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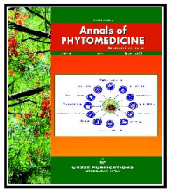

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A review on *Terminalia arjuna* (Roxb.) Wight & Arn.: The wonder medicinal plant with prodigious potential in therapeutics

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Abstract

Terminalia arjuna (Roxb.) Wight & Arn., a medicinal plant belonging to the family *Combretaceae* is known to display rich phytochemical profile. TA harbors several bioactive molecules such as glycosides, flavonoids, tannins, triterpenoids, phenolics and minerals. This review is an attempt to cover various clinical and experimental studies that reveals the clinical relevance of this plant. Most of the studies have indicated that TA possesses various medicinal properties like cardioprotective, hepatoprotective, antitumor, antibacterial, antioxidant, gastric, molluscicidal, anthelmintic, antidiabetic, antiviral and anti-inflammatory. This plant is also reported to enhance wound healing and bone mineralization process. This review presents no potential toxicity imposed by this plant extract but reflects the requirement of more extensive studies to be conducted in order to understand the long-term effect along with its molecular mechanism. This comprehensive review also provides information on various food products made using TA plant extract.

1. Introduction

From ancient times till today, medicinal plants have been a source of major components for traditional sources of medicine to cure human diseases owing to the concept of green medicine which serves as a healthier option when compared to the synthetic medicinal therapies. WHO also supports this fact that about 80% of the world population is dependent on traditional medicine and in India, 60% of the people in rural areas use herbal medicine (Heinrich, 2000). This plant based traditional system of medicine is a part of Indian culture and heritage which is dependent on Ayurveda, Siddha and Unani. This traditional medicine system encompasses practices and skills based on presumptions, knowledge, experience, belief of communities to cure various health problems (Ghosh, 2003). Use of herbal supplements in human consumption to promote health and nutritional status has seen an upsurge from 2.5% to 12% in the last few years owing to the increasing awareness about the importance of medicinal plants (Stickel and Schuppan, 2007). Use of herbal drugs made from bark, seeds, root, leaves, flowers and berries of medicinal plants seeks high demand from consumers as it offers plenty of advantages such as easy access, abundant availability, cost-effectiveness, highly efficient and possesses rare side effects. The medicinal use of plants is often attributed to the presence of secondary metabolite or bioactive compounds such as glycosides, alkaloids, tannins, steroids, flavonoids, phenols, volatile oil that is naturally accumulated in them and imparts definite physiological actions on human body when consumed. The evaluation of new drugs that incorporates utilization of phytochemicals has altogether opened new doors for extensive research and further assists in smoother transition from traditional medicine to modern medicine in India (Amalraj and Gopi, 2016).

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2. *Terminalia arjuna* (Roxb.) Wight & Arn.

Terminalia arjuna (Roxb.) Wight & Arn., is an ayurvedic plant which holds important medicinal value. It is commonly known as Arjuna, Dhavala, Kaubha, Nadisaraja Partha, Indradru and Veeravriksha belonging to the family Combretaceae. Almost 24 species of *Terminalia* have been reported in various part of India, of which few are *T. arjuna, T. bellirica, T. catappa, T. bialata, T. mantaly, T. elliptica, T. porphyrocarpa, etc.* It is a large evergreen deciduous tree that is found at several places in India and grows to a height of 60-80 feets. It commonly grows on banks of streams and rivers and is found to be distributed throughout the greater part of Indian sub-continent, Himalayan face of Uttar Pradesh, West Bengal, Deccan, Bihar, Madhya Pradesh, Orissa, Punjab and Konkan (Asif Ali *et al*., 2003; Kapoor *et al*., 2014; Sharma *et al*., 2000). It is also known by various vernacular names like Arjun (Hindi), Tella Maddi (Telugu), Marudhu (Malayalam and Tamil), Arjhan (Bengali), Sadado (Gujarati), Sadaru (Marathi), Neer matti (Kannada) and some traditional formulation is given in name of Arjunaghrita and Arjunarishta (Amalraj and Gopi, 2016). This tree displays spreading crowns, drooping branches and new leaves during the hot season (February to April). TA is grown through ripe seeds, pollarding, stumps, coppicing and air layering. Initial phase of its growth is

noticed to be slow but later faster growth rate is attained and this tree grows 2-3 meters in three years (Asif Ali *et al*., 2003).

3. Structure characteristics

Leaves of TA grow to about 15-25 cm in length and 6-7.5 cm in width. They are simple, alternate thick-coriaceous, base obtuse-subcordate. Margin of the leaves are crenate-serrate, apex is subacute or obtuse, pale brown beneath and pale green above. Petiole is 0.6-0.9 cm long and leaves exhibit oil glands at the abaxial surface of the leaf near petiole. The stem bark is smooth, simple, pinkish gray externally whereas the inner surface is soft, longitudinally striated and red in color. Barks have pieces that are curved, flat and rectangular in shape (Gupta *et al*., 2018). Flower of TA is white or yellowish and is found in groups with short auxiliary spikes or terminal panicle arrangement. Flowering phase of this plant occurs in summer and fruit appears in winter or spring season. Fruits of this plant are 1-1.5 inch in diameter with 5-7 longitudinal lobes. Fruits are glabrous with 5-7 wings, fibrous and woody. These fruits are drupe and are found to be notched near the top along with oblique upward curving striations (Ali, 2019).

4. Phytochemical constituent

TA harbors many phytochemicals in root bark, stem bark, leaves, fruits and seeds. Root exhibits presence of triterpenoids and glycosides whereas fruit contains triterpenoids and flavonoids. Seeds and leaves are known to contain flavonoid and glycosides. Amongst all the plant parts, bark of *T. arjuna* is considered most crucial constituent from medicinal point of view due to presence of flavonoids, tannins, glycosides, polyphenols, saponins, triterpenoids, sterols and minerals such as zinc, calcium, magnesium, copper, amino acids (Chaudhari and Mahajan, 2015; Chaudhari and Mengi, 2006).

