Chapter 6

Resveratrol and SIRT1 Activators for the Treatment of Aging and Age-Related Diseases

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Abstract

Reduced calorie intake is a religious and medical practice known since very old times, but its direct influence on life span in all organisms, included humans, has been demonstrated in the modern era. Not only periodic fasting, but also natural or synthetic compounds that mimic this phenomenon are growing to slow aging and the onset of chronic morbidities. Resveratrol (RSV), a plant polyphenol, is an elixir of longevity for simple organisms and preclinical rodent models even if a beneficial role in humans is still debated. Its main rejuvenating mechanism copes with the activation of specific longevity genes called sirtuins. Among seven known mammalian sirtuins, sirtuin 1 is the most studied. This pleiotropic nicotinamide adenine dinucleotide (NAD)-based deacetylase maintains longevity by removing acetyl group in nuclear histones, transcription factors, and other DNA repairing proteins. Actually, an exciting challenge is to discover and test novel sirtuin 1 activators to extend life span and to treat age-associated disabilities. This chapter updates on the antiaging effect of RSV and sirtuin 1 activators in experimental animals and in humans. Finally, pros and cons on RSV analogues and sirtuin 1 activators tested in preclinical and clinical trials to hamper neurological deficit, cardiovascular complications, diabetes, bone and muscle deterioration, and cancer are discussed.

Keywords: sirtuin 1, resveratrol, aging, neurodegeneration, diabetes, myopathy

1. Introduction

The increase in average life expectancy is a global consequence of sanitary welfare, proper nutrition, and healthy life style [1, 2], but unfortunately, longevity is linked to the onset of chronic irreversible diseases like neurological decline, cardiovascular damage, bone and muscle frailty, diabetes, and metabolic diseases with high economic and social costs [3–5]. Specific international clinical objectives are to maintain a "healthy aging" defined by World Health Organization (WHO) as the "functional ability that enables wellbeing in old age" by firstly preserving the quality of life together with its duration [6, 7]. Besides unchangeable genetic background, in this context, great credit is due to the quality but also the quantity of dietary nutrients [8–10].

Historically, since fifth century BC, the famous Greek physician Hippocrates declared that fasting was the best practice to block sickness progression, and, on the contrary, too much feeding gave rise to a disease. This old and simple medical concept, i.e., caloric restriction without malnutrition, has maintained for centuries but without a direct impact on life extension. Only in modern times since early 1930s, a pioneering Mc Cay discovery confirmed that undernutrition caused prolonged life span in laboratory rats [11]. By 2000s, Longo and coworkers systematically studied dietary restriction as a therapy for slowing aging and related diseases in human settings [12–15]. Periodic reduction of dietary calorie intake or an intermittent fasting, under medical control, appears alternative tools to pharmacology to delay the onset of aging comorbidities, like metabolic diseases, and to improve health outcomes [16–19]. "Geroscience," a definition coined by Burch et al. [20], identifies the branch of aging biology aimed to reduce human frailty and the impact of associated chronic diseases. However, considering the difference in the duration of life between lower organisms versus humans, to fill this gap, caloric limitation has been used also in nonhuman primates like monkeys. Anyway, significant translational value has been attributed to dietary studies in short-life animals versus nonhuman primates and humans that enhanced their life span under reduced nutrients intake.

