Review Article

Pharmacology, Phytochemistry and Toxicology of *Semecarpus anacardium*

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ABSTRACT

Semecarpus anacardium Linn. (SA) or Bhallataka is a plant well-known for its medicinal value in Ayurvedic and Siddha system of medicine. *Bhallataka* is a semi-poisonous plant. However, before using therapeutically Shodhanasanskara of Bhallataka is carried out to avoid its toxic effect on the body. *SA* contains a variety of biologically active compounds such as biflavonoids, phenolic compounds, alkaloids etc. There are reports of antiatherogenic, anti-inflammatory, antioxidant, antimicrobial, anti-tuberculous, anthelmintic, hepatoprotective, anti-spermatogenic, nootropic, analgesic, hypoglycaemic, and anti-carcinogenic activity. Hence this review article is an attempt to highlight chemical constituents, toxicological aspects and various pharmacological activities of *S. anacardium*.

Keywords: *Semecarpus anacardium,* Bhallataka, toxicity, phytochemistry, pharmacology.

INTRODUCTION

The Indian knowledge of herbal medicines is gaining widespread acceptance globally. In Ayurveda, almost all medicinal preparations are derived from plants, whether in the simple form of raw plant materials or in the refined form of crude extracts, mixtures and so on.

In other parts of the world, the term Complementary and Alternative Medicine (CAM) is used for various forms of traditional drugs.

Complementary and Alternative Medicine (CAM) can be defined as any treatment used in conjugation (complementary) or in place of (alternative) standard medical treatment.

In the recent years complementary and alternative medicine (CAM) has upsurge globally for the treatment and prevention of many aliments which are non-communicable and chronic in nature. However, alternative medicine, medicinal plant preparations have found widespread use particularly in the case of diseases not amenable to treatment by modern method[1-4].

Semecarpus anacardium Linn. (Family: Anacardiaceae) is distributed in sub-Himalayan region, tropical and central parts of India. *Semecarpus anacardium* (SA) is a deciduous tree, medium in size. The height of the tree is normally 12-15 m. The leaves are large and simple; they are up to 60 cm long and 30 cm wide. The colour of the bark is deep brown and it is quite rough in texture. The flowers are more of a dull greenish yellow color. The color of the fruit is black when ripe; it is quite smooth and shiny in texture however, it is toxic in nature. The nut is about 1 inch long.

In Ayurvedic, Unani and Siddha system of medicine, it is called as Bhallataka, Bhilaavaa, and Sorankottai respectively.

The parts generally used are detoxified nut and oil[4-6]. The aim of this review is to further highlight recently discovered effects and applications of *S. anacardium*.

Toxicity

Toxicology is the science which deals with poisons with reference to their sources, properties, mode of action, symptoms which they produce, lethal dose, and nature of fatal results, treatment, method of their detection, estimation and autopsy findings.

Forensic toxicology deals with medical and legal aspect of harmful effects of poisonous substances on human body.

A poison is a substance which when administered, inhaled or ingested is capable of having deleterious effects on human body.

Thus almost anything is a poison. There is little difference between a medicine and poison, as a medicine in a toxic dose is a poison and a poison in a small dose may be medicine[7].

Agadatantra is the branch of Ayurveda which is meant for diagnosis and treatment of various poisoning such as bites by snakes, insects, spiders, rats etc. and also other poisonous substances like plants and minerals. In western medicine agadtantra is named as toxicology.[7-8]

Since Bhallataka is extremely hot and sharp in its attributes, it should be used with caution. Individuals showing allergic reactions to it should stop and avoid the usage of Bhallataka. It should not be used in small children, very old persons, pregnant women and individuals of predominant pitta constitution.

The use of the same should be restricted in summer season. For its allergic reactions like rash, itching and swelling, the antidotes used externally are coconut oil, ghee, coriander leaves pulp or butter mixed with musta (*Cyperus rotundus*).

The salt and spices should be strictly restricted during Bhallataka treatment, and it is recommended to avoid exposure to sun, heat and excessive sex. The oily part of the nut is toxic and its degree of removal is proportional to its safety margin. Nephropathy is associated with exposure to toxins of this plant. It was noted that SA toxins lead to acute renal failure due to hemodynamic effects[9].

Patwardhan induced toxicity by oral route administration of SA extract with peanut oil and compared against the same extract emulsified with Tween-80 saline. The traditional way of administration with peanut oil was found to be safe upto 25 mg/kg/day for 9 days, and increase in weight, RBCs & haemoglobin % was observed without mortality. Same dose with Tween-80 saline was found to have adverse effects with 16.5% mortality[10].