TA bark contains a large amount of triterpenoids like arjunin, arjunic acid, arjunolic acid, arjungenin and terminic acid. Glycosides like triterpane, arjunetin, arjunoside I, arjunoside II, arjunaphthanoloside, terminoside A, termiarjunoside 1, termiarjunoside 2 and Sitosterol are also reported in stem bark. Arjunglucoside IV and V, arjunasides A-E were also found in ethanolic extract of the stem bark of *T. arjuna* (Deshpande *et al*., 2003; Khaliq and Fahim, 2017) (Table 1). TA bark is known to contain a very high level of flavonoids in comparison to other commonly used plants in Ayurveda. Types of flavonoids found in the bark of the plant are arjunone, luteolin, quercetin, flavones, gallic acid, ethyl gallate, baicalein, proanthocyanidins, catechin, gallocatechin, pelargonidin and kaempferol (Table 1). Flavonoids are popular phytochemicals owing to their antimutagenic and antibacterial properties. The aqueous extract from TA was revealed to harbor 70% polyphenols with molecular weight greater than 3.5 kDa (Dwivedi, 2007; Khaliq and Fahim, 2017). The antibacterial property of this plant is mainly attributed to the presence of such bioactive compounds which serves as strong antioxidant and antiproliferative agents. Various constituents of tannins that are found in the bark of TA are pyrocatechol, castalagin, punicallin, punicalagin and terflavin (Khaliq and Fahim, 2017) (Table 1). Tannins have been speculated to possess hypotensive, astringent, antioxidant, wound- healing, and antimicrobial effects (Dwivedi and Agarwal, 1994).

Table 1: Bioactive compounds of *T. arjuna* bark extract

Chemical type	Major chemical constituents	Molecular formula	Molecular weight	Reference
Triterpenoids	Arjunin	$C_{41}H_{26}O_{26}$	934.6 g/mol	Row *et al*., 1970
	Arjunic acid	$C_{30}H_{48}O_5$	488.7 g/mol	Row *et al*., 1970
	Arjungenin	$C_{30}H_{48}O_6$	504.7 g/mol	Honda *et al*., 1976
	Terminic acid	$C_{30}H_{48}O_4$	472.7 g/mol	Anjaneyulu and Prasad, 1983
	Arjunolic acid	$C_{30}H_{48}O_5$	488.7 g/mol	Singh *et al*., 2002
Glycosides	Arjunetin	$C_{36}H_{58}O_{10}$	650.8 g/mol	Row *et al*.,1970
	Arjunolone	$C_{16}H_{12}O_5$	284.2 g/mol	Sharma *et al*., 1982
	Arjunglucoside I	$C_{36}H_{58}O_{11}$	666.8 g/mol	Wang *et al*., 2010
Flavonoids and phenolics	Arjunone	$C_{19}H_{20}O_6$	344.4 g/mol	Sharma *et al*., 198
	Luteolin	$C_{15}H_{10}O_6$	286.24 g/mol	Pettit *et al*., 1996
	Baicalein	$C_{15}H_{10}O_5$	270.24 g/mol	Gaikwad and Jadhav, 2018
	Ethyl gallate	$C_9H_{10}O_5$	198.17 g/mol	Gaikwad and Jadhav, 2018
	Gallic acid	$C_7H_6O_5$	170.12 g/mol	Gaikwad and Jadhav, 2018
	Kaempferol	$C_{15}H_{10}O_6$	286.24 g/mol	Gaikwad and Jadhav, 2018
	Proanthocyanidin	$C_{31}H_{28}O_{12}$	592.5 g/mol	Gaikwad and Jadhav, 2018
	Pelargonidin	$C_{15}H_{11}O_5^+$	271.24 g/mol	Gaikwad and Jadhav, 2018
	Quercetin	$C_{15}H_{10}O_7$	302.23 g/mol	Gaikwad and Jadhav, 2018
	(+) catechin, (+) gallocatechin	$C_{15}H_{14}O_6$ $C_{15}H_{14}O_7$	290.27 g/mol 306.27 g/mol	Saha *et al*., 2012
Tannins	Pyrocatechols	$C_6H_6O_2$	110.11 g/mol	Takahashi *et al*., 1997
	Punicalin	$C_{34}H_{22}O_{22}$	782.5 g/mol	Lin *et al*., 2000
	Castalagin	$C_{41}H_{26}O_{26}$	934.6 g/mol	Kuo *et al*., 2005
	Punicalagin	$C_{48}H_{28}O_{30}$	1084.7 g/mol	Kuo *et al*., 2005
	Terflavin C	$C_{41}H_{26}O_{26}$	934.6 g/mol	Kuo *et al*., 2005

