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Role of Herbal Analgesic Drugs and Their Clinical Applications In Osteosarcoma Induced Pain

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ABSTRACT

Abstract- Recently, there has been a rapid rise in deforming problems like cancer, in which bone cancer is a problem that takes a long time to move. Primary bone sarcomas are rare tumors, comprising approximately 0.2% of all cancers. Their true incidence is difficult to estimate because of their rarity.¹ Osteosarcoma, chondrosarcoma, and Ewing sarcoma/primitive neuroectodermal tumor are the common bone sarcomas, as per Western data, with rare tumors such as fibrosarcomas, chordomas, and undifferentiated pleomorphic sarcoma constituting as the remaining subtypes. Bone sarcomas constitute as the third most common cause of mortality in adolescents. Remarkable achievements with multimodality management of these tumors have led to an increase in their 5-year survival rates, from approximately 50% in the year 1970, to the range of 75–80%, presently, in the adolescent age-group.² Osteosarcoma the second highest cause of cancer-related death in these age groups, mainly due to development of often fatal metastasis, usually in the lungs. Survival for these patients is poor despite the aggressive use of surgery, chemotherapy, and/or radiotherapy. Thus, new effective drugs and other forms of therapy are needed.³ This article reviews is about the Ayurvedic medicines that are beneficial in cancer disease. Is some of these special medicines are being discussed in this article to treat diseases like Osteosarcoma. Hadjod, and nirgundi which is used to reduce the inflammation of the joints, also works as a treatment in bone diseases. Similarly, medicines like Shallaki and Parijat work in treating bone diseases, reducing inflammation and increasing immunity.

Keywords: Hadjod, Shallaki, Parijat, Babool, Nirgundi, Anti cancerous, Bone healing.

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INTRODUCTION

एकादशोऽध्यायः ग्रन्थ्यपच्यर्बुदगलगण्डानां -

‘अथातो ग्रन्थ्यपच्यर्बुदगलगण्डानां निदानं व्याख्यास्यामः ॥ १ ॥

यथोवाच भगवान् धन्वन्तरिः ॥ २ ॥‘

Now its inner glands describe the diagnosis of dyspepsia, tumor and goiter, as said by Lord Dhanvantari to Sushruta.⁴

Osteosarcoma is a primary malignant tumour of the skeleton characterized by the direct formation of immature bone or osteoid tissue by the tumour cells. More rarely osteosarcoma may arise in the soft tissue.⁵

OSTEOSARCOMA:

Osteosarcoma (OS) is the most common malignancy in primary bone among children and adolescents. This malignancy comprises 2.4% of all childhood cancers and 20% of primary bone sarcomas. Every year 400 new cases of OS are diagnosed in children and adolescents below 20 years of age. Osteosarcoma is more commonly found in males than females with a ratio of 28:1. OS presents a bimodal age distribution with the first incidence peak of the disease between 10 and 14 years. The second peak of incidence occurs in older adults aged over 65 years.⁶

Osteosarcoma can occur in any bone of body but preferentially in distal femur (40%), proximal tibia (20%) and proximal humerus (10%), may also occur in the axial skeleton which is more frequent in older patients. Axial bone involvement in pediatric patients represents less than 10% of clinical cases. Radiologically detectable metastases in patient showed 80% of the cases present localized disease associated with a poor prognosis and short-time survival.⁷ OS is a destructive process that initiates in the intramedullary region and most of the cases grows radially towards the bone cortex resulting in cortex perforation. OS lesions can also extend to surrounding soft tissues like muscles compressing them into a pseudo capsular layer determined “reactive zone.” The OS lesions are characterized by the production of malignant osteoid by the neoplastic cells which can be detected through imaging studies. The imaging techniques used in osteosarcoma diagnosis are plain-film radiography, Computerized Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and bone scintigraphy. The most common symptoms of OS are pain and swelling. Pain can emerge after strenuous exercise or trauma, usually 2-4 months before diagnosis, and increases progressively along time. Swelling appears later with a hard painful mass in the affected region. Despite being uncommon, the pathologic fracture can occur in

OS cases. In addition to the physical symptoms, OS patients usually present abnormal high levels of Alkaline Phosphatase (AP) and Lactate Dehydrogenase (LDH). These features are reported to be related to prognosis and tumor volume. The World Age-Standardized (AS) mortality rate shows that there are 126 men and 83 female for every 100,000 of populations due to cancer in 2015.⁸ There was an increase of 1.5 million new cancer cases predicted every year. Globally, India has a lower rate of cancer, but, there is an increase in the incidence from over 700 to 1000 new cases per million of the population. Currently, more than 70% of the cases are in the advanced stage accounting for poor survival and high mortality. The early detection reduces the risk factors and mortality rate that helps to provide better treatment.⁹

Classical Osteosarcoma

Classical osteosarcoma is common among adolescents and 30 years old, which is located in the metaphysis region and knee joint or upper part of the arm. The tumor consists of malignant osteoid or calcified bone and also associated with chondroblastic or fibroblastic differentiation.¹⁰

Well-differentiated Intraosseous Osteosarcoma

It is a spindle cell osteosarcoma with few mitotic cells with varying bone trabeculas.¹¹

Telangiectatic Osteosarcoma

It is quite a rare variant of Osteosarcoma that appears as a benign, aneurysmal bone cyst. It is high grade, blood-containing cysts with the expansion of the cortex.¹⁰

Parosteal Osteosarcoma

It is low-grade sarcoma located distally on the femur. In some cases, infiltrated bone marrow can be seen designated with dedifferentiated parosteal osteosarcomas. These have worse prognosis and investigation will demonstrate ring like chromosomes.¹²

Ewing`s Sarcoma

This tumor occurs as soft tissue in bone and is a small cell tumor with varying degree of neuroectodermal differentiation. Histologically, they stain positive for Periodic acid-Schiff stain (PAS) as the cytoplasm of these cells contains glycogen and some show pleomorphic nature. It can also be related to neuroectodermal differentiation exhibiting rosettes with no matrix production and known to be high-grade sarcoma with high malignancy. Some confirmatory analyses are performed to include along with other diagnoses such as cytogenetic, immunohistochemistry and molecular methods. Immunohistochemical analysis demonstrates positivity for vimentin, (sensitive, but not specific). These shows positive for synaptophysin, S-100 protein and chromogranin for neuroectodermal markers. It has a diagnostic genetic finding where common translocation of gene fusion with later appears to be a malignant tumor.^{10,11,12}

SITES OF PAIN

The sense organs are the most important sites for the manifestation of happiness and miseries. In Ayurvedic literature attention has been directed towards origin, nature of pain as well as classification of pain.

