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Ethnomedicinal and Possible Mechanism of Anti-cancer Properties of Elephant Foot - A Review

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ABSTRACT

Elephant foot (*Elephantopus scaber* Linn.), a medicinal plant widely used in traditional medicine, holds significant promise as a potential anticancer agent. Ethnomedicinal practices across various countries employ *E. scaber* extracts for their anti-inflammatory, antipyretic, diuretic, anticough, antibiotic, emollient, and tonic properties. Recent scientific investigations have shed light on several mechanisms through which *E. scaber* exhibits anticancer effects. These include the induction of apoptosis (programmed cell death), inhibition of cell proliferation, suppression of angiogenesis (formation of new blood vessels essential for tumour growth), and modulation of signalling pathways crucial for tumour progression. Additionally, the plant's antioxidant properties play a role in protecting cells from oxidative stress-induced damage, a common feature in cancer development. Furthermore, *E. scaber* has been shown to enhance the immune response against cancer cells, adding another layer to its anticancer potential. It also demonstrates synergistic interactions with conventional chemotherapy drugs, potentially improving their efficacy and reducing side effects. The plant's diverse pharmacological properties, combined with its traditional use, underscore its value as a natural resource with significant anticancer potential. Overall, Elephant foot represents a promising avenue for the development of novel anticancer therapies, warranting further research and exploration.

1.Introduction

Elephantopus scaber Linn., a member of the Asteraceae family, is a small herb native to tropical and subtropical regions across the Neotropics, Europe, Asia, Africa, and Australia. Known as «Prickly leaved elephant foot» or «elephant's foot» in English, and locally referred to as «Gojivha» or «Hastipadi» in Sanskrit and «Gobhi» in Hindi, this plant is widespread in the Western Ghats of India and other forested areas like Achanakmar in Chhattisgarh.

The plant exhibits a coarse, rigid, and erect structure, typically reaching heights of 30–60 cm. Its leaves form a basal rosette, oblong-ovate to oblong-lanceolate, and are commonly notched along the margins. Flower heads are clustered at branch ends, encased in leaf-like bracts, and bear small purple flowers, while fruits are ribbed achenes with rigid pappus bristles.

Throughout various cultures, *E. scaber* has been traditionally valued for its diverse medicinal properties. Decoctions of the whole plant or its roots have been widely used across India, China, Vietnam, the Philippines, Thailand, Madagascar, Nepal, and Brazil as anti-inflammatory, antipyretic, diuretic, cough suppressant, antibiotic, emollient, and tonic. In India, it is used for cardiovascular and respiratory conditions, and in cases of smallpox and gonorrhea. Root powder is mixed with boiling water for internal relief from burning sensations, while fresh root extracts are used to treat reproductive and menstrual disorders. Various parts of the plant are also applied externally for rheumatism, headaches, and wounds.

In Ayurvedic medicine, E. scaber has been combined with other herbs for treating neoplasms and was historically used as an anti-venom, antiseptic, and treatment for digestive and respiratory ailments. Extensive phytochemical research on E. scaber has revealed an abundance of bioactive compounds. Notably, sesquiterpene lactones such as deoxyelephantopin, isodeoxyelephantopin, scabertopin, and isoscabertopin are key components known for their anticancer properties. Other significant compounds include triterpenoids, steroids, flavonoids, and essential oils, which contribute to the plant's pharmacological activities.

E. scaber has shown promise in modern pharmacological studies, particularly for its anticancer properties. Modern research has identified several bioactive compounds in *E. scaber*, such as sesquiterpene lactones like Elephatopin, deoxyelephantopin, flavonoids: Luteolin, quercetin, steroids: Stigmasterol, beta-sitosterol[5], Triterpenoids : Lupeol, epifriedelinol[6], which contribute to its extensive pharmacological activities including anti-inflammatory[7], antiasthamatic[8], antimicrobial9, hepatoprotective[10], nephroprotective[11], antidiabetic[12], antimalarial[13] ntiprotozoal, diuretic[14], antipyretic , anticancer, and antioxidant properties[15]. These multifaceted biological activities have prompted ongoing research to explore and expand upon the therapeutic potential of *E. scaber*, both as an ethnomedicinal remedy and as a source for developing new drugs.

