# Anti-proliferative effects of natural compounds on human melanoma cells

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Cancer is a growing health problem in the world, in 2016 1.685.210 new cancer cases and 595.690 cancer deaths are projected to occur in USA[1]. It has been estimated that more than 2/3 of human cancers could be prevented through appropriate lifestyle modification and, in particular, about 35% of human cancer mortality is attributable to diet[2]. Vegetables, fruit and spices are excellent sources of cancer preventive substances and the NCI has identified about 35 plant-based foods that possess anti-cancer properties. These include garlic, soybeans, ginger, onion, turmeric, tomatoes and cruciferous vegetables. Many of the molecular alterations that are associated with carcinogenesis occur in cell-signaling pathways that regulate cell proliferation and differentiation. One of the central components of the intracellular signaling network that maintains homeostasis is the mitogen-activated protein kinases (MAPKs). Abnormal or improper activation of the MAPK pathway can result in uncontrolled cell growth, leading to malignant transformation. Phosphatidylinositol 3-kinase (PI3K) are also important targets of certain chemopreventive phytochemicals[4]. These two pathways play an important role in melanoma development and are involved in the mechanism of resistance to targeted therapy. Moreover, these upstream kinases activate a distinct set of transcription factors, including nuclear factor κB (NF-κB). Several reports have shown that in melanoma the constitutive activation of NF-κB confers tumor survival capacity and avoidance of apoptosis[5]. So we investigated on the role of different phytochemicals on cancer progression, in particular on melanoma. In our study, compounds isolated from *Ferula assa-foetida L*, *Laurus nobilis L, Opuntia Ficus Indica* and *A.Sativum* were assessed for their antiproliferative effect on human melanoma cell line A375. We firstly demonstrated that all compounds tested inhibited the growth of A375 melanoma cells in a time- and concentration-dependent manner . The inhibition of cells proliferation was due to the induction of apoptosis as demonstrated by FACS analysis with Annexin V/PI staining and further confirmed by the cleavage of caspase-3, and of its substrate PARP. We hypothesized that the pro-apoptotic effect could be associated with suppression of NF-κB activation. Incubation of A375 cells with these compounds inhibited IκBÎ± degradation and consequently NF-κB nuclear translocation and activation. Moreover, the expression of the anti-apoptotic proteins c-FLIP, XIAP and Bcl-2, that is transcriptionally regulated by NF-κB[6], was greatly reduced. In order to better define the mechanism through which this latter effect is achieved, we investigated on the possible involvement of the MAPK/ERK and PI3K/AKT pathways, two of the most frequently deregulated pathways in melanoma[7]. Western blot analysis revealed that the treatment of A375 cells with several of the phytochemicals tested inhibited the phosphorylation and activation of both AKT and ERK proteins at the time points considered. In conclusion, all these findings suggest phytochemicals as new potential agents in the treatment of human metastatic melanoma and represent a very promising strategy to improve the fight against cancer.

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