TERMINALIA *ARJUNA*: A POTENTIAL SOURCE OF NUTRACEUTICALS CUM THERAPEUTIC AGENT

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Contents

Summary

Medicinal plants are considered as one of the chief sources of therapeutic agents since ancient time to cure various human diseases. Terminalia *arjuna* is broadly used as medicinal plant for several indigenous system of medicine like Ayurveda, Sidda and Unani. Earliest Indian physicians used the powdered tree bark of Terminalia *arjuna* Wight & Arn. for improving ―hritshool (angina) and other cardiovascular conditions. This study highlights the phytochemical and pharmacological activities of Terminalia *arjuna* and its application in Ayurveda and food products. Several studies of this plant have been reported to contain phytochemical constituents like triterpenoids, glycosides, flavonoids, tannins, β- sitosterol, minerals (calcium, magnesium, zinc, copper etc.) etc. which are used to treat various non-communicable diseases as these constituents exhibit various pharmacological activities like cardioprotective, antioxidant, antidiabetic, anticancer, antimicrobial, anti-fungal, anti-inflammatory, hypolipidemic, anti-helminthic, insecticidal, wound healing, anti-acne, hepato-renal protective, gastroprotective etc. Experimental studies have shown that the bark is utilized as significant ionotropic and hypotensive agent, increasing coronary artery flow and protecting myocardium against ischemic damage. The effectiveness of Terminalia *arjuna* as an anti-ischemic agent and as a powerful antioxidant preventing oxidation of LDL cholesterol and reperfusion ischemic injury to heart, and its potential to decrease atherogenic lipid levels have been satisfactorily confirmed in several experimental and clinical studies. It can be considered as a useful drug for coronary artery disease, hypertension and ischemic cardiomyopathy. The proposition to administer it along with statin deserves to be examined. In certain cases, the active phytochemicals have been conventionally recognized, although for several medicinal properties the active principles have been only partially considered. Therefore, the present comprehensive study is an effort to give detailed and up to date information on botanical description, phytochemical constituents, pharmacological studies and its applications in Ayurveda and food products of Terminalia *arjuna*.

1. Introduction

Medicinal plants play a significant role in health care and are main natural materials used for both conventional and traditional medicine preparations as most people choose herbal medicines than conventional medicines. Herbal medicinal usage continues to play an important role for the treatment of various diseases. People expanded their attention on herbal medicines due to its effectiveness, lack of current medical alternatives, cultural preference and increasing cost of modern medicines (Heinrich, 2000). From past decades plants are used as therapeutic agents and are the major source of medicines. In many developing countries, Ayurvedic medicine is usually practiced for the treatment of wide variety of disorders and diseases (Kamboj, 2000). According to WHO, almost 80% of the world's population depends on

traditional herbal medicine and in India still now 85% of peoples use crude plant preparation for the treatment of various diseases (WHO, 2002). The usage of herbal medicines is more dominantly preferred because they are usually safer alternative than allopathic drugs. Plant based medicines have been conventionally used as crude formulations, such as extracts and mixtures, essential oils and other herbal preparations. However, the modern trend is to isolate and characterize the individual phytochemical component with the aim of producing an analogue of elevated bioactivity. Several related studies have given rise to the development of various useful drugs such as digoxin (from Digitalis spp.) and quinine (from Cinchona spp.) as well as the anticancer drugs vincristine and vinblastine (from Vinca rosea). However, enhanced bioactivities were found in crude plant extracts. The plant extracts may contain thousands of different chemical components that act together in complex ways having therapeutic benefits (Karalliedde and Gawarammana 2008; Choi and Chung 2003) where phytomolecules acting in synergistic fashion. In recent years awareness about the significance of medicinal plants is increasing in community. Herbal drugs are efficient, easy accessible, secure, cost-effective and have less side effects. The studies shown that bark extract has been used in Indian system of medicine to cure number of diseases and hold an essential position in Ayurvedic medicine since ancient times. Various parts of this tree generally bark and fruit which are used as consumable parts to maintain good health (Kiritiker and Basu 1987).

