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S9. 2-CHLORO-1, 4-NAPHTHOQUINONE DERIVATIVE of QUERCETIN EXERTS ANTICARCINOGENIC ACTIVITY THROUGH the INDUCTION of APOPTOSIS and OXIDATIVE STRESS RELATED AUTOPHAGY in COLORECTAL CANCER

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Phytochemical therapeutics such as Quercetin (Qc) have strong antitumor effects by inducing cell cycle arrest and apoptotic cell death, inhibiting enzymes activating carcinogens and modifying key signal transduction pathways. However, its clinical application is limited due to poor water solubility and low bioavailability. In a screening of novel semi-synthetic derivatives of Qc, 3, 7-dihydroxy-2-[4-(2-chloro-1,4-naphthoquinone-3-yloxy)-3-hydroxyphenyl]-5-hydroxychromen-4-one (CHNQ) was the most promising in terms of biological efficacy. Using a rat model of colitis, we have previously shown that CHNQ could ameliorate the effects of acetic acid induced acute colitis more efficiently that Qc. Since chronic inflammation very significantly contributes towards neoplastic transformation, we have hypothesized that CHNQ may also have potential as an anti cancer agent. Using colon cancer cell lines HCT-116 and HT-29, we have carried out detailed functional analyses comparing the anti-carcinogenic activities of CHNQ and Qc on cellular proliferation, cytotoxicity, cell cycle, apoptosis as well as autophagy and the associated signal transduction pathways.

BrdU incorporation and cytotoxicity assays showed that CHNQ strongly inhibited cell proliferation with an IC_{50} value of ≤ 20 μM, which was nearly 3 fold lower than the IC_{50} value of Qc (≥ 100 μM). Apoptosis was examined by Annexin V staining and flow cytometry, multi caspase activity assay and the expression of pro- and anti-apoptotic proteins using immunoblotting showing that treatment of cells with CHNQ resulted in a more robust induction of apoptosis compared to Qc. Treatment with CHNQ also resulted in the induction of oxidative stress as determined by the increased production of superoxide anions, leading to cell cycle arrest at G2/M. This was accompanied by the increased phosphorylation of MAP Kinases including; ERK1/2, p38 and JNK and decreased phosphorylation of Akt/PKB. Interestingly, the cells treated with CHNQ resulted in a dramatic increase in oxidative stress related autophagy as shown by increased expression and conversion of LC-3I to LC-3II, increased expression of Beclin 1, acidic vesicle accumulation and GFP-LC-3 puncta formation. All of these effects were also seen when cells were treated with Qc, however, the effect was weak and observed only at high doses. Overall, we propose that CHNQ, a semi-synthetic derivative of Qc, induces cancer cell death through the induction of oxidative stress and autophagy.