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Review Article

SEMECARPUS ANACARDIUM - A WONDERFUL PLANT WITH VARIED MEDICINAL PROPERTIES

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Abstract:

Purpose: Traditional herbal plants have been used ever since human civilization started for treating various notable disorders. Semecarpus anacardium (SA) commonly called as Bhilwa is an ancient plant known as half physician for its ability to cure almost half of the known disorders and is available in form of various formulations in Ayurveda and siddha system of medicine. In the current review, complete pharmacological utility of the plant along with its geographical location, chemical constituents, its role in apoptosis and various other uses will be discussed.

Approach: Information from the published research article available from Pubmed, google scholar and other sources were used in the preparation of this review article.

Finding: SA has been reported to be a potential plant for the cure of diseases such as diabetes, myocardial infraction, asthma, rheumatoid arthritis, piles, cancer of liver, oesophagus, breast, mouth etc. It is a rich source of antioxidant having high free radical scavenging effect and is useful in treating heart diseases, CNS disorders and in cancer such as hepatocellular carcinoma, mammary carcinoma etc.

Conclusion: SA can be used as an alternative therapy for various ailments however the precise mechanism underlying its various effects has not been determined fully. The phyto constituents present in this plant need to be isolated and can be developed into phyto-pharmaceuticals.

Keyword: *Semecarpus anacardium, anticancer, Apoptosis, Indigenous system of medicine.*

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Introduction:

Herbs have been consumed since time immortal by humans as a part of their diet to prevent and treat various ailments. Plants are highly enriched with various bioactive components which are highly beneficial for maintaining good health. With an increase in globalisation, harmful chemical exposure, unhealthy lifestyle, environmental pollutants, etc. bio burden of diseases are increasing day by day. In such scenario, herbal medicine has formed itself as an integral part of healthcare system throughout the world. Although, modern medicines are available, traditional practice is still popular due to its cultural value. Several scriptures and text books are available till today which has mentioned the list of herbal plants with their medicinal values. Drugs such as taxol, quinine, vincristine, epinephrine etc. has all been obtained from medicinal plants therefore further studies on such traditionally important plants are required in order to develop potent and more effective treatment for lethal diseases. Semecarpus anacardium (SA) commonly known as bhallataka, is one of the ancient traditional herb whose importance has been mentioned in Valmiki

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Ramayana, one of the most sacred book of north India written somewhere before 3000 BC [1]. It is a potent medicinal plant names as Ardha-Vaidya in Ayurveda meaning half physician as it can cure almost all ailments and the fruit is considered as a golden acorn during the period of Galen and Avicenna in western society. However, it is lethal and toxic if consumed without detoxification. It has been used in both Ayurveda as well as Siddha system of medicine for treatment of various diseases such as cancer, asthma, arthritis, myocardial infraction, diabetes, piles, worm infestation, urticaria, etc. In this review, an attempt has been done to incorporate the details of this medicinal plant along with its pharmacological utilization highlighting its role in the treatment of various kind of cancer.

Language	Common name	Language	Common name
Ayurveda	Agnimukh, Bhallatak	**Hindi**	Bhilawa, Bhilawan
Siddha	Serangkottai	**Urdu**	Baladur, Bhilavan
Sanskrit	Agnimukh, Bhallatak	**Gujrati**	Bhilamo
Latin	Semecarpus anacardium linus	**Punjabi**	Bhilawa,
English	Marking nut, Oriental cashew nut, Marany nut, Varnish tree	**Oriya**	Bhollataki, Bholai
Arabic	Anaqardhiyae, Balaadhur	**Kannada**	Karee geru
French	Anarcardischer, Noix a marquer	**Malyalum**	Alakkucheru, Thenkotta
Persian	HabbulQalb, Biladur	**Tamil**	Senkottai, Tatamkottai
Nepali	Bhalaayo	**Marathi**	Bibba

Etymology:

Semecarpus anacardium, commonly known as oriental cashew nut belongs to family-anacardiaceae. The word Semecarpus is derived from a Greek word “simeion” which means marking and “carpus” meaning nut while anacardium means like cardium i.e, heart. As it produces water insoluble permanent mark on clothes, washer men on olden days used the nuts to mark clothes which gave the name "marking nut" to the plant by the Europeans.

