

Nutraceuticals for Promoting Longevity

Ivan Pavlović¹, Soliman Khateb^{2,3}, Irina Milisav^{4,5} and Jamal Mahajna^{6,7,*}

¹Laboratory of Molecular Biology and Endocrinology, Vinca Institute of Nuclear Sciences, University of Belgrade, Mike Petrovica Alasa 12-14, 11351 Belgrade, Serbia; ²Laboratory of Natural Compounds and Analytical Chemistry, Migal-Galilee Research Institute Kiryat Shmona, Kiryat Shmona, 11016, Israel; ³Department of Biotechnology, Faculty of Sciences and Technology, Tel-Hai College, Kiryat Shmona, Israel; ⁴Faculty of Medicine, Institute of Pathophysiology, University of Ljubljana, Zaloska 4, SI-1000 Ljubljana, Slovenia; ⁵Laboratory of Oxidative Stress Research, Faculty of Health Sciences, University of Ljubljana, Zdravstvena Pot 5, SI-1000 Ljubljana, Slovenia; ⁶Department of Nutrients and Natural Products, Migal-Galilee Research Institute, Kiryat Shmona, 11016, Israel; ⁷Department of Nutritional Sciences, Faculty of Sciences and Technology, Tel-Hai College, Kiryat Shmona, Israel

Abstract: Objective: To summarize the main findings on nutraceuticals that slow aging processes by delaying and even preventing the development of multiple chronic diseases and improve productivity and quality of life in the elderly.

Methods: Literature search of the relevant papers known to the authors was conducted.

Results: The most robust environmental manipulation for extending lifespan is caloric restriction without malnutrition. Some nutraceuticals can mimic caloric restriction effects. This review will focus on the nutraceuticals that impact insulin-like growth factor 1 receptor signaling and sirtuin activity in mediating longevity and healthspan.

Conclusion: Aging is considered to be synonymous with the appearance of major diseases and an overall decline in physical and mental performance. Caloric restriction is well established as a strategy to extend lifespan without malnutrition. A variety of nutraceuticals were reported to mimic the effect of caloric restriction by modulating the activity of insulin-like growth factor 1 receptor signaling and sirtuin activity and consequently promote longevity and healthspan.

ARTICLE HISTORY

Received: October 30, 2019
Revised: January 22, 2020
Accepted: January 22, 2020

DOI:
10.2174/2665978601666200213121512



Keywords: Nutraceuticals, longevity, caloric restriction, insulin-like growth factor 1 receptor (IGF1R), silent mating type information regulation 2 homology 1 (SIRT1).

1. INTRODUCTION

Caloric restriction (CR) without malnutrition is the most robust environmental manipulation known to increase active and healthy lifespan in diverse species. CR exhibited beneficial effects in reducing the incidence of age-related diseases such as obesity, diabetes mellitus, hypertension, cardiovascular disease, and cancer. Thus, CR may be a physiological strategy for extending lifespan through a slower cell growth and metabolism and a decreased accumulation of senescent cells; however, it is recommended only for selected segments of an adult human population.

Studies using model organisms and in human centenarians implied molecular mechanisms of longevity such as reducing the activity of mammalian target of rapamycin (mTOR) and insulin-like growth factor 1 receptor (IGF1R) signaling. It was observed from CR and genetic manipulation

studies that the silent mating type information regulation 2 homolog 1 (sirtuin1 or SIRT1) activity also modulated longevity and healthspan. These pathways were modulated also by some nutritional substances, nutraceuticals. As CR is neither a practical nor an advisable practice for all human populations, nutraceuticals are being investigated as an alternative. Their impact on IGF1R signaling and SIRT1 activity in mediating longevity and healthspan is described below and summarized in Table 1.

2. INSULIN-LIKE GROWTH FACTOR 1 RECEPTOR (IGF1R) AND LONGEVITY

IGF1R is conserved evolutionarily from worms to humans [1] and activated by insulin and insulin-like growth factor 1 (IGF1). IGF1 is mainly produced in the liver by stimulation of growth hormone (GH) secreted from somatotrophs in the anterior pituitary [2]. Circulating IGF1 binds to insulin/IGF1 receptors on the cell membrane of organs and primarily promotes tissue growth at an early developmental stage. IGF1R, through insulin receptor substrate 1 (IRS1), IRS2, phosphoinositide 3-kinase (PI3K),

*Address correspondence to this author at the Department of Nutrients and Natural Products, Migal-Galilee Research Institute, Kiryat Shmona, 11016, Israel and Department of Nutritional Sciences, Faculty of Sciences and Technology, Tel-Hai College, Kiryat Shmona, Israel;
E-mail: jamalm@migal.org.il

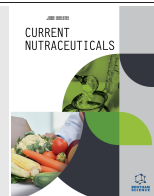


Table 1. Effect of nutraceuticals on longevity and healthspan through IGF1R signaling and SIRT1 activity modulation. Listed are the classification, chemical structures and sources of natural compounds along with experimental models and studies confirming their effects on longevity.

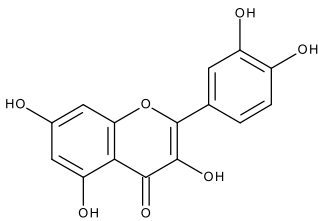
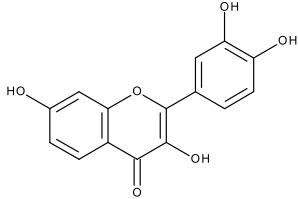
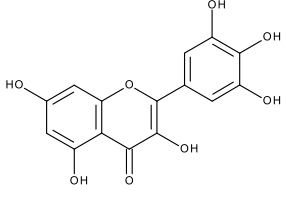
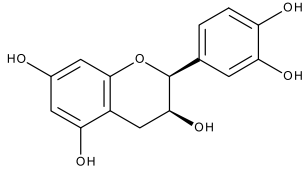
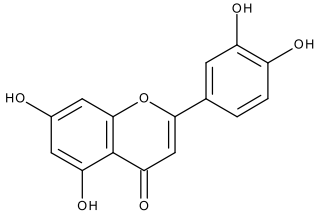
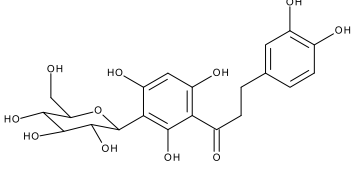
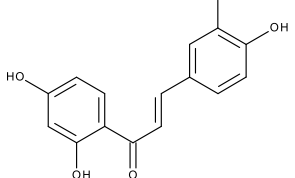
-	Compound Name	Structure	Sources	Experimental Model	Effect on Longevity	Refs.
POLYPHENOLS	Flavonols	Quercetin 	Spices, vegetables, and fruits	Worms	Extended lifespan by 21%	[39]
		Fisetin 	Fruits and vegetables	Mice	Extended the median and maximal lifespan	[120-125]
		Myricetin 	Fruits, (berries), vegetables, tea	<i>C.elegans</i>	Improved healthspan and lifespan.	[126-127]
	Flavanol	Epicatechin 	Cacao and tea	Obese diabetic mice	Decreased mortality from 50% in control to 8% in epicatechin treated mice	[41]
	Flavones	Luteolin 	<i>Reseda luteola</i> , broccoli, parsley, olive oil, celery	Human monocytic cells (THP-1)	Induced expression of SIRT1, SIRT3, SIRT6, FOXO3a	[125]
	Chalcones	Aspalathin (Dihydrochalcone glucoside) 	Rooibos tea leaves	Worms	Extended lifespan by 20% to 25% under high glucose feeding	[38]
		Butein 	Citruses, vegetables (tomatoes, bean sprouts, potatoes)	<i>S. cerevisiae</i>	Increased the average lifespan by 31 % and prolonged maximal lifespan	[110] [128-132]

Table 1. Contd...

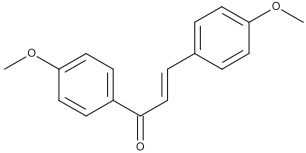
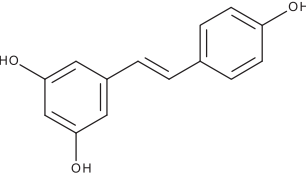
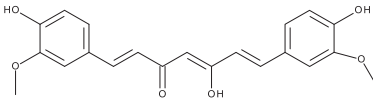
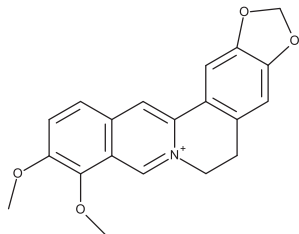
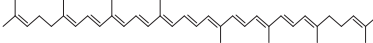
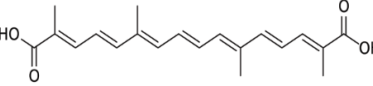
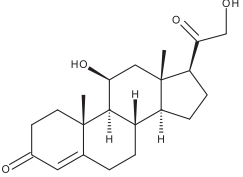
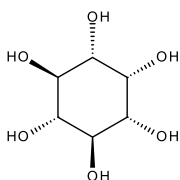
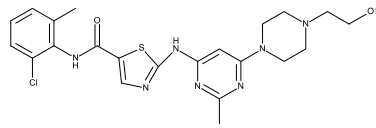
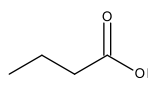
-	Compound Name	Structure	Sources	Experimental Model	Effect on Longevity	Refs.
Stilbene	4,4'-dimethoxychalcone (DMC)		<i>Angelica keiskei koidzumi</i>	<i>S.cerevisiae</i> <i>C. elegans</i> <i>D.melanogaster</i>	Extended lifespan	[133-135]
	Resveratrol		Grapes, blueberries, and red wine	Mice	Increased lifespan by 9% in old female mice SIRT1 activator	
	Curcumin		Ginger Fam: Zingiberaceae.	<i>C. elegans</i> , <i>D. melanogaster</i> , mice; HUVECs	Increased lifespan; attenuated senescence in human cells	[109] [136-140]
Alkaloids	Berberine		Fam: Berberidaceae	<i>Drosophila</i> ;	Prolonged lifespan under the high-temperature conditions	[141-142]
				Human cells (L-02)	Increased SIRT1 expression and cell viability (19%)	[143-144]
Carotenoid	Lycopene		Tomatoes	Human (Clinical trial)	Reduction in plasma IGF-1 and IGFBP-3 levels, and inhibit activation of IGF-1R	[45-50]
	Crocin		<i>Crocus sativus</i> (saffron spice)	Mice	Antioxidant protection of ovaries	[145]
Hormone	Corticosterone		Steroid hormone	Human	Decreased plasma levels of IGF-1 and reduced IGF-1R levels	[51]

Table 1. Contd...

-	Compound Name	Structure	Sources	Experimental Model	Effect on Longevity	Refs.
Others	Inositol		Fruits, beans, and nuts,	Fruit flies	Extended lifespan of males by 17 % and females by 13%	[40]
	Mixture of dasatinib and quercetin		Senolytic compounds	Old mice	Reduced number of senescent cells and increase mouse lifespan	[55-60]
	Butyrate		Gut microbiota	Worms	Increased lifespan by 20%	[52-54]

and protein kinase B (AKT) [3] activates mTOR. Moreover, the IGF1R pathway modulates gene expression through transcription factors such as forkhead box O (FOXOs) [4], which control the expression of genes implicated in age-related processes (oxidative stress, apoptosis, cell-cycle) [5]. Initial studies in *C. elegans* using reduced functionality have identified gene mutations such as *age-1* and *daf-2* that resulted in a profound extension of lifespan [1, 6]. Subsequent cloning studies identified the *daf-2* gene as being homologous to both mammalian insulin receptor (IR) and IGF1R that have been conserved in yeast, worms, fruit fly, mice and humans, and are causally linked to aging and longevity across species [7].

IGF1, the major energy sensing pathway, exerts pleiotropic effects *via* several intracellular signaling pathways promoting growth mediated by IGF1R. Circulating levels of IGF1 and IGF binding protein-3 (IGFBP-3) vary among individuals and are affected by genetic, environmental or lifestyle factors. A positive correlation was found between bioavailable levels of IGF1 and increased risk of age-related diseases including cancer [8]. Moreover, decreased IGF1R signaling pathway activity has been observed as a result of either genetic or environmental manipulation, and was found to be accompanied by the extension of lifespan in worms, flies, mice and likely humans [9]. Mutations in the IGF1R gene in mice and humans have also been implicated in longevity signaling. For example, female mice harboring loss-of-function mutations in the *igf1* gene in the liver are smaller than controls but live 16% longer [10]. Furthermore, mice that are heterozygous for a mutated allele of the IGF1R (*Igf1r*^{+/-}) are ~10% smaller than wild-type mice, expressing ~50% of wild-type IGF1R levels; they exhibit a significant reduction in IGF1-induced intracellular signaling and become insulin-resistant with age [11, 12]. Nevertheless, female *Igf1r*^{+/-} mice have a 33% longer mean lifespan than wild-type littermates.

Several studies have identified IGF1R alterations in humans and correlated them with human longevity. The G/A polymorphism in IGF1R was associated with long-living Italian individuals compared to other Italians, resulting in reduced IGF1 plasma levels [13]. A combination of

IGF1R/Asp-IRS2/Val-UCP2 allele was also associated with longevity, as was reported in another study involving Italian people [14]. Genetic alterations in IGF1R affecting longevity were not limited to Italian people. Other studies conducted on Ashkenazi Jews revealed a genetic variation in IGF1R among centenarians. Two heterozygous IGF1R gene mutations, Ala37Thr and Arg407His, were found to be more frequent in a cohort of Ashkenazi Jewish centenarians than in control individuals [15]. These mutations suppressed IGF1 signaling and decreased transcription of target genes [15]. Female carriers of these mutations have high IGF1 levels and slightly short stature, implying that they are IGF1-resistant [16]. These studies provide evidence that reduced IGF1 signaling can positively affect the human lifespan.

