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Resveratrol White Paper

Resveratrol is a polyphenolic natural substance found in grapes, various berries, peanuts and Japanese Knotweed (*Polygonum cuspidatum*). This therapeutic compound has undergone considerable evaluation by the scientific research community over the last ten years. Resveratrol was the first substance discovered to activate a class of enzymes called sirtuins (histone deacetylases) that "turn on" and "turn off" several important genes involved in longevity, inflammation, cardiovascular function, metabolic signaling, muscle activity, bone growth and anti-cancer activity. Sirtuin activation also is induced by exercise and dietary restriction, which is defined as reduced caloric intake without malnutrition. Thus, resveratrol administration, caloric restriction and exercise may offer many of the same health benefits through their similar effects on sirtuin enzyme production. Laboratory and clinical data suggest resveratrol administration can reduce the incidence of many aging related illnesses that occur in low frequencies in individuals undergoing dietary restriction or in individuals that exercise routinely.

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Mech Ageing Dev. 2010 Apr;131 (4):261-9. Epub 2010 Feb 26. **Resveratrol, sirtuins, and the promise of a DR mimetic.** Baur JA.

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J Appl Physiol. 2007 Sep;103 (3):1093-8. Epub 2007 Mar 8. **Role of myokines in exercise and metabolism.** Pedersen BK, Akerström TC, Nielsen AR, Fischer CP.

Nat Rev Drug Discov. 2006 Jun;5 (6):493-506. Epub 2006 May 26. **Therapeutic potential of resveratrol: the in vivo evidence.** Baur JA, Sinclair DA.

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J Appl Physiol. 2005 Apr; 98 (4):1154-62. **The anti-inflammatory effect of exercise.** Petersen AM, Pedersen BK.

Mechanisms of Action and Clinical Implications: Laboratory studies have determined that resveratrol has anti-oxidant, anti-inflammatory, anti-diabetic, anti-cancer, anti-aging, cardioprotective and neuroprotective effects. The effects of resveratrol administration upon various tissues and in various health conditions will be summarized in the following pages.

Muscle performance: Resveratrol enhances muscle performance by increasing muscle metabolism and insulin sensitivity and decreasing muscle inflammation. Resveratrol increases the density and size of mitochondria in cells (mitochondrial biogenesis) and improves the efficiency of energy producing metabolic reactions that occur in mitochondria. Mitochondria are the "powerhouse" organelles that supply energy to the cell and muscle tissue. Resveratrol also increases insulin sensitivity in the muscle, thereby improving the ability of the muscle cell to uptake glucose or readily use glucose to increase the activity of muscle tissue. Resveratrol inhibits muscle inflammation by decreasing the production of inflammatory mediators called cytokines. This is important because after a bout of exercise, inflammation can continue for a prolonged period of time and delay muscle recovery. Resveratrol also has been shown to prevent muscle wasting that occurs with old age. Resveratrol prevents muscle wasting by acting as an exercise mimetic to increase muscle mass and decrease muscle oxidative damage.

Am J Physiol Endocrinol Metab. 2011 Jul 26. [Epub ahead of print] **Resveratrol ameliorates metabolic disorders and muscle wasting in streptozotocin-induced diabetic rats.**Chen KH, Cheng ML, Jing YH, Chiu DT, Shiao MS, Chen JK.

FASEB J. 2011 Jun 29. [Epub ahead of print] **Resveratrol prevents the wasting disorders of mechanical unloading by acting as a physical exercise mimetic in the rat.** Momken I, Stevens L, Bergouignan A, Desplanches D, Rudwill F, Chery I, Zahariev A, Zahn S, Stein TP, Sebedio JL, Pujos-Guillot E, Falempin M, Simon C, Coxam V, Andrianjafiniony T, Gauquelin-Koch G, Picquet F, Blanc S.

Arch Surg. 2011 May;146 (5):556-64. **Improving glucose metabolism with resveratrol in a swine model of metabolic syndrome through alteration of signaling pathways in the liver and skeletal muscle.** Burgess TA, Robich MP, Chu LM, Bianchi C, Sellke FW.

Metabolism. 2008 Jul;57 (7):986-98. **Endurance exercise increases the SIRT1 and peroxisome proliferator-activated receptor gamma coactivator-1alpha protein expressions in rat skeletal muscle.** Suwa M, Nakano H, Radak Z, Kumagai S.

