Olive leaf extract inhibits metastatic melanoma spread through suppression of epithelial to mesenchymal transition

Paola De Cicco¹, Giuseppe Ercolano¹, Gian Carlo Tenore¹ and Angela Ianaro¹.

¹Department of Pharmacy, School of Medicine, University of Naples Federico II, Naples, Italy.

Olive tree leaves are an abundant source of bioactive compounds with several beneficial effects for human health, including anti-oxidant, anti-hypertensive, cardioprotective and anti-inflammatory activity. However, data about the anticancer activities of the whole olive leaf extract are quite rare. Therefore, in this study we investigated the anti-tumor effect of an extract obtained from olive leaves of *Olea europea* L cultivar Ravece (OLE) in metastatic melanoma, the highly aggressive form of skin cancer and the deadliest diseases. Our results demonstrated that OLE inhibited the proliferation of different metastatic melanoma cell lines in a dose-dependent manner. This effect was exerted through diverse mechanisms, including cell cycle arrest and induction of apoptotic cell death in a caspase 3-dependent manner. Moreover, OLE suppressed the migration, invasion and colonies formation of human melanoma cells. Similar to our *in vitro* findings, we demonstrated that the oral administration of OLE inhibited cutaneous tumor growth and lung metastasis formation *in vivo* by modulating the expression of EMT related factors. Finally, we found that the anti-proliferative and anti-invasive effects of OLE against melanoma were also related to a simultaneous targeting of MAPK and PI3K pathways, the most commonly dysregulated pathways in melanoma. In conclusion, our findings suggest that OLE has the potential to inhibit the development and the metastatic spread of melanoma thanks to its multifaceted mechanistic effects, and may represent a new adjuvant agent for the management of metastatic melanoma.