A Review on *Semecarpus anacardium* L.: An Anticancer Medicinal Plant

T. Gouthaman¹, M.S. Kavitha¹, Bakkudeen Ali Ahmed¹, T. Senthil Kumar² and M.V. Rao*  

**Abstract**

*Semecarpus anacardium* L. is a well known medicinal plant in Ayurvedic and Siddha medicine. It has been found to have a lot of medicinal Properties, particularly for its anti-cancerous activity. The present review deals with distribution, phytochemical and pharmacological aspects of *S. anacardium*. Furthermore, the safety evaluation of Siddha preparation of *S. anacardium* nut extract has been discussed. Plant improvement studies (seed germination and in vitro propagation) of *S. anacardium* are also discussed.

**Key words**: *Semecarpus anacardium*, Medicinal plant, Phytopharmaceuticals, Anticancer activity, Seed germination, *In vitro* propagation

**Introduction**

Plants have been used in traditional medicine for a long time. About 13,000 plant species have been used as drugs throughout the world and approximately 25% of our current materia medica is derived from plants (Kutchan, 1996). Eighty percent of the world population relies on the plant-
based drugs for their primary health care needs as estimated by World Health Organization. International market of medicinal plants is over US $ 60 billion per year which is growing at a rate of 7 %. The herbal drug market in India is about Rs.644.63 crores and it can be raised to Rs.3000 crores by 2006. The growing demand for plant based medicine, health products and pharmaceuticals etc. led to the depletion of plant resources. Hence immediate focus on conservation and sustainable use of medicinal plants is required.

*Semecarpus anacardium* L. popularly known as marking nut tree has many therapeutic applications in Indian system of medicine (Saraf et al., 1989). Preparations of the nut from *S. anacardium* were used in ancient medicine and still find a place in indigenous medicine. Trade in the bhilawa (*S. anacardium*) nut is very ancient (King, 1957). Recent reports from all over the world reveals several scientific studies have been conducted on *S. anacardium* to evaluate its medicinal value. The present review summarizes the phytochemical profile, pharmacological activity and plant improvement studies of *S. anacardium*.

**Plant description**

*Semecarpus anacardium* is a deciduous tree distributed in Sub-Himalayan region, tract east of the Beas, ascending to 1050m in Assam (Khasia hills), Madhya Pradesh, Gujarat, Konkan, Kanara forests of Tamilnadu state (Gothoskar et al., 1971), Western Peninsula and N. Australia (Kirtikar and Basu, 1975). It belongs to the family Anacardiaceae. It is commonly called by various names throughout the country as mentioned below.

<table>
<thead>
<tr>
<th>Language</th>
<th>Common name</th>
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<tbody>
<tr>
<td>English</td>
<td>Marking nut tree, oriental cashew</td>
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<tr>
<td>Hindi</td>
<td>Bhela, bhilva</td>
</tr>
<tr>
<td>Kannada</td>
<td>Godduguru, karigeri, bhallika</td>
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<tr>
<td>Malayalam</td>
<td>Ceru, allakkuceru</td>
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<tr>
<td>Sanskrit</td>
<td>Bhallatakah, aruskarah</td>
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<tr>
<td>Tamil</td>
<td>Senkottai, erimugi</td>
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<tr>
<td>Telugu</td>
<td>Bhallatamu, jidi</td>
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It is a medium sized to large tree, 15-25 m in height, with grey bark exfoliating in small irregular flakes (Fig. 1a). Leaves are simple, alternate, obovate oblong, rounded at the apex, coriaceous, glabrous above and more or less pubescent beneath, main nerves 15-25 pairs. Flowers are greenish white fascicled in pubescent panicles (Warrier et al., 1996). Fruits are obliquely ovoid or oblong drupes and 2.5 cm long. The upper portion of the fruit is cup-shaped, smooth, fleshy, orange red in colour and sweet and edible.
when ripe. It is formed of the thickened disc and accrescent calyx base. The lower base which may be turned the nut, consists of smooth, black, shining pericarp which is thick, containing between its outer and inner laminae oblong cells full of a corrosive resinous juice. This juice is white when the fruit is immature, but brownish or quite black when the fruit is ripe. The nut is approximately 1” × 0.75” × 0.33” and weighs on an average 3.5 g (Fig. 1b). The black corrosive juice is largely used throughout the India as an efficacious drug: internally in the cases of dyspepsia, nervous debility, acute rheumatism, asthma and cough; externally for swellings, piles and various cutaneous affections. It is also largely used by dhobis as an indelible marking ink, and in certain parts of the country an aqueous extract of the crushed seeds is used in conjunction with iron salts for producing a jet-black dye on the cloth. Inside the nut and protected by the hard shell is a white kernel which is sweet and nutritious as the almond or cashew-nut kernel (Naidu, 1925).

The Nutritive value of unusual food (kernels of *S. anacardium*), which is known to be consumed by some populations, was extensively studied (Ramasastri and Shenolikar, 1974) (Table 1).

The oleic acid content present in the kernel indicated that it could be used as a good source of salad oil. The marking nut kernels are being used for consumption especially during pregnancy and lactation because of its amino acid profile. They can replace the usage of other oil seed because of its high protein and fat content. However the vesicant nature of bhilwa juice and manufacturing difficulties of kernels prevents its usage (Ramasastri and Shenolikar, 1974). If this vesicant nature is abolished, this juice forms a good source for pharmaceutical industry.

