Resveratrol: Unique Nutrient for Extending Health Into Old Age

by Parris M. Kidd, PhD

Living a very long life with youthful vitality is a universal human longing. Now a nutrient is available with real promise to deliver this reality. The nutrient is resveratrol (res-ver-a-trol).

After almost two decades of intensive study, resveratrol has an exciting spectrum of benefits:

- Potent antioxidant, working through multiple pathways.
- Anti-inflammatory, and analgesic—reduces pain.
- Counters metabolic activation of chemicals to more toxic forms.
- Blocks new blood vessels that may enable tumor metastasis.
- Promotes DNA repair, delays self-destruction in damaged cells (apoptosis).
- Potent protectant for the brain, heart, and other organs.
- Down-regulates C-reactive protein (CRP), cardiovascular risk indicator.
- Blocks harmful effects of high-calorie diet on healthy aging.
- Extends lifespan in lower animals and in mice fed high-calorie diets.

But another, extremely rare property elevates resveratrol into a category all its own—this simple nutrient is a master gene regulator.

As a dietary supplement, resveratrol can turn on or off a large number of genes that are important for lifespan and quality of life. Resveratrol's pattern of gene regulation parallels that of caloric restriction (CR), the only other intervention known to extend healthy lifespan. Unlike CR, resveratrol is convenient and safe for long-term use.

Simple Molecule with Unique Attributes

Resveratrol is a relatively simple molecule found in small amounts in many plants, but mostly in the skin and seeds of grapes. Red wine has the highest resveratrol content of any foodstuff. Two molecular forms of resveratrol exist, the trans and the cis, of which the trans form has virtually all the biological activity and predominates in foods.

Technically, resveratrol is a stilbene substance belonging to the large family of polyphenol nutrients, which are widespread in plant foods. It is likely produced in plants as a protective response to stress. But resveratrol has unusual properties that make it unique among all nutrients (or drugs).

Resveratrol's especially rare property is its epigenetic action: it can selectively activate and deactivate genes in patterns that enhance healthy life processes AND extend healthy lifespan. Resveratrol even can activate the "master" gene that prolongs lifespan in higher animals (mammals).

This master gene is known as silent information regulator 2 (SIR2) in lower animals, and in the mammals as sirtuin-1 (SIRT1). Both resveratrol and CR extend lifespan via SIR2 in yeast, roundworms, and fruit flies, and via SIRT1 in mammals (mice).

Resveratrol is very safe and well tolerated by humans. Currently, healthy and diseased human subjects, young and old, are being recruited to receive resveratrol supplements in at least ten clinical trials.

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The Breakthrough Mouse Study

In 2006, a landmark research report was published in the prestigious journal Nature, by 27 researchers based at Harvard Medical School, the U.S. government's National Institute of Aging, and other internationally recognized institutions on three continents. The study reported that resveratrol improved the health and survival of mice maintained from middle age into old age on a high-calorie diet.

The gene AMPK was activated. This gene is known to manage insulin and is also up-regulated by CR.

Organ Damage Prevented in Mice on High Calories

The HC mice without resveratrol developed greatly increased liver size and weight, with liver cell damage and fat accumulation. They also displayed subtle pancreatic damage. Giving resveratrol protected against all these negative changes. In addition, resveratrol protected the heart against inflammatory damage and fat accumulation, and improved aorta wall structure.

CR (and exercise, incidentally) can increase the liver's density of mitochondria, the cell compartments that generate most of our energy. In this Nature study resveratrol also increased the liver's mitochondria density. Biochemical analysis linked resveratrol to increased enzyme activity from SIRT1, and from other genes probably activated by SIRT1.

Sophisticated gene monitoring revealed also that resveratrol changed the "expression" (on or off) of 782 mouse genes, including down-regulating three genes that can transform various chemicals to carcinogens. Resveratrol blocked the harmful high-calorie effects in 144 of the total 153 pathways found to be altered. Some 19 pathways were identified in which resveratrol's gene regulatory benefits paralleled those from caloric restriction.

Enhanced Life Quality and Lifespan

Those mice on high calories that received resveratrol showed improved function as they aged. On a test of balance and motor coordination, these mice steadily improved their motor skills.
over time. This positive effect resembled the improvement of motor activity that accompanies resveratrol's lifespan extension in the fish *Nothobranchius*.

As the *Nature* study findings suggest, resveratrol likely enhances life quality by influencing many genes, in addition to SIRT1 and AMPK. SIRT1 itself influences many other genes, and through them a variety of life processes. Resveratrol additionally influences genes for quinone reductase 2 and other enzymes that regulate energetics; SOD and other antioxidant genes; NF-kappa B and other genes that control apoptosis and cell survival; genes that control cell proliferation; and numerous others.