Table 2: Pharmacological studies on *T. arjuna* plant extract

Role of TA	Extract	Model	Research findings	References
Cardioprotection and antioxidant	Methanolic extract of bark	Rats (*in vitro* model of myocardial ischemic-reperfusion injury)	TA induced myocardial heat shock protein 72 and augmented endogenous antioxidants, without causing any cellular injury.	Karunakaran, 2015
Cardioprotection	Aqueous extract of the bark	Wistar male rats (isoproterenol-induced cardiac hypertrophy)	TA partially or completely restored the gene regulatory network by ISO treatment in rat heart.	Kumar *et al*., 2019
Cardioprotection and antioxidant	Aqueous extract of the bark	Swiss albino mice	TA protected the liver and kidney tissues against CCl_4 induced oxidative stress probably by increasing antioxidative defense activities.	Manna *et al*., 2006
Cardioprotection and antioxidant	Ethanol and aqueous extract of bark	Adult Wistar rats (isoproterenol induced myocardial infarction)	TA offered biochemical and histo-pathological protection as that of standard drug (Verapamil)	Sivakumar and Shanmugam, 2014
Cardioprotection and antioxidant	50% aqueous ethanol extract	Wistar albino rats (isoproterenol-induced chronic heart failure)	TA offered prophylactic and therapeutic benefits by maintaining endogenous antioxidant enzymeac-tivities, inhibiting lipid peroxidation and cytokine levels.	Parveen *et al*., 2011
Cardioprotection and antioxidant	Ethanol extract of the bark	Male Swiss albino mice (sodium fluoride-induced oxidative stress)	TA balanced the prooxidant-antioxidant status of the heart and enhanced the cardiac intracellular antioxidant activity.	Sinha *et al*., 2008
Cardioprotection and antioxidant	Alcoholic and aqueous	Wistar rats, Human monocytic cells and Human aortic endothelial cells	TA inhibited the lipid peroxidation and HMG-CoA reductase but had no effect on LpL. The extracts attenuated H_2O_2 mediated ROS generation in THP-1 cells by promoting antioxidant enzymes, and by sustaining cellular reducing power. Extracts decreased the levels of typical inflammatory marker proteins, viz. LPS induced TNF-α, VCAM-1 and E-selectin.	Kokkiripati *et al*., 2013
Cardioprotection	Hydroalcoholic extract of bark	Experimental rats	TA significantly reversed the STZ/ISP induced increase in CPK-MB, hs-CRP levels and marked protection against cardiac damage.	Suman *et al*., 2018
Cardioprotection	Ethanolic extract of bark	Chronic coronary artery disease (CAD) patients	Arjuna is safe and effective in patients with chronic coronary artery disease till 4.5 years. Mild symtoms like gastritis and constipation were reported.	Dwivedi *et al*., 2019
Cardioprotection	90% alcoholic extract	*In vitro* isolated perfused rabbit's heart	Cholinergic and adrenergic receptors are not involved in mechanism of TA action.	Jassal *et al*., 2013
Cardioprotection	70% ethanol	Male Swiss albino mice (caffeine induced coronary artery disease)	Amelioration of body weight, heart weight, biochemical parameter and antioxidant enzymes.	Palanivelu, 2015
Cardioprotection and antioxidant	Oral suspension (30mg)	Rats subjected to myocardial ischemia induced by isoproterenol and treated with abana	The reversal of cardiac injury enzyme and improved heart mitochondrial uptake.	Tandon *et al*., 1996
Hypotensive actions	Aqueous and alcoholic bark extract	Dog (*in vivo*)	Dose dependent decrease in blood pressure.	Singh *et al*., 1982
Cardioprotection	Ethanolic extract of bark	Rabbit fed with high fat diet	Reduced hyperlipidemia.	Ram *et al*., 1997

Antitumor	Methanolic extract of bark	MCF-7 cell line	Inhibitory and anti-proliferative action on breast cancer cell line.	Shalini *et al*., 2015
Antitumor	Aqueous bark extract	Human lymphocyte culture and bone marrow cells of albino mice	Reduced metaphase aberration, sister chromatid exchanges and frequencies in aberrant cells when compared to mutagen treated positive control.	Ahmad *et al*., 2014
Antitumor	Isolated arjunic acid from bark	Human oral, ovarian, and liver cancer cell lines	Inhibitory and anti-proliferative action on cell lines.	Saxena *et al*., 2007
Antitumor	Bark extract	Cultured human peripheral blood lymphocytes	Protects DNA against ADR-induced damage.	Reddy *et al*., 2008
Antimicrobial	Methanol, ethanol, acetone and aqueous extracts from theleaves and bark	*Staphylococcus aureus Acinetobacter* sp., *Proteusmirabilis, Escherichia coli* and *Pseudomonas aeruginosa*	Acetone leaf extract was found to be best against *S. aureus*. Organic extract showed almost equal inhibition of all Gram-negative bacteria except *P. aeruginosa*.Aqueous extract of TA bark exhibited good activity against S. aureus.	Aneja *et al*., 2012
Antimicrobial	Ethanolic extract and its different solvent fractions (chloroform, ethyl acetate, n-butanol and aqueous fraction) of bark and leaves	*Bacillus subtilis, Staphylococcus aureus, Eschericia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and Salmonella typhi*	The n-butanol fraction of bark showed more antioxidant potential as compared to other solvents.	Kumar *et al*., 2018
Antimicrobial	Aqueous	*Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Tanerella forsythus*	Significant antimicrobial efficacy on single and mixed cultures.	Karmakar *et al*., 2020
Antimicrobial	Methanol and aqueous extract of bark	Multidrug resistant *Salmonella typhi*	Strong antibacterial activity.	Rani and Khullar, 2004
Antimicrobial	Dichloromethane and methanol extract	*Staphylococusaureus, Pseudomonas aeruginosa, Microspormcanis, Aspergillusflavus, Fusariumsolani*	Inhibitory action.	Javed *et al*., 2016
Hepatoprotection and antioxidant	Aqueous extract of bark	Wistar albino rats (Paracetamol/ CCl_4 induced liver damage)	Amelioration of liver marker enzymes and histopatological changes.	Vishwakarma *et al*., 2013
Hepatoprotection and antioxidant	Aqueous extract of bark	Mice model(CCl_4 challenged)	Modulated levels of antioxidant enzymes and mitigated the CCl_4 induced changes as comparable to vitamin C.	Manna et al., 2006
Hepatoprotection and antioxidant	70% ethanol of bark	Experimental mice (CCl_4 challenged)	Oral treatment of the active constituents of TA at a dose of 50mg/kg body weight for 7 days prior to CCl_4 administration significantly restored the activities of all antioxidant enzymes.	Manna et al., 2007
Hepatoprotection and antioxidant	Aqueous bark powder extract	Rats (alcohol induced hepato and nephrotoxicity)	Reduced lipid peroxidation and restored levels of enzymatic and non-enzymatic antioxidants.	Hebbani *et al*., 2015
Hepatoprotection and antioxidant	Ethyl acetate extract of the heartwood	HepG2 cells	Significantly ameliorated levels of antioxidant enzymes, normalised the PPARγ expression, reduced steatosis and MNC infiltration.	Toppo *et al*., 2018
Hepatoprotection	Aqueous extract	Wistar albino male rats	The biochemical,antioxidant, histopathological, CYP2E1 enzyme, PI3K, AKT protein expression analysis were shown increased	Kannappan *et al*., 2020

