A REVIEW OF ANTICANCER POTENTIAL OF ELEPHANTOPUS SCABER AND ITS PHYTOCONSTituENTS

Rupali Dutta Roy, Md. Shahadat Hossan, Mohammed Rahmatullah*

Department of Pharmacy, University of Development Alternative, Lalmatia, Dhaka-1207, Bangladesh.

ABSTRACT

Elephantopus scaber L, otherwise known as Prickly-leaved elephant’s foot in English is a tropical plant belonging to the sunflower family (Asteraceae). It is native to Tropical Africa, Eastern Asia, Indian sub-continent, Southeast Asia and Northern Australia. A number of scientific reports have described anticancer activities of the plant or its phytoconstituents. In this review, we explore the various studies conducted with Elephantopus scaber and its phytoconstituents and the possible molecular mechanisms behind their anticancer activities.

KEY WORDS: Elephantopus scaber, Asteraceae, phytoconstituents, anticancer.

INTRODUCTION

Elephantopus scaber L, otherwise known as Prickly-leaved elephant’s foot in English is a tropical plant belonging to the sunflower family (Asteraceae). It is native to Tropical Africa, Eastern Asia, Indian sub-continent, Southeast Asia and Northern Australia. In Bangladesh, the plant is fairly common and known as Gojia lota as well as Hasti pada and considered as a medicinal plant. It is also considered a medicinal plant in India and the Philippines. The plant is known as Samduri in Hindi, Anashovadi in Tamil, Hastipata in Marathi, and Anayatiyan in Malayalam in the different vernaculars in India. In the Philippines, the plant is known as Dila-dila.

Anticancer activity reports on the plant and its phytoconstituents

Deoxyelephantopin (ESD) and isodeoxyelephantopin (ESI) are two sesquiterpene lactones derived from the plant. ESI has been reported to enhance apoptosis and inhibit invasion and
Rahmatullah et al.

World Journal of Pharmacy and Pharmaceutical Sciences

osteoclastogenesis, through inhibiting NF-κB (nuclear factor-κB) activation and NF-κB-regulated gene expression.\(^1\) The two compounds, along with an elemanolide sesquiterpene lactone, named elescarberin, isolated from the plant exhibited significant inhibitory activities against human SMMC-7721 liver cancer cells in vitro (IC\(_{50}\): 8.18-14.08 micromol/l).\(^2\)

The ethyl acetate fraction from the ethanolic extract of *Elephantopus scaber* showed the highest effect with IC\(_{50}\) values of less than 25 microg/mL on three susceptible cell lines, namely, PC-3 (human prostate carcinoma cell), CNE (human nasopharyngeal carcinoma epithelial cell) and HL-60 (human acute promyelocytic leukemia cell). Among the active compounds, compounds, deoxyelephantopin, exhibited the strongest effect on the PC-3, CNE and HL-60 cells, with IC\(_{50}\) values of 4.6, 2.6 and 0.9 microM, respectively. It was further shown that treatment with deoxyelephantopin caused subG1 population augmentation in PC-3, CNE and HL-60 cells, suggesting that apoptosis was induced in these cells.\(^3\) In human nasopharyngeal cancer CNE cells, ESD inhibited the CNE cell proliferation. Cell cycle arrest in S and G2/M phases was also found. ESD treatment also led to apoptosis in the cells. Dysfunction in mitochondria was found to be associated with the ESD-induced apoptosis as evidenced by the loss of mitochondrial membrane potential, the translocation of cytochrome c, and the regulation of Bcl-2 family proteins. Both intrinsic and extrinsic apoptotic pathways were triggered by ESD. Akt, ERK (extracellular signal regulated kinase) and JNK (Jun kinase) pathways were found to be involved in the apoptotic cell death. The results suggest that ESD can be an effective therapeutic agent in nasopharyngeal cancer.\(^4\)

