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Medicinal properties of Arjuna (*Terminalia arjuna Roxb.)*: A review

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Abstract

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. This comprehensive review provides various aspects of its ethnomedical, phytochemical, pharmacognostical, pharmacological and clinical significance to different diseases particularly in cardiovascular conditions. This plant has a good safety outline when used in combination with other conventional drugs. This review highlights various medicinal properties of *T. arjuna* through different studies such as antioxidant, hypotensive, anti-atherogenic, anti-inflammatory, anti-carcinogenic, anti-mutagenic and gastro-productive effect.

Keywords: *Terminalia arjuna*, Medicinal property, Phytochemistry, Coronary artery disease, Triterpenoids

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.[1] They expanded attention due to their effectiveness, lack of current medical alternatives, increasing cost of modern medicines and cultural preferences.[2, 3]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. The quantitative ethnobotanical studies were used to identify the plant uses as food,[4] human health care medicines,[5] veterinary medicine[6] and economically important.[7]

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.[1] 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.[10, 11, 12]

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, Unanai, etc. In recent years there has been an increasing awareness about the importance of medicinal plants. Herbal drugs are easily accessible, secure, less pricey, efficient and have very rare side effects. The evaluation of new drugs, especially the phytochemical obtained materials has opened a vast area for research and helpful in making a transition from traditional to modern medicine in India. Medicinal plants contain some organic compounds which provide definite physiological action on the human body and these bioactive substances include tannins, alkaloids, carbohydrates, terpenoids, steroids, flavonoids, and phenols.[13]

Even though numerous medicinal plants have been explained in the Indian customary therapeutic system for treatment of several diseases, very few plant products are nowadays utilized in the modern medical system to treat most of the diseases, particularly; cardiovascular diseases (CVD), ulcers, diabetes, cough, excessive perspiration, asthma, tumor, inflammation and skin disorders. Among the plants, one of the medicinal plants indigenous to India is *Terminaliaarjuna (Roxb.) Wight and Arn.*, (*T. arjuna*) commonly known as 'Arjuna', which has been used as a cardiotonic in heart failure, ischemic, cardiomyopathy, atherosclerosis, myocardium necrosis and has been used for the treatment of different human diseases like blood diseases, anemia, venereal and viral disease; and to continue excellent healthiness. It is used in the treatment of fractures, ulcers, hepatic and showed hypocholesterolemic, antibacterial, antimicrobial, antitumoral, antioxidant, antiallergic and antifeedant, antifertility and anti-HIV activities.[14, 15, 16]*T. arjuna* is reported that to possess strong hydrolipidemic properties. It is trusted that the saponin glycosides in *T. arjuna* may be responsible for its inotropic effects, while the flavonoids/phenolics may supply antioxidant activity as well as vascular amplification activity, in this manner authenticating the multiple activities of this plant for its cardio-protective function.[17, 18, 19]The aim of this review is to summarize the information and knowledge about the *T. arjuna* and updating available research data on the aspects of botany, ethnopharmacology, phytochemistry and clinical studies.

Pharmacological studies

Cardioprotective potential of *T. arjuna* stem bark on the molecular basis was evaluated by Kokkiripati et al,[56] using cell cultures of human monocytic (THP-1) and human aortic endothelial cells (HAECs). Inhibitory effect of alcoholic (TAAE) and aqueous (TAWE) extracts of *T. arjuna* stem bark was assessed on human 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, lipoprotein lipase (LpL) and lipid peroxidation in rat (Wistar) liver and heart homogenates. TAAE and TAWE inhibited the lipid peroxidation and HMG-CoA reductase. Both the extracts attenuated H_2O_2 mediated ROS generation in THP-1 cells by promoting catalase (CAT), glutathione peroxidase (GPx) activities, and by sustaining cellular reducing power. TAAE was highly effective in satisfying proinflammatory gene transcripts in THP-1 cells and HAECs, whereas the response to TAWE depended on the type of transcript and cell type. Both extracts decreased the levels of typical inflammatory marker proteins, viz. LPS induced tumor necrosis factor (TNF)-α secreted by THP-1 cells and TNF-α induced cell surface adhesion molecules on HAECs, namely vascular cell adhesion molecule-1 (VCAM-1) and E-selectin. The marked effects on cultured human monocytic and aortic endothelial cells (HAEC) provide the biochemical and molecular basis for the therapeutic potential of *T. arjuna* stem bark against cardiovascular diseases (CVD).

