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Review article

Therapeutic values of *Simarouba glauca* with reference to its anticancer potentiality

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ABSTRACT

Simarouba glauca, commonly known as Paradise Tree, has sparked considerable scientific attention due to its diverse phytochemical profile and potential medicinal uses. Traditionally it was used in many cultures to cure maladies such as malaria, diarrhoea and inflammatory disorders. Contemporary studies have focused on its anticancer potential, which is supported by a varied array of bioactive ingredients such as quassinoids, alkaloids and triterpenoids. Our review includes a wide range of pharmacological evidence, particularly in vitro and in vivo studies, that highlight its antiproliferative, apoptotic and immunomodulatory actions in a variety of cancer models, including breast, prostate, lung, ovary and leukaemia. Furthermore, the safety profile of its leaf and seed oil extracts has been investigated in a number of toxicity studies, all of which indicate a wide margin of safety. Despite these encouraging findings, we recognise many limitations, including a lack of standardised formulations, clinical data and sophisticated drug delivery methods. In this review, we emphasise the importance of future pharmacokinetic investigations, formulation development and clinical trials to convert Simarouba glauca from a traditional treatment to a proven anticancer therapy.

Keywords: Anticancer activity, Quassinoids, Simarouba glauca, Traditional medicine.

INTRODUCTION

Simarouba glauca, often known as 'Laxmitaru' or 'Paradise tree', belongs to the Simaroubaceae family. *Simarouba glauca* has been used in traditional medicine as an anticancer, antibacterial, antiviral and antihelminthic agent, especially in Southern Florida, the Caribbean and Brazil. Aside from these applications, it can treat anaemia, menstrual disorders, painful periods, menopausal issues, white discharge, leukaemia, dengue fever, ulcers and gastritis caused by Helicobacter pylori. Also used to treat dyspepsia, amoebiasis, diarrhoea, fever, colitis, anaemia, rheumatoid arthritis and haemorrhage [2]. *Simarouba glauca* contains a high concentration of quassinoids (degraded triterpene lactones) [1]. Quassinoids discovered in *Simarouba glauca* include ailanthinone, benzoquinone, canthin, dehydroglaucarubinone, glaucarubine, glaucarubolone, glaucarubinone, holocanthone, melianone, simaroubidin, simarolide, simarubin, simarubolide, sitosterol and tirucalla [2].

The tree is best suited to warm, humid tropical environments. Its cultivation is dependent on rainfall distribution, soil water-holding capacity and subsoil moisture. It is suitable for temperatures ranging from 10°C to 50°C. It can grow at elevations ranging from sea level to 1,000 meters (3,300 feet) and reaches a height of 40 to 50 feet (12 to 15 metres). *Simarouba glauca* has high levels of carbohydrates, fatty acids, lipids and proteins. *Simarouba glauca* decoction has been used in traditional medicine to treat cancer and tumours. Simarouba leaf decoction, when taken in moderation, can boost immunity, prevent appetite loss, and improve cancer patients' quality of life [3].

Simarouba glauca products are now available in the market as herbal skin lotion and dry leaf powder / dried seeds for the treatment of skin diseases. Traditionally, the bark was used to cure malaria. Brazilian tribes have also employed *Simarouba glauca* extract as an efficient natural medicine to treat chronic and severe

dysentery. In this review, we evaluated the literature on anticancer agents extracted from *Simarouba glauca* and highlighted future investigations that would require a deeper understanding of the phytochemicals.

Botanical description and distribution

Common name - Aceituno, Paradise tree, Simaba, Bitter wood tree.

Malayalam - Lakshmi Tharu

Tamil - Shorgum Maram

Hindi - Laxmitaru

Bengali - Lakshmi Tara

Taxonomical classification

Kingdom	Plantae
Phylum	Streptophyta
Class	Equisetopsida
Subclass	Magnoliidae
Order	Sapindales
Family	Simaroubaceae
Genus	Simarouba
Species	*Simarouba glauca*

Figure 1: *Simarouba glauca* plant

Figure 2: Leaf of *Simarouba glauca*

Figure 3: Seed of *Simarouba glauca*

Distribution

Simarouba glauca grows in Central America's tropical climate from Mexico to Panama, South Florida and the Caribbean Islands. *Simarouba glauca* was introduced to both Kenya and Burundi in 1957. *Simarouba glauca*, found in Mexico, Cuba, Haiti and Central America, is a rainforest and other tropical zone native. It is grown in some regions of India. Genetic Resources brought it to India in the 1960s at its Amravati research facility in Maharashtra. India's wastelands of Orissa, Karnataka and Gujarat show good plant growth. Furthermore, Andhra Pradesh, Bihar, Maharashtra and Tamil Nadu have substantially increased their growth rates [4].