			antioxidant level, increased PI3K/AKT level, decreased liver function marker level and decreased CYP2E1 level in animals treated with TA.	
Anti-inflammatory	Arjuna Ksheera paka and hydroalcoholic extract	Carrageenan-induced hind paw biphasic edema in C57BL/6 mice	Both the extracts, showed significant anti-inflammatory activity in reducing paw edema in mice.	Dube *et al*., 2017
Anti-inflammatory	Aqueous extract of bark	*Sprague dawely* rats	400mg/kg dose of TA aqueous extract of bark decreased the size of paw edema in carrageenan induced edema in rats.	Rana *et al*., 2016
Wound healing	Bark powder mixed with coconut oil	65 years old male patient of non-healing multiple ulcers	TA healed large, non healing, tender, recurrent ulcers with secondary infection.	Dudhamal, 2016
Wound healing	Herbal formulations (Himax ointment and lotion)	Rats (wound model)	Improved wound contracting ability, epithelization period, tensile strength and regeneration of tissues at the wound area. The results were found comparable to standard drug nitrofurazone.	Mukherjee *et al*., 2003
Wound healing and antimicrobial	Hydroalcohol extract of the bark	Rats (wound model), *Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Streptococcus pyogenes*	Increase in the tensile strength of the incision wounds, increased percent epithelialization of excision wounds and potential antimicrobial activity against microorganisms.	Chaudhari and Mengi, 2006
Gastroproductive effect	Methanolic extract	Diclofenac sodium induced gastric ulcer in male albinorats of Wistar	TA extracts ameliorate various impairments associated with DNA damage and free radical formation. Significant reduction in lesion index was observed in ulcer induced animals.	Devi *et al*., 2007
Molluscicidal	Column purified fractions, arjunolic acid and procynadine	Snail *Lymnaea acuminata*	Inhibited acetylcholinesterase (AChE), acid phosphatase (ACP) and alkaline phosphatase (ALP) activities in the cerebral ganglion of *L. acuminata*.	Soni *et al*., 2017
Molluscicidal	Ethanolic extract	Snail (*Indoplanorbis exustus. I. exustus)*	Time and concentration dependent molluscicidal activity.	Soni and Singh, 2015
Anthelmintic	Stem bark extract using chloroform, ethanol and water	Live earthworms *Pheretima posthuma*	Significant antioxidant and anthelmintic activity.	Bodke *et al*., 2013
Anthelmintic	Methanolic extract of bark	*Haemonchus contortus* ova and larva	Dose-dependent anthelmintic activity both in the *in vitro* and *in vivo* studies.	Bachaya *et al*., 2009
Antidiabetic	Ethanolic extract	Alloxan induced diabetic rats	Reduction inlipid peroxidation, amelioration of antioxidant enzyme activity and oxidative stress.	Raghavan and Kumari, 2006
Antiviral	Casuarinin, isolated from TA	Herpes simplex type 2 (HSV-2) *in vitro*	Casuarinin possessed anti-herpes virus activity in inhibiting viral attachment and penetration, and also disturbing the late event of infection.	Cheng *et al*., 2002
Antiviral	Ethanolic extract	Human hepatoma cell line (HepG2)	Inhibited the proliferation of HepG2 cells in a concentration-dependent manner along with DNA fragmentation, accumulation of p53, cleavage of procaspase-3 protein and depletion of GSH.	(Sivalokanathan *et al*., 2006
Improving endothelial dysfunction	TA capsule (500 mg)	Healthy male smokers	Improvement in flow-mediated dilation from baseline values and significant regression of endothelial abnormality in 2 weeks of treatment.	Bharani *et al*., 2004

Bark also contains 34% ash entirely constituting calcium carbonate. Aqueous extract of TA has previously been reported to show 16% tannins content and 23% calcium salts (Chitlange *et al*., 2009). The major chemical constituent found in the roots on TA are sitosterol, triterpenoids (arjunic acid, arjunolic acid, oleanolic acid, terminic acid) and glycosides (arjunoside I-IV). Leaves and fruits have also been revealed to be rich sources of glycosides and luteolin like flavonoids (Khaliq and Fahim, 2017).

5. Pharmacological significance of *T. arjuna*

Since ancient times TA is known to treat many dreadful diseases. It has been an important constituent of our Ayurveda as well as Allopathy medicinal system due to its wide range of therapeutic properties. It holds immense potential to cure various disease and medical conditions (Table 2).