2.Ethnomedicinal uses

Elephantopus scaber (commonly known as Elephant's Foot) has a long-standing history of ethnomedicinal use across diverse cultures. In India, it is traditionally used for cardiovascular support, where root powder mixed with boiling water is consumed to alleviate heart-related issues is also valued for respiratory health, with fresh roots chewed to relieve bronchitis, coughs, and colds. For skin conditions like smallpox and chickenpox, its roots are applied externally as an antiseptic and anti-venom for wounds and lesions. The powder is used to alleviate burning sensations and treat conditions like gonorrhoea, while both root powder and root decoctions address liver disorders.

E. scaber is commonly employed for gastrointestinal issues, treating ailments such as dysentery, diarrhoea, and other stomach troubles, and is even used for managing haemoptysis in tuberculosis. The plant's fresh utilized for various gynaecological conditions, including spermatorrhea, leucorrhoea, menstrual irregularities, and dysmenorrhea [16]. A paste of the roots and leaves is also applied externally to relieve headaches and menstrual bleeding. Beyond these uses, the plant's paste is traditionally used for

rheumatism and tetanus, and its decoction is valued for assisting in childbirth by expediting delivery and placenta expulsion. Moreover, leaf juice is appends for its antiseptic properties, highlighting its importance in traditional medicine for wound healing[17].

In Africa, *E. scaber* is used to treat inflammation, malaria, respiratory issues, wounds, rheumatism, arthritis, and various infections. In Latin America and the Caribbean, troves as a diuretic, antiulcer, anti-inflammatory, and analgesic, and is employed to treat urinary tract infections[18]. In Brazil, it is used for bladder stones, in Taiwan for hepatitis, and in Malaysia used to relieve flatulence. The plant also finds applications in Nigeria for arthritis, in Pakistan for venereal diseases, and in Mauritius for urinary and skin issues. This extensive ethnomedicinal usage highlights *E. scaber* therapeutic potential in addressing a wide array of health conditions[19-22].

Figure 1: *Elephantopus scaber*

3.Botanical Information:[23]

Kingdom: Plantae
Division: Magnoliophyta
Class: Magnoliopsida
Order: Asterales
Family: Asteraceae
Genus: Elephantopus
Species: *Elephantopus scaber*
Vernacular names of Elephant Foot:
Hindi: Gaathi Paanv
Kannada: Aane Haalu
Telugu: Eruvu Mullu
Tamil: Yanai Patam,
Arabic Qadam al Feel

4. Mechanism of Antitumor Activity of Elephant Foot

The antitumor activity of *E. scaber* is believed to involve multiple mechanisms, supported by scientific evidence from various studies.

4.1. Induction of Apoptosis.

Anticancer potential of *E. scaber*, focusing on its mechanism of inducing apoptosis via downregulation of Bcl-2 and Bcl-xL proteins in MCF-7 breast cancer cells. The extract's effect on cell viability was assessed using MTT and lactate dehydrogenase (LDH) assays, while apoptotic induction was confirmed by AO/EtBr staining and phase contrast microscopy. The results showed significant reduction in cancer cell viability, with an IC50 of 80 μM, while sparing normal breast cells (MCF-10A). Morphological changes consistent with cell death were observed in treated MCF-7 cells, along with the downregulation of key anti-apoptotic proteins. These findings suggest that *E. scaber* induces apoptosis through inhibition of survival pathways, making it a promising candidate for breast cancer therapy. Further studies are needed to explore additional molecular targets[24,25].

4.2. Inhibition of Cell Proliferation*:*

E. scaber ethanol extract (EEES) on HepG2 hepatocellular carcinoma cell proliferation. Initial in vitro screenings using the MTT assay demonstrated that EEES effectively inhibited HepG2 cell proliferation, while showing low toxicity toward normal cells. Further analysis revealed that EEES induced cell cycle

