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A REVIEW ON ANTI-CANCER POTENTIAL OF PHYTOCHEMICALS ISOLATED FROM *SIMAROUBA GLAUCA*

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Abstract:
Cancer is a dreadful disease affecting humans of all age groups. The conventional method of treatment like chemotherapy, radiation therapy, surgery or hormone therapy use synthetic drugs which are both toxic with severe side effects and expensive. Focus is now on phytochemicals derived from plants which are much less toxic and cost effective.
Simarouba glauca also known as "Paradise Tree" or "Laxmitaru" is an evergreen tree belonging to the family Simaroubaceae. The extracts isolated from S.glauca possess many pharmacological and medicinal properties and are being used to cure a number of ailments the world over since time immemorial. The extracts are used for treating acute dysentery, fever, malaria, colitis as a vermifuge, antimicrobial, heamostatic skin moisturizer and emmenagogue. The tree is a rich source of quassinoids which include ailanthinone, canthin, dehydroglaucarubinone, glaucarubine, glaucarubolone, glaucarubinone, holacanthone, melianone, simaroubidin, simarolide, simarubin, simarubolide. The anti-cancer activity of these quassinoids on various human cancer cell lines is well established through research. This article is a review of the anti-cancer activity of S.glauca collected by scrutinizing a number of papers dedicated to the said topic.
***Keywords**: Antimicrobial, Anti-Cancer , Cell lines , Glaucarubine, Quassinoids,*

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INTRODUCTION:

Simarouba glauca (S.*glauca, abbreviated as SG*), commonly known as 'Laxmitaru' or 'Paradise tree' belongs to the family Simaroubaceae **[Figure 1]**. *Simarouba glauca* is a medium sized evergreen tree which grows to a height around 20 m. It bears bright green leaves and produces small white flowers. The fruits are purple or yellowish green. It is native to rain forest of Amazon. It is indigenous to Southern Florida, the West Indies and Brazil. It is native to the Bahamas, Costa Rica, Cuba, EI-Salvador, Guatemala, Haiti, Honduras, Jamaica, Mexico, Puerto Rico and United States of America but exotic to India, Myanmar, The Phillippines and Srilanka. It grows under tropical conditions in Central America spreading from Mexico to Panama, Southern Florida as well as Caribbean Islands. *S. glauca* was introduced in African countries like Burundi and Kenya **[1].**

Fig: 1 *Simarouba glauca* tree

In India it was first introduced by National Bureau of Plant Genetic Resources in the research station at Amravati in Maharashtra in 1966 and to the university of Agricultural Sciences, Bangalore in 1986 by the scientists' Dr Syamasundar Joshi and Dr Shantha Joshi. It is now cultivated in Orrisa, Maharashtra, Karnataka, Gujarat and Tamil Nadu. *S. glauca* tree has an ability to grow well even in marginal wastelands or dry lands with degraded soil. However, systematic research and developmental activities of *S. glauca* began only from the year 1992 **[2]**.

Pharmacological applications of *Simarauba glauca*:

Simarauba glauca is a versatile evergreen tree. Every part of the tree, be it the wood, leaves, twigs, bark fruit or seeds, exhibit some medicinal or pharmacological property **[Figure 2]**. The bark extract of SG is traditionally used as an effective remedy for acute dysentery; thus, it is rightly called the "dysentery bark". The bark is also used to treat malaria, colitis and fever. The leaf, fruit, pulp and seed of *S. glauca* are known to possess medicinal properties such as analgesic, antimicrobial, antiviral, astringent, emmenagogue, (medicine to regulate menstrual flow) indigestion and vermifuge **[3].** The leaves are boiled in water and used to wash wounds and sores. The bark and leaf extract are used as haemostatic (stop bleeding). *Simarouba* leaf extract is used for reducing patchy skin pigmentation. The water extract of *S.glauca* helps in skin hydration and is used as a moisturizer. The health promoting oil prepared using SG extract contains oleic acid and devoid of bad cholesterol **[4]**. The crushed seeds of the tree are used as anti- dote for snake bites. A number of phytochemicals isolated from *S.glauca* have shown potential cancer inhibiting properties. In the present review paper, the focus is mainly on the anti-cancer properties of these bio- molecules.

