International Journal of Pharmaceutical Archive-2(8), 2013, 189-201
Available online through www.ijpaonline.info ISSN 2319-7226

REVIEW ARTICLE

MAGICAL REMEDIES OF TERMINALIA ARJUNA (ROXB.)

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(Received on: 21-07-13; Revised & Accepted on: 12-08-13)

ABSTRACT

T*erminalia arjuna (Roxb.) Wt. and Arn. (Arjuna; combretaceae) is a widely used medicinal plant throughout India and popular in various indigeneous system of medicine like Ayurveda, Siddha and Unani. In the Indian system of medicine, the bark is used as astringent, cooling, aphrodisiac, cardiotonic, tonic, infractures, 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 plants.*

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

INTRODUCTION

To cure human disease medicinal plant has been a major source of therapeutic a gents since ancient times. By definition, 'traditional' use of herbal medicines implies substantial historical use, and this is certainly true for many products that are available as 'traditional herbal medicines'. In many developing countries, a large proportion of the population relies on traditional practitioners and their armamentarium of medicinal plants in order to meet health care needs. Although modern medicine may exist side-by-side with such traditional practice, herbal medicines have often maintained their popularity for historical and cultural reasons. The pharmacological treatment of disease began long ago with the use of herbs (Schulz *et al*., 2001). Methods of folk healing throughout the world commonly used herbs as part of their tradition. Some of these traditions are briefly described below, providing some examples of the array of important healing practices around the world that used herbs for this purpose. Arjuna, large evergreen tree distributed yhroughout the greater part of the Indian Peninsula along rivers and found in Sub-Himalayan tract, Chita Nagpur, Orissa, West Bengal, Punjab, Deccan and Konkan (Warrier *et al*., 1994; Nadkarni, 1976).

Arjuna (Terminalia arjuna) is a widespread medicinal plant used in the ayurvedic system of medicine to care for various ailments and is one of the active ingredients in numerous polyherbal hepatoprotective formulations now used in India. Its stem, bark, leaves possesses glycosides, large quantities of flavonoids, tannins and minerals. Flavonoids have been detected to exert antioxidant, anti-inflammatory and lipid lowering effects whereas glycosides are cardiotonic, therefore making Terminalia arjuna distinctive amongst currently used medicinal plants. Terminalia arjuna leaves, (Flavonoids) antimicrobial and antifungal activity study has been restricted that's why in the present study we have addressed and provides an overview of extraction, phytochemical analysis, flavonoid quantification and FTIR Spectroscopy (Fourier Transform Infrared) analysis of Terminalia arjuna leaves**.** (Nema *et al.*, 2012).

Experiments conducted with the bark of *Arjuna* have been shown to possess hypolipidemic, hypocholesterolemic, hypotensive, antidiabetic, and anti-infilammatory activities (Dwivedi, 2007). In addition the thick, white to pinkish gray bark has been shown to posses' anticancer, antiulcer, antimutagenic and wound healing activities (warrier *et al*., 1996).

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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, Daccan and Konkan (Warrier *et al*., 1994 Nadkarni., 1976).

Taxonomical/scientific classification-
Kingdom – Plantae
Division- Magnoliopsida
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 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 cm. long, nearly glabrous with 5 -7 hard, winged angles (Nadkarni, 1976; Gupta, 1998; Cooke, 1967).

Climate, soil and propogation: 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 as propagated by seeds and stump planting (Kumari, 1996). Cotyledonary node explant excised from 21 days old seedings Climate, soil and propogation: *T. arjuna* produced multiple shoots ehen cultured on full strength MS or modified MS (1/2 strength major salts and Fe-EDTA) medium supplemented with different concentration (0.1 – 1.0 mg /L) of BAP. Maximum 8.9 shoots and explants could be recorded after 30 days of innculation on modified MS medium supplemented with BAP 0.5 mg /L. A proliferating shoot culture was established by reculturing the original cotyledonary nodes (2-3 times) on shoot multiplication medium after each harvest of newly formed shoots. Shoots (each having 2-3 nodes/shoots) thus obtained were also used as the source of nodel explants that gave rise to 1-2 shoots when cultured on modified MS+BAP (0.5 mg/L) medium. Thus 45-55 shoots 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 per L) 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 characteristic (Ali, 1994)



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

Leaves: Leaves are like that of guava leaves, oblong and 4 – 6 inch wide, sub opposite, glabrous and often inequilat *eral*. 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 – 1.3 cm.

