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# Caloric restriction, resveratrol and melatonin: Role of SIRT1 and implications for aging and related-diseases

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ABSTRACT

Aging is an inevitable and multifactorial biological process. Free radicals have been implicated in aging processes; it is hypothesized that they cause cumulative oxidative damage to crucial macromolecules and are responsible for failure of multiple physiological mechanisms. However, recent investigations have also suggested that free radicals can act as modulators of several signaling pathways such as those related to sirtuins. Caloric restriction is a non-genetic manipulation that extends lifespan of several species and improves healthspan; the belief that many of these benefits are due to the induction of sirtuins has led to the search for sirtuin activators, especially sirtuin 1, the most studied. Resveratrol, a polyphenol found in red grapes, was first known for its antioxidant and antifungal properties, and subsequently has been reported several biological effects, including the activation of sirtuins. Endogenously-produced melatonin, a powerful free radical scavenger, declines with age and its loss contributes to degenerative conditions of aging. Recently, it was reported that melatonin also activates sirtuins, in addition to other functions, such as regulator of circadian rhythms or anti-inflammatory properties. The fact that melatonin and resveratrol are present in various foods, exhibiting possible synergistic effects, suggests the use of dietary ingredients to promote health and longevity.

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**Contents**



*Abbreviations:* Aβ, amyloid β protein; AMPK, adenosine monophosphate activated protein kinase; CGNs, cerebellar granule neurons; ETC, electron transport chain; $H_2O_2$, hydrogen peroxide; HO-1, heme oxygenase-1; LXR, liver X receptor; MAPK, mitogen-activated protein kinase; mtDNA, mitochondrial DNA; NF-κB, nuclear factor-κ B; $O_2$, oxygen; $O_2^{\bullet-}$, superoxide; OA, osteoarthritis; PCa, prostate cancer; PGC-1α, peroxisome proliferator activated receptor G coactivator-1α; PPAR-γ, peroxisome proliferator activated receptor-γ; RNS, reactive nitrogen species; ROS, reactive oxygen species; SAMP8, senescence-accelerated prone 8 mice; SAMR1, senescence-accelerated-resistant 1; Sir2, sirtuin 2; SIRT1, sirtuin 1.

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## 1. Introduction

During the past century, treatments for the diseases of youth and middle age have helped raise life expectancy significantly. However, a variety of aging-related diseases are emerging as the greatest health threats of the twenty-first century. Thus, understanding the basis of the molecular effects of aging may help to reveal important aspects of organismal aging, as well as processes that lead to age-related dysfunction for developing therapeutic interventions (Jiang et al., 2001; Bishop et al., 2010). In addition, a number of healthy lifestyles and anti-aging therapies that can reduce or delay the physiological decline and age-related disease progression have been documented (Smith et al., 2010; Dabhade and Kotwal, 2013).

