

Colorectal cancer chemoprevention by 2 β -cyclodextrin-inclusion compounds of auraptene and 4'-geranyloxyferulic acid

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The inhibitory effects of novel prodrugs, inclusion complexes of 3-(4'-geranyloxy-3'-methoxyphenyl)-2-trans propenoic acid (GOFA) and auraptene (AUR) with β -cyclodextrin (CD), on colon carcinogenesis were investigated using an azoxymethane (AOM)/dextran sodium sulfate (DSS) model. Male CD-1 (ICR) mice initiated with a single intraperitoneal injection of AOM (10 mg/kg body weight) were promoted by the addition of 1.5% (w/v) DSS to their drinking water for 7 days. They were then given a basal diet containing 2 dose levels (100 and 500 ppm) of GOFA/ β -CD or AUR/ β -CD for 15 weeks. At Week 18, the development of colonic adenocarcinoma was significantly inhibited by feeding with GOFA/ β -CD at dose levels of 100 ppm (63% reduction in multiplicity, $p < 0.05$) and 500 ppm (83% reduction in the multiplicity, $p < 0.001$), when compared with the AOM/DSS group (multiplicity: 3.36 ± 3.34). In addition, feeding with 100 and 500 ppm ($p < 0.01$) of AUR/ β -CD suppressed the development of colonic adenocarcinomas. The dietary administration with GOFA/ β -CD and AUR/ β -CD inhibited colonic inflammation and also modulated proliferation, apoptosis and the expression of several proinflammatory cytokines, such as nuclear factor-kappaB, tumor necrosis factor- α , Stat3, NF-E2-related factor 2, interleukin (IL)-6 and IL-1 β , which were induced in the adenocarcinomas. Our findings indicate that GOFA/ β -CD and AUR/ β -CD, especially GOFA/ β -CD, are therefore able to inhibit colitis-related colon carcinogenesis by modulating inflammation, proliferation and the expression of proinflammatory cytokines in mice.

There were ~1 million new cases of colorectal cancer (CRC) in 2002 (9.4% of the total cancers).¹ Globally, the mortality of CRC was reported to be 655,000 deaths per year in 2005.² There is at least a 25-fold variation in the occurrence of CRC worldwide.¹ The highest rates of incidence are in North America, Australia/New Zealand, Western Europe and Japan,

especially in Japanese men.¹ These large geographic differences for CRC are probably explained by differences in environmental exposures and lifestyles.

There are several types of pathogenesis of CRC.³ Among them, inflammation is linked with CRC development.⁴ The risk of CRC in patients with inflammatory bowel disease

Key words: β -cyclodextrin, 4'-geranyloxyferulic acid, auraptene, inclusion compounds, antitumor activity

Abbreviations: AOM: azoxymethane; AUR: auraptene; CDs: cyclodextrins; COX: cyclooxygenase; CRC: colorectal cancer; DSS: dextran sodium sulfate; dUTP: deoxyuridine triphosphate; GOFA: 3-(4'-geranyloxy-3'-methoxyphenyl)-2-trans propenoic acid (4'-geranyloxy-ferulic acid); IBD: inflammatory bowel disease; IL: interleukin; iNOS: inducible nitric oxide synthase; NF- κ B: nuclear factor-kappaB; Nrf2: NF-E2-related factor 2; TdT: terminal deoxynucleotidyl transferase; Tnf: tumor necrosis factor; TUNEL: TdT-mediated dUTP-biotin nick end labeling

Additional Supporting Information may be found in the online version of this article

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