The genus Terminalia belongs to the family Combretaceae that consist of nearly 200-250 species of flowering trees. Generally Terminalia species are broadly distributed through the tropical and subtropical regions of Asia, Africa and Australia. Possibly, with greatest number and variety the Asian Terminalia covers several useful species with most widespread therapeutic effect. Mostly these species are used in traditional medicinal system (Mc Gaw et al., 2001). Mainly Terminalia *arjuna* and Terminalia chebula are well recognized in Asia due to their usage in Ayurvedic medicine. In Australia and South Pacific region approximately 28 species are present. Among these Terminalia *ferdinandiana* has received much attention due its phytochemistry and high antioxidant property. Further, in Africa approximately 30 species are present, with majority of these occurring in the southern part of the continent. The bark of Terminalia species is fissured and the branches are arranged in rows. The genus name is derived from the Latin word terminus, denoting that leaves are present at the shoot tips. In most Terminalia species the leaves are large and have leathery appearance. The flowers appear on spikes and are greenish white in color. The fruits are generally dark red, yellow or black drupes which are winged or angled. The fruit of the plant is edible and are highly nutritious. Mainly Terminalia species are well known for their high anti-oxidant properties. Similarly, studies shown that Terminalia *arjuna* also have high antioxidant potential. The higher antioxidant content in the stem bark of Terminalia *arjuna* is due to the presence of greater amount of phenolic and flavonoids (Mety and Mathad 2011). Chemical studies had indicated that the plant contains many bioactive components like saponins (arjunolic acid, arjunic acid), flavonoids (arjunone, arjunolone, and luteolin), tannins, triterpenoid, ellagic acid, gallic acid, phytosterols, oligomeric proanthocyanidins and minerals (Ca, Mg, Zn and Cu) (Kiritiker and Basu 1987; King et al. 1954) (Table 1). Terminalia *arjuna* is mainly responsible for several biological functions, including cardioactive properties, anti-diabetic, anti-ischemic, anti-oxidant action, anti-inflammatory, anti-bacterial, anti-fungal, anti-asthmatic, anti-

cholinesterase, immunomodulatory, anti-tumor (Tripathi and Singh 1996; Dwivedi and Udupa 1989; King et al. 1954). It also has properties to cure obesity, hyperglycemia and hypertension (Amalraj and Gopi, 2017) (Figure 1a).

