

Terminalia Arjuna: A Miraculous Medicinal Plant from India

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ABSTRACT:

Ancient Indian physicians used the powdered tree bark of Terminalia arjuna Wight & Arn. for alleviating "hritshool" (angina) and other cardiovascular conditions. Its stem bark possesses glycosides, large quantities of flavonoids, tannins and minerals. Flavonoids have been detected to exert antioxidant, anti-inflammatory and lipid lowering effects while glycosides are cardiogenic, thus making Terminalia arjuna unique amongst currently used medicinal plants. In this review an attempt has been made to discuss various aspects of its ethnomedical, pharmacognostical, phytochemical, pharmacological and clinical relevance to cardiovascular conditions. Experimental studies have revealed its bark exerting significant inotropic and hypotensive effect, increasing coronary artery flow and protecting myocardium against ischemic damage. It has also been detected to have mild diuretic, antithrombotic, prostaglandin E2 enhancing and hypolipidaemic activity.

KEYWORDS: Terminalia Arjuna, T.S. Of Leaf, Mechanism, Powder Character, Identification of Samples, Uses, Future Strategies.

I. INTRODUCTION:

Medicinal plants play an essential role in health care and are the major raw materials for both traditional and conventional medicine preparations; still most of the people choose herbal medicines than conventional medicines. They expanded attention due to their effectiveness, lack of current medical alternatives, increasing cost of modern medicines and cultural preferences. Ethnobotanical studies are most important to expose the ancient times and current culture about plants in the world and reserving original knowledge of medicinal plants. [20]

The quantitative ethnobotanical studies were used to identify the plant uses as food, human health care medicines, veterinary medicine and economically important. Around the world, the traditional knowledge system has expanded chief importance in perspective with protection, sustainable growth and search for new utilization patterns of plant resources. Traditional medicine system includes the knowledge, skills and practices based on the presumptions, beliefs and experiences of folk communities to protect their health problems. Traditional herbal medicines are considered to be of huge importance among different rural or native communities in many developing countries.[8]

According to WHO, almost 80% of the world's population depending on traditional medicine and in India 60% of the people in rural areas use herbal medicines. During the last few years, use of herbal supplements increased from 2.5% to 12%.⁹ In recent years, there has also been an increasing demand for nanoparticles derived from medicinal plants like Terminalia family due to their applications in various fields of research like medicine, catalysis, energy and materials.

In the earliest India, medicinal plants were used to prevent different critical diseases and they would be the best source to obtain a variety of drugs. The Indian traditional medicine is based on various systems such as Ayurveda, Siddha, Unani, etc.[1]

II. LITERATURE SURVEY:

a. Amalraj Augustine, Gopi Sreeraj.

Medicinal plants have been a main source of therapeutic agents from ancient time to cure diseases. Terminalia arjuna (Roxb.) Wight & Arn. (T. arjuna) is one of the most accepted and beneficial medicinal plants in indigenous system of

medicine for the treatment of various critical diseases. [1]

b. Choudhari Amol B., Seyyed Nazim, Gomase Pravin V., Khairnar Ashish S., Shaikh Afsar, Choudhari Pritam.

The use of medicinal plant either as a single drug or in combination is increasing in the health care of human being. Medicinal plants can be important source of previously unknown chemical substances with potential therapeutic effect. Terminalia arjuna bark is commonly known as arjuna bark or arjun and abundantly available throughout the India. This plant contains 15 % tannins, triterpenoids, saponins, flavonoids, calcium, aluminum and magnesium salts along with colouring matter and sugars are the other constituents of arjun. [2]

c. Chatha Shahzad Ali Shahid, Hussain Abdullah Ijaz, Asad Rehan, Mudasar Majeed and Nosheen Aslam

