ANTICANCER ACTIVITY OF UPAVISHA SNUHI: A COMPREHENSIVE UPDATE
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ABSTRACT
Cancer is one of the dreaded diseases of 20 th century responsible for causing most fatalities and spreading further with increasing incidence in 21 st century. Ayurveda an ancient science provides many useful remedies for these types of advanced diseases. Upavishas narrated in Agadtrans contribute for many fruitful therapeutic formulations. Snuhi (Euphorbia neriifolia Linn.) is one among these upavishas is knocking out as an effective Anticancer agent. Traditionally it is mainly used in Kushtha, Udara, Shotha, Pandu, Gulma, Dushivisha, Visha chikitsa. Various In Vitro & In Vivo studies has been conducted to evaluate the anticancer activity of Upavisha Snuhi (Euphorbia neriifolia Linn.) in the form of its extracts. In this study a special emphasis is on gathering details of Upavisha Snuhi from available classical text and assemble data related to the In Vivo and In Vitro Anticancer activity of Upavisha Snuhi. Keywords: Agadtrans, Upavisha, Snuhi (Euphorbia neriifolia Linn.), Anticancer activity, In Vivo, In Vitro.

INTRODUCTION
Therapeutic use of medicinal plant is as old as humankind. There are about 45,000 medicinal plant species in India. Samhitas, Vedas and holy books has mentioned effective therapeutic use of various medicinal plants. Snuhi is an important medicinal plant included in Upavisha by Rasatarangini.1 It is botanically identified as Euphorbia neriifolia Linn. It grows widely around the dry, rocky, & hilly areas of north, central and south India. Snuhi has been attributed with a number of synonyms depending on its morphology and pharmacological actions. Almost all the parts of Snuhi are of medicinal use. About 462 formulations, having Snuhi as an ingredient are used to combat almost 62 varied diseases.2 Acharya Charaka has given its twenty Virechana formulations in Sudha kalpa Adhyaya of Kalpathrama.3 Traditionally it is mainly used in Kushtha, Udara, Shotha, Pandu, Gulma, Dushivisha, Visha chikitsa. Snuhi (Euphorbia neriifolia Linn.) extracts and isolates have been reported for its analgesic, anesthetic, anti-anxiety, anti-convulsant, anti-psychotic, anti-arthritis, anti-diabetic, anti-inflammatory, anti-diuretic, anti-microbial, antioxidant, anti-ulcer, diuretic, hemolytic, immunomodulatory, pesticidal effect, radioprotective, wound healing property, cytotoxic and anticarcinogenic properties using various In Vitro and In Vivo methods.4

Cancer in the broader sense refers to more than 277 different types of cancer disease indicating several gene mutations which lead to abnormal cell proliferation.5 Cancer is the second leading cause of death globally.6 Chemotherapy and surgery have always been the standard methods of treatment but has not been fully effective. Chemotherapeutic agents are responsible for causing severe adverse effects.7 As medicinal herbs are known for less side effect; they are moving from border line to mainstream to treat cancer. Nowadays researches are mainly focused to develop new methods for cancer treatment predominantly using different plant species. Likewise, Snuhi (Euphorbia neriifolia Linn.) has been studied for various ethnomedical properties including anticancer. But no effort is made to formulate a single-handed document of In Vitro and In Vivo studies done with anticancer activity of Snuhi. Hence present review is mainly concerned with the documentation of In Vivo and In Vitro anticancer activity of Upavisha Snuhi.

LITERATURE REVIEW
Upavisha Snuhi 8-13 Snuhi (Euphorbia neriifolia Linn.) is commonly known as Indian Spurge tree, it is characterized by presence of latex which exudes when broken and is regarded as toxic part of the plant. It is found throughout the Deccan Peninsula of India.

Botanical Name - Euphorbia neriifolia Linn.
Family - Euphorbiaceae
Description – It is a Xerophytic, erect, prickly, succulent, large, much branched shrub, which grows up to 2-6 meters.
Classification -
   i. Ayurveda – Sthavara Upavisha
   ii. Modern Toxicology – Organic irritant poison
Common Names
   Sanskrit - Vaji, Snuhi, Sudha, Samantadugdha, Snuk, Sehunda
   Hindi - Sehunda, Thobhar
   Marathi - Nivdunga
   English - Common Milk Hedge
Gana -
   i. Charaka - Virechana, Shatashodhanavruksha
   ii. Sushruta - Adhobhagahara, Shyamadi
Rasa Panchak -
   a. Gunas - Laghu, Tikshna, Guru
b. Rasa - Katu
c. Veerya - Ushna
d. Vipaka - Katu
e. Doshaghnata - Kaphavatagyna
f. Karma - Vishaghnaha