Synonyms:

Taxonomic classification:

Kingdom:	**Plantae**
Subkingdom:	Tracheobionta
Superdivision:	Spermatophyta
Division:	Magnoliophyta
Class:	Magnoliopsida
Order:	Sapindales
Family:	Anacardiaceae
Genus:	Semecarpus
Order:	anacardium

Plant Description:

Picture of *Semecarpus anacardium*

Geographical Availability[2, 3]:

SA is found in various parts of the world right from the outer Himalayas to the Coromandel Coast Africa, East Asia to Indian subcontinent, Indo –Malaysian region, western peninsula, North Africa & in countries such as China, Nepal, India, N. Australia. With respect to India, it is available in hotter region up to the altitude of 3500ft and in places such as Bihar, West Bengal, Orissa, Karnataka, Konkan, Kanara forest of Tamil Nadu, Madhya Pradesh, Maharashtra etc. It grows naturally in the tropical region having dry climate.

Plant Morphology:

It is a medium sized average growing deciduous tree of around 10-15 m height. Leaves are 30-60 cm long, 12-30 cm wide, large and simple, alternative and obviate-oblong, glabrous above and less pubescent below. The leaf base is rounded, heart shaped, narrowed into the stalk. Flowers are greenish white, in panicles and appear with new leaves in May and June, easily recognized by large leaves and the red blaze exuding resin, which blackens on exposure. The fruit ripens from December to March, shining black in colour and is 2–3 cm broad. It is a moderate shade bearer, obliquely ovoid or oblong drupe, 2.5 to 3.8 cm long, compressed, held on an orange-coloured receptacle form of the disk, the base of the calyx and the extremity of the peduncle[4]. However, it is toxic in nature. The nut is about 1 inch long, ovoid and smooth lustrous black. It is frequently found in drier rather than damp localities. No specific soil affinity. The bark is dark grey in colour, quiet rough in texture and exudes an irritant secretion on incising. Seed appears brown in colour and its kernel is eatable after removing the pericarp but sometimes may cause cutaneous eruption and seed oil has high medicinal value. Seeds are generally collected during December- march. Each kilogram of fruit consists of 460-480 seeds.

Phytochemical constituents:

Preliminary phytochemical analysis of fruit reveals the presence of tannins, steroids, phenolic compounds, flavonoids, oils and fat[5]. It also contains vitamins such as: nicotinic acid, thiamine and riboflavin, amino acids like histidine, isoleucine, leucine, lysine, methionene, phenylalanine, arginine, threonine, tryptophan and valine.

Nut shell extract of the plant has been reported to contain various phytoconstituents such as anacardic acid; biflavonoids like: biflavone-A, C, A1, A2, tetrahydrorobustaflavone, jeediflavanone, semecarpuflavanone, galluflavanone and anacardoflavanone; Phenolic compounds such as: bhilawanols, semecarpol & anacardol. Bhilwanol is a mixture of 3-pentadec (en) yl catechols and its main components are: 8Z, 11Z-diene and 8Z-monoene. More than seven components has been isolated from the methylated bhilawanol and two of them has been identified as dimethyl ethers of 1-pentadeca- 8enyl-2, 3- dihydroxybenzene and 1-pentadeca- 7, 10 dienyl-1, 3-dihydroxybenzene[6]. Bhilwanol from fruits is a mixture of cis and trans isomers of ursuhenol; consisting of 1,2-dihydroxy-3(pentadecadienyl 8',11')benzene and 1,2-hydroxy-3(pentadecadienyl 8')benzene.

Nut consists of tetrahydroamentoflavone, 3'8-billiquiritigenin and nallaflavanone. An active anticancer catechol compound 3-[8_(Z),11_(Z)-pentadecadienyl]catechol (SA-3C) has been isolated from the kernels of the nut which is an amphiphilic non-isoprenoid phenolic lipid being derivatives of mono and dihydroxy phenols like catechol, resorcinol and hydroquinone[7].

Leaves contain amentoflavone as the exclusive compound[8] along with several minerals shown in the table 1 below.

The juice of the fruit has been reported to contain anacardol, catechol and fixed oil. The corrosive nature of the juice is attributed to its phenolic acids $C_{16}H_{15}O_3$.COOH and $C_{14}H_{13}O_3$.COOH[9].

From the seeds, a new phenolic glucoside: anacardoside has been identified as-l-O-ß-D-glucopyranosyl- (1 6) - ß-D-glucopyranosyloxy-3-hydroxy-5-methylbenzene[10].

