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Esculentoside B (ESB) in anti-inflammatory responses and cellular roles of ganglioside GM3 biosynthesis in human cancer cells

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The natural compound Esculentoside B (ESB) is evidenced to inhibit the conjunctivae edema and release of NO, TNF-a, and IL-1b from macrophages upon inflammatory reactions. Then, ESB has been isolated and identified from the roots of *Phytolacca americana* L. (Phytolaccaceae). Anti-inflammatory effects of the esculentoside B have been investigated in LPS-induced RAW264.7 macrophage cells as a model cell line. ESB inhibited the production of Nitric Oxide (NO) and prostaglandin E2 (PGE2) in a dose dependent manner in RAW264.7 macrophage cells. ESB inhibited the gene expression of inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2). In addition, ESB suppressed the mRNA expression of inflammatory cytokines IL-1β, IL-6 and TNF-α in LPS-induced RAW264.7 macrophage cells. Moreover, ESB inhibited nuclear translocation of nuclear factor kB (NF-kB) and decreased the expression level of phospho-extracellular signal regulated kinase 1/2 (p-ERK), p-p38. These results suggest that ESB exhibits anti-inflammatory effects in LPS-induced RAW 264.7 macrophage cells. Cisplatin (cis-diamminedichloroplatinum, CDDP) is a commonly used chemotherapeutic agent for the treatment of several solid tumors. CDDP binds to DNA to generate DNA adducts. CDDP regulates the activity of certain ion channels, transport proteins and various plasma membrane enzymes, and induces Reactive Oxygen Species (ROS) during cancer chemotherapy However; the precise mechanism underlying apoptosis of cancer cells induced by CDDP remains unclear. Specific gangliosides such as GM3, GD3, and GD1b induce apoptosis in various types of cells. GM3 treatment in immature proliferating glial and neuronal cells results in suppression of cell proliferation and the induction of apoptosis. Additionally, GM3 is involved in cell death through the accumulation of ROS and intracellular calcium ion influx into the neuronal cells. In murine bladder cancer cells, GM3 overexpression induces apoptosis and reduces malignant potential. Among the gangliosides, CDDP augmented the expression of only GM3 synthase and its product GM3. Reduction of the GM3 synthase level through ectopic expression of GM3 small interfering RNA (siRNA) rescued HCT116 cells from CDDP-induced apoptosis. This was evidenced by inhibition of apoptotic signals by reducing ROS production through the regulation of 12-lipoxigenase activity. Furthermore, the apoptotic sensitivity to CDDP was remarkably increased in GM3 synthase-transfected HCT116 cells compared to that in controls. In addition, GM3 synthase-transfected cells treated with CDDP exhibited an increased accumulation of intracellular ROS. These results suggest the CDDP-induced oxidative apoptosis of HCT116 cells is mediated by GM3.

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