5.1 Cardioprotective activity

The arjuna plant has been called by name "Guardian of the heart" owing to its property of treating heart diseases since time immemorial. Researchers have demonstrated cardioprotective role of TA extract in isoproterenol induced myocardial infarction, isoproterenol induced cardiac hypertrophy, myocardial ischemic reperfusion injury, hypertension and ischaemic heart disease, *etc*., (Karunakaran, 2015; Kumar *et al*., 2019; Manna *et al*., 2006; Sivakumar and Shanmugam, 2014). The reversal of cardiac injury enzyme and improved heart mitochondrial uptake is also reported in rats, subjected to myocardial ischemia induced by isoproterenol when TA was supplemented in 30 mg oral dose (Tandon *et al*., 1996). Ethanolic extract of TA bark has been reported to exhibit oxidative stress ameliorating activity in murine heart and incase of ISO-induced chronic heart failure by inhibiting process of lipid peroxidation as well as maintenance of endogenous antioxidant enzyme activities (Parveen *et al*., 2011; Sinha *et al*., 2008). Another report indicated the cholesterol level maintenance property of TA owing to its vitamin E like antioxidant properties that strengthens the heart muscles and ensures its functioning adequately. It was also found to be effective in treatment of coronary artery disease (CAD), angina, hypercholesterolemia, heart failure, asthma, diuretic and coronary related risk factors (Sivakumar and Shanmugam, 2014). At molecular levels, TA extract is revealed to be a potent inhibitor of human 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), CYP3A4, CYP2C9 and CYP2D6 and displays non-competitive binding ability to these enzymes in human liver microsomes (Kokkiripati *et al*., 2013; Varghese *et al*., 2015). Various aspects of the effect of TA on cardiovascular function, its molecular mechanism along with histological studies are well established (Khaliq and Fahim, 2017) . Suman *et al*., (2018) have suggested a modulatory role of TA extract in diabetic experimental models co-existing with cardiovascular problems (Suman *et al*., 2018). A recent pharmacovigilant study on 35 chronic CAD patients supplemented with 500 mg of bark extract thrice daily, claimed the long term safety of TA and proposed it as an adjunct drug in CAD (Dwivedi *et al*., 2019). Studies have been conducted to understand the pharmacological effects of 90% alcoholic extracts of TA on heart and coronary blood flow. This study revealed the cardiac depressant activity of the arjuna plant that is routed without involvement of cholinergic and adrenergic receptors (Jassal *et al*., 2013). Researchers have also unfolded the antihyperlipidemic activity of the bark extract in caffeine induced mice thereby suggesting its relevance in caffeine induced coronary heart diseases (Palanivelu, 2015). Cardiac-hemodynamics study on aqueous as well as alcoholic bark extract on isolated frog atria showed reduction in the heart rate whereas increased coronary flow in the isolated rabbit heart (Gaikwad and Jadhav, 2018). Hypotensive action of aqueous and ethanolic extract was also found to cause dose dependent decrease in blood pressure in an *in vivo* study on dogs (Singh *et al*., 1982) Alcoholic extracts of TA powder are also reported to reduce hyperlipidemia and cause no alteration in prothrombin time in rabbit model system (Gaikwad and Jadhav, 2018; Ram *et al*., 1997). Patients with dilated cardiomyopathy with or without heart failure and reduced left ventricular ejection fraction owing to either idiopathic or ischemic, when received 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*., 2013). Aqueous extract of TA induced cardiotonic action in adult ventricular myocytes isolated from hearts of male sprague-dawley rats is reported by enhancing sarcoplasmic reticular function thereby, minimizing the occurrence of arrhythmias, suggesting the promising and safe cardiotonic effect to the heart health and the treatment for chronic heart diseases (Oberoi *et al*., 2011). Overall the prophylactic and therapeutic repercussions of TA extract are well established and understood.

5.2 Antitumor potential

TA has been previously reported to display anti-proliferative effect in human breast cancer cell lines owing to its rich bioactive constituent profile (Shalini *et al*., 2015). The anticancer properties of this plant extract is investigated in detail using *in vivo* and *in vitro* model systems which has revealed its cytotoxic activity (Ahmad *et al*., 2014). It has been reported to be active in carcinoma, lymphoma, human oral, ovarian and liver cancer cell lines unfolding its superior potential to be have as antineoplastic agent (Ramesh *et al*., 2012; Saxena *et al*., 2007). Bark extract of TA is also recognized to protect DNA against ADR induced damage by minimizing the oxidative stress levels along with inhibition of anaerobic metabolism, thereby flaunting its excellent application as herbal medicine against environmental carcinogenicity (Reddy *et al*., 2008). Anti-carcinogenic and antimutagenic potential of TA was also evaluated using human lymphocytes and bone marrow of albino mice as assay systems. The researchers stated that TA causes significant reduction in metaphasic aberrations and sister chromatid exchanges induced by aflatoxin B1 both in the *in vitro* and *in vivo* system. On the other hand, the replication index was enhanced suggesting the dose and time dependent ameliorating potential of *Terminalia* extract (Ahmad *et al*., 2014).

5.3 Antibacterial activity

Extract of TA in various solvent systems have been found to be harboring antibacterial activity against various gram-positive and gram-negative organisms such as *Pseudomonas aeruginosa*, *Eschericia coli*, *Bacillus subtilis*, *salmonella typhi* and *staphylococcus aureus* (Kumar *et al*., 2018). A potent antibacterial activity of methanolic extract of this plant has been reported to be antimicrobial against multidrug resistant, *Salmonella typhi*, *Pseudomonas aeruginosa and Staphylococcus aureus* along with moderate antifungal effect against *Microsporum canis* (Javed *et al*., 2016; Rani and Khullar, 2004). The arjuna leaves and bark extract has

been investigated to harbor excellent antigrowth properties that retards the growth of organisms causing ear infections and, thus are used to formulate herbal ear drops. These herbal ear drops have been found to be more effective when compared to the standard ear drops (Aneja *et al*., 2012). Antimicrobial efficacy of this plant is also reported against periodontopathogens like *Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia and Tannerella forsythia*, thereby suggesting its potential in treating periodontal diseases (Karmakar *et al*., 2020). TA extracts have been found to be medicinal in nature by inhibiting respiratory pathogens also that cause infections in the lower and upper respiratory tract region (Kumar *et al*., 2014).

