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Molecular analysis of differential antiproliferative activity of resveratrol, epsilon viniferin and labruscol on melanoma cells and normal dermal cells

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ABSTRACT

Very recently, we have produced new resveratrol derived compounds, especially labruscol by culture of elicited grapevine cell suspensions (*Vitis labrusca* L.). This new polyphenolic oligomer could function as cancer chemopreventive agent in similar manner of resveratrol. In this study, we have determined the efficiency of resveratrol, ε-viniferin and the labruscol on human melanoma cell with or without metastatic phenotype. Our results show a differential activity of the three compounds where the resveratrol remains the polyphenolic compound with the most effective action compared to other oligomers. These three compounds block cell cycle of melanoma cells in S phase by modulating key regulators of cell cycle i.e. cyclins A, E, D1 and their cyclin–dependent kinases 1 and 2. These effects are associated with an increase of cell death while these compounds have no cytotoxic action on normal human dermal fibroblasts.

1. Introduction

Dietary polyphenols are of great interest due to their antioxidative and anticarcinogenic activities. Indeed, polyphenols are considered as chemopreventive agents since they exhibit pharmacological properties to promote the arrest or the regression of cancer process. Among these bioactive compounds, several epidemiological studies (Renaud et al., 1998) revealed that resveratrol may be one of the main wine microcomponents responsible for health benefits. Indeed, resveratrol (*trans*-3,4',5-trihydroxystilbene) can prevent important pathologies, *i.e,* vascular diseases, cancers or neurodegenerative processes (see for review (Delmas et al., 2005; Delmas et al., 2006)). We and others previously showed that oligomers of resveratrol such as viniferins, were suggested to block the proliferation of several tumoral cell lines (Kang et al., 2003; Kim et al., 2002; Marel et al., 2008; Yamada et al., 2006) and that a vineatrol preparation containing both *trans*-resveratrol and ε-viniferin exhibited a greater anti-proliferative effect on malignant cell lines than each compound tested separately (Billard et al., 2002; Colin et al., 2008, 2009; Marel et al., 2008). Very recently, we have isolated and identified various oligomeric derivatives of resveratrol produced in a bioreactor culture of elicited grapevine cell suspensions (*Vitis labrusca* L.) that could present potential biological effect on tumoral cell lines (Nivelle et al., 2017). Among them, a newly characterized dimer, the labruscol was recovered and seemed affected the growth of melanoma cells (Nivelle et al., 2017). Nevertheless, the ability of this new polyphenol bioproduct to inhibit tumor cells proliferation remained to be explored. In the present study, we compare the effects of *trans*-resveratrol (RSV), the resveratrol oligomer ε-viniferin (εV) and the labruscol (LAB) (Fig. 1A). We demonstrate that the three stilbenes present similar effects on human melanoma cells with a better effect on the metastatic phenotype. Moreover, we show for the first time that the labruscol is able to act on melanoma proliferation through a disruption of the cell cycle in S phase. This result seems to be the consequence of a modulation of the key regulator of the cell cycle such as cyclin A and their cyclin-dependent kinase. Subsequently, RSV and its oligomers induce melanoma death without affecting

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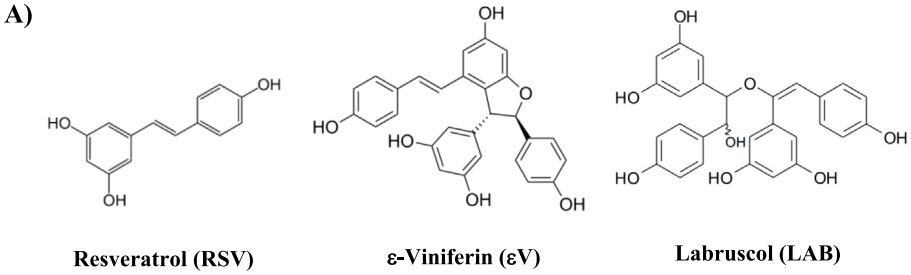

