Chemoprevention of colonic tumorigenesis by dietary hydroxylated polymethoxyflavones in azoxymethane-treated mice

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Hydroxylated polymethoxyflavones (OH-PMFs), existing exclusively in citrus genus, have been reported to exhibit a broad spectrum of biological activity and have potential to be a functional food ingredient. We investigated the chemopreventive effects and underlying molecular mechanisms of dietary administration of OH-PMFs in an azoxymethane (AOM)-induced colonic tumorigenesis model. ICR mice at age of 6 wk were injected with AOM twice weekly at a dose of 5 mg/kg for 2 wk and continuously fed control diet or diets containing 0.01 and 0.05% OH-PMFs, respectively. Mice were then sacrificed at 6 and 20 wk, and colonic tissues were collected and examined. OH-PMFs feeding dose-dependently decreased the number of aberrant crypt foci in colonic tissues of mice. More importantly, we found that OH-PMFs caused a strong reduction in numbers of large aberrant crypt foci and tumors in colonic tissue. Molecular analysis exhibited the anti-proliferative, anti-inflammatory, anti-angiogenic and pro-apoptotic activities of OH-PMFs. OH-PMF treatment significantly decreased the levels of inducible nitric oxide synthase, cyclooxygenase, cyclin D1 and vascular endothelial growth factor through interfering with Wnt/b-catenin and epidermal growth factor receptor/Ras/mitogen activated protein kinase signaling pathways as well as the activation of transcription factors NF-κB and STAT3 in colonic tissue, thus resulting in suppression of colonic tumorigenesis. These results demonstrated for the first time the in vivo chemopreventive efficacy and molecular mechanisms of dietary OH-PMFs against AOM-induced colonic tumorigenesis.