5.4 Hepatoprotective effect

TA has shown to bear excellent hepatoshielding effect against carbon tetrachloride (CCl_4) or paracetamol induced damage in wistar rats. This biochemical effect was revealed to be due to significant reduction in activity of various enzymes like serum alkaline phosphatase, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase and serum bilirubin which was found to be in the same levels when rats were treated with standard hepatoprotective agent (Vishwakarma *et al*., 2013). Manna and his team indicated the modulatory role of arjunolic acid against arsenic induced cytotoxicity in murine hepatocytes in 2007 and protective consequence of bark extract against CCl_4 induced liver damage in 2006 (Manna *et al*., 2006, 2007). TA bark aqueous extract have been also reported to be active in reducing the alcohol induced nephrotoxicity in experimental rats by mitigating the levels of lipid peroxides and restoration of enzymatic along with nonenzymatic antioxidants in liver (Hebbani *et al*., 2015). The hepatoprotective and antioxidative effect of TA bark extract has been evidently suggested in cadmium mediated hepatotoxicity (Haidry and Malik, 2014). Furthermore, arjuna extract has extended beneficial effect in curing nonalcoholic fatty acid liver disease by decreasing the lipid levels in palmitateoleate incubated HePG2 cell and by minimizing the activity of lactate dehydrogenase (LDH), alanine amino-transferase (ALT), aspartate transaminase (AST) and gamma glutaryl transferase (GGT) in HFD models (Toppo *et al*., 2018). Kannappan and his team have also suggested the antioxidant effect of this plant extract against acetaminophen induced hepatotoxicity *via* the regulation of cytochrome P450 2E1, phosphatidylinositol-3- kinase/ protein kinase B (Kannappan *et al*., 2020).

5.5 Antioxidant activity

The cardioprotective, antitumor activity, antibacterial and hepatoprotective effect of TA can be attributed to its antioxidant nature which has been reported by several studies mentioned before. Bioactive constituent profiling of bark extract has revealed it to be a superior source of antioxidants like flavonoids, tannins, proanthocyanidins, *etc*. Arujunic acid and aglycone found in the fruits of this plant has been suggested to be a very strong antioxidant or free radical scavenger and more effective than ascorbic acid (Sun *et al*., 2008). Extract of TA harboring casuarinin is reported to defend Madin Darby canine Kidney (MDCK) cells against hydrogen peroxide induced stress by alleviating the DNA damage and replenishing the levels of intracellular reduced glutathione (Chen *et al*., 2004). TA is also recognized as a hypocholesterolemic and hypolipidemic agent that can mitigate oxidative stress induced by a high fat high cholesterol diet (Sharma and Agarwal, 2012). *In vitro* investigation comparing the antioxidant properties of TA bark and core wood revealed that the core wood of the tree possesses more antioxidant molecules in comparison to bark. This study also supports methanol as the best solvent to extract antioxidant compounds from this plant (Ramesh *et al*., 2013).

5.6 Anti-inflammatory activity

The effect of TA extract was revealed to inhibit nitric oxide production in lipopolysaccharide induced rat peritoneal macrophages by expressing a strong antioxidant activity (Ali *et al*., 2003). The extract of TA along with *Datura stramonium* and *Withania somnifera* have been reported to exhibit anti-inflammatory activity. The anti-inflammatory and analgesic action of this formulation can be attributed to the inhibition of cyclooxygenase (COX) enzyme, thereby interfering with the production of prostaglandins (Mukesh *et al*., 2010). Dube and his colleagues investigated the anti-inflammatory efficacy TA ayurvedic formulation prepared in cow milk, *i.e*., Arjuna Ksheera paka and unfolded the better efficacy of Ksheera paka when compared to hydroalcoholic extract. The researchers proposed that presence of milk solids behaves as an adjuvant to arjuna bioactive, constituents thereby causing enhanced bioavailability and efficacy of the drug at lower concentration (Dube *et al*., 2017). Saxena and his team conducted a detailed investigation of TA bark and revealed that its bioactive constituent expressed immunostimulatory response at lower dose whereas, at higher concentration, they were found to exhibit immunosuppressive activity (Saxena *et al*., 2008). Another team of researchers proposed and proved anti-inflammatory activity on carrageenan induced paw edema in the rat model system. They stated that the aqueous extract of the plant bark can significantly reduce the carrageenan induced edema in experimental animals (Rana *et al*., 2016).

5.7 Wound healing activity

The TA bark powder has been reported to treat chronic wounds along with the coconut oil (Dudhamal, 2016). A study reports wound healing potential of arjuna extract in form of a formulation of Himax ointment and lotion which was comparable to standard nitrofurazone drugs (Mukherjee *et al*., 2003). TA hydroalcohol extract has also been documented for its beneficial effect on rat dermal wounds when applied topically owing to its superior tannin content (Chaudhari and Mengi, 2006).

5.8 Gastric activity

Various studies have reported that arjuna has greater potential to curb the damage caused to gastric mucosa by different agents. Devi and her team investigated and confirmed the antiulcer repercussions of methanolic extract of TA against *Helicobacter pylori* lipopolysaccharide mediated gastric damage in experimental rats (Devi *et al*., 2008). Not only this, these extract can enhance the adherent mucus in the gastric walls along with the protein bound carbohydrate molecules of gastric juices in diclofenac treated rats models (Devi *et al*., 2007).

5.9 Molluscicidal and anthelmintic properties

The molluscicides activity of TA is established on *Lymnaea acuminata* and *Indoplanorbis exustus* (Soni and Singh, 2015; Soni and Singh 2019a). The thin layer chromatography analysis showed the presence of bioactive components from TA extract to cause molluscicidal activity against *L. acuminata*. Further, the consequence

of arjunolic acid on key enzymes AchE, ACP and ALP activity was investigated in the nervous tissue of *L. acuminata* snail and displayed its dose dependent inhibition of these enzymes (Soni *et al*., 2017). Upon a detailed study on the kinetics of these enzymes, it was putforth that inhibition of AchE was noncompetitive, whereas inhibition of ALP and ACP was competitive-non-competitive and non-competitive respectively. Also, inhibition of ALP by TA extract was more evident and visible as compared to the other two enzymes. A different team of researcher determined the toxicity and safety aspects of a molluscicidal drug made from TA on *Colisa fasciatus* (an aquatic model) and added that lethal concentration 90 reported in *L. acuminata* and *I. exustus* did not impose any toxic effect on nervous tissue of fish in 24 h (Soni and Singh, 2019b).