The word shoola also used for painful sensation. Indeed Ayurveda has not only considered shoola as a symptom or as an independent disease entity but they have taken more comprehensive view regarding the etiology, pathology and management of pain. Shoola has been described as outcome of vata vyadhi.

There cannot be pain (shoola) without involvement of vata¹³ but pitta and kapha influences the nature and intensity of pain. Thus all three doshas (vata, pitta, kapha) as a whole are responsible for the origin, development and perception of pain.¹⁴

Shoola produces focal symptoms in the body. In stree roga shoola in the yoni (reproductive system) has been considered as a symptom of Vatala yoni. Thus it is clear that shoola has been considered as symptom as well as a disease in Ayurveda. Thus vayu in a particular individual or in some individual at different time might be the guiding factor for the perception of painful stimulus varying from negligible to severe pain depending upon the predominance of vayu in the individual at that time. Pain from all over the body is felt in manas (brain) except from hairs, small hairs, tip of nails, ingested food, excreta, urine.¹⁵

TYPES OF PAIN

Description of exact nature of pain as experienced by the subject it so vividly described in Ayurveda that hardly any new adjective and adverb can be added. More surprisingly the different method which includes drugs, vomiting, fasting etc. are also described in detail for relieving all these types of pain.

Vedana is classified into five types based on the predominant f dosha in reference of vrana.¹⁶

Pain of Vatika Vrana:

When a vrana has pin pricking, stabbing, staffing, beating, cutting, girdling, stirring. throwing, irritating, burning, bursting, tearing or dividing type of pain or there is a cramp. radiating or filling type of pain rigidity numbness, penetrating pain or various type of non specific pain which occur repeatedly than it should be known as vedana due to excessive vitiation or predominance of vata. Similar idea is in susrutasamhita.¹⁷

Pain of Paittic Vrana:

When the pain of Vrana cause local, regional or generalized burning sensation and appears as if smoke coming out of wound or sensation of burning charcoal covered all over the body, with rise

of temperature and pain as if kschar has been applied on the cut, wound, predominance of pitta should be concluded. Same idea exists in susrutasamhita.¹⁸

Pain of Raktaj Vrana:

Pain caused by shonita rakta (vitiated blood) predominance is similar to that caused by vitiation of pitta.

Pain of Kaphaja Vrana:

Where Vrana has itching sensation, heaviness, numbness, a feeling of being covered with paste, mild pain, rigidity and feeling of coldness it is supposed to be caused by vitiation of shelesma or kapha. Some idea is also found in susrutasamhita.¹⁹

Pain in Sannipataj Vrana:

When there is mixed sense of all types of pain described above, it should be considered to be due to vitiation of all the three dosha. The same description exists in susrutasamhita.²⁰

Pain in Osteosarcoma:

Bone cancer pain is very common, and patients with this type of pain may be difficult to treat. Development of an experimental model for studying this condition is critical to advancing an understanding of the mechanisms that cause pain in patients with malignant disease.

Malignant bone disease creates a unique pain state that involves sensitization of the nervous system. Major contributors to the pain state within the bone tissue are osteoclastic bone resorption and the malignant disease itself.

The disease-related event that has the most significant impact on quality of life for patients with malignant disease is cancer-induced pain. Bone cancer pain is the most common source of pain in patients with malignant disease.^{21,22} It affects patients with bone sarcomas and patients with malignant tumors that have spread to bone. Breast carcinoma and prostate carcinoma are the most common cause of pain from malignant bone disease.²³ This fact underscores the prevalence of these two types of carcinoma and their affinity for metastasizing to bone. In fact, 70% of patients with advanced breast or prostate carcinoma have skeletal metastases, and skeletal metastases are present in > 90% of patients who die from breast or prostate carcinoma.⁵ At its onset, bone cancer pain can be intermittent, but it progresses rapidly into continuous pain that is exacerbated by episodes of breakthrough pain. Once this chronic pain is established, the circumstance further deteriorates when mechanical allodynia develops. Mechanical allodynia occurs when normally non painful activity or stimulation is perceived as painful. For example, coughing, turning in bed, or gentle limb movements can cause intense pain.^{21,23}

THERAPIES:**Chemotherapy:**

Numerous drug combinations have been assessed for palliative treatment in metastatic or relapsed osteosarcoma. The most effective of these contained agents used for non metastatic disease are cisplatin, doxorubicin, methotrexate and ifosfamide .^{24,25}

Surgery:

In the face of local recurrence and metastatic disease, surgery is probably the best therapeutic option. Local and metastatic resections, when feasible, should always be considered. In a retrospective analysis performed at the Rizzoli Institute, the only patients who survived long term were those who achieved complete surgical removal of their recurrent tumor.²⁶ Specifically, the patients did not achieve surgical resection, and none of these patients survived long term. By contrast, the patients achieved surgical resection with a 5-year post-relapse EFS rate of 27.6%. These patients received either multi agent or no chemotherapy, but they shared the common feature that everyone had achieved a second surgical remission. Conversely, for those treated with chemotherapy or radiation therapy without surgery, there were no survivors. Our results seem to be confirmed by Kempf-Bielack et al., who reported a 5-year post-relapse survival rate of 23%, and found surgery to be an essential element of second-line cure.²⁷ Similarly, the resection of all identified tumor sites is essential for survival, as shown by Daw et al.²⁶ In general, most reports confirm the poor prognosis of metastatic or recurrent osteosarcoma. An aggressive surgical resection, if feasible, remains the most effective treatment.²⁷