Aging is a universal, intrinsic, progressive and multifactorial process characterized as degenerative in nature, which causes progressive loss of function and an increased risk of death (Acuña-Castroviejo et al., 2001; Mandavilli et al., 2002; Viña et al., 2007; Dabhade and Kotwal, 2013; López-Otín et al., 2013; Shokolenko et al., 2014). Aging occurs in spite of complex pathways for maintenance, repair and defense; this process progressively develops in every individual that survives beyond a certain duration of life within the evolutionary framework (Rattan, 2014). Among the numerous theories that explain the process of aging, the free radical theory of aging (Harman, 1956) has the longest history. This theory hypothesizes that aging is the result of the failure of various protective mechanisms to counteract reactive oxygen species (ROS)-induced damage, especially at the mitochondrial level. Mitochondria are in large part responsible for energy generation involving oxidative phosphorylation to produce ATP, a molecule essential for cellular function (Walker, 1992). The electron transport chain (ETC) consumes more than 90% of the oxygen ($O_2$) taken up by the cell (Boveris et al., 1972). As part of this process, however, ROS are produced as by-products of the incomplete four-electron reduction of molecular oxygen to water, the final electron acceptor in the process of ATP generation (Boveris et al., 1972; Ambrosio et al., 1993). About 1–5% of inhaled $O_2$ is converted to superoxide ($O_2^{\bullet -}$) even during the normal physiological state (Turrens and Boveris, 1980). In normal healthy cells, oxidation and the generation of ROS occur at controlled rates, but under high stress conditions or in disease states, ROS production becomes elevated. The ROS produced during aerobic respiration causes cumulative oxidative damage to crucial macromolecules, such as proteins, lipids and DNA, resulting in cellular death (Mariani et al., 2005; Scheibye-Knudsen et al., 2015), and affecting to the healthspan of many vital organ systems (Dai et al., 2014). Mitochondria are the principal source of ROS and are also the major target of these toxic species. The biological consequences of increased levels of molecular damage are wide ranging and include altered gene expression, genomic instability, mutations, molecular heterogeneity, loss of mitotic potential, impaired intercellular communication, tissue disorganization, organ dysfunctions, increased vulnerability to stress and other sources of disturbance, and eventually cell and organism death (Rattan, 2006). The lack of protective histones around mitochondrial DNA (mtDNA) and its close proximity to the ETC can make mtDNA extremely vulnerable to oxidative injury. As a result, the levels of oxidized bases in mtDNA are 2–3 times greater than in nuclear DNA (Ames et al., 1993; Shigenaga et al., 1994; Hudson et al., 1998; Alexeyev et al., 2004; Chistiakov et al., 2014; Scheibye-Knudsen et al., 2015). If damage to mtDNA is not repaired, it can lead to diminished function of the ETC and production of more ROS. This vicious cycle of ROS production and mtDNA damage ultimately leads to energy depletion in the cell and apoptosis (Mandavilli et al., 2002; Alexeyev et al., 2004; Shokolenko et al., 2014). However, recent studies have indicated that oxidative damage does not contribute to aging-associated mtDNA mutagenesis (Greaves et al., 2012; Kennedy et al., 2013; Shokolenko et al., 2014). Clearly, additional studies are required to elucidate the cause of the mtDNA mutagenesis and the possible role of ROS in mitochondrial dysfunction produced during aging.

Aging and related-diseases also are accompanied by structural changes in mitochondria, with corresponding alterations in the biophysical properties of the membrane such as asymmetry and decreased fluidity; alteration in the ETC complexes activities also occur causing mitochondrial failure and an energy imbalance. These perturbations impair mitochondrial function, endanger cellular homeostasis and enhance vulnerability to additional oxidative stress (Pu et al., 1999; Acuña-Castroviejo et al., 2001; Omodei and Fontana, 2011; Eckmann et al., 2013; Chistiakov et al., 2014). The progressive failure of homeostasis leads to physiological malfunction manifested as a general functional decline, diseases and ultimately death (Rattan, 2006).

Although as indicated above, in recent years there has been a re-evaluation of the effects of ROS generation in the process of aging; these effects indicate that oxidative damage may not be the essential cause of aging (Hekimi et al., 2011; López-Otín et al., 2013). Several investigations have demonstrated a lack of correlation between the level of ROS production and longevity in some species. Based on these observations, some workers have concluded that increased ROS may actually prolong lifespan in yeast and worms (Doonan et al., 2008; Van Raamsdonk and Hekimi, 2009; Mesquita et al., 2010), and genetic manipulations that increase mitochondrial ROS and oxidative damage do not accelerate aging in mice (Van Remmen et al., 2003; Zhang et al., 2009). Furthermore, it was recently noted that the location of the ROS is crucial in determining its effects on lifespan (Schaar et al., 2015); elevated ROS in the mitochondria can act to increase lifespan, while elevated ROS in the cytoplasm reduces lifespan. In addition, several studies indicate that ROS not only cause oxidative stress, but may also function as signaling molecules that promote health by preventing or delaying a number of chronic diseases, and ultimately extend lifespan (Sena and Chandel, 2012). Thus, ROS can play a role in mediating a stress response to age-dependent damage, which could cause the observed correlation between aging and ROS without implying that ROS cause aging (Hekimi et al., 2011). Moreover, while high levels of ROS are generally accepted to induce cellular damage and to promote aging, low levels of these may actually improve systemic defense mechanisms by inducing an adaptive response (Fig. 1), a concept known as hormesis (Masoro, 2005; Ristow and Schmeisser, 2014). This occurs because ROS have numerous crucial biological roles in signaling and stress response (Dai et al., 2014; Shokolenko et al., 2014). Accordingly, Hekimi et al. (2011) proposed that the level of ROS generation increases gradually with chronological age until it reaches a level at which the toxicity of ROS now participates in creating the damage that it was meant to help alleviate. Thus, ROS-mediated low-dose signaling events, including caloric restriction and the more recently-discovered sirtuins, may converge to improve cell physiology and homeostatic control (Cristòfol et al., 2012; Ristow and Schmeisser, 2014).

