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Review

Lifespan and healthspan extension by resveratrol ☆

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ABSTRACT

A number of small molecules with the ability to extend the lifespan of multiple organisms have recently been discovered. Resveratrol, amongst the most prominent of these, has gained widespread attention due to its ability to extend the lifespan of yeast, worms, and flies, and its ability to protect against age-related diseases such as cancer, Alzheimer's, and diabetes in mammals. In this review, we discuss the origins and molecular targets of resveratrol and provide an overview of its effects on the lifespan of simple model organisms and mammals. We also examine the unique ability of resveratrol to extend the healthy years, or healthspan, of mammals and its potential to counteract the symptoms of age-related disease. Finally, we explore the many scientific, medical, and economic challenges faced when translating these findings to the clinic, and examine potential approaches for realizing the possibility of human lifespan extension. This article is part of a Special Issue entitled: Resveratrol: Challenges in translating pre-clinical findings to improved patient outcomes.

1. In pursuit of an elixir of life

The quest to discover of an elixir capable of prolonging lifespan and retarding aging has been on-going since ancient times. However, only recently has modern molecular genetics succeeded in identifying key genes and pathways involved in the aging process, bringing us closer to realizing this goal. Experimental manipulations of insulin signaling [1], AMPK signaling [2], TOR signaling [3], and the Sir2 gene [4] have all been demonstrated to modulate lifespan in diverse organisms. Furthermore, a number of dietary and pharmacological interventions have recently been described that can extend lifespan and prevent age-related diseases, bolstering hope that it may one day be possible to extend human lifespan. For example, caloric restriction (CR), a dietary regimen involving a reduction in caloric intake, extends the lifespan of yeast [5], worms [6], flies [7], and rodents [8]. Moreover, while one study found that CR had no effect on the lifespan of monkeys [9], a series of more recent studies reported that CR can reduce age-related and all-cause mortality in rhesus monkeys [10–12]. As an alternative to CR, dietary supplementation with a small molecule such as rapamycin [13], metformin [14], spermidine [15], or resveratrol [16] has also been shown to extend the lifespan of multiple model organisms. Of these compounds, resveratrol has been the most widely studied molecule in the context of aging-research, not only due its apparent lack of toxicity [17], but also due to its remarkable ability to treat and counteract a number of age-related diseases in mammals, including heart disease, cancer, Alzheimer's disease, and diabetes [17,18]. Here, we provide an overview of lifespan extension by resveratrol in numerous organisms, and discuss its ability to extend the healthspan of mammals. Furthermore, we provide perspective on the many controversies, challenges, and future promises of translating these findings to the clinic.

2. Discovery of resveratrol and its link to the sirtuin longevity pathway

Resveratrol (3,5,4′-trihydroxystilbene) was first described in 1939 in ethanol extracts of the white hellebore *Veratrum grandiflorum*, and initially characterized as a phytoalexin [17,19]. Subsequently, resveratrol was shown to be present in grapevines and in wine [17]. Resveratrol exists in two isomeric configurations, *trans*-(*E*) and *cis*-(*Z*), which may undergo isomerization upon exposure to ultraviolet radiation [20]. The 4-hydroxystilbene skeleton in resveratrol has been shown to act as an antioxidant pharmacophore, displaying a potent ability to scavenge free radicals [21,22].

Following its discovery, multiple studies have demonstrated health-enhancing properties of resveratrol both *in vitro* and *in vivo* in a number of model organisms [18]. Early studies focused on the antioxidant capacity of resveratrol, demonstrating that resveratrol can inhibit formation of copper-catalyzed LDL oxidation [23], and inhibit peroxidation of membrane lipids in liver microsomes [24]. Later, it was discovered that resveratrol could restrict the release of inflammatory mediators contributing to cardiovascular disease [25]. This finding was proposed to resolve the 'French paradox', that certain European populations consuming large amounts of wine have low rates of cardiovascular disease despite their high-fat diets [18]. Furthermore, a landmark study in 1997 demonstrated that topical application of resveratrol is extremely

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chemopreventive in a model of skin cancer [26], a finding that was extended by reports showing that resveratrol can prevent both the formation and growth of multiple types of cancers [17]. Shortly thereafter, a neuroprotective role for resveratrol was identified [27]. Many of these beneficial effects were shown to be mediated by cyclooxygenases, NF-κB, and AP-1, key mediators of inflammation and carcinogenesis [28,29]. While few studies have reported negative health effects of resveratrol, two early studies implicated dietary administration of resveratrol in increased atherosclerosis [30] and DNA damage [31].

A small molecule screen for activators of the mammalian sirtuin SIRT1 led to the discovery that resveratrol can extend the lifespan of budding yeast [32]. Sirtuins comprise an evolutionary conserved family of NAD^+-dependent (class III) histone and protein deacetylases with a wide variety of biological functions [33,34]. The founding member of this protein class, Sir2, was initially characterized in yeast as a factor involved in transcriptional silencing at mating loci and telomeres [35]. Later, it was discovered that overexpression of Sir2 in yeast results in an ~30% lifespan extension [4,36], and that overexpression of Sir2 homologs in *Caenorhabditis elegans* [37] and *Drosophila melanogaster* [38] also increases lifespan. In mice, whole-body over-expression of SIRT6 extends the lifespan of males [39], and brain-specific over-expression of SIRT1 extends lifespan as well [40], while whole body overexpression of SIRT1 does not appear to affect longevity [41].

Because Sir2 consumes NAD^+, a metabolic intermediate linked to nutrient levels [33,34], it was proposed that the Sir2 enzyme could underlie lifespan extension by caloric restriction [42]. While initial reports [5,42] showing Sir2-dependent lifespan extension by CR in yeast were challenged [43], a critical role for sirtuins in yeast CR was later re-affirmed [44]. In addition, studies in mammals have shown that the Sir2 homologs SIRT1 and SIRT3 are implicated in several of the health benefits attributed to CR [45–48].

SIRT1, which has been proposed to be a central target of resveratrol in mammals [32,49], has been the most well-characterized of the seven mammalian sirtuins (SIRT1–7) [50]. SIRT1 regulates numerous cellular processes such as DNA repair, fat differentiation, glucose output, insulin sensitivity, fatty acid oxidation, and neurogenesis, through deacetylation of a number of key histone and protein targets including H3-K9, H4-K16, H1-K26, nuclear factor NF-κB, PPAR-gamma co-activator 1α (PGC1α), forkhead box transcription factors (FOXOs), and numerous others (Fig. 1) [18,34,50,51]. Importantly, overexpression of SIRT1 has been demonstrated to guard against Alzheimer's disease [52,53], cancer [41,54], type II diabetes [55], and cardiovascular disease [18,56]. Resveratrol and similar polyphenols (*e.g.* flavones, stilbenes, and chalcones) were initially reported to activate SIRT1 *in vitro* through a direct allosteric mechanism involving a lowering of the peptide substrate K_M [32]. Consistent with this hypothesis, lifespan extension in yeast by resveratrol was shown to be Sir2-dependent [32]. Whether or not SIRT1 is directly activated by resveratrol has been the subject of a contentious debate [18]. A series of studies challenged the early *in vitro* data, suggesting that resveratrol could be binding to an artificial fluorophore on the peptide used in the initial high-throughput screening assay, rather than allosterically modulating SIRT1 [57,58]. Furthermore, it was suggested that the *in vivo* effects of resveratrol on SIRT1 could simply be due to off-target effects on other enzymes such as phosphodiesterase (PDE) [59]. However, several recent reports have validated the initial model by identifying an allosteric site on SIRT1 to

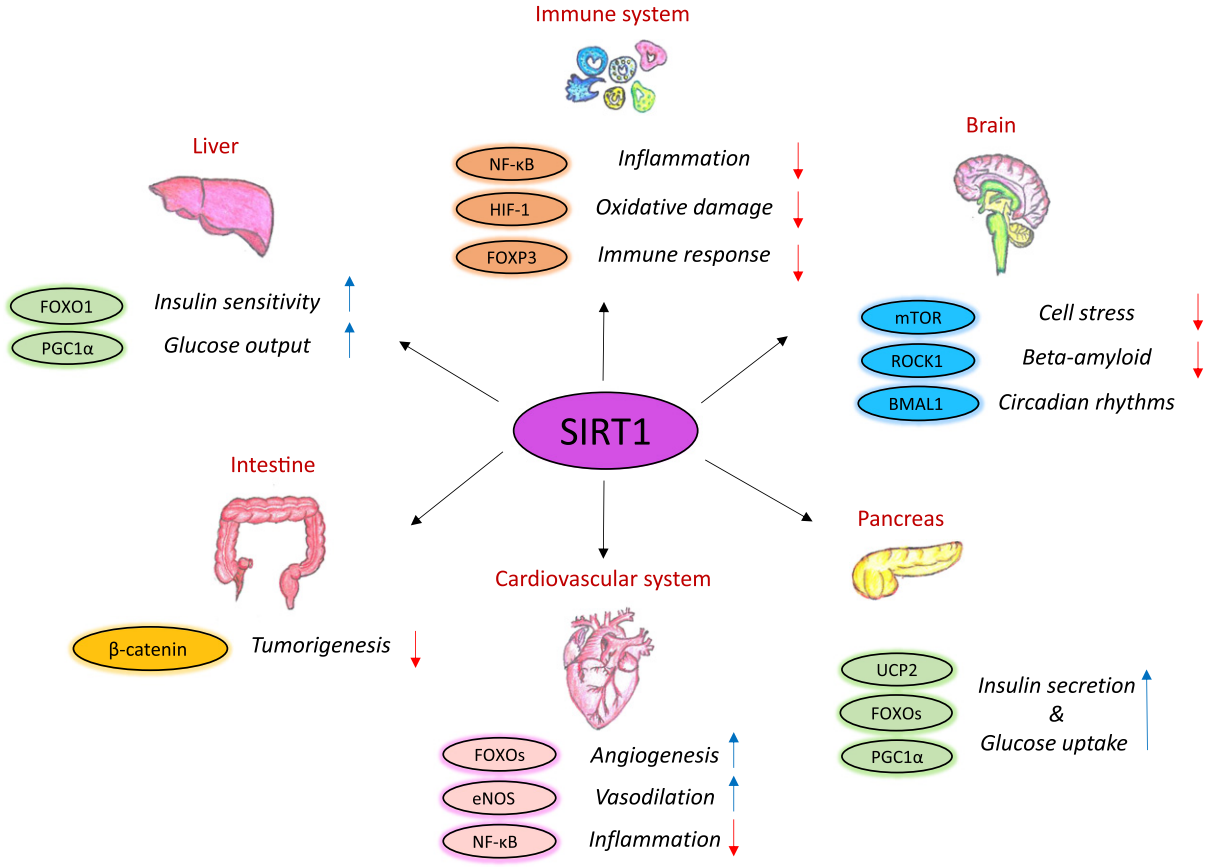

Fig. 1. Physiological functions and molecular targets of SIRT1. SIRT1 deacetylates a wide array of important non-histone targets, resulting in effects on many cellular processes. BMAL: Brain and muscle Arnt-like protein-1, eNOS: Endothelial NOS synthase, FOXO1: Forkhead box O1, FOXOs: Forkhead box proteins, FOXP3: Forkhead box P3, HIF-1: Hypoxia-inducible factor 1, mTOR: Mammalian target of rapamycin, ROCK1: Rho-associated protein kinase 1, NF-κB: Nuclear factor kappa-B, PGC1α: Peroxisome proliferator-activated receptor gamma co-activator 1-alpha, UCP2: Uncoupling protein 2.

which resveratrol binds and enhances deacetylation of non-tagged peptide substrates [60,61], supporting the hypothesis that SIRT1 is indeed a primary target of resveratrol action *in vivo*.