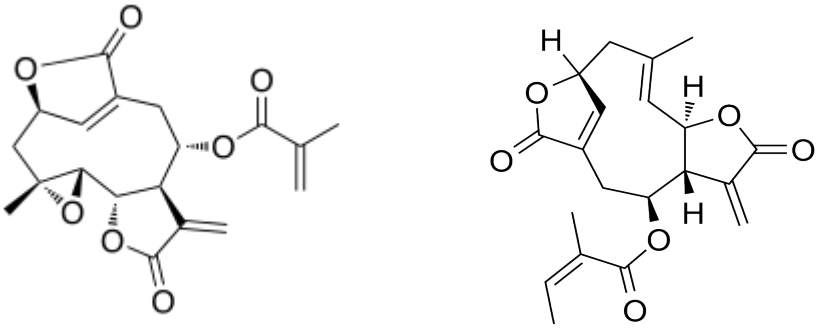

***Figure** 2. Elephantopin and Isoscabertopin*

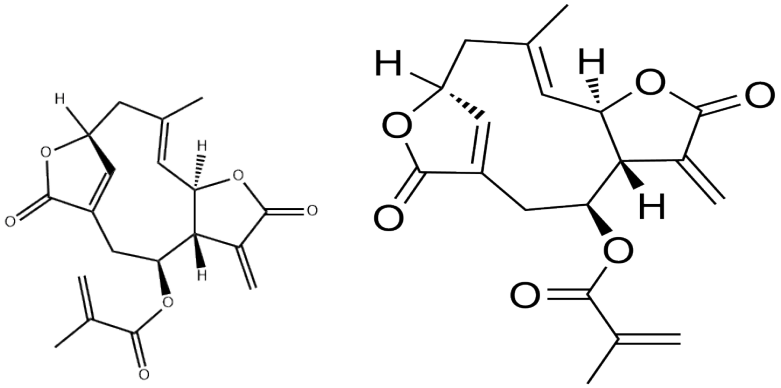

***Figure** 3. Deoxyelephantopin and Isodeoxyelephantopin*

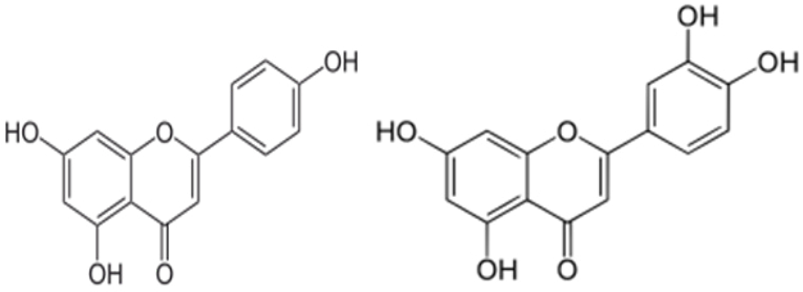

Figure 4. Apigenin and Luteolin

arrest at the G2/M phase, evidenced by the down-regulation of cyclin B1 and CDK1, two critical G2/M checkpoint proteins. In addition, EEES significantly promoted apoptosis in HepG2 cells, as confirmed by increased levels of cleaved caspase-3 and PARP. A bioinformatics analysis identified the PI3K/Akt pathway as a key target of EEES, which was validated through western blotting, showing reduced phosphorylation of PI3K and Akt. These findings highlight EEES's potential to inhibit HepG2 proliferation by modulating key cancer-related pathways[26].

4.3. Suppression of Angiogenesis.

The study investigates the effect of *E. scaber* on A549 lung cancer cells, focusing on its role in

Table 1: **Phytochemicals Responsible for Anticancer activity**

Phytochemicals	Mechanism of action	References
Sesquiterpene lactones (Elephantopin, scabertopin, isodeoxyelephantopin, and isoscabertopin, Deoxyelephantopin)	Induction of apoptosis, cell cycle arrest	[40]
Flavonoids (Quercetin, Luteolin, Apigenin)	Antioxidant activity, anti-inflammatory effects	[41]
Triterpenoids (Lupeol, Betulinic acid)	Induction of apoptosis, inhibition of metastasis	[42,43]
Steroids (Stigmasterol, Beta-sitosterol)	Cytotoxic effects, modulation of cell cycle	[44]
Phenolic compounds (Caffeic acid, Chlorogenic acid)	Antioxidant activity, anti-inflammatory effects	[45]

downregulating vascular endothelial growth factor (VEGF), a critical factor in tumour angiogenesis and metastasis. The methanolic extract of *E. scaber* significantly inhibited the metastatic potential of A549 cells, as demonstrated by decreased cell invasion and migration. Additionally, *E. scaber* treatment resulted in the downregulation of VEGF expression, which plays a key role in the formation of new blood vessels that support tumor growth. This reduction in VEGF levels was accompanied by the inhibition of pro-metastatic proteins such as MMP-2, MMP-9, and urokinase-type plasminogen activator, further highlighting its potential as an anti-metastatic agent in lung cancer therapy[27,28].