Radiotherapy:

Radiotherapy has a limited role in the management of osteosarcoma because of the natural history of the disease, the relative radio resistance, and the need for a large dose of radiation (>70 Gy) to achieve a clinical response.^{28,25} However, the value of radiation therapy in osteosarcoma has not yet been resolved.²⁹ Radiotherapy could be an alternative option to standard treatments as a palliative therapy in cases where surgery is unfeasible. Chemotherapy seems to markedly improve the effectiveness of local control radiotherapy. Chemotherapy agents that combine systemic osteosarcoma control and also increase radiation effectiveness include ifosfamide, cisplatin, high-dose methotrexate or gemcitabine.³⁰

Therefore both Charaka and Sushruta have said:

'ग्रन्थ्यर्बुदानां च यतोऽविशेषः प्रदेशहेत्वाकृतिदोषदूष्यैः' (च.चि. १२)

तथा 'तस्य च लक्षणानि ग्रन्थेः समानानि सदा भवन्ति' सु. नि. 11²

The symptoms which Sushruta has described as mild-pain, stagnant, apaki etc., should be understood only as benign tumors. Vatik, Pittik, Mucosal and Meadows tumor are the tumor of benign category. They have not been described in detail because of having similar symptoms and being endowed with the gland.²

Tumor differences-

महत्तु ग्रन्थितोऽर्बुदम् ॥१४॥

तल्लक्षणंचमेदोऽन्तःषोढादोषादिभिस्तुतत्। प्रायोमेदःकफाढ्यत्वात्स्थिरत्वाच्चनपच्यते ॥१५॥

The one that is bigger than the gland is a tumor. These tumors are of six types - three from Vataadi doshas, three born from blood, flesh and fat.⁶

Erythematous

सिरास्थं शोणितं दोषः सङ्कोच्यान्तः प्रपीड्य च । पाचयेत तदानद्धं सास्त्रावं मांसपिण्डितम् ॥१६॥

मांसाङ्कुरैश्चितं याति वृद्धिं चाशु सवेत्ततः । अजसं दुष्टरुधिरं भूरि तच्छोणितार्बुदम् ॥ १७ ॥

Vatadi any dosha mack by constricting the cerebrospinal blood and pressing it inside. Then it grows by filling with ripe, bloated and secretive fleshy flesh, fleshy spores. Then, soon after this, continuously contaminated blood flows in large quantities, it is called Sonitarbud. (The symptoms of carcinoma and atheroma are similar to that of the gland). (Nowadays it is called cancer and sarcoma.)²

Madhav Nidan (madhukosh)- Two distinctions have been given to cancer under the , first (somyarbud) cancer in benign, second malignant cancer. in which (Asthyarbud) osteoma is kept in benign tumor(somyarbud).³¹

Astanghridayam-

वृत्तं स्थिरं मन्दरुजं महान्तमनल्पमूलं चिरवृद्ध्यपाकम् ॥ १३ ॥

कुर्वन्ति मांसोपचयं तु शोफं तदर्बुदं शास्त्रविदो वदन्ति ।

वातेन पित्तेन कफेन चापि रक्तेन मांसेन च मेदसा च ॥ १४ ॥

तज्जायते तस्य च लक्षणानि ग्रन्थेः समानानि सदा भवन्ति ॥ १५ ॥

Arbudnidan- Vatadi Dosha, enlarged in any region of the body contaminating the flesh, is round, stable, less painful, large, spread in serious metals, slowly growing, never ripening and due to anabolic (growth) of meat Contains produce such edema. Knowing scholars of Ayurveda

scriptures call this edema disease as Arbud. It originates from Vata, from Pitta, from flesh and from fat and has symptoms similar to that of a gland.³²

Malignant tumor caused by valence metal

Sarcoma this tumor is often generated in the asthenia, bone, marrow and skin. There is a possibility of bleeding due to excessive blood circulation in them. The cells or small parts of the tumor separate from the tumor and reach the distant organs through the ends and start secondary growth there. The differences of sarcoma are small round celled, large round celled etc. according to the cell and fibro sarcoma, osteo sarcoma, myo sarcoma etc. are examples of metal excess.³³

Importance of Herbal Medicine In Osteosarcoma-

Medicinal herbs and their derivative phytochemicals are being increasingly recognized as useful complementary treatments for cancer. A large volume of clinical studies have reported the beneficial effects of herbal medicines on the survival, immune modulation, and quality of life (QOL) of cancer patients, when these herbal medicines are used in combination with conventional therapeutics. Here, we briefly review some examples of clinical studies that investigated the use of herbal medicines for various cancers and the development of randomized controlled trials (RCTs) in this emerging research area. In addition, we also report recent studies on the biochemical and cellular mechanisms of herbal medicines in specific tumor microenvironments and the potential application of specific phytochemicals in cell-based cancer vaccine systems. This review should provide useful technological support for evidence-based application of herbal medicines in cancer therapy.^{34,35,36}

Concept of Analgesic In Ayurveda -

(Asthisamhaara) Haadajodaa³⁷ 2. Shallaki⁴⁹ 3. Babbula⁵⁸ 4. Paarijaata⁶⁴ 5. Nirgundi⁸¹

Pharmacodynamic concept of herbal analgesic

Sl No	Name of The Drug	Botanical Name	Rasa	Guna	Virya	Vipaka	Pravah
1	(Asthisamhaara) Haadajodaa	Cissus Quadrangularis L.	Madhura	Laghu, Ruksa, Sara	Ushna	Usna	Kapha Vaata Shaamaka, Pitta Vardhaka
2	Shallaki	Boswellia Serrata Roxb	Kashaya, Tikta, Madhur	Laghu, Ruksha	Ushana	Katu	Kaphapittashamak
3	Babbula	Acacia Nilotica Delile Ssp.	Kasaaya, Madhura	Guru, Ruksa, Snigdha	Shita	Katu, Madhura	Kapha Pitta Shaamaka, Vaata Pitta Shaamaka
4	Paarijaata	Nyctanthes arbor-tristis L	Tikta	Laghu, Ruksha	Ushana	Katu	Vednahar
5	Nirgundi	Vitex Nergundo	Katu, Tikta	Laghu, Ruksha	Ushana	Katu	Vednahar

ASTHISAMHAARA

(Haadajodaa) *Cissus quadrangularis* L.

