Journal of Traditional and Complementary Medicine 7 (2017) 65–78

Contents lists available at ScienceDirect

Journal of Traditional and Complementary Medicine

journal homepage: http://www.elsevier.com/locate/jtcme

Review article

Medicinal properties of *Terminalia arjuna (Roxb.) Wight & Arn.*: A review

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ARTICLE INFO

Article history:
Received 20 January 2016
Received in revised form
10 February 2016
Accepted 12 February 2016
Available online 20 March 2016

Keywords:
Terminalia arjuna
Medicinal property
Phytochemistry
Coronary artery disease
Triterpenoids

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.

1. 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.[10–12]

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,

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Peer review under responsibility of The Center for Food and Biomolecules, National Taiwan University.

http://dx.doi.org/10.1016/j.jtcme.2016.02.003

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 (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.[14–16] *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.[17–19] 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.

2. Methods

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, SciFinder, 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.

3. Occurrences, botanical description and ethnopharmacology

T. arjuna is an ayurvedic plant with important medicinal value. It is commonly known as Arjuna, Indradru, Partha and Veeravriksha[20] 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*, *Terminalia bialata*, *Terminalia catappa*, *Terminalia elliptica*, *Terminalia porphyrocarpa*, *Terminalia mantaly 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.[19,21,22] *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.

Leaves of *T. arjuna* are simple, often crenulations, borne subopposite, shortly acute or obtuse at the apex, coriaceous and oblong or elliptic. Their upper face is pale or dark green and the lower face is pale brown. The tree bears white sessile bisexual flowers in short auxiliary spikes or in a terminal panicle arrangement. Fruits of *T. arjuna* are drupe, ovoid, fibrous-woody and smooth-skinned with five hard wings or angles which are oblique and curved upwards. Stem bark is simple, smooth and pinkish-gray in color in external view. An internal view, the bark is soft and reddish in color.[23]

4. 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[54] 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.[26,27,55,56] 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*.[24,29,31,57]

4.1. 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 (Fig. 1). Honda et al[25,32] initially confirmed that the presence of arjunic acid and arjungenin and latterly reported that two more glucosides namely arjunglucoside I and II (Fig. 1) in the stem bark of *T. arjuna*. Anjaneyulu and Prasad[48,49] 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* (Fig. 1). Hexane extraction of stem of *T. arjuna* authenticated that the presence of terminic acid and β-sitosterol.[28] Ali et al[36] 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-1α,3β,22β-triol-12-en-28-oic acid-3β-D-glucopyranoside. It was exhibited that terminoside A inhibits nitric oxide production and decreases inducible nitric oxide synthase levels in lipopolysaccharide stimulate macrophages.[35,36] Five ursane type triterpene glucosyl ester including new one, 2α, 3β-dihydroyurs-12,18-dien-28-oic acid 28-O-β-D-glucopyranosyl ester, and four known ursane triterpene glycosyl esters namely, 2α, 3β, 23-trihydroxyurs-12,18-dien-28-oic acid 28-O-β-D-glucopyranosyl ester, quadranosie VIII, kajiichigoside and 2α, 3β, 23-trihydroxyurs-12, 19-dien-28-oic acid 28-O-β-D-glucopyranosyl ester were isolated from bark of *T. arjuna* (Fig. 2).[30] 3-O-β-D-glucopyranosyl-2α, 3β, 19α-trihydroxyolean-12-en-28-oic acid, 28-O-β-D-glucopyranoside and 2α, 19α-dihydroxy-3-oxo-olean-12-en28-oic acid 28-O-β-D-gluco-pyranoside are isolated from bark of *T. arjuna* by Choubey and Srivastava[50] and Upadhyay et al[51] through spectrochemical analysis. Patnaik et al[38] using chromatography technique isolated a triterpenoid glycoside from the bark of *T. arjuna* and identified it is an olean-3β, 22β-diol-12-en-28 β-D-glucopyranoside-oic acid. Alam et al[39] were isolated two more glycosides namely Termiarjunoside I (olean-1α,3β,9α,22α-tetraol-12-en-28-oicacid-3β-D-glucopyranoside) and Termiarjunoside II (Olean-3α,5α, 25-triol-12-en-23,28-dioicacid-3β-D-glucophyranoside) from the ethanolic extract of TA 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.[30,58]