Longevity in several animal species, including worms, fruit flies and mice, was associated with increased resistance to stress [17, 18]. Cellular stress can be caused by diverse extracellular or intracellular stimuli such as heat, hypoxia, irradiation, glucose deprivation and the accumulation of reactive oxygen species (ROS) [19]. To avoid organelle and DNA damage, as well as aggregation of unfolded proteins, the cell's stress response is through activation of survival mechanisms such as autophagy or apoptosis induction [19]. Various stress stimuli inhibit mTOR, a central signal transducer that promotes cell growth, metabolism and survival in conditions of nutrient abundance. Inhibiting mTOR by rapamycin and CR decreased IGF1 signaling stimulated autophagy and induced improved response to cellular stress and increased lifespan [9, 19, 20].

The reduction in IGF1 signaling could upregulate the expression of FOXO transcription factors (tumor suppressor) and antioxidant genes to elicit stress resistance [18, 21]. Resistance to cellular stress was accompanied by extended lifespan in mice. As in the case of IGF1R, also FOXO mutations were reported in humans and were implicated in human longevity. For example, an association between single nucleotide polymorphisms (SNPs) in FOXO3A gene and longevity was confirmed in several independent studies involving human participants [22-25]. Interestingly, a SNP rs2802292 upregulated FOXO3A expression was associated with human longevity. The SNP rs2802292 is located in the

FOXO3A enhancer region, which can lead to the upregulation of FOXO3A expression. The presence of the SNP rs2802292 can partially explain the differences in FOXO3A association with longevity between genders, since its activity in females may be modulated by estrogens through estrogen receptor response elements located within the rs2802292-encompassing region [26].

3. DIETARY INTERVENTIONS LIMIT IGF1R SIGNALING AND PROMOTE LONGEVITY

Caloric restriction (CR) refers to dietary intervention with an overall 20-40% reduction in total caloric intake. CR is the most studied and reproducible non-genetic intervention known to extend the health span and/or lifespan in organisms, ranging from unicellular yeast to monkeys. It started with a simple experiment where a dietary intake reduction extended the lifespan of rats [27], providing a foundation to study experimentally the relationship between nutrition and the biology of aging. Animals fed a calorie-restricted diet are less likely to suffer from common age-related conditions such as obesity, neurodegenerative disorders, autoimmune disorders and neoplastic lesions [28]. No data exist that correlate the human lifespan and calorie-restricted diet, however, several reports support protection from age-related diseases [29, 30]. Since feeding studies are difficult to conduct in humans, the best information is from CR studies in nonhuman primates. Two studies in rhesus monkeys revealed disparate results; one showed that a CR diet extended lifespan [31], the other found no effects of CR on longevity [32].

Despite differences in which CR is carried out in diverse organisms, CR is the most robust environmental manipulation known to increase active and healthy lifespan by modulating nutrient-signaling pathways, including mTOR, insulin/IGF1-like signaling and SIRT1 [33].

Dietary factors may influence IGF1 signaling by affecting IGF1 bioavailability, IGF1R activity or expression levels. CR decreases serum IGF1 concentrations and consequently signaling mediated by the IGF1R pathway. Factors determining IGF1 circulating levels include genetic variation affecting expression levels of IGF1 and IGFBPs [34, 35], as well as exogenous factors (*e.g.*, dietary habits or other lifestyle factors). In the cases of chronic or acute CR, serum levels of IGF1 are strongly reduced [36, 37].

4. NATURAL PRODUCTS AS A CALORIES RESTRICTION (CR) MIMETIC

Many compounds isolated from plants and fungi prolong lifespan and prevent age-related diseases in model organisms. They modulate the same cellular and physiological pathways as CR, including those involving insulin and IGF1, mTOR and SIRT1 functions. Modulating these age-related pathways results in the activation of various cellular processes such as autophagy, DNA repair and ROS neutralization to delay aging and prevent chronic diseases by improving bodily functions and stress resistance. Various plant and fungal molecules described below modulate the insulin/IGF1/FOXO pathway in worms, fruit flies and rodents (Table 1).

Aspalathin, a dihydrochalcone glucoside compound isolated from rooibos tea leaves extends the lifespan of worms by 20-25% under high glucose feeding [38]. Its life extension effect is associated with reduced cellular ROS accumulation and activation of *daf-16*, the ortholog of FOXO in worms (Table 1).

Quercetin, a major flavonoid polyphenol in the human diet, found in spices, vegetables and fruits, also extends the lifespan of worms [39]. It increases mean and median lifespan by 18% and 21%, respectively, while maximal lifespan is not affected [39]. Quercetin does not increase lifespan in worms lacking *daf-2* gene, which encodes an ortholog of the human IGF1R [39] (Table 1).

Inositol, a small carbohydrate compound found in fruits, beans and nuts, extends the lifespan of male and female fruit flies by 17% and 13%, respectively [40]. Its life extension effect is attributed to dfoxo (the ortholog of FOXO in fruit flies) pathway activation. Inositol also improves the climbing ability of flies, thereby improving healthspan. Pinitol, an inositol-related compound, also extended lifespan similarly [40] (Table 1).

Epicatechin, a flavone compound isolated from cacao and tea, extends the lifespan of obese diabetic mice (50% mortality was observed in untreated mice vs 8% in epicatechin-treated mice) [41]. It reduces systemic inflammation and improves muscle stress output and antioxidant levels in the liver. Notably, it reduces blood IGF1 levels, suggesting reduced activation of the IGF1 signaling pathway (Table 1).

Resveratrol (RSV), a phenolic compound found in grapes, blueberries and red wine, increases the lifespan of mice [42], enhances insulin sensitivity and reduces blood IGF1 levels and consequently reduces insulin/IGF1 pathway signaling. It reduces age-related degeneration in cognitive function, blood vessels and bones, but fails to extend lifespan in mice in the absence of a high-calorie diet or high-fat diet (HFD) [43, 44] (Table 1).

Lycopene, a carotenoid found in tomatoes, increased serum IGFBP-3 and decreased serum IGF1/IGFBP-3 ratio in lycopene-fed animals [45]. Consumption of tomato products and/or intake of lycopene was inversely associated with IGF1 (or the ratio of IGF1/IGFBP-3) and positively associated with IGFBP-3. Moreover, lycopene inhibited the activation of IGF1R (*i.e.*, reduced tyrosine phosphorylation of IGF1R) [46]. In a clinical trial of lycopene supplementation, a reduction in plasma IGF1 and IGFBP-3 levels was observed [47]. In cross-sectional epidemiologic studies, a high consumption of cooked tomatoes was associated with low serum IGF1 levels [48], and a high lycopene intake was associated with high IGFBP-3 levels [49]. The Third National Health and Nutrition Examination Survey (NHANES III, 1988-1994) revealed that dietary interventions with carotenoids, fruits and vegetables may affect the IGF1 system positively or negatively. For example, statistically significant positive associations were observed between serum concentrations of α -carotene and lutein/zeaxanthin and intake of fruits with serum IGFBP-3 concentrations in women, but not in men [50] (Table 1).

Corticosterone, which usually increased during CR, decreased plasma IGF1 concentrations and also reduced

IGF1R levels and consequently the inhibition of several downstream signaling pathways [51] (Table 1).

Butyrate, a short-chain fatty acid (SCFAs), is a fermentation product of dietary fiber and polysaccharides produced by the gut microbiota of the large intestine. Butyrate is converted into the ketone body β -hydroxy butyrate (BHB), which enhances the mean lifespan of worms by ~20% [52]. BHB levels in the blood also increase during fasting, intense exercise, or CR, and serve as a source of energy independent of glucose, possibly delaying aging by increasing stress resistance [53, 54]. Based on these observations, some authors proposed that the life-extension effects of CR may be mediated at least in part by BHB [53, 54] (Table 1).

Senolytic compounds are a new class of compounds that target cellular senescence, a process in which damaged cells persist and become toxic to cells around them. Cellular senescence drives multiple age-related diseases. Dasatinib, a tyrosine kinase inhibitor that blocks the Bcr-Abl and Src kinase family [55], interferes with ephrin dependence receptor ligands (EFNB)-dependent suppression of apoptosis [56]. They reduce viability and cause cell death to senescent human cells. Quercetin, a natural flavonoid, inhibits PI3K and other kinases [57, 58] and induces apoptosis of senescent cells without affecting normal cells [59]. A mixture of dasatinib and quercetin reduced the number of senescent cells in old mice [59] and increased mouse lifespan compared to controls [60] (Table 1). Furthermore, in an open-label pilot study in humans, treatment with dasatinib and quercetin was successful in alleviating physical dysfunction in idiopathic pulmonary fibrosis (IPF).

Interestingly, a recent study showed that targeting the IGF1R with a monoclonal antibody was associated with a reduction in inflammation and increased lifespan by 9% in old female mice [61]. However, it remains to be seen whether this intervention targeting IGF1R may be viable in humans. Finally, CR not only reduces the bioavailability of IGF1 but is also causing the activation of sirtuin proteins such as SIRT1 and both directly and indirectly to promote longevity [62].

5. SIRTUINS AND LONGEVITY

Sirtuins are nicotinamide adenine dinucleotide (NAD⁺)-dependent histone deacetylases (HDACs) [63] involved in the modulation of structure and function of cellular proteins. Their protein targets are not only histones but many other proteins responsible for genome integrity [64], inflammation, antioxidative defense [65], apoptosis [66], metabolism [67], aging [68] and circadian rhythm [69].

Sirtuins are highly conserved proteins present in all eukaryotes and the majority of prokaryotes [70]. The number of sirtuin family members increases with the complexity of the organism's biological organization. Yeasts have only one sirtuin (Sir2) while *C. elegans* and *D. melanogaster* have four (Sir 2.1-Sir 2.4) and five sirtuins (dSirt1, dSirt2, dSirt4, dSirt6, and dSirt7), respectively [71]. In mammals, including humans, the sirtuin family is constituted of seven proteins (SIRT1-SIRT7) [70] with different subcellular distributions and catalytic activity. SIRT2 is located in cytoplasm but migrates to the nucleus during G2/M transition to deacetylate

histone H4 and modulate chromatin condensation [72]. SIRT1, SIRT6, and SIRT7 are mostly found in the nucleus. SIRT7 is the only sirtuin present in nucleoli, and as previously shown by Michishita and colleagues [73], along with SIRT6, but not SIRT1, was associated with condensed mitotic chromosomes. Nucleocytoplasmic shuttling is a feature of SIRT1 and depends on post-translational modifications of this protein [63]. Sirtuins (SIRT3, SIRT4, and SIRT5) reside in the mitochondrial matrix in human cells [74].

All SIRTs are deacetylases that cleave NAD⁺ into nicotinamide (NAM), which is followed by the removal of acetyl group from N-epsilon lysine residue of the target protein and formation of 2'-O-acetyl-ADP-ribose (2'-O-AADPr). SIRT1-3 exhibit strong deacetylase activity, while SIRT4 predominantly catalyzes ADP-ribosylation [75]. SIRT5 can modify target proteins by demalonylation, desuccinylation and deglutarylation [76-78]. Similar to SIRT4, SIRT6 shows ADP-ribosylation activity [79].

The catalytic activity of sirtuins depends on NAD⁺ availability or NAD⁺/NADH ratio. This relation links sirtuin enzymatic activity to the cell metabolism and antioxidant defense making them important stress sensors [80]. Indirectly, sirtuin activity depends on processes that influence NAD⁺ level in cells such as exercise, CR and low-glucose availability [81]. The activity of nicotinamide phosphoribosyltransferase (NAMPT), an enzyme essential for NAD⁺ synthesis, regulates levels of key NAD⁺ intermediates NAM and NMN (nicotinamide mononucleotide), as well as the activity of NAD⁺ consuming enzymes like Poly(ADP-ribose) polymerases (PARPs), all of which also modulate sirtuin activity [82-84]. The presence of sirtuins in almost all living systems and main cellular compartments indicates that lysine acetylation of proteins is a highly conserved and common regulatory mechanism of homeostatic processes in nature.

6. SIRTUINS AND THE AGING MECHANISM

Sirtuins play an important role in delaying cellular senescence through the repression of telomere shortening and the prevention of genomic instability, one of the most prominent hallmarks of the aging process. Sasaki and colleagues [85] reported that cellular senescence was accompanied by a decrease in SIRT1 protein, but not mRNA level, in embryonic mice and human lung fibroblasts. In contrast, Stamatovic and colleagues [86] revealed a decline in SIRT1 mRNA and protein levels followed by lower enzyme activity in brain micro-vessels of both aged mice and humans. The age-related decrease in SIRT1 and SIRT3 expression was found in the heart tissue of women but not in men's hearts [65]. Thus, age-related changes in sirtuin expression might be cell-, tissue- or even sex-specific [87-89]. SIRT1 and SIRT6 overexpression suppressed both replicative senescence with telomere attrition and stress-induced premature senescence of cells without telomere involvement [71]. Increased human telomerase (hTERT) expression as a result of SIRT1 upregulation of FOXO3A protein, prolonged the lifespan of the human umbilical cord fibroblast (HUC-F2) cells [90]. SIRT6 deficiency also caused telomere dysfunction, followed by chromosomal fusions and premature development of cellular aging

phenotype [91]. SIRT1 deacetylation of FOXO4 induces cell cycle arrest while deacetylation of p53 prevents stress-induced cellular senescence [92, 93]. Nuclear sirtuins (SIRT1, SIRT6, and SIRT7) interact with histones and stabilize chromatin structure [94]. SIRT1 deacetylates histones H4, H3, H1 at specific lysine sites and promotes heterochromatin formation and transcriptional silencing [95].