Anthelmintic effect of TA was studied on *Pheretima posthuma* and was found to retard the spontaneous movement of these helminthes and cause death of trematodes (Bodke *et al*., 2013). Also, methanolic extract of TA was revealed to be efficient against larvae and hatched eggs of *Haemonchus contortus* at the dose of 467 and 645 µg/ml, respectively suggesting the medicinal nature of TA (Bachaya *et al*., 2009).

5.10 Antidiabetic activity

A previously cited work has shown the modulatory role of TA extract in diabetes existing along with cardiovascular complications (Suman *et al*., 2018). The ethanolic extract of TA was found to ameliorate the alloxan induced diabetes in experimental rat models by stabilizing the enzymatic, non-enzymatic activity and minimizing the levels of oxidative stress in liver and kidney tissues (Raghavan and Kumari, 2006).

5.11 Antiviral and apoptosis related studies

Casuannin, a bioactive component of TA has proven to be antiviral in nature. Studies have been conducted on Herpes simplex type II virus *in vitro* condition and showed that the active molecule potently inhibited viral attachment and penetration of the virus (Cheng *et al*., 2002).

Apoptosis is a form of programmed cell death (PCD) that brings about characteristic change in the cell and leads to cell death. The changes encompass cell shrinkage, blebbing, nuclear DNA fragmentation, chromatin condensation, and mRNA decay. The role of TA bark extract in inducing apoptosis of a human liver cancer cell line (HepG2) was investigated and showed that the apoptotic effect was due to induction of DNA damage and over expression of apoptotic proteins along with possible exhaustion of reduced glutathione levels (Sivalokanathan *et al*., 2006). TA also is proposed to promote foam cell and macrophage apoptosis by enhancing UPR-mediated JHN/p38MAOK-CHOP pathway activation in a DUSP1-dependent manner, thereby suggesting a possible connection between ox-LDL-induced ER stress and TA mediated MAPK signaling (Bhansali *et al*., 2019). A double blind, placebo controlled, crossover designed study on 18 symptomatic smokers revealed the modulatory effect of TA on endothelial dysfunction by revealing the improved brachial artery flow mediated dilation (Bharani *et al*., 2004).

5.12 Other physiological effects

A study validated that arjuna bark extract exhibits synergistic effect with phytochemicals on different pathways leading to better bioactivity and bone mineralisation. The biocomposite prepared using bark extract displayed enhanced compression strength and stability. The functional groups of arjuna extract help in biomineralization *in vitro* and showed positive influence on cell differentiation and cell viability in MG-63 cells. Such biocomposite can be used as excellent bone filler or as a coating agent in metallic implants to impart bioactivity (Krithiga *et al*., 2014).

6. Toxicity or side effects

A study was conducted in order to understand an acute and sub-chronic toxicity of TA leaf in Swiss albino mice. No mortality was observed during the course of the entire study period and no noticeable alterations were revealed in hematological, biochemical and histological parameters treated group when compared to vehicle control group post 28 days emphasizing its safe nature (Moulisha *et al*., 2011). The effect of arjuna extract on tissue lead (Pb) concentration in rats was experimented by Senapati *et al*. (2005). Their study reported no synergistic toxicity of arjuna and extract but revealed the prophylactic efficacy of extract. Their report suggests that concomitant use of arjuna bark extract at three different doses was found to reduce Pb concentration considerably in these vital organs indicating the potential therapeutic activity of arjuna against lead toxicity (Senapati *et al*., 2005).

TA is usually used in the dose between 1 to 2 g per day and is found to be the optimum and effective dose in the patients with cardiovascular diseases. Few reports have suggested the mild side effects of these doses such as headache, mild gastritis and constipation. There are no reports in context to hematological, hepatic, metabolic and renal toxicity even after 24 months and more than two years of its administration (Gupta *et al*., 2018).

Overall, this review presents that TA possesses various medicinal properties like cardioprotective, hepatoprotective, antitumor, antibacterial, antioxidant, gastric, molluscicidal, anthelmintic, antidiabetic, antiviral and anti-inflammatory with no reported side effects (Figure 1).

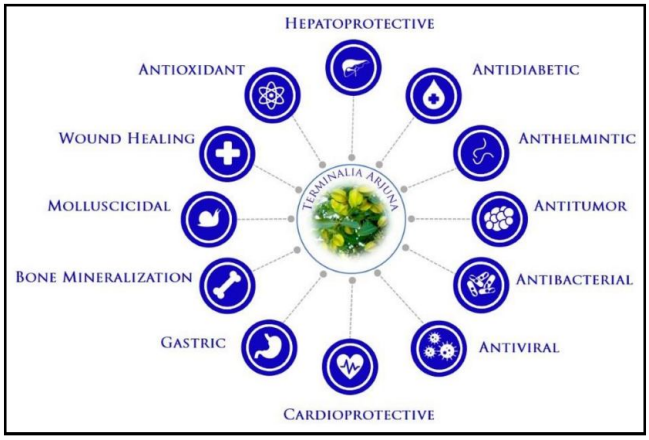

Figure 1: Beneficial medicinal properties of *T. arjuna*.

7. Studies on incorporation of *T. arjuna* in food products

About 39% of the total milk produced in India is converted into butter and ghee. The clarified milk fat, *i.e.*, ghee has a unique property of absorbing the medicinal characteristics of the fortified herbs without diminishing or losing its own qualities. The herbal ghee presently is being marketed and sold as medicine, *i.e.*, medicinal ghee. These types of products harbor a typical flavor, a bitter or pungent taste and a dark color. Such therapeutic products or preparations are not suitable for regular consumption by consumers.

