

## **ANTHOCYANIDINS MODULATE THE CYTOTOXICITY OF IRINOTECAN AND OXALIPLATIN IN HUMAN COLON ADENOCARCINOMA CELLS**

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Colon cancer is the second leading cause of cancer death in most western countries; 40 to 50 percent of patients who undergo potentially curative surgery alone ultimately relapse and die of metastatic disease. Chemotherapy is used as a first-line treatment for metastatic colorectal cancer to destroy cancer cells that have spread; the new agents incorporated into frontline therapies, irinotecan and oxaliplatin, have improved the prognosis, but still, drug resistance is the major cause of chemotherapy failure due to overexpression of ABC efflux pumps and glutathione-S-transferase. Flavonoids, the most common and widely distributed group of polyphenols in plants, show strong antioxidant activities and inhibitory effect on the growth of some cancer cells; these agents interact with ABC transporters and reduce the expression of GSTP in tumor cells and therefore are of interest for increasing the efficacy of antitumor agents. The aim of this study was to evaluate the cytotoxicity of anticancer agents irinotecan and oxaliplatin alone or in combination with anthocyanidins, a class of flavonoids widespread in fruits and vegetables, in LoVo human colon adenocarcinoma cells. Cytotoxicity assay (MTT test) was performed to determine IC<sub>50</sub> of anticancer agents and anthocyanidins and to evaluate the effect of their combination in LoVo cells. IC<sub>50</sub> for the antitumour drugs was respectively 37,0nM±5,3 for camptothecin, 876,2nM±245,5 for oxaliplatin, 2,5µM±0,5 for SN-38 (the active metabolite of irinotecan) and 130,5µM±10,89 for irinotecan. IC<sub>50</sub> for anthocyanidins was: 37,6µM±3,3 (delphinidin), 46,9µM±1,8 (cyanidin), 80,5µM±9,8 (malvidin). IC<sub>50</sub> for pelargonidin was not determined since it did not show any cytotoxic effect. The effect of the combination of anthocyanidins and antineoplastic drugs was also studied. Delphinidin (25µM) significantly increased the cytotoxic effect of camptothecin 0,01µM (p<0,001), oxaliplatin 0,1µM (p<0,001) and SN-38 0,5µM (p<0,01). The same concentration of cyanidin had similar effect in combination with camptothecin (p<0,001) but 50µM cyanidin significantly increased cytotoxicity of all three drugs (p<0,001). Our results show that anthocyanidins, in particular delphinidin and cyanidin, exert an important cytotoxic action in the LoVo colon cancer cell line and increase the cytotoxicity of oxaliplatin, camptothecin and SN-38. Studies are in progress to clarify the mechanisms of this cytotoxic action such as detection of apoptosis, GSH level measurements and expression of drug transport proteins in cells treated with different concentrations of the antineoplastic drugs and flavonoids.