J Appl Physiol. 2007 Sep;103 (3):1093-8. Epub 2007 Mar 8. **Role of myokines in exercise and metabolism.** Pedersen BK, Akerström TC, Nielsen AR, Fischer CP.

Metabolic Support: Resveratrol has been shown to lower blood pressure, blood glucose levels and insulin resistance by altering activities of key enzymes involved in metabolism. The compound was found to reduce blood insulin in animals with chronically high insulin levels (hyperinsulinemia). Moreover, numerous data indicate that resveratrol is able to reduce high blood sugar levels (hyperglycemia). Resveratrol has been shown to safely improve insulin resistance in diabetic rodents and is currently in human clinical trials (Trial #NCT00823381) as a potential treatment for Type II diabetes. Supplemental resveratrol also positively influences glucose metabolism pathways in the liver, skeletal muscle and adipose tissue. In fact, resveratrol has the ability to reverse obesity-induced metabolic syndrome and reduce blood lipid levels in individuals with dyslipidemia.

Diabetes. 2011 Sep;60 (9):2274-84. Epub 2011 Aug 1. **Continued postnatal administration of resveratrol prevents diet-induced metabolic syndrome in rat offspring born growth restricted.** Dolinsky VW, Rueda-Clausen CF, Morton JS, Davidge ST, Dyck JR.

Eur J Pharmacol. 2011 Aug 16;664 (1-3):45-53. Epub 2011 May 7. **Resveratrol modifies risk factors for coronary artery disease in swine with metabolic syndrome and myocardial ischemia.** Robich MP, Osipov RM, Chu LM, Han Y, Feng J, Nezafat R, Clements RT, Manning WJ, Sellke FW.

J Nutr Biochem. 2011 Aug 1. [Epub ahead of print] **Resveratrol up-regulates SIRT1 and inhibits cellular oxidative stress in the diabetic milieu: mechanistic insights.** Yun JM, Chien A, Jialal I, Devaraj S.

Biochem Pharmacol. 2011 Jun 1;81 (11):1343-51. Epub 2011 Mar 31. **Resveratrol exerts anti-obesity effects via mechanisms involving down-regulation of adipogenic and inflammatory processes in mice.** Kim S, Jin Y, Choi Y, Park T.

Nutrition. 2011 Jun;27 (6):617-23. Epub 2011 Mar 2. **Polyphenols: planting the seeds of treatment for the metabolic syndrome.** Cherniack EP.

Weight Control and Fat Tissue: Adipose or fat tissue is considered an active organ in which adipocytes (fat cells) have the ability to produce inflammation that contributes to disease states such as metabolic syndrome and cardiovascular disease. Resveratrol is therapeutic in these disease states due to the fact that it acts on fat tissue. Resveratrol decreases fat mass, increases lipolysis (fat break down), decreases adipogenesis (maturation and growth of fat cells) and viability in maturing preadipocytes. These effects are mediated through down-regulation of adipocyte specific transcription factors and enzymes but also by genes that modulate mitochondrial function in fat cells. More importantly resveratrol decreases inflammatory cytokine production by adipocytes.

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Nutr Metab (Lond). 2011 May 10;8 (1):29. **Changes in white adipose tissue metabolism induced by resveratrol in rats.** Alberdi G, Rodríguez VM, Miranda J, Macarulla MT, Arias N, Andrés-Lacueva C, Portillo MP.

J Nutr Biochem. 2011 May 2. [Epub ahead of print] **Resveratrol regulates lipolysis via adipose triglyceride lipase.** Lasa A, Schweiger M, Kotzbeck P, Churruca I, Simón E, Zechner R, Portillo MD.

Obes Surg. 2011 Mar;21 (3):356-61. **Resveratrol upregulated SIRT1, FOXO1, and adiponectin and downregulated PPARγ1-3 mRNA expression in human visceral adipocytes.** Costa Cdos S, Rohden F, Hammes TO, Margis R, Bortolotto JW, Padoin AV, Mottin CC, Guaragna RM.

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Mol Cell Endocrinol. 2010 Mar 25;316 (2):129-39. Epub 2009 Aug 31. **Adipose tissue as an endocrine organ.** Galic S, Oakhill JS, Steinberg GR.

