quinone reductase II (QRII),[186] and S6 kinase (S6K),[187] amongst others.[109] Yet, the cumulative effect of these many interactions on health appears to be generally positive,[188] and resveratrol demonstrates an apparent lack of toxicity in animal models.[109] This observation has given rise to the 'xenohormesis' hypothesis, which states that resveratrol and similar molecules produced by plants during times of stress could act as chemical cues to trigger a physiological defense mechanism in animals to aid in their survival.[188] Because it is multifaceted, resveratrol may protect against several disease-related phenotypes that a specific SIRT1 activator might not guard against. However, this property could also increase the occurrence of unforeseen and possibly detrimental off-target effects when using resveratrol to treat specific diseases. For example, while resveratrol-mediated SIRT1 activation might help treat type II diabetes,[189] its off-target effects could aggravate other pre-existing conditions in these patients. In this regard, second generation synthetic STACs such as SRT1720 and SRT1460, which were designed to specifically activate SIRT1, may be more appropriate.[24] However, while these molecules also appear to be well-tolerated,[190] they too display off-target effects.[191] No work has yet been published on the molecular specificity or toxicity of third generation STACs.

Poor bioavailability and pharmacokinetics are additional clinical challenges facing STACs.[27] Studies have shown that while resveratrol absorption in humans is dose-dependent,[115] low plasma levels are achieved due to poor bioavailability and rapid metabolism.[27] For example, one study showed that supplementation of a 5 g dose of resveratrol in humans resulted in a mean plasma concentration of only ~52 μg L^{-1} over a one day period.[192] The maximum plasma concentration (C_{max}) reached during this period was 540 μg L^{-1}, which occurred 1.5 hours after administration.[192] It is thought that human gut microbiota could limit the bioavailability of resveratrol through conversion into non-absorbable metabolites such as 3,4′-dihydroxy-*trans*-stilbene and 3,4′-dihydroxybibenzyl.[193] Time of intake (morning or night), prior food intake, and fat content in food are other factors that appear to affect absorption.[194] Once in the blood stream, resveratrol is rapidly metabolized into sulfate, disulfate, and glucuronide derivatives that are quickly excreted from the body,[109,195,196] resulting in a short half-life of only 8–14 minutes for the primary molecule.[196] To circumvent these issues, a proprietary micronized formulation of resveratrol, SRT501, with improved bioavailability has been developed.[197] In clinical trials, SRT501 has achieved blood levels 5–8 times higher than standard resveratrol, suggesting that this formulation may represent a promising pharmaceutical.[198] Likewise, SRT2104 shows moderate bioavailability of roughly 14%, and a mean clearance of ~400 mL min^{-1} in human patients.[199]

11.5.2 Regulatory Paradigms

Regulatory agencies do not typically consider aging a disease given its widespread prevalence. Furthermore, funding for research promoting health is far scarcer than funding for disease-related research. The cost of testing STACs in clinical trials for healthy aging would be enormous given the length of time and logistical complications associated with completing such a study.