In lower organisms, the SIRT1 protein extended the lifespan of yeasts by suppressing genomic instability [96]. Later studies confirmed that sirtuins modulate the lifespans of worms, flies and mice [97-99]. Among seven sirtuins in mammals, only SIRT1, SIRT6 and SIRT7 were related to the extension of lifespan. Overexpression of SIRT1 protein in mice hypothalamus increased lifespan by 9% in males and by 16% in females [100]. *Sirt7*^{-/-} mice had increased perinatal lethality and reduced lifespan [101], while SIRT6-deficient mice (*Sirt6*^{-/-}) developed abnormalities, severe metabolic defects and died at about four weeks after birth [102]. A recent study has shown that SIRT6 homozygous inactivating mutation leads to severe congenital anomalies and perinatal death in human fetuses [103]. The key molecular mechanisms through which sirtuins affect an organism's lifespan include the reduced activity of mTOR and IGF1R1 signaling. Under stress conditions, SIRT1 modulates mTOR through interaction with the TSC1-TSC2 inhibitory complex and reduces protein synthesis and cell growth [104]. Sirtuins such as SIRT1 and SIRT2 were reported to activate FOXO proteins [63]. Overexpression of SIRT6 in mice was accompanied by a decreased level of IGF1 and increased lifespan [99]: this pathway has a significant role in human lifespan extension as was indicated above.

It is believed that the increased expression of sirtuins, due to increased stress mediates the beneficial effects of CR on health and lifespan [71]. Sirtuins could be activated by two types of stress: metabolic/energy stress as a result of nutrient/calorie restriction and genotoxic stress [64]. CR upregulates SIRT1 expression in rodent and human metabolically active tissues such as kidney, liver, skeletal muscle and brain [105-107]. One of the major molecular pathways involved in sirtuin's modulation of lifespan is the upregulation of 5' adenosine monophosphate activated protein kinase (AMPK) and the increase of NAD⁺ levels. SIRT1 and AMPK comprise a reciprocal positive regulating loop. AMPK indirectly activates SIRT1 by upregulating NAMPT gene expression leading to increased NAD⁺ availability, while SIRT1 activates AMPK by deacetylating liver kinase B1 (LKB1), an AMPK activator [108].

7. NUTRACEUTICALS THAT ACTIVATE THE SIRTUIN PATHWAY

More than 14000 sirtuin-activating compounds (STACs) [71] including natural products (nutraceuticals) and synthetic compounds have been identified.

Resveratrol (**RSV**) is the most prominent SIRT1 activator [109]. Other phenolic compounds such as fisetin, butein and quercetin also activate sirtuins in different organisms [110]. Resveratrol activation of SIRT1 is an upstream effect through AMPK signaling [111]. Therefore, AMPK knock-out mice are resistant to the metabolic effect of dietary RSV

[112]. Moreover, Park and colleagues have shown that *in vivo* RSV indirectly activates SIRT1 through the cAMP-Epac1-AMPK-Sirt1 pathway [113]. RSV competitively inhibits cAMP-degrading phosphodiesterases, thus increasing cAMP levels, AMPK signaling, NAD⁺ levels and activation of SIRT1. RSV has limited therapeutic potential in the treatment of age-related disorders. In humans, 75% of orally administered RSV is absorbed by oral and intestinal mucosa but the availability of this polyphenol is less than 1% as a result of rapid detoxification in the liver and a short half-life [114]. Furthermore, RSV increases the activity of phase II detoxifying enzymes in the liver and thus further induces its own degradation [115]. Interestingly, Giovannini and colleagues have demonstrated the synergistic effect of RSV and eight additional compounds (berberine, tyrosol, quercetin, catechin, ferulic acid, curcumin, niclosamide and malvidin) that increased SIRT1 expression in Human Cervical Carcinoma (HeLa) cells [114]. The main molecular pathway by which these compounds affect SIRT1 expression involves the stimulation of AMPK and inhibition of mTOR activity [114]. Although the beneficial effect of CR on longevity has been appreciated in a number of species, the safety of this dietary regime limits its utilization to some groups of healthy adults [116]. In contrast, nutraceutical mimetics may serve as an alternative. A clinical study on 48 healthy subjects reported that the administration of 500 mg/day of RSV had the same effect on SIRT1 activity as CR (1000 cal/day). Both RSV and CR treatment increased SIRT1 serum levels to 5.5- and 3.6- fold, respectively [117]. Results of two independent studies imply a protective effect of an RSV- rich diet on the cardiac system indicating that RSV may play a role in primary prevention of cardiovascular disease [118, 119] (Table 1).

Fisetin, a flavonoid found in fruits and vegetables has a senotherapeutic effect in mouse and human tissues. In their recent study, Yousef zadeh and colleagues showed that a fisetin-enriched diet reduced senescence markers in mouse tissues and reduced age-related pathology as a result of restored tissue homeostasis [120]. Furthermore, fisetin decreased levels of senescence-associated β -galactosidase activity in human adipose tissue, indicating the translational potential of fisetin treatment. Moreover, fisetin showed a neuroprotective role by decreasing both inflammation and oxidative stress [121, 122]. The anti-inflammatory effect of fisetin was exerted through the downregulation of inflammatory genes (IL-1 β and TNF- α) [123] and was related to increased SIRT1 expression and activity [124]. In nerve cells, fisetin upregulated activating transcription factor 4 (ATF4) and NF-E2-related factor 2 (Nrf2) in a dose- and time-dependent manner, increased GSH level and reduced oxidative stress [122]. An *in vitro* study on human monocytic cells (THP-1) revealed that fisetin and flavone, luteolin independently reduced ROS production by decreasing expression of p47phox (a cytosolic protein, a component of NADPH oxidases) and increasing the expression of SIRT1, SIRT3, SIRT6 and FOXO3A [125] (Table 1).

Myricetin is another flavonoid found in fruits, vegetables and tea that affected worms' longevity (*C. elegans*) in a sirtuin dose-dependent manner [126]. Namely, mutations in SIRT1 homolog (*Sir-2.1*) abolished the myricetin extension of lifespan in wild-type *C. elegans*. In

mammals, myricetin induced oxidative phosphorylation in skeletal muscle and brown adipose tissue by increasing SIRT1 deacetylation of PGC-1 α [126]. Akindehin and colleagues reported an *in vivo* effect of myricetin treatment on the expression of mitochondrial sirtuins (SIRT3 and SIRT5) resulting in a bodyweight reduction in mice by 11% [127] (Table 1).

Butein, a chalcone found in citrus and vegetables like tomatoes, bean sprouts and potatoes, was reported as an activator of SIRT1 [128]. It prolonged the lifespan of *S. cerevisiae* by 31% [110] but no such effect was found in higher organisms. Nevertheless, butein may indirectly extend the human lifespan by its beneficial effect on health [129]. Preclinical studies have shown that butein has enormous potential as an anti-cancer agent [130]; it also has antihypertensive [131], anti-inflammatory and antioxidant [128], anti-adipogenic effects [132] (Table 1). These positive effects of butein require clinical confirmation.

4,4'-dimethoxychalcone (DMC) is a chalcone found in *Angelica keiskei koidzumi*, a Japanese plant, which prolongs the survival of several species such as yeasts, worms and flies, and decreases senescence in human cell cultures by the induction of autophagy [133]. Unlike RSV and CR [134], DMC affects autophagy in a SIRT1-independent manner [133, 135] (Table 1).

Curcumin, a polyphenol found in ginger and *Curcuma longa* plants, is a well-established nutraceutical examined extensively as an anti-aging, anti-cancer and anti-inflammatory agent [109]. *In vivo* studies showed that curcumin treatment mediated lifespan extension in *C. elegans* and *D. melanogaster* by increasing antioxidant capacity and inducing the expression of age-related genes [136]. Mice that were fed with a curcumin metabolite, tetrahydrocurcumin (ThC), had a significantly longer average lifespan (by 12%) compared to the control group [137], but only if the ThC diet started at a young age. Curcumin attenuates senescence mainly through its ability to reduce ROS production by increasing the activity of antioxidant enzymes [136]. Moreover, curcumin pretreatment of human umbilical vein endothelial cells (HUVECs) decreased the levels of aging parameters (senescence-associated β -galactosidase and p21) by increasing the expression and activity of SIRT1 [138]. Inhibition of SIRT1 diminished the protective role of curcumin. Anti-cancer and cardioprotective activities of curcumin are related to the upregulation of the SIRT1 [139, 140] (Table 1).

Berberine, an alkaloid found in berries prolonged *Drosophila* lifespan by attenuating an aging-accelerating effect of temperature [141]. Berberine has multiple targets in cells but its anti-aging impact is mainly through the AMPK activation [142]. Berberine affected SIRT1 expression in human cells (L-02) causing increased cell viability (by 19.1%) and decreased apoptosis [143]. *In vivo* berberine activated AMPK/SIRT1/PGC-1 α pathway and significantly improved cognitive and muscular function of 24-month-old rats [144] (Table 1).

Crocin is a natural carotenoid found in *Crocus sativus* (saffron spice); it exhibited antioxidative activity in cyclophosphamide (CPM)-treated ovaries by increasing SOD2 and PGC-1 α levels. SIRT1 level decreased as a result of a re-established redox balance [145] (Table 1).

A combination of polyphenols could have a positive synergistic effect on deacetylase activity of sirtuins. Giovannini and colleagues [114] demonstrated the stimulating effect of RSV and eight additional compounds (berberine, tyrosol, quercetin, catechin, ferulic acid, curcumin, niclosamide and malvidin) on the expression of SIRT1 in HeLa cells. The authors showed that the combined use of berberine and tyrosol or ferulic acid and quercetin or tyrosol and ferulic acid had a synergistic effect, as they increased SIRT1 expression for more than the sum of the two substances administered separately. A mixture of total flavonoids from Chinese hickory (*Carya cathayensis Sarg.*) prevented senescence of HUVEC cells by decreasing miR-34a and consequently increasing levels of SIRT1 mRNA [146].

Compounds that activate sirtuins may either increase NAD⁺ synthesis or its bioavailability. Thus, therapies that maintain high NAD⁺ levels may slow down aging, promote longevity and mitigate age-associated diseases [81]. An increase in NAD⁺ level can be achieved either by the administration of NAD⁺ precursors (NAD⁺-boosters), increasing NAMPT expression or reduction of NAD⁺ consumption [147]. Supplementation of key NAD⁺ intermediates, such as nicotinamide riboside (NR) and NMN, can improve age-related conditions [84]. Treatment of aged cerebrovascular endothelial cells (CMVECs) with NMN in rats improved their angiogenic ability and decreased oxidative stress counteracting the adverse effects of aging [148]. Pre-treatment with pharmacological SIRT1 inhibitor prevented these effects. Gomes and colleagues reported that NMN increased NAD⁺ level and restored mitochondrial function in the muscles of elderly mice to that of a young mouse in a SIRT1-dependent manner [149]. Supplementation with the amino acid tryptophan (Trp) or all three forms of vitamin B3 (NAM, niacin and NR) and possibly with nicotinic acid riboside (NaR), increase NAD⁺ synthesis through different anabolic pathways [150]; however, not all NAD⁺ precursor supplements are equally tolerated and thus suitable as supplements for slowing aging and promoting longevity [151]. Dietary intake of Trp or less than 20 mg/day of niacin for adults meet the baseline requirements for NAD⁺ [150]. Treatment of diabetic patients with high doses of NAM was hepatotoxic [152]. Trammell and colleagues reported that NR is more orally bioavailable than NAM and has no side effects after administration to mice and human participants [153]. Results from a recent clinical study involving 24 healthy male subjects implied that oral administration of 1000 mg/day of NR was well tolerated and lowered systolic blood pressure and aortic stiffness [154]. No improvement in insulin sensitivity or blood glucose control was attributed to the good health of the participants. In a study involving 40 obese and insulin-resistant men, Døllnerup and colleagues reported no effects of NR (1000 mg x 2, 12 weeks) on glucose tolerance and function of β -cells of pancreas suggesting that NMN and NRPT (nicotinamide riboside and pterostilbene) could be considered in future clinical trials [155]. In 2016, the first

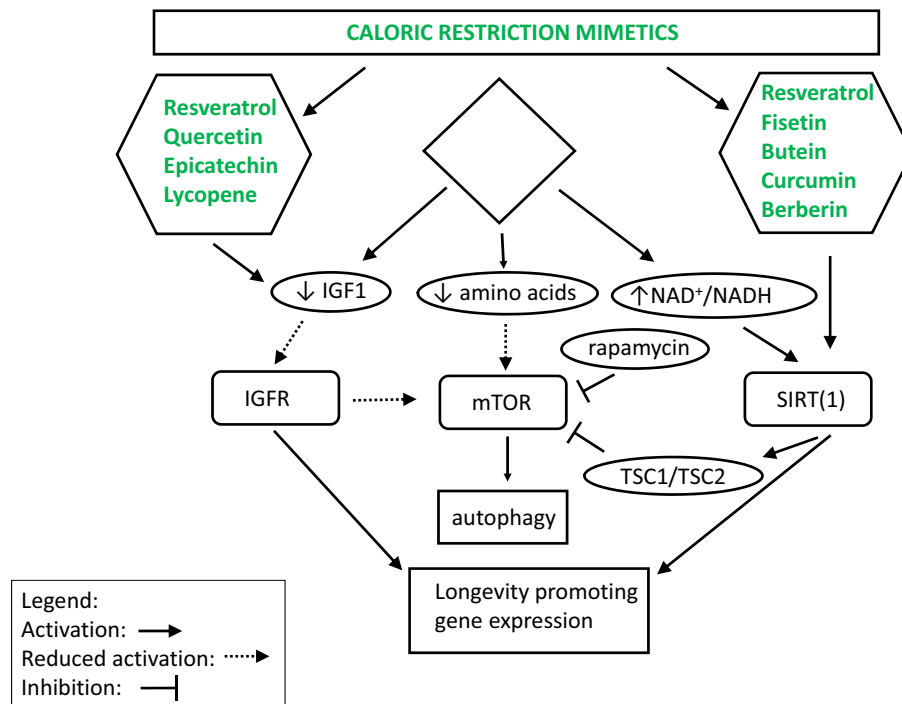


Fig. (1). Effect of CR mimetics on the modulation of IGF1R signaling and SIRT1 activity in promoting longevity.

human clinical study for assessment of NMN effect started in Japan [156], but no data are yet available¹.

