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Activity of the dietary flavonoid, apigenin, against multidrug-resistant tumor cells as determined by pharmacogenomics and molecular docking

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Natural products have been extensively studied and involved in cancer therapy field [1], apigenin has considerable cytotoxic activity in vitro and in vivo. Despite many mechanistic studies, less is known about resistance factors hampering apigenin's activity. We investigated the ATP-binding cassette (ABC) transporters BCRP/ABCG2, P-glycoprotein/ABCB1 and its close relative ABCB5. Apigenin inhibited not only P-glycoprotein, but also BCRP by increasing cellular uptake of doxorubicin and showed synergistic inhibitory effect in combination with doxorubicin or docetaxel against multidrug-resistant cells. To perform in silico studies, we first generated homology models for human P-glycoprotein and ABCB5 based on the crystal structure of murine P-glycoprotein. Their nucleotide binding domains (NBDs) revealed the highest degrees of sequence homologies (89%-100%), indicating that ATP binding and cleavage is of crucial importance for ABC transporters. In silico studies showed a pigenin bound to the NBDs of P-glycoprotein and ABCB5. Hence, apigenin may compete with ATP for NBD-binding leading to energy depletion to fuel the transport of ABC transporter substrates. Furthermore, we performed COMPARE and hierarchical cluster analyses of transcriptome-wide mRNA expression profiles of the National Cancer Institute tumor cell line panel. Microarray-based mRNA expressions of genes of diverse biological functions significantly predicted responsiveness of tumor cells to apigenin [2].

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