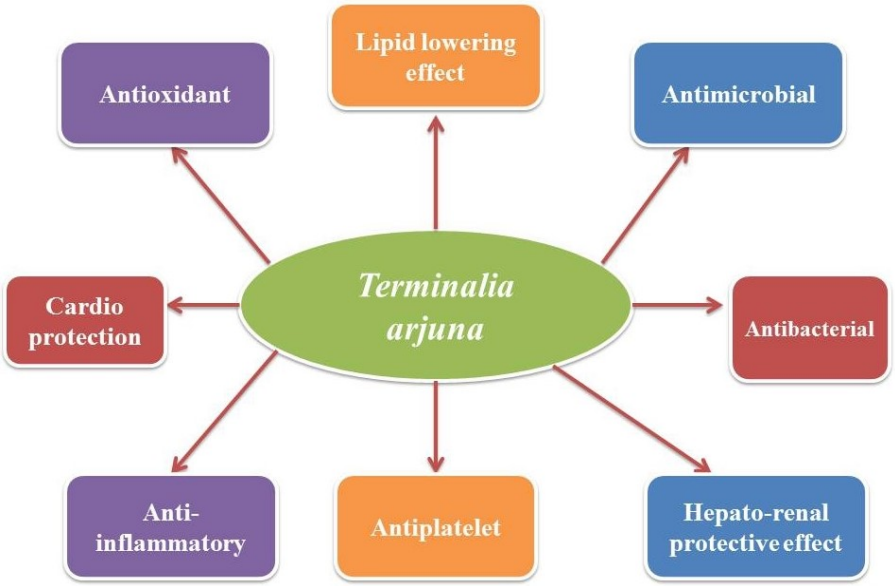

Figure 1a. Various Biological Activities of Terminalia *Arjuna*

It has been reported that Terminalia *arjuna* possess strong hydrolipidemic properties. Generally the studies suggest that glycosides and saponins are responsible for its inotropic effects, while phenolics and flavonoids are responsible for its antioxidant and vascular amplification activity. In this way the various activities of this plant is authenticated for its cardioprotective function (Dwivedi, 2007; Kapoor et al., 2014). This present chapter highlights the Ayurvedic formulation, phytochemical, pharmacological properties and clinical aspects of Terminalia *arjuna* as potential nutraceutical for the treatment of various diseases.

2. Ethnopharmacology

The leaves, fruit and barks of Terminalia *arjuna* have been used in traditional system of medicine for multiple different disorders and diseases (Warrier et al., 1993). Generally, the bark of the tree is acrid, sweet, aphrodisiac, styptic, expectorant, tonic, and used as cardiotonic, antidysenteric and diuretic (Udupa 1986; Kritikar and Basu 1975). It has been supported in several medicinal uses such as leucoderma, asthama, hydrosis, urinary discharge and tumors (Pettit et al. 1996). The fruits are used as tonic and deobstruent (Kritikar and Basu 1975). The leaves are mainly used as remedy for earache (Khory, 1867).

An Ayurvedic practitioner uses Terminalia *arjuna* as anticoagulant, anti-thrombotic, antihypertensive, hypocholsteremic, hypolipidemic agent. It has been conventionally used to treat viral, bacterial and fungal infections and diseases (Tripathi and Singh 1996).

3. Pharmacogonosy

3.1. Botanical Characteristics

Figure 1(b) shows the taxonomic placement of Terminalia *arjuna* in the plant kingdom.

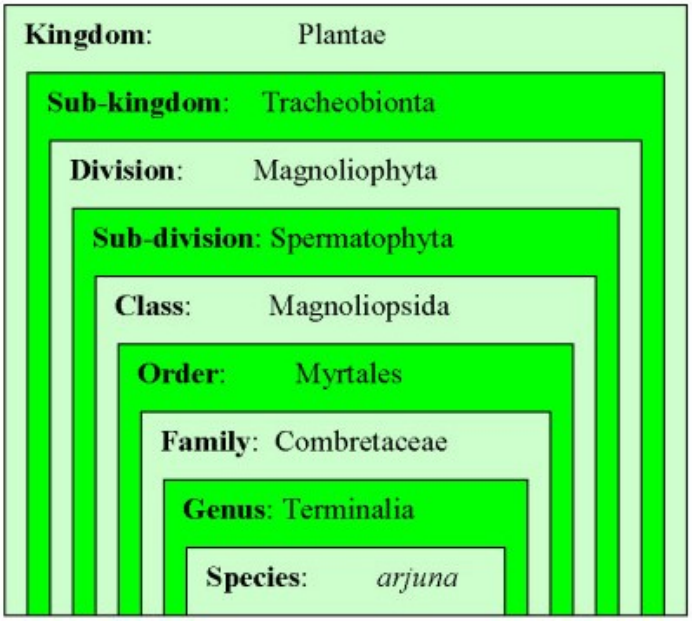

Figure 1(b). Taxonomic placement of Terminalia *arjuna* in the plant kingdom

Figure 1(c). Photographic representation of i) leaves, ii) flowers and iii) fruits of Terminalia *arjuna*

Terminalia *arjuna* Wight & Arn. is a deciduous and evergreen tree distributed throughout India standing 20-30 m above ground level (Figure 1c). The classical names are *Arjuna*, Kakubha, Dhavala, Veervriksha, Nadisarja, Partha, Indradru (Sarwar et al., 2008). Unusually the tree is pest and disease free. It has huge, buttressed trunk and horizontally spreading branches (Figure 2).

