Synergistic Effects of Phenolic Mixtures in Human Cell Models of Aging

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EB 2015 BOSTON

608.36

ABSTRACT

The health benefits associated with fruit and vegetable consumption are attributed, in the main, to fiber and micronutrients and recent research has focused on the role of phenolics (polyphenols) in mediating healthful dietary effects. While most plants contain complex mixtures of polyphenols, isolated compounds, such as resveratrol, have been widely studied and shown to influence the activity of multiple cellular metabolic and signaling pathways. Indeed, based on its actions on several cellular regulatory systems, resveratrol has been proposed to be the active molecule underlying the benefits of grape and red wine consumption. To test the hypothesis that phenolic mixtures containing resveratrol produce variable and non-additive effects versus resveratrol alone, their antioxidant capacity (ORAC) and their effects in several *in vitro* models of cellular aging were compared using identical concentrations (µg phenolics/ml). Compared to resveratrol alone, the same concentration of a mixture of muscadine grape polyphenols plus resveratrol produced synergistic effects on $ORAC_{lipophilic}$ but not $ORAC_{hydrophilic}$. Likewise, the phenolic mixture exhibited 10X greater potency versus resveratrol in inhibiting protein glycation. Non-additive/synergistic effects ($p<0.01$) of the mixture versus resveratrol on mitochondrial mass, oxygen consumption and gene expression were measured in human skeletal muscle cells. Finally, synergistic effects ($p<0.01$) of the phenolic mixture in preventing oxidative damage to DNA (COMET assay) were observed in human pancreatic cells. These results suggest that, compared to isolated plant phenolics, the complex mixtures occurring naturally in plants have greater potency to influence various mechanisms of cellular aging.

INTRODUCTION

The grape polyphenol resveratrol is demonstrated to influence the activity of multiple cellular signaling pathways including those involved in cellular aging. Grapes and red wine, however, contain complex mixtures of polyphenols of which resveratrol represents a very minor component. It is possible that complex mixtures of polyphenols have different cellular actions than those of any single polyphenol comprising the mixture. To test this notion, the effects of resveratrol were compared to those of a mixture of resveratrol plus muscadine grape polyphenols in multiple models of cellular aging.

METHODS

Assay	Investigator	Method
Antioxidant activity	Brunswick Laboratories, Southborough, MA	Ou et al., J. Agric. Food Chem. 49:4619-4626, 2001
Glycation of albumin	Dr. Phillip Greenspan, University of Georgia, Athens, GA	Farrar et al., BioFactors 30:193-200, 2007
Mitochondrial function	Dr. Michael Zemel, University of Tennessee, Knoxville, TN	Sun and Zemel, Nutr Metab (Lond). 2009 Jun 5;6:26. doi: 10.1186/1743-7075-6-26.
Oxidative DNA damage	Dr. Phillip Greenspan, University of Georgia, Athens, GA	Ramos et al., J Agric. Food Chem. 58:7465-7471, 2010