## 2. Caloric restriction and regulation by sirtuins

### 2.1. Caloric restriction

Caloric restriction, *i.e.*, the reduction of calorie intake without causing malnutrition, is the only known intervention that robustly increases lifespan in many species, including yeast, fruit flies, nematodes, fish, rats, mice, hamsters, and dogs (Weindruch, 1996; Masoro, 2005; Ingram and Roth, 2015) and possibly even primates (Ingram et al., 2006; Colman et al., 2009). Evidence that mammalian longevity could be increased emerged in 1935 in a rodent study showing that caloric restriction extended average and

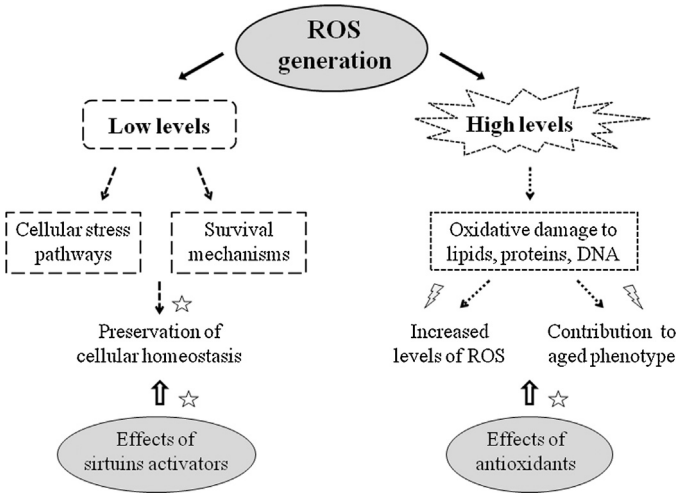


**Fig. 1.** Dual role of reactive oxygen species (ROS) levels. Low levels of ROS are implicated in cellular stress responses and survival mechanisms, while chronic high levels of ROS can produce oxidative damage to crucial macromolecules and cellular damage, contributing to the aged phenotype. Accordingly, compounds that activate sirtuins, one of the protective stress-response pathways, may exert beneficial effects promoting healthspan, and antioxidants can also play an important role, especially when there are elevated levels of ROS.

maximal lifespan and delayed the onset of age-associated pathologies in rats (McCay et al., 1935). It was not until the 1990s, however, that caloric restriction became widely viewed as a scientific model that could provide insights into the retardation of the aging process and thereby identify underlying mechanisms of aging (Kennedy et al., 2007).

Although a variety of different caloric restriction protocols have been reported, in general, studies in numerous species (both invertebrate and vertebrate) have demonstrated that reduction of calories 30–60% below *ad libitum* levels of a nutritious diet can increase lifespan 20–50% (Weindruch, 1996; Kennedy et al., 2007). Nevertheless, in recent investigations using several mouse strains, 40% caloric restriction shortened lifespan in more strains than strains in which lifespan was prolonged (Liao et al., 2010). Similarly, a study at the National Institute of Aging revealed no beneficial effect of caloric restriction on longevity in primates (Austad, 2012; Mattison et al., 2012).