Table 1
Phytochemical constituents of various parts of *Terminalia arjuna (Roxb.) Wight and Arn.*

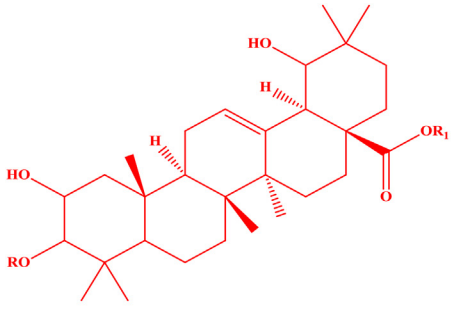
Part used	Major chemical constituents	References
Stem bark	**Triterpenoids**	
	Arjunin	Row et al[24]
	Arjunic acid	
	Arjungenin	Honda et al[25]
		Singh et al[26,27]
	Terminic acid	Anjaneyulu and Prasad[28]
	Terminoltin	Singh et al[29]
	Arjunolic acid	Singh et al[26,27]
	Ursane triterpenoids	
	2α,3β-dihydroyurs-12,18-oic acid 28-O-β-D-glucopyranosyl ester	Wang et al[30]
	2α,3β,23-trihydroxyurs-12,18-dien-28-oic acid 28-O-β-glucopyranosyl ester	
	Qudranoside VIII	
	Kajiichigoside F1	
	2α,3β,23-trihydroxyurs-23-trihydroxyurs-12,19-dien-28-oic acid 28-O-β-D-glucopyranosyl ester	
	Glycosides	
	Arjunetin	Row et al[24,31]
		Singh et al[26,27]
	Arjunoside I, II	Honda et al[25,32]
	Arjunolone	Sharma et al[33]
	Arjunolitin	Tripathi et al[34]
	Arjunaphthanoloside	Ali et al[35,36]
	Arjunglucoside IV and V, Arjunasides A-E	Wang et al[34,37]
	Olean-3β, 22β-diol-12-en-28 β-D-glucopyranosie-oic acid	Patnaik et al[38]
	Terminarjunoside I and II	Alam et al[39]
	Terminoside A	Ahmad et al[40]
	Termionic acid	
	Flavonoids and phenolics	
	Arjunone	Sharma et al[33]
	Luteolin	Pettit et al[41]
	Baicalein	Anonymous[42]
	Ethyl gallate	
	Gallic acid	
	Kempferol	
	Oligomeric proanthocyanidins	
	Pelargonidin	
	Quercetin	
	(+)-catechin, (+)-gallocatechin and (−)-epigallocatechin	Saha and Pawar[43]
	Gallic acid, ellagic acid and its derivatives such as 3-O-methyl-ellagic acid 4-O-β-D-xylopyranoside, 3-O-methyl ellagic acid 3-O-rhamnoside	
	3-O-methyl ellagic acid 4′-O-α-L-rhamnophranoside	Wang et al[30]
	(−)-epicatechin	
	Tannins	
	Pyrocatechols	Takahashi et al[44]
	Punicallin	Lin et al[45]
	Castalagin	Kuo et al[46]
	Casuariin	
	Casuarinin	
	Punicalagin	
	Terchebulin	
	Terflavin C	
	Minerals and trace elements	
	Calcium, magnesium, aluminum, zinc, copper, silica	Dwivedi and Udupa[47]
	Other compounds	
	β-Sitosterol	Anjaneyulu and Prasad[28]
Roots	**Triterpenoids**	
	Arjunoside I-IV	Anjaneyulu and Prasad[48,49]
	Arjunolic acid	Anjaneyulu and Prasad[28]
	Oleanolic acid	
	Terminic acid	
	2α,19α-Dihydroxy-3Oxo-Olean-12-En28-Olic acid 28-O-β-D-glucopyranoside	Choubey and Srivastava[50]
	Arjunic acid	Singh et al[26,27]
	Glycosides	
	Arjunetosie (3-O-β-D-glucopyranosyl-2α, 3β, 19α-trihydroxyolean-12-en-28-oic acid 28-O-β-D-glucopyranoside)	Upadhyay et al[51]
Fruits	**Triterpenoids and flavonoids**	
	Arjunic acid, Arjunone, Arachidic stearate, Cerasidin, Ellagic acid, Fridelin, Gallic acid, Hentriacontane, Methyl oleaolate, Myristyl oleate, β-Sitisterol	Rastogi and Mehrotra[52]
Leaves and seeds	**Flavonoids and glycosides**	
	Luteolin, 14,16-dianhydrogitoxigenin 3-β-D-xylopyranosyl-(1 > 2)-O-β-D-galactopyranoside	Pettit et al[41]
		Yadava and Rathore[53]

Table 2
Preliminary tests for phytochemical analysis of the *Terminalia arjuna (Roxb.) Wight and Arn.* extract.