Bahyantar - Raktashodhak, Shothahara, Twakdosahara,
Tikshnavirechak, Kaphanissarak

Rogaghnata - Gulma, Udararoga, Yakrutplhavruddhi, Shotha,
Kushtha, Vatarakta, Upadanhsa, Kasa, Shwas, Pratishyay,
Dushivisha, Visha

Prayojyanga - Moola, Kanda, Patra, Kshira

**Actions and Uses** – Plant is laxative, carminative, alexipharmic,
appetizing, useful in abdominal troubles, bronchitis, tumors,
ulcers.
Juice is useful in – Glandular swellings

Leaves are useful in – Tumors, inflammation, abdominal
swelling.

**Types** - 1) Tridhara (*Euphorbia antiquorum* Linn.)
2) Saptadhara (*Euphorbia royleana* Boiss.)
3) Chimiya (*Euphorbia tirucalli* Linn.)

**According to Charak Samhita** – Alpakantaka, Bahukantaka

**Fatal Dose** - Uncertain

**Fatal Period** - Uncertain

**Formulations** - Citrakadi taila, Abhaya lavana, Avitttoladi
bhasma, Vajrakarsa.

| Powdered plant, stem and leaves | Several triterpenoids like Glut-5-en-3S-ol, Glut-5(10)-en-1-one, taraxerol and $\alpha$-amyrin |
|--------------------------------|-------------------------------------------------------------------------------------------------
| Latex                         | Triterpene – nerifolione, euphol, nerifolien, nerifolene, euphorphon, resin, gum, caoutchouc, malate of calcium, euphol, monohydroxy triterpene, nerifoliol, taraxerol, beta- amyrion, glut-5(10)-en-1-one, nerifolione, cycloartenol |
| Leaf                          | Friedelan-3, D-B-friedol-5-(10)-en-1-one, taraxerol |
| Bark                          | Euphol, Euphorbol, hexacosanoate, n- hexacosanol, 12- deoxy 4-$\beta$- hydroxyphorbol-13-dodecanoate-20- acetate, pelargonin – 3, 5- diglucoide, 24-methylenecycloartenol, tulipanin-3, 5- diglucoide |
| Stem                          | Euphol, friedelan-3, D B friedol-5(10)-en-1-one, glut-5(10)-en-1-one, taraxerol |
| Root                          | Alnus-5(10)-ene-1-one, anthocyanins, euphol, pururate dikinsae, terpenes, 24-methylenecycloartenol, tulipanin-3, 5- diglucoide |

**Anticancer Activity of Upavisha Snuhi (*Euphorbia neriifolia* Linn.)** – Various research articles on Snuhi (*Euphorbia neriifolia* Linn.) were studied and data related anticancer activity of Snuhi (*Euphorbia neriifolia* Linn.) was extracted. Both In Vivo and In Vitro models are included. Data regarding plant part used, phytoconstituent studied and extractive solvent used is also collected.

| Sr. No. | Plant Part Used | Extractive Solvent | Phytoconstituent Studied | Study Design | Assessment | Results |
|---------|-----------------|---------------------|--------------------------|-------------|------------|---------|
| 1.      | Dried Powder of Leaf*16 | Ethanol | Sapogenin | Murine F,B16 Melanoma cell line | Cytotoxicity Assay | cell viability - At 10 µg/ml: 76.6% At 500 µg/ml: 13.6% |
| 2.      | Whole Plant*17 | Methanol | - | B16F10 Melanoma | SRB Assay | IC50 by – SRB Assay – 198.26 MT Assay – 212.78 |
| 3.      | Leaves and Bark - Dried Powder*20 | Methanol | - | HepG2 cell line | MTT Assay | Cytotoxicity for HepG2 cell line: 89.25% |
| 4.      | Whole Plant*18 | - | MacKay-03 (3,12-o-diacyl-7-o-angeloyl-8-methoxyglycol) | K562 HEL cells | MTT Assay | Inhibited growth of Human leukemic cells |
| 5.      | Dried Powder of Leaves*22 | MeOH | Nenifiol 1 Nenifiol 2 Nenifiol 3 | HCT116 cell line MCF7 cell line MDA-MB-231 cell line | MTT Assay | Compound 1-3 showed cytotoxicity to MCF 7 cell line |
| 6.      | Aarial parts*23 | Ethyl Acetate | Four Triterpenoids a) 3 beta -friedelinol b) 3 alpha- taraxerol c) 3 beta - taraxerol d) 3 alpha-friedelinol. Four lingols – a) 3,7,12 o-triacetyl-8-o-tiglioylingol b) 3,7,12 o-triacetyl-8-o-benzyolingol. c) 3,12-o-diacetyl-7-o-angeloyl8-methoxyglycol. d) 3,12-o-diacetyl-8-methoxy-7-o-benzyolingol. | K562 cell line Panc-1 cell line 8T1 cell line BE3 cell line | MTT Assay | 3 beta -friedelinol 3 beta -taraxerol and 3 alpha-friedelinol cytotoxic on - Panc-1 cell line 8T1 cell line BE3 cell line Inhibition 60% at conc. 10 µm. and 3 beta -friedelinol, 3,7,12 o-triacetyl-8-o-tiglioylingol and 3,12 o-diacetyl-7-o-angeloyl8-methoxyglycol, cytotoxic on - K562 cell line with 45%, 42%, & 53% inhibition at conc. 10 µm |
| 7.      | Latex*24 | Acetone | Terpenoids | EAC cell line DLA cell line | Tryphane blue exclusion method | DLA cell line – IC50 Conc. 51 µg/ml EAC cell line – IC50 Conc. 82 µg/ml |

