Deoxyelephantopin from *Elephantopus scaber* Inhibits HCT116 Human Colorectal Carcinoma Cell Growth through Apoptosis and Cell Cycle Arrest

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Abstract: Deoxyelephantopin (DET), one of the major sesquiterpene lactones derived from *Elephantopus scaber* was reported to possess numerous pharmacological functions. This study aimed to assess the apoptosis inducing effects and cell cycle arrest by DET followed by elucidation of the mechanisms underlying cell death in HCT116 cells. The anticancer activity of DET was evaluated by a MTT assay. Morphological and biochemical changes were detected by Hoescht 33342/PI and Annexin V/PI staining. The results revealed that DET and isodeoxyelephantopin (isoDET) could be isolated from the ethyl acetate fraction of *E. scaber* leaves via a bioassay-guided approach. DET induced significant dose- and time-dependent growth inhibition of HCT116 cells. Characteristics of apoptosis including nuclear morphological changes and externalization of phosphatidylserine were observed. DET also significantly resulted in the activation of caspase-3 and PARP cleavage. Additionally, DET induced cell cycle arrest at the S phase along with dose-dependent upregulation of p21 and phosphorylated p53 protein expression. DET dose-dependently downregulated cyclin D1, A2, B1, E2, CDK4 and CDK2 protein expression. In conclusion, our data showed that DET induced apoptosis and cell cycle arrest in HCT116 colorectal carcinoma, suggesting that DET has potential as an anticancer agent for colorectal carcinoma.

Keywords: deoxyelephantopin; apoptosis; cell cycle; colorectal cancer; *Elephantopus scaber*

1. Introduction

Colorectal cancer is the third ranked deadliest malignancy in the world. Chemotherapy is the current mode of treatment for colorectal cancer but it has limited efficacy with escalating side effects. Plants are an important source in the development of naturally-derived pharmaceutical agents for the treatment or prevention of various pathologies. To date, plants continue to contribute novel leads for drug discovery targeting a multitude of ailments, including cancer [1]. Currently, more than 50% of all approved drugs are natural products and their derivatives [2].

Phytochemicals have been reported to mediate diverse mechanisms against cancer including apoptosis, autophagy and cell cycle modulation. Apoptosis induction is a classical approach in initiating cell death characterized by biochemical (phosphatidylserine externalization, depolarization of mitochondrial membrane potential and caspase activation) and morphological hallmarks (DNA fragmentation, cell shrinkage and chromatin condensation) [3,4].

Various cytotoxic agents and DNA damaging inducers are capable of arresting cell cycle at the G0/G1, S or G2/M phase, consequently resulting in apoptosis induction in cancer [5–7].