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Arjuna: Exploring Therapeutic Potential of an Ancient Herb

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In the prehistoric past, the primary source of curative substances was herbal medicines. Among these therapeutic plants, Terminalia arjuna (TA) is well-known for its numerous health benefits, particularly those related to the cardiovascular system, heart failure, angina pectoris, liver health etc. Additionally, it has anti-inflammatory, antioxidant, lipid-lowering, anticoagulant, antihypertensive, antiviral, antithrombotic, antifungal and antibacterial and wound-healing potential. The aforementioned therapeutic effects are attributed to a variety of phytochemicals found in them, including flavonoids, polyphenols, triterpenoids, tannins, glycosides, and various minerals and proteins. Its therapeutic effects on patients with heart failure, endothelial dysfunction, chronic stable angina, and even ischemic mitral regurgitation have also been documented in a number of clinical investigations. Nevertheless, before its usage by modern medicine is deemed acceptable, there are some identified lacunae, such as standardization of the herb, toxicity studies along with pharmacological interactions with other medications and big multicentre randomized clinical trials. Standardization is a very important parameter that helps maintain high-quality herbal products by establishing criteria for identity, purity, and potency. The current review gives a brief understanding about various analytical techniques used for standardization of Arjuna. This comprehensive analysis also includes a detailed discussion of its ethnomedical, botanical compounds, pharmacognostical, pharmacological, pre-clinical, and clinical significance to various illnesses.
Keywords: Traditional medicine, cardiovascular, pre-clinical, clinical.

1. Introduction

Ayurveda, an age-old Indian medical science, is important as a medical system for both prevention and treatment. The majority of ingredients in ayurvedic medications are derived from plants. One such plant, Terminalia arjuna, is frequently used to make significant ayurvedic formulations This botanical marvel has been revered for centuries for its

multifaceted therapeutic properties and has found its way into various cultural and historical narratives. A member of the Combretaceae family, T. arjuna is a big deciduous plant with around 24 species in India. Table 1.1 depicts the in detail biological source of Arjuna. [1]

Table 1.1: Biological source of Arjuna

Vernacular name	Arjun, Mathi, Neer Marudhu, Aatumuruthu
Parts used	Bark, Leaves, Stem, Roots and fruits
i) Kingdom	Plantae
ii) Division	Magnoliophyta
iii) Class	Magnoliopsida
iv) Order	Myrtales
v) Family	Combretaceae
vi) Genus	Terminalia
vii) Species	arjuna

Ethnohistorical significance

The ethnohistorical use of Arjuna is deeply rooted in the rich tapestry of Indian traditional medicine. Its name itself carries historical weight, drawing a direct connection to the heroic figure Arjuna from the ancient Indian epic, the Mahabharata. Just as the legendary Arjuna was known for his strength, courage, and prowess on the battlefield, the Arjuna tree symbolizes vitality and resilience in the realm of herbal medicine.Throughout history, Arjuna has been extensively documented and utilized by indigenous communities and traditional healers across the Indian subcontinent. Its bark, leaves, and extracts have been employed to address a myriad of health concerns, particularly those related to cardiovascular health. From managing heart ailments to promoting overall well-being, Arjuna's therapeutic potential has been celebrated and passed down through generations. [2]

According to the Ayurveda, T.arjuna is said to be Laghu (light), ruksa(dry), sita (cold), kasaya (astringent), katu (pungent), hydra (cardiotonic). And by using it in combination with other drugs can be utilized for treating tridosha disturbances [3]. The renowned ancient physician Chakradatta advised giving it as a ghrita, or preparation made with butter or ghee, or as a decoction of bark and milk. [4]. Bark ashes have been employed as a remedy for scorpion stings and snakebite, while the decoction of the bark has been used as an ulcer wash [5]. The bark of T. arjuna was used to treat sores in the Punjabi Kangra area. The bark is used for leucorrhoea in Andhra Pradesh's tribal coastal districts. Additionally, it was reported that the Golaghat district of Assam treats cardiac ailments with boiled bark mixed with sugar and clarified butter. The bark powder is boiled with water and inhaled by traditional healers from Kancheepuram district in Tamil Nadu to treat headaches and eliminate tooth worms. On wounds, they also apply fruit paste topically. While tribes in the Malkangiri area of Orissa chew fresh bark and sip the juice as an antacid, tribes in the Sundargarh district use dry bark powder mixed with rice-washed water to treat blood in urine. In the most basic of cardioactive medications, T. arjuna is used as a single pharmacological cure in five different methods, according to Ayurveda. Sugar-infused milk decoction of bark can be used to treat pitta-related heart disease. Heart disorders can also be treated using a finely ground bark paste fermented in grape juice or combined with clarified butter. Due to its capacity to lower the pitta, arjuna was also utilized to treat liver-related illnesses. Because of its capacity to address the kapha, it is also utilized in the treatment of urological conditions [3].

Macroscopy and Microscopy

1. Bark: On the outside, it is smooth, drab, and basic. The thick, supple bark has a scarlet hue inside.

2. The leaves of this plant resemble those of guavas; they are oblong, subopposite, glabrous, and frequently inequilateral, measuring 4-6 inches long and 2-3 inches wide. In close proximity to the petiole's base are two glands. The edge is rounded, with an obtuse or subacute angle serving as the apex. The base is cordate or rounded. The length of petioles is 0.5–1.3 cm.

