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Terminalia arjuna (Roxb.) Wt. and Arn.: A Review

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Abstract: *Terminalia arjuna* (Roxb.) Wt. and Arn. (Arjuna; Combretaceae) is a widely used medicinal plant throughout India and popular in various Indigenous System of Medicine like Ayurveda, Siddha and Unani. In the Indian System of Medicine, the bark are used as astringent, cooling, aphrodisiac, cardiotonic, tonic, in fractures, ulcers, spermatorrhoea, leucorrhoea, diabetes, cough, tumour, excessive perspiration, asthma, inflammation and skin disorders etc. The present review is therefore, an effort to give a detailed survey of the literature on pharmacognosy, phytochemistry and pharmacological activities of the plant.

Key words: *Terminalia arjuna*, arjuna, pharmacognosy, phytochemistry, pharmacology, review, combretaceae, medicinal plant, bark

INTRODUCTION

To cure human disease, medicinal plants has been a major source of therapeutic agents since ancient times. The revival of interest in natural drugs started in last decade mainly because of the wide spread belief that green medicine is healthier than synthetic products. Nowadays, there is manifold increase in medicinal plant based industries due to the increase in the interest of use of medicinal plants throughout the world which are growing at a rate of 7-15% annually. Despite the major advances in the modern medicine, the development of new drugs from natural products is still considered important. This seems to be even more relevant for the developing countries, where the cost to develop a drug is prohibitive. Since 1980, the World Health Organization has been encouraging countries to identify and exploit traditional medicine and phytotherapy. The main Indian Traditional System of Medicine namely Ayurveda and Siddha are primarily plant based system. The evaluation of new drugs especially phytochemically obtained materials has again opened a vast area for research and development. As per WHO, about 80% of the population in the world relays on the traditional medicine for the treatment of various diseases. Therefore, the evaluation of rich heritage of traditional medicine is essential (Padmaa *et al*., 2008; Padmaa, 2009a-d; Salim and Padmaa, 2009; Sandeep and Padmaa, 2009). In this regard, one such plant is *Terminalia arjuna* (Roxb.) Wt. and Arn. which is a large evergreen tree (Anonymous, 1976) distributed throughout the greater part of the Indian Peninsula along rivers and found in Sub-Himalayan tract, Chota Nagpur, Orissa, West Bengal, Punjab, Deccan and Konkan (Warrier *et al*., 1994; Anonymous, 1999; Chopra *et al*., 1958; Kirtikar and Basu, 1989). In the Indian System of Medicine, the bark are used as astringent, cooling, aphrodisiac, cardiotonic, tonic, in fractures, ulcers, spermatorrhoea, leucorrhoea, diabetes, cough, tumour, excessive perspiration, asthma, inflammation and skin disorders etc (Warrier *et al*., 1994; Dwivedi and Udupa, 1989). The aim of present review is to highlight the traditional uses, pharmacognostical, phytochemical and pharmacological investigation carried out on the plant so that more pharmacological studies could be conducted to investigate the unexploited potential.

PLANT PROFILE

Terminalia arjuna (Roxb.) Wt. and Arn. (Combretaceae) commonly known as Arjuna, large evergreen tree distributed throughout the greater part of the Indian Peninsula along rivers and found in Sub-Himalayan tract, Chota Nagpur, Orissa, West Bengal, Punjab, Deccan and Konkan (Warrier *et al*., 1994; Nadkarni, 1976).

Taxonomical/ Scientific classification (Web page):

- Kingdom : Plantae
- Division : Magnoliophyta
- Class : Magnoliopsida
- Order : Myrtales
- Family : Combretaceae

- Genus : *Terminalia*
- Species : *arjuna*

Classical names: Arjuna, Dhavala, Kakubha, Nadisarja, Veeravriksha, Partha, Indradru (Sharma *et al*., 2005).

Botanical description: The tree is about 60-80 feet height. Arjuna is large, evergreen with a spreading crown and dropping branches. In favorable localities and especially along the banks of streams, the tree attains very large sizes. Two trees of 26 feet and 32 feet in girth at 5 feet from the ground have been recorded in the village of Manipur in Jammu and Kashmir. Leaves sub-opposite, oblong or elliptic, coriaceous, cordate, shortly acute or obtuse at the apex. Flowers in panicled spikes. Fruits ovoid or ovoid-oblong, 2.5-5.0 cm long, nearly glabrous, with 5-7 hard, winged angles (Nadkarni, 1976; Gupta, 1998; Cooke, 1967).

Climate, soil and propagation: It is generally cultivated on variety of soils but prefers fertile alluvial loam and deep sandy well drained soil (Nadkarni, 1976; Atal and Kapur, 1982; Handa and Kaul, 1996). It is propagated by seeds and stump planting (Kumari, 1998). Cotyledonary node explants excised from 21 day old seedlings of *T. arjuna* produced multiple shoots when cultured on full strength MS or modified MS (1/2 strength major salts and Fe-EDTA) medium supplemented with different concentrations (0.1-1.0 mg L^{-1}) of BAP. Maximum 8.9 shoots/explants could be recorded after 30 days of inoculation on modified MS medium supplemented with BAP (0.5 mg L^{-1}). A proliferating shoot culture was established by reculturing the original cotyledonary nodes (2-3 times) on shoot multiplication medium after each harvest of the newly formed shoots. Shoots (each having 2-3 nodes/shoot) thus obtained were also used as a source of nodal explants that gave rise to 1-2 shoots when cultured on modified MS+BAP (0.5 mg L^{-1}) medium. Thus, 45-55 shoots could be obtained after 60 days of culture initiation from a single cotyledonary node. About 88% shoots rooted well after 15 h pulse treatment with IBA (1 mg L^{-1}) in liquid MS medium followed by transfer to modified MS medium without IBA. About 80% of these plantlets were successfully acclimatized in plastic pots containing sand and soil mixture and 70% plantlets transferred in the field those survived even after 6 months of transplantation (Pandey and Jaiswal, 2002).

PHARMACOGNOSTICAL STUDIES

Macroscopical characteristics (Ali, 1994)

Stem bark: It is simple, grey and smooth on external surface. The bark is thick, soft and of red color from inside. Taste is bitter.

Leaves: Leaves are like that of guava leaves, oblong and 4-6 inch long and 2-3 inch wide, sub opposite, glabrous and often inequilateral. There is two glands near the base of the petiole. The margin is crenulate with apex at obtuse or sub acute angle. The base is rounded or cordate. Petioles run for 0.5 to 1.3 cm.

Flowers: White or yellowish flowers are found in groups. Flowering occurs in summer and fruit appears in winter or spring season.

Fruits: The fruits are 1-1.5 inch in diameter and with 5-7 longitudinal lobes. These are glabrous with 5-7 wings, woody and fibrous. Fruit is drupe and is often notched near the top, marked with oblique upward curving striations.

Microscopical and powder characteristics

Stem bark: Transverse section of Stem bark shows cork, thin-walled parenchymatous ground tissue with embedded crystals of calcium oxalate and secondary phloem with patches of sclerchyma fibres, mucilage secreting ducts and tanniferous cells. Mature bark shows a broad zone of phloem consisting of ceratenchyma, phloem parenchyma, phloem fibres and crystal fibres with rosette crystals of calcium oxalate (Ali, 1994; Mitra, 1985; Raghunathan and Mitra, 1982).

Leaves: It shows dorsiventral, epidermis is single layered, cuticularised. Upper and lower epidermis bear unicellular glandular and non- glandular trichomes and lower epidermis is provided with ranunculaceous stomata. In the midrib region inside epidermis, several layers of thick walled collenchymatous and thin walled parenchymaatous tissues surrounds the central vascular bundle which is open, bicollateral type. Few secretory canals are observed in parenchymatous tissue and central region. Abundant cluster crystals of calcium oxalate are present in phloem and parenchymatous tissues. Palisade is double layered. Stomatal index is 14.0 -15.5; vein islet number 11-19 per sq mm and palisade ratio from 7-12 (Ali, 1994; Mitra, 1985; Raghunathan and Mitra, 1982).

Fruit: It shows epidermis and hypodermis. Secretory canals, ducts and vascular supply are present. Seeds are

composed of stone cells, fibres and vascular bundle (Ali, 1994; Mitra, 1985; Raghunathan and Mitra, 1982).

The powdered bark showed pinkish white fluorescence in ether solvent. In petroleum ether, it shows pinkish red fluorescence. Fibrous powder exhibits parenchymatous cells of the cortex and phloem containing clusters and rosette of calcium oxalate crystals, starch grains, tannins and reddish brown pigment; fragments of thin walled phloem fibres associated with idioblasts containing rosette and cluster crystals of calcium oxalate and longitudinal radially cut medullary rays (Sarin, 1996).

Physical constants of the stem bark: Foreign matter: not more than 2 % w/w; total ash: not more than 27.0% w/w; acid insoluble ash: not more than 2.0% w/w; alcohol soluble extractive: not less than 16% w/w; water soluble extractive: not less than 17% w/w (Anonymous, 2005).

Important marketed formulations: Arjunarishta, Arjuna ghrita, Arjunadisiddha kshira, Kakubhadi kshira, Shankara vati, Kakubhadi churna, Dhatakyadi taila (Anonymous, 1999).

