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Pro-apoptotic Effects of Ethanol Extract of *Hizikia fusiforme* in Human Leukemic U937 Cells

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Hizikia fusiforme, well known as Sea weed fusiforme, is reported to possess many pharmacological activities including antioxidant, antimutagenic and anticoagulant effect. However, the molecular mechanisms of *H. fusiforme* on biochemical actions in cancer have not been clearly elucidated yet. The purpose of the present study was to examine the effect of the ethanol extract of *H. fusiforme* (EEHF) on the anti-proliferative effects of human leukemic U937 cells. It was found that EEHF could inhibit the cell proliferation of U937 cells in a concentration-dependent manner, which was associated with apoptotic cell death such as formation of apoptotic bodies, DNA fragmentation and increased populations of apoptotic-sub G1 phase. The induction of apoptotic cell death by EEHF was connected with a down-regulation of anti-apoptotic Bcl-2, Bcl-X_L and IAPs expression. MEHC treatment induced the proteolytic activation of caspase-3, caspase-8 and caspase-9, and a concomitant inhibition of PARP, β-catenin, PLC-γ1 and DFF45/ICAD proteins. Furthermore, caspase-3 specific inhibitor, z-DEVD-fmk, significantly inhibited EEHF-induced apoptosis demonstrating the important role of caspase-3 in the observed cytotoxic effect. Taken together, these findings suggest that EEHF may be a potential chemotherapeutic agent for the control of human leukemic U937 cells and further studies will be needed to identify the active compounds that confer the anti-cancer activity of EEHF. [This work was supported by a grant from Marine Bioprocess Research Center of the Marine Bio 21 Center funded by the Ministry of Land, Transport and Maritime, Republic of Korea.]

Key words: *Hizikia fusiforme*, U937, apoptosis, Bcl-2, caspase-3

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Induction of Apoptosis and Inhibition of Cell Migration by Ethyl Alcohol Extract of *Hizikia fusiforme* in Human Breast cancer Cells

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Hizikia fusiforme is a kind of brown edible seaweed that mainly grows in the temperate seaside areas of the northwest Pacific including Korea, Japan and Chine. Recently, *H. fusiforme* has been known to exert antioxidant, antimutagenic and anticoagulant activity, however, the molecular mechanisms of *H. fusiforme* in malignant cells have been poorly studied until now. In this study, we investigated the effects of ethyl alcohol extract of *H. fusiforme* (EAHF) on the anti-proliferative effects of MDA-MB-231 and MCF-7 human breast cancer cells. EAHF treatment resulted in a concentration-dependent growth inhibition by including apoptosis in MDA-MB-231 cells and G1 phase arrest in MCF-7 cells. In MDA-MB-231 cells, the increase in apoptosis induced by EAHF was correlated with up-regulation of pro-apoptotic Bax and down-regulation of cIAP-2 expression. EAHF treatment induced the proteolytic activation of caspase-3 and caspase-9, and a concomitant inhibition of poly (ADP-ribose) polymerase (PARP), β-catenin, phospholipase (PLC)-γ1 protein and DNA fragmentation factor 45/inhibitor of caspase-activated DNase (DFF45/ICAD). Furthmore, the EAHF inhibited cell migration in a concentration- and time-dependent manner of MDA-MB-231 and MCF-7 cells, as evidenced by the results of the wound healing assay. Taken together, these findings provide important new insights into the possible molecular mechanisms of the anti-cancer activity of *H. fusiforme*. [This work was supported by a grant from Marine Bioprocess Research Center of the Marine Bio 21 Center funded by the Ministry of Land, Transport and Maritime, Republic of Korea.]

Key words: *Hizikia fusiforme*, breast cancer, apoptosis, Bax, migration