Bhallatak (Semecarpus anacardium Linn.)—A Review

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Received 7 November 2005; revised 5 October 2006

Bhallatak (Semecarpus anacardium Linn.) has been used for medicinal and non-medicinal purposes since ancient times. The toxicity of bhallatak precludes its mega scale production particularly as a medicine at the industrial level. However, traditional healers and physicians of Indian Systems of Medicine continue to use bhallatak in various forms in their clinical practice. Several experimental investigations have been undertaken in diverse in vitro and in vivo models. The major focus of these investigations reported in the current literature, remains on anticancer and antiarthritic activity. The purpose of this review is to get a better insight in the activity of S. anacardium Linn. and comprehend its narrow therapeutic margin. It is important to understand the significance of Ayurveda inspired investigation of this traditionally acclaimed medicinal plant.

Keywords: Bhallatak, Ayurvedic drugs, Traditional medicine, Antiinflammatory activity, Antirheumatic activity, Anticancer activity, Review

IPC Int. Cl.8: A61K36/00, A61P19/00, A61P19/02, A61P21/00, A61P29/00

The word, Semecarpus is derived from Simeion in Greek means marking/tracing and carpus in Greek means nut. Anacardiaceae means like cardium, i.e. heart shaped marking nut. Bhallatak literary means sharp like spear. Bhallatak or marking nut is known to the world since ancient times. The stem, sap, fruit and seeds are used by mankind for diverse purposes such as timber, paint, waterproofing, food and medicine. In view of its several potent medicinal properties, it is acclaimed as Ardhavaidya in Ayurveda and as a Golden acorn at the time of Galen in the western world. Severe skin manifestations, precludes its use for medical purposes. In India, the plant is used by Ayurvedic practitioners/traditional healers across the country albeit with caution. However, manufacturing units are overtly scared in view of its apparent toxic nature, and hence there are a few takers. The plant belonging to Anacardiaceae family has potential to produce allergic manifestations through contact dermatitis. Phytoconstituents, viz. alkyl catechols, phenols, quinols and resorcinols are believed to be responsible for skin reactions. The plant growing naturally in tropical and dry climate is a deciduous tree having a height of about 10 m. Flowering time is May to October (Fig. 1), whereas fruiting time is December to March. The fruit is eaten when ripe, whereas the kernel of the seed is eaten after removing the pericarp. Marking nut seed, which sinks in water, is used for medicinal purposes (Fig. 2).

Ayurvedic properties of Bhallatak are madhur, kashay ras, ushna virya, madhur vipak and laghu, snigdha, tikshna, and ushna gunas. It has several karmas like Kaphavatashamak (alleviates kapha & Vata dosha), Bhootanashan (anti-devil) Pittasanshodhak (expels out pitta dosha), Medhya (beneficial to brain), Vanhikar (improves digestive fire), Vrishya (aphrodisiac), Chedana (excisional functions), Bhedan (incisional function), Bruhan (anabolic in effect), and hence indicated for many diseases like Arsha (haemorrhoids), Udar (ascites), Grahani (inflammatory bowel diseases), Shotha (inflammation), Kruni (helminthiasis), Kushtha (skin disorders, like psoriasis), Vran (wounds), Shwitra (vitiligo), Gulma (abdominal mass), Jwar (fever), Adhman (flatulence), etc. The seeds oil is mainly used for medicinal purpose. Seeds (1/4th-1/2 piece) are usually administered boiled in milk and the milk is consumed. The number of pieces may be increased gradually depending on the patient’s response up to 3 whole nuts and subsequently it is reduced gradually in a same fashion. The method of gradual dose escalation and subsequently gradual decrease of dosage over the period of weeks is called Vardhaman prayog in classical Ayurveda. The seeds oil is also

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used usually mixed with food items. For topical purpose, the oil is applied in a minimum possible quantity or mixing it with other commonly used non-toxic oils.

