Review of Terminalia Arjuna an Ancient Drug as an Alternative Remedy for Cardiovascular Diseases

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Abstract

Modern medical sciences have progressed a lot to treat aliments concerning heart.A simple medications like Aspirin to sophisticated open heart surgeries are common now days to treat heart diseases. In spite of the advancement in ultramodern technologies heart diseases like Angina pectoris and Myocardial Infarction are creating alarming situations in the society. Terminalia arjuna, commonly known as arjuna, is an ancient cardio protective herbal remedy. In traditional herbal system of medicine in India- Ancient medical scientists have mentioned the remarkable cardio protective, heart muscle strengthening properties of Terminalia arjuna herb. Terminalia arjuna bark decoction is being used in the Indian subcontinent for anginal pain, hypertension, and congestive heart failure based on the observations of ancient physicians for centuries. The role of arjuna in various cardiovascular diseases needs to be reviewed further. Ancient medicines expanded attention due to their effectiveness, lack of current medical alternatives, also due to increasing side effects and cost of modern medicines. Therefore, this study is an effort to survey the literature summarizing the experimental and clinical studies relating to arjuna in cardiovascular disorders. Both experimental and clinical studies, have suggested that Terminalia arjuna possesses anti-ischemic, antioxidant, hypolipidemic, and antiatherogenic activities. Ethno botanical studies are most important to expose the ancient times and current culture about plants in the world and reserving original knowledge of medicinal plants. Useful phytoconstituents of arjuna like triterpenoids and flavonoids are considered to be responsible for its beneficial antioxidant cardiovascular properties. The drug has shown promising effect on ischemic cardiomyopathy and found quite useful in angina pectoris, mild hypertension, dyslipidemia and heart palpitations, as well as high cholesterol. Though no serious side effects have been reported with arjuna therapy, its long-term safety still remains to be elucidated.

Keywards

Terminalia arjuna, Medicinal property, Antioxidant, Cardiovascular disorders, cholesterol, Coronary prevention; Ethno botanical, Flavonoids, Triterpenoids.

Introduction

Terminalia arjuna, commonly called Indradru, Arjuna, Dhavala, Kakubha, Veeravriksha and Nadisarja[1] is a potential cardio protective 20-25 meters tall large evergreen herbal drug belonging to the Combretaceae family found in many parts of the world. The Indian physician Charaka and Susruta have mentioned this ancient ayurvedic plant in their Samhitas. This ancient ayurvedic remedy has been also mentioned in Astang Hridayam. It was Vagabhatta who, for the first time, advocated the use of stem bark powder in heart ailments.[2] Terminalia arjuna has been known to possess cardiovascular benefits as early as 500 BC and its bark has been used in Indian traditional system of medicine for over three centuries as a cardiotonic.[3,4].The medicinal importance of this tree is also well documented in Indian pharmacopeia. It contains number of elements beneficial for human health, thus it has been used for centuries in the traditional medicine of India.

Ethnomedical Uses

The bark has been described as an astringent, demulcent, expectorant, cardiotonic, styptic, anti-dysenteric, urinary astringent, and has shown to be useful in fracture, ulcers, leukorrhea, diabetes, anemia, cardiopathy, and cirrhosis.[5] Chakradatta, the great ancient physician, recommended it to be given as a decoction of bark with milk or as a ghrita (a preparation with ghee or butter).[6] Fresh leaf juice is used for the treatment of ear-ache and bark powder for treating heart ailments by Malabar tribe, Kerala.[7]

Occuranve Botanical Description –

It is commonly known as Arjuna, Indradru, Partha and Veeravriksha[8] which is belongs to Combretaceae family. *T. arjuna* is about 60–80 feet in height, buttressed trunk and horizontally spreading crown and drooping branches distributed in India, Burma, Mauritius and Sri Lanka.[9, 10, 11] *T. arjuna* is distributed throughout sub Indo-Himalayan tracts of Uttar Pradesh, Punjab, Deccan, South Bihar, Orissa, West Bengal and

Madhya Pradesh mainly along riverside, rivulets and ponds. It is known by its various vernacular names, the most commonly used ones are Arjuna (Common Name), Arjun (Hindi), Marudhu (Tamil and Malayalam), Tella Maddi (Telugu), Arjhan (Bengali), Sadaru (Marathi), Sadado (Gujarati), Neer matti (Kannada) and some traditional formulations prescribe in the name of Arjunarishta and Arjunaghrita.

Leaves of *T. arjuna* are simple, often crenulations, borne sub-opposite, shortly acute or obtuse at the apex, coriaceous and oblong or elliptic. Their upper face is pale or dark green and the lower face is pale brown. The tree bears white sessile bisexual flowers in short auxiliary spikes or in a terminal panicle arrangement. Fruits of *T. arjuna* are drupe, ovoid, fibrous-woody and smooth-skinned with five hard wings or angles which are oblique and curved upwards. Stem bark is simple, smooth and pinkish-gray in color in external view. An internal view, the bark is soft and reddish in color.[12] 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.[13]

Experimental Studies-

Experimental studies regarding effects on cardiac hemodynamics, coronary flow, and blood pressure

Bark stem of *arjuna* possesses diuretic, inotropic, and chronotropic properties.[14] In the Langendorff's rabbit heart preparation, the aqueous extract has demonstrated to cause an increase in the coronary flow.[15] The inotropic effect is considered to be mediated through the high concentration of Ca^{++} present in the plant.[16]