Triterpenoids are essentially responsible for cardiovascular properties. Alcoholic and aqueous bark extracts of *T. arjuna*, arjunic acid, arjunetin and arjungenin were evaluated for their potential to inhibit CYP3A4, CYP2D6 and CYP2C9 enzymes in human liver microsomes by Varghese et al.[66] They have demonstrated that alcoholic and aqueous bark extract of *T. arjuna* showed effective inhibition of all three enzymes in human liver microsomes with IC_{50} values less than 35 µg/ml. Enzyme kinetics studies suggested that the extracts of *T. arjuna* showed rapidly reversible non-competitive inhibition of all three enzymes in human liver microsomes. They suggest strongly that *T. arjuna* extracts significantly inhibit the activity of CYP3A4, CYP2D6 and CYP2C9 enzymes. Ahmad et al[70] investigated and highlighted the anticarcinogenic and antimutagenic potential of extracts of *T. arjuna*. They have used human lymphocyte culture and bone marrow cells of albino mice as assay system. The parameters of studied were included chromosomal aberrations (CA), sister chromatid exchanges (SCEs) and cell growth kinetics (RI) both in the presence and in the absence of exogenous metabolic activation system for *in vitro* experiment, whereas total aberrant cells and the total frequencies of aberrations were taken for *in vivo* study. The role of *T. arjuna* extracts in reducing metaphase aberrations due to aflatoxin B_1 (AFB1) is quite significant, the reduction varying from 23.49%, 42.47%, and 59.65% down to 12.32%, 28.00%, and 36.88% respectively at the highest dose *T. arjuna* for the three different durations viz., 24, 48 and 72 h. Similarly the number of sister chromatid exchanges got reduced from a higher level of 15.00 ± 1.40 per cell to 7.70 ± 0.50 per cell with liver microsomal metabolic activation system mix at 48 h of treatment. The replication index was enhanced from 1.33 to 1.55 in the *in vitro* experiment. Similar trends were noticed in the *in vivo* experiments that are effective reductions in clastogeny ranging from 15.22% to 54.82% from the mutagen treated positive control and the total frequencies in aberrant cells got reduced from 429 due to AFB1 to 141 due to 5th concentration of *T. arjuna* extracts at 32 h of exposure. Arjungenin and its glucoside are extracted from *T. arjuna* and exhibited a moderate free radical scavenging activity on the superoxide release

from PMN cells. Arjungenin also exhibited greater inhibitory action on the hypochlorous acid production from human neutrophils.[67]Viswanatha et al[69] investigated the antioxidant and antimutagenic activities of alcoholic extract of TA bark. The alcoholic extract of the stem bark of *T. arjuna* (ALTA) has shown potent antioxidant activity with EC_{50} in DPPH assay, superoxide radical scavenging activity and lipid peroxidation assay. In micronucleus test ALTA showed significant reduction in percentage of micronucleus in both polychromatic erythrocytes (PCE) and normochromatic erythrocytes (NCE) and also shown a significant reduction in P/N ratio. Singh et al[68] investigated the effects of butanolic fraction of *T. arjuna* bark on Doxorubicin (Dox) induced cardiotoxicity using *in vivo* study with male Wistar rats and they found that *T. arjuna* bark has protective effects against Dox-induced cardiotoxicity and may have potential as a cardioprotective agent.

Dried pulverized bark of *T. arjuna* was administered orally to Wistar albino rats (120–150 g) in two doses (500 and 750 mg/kg in 2% carboxy methyl cellulose (CMC)), 6 days per week for 12 weeks. The determination of baseline changes in cardiac endogenous antioxidant compounds [superoxide dismutase (SOD), reduced glutathione (GSH) and catalase (CAT)] or the hearts were subjected to oxidative stress associated with *in vitro* ischemic-reperfusion injury (IRI). Significant rise in myocardial thiobarbituric acid reactive substance (TBARS) and loss of SOD, GSH and CAT occurred in the vehicle-treated hearts subjected to *in vitro* IRI. Hearts of rats were significantly protected from oxidative stress, when subjected to *in vitro* IRI. The crude bark of TA augments endogenous antioxidant compounds of rat heart and also prevented oxidative stress associated with IRI of the heart.[71] Vascular complications are a leading cause of mortality and morbidity in diabetic patients. Therapeutic potential of *T. arjuna*bark extract was examined in improving myocardial function in streptozotocin (STZ) induced diabetic rats. After 8 weeks of STZ administration, rats showed a decline in left ventricular pressure (LVP), maximal rate of rise and fall in LVP (LV [dP/dt] max and LV [dP/dt] min), cardiac contractility index (LV [dP/dt] max/LVP), and a rise in LV end-diastolic pressure. Altered lipid profile, oxidative stress, and increased levels of endothelin 1 (ET-1), tumor necrosis factor-α (TNF-α), and interleukin 6 (IL-6) along with histological changes in heart and pancreas were observed in diabetic rats. *T. arjuna* significantly attenuated cardiac dysfunction and myocardial injury in diabetic rats. It also reduced oxidative stress, ET-1, and inflammatory cytokine levels.[72] Sinha et al[73] has investigated the antioxidative properties of an ethanol extract of the bark of *T. arjuna* (TAEE) against sodium fluoride (NaF)-induced oxidative stress in the murine heart. NaF intoxication significantly altered all the indices related to the prooxidant–antioxidant status of the heart. In addition, the ferric reducing/antioxidant power assay revealed that TAEE enhanced the cardiac intracellular antioxidant activity. Finally, they concluded that TAEE protects murine hearts from NaF-induced oxidative stress, probably via its antioxidant properties.