Deoxyelephantopin has been described to have good potential for mammary cancer therapy. The compound showed significant antitumor growth and antimetastatic effect on murine mammary adenocarcinoma TS/A cells in vitro and in vivo in mice, which was superior to that of paclitaxel. Treatment with deoxyelephantopin resulted in regulation of molecules involved in proteolysis and calcium ion transport, suggesting effects on proteasome and endoplasmic reticulum machinery in TS/A cells. Induction of endoplasmic reticulum stress was associated with apoptosis.\(^5\) In another report on the effect of deoxyelephantopin on mammary adenocarcinoma, the authors observed that the compound significantly inhibited colony formation, cell proliferation, migration and invasion of TS/A cells and induced G(2)/M arrest and apoptosis in TS/A cells. c-Jun N-terminal kinase-mediated p21(Waf1/Cip1) expression and caspase activation cascades were up-regulated by the compound (these would lead to cell cycle arrest and induction of apoptosis). Moreover, tumor necrosis factor α-induced matrix
metalloproteinase-9 (MMP-9) enzyme activity and expression and nuclear factor-κB activation were abolished by deoxyelephantopin.\(^6\) Since MMP-9 can protect cells from apoptosis, abolishment of its activity can promote apoptosis.

The effect of active fraction of the plant has been investigated on skin papillomas induced by 7,12-dimethylbenz(a)anthracene (DMBA) as an initiator and croton oil as promoter in mice. Topical application of the active fraction (100 mg/kg) delayed the onset of papilloma formation and reduced the mean number of papillomas and the mean weight of papillomas per mouse. In soft tissue sarcomas in mice induced by subcutaneous injection of 20-methylcholanthrene, intraperitoneal administration of the active fraction inhibited the incidence of sarcomas and reduced the tumor diameter, suggesting that the active extract of the plant contains constituent(s) effective against papillomas and sarcomas.\(^7\)

Enriched portion of ethanol extract of the plant has been studied for cytotoxic activity in human epithelial cancer cells and found to exhibit potent dose-dependent cytotoxicity. Furthermore, treatment of cancer cells (HeLa, A549, MCF-7, and Caco-2) with the enriched portion demonstrated induction of apoptosis with signs like membrane blebbing and nuclear condensation, which are hallmarks of apoptosis. The enriched fraction furthermore inhibited MDR (multidrug resistant) transporters (ABC B1 and ABC G2) in cancer cells.\(^8\)

Ethanol extract of the plant and subsequent fractions reportedly also inhibited the growth of HCT116 human colorectal carcinoma cells and HT-29 cells and induced apoptosis. Apoptosis was associated with an upregulation of proapoptotic Bax, elevation of Bax/Bcl-2 ratio, dissipation of mitochondrial membrane potential, activation of caspase-3 and cleavage of poly (ADP-ribose) polymerase (PARP). Mitochondrial membrane potential was compromised and ROS (reactive oxygen species) was overproduced, which results demonstrate the involvement of the mitochondrial signaling pathway in apoptosis. The increase in ROS subsequently incited the increase in p53 protein expression and led to oligomerization of Bax (Bax oligomers cause enhanced membrane permeability leading to apoptosis), depolarization of mitochondrial membrane potential and induction of caspase cascade (caspase-3/7 and -9) in a time-dependent manner. Caspase cascade resulted in the cleavage of PARP which ultimately activated DNA fragmentation and eventually apoptosis.\(^9\)
The cytotoxicity and apoptosis-inducing capacity of ESD has been evaluated in lung adenocarcinoma (A549) cells. The results showed that ESD exhibited cytotoxicity to A549 cells ($IC_{50} = 12.287 \mu M$) but no toxicity towards normal human lymphocytes. The colony forming ability of A549 cells was suppressed in a dose-dependent manner by ESD. Various staining assays showed cell shrinkage, chromosomal condensation and nuclear fragmentation, indicating induction of apoptosis, as also evidenced by more TUNEL-positive (Terminal deoxynucleotidyl transferase dUTP nick end labeling) cells. It was concluded from the study that cell growth was arrested at the G2/M phase and apoptosis was induced by both intrinsic and extrinsic pathways.\textsuperscript{[10]} In lung cancer adenocarcinoma A549 cells, another study has found deoxyelephantopin to inhibit the expression of matrix metalloproteinase-2 (MMP-2), MMP-9, urokinase-type plasminogen activator and urokinase-type plasminogen activator receptor at transcript level. Tissue inhibitors of metalloproteinase-2 (TIMP-2) mRNA levels were up-regulated in A549 tumor cells without any change in TIMP-1 expression. ESD inhibited the protein levels of p-ERK1/2 and p-Akt in A549 cells but it activated p-JNK, p-p38 protein expression. NF-$\kappa$B and I-$\kappa$B$\alpha$ expressions were downregulated. The results are consistent with anti-metastatic activity of ESD.\textsuperscript{[11]}

