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Review Article

Deoxyelephantopin: A cytotoxic sesquiterpene lactones from *Elephantopus scaber* Linn.

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Abstract:

Deoxyelephantopin is a novel sesquiterpene lactones found in the specific extracts such as chloroform, acetone, ethanol and aqueous extracts of *E. scaber* belonging to family asteracae. Deoxyelephantopin seems to be a potential anticancer agent among all other various sesquiterpene lactones such as isodeoxyelephantopin, scabertopin, isoscabertopin, elescaberin, 17,19dihydrodeoxyelephantopin, iso 17,19 dihydro-deoxyelephantopin. Present review focus on the cytotoxic potential of deoxyelephantopin from *E. scaber*.

Keywords*: Deoxyelephantopin, Elephantopus scaber, sesqueterpene,*

1. Introduction

In folk medicinal practices, various parts of plant and even the whole plant of *E. scaber* have been used in many countries for the treatment of number of diseases. In many countries decoction of whole plant or root is used as an anti-inflammatory, antipyretic, diuretic, anticough agent, antibiotics, emollient, bronchitis, wound healing and tonic [1,3,4,8-24]. In Ayurvedic medicinal system, various herbal combinations were used for an effective cancer treatment. Local application of mixture of polyherbal formulation containing *E. scaber,* along with other seven herbal drugs is used for the treeatment of minor neoplasm (*Vatika granthi*). For treatment of major neoplasm (*Pittaja arbuda*), a mixture of leaves of *E. scaber* along with few other herbal drugs is used [25].

The lectotype species of *Elephantopus* genus i.e. *Elephantopus scaber* was established in Asteraceae family by Linnaeus in 1753. It is a common wild weed that forms undergrowth in shady places [1]. *E. scaber* is a genus of about 32 species centered in the Neotropics (extending from southern Mexico through Central America and northern South America to southern Brazil), Europe, Asia (India, Nepal, Pakistan, Sri Lanka, China, Taiwan, Hong Kong, Japan, Malaysia, Indonesia, Vietnam, Philippines, Thailand and Myanmar), Australia and Africa [1-7].

2. Sesquiterpene lactones from *E. scaber*

Sesquiterpene lactones are a class of naturally occurring plant terpenoids that represent a diverse and unique category of natural products and characteristic constituents of family Asteraceae. Several studies on various plant species of genus *Elephantopus* reports the presence of large number of sesquiterpene lactones which have strong cytotoxic and antitumor activity [2,6,26-42]. Sesquiterpenoids generally inhibit tumor growth by selective alkylation of growth regulatory biological macromolecules such as key enzymes, which controls cell division, thereby inhibiting a variety of cellular functions, which directs the cell into apoptosis. These reactions are interceded chemically by α, β-unsaturated carbonyl system present in the sesquiterpene lactones. Being rich source of sesquiterpene lactones, there have been renewed interests of researcher all over the world in the phytochemistry of *E. scaber* [43].

Sesquiterpene lactones present in the various parts of the plant such as deoxyelephantopin, isodeoxyelephantopin, scabertopin, isoscabertopin, elescaberin, 17, 19-dihydrodeoxyelephantopin, iso-17,19-dihydrodeoxyelephantopin, 11,13-dihydrodeoxy-elephantopin, scabertopinol etc. have been reported to be the active constituents. Among these constituents deoxyelephantopin seems to be very promising compound for the treatment of cancer.

Deoxyelephantopin ($C_{19}H_{20}O_6$) is one of the main sesquiterpene lactone isolated from the aqueous, ethanol, chloroform, acetone extract of whole plant and ethanolic extract of root of *E. scaber*. The aqueous extract has been partitioned with ethyl acetate and then deoxyelephantopin has been isolated from the ethyl acetate fraction by silica gel column containing $CHCl_3$/EtOAc gradient elution [36]. From chloroform extract deoxyelephantopin has been isolated by silica gel column by Hexane/EtOAc gradient elution. Deoxyelephantopin (mp 198-200°) have been crystallized from petroleum ether-EtOAc mixture as colourless needles. The structure of deoxyelephantopin has been established by careful examination of chemical evidence and spectral data such as IR, ^{1}H-NMR, ^{13}C-NMR and MS [2,6,31,34,35,40,44]. The details of chemical structures and percent yield of deoxyelephantopin and other sesquiterpene lactones have been depicted in figure 1.

