

Modulation of cisplatin cytotoxic activity by *Medicago* saponins

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Cisplatin (cis-[Pt^{II}Cl₂(NH₃)₂]) is one of the most important anticancer drug displaying significant clinical activity in the treatment of a wide array of solid malignancies. However most patients respond only transiently to cisplatin treatment that often results in the development of chemoresistance (Galluzzi et al., 2012). Several molecular mechanisms underlying resistance to cisplatin have been suggested. Among them, decreased transport of cisplatin across the cell membranes plays an important role. The use of drugs that may affect membrane permeability influencing the transmembrane transport of cisplatin could then be relevant to bypass this chemoresistance. Saponins are a large group of plant metabolites with a broad spectrum of pharmacological properties such as fungicidal, nematicidal, molluscicidal, antibacterial, antiviral and antitumor activities. Especially the genus *Medicago* is a rich source of bioactive saponins consisting of a complex mixture of triterpene glycosides with medicagenic acid, hederagenin, zanhic acid, bayogenin and soyasapogenols as the main aglycones. Although some of their biological effects are known (Tava and Avato, 2006), cytotoxicity of saponins from *Medicago* has not been investigated in great details. Only recently (Balestrazzi et al., 2011) their capacity to induce apoptosis in a model system of white poplar suspension cultures has been investigated. In the present work we describe the cytotoxic effects of different saponins from *M. arabica*, *M. arborea*, *M. sativa* and pure soyasapogenin I from *M. sativa* seeds on HeLa and MCF-7 (cisplatin-resistant) tumor cell lines. Saponins were tested by *in vitro* assays (MTT) at doses in the range of 0.01-200 mg/μL. *Medicago* saponin-mediated potentiation of cisplatin activity was also investigated. Cisplatin alone was used in the bioassays as the reference anticancer drug. Saponins from *M. arabica* were the most active with a toxicity comparable to that of cisplatin at 100 and 200 mg/μL, especially against HeLa cell lines (~ 80% cell death). Saponin toxicity was in general increased in combination with cisplatin (1 and 10 μM), even the effect was not highly significant as compared to the administration of cisplatin alone. Interesting results were obtained with the cisplatin-resistant MCF-7 cell line: a saponin-mediated modulation of the toxic activity of cisplatin against these tumor cells was in fact evident down to 40-45 % cell survival when using soyasapogenin I and derived prosapogenins from *M. sativa* combined with cisplatin, compared to cisplatin alone (60%). Saponins are known to increase the permeability of cell membranes. The observed modulation of the cytotoxic effect of cisplatin in combination with some of the tested compounds suggests that saponins from *Medicago* may as well influence the cell uptake of the antineoplastic drug.

Galluzzi et al. (2012) *Oncogene* 31: 1869-1883.

Tava and Avato (2006) *NPC* 1: 1159-1180.

Balestrazzi et al. (2011) *Physiol. Plant.* 141: 227-238.