The bark of Terminalia *arjuna* is pinkish grey and smooth from outer side and flakes off in large, curved and flat pieces (Shah and Bhavsar, 1956). The size of each piece may vary up to 10 cm in width, 15 cm or more in length and 3-10 mm in thickness. Mostly the heart wood is brown and sapwood is reddish white and parti-colored with dark colored streaks. The histology of Terminalia *arjuna* indicates the presence of single layered epidermis with dispersed lenticels and hair like projections. Primarily epidermis is a thin layer of cortex. In the old bark of the tree periderm and secondary phloem are present (Prasad, 1941).

The leaves are simple, oblong or elliptic, often crenulating, and borne sub-opposite coriaceous. The margin of the leaves are crenate- serrate, apex is obtuse or sub-acute. The upper surface of the leaves is pale or dark green in color and the lower surface is pale brown in color. It measures 10- 15 cm long and 4-7 cm broad. The veins and veinlets on the lamina of the leaves are arranged in network of 10-15 pairs having reticulate fashion. Generally the petioles are 6-10 mm long with one or two protruding oil glands at the top observed at abaxial side closely near the leaf petiole. This is a distinctive pharmacognostic feature of Terminalia *arjuna* (Anjaneyulu and Prasad, 1983).

Figure 2. Tree of Terminalia *Arjuna* Wight &Arn.

The tree produces white or yellowish color sessile flowers that do not bear pedicel. The flowers are arranged in short axillary spikes or in terminal pannicule. The flowers are bisexual (both the male and female reproductive parts are present). Each flower comprises of 10 stamens and disk shaped ovary with reddish or yellowish hairs. Bracteoles are mainly linear and lanceolate like structure. Calyx is glabrous. Generally the flowering occurs in summer and fruit appears in winter or spring season. Fruits are ovoid, 1-1.5 inch in diameter, 2.5-5 cm long and 5-7 longitudinal lobes are present. These are fibrous, woody and smooth-skinned with 5-7 hard wings. The fruit is drupe and is often notched near the top; the wings are marked with oblique upward and curved striations.

4. Phytochemistry

The chemical constituents of Terminalia *arjuna* are present in root bark, stem, bark, leaves, fruits and seeds. The findings suggest that bark is the most important constituent from medicinal point. The bark contains polyphenols, glycosides, flavonoids, tannins, triterpenoids, sterols, saponins and minerals such as calcium, magnesium, zinc, copper and amino acids (Chaudhari and Mengi, 2006). Bark had 34% ash content consisting entirely of pure calcium carbonate. The aqueous extract has 23% calcium salts and 16% tannins (Chitlange et al., 2009). It was reported that root contains glycosides and triterpenoids, fruits contains flavonoids and triterpenoids, leaves and seeds contain flavonoid and glycosides. The Terminalia *arjuna* bark extract was prepared by sequential method with several organic solvents such as chloroform, methanol, ethanol, butanol, ethyl acetate etc. The active chemical constituents of Terminalia *arjuna* present in stem, bark, leaves, fruits and seeds are well characterized in Table 1. The chemical structures of these compounds were established by using several innovative techniques like thin layer chromatography (TLC), High performance liquid chromatography (HPLC), reverse phase liquid chromatography (RPHPLC) and ESI–LC-MS/MS analysis.

Part used Major	Chemical Constituents
Stem bark	Triterpenoids Ursane triterpenoids Glycosides Flavonoids and phenolics Tannins Minerals and trace elements
Roots	Triterpenoids Arjunic acid Glycosides
Fruits	Triterpenoids and Flavonoids
Leaves and seeds	Flavonoids and glycosides

