E-ISSN: 2278-3229

IJGHC, September 2023–November 2023; Sec. B; Vol.12, No.4, 335-345
DOI: 10.24214/IJGHC/HC/12/4/33545.

International Journal of Green and Herbal Chemistry

An International Peer Review E-3 Journal of Sciences

Available online at www.ijghc.com

Section B: Herbal Chemistry

Research Article

CODEN (USA): IJGHAY

Reviewing the recent advancements of *Terminalia arjuna*, the guardian of the Heart.

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Received: 20 September 2023; **Revised:** 18 October 2023; **Accepted:** 00 October 2023

Abstract: An herb that is anti-oxidant, lowers cholesterol and blood pressure, and helps with diabetes all at once – *Terminalia arjuna*, it is. Since ancient times, medicinal plants have been a significant source of therapeutic compounds used to treat human ailments. Ayurveda, Siddha, and Unani are just a few of the indigenous medical systems in India that utilize the *Terminalia arjuna* medicinal plant. The Combretaceae family tree known as the Arjuna (*Terminalia arjuna* Roxb) is a common sight throughout India. The majority of experimental and clinical research have revealed that the bark of T. arjuna has anti-ischemic, antihyperlipidemic and antioxidant properties. Triterpenoids, flavonoids, glycosides, tannins, phenolics, and arjunolic acid are some of its beneficial phytoconstituents. Experimental research has shown that the bark of T. arjuna has strong cardioprotective and potent antioxidant effects. This in-depth analysis covers numerous facets of its phytochemical, pharmacognostical, pharmacological, and clinical value to various disorders, particularly cardiovascular problems.

Keywords: *Terminalia arjuna,* antioxidant, cardioprotective, antihyperlipidemic.

1.INTRODUCTION

Despite the fact that medicinal plants are important to health care and are used as primary raw materials in both traditional and modern medicine formulations, most people still prefer herbal over modern treatment [1]. Due to the variety of chemicals found in natural sources, the scientific and pharmaceutical societies are paying more attention to them. The majority of the more recent research on medicinal plants focuses on the rediscovery of old effects at the cellular and molecular levels. *Terminalia arjuna* is a wonder herb that has been used for centuries to treat cardiac issues.

It is commonly referred to as Arjuna. In conventional medicine, it is employed to treat ulcers and promote wound healing as well as for its antibacterial, antioxidant, antimutagenic/ anticarcinogenic and hypolipidemic properties [2-7]. It is also helpful in the treatment of obesity, hypertension, and hyperglycemia. It has been widely reported that T. arjuna bark is used in the treatment of cardiovascular disorders. By boosting antoxidative defence capabilities, Terminalia arjuna can shield the liver and renal tissues from CCl4-induced oxidative damage [8].

Due to their use in numerous research areas like medicine, catalysis, energy and materials, nanoparticles generated from this Terminalia family have also seen an increase in demand over the past decade [9-11]. The bark powder has been discovered to possess anti-ischemic, antioxidant action, cardioprotective properties, hypercholesterolemia effect, fungicidal and antibacterial, antimicrobial, anti-inflammatory, immunomodulatory, and antinociceptive activity.

Flavonoids in the bark of Terminalia arjuna provide its antioxidant and anti-inflammatory qualities. Consuming the bark supports the body's defenses against free radicals, which are the root cause of the majority of chronic diseases [12-14]. This review's objective is to provide a summary of the information and understanding on T. arjuna while also updating the recent research data that is now available in the fields of botany, phytochemistry, ethnopharmacology and clinical studies.

2.PROFILE OF *T. ARJUNA*

2.1. Habitat and Distribution: A perennial and evergreen tree, Terminalia arjuna, can be found 20 to 30 metre above sea level. It's a member of the Combretaceae family (Figure i, a). The arjuna is a common plant all throughout the Indian Subcontinent, and it may be found in Uttar Pradesh, Bihar, Madhya Pradesh, West Bengal, Maharashtra, Odisha.

It typically grows on river banks or next to dry river beds. Additionally, it can also be seen in Malaysia, Sri Lanka, Bangladesh, Indonesia and Kenya [15-18]. Its indigenous names are Arjuna (common Name), Arjun (Hindi), Sadado (Gujarati), Marudhu (Tamil and Malayalam), Tella Maddi (Telugu), Sadaru (Marathi), Arjhan (Bengali), Neer matti (Kannada) [19].

2.2.Ethnopharmacology and Phytochemistry

(a).Stem Bark: It is simple, smooth, and pinkish-gray in colour from the outside and velvety and crimson in hue from inside (Figure 1, b).

Major phytoconstituents in bark are:

- Triterpenoids, such as arjunin, arjunic acid, arjungenin, arjunolic acid, terminic acid. [20-21].

