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## THE FOUR MAJOR EFFECTS OF TRANS-RESVERATROL

### 1. Effects on cancer

Resveratrol:

- Acts as an antioxidant and antimutagen
- Induces phase II drug-metabolizing enzymes (anti-initiation activity).
- Mediates anti-inflammatory effects and inhibits cyclooxygenase and hydroperoxidase functions (antipromotion activity).
- Induces human promyelocytic leukemia cell differentiation (antiprogession activity).
- Inhibits the development of preneoplastic lesions in carcinogen- treated mouse mammary glands in culture
- Inhibits tumorigenesis in a mouse skin cancer model [1, 2].
- A recent review on the anti-carcinogen effect of resveratrol [3] shows the effect in vitro and in vivo.
- In Sirt1(+/-), p53(+/-) mouse, resveratrol counteracts the tumor development [4].

### 2. Effects on longevity

- Resveratrol increases the lifespan of yeast treated through the activation of sirtuins (Sir/Sirt) [5].
  - Resveratrol is a potent activator of Sir protein in yeast. An increased activity of Sir protein leads to a calorie restriction, extending lifespan in several organisms .
  - Resveratrol in yeast mimics calorie restriction by stimulating Sir2, increasing DNA stability, extending lifespan by 70%.
- Long-term resveratrol treatment slows age-related degeneration and functional decline and mimics the gene expression patterns induced by dietary restriction [6].
- Resveratrol induces gene expression patterns in multiple tissues (Muscle, heart, adipose, liver) in mice models, which are parallel to those induced by dietary restriction and every-other-day feeding.
  - Resveratrol-fed elderly mice show a marked reduction in signs of aging, including reduced albuminuria, decreased inflammation, and apoptosis in the vascular endothelium, increased aortic elasticity, greater motor coordination, reduced cataract formation, and preserved bone mineral density.

### 3. Effects on obesity biomarkers

- Resveratrol improves mitochondrial function [7].
  - Resveratrol (400 mg/kg/day for 15 weeks) reduces the body weight and total fat level in mice fed a high-fat diet.
  - Mice on a high-fat-resveratrol diet increased their aerobic capacity, as evidenced by their increased running time and consumption of oxygen in muscle fibers.
  - The physiological effects of resveratrol are associated with an induction of genes for oxidative phosphorylation and mitochondrial biogenesis, which could be explained by a resveratrol-mediated decrease in PGC-1alpha acetylation and an increase in PGC-1alpha activity.
  - Resveratrol protects mice against diet-induced-obesity and insulin resistance.
  - Resveratrol's effect on obesity and hyperlipidemia [8]
- Administration of resveratrol (20 mg/kg/day for 8 weeks) to female rats fed a high-fat diet prevented the increase in blood pressure and preserved acetylcholine-dependent relaxation of isolated aortic rings. On the other hand, resveratrol failed to attenuate the perivascular fibrotic response.

#### 4. Anti-inflammatory effects

- Resveratrol inhibits activation of the NF- $\kappa$ B cascade [9]
  - Resveratrol is a potent inhibitor of both NF- $\kappa$ B activation and NF- $\kappa$ B-dependent gene expression.
  - Resveratrol inhibits I $\kappa$ B kinase activity, the key regulator in NF- $\kappa$ B activation. As a consequence of the NF- $\kappa$ B inhibition the expression of monocyte chemoattractant protein-1 is blocked.
- Resveratrol *for* acute pneumonia in rats [10]
  - Pretreatment of murines with resveratrol for 3 days markedly increases alveolar macrophage infiltration, elevates NK cell activity, and decreases bacterial burden in the infected lung with a subsequent decrease in mortality. These effects are associated with reduced neutrophil infiltration of the lungs, reduced phagocytosis activity, and reduced secretion of cytokines such as TNF $\alpha$ , IL-1 $\beta$ , and IL-6.
  - Resveratrol ameliorates acute pneumonia via inhibition of the NF- $\kappa$ B signaling pathway, including inhibition of I $\kappa$ B $\alpha$  phosphorylation and subsequent NF- $\kappa$ B activation.
- The anti-inflammatory effects of resveratrol on human airway epithelial cells [11].
  - Resveratrol inhibits IL-8 and granulocyte-macrophage colony-stimulating factor release from A549 cells.
  - Resveratrol inhibits NF- $\kappa$ B, activator protein-1, and cAMP response element binding protein-dependent transcription
  - Resveratrol inhibits cytokine-stimulated inducible nitric oxide synthase expression and nitrite production in human primary airway epithelial cells.
  - Resveratrol also inhibits granulocyte-macrophage colony-stimulating factor release, IL-8 release, and cyclooxygenase-2 expression in these cells.
- Recent review on the anti-inflammatory effect of resveratrol [3] giving tables with *in vitro* and *in vivo* studies shows anti-inflammatory effect of resveratrol.