3. Lifespan extension by resveratrol in small model organisms

In addition to extending the lifespan of yeast up to 70% in a Sir2-dependent manner [32], the ability of resveratrol to promote longevity is highly conserved in other organisms (Table 1). Treatment of flies in early adulthood with 100 μM resveratrol was shown to extend mean lifespan [16]. The same dose of resveratrol was demonstrated to increase mean worm lifespan also, without any changes in fecundity [16]. In both cases, lifespan extension was originally shown to be Sir2-dependent [16]. However, these findings were challenged by a report claiming that resveratrol supplementation only marginally increases lifespan of *C. elegans* and *D. melanogaster*, and that this small effect is preserved in Sir2-mutant strains [62]. Indeed, it has been questioned if the Sir2 gene itself even plays any role in determining longevity in worms or flies [63]. Recent work has supported the original findings [64] and sheds light on some of the subtleties of the debate. In flies, it appears as though the effect of resveratrol on lifespan depends on both gender and dietary nutrient composition [65].

Resveratrol dosed at 130 μM also extends the mean lifespan of the common honey bee by up to 33%, in addition to extending maximum lifespan [66]. While a Sir2-dependence for this phenomenon has not been tested, bees fed resveratrol ingest fewer quantities of food under *ad libitum* feeding conditions, suggesting a caloric restriction-like mechanism [66]. In the short-lived fish species *Nothobranchius furzeri* and *Nothobranchius guentheri*, resveratrol extends both median and maximum lifespan [67–69] and delays age-dependent decay of locomotor activity [67]. In contrast, resveratrol administration does not affect the lifespan of the crustacean *Daphnia pulex* [70].

Physiological and environmental stressors may promote the early onset of a number of age-associated diseases. In certain instances, shortened lifespan resulting from exposure to stressors such as radiation or oxidative stress may be counteracted by resveratrol supplementation [71]. For example, resveratrol treatment was found to increase resistance to oxidative stress and ameliorate damage caused by oxidative stress in *C. elegans* [72]. Similarly, resveratrol exhibits radioprotective effects and alleviates radiation-induced damage in worms [73], and in fruit flies [74]. Finally, resveratrol counteracts the effects of amyloid toxicity in worms, thereby attenuating symptoms of induced-neurodegeneration [75]. Thus, in addition to increasing the maximum lifespan of several species, resveratrol can attenuate the lifespan shortening effect caused by a number of diseases and physiological stressors.

4. Effects of resveratrol on the lifespan of healthy mammals

While there is now substantial evidence suggesting that the lifespan-extending effects of sirtuins are conserved in mice [39], no study has yet reported lifespan extension resulting from resveratrol treatment in healthy mammals. To date, three studies examining the effects of resveratrol supplementation on wild-type healthy mice have been performed [76–78]. The first of these studies employed mice fed a standard diet *ad libitum* with a resveratrol supplementation protocol beginning at 12 months of age (mid-life) [76]. Two subsequent studies, which utilized supplementation protocols beginning at 9 [77], and 4 months of age [78], confirmed that resveratrol treatment does not extend the lifespan of healthy, genetically heterogeneous mice. Rats dosed with red wine or equivalent pharmacological doses of resveratrol do not live longer, but do display improved vascular aging phenotypes [79]. No large-scale study has attempted to measure the effects of resveratrol on human lifespan.

5. Lifespan extension by resveratrol in metabolically compromised mammals

While no study has demonstrated lifespan extension by resveratrol in healthy, wild-type mammals, studies have shown that resveratrol supplementation can increase the lifespan of metabolically

Table 1
Lifespan extension by resveratrol in various species. The ability of resveratrol to extend organismal lifespan is conserved from yeast to mammals. HFD: high-fat diet, SD: standard diet, N.O.: not observed.

Organism	Species	Mean lifespan extension	Maximum lifespan extension	References
	*Saccharomyces cerevisiae*	70%		[32]
	*C. elegans*	10–14%		[16]
	C. elegans	9–18%		[156]
	*D. melanogaster*	29%	20–22%	[16]
	D. melanogaster	10–17%		[157]
	D. melanogaster (females only)	10–15%		[65]
	*Apis mellifera*	33–38%		[66]
	*N. fuzeri*	33–56% (mEd.)	27–59%	[67]
	N. guentheri	19%	28%	[68]
	*Mus musculus* (SD)	N.O.	N.O.	[76,78,80]
	M. musculus (HFD)	31%[a]		[80]

[a] Resveratrol supplementation reduced the risk of death from a high-calorie diet by 31%.

compromised mammals [80], and defend against age-related disease caused by environmental insult [81]. A landmark paper by Baur et al. [80] showed that resveratrol treatment shifts the physiology of mice on a high-calorie diet to that of mice on a standard diet, reducing the risk of death due to high-calorie feeding by ~31%. In addition, resveratrol increased insulin sensitivity, reduced IGF-1 levels, activated AMPK/PGC-1α signaling, improved mitochondrial parameters, and improved liver and motor function of mice fed a high-calorie diet in this study [80]. Subsequent studies have confirmed that resveratrol protects against hepatic steatosis by decreasing lipogenesis and inflammation in these mice [82]. Moreover, resveratrol has been shown to stimulate mitochondrial biogenesis, and attenuate oxidative stress in regulatory T cells when fed to mice on a high-fat diet [83]. At the molecular level, the effects of resveratrol on metabolically compromised mice appear to involve both AMPK and SIRT1 [49]. Studies using conditional SIRT1-knockout mice have shown that resveratrol activates AMPK in a highly dose-dependent manner; a low dose (~24 mg/kg) stimulates AMPK in a SIRT1-dependent manner via LKB1, while a high dose of resveratrol (~240 mg/kg) displays SIRT1-independent AMPK activation [49].

The ability of resveratrol to suppress the damaging effects of a high-fat/high-calorie diet does not appear to be confined to mice [84]. Two recent studies have illustrated the benefits of resveratrol supplementation on the health of rhesus monkeys fed a high-fat/high-sucrose diet [84,85]. In the first study, resveratrol improved adipose insulin signaling and reduced inflammation in adipose tissue caused by the diet [84]. A second study revealed that resveratrol prevents high-fat/high-sucrose diet-induced arterial wall inflammation and stiffening [85]. Findings from these studies could be very relevant to humans, as the modern 'Western diet' mimics a high-fat/high-sugar diet in many ways [80].

Currently, there exists no consensus regarding the effects of resveratrol on metabolically compromised humans. Some reports have shown that resveratrol supplementation improves metabolic parameters in humans [86], while other studies show no such benefits [87]. For example, one recent study examining the effects of 30-day resveratrol supplementation (150 mg/day *resVida*) on energy metabolism and metabolic profile showed that resveratrol caused a calorie restriction-like phenotype [86]. Patients in this study displayed a decrease in intrahepatic lipid content, circulating glucose, triglycerides, inflammatory markers, and systolic blood pressure [86]. Furthermore, resveratrol supplementation appears to improve bone mineral density in obese men [88], and improve insulin sensitivity in humans via modulation of the Akt pathway [89]. In contrast, a separate study found that resveratrol had no effect on blood pressure, energy expenditure, lipid metabolism or inflammatory markers in obese men [87]. Also, while one study reported an improvement in inflammatory biomarkers in patients with non-alcoholic fatty liver disease following 500 mg treatment with resveratrol for 12 weeks [90], a separate study showed no such benefit [91]. Lastly, thirty-day supplementation with resveratrol was reported to suppress postprandial glucagon in obese human patients, but had no effect on postprandial incretin hormone responses [92].

6. Lifespan extension by resveratrol in the context of other mammalian diseases

Specific individuals within a given population may be more or less susceptible to a particular set of diseases due to their genetic predisposition. In small-scale mammalian lifespan studies, it is difficult to resolve the effects of a compound such as resveratrol on relatively rare genetic disorders affecting only a small subset of the population. Nonetheless, directed lifespan studies using resveratrol in several disease models have uncovered very interesting results [93–95]. Resveratrol treatment has been documented to attenuate symptoms and prolong the lifespan of mammals suffering from several genetic diseases of the brain [93,94]. Two recent reports showed that resveratrol supplementation improves motor-neuron function and extends the lifespan of the SOD1(G93A) mouse model of amyotrophic lateral sclerosis (ALS) [93,94]. Furthermore, dietary resveratrol supplementation was shown to prevent Alzheimer's disease markers and increase the lifespan of the senescence-accelerated mouse (SAMP8), which over-produces amyloid precursor protein (APP) in the brain, leading to oxidative damage [95]. In a mouse knockout model of HtrA2 (Huntington's disease), resveratrol extended lifespan and delayed worsening of the motor phenotype via regulation of the Bax pathway [96]. Resveratrol administration also improves survival in a rat model of hypertension [97]. Importantly, however, disease morbidity has also been increased by resveratrol in certain cases: at concentrations ranging from 50–100 mg/kg/day, resveratrol worsened survival of mice with prostate cancer [98].

Lethality due to exposure to environmental toxins, pathogens, and radiation may be prevented by resveratrol supplementation in several instances. First, resveratrol has been shown to attenuate catecholamine-induced mortality in obese rats, partly by reducing oxidative stress via the Nrf2 pathway [99]. Likewise, resveratrol increases the lifespan of LPS-treated mice [100]. Resveratrol also appears to be effective in protecting against insults from bacterial pathogens [101]. In a mouse model of sepsis-induced acute kidney injury, resveratrol restored renal microcirculation and prolonged survival [101]. Finally, resveratrol alters tumor load and increases the lifespan of mice subjected to ionizing radiation [81]. Thus, while the effects of resveratrol in general population studies of mammalian lifespan have been minimal, its potential to extend lifespan in the context of a number of diseases has been remarkable.