4.4. Modulation of Signalling Pathways.

The anticancer potential of *E. scaber*, particularly in inhibiting key tumour signaling pathways. The bioactive compounds from *E. scaber* leaves have been shown to inhibit ERα and Nrf2, both of which are critical regulators in tumour progression, especially in breast cancer. By targeting these molecules, *E. scaber* reduces the crosstalk between the PI3K/AKT/mTOR, ERα, and Nrf2 signaling pathways, which are essential for cancer cell survival, proliferation, and metastasis. This inhibition leads to the suppression of breast cancer cell growth, indicating that *E. scaber* can disrupt multiple tumour promoting pathways simultaneously, positioning it as a promising candidate for cancer therapy targeting ERα and PI3K/AKT/mTOR signalling[29,30].

4.5. Antioxidant Effects.

E. scaber exhibits significant antioxidant activity, which may contribute to its chemopreventive effects against cancer. Studies have shown that the methanolic root extract of E. scaber reduces oxidative stress markers such as TBARS and conjugated dienes (CD), while increasing levels of protective antioxidants like glutathione (GSH). The extract also decreased liver enzyme levels (AST, ALT, ALP, GGT) and improved protein and albumin levels, indicating hepatoprotective effects. This antioxidant potential is crucial in mitigating cellular damage caused by free radicals, which are often linked to cancer development. In tumour models, deoxyelephantopin (DOE), an active compound from *E. scaber*, exhibited potent cytotoxicity and induced apoptosis in Ehrlich ascites carcinoma (EAC) cells. The ability of DOE to reduce oxidative stress and trigger

apoptosis suggests that the antioxidant properties of *E. scaber* play a role in its anticancer and chemopreventive effects[31-33].

4.6. Immunomodulation.

E. scaber leaf extract has been shown to significantly enhance the activity of T lymphocytes and natural killer (NK) cells, contributing to its immunomodulatory effects. In studies involving pregnant mice infected with Salmonella typhimurium, treatment with E. scaber leaf extract increased the relative number of CD4+ and CD8+ T cells, as demonstrated by flow cytometry analysis. These findings indicate that E. scaber helps to restore immune balance, particularly in conditions of infection. Additionally, the extract boosts NK cell activity, which plays a crucial role in early defense against infections and tumour cells. This immunostimulatory effect suggests that E. scaber may be a valuable natural remedy for enhancing immune response, especially in vulnerable populations[34,35].

4.7. Synergistic Effects.

The study examined the synergistic effects of *E. scaber* and tamoxifen on cytotoxicity against the MCF-7 breast cancer cell line using three-dimensional multicellular tumour spheroid (MCTS) cultures. This model more accurately reflects solid tumours than monolayer cultures. The combination of *E. scaber* ethanol extract with tamoxifen, at concentrations lower than their respective IC_{50} values, effectively induced apoptosis in the MCTS. The treatment significantly increased lactate dehydrogenase release (>58%), caused cell cycle arrest at the S phase, and resulted in a 1.3-fold increase in mitochondrial membrane potential depolarization. DNA fragmentation analysis revealed over a 64% increase in DNA-damaged cells. The findings suggest that the combination enhances cytotoxicity and reduces drug resistance, highlighting the potential for *E. scaber* to improve tamoxifen efficacy in breast cancer therapy[24, 36-39]

5. Phytochemicals responsible for anticancer activity.

The anticancer properties of *E. scaber* are well-supported by its diverse array of phytochemicals. These compounds work synergistically to induce apoptosis, inhibit cell proliferation, and modulate key signaling pathways involved in cancer development and progression. Below is a summary table of key phytochemicals and their mechanisms (Figures 2-4)

6. Conclusion

The phytochemical profile of *Elephantopus scaber* provides a strong basis for its anticancer properties. The synergistic action of sesquiterpene lactones, flavonoids, triterpenoids, steroids, and phenolic compounds underlies the plant's ability to induce apoptosis, inhibit cell proliferation, and combat oxidative stress and inflammation. These findings support the traditional use of *E. scaber* in cancer treatment and highlight its potential for development into an effective natural anticancer therapy. □

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