3. Flower: Groups of white or yellow-colored blooms are seen. Summer brings flowers, and winter or spring brings fruits.

4. Fruits: The fruits have 5-7 longitudinal lobes and a diameter of 1 to 1.5 inches. These are woody and fibrous, glabrous, and have five to seven wings. Fruit is drupe-shaped and frequently has a notch near the top, with striations that curve upward at an oblique angle. [6]

Mature bark microscopy shows a cork made up of nine to ten layers of tangentially elongated cells. The phelloderm, which consists of 4-6 rows of tangentially elongated and radially oriented cells, is narrow and has a thickness of 2-4 cells. The broad phloem is crossed by uniseriate medullary rays that are parallel and straight, but occasionally they curve slightly in the vicinity of the rosette crystals. A lignified, thin-walled, tangentially oriented group of phloem fibers is connected to idioblasts, which are made up of calcium oxalate clusters and rosettes. Reddish-brown pigment is present in certain parenchymatous cells of the cortex and secondary phloem, whereas starch granules are present in other cells [7]. (Fig 1.1)

Fig 1.1 Macroscopy and microscopy of T. Arjuna

Adulterants and Allied species [8]

1. Terminalia tomentosa (Asna): Terminalia tomentosa is a tree species closely related to Terminalia arjuna. It shares similarities in bark texture and overall appearance.

2. Terminalia bellirica (Bibhitaki): Terminalia bellirica, also known as Bibhitaki, is another member of the Terminalia genus. While it has distinct botanical characteristics, its bark may resemble that of Terminalia arjuna

3. Terminalia chebula (Haritaki): Terminalia chebula, commonly referred to as Haritaki.. While its uses differ from Terminalia arjuna, its bark may bear some resemblance.

4. Addition of Fillers or Contaminants: Adulterants may include fillers or contaminants added to bulk up the product or enhance its appearance. These fillers may include starches, sugars, or inert materials.

GEOGRAPHIC DISTRIBUTION, COLLECTION & CULTIVATION

Geographical distribution: Terminalia arjuna is distributed across different climatic regions of the Indian subcontinent where it is a native species. Superior accessions of the plant are obtained from Andhra Pradesh, Assam, Chhattisgarh, Jharkhand, Maharashtra, Madhya Pradesh, Orissa, Uttarakhand and Uttar Pradesh (Fig 1.2) [9,10].

Globally, the plant is also found in Sri Lanka(native), Burma, Mauritius, Australia and also in certain regions of Southern Asia, Africa and South America [10,11].

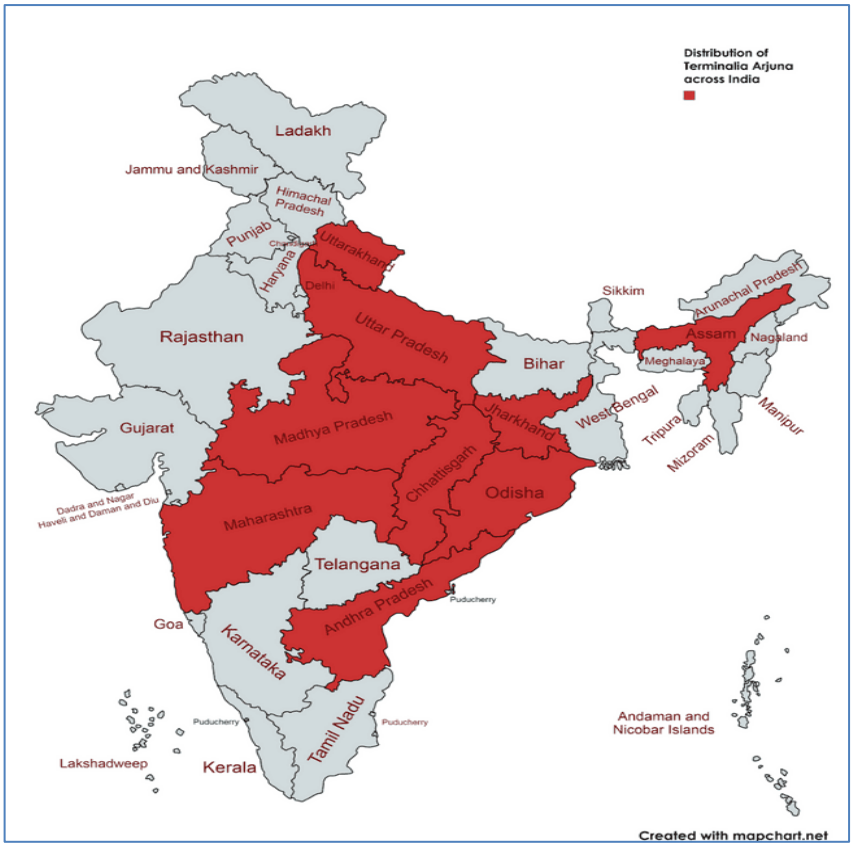

Fig 1.2: Distribution of Terminalia Arjuna across India

Cultivation and collection: Seed propagation is the most widely carried out method employed. Seeds belonging to plants over the age of six years are preferred and may be viable for about a year if correctly stored. [12]

a) Preparation of seeds: Seeds are planted in nursery beds following their collection and usually germinate within 8-12 days. Germination may be improved using pre-treated seeds.The pre-treatment consists of soaking the seeds in water for at least 24 hours. The process lasts for upto 8 weeks after which they are transplanted into a mixture containing equal proportions of soil, clay and manure. [12]

b) Preparation of land and planting: The land must be previously tilled and levelled. Pits are dug at well-spaced intervals and are enriched with fertilizers containing nitrogen, potassium and phosphorous. 10 month old saplings are the transferred to these pits. The plant may be grown alone or intercropped with climbers. The fields must always be devoid of weeds and pests. Fertiliser doses must be provided every three months. Irrigation must be done fortnightly during the summer months for younger plants and is generally not required during winter. [12]

c) Collection and post-harvest management: The bark is scrapped from trees that have attained an age of 10 years or more. This practice is generally carried out during winter. Scrapping is generally done is a vertical and spiral manner ensuring that a minimum length of 25cm and thickness of 5 cm is maintained for the strips. The bark is shade dried in well - ventilated sheds [12] (Fig 1.3,1.4)

Fig 1.3: T.Arjuna plant showing leaves, stem bark and fruit

Fig 1.4: Stem bark scrapping of T.Arjuna

Other methods of cultivation include coppicing, pollarding, root suckers, stumping and air layering. Shoot multiplication can also be carried out using nodal explants suspended in artificial media like Murashige and Skoog medium. [13]

PHYTOCONSTITUENTS

Table 1.2 provides a comprehensive list of the primary components found in T. arjuna's stem bark, root bark, fruits, leaves, and seeds.

