Potential benefits of *Terminalia arjuna* in cardiovascular disease

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Abstract

The bark of the tree of *Terminalia arjuna* has been used in cardiological disorders in Ayurveda. In the Rigveda, the word *Arjuna* is used for the first time. The preclinical studies in modern medicine suggest that there are strong antioxidant properties of *Terminalia arjuna* and reduction of ischemic perfusion injury. It also causes attenuation of oxidative stress and anti-fibrotic activity has been shown. Clinical trials suggest that the benefit of *arjuna* could be in patients with ischemic heart disease and heart failure. The mechanisms of action are not very clear, but some evidence of antioxidant action, inotropic action and hypopidemic action has been seen. The pre-clinical and clinical studies published so far are small and from limited regions, Myanmar and Sri Lanka. It grows predominantly beside water channels or marshy belts. It has a buttressed trunk. Bark of tree is grey brown in color and slightly rough in touch from outside and is thick, soft and of red color from inside. Leaves are sub-opposite, obovate or elliptical in shape and the shape resembles to the shape of guava leaves. Flowers are arranged in panicked spikes. Fruits are ovoid or ovoid-oblong, 2.5–5 cm and glabrous with five to seven wings.

Introduction

Few new drugs are being developed for heart diseases and an attempt is being made to look at other systems of medicine. The bark of the tree of *Terminalia arjuna* has been used in various cardiological disorders in Ayurveda including angina, hypertension and heart failure. In this article we trace the use of *Terminalia arjuna* in various cardiovascular ailments

History of use

In the Rigveda, the word *Arjuna* is used (R.V.1/122/5) for the first time. Both Carakacharya and Sushrutacharya have mentioned this plant in their Samhitas, but have not given its use for heart diseases. It was Vagbhattacharya who for the first time mentioned the use of *Arjuna* in the treatment of heart diseases and the same was endorsed by Cakradattam and Bhavamisram. Ayurveda recommends *Terminalia arjuna* 

**Keywords**
- *Terminalia arjuna*
- Ayurveda
- Phytochemistry
- Coronary artery disease
- Heart failure
- Hypertension

Botanical details

*Arjuna* tree is a large, evergreen tree. The tree is about 60–80 feet in height. *Arjuna* tree is native to Indian soil. It is seen all around the sub-Himalayan tracts, the Deccan regions, Myanmar and Sri Lanka. It grows predominantly beside water channels or marshy belts. It has a buttressed trunk. Bark of tree is grey brown in color and slightly rough in touch from outside.

The leaves of *ksadiamba*, *arjuna*, *nimba*, *patali*, *pippala* and *araka* are useful for healing of the wounds.

**Aqueous extract**

Aqueous extract of *Terminalia arjuna* bark was evaluated at 63, 125 and 250 mg/kg given orally for anti-atherogenic and antioxidant effects in rats given the selective beta-adrenoceptor agonist isoprenaline (5 mg/kg s.c.) for 28 days. Captopril was used as a positive control. Isoprenaline caused fibrosis, increased oxidative stress and cardiac hypertrophy (increased heart/body weight ratio and cardio-miyocyte diameter). The *Terminalia arjuna* bark extract and captopril significantly prevented the isoprenaline-induced increase in oxidative stress and decline in endogenous antioxidant level. Both also prevented fibrosis but not the increase in heart/body weight ratio. Therefore, *Terminalia arjuna* protects against myocardial changes induced by chronic beta-adrenoceptor stimulation.

**Hypolipidemic activity**

Hypolipidemic activity was studied earlier in experimental studies by Seth et al., 1998 and in the same year by Shaila 1998. In this experimental setting, Rabbits were fed a cholesterol-rich diet to induce atherosclerosis. *Arjuna* was fed along with cholesterol. At the end of the experimental period the animals were killed and their plasma and tissue lipid components estimated. Atherosclerotic lesions of the aorta were examined histologically. *Terminalia arjuna* was found to be a potent hypolipidemic agent and induced partial inhibition of rabbit atheroma.