An alternative approach to elevate NAD⁺ in cells is by increasing the activity of nuclear, cytoplasmic and mitochondrial isoforms of NAMPT (NAMPT1, NAMPT2, and NAMPT3), the key enzymes for NAD⁺ synthesis in main cellular compartments. This approach should be applied with caution since an increased expression of NAMPT has been measured in different cancers including breast, prostate, melanomas, *etc.* [157].

CONCLUSION

Delaying aging processes by reducing diseases may be an attractive strategy for promoting longevity. Several signaling pathways were implicated in the modulation of age-related diseases, the most understood are the IGF1 and SIRT1 pathways, which are modulated by nutrition. CR, which extends lifespan across species, mediates its function in part by modulating IGF1 and SIRT1 expression and function. CR reduces the bioavailability of IGF1 and also causes the activation of SIRT1, both directly and indirectly promoting longevity.

Nutraceuticals that are CR mimetics have the potential to promote longevity by modulating IGF1 and SIRT1 expression and function (Fig. 1). An increasing number of nutraceuticals were reported to modulate IGF1 and SIRT1. Many nutraceuticals promote longevity in rodents and there are limited data in non-rodent primates. Translation of animal data to humans is challenging, also because of human studies' limitations that include ethical study design, regulatory limitations and costs.

LIST OF ABBREVIATIONS

2'-OAADPr	=	2'-O-acetyl-ADP-Ribose
AKT	=	Protein Kinase B
AMPK	=	5' Adenosine Monophosphate-Activated Protein Kinase
ATF4	=	Activating Transcription Factor 4
BHB	=	β-Hydroxy Butyrate
CPM	=	Cyclophosphamide
CR	=	Caloric Restriction
DMC	=	4,4'-Dimethoxychalcone
EFNB	=	Ephrin Dependence Receptor Ligands
FOXO	=	Forkhead Box
HDAC	=	Histone Deacetylases
HFD	=	High-calorie Diet or High-fat Diet
hTERT	=	Human Telomerase
HUC-F2	=	Human Umbilical Cord Fibroblast
HUVEC	=	Human Umbilical Vein Endothelial Cells
IGF1	=	Insulin-like Growth Factor 1
IGF1R	=	Insulin-like Growth Factor 1 Receptor
IGFBP-3	=	IGF Binding protein-3
IPF	=	Idiopathic Pulmonary Fibrosis
IR	=	Insulin Receptor
IRS1	=	Insulin Receptor Substrate 1
IRS2	=	Insulin Receptor Substrate 2
LKB1	=	Liver Kinase B1

¹ https://upload.umin.ac.jp/cgi-open_bin/ctr_e/ctr_view.cgi?recptno=R000024575.

mTOR	=	Mammalian Target of Rapamycin
NAD+	=	Nicotinamide Adenine Dinucleotide
NAM	=	Nicotinamide Mononucleotide
NAMPT	=	Nicotinamide Phosphor-Ribosyl-Transferase
NaR	=	Nicotinic Acid Riboside
Nrf2	=	NF-E2-related factor 2
PARPS	=	Poly ADP-Ribose Polymerases
PI3K	=	Phosphoinositide 3-kinase
ROS	=	Reactive Oxygen Species
RSV	=	Resveratrol
SCFA	=	Short-Chain Fatty Acid
SIRT1	=	Silent mating Type Information Regulation 2 homolog 1
SNP	=	Single Nuclear Polymorphism
STACs	=	Sirtuin-Activating Compounds
Thec	=	Tetrahydro Curcumin

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None

CONFLICT OF INTEREST

Authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This article/publication is based upon work from COST Action CA16112 NutRedOx supported by COST (European Cooperation in Science and Technology). For further information see www.cost.eu.

REFERENCES

[1] Barbieri, M.; Bonafè, M.; Franceschi, C.; Paolisso, G. Insulin/IGF-I-signaling pathway: an evolutionarily conserved mechanism of longevity from yeast to humans. *Am. J. Physiol. Endocrinol. Metab.*, **2003**, 285(5), E1064-E1071. <http://dx.doi.org/10.1152/ajpendo.00296.2003> PMID: 14534077

[2] Junnila, R.K.; List, E.O.; Berryman, D.E.; Murrey, J.W.; Kopchick, J.J. The GH/IGF-1 axis in ageing and longevity. *Nat. Rev. Endocrinol.*, **2013**, 9(6), 366-376. <http://dx.doi.org/10.1038/nrendo.2013.67> PMID: 23591370

[3] Zhang, J.; Liu, F. Tissue-specific insulin signaling in the regulation of metabolism and aging. *IUBMB Life*, **2014**, 66(7), 485-495. <http://dx.doi.org/10.1002/iub.1293> PMID: 25087968

[4] Martins, R.; Lithgow, G.J.; Link, W. Long live FOXO: unraveling the role of FOXO proteins in aging and longevity. *Aging Cell*, **2016**, 15(2), 196-207. <http://dx.doi.org/10.1111/acel.12427> PMID: 26643314

[5] Carter, M.E.; Brunet, A. FOXO transcription factors. *Curr. Biol.*, **2007**, 17(4), R113-R114. <http://dx.doi.org/10.1016/j.cub.2007.01.008> PMID: 17307039

[6] Wolff, S.; Dillin, A. The trifeacta of aging in *Caenorhabditis elegans*. *Exp. Gerontol.*, **2006**, 41(10), 894-903. <http://dx.doi.org/10.1016/j.exger.2006.06.054> PMID: 16919905

[7] Kenyon, C. A conserved regulatory system for aging. *Cell*, **2001**, 105(2), 165-168. [http://dx.doi.org/10.1016/S0092-8674\(01\)00306-3](http://dx.doi.org/10.1016/S0092-8674(01)00306-3) PMID: 11336665

[8] Shi, R.; Berkel, H.J.; Yu, H. Insulin-like growth factor-I and prostate cancer: a meta-analysis. *Br. J. Cancer*, **2001**, 85(7), 991-996. <http://dx.doi.org/10.1054/bjoc.2001.1961> PMID: 11592771

[9] Fontana, L.; Partridge, L.; Longo, V.D. Extending healthy life span--from yeast to humans. *Science*, **2010**, 328(5976), 321-326. <http://dx.doi.org/10.1126/science.1172539> PMID: 20395504

[10] Svensson, J.; Sjögren, K.; Fäldt, J.; Andersson, N.; Isaksson, O.; Jansson, J.O.; Ohlsson, C. Liver-derived IGF-I regulates mean life span in mice. *PLoS One*, **2011**, 6(7), e22640. <http://dx.doi.org/10.1371/journal.pone.0022640> PMID: 21799924

[11] Holzenberger, M.; Dupont, J.; Ducos, B.; Leneuve, P.; Gélöën, A.; Even, P.C.; Cervera, P.; Le Bouc, Y. IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. *Nature*, **2003**, 421(6919), 182-187. <http://dx.doi.org/10.1038/nature01298> PMID: 12483226

[12] Bokov, A.F.; Garg, N.; Ikeno, Y.; Thakur, S.; Musi, N.; DeFronzo, R.A.; Zhang, N.; Erickson, R.C.; Gelfond, J.; Hubbard, G.B.; Adamo, M.L.; Richardson, A. Does reduced IGF-1R signaling in *Igf1r*^{-/-} mice alter aging? *PLoS One*, **2011**, 6(11), e26891. <http://dx.doi.org/10.1371/journal.pone.0026891> PMID: 22132081

[13] Bonafè, M.; Barbieri, M.; Marchegiani, F.; Olivieri, F.; Ragno, E.; Giampieri, C.; Mugianesi, E.; Centurelli, M.; Franceschi, C.; Paolisso, G. Polymorphic variants of insulin-like growth factor 1 (IGF-I) receptor and phosphoinositide 3-kinase genes affect IGF-I plasma levels and human longevity: cues for an evolutionarily conserved mechanism of life span control. *J. Clin. Endocrinol. Metab.*, **2003**, 88(7), 3299-3304. <http://dx.doi.org/10.1210/jc.2002-021810> PMID: 12843179

[14] Barbieri, M.; Boccardi, V.; Esposito, A.; Papa, M.; Vestini, F.; Rizzo, M.R.; Paolisso, G. A/ASP/VAL allele combination of IGF1R, IRS2, and UCP2 genes is associated with better metabolic profile, preserved energy expenditure parameters, and low mortality rate in longevity. *Age (Dordr.)*, **2012**, 34(1), 235-245. <http://dx.doi.org/10.1007/s11357-011-9210-z> PMID: 21340542

[15] Tazearslan, C.; Huang, J.; Barzilai, N.; Suh, Y. Impaired IGF1R signaling in cells expressing longevity-associated human IGF1R alleles. *Aging Cell*, **2011**, 10(3), 551-554. <http://dx.doi.org/10.1111/j.1474-9726.2011.00697.x> PMID: 21388493

[16] Suh, Y.; Atzmon, G.; Cho, M.O.; Hwang, D.; Liu, B.; Leahy, D.J.; Barzilai, N.; Cohen, P. Functionally significant insulin-like growth factor I receptor mutations in centenarians. *Proc. Natl. Acad. Sci. USA*, **2008**, 105(9), 3438-3442. <http://dx.doi.org/10.1073/pnas.0705467105> PMID: 18316725

[17] Harper, J.M.; Durkee, S.J.; Dysko, R.C.; Austad, S.N.; Miller, R.A. Genetic modulation of hormone levels and life span in hybrids between laboratory and wild-derived mice. *J. Gerontol. A Biol. Sci. Med. Sci.*, **2006**, 61(10), 1019-1029. <http://dx.doi.org/10.1093/gerona/61.10.1019> PMID: 17077194

[18] Murakami, S. Stress resistance in long-lived mouse models. *Exp. Gerontol.*, **2006**, 41(10), 1014-1019. <http://dx.doi.org/10.1016/j.exger.2006.06.061> PMID: 16962277

[19] Fulda, S.; Gorman, A.M.; Hori, O.; Samali, A. Cellular stress responses: cell survival and cell death. *Int. J. Cell Biol.*, **2010**, 2010, 214074. <http://dx.doi.org/10.1155/2010/214074> PMID: 20182529

[20] Wullschlegel, S.; Loewith, R.; Hall, M.N. TOR signaling in growth and metabolism. *Cell*, **2006**, 124(3), 471-484. <http://dx.doi.org/10.1016/j.cell.2006.01.016> PMID: 16469695

[21] Guevara-Aguirre, J.; Balasubramanian, P.; Guevara-Aguirre, M.; Wei, M.; Madia, F.; Cheng, C.W.; Hwang, D.; Martin-Montalvo, A.; Saavedra, J.; Ingles, S.; de Cabo, R.; Cohen, P.; Longo, V.D. Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. *Sci. Transl. Med.*, **2011**, 3(70), 70ra13. <http://dx.doi.org/10.1126/scitranslmed.3001845> PMID: 21325617

[22] Willcox, B.J.; Donlon, T.A.; He, Q.; Chen, R.; Grove, J.S.; Yano, K.; Masaki, K.H.; Willcox, D.C.; Rodriguez, B.; Curb, J.D. FOXO3A genotype is strongly associated with human longevity. *Proc. Natl. Acad. Sci. USA*, **2008**, 105(37), 13987-13992. <http://dx.doi.org/10.1073/pnas.0801030105> PMID: 18765803

