# Isocostunolide, a sesquiterpene lactone, induces mitochondrial membrane depolarization and caspase-dependent apoptosis in human melanoma cells.

賴基銘

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摘要

**Abstract**

Isocostunolide is a sesquiterpene lactone isolated from the roots of Inula helenium. Its chemical structure was determined by NMR and FAB-MS spectra. No biological activities of this compound have yet been reported. In this study, we found isocostunolide could effectively induce cytotoxicity in three cancer cell lines (A2058, HT-29, and HepG2), with an IC50 of 3.2, 5.0, and 2.0 μg/mL, respectively. DNA flow cytometric analysis indicated that isocostunolide actively induced apoptosis of cancer cells accompanied by a marked loss of G0/G1 phase cells. To address the mechanism of the apoptotic effect of isocostunolide, we analyzed the induction of apoptosis-related proteins in A2058. The levels of pro-caspase-8, Bid, pro-caspase-3, and poly(ADP-ribose) polymerase (PARP) decreased. However, the level of Fas was increased markedly in a dose-dependent manner. Furthermore, this compound markedly induced a depolarization of mitochondrial membranes to facilitate cytochrome c release into cytosol. The findings suggest that isocostunolide may activate a mitochondria-mediated apoptosis pathway. To address this, we found that isocostunolide-induced loss of mitochondrial membrane potential occurred via modulation of the Bcl-2 family proteins. The production of intracellular reactive oxygen species (ROS) in A2058 was not elicited. In summary, for the first time, we have isolated and characterized isocostunolide from I. helenium. This compound induces apoptosis through a mitochondria-dependent pathway in A2058 cells.

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