#### References

1. Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, Fong HH, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, and Pezzuto JM, Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* 275: 218-220, 1997.
2. Athar M, Back JH, Tang X, Kim KH, Kopelovich L, Bickers DR, and Kim AL, Resveratrol: A review of preclinical studies for human cancer prevention. *Toxicol.Appl.Pharmacol.* 224: 274-283, 2007.
3. Udenigwe CC, Ramprasath VR, Aluko RE, and Jones PJ, Potential of resveratrol in anticancer and anti-inflammatory therapy. *Nutr.Rev.* 66: 445-454, 2008.
4. Wang RH, Sengupta K, Li C, Kim HS, Cao L, Xiao C, Kim S, Xu X, Zheng Y, Chilton B, Jia R, Zheng ZM, Appella E, Wang XW, Ried T, and Deng CX, Impaired DNA damage response, genome instability, and tumorigenesis in SIRT1 mutant mice. *Cancer Cell* 14: 312-323, 2008.
5. Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, Zipkin RE, Chung P, Kisielewski A, Zhang LL, Scherer B, and Sinclair DA, Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature* 425: 191-196, 2003.
6. Pearson KJ, Baur JA, Lewis KN, Peshkin L, Price NL, Labinsky N, Swindell WR, Kamara D, Minor RK, Perez E, Jamieson HA, Zhang Y, Dunn SR, Sharma K, Pleshko N, Woollett LA, Csiszar A, Ikeno Y, Le CD, Elliott PJ, Becker KG, Navas P, Ingram DK, Wolf NS, Ungvari Z, Sinclair DA, and de CR, Resveratrol Delays Age-Related Deterioration and Mimics Transcriptional Aspects of Dietary Restriction without Extending Life Span. *Cell Metab* 8: 157-168, 2008.
7. Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, and Auwerx J, Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 $\alpha$ . *Cell* 127: 1109-1122, 2006.
8. Aubin MC, Lajoie C, Clement R, Gosselin H, Calderone A, and Perrault LP, Female rats fed a high-fat diet were associated with vascular dysfunction and cardiac fibrosis in the absence of overt obesity and hyperlipidemia: therapeutic potential of resveratrol. *J.Pharmacol.Exp.Ther.* 325: 961-968, 2008.
9. Holmes-McNary M and Baldwin AS, Jr., Chemopreventive properties of trans-resveratrol are associated with inhibition of activation of the I $\kappa$ B kinase. *Cancer Res.* 60: 3477-3483, 2000.
10. Lu CC, Lai HC, Hsieh SC, and Chen JK, Resveratrol ameliorates *Serratia marcescens*-induced acute pneumonia in rats. *J.Leukoc.Biol.*, 2008.
11. Donnelly LE, Newton R, Kennedy GE, Fenwick PS, Leung RH, Ito K, Russell RE, and Barnes PJ, Anti-inflammatory effects of resveratrol in lung epithelial cells: molecular mechanisms. *Am.J.Physiol Lung Cell Mol.Physiol.* 287: L774-L783, 2004.

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