- [23] van Heemst, D.; Beekman, M.; Mooijaart, S.P.; Heijmans, B.T.; Brandt, B.W.; Zwaan, B.J.; Slagboom, P.E.; Westendorp, R.G. Reduced insulin/IGF-1 signalling and human longevity. *Aging Cell*, **2005**, *4*(2), 79-85. <http://dx.doi.org/10.1111/j.1474-9728.2005.00148.x> PMID: 15771611
- [24] Pawlikowska, L.; Hu, D.; Huntsman, S.; Sung, A.; Chu, C.; Chen, J.; Joyner, A.H.; Schork, N.J.; Hsueh, W.C.; Reiner, A.P.; Psaty, B.M.; Atzmon, G.; Barzilai, N.; Cummings, S.R.; Browner, W.S.; Kwok, P.Y.; Ziv, E. Association of common genetic variation in the insulin/IGF1 signaling pathway with human longevity. *Aging Cell*, **2009**, *8*(4), 460-472. <http://dx.doi.org/10.1111/j.1474-9726.2009.00493.x> PMID: 19489743
- [25] Anselmi, C.V.; Malovini, A.; Roncarati, R.; Novelli, V.; Villa, F.; Condorelli, G.; Bellazzi, R.; Puca, A.A. Association of the FOXO3A locus with extreme longevity in a southern Italian centenarian study. *Rejuvenation Res.*, **2009**, *12*(2), 95-104. <http://dx.doi.org/10.1089/rej.2008.0827> PMID: 19415983
- [26] Sanese, P.; Forte, G.; Disciglio, V.; Grossi, V.; Simone, C. FOXO3 on the Road to Longevity: Lessons From SNPs and Chromatin Hubs. *Comput. Struct. Biotechnol. J.*, **2019**, *17*, 737-745. <http://dx.doi.org/10.1016/j.csbj.2019.06.011> PMID: 31303978
- [27] McCay, C.M.; Crowell, M.F.; Maynard, L.A. The effect of retarded growth upon the length of life span and upon the ultimate body size. *1935. Nutrition*, **1989**, *5*(3), 155-171. PMID: 2520283
- [28] Omodei, D.; Fontana, L. Calorie restriction and prevention of age-associated chronic disease. *FEBS Lett.*, **2011**, *585*(11), 1537-1542. <http://dx.doi.org/10.1016/j.febslet.2011.03.015> PMID: 21402069
- [29] Larson-Meyer, D.E.; Newcomer, B.R.; Heilbronn, L.K.; Volaufova, J.; Smith, S.R.; Alfonso, A.J.; Lefevre, M.; Rood, J.C.; Williamson, D.A.; Ravussin, E. Effect of 6-month calorie restriction and exercise on serum and liver lipids and markers of liver function. *Obesity (Silver Spring)*, **2008**, *16*(6), 1355-1362. <http://dx.doi.org/10.1038/oby.2008.201> PMID: 18421281
- [30] Heilbronn, L.K.; de Jonge, L.; Frisard, M.I.; DeLany, J.P.; Larson-Meyer, D.E.; Rood, J.; Nguyen, T.; Martin, C.K.; Volaufova, J.; Most, M.M.; Greenway, F.L.; Smith, S.R.; Deutsch, W.A.; Williamson, D.A.; Ravussin, E. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. *JAMA*, **2006**, *295*(13), 1539-1548. <http://dx.doi.org/10.1001/jama.295.13.1539> PMID: 16595757
- [31] Colman, R.J.; Anderson, R.M.; Johnson, S.C.; Kastman, E.K.; Kosmatka, K.J.; Beasley, T.M.; Allison, D.B.; Cruzen, C.; Simmons, H.A.; Kemnitz, J.W.; Weindruch, R. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science*, **2009**, *325*(5937), 201-204. <http://dx.doi.org/10.1126/science.1173635> PMID: 19590001
- [32] Mattison, J.A.; Roth, G.S.; Beasley, T.M.; Tilmont, E.M.; Handy, A.M.; Herbert, R.L.; Longo, D.L.; Allison, D.B.; Young, J.E.; Bryant, M.; Barnard, D.; Ward, W.F.; Qi, W.; Ingram, D.K.; de Cabo, R. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. *Nature*, **2012**, *489*(7415), 318-321. <http://dx.doi.org/10.1038/nature11432> PMID: 22932268
- [33] Kapahi, P.; Kaeberlein, M.; Hansen, M. Dietary restriction and lifespan: Lessons from invertebrate models. *Ageing Res. Rev.*, **2017**, *39*, 3-14. <http://dx.doi.org/10.1016/j.arr.2016.12.005> PMID: 28007498
- [34] Harrela, M.; Koistinen, H.; Kaprio, J.; Lehtovirta, M.; Tuomilehto, J.; Eriksson, J.; Toivanen, L.; Koskenvuo, M.; Leinonen, P.; Koistinen, R.; Seppälä, M. Genetic and environmental components of interindividual variation in circulating levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3. *J. Clin. Invest.*, **1996**, *98*(11), 2612-2615. <http://dx.doi.org/10.1172/JCI119081> PMID: 8958225
- [35] Hong, Y.; Pedersen, N.L.; Brismar, K.; Hall, K.; de Faire, U. Quantitative genetic analyses of insulin-like growth factor I (IGF-I), IGF-binding protein-1, and insulin levels in middle-aged and elderly twins. *J. Clin. Endocrinol. Metab.*, **1996**, *81*(5), 1791-1797. PMID: 8626837
- [36] Thissen, J.P.; Ketelslegers, J.M.; Underwood, L.E. Nutritional regulation of the insulin-like growth factors. *Endocr. Rev.*, **1994**, *15*(1), 80-101. PMID: 8156941
- [37] Underwood, L.E. Nutritional regulation of IGF-I and IGF-BPs. *J. Pediatr. Endocrinol. Metab.*, **1996**, *9*(Suppl. 3), 303-312. PMID: 8887175
- [38] Chen, W.; Sudji, I.R.; Wang, E.; Joubert, E.; van Wyk, B.E.; Wink, M. Ameliorative effect of aspalathin from rooibos (*Aspalathus linearis*) on acute oxidative stress in *Caenorhabditis elegans*. *Phytomedicine*, **2013**, *20*(3-4), 380-386. PMID: 23218401
- [39] Pietsch, K.; Saul, N.; Menzel, R.; Stürzenbaum, S.R.; Steinberg, C.E. Quercetin mediated lifespan extension in *Caenorhabditis elegans* is modulated by age-1, daf-2, sek-1 and unc-43. *Biogerontology*, **2009**, *10*(5), 565-578. <http://dx.doi.org/10.1007/s10522-008-9199-6> PMID: 19043800
- [40] Hada, B.; Yoo, M.R.; Seong, K.M.; Jin, Y.W.; Myeong, H.K.; Min, K.J. D-chiro-inositol and pinitol extend the life span of *Drosophila melanogaster*. *J. Gerontol. A Biol. Sci. Med. Sci.*, **2013**, *68*(3), 226-234. <http://dx.doi.org/10.1093/geron/gls156> PMID: 22843669
- [41] Si, H.; Fu, Z.; Babu, P.V.; Zhen, W.; Leroith, T.; Meaney, M.P.; Voelker, K.A.; Jia, Z.; Grange, R.W.; Liu, D. Dietary epicatechin promotes survival of obese diabetic mice and *Drosophila melanogaster*. *J. Nutr.*, **2011**, *141*(6), 1095-1100. <http://dx.doi.org/10.3945/jn.110.134270> PMID: 21525262
- [42] Baur, J.A.; Pearson, K.J.; Price, N.L.; Jamieson, H.A.; Lerin, C.; Kalra, A.; Prabhu, V.V.; Allard, J.S.; Lopez-Lluch, G.; Lewis, K.; Pistell, P.J.; Poosala, S.; Becker, K.G.; Boss, O.; Gwinn, D.; Wang, M.; Ramaswamy, S.; Fishbein, K.W.; Spencer, R.G.; Lakatta, E.G.; Le Couteur, D.; Shaw, R.J.; Navas, P.; Puigserver, P.; Ingram, D.K.; de Cabo, R.; Sinclair, D.A. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*, **2006**, *444*(7117), 337-342. <http://dx.doi.org/10.1038/nature05354> PMID: 17086191
- [43] Pearson, K.J.; Baur, J.A.; Lewis, K.N.; Peshkin, L.; Price, N.L.; Labinskyy, N.; Swindell, W.R.; Kamara, D.; Minor, R.K.; Perez, E.; Jamieson, H.A.; Zhang, Y.; Dunn, S.R.; Sharma, K.; Pleshko, N.; Woollett, L.A.; Csiszar, A.; Ikeno, Y.; Le Couteur, D.; Elliott, P.J.; Becker, K.G.; Navas, P.; Ingram, D.K.; Wolf, N.S.; Ungvari, Z.; Sinclair, D.A.; de Cabo, R. Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. *Cell Metab.*, **2008**, *8*(2), 157-168. <http://dx.doi.org/10.1016/j.cmet.2008.06.011> PMID: 18599363
- [44] Miller, R.A.; Harrison, D.E.; Astle, C.M.; Baur, J.A.; Boyd, A.R.; de Cabo, R.; Fernandez, E.; Flurkey, K.; Javors, M.A.; Nelson, J.F.; Orihuela, C.J.; Pletcher, S.; Sharp, Z.D.; Sinclair, D.; Starnes, J.W.; Wilkinson, J.E.; Nadon, N.L.; Strong, R. Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice. *J. Gerontol. A Biol. Sci. Med. Sci.*, **2011**, *66*(2), 191-201. <http://dx.doi.org/10.1093/geron/gdq178> PMID: 20974732
- [45] Liu, C.; Lian, F.; Smith, D.E.; Russell, R.M.; Wang, X.D. Lycopene supplementation inhibits lung squamous metaplasia and induces apoptosis via up-regulating insulin-like growth factor-binding protein 3 in cigarette smoke-exposed ferrets. *Cancer Res.*, **2003**, *63*(12), 3138-3144. PMID: 12810641
- [46] Karas, M.; Amir, H.; Fishman, D.; Danilenko, M.; Segal, S.; Nahum, A.; Koifmann, A.; Giat, Y.; Levy, J.; Sharoni, Y. Lycopene interferes with cell cycle progression and insulin-like growth factor I signaling in mammary cancer cells. *Nutr. Cancer*, **2000**, *36*(1), 101-111. http://dx.doi.org/10.1207/S15327914NC3601_14 PMID: 10798222
- [47] Kucuk, O.; Sarkar, F.H.; Sakr, W.; Djuric, Z.; Pollak, M.N.; Khachik, F.; Li, Y.W.; Banerjee, M.; Grignon, D.; Bertram, J.S.; Crissman, J.D.; Pontes, E.J.; Wood, D.P., Jr Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. *Cancer Epidemiol. Biomarkers Prev.*, **2001**, *10*(8), 861-868. PMID: 11489752
- [48] Ma, J.; Giovannucci, E.; Pollak, M.; Chan, J.M.; Gaziano, J.M.; Willett, W.; Stampfer, M.J. Milk intake, circulating levels of insulin-like growth factor-I, and risk of colorectal cancer in men. *J. Natl. Cancer Inst.*, **2001**, *93*(17), 1330-1336. <http://dx.doi.org/10.1093/jnci/93.17.1330> PMID: 11535708
- [49] Holmes, M.D.; Pollak, M.N.; Willett, W.C.; Hankinson, S.E. Dietary correlates of plasma insulin-like growth factor I and