Choudhari studied the toxicity study on a few blood parameters in male albino rats at acute and sub-chronic levels with SA nut oil extract (50% w/v) in ground nut oil. Albino rats (wistar strain) were treated orally with three sub-lethal doses. There was a significant decrease in hemoglobin percent and lowering of erythrocytes, indicating anaemia during toxicity study. He also evaluated the acute and sub-chronic effect of crude extract on activity of some marker enzymes like GOT, GPT, SDH, LDH and histology of kidney of albino rat (wistar strain) in either sex. Significant alteration in activity levels of marker enzymes of kidney as well as histological structure leading to nephritis were observed, indicating renal dysfunctioning in albino rat. Results exhibited nephrotoxicity inducing potential of SA nut oil extract[11-12].

Shodhana Sanskara of Bhallataka

The process in which specific substances are treated with process like rubbing, steaming etc. so as to remove its harmful or toxic effects is known as *shodhanasanskara* (purification process). Poisonous plants are subjected to *shodhanasanskara*, before its therapeutic use. This process reduces toxicity of poisonous plant considerably and keeps it at required optimum level. SA is one such toxic plant which is still used in the Indian system of medicine with bhilawanols as the toxic components present in it. Sodhana (detoxification/purification) process involves the purification as well as reduction in the levels of toxic principles which may sometimes result into enhanced therapeutic efficacy[13-15].

If juice of Bhallataka (even in traces) comes in contact with body produce severe *daha* (burning sensation), and *Vrana* (ulcer). When it comes in contact with face, it produces acute burning sensation with *shotha* (inflammation) and *Visarpa* (skin disease). Hence it is necessary to undertake *shodhana sanskara* of *Bhallataka* with precaution before using it in medicine to avoid toxic effects of *Ashuddha* (impure) *Bhallataka*[14-16].

We have done the shodhana of dried nuts of SA as per the method given in Ayurvedic texts. The thalamus part of the fruit was removed with a steel knife. Then, the nuts were subjected to fresh cow urine daily for 7days followed by cow milk (OMFED) daily for 7 days followed by rubbing thoroughly with brick powder for 3 days. During the treatment with cow urine and cow milk, the nuts were washed with water before adding fresh cow urine or milk. On the final day (18th day), the nuts were washed with hot water to remove the brick powder. This shodhana procedure was repeated three times[17-20].

Phytochemistry of *Semecarpus anacardium*

The phyto-components present in S. anacardium Linn. are alkaloids, phenolic compounds, biflavonoids, sterols and glycosides. An alkaloid, Bhilawanol, has been isolated from oil and seeds. Bhilwanol from fruits was shown to be a mixture of cis and trans isomers of ursuhenol. Oil from nuts contains Bhilavanol and the leaves contain amentoflavone as a sole biflavonoid. The phenolic compounds are bhilavanol A (monoenepentadecyl catechol I) and bhilavanol B (dienepentadecyl catechol II). The biflavonoids present in the nuts were biflavones A, C, A1, A2; tetrahydrorobustaflavone, tetrahydroamentoflavone, jeediflavone, jeediflavanone, semecarpuflavanone, galluflavanone, amentoflavanone, nallaflavanone, semicarpetin, anacarduflavanone, o-trimethyl bioflavanone A1, o-trimethyl bioflavanone A2, o-tetramethyl bioflavanone A1, o-hexamethl bichalcone A, o-dimethyl biflavanone B, o-heptamethyl bichalcone B1, o-hexamethyl bichalcone B2, o-tetramethyl biflavanone C etc. Other components isolated from the nuts are anacardic acid, cardol, catechol, alkenyl catechols, fixed oil, semecarpetin, anacardol, anacardoside, semecarpol. Monolefin I, diolefin II, oleic acid, linoleic acid, palmitic acid, stearic acid, and arachidic acid.[21-40]

Pharmacological Activity

Analgesic Activity

The analgesic activity of petroleum ether, chloroform and methanol extracts of SA was investigated by tail flicking and writhing method using acetyl salicylic acid as the standard reference. The methanol extract at 50 mg/kg showed a significant analgesic activity. However, methanol extract was more potent than the petroleum ether and chloroform extracts[41].