Local application

Simarouba glauca leaves and bark have long been used as a natural cure in tropical climates. *Simarouba glauca* bark has been used successfully to treat malaria and diarrhoea. Another South American group utilises bark as a hemostat to prevent bleeding and as a tonic to treat fever, diarrhoea and malaria. Externally, it treats wounds and cuts. The bark is cooked in water and used as a powerful astringent and tonic to cleanse the skin and treat dysentery, intestinal problems, blood loss and internal bleeding. *Simarouba glauca* is a robust and flexible dioecious oil crop plant with an annual output potential of 2000-2500 kg [5].

The oil extracted from this plant is mostly utilised in the making of bread items; however, it may also be used to make vanaspati and vegetable oil. The oil is devoid of harmful cholesterol. It may also be used industrially to make soaps, detergents, lubricants, varnishes, cosmetics, medicines and other products [6].

Simarouba glauca is also used as a biofuel, which is currently required to help the economic situation. *Simarouba glauca* Biodiesel is produced from processed seeds using the transesterification technique. Simarouba biodiesel is an alternative to regular petro-diesel. *Simarouba glauca* blends have shown improved performance and emission characteristics than other diesel fuels [2].

The seeds extracted in alcohol are used to treat snake bites. An infusion of the leaves or bark is considered astringent and used as a digestive and menstrual stimulant. Consuming a decoction produced from the tree's leaves and bark can successfully heal rheumatoid arthritis [6].

Phytochemical constituents

Simarouba glauca, a medicinally important member of the Simaroubaceae family, has been extensively explored due to its high phytochemical variety, especially its quassinoid and alkaloid content. A total of 11 (eleven) quassinoids, including glaucarubin, glaucarubolone, glaucarubinone, ailanthinone and dehydroglaucarubinone, have been isolated and identified as important bioactive elements contributing to the therapeutic efficacy of *Simarouba glauca* [1-2, 5-7]. Quassinoids are well-known for their

powerful anti-tumour, antifungal, antiviral and antiparasitic effects. Glaucarubin, initially identified by Ham E.A. in 1954, is still one of the most intensively researched compounds from *Simarouba glauca* [1]. *Simarouba glauca* contains canthin alkaloids, which include canthin-6-one, its methoxy and hydroxy derivatives, and β-carboline alkaloids, which have been shown to have antibacterial and cytotoxic activities [1,2,6]. Coumarins, including scopoletin and fraxidin, have been identified and shown to have pharmacological properties such as analgesic, antibacterial and antileishmanial actions [2, 6].

The plant also contains squalene-type triterpenoids such as 14-deacetyleurylene, as well as other triterpenes such as simarubolide, simarolide, melianone and tirucalla, which contribute to its antimalarial and antidiarrheal properties [1, 6, 7]. The fatty acid and triglyceride components of *Simarouba glauca*, such as triolein, trilinolein and oleic acid, are recognised to help manage metabolic, neurological and cardiovascular problems [2, 7]. In addition to these fundamental chemicals, qualitative screenings have revealed the presence of flavonoids, sterols (such as sitosterol), saponins, glycosides, cardenolides, phenolic compounds and fixed oils in various plant sections [5-7]. Furthermore, advanced GC-MS analysis of the ethanolic and aqueous extracts revealed modest but significant chemicals such as benzenamine derivatives, pyridines, thujopsene, phytol and androstane-type steroids, revealing a considerable chemical diversity within *Simarouba glauca* [8]. All the phytochemical constituents mentioned above are summarized and categorized in Table 1 for clarity and comprehensive reference.