3. Cytotoxicity study of deoxyelephantopin and other sesquiterpene lactones

Review of ethnomedical history of *E. scaber* clearly indicates its use in various part of the world for the treatment of variety of disease conditions. Many of these ethnomedical uses have been scientifically validated by the results of biological activity studies. About a dozens of multifarious activities ranging from anticancer, antibacterial [45-54], antifungal [55], hepatoprotective [56-61], antidiabetic [62-67], antioxidant [52,59], anti-inflammatory, analgesic [10,68-70], antiplatelet [71], antiasthamatic [72] and nephroprotective [73] to that of wound healing activity [5] has been reported in the literature. Apart from these various biological activity studies the present review focus on the *in vivo* and *in vitro* antitumor activity of sesquiterpene lactones from *E. scaber*. An antitumor activity study of *E. scaber* supersedes all other activities as evident from the studies of various

researchers. Several sesquiterpenoids (deoxyelephantopin, isodeoxyelephantopin, scabertopin, isoscabertopin, elescaberin, 17,19dihydrodeoxyelephantopin, iso 17,19 dihydrodeoxyelephantopin) have been isolated from the *E. scaber* and almost all of them have indicated significant antitumor activity [6, 31-41 ,44].

3.1 *In vitro* antitumor activity

Deoxyelephantopin and other analogs sesquiterpenoids from *E. scaber* have been demonstrated in numerous laboratories worldwide to have broad-spectrum antitumor activity against many tumor models.

Deoxyelephantopin exhibited strong effect on the PC-3 (human prostate carcinoma cell), CNE (human nasopharyngeal carcinoma epithelial cell) and HL-60 (human acute promyelocytic leukemia cell). In CNE cell it inhibited the CNE cell proliferation by arresting cell cycle in S and G2/M phases and also triggered apoptosis in CNE cells. Dysfunction in mitochondria was found to be associated with the deoxyelephantopin-induced apoptosis as evidenced by the loss of mitochondrial membrane potential, the translocation of cytochrome C, and the regulation of Bcl-2 family proteins [35,37].

Isodeoxyelephantopin mediated its effects by suppressing nuclear factor κB (NF-κB) activation and potentiate apoptosis. It inhibited activation of NF-κB by a variety of inflammatory agents and in a variety of cell lines such as KBM-5 (human chronic myeloid leukemia), H1299 (lungadenocarcinoma), HL60 (human promyelocytic leukemia), A293 (human embryonic kidney carcinoma), MCF-7(human breast adenocarcinoma), MM.1S (human multiple myeloma), and U266 (human multiple myeloma cell lines) and RAW 264.7. Specifically, NF-κB activity was inhibited because isodeoxyelephantopin suppressed IKK activation, resulting in inhibition of IκBα phosphorylation and degradation. Consequently, isodeoxyelephantopin also blocked p65 phosphorylation and p65 nuclear translocation. Furthermore, it suppressed expression of gene products involved in cell proliferation, antiapoptosis, and invasion. Suppression of NF-κB by isodeoxyelephantopin enhanced the apoptosis induced by TNF and inhibited TNF-induced cellular invasion and osteoclastogenesis [32].

Against DLA tumor cells, deoxyelephantopin and isodeoxyelephantopin act selectively on quiescent and PHA-stimulated proliferating human lymphocytes and inhibited tritiated thymidine incorporation into cellular DNA of DLA tumor cells and cause apoptosis. Therefore, the result indicated that deoxyelephantopin and isodeoxyelephantopin are not cytotoxic to normal human lymphocytes and only the proliferating cells were affected and hence could be used in regimens for treating tumors with extensive proliferative potencies [40].

