POLYMERIC STILBENE DERIVATIVES IN WINEMAKING BYPRODUCTS AFFECT NF-κB MEDIATED INFLAMMATORY RESPONSE IN CACO-2 CELLS

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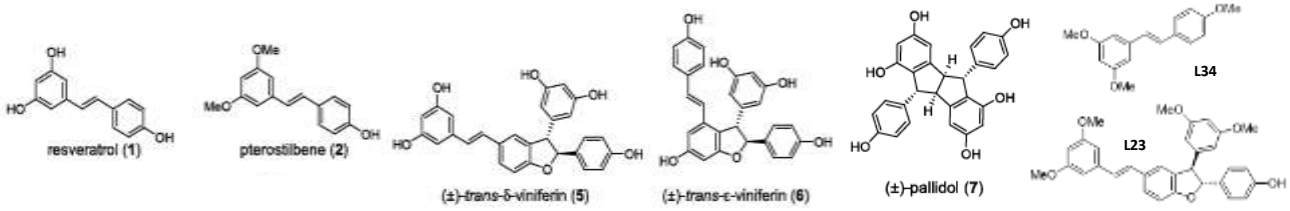
Residuals from winemaking represents one of the most important byproducts in the Italian agri-food scenario. Grape skins and stems reportedly contain high levels of various phenolics-based bioactives that - in the family of stilbenoids - include resveratrol and the products ensuing from its radical-based polymerization. Among these is the family of viniferins, that reportedly are able to interfere with the glucose metabolism in the gut, by inhibiting extracellular or membrane enzymes involved in the final steps of starch breakdown and – eventually - in glucose uptake[1, 2]. These same reports also highlighted the possibility that molecules in the stilbenoids family could display some physiologically relevant synergism in their inhibitory activities[2].

Whereas resveratrol is known to interfere with a number of cellular processes, including suppression of NF-κB mediated responses, little is known about the ability of polymeric or modified stilbenoids in this regard. Therefore, we took advantage of the introduction of a RT-qPCR-based assay for intracellular expression of NF-κB[3] to assess whether a number of naturally occurring and semi-synthetic resveratrol polymers (at concentrations in the 5-25 μM range) may affect intracellular expression of NF-κB in response to the addition of IL-1β, and to verify whether any effect of these species was synergistic with those observed for resveratrol alone (at a fixed 5 μM concentration).

In short, we observed concentration-dependent suppression of NF-κB expression for all the tested compounds but pterostilbene and pallidol (see structures here below). The inhibitory effect was in the order δ-viniferin > L34 ≥ ε-viniferin > L23> resveratrol, where L34 (trimethoxy-resveratrol) and L23 (pterostilbene-trans-dihydrodimer) represent a fully methylated analogue of resveratrol and a vastly methylated analogue of δ-viniferin, respectively. However, L23 and L34 elicited only modest effects when added at 5-20 μM to 5 μM resveratrol in synergistic studies. On the contrary, similar concentrations of the naturally occurring viniferins significantly increased the effects of 5 μM resveratrol, with δ-viniferin providing the largest suppressive effects, evident already at viniferin concentrations as low as 5 μM.



These data suggest that the bioactivities associated with resveratrol derivatives in wine and winemaking byproducts are dictated by specific molecular features, and are not limited to the inhibition of extracellular enzymes. Evidence is also provided as for possible co-operativity occurring – rather than competition – among chemically related species. Further studies will verify whether these observations can be of practical relevance, but these data circumstantially appear to support the "food better than pills" working hypothesis as for outlining possible intervention strategies.

[1] Lavelli V., Harsha P. S. C. S., Ferranti P., Scarafoni A. & Iametti S. (2016) Grape skin phenolics as inhibitors of mammalian alpha-glucosidase and alpha-amylase - effect of food matrix and processing on efficacy. Food & Function 7, 1655-1663.

[2] Mattio L. M., Marengo M., Parravicini C., Eberini I., Dallavalle S., Bonomi F., Iametti S. & Pinto A. (2019) Inhibition of pancreatic alpha-amylase by resveratrol derivatives: Biological activity and molecular modelling evidence for cooperativity between viniferin enantiomers. Molecules 24, Art. Nr: 3225, DOI: 10.3390/molecules24183225

[3] Barbiroli, A., Capraro, J., Marulo, S., Gamba, M. & Scarafoni, A. (2019). Effects on the Caco-2 cells of a hypoglycemic protein from lupin seeds in a solution and adsorbed on polystyrene nanoparticles to mimic a complex food matrix. Biomolecules, 9(10), 606; https://doi.org/10.3390/biom9100606