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Role of *Simarouba glauca* DC Plant in Cancer: A Short Review

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Abstract

Cancer is the second leading cause of death worldwide, an estimated 9.6 million deaths in 2018. Cancer is responsible for one in six deaths globally. Use of chemotherapy, radiotherapy and hormone therapy on the rise across globe, high cost and side effects forced to search for an alternate. Ayurveda is time tested medical science having its roots in India widely used in treating chronic diseases. There are many herbs available around the world with diverse medicinal properties. *Simarouba glauca* DC plant is widely used to treat the different types of cancers. *Simarouba* contains many phytochemicals which have anti-cancerous properties. Present short review is an attempt to compile the evidences from the classical Ayurveda texts and modern sciences. A few preliminary research studies verified its safety and efficacy in cancer and other ailments. The outcome of these studies showed widely scattered evidences. This study focuses on concomitantly consumed/ prescribed drugs having the potential to interact with *Simarouba*, which will help to explore role of *Simarouba* in the integrative management of oncology and its associated complications.

Keywords: *Simarouba glauca*, cancer, integrative oncology, herb

Introduction

Cancer is one among the life threatening diseases, where abnormal cell growth involves the other systems of the body and these cells will be multiplying which cannot be controlled or stopped [1]. In September 2018, the International Agency for Research on Cancer (IARC) estimated the incidence and mortality rate for 36 types of cancers in about 185 countries. The global cancer burden is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. One in five men and one in six women worldwide develop cancer during their lifetime, and one in eight men and one in 11 women

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die from the disease [2]. Present-day treatments like chemotherapy, radiotherapy and hormone therapy are widely practiced, but each has its own side effects. There is need of treating the patients with fewer side effects by using the alternative therapies. In India, since ancient days different conventional therapies are being used to treat many chronic diseases. There are many herbs available around the world with diverse medicinal properties. In past few years, due to availability of several treatment options and efficacy of the treatment modalities, people prefer conventional therapies [3]. WHO data shows that around 80% population takes one or other form of herbal/complementary alternative systems of medicine (CAM) formulations [4].

During recent years, the evidenced data demonstrate and portray the use of the *Simarouba* plant and its formulations for their therapeutic effect against cancer. Present article aims at to review the recent studies for the safety, efficacy of *Simarouba* plant in cancer treatment. Many research studies are carried out in different types of cancer cell lines to update regarding efficacy of *Simarouba* plant and its action. This review also focuses concomitantly consumed/ prescribed drugs having potential to interact with *Simarouba.* This will help to get an idea for integrative management of disease and its associated complications. This will help to increase the safety, efficacy, potency and rationalization of *Simarouba* based integrative therapeutic management [5].

Simarouba glauca, commonly named as Paradise Tree or Bitter Wood and in local language known as 'Laxmitaru' belongs to Simaroubaceae family [6]. It is native of El-Salvador that has been introduced to India in 1960s [7]. The bark, leaf, fruit, pulp and seed are widely used to treat different diseases. It has many pharmacological properties such as anticancer, antibacterial, antifungal, antipyretic, anti-helminthic as well as anti- spasmodial actions [8]. It is evidenced that, *S. galuca* has also been used in traditional medicine, as the plant is reported to have active chemical ingredients that show medicinal value [9]. Bhattacharjee (2008) et al., reported that because of the presence of quassinoids, the whole family, including *S. galuca*, are known to have antitumor, antiparasitic, herbicide, insecticide, antiviral etc. activities [10].

Now a days in market there are different formulations of *Simarouba glauca* are available and are widely used as herbal formulations to treat diseases like skin disorders, chronic and acute dysentery, malaria etc. [11]. Literature review shows that *Simarouba glauca* is having the anti-cancerous properties and is widely used by some of the Ayurvedic folk practitioners to treat cancer patients.