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. Fruits is drupe and is often notched near the top, marked with oblique upward curving striations.

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

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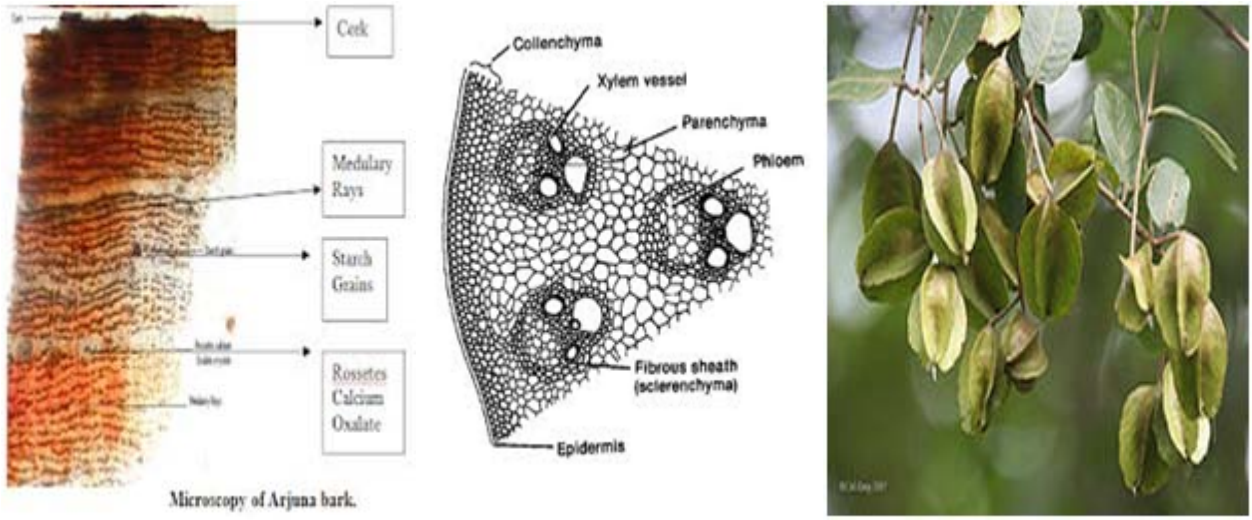
Microscopical and powder characteristics



Microscopy of Arjuna bark.

Stem bark: Transverse section of stem bark shows cork, thin-walled parenchymatius 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 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 parenchymatous 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 tissue. 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, 1982).

Fruits: It shows epidermis and hypodermis. Sedretory canals, ducts and vascular supply are present. Seeds are composed of stone cells, fibres and vascular bundle. 12 (Ali, 1994; Mitra, 1985; Raghunathan, 1982).

bark: The powdered bark is showed pinkish white 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 pigments; fragments of thin walled phloem fibres associated with idioblasts containing

rosette and cluster crystals of calcium oxalate and longitudinal radially cut medullary rays (Sarin S., 1996).

Physical constants of stem bark:
Foreign matter: not more then 2% w/w; total ash: not more then 27.0% w/w; acid insoluble ash : not more then 2.0% w/w; alchohal soluble extractive : not less then 16% w/w; water soluble extractive: not less then 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 gm; decoction : 50 – 100 ml; (Anonymous, 1999).

Important polyherbal formulations with Arjuna: Hepacef, Liv- 52, Ajar.

Traditional uses:

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, tumour, excessive perspiration, fatigue, asthma, bronchitis, intrinsic hemorrhage, otalgia, diarrhea associated with blood, cirrhosis of liver, hypertension, inflammation and skin disorders.

Fruits: Tonic and deobstruent

Leaves: Juice for earache

Plant parts used: Stem bark, fruit and leaves (Warrier et al, 1994; Kumar and Prabhakar, 1987).

Ayurvedic properties:

Rasa: Kasaya

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

Stem bark : Arjunolic acid, tomentosic acid, β-sitosterol, ellagic acid, (+) – leucodelphinidin (Rastogi and mahrotra., 1993a), arjunic acid (Row et al., 1970a), arjunetin (Row et al., 1970b), arjungenin, arjunglucoside I and II (Rastogi and mahrotra., 1993c), tannins containing catechin, gallocatechin, epicatechin, epigallocatechin (Rastogi and mahrotra., 1993c), arjunolone, baicalein (Sharma et al., 1982; Sharma., 1996), arjunglucoside III (Rastogi and mahrotra., 1993c), terminoic acid (Ahmad et al., 1983), arjunolitin (Tripathi et al.,1992), arjunglucoside IV, V (Wang et al., 2010a), arjunasides A – E (Wang et at., 2010b), 2α, 3β – dihydroxy urs 12, 18 dien – 28 oic acid 28 o – β – Dglucopyranosyl 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), termiarjunoside I and II (Alam *et al.*, 2008).