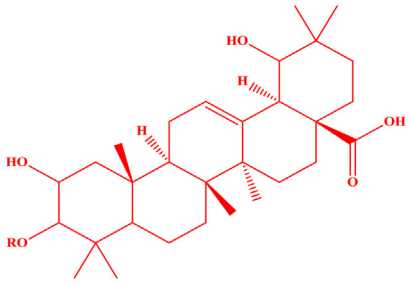
Phytoconstituents	Test
Alkaloides	Dragendroff's test
Carbohydrates	Molisch's test
Flavonoids	Lead acetate test
Glycosides	Keller–Killiant test
Lactones	Legal's test
Phenolic compounds and tannins	5% $FeCl_3$ test
Proteins	Ninhydrin test
Phytosterols	Salkowski's test
Saponins	Foam test
Triterpenoids	Liebermann–Burchard's test

4.2. Flavonoids and phenolics

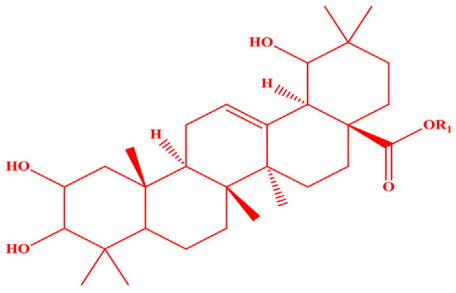
Bark of *T. arjuna* contains a very high level of flavonoids, namely arjunolone, flavones, luteolin, baicaleiin, quercetin, kempferol, and pelargonidin evaluated with other medicinal plants particularly having favorable effects on cardiovascular diseases. The compound luteolin has been isolated from the butanolic fraction of *T. arjuna* and it has been found to be antimutagenic and antibacterial activity. It inhibited gram negative pathogen growth with a minimum inhibitory concentration of 12.5 μg/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 LC-MS. 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-β-D-xylopyranoside and 3-O-methyl ellagic acid 3-O-rhamnoside



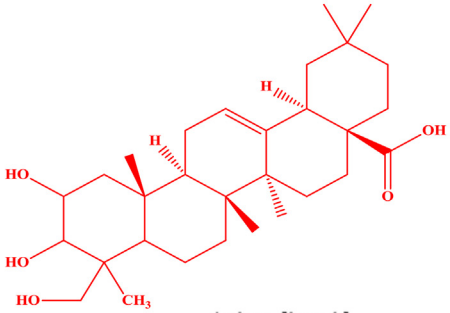
1. R = Galactose; R_1 = H; Arjunoside I
2. R = β-D-(+)-glocosyl-L-(-)-2-deoxyrhamanose, R_1 = H; Arjunoside II
3. R = H, R_1 = Gluconic acid; Arjunoside III
4. R = α-L-rhamnopyranose, R_1 = H; Arjunoside IV



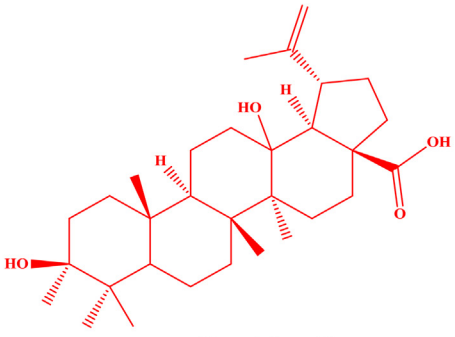
1. R = H; Arjunic acid
2. R = β-D-(+)-galactose, Arjunoside I
3. R = β-D-(+)-glocosyl-L-(-)-2-deoxyrhamanose, Arjunoside II
4. R = α-L-rhamnopyranose, Arjunoside IV