Taxonomy of Simarouba glauca

One among the 32 genera and 170 species of *Simaroubaceae* is *Simarouba glauca*. The family is characterized by the presence of bitter substances important in pharmacological applications [12]. The members of this family are distributed in tropical America, Africa, Madagascar, Asia, and Australia. All the members of the family have chemical diversity, therefore, are the promising sources of bioactive compounds [13]. *S glauca* also has important biologically active phytoconstituents; nevertheless, the plant has not been explored to its fullest. Here in this short review we try to invade the different pharmacological and mainly anti-proliferative property of *S glauca* plant. Below provided table 1 summarizes the same.

Anticancer Activity of S glauca

In recent years, pharmacological research is focusing on ethnopharmacology (scientific study of traditional medicine), which has less toxicity and fewer side effects. The phytochemicals from medicinal plants is an alternative treatment for cancer. The phytochemicals such as alkaloids, flavonoids as well as others are used to treat the cancer. Many research studies results that the plant *Simarouba* contains many phytochemicals, which act as anti-cancerous [14]. Hence in this study we are more emphasizing on its anticancer activity.

The trait of *S. galuca*, having cytotoxic property, is due to the presence of quassinoids. In addition, the phytochemicals, canthinone alkaloids and terpenoids of the plant elicit cytotoxic activity [15]. Umesh (2014) studied leaf methanol, water extracts by using a range of concentrations from 10-320 µg/ml with

10 μg variations on SCC9, MCF-7, A549 and HCT116 cell lines. On SCC9 and HCT116, water extract showed negligible effect on cell growth inhibition, methanol extract visualized effective growth inhibition on SCC9 cell lines, whereas, the same extract showed only 30% inhibition on HCT116 cell lines. Methanol and water extracts exhibited none cytotoxic activity in MCF-7 (breast cancer cell lines) and A-549 (lung adenocarcinoma epithelial cell lines). This study specifies the activity of leaf extracts vary depending on the active compounds present in the extracts [16].

Table 1. Chemical constituents of *S. glauca*

Phyto-constituents	Plant part	Reported pharmacological activity	Probable molecular target for cancer	Reference
Glaucarubinone	Leaf	Anticancer& cytotoxicity activity	KB cells	Karthikeyan et al. (2016)
Glaucarubolone	Leaf	Antioxidant & anticancer activity	Bladder cell lines	Sridevi et al. (2017)
Canthin-6-one	Wood	Cell growth inhibition against NF1-deficient cancer cells	P53 & NF-1	Krishna et al. (2014)
Fraxidin	Leaf	Anticancer activity	P21	Asha Jose et al. (2018)
Scopoletin	Wood	HDAC inhibition	Histone deacetylases	Asha Jose et al. (2018)
Triolein	Leaf	Apoptosis	Bax	Asha Jose et al. (2018)
Trilinolein	Leaf	Anticancer agent	P53	Asha Jose et al. (2018)
Tannins	Seed	Tumor growth inhibition	P21	Asha Jose et al. (2018)
Saponins	Seed	Cytotoxicity	Immune cells	Rout et al. (2014)
Flavonoids	Seed & leaf	Cytotoxicity	Immune cells	Jeyalakshmi et al.(2016)
Melyanodiol	Twigs	Inhibition of colorectal carcinoma cell growth	P53	Asha Jose et al. (2018)
Nilocitina	Twigs	Anticancer activity	P53	Asha Jose et al. (2018)
3-episapelin	Fruit	Cytotoxicity	Immune cells	Michel et al. (2016)