Proc Nutr Soc. 2001 Aug;60 (3):329-39. **Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ.** Trayhurn P, Beattie JH.

Cardiovascular Support: Resveratrol's cardioprotective effects are attributable to its ability to act on multiple cellular targets both extrinsically and intrinsically. These include the inhibition of LDL oxidation, suppression of platelet aggregation and inhibition of smooth muscle and endothelial cell proliferation and function. Resveratrol also exhibits a preconditioning-like action on the heart. The compound promotes an adaptive stress response by increasing the expression of cardioprotective genes that are involved in the production of heat shock and antioxidant proteins. This adaptive stress response enhances cardio performance as well as providing cardioprotection.

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J Nutr Biochem. 2011 Aug 16. [Epub ahead of print] **Effects of long-term consumption of low doses of resveratrol on diet-induced mild hypercholesterolemia in pigs: a transcriptomic approach to disease prevention.** Azorín-Ortuño M, Yáñez-Gascón MJ, González-Sarrías A, Larrosa M, Vallejo F, Pallarés FJ, Lucas R, Morales JC, Tomás-Barberán FA, García-Conesa MT, Espín JC.

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Ann N Y Acad Sci. 2011 Jan; 1215:16-21. **Resveratrol: a cardioprotective substance.** Wu JM, Hsieh TC.

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Recent Pat Cardiovasc Drug Discov. 2010 Jun;5 (2):97-102. **Targeting resveratrol to mitochondria for cardiovascular diseases.** Fan E, Zhang K.

Neuroprotection: Neuroinflammation is an important contributor to the pathogenesis of neurological disorders. Resveratrol has been shown to protect against various neurological disorders in experimental models, including brain ischemia, seizures, and neurodegenerative disease models. Resveratrol provides neuroprotection by decreasing inflammation and oxidation in the brain and nervous system and has also been shown to inhibit neuro-related angiogenesis (tumor growth).

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Brain Res. 2011 Feb 16; 1374:100-9. Epub 2010 Nov 25. **Resveratrol improves neuron protection and functional recovery in rat model of spinal cord injury.** Liu C, Shi Z, Fan L, Zhang C, Wang K, Wang B.

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Digestive System Support: Resveratrol has been shown to have significant therapeutic potential in the gastrointestinal tract. Resveratrol reduces colon inflammation and prevents oxidative damage in the colon. Resveratrol therapy also is a novel and promising approach to the treatment of chronic intestinal inflammation such as colitis. Resveratrol administration also has been shown to repair mucosal barrier imbalances thereby preventing or alleviating diarrhea.

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chronic colitis in IL-10(-/-) mice. Singh UP, Singh NP, Singh B, Hofseth LJ, Taub DD, Price RL, Nagarkatti M, Nagarkatti PS.

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Pulmonary Support: Inflammatory conditions of the lung, such as Reactive Airway Obstruction (RAO) and Chronic Obstructive Pulmonary Disorder (COPD), are difficult to treat without using steroidal drugs. Resveratrol has been shown to inactivate cells in the lung responsible for the production of inflammation. Resveratrol is one of the few natural compounds that significantly decreases lung inflammation, in turn alleviating symptoms of airway disease, including asthma.

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Cartilage Protection and Bone Health: Resveratrol protects joint cartilage by decreasing oxidative damage and synovial fluid inflammation and is a potent prophylactic treatment for osteoarthritis. By decreasing inflammation in the joint locally, resveratrol protects cartilage from the catabolic processes initiated by pro-inflammatory cytokines and thereby prevents the death of chondrocytes or cells that produce and make up cartilage. Resveratrol has also been shown to prevent bone loss with aging.

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Biochem Pharmacol. 2008 Feb 1;75 (3):677-87. Epub 2007 Sep 18. **Regulation of inflammation signalling by resveratrol in human chondrocytes in vitro.** Csaki C, Keshishzadeh N, Fischer K, Shakibaei M.

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Arthritis Rheum. 2008 Sep;58 (9):2786-97. **The antioxidant resveratrol protects against chondrocyte apoptosis via effects on mitochondrial polarization and ATP production.** Dave M, Attur M, Palmer G, Al-Mussawir HE, Kennish L, Patel J, Abramson SB.