7. Healthspan increase and disease prevention in mammals by resveratrol

Aging in mammals is marked by a complex set of physiological declines that do not always correlate with maximum lifespan. Thus, the concept of 'healthspan', the number of healthy or disease-free years of an organism's lifespan, may be a comparably important measure of the aging process. Several studies have demonstrated that resveratrol can prevent/revert a number of physiological changes associated with aging in mammals, and promote optimal health [17]. Pearson et al. reported that resveratrol supplementation induces gene expression patterns in several tissues that mimic those observed during dietary restriction or every-other-day feeding in mice [76]. Furthermore, resveratrol treated mice show a reduction in a number of physiological declines linked to aging, including decreased inflammation, decreased apoptosis in the vascular endothelium, increased aortic elasticity, improved motor coordination, reduced cataract formation, and decreased osteoporosis, relative to non-treated counterparts [76]. An independent study confirmed the striking resemblance in the transcriptional profile of mice on a caloric restriction regimen, and mice given resveratrol [102]. Also, it was shown that resveratrol has the ability to mimic the effects of caloric restriction on insulin-mediated glucose uptake in muscle [102]. These effects appear to be conserved in higher organisms as well, as both caloric restriction and resveratrol supplementation result in improved insulin sensitivity markers in the primate *Microcebus murinus* [103]. In humans, resveratrol supplementation improves glycemic control [104] and modulates inflammatory-related microRNAs in patients with type 2 diabetes mellitus [105], but has no effect on insulin sensitivity in obese men [87].

A large amount of data shows that resveratrol may delay or prevent the onset of common diseases of aging including cancer, Alzheimer's disease, and diabetes [18]. Resveratrol was shown to substantially reduce both overall tumor development and especially thymic lymphomas and sarcomas in mice subjected to gamma irradiation [81]. The latter effects were SIRT1-dependent [81]. Resveratrol also slows the growth of a number of tumors including colon and prostate [54,158], while its effects on tumors of the breast remain more controversial [18]. A clinical study using the resveratrol formulation SRT501 reported a 39% increase in apoptosis markers in malignant hepatic tissue following treatment [106].

Resveratrol is able to cross the blood–brain barrier, where it can act to prevent accumulation of beta-amyloid peptide [107], and reduce plaque formation [108], two processes which likely contribute to the onset of Alzheimer's disease [108]. Finally, roles in protecting against both type I and type II diabetes have been demonstrated for resveratrol [17,109]. For example, resveratrol is able to prevent chemically-induced diabetes in mice by inhibiting apoptosis of pancreatic β-cells [110], and it prevents β-cell de-differentiation in monkeys subjected to a high-fat/high-sugar diet [111].

Resveratrol mediates its protection against inflammatory disorders and cardiovascular disease through several mechanisms [17]. In part due to its inhibition of the cyclooxygenase enzymes COX-1 and COX-2, resveratrol is able to inhibit inflammation caused by infectious agents such as *Listeria monocytogenes*, which typically infects patients who are either immunocompromised or elderly [112]. Debilitating muscle and joint diseases associated with old age may be averted by resveratrol supplementation; a study in rabbits demonstrated protection against experimentally-induced arthritis [113]. The cardioprotective effects of resveratrol have been extensively documented previously [114], and may arise from the antioxidant and metal chelating properties of resveratrol, which prevent oxidation of low-density lipoprotein (LDL) particles [17]. Few studies have yet to examine the effects of resveratrol on disease prevention in healthy humans. One recent study reported that resveratrol supplementation in humans (70 mg/day) does not improve metabolic function, or have any effect on plasma lipids or inflammatory makers throughout a 12-week trial period [115]. The controversial effects of resveratrol in healthy humans have been previously summarized [109]. However, further longer-term and larger-scale studies will need to be conducted to determine if the many disease-preventing actions of resveratrol observed in mice are conserved in humans.

8. Lifespan and healthspan extension by resveratrol in humans: clinical challenges and promises

Resveratrol has demonstrated great promise in the laboratory as both a lifespan and healthspan extending molecule [17]. However, translating findings with resveratrol from model systems to the clinic will require overcoming several challenges and obstacles. First, there are numerous logistical and economic hurdles that would need to be addressed if a large-scale study of the effects of resveratrol on human lifespan were to be performed. Logistically, it would be very difficult to carry on such a long-term clinical study, due to both patient and researcher compliance. Furthermore, the cost of such a study would be enormous. A general study on the disease preventing benefits of resveratrol in humans would face similar challenges. Therefore, it is likely that any general beneficial effects of resveratrol on human health will first be reported as ancillary observations in disease-specific clinical trials, or from non-governmentally regulated studies. Indeed, it has been estimated that 66% of people in the US who consume multiple dietary supplements consume resveratrol [109,116].

Resveratrol regulates a wide array of proteins within the cell, resulting in complex pharmacodynamics that could complicate its use in the clinic. Whether SIRT1 is a direct target of resveratrol has been the subject of intense debate [57,58,117,118]. Moreover, resveratrol targets a number of other enzymes, kinases, and receptors (Fig. 2) [17,50,118,125,127]. For example, resveratrol inhibits the activity of various cytochrome P450s (CYPs), enzymes that are involved in phase I drug metabolism [17,119,120], and also decreases their transcription via inhibition of the aryl hydrocarbon receptor (AHR) [17,121]. Quinone reductase 2 (QR2), also involved in drug metabolism, is potently inhibited by resveratrol [122]. In addition to these, resveratrol inhibits the cyclooxygenase enzymes COX-1 and COX-2, resulting in potent anti-inflammatory effects [123]. Finally, resveratrol inhibits a number of important kinases including PKD, which plays an important role in cell proliferation, and S6 kinase, which acts to mediate cell autophagy [124,125]. The striking ability of resveratrol to simultaneously regulate a number of key enzymes, all in a manner which appears to enhance health and longevity, has led to the 'xenohormesis hypothesis' [126]. This hypothesis states that an organism can sense chemical cues from other species about harsh environmental conditions or a low food supply, and can respond by initiating a physiological defense mechanism to increase its odds of survival; the production of resveratrol is thought to be one such cue [127]. Thus, the chemical structure of resveratrol may have evolved to influence multiple stress-defense targets such as SIRT1, COX-2, and QR2 [17,127]. While the

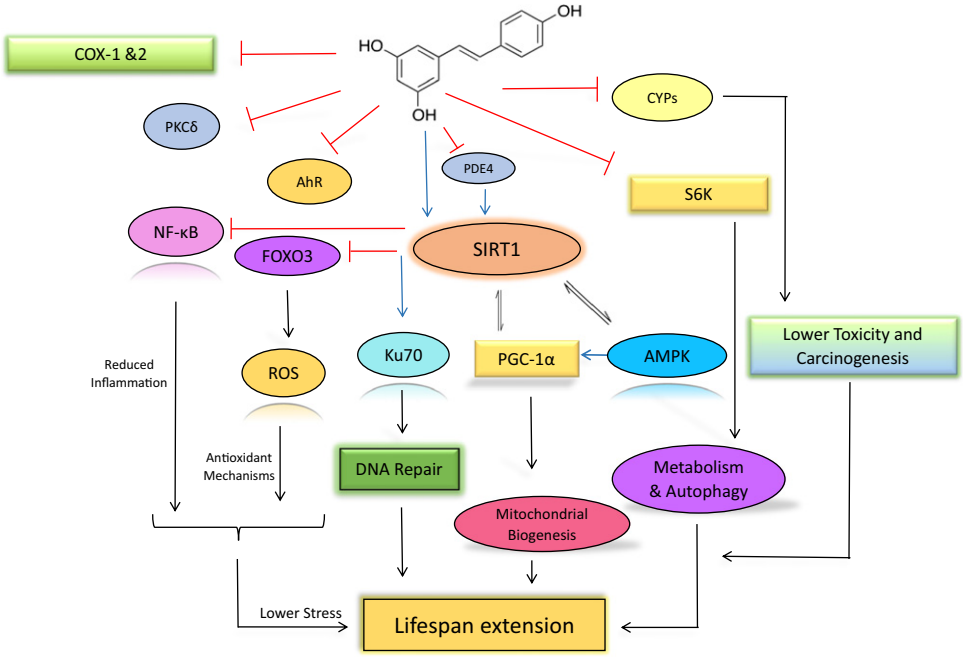

Fig. 2. Molecular targets of resveratrol. Principal targets of resveratrol regulate critical cellular processes that mediate its ability to extend lifespan and prevent age-related diseases. AhR: Aryl hydrocarbon receptor, AMPK: AMP-activated protein kinase, COX: Cyclooxygenase, CYPs: Cytochrome P450 family, FOXO3: Forkhead box O3, NF-κB: Nuclear factor kappa-B, PDE4: Phosphodiesterase 4, PGC-1α: Peroxisome proliferator-activated receptor gamma co-activator 1-alpha, PKCδ: Protein kinase C-δ, ROS: Reactive oxygen species, S6K: Ribosomal protein S6 Kinase.

pleiotropic effects of resveratrol strengthen its ability to influence a wide range of diseases, they also complicate its pharmacological analysis, making it difficult to predict how resveratrol would be tolerated by different sub-groups of patients in a large-scale clinical setting.

Studies on the bioavailability, pharmacokinetics, and tissue distribution of resveratrol suggest that it may not be an ideal clinical drug candidate [18,159]. Resveratrol from natural sources appears to be poorly absorbed by humans [128]. Humans receiving 25 mg/70 kg of body weight of resveratrol formulated in a wine-based matrix for 4 weeks failed to achieve plasma concentrations within the therapeutic window of 5–100 μM [128]. Similarly, Gresele et al. [129] determined that after 15 days of consumption of 300 mL of wine (white or red), the total plasma resveratrol concentration, including metabolites, was only slightly increased above background. Moreover, studies with purified resveratrol supplements have demonstrated poor systemic absorption [109]. For example, dietary supplementation with 5 g of *trans*-resveratrol in humans yielded a 24-hour mean plasma concentration of ~52 ug/L over the course of a day, with maximum plasma concentration (C_{max}) being observed 1.5 h after administration [109]. Multiple studies have now confirmed that resveratrol has a short half-life *in vivo* and reaches a low C_{max} due to its rapid metabolism and conversion into byproducts such as *trans*-resveratrol-3-sulfate, *trans*-resveratrol-disulfates, and *trans*-resveratrol-glucuronides [17,130,131]. Indeed, peak levels of two resveratrol metabolites, sulfate-conjugates and glucuronic acid-conjugates, have been reported to have blood levels 3- and 8-fold higher, respectively, than the unmodified molecule [132]. Interestingly, a recent report has demonstrated that resveratrol sulfate-conjugates can be taken up by several tissues, and that subsequent processing can regenerate free unmodified resveratrol inside cells [133]. Human gut microbiota may also limit bioavailability of resveratrol through conversion into metabolites such as 3,4′-dihydroxy-*trans*-stilbene and 3,4′-dihydroxybibenzyl [134]. Other factors affecting the bioavailability of unmodified resveratrol include the time of intake (high bioavailability after morning intake), prior food intake, and fat content in food [135–137]. Lastly, resveratrol and its metabolic derivatives seem to partition *in vivo* in a tissue specific manner, adding further complexity to its overall pharmacology [138].