RESULTS

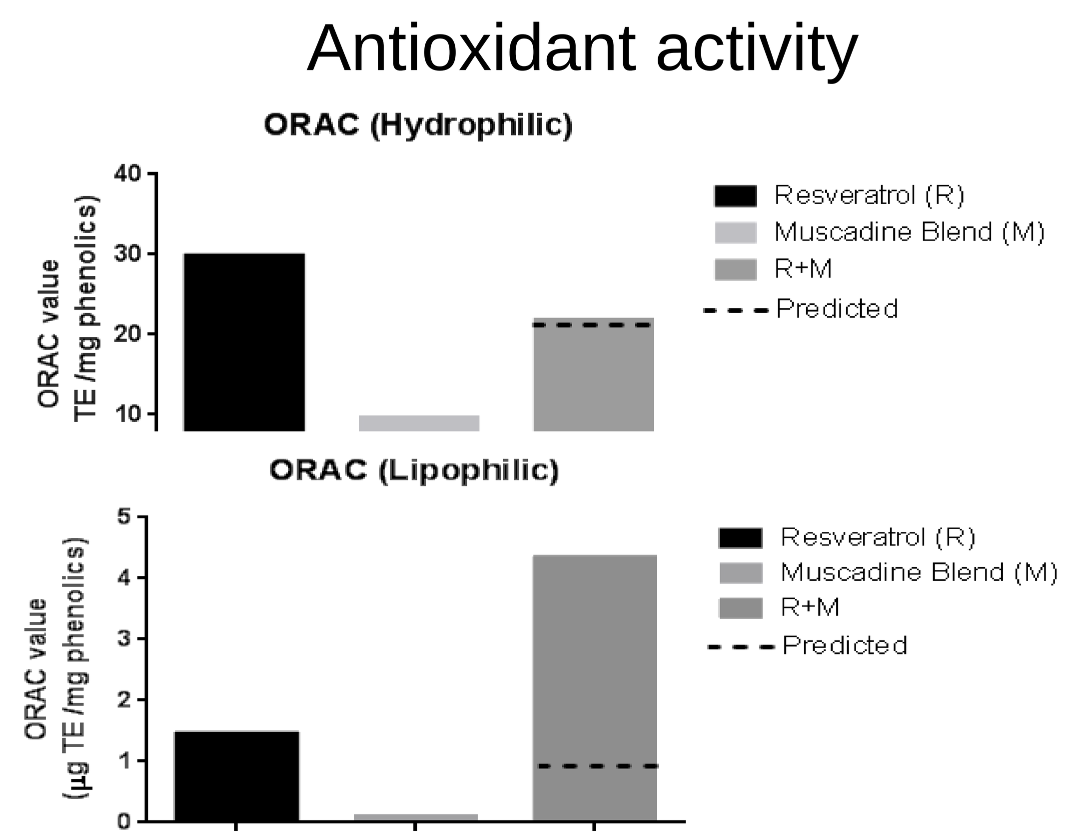


Figure 1. Additive and non-additive antioxidant effects of resveratrol and muscadine polyphenols.

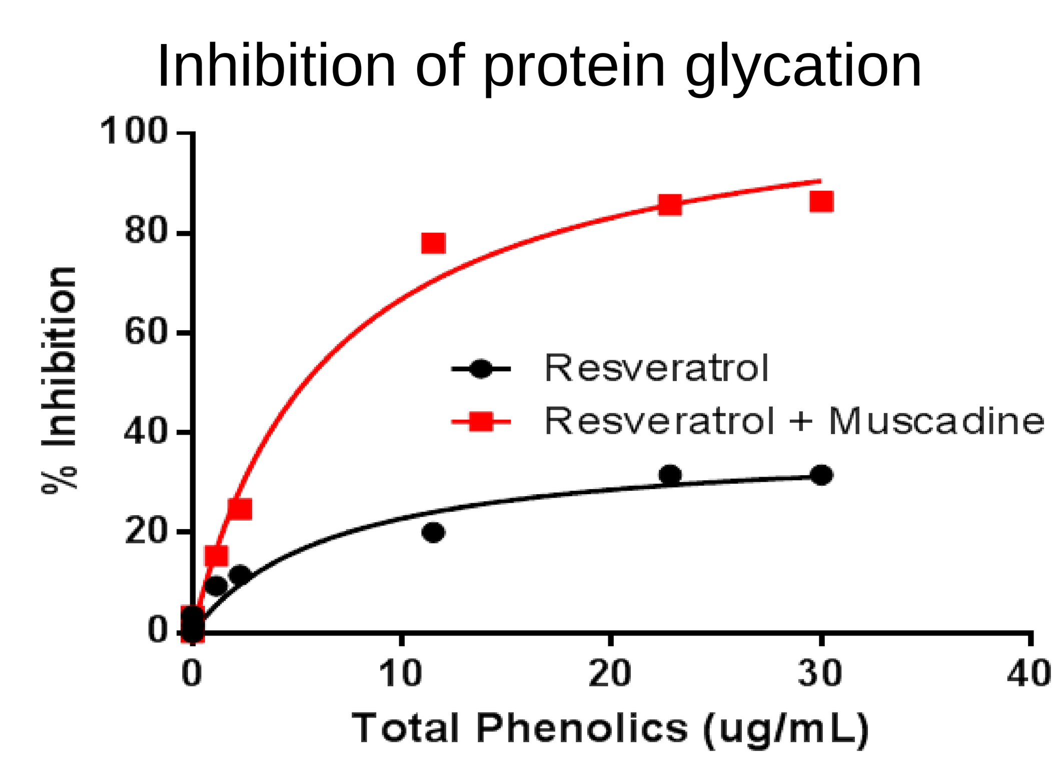


Figure 2. Compared to resveratrol alone, a mixture of resveratrol and muscadine polyphenols produced more potent inhibition of albumin glycation.

