Flavone inhibition of tumor growth via apoptosis in vitro and in vivo

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Abstract

Colorectal carcinoma is a human malignant tumor, which is very resistant to currently available methods of treatment. Therefore, developing an effective agent with anti-colorectal carcinoma activity is important. In the present study, 8 structurally related flavones including flavone, 3-OH flavone, 5-OH flavone, 7-OH flavone, quercetin, kaempferol, quercetin, and morin were used to study their effects on colorectal carcinoma cells (HT29, COLO205, COLO320-HSR). Results of MTT assay indicated that flavone shows the most potent cytoxic effect among them on these three cell types. The cytotoxicity induced by flavone is mediated by inducing the occurrence of apoptosis characterized by the appearance of DNA ladders, apoptotic bodies and hypodiploid cells. Activation of caspase 3 protein procession and enzyme activity with inducing cleavage of caspase 3 substrates PARP was identified in flavone-treated cells, and an inhibitory peptide Ac-DEVD-FMK for caspase 3, but not Ac-YVAD-FMK for caspase 1, attenuates the cytotoxic effect of flavone in COLO205 and HT29 cells. Elevation of p21 but no p53 protein was observed in flavone-treated cells. Increasing intracellular peroxide level was detected in flavone-treated cells by DCHF-DA assay, and antioxidants such as tiron, catalase, SOD, PDTC, but not DPI, suppress flavone-induced cytotoxic effect. In vivo anti-tumor study indicates that flavone exhibits ability to inhibit tumor formation elicited by s.c. injection of COLO205 cells in nude mice, and apoptotic cells and an increase in p21, but not p53, protein were observed in tumor tissues derived from flavone-treated group. Additionally, flavone induced apoptosis in primary colon carcinoma cells COLO205-X with appearance of DNA ladders, caspase 3 protein procession, PARP protein cleavage, and an increase in p21 (not p53) protein. These data provide evidence to suggest that flavone is an effective agent to induce apoptosis in colorectal carcinoma cells in vitro and in vivo; activation of caspase 3, ROS production, and increasing p21 protein are involved.