The effect of ESI has also been checked against nasopharyngeal carcinoma cell lines. It was found that ESI could induce G2/M arrest and subsequently stimulate cell apoptosis in dose- and time-dependent manners. It was found that ESI caused alterations in 124 cellular proteins. These proteins were mainly involved in the regulation of oxidative stress and inflammation response. Functional studies demonstrated that ESI induced G2/M arrest and apoptosis by inducing ROS generation. Accumulated ROS resulted in DNA breakage, subsequent G2/M arrest and mitochondrial-mediated apoptosis. ESI upregulated the expression of anticancer inflammation factors IL-12a (interleukin-12a), IFN-$\gamma$, interferon-$\gamma$, and IFN-$\beta$ through ROS-dependent and independent pathways. Thus it appears that three sorts of mechanisms are involved in ESI action, namely, ROS-dependent DNA damage, mitochondrial-mediated apoptosis mechanism and antitumor inflammation factor pathway.\textsuperscript{[12]}

In breast carcinoma T47D cells and lung carcinoma A549 cells, ESI inhibited the growth of A549 and T47D cells in a dose- and time-dependent manner with $IC_{50}$ values of 10.46 and 1.3 $\mu g/mL$, respectively. The cells became detached from the monolayer and rounded up, had fragmented nuclei and condensed chromatin, and the numbers of apoptotic cells
increased. ESI-induced cell death was found to be associated with activated caspase-3 expression followed by cell cycle arrest at G2/M phase.\textsuperscript{[13]}

ESD has been found to be effective against cervical carcinoma SiHa cells. The compound inhibited growth of the cells and triggered apoptosis. Apoptosis was accompanied by sequential activation of caspases (8, 9, 3, and 7) and reactive oxygen species (ROS) production. There was also downregulation of antiapoptotic proteins (Bcl2 and Bcl-xL) and upregulation of apoptotic protein (Bax). ESD-induced G2/M phase arrest was associated with a marked increase in the levels of p53 and p21 and a decrease in phospho-signal transducer and activator of transcription 3 (pSTAT3-Tyr705), cyclin-dependent kinase 1 (cdc2), and cyclin B1. The expression of p-Akt and p-mTOR was downregulated. p-ERK was inhibited while p-JNK and p-p38 was activated on ESD treatment, suggesting that multiple pathways are involved in the G2/M phase growth arrest and apoptosis of SiHa cells.\textsuperscript{[14]}

Lupeol is another compound that has been isolated from the plant. The effect of lupeol has been studied on MCF-7 breast cancer cells. Lupeol induced an effective change in the cell viability of MCF-7 cells with IC\textsubscript{50} concentration as 80 μM. Induction of cell death, change in cell morphology and population of the cancer cells was observed in the lupeol treated cells. Lupeol effectively caused the downregulation of the protein expressions of Bcl-2 and Bcl-xL within the cells, which contributed to induction of apoptosis in the cells.\textsuperscript{[15]}

Interestingly, lupeol by itself, or as a constituent present in various plant extracts, has been demonstrated to be effective against multiple cancer cell lines. Lupeol treatment by itself led to decreased cell viability in two hepatocellular carcinoma (HCC) cell lines. It also induced apoptosis and caused cell accumulation in S phase. Further analysis revealed the induction of active caspase-3 and poly(ADP-ribose)polymerase (PARP) cleavage by treatment with lupeol. In the \textit{in vivo} studies, nude mice implanted with SMMC7721 (human hepatoma) cells subcutaneously were treated with lupeol three times a week and tumor development was significantly inhibited.\textsuperscript{[16]} Lupeol has been found to be a promising candidate against prostate cancer.\textsuperscript{[17]}