The results indicate that *Terminalia arjuna* may play an anti-atherogenic role. Studies have shown that aqueous extracts of *arjuna* exerted positive inotropy, accelerated myocyte relaxation and increased catecholamine-induced contraction concentration-dependently. In contrast, *arjuna* organic extracts caused interruption of excitability and arrhythmias without consistent inotropic action. This suggested that *arjuna* induced cardiotoxic action via enhancing sarcoplasmic reticulum function, a unique action minimizing the occurrence of arrhythmias, makes *Terminalia arjuna* (Aql) a promising and relatively safe cardio-tonic beneficial to the healthy heart and the treatment for chronic heart disease. Effect of *Terminalia arjuna* effect on adriamycin-induced DNA damage was proved in a study by (Reddy 2008). Most of the preclinical studies have focused on the myocardial necrosis model and have shown that *arjuna* prevents injury induced by various stresses. Earlier in 2003, in a study cardioprotective effect of the alcoholic extract of *Terminalia arjuna* in vivo model of myocardial ischemic reperfusion injury was proved (Karthikeyan 2003). This suggested the potential of *arjuna* in the prevention of ischemic heart disease. (Nammi et al., 2003) showed its anti-hypertensive property in dogs. In the year 2006, Parmar et al. showed its
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**Introduction**

Few new drugs are being developed for heart diseases and an attempt is being made to look at other systems of medicine. The bark of the tree of *Terminalia arjuna* has been used in various cardiac disorders in Ayurveda including angina, hypertension and heart failure. In this article we trace the use of *Terminalia arjuna* in various cardiac ailments.

**History of use**

In the Rigveda, the word Arjuna is used (R.V.1/122/5) for the first time. Both Carakacharya and Sushrutacharya have mentioned this plant in their Samhitas, but have not indicated its use for heart diseases. It was Vagbhattacharya who for the first time mentioned the use of Arjuna in the treatment of heart diseases and the same was endorsed by Cakradattam and Bhamvamisram. Ayurveda recommends the *Terminalia arjuna* bark as a readily available and safe strategy to improve myocardial function in the face of acute coronary syndromes. It also offers an effective alternative to statins to lower lipids in hypercholesterolemic patients.

**Botanical details**

Arjuna tree is a large, evergreen tree. The tree is about 60–80 feet in height. Arjuna tree is native to Indian soil. It is seen all around the sub-Himalayan tracts, the Deccan regions, Myanmar and Sri Lanka. It grows predominantly beside water channels or marshy belts. It has a buttressed trunk. Bark of tree is grey brown in color and slightly rough in touch from outside and is thick, soft and of red color from inside. Leaves are sub-opposite, oblong or elliptical in shape and they resemble to the shape of guava leaves. Flowers are arranged in panicked spikes. Fruits are ovoid or ovoid-oblong, 2.5–5.0 cm and glabrous with five to seven wings.

**Phytochemistry of *Terminalia arjuna***

Phytochemical analysis reveals that it contains triterpenes (like arjunic acid), arjunolic acid, arjunglucoside-I, arjunglucoside-II, arjunolitin, arjunaphthanoloside-1 and very high amounts of flavonoids (quecetin, kaempferol, luteolin, and pellargonidin), ellagic acids and phytosterols as well as minerals such as calcium, magnesium, zinc, and copper. Some other compounds in *Terminalia arjuna* are termic acid, arjunin, Cuscinarin, sapogenins, serine, valine, proline, methionine, histidine, lysine, etc.

**Preclinical studies done on *Terminalia arjuna***

Although descriptions of cardiac ailments in the ancient medical texts did not match well with the modern classification of cardiovascular diseases, Ayurvedic physicians nevertheless widely prescribed the ‘drug’ for a wide range of cardiac conditions, from angina pectoris to heart failure. Evidence-based preclinical and clinical studies with *Terminalia arjuna* have only been reported during the last few decades. The preclinical studies suggest that there are strong antioxidant properties of *Terminalia arjuna* and wound healing and reduction of ischemic perfusion injury (Gauthaman et al., 2003), effect of this drug on the process of respiratory oxygen (Pawar et al., 2005), and anti-fibrotic activity (Kumar et al., 2009) have been shown. Kumar et al. have studied the effects of *Terminalia arjuna* bark extract on myocardial fibrosis and oxidative stress induced by chronic beta-adrenoceptor stimulation.

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cardioprotective property through alterations in thyroid hormones.

Arjuna is useful in various domains, e.g., Hepatic renal disorders (Manna et al. 2009) and due to its antioxidant properties used for the treatment of cancers Verma et al. 2009. In the same year Halder et al. proved its anti-inflammatory, immune modulatory and antiinfective property. Praveen et al. in 2011 gave mechanistic clues in its cardioprotective effect and in 2012 proves that the drug enhances baroreflex sensitivity and myocardial function. Obro et al. in 2011 concluded that bark of Terminalia arjuna exerts cardio protective effect on ventricular myocardial cells.

### Clinical studies done on Terminalia arjuna

In the Indian system of medicine the physicians are using arjuna in various heart problems, but in the era of evidence based medicine to prove the efficacy of arjuna a series of clinical trials have been going on since the early 20th century.