Pericarp oil contains flavonoids, phenols like catachol and anacardic acid[11]. The mineral present in the methanolic extract of its leaves are depicted in the table 1[12].

Table1: Minerals present in methanolic extract of leaves of SA.

S.No.	Minerals	Conc. in ppm (approx.)
1.	Potassium(K)	588
2.	Sodium (Na)	47
3.	Magnesium (Mg)	45
4.	Silicon (Si)	27
5.	Sulphur (S)	17
6.	Phosphorus (P)	10
7.	Calcium (Ca)	9
8.	Boron (B)	6
9.	Copper (Cu)	0.9
10.	Zinc (Zn)	0.6
11.	Manganese (Mn)	0.6
12.	Nickel (Ni)	0.4

Various physicochemical and phyto-constituents content of the seed oil of plant has been mentioned in the below table 2[5,13].

Table 2: Physicochemical properties & phyo-constituents present in seed oil of SA:

Parameters	Amount	Physicochemical Properties	Amount
Total phenols (mg/g)	157.7	Saponification value (mg KOH/g)	195.74
Saponins(mg/g)	133	Acid value (mg KOH/g)	420.25
Flavonoids(mg/g)	83.8	Iodine value (mgI2/g)	647.16
Tannins(mg/g)	17.5	Peroxide value (meqO2/kg)	11.42
Loss on drying 110 ℃ (%W/W)	6.68	PH	3.1
Ash value (%W/W)	2.68	Viscosity (cP)	290
Methanol soluble extractive (%W/W)	35.40	Relative density (g/ ml)	0.8476
Water soluble extractive (%W/W)	6.99		

Plant utility as per indigenous system of medicine:

- As per Ayurveda system of medicine:
  Nut of SA has properties such as; Rasa (taste): Katu (Pungent), Tikta (Bitter) & Kashava (Astringent), Guna (qualities): Laghu meaning light to digest, Teekshna (piercing), Snigda (unctous) and ushna meaning hot. Sweet ripe fruit of Bhallataka promotes digestion, cures vata-kapha dosha, heals-wound, skin anomalies, piles, inflammation, bloating, ascite infestation, improves malabsorption etc. Seed balances vata and pitta dosha & have high nutritional value. Fruit cap pacifies pitta dosha, stimulate