Benzene and ethanolic bark extracts of T.arjuna consist of arjunic acid, arjungenin, arjunglucoside I and II [14]. Presence of arjunoside III and IV, terminic acid, and a triterpene carboxylic acid by ethyl acetate extraction of roots of T. arjuna and terminic acid and β-sitosterol in the hexane extract was also reported [15]. Two glycosides namely Termiarjunoside I and Termiarjunoside II were isolated from ethanolic extract of bark of T.arjuna. Arjunglucoside IV and V, Arjunasides A-E were isolated from the ethanolic extract of the stem bark of T.arjuna. Arjunolone, flavones, luteolin, baicaleiin, quercetin, kempferol, and pelargonidin, all of which have been linked to beneficial effects on cardiovascular diseases are among the many flavonoids found in very high concentrations in T. arjuna bark. The butanolic extract of bark of T. arjuna, consisting of luteolin, was discovered to have antimutagenic and antibacterial properties. A minimum inhibitory dose of 12.5 μg/disc was found to suppress the growth of gram-negative pathogens. The bark of T. arjuna consist of hydrolyzable tannins castalagin, casuariin, casuarinin, punicalagin, pyrocatechols, punicallin, terchebulin, and terflavin C. Numerous minerals and trace elements, including magnesium (4000 μg/g), calcium (3133 μg/g), zinc (119 μg/g), and copper (19 μg/g), are abundant in T. arjuna bark. It also contains a few amino acids, including cysteine, histidine, tyrosine, and tryptophan.

Table 1.2: Major Constituents of T.Arjuna [9-16]

Class	Constituent	Part of plant	Solvent fraction
Triterpenoids (Fig. 1.5)	Arjunolic acid Arjunic acid,Terminoltin, arjunetin, arjungenin, arjunglucoside I and II, and terminoic acid oleanolic acid, Qudranoside VIII, Kajiichigoside F1	Stem bark	
	Arjunaphthanoloside, Terminoside, Termiarjunoside		Ethanolic
	Terminic acid, Arjunoside III and IV, Arjunin, arjunetin, hentriacontane, myristyl oleate and arachidic stearate	Fruit	Ethyl acetate
	Arjunoside I-IV, Oleanolic acid, Terminic acid, Arjunic acid, 2α,19α-Dihydroxy-3Oxo-Olean-12-En28-Olic acid 28-O-β-d-glucopyranoside	Root	Ethanolic and benzene
Glycoside	Arjunolone,Arjunoltin, Arjunaphthanoloside Arjunetin, Terminoside A, Arjunic acid Arjungenin,Arjunglucoside I and II	Stem bark	Aqueous, ethanolic and methanolic extracts
	Arjunone, Arachidic stearate, Cerasidine,Friedelin	Fruit	
Tannins and Polyphenols	Epicatechol, epigallocatechol, (+) catechol, (+) gallocatechol pyrocatechols, punicallin, punicalagin, terchebulin, castalagin,casuarin Terflavin C Gallic acid, Ellagic acid	Stem bark,	Aqueous, ethanolic and methanolic extracts
Flavonoids (Fig.1.6)	Arjunolone, Quercetin, kaempferol	Stem bark	Methanol and ethyl acetate
	Luteolin, gitoxigenin derivatives	Leaves and seeds	