Family: Vitaceae

Synonym : *Vitis quadrangularis* Wall. ex W. & A.

Ayurvedic syn. : Asthishrnkhalaa, Vajravalli, Granthimaana, Vajraanga, Kandavalli, Asthisamyojaka, Asthi-samhrta

Trade name: Adamant creeper

Local name: Haadajodaa, Haadabhangaa, Haadashikuli

Description: A rambling shrub; often climbing over bushes and trees to some length; stems fleshy, 4-angled, jointed, 4-winged or margined, often 2.5 cm diam; bearing leaves at the nodes during rainy and cold seasons. Leaves simple, alternate, short-petioled, very broadly ovate or reniform, 2.5-6 cm long and broad, rarely lobed, crenate-serrate, glabrous; stipules foliaceous. Tendril simple. Flowers pinkish-white in short-peduncled umbellate cymes. Calyx cup-shaped, entire. Petals 4, triangular-ovate, disc small; stamens 4, style subulate, stigma small. Barries obovoid or globose, 6-7 mm diam., red when ripe.³⁷

Parts used: Whole plant, root, stem & leaves.

Ayurvedic properties: Rasa: madhura; **Guna:** laghu, ruksa, sara ; **Virya:** usna; **Vipaaka:** usna, **Dosakarma:** kapha vaata shaamaka, pitta vardhaka

Actions & Uses: Digestive, stomachic, carminative, laxative, anthelmintic, depurative, haemostatic, aphrodisiac, anodyne, ophthalmic, union-promoting & useful in dyspepsia, colic, flatulence, haemorrhoids, colonopathy, skin diseases, leprosy, hemorrhages, haemoptysis, ophthalmopathy, otorrhoea, chronic ulcers, tumours, epilepsy, convulsions, scanty menstruation, scurvy, asthma, burns, wounds, fractures & swellings.³⁸

Formulations: Asthisamhaara tl, Laaksa ggl, Asthisamhaaraa ch, Daasyaadi kw, Daarvi kw.

Therapeutic uses:

- i. Bone fracture - Sarbat: Asthisamhaara + Arjuna + lac + wheat flour + milk - Topically - bandage with stem paste
- ii. Constipation - Juice of young shoots / leaves 10 ml at bed time
- iii. Dysmenorrhoea - Stem juice 10 ml

Chemical composition

Major &-Amyrin, &-amyrone, unsymmetric tetracyclic triterpenoids: onocer-7-ene-3a, 213-diol and onocer 7-ene-33, 21a-diol ²:33,3,4,4-Tetrahydroxybiphenyl³; stilbene derivatives: quadrangularin A, quadrangularin B, quadrangularin C, resveraterol, piceatannol, pallidol,

parthenocissine A; flavanols: quercetin, kaempferol: unsymmetric tetracyclic triterpenoid: 7-oxo-onocer-8-ene-33, 21a-diol, 4-hydroxy 2-methyl-tricos-2-en-22-one, friedelan-3-one, taraxerol, β -sitosterol, isopentacosanoic acid. 31-methyltritriacontanoic acid.³⁹

PHARMACOLOGICAL STUDIES

Bone Healing Activity:

The main traditional use of *Cissus quadrangularis* is in the field of bone remineralisation and fracture. It is commonly known as the 'Bone Setter,' the plant is referred to as 'Hadjod' in Hindi because of its ability to join bones. Modern research has shed light on the capability of *Asthisanharak* to speed up bone healing as it acts as a glucocorticoid antagonist.^{40,41}

Anti-Osteoporotic Activity:

C. quadrangularis has been stated in Ayurveda for its anti-osteoporotic activity. The phytoestrogen rich fraction (IND- HE) from the aerial parts of plant reveals its activity. Plant has phytoestrogen and triterpenoides. The phytoestrogen steroids isolated plant illustrates influence on early regeneration and quick mineralization of bone. The ethanolic and petroleum ether extract of *C. quadrangularis* L. confirms prominent effect.⁴²

Anti-Oxidant and Free Radical Scavenging Activity:

Methanol extract of *Cissus quadrangularis* exhibits strong antioxidant and free radical scavenging activity in vitro and in vivo systems mainly due to the presence of β carotene.^{43,44}

Central Nervous System Activity:

The root extract has central nervous system depressant activity indicated by decline in exploratory behaviour. Methanol extract of roots contains saponins which reveal potent sedative activity and also inhibit spontaneous motor activity in mice.⁴⁵

Analgesic, Anti-Inflammatory and Stimulatory Activity:

Cissus quadrangularis is potent as aspirin which was taken as standard in the treatment of acetic acid writhing mice, formalin test and tail-flick test in rats. The plant is also effective in the treatment of yeast infection induced hyper-pyrexia.⁴⁶

Anti-Obesity Activity:

Obesity and obesity-related complications (such as metabolic syndrome) are a common problem around the globe. To investigate the usefulness of *Cissus quadrangularis* in metabolic syndrome, particularly for weight loss and central obesity a randomized, double blind, placebo-controlled study was performed, 123 overweight and obese persons were treated with *Cissus* for eight weeks, while consuming a normal or calorie-controlled diet.⁴⁶

Anti-Tumour and Cytotoxic Activity:

Cytotoxic studies of *Cissus quadrangularis* ethanolic and chloroform extract was validated both on HeLa and Vero cell lines in a study, the cell lines were maintained in minimal essential media in a humidified atmosphere. The IC₅₀ Value of extracts was found to be 62.5 µg/ml and 125 µg/ml for HeLa and Vero cell lines respectively.⁴⁷

Anti-Ulcer Activity:

Methanol extract showed significant antiulcer activity in experimentally induced ulcer in rat model by decreasing gastric secretions and by enhancing glycoprotein levels. Methanol extract produce healing effect on aspirin induced gastric mucosal damage in rats through its antioxidative mechanism. Triterpenoids and β-sitosterol present in methanol extract possess anti-lipid peroxidating effect and thus prevent gastric damage.⁴⁸

SHALLAKI (*Boswellia serrata* Roxb. ex Colebr.)