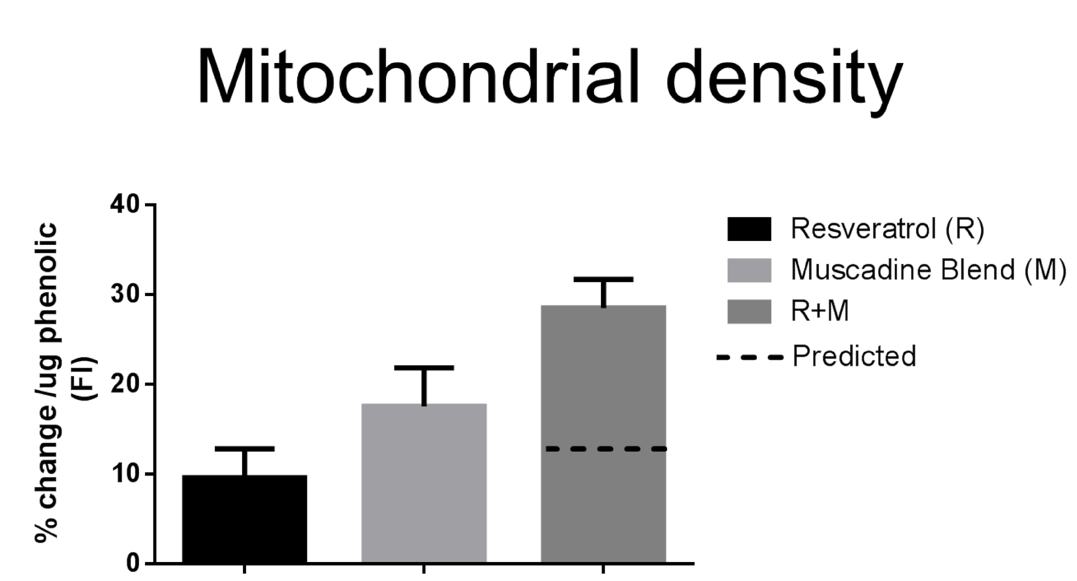


Figure 3. Non-additive effects of resveratrol and muscadine polyphenols on mitochondrial density in human myotubes.

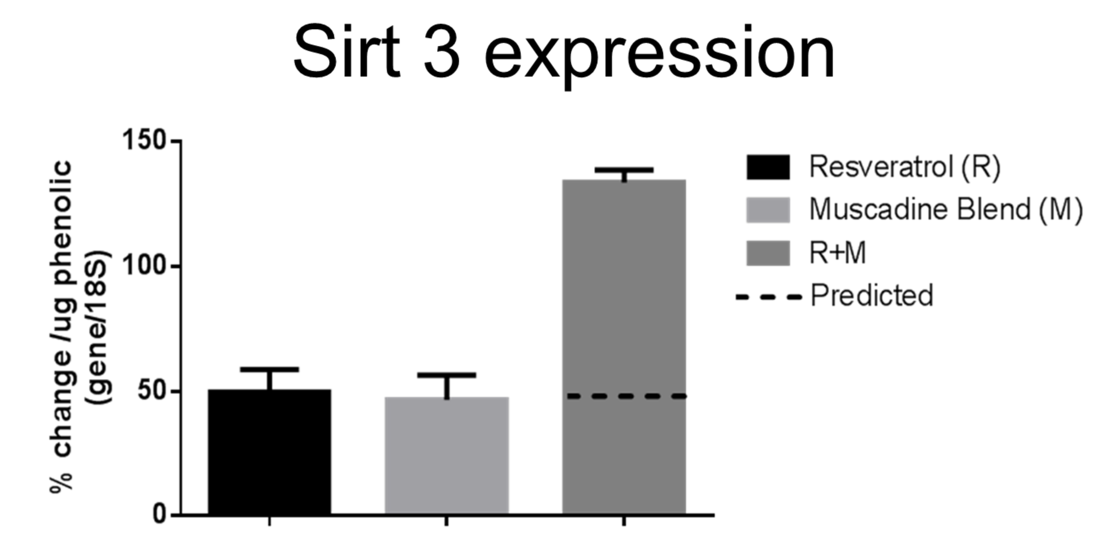


Figure 4. Non-additive effects of resveratrol and muscadine polyphenols on Sirt 3 mRNA expression in human myotubes.

