

Modulation of Anticancer Drug-Induced P-Glycoprotein Expression by Naringin

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Multidrug resistance (MDR) is a phenomenon that is often associated with decreased intracellular drug accumulation in the tumour cells of a patient, resulting from enhanced drug efflux. It is often related to the overexpression of P-glycoprotein (P-gp) on the surface of tumour cells, thereby reducing drug cytotoxicity. In the present study, naringin (the predominant flavonone found in grapefruit and other related citrus species) was tested for its potential ability to modulate the expression of P-gp in a short-term animal bioassay, in comparison with verapamil (a calcium channel blocker and positive MDR reversal agent). Western blot analysis showed that pre-treatment by i.p. administration of 5 mg naringin/kg body weight for 3 consecutive days prior to doxorubicin (the most common used anticancer drug which induces MDR) administration was able to significantly lower the P-gp expression reaching nearly the level of animals treated with verapamil. Moreover, pre-treatment with naringin prior to doxorubicin increased the sensitivity to the drug. Naringin inhibited the doxorubicin-stimulated ATPase activity demonstrating that naringin may interact directly with the transporter. In addition, the results demonstrated that induction of both glutathione (GSH) and glutathione-S-transferase (GST) by doxorubicin is consistent with an increased ATP-dependent doxorubicin transport. Thus, naringin seems to modulate the *in vivo* expression of P-gp. In summary, the present study describes the dual modulation of P-gp expression and function by the flavonoid naringin, which may be an attractive new agent for the chemosensitization of cancer cells.

Key words: P-Glycoprotein, Multidrug Resistance, Naringin