Family : Burseraceae Synonym : *B. glabra* Roxb., *B. serrata* Roxb. var. *glabra* (Roxb.) **Ayurvedic syn. :** Susrava, Gajabhaksya, Kunduru.

Trade name: Indian olibanum

Local name: Shaalai

Description: A deciduous tree with reddish, grey bark. Dry barks peeling off in thin flakes; blaze pinkish and exuding small drops of resin. Leaves alternate, compound, imparipinnate and crowded at the ends of the branches, 30-45 cm long; leaflets 9-16 pairs, opposite, sessile or subsessile, lanceolate or ovate-lanceolate, 3-5-7.5 cm long, crenate-serrate, apex obtuse or acute, glaucous beneath. Racemes at the ends of the branches, usually appearing when the tree is leafless. Flowers small, white. Fruit 1.2 cm, 3-gonous, with three valves and 3 winged hard pyrenes.⁴⁹

Parts used: Bark, gum resin(called as Kunduru), leaves, fruits.

Ayurvedic properties: Rasa:

Kasaaya, tikta, madhura; **Guna:** laghu, ruksa; **Virya:** usna; **Vipaaka:**katu; **Dosakarma:** kapha pitta shaamaka

Actions & uses:

Bark: cooling, tonic, & useful in asthma, diarrhoea, dysentery, ulcers, gonorrhoea, haemorrhoids & skin diseases. Gum resin: antidysenteric, expectorant, diaphoretic, febrifuge, diuretic, ecboic, lithontriptic, antiseptic, stomachic, antiinflammatory, ophthalmic, emmenagogue & useful in fever, diaphoresis, convulsions, piles, urethrorrhoea, renal & vesical calculi, orchioopathy, cough, asthma, bronchitis, stomatitis, paittika conjunctivitis, seminal weakness, leucorrhoea, syphilitic diseases, skin diseases, ulcers, tumours, goiter, cystic breast, chronic laryngitis, jaundice, arthritis & psychic

disorders.⁵⁰

Formulations:

Vidangaadi kw, Sarjaadi kw, Karanjaadi gt, Surasaadigana kw, Balaa tl, Nyagrodhaadi kw, Trutyaadi yg.

Therapeutic uses:

- i. Wound - Dusting fruit powder
- ii. Diarrhoea - Barks of Shallaki + Priyaala + Tinisha + Shaalmali + Plaksa- pounded with milk +honey
- iii. Conjunctivitis- Col.: exudates of Palaasha +Shallaki +candy + honey

Chemical composition

Boswellia contains oils, terpenoids, sugars, and volatile oils. Up to 16 % of the resin is essential oil, the majority being alpha thujene and p-cymene. Four pentacyclic triterpene acids are also present, with beta-boswellic acid being the major constituent. Similar to turpentine oil, this oil is soluble in colophony & dammer, but more volatile in nature. Gum is mainly composed of arabinose with small amounts of xylose and galactose. Gum also contains oxidizing and diastatic enzymes. The highly brittle resin is soluble in various organic solvents. It softens between 65-72°C and melts between 73-78°C. Resin is mainly employed in preparation of varnishes.⁵¹

Thus, Indian olibanum contains β -boswellic acid in resin portion; Volatile oil contains P-cymene, a-limonene, terpinolene, a-thujone, a-phellandrene, a-terpiol, bornyl acetate, and methyl chacicol. A diterpene alcohol viz. serratol has been reported from gum resin. Further, Boswellia consists of 6 Major acids 50. The various boswellic acids, 3 - Acetyl - 11- keto β Boswellic Acid or AKBA, is considered the most active and powerful acid. AKBA helps preserve the structural integrity of joint cartilage, 51 promotes gastrointestinal health and maintains a healthy immune mediator 32 cascade at the cellular level. It is a pyrazaline derivative [C₃₈H₅₂N₃O₄, m p 145-47°] exhibited maximum anti-inflammatory activity.⁵²

PHARMACOLOGICAL STUDIES

Anti-inflammatory and Anti-arthritis activity:

In 2012, researchers found that boswelli works in part by altering the expression of the cytokine tumor necrosis factor alpha (TNF-a) another integral component in inflammation. and effect of a herbal based, non-steroidal anti-inflammatory product kundur, prepared from the gum resin exudates of Boswellia serrata active principle “boswellic acids” on glycosaminoglycan metabolism has been studied in male albino rats. The biosynthesis of sulphated glycosaminoglycan was evaluated by the uptake of sulphate, and the content of glycosaminoglycan was measured in

specimens of skin, liver, kidney and spleen. The degradation of glycosaminoglycan was found to be reduced markedly in all drug treated animals as compared to control (ketoprofen).⁵³

Antidepressant Activity:

The drug *Boswellia serrata* in a dose of 100mg /kg in swiss albino mice rat significantly reduced immobility period in FST (Forced Swim Test) compared to the control group. Hence *Boswellia serrata* has significant antidepressant activity in the experimental animal model.^{54,53}

Hepatoprotective Activity:

The aqueous bark extract 250mg /kg, aqueous leaves extract 500mg /kg and aqueous gum extract 250mg /kg of *Boswellia serrata* showed marked reduction in the elevated levels of ALT, AST, ALP, and bilirubin and increased membrane bound enzymes and total proteins in paracetamol induced liver injury.^{55,53}

Nephroprotective Activity:

A study revealed significant nephroprotective activity against Gentamicin induced nephrotoxicity in the experimental model.^{56,53}

Antimicrobial Activity:

A study conducted to evaluate the antimicrobial activity of *Curcuma longa* and *Boswellia serrata* revealed that methanolic extract of the two drugs has a potent antimicrobial activity.^{57,53}

BABBULA (*Acacia nilotica* Delile ssp. *indica* (Benth.) Brenan.)

