Modulation of cancer signalling pathway(s) in two-stage mouse skin tumorigenesis by annonacin

ABSTRACT

Background: Annonacin, an annonaceous acetogenin isolated from Annona muricata has been reported to be strongly cytotoxic against various cell lines, in vitro. Nevertheless, its effect against in vivo tumor promoting activity has not been reported yet. Therefore, this study was aimed to investigate antitumor-promoting activity of annonacin via in vivo two-stage mouse skin tumorigenesis model and its molecular pathways involved. Methods: Mice were initiated with single dose of 7,12-dimethylbenz[α]anthracene (DMBA) (390 nmol/100 μL) followed by, in subsequent week, repeated promotion (twice weekly; 22 weeks) with 12-O-tetradecanoylphorbol-13-acetate (TPA) (1.7 nmol/100 μL). Annonacin (85 nM) and curcumin (10 mg/kg; reference) were, respectively, applied topically to DMBA/TPA-induced mice 30 min before each TPA application for 22 weeks. Upon termination, histopathological examination of skin, liver and kidney as well as genes and proteins expression analysis were conducted to elucidate the potential mechanism of annonacin. Results: With comparison to the carcinogen control, Annonacin significantly increased the tumor latency period and reduced the tumor incidence, tumor burden and tumor volume, respectively. In addition, it also suppressed tumorigenesis manifested by significant reduction of hyperkeratosis, dermal papillae and number of keratin pearls on skin tissues. Annonacin also appeared to be non-toxic to liver and kidney. Significant modulation of both AKT, ERK, mTOR, p38, PTEN and Src genes and proteins were also observed in annonacin-targeted signaling pathway(s) against tumorigenesis. Conclusions: Collectively, results of this study indicate that annonacin is a potential therapeutic compound targeting tumor promoting stage in skin tumorigenesis by modulating multiple gene and protein in cancer signaling pathways without apparent toxicity.

Keyword: Annonacin; Antitumor promotion; Gene expression; Skin tumorigenesis