via deacetylation by sirtuins.[234,311–314] However, it has recently been found that human sirtuin Sirt1 can activate AMPK *via* upstream kinase LKB1 (*l*iver *k*inase *B1*; also known as STK11, *s*erine/*t*hreonine *k*inase *11*).[315] Thus, sirtuin activation may link both mTOR and insulin signaling pathways of life span extension. The strength of the effect and thus the difference between the life-prolonging effects of CR mimetics, which act through the sirtuin-AMPK-mTOR axis, may depend on probable side effects and the degree of sirtuin activation. Extract of *Rhodiola rosea* and its main component, salidroside, which we already mentioned as possible activators of FOXO, were also found to affect mTOR signaling in cultured cells.[316] Many recent studies show that AMPK can be activated by a vast number of natural chemicals, including curcumin, berberine, quercetin, epigallocatechin-3-gallate, ginsenoside, hispidulin, caffeine, and others,[317] for some of which a life-prolonging effect was also found. Further studies are necessary to reveal a possible interplay between insulin and mTOR signaling pathways, along with the AMPK pathway.

Interestingly, p70 S6 kinase, a downstream, positively regulated target of mTOR, was shown to suppress food consumption itself *via* down-regulation of neuropeptide expression.[318,319] Thus, regulation of feeding behavior by mTOR signaling closes the negative feedback regulatory loop between mTOR and food consumption.

10.6.2.3 Nrf2/Keap1 Signaling Pathway

A growing body of evidence suggests a role of the Nrf2/Keap1 signaling pathway in prolonging life span by natural and synthetic geroprotectants, including CR mimetics.[161,239–241] The pathway is conserved among mammals, fruit flies and nematodes. In fruit flies, a homolog of Nrf2 called CncC (***c***ap-***n***-***c***ollar isoform ***C***) was found to be involved in life span extension.[320] A similar role in prolonging life span was declared for SKN-1, a homolog of Nrf2 in *C. elegans*.[321–323] It was also revealed that transcription factor Nrf2 is activated by many CR mimetics, such as resveratrol, curcumin[241] metformin,[239] epigallocatechin gallate,[324,325] and others. Nrf2 is activated by reactive oxygen species (ROS) *via* Keap1 protein. It is also activated by xenobiotic compounds with electrophilic properties, including plant phenols and alkaloids. Many xenobiotics undergo oxidation by P-450 type cytochromes, the enzymes that produce ROS as by-products.[326,327] Then, in phase II of detoxification, oxidized xenobiotics are conjugated with glutathione. After this conjugation, xenobiotics are decomposed by cellular metabolic systems and/or excreted from cells. Activation of Nrf2 by xenobiotics directly or indirectly *via* ROS produced by cytochromes P-450 leads to increased synthesis of low molecular weight antioxidants, glutathione and NADPH,[240,327] as well as antioxidant and related enzymes, such as superoxide dismutase, catalase, thioredoxin reductase, glutathione reductase, glutathione peroxidase, and glutathione-*S*-transferase.[161,239] Thus, Nrf2 governs potential pro-longevity processes, saving cell components from