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## TRANS-RESVERATROL – INDICATED HEALTH BENEFITS

### Life extension

In 2003, Howitz and Sinclair reported in the journal *Nature* that resveratrol significantly extends the lifespan of the yeast *Saccharomyces cerevisiae*.<sup>[1]</sup> Later studies conducted by Sinclair showed that resveratrol also prolongs the lifespan of the worm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*.<sup>[2]</sup>

In 2007, a different group of researchers were able to reproduce Sinclair's results with *C. elegans*<sup>[3]</sup> but a third group could not achieve consistent increases in lifespan of *Drosophila* or *C. elegans*.<sup>[4]</sup>

In 2006, Italian scientists obtained the first positive result of resveratrol supplementation in a vertebrate. Using a short-lived fish, *Nothobranchius furzeri*, with a median life span of nine weeks, they found that a maximum dose of resveratrol increased the median lifespan by 56%. At nine weeks the fish supplemented with resveratrol showed a significantly higher level of general swimming activity and better learning to avoid unpleasant stimulus than the control fish.

The authors noted a slight mortality increase in young fish fed resveratrol and hypothesized that it was its weak toxic action that stimulated the defense mechanisms and resulted in the life span extension.<sup>[5]</sup>

Later the same year, Sinclair reported that resveratrol counteracted the detrimental effects of a high-fat diet in mice. The high fat diet was compounded by adding hydrogenated coconut oil to the standard diet; providing 60% of energy from fat, where the mice consumed about 30% more calories than the mice on standard diet. Both the mice fed the standard diet and the high-fat diet plus 22 mg/kg resveratrol had a 30% lower risk of death than the mice on the high-fat diet without resveratrol. Gene expression analysis indicated that the addition of resveratrol opposed the alteration of 144 out of 155 gene pathways changed by the high-fat diet.

Insulin and glucose levels in mice on the 'high-fat+resveratrol diet' were closer to the mice on standard diet than to the mice on the high-fat diet. However, addition of resveratrol to the high-fat diet did not change the levels of free fatty acids and cholesterol, which were much higher than in the mice on standard diet.<sup>[6]</sup>

### Cancer prevention

In 1997 Jang reported that topical resveratrol applications prevented skin cancer development in mice treated with a carcinogen.<sup>[7]</sup> There have since been dozens of studies of the anti-cancer activity of resveratrol in animal models.<sup>[8]</sup>

No results of human clinical trials for cancer have been reported.<sup>[9]</sup> However, clinical trials to investigate the effects on colon cancer and melanoma (skin cancer) are currently recruiting patients.<sup>[10]</sup>

In vitro resveratrol interacts with multiple molecular targets, and has positive effects on the cells of breast, skin, gastric, colon, esophageal, prostate, and pancreatic cancer, and leukemia.<sup>[11]</sup> The strongest evidence of anti-cancer action of resveratrol exists for tumors it can come into direct contact with, such as skin and gastrointestinal tract tumors. For other cancers, the evidence is equivocal, even if massive doses of resveratrol are used.<sup>[12]</sup>

## Athletic performance

Johan Auwerx (at the Institute of Genetics and Molecular and Cell Biology in Illkirch, France) and coauthors published an online article in the journal *CELL* in November 2006. Mice fed resveratrol for 15 weeks had better treadmill endurance than controls.

The study supported Sinclair's hypothesis that the effects of resveratrol are indeed due to the activation of SIRT1.

Nicholas Wade's interview-article with Dr. Auwerx<sup>[13]</sup> states that the dose was 400 mg/kg of body weight (much higher than the 22 mg/kg of the Sinclair study). For an 80 kg (176 lb) person, the 400 mg/kg of body weight amount used in Dr. Auwerx's mouse study would come to 32,000 mg/day. Compensating for the fact that humans have slower metabolic rates than mice would change the equivalent human dose to roughly 4,571 mg/day.

Again, there is no published evidence anywhere in the scientific literature of any clinical trial for efficacy in humans, and there is limited human safety data (see above). However, in a study of 123 Finnish adults, those born with certain increased variations of the SIRT1 gene had faster metabolisms, helping them to burn energy more efficiently—indicating that the same pathway shown in the lab mice works in humans.<sup>[14]</sup>

## References

1. Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, Zipkin RE, Chung P, Kisielewski A, Zhang LL, Scherer B, Sinclair DA. "Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan". *Nature*. 2003 Sep 11;425(6954):191-6. Epub 2003 Aug 24.
2. Wood JG, Rogina B, Lavu S, Howitz K, Helfand SL, Tatar M, Sinclair D. "Sirtuin activators mimic caloric restriction and delay ageing in metazoans". *Nature*. 2004 Aug 5; 430(7000):686–689. Epub 2004 Jul 14.
3. JAN GRUBER et al, "Evidence for a Trade-Off between Survival and Fitness Caused by Resveratrol Treatment of *Caenorhabditis elegans*" *Ann. N.Y. Acad. Sci.* 1100: 530–542 (2007).
4. Bass TM, Weinkove D, Houthoofd K, Gems D, Partridge L. (2007). "Effects of resveratrol on lifespan in *Drosophila melanogaster* and *Caenorhabditis elegans*". *Mechanisms of ageing and development* **128** (10): 546–552.
5. Valenzano DR, Terzibasi E, Genade T, Cattaneo A, Domenici L, Cellarino A "Resveratrol Prolongs Lifespan and Retards the Onset of Age-Related Markers in a Short-Lived Vertebrate." *Current Biology* 2006 Feb 7;16 (3):296–300
6. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, Prabhu VV, Allard JS, Lopez-Lluch G, Lewis K, Pistell PJ, Poosala S, Becker KG, Boss O, Gwinn D, Wang M, Ramaswamy S, Fishbein KW, Spencer RG, Lakatta EG, Le Couteur D, Shaw RJ, Navas P, Puigserver P, Ingram DK, de Cabo R, Sinclair DA. "Resveratrol improves health and survival of mice on a high-calorie diet" *Nature* 2006 advanced publication
7. Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, Fong HH, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM (1997). "Cancer chemopreventive activity of resveratrol, a natural product derived from grapes". *Science* **275** (5297): 218–20.
8. See review:Baur JA, Sinclair DA (2006). "Therapeutic potential of resveratrol: the in vivo evidence". *Nat Rev Drug Discov* **5** (6): 493–506.
9. See review:Athar M, Back JH, Tang X, Kim KH, Kopelovich L, Bickers DR, Kim AL (2007). "Resveratrol: a review of preclinical studies for human cancer prevention". *Toxicol. Appl. Pharmacol.* **224** (3): 274–83.
10. Resveratrol. From Clinicaltrials.gov. Retrieved August 15, 2008.
11. Boocock DJ, Faust GE, Patel KR, et al (June 2007). "Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent". *Cancer Epidemiol. Biomarkers Prev.* **16** (6): 1246–52.
12. Kimura Y, Okuda H (June 2001). "Resveratrol isolated from *Polygonum cuspidatum* root prevents tumor growth and metastasis to lung and tumor-induced neovascularization in Lewis lung carcinoma-bearing mice". *J. Nutr.* **131** (6): 1844–9.
13. Wade, Nicholas (November 16 2006). "Red Wine Ingredient Increases Endurance, Study Shows". *New York Times*
14. M. Stefani, A. Markus, R.C.Y. Lin, M. Pinese, I.W. Dawes, B.J. Morris, The effect of resveratrol on a cell model of human aging, *Annals N.Y. Acad. Sci.* 1114 (2007) 407–418.

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