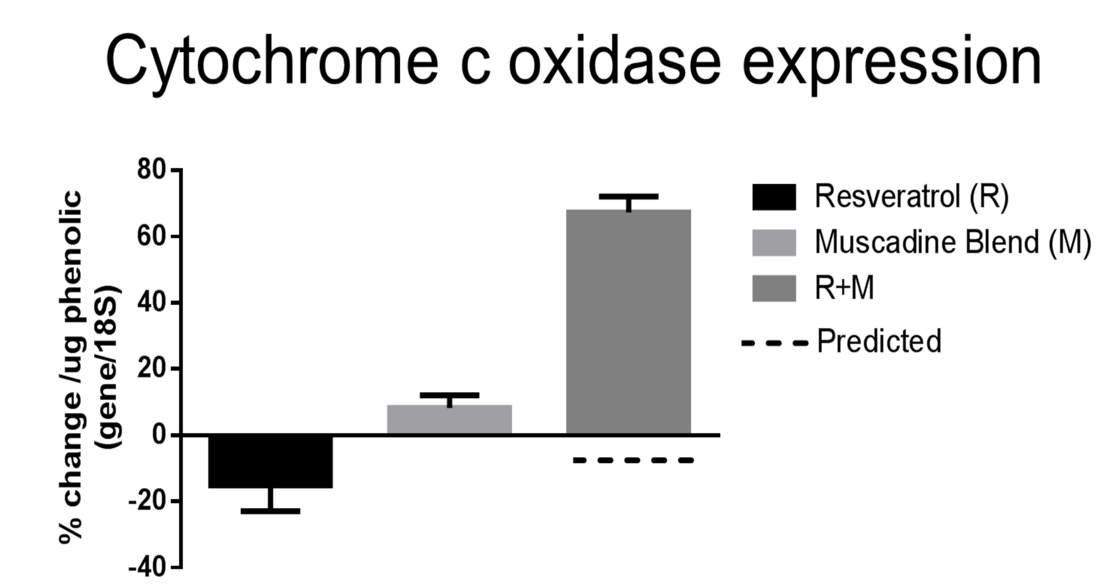


Figure 5. Non-additive effects of resveratrol and muscadine polyphenols on cytochrome c oxidase mRNA expression in human myotubes.

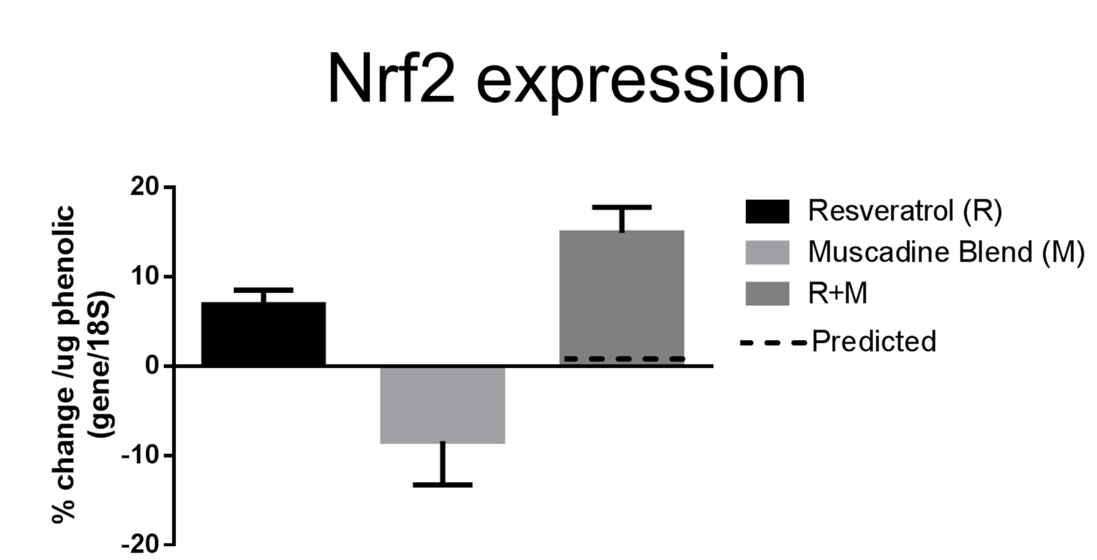


Figure 6. Non-additive effects of resveratrol and muscadine polyphenols on nrf2 mRNA expression in human myotubes.