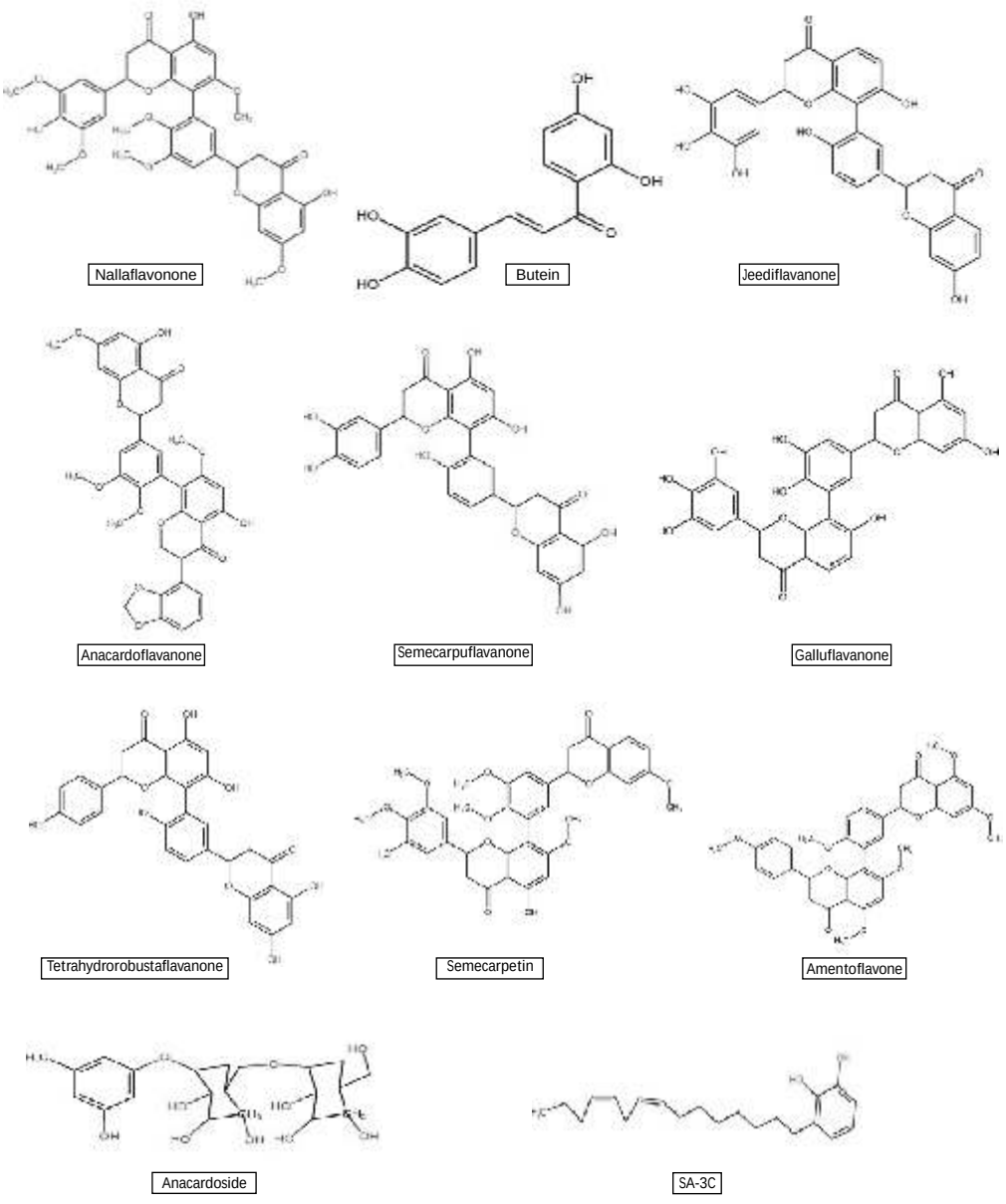

Fig: Phytoconstituents present in SA.

digestive system & is very useful for hair growth.

Fruits and oil are effective in treatment of neuritis, rheumatic pain & gout[14]. Fruits after detoxification have been used for improvement of eye sight, prolongation of life and in certain skin conditions. It has been reported to be used in treatment of asthma, piles, leprosy, arthritis, STDs such as syphilis & gonorrhoea, skin ailments like leucoderma[15]. Nut has been used in Ayurveda for management of diabetes, wound healing, urinary tract infections and anaemia. It is a nerve tonic and an aphrodisiac, also useful in treatment of tumors of oesophagus, skin, liver, etc.

There are many Ayurvedic preperations marketed in India such as- sanjivani vathi – poisoning & fever; Bhallataka Rasavana- anti aging, skin diseases; Amrita Bhallataka Ghrita- skin disorders & haemorrhoids.

- As per siddha system of medicine:
  Serankottai nei is a medicated ghee preparation consisting of nut extract of SA. It is a popular siddha drug and is used in treatment of cancer, neurological pain, lung infection such as tuberculosis and in auto immune disorders like osteoarthritis & rheumatoid arthritis[16].

  Another modified siddha formulation is also available named Kalpaamruthaa & it contains SA nut milk extract along with dried powder of Emblica officinalis fruit and honey. This formulation has been evaluated for numerous ailments such as analgesic, antipyretic, ulcerogenic[17], anti-carcinogenic, anti-arthritic etc.

Antioxidant & medicinal properties of the plant:

1. Antioxidant:
   Antioxidants offer protection against free radical mediated diseases such as cancer & cerebro-cardiovascular disorders due to its ability to scavenge free radicals. SA is a good antioxidant & has strong reactive oxygen species (ROS) scavenging activity. Its efficacy as an antioxidant has been established by several tests using almost all parts including nut, fruit, seed, bark etc. Bark extract of SA was subjected to total antioxidant; 1,1-Diphenyl-2-picrylhydrazyl (DPPH); superoxide scavenging activity and hydrogen peroxide scavenging assay. Methanol extract was able to scavenge DPPH similar to standard antioxidant Quercetin (78.35%) and had high ferric reducing antioxidant power (FRAP)[18].

   Sahoo et al., in their investigation isolated bright yellow crystal identified as butein from ethyal acetate extract of the bark and the compound exhibited antioxidant activity (IC50 values of 43.28 ± 4.34 µg/ml) which was comparable to the standard rutin[19].