Deoxyelephantopin, isodeoxyelephantopin scabertopin, isoscabertopin and elescaberin have been studied against SMMC-7721, Caco-2 and HeLa cell lines *in vitro*. All the above compounds exhibited significant antitumor effect in a concentration-dependent manner except isoscabertopin. The effect of isoscabertopin on the growth of tested cell lines was relatively weak [34,44].

Deoxyelephantopin, 17,19 dihydro-deoxyelephantopin, Iso-17,19 dihydro-deoxyelephantopin were investigated for anticancer activity *in vitro* in a panel of 34 human tumor cell lines. The screening comprised cell lines derived from bladder,

central nervous system, colon, gastric, head & neck, lung, mammary, ovarian, pancreatic, prostate, renal and uterus cancers, as well as cell lines established from melanomas and pleuramesothelioma. However, with regard to the tumor selectivity, some differences were found between the compounds. The melanoma derived cell line MEXF 394NL was sensitive to all three compounds. Deoxyelephantopin effected pronounced activity in the mammary cancer cell line MAXF 401NL while 17,19-dihydrodeoxyelephantopin was found highly effective in the renal cancer cell line RXF 944L, and iso-17,19 dihydrodeoxy-elephantopin showed marked activity to the large cell lung cancer LXFL 529L [6].

The literature review clearly indicates that the sesquiterpenoids lactones which have been reported from the ethanolic and aqueous extract of *E. scaber* are the only constituents responsible for significant antitumor activity. The ethanolic extract of *E. scaber* could inhibit growth and triggered time dependent and dosage dependent cell death in the MCF-7 breast cancer cell line via a p53 dependent apoptotic pathway. The extract triggered cell death with increased phosphatidyl serine externalization, DNA breaks and significant morphological apoptotic characteristics in the MCF-cells [23]. While the aqueous extract of leaves of *E. scaber* have been subjected to *in vivo* study described in later section.

3.2 *In vivo* antitumor activity

From the *in vitro* antitumor studies, it has been observed that deoxyelephantopin is the major sesquiterpenoids isolated from the *E. scaber* and seems to be very promising compound for the treatment of cancer. Hence only deoxyelephantopin has been subjected to *in vivo* antitumor activity studies against various cell lines tested in mice.

Deoxyelephantopin significantly reduced the growth rate of primary tumors *in vivo* of stably transfected HeLa cell [44]. Against a murine mammary adenocarcinoma cell line (TS/A), human breast adenocarcinoma cell line (MCF-7), human breast skin fibroblast cell line (CCD966SK), metastatic human breast cancer cell line (MDA-MB-231) and noncancerous human mammary epithelial cell line, deoxyelephantopin has potential as a chemopreventive agent for breast cancer and suppresses mammary adenocarcinoma and lung metastasis and double survival time in mice by several mechanism [44].

Later Lee and Shyur (2012) observed that deoxyelephantopin exhibits more profound suppression than paclitaxel (PTX) of lung metastasis of mammary adenocarcinoma TS/A cells in mice. Deoxyelephantopin significantly deregulate adhesion formation in TS/A cells, probably through inhibition of m-calpain activity. Epithelial growth factor (EGF)-mediated activation of Rho GTPase Rac1 and formation of lamellipodia in TS/A cells were remarkably suppressed by deoxyelephantopin treatment. Further, deoxyelephantopin impaired vesicular trafficking of EGF and induced protein carbonylation and formation of centrosomal aggregates in TS/A cells. Deoxyelephantopin-induced reactive oxygen species were observed to be the upstream stimulus for the formation of centrosomal ubiquitinated protein aggregates that might subsequently restrict cancer cell motility [41].

Shyur *et al*. (2012) has patented the isolated constituent, deoxyelephantopin and their analogues (isodeoxyelephantopin, scabertopin and isoscabertopin) from the *E. scaber* plant for the treatment of melanoma.