Parveen et al[74] examined the protective effect of *T. arjuna* bark extract on left ventricular (LV) and baroreflex function in chronic heart failure and to elucidate the possible mechanistic clues in its cardioprotective action. Fifteen days after isoproterenol administration, rats exhibited cardiac dysfunction, hypertrophy, and LV remodeling along with reduced baroreflex sensitivity. Prophylactic and therapeutic treatment with *T. arjuna* improved cardiac functions and baroreflex sensitivity. It has also attenuated hypertrophy and fibrosis of the LV. *T. arjuna* exerts beneficial effect on LV functions, myocardial remodeling, and autonomic control in chronic

heart failure possibly through maintaining endogenous antioxidant enzyme activities, inhibiting lipid peroxidation and cytokine levels. Diethyl ether, ethyl acetate and ethanol extractions of *T. arjuna* exerted hypolipidemic and antioxidative effects at two different dose levels of 175 and 350 mg/kg body weight in Poloxamer (PX)-407 induced hyperlipidemic albino Wistar rats. The results suggested that the ethanolic fraction of *T. arjuna* possesses the potent properties of being an antioxidant and hypolipidemic than other fractions.[75] Kumar et al[76] evaluated the effects of *T. arjuna* bark extract on myocardial fibrosis and oxidative stress induced by chronic β-adrenoceptor stimulation. Because myocardial fibrosis and oxidative stress accompany a number of cardiac disorders such as hypertrophic cardiomyopathy, hypertensive heart disease and cardiac failure. Aqueous extract of *T. arjuna* bark was evaluated at 63, 125 and 250 mg/kg given orally for antifibrotic and antioxidant effects in rats given the selective β-adrenoceptor agonist isoprenaline for 28 days. The *T. arjuna* bark extract significantly prevented the isoprenaline-induced increase in oxidative stress and decline in endogenous antioxidant level and also prevented fibrosis. Gauthaman et al[79] studied that oral administration of *T. arjuna* for 12 weeks in rabbits caused augmentation of myocardial antioxidants; superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) along with induction of heat shock protein72 (HSP72). *In vivo* ischemic-reperfusion injury induced oxidative stress, tissue injury of heart and hemodynamic effects were prevented in the *T. arjuna* treated rabbit hearts.

Alcoholic extract of *T. arjuna* bark and its extracts were evaluated for DNA protection, protein oxidation and free radical scavenging activity. Ethanolic extract of *T. arjuna* bark (TAA) and its fractions, including dichloromethane (TAD), ethyl acetate (TAE), butanol (TAB) and water (TAW) has significant antioxidant activity and potential to prevent protein oxidation, DNA damage protection by pBR 322 DNA and SCGE assay. The potent antioxidative activity and DNA protection ability of *T. arjuna* bark extracts might be endorsed with phenolic/flavonoid compounds. A significant correlation was also observed between free radical scavenging activity, *in vitro* DNA damage activity and the total phenolic/flavonoid content.[16] Physicochemical property and inotropic effect of the aqueous extract of *T. arjuna* bark (TAAqE) were investigated by Oberoi et al[80] on adult rat ventricular myocytes in comparison with extracts prepared sequentially with organic extracts. They found that TAAqE decoctions exerted positive inotropy, accelerated myocyte relaxation and increased caffeine-induced contraction concentration dependently. TAAqE-induced cardiotonic action via enhancing SR function, a unique action minimizing the occurrence of arrhythmias, makes TAAqE a promising and relatively safe cardiotonic beneficial to the healthy heart and the treatment for chronic heart disease.