One of the remarkable pharmacological properties of resveratrol is its apparent lack of toxicity in animals [17]. In rats, doses of resveratrol up to 300 mg per kg of body weight show no detrimental effects [139]. Consistent with this finding, preclinical and phase I clinical trials have revealed that resveratrol is well tolerated in humans and that it does not induce any major toxic complications [132,140,141]. Speculation as to potential adverse effects of resveratrol center around its ability to act as a phytoestrogen, and thereby potentially stimulate the growth of breast cancer cells [142], and its ability to delay wound healing [143]. Resveratrol also inhibits topoisomerase II [144], which could potentially result in DNA damage and carcinogenesis. Moreover, several reports have suggested that resveratrol should not be taken by pregnant women since the fetus has diminished detoxification systems and may be more susceptible to these negative effects [145]. Overall, while preclinical and small-scale clinical studies have demonstrated a wide-array of health benefits stemming from resveratrol supplementation, further pharmacological optimization is necessary in order to make resveratrol more suitable for larger-scale clinical trials.

9. Alternatives to resveratrol that may be more appropriate for clinical use

Two parallel approaches are on-going to fully exploit resveratrol's clinical potential: the design of new resveratrol formulations and analogues with improved pharmacokinetics and bioavailability, and the identification of more potent synthetic SIRT1 activators. A proprietary formulation of micronized resveratrol, SRT501, was shown to achieve blood levels 5–8 times higher than resveratrol alone, concentrations which approach levels that have been shown in animal models to have numerous health-promoting effects [18,141,146]. In addition, a number of resveratrol derivatives with hydrophobic substituents (*e.g.* methyl, ethyl) at the 4′ position of the stilbene backbone display higher lifespan extension in yeast than the parent compound, and are more stable (Fig. 3A) [147].

While it is unlikely that all of resveratrol's health benefits rely solely on activation of SIRT1, several screens have successfully identified novel SIRT1 activators that mimic many of its effects on healthspan and lifespan [55,148]. Most notable are three classes of synthetic SIRT1 activators, or STACs, which have been developed by Sirtris Pharmaceuticals (structures are shown in Fig. 3B and C). First generation STACs based on an imidazothiazole scaffold, such as SRT1460, SRT1720, and SRT2183,

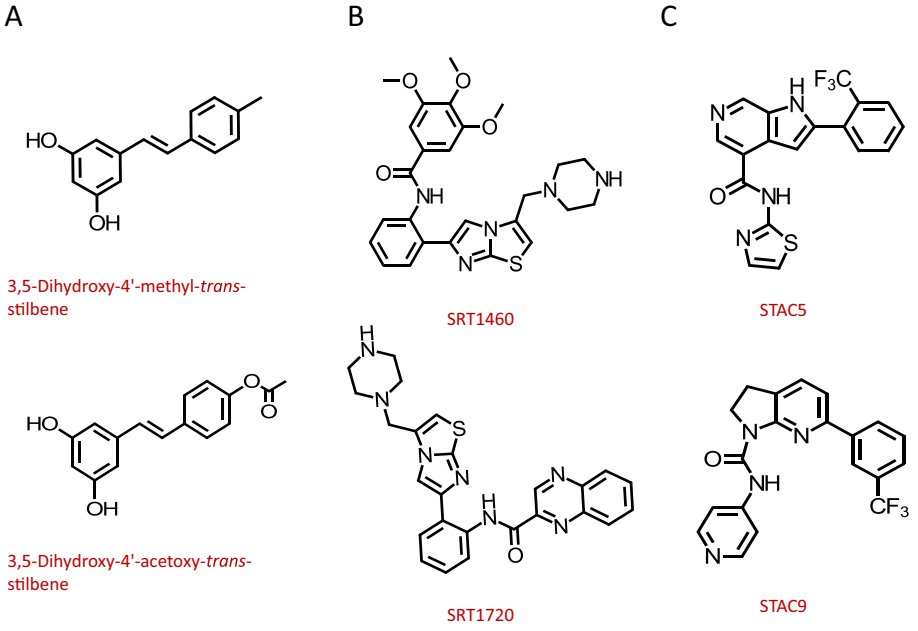

Fig. 3. Resveratrol analogues and synthetic SIRT1 activating compounds. A) Chemically modified derivatives of resveratrol, B) synthetic STACs based on the imidazothiazole scaffold, and C), benzimidazole and urea-based STACs (numbered according to a previously described convention [60]).

are stronger activators of SIRT1 than resveratrol, displaying nanomolar to low micromolar potency *in vitro* [55]. Like resveratrol, the ability of these compounds to activate SIRT1 has been questioned [117], and subsequently re-affirmed [60]. In addition to displaying benefits in a number of human disease models [149,150], SRT1720 extends both the lifespan and healthspan of mice fed a high-fat diet [151]. SRT1720 was also recently reported to extend the lifespan of mice fed a standard diet [152]. Similarly, SRT2104 has been shown to extend both mean and maximum lifespan of mice on a standard diet, concomitant with improvements in motor coordination, bone mineral density, insulin sensitivity, mitochondrial efficiency, and decreased inflammation [153]. This particular compound has also been the subject of extensive clinical trials in humans, where it displayed high bioavailability, lack of toxicity, and the ability to improve the serum lipid profile of patients [154,155]. Third generation STACs including benzimidazoles and urea-based scaffolds display even higher maximal efficacy and potency than second generation STACs [60], and may constitute a viable pharmaceutical alternative to resveratrol.

10. Concluding remarks

Given the ever growing list of molecules proven to extend the lifespan and health of mammals, it is likely that a molecule capable of extending human life has already been identified, or will be in the near future. In the case of resveratrol, there are currently 93 on-going or recently completed clinical trials (www.clinicaltrials.gov) in different disease models and clinical settings that will likely produce data answering critical questions regarding its effects on human health. However, governmental regulatory agencies currently do not consider aging a disease due its widespread occurrence, minimizing the possibility of testing resveratrol or similar molecules in clinical trials for aging. Thus, from a scientific and medical perspective, the major challenges moving forward will be determining how to identify molecules with the ability to extend human life, and how to implement strategies for testing them safely in the population. Additionally, many of the ethical and philosophical questions surrounding human lifespan extension will need to be examined in-depth. Although a tremendous amount of work still lies ahead, there is no doubt that the discovery of a single molecule capable of preventing and treating multiple age-related diseases in humans will revolutionize modern-day medicine.

Transparency Document

The Transparency document associated with this article can be found in the online version.