It has been shown that caloric restriction retards the age-associated cellular accumulation of oxidatively-damaged molecules. Caloric restriction attenuates the age-associated increase in lipid peroxidation (Matsuo et al., 1993), abrogates the accumulation of oxidized proteins and elevates protein turnover (Dubey et al., 1996; Lee et al., 1999), and reduces the oxidative damage of DNA (Chistiakov et al., 2014) as reflected in the levels of 8-oxo-2-deoxyguanosine (Sohal et al., 1994; Hamilton et al., 2001), the latter leads to an improvement of overall mitochondrial function and mitochondrial biogenesis (Civitarese et al., 2007; Chistiakov et al., 2014). In mammals, caloric restriction induces a complex pattern of physiological and behavioral changes, such as a reduction in blood glucose, triglycerides and growth factors, a depression in body temperature, and an increase in movement and foraging activity (Weindruch, 1996; Lane et al., 2002; Mattison et al., 2003; Speakman and Mitchell, 2011). Furthermore, caloric restriction can lead to improved healthspan, reducing the incidence and delaying the onset of age-related diseases, enhancing stress resistance and decelerating functional decline (Ingram et al., 2006; Allard et al., 2009; Omodei and Fontana, 2011; Ingram and Roth, 2015). For example, it prevents many age-dependent gene expression changes in the mouse brain (Park et al., 2009), reduces age-related brain atrophy in *Rhesus macaques* (Colman et al., 2009) and has significant beneficial effects on the age-dependent impairment of learning and memory in rodents (Ingram et al., 2006; Chouliaras et al., 2011) and humans (Witte et al., 2009). In addition, caloric restriction might lead to a decrease of the risk of Alzheimer's disease (Halagappa et al., 2007), cancer, autoimmune disease, cardiovascular disease and type II diabetes (Speakman and Mitchell, 2011).

It was repeatedly reported that caloric restriction is capable of inducing stress defense mechanisms, particularly those which are involved in the detoxification of ROS (Ristow and Schmeisser, 2014). Although the molecular basis of the efficacy of caloric restriction are not fully known, the lifespan extension effect of this procedure and some of the beneficial effects have been strongly associated with an increased level and activation of members of the sirtuin family (Mair and Dillin, 2008; Allard et al., 2009; Testa et al., 2014). The anti-aging effect of caloric restriction has also been related to other molecular signaling pathways, including peroxisome proliferator activated receptor G coactivator-1α (PGC-1α), adenosine monophosphate activated protein kinase (AMPK), insulin/insulin growth factor-1, and target of rapamycin (Testa et al., 2014).

Even if evidence could substantiate caloric restriction as an effective anti-aging strategy for humans, application of this intervention would be problematic due to the degree and length of restriction required. To meet this challenge for potential application of caloric restriction, research to create "caloric restriction mimetics" has emerged as an active research area within gerontology. This strategy focuses on identifying compounds that can mimic some of the beneficial effects associated to caloric restriction, such as targeting metabolic and stress response pathways affected by caloric restriction including compounds that activate sirtuins (Ingram et al., 2004; Ingram and Roth, 2015).

### 2.2. Sirtuins

A massive amount of research has suggested that lifespan extension and the principal health effects of caloric restriction are mediated by mechanisms involving sirtuins. Sirtuins are an ancient family of NAD+-dependent histone deacetylases (Imai et al., 2000; Landry et al., 2000; Smith et al., 2000; Morris, 2013) widely distributed in all phyla. Accumulating evidence indicates that sirtuins are important regulators of organismal lifespan (Sauve et al., 2006; Michan and Sinclair, 2007).