This chapter is focused on a natural dietary polyphenol, resveratrol (RSV), able to mimic calorie restriction and to prolong life duration in simple organisms and experimental animal models, but controversial in humans [21, 22]. RSV has been firstly identified as a modulator of conserved survival genes family called sirtuins [23]. Sirtuins, crucial modulators of life span extension and metabolism, have been firstly discovered by Guarente team as product of silent information regulator 2 (Sir 2) gene in yeast, *Saccharomyces cerevisiae* [24], worm, *Caenorhabditis elegans*, and fly fruit, *Drosophila melanogaster* [25]. In mammals, among seven known members, sirtuin 1 (SIRT1) enzyme was most beneficial against aging by mimicking calorie reduction [26, 27]. Moreover, other natural or synthetic compounds, more effective than RSV, like stimulate molecular longevity pathways via SIRT1 or pan-sirtuin activation, are currently under study [28–30]. Therefore, here major attention has been focused on newest preclinical experimental studies on laboratory animals, mainly rodents, and clinical trials based on RSV and other SIRT1 activators published over last 10 years. Due to the impressive wide scientific literature on longevity, we select only more recent articles or reviews and apologize in advance for unintentional omissions. We believe that a primary scope of this chapter is to steer readers, even if not expert in the field, to study in detail if interested, the newest antiaging therapeutic perspectives. Intriguingly, we stressed on the role of SIRT1 activators in cancer but a dichotomy exists based on specific type of cancer and clinical outcome. Indeed, SIRT1 activators (STACs) that will promote benefits in selected tumors may obtain opposite detrimental effects in others. Therefore, to date, particular caution must be taken in the pharmacological use of SIRT1 modulators in oncology. So best understanding on SIRT1 activation and maintenance by specific modulators is essential to fight age-derived inevitable disorders.

2. Sirtuin 1 history

The history of sirtuin family (silent information regulator 2—Sir 2) as antiaging proteins started in yeast, *Saccharomyces cerevisiae*, where they prolonged life span and regulated the number of replications from a mother cell [31]. Later, it was demonstrated in yeast that Sir 2 was further able to block the formation of extrachromosomal DNA linked to aging and genetic "toxicity." Indeed, an excess of Sir 2 gene ameliorated reproductive cycle and sustained longevity in yeast budding [32]. Moreover, sirtuins were able to influence longevity in other lower organisms like worms, *Caenorhabditis elegans* [33], and dose-dependently in fruit fly, *Drosophila melanogaster* [34, 35]. Guarente team in 2000 demonstrated that the main action of sirtuins was to remove, as deacetylase enzymes, acetyl groups from specific lysine sites in nuclear histones, so allowing DNA silencing and chromosome stability [36]. This peculiar role is basic for an epigenetic regulation of DNA and telomere health and stabilization. Besides on class III DNA histones, sirtuin deacetylation activity has been extended to a plethora of other nonhistone proteins, transcription factors, and cytoplasmic proteins, which, by this posttranslational event, changed their structure and consequently function or signaling [37]. Recently, sirtuins have been considered not only deacetylases but also able to perform other posttranslational changes in their targets and for this reason defined "deacylases" [38]. Moreover, for their enzymatic activity, sirtuins used nicotinamide dinucleotide (NAD+) as a specific substrate, so their role has been related to NAD+ availability in the cell and to the NAD+/NADH ratio. In particular, it is known that during dietary caloric limitation and regular physical exercise, abundant NAD+ is produced and sirtuins are more active. There are two different ways to produce NAD+: one *ex novo* and another by conversion of nicotinamide (NAM) into nicotinamide mononucleotide (NMN) then charged with adenine nucleotide to become NAD. For vertebrates, the limiting enzyme necessary for the final step in the NAD synthesis is nicotinamide phosphoribosyltransferase (NAMPT) that is regulated by circadian rhythm regulator and clock genes (CLOCK and BMALI) [39]. The strict connection between NAD+ availability and sirtuin activity has been recently demonstrated and implied that competition for NAD+ substrate by different enzymes may affect sirtuin level, so contributing to age-associated diseases in mice [40–42]. In particular, NAMPT-mediated NAD synthesis is associated to the transcription of circadian-regulated genes and sirtuin in metabolically active tissues [43]. However, another crucial step in the long sirtuin history was the characterization of mammalian sirtuins, seven different isoforms (sirtuin 1–7) [44]. SIRT1 is the most studied nuclear member, pleiotropic transcriptional factor that drives many cellular activities, like energy metabolism, cell survival, DNA stability, inflammation, and circadian rhythms [45, 46]. SIRT1 is involved not only in deacetylation of a specific histone but in complex chemical reactions for different pathways involved in metabolism, like target of rapamycin (mTOR)