Doses: Bark juice: 10- 20 mL; powder: 3- 6 g; decoction: 50-100 mL (Anonymous, 1999).

Traditional uses

- **Fruit:** Tonic and deobstruent
- **Leaves:** Juice for earache
- **Plant parts used:** Stem bark, fruit and leaves (Warrier *et al*., 1994; Kumar and Prabhakar, 1987)

Stem bark: Astringent, cooling, aphrodisiac, cardiotonic, demulcent, styptic, antidysentric, urinary astringent, expectorant, alexiteric, lithontriptic tonic, in fractures, ulcers, urethrorrhoea, spermatorrhoea, leucorrhoea, diabetes, anemia, cardiac disorders, cough, tumor, excessive perspiration, fatigue, asthma, bronchitis, intrinsic hemorrhage, otalgia, diarrhea associated with blood, cirrhosis of liver, hypertension, inflammation and skin disorders.

- Fruit: Tonic and deobstruent
- Leaves: Juice for earache

Ayurvedic properties

- Rasa: Kashaya
- Guna: Laghu, Ruksha
- Veerya: Sheeta
- Prabhava: Hridya
- Doshaghnata: Kaphapittashamaka
- Rogaghnata: Vrana, Raktasrava, Asthibhagna, Raktatisara, Raktapradara, Charmaroga, Arsha, Prahema, Jeernajwara
- Karma: Raktastambhana, Sandhaneeya, Vranaropana, Stambhana, Hridya, Hridayottejaka, Raktaprasadana, Kaphaghna, Mootrasangrahaneeya, Jwaraghna, Medohara, Vishaghna, Balya (Anonymous, 1999).

PHYTOCHEMICAL STUDIES

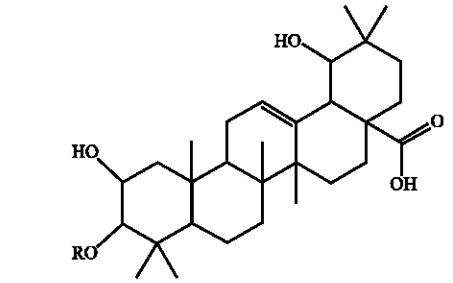
Very little phytochemical work has been carried out with the plant *Terminalia arjuna*. The structures of the compound isolated from the plant are given in Plate 1.

Stem bark: Arjunolic acid, tomentosic acid, β-sitosterol, ellagic acid, (+)- leucodelphinidin (Rastogi and Mehrotra, 1993a), arjunic acid (Row *et al*., 1970a); arjunetin (Row *et al*., 1970b), arjungenin, arjunglucoside I and II (Rastogi and Mehrotra, 1993b), tannins containing catechin, gallocatechin, epicatechin, epigallocatechin (Rastogi and Mehrotra, 1993c), arjunolone, baicalein (Sharma *et al*., 1982; Sharma, 1996), arjunglucoside III (Rastogi and Mehrotra, 1993c), terminoic acid (Ahmad *et al*., 1983), arjunolitin (Tripathi *et al*., 1992), arjunglucoside IV, V (Wang *et al*., 2010a), arjunasides A-E (Wang *et al*., 2010b), 2α, 3β-dihydroxy urs-12, 18 dien-28-oic acid 28-O-β-D-glucopyranosyl ester (Wang *et al*., 2010c), casuarianin (Kuo *et al*., 2005a), arjunophthanoloside (Ali *et al*., 2003a), terminoside A (Ali *et al*., 2003b), arjunin (Kandil and Nassar, 1998), terminarjunoside I, II (Alam *et al*., 2008).

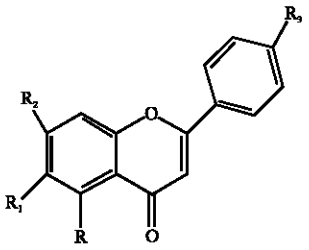
Fruit: Arjunone, cerasidin, β- sitisterol, friedelin, methyl oleanolate, gallic acid, ellagic acid, arjunic acid, hentriacontane, myristyl oleate, arachidic stearate (Rastogi and Mehrotra, 1993c), terminolitin (Singh *et al*., 1995).

Root bark: Arjunoside I, II, 8- hydroxyl hexadecanoic, oleanolic, arjunic acids, arjunolic acid, β-sitosterol (Anjaneyulu and Ram-Prasad, 1982a), terminic acid (Anjaneyulu and Ram-Prasad, 1983), arjunoside III, IV, arjunoside I, arjunetin, ellagic acid, gallic acid, leucocyanidin (Anjaneyulu and Ram-Prasad, 1982b), arjunetoside (Upadhyay *et al*., 2001), 16, 17-dihydroneridienone 3-O-β-D-glucopyranosyl-(1→6)-O-β-D-galactopyranoside (Yadav and Rathor, 2001).

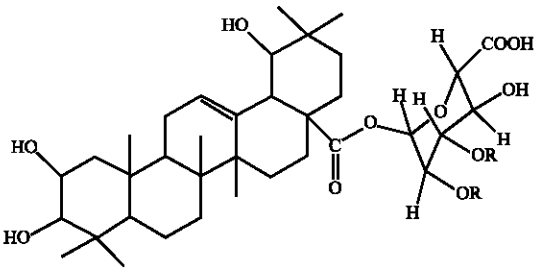
Seeds: 14, 16-dianhydrogitoxigenin 3-β-D-xylopyranosyl-(1>2)-O-β-D-galactopyranoside (Yadav and Rathore, 2000).



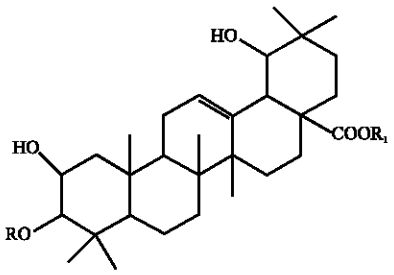
1: R = H, Arjunic acid
2: R = beta-D(+)-galactose, Arjunoside I
3: R = beta-D-(+)-ghicosyl-L-2-deoxyrhamnamnose, Arjunoside II
4: R = Alpha-L-rhamnopyranose, Arjunoside IV



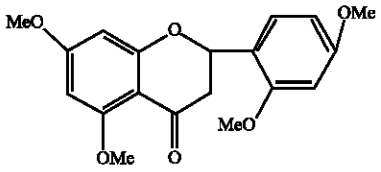
R = H; R1 = R3 = OH; R = OMe; Arjunolone
R = R1 R2 =OH; R3 = H; Baicalein



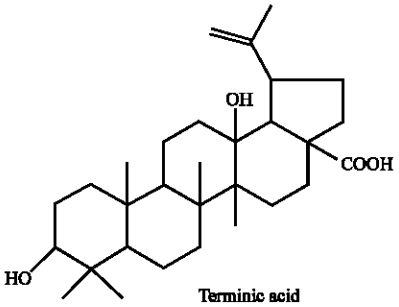
Arjunoside III



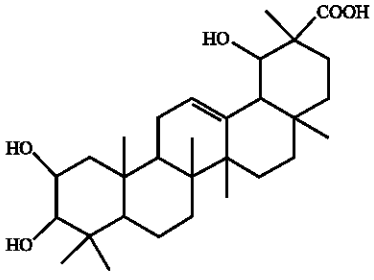
R = Gal, R1 = H; Arjunoside I
R = Ghi-2-Deoxyrha, R1 = H; Arjunoside II
R = H, R1 = Gluc. acid; Arjunoside III
R = Rha, R1 = H; Arjunoside IV



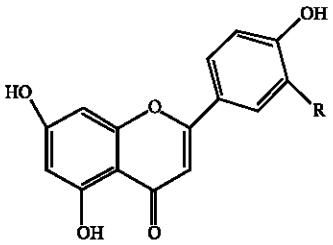
Arjunore



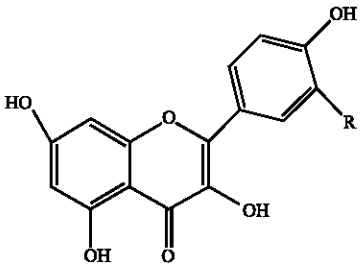
Terminic acid



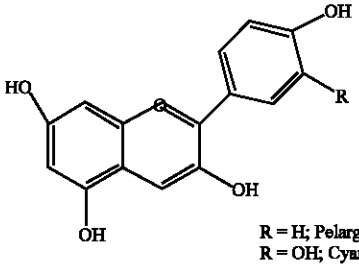
Terminoic acid



R = H; Apigenin
R = OH; Luteolin



R = H; Kaempferol
R = OH; Quercetin



R = H; Pelargonidin
R = OH; Cyanidin

Plate 1: Continued

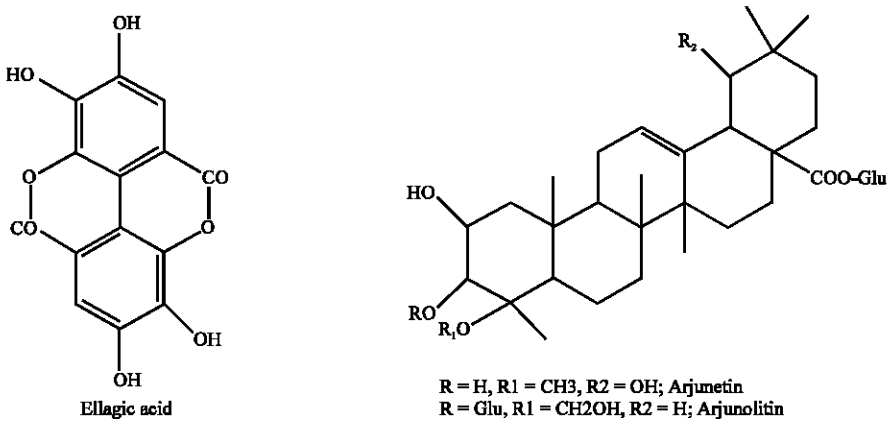


Plate 1: The structures of compounds isolated from *Terminalia arjuna*

PHARMACOLOGICAL STUDIES

The popularity of the plant was highly enhanced by the ideological belief in the herb as a cure for multiple diseases. The detailed pharmacological activities of *Terminalia arjuna* are given below:

Cardiovascular activity: The effect of aqueous extract of *T. arjuna* bark at 63, 125 and 250 mg kg^{-1} for antifibrotic and antioxidant effects in rats along with the selective beta-adrenoceptor agonist isoprenaline (5 mg kg^{-1} s.c.) for 28 days were evaluated. The *T. arjuna* bark extract significantly prevented the isoprenaline-induced increase in oxidative stress, decline in endogenous antioxidant level and also prevented fibrosis but not the increase in heart weight : body weight ratio suggesting it can prevent myocardial changes induced by chronic beta-adrenoceptor stimulation (Kumar *et al*., 2009).

The antioxidative properties of an ethanol extract of the bark of *T. arjuna* [TAEE] against sodium fluoride (NaF)-induced oxidative stress in murine heart was investigated. The activities of various antioxidant enzymes (superoxide dismutase, catalase and glutathione S-transferase), levels of cellular metabolites, reduced glutathione and oxidized glutathione, levels of lipid peroxidation end products and protein carbonyl contents were determined in the cardiac tissues. NaF intoxication significantly altered all the indices related to the prooxidant-antioxidant status of the heart; treatment with the active constituents prior to NaF administration prevented these alterations. In addition, the ferric reducing/antioxidant power assay revealed that TAEE enhanced the cardiac intracellular antioxidant activity. Histological studies also demonstrated a cardio protective action of TAEE. The combined results suggest that TAEE protects murine hearts from NaF-induced oxidative stress, probably via its antioxidant properties (Sinha *et al*., 2008).

The effects of butanolic fraction of *T. arjuna* bark (TA-05; 0.42, 0.85, 1.7, 3.4 and 6.8 mg kg^{-1} for 6 days $week^{-1}$ for 4 weeks) on Doxorubicin (Dox; 20 mg kg^{-1} i.p.)-induced cardio toxicity was evaluated in Male wistar rats. Co-treatment of TA-05 and Dox resulted in an increase in the cardiac antioxidant enzymes, decrease in serum CKMB levels and reduction in lipid peroxidation as compared to Dox-treated animals. Electron microscopic studies in Dox-treated animals revealed mitochondrial swelling, Z-band disarray, focal dilatation of Smooth Endoplasmic Reticulum (SER) and lipid inclusions, whereas the concurrent administration of TA-05 led to a lesser degree of Dox-induced histological alterations suggesting that butanolic fraction of *T. arjuna* bark has protective effects against Dox-induced cardio toxicity and may have potential as a cardio protective agent (Singh *et al*., 2008).

The cardio protective effect of the 70% ethanol extractable active constituents of the bark of *T. arjuna* (TA) against CCl_4 induced oxidative insult in cardiac tissue in mice was evaluated. Oral treatment of the active constituents of TA at a dose of 50 mg kg^{-1} b.wt. for 7 days prior to CCl_4 administration significantly restored the activities of all antioxidant enzymes as well as increased the level of GSH and decreased the level of lipid peroxidation end products. In addition, FRAP assay showed that the active constituents of TA enhanced the cardiac intracellular antioxidant activity. Histological studies also supported the cardio protective role of the active constituents suggesting cardio protective action against CCl_4 induced oxidative insult (Manna *et al*., 2006).

The possible involvement of thyroid hormones in the amelioration of cardiac and hepatic lipid peroxidation (LPO) by a bark extract of *T. arjuna* in albino rats was investigated. Simultaneous administration of 21.42 and 42.84 mg kg^{-1} of the plant extract decreased the level of thyroid hormones and also the cardiac LPO, suggesting

the possible mediation of the drug action through an inhibition in thyroid function. When the drug was administered to euthyroid animals, serum concentrations of thyroid hormones were decreased, whereas the hepatic LPO increased indicating a drug induced toxicity in euthyroid subjects. Since in euthyroid animals, thyroid hormones were decreased and hepatic LPO was increased which suggested that high amounts of this plant extract should not be consumed, as hepatotoxicity as well as hypothyroidism may be caused (Parmar *et al*., 2006).

The oleanane triterpenes arjunic acid, arjungenin and their glucosides, arjunetin and arjunglucoside II, were isolated from the bark of *T. arjuna*. Arjungenin and its glucoside exhibited a moderate free radical scavenging activity while all the compounds showed no effect on the superoxide release from PMN cells. Further arjungenin also exhibited greater inhibitory action on the hypochlorous acid production from human neutrophils suggesting that it is a very good cardio protective drug on the process of respiratory oxyburst (Pawar and Bhutani, 2005).

Oral administration of TA 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 TA treated rabbit hearts which provides scientific basis for the putative therapeutic effect of TA in ischemic heart disease (Ramesh *et al*., 2004).

The present study was aimed to find the effect of 70% alcoholic extract of *T. arjuna* (5 to15 mg kg^{-1}) on anaesthetized dog blood pressure and probable site of action. Intravenous administration of *T. arjuna* produced dose-dependent hypotension in anaesthetized dogs. The hypotension produced by 6 mg kg^{-1} dose of the extract was blocked by propranolol but not by atropine or mepyramine maleate. This indicates that muscarinic or histaminergic mechanisms are not likely to be involved in the hypotension produced by the extract. The blockade by propranolol of the hypotension produced by *T. arjuna* indicates that the extract might contain active compound(s) possessing adrenergic β2-receptor agonist action and/or that act directly on the heart muscle which lends support for the claims of its traditional usage in cardiovascular disorders (Nammi *et al*., 2003).

The effects of chronic administration of the alcoholic extract of *T. arjuna* (TAAE; [3.4 mg kg^{-1}: (T1), 6.75 mg kg^{-1}: (T2) and 9.75 mg kg^{-1}: (T3)] 6 days $week^{-1}$) bark on isoproterenol induced myocardial injury for 4 weeks was evaluated. The 6.75 mg kg^{-1} TAAE treatment group (baseline) shows a significant increase in myocardial TBARS as well as endogenous antioxidants (GSH, SOD and catalase), but not in the other treatment groups. In *in vivo* ischemic reperfusion injury of the TAAE treated rats there was a significant decrease in TBARS in all the groups. In 6.75 mg kg^{-1} treatment group, a significant rise in the levels of GSH, SOD and catalase were observed and it shows better recovery profile than the other groups subjected to *in vivo* ischemic reperfusion injury. In histological studies, all the groups, except the isoproterenol treated group, showed preserved myocardium. The present study demonstrates that the 6.75 mg kg^{-1} TAAE augments endogenous antioxidant compounds of the rat heart and also prevents the myocardium from isoproterenol induced myocardial ischemic reperfusion injury (Karthikeyan *et al*., 2003).

The antiatherogenic effect of a herbal formulation, Caps HT2 (methanolic extracts of selected parts of plants, *Commiphora mukul*, *Allium sativum*, *Plumbago indica*, *Semecarpus anacardium*, *Hemidesmus indicus*, *Terminalia arjuna*, *Tinospora cordifolia*, *Withania somnifera* and *Ocimum sanctum*) were evaluated as antioxidant, anticoagulant, platelet antiaggregatory, lipoprotein lipase releasing, anti-inflammatory and hypolipidaemic activity in rats. The Caps HT2 was found to scavenge superoxide and hydroxyl radicals; the IC_{50} required being 55.0 and 610.0 μg mL^{-1}, respectively. The lipid peroxidation was found inhibited (50%) by 48.5 μg mL^{-1} of Caps HT2. The intravenous administration of the formulation (5 mg kg^{-1}) delayed the plasma recalcification time in rabbits and enhanced the release of lipoprotein lipase enzyme significantly. The formulation also inhibited ADP induced platelet aggregation *in vitro*, which was comparable to commercial heparin. The anti-inflammatory action of the formulation was significant with acute and chronic inflammations induced by carrageenan and formalin respectively in rats. The hypolipidaemic effect of Caps HT2 changes such as decreased R amplitude and increased ST segment elevation and has resulted was significant with the administration of the formulation, in diet-induced hyperlipidaemia of rats for a period of 30 days. Oral administration of the formulation, Caps HT2 (100, 200, 300 and 400 mg kg^{-1}) significantly raised HDL cholesterol levels. The atherogenic index and the reduction in body weight were significant indicating the effectiveness against hyperlipidaemia and obesity. All these results revealed the therapeutic potential of Caps HT2 against vascular intimal damage and atherogenesis leading to various types of cardiovascular problems (Mary *et al*., 2003).