Table 1. Pytochemical Constituents of Various Parts of *Terminalia Arjuna*

4.1. Terpenoids and Glycosides

The bark of Terminalia *arjuna* contain large amount of triterpenoids. Mainly triterpenoids isolated from its bark are arjunin, arjunic acid, arjunetin, arjugenin. It was reported that stem bark contains arjunoglycoside (Desai and Chanda, 2014). Originally an oleanane triterpenoid is termed as arjunin and a lactone. Arjunetin was sequestered from the benzene and alcoholic bark extracts, respectively. Subsequently the presence of arjunic acid and arjungenin in the bark stem was established and mainly two more glucosides namely arjunglucoside I and arjunglucoside II were described (Honda et al., 1976) (Figure 3). Later on carboxylic acid, triterpene, terminic acid, arjunglucoside III and arjunglucoside IV were isolated from the ethyl acetate extract of its root (Anjaneyulu and Prasad, 1982). From the n-hexane extract of Terminalia *arjuna* heart wood terminic acid and β-sitosterol was isolated. Terminoside A, triterpane and two more glycosides namely Termiarjunoside 1, Termiarjunoside 2 was isolated from bark extract (Dube et al., 2016). From the ethanolic Terminalia *arjuna* stem bark extract Arjunglucoside IV and V, Arjunasides A-E were isolated (Dwivedi and Udupa, 1989). Additionally, oleanane type terminoside A, triterpane has been sequestered from the acetone fraction of the ethanolic extract of its stem bark (Ali et al., 2003a). Further the structure of this new compound was recognized as olean-1α,3β,22β-triol-12-en-28- oic acid-3β-d-glucopyranoside. The study established that terminoside A prevents nitric oxide production and reduces inducible nitric oxide synthase levels in lipopolysacchride stimulated macrophages. An arjunaphthanoloside possessing antioxidant activity has also been isolated from its bark (Ali et al., 2003b).

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Lin TC, Chien SC, Chen HF, Hsu FL. (2000) Tannins and related compounds from Combretaceae plants. *Chinese Pharmaceutical Journal*. 2000;52(1):1-26. [This study highlighted that several hydrolysable tannins such as punicallin, terchebulin, pyrocatechols, terflavin, castalagin, casuariin have been isolated from Terminalia *arjuna* extract].

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McGaw LJ, Rabe T, Sparg SG, Jäger AK, Eloff JN, Van Staden J. (2001) An investigation on the biological activity of Combretum species. *Journal of ethnopharmacology*. 2001 Apr 1;75(1):45-50. [This study highlighted that Terminalia *arjuna* species are used in traditional medicinal system].

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Pettit GR, Hoard MS, Doubek DL, Schmidt JM, Petrit RK (1996) Antineoplastic agents 338- the cancer cell growth inhibitory constituents of *Terminalia arjuna*. *J Ethnopharmacol* 53:57–63. [This study supported that Terminalia *arjuna* has several medicinal uses such as leucoderma, asthama, hydrosis, urinary discharge and tumors].

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study reported that the bioactive components such as tannins and flavones present in the Terminalia *arjuna* were mainly responsible for anticancer activity].

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Shah CS, Bhavsar GC. (1956) Pharmacognosy of the bark of *Terminalia tomentosaW*&Aand comparison with *Terminalia arjuna W*&A bark. *Indian Journal of Pharmacology*. 1956;18:81-4. [This study highlighted that the bark of Terminalia *arjuna* is pinkish grey and smooth from outer side and flakes off in large, curved and flat pieces].

Shaila HP, Udupa SL, Udupa AL. (1998) Hypolipidemic activity of three indigenous drugs in experimentally induced atherosclerosis. *International Journal of Cardiology*. 1998 Dec 1;67(2):119-24. [This study highlighted the cardioprotective effect of Terminalia *arjuna* bark extract which include reduced total lipid levels, mainly LDL lipids, with a coincident increase in HDL lipids].

Sharma PC, Yelne MB, Dennis TJ. (2005) *Database on medicinal plants used in Ayurveda* (Vol. 3, pp. 130-131). New Delhi: CCRAS. [This study revealed that the antioxidant activity and total polyphenol content of hydroalcoholic extract was higher than Arjun ksheera paka].