**Multiple Circulation Benefits**

Resveratrol has displayed circulatory benefits in various animal "models" and in humans. In the *Nature* mouse study, it blocked high-calorie damage to the heart and aorta. In other studies with animal and human tissues, resveratrol protected the blood vessel linings against atherosclerotic damage and against increased platelet aggregation, as can result from cigarette smoking, abnormal blood cholesterol, or homocysteine elevation. It also promoted healthy tone in the small blood vessels, perhaps through improved nitric oxide homeostasis.

Resveratrol is one of the few nutrients that can lower CRP, a proven risk factor for heart attack and stroke. In experimental animals it protected the heart against oxygen deprivation. In a clinical trial with type 2 diabetic subjects who had recently suffered heart attack (myocardial ischemia), resveratrol improved the heart's left ventricle function.

**Brain Protection and Memory Support**

As with the heart, resveratrol also protects the brain against damage caused by ischemia (including stroke). This small molecule seems able to readily cross the blood-brain barrier, and can protect against ischemic damage to the hippocampus, the brain region that initiates memories. Resveratrol seems to have strong neuro-protective effects, even at low doses. Currently two clinical trials are pending against Alzheimer's disease.

**Whole-Body Protection Grounded in DNA**

Human DNA is constantly exposed to potentially destructive influences, both from outside and inside the body. On average, each human cell takes at least 10,000 hits to its DNA each day, any one of which could cause a harmful gene mutation. Resveratrol protects DNA at a fundamental level: direct binding with the DNA strands. This ability to come into close proximity with DNA could explain resveratrol's capacities to block abnormal cell growth transformation and the premature cell aging or cell death scenarios associated with DNA damage.

Above the level of DNA, resveratrol can up-regulate the antioxidant defenses as it suppresses "free radical" activity. It boosts liver detoxification activity via the P450 enzyme system. Nor are its organ-protective effects limited to the heart and brain. Resveratrol can block experimental injury to the intestine, colon, liver, kidneys, lungs, joints, and spinal cord, and protect against hearing loss.

**Counters Inflammation, Supports Immunity**

Resveratrol is also a potent anti-inflammatory nutrient. It is a powerful inhibitor of cyclooxygenase-1 (COX-1), an enzyme that can promote inflammation especially in subjects with poor omega-3 fatty acid intakes. But resveratrol does not appreciably block COX-2 and so has none of the liability of COX-inhibitor pharmaceuticals.

Besides counteracting pro-inflammatory reactions, resveratrol promotes healthy immunity. It can correct the immune suppression that alcohol can cause, and protects mice from infection by herpes simplex viruses 1 and 2.

**A Must-Take Nutrient for Young and Old**

A new scientific paradigm of aging has emerged, one that recognizes practical possibility for extending the human lifespan in our lifetime. The most promising vehicle for human lifespan extension is not a wonder drug, but the wondrous nutrient resveratrol. Academic and private sector researchers in top-class institutions worldwide are sharply focused on resveratrol for a dazzling variety of health applications.

But resveratrol is not just for the old or the middle-aged. It is now entering clinical trials to combat obesity, insulin resistance, and diabetes, conditions that increasingly afflict young people. And the animal research suggests that to be assured of "anti-aging" benefit humans probably need to start on resveratrol before reaching middle age.

Young persons and others of any age also could investigate resveratrol for cancer prevention. Three of the pending clinical trials relate to prevention of cancers—melanoma, colon, and other solid tumors. Three others are targeted at cancer treatment—colon, rectal, and lymphoma.

Resveratrol absorption has been studied in humans, but much about its human metabolism remains unanswered. But in most of the animal studies, the effective intakes were within a range available from well-formulated resveratrol supplements (100 mg per day and more). In the landmark *Nature* mouse study, as the best example, using a reliable calculation the effective resveratrol dose translates to 145 per day for a 180-pound adult human. The amount of red wine needed to provide this amount of resveratrol would enter the zone of alcohol toxicity. For full and reliable benefit, it is best to take a potent resveratrol supplement.

Resveratrol is certainly not a panacea—already the most challenging of the clinical trials plan to employ it in combination with other nutrients. But this unique nutrient has sparked new optimism: that even our DNA can benefit from rational nutritional intervention. The rapidly-expanding knowledge base on resveratrol supports the proposition that it can help the human body attain excellent health and maintain it into a ripe old age.

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