Arjunolic acid from the bark of *T. arjuna*, has been shown to provide significant cardiac protection in isoproterenol induced myocardial necrosis in rats. To explore the mechanism of action of arjunolic acid as cardiac protective, antiplatelet activity, anticoagulant assays, electrocardiographic changes, serum marker enzymes, antioxidant status, lipid peroxide and myeloperoxidase (MPO) have been measured. Arjunolic acid at an effective dosage of 15 mg kg^{-1} b.wt. (pre and post treatment), when administered intraperitoneally (i.p.), effects a decrease in serum enzyme levels and the electrocardiographic changes get restored towards normalcy. Arjunolic acid treatment is also shown to prevent the decrease in the levels of superoxide dismutase, catalase, glutathione peroxidase, ceruloplasmin, alpha-tocopherol; reduced glutathione (GSH), ascorbic acid, lipid peroxide, MPO and the cardio protection is confirmed by the histopathological studies. This study shows that the cardio protection of arjunolic acid pre and post treatment could possibly be due to the protective effect against the damage caused by myocardial necrosis (Sumitra *et al*., 2001).

T. arjuna showed significant DPPH radical scavenging activity with EC_{50} 8.3±0.3 μg mL^{-1} (similar to L-ascorbic acid). In the deoxyribose damage protection assay, *T. arjuna* demonstrated no significant effect in the concentration range 0-20 μg mL^{-1}, but above -20 μg mL^{-1} concentration (20-125 μg mL^{-1}), a pro-oxidant activity was observed. At a dose of 90 mg kg^{-1} (single dose) *T. arjuna*, cardiac lipid peroxidation in male Wistar rats was reduced by 38.8%±2.6%. *T. arjuna* demonstrated the highest antioxidant activity which can be used in the therapy of cardiovascular disease by exerting its beneficial effects via antioxidant activity (Munasinghe *et al*., 2001).

Dried pulverized bark of *T. arjuna* (TA) was administered orally to Wistar albino rats (120-150 g) in two doses [500 and 750 mg kg^{-1} in 2% carboxy methyl cellulose (CMC)], 6 days per week for 12 weeks. There was significant increase in the baseline contents of thiobarbituric acid reactive substance (TBARS) with both doses of TA. However, only in the 500 mg kg^{-1} treated group, this was accompanied by a simultaneous increase in SOD, GSH and CAT levels, but not in the 750 mg kg^{-1} treated group, where only CAT was raised. Only hearts, harvested from the 500 mg kg^{-1} rats treated rats, were significantly protected from oxidative stress, when subjected to *in vitro* ischemic reperfusion injury. The results suggest that crude bark of TA augments endogenous antioxidant compounds of rat heart and also prevents oxidative stress associated with IRI of the heart (Gauthaman *et al*., 2005).

A test drug (Lipistat) comprising of equal-proportions of extracts of *Terminalia arjuna, Inula racemosa* Hook, latex of *Commiphora mukul*, in three different doses (225, 350, 450 mg kg^{-1}) were administered orally daily for 6 days a week for 60 days in rats. Thereafter, the rats were subjected to isoproterenol (ISO) induced (85 mg kg^{-1}, s.c. for 2 days) myocardial necrosis. Gross and microscopic examinations (histopathology) were done along with estimations of myocardial tissue High Energy Phosphates (HEP) stores and lactate content. Gross examination showed significant ($p<0.05$) cardio protection in Lipistat treated animals. On microscopic examination no statistically significant reduction in myocardial damage by 350 and 450 mg kg^{-1} of Lipistat were observed although loss of myocardial HEP stores and accumulation of lactate were significantly prevented. The results of the present study suggest the potential usefulness of Lipistat in the prevention of ischemic heart disease (Seth *et al*., 1998).

The present study was carried out to examine the underlying mechanism of the cardiovascular effects of aqueous solution of *T. arjuna* extract. Intravenous administration of the extract was found to induce dose dependent decrease in blood pressure and heart rate. These extracts also inhibited carotid occlusion response, without affecting the pressor responses, induced by intravenous injection of nor epinephrine and by electrical stimulation of preganglionic fibres of the abdominal splanchnic nerve. Hypotension and bradycardia were also observed following the injection of the extract into the lateral cerebral ventricle and vertebral artery which suggest that the hypotensive and bradycardiac effects of *T. arjuna* are mainly of central origin (Singh *et al*., 1982).

Antiinflammatory activity: *T. arjuna* bark powder (400 mg kg^{-1}, p.o.) significantly reduced formalin-indued paw edema at 24 h but not carrageenan-induced paw edema suggesting its role in prevention of inflammation (Halder *et al*., 2009).

The present study was undertaken to evaluate the antioxidant and anti-inflammatory effects of BHUx which is a polyherbal formulation consisting of water-soluble fractions of five medicinal plants (*Commiphora mukul*, *Terminalia arjuna*, *Boswellia serrata*, *Semecarpus anacardium* and *Strychnos nux vomica*). Under *in vivo* conditions, BHUx significantly reduced inflammation in the carrageenan-induced rat paw oedema model of inflammation, suggesting its anti-inflammatory properties. In order to test the mechanism of action of BHUx, further *in vitro* studies were undertaken on cumene-hydroperoxide-induced lipid peroxidation (CHP) in liver

homogenate, LPS-induced NO production in peritoneal macrophages and on key enzymes of arachidonic acid cascade, involved in the mediation of inflammation. BHUx showed concentration-dependent inhibition of CHP-induced lipid peroxidation in liver homogenate, suggesting its antioxidant properties. Similarly the potent anti-inflammatory effects of BHUx are evident by (a) preferential inhibition of COX-2 (IC_{50} for COX-2 = 80 μg mL^{-1} and IC_{50} for COX-1 = 169 μg mL^{-1}), (b) low ratios in the IC_{50} values of COX-2/COX-1 (0.47), (c) decreased production of NO in LPS-induced peritoneal macrophages and (d) inhibition of 5-LOX (IC_{50} = 795 μg mL^{-1}). BHUx also showed a preference for inhibiting 15-lipoxygenase (IC_{50} = 44 μg mL^{-1}), a key enzyme implicated in LDL oxidation. These studies suggest that BHUx is acting mainly at three levels, i.e., as a potent natural antioxidant, by reduction of key inflammatory mediators of arachidonic acid cascade and by preventing 15-LOX-mediated LDL oxidations, to prevent atherosclerosis (Tripathi *et al*., 2004).

Arjunaphthanoloside isolated from the stem bark of *T. arjuna* showed potent antioxidant activity and inhibited Nitric Oxide (NO) production in lipopolysaccharide (LPS)-stimulated rat peritoneal macrophages (Ali *et al*., 2003a).

Terminoside A isolated from the acetone fraction of the ethanolic extract of stem bark of *T. arjuna* potently inhibited Nitric Oxide (NO) production and decreased Inducible Nitric Oxide Synthase (iNOS) levels in lipopolysaccharide-stimulated macrophages (Ali *et al*., 2003b).

Antitumor activity: The effect of a bark extract of *T. arjuna* (TAE) was studied on the alteration of adriamycin (ADR)-induced micronuclei formation in cultured human peripheral blood lymphocytes. Pretreatment of lymphocytes with TAE before ADR treatment resulted in a significant decline in micronuclei formation. Prior exposure of lymphocytes to 15 μg mL^{-1} of TAE significantly reduced the frequency of lymphocytes bearing one, two and multiple micronuclei when compared with ADR-treated control. TAE-inhibited the induction of (*) OH (hydroxyl), O_2 (*-) (superoxide), DPPH (1, 1-diphenyl-2-picrylhydrazyl), ABTS (*+) (2, 2-azino-bis-3-ethyl benzothiazoline-6-sulphonic acid) radicals in a dose-dependent manner. These results demonstrate that TAE protects DNA against ADR-induced damage (Reddy *et al*., 2008).

The effect of aqueous extract of *T. arjuna* on antioxidant defense system in lymphoma bearing AKR mice was evaluated. Oral administration of different doses of aqueous extract of *T. arjuna* causes significant elevation in the activities of catalase, superoxide dismutase and glutathione S transferase. *T. arjuna* is found to down regulate anaerobic metabolism by inhibiting the activity of lactate dehydrogenase in lymphoma bearing mice, which was elevated in untreated cancerous mice. The results indicate the antioxidant action of aqueous extract of *T. arjuna*, which may play a role in the anti carcinogenic activity by reducing the oxidative stress along with inhibition of anaerobic metabolism (Verma and Vinayak, 2009).

(1) Arjunic acid, (2) arjungenin, (3) arjunetin and (4) arjunoglucoside I isolated from the bark of *T. arjuna* were evaluated for cytotoxicity activity. Out of the four compounds, arjunic acid (1) was significantly active against the human oral (KB), ovarian (PA 1) and liver (HepG-2 and WRL-68) cancer cell lines suggesting its role in anticancer treatment (Saxena *et al*., 2007).

The effect of ethanol extract of *T. arjuna* bark on carbohydrate metabolizing enzymes of N-nitrosodiethylamine induced hepatocellular carcinoma in Wistar albino rats were studied. The plasma and liver glycolytic enzymes such as hexokinase, phosphoglucoisomerase, aldolase were significantly increased in cancer induced animals while glyconeogenic enzyme; glucose-6-phosphatase was decreased. These enzymes were reverted significantly to near normal range in treated animals after oral administration of *T. arjuna* for 28 days. The modulation of the enzymes constitutes the depletion of energy metabolism leads to inhibition of cancer growth. This inhibitory activity may be due to the anticancer activity of constituents present in the ethanol extract of *T. arjuna* (Sivalokasnathan *et al*., 2005).