Sharma PN, Shoeb A, Kapil RS, Popli SP. (1982) arjunolone-a new flavone from stem bark of *Terminalia arjuna*. *Indian Journal of Chemistry Section B-Organic Chemistry Including Medicinal Chemistry*. 1982 Jan 1;21(3):263-4. This study highlighted that Terminalia *arjuna* contains high levels of antioxidant flavonoid compared to other plants. These flavonoids include quercetin, flavones, arjunolone, kampferol, bicalein, pelorgonidin and luteolin].

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Singh DV, Verma RK, Singh SC, Gupta MM. (2002) RP-LC determination of oleane derivatives in *Terminalia arjuna*. Journal of Pharmaceutical and Biomedical Analysis. 2002 May 15;28(3-4):447-52. [This study highlighted the antidiabetic effect of ethanolic extract of Terminalia *arjuna*].

Sinha M, Manna P, Sil PC. (2008) *Terminalia arjuna* protects mouse hearts against sodium fluoride-induced oxidative stress. J*ournal of Medicinal Food*. 2008 Dec 1;11(4):733-40. [In this study the ferric antioxidant assay revealed that ethanolic bark extract of Terminalia *arjuna* enhanced the cardiac intracellular antioxidant activity against sodium fluoride induced oxidative stress in the murine heart].

Sivalokanathan S, Ilayaraja M, Balasubramanian MP. (2006) Antioxidant activity of *Terminalia arjuna* bark extract on N-nitrosodiethylamine induced hepatocellular carcinoma in rats. *Molecular and Cellular Biochemistry*. 2006 Jan;281(1):87-93. [This study revealed that Terminalia *arjuna* bark extract has protective activity against oxidative stress and decreased levels of lipid peroxidase activity].

Srivastava RD, Dwivedi S, Sreenivasan KK, Chandrashekhar CN. (1992) Cardiovascular effects of Terminalia species of plants. *Indian drugs*. 1992;29(199):1. [This study highlighted that intravenous administration of Terminalia *arjuna* aqueous bark extract resulted in dose-dependent fall in blood pressure which established the hypotensive effect of Terminalia *arjuna*].

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study highlighted the cardioprotective effect of arjunolic acid helps to prevent against the damage caused by myocardial necrosis].

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Tandon S, Rastogi R, Kumar Kapoor N. (1996) Protection by abana, a herbomineral preparation, against myocardial necrosis in rats induced by isoproterenol. *Phytotherapy Research*. 1996 May;10(3):263-5. [This study revealed that Terminalia *arjuna* bark extract reverse cardiac injury and possess cardiotonic and cardiovascular protective effects including enhanced cardiac cell mitochondrial uptake].

Tripathi VK, Singh B, Tripathi RC, Upadhyay RK, Pandey VB. (1996) *Terminalia arjuna*: Its present status (A review). *Oriental Journal of Chemistry*. 1996;12:01-16. [This study investigated that Terminalia *arjuna* is used as anticoagulant, antithrombotic, antihypertensive, hypocholsteremic, hypolipidemic agent. It has been conventionally used to treat viral, bacterial and fungal infections and diseases].

Udupa KN. (1986) Scope of use of *Terminalia arjuna* in ischaemic heart disease. *Ann Natl Acad Indian Med*. 1986;1(1):54-8. [This study highlighted that bark of Terminalia *arjuna* tree is acrid, sweet, aphrodisiac, styptic, expectorant, tonic, and used as cardiotonic, anti-dysenteric and diuretic].

Upadhyay RK, Pandey MB, Jha RN, Singh VP, Pandey VB. (2001) Triterpene glycoside from *Terminalia arjuna*. *Journal of Asian natural products research*. 2001 Jul 1;3(3):207-12. [This study investigated that the antioxidant properties of Terminalia *arjuna* led their usage into fat rich dairy products for slowing down the auto-oxidation there by prolonging the shelf-life].

Wahal PK. (1991) A preliminary report on the inhibitory effect of Abana on platelet aggregation and adhesiveness in cases of coronary heart disease and hypertension. *Probe*. 1991;30:312-5. [This experimental study highlighted that the herbs- mineral preparation containing Terminalia *arjuna* 30 mg per tablet, known as abana, it was detected to have anti-thrombotic activity].