Fig : 2 Flowers, Seeds ,Leaves and Fruits of *Simarauba glauca*

Importance of the plant in Cancer treatment:

Cancer is a dreadful life-threatening disease having a high mortality rate. It is a condition where cells grow abnormally with a tendency to proliferate in an uncontrolled manner and if left undetected – metastasize.There are more than a hundred different and distinctive types of cancers. Any tissue of the body can become cancerous and can appear in a variety of forms in each body area. It can affect anybody irrespective of their age group. The present-day treatment involves chemotherapy, Radiation therapy, immunotherapy, targeted therapy or hormone therapy. All these require a patient to be exposed to high levels of toxic chemicals which have serious side effects. So, the focus is now on pharmacological research on natural products aimed at exploring plants to isolate active biomolecules and develop new plant based alternative medicines which are effective and have minimal side effects due to their reduced toxicity. A variety of medicinal plants are grown in India. These are used in the traditional Indian system of medicine (Ayurveda) as a cure for all ailments. Plants are rich in a variety of secondary metabolites such as tannins, terpenoids, alkaloids, flavonoids, phenols, steroids, glycosides', and volatile oils **[5]**. Medicines for a specific ailment is prepared by identifying and isolating the required bio-molecule from these secondary metabolites and using them in the pharmacological preparations. Extensive research is being carried out world over to use these phytochemicals to produce anti- cancer drugs. These drugs can be administered in parallel to the conventional modes of treatments. Research conducted on *Simarouba glauca* showed that the plant possessed active phytochemicals to treat various cancers. For this reason, it is called "TREE OF SOLACE OF CANCER" **[6]**. The main group of chemicals in *Simarouba glauca* is quassinoids, which belong to the triterpene family. This includes: Ailanthinone, Canthin, Dehydroglaucarubinone, Glaucarubine, Glaucarubolone, Glaucarubinone, Holacanthone, Melianone, Simaroubidin, Simarolide, Simarubin, Simarubolide, Sitosterol, Tirucalla etc **[4]**.

These quassinoids are shown to exhibit anti-proliferative and anti-inflammatory effects on tumor cells **[7]**. More over these natural quassinoids have reduced toxicity but are more aggressive in their mode of action than synthetic molecules. Quassinoids and triterpenoids helps to induce cell differentiation, downregulate c-Myc and promote apoptosis in cancer cells through a wide array of mechanisms **[8]**. Several quassinoid from *S. glauca* seed have exhibited cytotoxic activity *in vitro* against KB cells (human oral epidermoid carcinoma), including Glaucarubin, Glaucarubinone, Glaucarubol And Glaucarubolone **[9,10]**. The most potent and well researched compound isolated from seeds of SG is Glaucarubin. It shows distinct anti-cancer property **[11]**. Glaucarubinone is another key anti-cancer agent isolated from SG. Studies have revealed that the quassinoid Glaucarubinone shows cytotoxic reaction against human oral epidermoid carcinoma cells (KB cells), human prostate tumor cells, human lung cancer cells and human promyelocytic leukemia cells **[12]**. One more study demonstrated that Glaucarubinone present in *S. glauca* is active against solid tumors (human and mouse cell lines), multi-drug-resistant mammary tumors in mice, and antileukemic activity against leukemia in mice **[13]**.

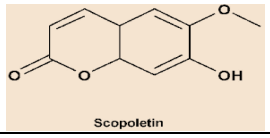
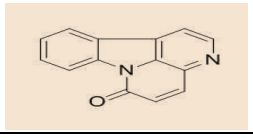
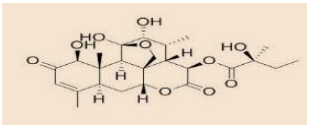
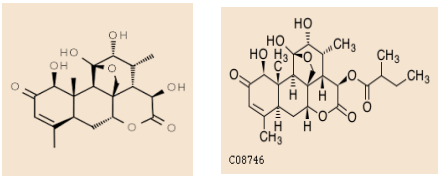
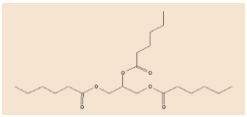
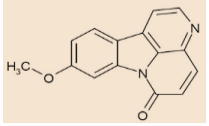
Studies on the efficacy of Glaucarubinone for inhibiting cell lines representing carcinomas of kidney (ACHN, TK10, UO-31,SN12C,RXF 393), breast (MCF7, MDA-N, BT549, T47D, MDAMB231, HS578T), ovaries (IGROVI, SKOV3, OVCAR-3, OVICAR-4, OVICAR-5, OVICAR-8), central nervous system (SF295, SF268, SF539, SNB-75, SNB-78, SNB-19, U251, XF498), lung (NCI-H23, DMS114, DMS273, HOP-92, NCI-H522, LXFL529, EKVX, NCI-H23, NCI-H226, NCI-H460, HOP-62, HOP-18), colon (HT29, Colo205, DLD-1, HCT15, KM12), skin (SKMEL-28, SK-MEL-2, SK-MEL5, UACC-62, LOX IMVI, M14, M19-MEL, MALME-3M, UACC-257) and prostate (PC-3, DU-145) have also been reported **[14]**.

