proteins were found in other organisms.[296,297] It was found that fruit flies consume less food when it is mixed with *Rhodiola rosea* extract.[227]

Generally, the CR mimetics that supposedly affect the insulin signaling pathway confer relatively slight and sometimes controversial life span extensions, as in the case with resveratrol. Insulin signaling pathway is activated by carbohydrates and regulates carbohydrate and lipid metabolism. Nevertheless, some components of this pathway, like PI3K and PKB, are at the crossroads of many signaling pathways that regulate processes of cell growth and division. The relatively weak effects of insulin signaling inhibition on life span suggest a moderate role of carbohydrates as nutrients for CR. Indeed, many studies reveal that restriction in the protein component of the diet plays a more important role in providing longevity.[3,5,7,8,227] The pathway responsible for protein metabolism is governed by the above-mentioned mTOR kinase.

10.6.2.2 Mechanistic Target-of-Rapamycin (mTOR) Kinase Pathway

Down-regulation of this pathway often provides a more profound life span extension than that of the insulin signaling pathway. Mimetics of CR that affect this pathway include rapamycin and metformin. The suppression of the mTOR pathway responds with pro-longevity processes, such as inhibition of protein synthesis and activation of autophagy. As was already mentioned, rapamycin binds immunophilin FKBP12 and this complex is, in turn, attached to a particular domain of mTOR kinase, suppressing its enzymatic activity.[247–249]

Metformin's influence is mediated by AMPK, which inhibits mTOR *via* phosphorylation of tuberous sclerosis complex proteins. Phosphorylation activates these proteins, whereas they, in turn, inhibit mTOR. There are several reports about the gerosuppressant activity of aspirin, another well-known activator of AMPK.[298–302] Moreover, the life-extending effect of the anticonvulsant valproic acid can be mediated by activation of AMPK.[303,304] Another anticonvulsant, ethosuximide, can prolong life span in *Caenorhabditis elegans*, likely by activation of insulin signaling components such as Daf-16, a homolog of FOXO in this nematode.[305–309] The other anticonvulsant, trimethadione, was shown to enhance the effects of valproic acid on *C. elegans* life span.[303,309] The latter findings suggest a possible link between AMPK, FOXO and mTOR. Indeed, mTOR activity is partly regulated by the insulin signaling pathway *via* Akt/PKB.[20,249,279,280] While AMPK activates TSC, Akt was shown to inhibit it by phosphorylation.[279] Overall, mTOR signaling is intrinsically linked with epilepsy,[310] thus anticonvulsants may represent a novel class of direct or indirect modulators of mTOR activity, simultaneously mimicking CR.

The mechanism of AMPK-mediated mTOR inhibition can also be suggested for resveratrol. It is widely accepted that this natural phenol activates FOXO, a pro-longevity transcription factor suppressed by insulin signaling,