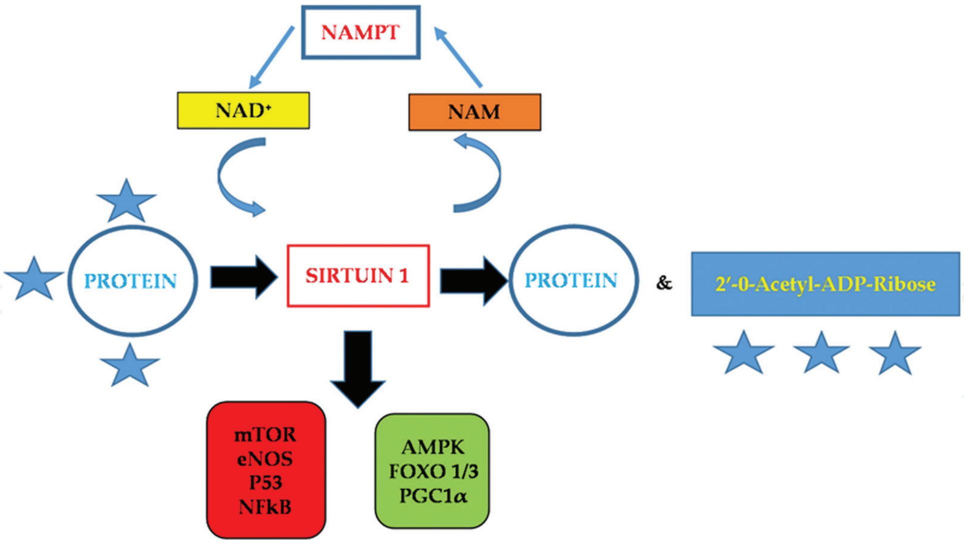

Figure 1. Sirtuin 1 deacetylase activity and its downstream substrates involved in longevity. The red square indicates the inhibited pathways and the green square the activated pathways. Stars indicate acetyl groups; (AMPK): 5′ AMP-activated protein kinase; (eNOS): endothelial nitric oxide synthase; (FOXO1/3): forkhead box protein O 1/3; (NAM): nicotinamide; (NAD$^+$): nicotinamide dinucleotide; (NAMPT): nicotinamide phosphoribosyltransferase; (NF-kB): nuclear factor k B; (p53): protein 53; (PGC1α): peroxisome proliferatoractivated receptor G coactivator 1α; (mTOR): mammalian target of rapamycin.

[47], insulin signaling [48], and forkhead box O (FOXO) [49] (**Figure 1**). Moreover, different mice overexpressing SIRT1 have been characterized that presented better metabolism, less inflammation, and cancer but a sex-dependent longevity (longer mean life span in males *vs* females) [50]. In these last 5 years, the involvement of SIRT1 in crucial cellular pathways has been demonstrated and the research of new drugs acting as SIRT1 modulators and relative patents exploded [28, 30, 51, 52]. A common intriguing idea is that if SIRT1 acts as a therapeutic target, specific drugs able to activate its signaling might be effective in specific age-related pathologies and in cancer. Herein, we resumed and discuss recent scientific data on SIRT1 modulators (STACs) and their potentiality assessed *in vivo*, in preclinical rodent models or in clinical settings.

3. Resveratrol and its derivatives as sirtuin 1 activators in aging

Since 2006 Sinclair's team in Harvard University reported that RSV, 3,5,4′-trihydroxystilbene, has a therapeutic potential to extend life span by miming caloric restriction to limit metabolic alterations in rodents in more than 140 genic pathways [23, 53]. RSV was added to the rodent diet at concentrations similar to human use (5.2 and 22.4 mg/kg/day) for 6 months. RSV was firstly isolated in late 1930s in leaves of white hellebore *Veratrum grandiflorum* and characterized as a phytoalexin [54], but later in 1990s, it was found in red wine and grapevines [55], in traditional herbs in Asia [56–58] in response to adverse conditions, in over 70 different plants and fruits like blueberry, raspberry, and mulberry [59]. Its first function was to reduce inflammation and to limit oxidant damage in cardiovascular diseases, the so-called “French paradox.” Intriguingly, the use of a glass of red wine reduced the extent of platelet aggregation and cardiovascular side effects in French people despite a high fat diet as reviewed in [60]. However, RSV is a photosensitive molecule, chemically composed by two aromatic rings linked by a methylene bridge, existing in two isomeric configurations, called *trans*-RSV and *cis*-RSV (**Figure 2**). Intriguingly, the most beneficial therapeutic properties are linked to *trans*-RSV even if, when exposed to light and high temperature, more than 80% of *trans*-RSV changes into *cis*-RSV with low solubility and stability [61].