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- Glycosides, such as arjunetin, arjunoside I, arjunoside II, arjunaphthanoloside, terminoside A[22-23].
- Flavonoids, such as arjunone, arjunolone, bicalein, luteolin, quercetin, gallic acid, ethyl gallate, kempferol, pelorgonidin, oligomeric proanthocyanidins.
- Tanins, such as punicallin, punicalagin, pyrocatechols, terchebulin, terflavin C, castalagin, casuarinin, casuariin.
- Sitosterol.
- Minerals/trace elements, such as calcium, copper, aluminium, magnesium, silica, zinc. [20-21].

(b).Roots: Its prominent buttress roots provide stability in rocky terrain and on riverbanks, where it is frequently found (Figure 1, c).Its main chemical constituents are:

- Glycosides, such as arjunoside I, II, III and IV, 2,19-dihydroxy-3-oxo-olean-12-en-28-oic acid-28-O-β-d-glucopyranoside.
- Triterpenoids, such as arjunic acid, arjunolic acid, oleanolic acid and terminic acid.
- Sitosterol [24-28].

(c)Leaves: T. arjuna's leaves are coriaceous, simple, frequently crenulate, borne sub-opposite, briefly acute or obtuse at the apex, and oblong or elliptic in shape. They have a light or dark green upper face and a pale brown lower face.Mainly Flavonoids, Alkaloids, Tannins, Steroids, Oxalic acid and phenolic compounds are active chemical constituents which are present in leaves (Figure 1, d).

(d).Fruits: The drupe-shaped, ovoid, fibrous-woody, smooth-skinned fruits of T. arjuna have five hard wings or angles that are oblique and curled upward. Glycosides and flavonoids (Luteolin) in fruits and Cardinolide in seeds are present as phytoconstituents (Figure 1, e).

(e). Flowers: The tree produces short auxiliary spikes or terminal panicles of white sessile bisexual flowers (Figure 1, f). [25].

(a) T. arjuna tree

(b) T. arjuna bark

(c) T. arjuna roots

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(d) T. arjuna leaves (e) T. arjuna fruits (f) T. arjuna flowers

Figure 1: Various parts of Terminilia arjuna tree

3.EXPERIMENTAL STUDIES

T. arjuna is a tree with considerable therapeutic promise, especially for cardiovascular ailments. Through many preclinical and clinical trials, scientific investigations of T. arjuna have been extensively reported and discussed.

3.1. Effects on cardiovascular system: Twelve patients with refractory chronic congestive heart failure, usually due to idiopathic dilated cardiomyopathy, received 500 mg of an aqueous extract from the bark of T. arjuna every eight hours. That therapy appeared safe and it improved symptoms and signs of heart failure for a considerable period of time and enhanced quality of life.

In another study, T. arjuna capsules with a dose of 500 mg at an interval of 8 hours were administered to ninety-three patients with dilated idiopathic and ischemic cardiomyopathy. Compared to patients receiving only standard therapy, those using herbal medication experienced a considerable improvement in their systolic and diastolic functions as well as in their functional capacity [29].

Chronotropic, inotropic and diuretic effects can be found in arjuna bark stem [22]. The extract in aqueous form has been shown to increase coronary flow in a rabbit heart preparation made by Langendorff [30]. Recent experimental research has confirmed the earlier findings by demonstrating that arjuna's aqueous extract increased the force of cardiac muscle contraction in in-situ frog hearts, in-situ hypodynamic frog hearts, and isolated perfused rabbit hearts. Increased coronary flow and bradycardia were the results in an isolated, perfused rabbit heart [31]. It is believed that the high concentration of Calcium in the plant serves as a mediator for the inotropic effect [32].

The rat atria that had a favourable inotropic response allowed the identification of the bark's aqueous extract [33]. When a water-based extract of the bark was discovered in the rat atria, further research led to the production of inotropic activity, which was demonstrated by cocaine and propranolol [34]. Arjuna root yields the novel compound 16, 17-Dihydroneridienone, 3-O-D-glucopyranosyl-(1-6)-O-D-galactopyranoside, which is useful as a cardiotonic[35] .

Analysis of the bark to maximise coronary flow by injecting an aqueous extract into a rabbit heart that has been isolated. The dose that caused the greatest increase in coronary flow was 1024 g/ml. [36].

Blood pressure in dogs was lowered in a dose-dependent manner after intravenous, intracerebral, and intravertebral administration of aqueous and alcoholic bark extract. It was observed that a dose-dependent

reduction in heart rate and blood pressure was caused by an aqueous solution of a 70% alcoholic bark extract in dogs, albeit the mechanism was not identified [37].