Therapeutic Approach

Simarouba glauca exhibits a wide range of therapeutic properties, including anti-amebic, antibacterial, antifungal, antioxidant, anti-cancer, anti-inflammatory, hepatoprotective and wound-healing actions, among others [6-8]. These bioactivities are primarily attributed to its rich phytochemical profile, which includes flavonoids, alkaloids and terpenoids [1, 5, 6]. Table 2 provides a detailed overview of the therapeutic applications and biological effects demonstrated by this plant**.**

Table 1: Phytochemical constituents in *Simarouba glauca*

Category	Phytochemicals
Quassinoids	Glaucarubin, Glaucarubol, Glaucarubolone, Glaucarubinone, Ailanthinone, 15-O-β-D-glucopyranosyl glaucarubolone, Dehydroglaucarubinone, Simarubin, Simarubolide, Simarolide, Simaroubidine, Holacanthone [1, 2, 6, 7].
Alkaloids	Canthin-6-one, 2-Methoxycanthin-6-one, 9-Methoxycanthin-6-one, 2-Hydroxycanthin-6-one, 4,5-Dimethoxycanthin-6-one, 4,5-Dihydroxycanthin-6-one, Canthin, β-carboline alkaloids [1, 2, 6, 7].
Coumarins	Scopoletin, Fraxidin [1, 2, 6, 7].
Triterpenoids	14-Deacetyleurylene (squalene-type), Tirucalla, Simarubolide, Melianone, Simarolide, Simaroubidine [1, 2, 6, 7].
Sterols	Sitosterol [6, 7].
Fatty Acids & Triglycerides	Triolein, Trilinolein, Oleic acid [1, 2, 7].
Phenolic Compounds	General phenolics [5-7].
Saponins	Present in extract [5-7].
Glycosides & Cardinolides	Glucosides (e.g., 15-O-β-D-glucopyranosyl glaucarubolone), Cardinolides [5-7].
Flavonoids	Flavone, Other unspecified flavonoids [5-7].
Volatile/Oil Components	Fixed oils, Thujopsene, Phytol [5-7].
Miscellaneous Compounds	Benzoquinone, Tricaproin, Androstane-3,17-dione 17-oxime, 5Alpha-androstane-3,17-dione 17 monoxime, N-ethyl aniline, 4-(3-pentyl)pyridine, 2,2-Bis(4-trimethylsiloxy)phenylpropane [1, 8].
Extract Effects	Antineoplastic, Antiviral, Anti-inflammatory, Antifungal, Antiprotozoal, Cytotoxic, Anti-tumor, Vermifuge, Emmenagogue, Analgesic, Immunomodulatory, Skin Hydration & Depigmentation [2, 5, 6, 7].

Table 2: Therapeutic Approaches of *Simarouba glauca*

Therapeutic Approach	Description
Anti-amebic action	Effective against *Entamoeba histolytica*, interferes with trophozoite stage to reduce infection severity [6-8].
Antibacterial action	Inhibits Gram-positive and Gram-negative bacteria like *E. coli* and *Staphylococcus aureus* [6-8].
Antifungal activity	Active against fungal strains such as *Candida albicans* and *Aspergillus niger* [6-8].
Antioxidant action	Rich in polyphenols and flavonoids; reduces oxidative stress and cellular damage [6-8].
Anti-cancer activity	Cytotoxic to cancer cells; exhibits antiproliferative and pro-apoptotic properties [6-8].
Antimalarial activity	Effective against *Plasmodium falciparum*; inhibits parasite growth [6-8].
Antiulcer activity	Protects gastric mucosa, reduces acid secretion, promotes ulcer healing [6-8].
Hepatoprotective activity	Restores liver enzyme levels and prevents histological damage in animal models [6-8].
Anti-inflammatory action	Inhibits pro-inflammatory mediators; useful in arthritis and bowel diseases [7].
Antimicrobial activity	Broad-spectrum activity against bacteria, fungi, and protozoa [7].
Antidysenteric action	Reduces intestinal inflammation and microbial load; relieves dysentery symptoms [7].
Analgesic activity	Demonstrates pain-relieving effects in animal models [7].
Anti-leukemic activity	Reduces leukemia cell proliferation through apoptosis and inhibition of abnormal cell division [7].
Acaricidal property	Toxic to ticks and mites; potential use in veterinary and agriculture [7].
Antihypertensive activity	May lower blood pressure by relaxing blood vessels and improving vascular function [7].
Reducing spotty skin pigmentation	Topical use helps reduce hyperpigmentation and improves skin tone [6,7].
Hemolytic activity	Exhibits red blood cell lysis; useful in immunological and toxicology research [7].
Antiproliferative activity	Inhibits abnormal cell division, especially in cancerous cells [7].
Pro-apoptotic action	Induces programmed cell death in cancer cells, aiding in selective tumor elimination [7].
Anti-inflammatory in bowel disorders	Reduces cytokine levels; beneficial in inflammatory bowel diseases like colitis [7].
Wound healing activity	Promotes wound contraction, reduces inflammation, and aids re-epithelialization [6, 7].
Antipyretic activity	Likely reduces fever by inhibiting prostaglandin synthesis (based on anti-inflammatory potential) [7].
Skin protective activity	Topical application improves skin texture and protects against oxidative damage [6, 7].
Gastroprotective action	Enhances gastric mucosal defense and mucin secretion, preventing peptic ulcer formation [6, 7, 8].