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

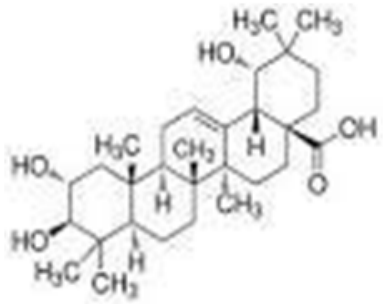
Root bark: Arjunoside I and II, 8 – hydroxyl hexadecanoic, oleanoic, arjunic acids, arjunolic acid, β – sitosterol (Anjaneyulu and Ram Prasad, 1982a), terminic acid (Anjaneyulu and Ram Prasad, 1983), arjunoside III, IV , arjunoside I, arjunetin, ellagic acid, gallic acid, leucocyanidin (Anjaneyulu and 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 Rathor., 2000).

(+)-Arjunic acid
Identificationname(+)-Arjunin acid,Synonyms-Arjuntriterpenic acid

(2α, 3β, 19α)-2, 3, 19-Trihydroxyolean-12-en-28-oic acid

Molicular structure

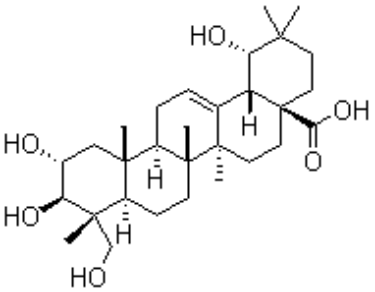


Molecular formula c30H48o5

Molicular weight 488.7

(+)-Arjungenin

Identification Name(+)-Arjungenin, Synonyms-Arjugenin; Arjungenin; 2alpha, 19alpha, 23-Trihydroxyoleanolic acid



Molecular Structure

Molecular Formula$C_{30}H_{48}O_6$

Molecular Weight504.70

PHARMACOLOGICAL STUDIES

Cardiovascular activity: The effect of aqueous extract of *T. arjuna* bark at 63, 125 and 250 mg per kg for antifibrotic and antioxidant effects in rats along with the selective β – adrenocepter agonist isoprenalin (5 mg per kg s.c.) for 28 days were evaluated. The T. arjuna bark extract significantlly prevented the isoprenalin 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 – adrenocepter stimulation (Kumar *et al.*, 2009).

The antioxidative properties of an ethanolic 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 lipid peroxidation end products and carbonyl contents were determined in the cardiac tissues. NaF intoxication significantly altered all the indices related to

the prooxidant – antioxidant status of 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 cardioprotective 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 effect of butanolic fraction of *T. arjuna* bark (TA 0.5, 0.42, 0.85, 1.7, 3.4 and 6.8 mg per kg for 6 days week-1 for 4 weeks) on Doxorubicin (Dox., 20 mg per kg i.p.) induced cardiotoxicity 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 compaired to Dox – treated animals. Electron microscopic studies in Dox treated animals revealed mitochondrial swelling, Z – band disarray, focal dilatation of Smooth Endoplasmic Raticulum (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 *Terminalia 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 CCL4 induced oxidative insult in cardiac tissue in mice was evaluated. Oral treatment of the active constituents of TA at a dose of 50 mg per kg b. wt. for 7 days prior to CCL4 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 CCL4 induced oxidative insult (Manna *et al*., 2006).

Anti-inflammatory activity: *T. arjuna* bark powder (400 mg per kg p.o.) significantly reduced formalin induced 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 evaluated the antioxidant and anti-inflammatory effect 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 the in vivo conditions, BHUx significantly reduced

inflammation in the carageenan induced rat paw odema model of inflammation properties. Hydroperoxide induced lipid peroxidation (CHP) in liver homogenate, LPS – induced NO production in peritoneal macrophage 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 per ml and IC-50 for COX – 1 = 169 µg per ml) (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 per ml). BHUx also showed a preference for inhibiting 15 – lipoxigenase (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 oxidation, to prevent athrosclerosis (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 macrophase (Ali *et al*., 2003a).

