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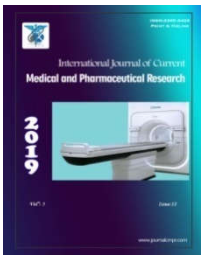

Research Article

THE PHARMACOLOGICAL ACTIVITIES OF VARIOUS EXTRACTS FROM TERMINALIA ARJUNA BARK: A REVIEW

Z.M. Anka[1]* Vijender Singh[1] Gunjan Singh[1] and S.N. GIMBA[2]

[1]Department of pharmacy, School of Allied Health science, Sharda University, Greater Noida U.P, India
[2]Department of Clinical Research, School of Allied Health science, Sharda University, Greater Noida, U.P, India

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ABSTRACT

Medicinal plants have been a main source of therapeutic agents from ancient time to cure diseases. Terminalia arjuna (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 ethno-medical, phyto-chemical, pharmacognostical, pharmacological and clinical significance to different diseases particularly in cardiovascular conditions. The 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, hypertensive, antiatherogenic, anti-inflammatory, anti-carcinogenic, anti-mutagenic and gastro-productive effect.

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.(WHO, 2002) They expanded attention due to their effectiveness, lack of current medical alternatives, increasing cost of modern medicines and cultural preferences.(Heinrich., 2000), (Tabuti *et al*., 2003) 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, (Pieroni., 2001) human health care medicines,(Kim *et al*., 2013) veterinary medicine(Upadhyay *et al*., 2011) and economically important.(Reyes-Garcia *et al*., 2006*)*

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.(Gosh., 2003) 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.(WHO., 2002) During the last few years, use of herbal supplements increased from 2.5% to 12%.(Stickel *et al*., 2007) 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.(Gopinath *et al*., 2013)*, (Yallappa et al*., 2013), (Edison *et al*., 2012)

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. (Sharma *et al*., 2012)

Corresponding author:* **Z.M. Anka
Department of pharmacy, School of Allied Health science, Sharda University, Greater Noida U.P, India

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 *Terminalia arjuna*, (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.(Ram *et al*., 1997), (Bachaya *et al*., 2009), (phani kumar *et al*., 2013)

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.(Dwivedi., 2007), (Maulik *et al*., 2012), (Kapoor *et al*., 2014)

METHODOLOGY

Systematic literature searches were carried out and the available information on various plants traditionally used for cardiovascular disorders was collected via electronic search (using Pubmed, Sci- Finder, Scopus, Scirus, ScienceDirect, Google Scholar and Web of Science) and a library search for articles published in peer-reviewed journals and also locally available books.

Occurrences, Botanical Description and Ethnopharmacology

Terminalia arjuna is an ayurvedic plant with important medicinal value. It is commonly known as Arjuna, Indradru, (Sharma *et al*., 2005) which is belongs to Combretaceae family comprising of nearly 200 species distributed around the world. Nearly 24 species of Terminalia have been reported from various parts of India, some selected species are T. arjuna, Terminalia bellirica (use for treatment of respiratory tract infection), Terminalia catappa (use for treatment of skin diseases, leprosy and scabies), Terminalia elliptica(use for treatment of diarrhea), Terminalia mantaly (use for cancer treatment), Terminalia tomentosa (use for bronchitis treatment), Terminalia ivorensis (use for treatment of dermal diseases) etc. In India, T. arjuna is about 60-80 feet in height, buttressed trunk and horizontally spreading crown and drooping branches distributed in India, Burma, Mauritius and Sri Lanka.(Kapoor *et* a*l* 2014), (Chopra *et al*., 1958), (Nadkarni., 1976)

T. arjuna is distributed throughout sub Indo-Himalayan tracts of Uttar Pradesh, Punjab, Deccan, South Bihar, Orissa,West Bengal and Madhya Pradesh mainly along riverside, rivulets and ponds. It is known by its various vernacular names, the most commonly used ones are Arjuna (Common Name), Arjun (Hindi), Marudhu (Tamil and Malayalam), Tella Maddi (Telugu), Arjhan (Bengali), Sadaru (Marathi), Sadado (Gujarati), Neer matti (Kannada) and some traditional formulations prescribe in the name of Arjunarishta and Arjunaghrita. This tree is usually an evergreen tree with new leaves (reddish in color) appearing in the hot season (February to April) before leaf fall.(Ali., 1994)