**Bhallatak formulations**

The compendium of Ayurvedic formulations, Bharat Bhaishajya Ratnakar has mentioned about 40 formulations of Bhallatak. Charak, Sushrut and Vagbhhatt, the main three treatises of Ayurveda have described diverse Bhallatak formulations. Charak describes 10 different types of Bhallatak formulations in Rasayanavidhi, while Sushrut and Vagbhhatt have indicated the use of about 1,000 seeds of Bhallatak during the schedule of one therapeutic course of Vardhman prayog. Bhallatak is being currently used in some of the formulations as a major or minor ingredient. The commonly used formulations are Amrithbhallatak Avaleha, Bhallatakasav, Suran vatak, Bhallatak Parpati, Sanjeevani Vati, Narsimha choorna, etc. (Table 1). Before using, Bhallatak for medical purpose, it is subjected to the process of shodhana (purification and detoxification). The most common shodhana involves rubbing the Bhallatak seeds with brick powder and washing the seeds later with warm water. In another method, it is recommended to tie the seeds in muslin cloth and suspend it in a vessel containing coconut water, which is then heated for about 3 hrs continuously.

**Phytochemistry**

The most significant components of the Semecarpus anacardium Linn. oil are phenolic compounds. On exposure to air, phenolic compounds get oxidized to quinones. The oxidation process can be prevented by keeping the oil under nitrogen. Two main phenolic compounds and a glucoside are bhilavanol A (monoenepentadecyl catechol I), bhilavanol B (dienepentadecyl catechol II) and anacardoside (glucoside). Vesicant reactions of Bhallatak are possibly attributable to these phenolic compounds. Important biflavanoids such as semecarpaflavanone, jeefflavanone, golluflanvanone, nallaflavanone, semecarpetin and anacarduflanvanone have also been isolated. Semecarpaflavanone and golluflanvanone group have potentially antioxidant activity on these flavanones. Analysis of the kernel has also been reported.

**Pharmacology**

Bhallatak has been evaluated pharmacologically on the isolated tissues and the whole animal.
Anticancer activity, antiinflammatory, antiarthritic and antioxidant activity have been reported in experimental animals. Very few studies have been reported on hypolipidemic, hypoglycemic, antitherogenic, antifungal, antifertility and neuroprotective activities. Antiinflammatory and antiarthritic activities of milk extract and chloroform extract have been documented in rats and mice. A significant protection against FeSO$_4$ induced lipid peroxidation with alcohol extract of *S. anacardium* pericarp has also been demonstrated. The oil rich fraction of water extract of nut has shown inhibition of lipopolysaccharide induced nitric oxide production. Cyclooxygenase inhibitory flavanoids from the ethyl acetate extract of the stem bark and biflavanoids, tetrahydromentoflavone from the seeds have been documented. These biflavanoids have demonstrated dose-dependant antiinflammatory activity in carrageenan induced paw oedema comparable to that of ibuprofen. Antiinflammatory activity of nut extract in acute and chronic models of inflammation was comparable with indomethacin. Further, the nut extracts have demonstrated antioxidant and immunomodulatory activity on the compounds of immune system in adjuvant-induced arthritis. Effective regulation of cartilage metabolism and bone turnover in experimental models of arthritis by the nut milk extract has been documented. The nut extract has also demonstrated inhibition of proinflammatory cytokine production in *in-vitro* model using peripheral blood and synovial fluid mononuclear cells of healthy and rheumatoid arthritis patients.