Family: Mimosaceae.

Synonym: *A. arabica* var. *indica* Benth., *A. arabica* auct. non (Lam.) Willd., *A. nilotica* (L.) Delile var. *indica* (Benth.)

Ayurvedic syn: Kimkiraata, Aabhaa, Satpadamodini, Yugmakanta, Suksmapatra, Drdharuha, Sapitaka, Mahaaphala.

Trade name: Babul; Local name: Babur, Baburi kantaa

Description: A small tree, with deeply cracked, brown to black bark. Branches with long, straight, white spines, 0.6-5cm long. Leaves compound, alternate, bipinnate; pinnae paripinnate, 3-6 pairs, 1.2-5 cm long; leaflets opposite, 10-20 pairs, sessile, linear, 3-6.2 mm long, apex subobtusate, glabrous. Flower-heads yellow, 1.2 cm across, on short axillary, peduncles with 2 bracts a little above the middle. Pods grey-downy, 7.5-22 x 1.5-1.8 cm long, moniliform, indehiscent.

Parts used Bark, gum, leaves, pods & seeds.

Ayurvedic properties:

Rasa: kasaaya(bark & fruit), madhura, kasaaya(gum); **Guna:** guru, ruksa(b,f), snigdha(g); **Virya:** shita; **Vipaaka:** katu(b,f), madhura(g); **Dosakarma:** kapha pitta shaamaka(b,f), vaata pitta shaamaka(g)

Actions & uses:

typtic, emollient, vulnerary, anthelmintic, liver tonic, febrifuge, haemostatic, constipating, depurative, aphrodisiac, diuretic, expectorant, alexeteric, emetic, nutritive & used in hemorrhages, ulcers, ascites, colic, chronic dysentery, leprosy, leucoderma, skin diseases, burning sensation, cough, asthma, strangury, bronchitis, leucorrhoea, haemorrhoids, proctoptosis, seminal weakness, pharyngodynia, uterovesical disorders, oral ulcers, odontopathy, pneumonosis, urinogenital discharges, burns, intermittent fevers & general debility.⁵⁸

Formulations: Babbula ch, B. ast, Lavangaadi vt, Mrtasanjivani suraa, Maalatyadyaama gt.

Therapeutic uses:

1. Lacrymation - Leaf juice + honey
2. Soft chancre - Dusting leaf powder
3. Obesity - Massage with leaf paste, then with Haritaki powder followed by bath

Chemical composition

The bark and pods contain 12- 20 % of tannin. Several polyphenolic compounds have been reported from bark and the pods of the plants acacia nilotica. The gum resin of the plants contain galactose, aldobio uranic acid and arabinobioses. It also contain about 52 % of calcium and 20% of magnesium. The flowers contain flavonoids-kaempferol-3-glucoside, iso-quercitrin and leucocyanidin.⁵⁹

PHARMACOLOGICAL STUDIES

Anti-hypertensive and anti-spasmodic activities:

A decrease in arterial blood pressure is reported by use of methanolic extract of *A. nilotica* pods and provides evidence of anti hypertensive activities independent of muscarinic receptor stimulation. In the in vitro studies, *A. nilotica* has inhibitory effect on force and rate of spontaneous contractions in guinea-pig paired atria and rabbit jejunum. *A. nilotica* also inhibits K⁺ induced contractions in rabbit jejunum advocating the antispasmodic action of *A. nilotica* which is mediated through calcium channel blockade and this may also be responsible for the blood pressure lowering effect of *A. nilotica*, observed in the in vivo studies.⁶⁰

Antibacterial and antifungal activities:

The assays of the stem bark extracts confirms the antimicrobial activity against *Streptococcus viridans*, *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis* and *Shigella sonnei* using the agar diffusion method. *A. nilotica* could be a potential source of antimicrobial agents.^{61,60}

Antioxidant activity:

Water extract/fractions of *A. nilotica* (L.) in lipid peroxidation assay possess the peroxy radical scavenging capacity and results prove the anti-oxidant activity of plant. The bark powder of the plant extracts with different solvents found the scavenging activity using maceration extraction.^{62,60}

Antiplasmodial activities:

The ethyl acetate extract holds the highest activity on *Plasmodium falciparum*. Phytochemical analysis indicated that the most active phase contained terpenoids and tannins and was devoid of alkaloids and saponins (El-tahir et al., 1999). Crude methanolic root extracts of *A. nilotica* reveals significant activity against chloroquine sensitive strain of *Plasmodium berghei* in mice.^{63,60}

PAARIJAATA (*Nyctanthes arbor-tristis* L).

Family: Oleaceae

Ayurvedic syn : Shephaali, Naalakumkumaka, Raagapuspi, Kharapatraka, Harashrngara, Praajakta.

Trade name: Coral jasmine

Local name: Ganga Siuli, Shingaraara

Description: A small tree; branchlets 4-angular, often drooping. Leaves simple, opposite, ovate, 5-14 x 3-10 cm, entire or coarsely toothed, apex acute or acuminate, very scabrous; petiole 8-10 mm long. Flowers in terminal trichotomous cymes, fragrant, 1.8-2.5 cm across. Corolla salver-shaped, tube cylindric, orange. Capsules elliptic or obovoid, 1.8-2.5 x 1.2-1.7 cm, compressed, 5 mm thick, glabrous. Seeds orbicular.⁶⁴

Parts used: Leaves, flowers, seeds.