They claimed for deoxyelephantopin and their analogues act by inhibiting proliferation, migration and/or metastasis of melanoma cell by comparing the data with cisplatin. Deoxyelephantopin and cisplatin exhibited dose dependent inhibition of B16 cell proliferation and showed little or no toxicity on normal human melanocytes. They also claimed for the synergistic effect of deoxyelephantopin with cisplatin and observed variable degree synergistic cytotoxicity in B16 melanoma cell in mice [74].

Because of sesquiterpenoids present in *E. scaber*, the aqueous extract of leaves of *E. scaber* against Dalton's lymphoma ascitic (DLA) in swiss albino mice showed a significant enhancement of mean survival time and hence tumor cell growth was found to be inhibited [75].

4. Possible mechanism of action of deoxyelephantopin

Sesquiterpene lactones have recently attracted a great deal of interest of researcher for their anticancer activities, their molecular mechanisms of action and potential chemopreventive as well as chemotherapeutic applications. Deoxyelephantopin is the germacranolide sesquiterpene lactone isolated from the *E. scaber* that contains an extra α, β-unsaturated ketone and α-methylene-γ-lactone without an epoxy group in its structure [36]. Such common functional features, indicates the thiol-reactivity of sesquiterpene lactones which may be an underlying mechanism responsible for their bioactivities. [76].

Ichikawa *et al.*, (2006) demonstrated that isodeoxyelephantopin, an isomer of deoxyelephantopin, suppresses NF-kB signalling by inhibiting TNF-a-induced phosphorylation and degradation of IkB and upstream activation of IKKα/β and IKK kinase activities [32]. Huang *et al.*, (2010) demonstrated that deoxyelephantopin blocked the nuclear translocation of NF-kB (p65) and it's binding to consensus DNA elements in TNF-α-stimulated TS/A cells in vitro and in vivo. The carbonyl group at position 16 of deoxyelephantopin can form hydrogen bonds with residue Lys122 of NF-kB (p65), which also forms hydrogen bonds with cis-acting DNA element of p65 on the basis of a molecular docking analysis. Hence deoxyelephantopin blocked the NF-kB(p65)/DNA binding. Thus, deoxyelephantopin is an effective blocker of TNF-α–NF-kB axis signalling, which implies that deoxyelephantopin may have potential in preventing NF-kB-mediated tumorigenesis and metastasis [36].

In another study deoxyelephantopin was found to be significantly inhibiting the proliferation of different cancer cells and induce apoptosis and cell cycle arrest at G2/M phase in HeLa cell. With the help of biochemical and biophysical assays and molecular docking with site-directed mutagenesis analyses, it is revealed that deoxyelephantopin acted as a specific partial agonist against PPARγ which is a nuclear hormone receptor peroxisome proliferator-activated receptor-γ. [77]. PPARγ is regarded as a potential target for the discovery of anti-cancer agents and several of PPARγ ligands have been discovered to exhibit anti-proliferation activities against a wide variety of cancer cells including colon, prostate and breast cancers, although the detailed mechanisms still remain unclear [78].

5. Conclusion

E. scaber Linn. family Asteraceae is a small herb spread all over the world. It has

been used as a medicine since a long period of time in almost all countries where it grows and

Deoxyelephantopin, a novel sesquiterpene lactones in the specific extracts such as chloroform, acetone, ethanol and aqueous extracts. Many sesquiterpene lactones have been identified as deoxyelephatopin, isodeoxyelephantopin, scabertopin, isoscabertopin and few others but deoxyelephantopin is the major sesquiterpenoids that contribute to the anticancer activity. The significant activities for which *E. scaber* have attracted the attention of drug researchers is its antitumor activity. The major sesquiterpenoids of *E. scaber* have been subjected to the variety of antitumor activity studies and very significant results have been reported. Certain patents related to anticancer activity have already been granted. Therapeutic effectiveness of deoxyelephantopin may possibly develop it as a potential anticancer drug in future.

