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Pharmacological Mechanisms of an Indolic Compound in Chemoprevention of Colonic Acf Formation in Azoxymethane-Induced Colon Cancer Rat Model and Cell Lines

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Abstract : Although number of indole containing compounds have been reported to have anticancer properties in vitro but only a few of them show potential as anticancer compounds in vivo. The current study was to evaluate the mechanism of cytotoxicity of selected indolic compound in vivo and in vitro. In this context, we determined the potency of the compound in the induction of apoptosis, cell cycle arrest, and cytoskeleton rearrangement. HT-29, WiDr, CCD-18Co, human monocyte/macrophage CRL-9855, and B lymphocyte CCL-156 cell lines were used to determine the IC50 of the compound using the MTT assay. Analysis of apoptosis was carried out using immunofluorescence, acridine orange/ propidium iodide double staining, Annexin-V-FITC assay, evaluation of the translocation of NF-kB, oxygen radical antioxidant capacity, quenching of reactive oxygen species content, measurement of LDH release, caspase-3/-7, -8 and -9 assays and western blotting. The cell cycle arrest was examined using flowcytometry and gene expression was assessed using qPCR array. Results displayed a potent suppressive effect on HT-29 and WiDr after 24 h of treatment with IC50 value of 2.52±0.34 µg/ml and 2.13±0.65 µg/ml respectively. This cytotoxic effect on normal, monocyte/macrophage and B-cells was insignificant. Dipping in the mitochondrial membrane potential and increased release of cytochrome c from the mitochondria indicated induction of the intrinsic apoptosis pathway by the compound. Activation of this pathway was further evidenced by significant activation of caspase-9 and 3/7. The compound was also shown to activate the extrinsic pathways of apoptosis via activation of caspase-8 which is linked to the suppression of NF-kB translocation to the nucleus. Cell cycle arrest in the G1 phase and up-regulation of glutathione reductase, based on excessive ROS production were also observed. These findings were further investigated for inhibitory efficiency of the compound on colonic aberrant crypt foci in male rats. Rats were divided in to 5 groups: vehicle, cancer control, positive control groups and the groups treated with 25 and 50 mg/kg of compounds for 10 weeks. Administration of compound suppressed total colonic ACF formation up to 73.4%. The results also showed that treatment with the compound significantly reduced the level of malondialdehyde while increasing superoxide dismutase and catalase activities. Furthermore, the down-regulation of PCNA and Bcl2 and the up-regulation of Bax was confirmed by immunohistochemical staining. The outcome of this study suggest sthat the indolic compound is a potent anti-cancer agent against colon cancer and can be further evaluated by animal trial.

Keywords : indolic compound, chemoprevention, crypt, azoxymethane, colon cancer
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