References

[1] C. Kenyon, The first long-lived mutants: discovery of theinsulin/IGF-1 pathway for ageing, Phil. Trans. R. Soc. B 366 (2011) 9–16. http://dx.doi.org/10.1098/rstb.2010.0276.
[2] D.G. Hardie, F.A. Ross, S.A. Hawley, AMPK: a nutrient and energy sensor that maintains energy homeostasis, Nat. Rev. Mol. Cell Biol. 13 (2012) 251–262.
[3] M. Hansen, S. Taubert, D. Crawford, N. Libina, S.J. Lee, C. Kenyon, Lifespan extension by conditions that inhibit translation in *Caenorhabditis elegans*, Aging Cell 6 (2007) 95–110.
[4] M. Kaeberlein, M. McVey, L. Guarente, The SIR2/3/4 complex and SIR2 alone promote longevity in *Saccharomyces cerevisiae* by two different mechanisms, Genes Dev. 13 (1999) 2570–2580.
[5] R.M. Anderson, K.J. Bitterman, J.G. Wood, O. Medvedik, D.A. Sinclair, Nicotinamide and PNC1 govern lifespan extension by calorie restriction in *Saccharomyces cerevisiae*, Nature 423 (2003) 181–185.
[6] G.D. Lee, M.A. Wilson, M. Zhu, C.A. Wolkow, R. de Cabo, D.K. Ingram, S. Zou, Dietary deprivation extends lifespan in *Caenorhabditis elegans*, Aging Cell 5 (2006) 515–524.
[7] L. Partridge, M.D. Piper, W. Mair, Dietary restriction in *Drosophila*, Mech. Ageing Dev. 126 (2005) 938–950.
[8] R. Weindruch, R.L. Walford, S. Fligiel, D. Guthrie, The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake, J. Nutr. 116 (1986) 641–654.
[9] J.A. Mattison, G.S. Roth, T.M. Beasley, E.M. Tilmont, A.M. Handy, R.L. Herbert, D.L. Longo, D.B. Allison, J.E. Young, M. Bryant, D. Barnard, W.F. Ward, W. Qi, D.K. Ingram, R. de Cabo, Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study, Nature 489 (2012) 318–321.
[10] R.J. Colman, T.M. Beasley, J.W. Kemnitz, S.C. Johnson, R. Weindruch, R.M. Anderson, Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys, Nat. Commun. 5 (2014) 3557.
[11] R.J. Colman, R.M. Anderson, S.C. Johnson, E.K. Kastman, K.J. Kosmatka, T.M. Beasley, D.B. Allison, C. Cruzen, H.A. Simmons, J.W. Kemnitz, Caloric restriction delays disease onset and mortality in rhesus monkeys, Science 325 (2009) 201–204.
[12] N.L. Bodkin, T.M. Alexander, H.K. Ortmeyer, E. Johnson, B.C. Hansen, Mortality and morbidity in laboratory-maintained Rhesus monkeys and effects of long-term dietary restriction, J. Gerontol. A: Biol. Med. Sci. 58 (2003) B212–B219.
[13] D.E. Harrison, R. Strong, Z.D. Sharp, J.F. Nelson, C.M. Astle, K. Flurkey, N.L. Nadon, J.E. Wilkinson, K. Frenkel, C.S. Carter, M. Pahor, M.A. Javors, E. Fernandez, R.A. Miller, Rapamycin fed late in life extends lifespan in genetically heterogeneous mice, Nature 460 (2009) 392–395.
[14] A. Martin-Montalvo, E.M. Mercken, S.J. Mitchell, H.H. Palacios, P.L. Mote, M. Scheibye-Knudsen, A.P. Gomes, T.M. Ward, R.K. Minor, M.J. Blouin, M. Schwab, M. Pollak, Y. Zhang, Y. Yu, K.G. Becker, V.A. Bohr, D.K. Ingram, D.A. Sinclair, N.S. Wolf, S.R. Spindler, M. Bernier, R. de Cabo, Metformin improves healthspan and lifespan in mice, Nat. Commun. 4 (2013) 2192.
[15] E. Morselli, L. Galluzzi, O. Kepp, A. Criollo, M.C. Maiuri, N. Tavernarakis, F. Madeo, G. Kroemer, Autophagy mediates pharmacological lifespan extension by spermidine and resveratrol, Aging 1 (2009) 961–970.
[16] J.G. Wood, B. Rogina, S. Lavu, K. Howitz, S.L. Helfand, M. Tatar, D. Sinclair, Sirtuin activators mimic caloric restriction and delay ageing in metazoans, Nature 430 (2004) 686–689.
[17] J.A. Baur, D.A. Sinclair, Therapeutic potential of resveratrol: the in vivo evidence, Nat. Rev. Drug Discov. 5 (2006) 493–506.
[18] B.P. Hubbard, D.A. Sinclair, Small molecule SIRT1 activators for the treatment of aging and age-related diseases, Trends Pharmacol. Sci. 35 (2014) 146–154.
[19] M. Takaoka, Resveratrol, a new phenolic compound from Veratrum grandiflorum, Nippon Kagaku Kaishi 60 (1939) 1090–1100.
[20] F. Mattivi, F. Reniero, S. Korhammer, Isolation, characterization, and evolution in red wine vinification of resveratrol monomers, J. Agric. Food Chem. 43 (1995) 1820–1823.
[21] H. Cao, X. Pan, C. Li, C. Zhou, F. Deng, T. Li, Density functional theory calculations for resveratrol, Bioorg. Med. Chem. Lett. 13 (2003) 1869–1871.
[22] A.N. Queiroz, B.A. Gomes, W.M. Moraes Jr., R.S. Borges, A theoretical antioxidant pharmacophore for resveratrol, Eur. J. Med. Chem. 44 (2009) 1644–1649.
[23] E. Frankel, A. Waterhouse, J.E. Kinsella, Inhibition of human LDL oxidation by resveratrol, Lancet 341 (1993) 1103–1104.
[24] J. Blond, M. Denis, J. Bezard, Antioxidant action of resveratrol in lipid peroxidation, Sci. Aliments 15 (1995) 347–358 (France).
[25] S. Rotondo, G. Rajtar, S. Manarini, A. Celardo, D. Rotilio, G. De Gaetano, V. Evangelista, C. Cerletti, Effect of *trans*-resveratrol, a natural polyphenolic compound, on human polymorphonuclear leukocyte function, Br. J. Pharmacol. 123 (1998) 1691–1699.
[26] M. Jang, L. Cai, G.O. Udeani, K.V. Slowing, C.F. Thomas, C.W. Beecher, H.H. Fong, N.R. Farnsworth, A.D. Kinghorn, R.G. Mehta, Cancer chemopreventive activity of resveratrol, a natural product derived from grapes, Science 275 (1997) 218–220.
[27] M. Virgili, A. Contestabile, Partial neuroprotection of in vivo excitotoxic brain damage by chronic administration of the red wine antioxidant agent, *trans*-resveratrol in rats, Neurosci. Lett. 281 (2000) 123–126.
[28] M. Ono, Molecular links between tumor angiogenesis and inflammation: inflammatory stimuli of macrophages and cancer cells as targets for therapeutic strategy, Cancer Sci. 99 (2008) 1501–1506.
[29] J.K. Kundu, Y.K. Shin, Y.-J. Surh, Resveratrol modulates phorbol ester-induced pro-inflammatory signal transduction pathways in mouse skin *in vivo*: NF-κB and AP-1 as prime targets, Biochem. Pharmacol. 72 (2006) 1506–1515.
[30] T. Wilson, T.J. Knight, D.C. Beitz, D.S. Lewis, R.L. Engen, Resveratrol promotes atherosclerosis in hypercholesterolemic rabbits, Life Sci. 59 (1996) L15–PL21.
[31] V.M. Breinholt, A.-M. Mølck, G.W. Svendsen, B. Daneshvar, A.M. Vinggaard, M. Poulsen, L.O. Dragsted, Effects of dietary antioxidants and 2-amino-3-methylimidazo [4, 5-f]-quinoline (IQ) on preneoplastic lesions and on oxidative damage, hormonal status, and detoxification capacity in the rat, Food Chem. Toxicol. 41 (2003) 1315–1323.
[32] K.T. Howitz, K.J. Bitterman, H.Y. Cohen, D.W. Lamming, S. Lavu, J.G. Wood, R.E. Zipkin, P. Chung, A. Kisielewski, L.L. Zhang, B. Scherer, D.A. Sinclair, Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan, Nature 425 (2003) 191–196.
[33] R.A. Frye, Phylogenetic classification of prokaryotic and eukaryotic Sir2-like proteins, Biochem. Biophys. Res. Commun. 273 (2000) 793–798.
[34] J.M. Denu, The Sir2 family of protein deacetylases, Curr. Opin. Chem. Biol. 9 (2005) 431–440.
[35] D. Shore, M. Squire, K.A. Nasmyth, Characterization of two genes required for the position-effect control of yeast mating-type genes, EMBO J. 3 (1984) 2817–2823.
[36] D.A. Sinclair, L. Guarente, Extrachromosomal rDNA circles—a cause of aging in yeast, Cell 91 (1997) 1033–1042.
[37] H.A. Tissenbaum, L. Guarente, Increased dosage of a sir-2 gene extends lifespan in *Caenorhabditis elegans*, Nature 410 (2001) 227–230.
[38] B. Rogina, S.L. Helfand, Sir2 mediates longevity in the fly through a pathway related to calorie restriction, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 15998–16003.
[39] Y. Kanfi, S. Naiman, G. Amir, V. Peshti, G. Zinman, L. Nahum, Z. Bar-Joseph, H.Y. Cohen, The sirtuin SIRT6 regulates lifespan in male mice, Nature 483 (2012) 218–221.
[40] A. Satoh, C.S. Brace, N. Rensing, P. Cliften, D.F. Wozniak, E.D. Herzog, K.A. Yamada, S. Imai, Sirt1 extends life span and delays aging in mice through the regulation of Nk2 homeobox 1 in the DMH and LH, Cell Metab. 18 (2013) 416–430.