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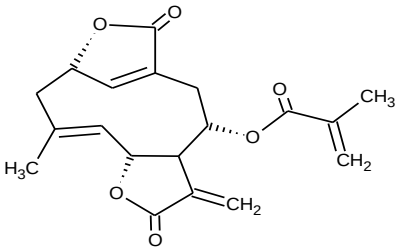
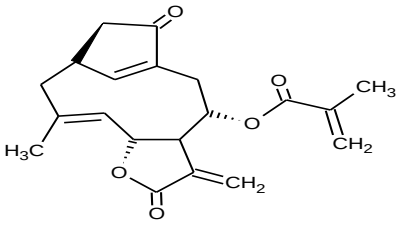
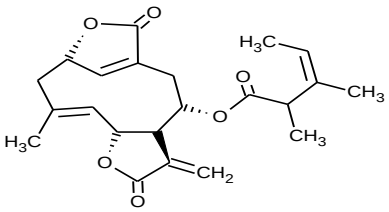
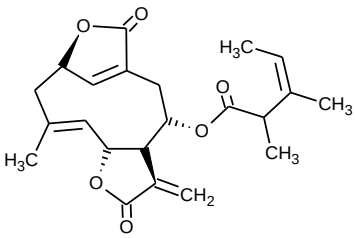
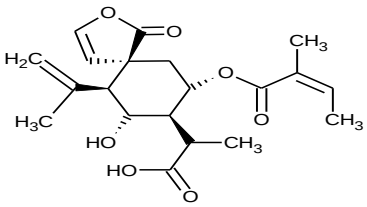
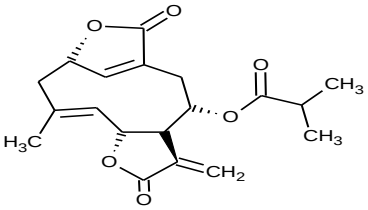
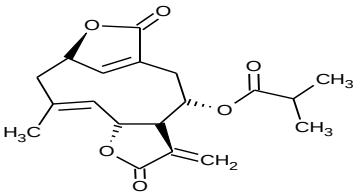
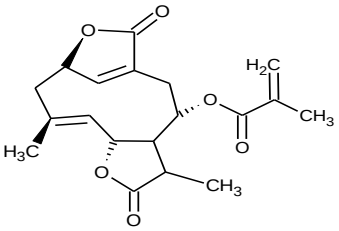
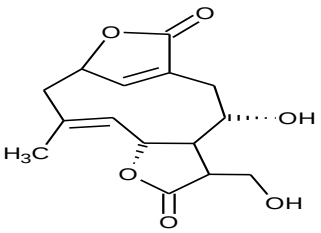
Table 1. Sesquiterpene lactones and their percent yield in *E. scaber*

S.N.	Sesquiterpene lactone	Extract	Part of plant	% yield in plant	Reference
1	Deoxyelephantopin 	Chloroform	Whole plant	0.106	Geetha et al. (2012; Kurokawa and Nakanishi (1970), Ichikawa et al. (2006)
		Acetone	Whole plant	0.096	Than et al. (2005).
		Ethanol	Whole plant	0.003	Liang et al. (2008),
				0.006	Than et al. (2005).
			Root	Not reported	Su et al. (2009).
		Aqueous	Whole plant	Not reported	Huang et al. (2010).
2	Isodeoxyelephantopin 	Chloroform	Whole plant	0.118	Geetha et al. (2012; Ichikawa et al. (2006)
		Ethanol	Whole plant	0.0008	Liang et al. (2008),
			Root	Not reported	Su et al. (2009).
3	Scabertopin 	Ethanol	Root	Not reported	Su et al. (2009).
4	Isoscabertopin 	-	-	-	Xu et al., 2006
4	Elescaberin 	Ethanol	Whole plant	0.0003	Liang et al. (2008),
5	Iso-17,19-dihydrodeoxyelephantopin	Acetone	Whole plant	0.0016	Than et al. (2005).

					
6	17, 19-dihydrodeoxyelephantopin 	Ethanol	Whole plant	0.002	Than et al. (2005).
7	11,13-dihydrodeoxyelephantopin 	Methanol	Whole plant	0.002	Desilva et al. (1982).
8	Scabertopinol 	Methanol	Aerial part	0.00011	Chang et al. (2011).