Ayurvedic properties: **Rasa:** tikta; **Guna:** laghu, ruksa; **Virya:** usna; **Vipaaka:** katu;

Dosakarma: kapha vaata shaamaka, pittasamshodhaka

Actions & uses:

Antibacterial, anthelmintic, antimalarial, antipyretic, anodyne, anti-inflammatory, digestive, carminative, laxative, cholagogue, depurative, sudorific, expectorant, diuretic, trichogenous, tonic & useful in rheumatic & osteo arthritis, sciatica, pruritus, ringworm, baldness, greyness of hairs, scurvy, dysuria, worms, splenomegaly, ophthalmopathy, hepatopathy, constipation, haemorrhoids,

cough, asthma, strangury, fever, intermittent fevers & malarial fever etc.⁶⁵

Formulations: Yakrt-plihodaraari louha.

Therapeutic uses:

- i. Sciatica - Leaf decoction 20-50 ml,
- ii. Arthritis - Root decoction 50 ml
- iii. Udakameha - Leaf decoction - 50 ml
- iv. Enlarged uvula, tonsillitis - Chewing its root
- v. Fever - Leaf juice 10 ml + honey 3ml

Chemical composition

The *N. arbor-tristis* Linn. leaves showed the presence of D-mannitol β -ainyrin, β -sitosterol, hentriacontane, benzoic acid along with free glucose and fructose . The ethanolic extract of the leaves yielded two flavonol glycosides, astragelin (Kaempherol-3-glucoside) and nicotiflorin (Kaempherol-3- rhamnoglucoside, and an unidentified alkaloid. Preliminary chemical study showed the traces of an alkaloid and the absence of saponins and flavonoids in the leaves , while the whole plant excluding the roots was devoid of tannins.The oil from the *N. arbortristis* flowers contained a pinene, p-cymene, L hexanal, methyl-heptanone, phenylacetaldehyde, L-delanol and anisaldehyde . The acetone extract of the corolla tubes yielded the β --monogentiobioside ester of acrocetin as a major component and the β - digentiobiosides ester of (x-acrocetin as minor components.⁶⁶

PHARMACOLOGICAL STUDIES

Antioxidant activity:

Recent studies have shown that the leaves and stem of *Nyctanthes arbor-tristis* are a potential source of natural antioxidants.⁶⁷ Phytochemical screening of the ethanolic extract of the leaves and stems of *Nyctanthes arbor-tristis* revealed the presence of flavonoids, tannins, saponins, glycosides, alkaloids, steroids, and phenolic compounds. Phenolic compounds have been recognized as antioxidant agents, which act as free radical terminators^{68,69} and have been known to show medicinal activity and exhibit physiological functions.⁷⁰

Anti-Inflammatory, anti-pyretic and antinociceptive activities:

Anti-inflammatory activity in leaves of Harsingar supports its use in various inflammatory conditions by the followers of the Ayurvedic system of medicine.⁷¹ The water-soluble fraction of the ethanol extract elicited significant anti-inflammatory activity against acute inflammatory oedema produced in rats by different phlogistic agents, namely carrageenin, formalin, histamine,

5-hydroxytryptamine and hyaluronidase.^{72,73} The extract significantly reduced acute inflammatory swelling in the knee joint of rats induced by turpentine oil.⁷²

Immunostimulent activity:

Plant extracts have been widely investigated for their possible immunomodulatory properties.⁷⁴ Aqueous leaf extract of *Nyctanthes arbor-tristis* has been found as a potent immunomodulator as evidenced by both humoral and cell mediated responses.^{75,76}

Anti-plasmodial activity:

Rengyolone, a cyclohexylethanoid isolated from the ethanolic extract of *Nyctanthes arbor-tristis* flowers and its acetate showed in vitro antiplasmodial activity against *Plasmodium falciparum* (K1, multidrug resistant strain). The extract also showed in vitro efficacy against *Leishmania donovani* and *Entamoeba histolytica*.⁷⁷

Sedative Activity:

Sedative potential of a hot infusion of the flowers was examined in rats.⁷⁸ In this test, male rats exhibited a dose-dependent conscious sedative activity while female rats remained unaffected. At these doses, muscle strength and coordination were not affected nor was blood glucose levels affected even at the highest dose. However, glucose absorption from the small intestine was significantly reduced. The sedation was attributed, in part, to the antioxidant and membrane stabilizing activity of the extract.⁷⁸

Anti-allergy Activity:

The pretreatment of guinea pigs exposed to histamine aerosol with a water soluble portion of the alcoholic extract of *N. arbor-tristis* leaves offered significant protection against the development of asphyxia.⁷⁹ *Arbortristoside A* and *arbortristoside C* present in *N. arbor-tristis* was reported to be anti-allergic.⁸⁰

NIRGUNDI (*Vitex negundo* L.)

Family: Verbenaceae

Ayurvedic syn. : Sungandhika, Sindhuvaara, Shephaali, Indraanikaa.

Trade name : Five-leaved chest tree ;

Local name: Beguniaa

Description: A large shrub; bark thin, grey, finely hoary-tomentose. Leaves opposite, compound, digitately 3-5-foliolate; petiole 2.5-4 cm long; leaflets lanceolate or narrowly lanceolate, 5-15 cm long, apex acute to acuminate, glabrescent or puberulous above, finely white-tomentose beneath, base obtuse, two lateral leaflets in 5-foliolate leaves sessile or subsessile; others petioluled, 1.2-2.5 cm long. Flowers bluish purple, in large terminal panicles, 5-20cm long. Calyx 2.5 mm long,

hoary-tomentose. Corolla 6.2-7.5 mm across. Stamens inserted near the base of the corolla. Drupe globose, 3 mm diam.⁸¹

Parts used: Root, bark, leaves, flowers, seeds.