*16 IC50, Conc. 51 µg/ml EAC cell line – IC50 Conc. 82 µg/ml
In Vivo Anticancer Activity of Snuhi (Euphorbia neriifolia Linn.) -

1. N-nitrosodiethylamine (DENA) Induced Renal Carcinogenesis

   Plant Part Used – Dried Leaves
   Extractive Solvent – Pet-ether, benzene, chloroform, ethyl acetate & ethanol.
   Phytoconstituents Studied – Isolated Flavonoids – ENF [2-(3,4-dihydroxy-5-methoxy-phenyl)-3,5-dihydroxy-6,7dimethoxy chromen-4-one], Hydro Ethanolic Extract of Euphorbia Neriifolia (EN).

   Experimental Animals – Healthy male Swiss albino mice
   Groups – Twelve groups of 6 mice each.
   Parameters Studied – Levels of renal markers - urea and creatinine, Xenobiotic metabolic enzymes - Cyt P450 and Cyt b5, Lipid peroxidation - LPO.
   Biochemical Parameters - AST, ALT, ALP, total protein (TP), total cholesterol (TC).

   The data obtained in this study reveals anticancer activity of Snuhi (Euphorbia neriifolia Linn.).

2. N-nitrosodiethylamine induced hepatocarcinoma in mice –

   Plant Part Used – Leaves
   Phytoconstituents Studied – ethanolic extract, isolated flavonoid.
   Parameters Studied – Levels of liver markers - AST, ALT & ALP, Xenobiotic metabolic enzymes - Cyt P450 and Cyt b5, Lipid peroxidation (LPO), Antioxidants - SOD, CAT, GST and GSH, Biochemical parameters – TP and TC.

   Experimental Procedure – Experimental mice were pretreated with 150 and 400 mg/kg body weight of EN, 0.5% and 1% mg/kg body weight of butylated hydroxylanisole (BHA) as a standard antioxidant and 50 mg/kg body weight of ENF for 21 days prior to the administration of a single dose of 50 mg/kg body weight of DENA. DENA administration significantly (p<0.001) decreased the body weight and increased the tissue weight. Activity of liver markers, antioxidants and TP content were significantly decreased (p<0.001), while Cyt P450, Cyt b5, LPO and TC levels were significantly (p<0.001) increased after DENA administration as compared with the normal control group (p<0.001). Pretreatment with EN and ENF counteracted DENA-induced oxidative stress (LPO) and exerted its protective effects by restoring the levels of antioxidants (SOD, CAT, GST and GSH), biochemical parameters (AST, ALT, ALP, TP and TC), renal markers (urea and creatinine) and xenobiotic enzymes (Cyt P450 and Cyt b5) in renal tissue.

   DISCUSSION

   The data obtained in this study reveals anticancer activity of Snuhi (Euphorbia neriifolia Linn.). Most studies reveal use of dried leaf as a plant part for extraction of phytoconstituents and methanol is a common extractive solvent used. Phytoconstituents studied like isolated flavonoids, sapogenin, triterpenoids, lignols are proven to be anticancerous on variety of cancer cell lines. Leukemia and melanoma cell lines are frequently used for anticancer study of Euphorbia neriifolia Linn. MTT assay was the most commonly found method of detection of cell cytotoxicity.