Phytochemistry

The major constituents of T. arjuna in stem bark, root bark, fruits, leaves and seeds are well characterized (Table 1). The preliminary phytochemical analysis of existing compounds in T. arjuna was carried out according to various standard protocols as mentioned by (Harbone., 1998) in (Table 2), 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.(Singh *et al*., 2002), (Chitlange *et al*., 2009), (Kokkiripati *et al*., 2013) 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.(Row *et al*., 1970), (singh *et al*., 1995), (Kandil *et al*., 1998) Extracts from T. arjuna bark are:

Terpenoids, Ursane Triterpenoids and Glycosides

At first, an oleanane triterpenoid named, arjunin, and a lactone, arjunetin were isolated from the benzene and ethanolic extracts of its bark respectively.(Honda *et al*., 1976) initially confirmed that the presence of arjunic acid and arjungenin and latterly reported that two more glucosides namely arjunglucoside I and II in the stem bark of T. arjuna. (Anjaneyulu *et al*., 1982) confirmed that the presence of arjunoside III and IV, terminic acid, and a triterpene carboxylic acid by ethyl acetate extraction of roots of T. arjuna. Hexane extraction of stem of T. arjuna authenticated that the presence of terminic acid and b-sitosterol.(Anjaneyulu *et al*., 1983)

(Ali *et al*., 2003) has isolated another oleanane type triterpane, terminoside A from the acetone fraction of the ethanolic extract of T. arjuna's stem bark. The structure of this new compound was established as olean-1a,3b,22b-triol-12-en-28-oic acid-3b-D-glucopyranoside. It was exhibited that terminoside A inhibits nitric oxide production and decreases inducible nitric oxide synthase levels in lipopolysaccharide stimulate macrophages. (Ali *et al*., 2003) Five ursane type triterpene glucosyl ester including new one, 2a, 3b-dihydroyurs-12,18-dien-28-oic acid 28-O-b Dglucopyranosyl ester, and four known ursane triterpene glycosyl esters namely, 2a, 3b, 23-trihydroxyurs-12,18-dien-28-oic acid 28-O-b-D-glucopyranosyl ester, quadranosie VIII, kajiichigoside and 2a, 3b, 23-trihydroxyurs-12, 19-dien-28-oic acid 28-O-b-Dglucopyranosyl ester were isolated from bark of T. arjuna.(Wang *et al*., 2010) 3-O-b-D-glucopyranosyl-2a, 3b, 19a-trihydroxyolean- 12-en-28-oic acid, 28-O-b-D-glucopyranoside and 2a, 19a-dihydroxy- 3-oxo-olean-12-en28-oic acid 28-O-b-D-gluco-pyranoside are isolated from bark of T. arjuna by (Choubey *et al*., 2001), (Upadhyay *et al*., 2001) through spectrochemical analysis.

(Patnaik *et al*., 2007) using chromatography technique isolated a triterpenoid glycoside from the bark of T. arjuna and identified it is an olean- 3b, 22b-diol-12-en-28 b-D-glucopyranoside-oic acid.

(Alam *et al*., 2008) isolated two more glycosides namely Termiarjunoside I (olean-1a,3b,9a,22a-tetraol-12-en-28-oicacid-3b-D-glucopyranoside) and Termiarjunoside II (Olean-3a,5a, 25-triol-12-en-23,28- dioicacid-3b-D-glucophyranoside) from the ethanolic extract of T. arjuna bark. Arjunglucoside IV and V, Arjunasides A-E were isolated from the ethanolic extract of the stem bark of T. arjuna by (Wang *et al*., 2010)

Flavonoids and Phenolics

Bark of T. arjuna contains a very high level of flavonoids, namely arjunolone, flavones, luteolin, baicaleiin, quercetin, kempferol, and pelargonidin evaluated with other medicinal plants particularly having favorable effects on cardiovascular diseases. The compound luteolin has been isolated from the butanolic fraction of T. arjuna and it has been found to have antimutagenic and antibacterial activities. It inhibited gram negative pathogen growth with a minimum inhibitory concentration of 12.5 mg/disc. Aqueous extract of T. arjuna contains 70% polyphenols having a molecular weight greater than 3.5 kDa and they are confirmed by the HPLC and LCMS. The aqueous extract contains flavon-3-ols, such as (+)-catechin, (+)-gallocatechin and (-)-epigallocatechin; gallic acid, ellagic acid and its derivatives such as 3-O-methyl ellagic acid 4-O-b-Dxylopyranoside and 3-O-methyl ellagic acid 3-O-rhamnoside.