R1 = Glucose; Arjunetin

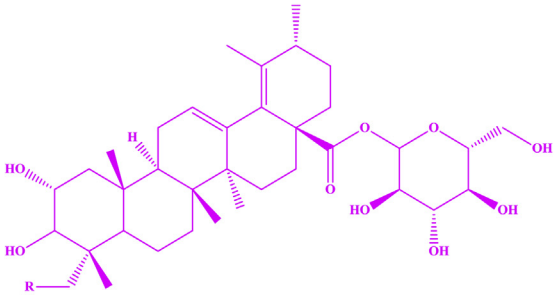


Arjunolic acid

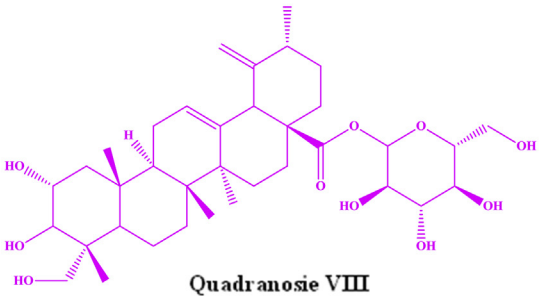


Terminic acid

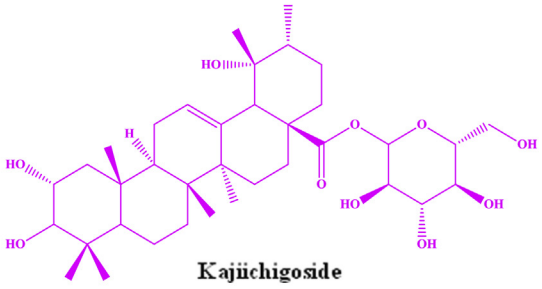
Fig. 1. Structure of important terpenoids and glycosides isolated from *Terminalia arjuna.*



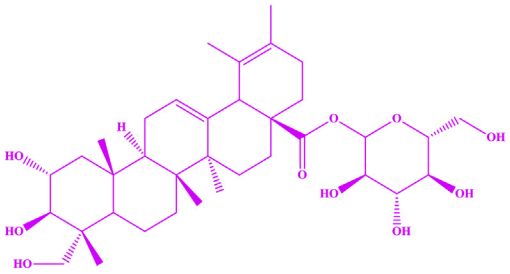
R = H; 2α, 3β-dihydroyurs-12,18-dien-28-oic acid 28-O-β-D-glucopyranosyl ester
R = OH; 2α, 3β, 23-trihydroxyurs-12,18-dien-28-oic acid 28-O-β-D-glucopyranosyl ester



Quadranosie VIII



Kajiichigoside



2α, 3β, 23-trihydroxyurs-12, 19-dien-28-oic acid 28-O-β-D-glucopyranosyl ester

Fig. 2. Structure of ursane triterpenoids isolated from *Terminalia arjuna*.

(Fig. 3). Various studies support the fact that bioflavonoids inhibit LDL oxidation, endothelial activation and platelet aggregation.[59–62] 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.[63] 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 TA is beneficial effects in CAD.

4.3. 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*.[45] Tannins are considered to have wound healing, astringent, hypotensive, antioxidant and antimicrobial effects.[64,65]

4.4. 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).[47] It contains some amino acids such as tryptophan, tyrosine, histidine and cysteine.[26,27,57]