Casuarinin, hydrolysable tannin isolated from the bark of *T. arjuna* was investigated for its antiproliferative activity in human breast adenocarcinoma MCF-7 cells. The results showed that casuarinin inhibited the proliferation of MCF-7 by blocking cell cycle progression in the G0/G1 phase and inducing apoptosis. An enzyme-linked immunosorbent assay showed that casuarinin increased the expression of p21/WAF1 concomitantly as the MCF-7 cells underwent G0/G1 arrest. An enhancement in Fas/APO-1 and its two forms of ligands, membrane-bound Fas ligand (mFasL) and soluble Fas ligand (sFasL), might be responsible for the apoptotic effect induced by casuarinin. The induction of p21/WAF1 and the activity of Fas/Fas ligand apoptotic system may participate in the antiproliferative activity of casuarinin in MCF-7 cells (Kuo *et al*., 2005a).

Casuarinin isolated from the bark of *T. arjuna* inhibits human non-small cell lung cancer A549 cells by blocking cell cycle progression in the G0/G1 phase and inducing

apoptosis. Enzyme-linked immunosorbent assay showed that the G0/G1 phase arrest is due to p53-dependent induction of p21/WAF1. An enhancement in Fas/APO-1 and the two forms of Fas ligand (FasL), membrane-bound FasL and soluble FasL, might be responsible for the apoptotic effect induced by casuarinin. The result suggests the antiproliferative activity of casuarinin in A549 cells (Kuo *et al*., 2005b).

The antigenotoxic properties of sequential extraction using acetone, methanol, methanol + HCl, chloroform, ethyl acetate and ethyl ether extracts were investigated by assessing the inhibition of genotoxicity of the direct acting mutagen 4-nitroquinoline-N-oxide (4NQO) using the comet assay and the micronucleus (MN) test. The results showed that acetone and methanol extracts were highly effective in reducing the DNA damage caused by 4NQO, whereas the acidic methanol, chloroform, ethyl acetate and ethyl ether extracts showed less marked or no antigenotoxic activity. In the MN test, a decrease in 4NQO genotoxicity was observed by testing this mutagen in the presence of acetone, methanol, chloroform and ethyl acetate extracts (Scassellati-Sforzolini *et al*., 1999).

Similar results were performed with the chloroform, acetone, methanol, methanol+HCl, diethyl ether and ethyl acetate extracts of *T. arjuna* bark. The 4-NQO mutagenicity was inhibited by more than 70% in the *Salmonella*/microsome test at the highest nontoxic extract dose of ethyl acetate (50 μg plate^{-1}), chloroform (100 μg plate^{-1}), acetone, (100 μg plate^{-1}) and methanol (500 μg plate^{-1}). A less marked antimutagenicity activity (inhibition of about 40-45%) was observed for the acidic methanol and diethyl ether extracts. The comet assay showed that acetone extract (100 μg mL^{-1}) was more effective in reducing the DNA damage caused by 4-NQO, whereas the chloroform, ethyl acetate and diethyl ether extracts were cytotoxic. In the MN test, the decrease in 4-NQO clastogenicity was observed by testing the mutagen especially with chloroform and ethyl acetate extracts (inhibition about 40-45%). The acetone and methanol extracts showed a less marked activity (33 and 37%, respectively). The results suggest that *T. arjuna* bark contains some nonpolar as well as polar compounds with antimutagenic activity against 4-NQO (Pasquini *et al*., 2002).

Similar experiments were performed with the fractionation of crude extracts from the bark of *T. arjuna* in order to isolate and purify the antimutagenic factors present. Most of the phenol fractions exhibited mutagen specificity against direct-acting mutagens, being effective in suppressing the frame shift mutagen 4-nitro-o-phenylenediamine (NPD) but failing to inhibit sodium azide (base pair substitution)-induced his+ revertants. ET-1 fraction triterpenoid diglycoside showed a marked effect against sodium azide but was ineffective against NPD. In the case of the indirect-acting mutagen 2AF, all the fractions were found to be quite potent in modulating its mutagenicity in both TA98 and TA100 tester strains of *Salmonella typhimurium* (Kaur *et al*., 2001).

The antimutagenic effect of benzene, chloroform, acetone and methanol fractions from *T. arjuna* was determined against Acid Black dye, 2-aminofluorene (2AF) and 4-nitro-o-phenylenediamine (NPD) in TA98 Frame shift mutagen tester strain of *Salmonella typhimurium*. Among the different fractions, the antimutagenic effect of acetone and methanol fractions was more than that observed with other fractions. Moreover, these fractions inhibited the S9-dependent mutagens, 2AF and Acid Black dye more effectively than the direct-acting mutagens (Kaur *et al*., 2002a).

The *in vitro* antiproliferative activity of extracts from *Emblica officinalis*, *Terminalia arjuna*, *Aphanamixis polystachya*, *Oroxylum indicum*, *Cuscuta reflexa*, *Aegle marmelos*, *Saraca asoka*, *Rumex maritimus*, *Lagerstroemia speciosa*, Red Sandalwood toward human tumor cell lines, including human erythromyeloid K562, B-lymphoid Raji, T-lymphoid Jurkat, erythroleukemic HEL cell lines were evaluated. Extracts from *Emblica officinalis* were the most active in inhibiting *in vitro* cell proliferation, after comparison to those from *Terminalia arjuna*, *Aphanamixis polystachya*, *Oroxylum indicum*, *Cuscuta reflexa*, *Aegle marmelos*, *Saraca asoka*, *Rumex maritimus*, *Lagerstroemia speciosa*, Red Sandalwood (Khan *et al*., 2002).

The antimutagenicity of phenol fractions of *T. arjuna* (soluble and insoluble in chloroform) against two direct-acting mutagens, 4-nitro-o-phenylenediamine (NPD) and sodium azide and against the S9-dependent mutagen 2-aminofluorene (2AF), in TA98 and TA100 tester strains of *Salmonella typhimurium*. The phenol fractions of *T. arjuna* inhibited revertants induced by the S9-dependent mutagen more remarkably than the direct-acting mutagens. Furthermore, the phenol fractions showed maximum inhibition of 98 and 101.55%, respectively, in the pre-incubation mode of treatment against the mutations induced by 2AF. Overall, the fractions inhibited the revertants induced by S9-dependent mutagens more effectively than those induced by direct-acting mutagens. The fraction insoluble in chloroform showed more inhibition than the soluble one, which corresponds to a higher polyphenol content in the insoluble fraction than in the soluble extract (Kaur *et al*., 2002b).

A fraction isolated from *T. arjuna* was studied for its antimutagenic effect against 4-nitro-o-phenylenediamine (NPD) in TA98, sodium azide in TA100 and 2-aminofluorene (2AF, S9-dependent), a promutagen, in both TA98 and TA 100 tester strains of *Salmonella typhimurium* using the Ames assay. The fraction inhibited the mutagenicity of 2AF very significantly in both strains while the revertant colonies induced by NPD and sodium azide were reduced moderately. ^{1}H-NMR, ^{13}C-NMR, IR and UV-spectroscopic data of the fraction revealed it to be tannin in nature (Kaur *et al*., 2000).

Antimutagenic potential of a fraction isolated from *T. arjuna* has been evaluated in TA98 and TA100 strains of *Salmonella typhimurium* against direct and indirect-acting mutagens. The fraction was quite effective against S9-dependent 2AF while it showed moderate effect against NPD. The fraction was analyzed to be ellagic acid (Kaur *et al*., 1997).

The effects of acetone and methanol extracts of *T. arjuna* on the growth of human normal fibroblasts (WI-38), osteosarcoma (U2OS) and glioblastoma (U251) cells *in vitro* were evaluated. Both extracts at 30 μg and 60 μg mL^{-1} concentrations inhibit the growth of transformed cells. In the extract treatment, the tumor suppressor protein, p53, was induced in U2OS but not in U251 and WI-38 cells. A cyclin-dependent kinase inhibitor, p21WAF1, was induced in transformed cells only which suggests that the bark extract of *T. arjuna* has components that can induce growth arrest of transformed cells by p53-dependent and -independent pathways (Nagpal *et al*., 2000).

By means of bioassay-guided separation methods, the cancer cell growth inhibitory constituents residing in the bark, stem and leaves of the *T. arjuna* were examined. The cancer cell line active components were found to be gallic acid, ethyl gallate and the flavone luteolin. Only gallic acid was previously known to occur in this plant. Luteolin has a well established record of inhibiting various cancer cell lines and may account for most of the rationale underlying the use of *T. arjuna* in traditional cancer treatments (Pettit *et al*., 1996).