Terminoside A isolated from the acetone fraction of 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 macrophase (Ali *et al.*, 2003b).

Antitumour activity: The effect of the 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 per ml 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), O2 (*_) (superoxide) DPPH (1, 1 diphenyl – 2 – picrylhydrazyl), ABTA (*+) (2,2 – azino – bis – 3 – ethyl benzothiazolin – 6 – sulphonic acid) radicals in a dose – dependent manner. These result demonstrate that TAE protects DNA against ADR induced damage (Reddy et al., 2008).

The effect of aqueous extract of *Terminalia 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 indicates the antioxidant action in 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) arjunitin 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 WRL – 68) cancer cell lines suggesting its role in anticancer treatment (saxena et al., 2007).

The effect of extract of *T. arjuna* bark on carbohydrate metabolizing enzymes of N – nitrisodiethyl amine 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 gluconeogenic 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 constituents 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 ethanolic 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 GO/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 GO/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 antiprolierative 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 casuaranin. The results suggests the antiprolifirative activity of casuarinin in A549 cells (Kuo *et al.*, 2005b).

The antigenotoxic properties of sequential extraction using acetone, methanol + HCL chloroform, ethyl acetate and ethyl ether extract were investigated by assessing the inhibition of genotoxicity of the direct acting mutagen 4 – nitroquinoiln – 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, where as the acetic methanol, chlorioform, 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, chloroform, methanol and ethyl acetate extracts (Scassellati – Sfor zolini *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 higest nontoxic extract dose of ethyl acetate (50 µg per plate), chloroform (100 µg per plate), acetone (100 µg per plate), methanol (500 µg per plate). A less marked antimutagenicity activity (inhibition of about 40 – 45%) was observed for the acedic methanol and diethyl ether extracts. The comet assay showed that acetone extract (100 µg per ml) was more effective in reducing the DNA damage caused by 4 – NQO clastogenicity was observed by testing the mutagen especially with chloroform and ethyl acetate extracts (inhibit about 40 – 45%). The acetone and methanol extracts showed a less marked activity (33 and 37% respectively). The results suggest that *T. arjuna* bark contents some nonpolar aS well as polar components with antimutagenic activity against 4 – NQO (Pasquini *et al*., 2002).

Similar experiments were performed with fractionation of crude extracts from the bark of *T. arjuna* in order to isolate and purify the antimutagenic factors present. Most of phenol fractions exhibited mutagen specificity against direct acting mutagens, being effective in suppressing the frame shift mutagen 4 – nitro – o – phenyl enediamine (NPD) but tailing to inhibit sodium azide (base pair substitution) – induced his + revertants. ET – 1 fraction triterpenoid digycoside 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 effects of benzene, chloroform, acetone and methanol fractions of *T. arjuna* was determined against Acid black dye, 2 – amino fluorine (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 then that observed with other fractions. Moreover, these fractions inhibited the S9 – dependent mutagens, 2AF and Acid black dye more effectly tnan the direct acting mutagens (Kaur *et al*., 2002a).

The in – vitro proliferative activity of extracts from Emblica officinalis, *Terminalia arjuna, Aphanamixis polystachya, Oroxylum indicum, Cuscuta reflexa, Aegle marmalos, 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 comparision to those from *Terminalia arjuna , Aphanamixis polystachya, Oroxylum indicum,*

*Cuscuta reflexa, Aegle marmelos, saraka asoka, rumex maritimus, Lagerstroemia speciosa, Red sandalwood (*Kaur *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 thyphimurium. The phenol fractions of *T. arjuna* inhibited revertants induced by the S9 – dependent mutagens 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 effectly 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 TA100 tester strains of salmonella tphimurium 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. 1H- NMR, 13C-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 analysed 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 per ml concentrations inhibit the growth of transformed cells. In the extract treatment, the tumour suppressor p rotein, 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 (Negpal *et al.*, 2000).

By means of bioassay–guided separation methods, the cancer 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 estabilished 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 per animal) 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 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 serve 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 anti ulcer and ulcer healing activity against 80% ethanol (ETH), diclofenac sodium (DIC) and dexamethasone (DEX) induced ulcer models dose dependently at dose 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 DAX induced ulcers as observed from the ulcer score. Co – administration with TAE in DEX rats (DEX + TAE) favorably altered the levels of protein and protein bound carbohydrate complexes were increased when compared with DEX rats. The results indicates that the gastro protective effects 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 agensts (Devi *et al*., 2007a).