Hypoglycemic Effect

Arul studied the effect of ethanolic extract of dried nuts of SA on blood glucose and investigated in both normal hypoglycemic effect and streptozotocin-induced diabetic antihyperglycemic effect rats. The ethanolic extract of SA 100 mg/kg reduced the blood glucose of normal rats but showed no antihyperglycemic activity[42].

Krishnamurthy developed Kalpaamruthaa (KA), a modified Siddha preparation, which contains SA, *Emblica officinalis* (EO) and honey, and studied for the variations in lipids, lipid-metabolizing enzymes and lipoproteins in cancerous animals and the effect of KA on the lipid metabolism. The increased levels of total cholesterol, free cholesterol, phospholipids, triglycerides and free fatty acids and decreased levels of ester cholesterol in plasma, liver and kidney found in cancer-suffering animals were normal on treatment with KA and SA[43].

Hepatoprotective Effect

Abirami carried out a study to understand the antioxidant and protective effect of SA against lead acetate induced toxicity by analyzing the phytochemicals flavanoids, alkaloids, resins, tannins, carbohydrates, proteins present in the plant which is probably responsible for the hepatoprotective efficacy[44].

Anthelmintic Activity

Pal have studied anthelmintic activity of different extracts of nuts of SA on adult Indian earthworm (*Pheritima posthuma*). It was found that petroleum ether, chloroform extract of SA (PESA and CESA, respectively) showed better anthelmintic activities than ethanol (EESA) and aqueous (AESA) extract of it[45].

Anti-Cancer Activity

Mathivadhani studied SA nut extract for inhibitory effect on human breast cancer cell line (T47D). At the molecular level, it showed decrease in Bcl and increase in Bax, cytochrome c, caspases and PARP cleavage, and ultimately by internucleosomal DNA fragmentation[46].

Sugapriya showed restoration of energy metabolism in leukemic in leukemic mice treated by SA nut milk extract. SA treatment was compared with standard drug imatinib mesylate. SA administration to leukemic animals resulted in clearance of the leukemic cells from the bone marrow and internal organs[47].

Arulkumaran investigated the protective efficacy of preparation named as Kalpaamruthaa (KA) (includes SA nut milk extract, dried powder of *Phyllanthus emblica* fruit and honey) on the per-oxidative damage and abnormal antioxidant levels. Dimethylbenzanthracene (DMBA) treated rats also showed decline in the activities of mitochondrial enzymes, while rats treated with SA and KA showed normal lipid peroxidation antioxidant defences in mitochondrial enzymes, and indicate the anticarcinogenic activity of KA during DMBA-initiated mammary carcinogenesis[48].

Prabhu studied the anti-mutagenic effect of SA under *in vivo* condition. Mice were intraperitoneally treated with 500 and 250 mg/kg of SA, which showed a significant inhibition of induced aberrations at the 12 h pre-treatment period. The results on the reduction of induced chromosome aberrations clearly show that SA serves as an antioxidant because of the presence of flavonoid and its administration may be protective and therapeutic[49].

Krishnarajua found that aqueous extracts of medicinal plants were screened for their cytotoxicity using brine shrimp lethality test. Out of the 120 plants tested, SA (Anacardiaceae) showed significant cytotoxicity with LC_{50} of 29.5 µg[50].

Joseph studied the anticancer effect of Ayurvedic preparation made from SA nuts. They have found that after 154 days of experiment both liver enzymes and hepatocellular carcinoma (HCC) marker were increased in HCC along with neoplastic changes in liver and were decreased in SA milk extract treated group. The Ayurvedic drug showed positive correlation with the action of doxorubicin. This study demonstrated the efficacy of SA milk extract for the treatment of HCC[51].

Neuroprotective Activity

Farooq evaluated the beneficial effects of nuts of SA, extracted with milk, on central nervous system (CNS), mainly for its locomotor and nootropic activities[52]. Vinutha studied that loss of cholinergic cells, particularly in the basal forebrain is accompanied by the loss of neurotransmitter acetyl choline (ACh). The SA is effective in prolonging the half-life of acetylcholine through inhibition of ACh esterase. SA *is* useful in treating cognitive decline, improving memory[53].

Anti-Inflammatory Activity

Sushma attempted to explore the anti-inflammatory activity of ethanolic extract of fruits of SA plant in albino rats by carrageenan induced rat hind paw edema model. Ethanolic extract of SA fruit exhibited a dose dependent anti-inflammatory activity[54].

Ramprasath investigated that SA significantly decreased the carrageenan-induced paw edema and cotton pellet granuloma[55].