Gastric activity: The anti-ulcer effect of methanol extract of *T.arjuna* (TA) against *Helicobacter pylori* lipopolysaccharide (HP-LPS; 50 μg animal^{-1}) induced gastric damage in rats was evaluated. The efficacy of TA on gastric secretory parameters such as volume of gastric juice, pH, free and total acidity, pepsin concentration and the cytoprotective parameters such as protein-bound carbohydrate complexes in gastric juice and gastric mucosa were assessed. The protective effect of TA was also confirmed by histopathological examination of gastric mucosa. HP-LPS-induced alterations in gastric secretory parameters and gastric defense factors were altered favorably in rats treated with TA, suggesting that TA has an anti-secretory role. These results suggest that the severe cellular damage and pathological changes caused by HP-LPS are mitigated by TA. The anti-ulcer effect of TA may reflect its ability to combat factors that damage the gastric mucosa and to protect the mucosal defensive factors (Devi *et al*., 2008).

The methanol extract of the bark of *T. arjuna* (TAE) showed marked antiulcer and ulcer healing activity against 80% ethanol (ETH), diclofenac sodium (DIC) and dexamethasone (DEX) induced ulcer models dose dependently at doses of 100, 400 and 200 mg kg^{-1} b.wt., respectively. Pre-, post and co-administration of TAE offered 100% protection to the gastric mucosa against ETH, DIC and DEX induced ulcers as observed from the ulcer score. Co-administration with TAE in DEX rats (DEX + TAE) favorably altered the levels of LPO, GSH and also the activities of SOD and CAT in gastric mucosa, whereas the activities of GPx remained unaltered in all groups. In DEX + TAE rats, the levels of protein and protein bound carbohydrate complexes were increased when compared with DEX rats. The results indicate that the gastro protective effect of TAE is probably related to its ability to maintain the membrane integrity by its antilipid peroxidative activity that protects the gastric mucosa against oxidative damage and its ability to strengthen the mucosal barrier, the first line of defense against exogenous and endogenous ulcerogenic agents (Devi *et al*., 2007a).

The effect of methanolic extract of *T. arjuna* (TA; 100 to 500 mg kg^{-1} b.wt.) on diclofenac sodium [DIC; 80 mg kg^{-1} b.wt. in water, orally] induced gastric ulcer in experimental rats were evaluated. A significant reduction in lesion index was observed in ulcer induced animals treated with TA (DIC+TA) compared to ulcerated rats (DIC). A significant increase was observed in 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. Histological studies confirmed the gastro protective activity of TA. It could be concluded that *T. arjuna* acts as a gastro protective agent probably due to its free radical scavenging activity and cytoprotective nature (Devi *et al*., 2007b).

Hepatoprotective activity: The preventive role of Arjunolic Acid (AA) against arsenic [Sodium arsenate; 1 mM]-induced cytotoxicity in isolated murine hepatocytes was

evaluated. Administration of AA (100 μg mL^{-1}) before and with the toxin almost normalized the altered activities of antioxidant indices. The cytoprotective activity of AA was found to be comparable to that of a known antioxidant, vitamin C suggesting that AA protects arsenic-induced cytotoxicity in murine hepatocytes (Manna *et al*., 2007b).

The protective role of the aqueous extract of the bark of *T. arjuna* (TA; 50 mg kg^{-1} b.wt.) on CCl_4 (1 mL kg^{-1} b.wt.) induced oxidative stress and resultant dysfunction in the livers and kidneys of mice was evaluated. Results showed that CCl_4 caused a marked rise in serum levels of GPT and ALP. TBARS level was also increased significantly whereas GSH, SOD, CAT and GST levels were decreased in the liver and kidney tissue homogenates of CCl_4 treated mice. Aqueous extract of TA successfully prevented the alterations of these effects in the experimental animals. The aqueous extract of the bark of TA could protect the liver and kidney tissues against CCl_4-induced oxidative stress probably by increasing antioxidative defense activities (Manna *et al*., 2006).

The effects of *T. arjuna* extract on human hepatoma cell line (HepG2) and its possible role in induction of apoptosis was evaluated. *T. arjuna* inhibited the proliferation of HepG2 cells in a concentration-dependent manner. Apoptotic morphology was observed in HepG2 cells treated with *T. arjuna* at the concentrations of 60 and 100 mg L^{-1}. DNA fragmentation, accumulation of p53 and cleavage of procaspase-3 protein were observed in HepG2 cells after the treatment with *T. arjuna*. The depletion of GSH was observed in HepG2 cells treated with *T. arjuna*. Apoptosis of HepG2 cells may be due to the DNA damage and expression of apoptotic proteins. Depletion of GSH may be involved in the induction of apoptosis of HepG2 cells suggesting it induces cytotoxicity in HepG2 cells (Sivalokanathan *et al*., 2006a). The antioxidant nature of ethanol extract of *T. arjuna* bark (EETA) on N-nitrosodiethylamine (DEN; 200 mg kg^{-1}) induced liver cancer in male Wistar albino rats was evaluated. The levels of lipid peroxides (LPO) under basal and also in the presence of inducers (H_2O_2, ascorbate and $FeSO_4$) were estimated in serum, liver and kidney of control and experimental animals. Enzymic antioxidants, such as superoxide dismutase, catalase, glutathione peroxidase and non-enzymic antioxidants like Vitamin C and Vitamin E levels were determined in all the groups of animals. A significant increase in LPO levels were observed while the levels of enzymic and non-enzymic antioxidants were decreased, when subjected to DEN induction. These altered enzyme levels were ameliorated significantly by administration of EETA at the concentration of 400 mg kg^{-1} in drug-treated animals. This protective effect of EETA was associated with inhibition of LPO induced by DEN and to maintain the antioxidant enzyme levels suggesting an antioxidant activity of *T. arjuna* bark against DEN-induced liver cancer (Sivalokanathan *et al*., 2006b).

Wound healing activity: The effect of topical application of phytoconstituents (fraction I, II and III) fractionated from a hydroalcohol extract of the bark of *T. arjuna*, was assessed on the healing of rat dermal wounds using *in vivo* models. The results indicated a statistically significant increase in the tensile strength of the incision wounds and the percent epithelialization of excision wounds compared with control. However, topical treatment with fraction I, consisting mainly of tannins, was found to demonstrate a maximum increase in the tensile strength of incision wounds. Even with respect to excision wounds, the fastest rate of epithelialization was seen with fraction I. Fraction I from the hydroalcohol extract of Arjuna bark possessed antimicrobial activity against tested microorganisms such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes* but not *Candida albicans*. These results strongly document the beneficial effects of fraction I, consisting mainly of tannins, of *T. arjuna* in the acceleration of the healing process well as corroborating the astringent effect of tannins by drawing the tissues closer together (Chaudhari and Mengi, 2006).

The effects of 50% ethanolic extract of the bark *T. arjuna* and tannins isolated from the bark were studied for wound healing activity in incision and excision wound models, after oral or topical application in form of a hydrogel. The findings revealed a statistically significant increase in the tensile strength of the incision wounds and increase in the percent reduction in wound size of excision wounds as compared to control. However, the topical treatment with tannins was found to be superior in both incision and excision wound studies. The estimated increase in hydroxyproline content of the granulation tissue of the excision wounds indicated rapid collagen turnover thus, leading to rapid healing of the wounds (Rane and Mengi, 2003).

The wound healing activity of two herbal formulations (Himax ointment and lotion) containing Indradaru extract, i.e., Arjuna bark (*Terminalia arjuna*), extract was evaluated for its wound healing potential in two types of wound models in rats (1) excision wound model and (2) incision wound model. Both the formulations responded significantly in both the wound models tested. The results were also comparable to that of the standard drug nitrofurazone. The results were also comparable in terms of wound contracting ability,

epithelization period, tensile strength and regeneration of tissues at the wound area. Thus, this investigation confirms the use of the Himax ointment and lotion containing *T. arjuna* extract as a wound-healing agent (Mukherjee *et al*., 2003).

Antibacterial activity: The antibacterial activity of acetone, hexane, dichloromethane leaf extract of five *Terminalia* species (*Terminalia alata* Heyne ex Roth., *Terminalia arjuna* (Roxb.) Wt. and Am., *Terminalia bellerica* (Gaertn.) Roxb., *Terminalia catappa* L. and *Terminalia chebula* Retz.) were tested by Agar-well-diffusion method against human pathogens *E. coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus* and *Staphylococcus epidermidis*. Hexane and dichloromethane extracts have shown more antibacterial components than the acetone extract suggesting the antibacterial activity in *T.arjuna* extracts (Shinde *et al*., 2009).

Antimicrobial activities of the crude ethanol extracts of five plants were screened against multidrug resistant (MDR) strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Candida albicans* and ATCC strains of *Streptococcus mutans*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus bovis*, *Pseudimonas aeruginosa*, *Salmonella typhimurium*, *Escherichia coli*, *Klebsiella pneumoniae* and *Candida albicans*. The MDR strains were sensitive to the antimicrobial activity of *Acacia nilotica*, *Syzygium aromaticum* and *Cinnamum zeylanicum*, whereas they exhibited strong resistance to the extracts of *T. arjuna* and *Eucalyptus globules* (Khan *et al*., 2009).

Strong antibacterial activity was shown by the methanol extracts of T.arjuna against multi-drug resistant *Salmonella typhi* (Rani and Khullar, 2004).

The extracts from the *T. arjuna* exhibited potent antibacterial activity against *Escherichia coli*, *Klebsiella aerogenes*, *Proteus vulgaris* and *Pseudomonas aerogenes* (gram-negative bacteria) at 1000-5000 ppm by the disc diffusion method (Perumal Samy *et al*., 1998).