- insulin-like growth factor binding protein 3 concentrations. *Cancer Epidemiol. Biomarkers Prev.*, **2002**, *11*(9), 852-861. PMID: 12223429
- [50] Diener, A.; Rohrmann, S. Associations of serum carotenoid concentrations and fruit or vegetable consumption with serum insulin-like growth factor (IGF)-1 and IGF binding protein-3 concentrations in the Third National Health and Nutrition Examination Survey (NHANES III). *J. Nutr. Sci.*, **2016**, *5*, e13 <http://dx.doi.org/10.1017/jns.2016.1> PMID: 27313849
- [51] Zhu, Z.; Jiang, W.; Thompson, H.J. Mechanisms by which energy restriction inhibits rat mammary carcinogenesis: *in vivo* effects of corticosterone on cell cycle machinery in mammary carcinomas. *Carcinogenesis*, **2003**, *24*(7), 1225-1231. <http://dx.doi.org/10.1093/carcin/bgg077> PMID: 12807724
- [52] Edwards, C.; Canfield, J.; Copes, N.; Rehan, M.; Lipps, D.; Bradshaw, P.C. D-beta-hydroxybutyrate extends lifespan in *C. elegans*. *Aging (Albany NY)*, **2014**, *6*(8), 621-644. <http://dx.doi.org/10.18632/aging.100683> PMID: 25127866
- [53] Veech, R.L.; Bradshaw, P.C.; Clarke, K.; Curtis, W.; Pawlosky, R.; King, M.T. Ketone bodies mimic the life span extending properties of caloric restriction. *IUBMB Life*, **2017**, *69*(5), 305-314. <http://dx.doi.org/10.1002/iub.1627> PMID: 28371201
- [54] Newman, J.C.; Verdin, E. Ketone bodies as signaling metabolites. *Trends Endocrinol. Metab.*, **2014**, *25*(1), 42-52. <http://dx.doi.org/10.1016/j.tem.2013.09.002> PMID: 24140022
- [55] Montero, J.C.; Seoane, S.; Ocana, A.; Pandiella, A. Inhibition of SRC family kinases and receptor tyrosine kinases by dasatinib: possible combinations in solid tumors. *Clin. Cancer Res.*, **2011**, *17*(17), 5546-5552. PMID: 21670084
- [56] Chang, Q.; Jorgensen, C.; Pawson, T.; Hedley, D.W. Effects of dasatinib on EphA2 receptor tyrosine kinase activity and downstream signalling in pancreatic cancer. *Br. J. Cancer*, **2008**, *99*(7), 1074-1082. <http://dx.doi.org/10.1038/sj.bjc.6604676> PMID: 18797457
- [57] Olave, N.C.; Grenett, M.H.; Cadeiras, M.; Grenett, H.E.; Higgins, P.J. Upstream stimulatory factor-2 mediates quercetin-induced suppression of PAI-1 gene expression in human endothelial cells. *J. Cell. Biochem.*, **2010**, *111*(3), 720-726. <http://dx.doi.org/10.1002/jcb.22760> PMID: 20626032
- [58] Bruning, A. Inhibition of mTOR signaling by quercetin in cancer treatment and prevention. *Anticancer. Agents Med. Chem.*, **2013**, *13*(7), 1025-1031. <http://dx.doi.org/10.2174/18715206113139990114> PMID: 23272907
- [59] Zhu, Y.; Tchkonina, T.; Pirtskhalava, T.; Gower, A.C.; Ding, H.; Giorgadze, N.; Palmer, A.K.; Ikeno, Y.; Hubbard, G.B.; Lenburg, M.; O'Hara, S.P.; LaRusso, N.F.; Miller, J.D.; Roos, C.M.; Verzosa, G.C.; LeBrasseur, N.K.; Wren, J.D.; Farr, J.N.; Khosla, S.; Stout, M.B.; McGowan, S.J.; Fuhrmann-Stroissnigg, H.; Gurkar, A.U.; Zhao, J.; Colangelo, D.; Dorronsoro, A.; Ling, Y.Y.; Barghouthy, A.S.; Navarro, D.C.; Sano, T.; Robbins, P.D.; Niedernhofer, L.J.; Kirkland, J.L. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell*, **2015**, *14*(4), 644-658. <http://dx.doi.org/10.1111/acel.12344> PMID: 25754370
- [60] Xu, M.; Pirtskhalava, T.; Farr, J.N.; Weigand, B.M.; Palmer, A.K.; Weivoda, M.M.; Inman, C.L.; Ogrodnik, M.B.; Hachfeld, C.M.; Fraser, D.G.; Onken, J.L.; Johnson, K.O.; Verzosa, G.C.; Langhi, L.G.P.; Weigl, M.; Giorgadze, N.; LeBrasseur, N.K.; Miller, J.D.; Jurk, D.; Singh, R.J.; Allison, D.B.; Ejima, K.; Hubbard, G.B.; Ikeno, Y.; Cubro, H.; Garovic, V.D.; Hou, X.; Weroha, S.J.; Robbins, P.D.; Niedernhofer, L.J.; Khosla, S.; Tchkonina, T.; Kirkland, J.L. Senolytics improve physical function and increase lifespan in old age. *Nat. Med.*, **2018**, *24*(8), 1246-1256. <http://dx.doi.org/10.1038/s41591-018-0092-9> PMID: 29988130
- [61] Mao, K.; Quipildor, G.F.; Tabrizian, T.; Novaj, A.; Guan, F.; Walters, R.O.; Delahaye, F.; Hubbard, G.B.; Ikeno, Y.; Ejima, K.; Li, P.; Allison, D.B.; Salimi-Moosavi, H.; Beltran, P.J.; Cohen, P.; Barzilai, N.; Huffman, D.M. Late-life targeting of the IGF-1 receptor improves healthspan and lifespan in female mice. *Nat. Commun.*, **2018**, *9*(1), 2394. <http://dx.doi.org/10.1038/s41467-018-04805-5> PMID: 29921922
- [62] Guarente, L.; Picard, F. Calorie restriction--the SIR2 connection. *Cell*, **2005**, *120*(4), 473-482. <http://dx.doi.org/10.1016/j.cell.2005.01.029> PMID: 15734680
- [63] Poulou, N.; Raju, R. Sirtuin regulation in aging and injury. *Biochim. Biophys. Acta*, **2015**, *1852*(11), 2442-2455. <http://dx.doi.org/10.1016/j.bbadis.2015.08.017> PMID: 26303641
- [64] Bosch-Presegué, L.; Vaquero, A. Sirtuin-dependent epigenetic regulation in the maintenance of genome integrity. *FEBS J.*, **2015**, *282*(9), 1745-1767. <http://dx.doi.org/10.1111/febs.13053> PMID: 25223884
- [65] Barcena de Arellano, M.L.; Pozdniakova, S.; Kühl, A.A.; Bacsko, I.; Ladilov, Y.; Regitz-Zagrosek, V. Sex differences in the aging human heart: decreased sirtuins, pro-inflammatory shift and reduced anti-oxidative defense. *Aging (Albany NY)*, **2019**, *11*(7), 1918-1933. <http://dx.doi.org/10.18632/aging.101881> PMID: 30964749
- [66] Verdin, E.; Hirshey, M.D.; Finley, L.W.; Haigis, M.C. Sirtuin regulation of mitochondria: energy production, apoptosis, and signaling. *Trends Biochem. Sci.*, **2010**, *35*(12), 669-675. <http://dx.doi.org/10.1016/j.tibs.2010.07.003> PMID: 20863707
- [67] Chang, H.C.; Guarente, L. SIRT1 and other sirtuins in metabolism. *Trends Endocrinol. Metab.*, **2014**, *25*(3), 138-145. <http://dx.doi.org/10.1016/j.tem.2013.12.001> PMID: 24388149
- [68] Guarente, L. Sirtuins in aging and disease. *Cold Spring Harb. Symp. Quant. Biol.*, **2007**, *72*, 483-488. <http://dx.doi.org/10.1101/sqb.2007.72.024> PMID: 18419308
- [69] Masri, S.; Sassone-Corsi, P. Sirtuins and the circadian clock: bridging chromatin and metabolism. *Sci. Signal.*, **2014**, *7*(342), re6. <http://dx.doi.org/10.1126/scisignal.2005685> PMID: 25205852
- [70] Frye, R.A. Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins. *Biochem. Biophys. Res. Commun.*, **2000**, *273*(2), 793-798. <http://dx.doi.org/10.1006/bbrc.2000.3000> PMID: 10873683
- [71] Lee, S.H.; Lee, J.H.; Lee, H.Y.; Min, K.J. Sirtuin signaling in cellular senescence and aging. *BMB Rep.*, **2019**, *52*(1), 24-34. <http://dx.doi.org/10.5483/BMBRep.2019.52.1.290> PMID: 30526767
- [72] Vaquero, A.; Scher, M.B.; Lee, D.H.; Sutton, A.; Cheng, H.L.; Alt, F.W.; Serrano, L.; Sternglanz, R.; Reinberg, D. SirT2 is a histone deacetylase with preference for histone H4 Lys 16 during mitosis. *Genes Dev.*, **2006**, *20*(10), 1256-1261. <http://dx.doi.org/10.1101/gad.1412706> PMID: 16648462
- [73] Michishita, E.; Park, J.Y.; Burneskis, J.M.; Barrett, J.C.; Horikawa, I. Evolutionarily conserved and nonconserved cellular localizations and functions of human SIRT proteins. *Mol. Biol. Cell*, **2005**, *16*(10), 4623-4635. <http://dx.doi.org/10.1091/mbc.e05-01-0033> PMID: 16079181
- [74] Osborne, B.; Bentley, N.L.; Montgomery, M.K.; Turner, N. The role of mitochondrial sirtuins in health and disease. *Free Radic. Biol. Med.*, **2016**, *100*, 164-174. <http://dx.doi.org/10.1016/j.freeradbiomed.2016.04.197> PMID: 27164052
- [75] Morigi, M.; Perico, L.; Benigni, A. Sirtuins in renal health and disease. *J. Am. Soc. Nephrol.*, **2018**, *29*(7), 1799-1809. <http://dx.doi.org/10.1681/ASN.2017111218> PMID: 29712732
- [76] Nishida, Y.; Rardin, M.J.; Carrico, C.; He, W.; Sahu, A.K.; Gut, P.; Najjar, R.; Fitch, M.; Hellerstein, M.; Gibson, B.W.; Verdin, E. SIRT5 Regulates both cytosolic and mitochondrial protein malonylation with glycolysis as a major target. *Mol. Cell*, **2015**, *59*(2), 321-332. <http://dx.doi.org/10.1016/j.molcel.2015.05.022> PMID: 26073543
- [77] Park, J.; Chen, Y.; Tishkoff, D.X.; Peng, C.; Tan, M.; Dai, L.; Xie, Z.; Zhang, Y.; Zwaans, B.M.; Skinner, M.E.; Lombard, D.B.; Zhao, Y. SIRT5-mediated lysine desuccinylation impacts diverse metabolic pathways. *Mol. Cell*, **2013**, *50*(6), 919-930. <http://dx.doi.org/10.1016/j.molcel.2013.06.001> PMID: 23806337
- [78] Tan, M.; Peng, C.; Anderson, K.A.; Chhoy, P.; Xie, Z.; Dai, L.; Park, J.; Chen, Y.; Huang, H.; Zhang, Y.; Ro, J.; Wagner, G.R.; Green, M.F.; Madsen, A.S.; Schmieging, J.; Peterson, B.S.; Xu, G.; Ilkayeva, O.R.; Muehlbauer, M.J.; Bralke, T.; Mühlhausen, C.; Backos, D.S.; Olsen, C.A.; McGuire, P.J.; Pletcher, S.D.; Lombard, D.B.; Hirshey, M.D.; Zhao, Y. Lysine glutarylation is a protein posttranslational modification regulated by SIRT5. *Cell Metab.*, **2014**, *19*(4), 605-617. <http://dx.doi.org/10.1016/j.cmet.2014.03.014> PMID: 24703693
- [79] Liszt, G.; Ford, E.; Kurtev, M.; Guarente, L. Mouse Sir2 homolog SIRT6 is a nuclear ADP-ribosyltransferase. *J. Biol. Chem.*, **2005**, *280*(22), 21313-21320. <http://dx.doi.org/10.1074/jbc.M413296200> PMID: 15795229

- [80] van de Ven, R.A.H.; Santos, D.; Haigis, M.C. Mitochondrial sirtuins and molecular mechanisms of aging. *Trends Mol. Med.*, **2017**, *23*(4), 320-331.
<http://dx.doi.org/10.1016/j.molmed.2017.02.005> PMID: 28285806
- [81] Poljsak, B.; Milisav, I. NAD⁺ as the link between oxidative stress, inflammation, caloric restriction, exercise, DNA repair, longevity, and health span. *Rejuvenation Res.*, **2016**, *19*(5), 406-415.
<http://dx.doi.org/10.1089/rej.2015.1767> PMID: 26725653
- [82] Costford, S.R.; Bajpeyi, S.; Pasarica, M.; Albarado, D.C.; Thomas, S.C.; Xie, H.; Church, T.S.; Jubrias, S.A.; Conley, K.E.; Smith, S.R. Skeletal muscle NAMPT is induced by exercise in humans. *Am. J. Physiol. Endocrinol. Metab.*, **2010**, *298*(1), E117-E126.
<http://dx.doi.org/10.1152/ajpendo.00318.2009> PMID: 19887595
- [83] Bitterman, K.J.; Anderson, R.M.; Cohen, H.Y.; Latorre-Esteves, M.; Sinclair, D.A. Inhibition of silencing and accelerated aging by nicotinamide, a putative negative regulator of yeast sir2 and human SIRT1. *J. Biol. Chem.*, **2002**, *277*(47), 45099-45107.
<http://dx.doi.org/10.1074/jbc.M205670200> PMID: 12297502
- [84] Imai, S.; Guarente, L. NAD⁺ and sirtuins in aging and disease. *Trends Cell Biol.*, **2014**, *24*(8), 464-471.
<http://dx.doi.org/10.1016/j.tcb.2014.04.002> PMID: 24786309
- [85] Sasaki, T.; Maier, B.; Bartke, A.; Scoble, H. Progressive loss of SIRT1 with cell cycle withdrawal. *Aging Cell*, **2006**, *5*(5), 413-422.
<http://dx.doi.org/10.1111/j.1474-9726.2006.00235.x> PMID: 16939484
- [86] Stamatovic, S.M.; Martinez-Revollar, G.; Hu, A.; Choi, J.; Keep, R.F.; Andjelkovic, A.V. Decline in Sirtuin-1 expression and activity plays a critical role in blood-brain barrier permeability in aging. *Neurobiol. Dis.*, **2019**, *126*, 105-116.
<http://dx.doi.org/10.1016/j.nbd.2018.09.006> PMID: 30196051
- [87] Rimmelé, P.; Bigarella, C.L.; Liang, R.; Izac, B.; Dieguez-Gonzalez, R.; Barbet, G.; Donovan, M.; Brugnara, C.; Blander, J.M.; Sinclair, D.A.; Ghaffari, S. Aging-like phenotype and defective lineage specification in SIRT1-deleted hematopoietic stem and progenitor cells. *Stem Cell Reports*, **2014**, *3*(1), 44-59.
<http://dx.doi.org/10.1016/j.stemcr.2014.04.015> PMID: 25068121
- [88] Gong, H.; Pang, J.; Han, Y.; Dai, Y.; Dai, D.; Cai, J.; Zhang, T.M. Age-dependent tissue expression patterns of Sirt1 in senescence-accelerated mice. *Mol. Med. Rep.*, **2014**, *10*(6), 3296-3302.
<http://dx.doi.org/10.3892/mmr.2014.2648> PMID: 25323555
- [89] Lafontaine-Lacasse, M.; Richard, D.; Picard, F. Effects of age and gender on Sirt 1 mRNA expressions in the hypothalamus of the mouse. *Neurosci. Lett.*, **2010**, *480*(1), 1-3.
<http://dx.doi.org/10.1016/j.neulet.2010.01.008> PMID: 20074616
- [90] Yamashita, S.; Ogawa, K.; Ikei, T.; Udono, M.; Fujiki, T.; Katakura, Y. SIRT1 prevents replicative senescence of normal human umbilical cord fibroblast through potentiating the transcription of human telomerase reverse transcriptase gene. *Biochem. Biophys. Res. Commun.*, **2012**, *417*(1), 630-634.
<http://dx.doi.org/10.1016/j.bbrc.2011.12.021> PMID: 22197555
- [91] Wątroba, M.; Dudek, I.; Skoda, M.; Stangret, A.; Rzdokiewicz, P.; Szukiewicz, D. Sirtuins, epigenetics and longevity. *Ageing Res. Rev.*, **2017**, *40*, 11-19.
<http://dx.doi.org/10.1016/j.arr.2017.08.001> PMID: 28789901
- [92] Brunet, A.; Sweeney, L.B.; Sturgill, J.F.; Chua, K.F.; Greer, P.L.; Lin, Y.; Tran, H.; Ross, S.E.; Mostoslavsky, R.; Cohen, H.Y.; Hu, L.S.; Cheng, H.L.; Jedrychowski, M.P.; Gygi, S.P.; Sinclair, D.A.; Alt, F.W.; Greenberg, M.E. Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science*, **2004**, *303*(5666), 2011-2015.
<http://dx.doi.org/10.1126/science.1094637> PMID: 14976264
- [93] Langley, E.; Pearson, M.; Faretta, M.; Bauer, U.M.; Frye, R.A.; Minucci, S.; Pelicci, P.G.; Kouzarides, T. Human SIR2 deacetylates p53 and antagonizes PML/p53-induced cellular senescence. *EMBO J.*, **2002**, *21*(10), 2383-2396.
<http://dx.doi.org/10.1093/emboj/21.10.2383> PMID: 12006491
- [94] Vaquero, A. The conserved role of sirtuins in chromatin regulation. *Int. J. Dev. Biol.*, **2009**, *53*(2-3), 303-322.
<http://dx.doi.org/10.1387/ijdb.082675av> PMID: 19378253
- [95] Das, C.; Lucia, M.S.; Hansen, K.C.; Tyler, J.K. CBP/p300-mediated acetylation of histone H3 on lysine 56. *Nature*, **2009**, *459*(7243), 113-117.
<http://dx.doi.org/10.1038/nature07861> PMID: 19270680
- [96] Sinclair, D.A.; Guarente, L. Extrachromosomal rDNA circles--a cause of aging in yeast. *Cell*, **1997**, *91*(7), 1033-1042.
[http://dx.doi.org/10.1016/S0092-8674\(00\)80493-6](http://dx.doi.org/10.1016/S0092-8674(00)80493-6) PMID: 9428525
- [97] Tissenbaum, H.A.; Guarente, L. Increased dosage of a sir-2 gene extends lifespan in *Caenorhabditis elegans*. *Nature*, **2001**, *410*(6825), 227-230.
<http://dx.doi.org/10.1038/35065638> PMID: 11242085
- [98] Rogina, B.; Helfand, S.L. Sir2 mediates longevity in the fly through a pathway related to caloric restriction. *Proc. Natl. Acad. Sci. USA*, **2004**, *101*(45), 15998-16003.
<http://dx.doi.org/10.1073/pnas.0404184101> PMID: 15520384
- [99] Kanfi, Y.; Naiman, S.; Amir, G.; Peshti, V.; Zinman, G.; Nahum, L.; Bar-Joseph, Z.; Cohen, H.Y. The sirtuin SIRT6 regulates lifespan in male mice. *Nature*, **2012**, *483*(7388), 218-221.
<http://dx.doi.org/10.1038/nature10815> PMID: 22367546
- [100] Satoh, A.; Brace, C.S.; Rensing, N.; Cliften, P.; Wozniak, D.F.; Herzog, E.D.; Yamada, K.A.; Imai, S. Sirt1 extends life span and delays aging in mice through the regulation of Nk2 homeobox 1 in the DMH and LH. *Cell Metab.*, **2013**, *18*(3), 416-430.
<http://dx.doi.org/10.1016/j.cmet.2013.07.013> PMID: 24011076
- [101] Vazquez, B.N.; Thackray, J.K.; Simonet, N.G.; Kane-Goldsmith, N.; Martinez-Redondo, P.; Nguyen, T.; Bunting, S.; Vaquero, A.; Tischfield, J.A.; Serrano, L. SIRT7 promotes genome integrity and modulates non-homologous end joining DNA repair. *EMBO J.*, **2016**, *35*(14), 1488-1503.
<http://dx.doi.org/10.15252/embj.201593499> PMID: 27225932
- [102] Mostoslavsky, R.; Chua, K.F.; Lombard, D.B.; Pang, W.W.; Fischer, M.R.; Gellon, L.; Liu, P.; Mostoslavsky, G.; Franco, S.; Murphy, M.M.; Mills, K.D.; Patel, P.; Hsu, J.T.; Hong, A.L.; Ford, E.; Cheng, H.L.; Kennedy, C.; Nunez, N.; Bronson, R.; Frendewey, D.; Auerbach, W.; Valenzuela, D.; Karow, M.; Hottiger, M.O.; Hursting, S.; Barrett, J.C.; Guarente, L.; Mulligan, R.; Demple, B.; Yancopoulos, G.D.; Alt, F.W. Genomic instability and aging-like phenotype in the absence of mammalian SIRT6. *Cell*, **2006**, *124*(2), 315-329.
<http://dx.doi.org/10.1016/j.cell.2005.11.044> PMID: 16439206
- [103] Ferrer, C.M.; Alders, M.; Postma, A.V.; Park, S.; Klein, M.A.; Cetinbas, M.; Pajkrt, E.; Glas, A.; van Koningsbruggen, S.; Christoffels, V.M.; Mannens, M.M.A.M.; Knekt, L.; Etchegaray, J.P.; Sadreyev, R.I.; Denu, J.M.; Mostoslavsky, G.; van Maarle, M.C.; Mostoslavsky, R. An inactivating mutation in the histone deacetylase SIRT6 causes human perinatal lethality. *Genes Dev.*, **2018**, *32*(5-6), 373-388.
<http://dx.doi.org/10.1101/gad.307330.117> PMID: 29555651
- [104] Ghosh, H.S.; McBurney, M.; Robbins, P.D. SIRT1 negatively regulates the mammalian target of rapamycin. *PLoS One*, **2010**, *5*(2), e9199.
<http://dx.doi.org/10.1371/journal.pone.0009199> PMID: 20169165
- [105] Nisoli, E.; Tonello, C.; Cardile, A.; Cozzi, V.; Bracale, R.; Tedesco, L.; Falcone, S.; Valerio, A.; Cantoni, O.; Clementi, E.; Moncada, S.; Carruba, M.O. Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. *Science*, **2005**, *310*(5746), 314-317.
<http://dx.doi.org/10.1126/science.1117728> PMID: 16224023
- [106] Cohen, H.Y.; Miller, C.; Bitterman, K.J.; Wall, N.R.; Hekking, B.; Kessler, B.; Howitz, K.T.; Gorospe, M.; de Cabo, R.; Sinclair, D.A. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. *Science*, **2004**, *305*(5682), 390-392.
<http://dx.doi.org/10.1126/science.1099196> PMID: 15205477
- [107] Civitarese, A.E.; Carling, S.; Heilbronn, L.K.; Hulver, M.H.; Ukropcova, B.; Deutsch, W.A.; Smith, S.R.; Ravussin, E. Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. *PLoS Med.*, **2007**, *4*(3), e76.
<http://dx.doi.org/10.1371/journal.pmed.0040076> PMID: 17341128
- [108] Lan, F.; Cacicedo, J.M.; Ruderman, N.; Ido, Y. SIRT1 modulation of the acetylation status, cytosolic localization, and activity of LKB1. Possible role in AMP-activated protein kinase activation. *J. Biol. Chem.*, **2008**, *283*(41), 27628-27635.
<http://dx.doi.org/10.1074/jbc.M805711200> PMID: 18687677
- [109] McCubrey, J.A.; Lertpiriyapong, K.; Steelman, L.S.; Abrams, S.L.; Yang, L.V.; Murata, R.M.; Rosalen, P.L.; Scalisi, A.; Neri, L.M.; Cocco, L.; Ratti, S.; Martelli, A.M.; Laidler, P.; Dulińska-Litewka, J.; Rakus, D.; Gizak, A.; Lombardi, P.; Nicoletti, F.; Candido, S.; Libra, M.; Montalto, G.; Cervello, M. Effects of resveratrol, curcumin, berberine and other nutraceuticals on aging, cancer development, cancer stem cells and microRNAs. *Aging (Albany NY)*, **2017**, *9*(6), 1477-1536.
<http://dx.doi.org/10.18632/aging.101250> PMID: 28611316