Anti-cancer activity study (*in vitro / in vivo*)

***In vivo* Study (Animal model)**

A study on breast cancer aimed to evaluate the tumour-reducing potential and safety of *Simarouba glauca* ethanolic extract in a mouse model. The researchers used an MDA-MB-231 xenograft model in immunocompromised Balb C Nu/Nu mice. Breast cancer cells were injected into the mice, and the animals were treated with plant extract (PTE) alone or in combination with standard chemotherapeutic drugs such as cisplatin or Taxol. Tumour size and body weight were regularly monitored. The study found that the PTE significantly reduced tumor volume, enhanced the effectiveness of chemotherapy, and did not produce any observable toxicity, as the mice maintained normal weight gain throughout the treatment period.

***In vitro* studies (Cancer cell line experiments)**

Research on breast cancer was conducted utilising human breast cancer cell lines MDA-MB-231 (triple-negative) and MCF-7 (oestrogen receptor-positive). Several tests, such as Annexin V/PI staining, reactive oxygen species (ROS) detection, mitochondrial membrane potential assays and the WST-1 assay on normal fibroblasts were used to assess the ethanolic extract of S. glauca. In addition to increasing ROS generation and mitochondrial malfunction, the extract was found to preferentially trigger apoptosis in cancer cells and to dramatically boost the anti-cancer effects of Taxol and Cisplatin while sparing healthy cells [9].

Another study was conducted on prostate cancer, utilising the PC-3 human prostate cancer cell line, and it was used to assess the cytotoxic and pro-apoptotic properties of S. glauca methanolic extract. To evaluate the expression of the VEGF-A and 5-LOX genes, the methanolic extract was prepared by Soxhlet extraction and examined using the MTT assay, mitochondrial membrane potential assay and real-time PCR. Its potential anti-cancer characteristics were indicated by the results, which showed that the extract suppressed cell growth with an IC_{50} value of 35.24 µg/mL, induced early apoptosis, disturbed mitochondrial activity and led to a downregulation of both VEGF-A and 5-LOX [10].

Now, another Research was conducted on lung cancer, in which the A549 human lung adenocarcinoma cell line was used to test an aqueous extract of dried S. glauca leaves. Cell viability was measured at different doses ranging from 12.5 to 200 µg/mL using the MTT test. The extract dramatically reduced the growth of cancer cells, according to the study, and this effect was dependent on both time and dose. Crucially, it demonstrated its selective anticancer activity by not being harmful to healthy alveolar cells [11].

Another finding indicates that the PA1 human ovarian cancer cell line was utilised to investigate the cytotoxic and antioxidant characteristics of S. glauca leaf extracts in ovarian cancer models. Solvents like methanol and acetone were used to extract the leaves one after the other. Antioxidant activity was evaluated using the DPPH and FRAP assays, whereas cytotoxicity was determined using the MTT assay. A dual involvement in oxidative stress management and cancer cell inhibition is suggested by the methanol extract's most cytotoxic effect and the substantial antioxidant activity of both methanol and acetone extracts [12].