   In-Vitro testing of total sapogenin against the murine F1 B16 Melanoma cell line showed 76.6 % cell viability at 10 µg/ml compared to 13.6 % at 500 µg/ml of total sapogenin. The assay data show that the IC50 (over a period of 72 h) concentration of total sapogenin that inhibited growth of mouse melanoma cells was tested for its anticancer properties. The percent viability was determined by SRB assay and MTT assay. IC50 and R2 value by SRB assay were 198.26 and 0.710 respectively. Whereas IC50 and R2 value by MTT assay was 212.78 and 0.762 respectively. Results have revealed the potential anticancer property of Euphorbia neriifolia Linn. (Table 2, Sr. No. 1).

   Methanolic extract of Euphorbia neriifolia was tested for its inhibitory action on B16F10 melanoma cell line under concentration range 10 µl to 100 µl. The percent viability was tested using Tryphan blue dye exclusion method and cytotoxicity by SRB assay and MTT assay. IC50 and R2 value by SRB assay were 198.26 and 0.710 respectively. Whereas IC50 and R2 value by MTT assay was 212.78 and 0.762 respectively. Results have
shown significant activity that means it can be used as anticancer agent. (Table 2, Sr. No 2)

In Vitro Antitumor study of methanolic extract of *Euphorbia neriifolia* Linn. extract was counted as active possessing (scoring >50%) in HepG2 cytotoxicity. (Table 2, Sr. No.3)

MacKay-03 compound from Euphorbia neriifolia is able to inhibit growth, induce megakaryocytic differentiation, and to a lesser extent cause apoptosis in K562 and HEL human leukemia cells. (Table 2, Sr. No. 4)

The isolated compounds Nerifolin 1, 2, and 3, were evaluated for their cytotoxicity against three cancer cell lines HCT-116 (colon) and MCF-7 and MDA-MB-231(Breast) by MTT assay. Doxorubicin was used as a positive control with IC50 values ranging from 1.59 to 2.13 μM. All three compounds (Nerifolin1,2,3) displayed more cytotoxicity on breast cancer MCF-7 cells than other two cell lines. The IC50 values of Nerifolin 1,2 and 3 on MCF-7 cells were 1.81, 7.12 and 55.50 μM, respectively. Compound showed more cytotoxicity on MCF 7 cell line which suggests that present compound is active on estrogen receptor positive cancer cell line but not on triple negative MDA- MB - 231. (Table 2, Sr. No. 5)

The triterpenoids, 3 beta -friedelinol, 3 beta - taraxerol and 3 alpha-friedelinol cytotoxic on Panc-1 cell line,81T and BE3 cell line having inhibition 60% at conc. 10 μM. Whereas 3 beta - friedelinol, 3,7,12-o-triacyt-8-o-ugloylingol and 3,12-o-diacyt-7-o-angeloyl-8-methoxyngol, cytotoxic on - K562 cell line with 45%, 42%, & 53% inhibition at conc. 10 μM. The triterpenoids were found cytotoxic on Panc-1 cell line,81T and BE3 cell line. Whereas lignols were found cytotoxic on only K562 cell line. (Table 2, Sr. No. 6)

The acetone extract was found to contain terpenoids as the major component which was screened for its cytotoxic activity against the DLA and EAC cancer cells. The IC50 value of the Acetone extract of the latex of the EN on DLA cells was 51μg/ml. On EAC cells the Acetone extract of latex of EN had an IC50 value of 82μg/ml. Study concluded that acetone extract of Euphorbia neriifolia has significant anticancer activity. (Table 2, Sr. No. 7)

Whereas animal models reveal the anticancer activity of Snuhi (*Euphorbia neriifolia* Linn.) against DENA-induced renal carcinogenicity using hydro-ethanolic extract *E. neriifolia* and ENF.

Hepatocarcinoma animal study showed significant anti- carcinogenic potential of the hydro-ethanolic extract of *E. neriifolia* and ENF against DENA induced hepatic carcinogenicity. Study also reveals that Snuhi (*Euphorbia neriifolia* Linn.) releases the oxidative stress and exerts its preventative effect which restores level of liver marker, antioxidants, biochemical parameters, and xenobiotics in liver tissue.

CONCLUSION

Present review accomplishes anticancer activity of Upavisha Snuhi (*Euphorbia neriifolia* Linn.). However, the studies conducted include only extracted phytoconstituents as an active anticancer agent. There are number of formulations which constitutes Snuhi (*Euphorbia neriifolia* Linn.) as an ingredient containing similar phytoconstituents. Hence the need is to conduct further studies on formulations of Upavisha Snuhi (*Euphorbia neriifolia* Linn.) as an anticancer agent. More thorough experimental studies and clinical data can suffice the validation of Snuhi as an anticancer agent.

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