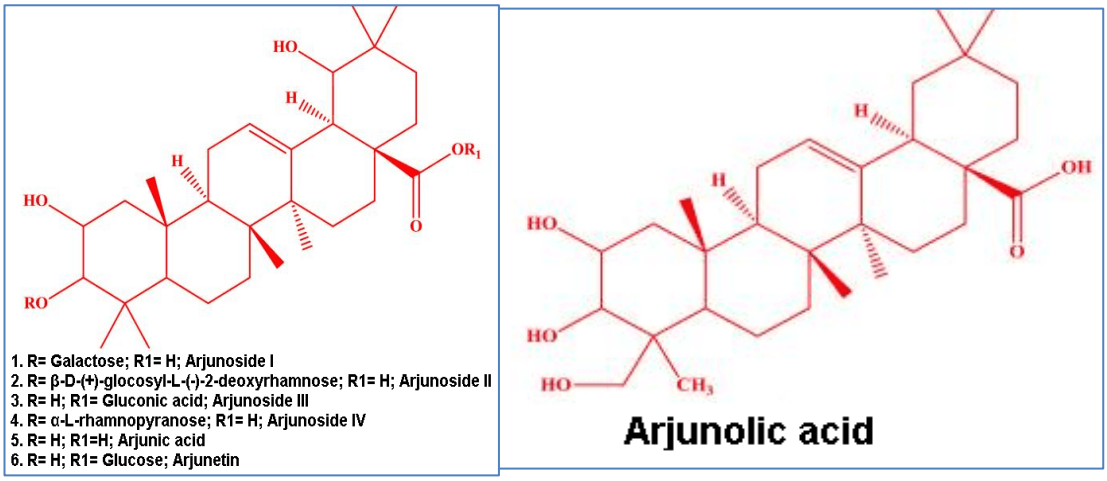

Fig.1.5 Important terpenoids from T.arjuna

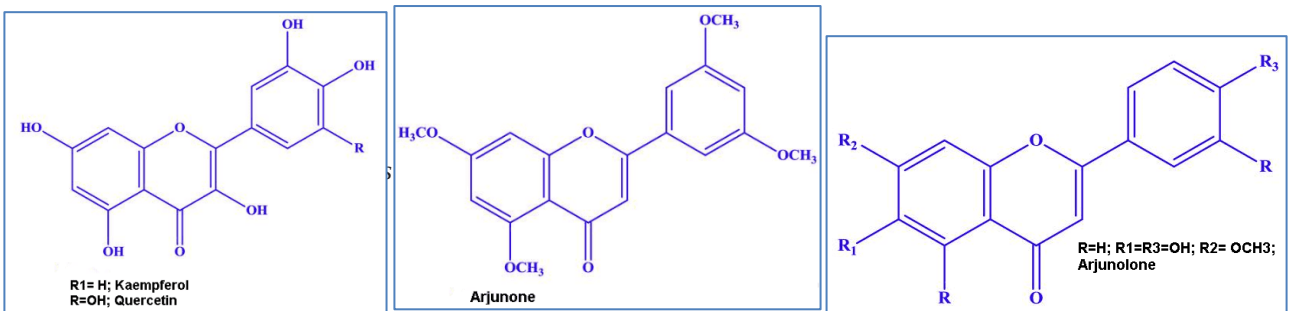

Fig.1.6 Important flavonoids from T.arjuna

ANALYTICAL METHODS FOR QUANTITATIVE ESTIMATION OF THE PHYTOCONSTITUENTS

The various analytical methods used for standardization of Arjuna bark are described below in the Table 1.3

Table 1.3: Analytical methods for estimation of Phytoconstituents

Analytical method	Conditions	Solvent fraction	Phyto constituents analyzed	Reference
HPLC and LCMS	Phenomenx phenyl-hexyl, 5 µm, 4.6×250 mm HPLC column. The mobile phase A 9% acetonitrile, 2% acetic acid with 20 µg/ml EDTA and mobile B 80% acetonitrile, 2% acetic acid with 20 µg/ml EDTA. 1 ml/min flow rate at 40° and detection at 278 nm. Binary gradient elution	Aqueous and methanolic bark extract	Polyphenols	[17]
HPLC-PDA	KROMASIL C-18 (250 mm × 4.6 mm × 7 m) column, Shimadzu HPLC System LC 2010-CHT with LC solution software, a diode array detector (PDA) and 20-L injector loop. Solvent A: 0.136 g of potassium dihydrogen orthophosphate in 900 mL Milli-Q-water and added 0.5 mL of ortho-phosphoric acid and made up it to 1000 mL with Milli-Q-water. Acetonitrile (solvent B, pH 2.5) was used as the mobile phase with a gradient elution as follows: 0.01– 18 min, 70–40% A; 18–20 min, 40–15% A; 20–22 min, 15% A; 22–25 min, 15–70% A; 25–30 min, 70% A. Flow rate 1.5 mL/min for 20 min to elute out arjunic acid and arjunolic acid at 16.98 min and 15.04 min. 28ºC, injection volume 20 uL	Ethyl acetate fraction	Arjunic acid, Arjunolic acid	[18]
HPTLC	HPTLC Precoated plates Silica Gel Merck 60F25. Ethyl acetate: formic acid: glacial acetic acid: water (100:11:11:26). 100 uL Hamilton (Bonadzu, Switzerland). CAMAG Automatic TLC Sampler III. Development mode: Ascending. CAMAG TLC scanner 3 with Cats software. Temperature (25ºC) relative humidity 40%.	Aqueous extract	Rutin and Quercetin	[19]
HPTLC	Pre-coated silica gel TLC aluminum plates 60F254 on aluminum sheets (10 × 20 cm) as the stationary phase, while the mobile phase consisted of toluene–ethyl acetate–formic acid (5:4:1, V/V). Densitometric analysis at 420 and 475 nm.	Aqueous extract	Arjunetin and Arjungenin	[20]
HPLC-PDA	Shimadzu SPD-M10 A (Class VP-series, version 6.10), automatic gradient controller, LC-10AT pump, Rheodyne 7725 I manual injector (CA, USA), and phenomenex C-18 column (250 x 4.6 µm ID, 5 µm with a suitable guard column) comprise this Japanese-made HPLC system.	Arjunarishta	ellagic acid, gallic acid, ethyl gallate, quercetin and kaempferol	[21]
HPLC	Hypersil column at a temperature of 20 C, with a particle size of 5 m and a diameter of 250 4.6 mm. Acetonitrile and water (pH 7.0) made up the mobile phase. 0.8 mL/min was the flow rate. The UV wavelengths of 200, 210, 225, and 250 nm were employed to obtain chromatograms.	Arjuna churna formulation	Sapogenins	[22]
HPLC-ESI-QTOF-MS/MS	Thermo Betasil C8 column (250 mm×4.5 mm, 5µm) with a mobile phase consisted of 0.1% formic acid aqueous solution and acetonitrile at a flow rate of 0.5 mL/min in 55 min.	Aqueous extract	Gallic acid, Ellagic acid	[23]
HPTLC	TLC aluminum plate precoated with silica gel 60 GF 254.	Arjuna Tablet,	Andrographolide	[24]

	Mobile phase Toluene: Methanol (4:3), UV detector, wavelength 254nm.	Alcoholic extract		
HPTLC	TLC aluminum plate precoated with silica gel 60 GF 254. Chloroform: Toluene: Ethanol (4:4:1), wavelength 254nm	Alcoholic extract	Arjunolic acid	[25]

PRECLINICAL/PHARMACOLOGICAL ACTIVITIES:

Table 1.4 Pharmacological activities of T.arjuna

Pharmacological activity	Model used and study design	Type of extract	Observations	References
Antioxidant and Cardioprotective	Ischemic–reperfusion injury of the rat heart	Aqueous extract of T.arjuna	Prevents oxidative stress by inducing myocardial heat shock protein 72 and augments myocardial endogenous antioxidants.	[26, 27]
Anti-inflammatory, immune-modulating, and antioxidant	Enzymes CYP2D6, CYP3A4, and CYP2C9 in human liver microsomes	T. arjuna alcoholic and aqueous extract at a dosage level of 35 μg/ml	Inhibition activity of CYP3A4, CYP2D6 and CYP2C9 enzyme. Enzyme kinetic studies suggested that the extract showed rapidly reversible non-competitive inhibition of all three enzymes in human liver microsomes.	[28]
Antioxidant	Human polymorphonuclear (PMN) cells and hypochlorous acid from human neutrophils	Methanolic extract of T. arjuna	Shown a moderately inhibiting effect on the respiratory oxyburst process.	[29]
Cardiac hemodynamics, coronary flow	Langendorff's rabbit heart preparation	Aqueous bark extract of T.arjuna	Increased coronary flow and the heart muscle's contraction force. Positive ionotropic effect as a result of the plant's high calcium concentration	[30, 31]
Cardioprotection	Doxorubicin-induced rat cardiotoxicity and DNA damage	Aqueous bark extract of T.arjuna	Preserving the activity of natural antioxidant enzymes and reducing cytokine and LPO levels.	[32, 33]
Antioxidant and antimutagenic activity	Wistar rats (200–250 g) and Swiss albino mice (18–22 g)	Aqueous and ethanolic extraction of T. arjuna	With EC50 values of 2.491 ± 0.160, 50.110 ± 0.150, and 71.000 ± 0.025 in the DPPH assay, superoxide radical scavenging activity, and lipid peroxidation assay, respectively, the alcoholic extract of T. arjuna (ALTA) has demonstrated strong antioxidant activity. In the micronucleus test, the percentage of micronucleus in ALTA (100 and 200 mg/kg p.o) with EC50 values of 2.410 ± 0.140, 40.500 ± 0.390, and 63.000 ± 0.360 demonstrated a considerable decrease in both polychromatic and normochromatic erythrocytes, along with a noteworthy decrease in the P/N ratio.	[34]
Anticarcinogenic and antimutagenic potential	In vitro and in vivo method	Aqueous extracts from 75 μg/ml to 200 μg/ml for lymphocyte culture	Used bone marrow from albino mice (8–10 weeks old, weighing 25–35 g) and human lymphocyte culture	[35]

		for in vitro experiments Aqueous extracts from 50 mg/kg to 350 mg/kg body weight for in vivo experiments	After 48 hours of treatment, the number of sister chromatid exchanges decreased with S9 mix, from a higher level of 15.0 ± 1.4 per cell to 7.7 ± 0.5 per cell. In vitro, the replication index increased from 1.33 to 1.55. In the in vivo studies, the total frequencies in aberrant cells decreased from 429 due to AFB1 to 141 due to the fifth concentration of T. arjuna extracts at 32 hours of exposure. The effective reduction in clastogeny ranged from 15.22% to 54.82% from the mutagen treated positive control.	
Antioxidant, anti-inflammatory and immunomodulatory	Cell cultures of human monocytic (THP-1) and human aortic endothelial cells (HEACs)	T. arjuna alcoholic extract (TAAE) and T. arjuna Aqueous extract (TAWE) from steam bark at a dose of 1–50 μg/ml	HMG-CoA reductase and lipid peroxidation were suppressed by TAAE and TAWE, while LpL was unaffected. Both extracts sustained cellular reducing capacity and enhanced the activities of catalase (CAT) and glutathione peroxidase (GPx), thereby attenuating H2O2-mediated ROS production in THP-1 cells. While the reaction of TAWE varied according to the kind of transcript and cell type, TAAE was very efficient in attenuating proinflammatory gene transcripts in THP-1 cells and HAECs.	[36]
Hypotensive effect	Pretreatment of rats with propranolol	Acqueous bark extract	Adrenergic β2-receptor agonistic and/or direct action on the heart muscle	[37]
Hypolipidemic	Hyperlipidemic rats	Ethanolic extract	Reduction in the lipids' plasma levels. decreased expression of lipogenic enzymes, suppression of HMG-CoA reductase, and increased hepatic clearance of cholesterol.	[38]
Antioxidant	Male Wistar albino rats, weighing between 250 and 300 g; treated with STZ at a dose of 65 mg/kg	After eight weeks of STZ treatment, rosuvastatin (20 mg/kg) and a 50% ethanolic extract of T. arjuna were administered orally for 30 days as a therapeutic intervention.	Rats with uncontrolled diabetes showed improved cardiovascular autonomic neuropathy by lowering cytokine levels and preserving endogenous antioxidant enzyme activity.	[39]
Antioxidant and antimicrobial activity	DPPH methods and Agar well diffusion method	Methanol extracts	Methanolic extracts are excellent at scavenging free radicals. It has a large concentration of flavonoid chemicals. When tested against two gram negative bacteria, it demonstrated good antibacterial action (E. coli and K pneumonia).	[40]
Antimicrobial	Five microorganisms	Methanol, ethanol,	It was discovered that acetone	[41]

activity	were used: Proteus mirabilis, Acinetobacter sp., Escherichia coli, Pseudomonas aeruginosa (Gram negative), and Staphylococcus aureus (Gram positive).	acetone aqueous extracts from the leaves and bark of T. arjuna	leaf extract worked best against S. aureus.With the exception of P. aeruginosa, all studied Gram-negative bacteria were nearly equally inhibited by organic extract. T. arjuna bark aqueous extract showed good anti-S. aureus efficacy.	
Anticarcinogenic potential	Adult ventricular myocytes isolated from hearts of adult male Sprague-Dawley rats (250–300 g)	Ethanolic and aqueous extract of T. arjuna at a dose of 0.05–100 μg/ml	T. arjuna aqueous extract is a promising and reasonably safe cardiotonic that is useful to the health of the heart and the treatment of chronic cardiac illnesses because it enhances sarcoplasmic reticular function, a unique action that minimizes the incidence of arrhythmias.	[42]
DNA damage protecting and free radical scavenging	Using rat adrenal PC-12 cells and the pBR 322 plasmid, the DNA stand breakage assay and comet assay analysis were performed.	Ethanolic extracts and its fractions	T. arjuna bark fractions and ethanolic extracts prevented H2O2-induced DNA damage. The ethyl acetate fraction showed the highest level of suppression of metal chelation, hydroxyl, ABTS, nitric oxide radicals, and DPPH. Extracts from T. arjuna improve a number of conditions linked to DNA damage and the production of free radicals.	[43]
Gastro-productive effect	Gastric ulcers caused by Diclofenac sodium (DIC) were observed in experimental rats (male Wistar albino rats weighing 150–200 g).	Methanolic extract of T. arjuna	Compared to ulcerated rats (DIC), ulcer-induced animals treated with T. arjuna (DIC + TA) showed a substantial decrease in lesion index. Comparing DIC + TA rats to DIC rats, there was a significant decrease in the volume of gastric juice, free and total acidity, pepsin concentration, acid output, LPO levels, and MPO activities, but a significant increase in pH, NP-SH, GSH, enzymatic antioxidants, protein-bound carbohydrate complexes, adherent mucus content, and nucleic acid.	[44]