Arjuna ghee has been developed for extending beneficial health effects against cardiovascular disease. The ghee has exhibited more stability to oxidative deterioration as compared to conventional ghee owing to the rich phenolic bioactive compounds present in TA plants. The consumer acceptability of this product on the basis of sensory analysis has been reported to be very good. In daily diet, arjuna ghee can be replaced with regular ghee unlike medicated ghee preparations that is not used for regular purpose. The rich repository of the antioxidants present in the arjuna herbs lead to their usage into fat rich dairy products for retarding auto-oxidation there by prolonging the shelf-life (Upadhyay *et al*., 2001).

Churna is a mixture of powdered herbs and minerals which are used in Ayurvedic medicine. Arjuna churna is sold under different names by popular brands like Patanjali, Baidyanath and Dabur. This churna is used to prevent heart ailments most popularly. Systematic comparison of high-performance liquid chromatogram of standardized and marketed Arjuna churna formulation revealed eight common peaks in an acetonitrile-water gradient program that can serve as a fingerprint to this formulations. This has been the basis of preparation of churna (Chitlange *et al*., 2009).

Bishnoi and Ahlawat (2015). have used TA extract for development of buffalo meat rolls by supplementing the extracts at 2, 4 and 6% level each so as to optimize the amount of extract incorporation. The effect of co-supplementation on the texture profile of the developed products was also studied. 2% extract of arjuna tree bark was suitable for incorporation and selected for further studies on the basis of sensory scores. The physical properties of the developed products were also studied and compared to control samples. Their report overall indicated that male buffalo calf meat rolls can be developed by incorporating 2% arjuna tree bark extracts with good sensory and textural properties thereby, unfolding new application of TA extract (Bishnoi and Ahlawat, 2015).

Recently, utilization of TA at 2, 4 and 6% was evaluated for development of herbal multigrain biscuits as cardiotonic. The results revealed that 2% TA containing biscuits had lesser ash content, lower spread ratio, nominal diameter, less moisture and more thickness in comparison to control biscuits. Incorporation of TA at 2% did not affect the overall acceptability of the biscuits and possesses potential to enhance the nutritional status for people with cardiac diseases, without minimizing the sensory acceptability of the composite biscuits. Co-supplementation of higher percentage of TA resulted in darker color along with undesirable taste, thereby affecting the overall acceptability of the bakery product (Alifiya *et al*., 2018).

Furthermore, a herbal green tea was developed using *Withania somnifera* stems, TA bark, Cinnamon bark and *Tinospora cordifolia* stems. The phytochemical, nutritional, antioxidant and antibacterial activity analysis showed that the formulation mixture of these herbs reflected them to be an excellent source of nutraceuticals and flavoring agents. A perfect physical and psychological health rejuvenator was made from these herbs that possesses potential to extend multiple health benefits to the diet conscious consumers. This report also presents this herb formulation based infusion as a new alternative to the traditional flavored teas (Namdev and Gupta, 2015).

Sawale and team, 2016 evaluated the hypolipidemic potential along with the antioxidative properties of encapsulated herb (TA in 1.8%) added with vanilla chocolate dairy drink in high cholesterol fed Wistar rats for 60 days. A significant decrease in serum lipids such as total cholesterol, triglycerides, very-low-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and atherogenic index was observed with encapsulated herb. The results obtained from their study revealed that the bioactive components (flavonoids, phytosterols, saponins, tannins, *etc*.) which are present in encapsulated TA gets effectively released in the intestine to display their effects and can also withstand the adverse processing conditions. This encapsulated herb study also supports and presents TA as a potential medicinal plant candidate bearing hypolipidemic and antioxidant activities that can treat cardiovascular disease (Sawale *et al*., 2016).

Sharma *et al*. (2012). developed arjuna omelette and arjuna upma composition with good sensory properties of arjuna omelette in comparison to upma. Their results showed that coconut chutney with sambar soppu scored highest for all sensory attributes followed by bisebilebath and little millet upma with drumstick leaves and the least scores were obtained for barnyard millet upma with drumstick leaves (Sharma *et al*., 2012).

8. A global perspective of research on *T. arjuna*

A total of 683 publications on TA have been reported upon on a global search and retrieval from Scopus database ranging from 1997-2019 publication year. The cumulative global research registers 169.19% growth and 8% as annual increase in the publications. The plant global citation impact averaged to 16.92 citations per paper (CPP) in twenty-two years, which decreased from 36.02 to 9.82 CPP from 1997-2007 to 2008-2018. India accounts for the highest and largest publication share of 82.43% and other 9 countries from 1.02% to 5.27% during 1997-2018. Pharmacology, toxicology and pharmaceutics, among seven broad subjects, contributed the largest publications share of 50.51%, followed by medicine (30.31%), biochemistry, genetics and molecular biology (26.52%), agricultural and biological sciences (21.52%) and other 3 sub-fields contribution varying from 4.54% to 10.83% during 1997-18 (Ahmed *et al*., 2020). This data certainly points out the potential of TA and extensive studies conducted on it with the objective of exploring its potential in curing various diseases and expounding its therapeutic role in development of novel formulation.

9. Conclusion

Experimental and clinical studies compiled in this review indicate that TA possesses immense ethanopharmacological significance owing to its various medicinal properties. The properties of this plant are attributed to the presence of various phytoconstituents such as glycosides, flavonoids, tannins, triterpenoids and phenolics.

TA is been reported to possess cardioprotective, hepatoprotective, antitumor, antibacterial, antioxidant, gastric, molluscicidal, anthelmintic, antidiabetic, antiviral and anti-inflammatory properties. Such medicinal phytochemical rich plants behave as potent resource for future drug discoveries. Maximum efforts and extensive investigation should be undertaken to characterize all phytochemicals in such medicinal plants at molecular level. Such investigation can establish new standard drugs with lesser toxicity when accompanied with *in-silico* analysis and clinical trials so as to benefit global population.

Conflict of interest

The authors declare that there is no conflicts of interest, relevant to this article.

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