**Ayurvedic usage**

Ayurveda, literally meaning ‘science of life’, is based on the principle of subjectivity. It is a well-organized system of traditional health care in large

<table>
<thead>
<tr>
<th>Proximate principles (g / 100 g)</th>
<th>Minerals and vitamins (mg / 100 g)</th>
<th>Essential amino acids (mg / g protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moisture 3.8</td>
<td>Iron 6.1</td>
<td>Arginine 9.6</td>
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<tr>
<td>Protein 26.4</td>
<td>Phosphorous 836</td>
<td>Histidine 1.8</td>
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<td>Fat 36.4</td>
<td>Calcium 295</td>
<td>Lysine 4.1</td>
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<tr>
<td>Fiber 1.4</td>
<td>Thiamine 0.38</td>
<td>Leucine 7.3</td>
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<tr>
<td>Minerals 3.6</td>
<td>Riboflavin 0.17</td>
<td>Isoleucine 4.4</td>
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<tr>
<td>Carbohydrates 28.4</td>
<td>Nicotinic acid 1.06</td>
<td>Methionine 1.5</td>
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<tr>
<td>Calories 5.87</td>
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<td>Tryptophan 1.1</td>
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Fig. 1. Habit and seeds of *Semecarpus anacardium*

a. Habit

b. Seeds with ripening yellow fruits

*Fig. 1. Habit and seeds of Semecarpus anacardium*
parts of the eastern world, especially in India (Chopra et al., 1956). Ayurvedic medicinal system has identified more than 700 individual herbs, as well as several complex herbal drug preparations, as useful in the treatment and/or prevention of diseases including cancer, and improvement of quality of life of both healthy and diseased individuals (Joseph et al., 1999; Premalatha 2000; Diwanay et al., 2004). Ayurveda describes *S. anacardium* to be a potent drug against a variety of ailments and is popularly known as Ardha Vaidhya. The fruits and oil have been claimed to be highly efficacious in the treatment of neuritis (Charaka, 1941) and helmintic infection (Chattopadhayaya and Khare, 1969). *S. anacardium* has found many applications in Indian medicine in the treatment of gout and rheumatic pain (Nadkarni, 1954). The fruits of *S. anacardium* are subjected to a purification process before they are used for ayurvedic medicines because they are considered to be toxic. Purified fruits are claimed to possess rejuvenating properties, increasing longevity, bringing a glow to the face, sweetness in tone and improvement in vision (Sreenivasacharyulu, 1931). The fruits of plants are also largely used in Ayurvedic system of medicine for various ailments, particularly alimentary tract and certain dermatologic conditions. It has beneficial action on heart, blood pressure, respiration and neurological disorders (Kurup et al., 1979, Raghunath and Mitra, 1982, Sharma et al., 1995). The fruits of *S. anacardium* are claimed to be useful in treating leprosy, rheumatoid arthritis, piles, asthma and cough, sexually transmitted diseases such as syphilis and gonorrhoea, and skin diseases such as leucoderma (Nadkarni, 1976; Kirthikar and Basu, 1933). The nuts are also used for management of rheumatisim, wound healing, diabetes and urinary diseases. It is also used as aphrodisiac, nerve- tonic and as anabolic medicine in the Ayurvedic system of therapy (Pandey et al., 1967 and Thakur and Puri, 1978). The chloroform soluble fraction of the whole nut has been reported to be very useful in the treatment of cancer of oesophagus and leukemias (Vad and Kulkarni, 1975). The seeds are eaten in certain regions of India and are considered nutritious. Several Ayurvedic preparations such as “Bhallataka rasayana”, “Amritha bhallataki” and “Brihat bhallataka lehya” are marketed in India (Sreenivasacharyulu, 1931).

**Phytochemical profile**

In alternative medicine, medicinal plant preparations have found widespread use particularly in the case of diseases not amenable to treatment by modern methods. A variety of nut extract preparations from *S. anacardium* are effective against many diseases viz. arthritis, tumours, infections etc (Premalatha, 2000). Understanding the mechanism of the pharmacological action of *S. anacardium* can be greatly aided by the isolation of its active principle and determination of structure and function relationship. Based on this principle a lot of phytopharmaceuticals from different parts of *S. anacardium* have been isolated.

Phytochemical examination revealed 3.85% of total ash, 0.33% of acid insoluble ash, 11.27% alcohol soluble extractive, 11.84% water soluble
extractive and 12.71 % moisture content in *S. anacardium* nuts (Gulati *et al*., 1984). Analysis by Bose *et al.* (1967) revealed the presence of iron, copper, sodium, calcium and aluminium in traces.