Satayavati and Bajpai reported the anti-inflammatory activity of SA for both immunological and non-immunological origin[56].

Premlatha have been reported SA for immune-modulatory potency, anti-oxidative, membrane stabilizing, tumor marker regulative, glucose level restoring and mineral regulation properties of nut extract in hepatocellular carcinoma and found potent against hepatocarcinogen aflatoxin B1[57]. Salvem investigated that ethyl acetate extract of SA led to the isolation of major active principle, tetrahydroamentoflavone (THA), a biflavonoid.

The *in vitro* cyclooxygenase (COX-1)-catalyzed prostaglandin biosynthesis assay of THA gave an IC_{50} value of 29.5 µM (COX-1) and 40.5% inhibition at 100 g/mL (COX-2). The *in vivo* carrageenan-induced paw edema assay resulted in dose-dependent anti-inflammatory effect and the activity was comparable to the ibuprofen[58].

Bhitre prepared the methanolic, ethanolic, chloroform, ethyl acetate and petroleum ether extracts of fruits of SA and studied the anti-inflammatory activity using the technique of carrageenan-induced paw oedema in albino rats. The extract showed significant anti-inflammatory activity comparable to aspirin[59].

Singh evaluated that *SA* extract can inhibit proinflammatory cytokine production. Crude ethanolic extract of *SA* nuts was studied for its anti-inflammatory activities *in vitro* using peripheral blood and synovial fluid mononuclear cells of healthy individuals and rheumatoid arthritis (RA) patients. SA extract inhibited the spontaneous and LPS-induced production of pro-inflammatory cytokines IL-1beta and IL-12p40 but had no effect on TNF-alpha and IL-6 production, both at protein and mRNA level. The crude extract also suppressed LPS-induced nuclear translocation of transcription factors[60].

Kalpaamruthaa (KA), an indigenous-modified Siddha formulation, consists of SA nut milk extract and fresh dried powder of *Emblica officinalis* (EO) fruit along with honey. Kalpaamruthaa was found to be nontoxic up to the dose level of 2000 mg/kg. Further, KA has been reported for its potent antioxidant analgesic, antipyretic and non-ulcerogenic properties.

Mythilypriya studied the antiinflammatory activity of SA in adjuvant-induced arthritic rat (AIA) model with reference to mediators of inflammation (lysosomal enzymes) and its effect on proteoglycans. The activities of various enzymes and levels of plasma protein bound carbohydrate components of glycoproteins were determined and were found to be elevated in arthritic rats when compared to control animals[61].

Antioxidant Activity

Shanmugam observed that rats treated with Kalpaamruthaa showed normal lipid peroxide level and antioxidant defences[62]. Veena measured antioxidant status in blood, and vital organs (liver, kidney and breast tissue) of control and experimental animals. In cancer condition, lipid peroxidation (LPO) was increased and antioxidant levels were decreased. On drug (SA and KA) administration, decreased LPO and increased antioxidant[63].

Sahoo investigated the antioxidant activity of ethyl acetate extract of stem bark of SA. Ethyl acetate extract showed the stronger antioxidant activity (due to presence of highest total phenolic content of 68.67% measured as pyrocatechol equivalent) compared to the other (hexane, chloroform and methanol) extracts. The isolation of the ethyl acetate extract of SA stem bark yielded a bright-yellow solid crystal, which was identified as butein. This compound exhibited antioxidant activity (IC50 values of 43.28 ± 4.34 µg/ml)[64].

Antimicrobial Activity

Sharma also found that due to presence of flavonoid, alcoholic extract of dry nuts of *SA* show antifungal activity (*Aspergillus fumigatus* and *Candida albicans*) at 400 mg/ml concentration. Both the fungi showed inhibition in growth, reduction in size of cells and sporulation also decreased[65].

Sharma investigated that its nut oil show significant anti-microbial activity against several Gram positive (Bacillus subtilis, Staphylococcus aureus) and Gram negative (Proteus volgaris, Escheria coli) Bacteria[66].

Mohanta prepared the aqueous and organic solvent extracts of the plant and screened for antimicrobial (disc diffusion method) and phytochemical properties. The petroleum ether (PEE) and aqueous extract fractions (AQE) showed inhibitory activity against *Staphylococcus aureus* (10 mm) and *Shigella flexneri* (16 mm) at 100 mg/ml, respectively while chloroform extract showed inhibition against *Bacillus licheniformis, Vibrio cholerae* and *Pseudomonas aeruginosa*. The ethanol extract showed inhibition to *Pseudomonas aeruginosa* and *S. aureu6*[67].