Ayurvedic properties: **Rasa:** katu, tikta; **Guna:** laghu, **ruksha;** Virya: usna; **Vipaaka :** katu;

Dosakarma:kapha vaata shaamaka

Actions & uses:

Thermogenic, anthelmintic, expectorant, antiinflammatory, antibacterial, antifertility, antispasmodic, analgesic, hepatoprotective, anticonvulsant, antimicrobial, mosquito repellent, rejuvenative, vulnerary, tonic & useful in hepato-splenomegaly, cephalalgia, otalgia, arthritis, uropathy, cough, bronchitis, malarial fever, haemorrhoids, dysmenorrhoea, ophthalmopathy, otorrhoea, diarrhoea, cholera, cardiac disorders & hemorrhages etc.

Formulations:

Nirgundi tl, N.gt, N.kalpa, N.asv, Trivikrama rs, M.vaatavidhwamsana rs, Anutl, Sri jayamangala rs, Pusparaaja prasaarini tl, Laangali tl, Trinetra rs, Guduchi tl, Agninaamaa rs, Swachchhandabhairava rs, Manthaaanabhairava rs, Louha rsyn, Karaanjaadi lp, Raamabaana rs, Raasnaadi ksy, M.sugandhi tl, Laaksaadi tl.⁸²

Therapeutic uses:

- i. Cough - Ghee cooked with leaf juice
- ii. Guinea worm - Taking ghee for first three days, then taking Nirgundi juice next three days
- iii. Cervical adenitis - Snuff : root juice

Chemical composition

The freshly collected leaves, on steam-distillation, yielded a pale greenish yellow oil (0.04-0.07%); the maximum yield of the oil is during Oct.-Nov., Just before flowering. The oil is slightly soluble in water, soluble in 10 volumes of alcohol and all proportions in ether and chloroform. Physio-chemical constants of the oil were : sp. gr. 23°, 0.9215; np 20°, 1.475; acid val., 2.7; ester val., 24.9; acetyl val., 143.8. The constituents of the oil were: aldehydes and ketone, 22.5; phenolic derivatives 15; and cineol, 10% .⁸³

The leaves contain 2 alkaloids nishindine (C₁₅H₂₃ON; m.p.266°) and hydrocotylene (C₂H₃ON), glucononitol (C₂H₂O₂; m.p. 196-98°), p-pydroxybenzoic acid, an amorphous glucoside (C₂₀H₂₆O₁₁; m.p. 93-95), tannic acid, aucubin, arguside (C₂₂H₂O₁, m.p. 146°) casticin, orientin, iso-orientin, a-D-glucoside of a tetrahydroxymonomethyl flavone (C₂₂H₂₄O₁₂; m.p. 245°), 5-hydroxy-3,6,7,3'4' pentamethoxy flavone (C₂₀H₂₀O₈; m.p. 163°). Vit. C (150 mg/100gm, fresh wt. basis).⁸⁴

NEW CHEMICAL COMPOUNDS:

n-Tritriacontane, n-hentriacontane, n-pentatriacontane, n-nonaacosane, β sitosterol, p-hydroxybenzoic acid and 5-oxyisophtlic acid from seeds (J. Indian Chem. Soc., 1973); vanillic acid and p-hydroxybenzoic acids and luteolin isolated from bark; two new leuconthocyanidins isolated from stem bark and their structures determined as 6, 8-di-O-methyl- leucodelphinidin and 3', 4'-di-o-methyleucocyanidin-7-o rhmnoglucoside.⁸⁵

PHARMACOLOGICAL STUDIES**Cardiotonic Activity:**

Cardiotonic activity of the aqueous extract of *Vitex negundo* leaves was proven by significant increase in the height of contraction even at the lower doses. The extract showed wide therapeutic index as it produced therapeutic effect in the dose range of 0.25mg to 2mg without producing cardiac arrest, while digoxin showed cardiac arrest at dose 0.2mg. In view of the above findings, extract of the *Vitex negundo* can be safe and potent alternative to digoxin in management of congestive heart failure.⁸⁶

Anti cancer Activity:

In studies to assess the histomorphological effects of *Vitex negundo* extracts in rats, it was observed that even by toxic doses, the stomach tissues remained unaffected.⁸⁷ The study observed that there were changes in lung, liver and heart tissues, which were dose dependent. COLO-320 tumour cells were used to affirm the cytotoxic effects of leaf extracts of *Vitex negundo*.⁸⁸ The chloroform extract of the leaves of *Vitex negundo* was found to be toxic to the human cancer cell line panel⁸⁹ but was non cytotoxic on genitourinary and mammary cells of mice.⁹⁰

Anti-inflammatory Activity:

A study conducted to evaluate the anti- inflammatory effect of leaf oil of *Vitex Negundo* showed that oil of *Vitex negundo* prevented carrageen induced inflammation via COX-2 inhibition, this indicates that *Vitex negundo* leaf oil possesses potent anti-inflammatory property and acts via the inhibition of COX-2 receptor without interfering COX- 1 inhibition .⁹¹

Anti-oxidant Activity:

Plant of the *Vitex negundo* is a source of many natural antioxidants.⁹² A phytochemical which is very strong antioxidant, named as Vitedoin A,⁹³ is present in the plant and is reported to have more antioxidant activity than L-cystine and Vit E. A study conducted to validate the antioxidant potential of leaf extract of *Vitex negundo* showed that it reduced the levels of catalase, superoxide dismutase and glutathione peroxidase in Freund's adjuvant induced arthritic-rat.⁹⁴

CONCLUSION

For the betterment, while treating cancer with the drugs, it is more effective when treated with the herbal medicine. Thus, the above review replenishes the usage of the medicinal herbs for especially the treatment of bone cancer, and it has the potential access to cancer treatment. Traditional system of medicine continues to be widely practised for various reasons. Fast population growth, inadequate supply of branded medicines, alarmingly prohibitive cost of treatment, adverse side-effects of several allopathic drugs and ever increasing resistance to current drugs for infectious diseases have led to growing emphasis on the use of plant-materials as a source of medicines for a wide variety of human ailments.

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