Mandal et al[77] investigated antioxidative and antimicrobial properties of methanolic extract of *T. arjuna* bark. The antimicrobial activity showed that higher inhibition against Gram negative bacteria than gram positive bacteria and showed a promising antioxidant activity, as absorption of DPPH radicals decreased in DPPH free radical scavenging assay. Methanol extract from bark of *T. arjuna* exhibited medicinal as well as physiological activities. Methanol, ethanol, acetone, aqueous both hot and cold extracts from the leaves and bark of *T. arjuna* were tested for their antimicrobial activity against *Staphylococcus aureus*, *Acinetobacter* sp., *Proteus mirabilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans*, pathogens causing ear infections. Three organic solvents evaluated, acetonic leaf extract was found to be best against *S. aureus*. Organic bark extract

showed almost equal inhibition of all tested Gram negative bacteria except *P. aeruginosa*. Aqueous extract of *T. arjuna* bark exhibited good activity against *S. aureus*.[78] Devi et al[81] evaluated the effect of methanolic extract of *T. arjuna* (100 mg/kg to 50 mg/kg body weight) on diclofenac sodium (80 mg/kg bodyweight in water, orally) induced gastric ulcer in rats. The gastroprotective effect of *T. arjuna* was assessed from volume of gastric juice, pH, free and total acidity, pepsin concentration, acid output in gastric juice, the levels of non-protein sulfhydryls (NP-SH), lipid peroxide (LPO), reduced glutathione (GSH), and activities of enzymic antioxidants-super oxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST) and myeloperoxidase (MPO) in gastric mucosa. The levels of DNA, protein bound carbohydrate complexes-hexose, hexosamine, sialic acid, fucose in gastric mucosa and gastric juice and the levels of RNA in gastric mucosa were assessed. The stomach tissues were used for adherent mucus content and also for the histological examination. A significant reduction in lesion index was observed in ulcer induced animals treated with *T. arjuna* (DIC + TA) compared to ulcerated rats (DIC). A significant increase was observed at pH, NP-SH, GSH, enzymic antioxidants, protein bound carbohydrate complexes, adherent mucus content, nucleic acids with a significant decrease in volume of gastric juice, free and total acidity, pepsin concentration, acid output, LPO levels and MPO activities in DIC + TA rats compared to DIC rats. It is proved that *T. arjuna* could act as a gastroprotective agent probably due to its free radical scavenging activity and cytoprotective nature.

Clinical studies

The therapeutic potential of *T. arjuna* on the inflammatory markers in subjects with stable coronary artery disease (CAD). In a placebo-controlled, randomized double-blind study, 116 patients with stable CAD who were on standard cardiac medications for more than three months were enrolled and received either placebo or 500 mg of *T. arjuna* from Himalayan Herbal Healthcare, Bangalore, India twice a day in addition to receiving the conventional treatment. A significant decrease in serum triglycerides as well as in various inflammatory cytokines such as hsCRP, IL-18 ($P < 0.001$), IL-6 and TNF-α ($P < 0.05$) was observed at 3 months in patients who were on drug treatment as compared to the placebo. The effects were maintained till 6 months follow-up and showed a further reduction in hyperlipidemia and inflammatory markers with time. An observational study was conducted to find out the effects of *T. arjuna* in patients with dilated cardiomyopathy (DCMP) of idiopathic and ischemic cause. Ninety three patients with DCMP receiving standard therapy and/or bark extract of *T. arjuna* 500 mg 8 hourly were enrolled. Three groups as standard therapy (ST, Group 1), *T. arjuna* therapy (TA, Group 2) and standard therapy with *T. arjuna* (ST + TA, Group 3) were formed. At the end of the study period, patients of group 3 showed significant improvement in percentage of left ventricular ejection fraction (LVEF%) (7 ± 1.6, $P < 0.00001$) compared to group 1 and 2 ($P < 0.00001$, $P < 0.0001$). Reductions in Left ventricular end systolic and diastolic diameters and volumes were most significant in group 3 (8.3 ± 4.7, $P < 0.0001$ and 3.1 ± 5.7, $P < 0.001$) and (11 ± 26, 9 ± 21 $P < 0.01$) respectively in comparison to other groups. Pulmonary artery pressure reduced significantly in group 1 and 3 ($P < 0.0001$). A similar reduction in diastolic score and mitral regurgitation ($P < 0.01$ and $P < 0.0001$) was observed in groups 1 and 3. From the results, dilated cardiomyopathy with reduced LVEF due to either idiopathic or ischemic cause receiving standard

therapy with *T. arjuna* showed significant improvement in left ventricular parameters as well as functional capacity.[82]

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. It is also used for earaches and diseases of the urinary tract. The effectiveness *T. arjuna* as an anti-ischemic agent and as 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, 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.

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