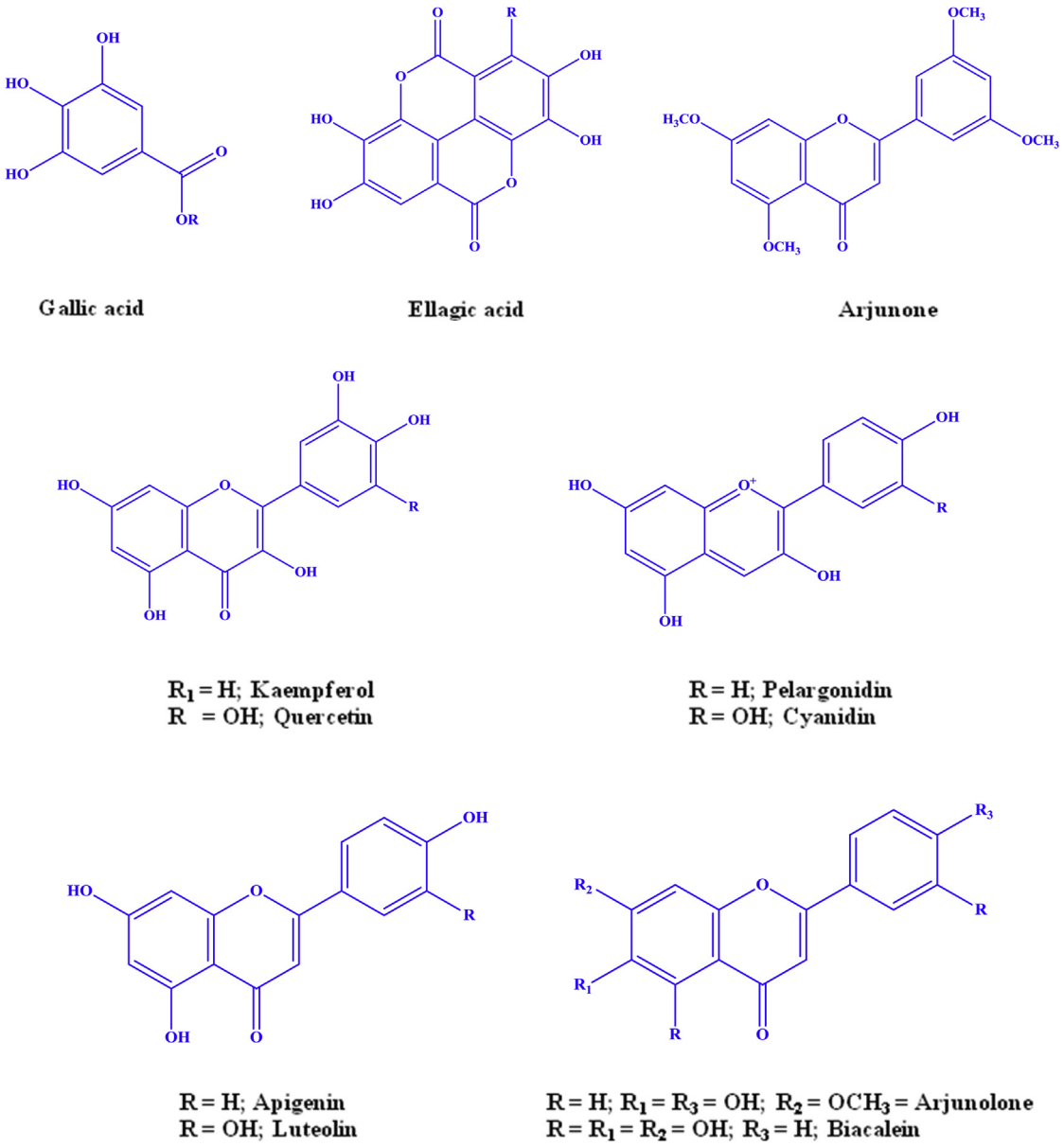


Fig. 3. Structure of important flavonoids isolated from *Terminalia arjuna*.

5. Pharmacological and clinical studies

T. arjuna is a tree having an widespread medicinal potential in most of the diseases particularly cardiovascular disorders. Scientific investigations of *T. arjuna* extensively reported and discussed through various preclinical and clinical studies (Tables 3 and 4).

