**CO-ORDINATED AUTOPHAGY WITH RESVERATROL AND**

γ-**TOCOTRIENOL CONFERS SYNERGETIC CARDIOPROTECTION**

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This study compared two dietary phytochemicals, grape-derived resveratrol and palm oil-derived γ-tocotrienol, either alone or in combination, on the contribution of autophagy in cardioprotection during ischemia and reperfusion. Sprague Dawley rats weighing between 250-300 gm were randomly assigned to one of the following groups: vehicle, ischemia/reperfusion (I/R), resveratrol+I/R, γ-tocotrienol+I/R, resveratrol+

γ-tocotrienol+I/R. For resveratrol experiments, the rats were gavaged with resveratrol

[2.5 mg/kg] for 15 days while for γ-tocotrienol experiments the rats were gavaged with γ-tocotrienol for 30 days.  For the combined resveratrol+γ-tocotrienol experiments, the rats were gavaged with g-tocotrienol for 15 days, and then gavaging continued with resveratrol along with tocotrienol for a further period of 15 days. After 30, days, isolated perfused hearts were subjected to 30 min of global ischemia followed by 2h of reperfusion. Our results showed for the first time that at least in part, the cardioprotection (evidenced from the ventricular performance, myocardial infarct size and cardiomyocyte apoptosis) with resveratrol and γ-toctrienol was achieved by their abilities to induce autophagy. Most importantly, resveratrol and γ-tocotrienol acted synergistically providing greater degree of cardioprotection simultaneous generating greater amount of survival signal through the activation of Akt-Bcl2 survival pathway.  Autophagy was accompanied by the activation of Beclin and LC3-II as well as mTOR signaling, which were inhibited by either 3-methyl adenine (3-MA) or Wortmannin. The autophagy was confirmed from the results of transmission electron microscopy and light microscopy as well as with confocal microscopy. Furthermore, AMPK, a well known redox sensor was also activated with both resveratrol and γ-tocotrienol. It is tempting to speculate that autophagy along with enhanced survival signals helps to maintain basic cell function during ischemia and reperfusion, and after reperfusion survival signals helps to rec