3.2. Antioxidant effect: 30 mg of Terminalia arjuna stem bark suspension was administered orally to rats which were previously given isoproterenol to cause myocardial ischemia and later Abana was given to alleviate it [38].

It has been demonstrated that dried, ground bark can increase the heart's natural antioxidant molecules and guard against oxidative stress brought on by ischemic-reperfusion injury [39].

Arjuna's alcoholic extract was said to promote myocardial heat shock protein 72 in rabbits and increase endogenous antioxidants in the heart, providing cardioprotection against oxidative stress brought on by myocardial ischemic-reperfusion injury [40]. It has also been shown that the active phytoconstituents of arjuna bark have cardioprotective effects against oxidative stress caused by sodium fluoride and carbon tetrachloride, perhaps due to its antioxidant capabilities. The ferric reducing/antioxidant power assay performed on the models mentioned above showed that the ethanol extract increased the cardiac intracellular antioxidant activity [41, 42].

In a recent study, it was discovered that the methanol extract had the highest total antioxidant capacity and produced the highest levels of phenolic and flavonoid content. Thus, it can be concluded that there is a linear relationship between the extracts' overall phenolic concentration and antioxidative capacity [43].

In a different study, the bark's alcoholic and aqueous extracts reduced the production of H O-mediated reactive oxygen species in human monocytic cells by enhancing the activities of the antioxidant enzymes catalase and glutathione peroxidase (GPO) and maintaining the cellular reducing power.

Recent research by Mythili et al. has validated prior findings that triterpenoids from arjuna extract with arjunolic acid have cardioprotective effects by enhancing the body's natural antioxidant defence mechanism [44].

3.3. Antihyperlipidemic and antiatherogenic activity: In a placebo-controlled double-blind study, 500 mg of T. arjuna twice daily was given to 100 patients with stable CAD in addition to receiving standard care. At 3 months, a significant reduction in hyperlipidemia as well as in various inflammatory cytokines including hsCRP, IL-18 (P, 0.001), IL-6 and TNF- (P 0.05) was seen in patients [45].

T. arjuna bark powder dosage of 500 mg was given to 30 individuals with coronary artery disease along with standard medication. In addition, there was a marginal decline in nitrite levels and a 16% drop in LDL cholesterol, 15% in total cholesterol, 11% in triglycerides, and 15% in LDL cholesterol [46].

Increased hepatic cholesterol clearance, decreased lipogenic enzyme activity, and inhibition of HMG-CoA reductase are hypothesised to be the mechanisms by which the hypolipidemic action occurs [47]. The improvement of cardiac and hepatic lipid peroxidation by the bark extract in albinorats was further demonstrated by Parmar et al., who also suggested that thyroid hormones may be involved (suppressing thyroid activity) [48].

The rabbits, which were fed a high-fat diet, were given an oral dose of 100–500 mg/kg of ethanolic extract of bark. An in vivo investigation demonstrates a decrease in hyperlipidemia [49].

Prior to intoxicating experimental mice with sodium arsenite, arjunolic acid (20 mg/kg) treatment was continued, and the results showed a decrease in total cholesterol, triglycerides, and LDL-C levels and an increase in HDL-C levels [50].

500 mg/kg of an aqueous ethanol extract (50%) were administered orally to rats with diabetic cardiomyopathy. After taking streptozotocin for eight weeks, the T. arjuna treatment began and was given for 30 days. The levels of total cholesterol, triglycerides, and LDL-C decreased, while the levels of HDL-C increased [51].

3.4. Advancement in Angina/myocardial infarction: In 30 patients with post-infarction stable angina, the anti-ischemic impact of bark powder (500 mg tds) was assessed. In addition to a considerable decline in systolic blood pressure, an improvement in the electrocardiogram, and a decrease in plasma cortisol and serum cholesterol levels, the authors also noticed a significant decline in mean anginal frequency [52]. Then, for three months, 25 patients with coronary artery disease (CAD) received 500 mg of bark powder twice daily. Six patients showed improved exercise tolerance, a decline in the frequency of angina events, and a decreased need for sublingual nitrates, all of which were accompanied with a decrease in the grade of positive of the treadmill test (TMT) response [53].

After receiving arjuna therapy, stable angina patients showed a fifty percent decrease in angina episodes, a substantial delay in the first symptoms of angina on TMT, and the emergence of ST-T alterations in their electrocardiograms. This was demonstrated in a trial. Significant reductions in blood pressure and body mass index were also seen, along with slight gains in the left ventricular ejection fraction (LVEF) and high-density lipoprotein (HDL) values. There was a negligible decrease in anginal frequency in patients with unstable angina. These findings imply that monotherapy with arjuna has a restricted impact on unstable angina patients but is reasonably beneficial in those with stable angina [54].