[41] D. Herranz, M. Muñoz-Martin, M. Cañamero, F. Mulero, B. Martinez-Pastor, O. Fernandez-Capetillo, M. Serrano, Sirt1 improves healthy ageing and protects from metabolic syndrome-associated cancer, Nat. Commun. 1 (2010) 3.
[42] L. Guarente, F. Picard, Calorie restriction—the SIR2 connection, Cell 120 (2005) 473–482.
[43] M. Kaeberlein, K.T. Kirkland, S. Fields, B.K. Kennedy, Sir2-independent life span extension by calorie restriction in yeast, PLoS Biol. 2 (2004) e296.
[44] D.W. Lamming, M. Latorre-Esteves, O. Medvedik, S.N. Wong, F.A. Tsang, C. Wang, S.J. Lin, D.A. Sinclair, HST2 mediates SIR2-independent life-span extension by calorie restriction, Science 309 (2005) 1861–1864.
[45] H.Y. Cohen, C. Miller, K.J. Bitterman, N.R. Wall, B. Hekking, B. Kessler, K.T. Howitz, M. Gorospe, R. de Cabo, D.A. Sinclair, Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase, Science 305 (2004) 390–392.
[46] O.M. Palacios, J.J. Carmona, S. Michan, K.Y. Chen, Y. Manabe, J.L. Ward Iii, L.J. Goodyear, Q. Tong, Diet and exercise signals regulate SIRT3 and activate AMPK and PGC-1α in skeletal muscle, Aging (Albany NY) 1 (2009) 771.
[47] G. Boily, E.L. Seifert, L. Bevilacqua, X.H. He, G. Sabourin, C. Estey, C. Moffat, S. Crawford, S. Saliba, K. Jardine, SirT1 regulates energy metabolism and response to caloric restriction in mice, PLoS One 3 (2008) e1759.
[48] X. Qiu, K. Brown, M.D. Hirschey, E. Verdin, D. Chen, Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation, Cell Metab. 12 (2010) 662–667.
[49] N.L. Price, A.P. Gomes, A.J. Ling, F.V. Duarte, A. Martin-Montalvo, B.J. North, B. Agarwal, L. Ye, G. Ramadori, J.S. Teodoro, B.P. Hubbard, A.T. Varela, J.G. Davis, B. Varamini, A. Hafner, R. Moaddel, A.P. Rolo, R. Coppari, C.M. Palmeira, R. de Cabo, J.A. Baur, D.A. Sinclair, SIRT1 is required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function, Cell Metab. 15 (2012) 675–690.
[50] B.J. Morris, Seven sirtuins for seven deadly diseases of aging, Free Radic. Biol. Med. 56 (2013) 133–171.
[51] T. Finkel, C.X. Deng, R. Mostoslavsky, Recent progress in the biology and physiology of sirtuins, Nature 460 (2009) 587–591.
[52] G. Donmez, D. Wang, D.E. Cohen, L. Guarente, SIRT1 suppresses β-amyloid production by activating the α-secretase gene ADAM10, Cell 142 (2010) 320–332.
[53] D. Kim, M.D. Nguyen, M.M. Dobbin, A. Fischer, F. Sananbenesi, J.T. Rodgers, I. Delalle, J.A. Baur, G. Sui, S.M. Armour, SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis, EMBO J. 26 (2007) 3169–3179.
[54] T. Liu, P.Y. Liu, G.M. Marshall, The critical role of the class III histone deacetylase SIRT1 in cancer, Cancer Res. 69 (2009) 1702–1705.
[55] J.C. Milne, P.D. Lambert, S. Schenk, D.P. Carney, J.J. Smith, D.J. Gagne, L. Jin, O. Boss, R.B. Perni, C.B. Vu, Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes, Nature 450 (2007) 712–716.
[56] N.M. Borradaile, J.G. Pickering, NAD+, sirtuins, and cardiovascular disease, Curr. Pharm. Des. 15 (2009) 110–117.
[57] M.T. Borra, B.C. Smith, J.M. Denu, Mechanism of human SIRT1 activation by resveratrol, J. Biol. Chem. 280 (2005) 17187–17195.
[58] M. Kaeberlein, T. McDonagh, B. Heltweg, J. Hixon, E.A. Westman, S.D. Caldwell, A. Napper, R. Curtis, P.S. DiStefano, S. Fields, A. Bedalov, B.K. Kennedy, Substrate-specific activation of sirtuins by resveratrol, J. Biol. Chem. 280 (2005) 17038–17045.
[59] J.H. Chung, Using PDE inhibitors to harness the benefits of calorie restriction: lessons from resveratrol, Aging (Albany NY) 4 (2012) 144–145.
[60] B.P. Hubbard, A.P. Gomes, H. Dai, J. Li, A.W. Case, T. Considine, T.V. Riera, J.E. Lee, S. Yen, D.W. Lamming, Evidence for a common mechanism of SIRT1 regulation by allosteric activators, Science 339 (2013) 1216–1219.
[61] M. Lakshminarasimhan, D. Rauh, M. Schutkowski, C. Steegborn, Sirt1 activation by resveratrol is substrate sequence-selective, Aging (Albany NY) 5 (2013) 151–154.
[62] T.M. Bass, D. Weinkove, K. Houthoofd, D. Gems, L. Partridge, Effects of resveratrol on lifespan in *Drosophila melanogaster* and *Caenorhabditis elegans*, Mech. Ageing Dev. 128 (2007) 546–552.
[63] C. Burnett, S. Valentini, F. Cabreiro, M. Goss, M. Somogyvári, M.D. Piper, M. Hoddinott, G.L. Sutphin, V. Leko, J.J. McElwee, Absence of effects of Sir2 overexpression on lifespan in *C. elegans* and *Drosophila*, Nature 477 (2011) 482–485.
[64] M. Viswanathan, L. Guarente, Regulation of *Caenorhabditis elegans* lifespan by sir-2.1 transgenes, Nature 477 (2011) E1–E2.
[65] C. Wang, C.T. Wheeler, T. Alberico, X. Sun, J. Seeberger, M. Laslo, E. Spangler, B. Kern, R. de Cabo, S. Zou, The effect of resveratrol on lifespan depends on both gender and dietary nutrient composition in *Drosophila melanogaster*, Age 35 (2013) 69–81.
[66] B. Rascón, B.P. Hubbard, D.A. Sinclair, G.V. Amdam, The lifespan extension effects of resveratrol are conserved in the honey bee and may be driven by a mechanism related to caloric restriction, Aging (Albany NY) 4 (2012) 499.
[67] D.R. Valenzano, E. Terzibasi, T. Genade, A. Cattaneo, L. Domenici, A. Cellerino, Resveratrol prolongs lifespan and retards the onset of age-related markers in a short-lived vertebrate, Curr. Biol. 16 (2006) 296–300.
[68] X. Yu, G. Li, Effects of resveratrol on longevity, cognitive ability and aging-related histological markers in the annual fish *Nothobranchius guentheri*, Exp. Gerontol. 47 (2012) 940–949.
[69] T. Genade, D. Lang, Resveratrol extends lifespan and preserves glia but not neurons of the *Nothobranchius guentheri* optic tectum, Exp. Gerontol. 48 (2013) 202–212.
[70] E. Kim, C.M. Ansell, J.L. Dudycha, Resveratrol and food effects on lifespan and reproduction in the model crustacean *Daphnia*, J. Exp. Zool. A Ecol. Genet. Physiol. 321 (2014) 48–56.
[71] Resveratrol supplementation, Prevention of short-term ultraviolet B radiation-mediated damages by resveratrol in SKH-1 hairless mice, Toxicol. Appl. Pharmacol. 186 (1) (2003) 28–37.
[72] W. Chen, L. Rezaizadehnajafi, M. Wink, Influence of resveratrol on oxidative stress resistance and life span in *Caenorhabditis elegans*, J. Pharm. Pharmacol. 65 (2013) 682–688.
[73] K. Ye, C.-B. Ji, X.-W. Lu, Y.-H. Ni, C.-L. Gao, X.-H. Chen, Y.-P. Zhao, G.-X. Gu, X.-R. Guo, Resveratrol attenuates radiation damage in *Caenorhabditis elegans* by preventing oxidative stress, J. Radiat. Res. 51 (2010) 473–479.
[74] C.L. Chang, P. Follett, Resveratrol modifies tephritid fruit fly response to radiation but not nutritional stress, Int. J. Radiat. Biol. 88 (2012) 320–326.
[75] H. Yin, J. Si, H. Xu, J. Dong, D. Zheng, X. Lu, X. Li, Resveratrol-loaded nanoparticles reduce oxidative stress induced by radiation or amyloid-beta in transgenic *Caenorhabditis elegans*, J. Biomed. Nanotechnol. 10 (2014) 1536–1544.
[76] K.J. Pearson, J.A. Baur, K.N. Lewis, L. Peshkin, N.L. Price, N. Labinskyy, W.R. Swindell, D. Kamara, R.K. Minor, E. Perez, Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span, Cell Metab. 8 (2008) 157–168.
[77] R.A. Miller, D.E. Harrison, C. Astle, J.A. Baur, A.R. Boyd, R. de Cabo, E. Fernandez, K. Flurkey, M.A. Javors, J.F. Nelson, Rapamycin, but not resveratrol or simvastatin, extends life span of genetically heterogeneous mice, J. Gerontol. A: Biol. Med. Sci. (2010) glq178.
[78] R. Strong, R.A. Miller, C.M. Astle, J.A. Baur, R. de Cabo, E. Fernandez, W. Guo, M. Javors, J.L. Kirkland, J.F. Nelson, Evaluation of resveratrol, green tea extract, curcumin, oxaloacetic acid, and medium-chain triglyceride oil on life span of genetically heterogeneous mice, J. Gerontol. A: Biol. Med. Sci. 68 (2013) 6–16.
[79] P.L. da Luz, L. Tanaka, P.C. Brum, P.M.M. Dourado, D. Favarato, J.E. Krieger, F.R.M. Laurindo, Red wine and equivalent oral pharmacological doses of resveratrol delay vascular aging but do not extend life span in rats, Atherosclerosis 224 (2012) 136–142.
[80] J.A. Baur, K.J. Pearson, N.L. Price, H.A. Jamieson, C. Lerin, A. Kalra, V.V. Prabhu, J.S. Allard, G. Lopez-Lluch, K. Lewis, Resveratrol improves health and survival of mice on a high-calorie diet, Nature 444 (2006) 337–342.
[81] P. Oberdoerffer, S. Michan, M. McVay, R. Mostoslavsky, J. Vann, S.K. Park, A. Hartlerode, J. Stegmuller, A. Hafner, P. Loerch, S.M. Wright, K.D. Mills, A. Bonni, B.A. Yankner, R. Scully, T.A. Prolla, F.W. Alt, D.A. Sinclair, SIRT1 redistribution on chromatin promotes genomic stability but alters gene expression during aging, Cell 135 (2008) 907–918.
[82] J.M. Oliveira Andrade, A.F. Paraíso, M.V. Macedo de Oliveira, A.M.E. de Barros Lima Martins, J.F. Rodrigues Neto, A.L. Sena Guimarães, A.M. Batista de Paula, M. Qureshi, S.H. Sousa Santos, Resveratrol attenuates hepatic steatosis in high-fat fed mice by decreasing lipogenesis and inflammation, Nutrition 30 (7–8) (2014) 915–919. http://dx.doi.org/10.1016/j.nut.2013.11.016.
[83] B. Wang, J. Sun, Y. Ma, G. Wu, Y. Tian, Y. Shi, G. Le, Resveratrol preserves mitochondrial function, stimulates mitochondrial biogenesis, and attenuates oxidative stress in regulatory t cells of mice fed a high-fat diet, J. Food Sci. 79 (9) (2014) H1823–H1831. http://dx.doi.org/10.1111/1750-3841.12555.
[84] Y. Jimenez-Gomez, J.A. Mattison, K.J. Pearson, A. Martin-Montalvo, H.H. Palacios, A.M. Sossong, T.M. Ward, C.M. Younts, K. Lewis, J.S. Allard, D.L. Longo, J.P. Belman, M.M. Malagon, P. Navas, M. Sanghvi, R. Moaddel, E.M. Tilmont, R.L. Herbert, C.H. Morrell, J.M. Egan, J.A. Baur, L. Ferrucci, J.S. Bogan, M. Bernier, R. de Cabo, Resveratrol improves adipose insulin signaling and reduces the inflammatory response in adipose tissue of rhesus monkeys on high-fat, high-sugar diet, Cell Metab. 18 (2013) 533–545.
[85] J.A. Mattison, M. Wang, M. Bernier, J. Zhang, S.S. Park, S. Maudsley, S.S. An, L. Santhanam, B. Martin, S. Faulkner, C. Morrell, J.A. Baur, L. Peshkin, D. Sosnowska, A. Csiszar, R.L. Herbert, E.M. Tilmont, Z. Ungvari, K.J. Pearson, E.G. Lakatta, R. de Cabo, Resveratrol prevents high fat/sucrose diet-induced central arterial wall inflammation and stiffening in nonhuman primates, Cell Metab. 20 (2014) 183–190.
[86] S. Timmers, E. Konings, L. Bilet, R.H. Houtkooper, T. van de Weijer, G.H. Goossens, J. Hoeks, S. van der Krieken, D. Ryu, S. Kersten, Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans, Cell Metab. 14 (2011) 612–622.
[87] M.M. Poulsen, P.F. Vestergaard, B.F. Clasen, Y. Radko, L.P. Christensen, H. Stodkilde-Jorgensen, N. Moller, N. Jessen, S.B. Pedersen, J.O. Jorgensen, High-dose resveratrol supplementation in obese men: an investigator-initiated, randomized, placebo-controlled clinical trial of substrate metabolism, insulin sensitivity, and body composition, Diabetes 62 (2013) 1186–1195.
[88] M.J. Ornstrup, T. Harslof, T.N. Kjaer, B.L. Langdahl, S.B. Pedersen, Resveratrol increases bone mineral density and bone alkaline phosphatase in obese men: a randomized placebo-controlled trial, J. Clin. Endocrinol. Metab. (2014) jc20142799.
[89] P. Brasnyó, G.A. Molnár, M. Mohás, L. Markó, B. Laczy, J. Cseh, E. Mikolás, I.A. Szijártó, A. Mérei, R. Halmai, Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients, Br. J. Nutr. 106 (2011) 383–389.
[90] F. Faghihzadeh, P. Adibi, R. Rafiei, A. Hekmatdoost, Resveratrol supplementation improves inflammatory biomarkers in patients with nonalcoholic fatty liver disease, Nutr. Res. 34 (10) (2014) 837–843. http://dx.doi.org/10.1016/j.nutres.2014.09.005.
[91] V.S. Chachay, G.A. Macdonald, J.H. Martin, J.P. Whitehead, T.M. O'Moore-Sullivan, P. Lee, M. Franklin, K. Klein, P.J. Taylor, M. Ferguson, J.S. Coombes, G.P. Thomas, G.J. Cowin, C.M. Kirkpatrick, J.B. Prins, I.J. Hickman, Resveratrol does not benefit patients with nonalcoholic fatty liver disease, Clin. Gastroenterol. Hepatol. 12 (12) (2014) 2092–2103.e1-6. http://dx.doi.org/10.1016/j.cgh.2014.02.024.
[92] F.K. Knop, E. Konings, S. Timmers, P. Schrauwen, J.J. Holst, E.E. Blaak, Thirty days of resveratrol supplementation does not affect postprandial incretin hormone responses, but suppresses postprandial glucagon in obese subjects, Diabet. Med. 30 (2013) 1214–1218.

