



## The Health Benefits of Resveratrol

For the past few years, resveratrol, a compound found in red grapes, has attracted widespread medical attention as the long sought-after fountain of youth. This is because research has begun to indicate that this phytonutrient does indeed seem to have longevity-enhancing effects and that it also can play a critical role in heart health. Since 2003, when Harvard researchers discovered that resveratrol increases the life span of yeast cells by as much as 70 percent, scientists have eagerly studied its effects in increasingly complex forms of life. Following up on research that resveratrol extended the life of roundworms and fruit flies, the most recent studies reveal for the first time that resveratrol also extends life span in mammals.

### Resveratrol Promotes Longevity

A groundbreaking study in 2006, investigating resveratrol in mammals, found that dietary supplementation with resveratrol protected obese mice on a high-calorie diet, improving their health and extending their life span.<sup>1</sup> The study, conducted by the National Institute on Aging and a group co-led by pioneering researcher Dr. David Sinclair, compared three groups of middle-aged mice on three diets: a standard diet and a high-calorie diet (60 percent of calories from fat) with and without resveratrol (22.4 mg/kg/day). As expected, the mice in the untreated high-calorie group showed signs of obesity, developing enlarged livers, muscle inflammation, early signs of diabetes and heart disease, and dying much sooner than those on the standard diet. However, the resveratrol-supplemented mice developed none of these complications despite being obese. The mice given the high-fat diet and resveratrol lived as long as the mice fed the standard diet and up to 31 percent longer than the untreated obese group. This study dramatically showed for the first time that resveratrol increases life span for obese mammals, which would otherwise be expected to develop chronic diseases, especially type II diabetes, and to die sooner. Of the 153 biochemical pathways significantly altered in the high-calorie group, resveratrol opposed the effects of high-caloric intake in 144 of them (94 percent). Although the resveratrol-treated mice lost no weight, the supplement effectively offset the detrimental effects of a high-calorie diet by shifting their overall physiology towards that of the control group and preventing many of the obesity-associated pathologies.<sup>1</sup>

### Increasing Energy Expenditure

Soon after this study, French researchers shed some light as to what was going on. They fed healthy young mice large amounts of resveratrol (400 mg/kg/day) for 15 weeks.<sup>2</sup> The team discovered that it greatly enhanced the aerobic

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capacity of the mice, doubling their physical endurance during exercise, increasing oxygen consumption efficiency, and significantly increasing grip strength.

The investigators also found that the size and number of mitochondria, the powerhouses of cells, were dramatically increased in muscle fibers, which explained the greater energy-output capacity and endurance of the mice. As a result of the increased energy expenditure, the resveratrol-treated mice in the high-calorie group were able to burn off most of their excess calories rather than storing them as fat, preventing weight gain.<sup>2</sup>

### **SIRT1: The Longevity Gene**

Scientists are still uncertain of the exact mechanism by which resveratrol works, but believe it acts in a similar way to calorie restriction, which switches on a longevity gene called SIRT1.<sup>1-2</sup> SIRT1 is thought to be triggered in times of famine to ensure the survival of a species. In times of caloric restriction, SIRT1 appears to act both as a sensor of nutrient availability and a regulator of gluconeogenic and glycolytic pathways in the liver.<sup>3</sup>

The activity of SIRT1 increases in fat cells after food limitation, which plays a key role in lipid metabolism by moving fat stores from the cells into the bloodstream for conversion to energy in other tissues. Researchers have found that mice genetically engineered to have increased levels of SIRT1 and fed a high-calorie diet do not gain any more weight than controls since the excess calories are offset by increased energy expenditure.<sup>4</sup>

Another recent study supports these findings. It showed that SIRT1 levels are reduced in insulin-resistant cells and tissues.<sup>5</sup> Furthermore, treatment with SIRT1 inhibitors causes insulin resistance, while resveratrol improves insulin sensitivity *in vitro* in a SIRT1-dependent manner. *In vivo*, resveratrol, 2.5 mg/kg/day, reduces insulin resistance in the cells of animals fed a high-fat diet.<sup>5</sup>

### **A Calorie-Restriction Mimetic**

Studies in the past year confirm that resveratrol mimics the favorable gene-expression changes seen with calorie restriction. In a study co-led by Sinclair, middle-aged mice were placed on three different diets: a standard diet, dietary restriction by every-other-day feeding of a nutritious diet, and a high-calorie diet (60 percent calories from fat).<sup>6</sup> The mice in each group were also divided into treatment with and without resveratrol (up to 30 mg/kg/day). As with the previous Sinclair study,<sup>1</sup> the resveratrol-supplemented mice in the high-calorie group did not lose weight, but lived longer than the untreated high-calorie group. The researchers speculated that an improvement in several markers for heart health

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and a reduction both in aortic stiffness and the severity of albuminuria may have contributed to animals' increased life span.<sup>6</sup>

They also found that even in mice in the standard diet group, resveratrol improved cardiovascular function, bone density, and motor function, and delayed cataracts.<sup>6</sup>

The team also performed a gene-expression analysis in liver, skeletal muscle, fat, and heart tissue to see if resveratrol mimicked the physiological effects of dietary restriction in terms of gene activity. They found that resveratrol induced transcriptional changes in key metabolic tissues that closely resembled those induced by dietary restriction in the group fed every other day. However, they were unable to confirm SIRT1's role in the anti-aging effects seen in this study. The team concluded, "long-term resveratrol treatment of mice can mimic transcriptional changes induced by dietary restriction and allow them to live healthier, more vigorous lives."<sup>6</sup>