Based on the findings of Patil and Gaikwad (2011), traditionally, *S. glauca* plant parts are widely used to treat different cancers. The National Cancer Institute in the United States demonstrated in their preliminary study that the alcohol extracts at a dose of 25μg/ml of *S. glauca* leaves the growth of cancer cells inhibited [17]. Recent findings by Puranik (2017) showed that the leaf ethanolic extract has an anti-bladder cancer activity on T-24 cell lines. Chloroform extract of *S. glauca* twig extract contained phyto-constituents like six canthin-6-one type alkaloid derivatives, canthin-6-one (1), 2-methoxycanthin-6 -one (2), 9-methoxycanthin-6-one (3), 2-hydroxy-canthin-6-one (4), 4,5-dimethoxycanthin-6-one (5) and 4,5-dihydroxycanthin-6-one (6), a limonoid, melianodiol (7), an acyclic squalene-type triterpenoid, 14-deacetyleurylene (8), two coumarins, scopoletin (9) and fraxidin (10), and two triglycerides, triolein (11) and trilinolein (12), which are considered to have anticancer properties [18]. When tested, it is noted that only canthin-6-one (1), 2-methoxycanthin-6-one (2), 9-methoxycanthin-6-one (3), 2-hydroxycanthin-6-one (4), a limonoid, melianodiol (7), 14-deacetyl-eurylene (8) having the function of inhibiting human cancer cell lines [19].

Reynertson et al., (2011) isolated the chemicals from wood extract like scopoletin, canthin-6-one, canthine-6-one dimethoxy derivatives and used

human breast cancer cell lines, MCF-7 and SK-BR-3 to test their efficacy at a concentration of 2.0 µg/ml and 5.5 µg/ml respectively. The isolated phytochemical, 4-canthin-6-one, an alkaloid derived from the twigs of *S. glauca* confirmed cytotoxic activity on different cancers of human *viz,* colon cancer, oral epidermoid cancer, hormone dependent prostate cancer and lung cancer cells. Among the identified phytochemicals of *Simarouba*, quassinoids and alkaloids are considered to be having anti-tumor property. The good anti-leukemic activity was displayed by chaparrinone, chaparrin of the selected plant species [20].

Houel et al., (2009) demonstrated a promising cytotoxic activity against mammary humanadeno-carcinoma cells [21]. During phytochemical analysis Michel Feussi Tala (2016) assessed CH_2Cl_2-soluble extract, sub-fractions and isolated compounds (1–3, 16) against the human lung carcinoma A-549, the human gastric cancer BGC-823, and the human cervical cancer HeLa cell lines. And they reported first time that the active compound present in it shows inhibitory effects towards cancer cell lines A-549, BGC-823 and Hela etc. [22].

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The fruits and seeds of *S. glauca* contain Ailantinone and Glaucarubinone. It is known that these compounds have anticancer properties when tested on human pharynx epidermoid carcinoma. When tested in rats on solid and meltiersilent mammary tumors by Valeriote et al., (1998), it is concluded that glaucarubinone showed beneficial activity [23].

Subburayan Karthikeyan et al., (2016) aimed to study the beneficial effects of Glucarubinone (GLU), one among the major quassinoids of *S. glauca*. Though it has been identified as an antimalarial drug, recent research results conclude that it has got anticancer properties too, essentially, on multidrug resistant KB cells. They studied how this phyto-chemical potentiates the cytotoxic effects of paclitaxel (PTX) in KB cells. While working, they found interesting results that there is a positive association between anticancer effectiveness of GLU and PTX-induced cell cycle arrest at G2/M phase. The illustrations of this study showed greater anticancer property of GLU-PTX combination than alone of both GLU and PTX. The investigation concludes that GLU from *S. glauca* may be promising supplementary dietary for cancer patients. Glaucarubinone sensitizes KB cells to paclitaxel by inhibiting ABC transporters via ROS-dependent and P53-mediated activation of apoptotic signaling pathways [24].

The similar kind of work has been carried out by Yeo et al., (2014) on pancreatic cancer growth. While working with glaucarubinone, from seeds of *S. glauca* and the front-line chemotherapeutic drug, gemcitabine alone or in combination for inhibition of pancreatic cell proliferation in vitro and in vivo concluded that there is a combined effect by both glaucarubinone and gemcitabine. This opens up an avenue to use glaucarubinone as an additional drug along with commercial drugs (Glaucarubinone and gemcitabine synergistically reduce pancreatic cancer growth via down-regulation of P21-activated kinases) [25].