There are approximately 250 amino acids in the sirtuin's catalytic core domain that exhibits 25 ± 60% sequence identity between different organisms (García-Salcedo et al., 2003; Sauve et al., 2006). The sirtuin fold consists of two characteristic domains (García-Salcedo et al., 2003; Zhao et al., 2004; Avalos et al., 2005); the larger domain adopts the classic pyridine dinucleotide binding fold, or Rossman fold, found in proteins that bind NAD + /NADH or NADP + /NADPH.

Studies continue to uncover the roles that members of the sirtuin family play in important biological processes (Sauve et al., 2006; Michan and Sinclair, 2007; Morris, 2013), such as transcriptional silencing, DNA recombination and repair mechanisms (Gottlieb and Esposito, 1989; Brachmann et al., 1995; Smith and Boeke, 1997; Bennett et al., 2001; McMurray and Gottschling, 2003; O'Hagan et al., 2008 Oberdoerffer et al., 2008), apoptosis (Luo et al., 2001; Vaziri et al., 2001; Motta et al., 2004), cellular response to stress (Anderson et al., 2003; Brunet et al., 2004; Cohen et al., 2004), insulin secretion (Moynihan et al., 2005), fat mobilization from human cells (Picard et al., 2004), axonal protection (Araki et al., 2004), and aging (Guarente, 2000; Lin et al., 2000; Kaeberlein et al., 2004; Oberdoerffer et al., 2008).

The NAD+-dependent deacetylase sirtuin 2 (Sir2) was one of the earliest genes to be implicated in the response to caloric restriction,

initially in a yeast model (Lin et al., 2000; Mair and Dillin, 2008). Homologues of Sir2 have subsequently been shown to mediate some of the effects of caloric restriction in flies (Rogina and Helfand, 2004), worms (Tissenbaum and Guarente, 2001) and in mammals (Chen et al., 2005a; Boily et al., 2008). Mammals have 7 homologues of the Sir2 protein, sirtuins 1-7 (SIRT1-7), which appear to regulate a diverse set of pathways related to energy metabolism, cell survival and longevity (Michan and Sinclair, 2007). SIRT1, located in the nucleus, is the family member sharing the most homology to Sir2, is considered to be its orthologue and is the most studied (Haigis and Guarente, 2006). Despite this, in recent years the other sirtuins, such as the mitochondrial sirtuin 3, also received significant attention regarding its actions on different aspects of cellular regulation (Someya et al., 2010; Ingram and Roth, 2015; Herskovits and Guarente, 2014; Sidorova-Darmos et al., 2014).

SIRT1 can deacetylate histones (Imai et al., 2000; Vaquero et al., 2004) as well as a large number of substrates (Yamamoto et al., 2007), including the tumor suppressor p53 protein, the DNA repair factor Ku70, nuclear factor-κ B (NF-κB), the signal transducer and activator of transcription 3 and the FOXO family of forkhead transcription factors, proteins that affect stress resistance in cells (Luo et al., 2001; Vaziri et al., 2001; Brunet et al., 2004; Cohen et al., 2004; Motta et al., 2004; Yeung et al., 2004; Bernier et al., 2011). This may relate to the observed stress resistance conferred by caloric restriction.

Several studies also suggest that SIRT1 plays a role in energy metabolism. The dependence on $NAD^+$ as a cofactor for catalysis is thought to link SIRT1 activity to the energetic and metabolic state of the cell (Imai et al., 2000; Landry et al., 2000). In fact, observations suggest that SIRT1 is an important regulator of metabolic activity because SIRT1-null mice utilize ingested calories inefficiently and because SIRT1-null mice do not adapt normally to caloric restriction or to fasting (Boily et al., 2008). In addition, the metabolism of glucose, fatty acids and cholesterol is modulated in various cell types by the effects of SIRT1 on known regulators of metabolic enzymes such as the PGC-1α, the peroxisome proliferator activated receptor-γ (PPAR-γ) (Picard et al., 2004) and liver X receptor (LXR) (Gerhart-Hines et al., 2007; Rodgers and Puigserver, 2007). The vital role that sirtuins play in cellular metabolic control indicates that they could be important determinants of whole-body metabolism and may help in designing strategies to provide the health benefits of caloric restriction, thereby protecting against many chronic diseases associated with metabolic dysfunction (Yamamoto et al., 2007; Boily et al., 2008).

