandhi S, Antani NJ. Terminalia arjuna in congestive heart failure (Abstract). *J Assoc Physicians India* 1991;39:801.
  59. Dwivedi S, Aggarwal A, Agarwal MP, Rajpal S. Role of Terminalia arjuna in ischaemic mitral regurgitation. *Int J Cardiol* 2005;100:507-8.
  60. Bhawania G, Kumar A, Murthy KS, Kumari N, Swami CG. A retrospective study of effect of Terminalia arjuna and evidence based standard therapy on echocardiographic parameters in patients of dilated cardiomyopathy. *J Pharm Res* 2013;6:493-8.
  61. Malik N, Dhawan V, Bahl A, Kaul D. Inhibitory effects of Terminalia arjuna on platelet activation *in vitro* in healthy subjects and patients with coronary artery disease. *Platelets* 2009;20:183-90.
  62. Pingali U, Fatima N, Nizampatnam M. Evaluation of Terminalia arjuna on cardiovascular parameters and platelet aggregation in patients with Type II diabetes mellitus. *Res J Life Sci* 2013;1:7-12.
  63. Tripathi VK, Singh B, Jha RN, Pandey VB, Udupa KN. Studies on Arjuna in coronary heart disease. *J Res Ayur Siddha* 2000;21:37-40.
  64. Gupta R, Singhal S, Goyle A, Sharma VN. Antioxidant and hypocholesterolaemic effects of Terminalia arjuna tree-bark powder: A randomised placebo-controlled trial. *J Assoc Physicians India* 2001;49:231-5.
  65. Khalil S. Effect of statin versus Terminalia arjuna on acute myocardial infarction. *DNB thesis (Medicine)*, 2005 National Board of Examination, New Delhi, India.
  66. Kumar G, Srivastava A, Sharma SK, Gupta YK. Safety and efficacy evaluation of Ayurvedic treatment (Arjuna powder and Arogyavardhini Vati) in dyslipidemia patients: A pilot prospective cohort clinical study. *Ayu* 2012;33:197-201.

67. Dwivedi S, Kumar V. Beta-thalassemia, hyperlipoproteinaemia(a) and metabolic syndrome: Its low cost holistic therapy. *J Altern Complement Med* 2007;13:287-9.
68. Bharani A, Ahirwar LK, Jain N. Terminalia arjuna reverses impaired endothelial function in chronic smokers. *Indian Heart J* 2004;56:123-8.
69. Shahriar M, Sharmin FA, Islam SMA, Dewan I, Kabir S. Membrane stabilizing and anti-thrombolytic activities of four medicinal Plants of Bangladesh. *Experiment* 2012;4:265-70.
70. Varghese A, Pandita N, Gaud R S. *In vitro* and *in vivo* evaluation of CYP1a interaction potential of terminalia arjuna bark. *Indian J Pharm Sci* 2014;76:138-47.