[93] L. Song, L. Chen, X. Zhang, J. Li, W. Le, Resveratrol ameliorates motor neuron degeneration and improves survival in SOD1 G93A mouse model of amyotrophic lateral sclerosis, BioMed Res. Int. 2014 (2014).
[94] R. Mancuso, J. del Valle, L. Modol, A. Martinez, A.B. Granado-Serrano, O. Ramirez-Núñez, M. Pallás, M. Portero-Otin, R. Osta, X. Navarro, Resveratrol improves motoneuron function and extends survival in SOD1G93A ALS mice, Neurotherapeutics 11 (2014) 419–432.
[95] D. Porquet, G. Casadesús, S. Bayod, A. Vicente, A.M. Canudas, J. Vilaplana, C. Pelegrí, C. Sanfeliu, A. Camins, M. Pallàs, Dietary resveratrol prevents Alzheimer's markers and increases life span in SAMP8, Age 35 (2013) 1851–1865.
[96] E. Gerhardt, S. Gräber, É.M. Szegő, N. Moisoi, L.M. Martins, T.F. Outeiro, P. Kermer, Idebenone and resveratrol extend lifespan and improve motor function of HtrA2 knockout mice, PLoS One 6 (2011) e28855.
[97] S. Rimbaud, M. Ruiz, J. Piquereau, P. Mateo, D. Fortin, V. Veksler, A. Garnier, R. Ventura-Clapier, Resveratrol improves survival, hemodynamics and energetics in a rat model of hypertension leading to heart failure, PLoS One 6 (2011) e26391.
[98] J.C. Klink, A.K. Tewari, E.M. Masko, J. Antonelli, P.G. Febbo, P. Cohen, M.W. Dewhirst, S.V. Pizzo, S.J. Freedland, Resveratrol worsens survival in SCID mice with prostate cancer xenografts in a cell-line specific manner, through paradoxical effects on oncogenic pathways, Prostate 73 (2013) 754–762.
[99] P.R. Avila, S.O. Marques, T.F. Luciano, M.F. Vitto, J. Engelmann, D.R. Souza, S.V. Pereira, R.A. Pinho, F.S. Lira, C.T. De Souza, Resveratrol and fish oil reduce catecholamine-induced mortality in obese rats: role of oxidative stress in the myocardium and aorta, Br. J. Nutr. 110 (2013) 1580–1590.
[100] H. Sebai, M. Sani, N. Ghanem-Boughanmi, E. Aouani, Prevention of lipopolysaccharide-induced mouse lethality by resveratrol, Food Chem. Toxicol. 48 (2010) 1543–1549.
[101] J.H. Holthoff, Z. Wang, K.A. Seely, N. Gokden, P.R. Mayeux, Resveratrol improves renal microcirculation, protects the tubular epithelium, and prolongs survival in a mouse model of sepsis-induced acute kidney injury, Kidney Int. 81 (2011) 370–378.
[102] J.L. Barger, T. Kayo, J.M. Vann, E.B. Arias, J. Wang, T.A. Hacker, Y. Wang, D. Raederstorff, J.D. Morrow, C. Leeuwenburgh, A low dose of dietary resveratrol partially mimics caloric restriction and retards aging parameters in mice, PLoS One 3 (2008) e2264.
[103] J. Marchal, S. Blanc, J. Epelbaum, F. Aujard, F. Pifferi, Effects of chronic calorie restriction or dietary resveratrol supplementation on insulin sensitivity markers in a primate, *Microcebus murinus*, PLoS One 7 (2012) e34289.
[104] J.K. Bhatt, S. Thomas, M.J. Nanjan, Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus, Nutr. Res. 32 (2012) 537–541.
[105] J. Tome-Carneiro, M. Larrosa, M.J. Yanez-Gascon, A. Davalos, J. Gil-Zamorano, M. Gonzalvez, F.J. Garcia-Almagro, J.A. Ruiz Ros, F.A. Tomas-Barberan, J.C. Espin, M.T. Garcia-Conesa, One-year supplementation with a grape extract containing resveratrol modulates inflammatory-related microRNAs and cytokines expression in peripheral blood mononuclear cells of type 2 diabetes and hypertensive patients with coronary artery disease, Pharmacol. Res. 72 (2013) 69–82.
[106] L.M. Howells, D.P. Berry, P.J. Elliott, E.W. Jacobson, E. Hoffmann, B. Hegarty, K. Brown, W. Steward, A.J. Gescher, Phase I randomized, double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases—safety, pharmacokinetics, and pharmacodynamics, Cancer Prev. Res. 4 (2011) 1419–1425.
[107] P. Marambaud, H. Zhao, P. Davies, Resveratrol promotes clearance of Alzheimer's disease amyloid-beta peptides, J. Biol. Chem. 280 (2005) 37377–37382.
[108] S.S. Karuppagounder, J.T. Pinto, H. Xu, H.L. Chen, M.F. Beal, G.E. Gibson, Dietary supplementation with resveratrol reduces plaque pathology in a transgenic model of Alzheimer's disease, Neurochem. Int. 54 (2009) 111–118.
[109] J.M. Smoliga, J.A. Baur, H.A. Hausenblas, Resveratrol and health—a comprehensive review of human clinical trials, Mol. Nutr. Food Res. 55 (2011) 1129–1141.
[110] C.R. Ku, H.J. Lee, S.K. Kim, E.Y. Lee, M.K. Lee, E.J. Lee, Resveratrol prevents streptozotocin-induced diabetes by inhibiting the apoptosis of pancreatic beta-cell and the cleavage of poly(ADP-ribose) polymerase, Endocr. J. 59 (2012) 103–109.
[111] J.L. Fiori, Y.K. Shin, W. Kim, S.M. Krzysik-Walker, I. Gonzalez-Mariscal, O.D. Carlson, M. Sanghvi, R. Moaddel, K. Farhang, S.K. Gadkaree, M.E. Doyle, K.J. Pearson, J.A. Mattison, R. de Cabo, J.M. Egan, Resveratrol prevents beta-cell dedifferentiation in nonhuman primates given a high-fat/high-sugar diet, Diabetes 62 (2013) 3500–3513.
[112] D.W. Park, J.S. Kim, B.R. Chin, S.H. Baek, Resveratrol inhibits inflammation induced by heat-killed *Listeria monocytogenes*, J. Med. Food 15 (2012) 788–794.
[113] N. Elmali, O. Baysal, A. Harma, I. Esenkaya, B. Mizrak, Effects of resveratrol in inflammatory arthritis, Inflammation 30 (2007) 1–6.
[114] J.M. Wu, T.C. Hsieh, Resveratrol: a cardioprotective substance, Ann. N. Y. Acad. Sci. 1215 (2011) 16–21.
[115] J. Yoshino, C. Conte, L. Fontana, B. Mittendorfer, S. Imai, K.B. Schechtman, C. Gu, I. Kunz, F. Rossi Fanelli, B.W. Patterson, S. Klein, Resveratrol supplementation does not improve metabolic function in nonobese women with normal glucose tolerance, Cell Metab. 16 (2012) 658–664.
[116] G. Block, C.D. Jensen, E.P. Norkus, T.B. Dalvi, L.G. Wong, J.F. McManus, M.L. Hudes, Usage patterns, health, and nutritional status of long-term multiple dietary supplement users: a cross-sectional study, Nutr. J. 6 (2007) 30.
[117] M. Pacholec, J.E. Bleasdale, B. Chrunyk, D. Cunningham, D. Flynn, R.S. Garofalo, D. Griffith, M. Griffor, P. Loulakis, B. Pabst, SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of SIRT1, J. Biol. Chem. 285 (2010) 8340–8351.
[118] J.H. Chung, Metabolic benefits of inhibiting cAMP-PDEs with resveratrol, Adipocyte 1 (2012) 256–258.
[119] C. Yu, Y.G. Shin, J.W. Kosmeder, J.M. Pezzuto, R.B. van Breemen, Liquid chromatography/tandem mass spectrometric determination of inhibition of human cytochrome P450 isozymes by resveratrol and resveratrol-3-sulfate, Rapid Commun. Mass Spectrom. 17 (2003) 307–313.
[120] B. Piver, F. Berthou, Y. Dreano, D. Lucas, Inhibition of CYP3A, CYP1A and CYP2E1 activities by resveratrol and other non volatile red wine components, Toxicol. Lett. 125 (2001) 83–91.
[121] H.P. Ciolino, P.J. Daschner, G.C. Yeh, Resveratrol inhibits transcription of CYP1A1 in vitro by preventing activation of the aryl hydrocarbon receptor, Cancer Res. 58 (1998) 5707–5712.
[122] J.B. Cai, Z.H. Zhang, D.J. Xu, Z.Y. Qian, Z.R. Wang, Y.Z. Huang, J.G. Zou, K.J. Cao, Negative regulation of quinone reductase 2 by resveratrol in cultured vascular smooth muscle cells, Clin. Exp. Pharmacol. Physiol. 35 (2008) 1419–1425.
[123] M. Murias, N. Handler, T. Erker, K. Pleban, G. Ecker, P. Saiko, T. Szekeres, W. Jager, Resveratrol analogues as selective cyclooxygenase-2 inhibitors: synthesis and structure–activity relationship, Bioorg. Med. Chem. 12 (2004) 5571–5578.
[124] R.S. Haworth, M. Avkiran, Inhibition of protein kinase D by resveratrol, Biochem. Pharmacol. 62 (2001) 1647–1651.
[125] S.M. Armour, J.A. Baur, S.N. Hsieh, A. Land-Bracha, S.M. Thomas, D.A. Sinclair, Inhibition of mammalian S6 kinase by resveratrol suppresses autophagy, Aging (Albany NY) 1 (2009) 515–528.
[126] D.W. Lamming, J.G. Wood, D.A. Sinclair, Small molecules that regulate lifespan: evidence for xenohormesis, Mol. Microbiol. 53 (2004) 1003–1009.
[127] K.T. Howitz, D.A. Sinclair, Xenohormesis: sensing the chemical cues of other species, Cell 133 (2008) 387–391.
[128] D.M. Goldberg, J. Yan, G.J. Soleas, Absorption of three wine-related polyphenols in three different matrices by healthy subjects, Clin. Biochem. 36 (2003) 79–87.
[129] P. Gresele, P. Pignatelli, G. Guglielmini, R. Carnevale, A.M. Mezzasoma, A. Ghiselli, S. Momi, F. Violi, Resveratrol, at concentrations attainable with moderate wine consumption, stimulates human platelet nitric oxide production, J. Nutr. 138 (2008) 1602–1608.
[130] H.H. Chow, L.L. Garland, C.H. Hsu, D.R. Vining, W.M. Chew, J.A. Miller, M. Perloff, J.A. Crowell, D.S. Alberts, Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study, Cancer Prev. Res. (Phila.) 3 (2010) 1168–1175.
[131] J.F. Marier, P. Vachon, A. Gritsas, J. Zhang, J.P. Moreau, M.P. Ducharme, Metabolism and disposition of resveratrol in rats: extent of absorption, glucuronidation, and enterohepatic recirculation evidenced by a linked-rat model, J. Pharmacol. Exp. Ther. 302 (2002) 369–373.
[132] D.J. Boocock, G.E. Faust, K.R. Patel, A.M. Schinas, V.A. Brown, M.P. Ducharme, T.D. Booth, J.A. Crowell, M. Perloff, A.J. Gescher, W.P. Steward, D.E. Brenner, Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent, Cancer Epidemiol. Biomarkers Prev. 16 (2007) 1246–1252.
[133] K.R. Patel, C. Andreadi, R.G. Britton, E. Horner-Glister, A. Karmokar, S. Sale, V.A. Brown, D.E. Brenner, R. Singh, W.P. Steward, Sulfate metabolites provide an intracellular pool for resveratrol generation and induce autophagy with senescence, Sci. Transl. Med. 5 (2013) (205ra133-205ra133).
[134] L.M. Bode, D. Bunzel, M. Huch, G.-S. Cho, D. Ruhland, M. Bunzel, A. Bub, C.M. Franz, S.E. Kulling, In vivo and in vitro metabolism of *trans*-resveratrol by human gut microbiota, Am. J. Clin. Nutr. 97 (2013) 295–309.
[135] M. Vaz-da-Silva, A. Loureiro, A. Falcao, T. Nunes, J. Rocha, C. Fernandes-Lopes, E. Soares, L. Wright, L. Almeida, P. Soares-da-Silva, Effect of food on the pharmacokinetic profile of trans-resveratrol, Int. J. Clin. Pharmacol. Ther. 46 (2008) 564–570.
[136] L. Almeida, M. Vaz-da-Silva, A. Falcão, E. Soares, R. Costa, A.I. Loureiro, C. Fernandes-Lopes, J.F. Rocha, T. Nunes, L. Wright, Pharmacokinetic and safety profile of *trans*-resveratrol in a rising multiple-dose study in healthy volunteers, Mol. Nutr. Food Res. 53 (2009) S7–S15.
[137] C. la Porte, N. Voduc, G. Zhang, I. Seguin, D. Tardiff, N. Singhal, D.W. Cameron, Steady-state pharmacokinetics and tolerability of *trans*-resveratrol 2000 mg twice daily with food, quercetin and alcohol (ethanol) in healthy human subjects, Clin. Pharmacokinet. 49 (2010) 449–454.
[138] K.R. Patel, V.A. Brown, D.J. Jones, R.G. Britton, D. Hemingway, A.S. Miller, K.P. West, T.D. Booth, M. Perloff, J.A. Crowell, D.E. Brenner, W.P. Steward, A.J. Gescher, K. Brown, Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients, Cancer Res. 70 (2010) 7392–7399.
[139] J.A. Crowell, P.J. Korytko, R.L. Morrissey, T.D. Booth, B.S. Levine, Resveratrol-associated renal toxicity, Toxicol. Sci. 82 (2004) 614–619.
[140] M. Athar, J.H. Back, X. Tang, K.H. Kim, L. Kopelovich, D.R. Bickers, A.L. Kim, Resveratrol: a review of preclinical studies for human cancer prevention, Toxicol. Appl. Pharmacol. 224 (2007) 274–283.
[141] L.M. Howells, D.P. Berry, P.J. Elliott, E.W. Jacobson, E. Hoffmann, B. Hegarty, K. Brown, W.P. Steward, A.J. Gescher, Phase I randomized, double-blind pilot study of micronized resveratrol (SRT501) in patients with hepatic metastases—safety, pharmacokinetics, and pharmacodynamics, Cancer Prev. Res. (Phila.) 4 (2011) 1419–1425.
[142] J.L. Bowers, V.V. Tyulmenkov, S.C. Jernigan, C.M. Klinge, Resveratrol acts as a mixed agonist/antagonist for estrogen receptors alpha and beta, Endocrinology 141 (2000) 3657–3667.
[143] E. Brakenhielm, R. Cao, Y. Cao, Suppression of angiogenesis, tumor growth, and wound healing by resveratrol, a natural compound in red wine and grapes, FASEB J. 15 (2001) 1798–1800.
[144] S. Leone, E. Basso, F. Polticelli, R. Cozzi, Resveratrol acts as a topoisomerase II poison in human glioma cells, Int. J. Cancer 131 (2012) E173–E178.
[145] M. Paolini, A. Sapone, L. Valgimigli, Avoidance of bioflavonoid supplements during pregnancy: a pathway to infant leukemia? Mutat. Res. 527 (2003) 99–101.
[146] P.J. Elliott, M. Jirousek, Sirtuins: novel targets for metabolic disease, Curr. Opin. Investig. Drugs 9 (2008) 371–378.
[147] H. Yang, J.A. Baur, A. Chen, C. Miller, D.A. Sinclair, Design and Synthesis of Compounds That Extend Yeast Replicative Lifespan, Aging Cell 6 (2007) 35–43.