Various studies support the fact that bioflavonoids inhibit LDL oxidation, endothelial activation and platelet aggregation.(Fuhrman *et al*., 2001), (Carluccio *et al*., 2003), (Ruff., 2003), (Martikainen *et al*., 2007) Due to the presence of free radical scavenging action of the various phenolic contents in T. arjuna, it acts as strong anti proliferative and anti-oxidant agent.(Baipai *et al*., 2005) There is an inversely relationship between the high intake of dietary flavonoids and the risk of coronary artery disease (CAD), so possible account for intake of high flavonoids content Tarjuna is beneficial effects in CAD.

Tannins

Tannins are known to enhance the synthesis of nitric oxide and relax vascular segments pre-contracted with norepinephrine. In addition to a flavonoids variety of tannins have been isolated from the bark of T. arjuna. Around fifteen types of tannins and their related compounds were isolated from the bark of T. arjuna and their structures were elucidated with the help of spectral analysis. Hydrolyzable tannins are castalagin, casuariin, casuarinin, punicalagin, pyrocatechols, punicallin, terchebulin and terflavin C were isolated from the bark of T. arjuna.(Lin *et al*., 2001) Tannins are considered to have wound healing, astringent, hypotensive, antioxidant and antimicrobial effects.(Kolodziej *et al*., 2005), (Chaudhari *et al*., 2006)

Minerals and Amino Acids

The bark of T. arjuna contains large amount of various minerals and trace elements such as magnesium (4000 µg/g), calcium (3133 µg/g), zinc (119 µg/g) and copper (19 µg/g).(Dwivedi *et al*., 1989) It contains some amino acids such as tryptophan, tyrosine, histidine and cysteine.(Singh *et al*., 2002), (Kandil *et al*., 1998)

Table 1 Phytochemical Constituents of various Parts of Terminalia Arjuna

Part used Major	Chemical Constituents	Reference
Stem bark	Triterpenoids	Row *et al*[24] Honda *et al*[25] Singh *et al*[26,27] Anjaneyulu *et al*[28] Singh *et al*[29] Wang *et al*[30]
	Ursane triterpenoids	
	Glycosides	Row *et al*[24,31], Singh *et al*[26,27]Honda *et al*[25,32] Tripathi *et al*[34] Ali *et al*[35,36] Wang *et al*[34,37] Patnaik *et al*[38]Alam *et al*[39] Ahmad *et al*[40] Sharma *et al*[33]
	Flavonoids and phenolics	Sharma *et al*[33] Pettit *et al*[41] Anonymous[42] Saha *et al*[43] Wang *et al*[30]
	Tannins	Takahashi *et al*[44] Lin *et al*[45] Kuo *et al*[46]
	Minerals and trace elements	Dwivedi *et al*[47]
	Other compounds	Anjaneyulu *et al*[28] Anjaneyulu *et al*[48,49]
Roots	Triterpenoids Arjunic acid	Singh *et al*[26,27]
	Glycosides	Upadhyay *et al*[51]
Fruits	Triterpenoids and flavonoids	Rastogi *et al*[52]
Leaves and seeds	Flavonoids and glycosides	Pettit *et al*[41], Yadava *et al*[53]

Pharmacological and Clinical Studies

Pharmacological studies

Cardioprotective potential of T. arjuna stem bark on the molecular basis was evaluated by (Kokkiripati *et al*., 2013), 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)-a secreted by THP-1 cells and TNF-a induced cell surface adhesion molecules on HAECs, namely vascular cell adhesion molecule-1 (VCAM-1) and Eselectin. 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*., 2015) They have demonstrated that alcoholic and aqueous bark extract of T. arjuna showed effective inhibition of all three enzymes in human liver microsomes with IC50 values less than 35 µg/ml. Enzyme kinetics studies suggested that the extracts of T. arjuna showed rapidly reversible noncompetitive 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*., 2014) 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 B1 (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.(Pawar *et al.*, 2005)