Anti-cancer Activity: Resveratrol inhibits or retards the growth of various cancer cells in culture and implanted tumors *in vivo*. The compound significantly inhibits experimental tumorigenesis in a wide range of animal models. Resveratrol targets many components of intracellular signaling pathways involved in cancer including pro-inflammatory mediators, regulators of cell survival and apoptosis and tumor angiogenic and metastatic switches. Resveratrol modulates signaling pathways in a variety of different cancers including skin cancer (melanomas), breast cancer, lung cancer, prostate cancer, fibrosarcomas, hepatoma, and leukemia. Resveratrol currently is in human clinical trials as a treatment for cancer.

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Cancer Prev Res (Phila). 2009 May;2 (5):409-18. Epub 2009 Apr 28. **Cancer prevention and treatment with resveratrol: from rodent studies to clinical trials.** Bishayee A.

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Anti-Aging Effects: One of the most striking biological activities of resveratrol is its ability to promote longevity. Resveratrol has been shown to promote healthy aging and to increase lifespan primarily through the activation of the histone deacetylases (sirtuins). Resveratrol not only activates longevity enzymes or sirtuins but it can induce the expression of several longevity genes which prevent aging-related decline in a variety of tissues, thereby slowing down the onset of age-related diseases. More recently, resveratrol has been shown to exert its anti-aging effects through the induction of autophagy. Autophagy is the body's natural catabolic process responsible for cellular cleanup in tissues and organs. Autophagy decreases with age, and this reduced function has been blamed for the accumulation of damaged proteins in old organisms, thus leading to decreased function of organ systems and increased inflammatory conditions and cancers. Therefore, resveratrol's ability to activate autophagy stimulates the body's natural defense system to cleanse, promoting continued health with aging.

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Heart Fail Rev. 2011 Jul;16 (4):425-35. **Erratum to: resveratrol and red wine, healthy heart and longevity.** Das DK, Mukherjee S, Ray D.

Autophagy. 2010 Jan;6 (1):186-8. Epub 2010 Jan 2. **The life span-prolonging effect of sirtuin-1 is mediated by autophagy.** Morselli E, Maiuri MC, Markaki M, Megalou E, Pasparaki A, Palikaras K, Criollo A, Galluzzi L, Malik SA, Vitale I, Michaud M, Madeo F, Tavernarakis N, Kroemer G.

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Cell Death Dis. 2010; 1:10. **Caloric restriction and resveratrol promote longevity through the Sirtuin-1-dependent induction of autophagy.** Morselli E, Maiuri MC, Markaki M, Megalou E, Pasparaki A, Palikaras K, Criollo A, Galluzzi L, Malik SA, Vitale I, Michaud M, Madeo F, Tavernarakis N, Kroemer G.

Curr Aging Sci. 2008 Dec;1 (3):145-51**. Metabolic effects of resveratrol in mammals--a link between improved insulin action and aging.** Fröjdö S, Durand C, Pirola L.

Mol Nutr Food Res. 2005 May;49 (5):405-30. **Resveratrol as an anti-inflammatory and anti-aging agent: mechanisms and clinical implications.** de la Lastra CA, Villegas I.

Anti-inflammatory/Anti-oxidant Activity: Many studies have documented the anti-inflammatory and anti-oxidant activity of resveratrol using various models of inflammation. Resveratrol interferes with immune activation and cytokine cascades responsible for inflammation. These studies have shown that resveratrol inhibits a

potent cellular factor (Nuclear factor kappaB) which is responsible for initiating inflammation in a variety of tissues and in the blood, thereby providing a broad anti-inflammatory protection. Resveratrol administration reduces inflammation by: decreasing synthesis or production of pro-inflammatory mediators, modifying eicosanoid synthesis, inhibiting activated immune cells and inhibiting pro-inflammatory enzymes such as cyclooxygenase-2 (COX-2).

Resveratrol is also a potent anti-oxidant. Mitochondrial redox metabolism is a major contributor to oxidative damage in the body and has long been considered to play an important role in mammalian aging and the development of disease pathologies. Resveratrol has been shown to manipulate the mitochondrial redox metabolism system such that there is reduced oxidative damage in a variety of cells and tissues.

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Int J Mol Med. 2001 Jul;8 (1):3-17. **Mechanism of cardioprotection by resveratrol, a phenolic antioxidant present in red wine (Review).** Wu JM, Wang ZR, Hsieh TC, Bruder JL, Zou JG, Huang YZ.