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.[17] 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 reducing/antioxidant power assay revealed that ethanol extract enhanced the cardiac intracellular antioxidant activity.[18,19]

Clinical Uses

Angina Pectoris-

Study of Terminalia use in stable and unstable angina demonstrated a 50-percent reduction of angina in the stable angina group after three months testing. Indicating an improvement in exercise tolerance. Evaluation of overall clinical condition, treadmill results, and ejection fraction showed improvement in 66 percent of stable angina patients and 20 percent of unstable angina patients after three months.[20] Two clinical studies found similar results when Terminalia arjuna was compared to isosorbide mononitrate in stable angina patients.[21,22]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.[23]

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.[24] *Terminalia arjuna* has been clinically tested in a number of cardiovascular conditions including ischaemic heart disease, [25] Nine clinical studies have been conducted to study the effects of *Terminalia arjuna* in patients with angina alone [26–34]. No systematic review has been conducted for *Terminalia arjuna* in patients of chronic stable angina.

CHF/ hypertension/ Congestive Heart Failure

A double-blind, placebo-controlled of Terminalia extract in 12 patients with severe refractory heart failure (NYHA Class IV) was conducted, in which either 500 mg Terminalia bark extract or placebo was given every eight hours for two weeks, in addition to the patients' current pharmaceutical medications (digoxin, diuretics, angiotensin-convertingenzyme inhibitors, vasodilators, and potassium supplementation).

Dyspnea, fatigue, edema, and walking tolerance all improved while patients were on Terminalia therapy. Treatment with Terminalia was also associated with significant improvements in stroke volume and left ventricular ejection fraction, as well as decreases in end-diastolic and end-systolic left ventricular volumes compared to placebo.[35]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.[36]

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 interventricular septal thickness.[37] hypertension, [38] heart failure, [39]. mitral regurgitation, [40] endothelial dysfunction, [41] Recently, *arjuna* has also been shown useful in improving cardiovascular endurance and in lowering SBP in normal healthy subjects.[42]

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.[43]

Cardiomyopathy/Post-Myocardial Infarction

A study was conducted on 10 post-myocardial-infarction patients and two ischemic cardiomyopathy patients, utilizing 500 mg Terminalia extract every eight hours for three months, along with conventional treatment. Significant reductions in angina and left ventricular mass, in addition to improved left ventricular ejection fraction, were noted in the Terminalia group; whereas, the control group taking only conventional drugs experienced decreased angina only. The two patients with cardiomyopathy improved from NYHA Class III to NYHA Class I during the study.[44] A*rjuna* was found to reduce LVM and improve LVEF.[45] 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.[46]

Hyperlipidemia –

Animal studies suggest Terminalia might reduce blood lipids. Rabbits made hyperlipidemic on an atherogenic diet were given an oral Terminalia extract, and had a significant, dose-related decrease in total- and LDL-cholesterol, compared to placebo ($p<0.01$) [47] In another study, rabbits were fed a cholesterol-rich diet in combination with three indigenous Terminalia species; Terminalia arjuna, T. belerica, and T. chebula. Upon histological examination, the rabbits fed the diet and T. arjuna exhibited the most potent hypolipidemic effect, with partial inhibition of atheroma.[48] In a randomized, controlled trial, Terminalia bark was compared to vitamin E. The Terminalia group had a significant decrease in total cholesterol and LDL cholesterol. Lipid peroxidase levels decreased significantly in both vitamin E and Terminalia groups; however, there was a greater decrease in the vitamin E group.[49]

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.[50]

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.[51]

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.[52]

Lipoprotein(a)

A significant reduction in lipoprotein(a) levels amounting to 24.71% following the administration of *arjuna* in a patient of β-thalassemia associated with hyperlipoproteinemia and metabolic syndrome has been reported.[53]

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.[54]

Toxicity And Side Effects

T. arjuna has been used in the dose between 1 to 2 g per day in different clinical studies and found that this is an optimum dose in the patients particularly CAD.Mild side effects like nausea, gastritis, headache, bodyache, constipation, and insomnia have been reported. No metabolic toxicity has been reported even after more than 24 months of its administration.[55,56,57,58]. High amounts of the plant extract should not be consumed, as it may induce hepatotoxicity as well as hypothyroidism.[59] 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.[60] Recently Bhawani et al reported that there was no significant variation in the body and organ weights between the control and the treated group of 93 patients with dilated cardiomyopathy (DCMP) of idiopathic and ischemic cause was observed after 28 days of treatment under the treatment of *T. arjuna* capsules (500 mg at 8 h)

Conclusion

On the basis of the available literature evidences, *T. arjuna* is widely used for treatment of cardiovascular diseases, including heart diseases and related chest pain, high blood pressure and high cholesterol. Its efficacy as an anti-ischemic agent, a potent antioxidant, preventing LDL, reperfusion ischemic injury to the heart and its potential to reduce atherogenic lipid levels have been sufficiently demonstrated in different experimental and clinical studies. However, major lacunae of these studies include the lack of phytochemical standardization of the extract, bioavailability studies, and continuous research progress of using *T. arjuna* is very much needed in the regards of exact molecular mechanism, drug administration, drug-drug interactions and toxicological studies.Also well-designed study to evaluate its long-term toxicity effects is needed. Increasing the awareness regarding its medicinal usage can give a direction to the physicians to respond to the challenges in treating cardiovascular diseases.

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