While assessing the anticancer activity of *S glauca* leaf methanol extract on K-562, MOLT-3 and KG-1 leukemic cell lines; Prajapati (2018) et al. reported that extracts effectively inhibited the growth of these cell lines in a dose-dependent manner, with an IC50 range from 74.21, 69.69 and 131.1 µg/ml respectively. The inhibitory activity of *S glauca* methanolic leaf extract against MOLT-3 was highest as compared to K-562, and KG-1. These data indicate clearly that *S glauca* leaf methanol has the good anti-cancer influence towards MOLT-3 and K-562, but it has limited activity against KG-1 cell line, therefore, methanol leaf extract can be a good drug against leukemia. And also, it is necessary to identify and purify the active compounds before taking to trials [26].

Study conducted by Asha Jose (2019) et al., on tricaproin, isolated from *S glauca* inhibits the growth of human colorectal carcinoma cell lines. The authors used different solvent extracts of the leaves namely, hexane, chloroform, ethyl acetate, 70% ethanol, water. They tested the efficiency of these extracts on

colorectal cancer cells, HCT-116, and HCT-15 by Sulforhodamine-B assay. Among the studied solvent extracts, chloroform extract exhibited maximum cell proliferation or anticancer property. After spectral analysis and structural characterization, the compound has been confirmed as tricaproin (TCN). Comparison was made between the selected cancer cells and normal cell lines, BEAS-2B and the results concluded that TCN inhibited greatly the viability of cancer cells in dose and time dependent manner. The mode of action result demonstrated that TCN showed reduced action on class-1 Histone Deacetylase enzyme. Also it induced the apoptosis in cells [27]. Table 2 summarizes the in vitro and in vivo studies.

Table 2. In vitro and in vivo studies of *S glauca*

Sl. no	Study type	Cell lines	Conclusion	Author name
1.	In vitro	SCC9, MCF-7, A549 and HCT116 cell lines	On SCC9 and HCT116, water extract showed negligible effect on cell growth inhibition, methanol extract showed effect on growth inhibition of SCC9 & MCF-7 cell lines.	Umesh T.G et al.
2.	In vitro	Cancer cell line	Alcohol extract of leaves inhibited cancer cell growth.	Patil Manasi et al.
3.	In vitro	T-24 cell lines	Ethanolic extract showed anti-cancer activity on T-24 cell line(bladder cell line)	Puranik et al.
4.	In vitro	Cancer cell lines (Colon cancer, oral epidermoid cancer, prostate etc.)	Isolated chemicals from wood extract showed cytotoxic activity on different cancer cell lines like colon cancer, oral epidermoid cancer, hormone dependent prostate cancer and lung cancer cells etc.	Reynertson et. al
5.	In vitro	Mammary human adenocarcinoma cells	Leaf extract inhibited human adenocarcinoma cell line.	Houel et. al
6.	In vitro	Cancer cell lines A-549, BGC-823 and Hela	CH_2Cl_2-soluble extract showed inhibitory effect on human lung carcinoma A-549, the human gastric cancer BGC-823, and the human cervical cancer HeLa cell lines.	Michel Feussi Tala et al.
7.	In vitro	Cancer cell lines	Isolated phytochemicals derived from twigs showed anti-tumor, anti-leukemic activity.	Rivero-Cruz JF, Lezutekong R et al.
8.	In vitro	Cancer Cell lines (KB Cells)	Showed Anticancer activity on KB cells.	Subburayan Karthikeyan et al.
9.	In vitro	Leukemic cell lines	Leaf extract inhibited the growth of cancer & leukemic cell lines.	Prajapati CK et al.
10.	In vitro	Colorectal carcinoma cell lines	Isolated phytochemicals inhibited the growth of Colorectal carcinoma cell lines.	Asha Jose et al.
11.	In vitro	Pancreatic cancer cell lines	Inhibition of pancreatic cell proliferation	Yeo et al.

In summary, all these studies conclude that the extracts of *S glauca* contain potential anticancer agents.

