resveratrol is necessary in plasma for therapeutic activity, but *in vivo* studies indicated that a high concentration of resveratrol in plasma may not be achieved. In models involving rabbit, rat, and mice, the highest concentration of resveratrol—reached in the first 5 min after oral administration of 20 mg kg^{-1} resveratrol—was less than 3 μM in the plasma.[107] In addition, the level of resveratrol dropped to half after only 14.4 min of intravenous administration of 20 mg kg^{-1} resveratrol in rabbits.[107] Furthermore, the concentration of resveratrol in the plasma of rats generated a peak value not greater than 6.6 μM in 5–10 min after oral administration of 50 mg kg^{-1} resveratrol, and it dropped to 50 nM in 2 h.[108,109] Similarly, neither resveratrol nor resveratrol conjugates were detected in the plasma after 24 h fasting in rats fed for 8 weeks with a diet containing 50 mg kg^{-1} resveratrol.[110] Although the conjugates of resveratrol seem to reach much higher plasma levels than resveratrol,[111] the peak plasma levels of resveratrol were 2 μM after an oral ingestion of 25 mg resveratrol with a half-life of 9.2 ± 0.6 h.[104,112] Human plasma concentrations as high as 0.5 μM for resveratrol and 2 to 10 μM for its 4′-*O*-sulfate conjugate have been reported after oral administration of pure resveratrol.[111] Resveratrol absorbed and modified in the intestine is secreted back into the intestine, where it may be de-conjugated, reabsorbed, or excreted in the feces.[104] Interestingly, a recent report demonstrated that resveratrol sulfate conjugates can be taken up by several tissues, and that subsequent processing can regenerate free unmodified resveratrol inside the cells.[113] In addition, human gut microbiota may also limit the bioavailability of resveratrol through conversion into metabolites, such as 3,4′-dihydroxy-trans-stilbene and 3,4′-dihydroxybibenzyl.[114] To improve the low bioavailability of resveratrol, several theoretical solutions have been tried, such as a combination with additional phytochemicals and nano materials. In the report using rats, piperine—a polyphenol found in black pepper—is reported to increase the maximal plasma concentration of resveratrol.[115] Moreover, the load of resveratrol on lipid-core nanocapsules was reported to improve the bioavailability of resveratrol in rats and mice.[116–118] The issue of low bioavailability of resveratrol and its solutions are well reviewed by Smoliga *et al.*[119]

Despite the uncertainty of resveratrol as a clinical drug, the investigation of resveratrol is sufficiently valuable. As resveratrol has low bioavailability and interacts with multiple molecular targets, the development of new molecules with better bioavailability and higher affinity with sirtuin is a promising direction for the field of medicinal chemistry.

13.3 Other Phytochemicals with Lifespan-Extending Effects

13.3.1 Curcumin

Curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] is a non-flavonoid polyphenolic yellow pigment, extracted from the rhizome of the plant *Curcuma longa* (turmeric). It has been widely used as a spice,