It has been suggested that persistent activation of a DNA damage response leads to a loss of SIRT1 activity. This is mediated through the DNA damage recognizing protein poly[ADP-ribose] polymerase 1, which depletes $NAD^+$, attenuates SIRT1-activity and induces mitochondrial dysfunction (Scheibye-Knudsen et al., 2014). In addition, recent studies have shown that DNA damage can induce changes in gene expression and histone modification patterns that may be mediated, in part, by the regulatory gene SIRT1. This suggests a possible mechanistic link between DNA damage, the epigenomic state and aging. Consistent with this idea, the yeast homologue of SIRT1, Sir2, is a long-established regulator of lifespan, DNA damage repair and epigenetic gene silencing (Guarente, 2000; O'Hagan et al., 2008; Oberdoerffer et al., 2008).

Likewise, potential applications of the sirtuins in neuronal cell survival and response to stress and cell-cycle control hint at the eventual importance of this gene family in the pathogenesis of neurodegenerative diseases and cancer (Yamamoto et al., 2007). SIRT1 plays a role in the maintenance of neural systems and behavior during normal aging, including the modulation of synaptic plasticity and memory processes (Herskovits and Guarente, 2014). Accordingly, SIRT1 is expressed in neurons of the hippocampus and the absence of SIRT1 impaired cognitive abilities, including immediate memory, classical conditioning, and spatial learning (Michán et al., 2010); thus, SIRT1 can offer a promising approach in the treatment of several neurodegenerative diseases (Herskovits and Guarente, 2014). For example, evidence for the benefits of SIRT1 in brain aging includes the finding that increased SIRT1 activity protects against amiloid β protein (Aβ) toxicity in cell cultures and neurodegeneration in the p25/CDK5 mouse model, which recapitulates aspects of Alzheimer's disease pathology and tauopathy (Kim et al., 2007).

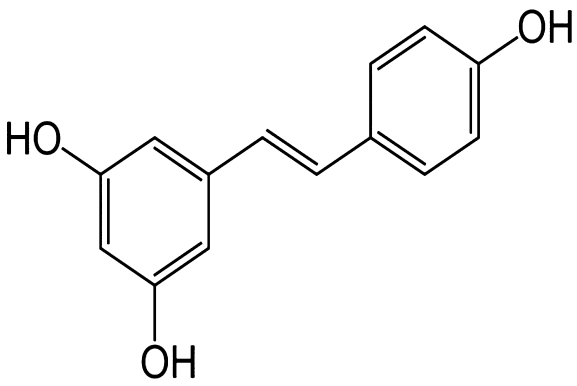


**Fig. 2.** Chemical structure of *trans*-resveratrol.

A number of small molecular agents have been identified that either inhibit or activate sirtuin enzymes in diverse organisms including yeast, flies, and mammals. These activators include several polyphenols, such as resveratrol, which is present in various foods; melatonin, an indoleamine produced endogenously and also present in many edible foods, and another compound that can antagonize nicotinamide inhibition of sirtuin deacetylation activity, *i.e.*, isonicotinamide (Sauve et al., 2005, 2006; Baur, 2010; Yu et al., 2014). In addition, there are a series of pharmaceutical compounds, including SRT1720, that activate sirtuins; they are being investigated for their potential efficacy in the treatment of metabolic and chronic diseases associated with aging (Minor et al., 2011). We have focused on resveratrol and melatonin due to the presence of these compounds in the diet and their possible synergistic effects.