Nevertheless, it has been calculated that more than 110 glasses of wine should be drunk to achieve an anticancer effect in humans [62]. Unfortunately, lipophilicity of RSV conditioned its bioavailability, low intestinal absorption, and rapid clearance from the plasma, making necessary a high dosage in preclinical and clinical trials [63, 64]. In humans, RSV was administered as a dose of 25 mg, then grew in the range from 25 to 1000 mg, up to 5 g daily for almost 1 month still well tolerated [65]. However, when administered in healthy volunteers in the morning, RSV bioavailability and pharmacokinetic ameliorated [66] and tolerability was maintained if associated with other drugs, like quercetin and alcohol [67]. To ameliorate half-life in the plasma, a modified version of RSV was produced, called Longevinex, able to prevent isomerization from *trans* to *cis* and it is rich of vitamin D3 (at a dose 1200 IU) and quercetin very effective in the metabolic syndrome [68] and cardiac health in mice [69]. Interestingly, also in humans, RSV mimicked caloric restriction [70] and attenuated obesogenic changes in the metabolic syndrome but had no effects under normal weight patients [71]. Herein, the RSV ability to sustain SIRT1 expression/activity is effective when the deacetylase is scarce, but unnecessary if SIRT1 level/activity is normal like in postmenopausal women with normal glucose tolerance or in slightly obese men and women (*trans*-RSV was taken at a dose 150 mg daily for 4 weeks) [72]. However, despite extensive data on efficacy of RSV in rodent preclinical trials, actually its beneficial role in humans is still debated, greatly depending

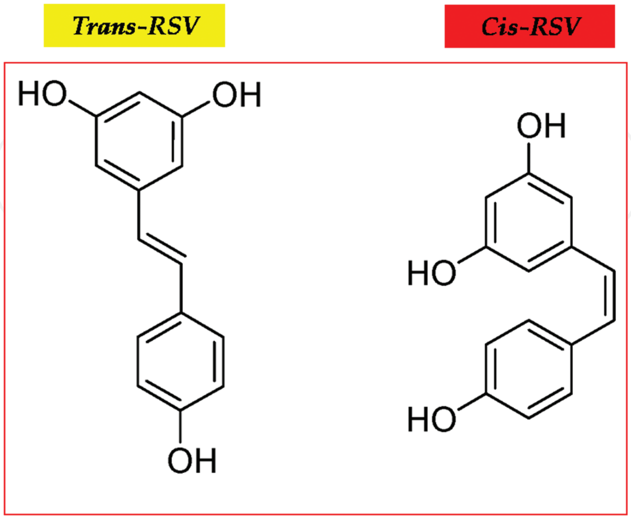

Figure 2. Resveratrol, 3′,5, 4′-trihydroxystilbene, isomers adapted from Nawaz et al. [78].

