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Inhibitory Effects of Crocin from Crocus sativus L. on Cell Proliferation of a Medulloblastoma Human Cell Line

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Abstract : Medulloblastoma is a highly invasive tumour, as it tends to disseminate throughout the central nervous system early in its course. Despite the high 5-year-survival rate, a significant number of patients demonstrate serious long- or short-term sequelae (e.g., myelosuppression, endocrine dysfunction, cardiotoxicity, neurological deficits and cognitive impairment) and higher mortality rates, unrelated to the initial malignancy itself but rather to the aggressive treatment. A strong rationale exists for the use of Crocus sativus L (saffron) and its bioactive constituents (crocin, crocetin, safranal) as pharmaceutical agents, as they exert significant health-promoting properties. Crocins are water soluble carotenoids. Unlike other carotenoids, crocins are highly water-soluble compounds, with relatively low toxicity as they are not stored in adipose and liver tissues. Crocins have attracted wide attention as promising anti-cancer agents, due to their antioxidant, anti-inflammatory, and immunomodulatory effects, interference with transduction pathways implicated in tumorigenesis, angiogenesis, and metastasis (disruption of mitotic spindle assembly, inhibition of DNA topoisomerases, cell-cycle arrest, apoptosis or cell differentiation) and sensitization of cancer cells to radiotherapy and chemotherapy. The current research aimed to study the potential cytotoxic effect of crocins on TE671 medulloblastoma cell line, which may be useful in the optimization of existing and development of new therapeutic strategies. Crocins were extracted from stigmas of saffron in ultrasonic bath, using petroleum-ether, diethylether and methanol 70%v/v as solvents and the final extract was lyophilized. Identification of crocins according to high-performance liquid chromatography (HPLC) analysis was determined comparing the UV-vis spectra and the retention time (tR) of the peaks with literature data. For the biological assays crocin was diluted to nuclease and protease free water. TE671 cells were incubated with a range of concentrations of crocins (16, 8, 4, 2, 1, 0.5 and 0.25 mg/ml) for 24, 48, 72 and 96 hours. Analysis of cell viability after incubation with crocins was performed with Alamar Blue viability assay. The active ingredient of Alamar Blue, resazurin, is a blue, nontoxic, cell permeable compound virtually nonfluorescent. Upon entering cells, resazurin is reduced to a pink and fluorescent molecule, resorufin. Viable cells continuously convert resazurin to resorufin, generating a quantitative measure of viability. The colour of resorufin was quantified by measuring the absorbance of the solution at 600 nm with a spectrophotometer. HPLC analysis indicated that the most abundant crocins in our extract were trans-crocin-4 and trans-crocin-3. Crocins exerted significant cytotoxicity in a dose and time-dependent manner ($p < 0.005$ for exposed cells to any concentration at 48, 72 and 96 hours versus cells not exposed); as their concentration and time of exposure increased, the reduction of resazurin to resofurin decreased, indicating reduction in cell viability. IC50 values for each time point were calculated ~3.738, 1.725, 0.878 and 0.7566 mg/ml at 24, 48, 72 and 96 hours, respectively. The results of our study could afford the basis of research regarding the use of natural carotenoids as anticancer agents and the shift to targeted therapy with higher efficacy and limited toxicity. Acknowledgements: The research was funded by Fellowships of Excellence for Postgraduate Studies IKY-Siemens Programme.

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