

Resveratrol treatment has been documented to attenuate symptoms and prolong the lifespan of mice with age-related diseases. In 2011, supplementation of 25 mg kg⁻¹ resveratrol to *KtrA2* knock-out mice exhibiting Parkinsonian phenotype increased the lifespan by 30%, delaying the deterioration of motor activity.⁴⁰ Furthermore, supplementation of 1 g kg⁻¹ resveratrol to age-accelerated mice (SAMP8)—a model with Alzheimer's disease—reduced cognitive impairment, amyloid accumulation in the brain, and levels of phosphorylated tau, a marker of Alzheimer's disease severity.⁴¹ In addition, resveratrol treatment increased the levels of Sirt1 and pAMPK, and extended the lifespan of SAMP8 mice by 33%.⁴¹ In an experiment using an amyotrophic lateral sclerosis model of SOD1^{G93A} transgenic mice, 25 mg kg⁻¹ day⁻¹ of resveratrol reduced the disease onset, increased lifespan, and attenuated the loss of motor neuron and atrophy of mitochondria.⁴² Similarly, it was independently reported that resveratrol supplementation at 160 mg kg⁻¹ day⁻¹ extended the lifespan by 10% and improved the motor function in SOD1^{G93A} mice.⁴³ Resveratrol was also effective in rodents with hypertension. Supplementation of resveratrol at 18 mg kg⁻¹ day⁻¹ to Dahl salt-sensitive rats extended the lifespan by 64%, and improved mitochondrial respiration and biogenesis.⁴⁴ However, supplementation of 50 mg kg⁻¹ day⁻¹ resveratrol decreased the survival of immunodeficient mice with prostate cancer xenografts.⁴⁵ These conflicting effects of resveratrol on lifespan between the healthy and diseased animals can be explained by the requirement of metabolic stresses to achieve lifespan-extending properties of resveratrol.

13.2.3 Clinical Trials of Resveratrol in Human Subjects

Although there have been no trials investigating the longevity effect of resveratrol in primates, including human subjects, an inference can be made from previously published reports with respect to the beneficial effects of resveratrol on human health. Recently, two studies reported by the National Institute on Aging showed that the supplementation of resveratrol improved insulin sensitivity in adipose and ameliorated arterial wall inflammation in rhesus monkeys fed with a high-fat/high-sucrose diet.^{46,47} Several clinical trials of resveratrol have been attempted, especially in patients with metabolic disease, cardiovascular disease, and cancer, but the results have been controversial thus far. Daily supplementation of 500–600 mg resveratrol for 12 weeks to patients with non-alcoholic fatty liver reduced alanine aminotransferase, hepatic steatosis, tumor necrosis factor- α , and low-density lipoprotein cholesterol, but did not affect insulin sensitivity, lipid profile, and blood pressure.^{48,49} Higher doses of resveratrol were also attempted to treat patients with non-alcoholic fatty liver. The supplementation of 1.5 g of resveratrol for 6 months or 3 g of resveratrol for 8 weeks was reported to decrease liver lipid contents, but did not change the histological features of the liver and insulin sensitivity.^{50,51} In addition, daily supplementation of 3 g of resveratrol for 12 weeks significantly increased the expression of SIRT1 and the phosphorylation of AMPK in type 2 diabetes.⁵² Inconsistently with the data from