SAN-AB, an extract of marking nut was studied for its antitumour and anticancer activity. Chloroform extracts of nuts in wide spectrum of murine tumour system showed significant increase in the animal lifespan in the models of leukaemias L1210, P388, advanced P388, sublines of P388 resistant to adriamycin/vincristine and B16 melanoma and glioma 26,27. Cytotoxic effects on the cells of P388 lymphocytic leukemia was demonstrated by acetylated oil of nut. Potentiation of the cytotoxic activity was further demonstrated against P388 lymphocytic leukemia and Sarcoma 180 by a combination of acetylated oil of *S. anacardium* with anticancer drugs, mitomycin –C, 6 mercaptopurine and methotrexate. Antimutagenic activity has been shown by Ames test with water, alcoholic and oil extract of the nut. Cytotoxic activity against colo-320 tumour cells has been documented with an alcoholic extract of the nut and against Eagles 9 KB, nasopharyngeal carcinoma cell culture system has been shown with Pentadecyl catechols I & II derived from *S. anacardium*. Traditional milk extract of the nut studies in aflatoxin B (1) induced hepatocellular carcinoma model has recorded several interesting & favourable biological activities on glucose metabolizing activities, tumour marker enzymes, antioxidant defence system, aflatoxin B (1) biotranformation, microsomal biotranformation enzymes and lysosomal membrane & cell membrane glycoprotein profile. Similar milk extract of nut has been studied further in mammary carcinoma bearing rats with interesting results. Marking nut oil studied in AML (acute myeloid leukemia) cell line (HL60) and CML (Chronic myeloid leukemia) cell line (K-562) have shown apoptotic activity suggesting to be mediated by activation of caspases. The traditional Siddha product, *Semecarpus lehyam* studied in breast cancer demonstrated a potent antitumour activity against ER-ve (estrogen receptor-ve) cancer cell line.

**Clinical studies**

*Bhallatak* is used topically and systemically for served clinical conditions. Topically, it is used in migraine, wounds, vulvitis, eczema, boils, earache, hydrocele, localized pain, etc. For inducing abortion, oil is applied to cervix. Orally, it is used for conditions, mainly like bronchitis, asthma, helminthiasis, hemorrhoids, psoriasis, rheumatic complaints, neuralgias, tumors, etc. Series of case studies of diverse cancerous conditions clinically responding to the SAN-AB, a *Bhallatak* based formulation has been reported. At least 45 dissertations are recorded for post graduate studies in *Ayurveda* to investigate various aspects of *Bhallatak*; its role in rheumatoid arthritis emerges to be the most common topic. *Ayurvedic* periodicals have also been publishing clinical studies of *Bhallatak* in rheumatic diseases. Serial investigations carried out in rheumatic diseases are interesting and have reported role of *S. anacardium* in the management of sciatica, where *Bhallatak* *ksheerpak* was administered in a classical mode of *vardhaman prayog* over the period of 3 weeks. Taking the positive lead from this clinical trial, patients with various rheumatic diseases such as rheumatoid arthritis, ankylosing spondylitis, sciatica, periarthritic of shoulder and osteoarthritis were
studied in controlled clinical trial. This 4 weeks study again of \textit{vardhman prayog} has shown positive response in cases of periarticular arthritis of shoulder, sciatic neuralgia and early stages of rheumatoid arthritis and ankylosing spondylitis\textsuperscript{62}. However, the study reports adverse drug reactions in 25\% of patients in the form of itching, maculo-papular rashes, urethritis and stomatitis, which were dose dependant and could be controlled by the withdrawal of the drug or administration of antihistamines. Further controlled clinical study in defined patients of rheumatoid arthritis, the dose used of \textit{Bhallatak ksheerpak} was in the range of 1.5-9 gm/day in a classical fashion of \textit{vardhman prayog} over a period of 28 days. About 65\% of patients showed good subjective response\textsuperscript{63}. 

\textbf{Toxicity and antidotes}

\textit{Bhallatak} is generally classified in \textit{Ayurveda} under the category of toxic plants\textsuperscript{65}. \textit{Bhallatak} is usually avoided in pediatric age group, pregnant women, predominant \textit{pitta prakruti} persons and also in certain diseased conditions such as bleeding diatheses, renal function disorder, history of vesications and past history of intolerance to \textit{Bhallatak}. \textit{Bhallatak} is known to have a narrow therapeutic range. The commonly seen \textit{Bhallatak} - related adverse events are generalized itching, vesication, erythematous patches, mucocutaneous papular eruptions, stomatitis, gastritis, proctitis, urethritis, etc. Practitioners are known to use several antidotes either locally or systemically (Table 2). It is always advised to avoid substances, which would aggravate \textit{pitta} while consuming \textit{Bhallatak}\textsuperscript{66}. Taking \textit{Bhallatak} with \textit{Anupana} of \textit{ghee}, milk, sugar, rice (\textit{Shashitsali}) is believed to reduce the incidence of adverse events.