(Viswanatha *et al*., 2010) investigated the antioxidant and antimutagenic activities of alcoholic extract of Tarjuna bark. The alcoholic extract of the stem bark of T. arjuna (ALTA) has shown potent antioxidant activity with EC50 in DPPH (2,2-diphenyl-1-picryl-hydrate) 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*., 2008) 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.(Gauthaman *et al.*, 2001) 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-a (TNF-a), 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.(Khaliq *et al.*, 2013)

(Sinha *et al*., 2008) 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 prooxidante 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*., 2012) 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.(Subramaniam *et al.*, 2011)

(Kumar *et al*., 2009) evaluated the effects of T. arjuna bark extract on myocardial fibrosis and oxidative stress induced by chronic b-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 b-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*., 2005) 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 (SHP72). 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 (Single cell gel electrophoresis) assay. The potent antioxidative activity and DNA protection ability of T. arjuna bark extracts might be endorsed with phenolic/flavonoid compounds. A significant correlationwas also observed between free radical scavenging activity, *in vitro* DNA damage activity and the total phenolic/flavonoid content.(Phani Kumar *et al.*, 2013)

Physicochemical property and inotropic effect of the aqueous extract of T. arjuna bark (TAAqE) were investigated by (Oberoi *et al*., 2011) 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*., 2013) 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.(Aneja *et al.*, 2012)

(Devi *et al*., 2007) 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-Stransferase (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 acid 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

Recently, (Kapoor *et al*., 2014) investigated 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-a ($P < 0.05$) 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.(Bhawani *et al.*, 2013)

(Bharani *et al*., 1995) investigated the salutary effect of T. arjuna in patients with severe refractory heart failure. Twelve patients with refractory chronic congestive heart failure (Class IV NYHA), related to idiopathic dilated cardiomyopathy (10 patients); previous myocardial infarction (one patient) and peripartum cardiomyopathy (one patient), received T. arjuna,

as bark extract (500 mg 8 hourly) or matching placebo for 2 weeks each, separated by 2 week washout period, in a double blind crossover design as an adjuvant to maximally tolerable conventional therapy (Phase I). On long term evaluation in an open design (Phase II), wherein Phase I participants continued T. arjuna in fixed dosage (500 mg 8-hourly) in addition to flexible diuretic, vasodilator and digitalis dosage for 20-28 months (mean 24 months) on outpatient basis, patients showed continued improvement in symptoms, signs, effort tolerance and NYHA Class, with improvement in quality of life.

(Dwivedi *et al*., 2005) were conducted a study to evaluate the role of T. arjuna in ischemic mitral regurgitation (IMR) following acute myocardial infarction (AMI). 40 patients with fresh AMI showing IMR were randomly divided into 2 groups of 20 each. Two groups were observed between one and three months therapy with T. arjuna at a dose of 500 mg twice a day and showed significant decreases in IMR, improvement in E/A ratio and considerable reduction in angina frequency.

(Bharani *et al*., 2002) conducted a study on the efficacy of T. arjuna in chronic stable angina. Fifty eight males with chronic stable angina (NYHA class II-III) with evidence of provocable ischemia on treadmill exercise test received TA (500 mg 8 hourly), isosorbide (40 mg/daily) or a matching placebo for oneweek each, separated by a washout period of at least three days in a randomized, double-blind, crossover design. They underwent clinical, biochemical and treadmill exercise evaluation at the end of each therapy, which were compared during the three therapy periods. T. arjuna therapy was associated with a significant decrease in the frequency of angina and the need for isosorbide dinitrate. T. arjuna bark extract, 500mg 8 hourly, given to patients with stable angina with provocable ischemia on treadmill exercise, led to improvement in clinical and treadmill exercise parameters as compared to placebo therapy. These benefits were similar to those observed with isosorbide mononitrate (40 mg/day) therapy and the extract was well tolerated.

The effect of an Ayurvedic formulation of T. arjuna, known as'Arjuna Kwatha' was assessed by (Rao *et al*., 2001) in 36 hypertensive patients at stage III with increased LV mass. The patients were divided into two groups, one group received atenolol (50 mg twice daily) and the other group 'Arjuna Kwatha' (25ml twice daily) along with atenolol for 6 months. A significant decrease was observed in both SBP and DBP ($P < 0.001$) in both the groups. However, LV mass index was only significantly reduced in the atenolol-plus-'Arjuna Kwatha' group as compared to atenolol alone ($P < 0.001$), due to negative chronotropic and inotropic effects of the herbal preparation. (Khalil., 2005) reported that the administration of T. arjuna bark powder along with statins for 3months to 30 patientswith coronary artery disease resulted in a 16% in LDL-cholesterol, 15% decrease in total cholesterol and 11% in triglycerides, confirming its immense potential to correct dyslipidemia in conjunction with statins.