CLINICAL STUDIES

1. Thrombotic condition

T. arjuna was one of the four plants from Bangladesh who's in vitro thrombolytic and membrane stabilizing properties were assessed. It was discovered that methanolic extract has a notable thrombolytic activity (30.57%). Both heat-induced and hypotonic solution conditions decreased RBC hemolysis. [45]

2.Reduction in lipoprotein levels.

It has been observed that giving T.arjuna powder to a patient with β-thalassemia who also has hyperlipoproteinemia and metabolic syndrome considerably lowers their lipoprotein levels. 24.71% [46]

3. Antihyperlipidemic and Anti inflammatory effects.

For three months, in addition to getting the standard medication, 116 patients with coronary artery disease received either 500 mg of T. arjuna from Himalayan Herbal Healthcare, Bangalore, India, twice a day, or a placebo. At three months, individuals receiving medication treatment showed a significant reduction in serum triglycerides and several inflammatory cytokines, including hsCRP, IL-18 ($P < 0.001$), IL-6, and TNF-α ($P < 0.05$), as compared to those receiving a placebo. [47,48]

To determine the effects of T. arjuna in individuals with idiopathic and ischemic dilated cardiomyopathy, another investigation was carried out. 500 mg of T. arjuna bark extract administered every eight hours was the standard treatment for 93 individuals with cardiomyopathy. Three groups were created: group 1 was for regular therapy; group 2 was for T. arjuna therapy; and group 3 was for standard therapy combined with T. arjuna. Patients in group 3 had a significantly higher percentage of left ventricular ejection fraction (7 ± 1.6, $P < 0.00001$) at the conclusion of the study period than those in groups 1 and 2 ($P < 0.00001$, $P < 0.0001$). In compared to the other groups, group 3 had the greatest reductions in left ventricular end systolic and diastolic diameters and volumes (8.3 ± 4.7, $P < 0.0001$ and 3.1 ± 5.7, $P < 0.001$) and (11 ± 26, 9 ± 21 $P < 0.01$), respectively. Groups 1 and 3 experienced a significant decrease in pulmonary artery pressure ($P < 0.0001$). Groups 1 and 3 showed a comparable decrease in diastolic score and mitral regurgitation ($P < 0.01$ and $P < 0.0001$). According to the findings, patients with dilated cardiomyopathy who received T. arjuna as standard therapy significantly improved in terms of both functional ability and left ventricular metrics. [49]

4. Oxidative stress/dyslipidemia

In a 4-month research, the lipid profiles of 21 individuals with coronary heart disease who received 1 g of bark powder twice daily with milk improved. Additionally, following a month of treatment, individuals saw symptom improvement. [50] The antioxidant effect of 500 mg of bark powder was evaluated in 105 individuals with coronary heart disease, equivalent to 400 IU of vitamin E in a randomized, controlled, open trial. Significant decrease in the levels of LDL and lipid peroxide was observed. The flavonoids were responsible for the antioxidant impact, while the soluble fibers and sitosterol levels were thought to have a hypocholesterolemia effect. [51]

.5. Platelet aggregation

In vitro study, the bark extract was reported to have antithrombotic and antiplatelet activation characteristics in twenty patients with coronary artery disease confirmed by angiography and twenty age- and sex-matched controls. Competition with the platelet receptor or disruption of signal transmission are two possible causes of desensitization of platelets. [52] In a recent randomized, double-blind, parallel-group, placebo-controlled experiment, patients with type 2 diabetes mellitus received 500 mg of arjuna three times a day. The mean cardiac output increased significantly from 4.34 ± 0.38 to 4.86 ± 0.20 (l/min). In addition, the mean systemic vascular resistance (dyne sec/cm5) dropped from 1729 ± 93.52 to 1484 ± 115.5. Arjuna also considerably decreased the aggregation of platelets.[53]

6. Cardiomyopathy

According to a recent observational study, there was a significant improvement in left ventricular metrics and functional capacity in patients with dilated cardiomyopathy and lower LVEF who received T.arjuna in addition to their usual medication. It was found that T.arjuna improved LVEF and decreased LVM. [54]

In other study, salutary effect of T. arjuna in patients with severe refractory heart failure was evaluated. A total of twelve patients suffering from refractory chronic congestive heart failure (Class IV NYHA) were randomized to receive either matching placebo or T. arjuna bark extract (500 mg 8 hourly) as an adjuvant to maximally tolerable conventional therapy (Phase I). One patient had a history of myocardial infarction, and another had peripartum cardiomyopathy. The two groups were separated by a two-week washout period. Patients continued to improve in terms of symptoms, signs, effort tolerance, and NYHA Class with an increase in quality of life over a long-term evaluation in an open design (Phase II). Over the course of 20–28 months (mean 24 months), phase I participants continued to take T. arjuna at a set dosage of 500 mg eight hoursly in addition to flexible diuretics, vasodilators, and digitalis dosage on an outpatient basis. [55]

7. Ischemic mitral regurgitation

Arjuna was found to dramatically reduce anginal frequency and ischemic mitral regurgitation (IMR) in patients with IMR after an acute myocardial infarction in a randomized, double-blind, placebo-controlled research. Furthermore, diastolic dysfunction significantly improved as well (E/A ratio increased from 0.93 ± 0.31 to 1.38 ± 0.40 at 12 weeks). [56]