Bhilawanols, isolated from the nut shell of *S. anacardium*, is a mixture of 3-pentadec (en) yl catechols unsaturated in the lipophilic side chain. The chief components of bhilawanol are the 8Z, 11Z-diene (Fig. II1) and 8Z-monoene (Fig. II2) along with minor amounts of saturated bhilawanol (Fig. II2) (Nagabhushana *et al*., 2002). Studies on the methylated Bhilawanol showed that it contained more than seven components and two major compounds identified as dimethyl ethers of 1-pentadeca-8enyl-2,3-dihydroxybenzene (Fig. I1) and 1-pentadeca-7,10 dienyl-1,3-dihydroxybenzene (Fig. II) (Rao *et al*., 1973). Reexamination of bhilawanol showed that it was comprised of two components, 1,2-dihydroxy-3-pentadecylbenzene (Fig. III1) and its corresponding diene analogue (Fig. III2) (Gedam *et al*., 1974; Cordell and Shin, 1999). Three biflavonoids were isolated from the ethanol soluble fraction of the *S. anacardium* nut shells and characterized as I-4′, II-3′, 4′, I-5, II-5, I-7-hexahydroxy [I-3, II-8] biflavonone (Fig. III4), I-4′, II-4′, I-5, II-5, I-7, II-7-hexahydroxy [I-3, II-8] biflavonone (3′, 8-binarigenin) (Fig. III5) and I-4′, II-4′, I-7, II-7-tetrahexahydroxy [I-3, II-8] biflavonone (3′8-biliquiritigenin) (Fig. III6) (Rao *et al*., 1973). The three other biflavonoids, jeediflavonone (Fig. IVa), semecarpuflavonan (Fig. IVb), gauluflavanone (Fig. IVc) have also been isolated from the alcoholic fraction of nut shells and characterized (Murthy, 1983 a; Murthy, 1985 a; Murthy, 1983 b; Murthy, 1983 c; Murthy, 1985 b). The two other new biflavonoids a dimeric flavonoid nallaflavanone (Fig. IV10a), semecarpetin (Fig. IV10b) and anacardoflavonanone (Fig. IV11) have been isolated from the nut shells and characterized (Rastogi and Mehrotra, 1999; Murthy, 1988; Rastogi and Mehrotra, 1995). Ishratullai *et al.* (1977) isolated one more biflavonoid namely tetrahydrorobustaflavone (Fig. V) from the defatted nuts of the *S. anacardium* and structure characterized. The leaves of the *S. anacardium* found to contain amentoflavone (Fig. V) as the sole compound (Ishratullai *et al*., 1977). The corrosive juice from the pericarp of the fruit found to contain catechol, fixed oil and anacardol (C18H13O3.COOH) to which the corrosive properties of the juice are due to two phenolic acids C16H15O3.COOH and C14H13O3.COOH (Naidu, 1925). From the seeds of *S. anacardium*, a new phenolic glucoside, anacardoside, was isolated, and its structure and configuration were elucidated by a combination of NMR techniques as-l-O-β-D-glucopyranosyl- (1 → 6) -β-D-glucopyranosyloxy-3-hydroxy-5-methylbenzene (Fig. V14) (Gil *et al*., 1995).

**Pharmacological activity**

*Semecarpus anacardium* has been used in the treatment of a number of diseases. A vast number of clinical and pharmacological studies on different
types of Siddha preparations and also on the different parts of *S. anacardium* have been carried out.

**Siddha preparation of Semecarpus anacardium nut extract**

The Siddha preparation of *S. anacardium* nut extract called Serankottai nei is being used in the treatment of various ailments. The preparation of drug Serankottai nei is as follows: *S. anacardium* nuts, cow’s milk, and ghee are the main ingredients present in the drug. The drug was prepared by boiling the nuts (200 g) with 500 ml of milk. After decanting the decoction, 500 ml of milk was added to the boiled nuts and the mixture was again boiled...
for some time. The decoction was recovered and repeated the process again with the milk. All the three portions of the milk nut decoction were mixed with ghee and boiled till dehydrated, filtered and stored. Olive oil was used as the vehicle for the drug, since it is insoluble in water (Formulary of Siddha Medicine, 1972).

**Anti-inflammatory activity**

*Semecarpus anacardium* nut extract demonstrated significant anti-inflammatory activity against early phase of acute (carrageen induced), late phase of chronic (cotton pellet induced granuloma) inflammation and acute arthritis without any deleterious side effects. The response observed with the dose level of 150 mg/kg body weight and comparable to 30 mg/kg body weight of indomethacin. The ability of the drug to reduce the edema formation may be due to the inhibition of the release of early mediators such as histamine and serotonin and also due to the inhibition of cyclooxygenase. *S. anacardium* decreases the size of cotton pellet granuloma by inhibiting monocyte infiltration and fibroblast proliferation. It was reported that the flavonoids present in the nut extract could attribute to the anti-inflammatory activity (Ramprasath et al., 2004). Ayurvedic drug “Sandhika” (water extracts of the four plants *Commiphora mukul*, *Boswellia serrata*, *Strychnos nux-vomica* and *S. anacardium*) revealed significant anti-inflammatory activity at a dose level of 0.25 g/kg body weight in carrageen induced paw edema and cotton pellet induced granuloma of albino rats. It also showed significant protection against lipid peroxidation. This is accompanied by reduced glutathione levels and normal serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT) levels. These findings indicated that “Sandhika” can be used as a drug for inflammatory disorders and it might be acting through its free radical scavenging ability (Chaurasia et al., 1995).

**Anti-arthritic effect**

*Semecarpus anacardium* nut milk extract was found to be effective against adjuvant-induced arthritis in albino Wistar rat at the dose level of 150 mg/kg body weight on the basis of dose dependent study (Vijayalakshmi et al., 1996). The milk extract of the nut was found to inhibit acute tuberculin reaction in sensitized rats and also the primary phase of adjuvant arthritis (Satyavathi et al., 1968 and 1969). A chloroform extract of the nut significantly reduced acute carrageen induced paw edema in rats and was active against secondary lesions of adjuvant induced arthritis (Saraf et al., 1989). Vijayalakshmi et al. (1997a) suggested that the diseased state of adjuvant arthritis may be associated with augmented lipid peroxidation and the administration of the drug may exert its anti arthritic effect by retarding lipid peroxidation and causing a modulation in cellular antioxidant defense system. The antioxidant property of flavonoids (scavenge singlet O₂ and
terminate peroxides by their low redox potential) could augment for the inhibition of lipid peroxidation (Klopman and Dimayuga, 1988). The effect of *S. anacardium* nut milk extract on adjuvant induced arthritis associated carbohydrate metabolic changes was evaluated by Vijayalakshmi et al. (1998). This study indicates that *S. anacardium* nut milk extract reverted back the altered level of glycolytic and gluconeogenic enzymes to near normal levels. *S. anacardium* nut milk extract treatment brought back elevated levels of antioxidants (SOD, CAT, GPX, GSH) and the biochemical markers of inflammation (C-reactive protein (CRP) level and Erythrocyte sedimentation rate (ESR) to near normal levels in arthritis induced Wistar rats. The treatment with the drug also significantly reduced paw thickness and arthritic scores associated with arthritic rats (Ramprasath et al., 2004). Apart from this, *S. anacardium* also possess a capability to modulate the accumulation of neutrophils (Nada et al., 1999) and brings down the increased levels of lysosomal enzymes (Anderson, 1986) in adjuvant induced arthritis rats. Apart from this, *S. anacardium* nut milk extract exerts its action on adjuvant arthritis in rats through stabilizing action on lysosomal membrane and thereby preventing its leakage from lysosomes. This would prevent the injurious attack to normal tissue and also would tend to retard amplification and spread of the inflammatory process (Vijayalakshmi et al., 1997b). All these observations indicated that *S. anacardium* nut milk extract is a good therapeutic agent for the arthritis.