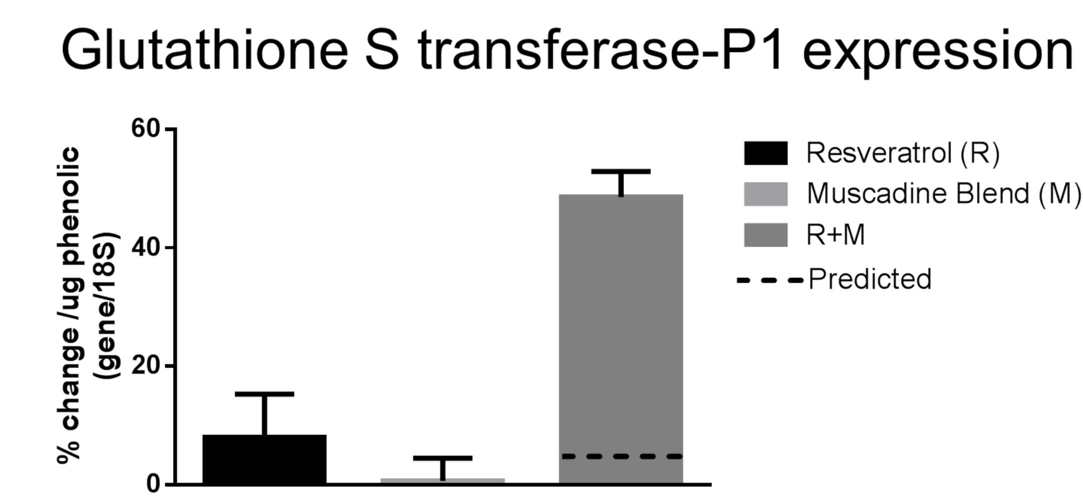
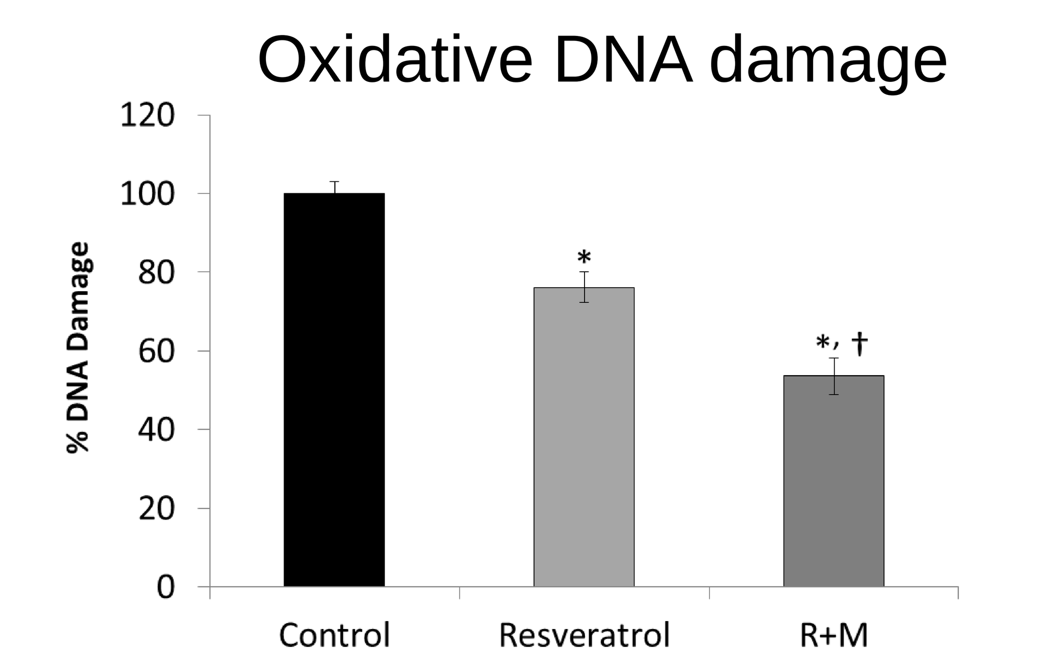


Figure 7. Non-additive effects of resveratrol and muscadine polyphenols on glutathione S transferase- P1 mRNA expression in human myotubes .



*significantly different from control; †significantly different from resveratrol; n= 42 per group.

Figure 8. Compared to resveratrol alone, a mixture of resveratrol and muscadine polyphenols produced greater protection against oxidative DNA damage in human pancreatic cells.

CONCLUSIONS

When compared to resveratrol alone, complex mixtures of polyphenols containing resveratrol produce non-additive effects in several models of cellular aging. Thus, the physiological effects of grape and red wine consumption may differ from those after consuming resveratrol alone.