In a randomized, double-blind, crossover trial, fifty-eight males with chronic stable angina (NYHA class II–III) and evidence of provocable ischemia on a treadmill exercise test were randomly assigned to receive TA (500 mg 8 hourly), isosorbide (40 mg/daily), or a matching placebo for one week each, followed by a minimum three-day washout period. At the conclusion of each therapy, they had evaluations for clinical, biochemical, and treadmill exercise, which were compared over the course of the three therapy periods. The frequency of angina attacks and the requirement for isosorbide dinitrate were shown to significantly decrease with T. arjuna medication. Compared to placebo medication, T. arjuna bark extract (500 mg 8 hourly) improved clinical and treadmill exercise parameters in patients with stable angina and provocable ischemia during exercise. The extract was well tolerated, and the advantages were comparable to those seen with isosorbide mononitrate treatment (40 mg/day). [57]

8. CHF/hypertension

Ten CHF patients were given 4 g of arjuna bark powder twice a day for a month as part of one of the first investigations. Breathlessness, overall well-being, and the functional class all improved, and there was a notable diuresis along with a decrease in both systolic and diastolic blood pressure. [58]

Twelve patients with refractory CHF participated in a double-blind, placebo-controlled, two-phase trial to examine the effects of bark extract (500 mg 8 hourly). Arjuna was given for two weeks during the first part of the study. Improvement was indicated by a decrease in the echo-left ventricular end-diastolic and end-systolic volume indices, a rise in the left ventricular stroke volume index, and an increase in LVEF. During the 20–28 month long-

term assessment, they reported improved quality of life along with ongoing improvement in symptoms and signs.

An investigation in hypertensive patients using a herbal formulation called abana, which contains arjuna, revealed improvement in cardiac function as indicated by a significant decrease in SBP, posterior wall thickness, interventricular septal thickness, and left ventricular internal diameter as well as an increase in ejection fraction [59].

36 hypertension patients at stage III with increased left ventricular mass were examined to assess the effects of "Arjuna Kwatha," an Ayurvedic preparation of T. arjuna. The patients were divided into two groups. One group was given 50 mg of atenolol twice day for six months, while the other group also received 25 ml of "Arjuna Kwatha" twice day. There was a significant drop in SBP and DBP in both groups ($P < 0.001$). However, as the herbal preparation showed negative chronotropic and inotropic effects, the LV mass index was only considerably lower in the atenolol-plus-'Arjuna Kwatha' group when compared to atenolol alone ($P < 0.001$). [60]

9. Angina/myocardial infarction

It was shown in an open-label trial that when arjuna therapy was given to individuals with stable angina, there was a 50% decrease in angina episodes as well as a significant delay in the time to the beginning of angina on TMT and the development of ST–T alterations in the ECG. Notable reductions in blood pressure and body mass index were also noted, along with a marginal enhancement in left ventricular ejection fraction (LVEF) and a little elevation in high density lipoprotein (HDL) levels. The reduction in anginal frequency was not statistically significant in patients with unstable angina. These findings imply that T.arjuna monotherapy has a limited role in treating unstable angina but is generally beneficial in treating patients with stable angina. [61]

In ten patients with stable angina, the effectiveness of Hartone, a herbal medicine containing arjuna, was investigated. The outcomes were contrasted with those of ten stable angina patients receiving twice-daily injections of 20 mg isosorbide mononitrate (ISMN). Observations showed that 80% of patients received symptomatic alleviation using Hartone, compared to 70% in the ISMN alone group. Arjuna was also more tolerable than ISMN. [62]

TOXICITY/ SIDE EFFECTS

T.arjuna has been utilized in a number of clinical trials at a dose of 1-2 g/day. It has less adverse effects, such as headaches, constipation, and moderate gastritis, at this dosage and is well tolerated [63]. Even after more than 24 months of therapy, no reports of hepatic, renal, hematological, or metabolic damage exist [64,65,66]. However in one of the studies it was reported that when T.arjuna was administered to euthyroid mice, the concentration of thyroid hormone decreased but the hepatic LPO increased. Therefore, consuming large amounts of the plant extract is not advised since it may cause hypothyroidism and hepatotoxicity[67].

It plays a part in obesity that is not advised. Because it is removed from the body, it usually results in a decrease in the quantity of fat. Because of this, it is necessary to assess the risk to benefit ratio of the cardiovascular advantages when considering an obese individual.

According to the findings of a recent acute and oral toxicological investigation conducted on animals, giving ethanolic extract orally to animals at a limit dose of 2000 mg/kg did not cause any form of toxicity or mortality [68].

Following 28 days of treatment with 500 mg of T. arjuna capsules every eight hours, there was no appreciable change in body and organ weights between the 93 patients with idiopathic and ischemic dilated cardiomyopathy (DCMP) in the treated group and the control group. Hematological investigations and biochemical indicators demonstrated the extract's safety. Pathologically, the histology showed no obvious anomalies or changes, and no mortality was reported in the next 28 days. [69].

To fully explore T. arjuna's medicinal potential, well-controlled multicentric clinical trials with a standardized product and a bigger subject design are essential.

DRUG INTERACTIONS

In one of the studies, the ability of T.arjuna bark extracts both alcoholic and aqueous, to inhibit the CYP3A4, CYP2D6, and CYP2C9 enzymes that are involved in metabolism of many drugs in human liver microsomes was assessed. The results demonstrated strong inhibition of all three enzymes with IC50 values less than 35 μg/mL. The inactivator was diluted after T. arjuna bark extracts, both alcoholic and aqueous, were pre-incubated in human liver microsomes with and without NADPH. This did not result in a discernible decrease in the activity of the enzymes CYP3A4, CYP2D6, and CYP2C9. Thus alcoholic as well as aqueous extract could be classified as rapidly reversible non-competitive inhibitors of CYP3A4, CYP2D6 and CYP2C9 enzymes. Hence, the drugs that are predominantly eliminated by the CYP3A4, CYP2D6, and CYP2C9 enzymes should be administered with caution when combined with extracts from the bark of T.arjuna.