**Antitumour, Antineoplastic, Cytotoxic and Cytostatic activity**

*Semecarpus anacardium* has been under investigation for its antitumour properties. A variety of marking nut preparations had been used in clinical practice and encouraging results have been reported, particularly for cancer of the esophagus, liver, urinary bladder and leukaemia (Vad, 1973). The investigation of pericarp oil revealed its anticancer activity (Gothoskar et al., 1971). The flavonoids present in the *S. anacardium* nut have the ability to prevent various cancers (Tumova, 1995). SAN-AB is a chloroform extract of the whole nut (pericarp and seed) and when administered at a dilution with peanut oil, it is nontoxic. It showed a differential action on tumour cells in Yoshida sarcoma (ascites tumour in rats) (Gothoskar et al., 1971). *S. anacardium* nut extract revealed potent anticarcinogenic activity against AFB1 mediated hepatocellular carcinoma. The adverse effects induced by AFB1 were reversed to near normal levels with reference to biochemical parameters and histological pattern (Premalatha and Sachdanandam, 1999a). The serum alpha protein level was also brought back to near normal levels after administration with the *S. anacardium* nut milk extract. This provided the additional evidence to use *S. anacardium* nut milk extract as an antitumour agent (Premalatha and Sachdanandam, 1999b). The depleted levels of non-enzymatic antioxidants (uric acid, vitamin C, vitamin E,
glutathione, total thiol, non-protein thiols, cytochrome P450) were brought back into normal values followed by the administration of the drug. The deleterious effects associated with decreased levels of antioxidant are also controlled by *S. anacardium* nut extract. Thus *S. anacardium* nut extract acts as a potential anticarcinogenic agent against radiation damage caused by AFB1 induced HCC through its antioxidant property and by the induction of *in vivo* antioxidant defence system (Premalatha and Sachdanandam, 1999c). Premalatha *et al.* (1999) evaluated the influence of the drug *S. anacardium* extract on hepatocarcinogenicity of aflatoxin B (AFB1) in adult albino male Wistar rats with reference to tumour marker enzymes (lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and γ-glutamyl transpeptidase). Administration of *S. anacardium* nut extract resulted in the recoupment of these enzyme levels to near normal values. The presence of flavonoids in the nut extract is responsible not only for inhibition of these enzymes (Sanz *et al.*, 1994) but also possess specific inhibitory action on AFB1-DNA adduct formation and they reflect their ability to afford protection against development of AFB1—induced neoplasia in susceptible species (Francis *et al.*, 1989). Bilawanols, which was localized maximally in the cell membrane fraction of *S. anacardium* extract, could exert its effect through membrane function. The extract would change the permeability of the membrane, affecting cellular growth (Patwardan *et al.*, 1988) and this may contribute to its anticancer property. Premalatha and Sachdanandam (2000a) reported that anticarcinogenic action by *S. anacardium* nut extract is possibly via suppression of AFB1 activation and through interaction with microsomal-activating components. This is responsible for the chemopreventive ability of *S. anacardium* nut extract against HCC. The effect of *S. anacardium* nut milk extract on host detoxification system in AFB1 induced hepatocellular carcinoma was evaluated in male albino rats. It shows that *S. anacardium* nut milk extract affords anticancer activity by enhancing both phase I (cytochrome P450, cytochrome b5, NADPH-cytochrome P450 reductase, NADH-cytochrome b5 reductase, and aniline hydroxylase) and phase II (glutathione-S-transferase and UDP-glucuronyl transferase) enzymes to near normal levels. The anticarcinogenic potency of *S. anacardium* nut extract against AFB1-induced hepatocarcinogenesis is mediated through the induction of hepatic biotransformation enzymes and by enhancing the oxidative metabolism of a carcinogen (Premalatha and Sachdanandam, 2000b). Stabilizing action on lysosomal membrane and altered glycoprotein profile exhibited by *S. anacardium* nut extract could augment for its anticancer potency against AFB1 induced hepatocellular carcinoma in male albino rats (Premalatha and Sachdanandam, 2000c). The antiperoxidative capacity of the nut extract may play a role in the stabilization of lysosomal membranes (Premalatha *et al.*, 1997a; Vijayalakshmi *et al.*, 1997a). The
potentiality of chloroform extract of *S. anacardium* to act as an antineoplastic agent was proved by its antitumour activity against a wide spectrum of experimental tumour systems such as leukaemia L1210, P388, advanced P388, B16 melanoma and glioma 26 (Chitinis et al., 1980; Cassady et al., 1981). *S. anacardium* nut extract was found to be effective in regulating the key enzymes (significant drop in the activity of glycolytic enzymes [hexokinase, phosphoglu-coisomerase and aldolase] and a concomitant elevation in the gluconeogenic enzymes [glucose-6-phosphatase and fructose 1, 6-diphosphatase]) related to carbohydrate metabolism in dimethyl benzanthracene-induced mammary carcinoma in Sprague-Dawley rats. Thus *S. anacardium* nut extract can be a potential antineoplastic agent against mammary carcinoma (Premalatha et al., 1997b, Sujatha and Sachdanandam, 2002) and also has a significant role in mitochondrial energy production (Arathi and Sachdanandam, 2003). Immunological deficiency (depleted levels of IgG, IgA, IgM, IgI) associated with mammary carcinoma was brought back to normal levels. This immunomodulatory activity of the drug could attribute to its potential antineoplastic property (Sachdanandam and Sujatha, 2001). The cytostatic activity of extracts of *S. anacardium* had been reported by various experiments. In one experiment the chloroform extract of the nuts showed an activity of 150 % T/C in a P388 test system in mice, at a dose of 50 mg/kg (Gothoskar et al., 1971). In another study a fraction of the aqueous methanolic extract of the nuts was tested on Eagles 9 KB nasopharynx carcinoma cell cultures, yielding an IC50-value of 2.3 µg/ml. This fraction consisted mainly of pentadecylcatechols. These pentadecylcatechols however showed no activity on *in vivo* P388 leukaemia tests in mice, up to a dose of 80 mg/ml (Hembree et al., 1978). The nuts of *S. anacardium* displayed the strongest cytotoxic effect with IC50-values of 1.6 µg/ml (Smit et al., 1995). *S. anacardium* oil prepared according to the Ayurvedic principle displayed strong cytotoxic activity in human leukaemia cell lines. It is surmised that this cytotoxic activity of *S. anacardium* oil in human leukaemia cells is attributed to its phenolic constituents, particularly biflavones (Chakraborty et al., 2004). *Semecarpus lehyam* (Sowmyalakshmi et al., 2005) and rasagenthi lehyam (Ranga et al., 2004) which contain *S. anacardium* as one of the components can be effectively utilized as complementary and alternative medicine against breast cancer and prostate cancer respectively.