#### Coronary artery disease

The Early clinical trials with Terminalia arjuna were done by Dwivedi and Pandey in 1994. Terminalia arjuna was studied in 15 stable and 5 unstable angina patients before and 3 months after therapy. There was 50% reduction in anginal episodes. The time to the onset of angina and appearance of ST changes on TMT after Terminalia arjuna was delayed significantly. However, in patients with unstable angina there was an insignificant reduction in anginal frequency. The adverse symptoms, blood pressure and body mass index to a significant level (p < 0.05) and increased HDL-cholesterol only slightly along with marginal improvement in left ventricular ejection fraction in the stable angina patients.

In 1997, in another study Dwivedi et al. studied patients with ischemic cardiomyopathy and showed significant symptomatic relief in coronary heart failure from NYHA class III to NYHA class I. Prolonged administration of Terminalia arjuna did not show any adverse effects on renal, hepatic and hematological parameters.

In 2001, Gupta et al. showed that Terminalia arjuna tree bark powder has significant antioxidant action that is comparable to vitamin E. In addition, it also has a significant hypcholesterolemic effect.

In the year 2002, Bharani et al. also worked on chronic stable angina cases and proved that Terminalia arjuna bark extract 500 mg, 8 hourly given to patients with stable angina with provable ischemia on treadmill exercise, led to improvement in clinical and treadmill exercise parameters as compared to placebo and their results suggest that monotherapy with arjuna is fairly effective in patients with symptoms of stable angina pectoris.

In the year 2003, Mary et al. studied the antiangogenic effect of Terminalia arjuna and observed the hypopilidemic action of a preparation which included a methanolic extract of arjuna. They also showed antioxidant and antplatelet activities. All these results revealed the therapeutic potential of arjuna against vascular intimal damage and atherosclerosis.

The work was followed by Bharani et al. in the year 2004, and result was that the Terminalia arjuna therapy for two weeks led to significant regression of endotheleal dysfunction amongst smokers. In 2009, Malik et al. worked to prove inhibitory effects of Terminalia arjuna on platelet activation in vitro in healthy subjects and patients with coronary artery disease.

### Heart failure

In 1995, Bharani et al. also worked on severe refractory heart failure. The results of a prospective clinical congestive heart failure received Terminalia arjuna (as bark extract 500 mg 8-hourly) or matching placebo for 2 weeks each, separated by 2 weeks washout period, in a double blind cross over design as an adjuvent to maximally improve in symptoms, signs, effort tolerance and NYHA Class, with improvement in quality of life.

Heart failure

Hypertension

In 2001, Rao BCS, Singh RH, Tripathi K worked to assess the effect of Terminalia arjuna (W&A) on regression of LVH in hypertensive subjects and stated that the efficacy of arjuna may be attributed to its negatively chronotropic as well as hypotensive action. In 2005, a study done by Dwivedi et al. worked for the role of Terminalia arjuna in ischemic mitral regurgitation.

Ongoing

Currently in the All India Institute of Medical Sciences (AIIMS), New Delhi, a clinical trial on Arjuna is going on. It is a double-blind, randomized placebo controlled clinical trial to study the add-on efficacy of a standardized preparation of Terminalia arjuna in 100 patients with Left Ventricular Dysfunction, already receiving a standard drug regimen. Patients are getting a dose of 750 mg twice a day of water extract of bark of Terminalia arjuna for a period of three months. Left ventricular function (by echocardiography), and functional capacity by New York Heart Association (NYHA) Class, Kansas City Cardiomyopathy Questionnaire-KCCQ (for quality of life), Six Minute Walk test and Brain Natriuretic Peptide (BNP) are the end points to be assessed. They are also being assessed by Dashvish Parkash (an ayurvedic method of assessment of the patient) before and after therapy. All safety end points are being assessed. This trial is expected to give conclusive evidence regarding the effects of Terminalia arjuna on heart failure as administered as an add-on therapy in the patients of heart failure.

### Conclusion

The bark of Terminalia arjuna has been used in Indian medicine for cardiovascular ailments for a long time. Current scientific literature suggests that the benefit of arjuna lies in patients with ischemic heart disease and heart failure. The mechanisms of action are not very clear but some evidence of antioxidant action, inotropic action and hypotensive action has been seen. The preclinical and clinical studies published so far are small and from limited centres. Large clinical studies and more mechanistic pre-clinical studies are needed to establish a firm role for arjuna in current cardiovascular practice.