T.arjuna might slow blood clotting. T. arjuna may make bruises and bleeding more likely, especially when used with drugs that also reduce blood coagulation. [70]

MARKETED FORMULATIONS OF T.ARJUNA

Because of its importance in cardiovascular health Arjuna has gained good importance in the market. Table 1.5 shows a list of herbal formulations containing Arjuna extract.

Table 1.5: Marketed formulations of T.Arjuna

Type of formulation	Manufacturer	Composition	Intended use (as health supplement)
Tablets	Himalya Wellness, India	Arjuna bark extract -250 mg	Cardiac wellness,blood circulation
Capsules	Zandu Care, India	Arjuna bark extract -250 mg	Promotes heart health, improves skin , strengthens bones, reduces urinary disorders
Concentrated liquid extract	Veda Oils, India	Arjuna bark extract	Improved cardiac functioning, mood enhancer, relieves urinary disorders, healthy cell growth
Arishta	Baidyanath Ayurveda , India	Arjun chhal (bark)- 3.3 g, Munakka - 1.7g, Jaggery- 3.3 g, Dhaiphool-0.7 g in arishta base	Relieves excessive palpitation, perspiration, dryness of mouth
Churna	Dabur, India	Arjuna bark powder	Heart health, maintains cholesterol levesl, prevents excessive thirst
Kwath	Patanjali Ayurved,	Prepared using coarse powder of Arjuna	Maintains heart health

	India	bark	
Vati	Nagarjun Pharmaceuticals, India	Arjun Twak Ghan - 350 mg	Heart health, management of cholesterol and hypertension

HOME REMEDIES

Traditional formulations of Arjuna have been used for treating a variety of ailments.

Common traditional remedies include Arjunarishta, Arjuna Ksheer paka, Arjuna Churna, Kwath, Lepa and Dhan [71]

Arjuna Churna can be ingested daily (2-5 grams) for management of lipid and cardiac disorders. Skin diseases can be treated using local application of Arjuna lepa.

Kwath kalpana is a decoction of arjuna powder in water which can be taken for hyperaciditiy and also to treat ulcerations due to its wound healing properties. It can also be administered alongside other medications to control hypertension. It is generally administered as is, or with honey or triphala as directed.

Kwath can be further heated to a paste like consistency and rolled into pills known as ghan which can be used for hypertension and to promote overall wellness

Arjuna Ksheer paka is a decoction prepared using cow milk and water. It can be given for management of angina, other cardiovascular disease and also for treating liver cirrhosis

Arjunarishta contains T. arjuna, Madhuca indica, Vitis vinifera and Woodfordia fruticosa. It is used to stimulate appetite, as a cardiotonic and immunomodulator [72,73]

RESEARCH GAPS AND FUTURE PROSPECTIVES

Although the T.arjuna potential benefit to human health is being thoroughly investigated by medical science. Still, it is undoubtedly a small portion of this multipurpose medicinal herb. Given that T. arjuna grows well throughout a wide range of climatic circumstances, it is expected to exhibit a high degree of genotypic variety. A thorough characterization and grouping of the genome and agronomy is required to find the prospective genes that could support breeding initiatives, targeted mutations, and genetic enhancement for resistance to abiotic stress.

Herbal toxicity can also arise from the interactions of T.arjuna with conventional medications. Quality standards of the T.arjuna formulations have been established in the last several decades. However, because of the high cost and specialized equipment required, some toxicological investigations are not practical for all research teams. However, researchers that possess the financial resources to carry out this type of research should prioritize toxicological evaluations as a major component of their study.

Pharmacokinetics: the body's interactions with the drug include distribution, excretion, metabolism, and absorption. The drug's bioavailability, or the rate and degree to which it reaches the site of action, determines its therapeutic efficacy. In contrast to pharmaceuticals, the pharmacokinetics of herbal products—which are mixtures of known and unknown components—are inherently difficult because of their complexity and lack of standards.

The largest obstacle to the modernization of herbal products is the lack of pharmacokinetic research, as there is no means to determine the bioequivalence of goods made using modified

methods against original methods.

Before herbal medications are put through clinical trials, pharmacokinetic studies are crucial to making natural treatments into pharmaceuticals with proof. Additionally, important information on bio-transformed metabolites, dosage forms, dosages, and possible herb-drug interactions is provided by pharmacokinetic investigations on the bioactive components of herbal medications. But very little data is available on the standardization of the T.arjuna with respect to its marker compounds and pharmacokinetic parameters.

2. Conclusion

In summary, Terminalia arjuna, often known as arjuna, is a medicinal plant that shows great potential. It has a long history of traditional use, and there is mounting scientific evidence to support its potential for therapeutic application, especially in the area of cardiovascular health. Empirical research and clinical trials have yielded strong proof of Arjuna's effectiveness in treating a range of cardiovascular conditions, including dyslipidemia, ischemic heart disease, hypertension, and congestive heart failure. Arjuna has also been shown to help with angina pectoris symptoms, enhance exercise tolerance, and improve cardiovascular health in general. Safety data regarding the use of T.arjuna in prescription dose forms has also been reviewed. Despite its lengthy history of use in medicine, more research is still required to fully comprehend the molecular mechanisms, the relationship between structure and activity, the possible antagonistic and synergistic effects of its phytocompounds, optimize dosage regimens, and evaluate long-term safety and efficacy in clinical settings the administration of drugs, interactions between drugs, and toxicological effects. Also, standardization will serve as a cornerstone for the sustainable utilization and integration of Arjuna into modern healthcare practices, thereby unlocking its full therapeutic potential and promoting the health and well-being of individuals worldwide. Embracing Arjuna as part of a comprehensive approach to cardiovascular health may pave the way for enhanced prevention, management, and treatment of cardiovascular diseases, ultimately contributing to improved patient outcomes and public health.

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