from doses and time of administration [73]. Antiaging properties of RSV via SIRT1 and mitochondrial health are addressed on amelioration of oxidative metabolism in crucial organs like heart and vessels, muscles, kidney but the mechanism is strictly cell-dependent [74–76]. Remarkably, at high doses, RSV has been reported to induce mild toxicity in humans where somnolence, headache, rash, and myalgia occurred [77]. Herein, to overcome these problems, in the past few years, different RSV derivatives have been synthesized *ex novo* by substituting hydroxyl with methoxy groups, so enhancing lipophilicity, or by adding a 4-hydroxy group in *trans*-RSV or a halogen group to potentiate the therapeutic efficacy [78], although different promising antimicrobial, antioxidant, and cardioprotective effects have been obtained *in vitro*. Moreover, to improve oral bioavailability of RSV-specific complexes with liposomes, lipid or synthetic nanoparticles have been made, even if they resulted with low therapeutic potential [79, 80]. In respiratory diseases reproduced in rodent like pulmonary hypertension, RSV ameliorates asthma and fibrosis via SIRT1 activation [81, 82] and also its derivative, trimethoxystilbene, demonstrated antioxidant and anti-inflammatory properties in rats exposed to hypoxia [83]. Recently, Bastin and Djouadi [84] reviewed RSV potentiality against mitochondrial damage and myopathies, and promising results in an animal model of a fatal genetic disease called Duchenne muscular dystrophy were reported. In dystrophic mice (mdx model), RSV supplementation (0.5% in the diet for 3 weeks) ameliorated muscle atrophy and prevented sciatic denervation signaling [85]. However, caution must be taken to extrapolate successful data obtained in animal models to humans where RSV might modulate different pathways in a dose-dependent manner. Autoimmune diseases represent an emerging type of chronic diseases often associated to aging that affect specific or multiple organs at the same time like rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and type I diabetes [86]. RSV inhibited transcription factors crucial in autoinflammation, like nuclear factor k B (NF-kB) [87], and curiously in these pathologies, stopped SIRT1 activity. Intriguingly, RSV behaves as a potent drug mainly in animal models, although actually poor patient outcome and reduced number of clinical trials made necessary further studies in humans to exclude side effects or competition with other drugs [88]. RSV has been tested successfully in neuronal inflammation, psychotic mice (up to 30 mg/kg/daily) [89, 90], depressed menopausal women (orally 25 mg/day for 12 weeks) [91], and in patients with minimal hepatic encephalopathy, a frequent complication of cirrhosis [92]. However, the oral dosing of RSV seemed to cross the blood-brain barrier but more potent polyphenols specifically addressed on brain with promising preventive and not only therapeutic properties are under research [93]. Moreover, RSV administered 48 h prior the induction of a subarachnoid hemorrhage activated SIRT1 thereby reducing mortality and improving neurological functions in rats [94]. Pterostilbene is a natural phenolic drug found in sandalwood and some fruits like grapes and blueberries that ameliorated neuronal aging and memory deficit in rats [95]. Chemically, it is a dimethylether analogue of RSV with better pharmacokinetic and oral bioavailability in rats (80% in comparison to 20% RSV) [96]. Recently, pterostilbene demonstrated better efficacy than RSV in the modulation of behavior and functional improving in SAMP8 mouse, a rodent model of accelerated aging validated to study Alzheimer’s disease [97]. Moreover, recent evidences indicated that pterostilbene worked well as cardioprotective and anti-inflammatory drug in rodents with ischemia-reperfusion [98]. However, both pterostilbene and RSV efficacy on aging and longevity have been reviewed recently by Li et al. [99], but conclusive data are lacking due to poor water solubility, low bioavailability, and rapid elimination (half-life only 9 h in humans), the main obstacles to work in clinical trials. However, different strategies have been also undertaken to optimize the delivery of RSV to strengthen its clinical utility: one strategy was to complex it to controlled release devices, another avenue was to use micronized powder (called SRT501) [100]. A crucial year in the history of RSV pharmacology was 1997 when Jang et al. [101] firstly reported an antitumoral effect *in vitro* and *in vivo* in a murine model of skin cancer. However, SIRT1 played a double opposite role in cancer linked to severity grade. Indeed, in early cancer phases, when cellular mutations are scarce, to activate SIRT1 is a good strategy, but in advanced stages with many mutations, SIRT1 may potentiate and accelerate oncogenesis, as demonstrated in breast cancer [102]. Remarkably, Li et al. [103] provided evidences that dietary RSV for 4–5 weeks reduced prostate neoplastic lesions by about 50% in mice through SIRT1-mediated autophagy. More recently in chondrosarcoma cells, xenografted in mice, RSV via SIRT1 stimulated apoptosis and decreased tumor growth [104].