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Clinical studies done on Terminalia arjuna

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Coronary artery disease

The Earliest clinical trials with Terminalia arjuna were done by Dwivedi and Prakash in 1984. Terminalia arjuna was studied in 41 stable and 5 unstable angina patients before and 3 months after therapy. There was 50% reduction in anginal episodes. The time to the onset of angina and appearance of ST-T changes on ECG after treatment with Terminalia arjuna was delayed significantly. However, in patients with unstable angina there was an insignificant reduction in anginal frequency. The adverse symptoms like blood pressure and body mass index to a significant level (p < 0.05) and increased HDL-cholesterol only slightly along with marginal improvement in left ventricular ejection fraction in the stable angina patients.

In 1997, in another study Dwivedi et al. studied patients with ischemic heart disease and showed significant symptomatic relief in coronary heart failure from NYHA class III to NYHA class-I. Prolonged administration of Terminalia arjuna in 100 patients with Left Ventricular Dysfunction, already receiving a standard drug regimen. Patients are getting a dose of 750 mg twice a day of water extract of bark of Terminalia arjuna for a period of three months. Left ventricular function (by echocardiography), and functional capacity by New York Heart Association (NYHA) Class, Kansas City Cardiomyopathy Questionnaire-KCCQ (for quality of life), Six Minute Walk test and Brain Natriuretic Peptide (BNP) are the end points assessed. They are also being assessed by Dashivuld Parkish (an ayurvedic method of assessment of the patient) before and after therapy. All safety end points are being assessed. This trial is expected to give conclusive evidence regarding the effects of Terminalia arjuna on patients with coronary artery disease.

Heart failure

In 1995, Bharani et al. 1995 also worked on severe refractory heart failure. They found that the ventricular congestive heart failure received Terminalia arjuna (as bark extract 500 mg 8-hourly) or matching placebo for 2 weeks each, separated by 2 weeks washout period, in a double blind cross over design as an adjunct to maximally tolerable conventional therapy (Phase I). The clinical, laboratory and echocardiographic evaluation was carried out at baseline and after 2 weeks of treatment. Terminalia arjuna and placebo therapy and results were compared. Terminalia arjuna, compared to placebo, was associated with improvement in symptoms and signs of heart failure, decrease in NYHA Class, decrease in left ventricular diastolic and end systolic volume indices, increase in left ventricle’s stroke volume index and increase in left ventricular ejection fraction (35.33 ± 7.85 vs. 30.24 ± 7.13%; P < 0.005).

On long term evaluation in an open design (Phase II), wherein Phase I participants continued Terminalia arjuna in fixed dosage (500 mg 8-hourly) in addition to flexible diuretics, vasodilator and digoxin doses for 20–28 months (mean 24 months) on outpatient basis, patients showed continued improvement in symptoms, signs, effort tolerance and NYHA Class, with improvement in quality of life. Therefore, arjuna appeared to be safe and caused long lasting improvement in symptoms and signs of heart failure along with improvement in left ventricular ejection phase indices with definite improvement in quality of life.

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In 1995, 2001, 2005 clinical trials have been going on since the early 20th century. In the Indian system of medicine the physicians are using arjuna in various heart problems, but in the era of evidence based medicine to prove the efficacy of arjuna a series of clinical trials have been going on since the early 20th century.

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The meta-analyses included around 280 trials of NSAIDs versus placebo (n = 124753 participants, 687342 person-years) and 474 trials of one NSAID versus another NSAID (N = 229729 participants, 1657456 person-years). The main outcomes studied were major vascular events, major coronary events, stroke, mortality, heart failure, and upper gastrointestinal complications.

The results of the comparative study showed that the vascular risks of high-dose diclofenac or ibuprofen, was comparable to coxibs, and thus NSAIDs should be used considering the increase in vascular and gastrointestinal risks, but the size of these risks can be predicted which can guide in clinical decision making.

3. Type 1 Diabetes Mellitus can increase the risk of cardiovascular risk

Urbina EM and others
Diabetes Care. 2013 Apr. 5. [Epub ahead of print]

The studies have revealed that Type 1 diabetes mellitus increases the risk of cardiovascular disease by narrowing carotid intima-media thickness (IMT) in adults. The young subjects with type 1 diabetes were evaluated for IMT.

Subjects enrolled for the study were 18.9 ± 3.3 years old (50% male, 82.7% non-Hispanic white). The results showed that Youth with type 1 diabetes had thicker bulb intima-media thickness and upper gastrointestinal complications. With better control over glycemic values the difference could be eliminated, which was attributed to poor glycemic control of the subjects.

Hence to prevent progression of atherosclerosis in young patients with type 1 diabetes, better control of diabetes helps in prevention and control of cardiovascular diseases.