(Gupta *et al*., 2001) evaluated the antioxidant and hypocholesterolaemic effects of T. arjuna tree bark and to compare it with a known antioxidant, vitamin E, also performed a randomized controlled trial. One hundred and five successive patients with coronary heart disease (CHD) were recruited and divided into 3 groups of 35 each in this study. Group I received placebo capsules; Group II vitamin E capsules 400 units/day; and Group III received finely pulverized T. arjuna tree bark-powder (500 mg) in capsules daily. Lipids and lipid peroxide levels were determined at 30 days follow-up. No significant changes in total, HDL, LDL cholesterol and triglycerides levels were seen in Groups I and II. In Group III, there was a significant decrease in total cholesterol (_9.7 ± 12.7%), and LDL cholesterol (_15.8 ± 25.6%) (paired t-test $P < 0.01$). Lipid peroxide levels decreased significantly in both the treatment groups ($P < 0.01$). This decrease was more in vitamin E group (_36.4 ± 17.7%) as compared to the T. arjuna group (_29.3 ± 18.9%). T. arjuna tree bark powder has significant antioxidant action that is comparable to vitamin E and also has a significant hypocholesterolaemic effect.

A study was conducted by (Bharani *et al*., 2004) to determine the improvement of endothelial dysfunction in smokers. Eighteen healthy male smokers (age 28.16 ± 9.45 years) and an equal number of age-matched, non-smoker controls participated in the study. The smokers were given T. arjuna (500 mg, 8 h) or matching placebo randomly in a double blind crossover design for two weeks each, followed by repetition of brachial artery reactivity studies to determine various parameters including flow-mediated dilation after each period. The flow-mediated dilation showed significant improvement from baseline values after T. arjuna therapy.

Table 2 Preliminary tests for Phytochemical Analysis of the Terminalia Arjuna Extract

Phytoconstituents	Test
Alkaloides	Dragendroff's test
Carbohydrates	Molisch's test
Flavonoids	Lead acetate test
Glycosides	KellereKilliant test
Lactones	Legal's test
Phenolic compounds and tannins	5% FeCl3 test
Proteins	Ninhydrin test
Phytosterols	Salkowski's test
Saponins	Foam test
Triterpenoids	Liebermanne Burchard's test

Toxicity and Side Effects

T. arjuna has been used in the dose between 1 to 2g per day in different clinical studies and found that this is an optimum dose in the patients particularly CAD. These doses have lesser side effect like headache, mild gastritis and constipation. There were no reports in the regards of hematological, hepatic, metabolic and renal toxicity after more than two years of its administration.(Bharani *et al.*, 1995)

Recently (Bhawani *et al*., 2013) reported that there was no significant variation in the body and organ weights between the control and the treated group of 93 patients with dilated cardiomyopathy (DCMP) of idiopathic and ischemic cause was observed after 28 days of treatment under the treatment of T. arjuna capsules (500 mg at 8 h).

Haematological analysis and biochemical parameters revealed no toxic effects of the extract. Pathologically, neither gross abnormalities nor histopathological changes were observed and there was no mortality recorded in 28 days.

(Yaidikar *et al*., 2015) reported that pre-treatment with arjunolic acid from the T. arjuna bark effectively prevented the cerebral I/R induced oxidative damage by virtue of its antioxidant potential and supplementation of arjunolic acid may be beneficial in stroke prone population. Arjunolic acid from T. arjuna attenuated sodium nitrite-induced cardiac

damage in rats and restored the normal balance between pro- and anti-inflammatory cytokines. Moreover, arjunolic acid protected cardiac tissues from both extrinsic and intrinsic cell death pathways.(Al-Gayyar *et al.*, 2014)

(Parmar *et al*., 2006) were observed a decrease in serum concentration of thyroid hormones as well as an increase in the hepatic LPO with higher doses of T. arjuna. There is a vital need for well controlled multicentric clinical trials in a larger setup of subjects with a standardized product for exploring the true therapeutic potential of T. arjuna.

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 of 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 regards to exact molecular mechanism, drug administration, drug-drug interactions and toxicological studies.

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