

LPS-stimulated macrophages by inhibiting the proteasome.¹⁶² Finally, resveratrol decreases inflammation in models of respiratory disorders, including chronic obstructive pulmonary diseases (COPD)¹⁶³ and asthma.¹⁶⁴ Given its pervasive anti-inflammatory activity and apparent safety, resveratrol may prove to be a practical treatment for many low-grade chronic inflammatory disorders.

In addition to its anti-inflammatory effects on the cardiovascular system,¹⁵⁴ SRT1720 has demonstrated promising effects in mouse models of chronic inflammation,¹⁶⁵ asthma¹⁶⁶ and COPD/emphysema.¹⁶⁷ Importantly, its effects in COPD occur *via* a FOXO3-mediated reduction in premature lung cell senescence, an effect that was shown to be SIRT1-dependent.¹⁶⁷ In addition, SRT1720 ameliorates colitis in mice through a mechanism involving PGC1 α .¹⁶⁸ In humans, clinical trials on inflammation using synthetic STACs have yielded mixed results. For example, SRT2104 has been reported to attenuate LPS-induced inflammation in human patients.¹⁶⁹ In addition, a randomized, placebo-controlled study demonstrated that SRT2104 may be a viable treatment for patients with moderate to severe psoriasis.¹⁷⁰ However, another study assessing the safety and clinical activity of SRT2104 in patients with mild to moderate ulcerative colitis failed to show any effect.¹⁷¹ This result is quite unexpected since SIRT1 has been shown to play an important role in colitis,¹⁷² but it could be the result of poor drug pharmacokinetics or pharmacodynamics.

11.4.7 Fertility and Development

Since fertility decreases in both males and females with age, it may be considered another marker for aging. Because resveratrol has been shown to have weak estrogenic activity (*via* activation of ER α),¹⁷³ initially there was concern that supplementation could alter male fertility and possibly influence the development of offspring in mammals.¹⁰⁹ The results of numerous studies, however, have led to dismissal of these concerns.¹⁰⁹ Treatment of pregnant mothers with resveratrol had virtually no effect on their offspring,¹⁷⁴ and even very high doses of resveratrol up to 300 mg kg⁻¹ do not appear to result in any observable toxic effects on fertility or development.¹⁷⁵ In fact, resveratrol appears to protect against age-associated infertility in female mice. In one study, young mice fed a diet containing resveratrol for 12 months retained the capacity to reproduce while their age-matched counterparts on the control diet did not.¹⁷⁶ This phenotype was associated with an increase in the number and quality of oocytes.¹⁷⁶ In male rodents, resveratrol protects sperm against a number of chemical and environmental insults.¹⁷⁷ While researchers have only started to investigate the use of synthetic STACs for the treatment of age-related infertility, one report has demonstrated that SRT1720 improves follicle reserve and prolongs the ovarian lifespan of obese female mice *via* a SIRT1-dependent mechanism.¹⁷⁸ Thus, recent work is supporting the notion that an extension of lifespan and healthy aging could also lead to an extension of the reproductive phase of life. Figure 11.4 summarizes the beneficial effects of STACs on age-related diseases and physiological declines.