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Naringenin Induces Mitochondria-Mediated Apoptosis and Endoplasmic Reticulum Stress by Regulating MAPK and AKT Signal Transduction Pathways in Endometriosis Cells.

Park S, Lim W, Bazer FW, Song G.

Abstract

STUDY QUESTION: Does the flavonoid naringenin inhibit proliferation of human endometriosis cells?

SUMMARY ANSWER: Naringenin suppresses proliferation and increases apoptosis via depolarization of mitochondrial membrane potential and generation of reactive oxygen species (ROS) in human endometriosis cells.

WHAT IS KNOWN ALREADY: For management of endometriosis, hormonal therapy is commonly used to decrease production of estrogens by the ovaries, but that has limitations including undesirable side effects with long-term therapies. To overcome these limitations, it is important to discover novel compounds which have no adverse effects, but inhibit expression of target molecules involved in the pathogenesis of endometriosis.

STUDY DESIGN SIZE, DURATION: Well-established endometriosis cell lines (VK2/E6E7 and End1/E6E7) were purchased from the American Type Culture Collection. Effects of naringenin on VK2/E6E7 and End1/E6E7 cells were assessed in diverse assays in a dose- and time-dependent manner.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Effects of naringenin on viability, apoptosis (Annexin V expression, propidium iodide staining, TUNEL and invasion assays), mitochondria-mediated apoptosis, production of ROS and endoplasmic reticulum (ER) stress proteins of VK2/E6E7 and End1/E6E7 cells were determined.

Signal transduction pathways in VK2/E6E7 and End1/E6E7 cells in response to naringenin were determined by western blot analyses.

MAIN RESULTS AND THE ROLE OF CHANCE: In the present study, we demonstrated that naringenin suppressed proliferation and increased apoptosis through depolarization of mitochondrial membrane potential and inducing pro-apoptotic proteins, Bax and Bak, in both endometriosis cell lines. In addition, naringenin increased ROS, ER stress, through activation of eIF2α and IRE1α, GADD153 and GRP78 proteins in a dose-dependent manner. Furthermore, the induction of apoptosis by naringenin involved activation of MAPK and inactivation of PI3K pathways in VK2/E6E7 and End1/E6E7 cells.

LIMITATIONS REASONS FOR CAUTION: Lack of in vivo animal studies is a major limitation of this research. Effectiveness of naringenin to induce apoptosis of human endometriosis cells requires further investigation.

WIDER IMPLICATIONS OF THE FINDINGS: Our results suggest that naringenin is a promising therapeutic compound for treatment of endometriosis in women.