4. Synthetic sirtuin 1 activators (STACs) in aging

RSV and natural polyphenols, like quercetin and butein, have been included into the first generation of SIRT1 activators (STACs). However, to overcome limitations in RSV pharmacology, its aspecific interaction with several sirtuins like human sirtuin 5 and the competition with SIRT1 for the catalytic site [105], Sinclair laboratory since 2000s produced novel synthetic STACs [28] to fight aging-associated disabilities. The screening of potential STACS began *in vitro* looking for more than 18,000 drugs and resulted in 21 compounds able to stimulate the catalytic site in SIRT1 deacetylase enzyme [106]. Using a fluorescence polarization assay verified by mass spectrometry, novel synthetic STACs were obtained but a strong scientific controversy occurred on the efficacy of different drugs on SIRT1 activation. To date, the research on synthetic STACs (came to the fifth generation) has produced more soluble and specific compounds [30] with an *in vitro* 1000-fold greater potency than RSV to mimic calorie restriction. Intriguingly, STACs extended life span in obese mice [107] but also in mice fed a standard diet. [108]. Interestingly, SRT2104 was able to preserve muscle mass, strength, and bone integrity in muscle-atrophy induced by hind limb suspension and fasting [109]. Moreover, also SRT1720 behaved as an effective SIRT1 agonist *in vivo* in two independent rodent models of osteoporosis, where after 1 month or 3 months of oral treatment, femoral bone mass grew about 30% [110]. These studies have great translational implications considering the high frequency of fractures in human osteoporosis. Oral administration of SRT3025 (50 or 100 mg/kg/day) for 6 weeks, starting 6 weeks after ovariectomy, successfully reversed scarcity of bone mass and osteoporosis in mice [111]. Remarkably, SRT1720 intraperitoneally injected daily in female obese mice for 6 weeks improved the vitality of follicles via sustained SIRT1 able to reduce atresia and the abnormal primordial follicles activation [112]. In human plasmacytoma xenografted mice, a model utilized to validate new therapies against multiple myeloma, oral treatment with SRT1720 (200 mg/kg) on five consecutive days/week schedule for 4 weeks reduced tumor growth in combination with other drugs, like bortezomib, potentiated antimyeloma effects [113]. Several STACS have been tested as SIRT1 modulators in preclinical rodent model to fight diabetes, obesity, neurodegeneration, atherosclerosis, bone and muscle mass [114], and most relevant diseases investigated in the preclinical trials have been resumed in **Figure 3**.

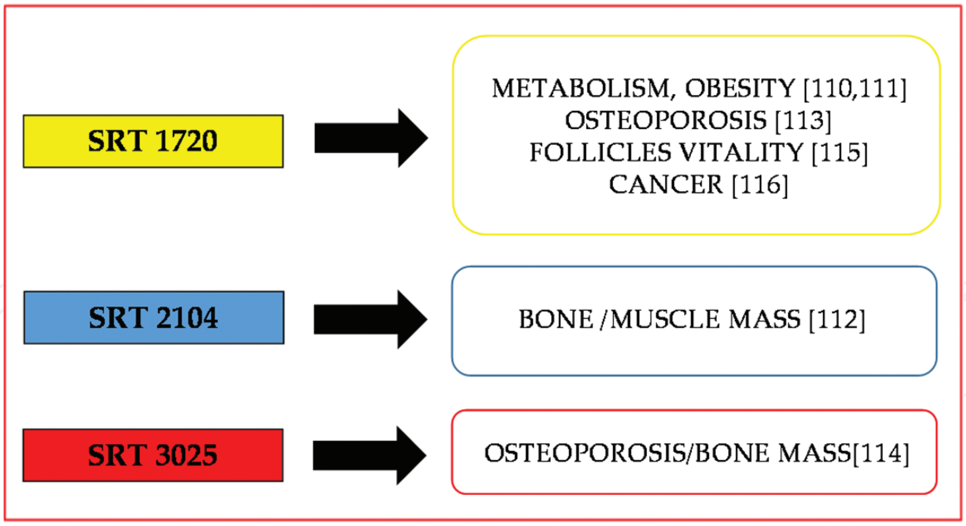

Figure 3. Synthetic SIRT1 activators (STACs) effective in rodent models.