Luteolin was also found to exhibit specific activity against the pathogenic bacterium *Neisseria gonorrhoeae* (Petit *et al*., 1996).

Antioxidant activity: The antioxidant and free radical scavenging capacities of arjunic acid, an aglycone obtained from the fruit of *Terminalia* was evaluated. Results showed that arjunic acid was a strong antioxidant and a free radical scavenger, more potent than ascorbic acid, in microsomes lipid peroxidation, DPPH, hydrogen peroxide induced RBCs hemolysis and 2', 7'-dichlorodihydrofluorcin diacetate (DCFH(2)-DA) assay. However, no significant difference was observed in the RBCs autoxidative hemolysis assay (Sun *et al*., 2008).

The study was designed to assess the ability of casuarinin, extracted from *T. arjuna*, to protect cultured Madin-Darby canine kidney (MDCK) cells against H_2O_2-mediated oxidative stress. Casuarinin caused a decrease in intracellular peroxide production as shown by dichlorofluorescein (DCF) fluorescence in a concentration-dependent manner. After 3 h exposure to 8 mM H_2O_2, the percentage of intracellular glutathione (GSH)-negative cells was reduced in the casuarinin-treated group. Addition of 32 mM H_2O_2 to MDCK cells for 3 h induced an increase in the percentage of cells containing 8-oxoguanine but the level of such cells declined in casuarinin-treated cells. The data suggest that casuarinin attenuates H_2O_2-induced oxidative stress, decreases DNA oxidative damage and prevents the depletion of intracellular GSH in MDCK cells (Chen *et al*., 2004).

Antidiabetic activity: The effect of ethanol extract (250 and 500 mg kg^{-1} b.wt.) of *T. arjuna* stem bark in alloxan induced diabetic rats and its lipid peroxidation, enzymatic and nonenzymatic activity was investigated in the liver and kidney tissues. The extract at a dose of 500 mg kg^{-1} produced significant reduction in lipid peroxidation (LPO). The extract also causes a significant increase in superoxide dismutase, catalase, glutathione peroxidase, glutathione-s-transferase glutathione reductase and glucose-6-phosphate dehydrogenase, reduced glutathione, vitamin A, vitamin C, vitamin E, total sulfhydryl groups (TSH) and non protein sulfhydryl groups (NPSH) in liver and kidney of alloxan induced diabetic rats, which clearly shows, the antioxidant property of *T. arjuna* bark. The result indicates that the extract exhibit the antioxidant activity through correction of oxidative stress and validates the traditional use of this plant in diabetic animals (Raghavan and Kumari, 2006).

Antiviral activity: Casuarinin isolated from the bark of *T. arjuna* was investigated for its antiviral activity on *Herpes simplex* type 2 (HSV-2) *in vitro*. Results showed that the IC_{50} of casuarinin in XTT and plaque reduction assays were 3.6±0.9 and 1.5±0.2 μM, respectively. The 50% cytotoxic concentration for cell growth (CC_{50}) was 89±1 μM. Thus, the Selectivity Index (SI) (ratio of CC_{50} to IC_{50}) of casuarinin was 25 and 59 for XTT and plaque reduction assays, respectively. Casuarinin continued to exhibit antiviral activity even added 12 h after infection. During the attachment assay, casuarinin was shown to prevent the attachment of HSV-2 to cells. Furthermore,

casuarinin also exhibited an activity in inhibiting the viral penetration. Interestingly, casuarinin was virucidal at a concentration of 25 μM, reducing viral titers up to 100, 000-fold which suggest that casuarinin possesses anti-herpesvirus activity in inhibiting viral attachment and penetration and also disturbing the late event(s) of infection (Cheng *et al*., 2002).

Antiathersclerotic activity: The effect of orally administered indigenous drugs *T. arjuna*, *T. belerica* and *T. chebula* were investigated on experimental atherosclerosis in rabbits. Atherosclerotic lesions of the aorta were examined histologically. *T. arjuna* was found to be the most potent hypolipidemic agent and induced partial inhibition of rabbit atheroma indicating that *T. arjuna* may act an anti-atherogenic role (Shailaa *et al*., 1998).

Diet-induced hyperlipidaemic rabbits were given 50% ethanol extract of *T. arjuna* tree bark in doses of 100 and 500 mg kg^{-1} and compared with controls. After 60 days, total cholesterol was 574±61, 320±29 and 217±44 mg dL^{-1}, respectively; LDL cholesterol was 493±57, 271±30 and 162±44 mg dL^{-1}; HDL cholesterol was 59±7, 36±3 and 35±4 mg dL^{-1}; triglyceride was 108±13, 67±6 and 101±26 mg dL^{-1}; cholesterol/HDL ratio was 10.1±1.3, 9.2±1.1 and 6.1±1.0 and LDL/HDL ratio was 8.7±1.3, 7.8±1.1 and 4.5±1.0. The extract did not adversely affect biochemical tests of liver and renal function and hematological parameters (Ram *et al*., 1997).

Immunomodulatory activity: *T. arjuna* bark powder (400 mg kg^{-1}, po) significantly increased the anti-SRBC antibody titre in the secondary phase of immune response suggesting its use as immunomodulator (Halder *et al*., 2009).

Antinociceptive activity: *T. arjuna* bark powder (400 mg kg^{-1}, p.o.) significantly reduced the duration of licks and bites in both phases of formalin-induced pain response and showed significant increase in tail flick latency at higher dose (800 mg kg^{-1}, p.o.). These effects of *T. arjuna* were antagonised by pretreatment with naloxone (1 mg kg^{-1}, i.p.). In another series of experiments, mice pretreated with morphine for three days in increasing doses (10, 15, 20 mg kg^{-1}, i.p., twice daily) showed a decreased response in antinociceptive activity of morphine (5 mg kg^{-1}, i.p.). Further these findings support the hypothesis that *T. arjuna* has antinociceptive action probably mediated via central opioid receptors (Halder *et al*., 2009).

Reproductive activity: The preventive role of arjunolic acid, a triterpenoid saponin isolated from the bark of *T. arjuna*, against arsenic (sodium arsenite, 10 mg kg^{-1} b.wt. for 2 days) -induced testicular damage in mice was evaluated. Pretreatment with arjunolic acid at a dose of 20 mg kg^{-1} b.wt. for 4 days could prevent the arsenic-induced testicular oxidative stress and injury to the histological structures of the testes. Arjunolic acid had free radical scavenging activity in a cell-free system and antioxidant power *in vivo*. The results suggest that the chemopreventive role of arjunolic acid against arsenic-induced testicular toxicity may be due to its intrinsic antioxidant property (Manna *et al*., 2008).

Analytical parameters: A novel, accurate and valid fingerprint method was developed using HPLC for quality control of a traditional Ayurvedic Arjuna churna formulation, which is used as a cardio tonic drug. Comprehensive comparison of chromatograms of standardized formulation of Arjuna churna and marketed formulations revealed eight characteristic peaks in chromatogram. An HPLC fingerprint was also developed for total sapogenins present in *T. arjuna*. The six common peaks observed in chromatograms of isolated sapogenins, standardized formulations and marketed formulations which can serve as a quality control tool for qualitative estimation of total saponin glycosides present in an Arjuna churna formulation (Chitlange *et al*., 2009).

A simple, precise and rapid high performance thin layer chromatographic method has been developed for the simultaneous quantitative determination of five oleane derivatives, namely, arjunic acid, arjunolic acid, arjungenin, arjunetin and arjunglucoside I from stem bark extract of *T. arjuna*. The isolation and separation of these compounds was carried out on 60F254 layers eluted with chloroform: methanol (90:10) and the analytes were visualized through color development with vanillin in concentrated sulphuric acid: ethanol. Scanning and quantification of the spots at 640 nm showed good recoveries in the range 96.40-101.7% (Singh *et al*., 2002a).

A rapid sensitive and reproductive reversed phase high performance liquid chromatographic method with photo diode array detection is described for the simultaneous quantification of major oleane derivatives: arjunic acid, arjunolic acid, arjungenin and arjunetin in *T. arjuna* extract. The method involves the use of a Waters Spherisorb S10 ODS column (250 x 4.6 mm, I.D., 10 μm) and binary gradient mobile phase profile. The various other aspects of analysis viz. Extraction efficiency, peak purity and similarity were validated using a photo diode array detector (Singh *et al*., 2002b).

Clinical trials: Several studies have been made to assess the efficacy of *T. arjuna* bark in cardiac disorders. Decoction of bark powder was found more useful in hypertensive heart disease as compared to congestive heart failure. Alcoholic decoction of bark was found to be beneficial in stable cases of ischemic heart disease. Prolonged use of the drug brought sense of well being in patients and increased euglobulin lysis time and prothrombin time. The drug also showed electrocardiographic improvement (Anand, 1994).

An adult male with Stokes-Adams attacks following acute chest pain became well after three months use of *T. arjuna* powder. In another study, 500 mg crude drug powder of *T. arjuna* was administered in 30 stable angina pectoris patients and found to alleviate angina pain. It was also found to be beneficial in ischemic heart disease associated with rhythm disturbances. It is also beneficial in modifying various known coronary risk factors like obesity, hypertension and hyperglycemia. No significant side effects were observed in these patients (Sharma *et al*., 2005).