This work was carried out to investigate the antioxidant activity and free radical scavenging capacity of leaves and stem bark extracts of Terminalia arjuna (arjuna) prepared in aqueous ethanol (water: ethanol 20:80v/v) and aqueous methanol (water: methanol 20:80v/v) solvents. [4]

d. Jain Sunyana, Yadav Prem Prakash, Gill Vikrant, Vasudeva Neeru, Singla Neelam

Terminalia arjuna Wight & Arn. (Combretaceae) is a tree having an extensive medicinal potential. The plant is used traditionally in the treatment of various ailments. T. arjuna is a very good hypocholesteremic, hypolipidemic, anticoagulant, anti-hypertensive, antithrombotic, antiviral, antifungal and antibacterial agent. Various parts of plant have been investigated for the presence of phytoconstituents and pharmacological activities. [5]

e. Dwivedi Shridhar, Chopra Deepti

Terminalia arjuna, commonly known as arjuna, belongs to the family of Combretaceae. Its bark decoction is being used in the Indian subcontinent for arthralgia, 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. [5]

4. TERMINALIA ARJUNA:



Plant Profile:

- Kingdom: Plantae
- Division: Magnoliophyta
- Class: Magnoliopsida
- Order: Myrtales
- Family: Combretaceae
- Genus: Terminalia
- Species: T. arjuna
- Zoological name: Terminalia arjuna [2]

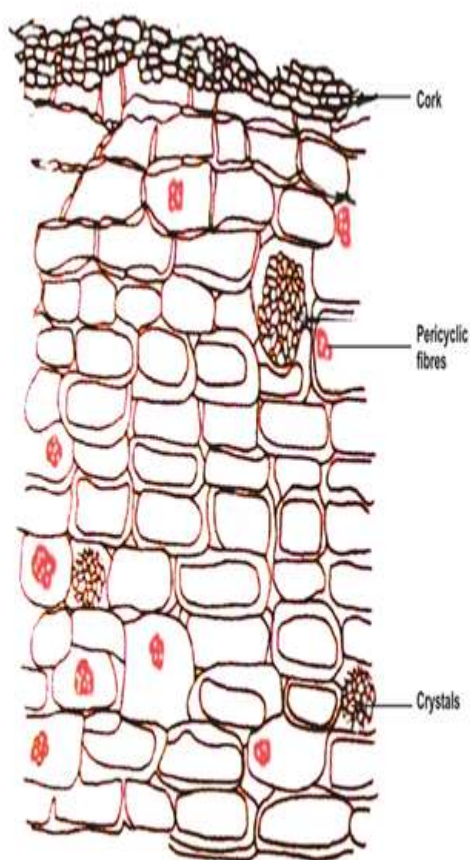
Arjuna is the large size deciduous tree. The height of the Arjuna tree reaches up to 100 feet. It is the evergreen tree with the yellow flowers and conical leaves. It has a smooth gray bark. Fruit is 2.5 -3.5 cm long, fibrous woody, glabrous with 5 hard wings, striated with numerous curved veins. It has a buttressed trunk and a vast spreading crown from which the branches drop downwards. Its leaves are dull green above and pale brown beneath. Arjuna flowers between March to June and fruits between September to November. [9]

Chemical Constituents:

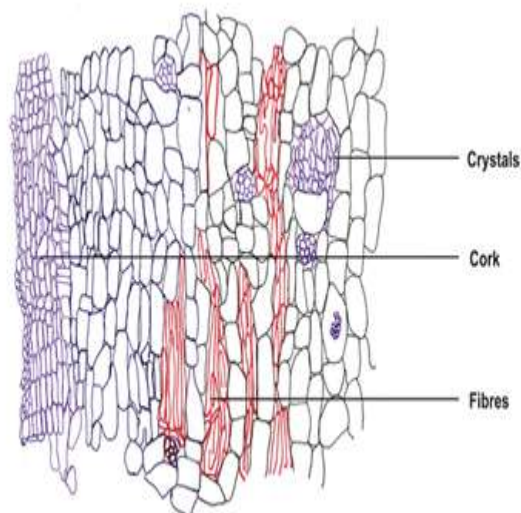
It was initially reported that the bark had 34% ash content consisting entirely of pure calcium carbonate. The aqueous extract revealed 23% calcium salts and 16% tannins, whereas the alcoholic extract contained very little colouring matter and tannins. Later chemical analysis of the bark showed evidence of sugar, tannins (12%), colouring matter, a glycoside, and carbonates of calcium, sodium and traces of chloride of alkali metals. Subsequently presence of an alkaloid as

well as a glycoside was confirmed. The glycoside was capable of increasing the force of contraction of the frog heart. Attempt to isolate the glycoside resulted into finding of an organic acid with a high melting point, a phytosterol, an organic ester easily hydrolyzed 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. [21]