**Contraceptive agent**

Narayan et al. (1985) reported that the water extract of the aerial part of *S. anacardium* exhibited a spermicidal activity. The administration of ethanolic extract of *S. anacardium* fruit leads to spermatogonic arrest in albino rats. The significant reduction in the sperm motility and density was observed. The fruit extract feeding also caused marked reduction in the
number of primary spermatocytes, secondary spermatocytes and spermatids. The number of mature leydig cells was also decreased and degenerating cells increased proportionately. These results clearly show the anti spermatogonic activity of *S. anacardium* (Sharma and Verma, 2003).

Gudibanda (1968) studied the activity of *S. anacardium* on the uterus and ovaries of albino rats. He observed that the cotyledons of *S. anacardium* were found to be effective in causing inhibition in both the number litters (from 12 to 3) and litter size (from 7.17 to 2.67). In the metabolic study he stated that *S. anacardium* has a selective action on the gonadotropin effects on the ovary and also have an antiestrogenic type of action (blockage of uterine metabolic functions). Murty (1974) observed that no signs of pregnancy were observed in 8 women patients treated for antifertility effect of the drug. Oligospermia and azoospermia were observed of the cases treated for male infertility effect of the drug. This implied that it might be
acting via the hypophysis. From these we can infer that *S. anacardium* can be a good oral contraceptive agent.

**Lipoxygenase inhibitory activity**

Bhilawanol diene present in the bhilawan nut shell liquid was found to be a potent inhibitor of both soybean and potato lipoxygenases with IC$_{50}$ values of 0.85 mM and 1.1 mM, respectively. However, two other compounds monoene and saturated bhilawanols exhibited relatively lower inhibitory activity. The unsaturated lipophilic side chain may be an absolute requirement for inhibitory activity of these compounds and it is proved by inhibition studies with the synthetic analogues of salicylic acid (Nagabhushana *et al.*, 2002).

**Hypoglycaemic activity**

Ethanolic extract of dried nuts (100 mg/kg) of *S. anacardium* reduced blood glucose levels of both normal (hypoglycaemic) and streptozotocin-induced (antihyperglycaemic) diabetic rats. The antihyperglycaemic activity of *S. anacardium* was compared with tolbutamide, a sulfonylurea derivative used in diabetes mellitus (Arul *et al.*, 2004). Kothai *et al.* (2005) also reported the antihyperglycaemic activity of *S. anacardium* against alloxan-induced diabetes and this was compared with tolbutamide, a sulfonylurea derivative used in diabetes mellitus. These results clearly indicate the hypoglycaemic activity of *S. anacardium* nut extract.