The esters of Glaucarubolone, Ailanthinone and Glaucarubinone exhibited significant activity in vivo in the P388 lymphocytic leukemia mode. The quassinoid, 2-acetylglaucarubine was found significantly to inhibit growth of murine lymphocytic leukemia **[15]**. Canthin-6-one is another potent anti-cancer agent tested using various *in vitro* and *in vivo* model **[16,17]**. Canthin-6-one are alkaloids isolated from species in the Simaroubacea family. They are found together with quassinoids and beta -carbolin alkaloids. Canthin-6-one is cytotoxic towards human jurkat cells (immortalized line of humanT lymphocyte cells). Canthin-6-one and its derivatives 9-methoxy canthin-6-one ,2-methoxycanthin-6-one and 2-hydroxy canthin-6-one are cytotoxic towards human colon cancer cell line, umbilical vein endothelial cells, prostate cancer cells, KB cells, lung cancer cell line. **[18]**.

Scopoletin is a coumarin isolated from the wood of SG. It showed cytotoxicity towards human epithelial connective tissue and human breast cancer cells. Also, Tricaproin a triglyceride isolated from the leaves of SG showed cytotoxicity against human colorectal carcinoma cell lines at lower concentrations. **[19]**. An alternative mode of treating cancers by combining extracts isolated from natural products with the available conventional synthetic drugs is also being researched. For example, Gemcitabine is a novel deoxycytidine analogue

developed as an anti-cancer therapy. A combination of Glacarubinone and Gemcitabine inhibited murine pancreatic cancer cell line *in vitro* **[20,21]**.

Phytochemicals isolated from *Simarouba glauca* showing cytotoxicity against certain cancer cell lines:

PHYTOCHEMICALS ISOLATED	PART OF THE SG PLANT	PHYTOTOXICITY
Scopoletine 	Wood and twigs	1. Pancreatic cell line of ductal cell origin 2. Colon adenocarcinoma cells 3. Human breast cancer cells
Canthin – 6 – one 	Wood and twigs	1. Human Jurkat cells 2. Prostate cancer cell lines 3. Colorectal carcinoma cell line. 4. Cancer of Cervix 5. Brain cancer cell line
Glaucarubinone 	Seeds	1. Cancer of Pancreatic cell 2. KB cells 3. Carcinoma of lungs 4. Colon cancer cell line 5. Breast cancer
Esters of Glaucarubolon and Ailanthinone 	Seeds	1. Human prostate cell line 2. Carcinoma of Kidneys 3. Central nervous system CA cells 4. Skin cancer cells 5. Ovary cancer 6. Leukaemia 7. Colon cancer cells
Canthin-6-one 2-mrthoxy canthin-6-one 2-hydroxy canthin-6-one 9-mrthoxy canthin-6-1	Twigs	1. Prostate cancer cell line 2. Human colon cancer line 3. Umbilical vein endothelial cancer cell lines 4. Lung cancer cell line 5. KB cells 6. Cancer cell of cervix
Tricaproin 	Leaves	Human colorectal carcinoma cell line
9-methoxy canthin-6-one 	Twigs	Human embryonic kidney cells

The proposed mechanisms to explain the mode of action of the cytotoxins isolated from *S.glauca* on cancer cells:

Induction of cancer cell death by the isolated phytochemicals is mediated by (a) upregulation of apoptosis (programmed cell death in multicellular organisms) ; (b) arrest of cells in cell cycle stages; (c) halting of proliferation through inhibition of cyclins with simultaneous induction of p21 and p27 inhibitors (d) modulation of autophagy (orderly degradation and recycling of cellular components) and (e) downregulation of oncogenes (genes having potential to cause cancer) and upregulation of tumor suppressors **[21, 22, 23, 24]**.

CONCLUSION:

It is evident from the above study that *S.glauca* has a number of phytochemicals which can act as potential cure for a number of ailments. The quassinoids, flavonoids, alkaloids, glycosides extracted from the tree show distinct anti-cancer properties both *in vivo* and *in vitro*. Their action reduces the size of tumors and increases the survival chances of the patient in the early stages of the disease. In future, the focus will be on generating natural (plant based) anti-cancer drugs which are less toxic but more aggressive. The mode of action specifically targeting cancer cells has to be further researched.

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