2. Anti-inflammatory[20]:
   Nut extract preparation of the plant has been reported to possess anti-inflammatory activity against carrageen induced, cotton pellet induced granuloma and adjuvant induced arthritis at the dose of 150 mg/kg body weight on wistar rats. Flavonoids present in the preparation could attribute to its anti-inflammatory activity as it was able to reduce the oedema formation which could be due to the inhibition of release of inflammatory mediators such as histamine and serotonin and inhibition of the enzyme cyclooxygenase. The effect produced on the acute and chronic phase of inflammation by nut preparation was comparable to 30 mg/kg body weight of indomethacin and such preclinical studies of the plant proves its effectiveness for inflammation.

3. Antiarthritic:
   Vijayalakshmi et al., conducted a study using nut milk extract of Semecarpus anacardium against adjuvant-induced arthritis in the rats at the dose of 150 mg/kg body weight for 14 days. Extract was able to decrease the increased level of lipid peroxides in plasma and tissues due to its ability to modulate the cellular antioxidant defence system. This study indicates that the treatment with milk extract can bring back increased level of antioxidants (SOD,CAT, GPX, GSH), biochemical markers of inflammation C-reactive protein (CRP) level, Erythrocyte sedimentation rate (ESR) and gluconeogenic enzymes to near normal levels in arthritis induced rats[21]. It also has an ability to modulate neutrophil accumulation & lysozomal membrane stabilizing action[22,23]. Such studies prove SA nut milk extract as a potential therapeutic agent in arthritis.

4. Antimicrobial:
   Bhallataka (SA) is a plant having good antibacterial properties & is active against Salmonella typhi. Its antibacterial activity is contributed by the secondary metabolites such as triterpenoids, steroids, phenol and anthraquinones. Possible mechanism of action is disruption of cytoplasmic membrane, change in phospholipid constituents leading to degradation of cell wall and disruption of cytoplasmic membrane ultimately causing defect in electron transport and nutrient uptake[24]. Methanolic leaf extract of SA when evaluated against bacteria like Staphylococcus epidermidis, Micrococcus luteus, Staphylococcus aureus , Propionibacterium acnes and yeast Malaassezia furfur by pednekar et al., using the MIC and MBC/MFC analysis, the

lowest MIC and MBC values for Staphylococcus epidermidis was found to be 100 mg/mL[25]. Similarly, dry nut extract of the plant holds good dose dependent fungicidal activity in-vitro against candida albicans & Aspergillus fumigatus. The growth of both the fungus was inhibited and the size of cells, hyphae & sporulation were reduced to greater extend at the concentration of 400 mg/ml[26].

5. Effect on CNS:

Nut of SA has been evaluated by Farooq et al., in their study to evaluate beneficial effect of it on locomotor and nootropic activities in several experimental animal models. Siddha preparation of the drug was found to possess nootropic activity & the effect was evaluated by interocepitve and exteroceptive models of amnesia & locomotor activity using photoactometer[27]. It has also been reported to possess immunomodulatory effect on rats bearing hepatocellular carcinoma[28]. It has been reported to show neuroprotective effect in stress induced neurodegenerating disorders like Alzheimer's disease. Treatment with 40 mg/kg/bodyweight of the nut extract was able to reduce the degenerating hippocampal neuronal cell bodies by 80%[29].

The nut extract has been reported by Bose et al., to have direct depressant effects on the isolated frog heart and rabbit intestine[30].

6. Effect on CVS:

Kalpaamruthaa, herbal preparation of SA was tested for its efficacy for cardiovascular damage on streptozotocin - induced diabetic rats. It was able to alter the lipid metabolizing enzymes (total lipase, cholesterol ester hydrolase, cholesterol ester synthetase) towards normal and was able to ascertain its efficacy through the modulation of metabolizing enzymes and mitochondrial dysfunction[31].

Cardioprotective:

Hydro-alcoholic extract of SA (SANE) at dose of 100 & 500 mg/kg when given orally to rats was able to ameliorate the myocardial damage caused by isoproterenol. SOD & CAT level were elevated while LDH level was reduced in serum by both the doses. Asdaq & Chakraborty reported in their study that the plant possess cardio protective activity of SANE against isoproterenol induced myocardial necrosis[32].