It may be that resveratrol alters not just SIRT1, but multiple proteins involved in the cellular stress response. A recent study focused on another target—an enzyme called AMPK (adenosine monophosphate-activated kinase), which is a sensor of cellular energy levels and is thought to be activated in brain neurons during calorie restriction. Using neuronal cell cultures and mice, the researchers found that many of resveratrol's effects including energy expenditure do indeed depend on AMPK.<sup>7</sup> Resveratrol activated AMPK in primary neurons *in vitro* as well as in the brain. It also stimulated mitochondrial biogenesis (the formation of increased numbers of mitochondria) in an AMPK-dependent manner, which plays an important part in neuronal energy homeostasis and contributes to the neuroprotective effects of resveratrol.<sup>7</sup>

While research into gene-expression changes induced by resveratrol continues, another study published this year builds on evidence that alcohol inhibits SIRT1 and AMPK. This study of alcoholic fatty liver showed that the accumulation of fat in the livers of mice fed alcohol and a low-fat diet could be prevented with resveratrol through its upregulation of both SIRT1 and AMPK.<sup>8</sup>

### **Cardiovascular Protection**

Results from the groundbreaking studies mentioned earlier revealed that mice in high-calorie groups given resveratrol had healthier hearts, essentially helping them to live normal, active lives despite becoming obese.<sup>1</sup>

A new study confirms that resveratrol confers special protection to the heart.<sup>9</sup> Researchers divided two groups of middle-aged mice (14 months) to receive resveratrol (4.9 mg/kg/day) or a calorie-restricted diet (reduction of daily energy

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intake by 40 percent) and followed them until old age (30 months). They found that while aging altered gene-expression profiles in the heart, calorie restriction and resveratrol mitigated these changes by 90 and 92 percent, respectively, thus preventing the decline in cardiovascular function associated with aging. The researchers stated that “resveratrol at doses that can be readily achieved through dietary supplementation in humans is as effective as calorie restriction in opposing the majority of age-related transcriptional alterations in the aging heart.”<sup>9</sup>

They also measured an indicator of cardiac function called the myocardial performance index, which normally increases with declining function and age. Both calorie restriction and resveratrol almost completely protected against this increase, unlike the control group, in which the index increased as expected. They concluded, “resveratrol mimics the effects of calorie restriction to prevent cardiac aging at both the transcriptional and functional levels.”<sup>9</sup>

Many studies have found that resveratrol acts through several mechanisms to protect against acute and chronic heart disease. In an experimental study of cardiac hypertrophy, resveratrol helped improve blood flow by increasing the production of nitric oxide, the universal vasodilator, by 90 percent,<sup>10</sup> while reducing levels of the artery-constricting angiotensin 2.<sup>10</sup>

In another experimental study, resveratrol showed a direct cardioprotective effect on diabetic myocardium in rats with streptozotocin-induced diabetes. Resveratrol also significantly reduced glucose levels in this study, improved left ventricular function, reduced the size of myocardial infarcts, and increased levels of superoxide dismutase, a powerful antioxidant.<sup>11</sup> Another study showed that resveratrol has potent cardioprotective properties following a reduction in oxygen and blood supply in ischemia-reperfused hearts.<sup>12</sup>

In addition, resveratrol inhibits platelet aggregation in high-risk cardiac patients,<sup>13</sup> which lowers the risk of deadly blood clots that can cause heart attacks. It also reduces the expression of endothelin (a potent vasoconstrictor) and cardiac apoptosis in ischemic-reperfused hearts,<sup>14</sup> and increases endothelial progenitor cells in patients with hypercholesterolemia (which helps repair arteries damaged by atherosclerosis).<sup>15</sup> In addition, resveratrol protects heart muscle by reducing the effects of cardiac fibrosis (stiffening of heart tissue).<sup>16</sup>

### **Osteoarthritis and Neurodegenerative Diseases**

Resveratrol may also hold promise in osteoarthritis following studies that it inhibits the expression of proinflammatory mediators such as COX-2 and that it has a cartilage-protecting effect.<sup>18</sup>

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Resveratrol also offers neuroprotective benefits. It has been shown to help degrade the destructive amyloid-beta protein implicated in Alzheimer's disease<sup>19</sup> and protect dopaminergic neurons against a neurotoxic compound that causes brain lesions in Parkinson's disease.<sup>20</sup>

## Conclusion

Resveratrol can harness the anti-aging benefits of calorie restriction without food deprivation by activating genes that influence a variety of aging-related metabolic functions. Resveratrol is metabolized very rapidly when ingested, but its bioavailability can be increased with substances such as quercetin (as found in Extension Resveratrol). In addition, resveratrol occurs naturally as two forms: cis and trans, but it is the trans form that is the most bioactive and clinically beneficial. Furthermore, the studies mentioned in this article used human equivalent doses of resveratrol of up to a few hundred milligrams per day. In fact, the leading resveratrol researcher, Dr. Sinclair, has been reported to take 5 mg/kg/day of resveratrol,<sup>21</sup> which translates to 300 mg/day for a 60-kg (132-lb) person.

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