Structurally-related anti-tumor effects of flavanones in vitro and in vivo: involvement of caspase 3 activation, p21 gene expression and reactive oxygen species production.

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Abstract

Flavonoids exist extensively in plants and Chinese herbs, and several biological effects of flavonoids have been demonstrated. The antitumor effects in colorectal carcinoma cells (HT29, COLO205, and COLO320HSR) of eight flavanones including flavanone, 2'-OH flavanone, 4'-OH flavanone, 6-OH flavanone, 7-OH flavanone, naringenin, nargin, and taxifolin were investigated. Results of the MTT assay indicate that 2'-OH flavanone showed the most potent cytotoxic effect on these three cells, and cell death induced by 2'-OH flavanone was via the occurrence of DNA ladders, apoptotic bodies, and hypodiploid cells, all characteristics of apoptosis. Induction of caspase 3 protein processing and enzyme activity associated with cleavage of poly(ADP-ribose)polymerase (PARP) was identified in 2'-OH flavanone-treated cells, and a peptidyl inhibitor (Ac-DEVD-FMK) of caspase 3 attenuated the cytotoxicity of 2'-OH flavanone in COLO205 and HT-29 cells. Elevation of p21 (but not p53) and a decrease in Mcl-1protein were found in 2'-OH flavanone-treated COLO205 and HT-29 cells. Elevation of intracellular reactive oxygen species (ROS) was detected in 2'-OH flavanone-treated cells by the 2',7'-dichlorodihydrofluorescein diacetate (DCHF-DA) assay, and ROS scavengers including 4,5-dihydro-1,3-benzene disulfonic acid (tiron), catalase, superoxide dismutase (SOD), and pyrrolidine dithiocarbamate (PDTC) suppressed the 2'-OH flavanone-induced cytotoxic effect. Subcutaneous injection of COLO205 induced tumorformation in nude mice, and 2'-OH flavanone showed a significant inhibitory effect on tumor formation. The appearance of apoptotic cells with H&E staining, and an increase in p21, but not p53, protein by immunohistochemistry were observed in tumor tissues under 2'-OH flavanone treatment. Primary tumor cells (COLO205-X) derived from a tumor specimen elicited by COLO205 were established, and 2'-OH flavanone showed an significant apoptotic effect in COLO205-X cells in accordance with the appearance of DNA ladders, caspase 3 protein processing, PARP protein

cleavage, and increasing p21 protein. These results revealed in vitro, ex vivo, and in vivo antitumor activities of 2'-OH flavanone via apoptosis induction, and indicates that 2'-OH flavanone is an active compound worthy of development for cancer chemotherapy.