Similarly, Wood *et al.* showed that resveratrol did not further extend the lifespan of flies under a restricted diet.[18] In this regard, resveratrol was considered as a calorie restriction mimetic—a compound producing the beneficial effects of caloric restriction without the actual restriction of energy intake. The concept of resveratrol having caloric restriction mimetic properties was supported by the fact that resveratrol shifts the physiology of mice fed with excess calories towards that of mice fed with a standard diet.[19] Supplementation of resveratrol make the mice fed with high calories healthier as indicated by survival, motor function, insulin sensitivity, organ pathology, and mitochondrial number.[19]

To find the link between resveratrol and caloric restriction, several studies compared the transcriptional profile of resveratrol treatment and caloric restriction implementation in rodents, and found that the transcriptional response to resveratrol resembles that by caloric restriction.[36,66,67] The gene expression alterations by low-dose resveratrol (4.9 mg kg^{-1}) or caloric restriction occurred in the same direction in the heart, skeletal muscle, and brain.[66] A strong repression of age-related transcriptional alterations by resveratrol and caloric restriction was shown in the heart.[66] Additionally, it was reported that the transcriptional effects of calorie restriction exhibited a variable degree of overlap with resveratrol in the liver of mice.[67] However, the transcriptional changes of resveratrol and caloric restriction were reported to be largely independent of the increase in SIRT1 activity.[66]

Although many studies indicate the possible role of resveratrol as a caloric restriction mimetic, not all studies support this notion. In a report published by Zou *et al.*, resveratrol supplementation still extended the lifespan of the tephritid fruit fly under caloric restriction.[29] Furthermore, caloric restriction reduced the circulating IGF-1 level but not resveratrol,[66] and resveratrol failed to slow down the heart rate, to decrease the core body temperature, and to extend the lifespan in non-obese animals unrelated to caloric restriction.[36,68,69]

13.2.4.2 NAD^+-Dependent Deacetylase Sirtuin

The NAD^+-dependent deacetylase sirtuins, including silent information regulator 1 (SIRT1), play a role in DNA damage response, metabolism, longevity, and carcinogenesis. SIRT1 regulates cellular processes such as proliferation, differentiation, and apoptosis through deacetylation of important regulatory proteins such as p53, transcription factor forkhead box O (FOXO), nuclear factor κB (NF-κB) subunit p65, and peroxisome proliferator-activated receptorγcoactivator-1α (PGC-1α). In addition, histones H1, H3, and H4 are also reported as substrates of SIRT1.[70] Much experimental evidence indicates that sirtuin is the major mediator of the health-improving and lifespan-extending effects of caloric restriction. Resveratrol was initially selected in the process of sirtuin activator screening in yeast, and it was revealed that resveratrol significantly increased SIRT1 activity through an allosteric interaction, resulting in an increase of SIRT1 affinity for both NAD^+ and acetylated substrate.[17,70]