**Hypolipidemic and Hypocholesterolemic activity**

*Semecarpus anacardium* nut extract oil fraction at a dose of 1 mg/100 g body weight significantly reduced serum cholesterol levels and increased HDL cholesterol levels in the rat fed with atherogenic diet (Tripathi and Pandey, 2004). The same oil fraction also prevented lipopolysachharide (LPS) induced nitric oxide (NO) production through its inhibitory activity on NFκB trascripting factor, which is responsible for the production of cytokines and other inflammatory factors. Thus it could be a better drug to treat CHD through mechanism of anti-inflammation, hypolipidemic and HDL cholesterol enhancing activity. The altered levels of cholesterol and phospholipids levels were reduced to near normal levels by *S. anacardium* nut extract in rabbits fed with athregenic diet. Further it lowered the elevated levels of LDL-cholesterol and promoted plaques regression (75.3-83.5 %). This indicated that CHD patients could use it as a potent antiatherosclerotic drug to halt the progression of atherosclerosis (Sharma *et al.*, 1995). The evaluation of the antiatherogenic effect of a herbal formulation, Caps HT2 (methanolic extracts of selected parts of plants, Commiphora mukul, Allium sativum, Plumbago indica, *S. anacardium*, Hemidesmus indicus, Terminalia arjuna, Tinospora cordifolia, Withania...
somnifera and Ocimum sanctum) revealed its antioxidant, anticoagulant, platelet antiaggregatory, lipoprotein lipase releasing, anti-inflammatory and hypolipidaemic activity (Mary et al., 2003).

**Antimicrobial activity**

Alcoholic and oil extracts of S. anacardium dry nuts have antimicrobial activity against Gram-positive and Gram-negative bacteria (Nair and Bhide, 1996). An Ayurvedic preparation of S. anacardium called “Bhallatakensava” was shown to have antibacterial activity against tetanus causing microorganism (Kulkarni et al., 1995). Alcoholic extract of dry nuts showed dose dependent antifungal activity in vitro against Aspergillus fumigatus and Candida albicans. At 400 mg/ml concentration, growth of both fungi were inhibited and considerable reduction in size of cells, hyphae, and reduced sporulation was also observed (Sharma et al., 2002). Anacardic acid from the nuts exhibited antimicrobial properties (Chattopadhyaya and Khare, 1969). Monoene and diene bhilawanols inhibit gram positive anaerobes but not gram positive anaerobes which is probably due to lipoprotein layer which prevents penetration of lipophilic agents like bhilawanols into the cell membranes. Bhilawanols are susceptible to atmospheric oxidation and complex polymerization in the presence of oxygen which makes them unable to inhibit aerobic bacteria (Patwardhan et al., 1988).

**Antistress activity**

Immobilization stress caused degeneration (karyorrhexis, membrane blebbing, chromatin condensation, chromatin fragmentation and intracellular spacing) of hippocampal neuron cell bodies of rats. Treatment with S. anacardium nut extract (40 mg/kg/bodyweight) reduced the degenerating cell bodies (80 %). This indicated that S. anacardium nut extract has neuroprotective effect and possibly it can be used as an “antistress” agent in human beings (Shukula et al., 2000).

**Other significant properties**

The nut extract has direct depressant effects on the isolated frog heart and rabbit intestine and antagonism to the spasmogenic effects of histamine, barium chloride and pitocin (Bose et al., 1967). Delayed type of hypersensitivity induced in mice by sheep red blood cells as an antigen was potentiated by the nut extract (Gothoskar et al., 1971). Immunomodulatory potency of the nut extract in hepatocellular carcinoma was also reported (Premalatha and Sachdanandam, 1998).

**Toxic characteristics**

Apart from having lot of medicinal properties S. anacardium also found to have some toxic characters. The powerful irritant properties of the juice of
pericarp have frequently been made use of by malingerers in producing ophthalmic and skin lesions and also in producing abortions (Nadkarni, 1976). Dermatitis occurs in those preparing the oil or in those applying it to clothing in their capacity as laudryman or in those wearing the marked clothing. There are two principal patterns of dermatitis (Behl et al., 1966). Those who use nut preparations medicinally may develop dermatitis of the
Hands and face. If the nuts are ground with a pestle in a mortar held between the knees, the legs and feet may also be affected. The second clinical pattern involves those who wear the marked clothing. Exposure to sap of the *S. anacardium* led to a development of skin lesions and anuria followed by diffused cortical necrosis. The mechanism of nephrotoxicity of the sap may be due to its phenolic constituents (Matthai and Date, 1979). External application of *S. anacardium* lead to the painful micturition and the urine was reddish and bloody and passing of stools was very painful (Murty, 1974). Certain side effects were also reported in patients treated with *S. anacardium* by Tripathi et al. (1965) and Satyavati et al. (1968). The occurrence of these side effects was related to the dose of the drug being administered to the patients in each case (Bajpai et al., 1970). They reported that 17 patients out of 70 patients developed reactions to the drug. They usually occur in the form of itching in the dorsal aspects of the hands and forearm, often associated with reddish maculo-papular rashes in the same area. There was intense itching and rashes all over the body associated with stomatitis, burning in the anal region, interfering with sleep of the individual occurs in severe most cases.

**Toxicological evaluation**

*Semecarpus anacardium* can be given orally with milk, ghee, peanut oil etc. Toxic effects are not observed in such routes of administration. On the contrary anabolic effects are obtained. Traditional methods recommended in Ayurveda and Siddha should be closely followed so as to get therapeutic effects without toxicity (Premalatha, 2000).