[148] V.M. Nayagam, X. Wang, Y.C. Tan, A. Poulsen, K.C. Goh, T. Ng, H. Wang, H.Y. Song, B. Ni, M. Entzeroth, W. Stunkel, SIRT1 modulating compounds from high-throughput screening as anti-inflammatory and insulin-sensitizing agents, J. Biomol. Screen. 11 (2006) 959–967.
[149] L.B. Gano, A.J. Donato, H.M. Pasha, C.M. Hearon Jr., A.L. Sindler, D.R. Seals, The SIRT1 activator SRT1720 reverses vascular endothelial dysfunction, excessive superoxide production and inflammation with aging in mice, Am. J. Physiol. Heart Circ. Physiol. 307 (12) (2014) H1754–H1763. http://dx.doi.org/10.1152/ajpheart.00377 (ajpheart 00377 02014).
[150] C. Gueguen, B. Palmier, M. Plotkine, C. Marchand-Leroux, V.C. Bessson, Neurological and histological consequences induced by in vivo cerebral oxidative stress: evidence for beneficial effects of SRT1720, a sirtuin 1 activator, and sirtuin 1-mediated neuroprotective effects of poly(ADP-ribose) polymerase inhibition, PLoS One 9 (2014) e87367.
[151] R.K. Minor, J.A. Baur, A.P. Gomes, T.M. Ward, A. Csiszar, E.M. Mercken, K. Abdelmohsen, Y.-K. Shin, C. Canto, M. Scheibye-Knudsen, SRT1720 improves survival and healthspan of obese mice, Sci. Rep. 1 (2011).
[152] S.J. Mitchell, A. Martin-Montalvo, E.M. Mercken, H.H. Palacios, T.M. Ward, G. Abulwerdi, R.K. Minor, G.P. Vlasuk, J.L. Ellis, D.A. Sinclair, The SIRT1 Activator SRT1720 extends lifespan and improves health of mice fed a standard diet, Cell Rep. 6 (2014) 836–843.
[153] E.M. Mercken, S.J. Mitchell, A. Martin-Montalvo, R.K. Minor, M. Almeida, A.P. Gomes, M. Scheibye-Knudsen, H.H. Palacios, J.J. Licata, Y. Zhang, SRT2104 extends survival of male mice on a standard diet and preserves bone and muscle mass, Aging Cell 13 (2014) 787–796.
[154] V. Libri, A.P. Brown, G. Gambarota, J. Haddad, G.S. Shields, H. Dawes, D.J. Pinato, E. Hoffman, P.J. Elliot, G.P. Vlasuk, E. Jacobson, M.R. Wilkins, P.M. Matthews, A pilot randomized, placebo controlled, double blind phase I trial of the novel SIRT1 activator SRT2104 in elderly volunteers, PLoS One 7 (2012) e51395.
[155] E. Hoffmann, J. Wald, S. Lavu, J. Roberts, C. Beaumont, J. Haddad, P. Elliott, C. Westphal, E. Jacobson, Pharmacokinetics and tolerability of SRT2104, a first-in-class small molecule activator of SIRT1, after single and repeated oral administration in man, Br. J. Clin. Pharmacol. 75 (2013) 186–196.
[156] M. Viswanathan, S.K. Kim, A. Berdichevsky, L. Guarente, A role for SIR-2.1 regulation of ER stress response genes in determining *C. elegans* life span, Dev. Cell 9 (2005) 605–615.
[157] J.H. Bauer, S. Goupil, G.B. Garber, S.L. Helfand, An accelerated assay for the identification of lifespan-extending interventions in *Drosophila melanogaster*, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 12980–12985.
[158] L.G. Carter, J.A. D'Orazio, K.J. Pearson, Resveratrol and cancer: focus on in vivo evidence, Endocr. Relat. Cancer 21 (3) (2014) R209–R225. http://dx.doi.org/10.1530/ERC-13-0171.
[159] T. Walle, Bioavailability of resveratrol, Ann N Y Acad Sci. 1215 (2011) 9–15. http://dx.doi.org/10.1111/j.1749-6632.2010.05842.x.