Lupeol has been found to inhibit tumor formation during 7,12-dimethylbenz(a)anthracene (DMBA) induced oral carcinogenesis.\textsuperscript{[18]} The pro-apoptotic potential of lupeol during 7,12-dimethylbenz(a) anthracene induced hamster buccal pouch carcinogenesis has been noted. Oral administration of lupeol at a dose of 50 mg/kg bw completely prevented the formation
oral tumors as well as decreased the expression p53 and Bcl-2, while increasing the expression of Bax and the activities of caspase 3 and 9.\(^{[19]}\)

Lupeol has been observed to inhibit the proliferation of gastric tumor cells in a dose-dependent manner.\(^{[20]}\) Treatment of colorectal cancer cells with lupeol led to a dose-dependent (i) decrease in cell viability, (ii) induction of apoptosis, (iii) decrease in colonogenic potential, (iv) decrease in β-catenin transcriptional activity, and (v) decrease in the expression of Wnt target genes. Lupeol inhibited the translocation of β-catenin from the cytoplasm to the nucleus.\(^{[21]}\) Systemic and local injections of lupeol reportedly inhibited tumor growth in a melanoma bearing mouse model.\(^{[22]}\) Lupeol inhibited the proliferation, migration, invasion, and induced apoptosis of gall bladder carcinoma GBC-SD cells in a dose-dependent manner \textit{in vitro}. Furthermore, the expression of p-EGFR (epidermal growth factor receptor), p-Akt and MMP-9 levels were significantly down-regulated. \textit{In vivo} studies with GBC-SD xenograft tumors established in male nude BALB/c mice showed that administration of lupeol decreased tumor growth in a dose-dependent manner. Since lupeol caused the down regulation of p-EGFR and MMP-9 in tumor tissues, lupeol-associated anticancer mechanism may have to do with the suppression of EGFR/MMP-9 signaling.\(^{[23]}\)

Lupeol has been shown to inhibit proliferation and induce apoptosis in human pancreatic cancer PCNA-1 cells. The compound induced apoptosis as well as cell cycle arrest in G0/G1 phase by upregulating p21 and p27 and downregulating cyclin D1. Cellular apoptosis was induced by lupeol through decreasing levels of p-AKT and p-ERK.\(^{[24]}\)

A novel mechanism for inhibition of hepatocellular carcinoma (HCC) HCCLM3 cells has been described. Inhibition of cell proliferation by lupeol has been shown to proceed in time- and dose-dependent manner, through caspase-3 dependent activation and Poly ADP-Ribose Polymerase (PARP) cleavage. Lupeol induced cell death was associated with a marked decrease in the protein expression of Brain-Derived Neurotrophic Factor (BDNF) and ser-9-phosphoryltion of Glycogen Synthase Kinase 3\(\beta\) (GSK-3\(\beta\)), with concomitant suppression of Akt1, phosphatidylinositol 3-kinase (PI3K), β-catenin, c-Myc and Cyclin D1 mRNA expression. The findings would suggest a link between caspase dependent pathway, BDNF secretion and Akt/PI3K/GSK-3\(\beta\) in HCC cells.\(^{[25]}\)

Thus a perusal of the scientific literature suggests that the plant \textit{Elephantopus scaber} contains at least three anticancer phytochemicals, namely, deoxyelephantopin, isodeoxyelephantopin,
and lupeol. These components have been shown to possess anticancer activity against a variety of cancer cell lines. Moreover, extract of the plant also have demonstrated anticancer activity against various cell lines suggesting that the plant may have more anticancer phytochemicals present. Thus, the plant is worth further study and the various anticancer phytochemicals be more researched upon as to their appropriate therapeutic potentials.

CONCLUSION

*Elephantopus scaber* has been found to contain at least three phytoconstituents, namely deoxyelephantopin, isodeoxyelephantopin, and lupeol, all three compounds having been reported for anticancer activity against a wide variety of cancer cell lines. The plant and its phytochemical constituents thus possess potential as promising anticancer drugs.

REFERENCES