The effect of methanolic extract of *Terminalia arjuna* (TA; 100 to 500 mg per kg b. wt.) on diclophenic sodium

(DIC; 80 mg per kg b. wt. in water, orally) induced gastric ulcers in experimental rats were evaluated. A sufficient 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 mucous content, nucleic acids with a significant decrease in volume of gastric juice. Free and total activity, 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 per ml) 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 proptective role of the aqueous extract of the bark of *T. arjuna* (TA; 50 mg per kg b. wt.) on CCL4 (1 ml per kg b. wt.) induced oxidative stress and resultant dysfunction in the livers and kidneys of mice was evaluated. Results showred that CCL4 caused a marked rise in serum levels of GPT and ALP. TBARS level was also increased significantly where as GSH, SOD, CAT and GST levels were decreased in the liver and kidney tissues homogenates of CCL4 treated mice. Aqueous extract of TA successfully prevented the alterations of these effects in experimental animals. The aqueous extract of the bark of TA could protects the liver and kidney tissues against CCL4 induced oxidative stress probably by increasing antioxidant defense activities (Manna *et al*., 2006).

The effect of *T. arjuna* extract on human hepatoma cell line (Hep G2) and its possible role in induction of apoptosis was evaluated. *T. arjuna* inhibited the proliferation of Hep G2 cells in a concentration dependent manner. Apoptotic morphology was observed in Hep G2 cells treated with *T. arjuna* at the concentrations of 60 and 100 mg per L. DNA

fragmentation, accumulation of p53 and cleavage of procaspase – 3 protein were observed in Hep G2 cells after the treatment with *T. arjuna*. The depletion of GSH was observed in Hep G2 cells treated with T. arjuna. Apoptosis of Hep G2 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 Hep G2 cells suggesting it induces cytotoxicity in Hep G2 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 ratswas evaluated. The levels of lipid peroxides (LPO) under basal and also in the presence of inducers (H2O2, ascorbate and FeSo4) 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 per kg 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 hydroalcohol extract of tha bark of *T. arjuna* was assassed on the healing of rat dermal wounds using invivo models. The results indicated a statistically significant increase in the tensile strength of the incision wound and the percent epithelialization of excision wounds compared with control. However topical treatment with fraction I, consisting mainly of tannin, 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, with hydroalcohol extract with *Arjuna* bark possessed antimicrobial activity against tested microorganisms such as Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus, Streptophylococcus 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 closure together (Chaudhari and Mengi., 2006).

The effect of 50% ethanolic extract of the bark *T. arjuna* and tannins isolated from the bark studied for wound healing activity in incision and excision wound models, after oral or topical application in form of the 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 wounds studies. The estimated increase in hydroxyproline content of the granulation tissues of the excision wounds indicated rapid collagen turnover thus, leading to rapid healing of 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 models and (2) incision wound models. Both the formulations responded significantly in both the models tested. The results were also comparable to that of the standard drug nitrofurazone. The results were also comparable in terms of wound contracting activity, epithelization period, tensile strength 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 agant (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, Staphylococcus epidermidis. Hexane and dichloromethane extract have shown more antibacterial components than the acetone extract suggesting the antibacterial activity in *Terminalia 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 pneumonia, Candida albicans and ATCC strains of Streptococcus mutans, Streptococcus aureus, Enterococcus faecalis, Streptococcus bovis, Pseudimonas aeruginosa, Salmonella typhimurium, Escherichia coli, Klebsiella pneumonia and candida albicans. The MDR strains were sensitive to the antimicrobial activity of *Acacia nilotica*, *Syzygium arimaticum* and *Cinnamum zeylanicum*, whereas they exhibited strong resistance to the extracts of *T. arjuna* and *Eucalyptus globules* (Khan *et al*., 2009).

Antioxidant activity: The antioxidant and free radical scanvenging capacities of arjunic acid, an aglycon obtained from the fruit of *Terminalia* evaluated. Results showed that arjunic acid was a strong antioxidant and a free radical scavenger, a 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 autooxidative hemolysis assay (Sun *et al*., 2008).

