rodents, daily supplementation of 1–2 g resveratrol for 2 weeks or 500 mg for 4 weeks to obese men did not affect the blood pressure, resting energy expenditure, visceral fat contents, and inflammatory biomarkers.[53,54] In addition, non-obese and postmenopausal women with normal glucose tolerance did not respond to daily administration of 75 mg of resveratrol for 12 weeks.[55] A 1 year supplementation of resveratrol-containing (8 mg) grape-extract in coronary artery disease patients increased the level of anti-inflammatory adiponectin and decreased the levels of high-sensitivity C-reactive protein, tumor necrosis factor α, and thrombogenic plasminogen activator inhibitor type 1.[56,57] Moreover, daily supplementation of 10 mg of resveratrol capsule for 3 months to patients with coronary artery disease after myocardial infarction showed an improvement in the ventricle function and lowered the LDL-cholesterol level.[58] The effect of resveratrol on the host metabolism and clinical trials related to metabolic diseases were well reviewed by Timmers *et al.*[59]

According to the data from these reports, the optimal concentration and duration of resveratrol treatment seem to be distinct for the specific disease. Thus, large-scale and long-term studies are required to further evaluate the clinical values of resveratrol.

13.2.4 Putative Target Molecules for Lifespan-Extending Effect of Resveratrol

The first identified molecular target of resveratrol was sirtuin, an NAD+ dependent deacetylase. However, sirtuins are not the only target of resveratrol, and resveratrol is reported to have numerous molecular targets, including AMP-activated protein kinase (AMPK), cyclooxygenases, lipoxygenases, adenylyl cyclase, DNA polymerase, ribonucleotide reductase, quinone reductase 2, aryl hydrocarbon receptors, cytochrome P450 enzymes, F1-ATPase, and phosphodiesterases.[8,12,60–65] In addition, the metabolic effects of resveratrol were recently reported to be mediated by inhibiting cAMP phosphodiesterases (PDEs), particularly PDE4.[64] The underlying mechanism of lifespan-extending effects by phytochemicals is well reviewed by Leonov *et al.*[1] In this section, we focus on the putative mechanisms of lifespan-extending effects by resveratrol.

13.2.4.1 Caloric Restriction Mimetics

Caloric restriction is defined as the reduction of calorie uptake without malnutrition, and is well established to extend the lifespan of almost all species, including non-human primates. Several studies have shown that resveratrol did not further increase the lifespan under caloric restriction conditions, indicating that caloric restriction and resveratrol share similar anti-aging mechanisms. In 2003, Howitz *et al.* showed that resveratrol did not further extend the lifespan of *S. cerevisiae* under glucose-restricted conditions.[17]