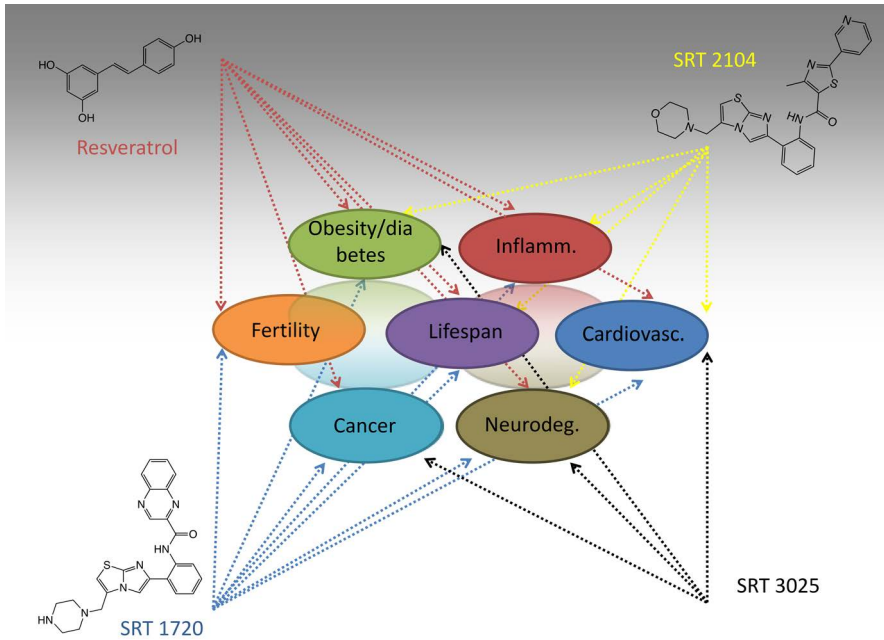

Figure 11.4 Documented effects of SIRT1 activators on lifespan and the treatment and prevention of various age-related diseases in mammals.

11.5 Clinical Challenges with STACs

11.5.1 Pharmacology

To date, resveratrol and synthetic STACs have been tested in over 125 phase I and phase II clinical trials (http://www.clinicaltrials.gov). Some of the most promising results from these trials include data showing that resveratrol supplementation can improve insulin sensitivity in patients suffering from metabolic syndrome,[179] and that it can reduce inflammation in patients with ulcerative colitis.[180] In addition, SRT2104 showed promising effects in the treatment of psoriasis in phase I trials.[170] Unfortunately, very few phase III trials have been performed using these molecules, and even fewer are in the pipeline (http://www.clinicaltrials.gov). Pharmaceutical companies may be discouraged from pursuing large-scale studies using resveratrol because it is a non-patentable natural compound that displays relatively poor pharmacological properties, including molecular promiscuitiy[181] and low bioavailabilty.[115] In the case of synthetic STACs, which are patented new chemical entities, much more work is still needed to adequately characterize their molecular pharmacodynamics and toxicity.[15]

Resveratrol exhibits complex pharmacodynamics.[15] In addition to activating SIRT1 and modulating cyclooxygenase enzymes,[109,182] PDE,[90] and the estrogen receptor,[173] resveratrol also targets cytochrome P450 enzymes (CYPs) involved in phase I drug metabolism,[183,184] the aryl hydrocarbon receptor (AHR),[185]