Red wine polyphenol compounds favor neovascularisation through estrogen receptor α independent mechanism in mice

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Red wine polyphenols compounds (RWPC) are known to protect against deleterious effects of cardiac and cerebral ischemia. However, they exert different effect depending on the dose on post-ischemic neovascularisation. Low dose (0.2 mg/kg/d) promotes angiogenesis, whereas high dose (20 mg/kg/d) has anti-angiogenic property. The vascular effect of RWPC is mediated through the activation of a redox-sensitive pathway, mitochondrial biogenesis and the activation of α isoform of the estrogen receptor (ERα). Here we evaluate the implication of ERα on angiogenic properties of RWPC. Using ovariectomized mice lacking ERα treated with high dose of RWPC after hindlimb ischemia, we examined blood flow reperfusion, vascular density, nitric oxide (NO) production, expression and activation of proteins involved in angiogenic process (eNOS, cav-1, VEGF) and muscle energy sensing network proteins (Sirt-1, AMPK and PGC-1). High dose of RWPC treatment reduced both blood flow and vascular density in muscles of mice expressing ERα. These effects were associated with reduced NO production resulting from diminished activity of eNOS. Surprisingly, high dose of RWPC increased blood flow and capillary density in mice lacking ERα. This effect is accompanied with increased NO pathway and production as well as VEGF expression. Interestingly, RWPC was able to activate Sirt-1, AMPK and PGC-1 in hindlimb from both strains. Altogether, the results highlight a pro-angiogenic property of RWPC via an ERα-independent mechanism that is associated with an up-regulation of energy sensing network proteins of the Sirt-1, PGC-1 network. This study depicts a novel way by which polyphenols may represent a therapeutic approach to treat pathologies associated with failed vascularisation.

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