5.1. 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

Table 3
Pharmacological studies on *Terminalia arjuna (Roxb.) Wight and Arn.*

Pharmacological activity	Model used and study design	Type of extract	Observations	References
Antioxidant, antiinflammatory, and immunomodulatory	CYP3A4, CYP2D6 and CYP2C9 enzymes in human liver microsomes	Alcoholic and aqueous extract of *T. arjuna* at 35 μg/ml dose level	Alcoholic and aqueous extracts of *T. arjuna* showed significant inhibition activity of CYP3A4, CYP2D6 and CYP2C9 enzyme. Enzyme kinetic studies suggested that the extracts of *T. arjuna* showed rapidly reversible non-competitive inhibition of all three enzymes in human liver microsomes.	Varghese et al[66]
Antioxidant	Human polymorphonuclear (PMN) cells and hypochlorous acid from human neutrophils	Methanolic extract of *T. arjuna*	Arjungenin is the most active compound than others and had moderate inhibitory effect on the process of respiratory oxyburst and its IC_{50} value is shown 60 μg/ml.	Pawar and Bhutani[67]
Antioxidant	Male Wistar albino rats (110 −140 g) − (6−7 weeks old)	*T. arjuna* was administrated orally to Wistar rat at different doses (0.42 mg/kg to 6.8 mg/kg) for 6 days/week for 4 weeks	Chromic administration of butanolic fraction of alcoholic extract of *T. arjuna* bark has cardioprotective potential against Dox-induced cardiotoxicity.	Singh et al[68]
Antioxidant and antimutagenic activity	Wistar rats (200−250 g) and Swiss albino mice (18−22 g)	Aqueous and ethanolic extraction of *T. arjuna*	The alcoholic extract of *T. arjuna* (ALTA) has shown potent antioxidant activity with EC_{50} of 2.491 ± 0.160, 50.110 ± 0.150 and 71.000 ± 0.025 in DPPH assay, superoxide radical scavenging activity and lipid peroxidation assay, respectively. In micronucleus test, EC_{50} of 2.410 ± 0.140, 40.500 ± 0.390 and 63.000 ± 0.360 in percentage of micronucleus in ALTA (100 and 200 mg/kg p.o) showed significant reduction in both polychromatic erythrocytes and normochromatic erythrocytes and also shown significant reduction in P/N ratio.	Viswanatha et al[69]
Anticarcinogenic and antimutagenic potential	*In vitro* and *in vivo* method	Aqueous extracts from 75 μg/ml to 200 μg/ml for lymphocyte culture for *in vitro* experiments Aqueous extracts from 50 mg/kg to 350 mg/kg body weight for *in vivo* experiments	Used human lymphocyte culture and bone marrow cells of albino mice (8−10 weeks old and weight ranges between 25-35 g) The number of sister chromatid exchanges got reduced from a higher level of 15.0 ± 1.4 per cell to 7.7 ± 0.5 per cell with S_9 mix at 48 h of treatment. The replication index was enhanced from 1.33 to 1.55 *in vitro*. In the *in vivo* experiments, effective reduction 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.	Ahmad et al[70]
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	TAAE and TAWE inhibited the lipid peroxidation and attenuated H_2O_2 mediated ROS generation in THP-1 cells by promoting catalase, glutathione peroxidase activities and by sustaining cellular reducing power. Marked effects of *T. arjuna* steam bark on cultured human monocytic and aortic endothelial cells provide the biochemical and molecular basis for therapeutic potential of *T. arjuna* steam bark against cardiovascular diseases (CVD).	Kokkiripati et al[56]
Antioxidant	Male albino Wistar rats (120 −150 g body weight) were subjected to oxidative stress associated with *in vitro* ischemic reperfusion injury (IRI)	Two doses (500 and 750 mg/kg in 2% carboxy methyl cellulose (CMC)), 6 days per week for 12 weeks	*T. arjuna* augments endogenous antioxidant compounds of rat heart and also prevents oxidative stress associated with IRI of the heart.	Gauthaman et al[71]

(*continued on next page*)

Table 3 (*continued*)