Nair found that the alcoholic extract of dry nuts of SA (Bhallatak) showed bactericidal activity *in vitro* against three gram negative strains (*Escherichia coli, Salmonella typhi* and *Proteus vulgaris*) and two gram positive strains (*Staphylococcus aureus* and *Corynebacterium diphtheriae*). Studies showed that the alcoholic extracts of different parts of the plant (leaves, twigs and green fruit) also possess anti-bacterial properties. No dermatoxic effect (irritant property) was observed in the mouse skin irritant assay[68].

Anti-Spermatogenic Effect

SA extract feeding caused Anti-spermatogenic effect evidenced by reduction in numbers of spermatogenesis cells and spermatozoa in male albino rats. Sharma studied reduction in sperm density in cauda epididymides may be due to changes in the androgen metabolism. Meiotic and postmeiotic germ cells were highly sensitive to androgen concentration and the alteration in androgen level in testes may affect the transformation of spermatocytes to spermatids[69].

Narayan reported that the water extract of the aerial part of SA exhibited a spermicidal activity. The administration of ethanolic extract of SA fruit leads to spermatogenic 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. These results clearly show the anti spermatogenic activity of SA[70]. SA extract feeding caused anti-spermatogenic effect evidenced by reduction in numbers of spermatogenic cells and spermatozoa in male albino rats[71].

Antiatherogenic Effect

Mary observed that the imbalance between the pro-oxidants and antioxidants is the main cause of development of atherosclerosis.

To prevent such condition, antioxidant therapy is beneficial. SA shows antioxidant property. It has capacity to scavenge the super oxide and hydroxyl radicals at low concentrations. The process of atherogenesis is initiated by peroxidation of lipids in low-density lipoproteins was found in SA[72].

Hypolipidemic and Hypocholesterolemic Activity

Tripathi have observed that SA nut extract oil fraction at a dose of 1 mg/100g body weight significantly reduced serum cholesterol levels and increased HDL cholesterol levels in the rat fed with atherogenic diet[73].

Memory Enhancing Effect

SA improves memory by increasing cholinergic function[53]. We have demonstrated the effect of shodhana on nootropic effect of SA. Methanolic extract of the nuts of S. anacardium possesses nootropic activity which may be attributed to inhibition of cholinesterase activity. Shodhana of the nuts decreases nootropic activity[17].

Cardioprotective Effect

Asdaq evaluated the cardioprotective effect of hyroalcoholic extract of *S. anacardium* nuts (SANE) against isoproterenol (ISO) induced myocardial damage in rats.

The CK-MB activities were fallen in serum and elevated in heart tissue of animals treated with low and high doses of SANE as compared to ISO control. The LDH activity were significantly reduced in serum with both low and high doses of SANE while no change was noted in heart tissue with both doses compared to ISO control.

Hence it is concluded that SA possesses potential to ameliorate the myocardial damage induced by isoproterenol in rats[74].

Aphrodisiac Activity

Gupta evaluated the effect of chloroform extract of SA (150mg/kg & 300 mg/kg' p.o.) in male mice.

Mounting behaviour & mating performance were determined and compared with the standard drug Penegra (Sildenafile citrate).

The extract of the SA were found to stimulate the mounting behaviour of male mice and also significantly increase their mating performance.

The extracts of SA enhanced the sexual behaviour of male mice[75].

Anti-Tuberculosis Activity

A study was carried out by Singh to isolate, identify and evaluate bioactive compounds of SA nuts extracted using GC-MS.

Solvent extraction of SA nuts was done with petroleum ether, ethyl acetate, methanol and finally with water.

All the extracts were tested for their bioactivity against potential pathogen *Mycobacterium tuberculosis*.

Water extract showed potential with MIC 6.25 µg/ml against M. tuberculosis during *in vitro* bioassay. Nuts extract showed anti-tuberculosis activity during *in vitro* bioassay investigations[76].

CONCLUSION

Semcarpus anacardium is a one of the medicinally important plants which may be used as an alternative medicine.

Traditional healers and physicians use SA in their clinical practice. Several studies show that SA nut's extract have various phytochemicals which are able to fight against several disease but due to its poisonous nature it should be used with caution. But there are limited studies on the effect of shodhana on various activities of SA.

The present review would thus be beneficial for the researcher working on shodhana of SA.

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