Ayurvedic Perspective of Simarouba glauca DC

Simarouba glauca DC is one among the folk drugs, now a days which is widely used to treat the cancer by some of the *Ayurvedic* or traditional folk practitioners in Indian subcontinent. But we won't get the explanation regarding *S glauca* DC in any major *Ayurvedic* textbook. In *Ayurveda*, pharmacological actions of the drugs are identified based on their *Rasa* (taste), *Guna* (quality), *Virya* (potency), *Vipaka* (transformation) and *Prabhava* (inexplicable nature) [28]. Based on fundamental principles of *Ayurveda* a pharmacological action can be predicted. As per some scientific evidences rasa of a substance can be scientifically used to assume the pharmacological actions [29]. *Acharaya Charaka* says *Rasa* is

experienced the moment a substance comes in contact with the tongue [30]. Each *Rasa* indicates a distinct *Mahabhautika* status of the substance. Each *Rasa* signifies *Mahabhautika utkarsata* of a combination of two *Mahabhutas*. The different properties and actions are attributed to a particular *Mahabhuta*, when it is in an activated state [31, 32]. Thus, by knowing *rasa* of a substance we can interpret pharmacological properties and action of that particular drug. With the help of some scientific research articles and *Ayurvedic* classical texts we made an attempt to identify the *rasa*, *guna*, *virya* and *vipaka* of the *Simarouba glauca* DC.

Rasa: Tikta (Bitter)
Guna: Laghu, Ruksha (Light and dry in nature)
Virya: Sheetavirya (cold in potency)
Vipaka: KatuVipaka
Mahabhuta predominance: Vayu + Akasha
Doshaghnata: Kapha pitta shamaka, Vatakaraka

All these properties and actions of *S glauca* DC based on general rule of *Rasa*, *Vipaka* and *Mahabhuta* predominance. These properties are important to produce anticancer activities. However this prediction needs to be validated by drug validation method with the help of experts.

Role of *Simarouba* and Cancer Stem Cells

As discussed, cancer is the most common causes for death and ill health in all around the world. Since decades stem cells are being used in cancer treatment for immune- modulation [33].

Stem cells are undifferentiated and it can rise from the multicellular organisms like humans. These cells are pluripotent under suitable condition; it can be differentiate into any type of cells. Stem cells have seemingly endless self-renewal potential property. Their undifferentiated state makes it possible from a single cell can multiply many healthy cells and formed to replace damaged cells. This forms the basis of cell-based therapies and newer treatment are the futile modality as for regeneration of organ [34].

Normal stem cells are more exposed to mutagenic factors; this may lead to cancer progression which happens in somatic stem cells by the carcinogenesis. This may affect signaling and transcription factors, the cellular proliferative pathways and signaling pathways Receptors can inhibit oligodendrocyte and cells can impede self-proliferation which eventual lead to oncogenesis. Many of stem cells exhibit characteristics like self-renewal, anchorage dependent growth factor, cloning efficiency and in-time expression proteins in anti-apoptotic cells. *Simarouba* enhances the ability to undifferentiate the down regulation of c-Myc, can create the genetic stability and effect the apoptotic mechanism in stem cells [35].

Conclusion

Present short review reveals that *Simarouba glauca* plant is widely used in treating cancer and other ailments. Phase I and Phase II studies revealed *Simarouba* is safe and effective herb in the management of cancer. But present literature lacks in the clinical trials to confirm its safety and efficacy, it also lacks in the studies to explore the underlying (molecular) mechanism of the S*imarouba glauca* DC on cancer cells. Hence, further studies need to be conducted in these areas before integrating *Simarouba* in the management of cancer.

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Ethical compliance

The authors have stated all possible conflicts of interest within this work. The authors have stated all sources of funding for this work. If this work involved human participants, informed consent was received from each individual. If this work involved human participants, it was conducted in accordance

with the 1964 Declaration of Helsinki. If this work involved experiments with humans or animals, it was conducted in accordance with the related institutions' research ethics guidelines.

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