Pharmacological activity	Model used and study design	Type of extract	Observations	References
Antioxidant	Human neutrophils isolated from fresh, heparinized human blood by using Histoprep and suspended in HBSS medium containing gelatin.	Ethanolic extraction of *T. arjuna* containing arjunic acid, arjungenin, arjunetin and arjunglucoside II	Arjungenin and its glucoside extracted from *T. arjuna* and are exhibited a significant free radical scavenging activity on the superoxide release from PMN cells. Arjungenin exhibited great inhibitor action on the hypochlorous acid productin from human neutrophils.	Pawar and Bhutani[67]
Antioxidant	Male Wistar albino rats, weighing between 250 and 300 g; treated with STZ at a dose of 65 mg/kg	Therapeutic treatment through 50% ethanolic extract of *T. arjuna* at a dose of 500 mg/kg and rosuvastatin (20 mg/kg) for 30 days orally after 8 weeks of STZ treatment	*T. arjuna* bark extract improved cardiovascular autonomic neuropathy in rats having uncontrolled diabetes through maintaining endogenous antioxidant enzyme activities and decreasing cytokine levels.	Khaliq et al[72]
Antioxidant	Male Swiss albino mice treated with NaF at a dose of 600 mg/L for 1 week.	Ethanolic extract of *T. arjuna* at a dose of 50 mg/kg of body weight and with vitamin C at a dose of 100 mg/kg body weight for 1 week	Ethanolic extract of *T. arjuna* protects murine hearts from NaF-induced oxidative stress via its antioxidant properties.	Sinha et al[73]
Antioxidant	Wistar rats weight between 200-240 g.	Ethanolic extract of *T. arjuna* at a dose of 500 mg/kg for 15 days was administrated orally	Prophylactic and therapeutic treatment with *T. arjuna* improved cardiac functions and baroreflex sensitivity. It is attenuated hypertrophy and fibrosis of the LV. *T. arjuna* significantly reduced oxidative stress and inflammatory cytokine level in CHF rats	Parveen et al[74]
Antioxidant	Poloxamer (PX)-407 induced hyperlipidemic albino Wistar rats	Three fractions diethyl ether, ethyl acetate and ethanol of *T. arjuna* exerted hypolipidemic and antioxidative effects at two different doses levels (175 and 350 mg/kg body weight)	Hypolipidemic and antioxidant effects of *T. arjuna* fractions were noticed as ethanol > diethyl ether > ethyl acetate. Ethanolic fraction of *T. arjuna* possesses the potent properties of antioxidant and hypolipidemic than other fractions and has therapeutic potential for the prevention of coronary arterial disease.	Subramaniam et al[75]
Antioxidant	Male Wistar rats treated with isoprenaline to produce LVH	Aqueous extract of *T. arjuna* bark was evaluated at 63, 125 and 250 mg/kg given orally for antifibrotic and antioxidant effects in male Wistar rats given selective β-adrenoceptor agonist isoprenaline (5 mg/kg) for 28 days Captopril has given orally 50 mg/kg per day, an inhibitor of angiotensin-converting enzyme used as a standard cardioprotective drug	Aqueous extract of *T. arjuna* significantly prevented isoprenaline-induced increase in oxidative stress and decline in endogenous antioxidant level and also prevented fibrosis.	Kumar et al[76]
Antioxidant and antimicrobial activity	DPPH methods and Agar well diffusion method	Methanol extracts	Methanolic extracts has great free radical scavenging properties. It contains liberal amount of flavonoid compounds. It is exhibited good antimicrobial activity against two gram negative bacteria (*E. coli* and K pneumonia).	Mandal et al[77]
Antimicrobial activity	Five bacteria namely *Staphylococcus aureus* (Gram Positive) *Acinetobacter* sp., *Proteus mirabilis*, *Escherichia coli* and *Pseudomonas aeruginosa* (Gram negative) were used	Methanol, ethanol, acetone aqueous extracts from the leaves and bark of *T. arjuna*	Acetone leaf extract was found to be best against *S. aureus*.Organic 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[78]
Antimicrobial activity	NZW albino rabbits subjected to 15 min coronary artery ligation followed by 60 min of reperfusion injury	Pretreatment of bark powder of 500–750 mg/kg/day for 12 weeks before ischemic-reperfusion injury	Chronic oral administration of the bark of *T. arjuna* in rabbit causes augmentation of myocardial endogenous antioxidants along with induction of HSP 72. It is offered further protection against oxidative stress associated with myocardial ischemic reperfusion injury.	Gauthaman et al[79]
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	Aqueous extract of *T. arjuna* induced cardiotonic action via enhancing sarcoplasmic reticular function, an unique action minimizing the occurrence of arrhythmias, makes aqueous extract of *T. arjuna* a promising and relatively safe cardiotonic beneficial to the health heart and the treatment for chronic heart diseases.	Oberoi et al[80]

DNA damage protecting and free radical scavenging	DNA stand breakage assay and comet assay analysis by using of pBR 322 plasmid and rat adrenal PC-12 cells	Ethanolic extracts and its fractions of *T. arjuna* bark protected H_2O_2, induced DNA damage. Maximum inhibition of DPPH, hydroxyl, ABTS, nitric oxide radicals and metal chelation was observed in ethyl acetate fraction. *T. arjuna* extracts ameliorate various impairments associated with DNA damage and free radical formation.	Phani Kumar et al[16]
Gastro-productive effect	Diclofenac sodium (DIC) induced gastric ulcer in experimental rats (male albino rats of Wistar – (150–200 g weight)	Methanolic extract of *T. arjuna*	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 in pH, NP-SH, GSH, enzymatic 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.	Devi et al[81]