**Animal studies**

Two different studies acute (72 h) and sub acute (30 days) were carried out on liver and kidney function by administrating the nut extract and the biochemical parameters were observed. The drug did not produce any mortality in the acute toxic studies at any dose level given (75 – 2000 mg/g body weight). During the sub acute toxicity studies (50, 100, 250 and 500 mg/kg body weight), there is no marked alteration were observed in haematological (total red cell and leukocyte counts and haemoglobin) and biochemical parameters (glutamate pyruvate transaminase, glutamate oxaloacetate transaminase and alkaline phosphatase). However, the highest dose (500 mg/kg body weight) alone showed a moderate increase in the level of blood glucose, plasma urea, uric acid and creatinine. The alteration in the lipid profile may be attributed by the ghee preparation of the drug. Decrease in urinary urea, uric acid and creatinine levels were also observed. No morphological disturbances were observed in vital organs during histopathological study (Vijayalakshmi et al., 1998). Ramprasath et al. (2004) clearly indicated that animals administered with the nut extract did not show any ulceration effect. Analysis of tumour marker enzymes in the case

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of normal *S. anacardium* nut extract (200 mg/kg body weight/day) administered animals no conspicuous deleterious side effects were observed, which suggests that the drug is safe pharmacologically in rats (Premalatha *et al.*, 1999). The drug has no toxic effect at the dose level used and has a very temporary effect on white blood corpuscles and neutrophil count. It kills malignant cells but does not affect normal blood cells (Gothoskar *et al.*, 1971). The drug administered animals showed no acute biochemical disturbances in glycolytic (hexokinase, phosphogluco isomerase, aldolase) and gluconeogenic enzymes (glucose-6-phosphatase and fructose-1, 6-biphosphatase) (Sujatha and Sachdanandam, 2002). The level of lysosomal enzymes (Acid phosphatase, α-glucuronidase, β-galactosidase, and N-acetyl β-D-glucuronidase and the glycoprotein profile did not alter during the administration of *S. anacardium* nut extract (Premalatha and Sachdanandam, 2000c). Siddha preparation of *S. anacardium* (SKx) did not produce any adverse effect up to an oral dose of 1000 mg/kg body weight in animals (Ghosh *et al.*, 1981). Acute and sub-acute toxicity studies of Anacarcin forte (Jam like preparation from *S. anacardium* nut) were carried out in rats and rabbits. The IC$_{50}$ value of this drug was found to be more than 40 g/kg in rats and rabbits. In sub-acute toxicity studies there was no significant abnormality in histopathological and haematological conditions. However the bone marrow of the rabbit showed hypocellularity with respect to granulocytes and thrombocytes, and also variable changes in the bone marrow ranging from hypocellularity to hypercellularity in rats. The toxic effects were detected after 6 weeks of drug treatment (Vaishnav *et al.*, 1983). This revealed that caution should be taken while using this drug for human treatment.

**Human studies**

*Semecarpus anacardium* was administered orally to 266 patients (189 man and 77– women between 30-45 years of age) in 3 formulations (Amrit Bhallatak- extract of both the cotyledons and pericarp of the fruit of *S. anacardium*, RB3-whole cotyledon (300mg) and Garsin - 200g of cotyledons). Daily dosage of Amrit Bhallatak, RB3 and Garsin was 10 g/day, 3.6 g/day and 2.4 g/day respectively. The treatment was restricted to internal medication by mouth and no external contact or application of the drug was applied. No toxicity and side effects were observed in this study and also the women patients tested showed normal pregnancy and none showed any teratogenicity (Murty, 1974).

The toxic side effects of the very high dose of drug are diarrhoea and vomiting, swelling all over the body, ulceration and vesication on the skin. The least appearance of a rash or redness of the skin or the itchy or uneasy sensation in any part of the body should be considered as a manifestation of undesirable effect during internal or external usage of the drug and it should be discontinued immediately (Premalatha, 2000).
From these we can infer that *S. anacardium* is nontoxic and can be used as a therapeutic agent in treating various diseases. However more clinical studies have to be conducted before using the *S. anacardium* as a complementary and alternative medicine.

**Plant improvement studies in *Semecarpus anacardium***

**Seed germination**

The seeds of *S. anacardium* have very poor viability, hence our study focused on improvement of seed germination using different treatments to reduce the seed germination time (Gouthaman and Rao, 2006). The seeds were treated with hot water, prechilling, GA₃, Conc. HNO₃, Conc. HCl and Conc. H₂SO₄. Each treatment consisted of 25 seeds and repeated twice for confirmation. The seeds were washed under running tap water for overnight after the treatment and surface scarified to remove the external coat. In *vivo* study they were sown in the garden soil. The same set of treatment was done in *in vitro* condition. The surface scarified seeds were soaked in teepol (1 %) solution for 5-10 min to reduce the level of superficial contamination. They were then treated with 95 % alcohol for 10-20 min and 0.2 % mercuric chloride for 15 min. After exposure to sterilants the seeds were rinsed with several changes of sterile distilled water to remove all traces of the sterilizing agent before it is placed *in vitro*. These sterilized seeds were then inoculated in culture tubes containing MS medium.

Culture conditions: The pH of the medium was adjusted to 5.8 using 0.1 % NaOH before autoclaving and sterilized by autoclaving at 1.05 kg/cm² and 121°C for 15 minutes. Culture medium contained 3 % sucrose (w/v) and solidified with 0.8 % agar (Bacteriological grade, HiMedia, India). Cultures were maintained in a culture room at 25 °C ± 2°C and under 16 h photoperiod provided by cool white fluorescent tubes (40 µEm⁻²S⁻¹) with 60-65 % relative humidity.

In *in vivo* conditions, GA₃ treatment improved seed germination percentage significantly (20 %) and the time duration of germination was 60-70 days (Fig. VIa), compared to the control seeds (20 % germination and the time duration was 50-60 days) (Fig. VIa). Similarly Conc.HNO₃ treated seeds showed a germination rate of 20 % but the germination was noticed between 50-70 days (Fig. VIc). In contrast the seeds treated with Conc. HCl and prechilling gave nil response and only 4 % germination was observed in case of seeds treated with the hot water (Fig. VIb). Compared to other treatments Conc. H₂SO₄ (40 % and 50 %) proved to be the best to increase the rate of germination (60 %) and the time duration was between 45-60 days after sowing in the garden soil (Fig. VIe).