Lastly, the K562 chronic myeloid leukaemia cell line was used to test the apoptotic qualities of S. glauca leaf extracts in relation to leukaemia. Multiple assays, such as MTT for viability, AO/EB dual staining, Hoechst dye staining, Annexin V binding assay, and caspase-3 flow cytometry, were used to assess the petroleum ether extract. Importantly, the extract was non-toxic to healthy lymphocytes and efficiently suppressed cell growth with an IC_{50} of 186 µg/mL. It also promoted apoptosis through death receptor and mitochondrial pathways [13].

Mechanism of action

The Phytochemicals derived from *Simarouba glauca* have shown promising anticancer activity through multiple biological mechanisms. These compounds primarily work by inducing apoptosis, which is a normal process of programmed cell death, while leaving healthy cells unharmed.

It has been discovered that ethanolic extracts of S. glauca increase oxidative stress in breast cancer models by increasing intracellular Reactive Oxygen Species (ROS), which destroys the mitochondrial membrane and causes cell death(apoptosis). This effect was further enhanced when the extract was used alongside conventional chemotherapies like Taxol and Cisplatin, allowing for lower doses of chemotherapy to be used with reduced side effects [9]. In another study, methanol extracts of S. glauca induced early apoptosis and depolarised the mitochondrial membrane in addition to inhibiting cell proliferation in prostate cancer (PC-3 cells). Crucially, it decreased the expression of genes that are frequently implicated in inflammation and tumour growth, such as VEGF-A and 5-LOX [10]. Adding to this, a comprehensive review highlighted that specific phytochemicals such as glaucarubinone inhibit main pathways in cancer cells by suppressing protein synthesis, blocking survival pathways like β-catenin & HIF-1α and activating apoptotic genes like p53 & Bax. Canthin-6-one is another active compound that interferes with the cancer cell cycle, disrupts mitotic spindles and suppresses signalling pathways like AKT, NF-κB and Wnt. Other compounds like Tricaproin modulate epigenetic changes through HDAC inhibition, further pushing cancer cells toward death [1]. Overall, these studies suggest that *Simarouba glauca* acts through a combination of oxidative stress induction, mitochondrial damage, gene regulation and pathway inhibition, which indicates that *Simarouba glauca* is a strong candidate for future anticancer therapies.

Toxicity and safety profile

The safety assessment of *Simarouba glauca* has been comprehensively studied through acute and sub-chronic toxicity models by using its leaf extracts and seed oil. The plant parts were extracted with aqueous and ethanolic solvents and the oil was studied in both crude and refined forms. A summary of the study is provided below.

Acute toxicity studies (LD_{50} Estimation)

In these studies, both the aqueous and ethanol leaf extracts of *S. glauca* were evaluated using Lorke's method. In both studies, there was no mortality or observable toxicity up to the maximum tested oral dose of 5000 mg/kg, suggesting an LD_{50} exceeding this threshold [14,15]. Similarly, the seed oil, which is first expeller-extracted by mechanical pressing, then solvent-extracted and then refined, was administered. The oil, administered at 15–30 mL/kg also showed no toxic symptoms or deaths in rats.

Sub-chronic toxicity (30-day repeated oral dosing)

In this study, the rats were administered 500, 1000, and 2000 mg/kg of either aqueous or ethanol leaf extracts daily for 30 days.

Body weight

The observation was that there was significant weight gain across all doses, which indicates good tolerance and no cachexic or catabolic effects.

Organ-to-body weight ratios

While minor dose-related changes in liver, kidney and heart weight ratios were observed, particularly reductions at higher doses. Histological evaluation confirmed that no structural damage.

Kidney markers

In both studies, plasma urea levels were significantly elevated at doses of 1000 and 2000 mg/kg, while plasma creatinine levels varied inconsistently, showing a slight increase at lower doses and a decrease at higher doses, suggesting only a mild and non-progressive effect on kidney function. Although there were reductions in sodium and bicarbonate levels, these changes were not considered toxicologically significant, as no related tissue damage was observed in the histopathological analysis.