The study was designed to assess the ability of casuarinin, extracted from *Terminalia arjuna*, to protect cultured Madin-Darby canine kidney (MDCK) cells against H2O2-mediated oxidative stress. Casuarinin caused a decrease in intracellular peroxide production as shown by dichlorofluorescein (DCF) fluorescence in a concentration dependent manner. After 3h exposure to 8mM H2O2, the percentage of intracellular glutathione (GSH) negative cells was reduced in the casuarinin treated group. Addition of 32mM H2O2 to MDCK cells for 3h 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 attenuatesH2O2 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 – 500 mg per kg b. wt.) of *T. arjuna* stem bark in alloxan induced diabetic rats and its lipids peroxidation, enzymatic and non-enzymatic activity was investigated in the liver and kidney tissues. The extract at a dose of 500 mg per kg produced significant reduction in lipid peroxidation (LPO). The extract also cause a significant increase in peroxide dismutase, catalase, glutathione peroxidase, glutathione-s-transferase, glutathione reductase and glucose-6-phosphate dehydrogenase, reduced gluytathione, 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 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 IC50 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 (CC50) was 89±1 µM. Thus the selectivity index (SI) (ratio of CC50 to IC50) of casuarnin was 25 and 59 for XTT and plaque reduction, assay s respectively. Casuarinin continued to exhibit antiviral activity even added 12 h after infection. During attachment assay of HSV -2 to cells. Furthermore, casuarinin also exhibited an activity inhibiting the viral penetration. Interestingly, casuarinin was virucidal at a concentration of 25 µM, reducing viral titers up to 100000 fold which suggest that casuarinin possesses antiharpsvirus activity in inhibiting viral attachment and penetration also disturbing the late events of infection (Cheng *et al*., 2002).

Antiatherosclerotic activity: The effect of orally administrated indigeneous drugs *T. arjuna*, *T. chebula* and *T. belerica* were investigated on experimental atherosclerosis in rabbits. Atherosclerotic lesions of the arota were examined histologically. *T. arjuna* was found to be the most potent hypolipidaemic agent and induced partial inhibition of rabbits 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 dose of 100 and 500 mg per kg and compared with controls. After 60 days total cholesterol was 574±61, 320±29 and 217±44 mg per dL, respectively. LDL cholesterol was 493±57, 271±30 and 162±44 mg per dL; HDL cholesterol was 59±7, 36±3

and 35±4 mg per dL; Triglyceride was 108±13, 67±6 and 101±26 mg per dL; Cholestrol /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).

Antinociceptive activity*: T. arjuna* bark powder (400 mg per kg, 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 per kg, p.o.). these effects of *T. arjuna* were antagonized by pretreatment with naloxone (1 mg per kg, i:p.). in another series of experiments, mice pretreated with morphine for three days in increasing doses (10, 15, 20 mg per kg, i.p., twice daily) showed a decreased response in antinociceptive activity of morphine (5 mg per kg, i.p.). further these findings support the hypothesis that *T. arjuna* has antinociceptive action probably mediated via central opioid receptors (Halder *et al.*, 2009).

Immunomodulatory activity: *T. arjuna* bark powder (400 mg kg-1, p.o.) significantly increased the anti-SRBC antibody titre in the secondary phases of immune

response suggesting its use as immunomodulator (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 invivo. The results suggests that the chemopreventive role of arjunolic acid against arsenic induced testicular toxicity may be due to its intrinsic antioxidant property (Manna *et al.*, 2008).

Clinical trials: Several studies have been made to assess the efficacy of *T. arjuna* bark 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 *et al.*, 1994).

An adult male with Stokes Adams attacks following acute chest pain become well after three months use of *T. arjuna* powder. In another study, 500 mg crude drug powder of *T. arjuna* was administrated 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).

Botanical-Drug Interactions

Terminalia arjuna extracts have been used in clinical studies concomitantly with standard heart medications, including digoxin, diuretics, angiotensin-converting-enzyme inhibitors, and vasodilators, with no reported adverse effects. Simultaneous use of Terminalia with other cardiac medications should be undertaken with caution. (Kapoor *et al*., 1990).

Dosage and Toxicity

A typical dose of dried bark is 1-3 grams daily, while 500 mg bark extract four times per day has been used in congestive heart failure. No toxicity has been documented (Kapoor et al., 1990).

ACKNOWLEDGMENT

The author wish to thank the chairman, Principal, guide Dr. Anand Chaorasia and batch mades and Sagar Institutes of Pharmaceutical Sciences Sagar, of the assistance provided for this study.

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Source of support: Nil, Conflict of interest: None Declared