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

Table 4
Clinical studies on *Terminalia arjuna (Roxb.) Wight and Arn.*

Highlights of the study	Clinical conditions	Drug formulation and dosage	Clinical outcome	References
Idiopathic and ischemic cause	93 patients with dilated cardiomyopathy (DCMP) of idiopathic and ischemic cause	*T. arjuna* capsules (500 mg at 8 hourly)	Patients with dilated cardiomyopathy with or without heart failure and reduced left ventricular ejection fraction due to either idiopathic or ischemic cause receiving combined standard therapy, and herbal medication showed significant improvement in systolic and diastolic functions as well as functional capacity in comparison to those receiving only standard therapy or only herbal medications	Bhawani et al[82]
Heart failure	12 patients with refractory chronic congestive heart failure	Aqueous extract from bark of *T. arjuna* was controlled 8 h at a dose of 500 mg	Adjuvant *T. arjuna* therapy in selected patients with refractory congestive heart failure, mostly related to idiopathic dilated cardiomyopathy, appeared safe and caused long lasting improvement in symptoms and signs of heart failure along with improvement in left ventricular ejection phase indices with definite improvement in quality of life	Bharani et al[83]
Anti-ischemic effects	40 patients with acute myocardial infarction with ischemic mitral regurgitation	Double-blind study with 500 mg thrice daily for 3 months along with conventional therapy	Reduction in mitral regurgitation jet area Improvement in E/A ratio	Dwivedi et al[84]
Anti-ischemic effects	58 males with chronic stable angina (NYHA class II–III) with evidence of provocable ischemia	*T. arjuna* (500 mg 8 h), isosorbide mononitrate (40 mg/daily) or a matching placebo for one week each, separated by a wash-out period of three days in a randomized, doubled blind crossover design	Significant decrease in the frequency of angina and need for isosorbide dinitrate Significant improvement in the treadmill exercise. The total duration of exercise increased	Bharani et al[85]
Hypertension	36 hypertensive patients (stage III) with increased LV mass	Ayurvedic formulation of *T. arjuna*, known as 'Arjuna Kwath' (25 ml twice a day)	A significant decrease in both SBP and DBP ($P < 0.001$) in both the groups LV mass index was only significantly reduced in the atenolol-plus-'Arjuna Kwatha' group as compared to atenolol	Rao et al[86]
Antioxidant, lowering effects of lipid and lipoprotein	100 patients with stable CAD	In a placebo-controlled double-blind study, 500 mg of *T. arjuna* along twice a day in addition to receive the conventional treatment	A significant decrease in hyperlipidemia 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	Kapoor et al[19]
Antioxidant activity	30 patients with coronary artery disease	500 mg bark powder of *T. arjuna* combined with conventional drugs	16% reduction in LDL cholesterol 15% decrease in cholesterol 11% decrease in triglycerides Marginal decrease in nitrite levels	Khalil[87]
Antioxidant activity	105 patients with stable coronary heart disease (CHD)	*T. arjuna* bark powder at a dose of 500 mg once daily for 30 days was compared with a known antioxidant, vitamin E (400 units once daily)	Significant reduction in lipids (total cholesterol, LDL-cholesterol) Lowering of lipid peroxide in *T. arjuna* group	Gupta et al[88]
Effect on endothelial dysfunction	Asymptomatic 18 health chronic smokers and 18 non-smokers	Double-blind, placebo-controlled, crossover design. 500 mg aqueous extract of *T. arjuna* bark powder administrated thrice daily	Improvement in brachial artery flow mediated dilation	Bharani et al[89]

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.

5.2. Clinical studies

Recently, Kapoor et al[19] 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-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]

Bharani et al[83] 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[84] 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[85] 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 one week 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, 500 mg 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[86] 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' (25 ml 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[87] reported that the administration of *T. arjuna* bark powder along with statins for 3 months to 30 patients with 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[88] 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 ($-9.7 \pm 12.7\%$), and LDL cholesterol ($-15.8 \pm 25.6\%$) (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 ($-36.4 \pm 17.7\%$) as compared to the *T. arjuna* group ($-29.3 \pm 18.9\%$). *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[89] 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.

6. Toxicity and side effects

T. arjuna has been used in the dose between 1 to 2 g 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.[83] Recently Bhawani et al[82] 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). Hematological 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[90] reported that pretreatment 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.[91] Parmar et al[92] 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*.

7. 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.

Conflict of interest statement

We declare that we have no conflict of interest.

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