Antiatherogenic:

SA is able to scavenge the free radicals which are the key players in the process of atherogenesis. At the dose of 1 mg/100g, it reduced serum cholesterol from 378.87 mg/dl to 197.99 mg/dl & increased serum HDL-cholesterol, inhibited LPS induced NO production in the dose dependent manner with IC_{50} value at 50 ng/ml.[33]

7. Antihyperglycemic[34]:

Anti-diabetic activity of SA was studied in high fat diet streptozotocin induced diabetic rat. SA could lower the level of blood glucose & glycosylated haemoglobin and improvement in glucose tolerance test was noted. It was also able to lower lipid profile level effectively at the dose of 200 mg/kg/body weight suggesting its potential anti-hyperglycemic effect.

8. Spermicidal[35,36]:

Aqueous extract of the aerial part of the plant has been reported to exhibit spermicidal effect. A marked reduction in sperm motility, spermatocytes, spermatids & spermatogonic arrest has been reported in albino rats. Such effect produced by the extract could be due to the selective effect on the release of gonadotropin & blockage of uterine metabolic function. However, chloroform extract of the plant was found to stimulate the mating performance & mounting behaviour of male mice indicating enhanced sexual behaviour. Therefore, SA could serve as a potential agent as an aphrodisiac and as a contraceptive agent.

9. Antineoplastic:

Both Ayurveda preparation as well as the extracts of various parts of SA has been reported to exhibit anti-tumour property. It being a rich source of phytoconstituents such as flavonoids, bioflavonoids (biflavones A, C, A1, A2), diterpenes, tannins & high amount of antioxidants; shows good cytotoxic, cytostatic & anticancer property. MTT assay when carried out on ethanolic extract of the same on HeLa and SiHa cell lines, IC_{50} value was reported to be 44.0µg/ml and 57.0µg/ml, respectively [37]. The chloroform soluble fraction of nut has been

reported to have beneficial effect on treatment of leukemia & oesophageal cancer.

Hepatocellular carcinoma:

Hepatocellular carcinoma is a primary liver cancer arising from the hepatocytes which constitute about 80% of liver tissue.

Mechanism of induction of hepatocellular carcinoma:

Induction of cancer is a slow multistep process with various processes like initiation, promotion and progression. Its induction and progression are due to:

- Injury to the healthy hepatocytes by agents such as dietary aflatoxins, infection with hepatitis B (HBV) or hepatitis (HCV) virus, excessive alcohol intake, smoking, anabolic steroids, cirrhosis of liver, mutation of P53 gene and repeated liver cell necrosis contributes to chronic inflammation of hepatocytes
- Increase in inflammatory cells results in excessive release of chemokines and cytokines resulting cellular transformation.
- Alteration in cell physiology due to mutation activates oncogenes, inactivates tumour suppressor genes (codon 249 p53 mutation), cell avoids apoptosis leading to uncontrolled cell replication , neoangiogenesis results and finally the tumour cell metastasize to other body parts resulting in hepatocellular carcinoma end stage.

Nut extract preparation of SA when given orally at dose of 200 mg/kg body weight of wistar rat for 14 days along with sunflower oil reversed the elevated enzymes level in aflatoxin induced HCC rats[38]. The plasma concentration of liver enzymes such as alkaline phosphatase and gamma glutamyltranspeptidase were elevated while lactate dehydrogenase and amino transferase level decreased in tumour bearing rats. Such altered enzymes level were reversed back to normal value by nut extract preparation and this might be due to its ability to induce hepatic biotransformation of enzymes. Oral administration of same preparation showed an effective induction of phase I and II biotransformation in another study. Decrease in phase I enzymes such as - cytochrome P450, cytochrome b5, NADPH cyt P450 reductase enzyme, NADH cytochrome b5 reductase, aniline hydroxylase & phase II enzymes- glutathione s- transferase, UDP- glucuronyltransferase was reported in tumour bearing wistar rats and these enzyme levels were reverted back to near normal level which attributes to SA nut extract anticancer potential[39]. It also has a membrane stabilizing effect in fragile lysosomal membrane from aflatoxin mediated HCC at the dose of 200 mg/kg/day when given for 14 days along with an increase in glycoprotein content[40].