Solidified aqueous extract of arjuna bark when administered in doses of 500 mg b.d. for 3 months along with antianginal drugs proved useful in reducing tread mill test positivity and increase in exercise tolerance in 25 angina patients. However, there was no reduction in the consumption of antianginal drugs (Sharma *et al*., 2005).

A clinical trial was taken on 51 patients of coronary heart disease to assess the effect of *T. arjuna*. All the patients were administered with 2 capsules of 500 mg in morning and in evening with milk for 4 months followed up each month. Reduction in systolic and diastolic blood pressure, pulse rate, serum cholesterol and HDL and LDL cholesterol was noticed (Arora *et al*., 1995).

The extract of arjuna, Vacha, Brahmi and Jatamansi in equal doses was administered to 22 hypertensive patients with no lipid derangement. A symptomatic improvement with fall in blood pressure was noted. various symptoms viz., Anidra, Dourbalya, Shirahshoola, kshubdhata Sharma *et al*. (2005) were graded as per their severity and recorded. A shift in symptom grade score was observed after 3 months of treatment with Arjuna Vacadi Yoga.

Administration of an herbal drug *T. arjuna*, *Emblica officinalis*, *Ocimum sanctum* and *Withania somnifera* resulted in significant reduction in systolic and diastolic blood pressure. There was a significant reduction in body mass index in patients treated with drug when compared to those on conventional drugs alone. Similarly a significant decline in levels of serum cholesterol, triglycerides and elevation in HDL cholesterol was observed at the end of 3 months in the indigenous drug group (Sharma *et al*., 2005).

The present study demonstrates *in vitro* effects of its ethanol bark extract (TAE) on platelet function indices in twenty patients of angiographically proven Coronary Artery Disease (CAD). Platelet activation was monitored by determining P-selectin (CD62P) expression, intracellular free calcium (Ca^{2+}) release and platelet aggregation. The results clearly demonstrates that the bark extract of TA decreases platelet activation and may possess antithrombotic properties. The possible mechanism of action could be by desensitizing platelets to the agonist by competing with platelet receptor or by interfering with signal transduction. Thus, TA can be exploited for its therapeutic potential in CAD and related cardiovascular disorders (Malik *et al*., 2009).

The efficacy of herbal medicine Liv-52 (consisting of *Mandur basma*, *Tamarix gallica* and herbal extracts of *Capparis spinosa*, *Cichorium intybus*, *Solanum nigrum*, *Terminalia arjuna* and *Achillea millefolium*) on liver cirrhosis outcomes was compared with the placebo for 6 months in 36 cirrhotic patients. The results demonstrated that the patients treated with Liv-52 for 6 months had significantly better child-pugh score, decreased ascites, decreased serum ALT and AST. In placebo administered patients all the clinical parameters recorded at beginning of the study were not significantly different than after 6 months suggesting that Liv-52 possess hepatoprotective effect in cirrhotic patients (Huseini *et al*., 2005).

The role of *T. arjuna* in Ischemic Mitral Regurgitation (IMR) following Acute Myocardial Infarction (AMI) in 40 patients were evaluated. They were given placebo or 500 mg of *T. arjuna* in addition to anti-ischemic treatment. After 1 and 3 months of follow up, patients receiving adjuvant *T. arjuna* showed significant decrease in IMR, improvement in E/A ratio and considerable reduction in anginal frequency suggesting its use as antiangina drug (Dwivedi *et al*., 2005).

Fifty-eight males with chronic stable angina (NYHA class II-III) with evidence of provocable ischemia on treadmill exercise test received *T. arjuna* (500 mg; 8 h), isosorbide mononitrate (40 mg $daily^{-1}$) or a matching placebo for one week each, separated by a wash-out period of at least three days in a randomized, double-blind, crossover design. *T. arjuna* therapy was associated with significant decrease in the frequency of angina and need for isosorbide dinitrate (5.69±6.91 mg $week^{-1}$ vs. 18.22±9.29 mg $week^{-1}$ during placebo therapy). The treadmill exercise test parameters improved significantly during therapy with *T. arjuna* compared to those with placebo. The total duration of exercise increased (6.14±2.51 min vs. 4.76±2.38 min), maximal ST depression during the longest equivalent stages of submaximal exercise decreased (1.41±0.55 mm vs. 2.21±0.56 mm), time to recovery decreased (6.49±2.37 min vs. 9.27±3.39 min) and higher double products were achieved

(25.75±4.81x10(3) vs. 23.11±4.83x10(3) during *T. arjuna* therapy. No significant untoward effects were reported during *T. arjuna* therapy suggesting that bark extract, 500 mg; 8 h, given to patients (Bharani *et al*., 2002).

To evaluate the antioxidant and hypocholesterolaemic effects of *T. arjuna* bark and to compare it with a known antioxidant, vitamin E a randomized controlled trial was performed on 105 patients with Coronary Heart Disease (CHD). There was a significant decrease in total cholesterol (-9.7±12.7%) and LDL cholesterol (-15.8±25.6%) with the drug group. Lipid peroxide levels decreased significantly in both the treatment groups. This decrease was more in vitamin E group (-36.4±17.7%) as compared to the *T. arjuna* group (-29.3±18.9%). *T. arjuna* tree bark powder has significant antioxidant action that is comparable to vitamin E. In addition, it also has a significant hypocholesterolaemic effect (Gupta *et al*., 2001).

The safety and efficacy of 'Hartone'--a proprietary herbal product primarily containing *T. arjuna* in 10 stable angina pectoris patients were evaluated. Hartone afforded symptomatic relief in 80% of patients and isosorbide mononitrate (ISMN) in 70%. The number of anginal attacks were reduced from 79/week to 24/week by Hartone and from 26/week to 7/week by ISMN. Hartone improved BP response to stress test in two patients and ejection fraction in one. Hartone was better tolerated than ISMN and showed no evidence of hepatic or renal impairment suggesting its use as antianginal drug (Kumar *et al*., 1999).

Bark stem powder of *T. arjuna*, 500 mg, 8 h (Group A) was administered to 10 patients of postmyocardial infarction angina and two patients of ischaemic cardiomyopathy postoperatively, for a period of three months. These patients were also on conventional treatment comprising of nitrates, aspirin and/or calcium channel blockers. Twelve ages-, sex-, body mass index- and ECG-matched patients of post myocardial infarction angina receiving only conventional treatment served as controls (Group B). Significant reduction in angina frequency was noted in both groups (3.5±1.98 to 1.08 + 1.08 per day vs. 3.10 + 0.72 to 1.17 + 0.84 per day). However, only Group A patients showed significant improvement in left ventricular ejection fraction (42.25 + 9.96 to 52.67 + 12.32% vs. 51.83 + 5.99 to 49.83 + 2.52%) and reduction in left ventricular mass (159.18 + 51.11 to 127.47 + 52.40 g m^{-2} vs. 159.11 + 38.92 to 160.78 + 54.23 g m^{-2}) on echocardiography following three months of therapy. Both patients with ischemic cardiomyopathy showed significant symptomatic relief in coronary heart failure from NYHA class III to NYHA class I. Prolonged administration of *T. arjuna* did not show any adverse effects on renal, hepatic and hematological parameters (Dwivedi and Jauhari, 1997).

The effect of *T. arjuna* on twelve patients with refractory chronic congestive heart failure (Class IV NYHA), related to idiopathic dilated cardiomyopathy for 2 weeks were evaluated. *T. arjuna*, compared to placebo, was associated with improvement in symptoms and signs of heart failure, improvement in NYHA Class (Class III vs. Class IV), decrease in echo-left ventricular end diastolic (125.28±27.91 vs. 134.56±29.71 mL m^{-2}) and end systolic volume (81.06±24.60 vs. 94.10±26.42 mL m^{2}) indices, increase in left ventricular stroke volume index (44.21±11.92 vs. 40.45±11.56 mL m^{-2}) and increase in left ventricular ejection fractions (35.33±7.85 vs. 30.24±7.13%; $p<0.005$). 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 (Bharani *et al*., 1995).

The effect of bark powder of *T. arjuna* on anginal frequency, blood pressure, body mass index, blood sugar, cholesterol and HDL-cholesterol was studied in 15 stable (Group A) and 5 unstable (Group B) angina patients before and 3 months after *T. arjuna* therapy. There was 50% reduction in anginal episodes in Group A cases. TMT performance improved from moderate to mild changes in 5 patients and one with mild changes became negative for ischemia. The time to the onset of angina and appearance of ST-T changes on TMT after *T. arjuna* was delayed significantly. However, in patients with unstable angina there was an insignificant reduction in anginal frequency. These patients also needed diltiazem, B-blockers and nitroglycerine in addition to *T. arjuna*. The drug lowered systolic blood pressure and body mass index to a significant level ($p<0.05$) and increased HDL-cholesterol only slightly along with marginal improvement in left ventricular ejection fraction in stable angina patients. There were no deleterious effects on liver or kidney functions which suggests that monotherapy with *T. arjuna* is fairly effective in patients with symptoms of stable angina pectoris. However, it has a limited role in unstable angina (Dwivedi and Agarwal, 1994).

On the basis of available experimental evidences, the drug is considered as cardioprotective and not as cardio tonic as previously assumed. Its antianginal properties along with its potential of modifying various coronary risk factors open up larger opportunities for its use in primary and secondary prevention of ischaemic heart disease.

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