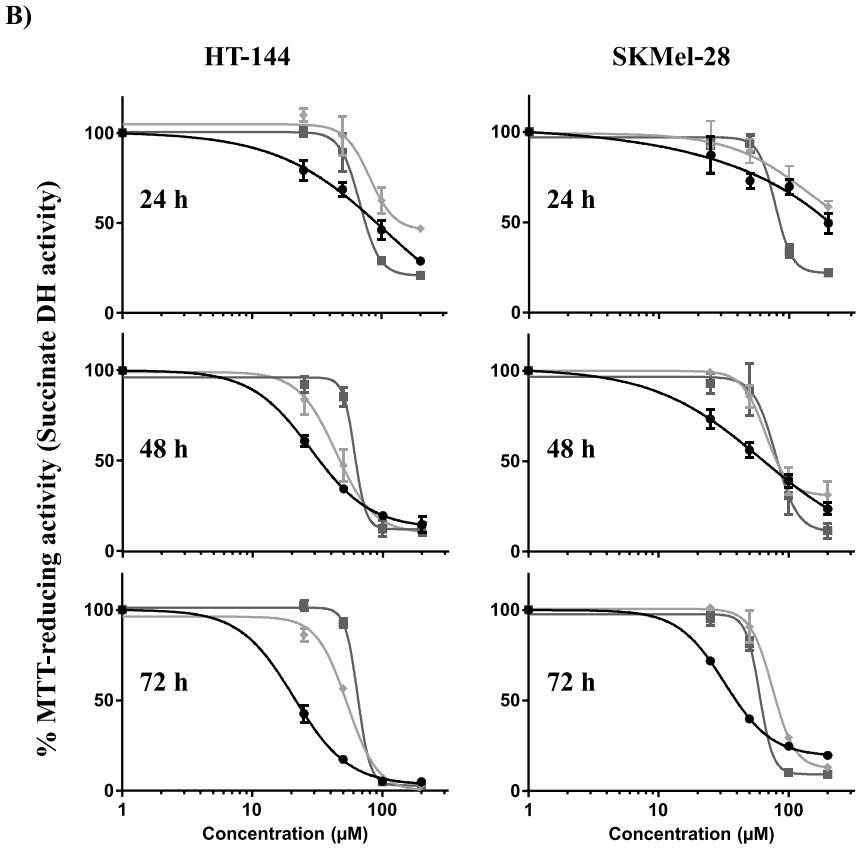

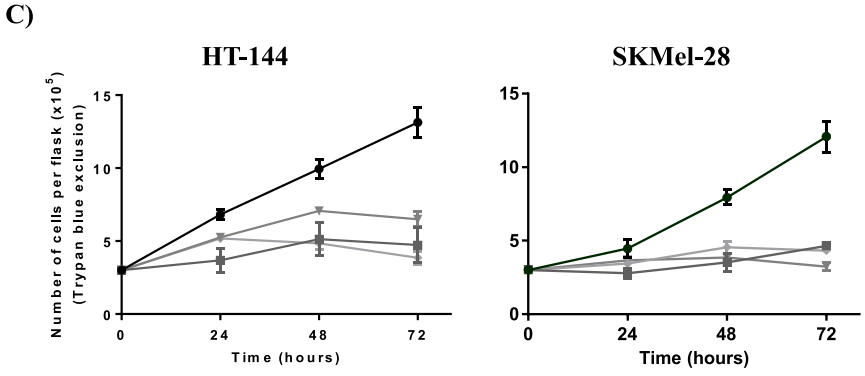

Fig. 1. A) Chemical structures of three stilbenes bioproducts, resveratrol (RSV) and two resveratrol oligomeres, ε-viniferin (εV) and Labruscol (LAB). B) Cell viability inhibition by stilbenes bioproducts. HT-144 and SKMel-28 cells were treated with various concentration (25–200 μM) of RSV (–●–), εV (–■–) and LAB (–◆–) for 24, 48 and 72 h. Cell viability was determined by the MTT assay. C) Cell growth inhibition by stilbenes bioproducts. HT-144 and SKMel-28 cells were treated during 72 h with the IC_{50} at 48 h of each stilbenes bioproducts, corresponding to 30 μM for RSV (–■–), 60 μM for εV (–▼–) and 50 μM for LAB (–◆–) on HT-144 cells and 60, 85 and 80 μM respectively on SKMel-28 cells. Control cells (–●–) were treated by a vehicle (ethanol) with a maximal final volume of 0.085%. Cell growth was determined by the method of trypan blue exclusion. Data are expressed as the means ± SD of 3 independent experiments. Each experiment was performed in triplicate.