In *in vitro* condition seed germination study revealed significant improvement (70 %) under Conc. H₂SO₄ treatment and the time duration
was 35-45 days (Fig. VIIId). The seeds treated with Conc. HNO$_3$ (Fig. VIIb) and GA$_3$ showed only 10% of seed germination (Fig. VIIc) from 45-60 days of time duration, whereas Conc. HCl, prechilling and hot water treatment failed to induce the germination. The control seeds showed better results than the above two treatments, the rate of germination was 30% and the number of days were between 35-45 days (Fig. VIIa).

While comparing the *in vivo* and *in vitro* seed germination, the *in vitro* kept seeds showed better results than the *in vivo* seeds (Table 2). The germination rate was high and the time duration for effective germination was low when compared to the *in vivo* condition. The seeds germinated from

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**Fig. V.** Chemical constituents of *Semecarpus anacardium.*

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the basal region by breaking the seed coat. The cotyledon is attached with the plant for a long time. In certain seeds the seed coat dies immediately after breaking. Similar results were also obtained in acid scarification study carried out by Airi et al. (1998), where the treatment with Conc. H$_2$SO$_4$ (50%) for 5-10 min significantly increased the percentage germination and reduced mean germination time (MGT).

**Tissue culture studies**

Raising the demand for wild source herbal drugs has abetted over the exploitation of medicinal plants, leading to cumulative and unsustainable use of forest wealth. The importance of conservation of genetic resources cannot be over emphasized. Germplasm storage in the form of seeds is very easy. But for the species whose seeds have poor viability, or the species, which do not produce seeds, the plants must be maintained in the vegetative state under field conditions. The maintenance of living material by traditional methods is expensive, laborious and risky. Tissue culture is an alternative method for conserving germplasm in a vegetative state so that a large number of plants can be produced on demand (Arora and Bhojwani, 1989). The shoot tip and nodal culture could be a valuable technique for the production of these secondary metabolites in large-scale (Sen and Sharma, 1999).

In our laboratory, attempts has been made to produce *S. anacardium* plants on large scale by *in vitro* methods such as micropropagation and organogenesis. In the present study apical bud, axillary bud and leaves collected from the 7 months old plants were used as explants. The MS basal medium supplemented with various concentrations of growth regulators either alone [BA (1 – 5 mg/l), kin (1 – 5 mg/l), 2ip (1-5 mg/l)] or in various combinations [BA (2.0 mg/l) + kin (0.5mg/l) + 10 % coconut water (CW) + 10 mg/l citric acid (CA) or 10 mg/l sodium citrate (SC)] were tested for multiple shoot induction. MS medium fortified with BA (2.0 mg/l) + kin (0.5mg/l) + 10mg/l SC induced the formation of stout and broad leaves and stem elongation in both the apical (Fig. VIIIa) and axillary buds (Fig. VIIIb).
Fig. VI. Effect of various treatments on seed germination from *Semecarpus anacardium* under *in vivo* conditions after 90 days.

- a. Control
- b. Hot water treatment
- c. Conc. HNO₃ treatment
- d. GA₃ treatment
- e. Conc. H₂SO₄ (40 % and 50 %) treatment
Fig. VII. Effect of various treatments on seed germination from *Semecarpus anacardium* under *in vitro* conditions after 75 days.

Apical bud explants alone produced 3 multiple shoots, when they were subcultured on to the same medium after 15 days (Fig. VIIIc). Shoot elongation occurred in the same medium when they were subcultured into the same medium after 15 days.

Leaf explants cultured on MS medium supplemented with 2, 4-D, NAA, IAA or IBA (2.0 – 8.0 mg/l) + 10% CW + 10 mg/l SC for callus induction.
Fig. VIII. Micropropagation of *Semecarpus anacardium*.

a. Shoot induction from apical bud explant on MS medium supplemented with BA (2.0 mg/l) + kin (0.5 mg/l) + SC (10.0 mg/l), after 15 days.
b. Shoot induction from axillary bud explant on MS medium supplemented with BAP (2.0 mg/l) + kin (0.5 mg/l) + SC (10.0 mg/l), after 15 days.
c. Shoot proliferation from apical bud explant on MS medium supplemented with BAP (2.0 mg/l) + kin (0.5 mg/l) + SC (10.0 mg/l), after 15 days.
d. Callus induction from leaf explant on MS medium supplemented with 2, 4-D (8.0 mg/l) + SC (10.0 mg/l), after 15 days.
They produced friable brown colour callus only on MS medium supplemented with 2, 4-D (8.0 mg/l) and SC (10 mg/l) (Fig. VIIId). The leaves placed on other media remained as such as greenish colour or turn into brown colour after two weeks. Our results indicated that only few multiple shoots had obtained from apical bud explants and also there was poor callus induction. The research is still going on in our laboratory to improve this protocol to produce large number plantlets through both direct and indirect organogenesis.

**Future strategies**

The wide spread use of *S. anacardium* in various treatments reveals its pharmacological importance. The following aspects should be focused for the effective conservation of these plants.

1. For the effective conservation of these plants, scientific efforts have to be made towards the clonal propagation of *S. anacardium* through *in vitro* techniques (plant tissue culture) to produce more number of diseases free, true – to – type plants.

2. Extensive investigation has to be conducted to explore the therapeutic utilities of phytopharmaceuticals in various diseases.

3. Productivity of phytopharmaceuticals can be increased by plant tissue culture and plant genetic engineering methods.

4. Finally the toxic components responsible for causing toxic dermatitis and renal problems have to be identified and altered by genetic transformation studies in future.

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