Table 2—Traditionally used antidotes for \textit{Bhallatak} toxicity

<table>
<thead>
<tr>
<th>Systematic</th>
<th>Local</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coconut albumen</td>
<td>Sesame oil</td>
</tr>
<tr>
<td>Coconut water</td>
<td>Coconut oil</td>
</tr>
<tr>
<td>Tamarind leaves</td>
<td>Ghee</td>
</tr>
<tr>
<td>\textit{Sesamum} seeds</td>
<td>Resin ointment</td>
</tr>
<tr>
<td>\textit{Sarivadi} gana</td>
<td>Coriander</td>
</tr>
<tr>
<td>\textit{Durvadi} gana</td>
<td>Gopichandanan</td>
</tr>
</tbody>
</table>

Although several phytoconstituents, viz. bhilawanols and biflavanoids have been isolated from the seed oil, clinical use based rationale approach for the study of chemical profiling will provide better insight in understanding the activity and toxicity of the plant\textsuperscript{8,11}. Better tolerability with traditionally prepared no mortality till 2,000 mg/kg in acute toxicity study, while subacute toxicity study (500 mg/kg) showed moderate increase in the levels of blood glucose, plasma urea, uric acid, creatinine & lipid alterations. However, histopathological examination of organs did not show any morphological disturbances\textsuperscript{77}.

\textbf{Conclusion}

Seeds of \textit{Semecarpus anacardium} have been used as a healthcare product and medicine since thousands of years\textsuperscript{5}. All the three \textit{Brihatrayee} (three major treatises), viz. \textit{Charak}, \textit{Sushrut} and \textit{Vagbhat} of \textit{Ayurveda} elaborately described \textit{Bhallatak} formulations. It is being continuously used over thousands of years\textsuperscript{51-56}. \textit{Bhallatak} is acclaimed as \textit{Ardha-Vaidya} meaning it does half the job of a physician. In spite of such a reputation, currently many physicians avoid using \textit{Bhallatak} based preparation due to fear of potential toxic nature and for the same reason many pharmaceutical units prefer keeping away from preparing \textit{Bhallatak} based formulations. However, few skillful \textit{Ayurvedic} experts have been using \textit{Bhallatak} based formulations successfully. Since, the seed pericarp contains toxic constituents, so after removing the pericarp, seed pulp as well as fruits is consumed. However, for medicinal purpose either the seed or the seed oil is used; which although makes it potentially toxic, is therapeutically effective. The important thing is to finetune this margin of efficacy and safety. The key probably lies in \textit{Ayurvedic} process of manufacturing and \textit{Ayurvedic} method of using it clinically. The \textit{shodhan} process is considered mandatory for any toxic plant material before its medicinal use; it would be interesting to study the differences if any in the phytochemical profiling of the \textit{shodhit} and \textit{ashodhit bhallatak}.
Bhallatak preparation and milk extract has already been reported in acute and subacute animal toxicity studies. It is desirable to study pharmacology of Bhallatak with addition of subgroups based on different Anupana, viz. milk, ghee, sugar, etc. to investigate the significance of Anupana used in Ayurveda. Clinical studies of Bhallatak based formulations have shown good clinical activity. However, what essentially required is to find out the effective safe dose, difference between the mode of administration in classical vardhmaan prayoga and fixed dose schedule, time suitable for drug administration, significance of patients’ constitution and relevance of ancillary instructions of dietary and behavioral modifications suggested in classical Ayurvedic practice. The significance of Ayurvedic pharmaceutical processing and Ayurvedic approach of clinical usage if documented through objective evidence would certainly provide a better insight in Ayurvedic concepts and fundamentals, which eventually would help in developing Ayurveda inspired evidence based natural drugs.

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