- [110] Howitz, K.T.; Bitterman, K.J.; Cohen, H.Y.; Lamming, D.W.; Lavu, S.; Wood, J.G.; Zipkin, R.E.; Chung, P.; Kisielewski, A.; Zhang, L.L.; Scherer, B.; Sinclair, D.A. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature*, **2003**, *425*(6954), 191-196.
<http://dx.doi.org/10.1038/nature01960> PMID: 12939617
- [111] Morris, B.J. Seven sirtuins for seven deadly diseases of aging. *Free Radic. Biol. Med.*, **2013**, *56*, 133-171.
<http://dx.doi.org/10.1016/j.freeradbiomed.2012.10.525> PMID: 23104101
- [112] Um, J.H.; Park, S.J.; Kang, H.; Yang, S.; Foretz, M.; McBurney, M.W.; Kim, M.K.; Viollet, B.; Chung, J.H. AMP-activated protein kinase-deficient mice are resistant to the metabolic effects of resveratrol. *Diabetes*, **2010**, *59*(3), 554-563.
<http://dx.doi.org/10.2337/db09-0482> PMID: 19934007
- [113] Park, S.J.; Ahmad, F.; Philp, A.; Baar, K.; Williams, T.; Luo, H.; Ke, H.; Rehmann, H.; Taussig, R.; Brown, A.L.; Kim, M.K.; Beaven, M.A.; Burgin, A.B.; Manganiello, V.; Chung, J.H. Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. *Cell*, **2012**, *148*(3), 421-433.
<http://dx.doi.org/10.1016/j.cell.2012.01.017> PMID: 22304913
- [114] Giovannini, L.; Bianchi, S. Role of nutraceutical SIRT1 modulators in AMPK and mTOR pathway: Evidence of a synergistic effect. *Nutrition*, **2017**, *34*, 82-96.
<http://dx.doi.org/10.1016/j.nut.2016.09.008> PMID: 28063518
- [115] Gambini, J.; Inglés, M.; Olaso, G.; Lopez-Grueso, R.; Bonet-Costa, V.; Gimeno-Mallench, L.; Mas-Bargues, C.; Abdelaziz, K.M.; Gomez-Cabrera, M.C.; Vina, J.; Borras, C. Properties of resveratrol: *In Vitro* and *In Vivo* Studies about metabolism, bioavailability, and biological effects in animal models and humans. *Oxid. Med. Cell. Longev.*, **2015**, *2015*, 837042.
<http://dx.doi.org/10.1155/2015/837042> PMID: 26221416
- [116] Martin, C.K.; Bhapkar, M.; Pittas, A.G.; Pieper, C.F.; Das, S.K.; Williamson, D.A.; Scott, T.; Redman, L.M.; Stein, R.; Gilhooly, C.H.; Stewart, T.; Robinson, L.; Roberts, S.B. Effect of caloric restriction on mood, quality of life, sleep, and sexual function in healthy nonobese adults: The calerie 2 randomized clinical trial. *JAMA Intern. Med.*, **2016**, *176*(6), 743-752.
<http://dx.doi.org/10.1001/jamainternmed.2016.1189> PMID: 27136347
- [117] Roggerio, A.; Strunz, C.M.C.; Pacanaro, A.P.; Leal, D.P.; Takada, J.Y.; Avakian, S.D.; Mansur, A.P. Gene expression of sirtuin-1 and endogenous secretory receptor for advanced glycation end products in healthy and slightly overweight subjects after caloric restriction and resveratrol administration. *Nutrients*, **2018**, *10*(7), E937.
<http://dx.doi.org/10.3390/nu10070937> PMID: 30037068
- [118] Zamora-Ros, R.; Urpi-Sarda, M.; Lamuela-Raventós, R.M.; Martínez-González, M.A.; Salas-Salvadó, J.; Arós, F.; Fitó, M.; Lapetra, J.; Estruch, R.; Andres-Lacueva, C. High urinary levels of resveratrol metabolites are associated with a reduction in the prevalence of cardiovascular risk factors in high-risk patients. *Pharmacol. Res.*, **2012**, *65*(6), 615-620.
<http://dx.doi.org/10.1016/j.phrs.2012.03.009> PMID: 22465220
- [119] Tomé-Carneiro, J.; González, M.; Larrosa, M.; Yáñez-Gascón, M.J.; García-Almagro, F.J.; Ruiz-Ros, J.A.; García-Conesa, M.T.; Tomás-Barberán, F.A.; Espín, J.C. One-year consumption of a grape nutraceutical containing resveratrol improves the inflammatory and fibrinolytic status of patients in primary prevention of cardiovascular disease. *Am. J. Cardiol.*, **2012**, *110*(3), 356-363.
<http://dx.doi.org/10.1016/j.amjcard.2012.03.030> PMID: 22520621
- [120] Yousefzadeh, M.J.; Zhu, Y.; McGowan, S.J.; Angelini, L.; Fuhrmann-Stroissnigg, H.; Xu, M.; Ling, Y.Y.; Melos, K.I.; Pirtskhalava, T.; Inman, C.L.; McGuckian, C.; Wade, E.A.; Kato, J.I.; Grassi, D.; Wentworth, M.; Burd, C.E.; Arriaga, E.A.; Ladiges, W.L.; Tchkonja, T.; Kirkland, J.L.; Robbins, P.D.; Niedernhofer, L.J. Fisetin is a senotherapeutic that extends health and lifespan. *EBioMedicine*, **2018**, *36*, 18-28.
<http://dx.doi.org/10.1016/j.ebiom.2018.09.015> PMID: 30279143
- [121] Ahmad, A.; Ali, T.; Park, H.Y.; Badshah, H.; Rehman, S.U.; Kim, M.O. Neuroprotective effect of fisetin against amyloid-beta-induced cognitive/synaptic dysfunction, neuroinflammation, and neurodegeneration in adult mice. *Mol. Neurobiol.*, **2017**, *54*(3), 2269-2285.
<http://dx.doi.org/10.1007/s12035-016-9795-4> PMID: 26944285
- [122] Ehren, J.L.; Maher, P. Concurrent regulation of the transcription factors Nrf2 and ATF4 mediates the enhancement of glutathione levels by the flavonoid fisetin. *Biochem. Pharmacol.*, **2013**, *85*(12), 1816-1826.
<http://dx.doi.org/10.1016/j.bcp.2013.04.010> PMID: 23618921
- [123] Singh, S.; Singh, A.K.; Garg, G.; Rizvi, S.I. Fisetin as a caloric restriction mimetic protects rat brain against aging induced oxidative stress, apoptosis and neurodegeneration. *Life Sci.*, **2018**, *193*, 171-179.
<http://dx.doi.org/10.1016/j.lfs.2017.11.004> PMID: 29122553
- [124] Zheng, W.; Feng, Z.; You, S.; Zhang, H.; Tao, Z.; Wang, Q.; Chen, H.; Wu, Y. Fisetin inhibits IL-1 β -induced inflammatory response in human osteoarthritis chondrocytes through activating SIRT1 and attenuates the progression of osteoarthritis in mice. *Int. Immunopharmacol.*, **2017**, *45*, 135-147.
<http://dx.doi.org/10.1016/j.intimp.2017.02.009> PMID: 28213268
- [125] Kim, A.; Lee, W.; Yun, J.M. Luteolin and fisetin suppress oxidative stress by modulating sirtuins and forkhead box O3a expression under *in vitro* diabetic conditions. *Nutr. Res. Pract.*, **2017**, *11*(5), 430-434.
<http://dx.doi.org/10.4162/nrp.2017.11.5.430> PMID: 28989580
- [126] Jung, H.Y.; Lee, D.; Ryu, H.G.; Choi, B.H.; Jo, Y.; Lee, N.; Lee, D.; Son, H.G.; Jeon, J.; Kim, S.H.; Yoon, J.H.; Park, S.M.; Lee, S.V.; Lee, I.K.; Choi, K.Y.; Ryu, S.H.; Nohara, K.; Yoo, S.H.; Chen, Z.; Kim, K.T. Myricetin improves endurance capacity and mitochondrial density by activating SIRT1 and PGC-1 α . *Sci. Rep.*, **2017**, *7*(1), 6237.
<http://dx.doi.org/10.1038/s41598-017-05303-2> PMID: 28740165
- [127] Akindehin, S.; Jung, Y.S.; Kim, S.N.; Son, Y.H.; Lee, I.; Seong, J.K.; Jeong, H.W.; Lee, Y.H. Myricetin exerts anti-obesity effects through upregulation of sirt3 in adipose tissue. *Nutrients*, **2018**, *10*(12), E1962.
<http://dx.doi.org/10.3390/nu10121962> PMID: 30545041
- [128] Zhu, Y.; Wang, K.; Ma, Z.; Liu, D.; Yang, Y.; Sun, M.; Wen, A.; Hao, Y.; Ma, S.; Ren, F.; Xin, Z.; Li, Y.; Di, S.; Liu, J. SIRT1 activation by butein attenuates sepsis-induced brain injury in mice subjected to cecal ligation and puncture via alleviating inflammatory and oxidative stress. *Toxicol. Appl. Pharmacol.*, **2019**, *363*, 34-46.
<http://dx.doi.org/10.1016/j.taap.2018.10.013> PMID: 30336174
- [129] Padmavathi, G.; Roy, N.K.; Bordoloi, D.; Arfuso, F.; Mishra, S.; Sethi, G. Butein in health and disease: A comprehensive review. *Phytomedicine*, **2017**, *25*, 118-127.
<http://dx.doi.org/10.1016/j.phymed.2016.12.002>
- [130] Padmavathi, G.; Rathnakaram, S.R.; Monisha, J.; Bordoloi, D.; Roy, N.K.; Kunnumakkara, A.B. Potential of butein, a tetrahydroxychalcone to obliterate cancer. *Phytomedicine.*, **2015**, *22*(13), 1163-1171.
<http://dx.doi.org/10.1016/j.phymed.2015.08.015>
- [131] Kang, D.G.; Kim, Y.C.; Sohn, E.J.; Lee, Y.M.; Lee, A.S.; Yin, M.H.; Lee, H.S. Hypotensive effect of butein via the inhibition of angiotensin converting enzyme. *Biol. Pharm. Bull.*, **2003**, *26*(9), 1345-1347.
<http://dx.doi.org/10.1248/bpb.26.1345> PMID: 12951484
- [132] Song, N.J.; Yoon, H.J.; Kim, K.H.; Jung, S.R.; Jang, W.S.; Seo, C.R.; Lee, Y.M.; Kweon, D.H.; Hong, J.W.; Lee, J.S.; Park, K.M.; Lee, K.R.; Park, K.W. Butein is a novel anti-adipogenic compound. *J. Lipid Res.*, **2013**, *54*(5), 1385-1396.
<http://dx.doi.org/10.1194/jlr.M035576> PMID: 23468131
- [133] Carmona-Gutierrez, D.; Zimmermann, A.; Kainz, K.; Pietroccola, F.; Chen, G.; Maglioni, S.; Schiavi, A.; Nah, J.; Mertel, S.; Beuschel, C.B.; Castoldi, F.; Sica, V.; Trausinger, G.; Raml, R.; Sommer, C.; Schroeder, S.; Hofer, S.; Bauer, M.A.; Pendl, T.; Tadic, J.; Dammbrueck, C.; Hu, Z.; Ruckenstein, C.; Eisenberg, T.; Durand, S.; Bossut, N.; Aprahamian, F.; Abdellatif, M.; Sedej, S.; Enot, D.P.; Wolinski, H.; Dengjel, J.; Kepp, O.; Magnes, C.; Sinner, F.; Pieber, T.R.; Sadoshima, J.; Ventura, N.; Sigris, S.J.; Kroemer, G.; Madeo, F. The flavonoid 4,4'-dimethoxychalcone promotes autophagy-dependent longevity across species. *Nat. Commun.*, **2019**, *10*(1), 651.
<http://dx.doi.org/10.1038/s41467-019-08555-w> PMID: 30783116
- [134] Morselli, E.; Maiuri, M.C.; Markaki, M.; Megalou, E.; Pasparki, A.; Palikaras, K.; Criollo, A.; Galluzzi, L.; Malik, S.A.; Vitale, I.; Michaud, M.; Madeo, F.; Tavernarakis, N.; Kroemer, G. Caloric