Role of SA on regulation of mineral status in aflatoxin induced HCC:

Anti-carcinogenic potency of SA nut milk extract against AFB induced HCC was biochemically assayed by B. Premalatha et al., where they reported positive modulation of tumour marker enzymes, anti-proliferative property & glucose level restoration capability of the extract against hypoglycemic status during HCC. An alteration in ATPase activity is observed which results in abnormal mineral content. Increase in calcium, magnesium and potassium level & decrease in sodium is noted in HCC rats however flavonoids (bhilwanol) present in the plant influences the permeability of bio membrane, interacts with Na^+/K^+ pump & has ability to catalyse electron transport chain and therefore recovers the mineral status of tumour bearing rats adding more evidence to anticancerogenic potential of nut against HCC[41].

Mammary carcinoma

SA nuts are also effective against the treatment of mammary carcinoma which is the most common form of cancer diagnosed among women accounting for around 26% of all cancers in women. Around 182,000 cases of breast cancer are diagnosed each year in United States alone[42]. In an in-vitro study on T47D breast cancer cell line, apoptotic effect of the extract was reported[43]. Cytoprotective effect of the same was established on MCF-7 breast cancer cell line by trypan blue exclusion method[44]. Significant elevation in the various glycolytic enzymes like aldolase, phospho-glucoisomerase and hexokinase while fall in glyconeogenic enzymes such as glucose-6-

phosphatase and fructose 1,6-diphosphatase are observed in mammary carcinoma bearing rats. Such changes have been restored after the administration of SA along with a significant rise in mitochondrial enzymes suggesting its role in mitochondrial energy production[45].

Similarly, in another study, protective effect of the drug on oxidative stress mediated erythrocyte damage was assessed whereby fluorescence spectra of bold sample was analysed for lipid peroxide level & antioxidant enzymes status in DMBA induced mammary carcinoma bearing rats. Endogenous fluorescence had been labelled to the erythrocyte to test its utility in diagnosis & treatment of malignancies. SA nut extract has been effective in reducing the oxidative stress on erythrocytes restoring the antioxidant level & the study suggests that erythrocytes might be the carriers of fluorophors which accumulates in malignant tissue which can also acts as new biomarkers for the diagnosis and treatment[46].

Role of SA in apoptosis:

Apoptosis is an essential physiological programmed cell death that controls the normal cell number necessary in the development of body organs in both healthy and diseased condition. It is characterised by series of morphological changes whereby cell undergoes shrinkage, chromatin condensation, bleb formation, DNA fragmentation followed by engulfment of the cell body by the macrophages. In order to maintain normal cell content several molecular events are necessary for activation, promotion and execution of apoptotic process. Deactivation of several apoptotic pathways due to either altered gene expression or mutation of gene encoding vital apoptotic proteins causes insufficient cell death which ultimately results in tumorogenesis. Natural polyphenols are the best cancer preventive agent since they exhibit minimum toxicity and possess free radical scavenging property contributing to anticancer activity. SA has been reported by Ramprasath et al., [47] as effective agent against tumour progression in hepatocellular carcinoma & breast cancer in animal model. A study on chronic myeloid leukemia (CML), a malignant clonal disorder of the hemopoietic stem cell carried out by Sugapriya et al., revealed its antileukemic activity. SA has been an effective agent for reversal of deranged energy metabolism in 2B1-induced BCR-ABL leukemic mice to normal[48].

12B1 leukemic cells were subjected to MTT assay for cell viability test, thymidine incorporation assay to evaluate the cell growth rate & morphological determination, mitochondrial membrane potential, RT-PCR, western blotting to evaluate apoptotic effect of SA on 12B1 cell line. Intracellular calcium & ROS level were significantly elevated which could be either due to impaired plasma membrane extrusion mechanism or excessive release of ca^{+2} from intracellular stores. Increased calcium level damages the mitochondria impairing the electron transport chain, ultimately resulting increased ROS concentration. Treatment with SA resulted in inhibition of mRNA expression of BCR-ALB gene (a potent cell death inhibitor) leading to release of cytochrome c, a key player for the aggregation of adaptor molecule Apaf1 which eventually mediates apoptosis. Down-regulation of Bcl- 2 (antiapoptotic gene) & upregulation of Bax (proapoptotic gene) were found in the study suggesting involvement of Bcl-2 family in the mediation of apoptosis. Therefore, decrease in Bcl2 & increase in Bax, increase in cytochrome c release and activation of caspase cascade signalling pathway leads to inter nucleosomal DNA fragmentation leading to apoptosis[49].