Later, since 2012, an STAC phase I clinical trials started in humans [115]. SRT2104 in doses ranged from 0.03 to 3 g was well tolerated with a bioavailability about 14% in male and female volunteers. Remarkably, the same drug was also tested in elderly volunteers with no side effects [116]. In these last years, various human clinical trials with STACs have been started but to date the only ended with SRT2104 in patients with moderate to severe psoriasis demonstrated a promising efficacy [117]. Despite some encouraging evidences, in other clinical trials, SRT2104 administration for 28 days to diabetic patients (n = 15) was ineffective on insulin resistance and endothelial function but induced a striking weight reduction not observed in placebo [118]. Moreover, patients with mild to moderate ulcerative colitis were treated with SRT2104 at 50–500 mg daily for 8 weeks, and they not presented any clinical remission so the clinical trials stopped [119]. However, the times are ripe to start further clinical trials and to test novel STACs for longer times, hoping in new exciting results.

5. Recommendation

RSV, the main member of the first generation STACs, is not found in meat or dairy but is present in vegetables and herbs. Renisalo et al. [120] have indicated main sources of RSV in vegetables and seeds like cocoa, grape, hop, peanuts, pistachios, tomato, and berries. However, RSV is also present in common Asian herbs like *Polygonum cuspidatum*, known as Japanese knotweed. Its dried roots have been infused to produce “Itadori” tea, which means “well-being” in Japanese, a folk beverage largely used for the treatment of heart disease and stroke [59].

To date, pleiotropic effects of *trans*-RSV in degenerative and metabolic diseases in elderly are recognized, but despite a lot of evidences *in vitro* and in rodent model, their therapeutic role in humans is still debated. Firstly, its beneficial effect is strictly dose-dependent, and to potentiate mitochondria health, it is required at least an oral dose of RSV of 1 g/day in Alzheimer’s patients and generally from 0.5 g up to 5 g/day to reach a therapeutic level in plasma (5 μM) [121]. Furthermore, RSV efficacy is also time-dependent, and an oral daily intake for 2 months is effective in patients with angina pectoris only if *trans*-RSV (at 20 mg) is associated with calcium fructoborate [122]. Moreover, controversial RSV effects reported on nonalcoholic fatty liver (NAFLD) are probably linked to different oral doses (from 500 mg/day up to 3000 mg/day), time of administration (from 56 days up to 6 months), and number of patients considered in clinical trials [123]. On the contrary, promising results have been recently obtained on 119 patients with mild to moderate Alzheimer's disease orally supplemented with RSV at 1 g twice a day for 52 weeks, which presented reduced inflammatory markers in plasma and cerebrospinal fluid [124]. Herein, there is still a lot of research to do on the RSV and other STACs drug and caution must be taken to sustain their definitive clinical therapeutic effects in humans.

6. Conclusions

A constant effort has been made to synthesize novel drugs to extend life span, to prolong the quality of the life in elderly, and to limit age-associated diseases. Unfortunately, to date, there is no drug that could be an elixir of longevity for humans even if more than a hundred clinical trials on natural or synthetic SIRT1 activators are ongoing worldwide. However, there are still many challenges to discover and test the efficacy of antiaging drugs in clinics together with the necessity to get funds for a long time. The main final message from this chapter may be that a big scientific awareness is placed in the aging research, as indicated by the tremendous number of published articles on this topic. Indeed, all actors in the biogerontology scenario agree that not only the extension of the life is important in elderly, but it is fundamental its quality, maintaining a good health. To reach this aim, dietary intervention with caloric restriction mimetics is crucial, but remember to start early during adult age to best adapt your metabolism to counteract aging.

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Conflict of interest

Authors declare no conflict of interest.

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