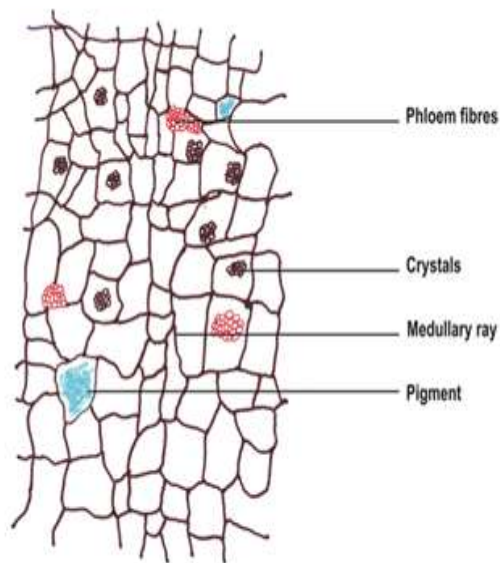
T.S. OF LEAF:



T.S. of outer part of the bark



L.S. of outer part of the bark



T.S. of inner part of bark

MICROSCOPY:

The transverse section of the arjuna bark shows the following tissues microscopically:

A. Cork:

It is composed of many uniformly arranged layers of small, tangentially elongated cells.[10]

B. Cortex:

It is a broad zone below the cork consisting of thin-walled, brick-shaped, rectangular parenchymatous cells containing cluster crystals of calcium oxalate. A few groups of sclerenchymatous

pericyclic fibers are found scattered in the cortex. [22]

C. Secondary phloem:

It consists of phloem parenchyma whose cells are polygonal with thin and wavy walls. It shows cluster crystals of calcium oxalate and pigmented cells. Phloem fibers are composed of sclerenchymatous cells and occur in groups and are also found scattered in the form of patches. Young stem bark also shows mucilage, secreting ducts, sclerenchyma of fibers and tanniferous cells. Mature bark shows a broad zone of phloem consisting of ceratenchyma, phloem parenchyma, phloem fibers and crystals fibers. The crystal fibers contain rosette crystals of calcium oxalate. [11]

D. Medullary rays:

These are narrow, many layered and almost straight. These rays are radially elongated and parenchymatous with small pits and starch grains. A few cluster crystals of calcium oxalate may appear. [3]

PHYTOCHEMISTRY:

The major constituents of *T. arjuna* in stem bark, root bark, fruits, leaves and seeds are well characterized. The preliminary phytochemical analysis of existing compounds in *T. arjuna* was carried out according to various standard protocols as mentioned by Harbone. [12] As bark was considered to be the most important constituent from the medicinal point of view, initially reported that the bark had 34% ash content consisting entirely of pure calcium carbonate. Aqueous extract of *T. arjuna* is reported to have 23% calcium salts and 16% tannins. Organic extracts of *T. arjuna* bark were also prepared using the sequential methods with a number of organic solvents such as hexane, benzene, chloroform, acetone, dichloromethane, ethyl acetate, butanol, ethanol, methanol and ether, etc., to extract various phytochemical constituents. The chemical structures of available compounds were confirmed by various advanced techniques like HPLC, UPLC, LC-ESI-MS/MS analysis. Polyphenols, flavonoids, tannins, triterpenoids, saponins, sterols and minerals are the major constituents of *T. arjuna*. Such amino acids like tryptophan, tyrosine, histidine and cysteine are also the main ingredients in *T. arjuna*. [23]

MECHANISM:

Improvement of cardiac muscle function and subsequent improved pumping activity of the

heart seems to be the primary benefit of *Terminalia*. It is thought the saponin glycosides might be responsible for the inotropic effect of *Terminalia*, while the flavonoids and OPCs provide free radical antioxidant activity and vascular strengthening. A dose-dependent decrease in heart rate and blood pressure was noted in dogs given *Terminalia* intravenously. Recently, two new cardenolide cardiac glycosides were isolated from the root and seed of *Terminalia*. The main action of these cardenolides is to increase the force of cardiac contraction by means of a rise in both intracellular sodium and calcium. [2]

POWDER CHARACTER:

The powder of arjuna bark appears pinkish or reddish brown with slight odour and astringent taste. It shows the following characters microscopically:-

a. Cork:

These cells are seen as with moderately thick walls and polygonal in surface view. If the bark is exfoliated as it is in commercial samples, only few fragments of cork cells are observed. [13]

b. Starch granules:

These are present in various tissues like cork, cortex and medullary rays and thus occur abundantly. Simple or compound grains (with two to seven components) occur and show a distinct central hilum.

c. Calcium oxalate crystals:

Cluster crystals of calcium oxalate are observed. A few are large in size. These are more in number in the case of matured stem bark powder.

d. Parenchymatous cells:

Fragments of parenchymatous cells are observed. These are thin walled and rectangular in shape. Some cells contain cluster crystals of calcium oxalate. Parenchymatous cells of phloem are polygonal with thin and wavy cell walls. A few of these cells also show cluster crystals of calcium oxalate. [14]

e. Medullary rays:

These are multiseriate and made up of lignified parenchymatous cells. Fragments are found attached to the cells of secondary phloem.

f. Fibres:

Phloem fibres made up of sclerenchymatous cells appear as scattered. Sclerenchymatous pericyclic fibres with tapering ends are also observed.[3]

COLLECTION AND IDENTIFICATION OF SAMPLES:

a. Pre-treatment of samples:

Upon arrival in the laboratory the leaves and stem bark samples were washed thoroughly with tap water to remove any wastes and dust particles. The remaining water in the plant material was removed using paper towel by pressing on them gently. The stem barks and leaves samples were dried by keeping them in open air under shade for three weeks till constant weight was achieved. The dried samples were ground to semi-powder form (10 to 20 meshes) using commercial grinder (TSK-949, WestPoint, France) and were stored in air tight polythene bags in refrigerator at 4°C for further analysis.[15]

b. Preparation of extracts:

Two different solvent systems aqueous ethanol (water: ethanol 20:80 v/v) and aqueous methanol (water: methanol 20:80v/v) were used for the preparation of extracts from the ground bark and leave samples of arjuna. Briefly, 15 gram of ground material was taken in conical flask followed by the addition of 150 mL of each solvent separately. The extraction was executed for 24 hours in an orbital shaker (Gallenkamp, U.K) at ambient temperature following the previously established method [4]. The residue from the extracts was separated using whatman no 4 filter paper and the crude extract was concentrated using rotary vacuum evaporator (EYELA, N-N Series, Rikakikai Tokyo, Japan) at reduced pressure and elevated temperature (45°C). The concentrated extract was allowed to dry at room temperature. The dried extract was weighed and stored in refrigerator (- 4°C) in air tight vials. The percentage yield of the extracts was calculated by using the following formula;
yield (%)= amount of extract/dryweight of sample*100[16]

c. Estimation of total phenolic contents:

The estimation of total phenolic contents (TPC) was carried out using Folin-Ciocalteu reagent method [12]. Briefly, 50mg of dry mass of extracts was mixed with 0.5mL of Folin-Ciocalteu reagent and 7.5mL of deionized water. The mixture was kept at room temperature for 10 minutes, and then 1.5mL of 20% sodium carbonate (w/v)

solution was added. Then the mixture was heated in a water bath at 40°C for 20 minutes and followed by cooling ice bath. Finally, absorbance at 755 nm was taken using the spectrophotometer (U-2001, Hitachi Instruments Inc, Tokyo, Japan). The amounts of total phenolic were calculated using a calibration curve Gallic acid (10-100ppm). The results were expressed as Gallic Acid Equivalent (GAE) gram per hundred grams of dry matter.

d. Estimation of total flavonoids contents:

The total flavonoids contents (TFC) were determined following the previously established spectrometric method [13]. 1 mL of aqueous arjuna extract containing 0.01 g/mL of dry matter was taken in a 10mL volumetric flask, then 5mL of distilled water was added followed by 0.3mL of 5% NaNO₂ solution. After 5 minutes, 0.6mL of 10% AlCl₃ solution was added. After another 5 minutes, 2mL of 1M NaOH solution was added and volume was made up 10 mL with distilled water. The solution was mixed and the absorbance was measured at 510nm using a spectrophotometer (U-2001, Hitachi Instruments Inc, Tokyo, Japan). TFC amounts were expressed as catechin equivalents per hundred grams of dry matter.[4]

ETHNIC USES OF TERMINALIA ARJUNA:

a. Bark:

Bark is acrid, sweet and used as a cardiogenic and diuretic. Powdered bark is taken internally with milk in case of cardiac disorders. A decoction of the bark is used as a wash in ulcers. The ashes of the bark and plant are prescribed for snakebite and scorpion sting. The bark of plant also possesses cardiac stimulant and cardiogenic properties. [24]

b. Fruits:

Fruits are used as a tonic and deobstruent.

c. Leaves:

Leaves are said to be the remedy for earache.

d.T. arjuna is also used as an hypocholesteremic, hypolipidemic, anticoagulant, antihypertensive, antithrombotic, antiviral, antifungal and antibacterial agent.

e.Its bark decoction is being used in the Indian subcontinent for anginal pain, hypertension, congestive heart failure, and dyslipidemia, based on the observations of ancient physicians for centuries. [25]

SOME CLINICAL USES:

a. 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.[54] 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. [17]

b. 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.

c. 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.

d. Cardiomyopathy:

In addition to its anti-ischemic property, arjuna was found to reduce LVM and improve LVEF.[59] 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. [18]

e. 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.

f. 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.

g. 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. [19]

h. 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.

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. However, Parmaretal. 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. 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.[7]

Terminalia arjuna has been used in the dose of 1–2 g/day in various clinical studies. This has been found to be the optimum dose in patients of CAD. At this dosage, it is well tolerated and has fewer side effects like mild gastritis, headache and constipation. No haematological, metabolic, renal and hepatic toxicity has been reported even more than 24 months of its administration. There have been few reports which have shown its hepatorenal protective property. [26] In a recent study the aqueous extract of its bark could protect the liver and kidney tissues of mice against carbon tetrachloride (CCl₄)-induced oxidative stress probably by increasing antioxidant defence activities. In another study using ethanolic extract, 500 mg/kg dose of its bark stem in alloxan-induced diabetic rats, it was found that the drug reduced the lipid peroxidation and raised endogenous antioxidant enzymes in liver and kidney tissues. Notwithstanding these evidences the need for a properly designed experimental study to assess its toxicity after long-term use needs no overemphasis. It is more pertinent in the light of the fact that Terminalia arjuna may often have to be given along with statins and blockers for a prolonged period.[6]

III. FUTURE STRATEGIES:

The efficacy of Terminalia arjuna as an anti-ischemic agent and as a potent antioxidant preventing LDL cholesterol oxidation and reperfusion ischemic injury to heart, and its potential to reduce atherogenic lipid levels have been amply demonstrated in various experimental and clinical studies. It can be considered as a useful drug for coronary artery disease, hypertension and ischemic cardiomyopathy. The proposition to administer it along with statin deserves to be examined. Major lacunae has been lack of a comprehensive study on its role in atherosclerosis employing the currently used LDL receptor knock out and/or Apo E deficient mouse model. Its impact on inflammatory and immunological markers, lipid biosynthesis, platelet aggregation, vascular reactivity and molecular actions in different cells of the cardiovascular system are few of the points which need to be addressed. Further, a well-designed study to evaluate its toxicity from its long-term use is another priority. Such a study will provide scientific basis for its clinical use and a basis for multicentric randomised double blind clinical trials. This will help define its exact status both in primary as well as secondary prevention and management of coronary artery disease.[6]

IV. 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 β -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 cardio-vascular diseases.

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