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EXPRESSION AND METABOLITE ANALYSES OF GRAPE SEED EXTRACTS SHOWING ANTICANCER ACTIVITY

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Grapevine (*Vitis vinifera* L.) is a plant rich of bioactive compounds that have beneficial cardiovascular, chemopreventive, and cytoprotective effects. These molecules include polyphenols that are known for anti-inflammatory, antimicrobial and antioxidant activities and are widely used in nutraceutical and cosmetic fields. Here we describe i) the biological activity of grape seed and skin semi-polar extracts of two Italian grape varieties, Aglianico (red) and Falanghina (white) in human mesothelioma cell lines, and ii) a transcriptional and metabolic profiling of peel and seed samples of both varieties carried out through LC-HRMS and RT-qPCR approaches, respectively. We have treated mesothelioma cell lines sensitive (MSTO-221H, NCI-H2452) or insensitive (Ist-Mes2) to standard chemotherapy using both seed and skin semi-polar extracts. We showed that grapes seed extracts were able induce apoptosis in dose- and time-dependent manners. Both extracts induced apoptosis by intrinsic pathway inducing mitochondrial cytochrome *c* release. The global metabolic analysis of the semi-polar fractions revealed a higher accumulation in phenylpropanoid precursors and proanthocyanidins (PAs) in the seed vs peel extracts in both varieties, and in their more elevated contents in Aglianico compared to Falanghina. Notably, the transcript abundance of structural genes (i.e. *ANR, LDOX, CHS, DFR*) and transcriptional factors (*MybPA1/PA2, MybF1, MybC2-L1/L3*) involved in both the aforementioned pathways was consistent with the metabolite levels detected in all comparisons. Taken as whole, the data might explain the growth inhibition of human mesothelioma cell lines determined by grape seed semi-polar extracts.