Wang W, Ali Z, Shen Y, Li XC, Khan IA. (2010) Ursane triterpenoids from the bark of *Terminalia arjuna*. *Fitoterapia*. 2010 Sep 1;81(6):480-4. [This study highlighted that Terminalia *arjuna* was also used to prepare herbal green tea. The phytochemical, nutritional, antioxidant and antimicrobial activity revealed that Cinnamon bark, Terminalia *arjuna* bark, Withania somnifera stem, Tinospora cordifolia stems, green tea and the formulation mixture of these herbs indicated that they can be proven to be an excellent source of nutraceuticals and flavoring agents].

Warrier PK. (1993) *Indian medicinal plants: a compendium of 500 species*. Orient Blackswan [This study highlighted that leaves, fruit and barks of Terminalia *arjuna* have been used in traditional system of medicine for multiple different disorders and diseases].

World Health Organization. (2002) WHO Traditional medicine strategy Report. Document WHO/EDM/TRM. [According to WHO, almost 80% of the world's population depends on traditional herbal medicine and in India still now 85% of peoples use crude plant preparation for the treatment of various diseases].

Yadav RN, Rathore K. (2001) A new cardenolide from the roots of *Terminalia arjuna*. *Fitoterapia*. 2001 May 1;72(4):459-61. [This study highlighted that 16, 17-Dihydro neridienone, 3-O-b-D glucopyranosyl (1 6) -O-β-D galactopyranoside isolated from the root of T. *arjuna*, is known to possess cardioprotective activity].

Yaidikar L, Thakur S. (2015) Arjunolic acid, a pentacyclic triterpenoidal saponin of *Terminalia arjuna* bark protects neurons from oxidative stress associated damage in focal cerebral ischemia and reperfusion. *Pharmacological Reports*. 2015 Oct 1;67(5):890-5. [This study reported that pre-treatment with arjunolic acid isolated from Terminalia *arjuna* bark extract efficiently prevented the cerebral I/R induced oxidative damage by virtue of its antioxidant activity and supplementation of arjunolic acid may be beneficial in stroke prone population].

Yegnanarayan R, Sangle SA, Sirsikar SS, Mitra DK. (1997) Regression of cardiac hypertrophy in hypertensive patients—comparison of Abana with propranolol. Phytotherapy Research: An *International*

Journal Devoted to Medical and Scientific Research on Plants and Plant Products. 1997 May;11(3):257-9. [This study highlighted the hypotensive effect of Terminalia *arjuna*].

Biographical sketches

Dr. Mousumi Mitra completed her Ph.D. degree from University of Calcutta in the field of herbal nanomedicines and nanotechnology. Her area of research is alternative management of liver and kidney disease through herbal nanomedicines. She also works in the field of stress management, nutritional health survey and management. She had published several scientific research articles in peer reviewed national and international journals. She had received Newton Bhabha Ph.D. Placement in 2019

Dr. Dilip Kumar Nandi worked as an Associate Professor and HOD, in the Department of Physiology, Food Science & Nutrition and BMLT of Raja Narendra Lal Khan Women's College. He has been actively associated with teaching profession for more than 41 years in undergraduate and postgraduate level. He advised more than 20 Ph.D. students and many research scholars are still working under him. His area of research is alternative management of liver and kidney disease through phytotherapy, functional foods, probiotics, and herbal nanomedicines. He also works in the field of stress management, nutritional health survey and management. Presently he supervises several students of Vidyasagar University, University of Calcutta, and Jadavpur University. He published more than 70 scientific research articles in peer reviewed national and international journals. Dr. Nandi is a Fellow of Physiological Society of India (FPSI) and Vice-President of South Asia Association of Physiology (SAAP). He was awarded B.B. Sarkar Memorial Oration in 2004 by the PSI. He is an active Member Secretary of Animal and Human Ethical Committee of the institution under CPCSEA and ICMR. He had also participated as the Principal investigator of several projects funded by DST, DBT, UGC, ICMR, WBDST and DRDO.