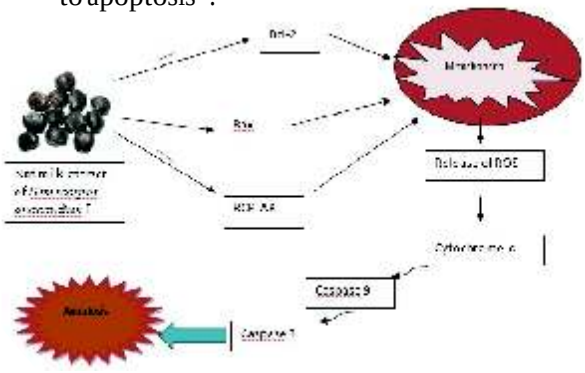

Fig: Proposed mechanism of induction of mitochondria dependant apoptotic pathway in BCR-ABL/ 12B1 Leukemia Cell Line by Semecarpus anacardium L nuts.[49]

Harmful effects of the plant and its prevention

- Urushiol-induced contact Dermatitis:
  Collection of this medicinal plant and its purification process has become a tedious job since it has harmful effect on those expose to it. It has been mentioned under Upavisha in Ayurveda to be administered internally only after sodhana (purification process) & has been described as poisonous plant having medicinal value in Drug & cosmetics act of India, 1940. Several cases of allergic contact dermatitis have been reported from its exposure to humans. The tarry oil obtained from pericarp of fruit of SA contains anacardic acid and it possesses urushiol, a constituent responsible for allergic contact dermatitis[50]. There is a traditional practice among women in village of India where seeds of the plant are burned to get rid of evil eye on new born babies. The smoke contains urushiol and produces allergic reactions with symptoms such as itchy, redness, blisters, swelling, papules, vesicles and streaking. Excessive scratching may result to secondary infection by staphylococcus & streptococcus species. In a case study by Bhatia et al., people exposed to the smoke of burnt seeds were evaluated by patch test for allergic contact dermatitis. All 40 patients with contact dermatitis had erythema and 39 of them had papular eruption out of which 4 had oozing, 2 had vesiculation and 2 had both oozing and vesiculation[51]. This study confirmed Urushiol as an active allergen responsible for contact dermatitis in patients exposed to the smoke of SA seeds. It is important to take precaution right from its collection to its purification and its processing has to be done in an open place.

Preventive measures:

As per Ayurveda, right from the collection to its purification following measures can be taken to avoid contact dermatitis:

- Coconut oil reduces irritation hence one should apply the oil on face, hands, legs and all exposed body parts during collection, drying, and processing.
- In case of allergy, albumin of coconut and drinking sufficient amount of coconut water helps.

  Plants such as Terminalia bellerica, Sesamum indicum, Terminalia chebula, Azadiracta indica are antidote to its poisoning. Topical application of neem leaf shows promising effect in eliminating the blisters while taking 'Triphala Churna' an ayurvedic preparation for 7 days helps curing the allergy rapidly[51].

- Neurotoxicity & disturbed function of the brain:
  Extraction of pericarp oil from the nut of SA requires large number of labours in rural village of India who get exposed to the fumes, highly toxic in nature during the extraction. Such oil has been reported to cause Semecarpus anacardium toxicosis in albino rats leading to serious problem of skin & deformities. In the study conducted by Choudhary et al., effect produced by SA on biochemical parameters and enzyme level was assessed & the level of GOT, GPT, SDH, LDH and AChE activity in the brain of experimental animals was increased which correlates to severe tissue damage causing necrosis. Severe behavioural change, convulsion and paralytic symptom appears due to its ill effect on brain physiology. Such studies provide an evidence for its measure of neurotoxicity and disturbed brain function after the sub-lethal dose of SA. Hence, it is required to adopt safety measures by the workers involved in the extraction of oil from SA[52].

Conclusion:

SA is one of the most valuable ancient plants having remarkable uses in treating various diseases. It is a rich source of antioxidant, flavonoids and tannins and has been used in treating various form of cancer like leukaemia, hepatocellular carcinoma; heart diseases; neurological disorders etc. Various preliminary & preclinical studies have been performed with the various extracts of this plant but its proper utilization as a phyto-pharmaceutical has not been fully explored. It is a poisonous plant and has to be used only after careful detoxification process. Hence it can be concluded that the plant can be utilized as one of the source of bioactive constituents to treat various diseases.

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