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Genistein Enhances TRAIL-induced Apoptosis of Human Hepatocellular Carcinoma Hep3B Cells through Inhibition of p38 Mitogen-activated Protein Kinase

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The cytotoxic effect of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is limited in some carcinoma cancer cells. However, treatment with TRAIL in combination with nontoxic concentrations of genistein (GEN) sensitizes TRAIL-resistant human hepatocarcinoma Hep3B cells to TRAIL-mediated apoptosis. Combined treatment with GEN and TRAIL induced chromatin condensation, DNA fragmentation and sub-G_1 phase DNA content. These indicators of apoptosis correlated with the induction of caspase activity that resulted in the cleavage of PARP. Both the cell viability and cleavage of PARP induced by combined treatment were significantly inhibited by caspase-3, -8 and 9 inhibitors, demonstrating the important role of caspases in the observed cytotoxic effect. Combined treatment also triggered the inhibition of p38 MAPK activation. Inhibition of p38 MAPK, but not ERK, JNK or Akt, resulted in significantly decreased cell viability, mitochondrial dysfunction, and increased caspase activation,suggesting that the caspases are key regulators of apoptosis through inhibition of p38 MAPK in response to combined GEN and TRAIL treatment in human hepatocellular carcinoma Hep3B cells. [This study was supported by the Technology Development Program for Agriculture and Forestry, Republic of Korea.]

Key words: Genistein, TRAIL, apoptosis, p38 MAPK, Hep3B

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Bcl-2 Inhibites Esculetin-induced Apoptosis in Human Leukemic U937 Cells through Inactivation of Extracellular-regulated Kinase Pathway

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Esculetin, a coumarin derivative contained in various plants, has been shown to exhibit anti-cancer effects. However, the cellular and molecular mechanism by which esculetin induced apoptosis are poorly understood. In the present study, we determined that esculetin could inhibit the cell growth of U937 cells, which was associated with apoptotic cell death such as increased populations of apoptotic-sub G1 phase, formation of apoptotic bodies, DNA fragmentation and increased the percentage of cells with depolized mitochondrial membrane. Esculetin induced apoptosis through activation of ERK phosphorylation, up-regulation of DR4, cleavaged Bid, induced the proteolytic activation of caspases, and a concomitant degradation and/or down-regulation of PARP and PLC-γ1. Although esculetin did not alter Bcl-2 expression, overexpression of Bcl-2 were significantly attenuated the change in mitochondrial membrane potential, ERK phosphorylation, up-regulation of DR4 and caspases activation during esculetin-induced apoptosis. Furthermore, Bcl-2 specific inhibitor, HA14-1, restored esculetin-induced apoptosis through activation of ERK phosphorylation in U937/Bcl-2 cells. Thus, our findings imply that some of the biological functions of Bcl-2 may be attributed to their ability to inhibit esculetin-induced apoptosis through inhibition of ERK activation. And esculetin can be used as a new therapeutic approach for the treatment of human monocytic leukemia cells. [Marine Bioprocess Research Center of the Marine Bio 21 Center (M2007-11) funded by the Ministry of Maritime Affairs & Fisheries, Republic of Korea.]

Key words: Esculetin, apoptosis, Bcl-2, ERK, U937