In 10 stable angina patients, the effectiveness of Hartone (an ayurvedic supplement incorporating arjuna) was examined. The outcomes were compared to those of 10 patients with stable angina receiving twice-daily doses of isosorbide mononitrate at a dose of 20 mg. It was found that 80% of patients receiving Hartone experienced symptomatic improvement compared to 70% of those in the isosorbide mononitrate alone group. Arjuna was also tolerated better than isosorbide mononitrate [55].

3.5.Effect on Thrombosis: Arjuna was one of four medicinal plants of Bangladesh origin which were examined in a recent study to determine their in-vitro membrane-stabilizing and thrombolytic activity. The methanol extract was found to have high thrombolytic activity (30.57%). Additionally, it greatly reduced both heat-induced and hypotonic solution-induced RBC hemolysis. Its modest thrombolytic action was demonstrated; however, more studies are required to identify the secondary metabolites responsible for the activity [56]. There isn't much information available to discuss how arjuna affects the cytochrome P450 (CYP450) enzyme. According to the findings of a recent in vitro investigation, arjuna extracts include components that have the potential to effectively suppress CYP1A action [57].

3.6.Effect on aortic prostaglandins: For an in vivo investigation, bark powder was administered to rabbits in suspension form twice daily for 90 days. In rabbits receiving Terminalia arjuna, aortic ring Prostaglandin E_2 levels increased, which boosted blood flow and improved heart functioning [58].

3.7. Effects on Endothelin 1 levels: Rats with diabetic cardiomyopathy received 500 mg/kg dose of a 50% aqueous ethanol extract orally. After eight weeks of STZ, T. arjuna treatment began and was given

for 30 days. T. arjuna improved the function of the vascular endothelium by bringing blood ET-1 levels in STZ-treated rats closer to normal levels, which decreased pro-inflammatory mediators and increased the cardioprotective impact [59].

3.8. Anti-inflammatory activity: Rats with carrageenan-induced paw edema were given bark powder, which reduced inflammation [61].

3.9. Anticancer activity: In a recent study human oral, ovarian, and liver cancer cell lines were treated with arjunic acid, which was extracted from the bark and was found to be an effective anti-cancer treatment.

3.10. Antiviral activity: Casuarinin, a substance extracted from the bark, is used in vitro to treat Herpes simplex Type 2 virus. It prevented viral attachment and penetration while also interfering with the infection's late stage [62].

3.11. Recent advancement in Antibacterial activity: The study was done to assess the antibacterial efficacy of silver nanoparticles made from Terminalia arjuna bark extract. Using an 80% methanolic extract of Terminalia arjuna bark, silver nanoparticles were created. They were then examined using atomic force microscopy, UV-Visible spectroscopy, and particle size analysis. Pseudomonas aeruginosa ATCC9027, Escherichia coli MTCC1687 and Staphylococcus aureus ATCC6538 were used as test organisms to determine whether synthesised silver nanoparticles had any antibacterial action.

These nanoparticles' antibacterial activity leads to the conclusion that they can be employed to treat bacterial skin infections [63].

4.RELEVANT IMPACTS

The bark of the T. arjuna plant is generally regarded as safe to use. But before ingesting it, there are a few unique safety precautions and warnings that should be followed.

1. **Pregnancy:** While the Terminalia arjuna plant MAY BE UNSAFE during pregnancy, it is advisable to stay away from any other Terminalia species also.
2. **Bleeding problems:** Consuming T. arjuna may make bruising and bleeding worse in those who have bleeding problems because it is known to slow down blood coagulation.
3. **Breast-feeding:** There is insufficient data to conclusively determine whether it is safe or hazardous to use the Terminalia plant while nursing. Therefore, it is best to avoid using it.
4. **Diabetes:** It is well known that Terminalia lowers blood sugar levels.
5. **Surgery:** It is advised to cease using Terminalia about two weeks prior to surgery because it slows down the blood clotting process and affects blood sugar regulation [49, 52].

CONCLUSION

Numerous experimental research has adequately established the effectiveness of Terminalia arjuna as a cardioprotective agent, anti-ischemic agent, anti-inflammatory and antioxidant reducing LDL cholesterol oxidation, and its potential to lower atherogenic lipid levels.

Its molecular activities in several cardiovascular system cells are also documented. The enhancement of cardiovascular functions is significantly aided by its role in increasing autonomic regulation. This herbal medication can modify current treatment plans because it has numerous positive effects without any negative ones. However, there are some known gaps that must be filled before its use in modern medicine can be considered appropriate. These include standardisation of the "drug," toxicity studies, pharmacological interactions with other medications, and significant multicenter randomised clinical trials

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Online publication Date: 00.10.2023