- restriction and resveratrol promote longevity through the Sirtuin-1-dependent induction of autophagy. *Cell Death Dis.*, **2010**, *1*, e10. <http://dx.doi.org/10.1038/cddis.2009.8> PMID: 21364612
- [135] Zimmermann, A.; Kainz, K.; Hofer, S.J.; Bauer, M.A.; Schroeder, S.; Dengjel, J.; Pietrocola, F.; Kepp, O.; Ruckenstein, C.; Eisenberg, T.; Sigrist, S.J.; Madeo, F.; Carmona-Gutierrez, D.; Kroemer, G. 4,4'-Dimethoxychalcone: A natural flavonoid that promotes health through autophagy-dependent and -independent effects. *Autophagy*, **2019**, *15*(9), 1662-1664. <http://dx.doi.org/10.1080/15548627.2019.1632623> PMID: 31248332
- [136] Shen, L.R.; Parnell, L.D.; Ordovas, J.M.; Lai, C.Q. Curcumin and aging. *Biofactors*, **2013**, *39*(1), 133-140. <http://dx.doi.org/10.1002/biof.1086> PMID: 23325575
- [137] Kitani, K.; Osawa, T.; Yokozawa, T. The effects of tetrahydrocurcumin and green tea polyphenol on the survival of male C57BL/6 mice. *Biogerontology*, **2007**, *8*(5), 567-573. <http://dx.doi.org/10.1007/s10522-007-9100-z> PMID: 17516143
- [138] Sun, Y.; Hu, X.; Hu, G.; Xu, C.; Jiang, H. curcumin attenuates hydrogen peroxide-induced premature senescence via the activation of SIRT1 in human umbilical vein endothelial cells. *Biol. Pharm. Bull.*, **2015**, *38*(8), 1134-1141. <http://dx.doi.org/10.1248/bpb.b15-00012> PMID: 26235577
- [139] Hu, A.; Huang, J.J.; Li, R.L.; Lu, Z.Y.; Duan, J.L.; Xu, W.H.; Chen, X.P.; Fan, J.P. Curcumin as therapeutics for the treatment of head and neck squamous cell carcinoma by activating SIRT1. *Sci. Rep.*, **2015**, *5*, 13429. <http://dx.doi.org/10.1038/srep13429> PMID: 26299580
- [140] Yang, Y.; Duan, W.; Lin, Y.; Yi, W.; Liang, Z.; Yan, J.; Wang, N.; Deng, C.; Zhang, S.; Li, Y.; Chen, W.; Yu, S.; Yi, D.; Jin, Z. SIRT1 activation by curcumin pretreatment attenuates mitochondrial oxidative damage induced by myocardial ischemia reperfusion injury. *Free Radic. Biol. Med.*, **2013**, *65*, 667-679. <http://dx.doi.org/10.1016/j.freeradbiomed.2013.07.007> PMID: 23880291
- [141] Navrotskaya, V.; Oxenkrug, G.; Vorobyova, L.; Summergrad, P. Berberine Attenuated aging-accelerating effect of high temperature in drosophila model. *Am. J. Plant Sci.*, **2014**, *5*(3), 275-278. <http://dx.doi.org/10.4236/ajps.2014.53037> PMID: 26167393
- [142] Xu, Z.; Feng, W.; Shen, Q.; Yu, N.; Yu, K.; Wang, S.; Chen, Z.; Shioda, S.; Guo, Y. Rhizoma coptidis and berberine as a natural drug to combat aging and aging-related diseases via anti-oxidation and ampk activation. *Aging Dis.*, **2017**, *8*(6), 760-777. <http://dx.doi.org/10.14336/AD.2016.0620> PMID: 29344415
- [143] Zhu, X.; Guo, X.; Mao, G.; Gao, Z.; Wang, H.; He, Q.; Li, D. Hepatoprotection of berberine against hydrogen peroxide-induced apoptosis by upregulation of Sirtuin 1. *Phytother. Res.*, **2013**, *27*(3), 417-421. <http://dx.doi.org/10.1002/ptr.4728> PMID: 22628222
- [144] Yu, Y.; Zhao, Y.; Teng, F.; Li, J.; Guan, Y.; Xu, J.; Lv, X.; Guan, F.; Zhang, M.; Chen, L. Berberine improves cognitive deficiency and muscular dysfunction via activation of the AMPK/SIRT1/PGC-1 α pathway in skeletal muscle from naturally aging rat. *J. Nutr. Health Aging*, **2018**, *22*(6), 710-717. <http://dx.doi.org/10.1007/s12603-018-1015-7> PMID: 29806860
- [145] Di Emidio, G.; Rossi, G.; Bonomo, I.; Alonso, G.L.; Sferra, R.; Vetuschi, A.; Artini, P.G.; Provenzani, A.; Falone, S.; Carta, G.; D'Alessandro, A.M.; Amicarelli, F.; Tatone, C. The natural carotenoid crocetin and the synthetic tellurium compound as101 protect the ovary against cyclophosphamide by modulating sirt1 and mitochondrial markers. *Oxid. Med. Cell. Longev.*, **2017**, *2017*, 8928604. <http://dx.doi.org/10.1155/2017/8928604> PMID: 29270246
- [146] Guo, Y.; Xing, L.; Chen, N.; Gao, C.; Ding, Z.; Jin, B. Total flavonoids from the *Carya cathayensis* Sarg. leaves inhibit HUVEC senescence through the miR-34a/SIRT1 pathway. *J. Cell. Biochem.*, **2019**, *120*(10), 17240-17249. <http://dx.doi.org/10.1002/jcb.28986> PMID: 31106472
- [147] Kida, Y.; Goligorsky, M.S. Sirtuins, Cell Senescence, and Vascular Aging. *Can. J. Cardiol.*, **2016**, *32*(5), 634-641. <http://dx.doi.org/10.1016/j.cjca.2015.11.022> PMID: 26948035
- [148] Kiss, T.; Balasubramanian, P.; Valcarcel-Ares, M.N.; Tarantini, S.; Yabluchanskiy, A.; Csipo, T.; Lipez, A.; Reglodi, D.; Zhang, X.A.; Bari, F.; Farkas, E.; Csiszar, A.; Ungvari, Z. Nicotinamide mononucleotide (NMN) treatment attenuates oxidative stress and rescues angiogenic capacity in aged cerebrovascular endothelial cells: A potential mechanism for the prevention of vascular cognitive impairment. *Geroscience*, **2019**, *41*(5), 619-630. <http://dx.doi.org/10.1007/s11357-019-00074-2> PMID: 31144244
- [149] Gomes, A.P.; Price, N.L.; Ling, A.J.; Moslehi, J.J.; Montgomery, M.K.; Rajman, L.; White, J.P.; Teodoro, J.S.; Wrann, C.D.; Hubbard, B.P.; Mercken, E.M.; Palmeira, C.M.; de Cabo, R.; Rolo, A.P.; Turner, N.; Bell, E.L.; Sinclair, D.A. Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. *Cell*, **2013**, *155*(7), 1624-1638. <http://dx.doi.org/10.1016/j.cell.2013.11.037> PMID: 24360282
- [150] Bogan, K.L.; Brenner, C. Nicotinic acid, nicotinamide, and nicotinamide riboside: a molecular evaluation of NAD+ precursor vitamins in human nutrition. *Annu. Rev. Nutr.*, **2008**, *28*, 115-130. <http://dx.doi.org/10.1146/annurev.nutr.28.061807.155443> PMID: 18429699
- [151] Poljsak, B.; Milisav, I. Restoring NAD(+) Levels with NAD(+) Intermediates, the Second Law of Thermodynamics, and Aging Delay. *Rejuvenation Res.*, **2018**, *21*(6), 506-509. <http://dx.doi.org/10.1089/rej.2017.2037> PMID: 29695187
- [152] Knip, M.; Douek, I.F.; Moore, W.P.; Gillmor, H.A.; McLean, A.E.; Bingley, P.J.; Gale, E.A. Safety of high-dose nicotinamide: a review. *Diabetologia*, **2000**, *43*(11), 1337-1345. <http://dx.doi.org/10.1007/s001250051536> PMID: 11126400
- [153] Trammell, S.A.; Schmidt, M.S.; Weidemann, B.J.; Redpath, P.; Jaksch, F.; Dellinger, R.W.; Li, Z.; Abel, E.D.; Migaud, M.E.; Brenner, C. Nicotinamide riboside is uniquely and orally bioavailable in mice and humans. *Nat. Commun.*, **2016**, *7*, 12948. <http://dx.doi.org/10.1038/ncomms12948> PMID: 27721479
- [154] Martens, C.R.; Denman, B.A.; Mazzo, M.R.; Armstrong, M.L.; Reisdorph, N.; McQueen, M.B.; Chonchol, M.; Seals, D.R. Chronic nicotinamide riboside supplementation is well-tolerated and elevates NAD+ in healthy middle-aged and older adults. *Nat. Commun.*, **2018**, *9*(1), 1286. <http://dx.doi.org/10.1038/s41467-018-03421-7> PMID: 29599478
- [155] Døllerup, O.L.; Trammell, S.A.J.; Hartmann, B.; Holst, J.J.; Christensen, B.; Møller, N.; Gillum, M.P.; Treebak, J.T.; Jessen, N. Effects of nicotinamide riboside on endocrine pancreatic function and incretin hormones in nondiabetic men with obesity. *J. Clin. Endocrinol. Metab.*, **2019**, *104*(11), 5703-5714. <http://dx.doi.org/10.1210/je.2019-01081> PMID: 31390002
- [156] Tsubota, K. The first human clinical study for NMN has started in Japan. *NPJ Aging Mech. Dis.*, **2016**, *2*, 16021. <http://dx.doi.org/10.1038/npjamd.2016.21> PMID: 28721273
- [157] Katsyuba, E.; Auwerx, J. Modulating NAD+ metabolism, from bench to bedside. *EMBO J.*, **2017**, *36*(18), 2670-2683. <http://dx.doi.org/10.15252/embj.201797135> PMID: 28784597