Seed oil safety and dietary study

A comprehensive 13-week feeding study on rats to assess *Simarouba glauca* seed oil as a dietary fat in comparison with groundnut oil, where no mortality or adverse effects were recorded during the trial. Growth parameters, organ weights and food efficiency were comparable to control animals. Digestibility was excellent (>94%), which is similar to that of edible oils. Haematological and biochemical parameters, including liver enzymes, renal markers and serum cholesterol, remained within normal limits. Histopathological analysis of liver, kidney, spleen, heart and testes revealed no abnormalities.

Across all studies, *Simarouba glauca* extracts and oils demonstrated excellent safety profiles, in both acute and sub-chronic exposure models. The minor biochemical changes did not correlate with organ damage, as confirmed by histology. These findings justify the continued exploration of *S. glauca* as a safe therapeutic and nutraceutical agent, provided dosing is optimised and standardised.

Challenges and limitations

Lack of standardised formulations

Despite extensive pharmacological evidence, there are currently no standardised pharmaceutical products like tablets, capsules, or injectables made from *Simarouba glauca*. Most of the studies utilize crude extracts (aqueous, ethanol, petroleum ether), which limits reproducibility and dosage precision [1, 5].

Absence of advanced delivery systems

There is a notable lack of modern drug delivery systems, such as nanoparticles, liposomes or targeted vehicles for active phytochemicals like quassinoids, which restricts its therapeutic potential, especially in cancer treatments [1, 5].

Early stage of research

Most of the pharmacological evidence for *Simarouba glauca* is based on in vitro and preclinical animal models. There is no clinical trial data in humans, which limits its current medical application [9-13].

Toxicological ambiguity

Although toxicity studies suggest high safety (LD_{50} > 5000 mg/kg), biochemical anomalies (e.g., raised plasma urea, enzyme level fluctuations) were observed, which indicate the need for longer-term safety evaluations [14].

Variability in extract composition

The composition of extracts varies depending on the plant part used, solvent type and geographic conditions, which creating difficulty in standardizing dosage and efficacy.

Limited bioavailability and pharmacokinetics data

There are no established pharmacokinetic or bioavailability studies for major phytoconstituents such as glaucarubinone or canthin-6-one, which slows down drug development and clinical translation [1, 5, 9].

Future perspective and research direction

Simarouba glauca holds significant promise as a source of bioactive compounds with diverse pharmacological properties, particularly in the area of anticancer therapeutics. However, its transition from traditional medicine to mainstream pharmacological application requires systematic advancements.

Future research should focus on standardisation of extract preparation, as current studies heavily rely on crude solvent-based methods, which make it difficult to get the same results and receive regulatory approval. Developing standardised dosages and identifying active lead compounds, especially among quassinoids and alkaloids, are critical for consistent therapeutic outcomes. In this

context, glaucarubinone, canthin-6-one and other quassinoids warrant further molecular characterisation and structural optimisation for drug development.

Additionally, there is an urgent need to explore advanced drug delivery systems such as Nano-emulsions, liposomes and polymeric nanoparticles to enhance the bioavailability and target specificity of these compounds. Such systems can overcome the solubility and stability challenges currently associated with phytochemical-based therapies.

Clinical trials should be initiated to assess the safety, tolerability and efficacy of purified extracts or isolated phytochemicals in humans. Concurrently, combinatorial studies with existing chemotherapeutic agents may help to establish synergistic effects and dose-reduction potentials, as observed in vitro with agents like cisplatin and Taxol [9].

Long-term toxicological evaluations should be conducted under Good Laboratory Practices (GLP) to further confirm the safety profile established by sub-chronic and acute animal studies [14]. Studies focusing on pharmacokinetics, metabolism, and mechanism-based toxicity will also help bridge the translational gap.

Finally, future investigations should also assess the plant's ecological impact, sustainable cultivation practices and economic viability for large-scale therapeutic and nutraceutical production.

CONCLUSION

Simarouba glauca demonstrates significant potential as a source of bioactive compounds with anticancer, antimicrobial and anti-inflammatory properties. Preclinical studies consistently report its effectiveness across various cancer models, which was supported by its rich phytochemical profile. Toxicological evaluations further indicated a favourable safety margin. However, its clinical translation remains limited by the absence of standardized formulations, pharmacokinetic data and human trials. Advancing this promising plant into therapeutic use will require focused research on formulation development, delivery systems and comprehensive clinical evaluation.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this review article.

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