## 3. Dietary activators of SIRT1: resveratrol and melatonin

### 3.1. Resveratrol

Resveratrol (3,4′,5-trihydroxyl-trans-stilbene, Fig. 2) is a plant-derived polyphenol produced in abundance by plants undergoing a variety of environmental stresses (Frémont, 2000; Lamming et al., 2004; Pallàs et al., 2013), where it has antifungal properties (Langcake and Pryce, 1977; Hain et al., 1990). Resveratrol exists in two isomers: *trans*- and *cis*-resveratrol, which may have different biological effects. It is known that *trans*-resveratrol is nontoxic and is the more widely studied (Pallàs et al., 2013; Zhao et al., 2013). It is found in grape skins, raspberries, blueberries, peanuts, some pine trees and medicinal plants, such as Japanese knotweed (*Polygonum cuspidatum*) (Baur and Sinclair, 2006; Allard et al., 2009). The most important dietary source of resveratrol is red wine, and it is often postulated to be an important factor in the French Paradox, a term coined to describe the observation that the French population has a low incidence of cardiovascular disease, despite a diet high in saturated fats (Renaud and de Lorgeril, 1992; Liu et al., 2007); epidemiological studies showed an inverse correlation between red wine consumption and incidence of cardiovascular diseases.

Resveratrol has also received widespread interest for its reported protective effects in a variety of pathologies (Robb et al., 2008; Smoliga et al., 2011). This natural compound has been shown

to have a wide range of biological effects, including antioxidant activity, anti-platelet, inhibition of lipid peroxidation, vasorelaxing activity, anti-inflammatory, anti-cancer, anti-mutagenic, and to function in protection from atherosclerotic disease and cardioprotective degeneration (Frémont, 2000; Das and Maulik, 2006; Allard et al., 2009; Smoliga et al., 2011), thereby improving general health in mammals (Baur et al., 2006). The beneficial actions of resveratrol involve its antioxidative capacity and the regulation of the activities and expression levels of enzymes and proteins associated with the survival signals, regulation of ion channels, and antioxidative actions (Baur and Sinclair, 2006; Kwon et al., 2010).

Some of the protective properties have been attributed to the ability of resveratrol to reduce oxidative stress. Similar to most polyphenols, resveratrol has intrinsic antioxidant capacity, but it also induces the expression of a number of antioxidant enzymes, making it difficult to decipher the precise contribution of each mechanism to an overall reduction of oxidative damage (Halliwell, 2007; Robb et al., 2008). However, the low bioavailability, and a weak ability to directly scavenge ROS, makes cytoprotection *via* direct chemical reactions unlikely (Leonard et al., 2003; Sale et al., 2004). Thus, the beneficial actions of resveratrol may be a result of its initiation of a cascade of intracellular events that lead to an upregulation of cellular defense systems, which in turn protect against oxidative stress-mediated death (Robb et al., 2008; Pallàs et al., 2013).

Studies of the biological responses to treatments with resveratrol, both *in vivo* and *in vitro*, have reported that resveratrol stimulates the activities of intracellular signaling molecules including sirtuins and AMPK; both of these regulate metabolism in multiple tissues (Howitz et al., 2003; Wood et al., 2004; Baur et al., 2006; Lagouge et al., 2006; Stefani et al., 2007; Zang et al., 2006). There is also speculation that metabolites of resveratrol may retain some of the activity of the parent molecule. In support of this, several metabolites have the ability to activate SIRT1 and inhibit cyclooxygenase *in vitro* (Baur and Sinclair, 2006). Resveratrol has previously been shown to extend lifespan by >60% in *Saccharomyces cerevisiae, Caenorhabditis elegans,* and *Drosophila* by stimulating sirtuins (Howitz et al., 2003; Wood et al., 2004; Valenzano and Cellerino, 2006), the same pathways activated by caloric restriction. Nevertheless, there is a disparity in the effects reported by resveratrol with respect to the activation of sirtuins, especially in higher organisms (Hector et al., 2012), and its capacity to extend lifespan. Thus, unlike the studies mentioned above, Bass et al. (2007) obtained that resveratrol did not increase lifespan in *Drosophila melanogaster*, and only in some trials did it cause slight increases in lifespan in *Caenorhabditis elegans* in both wild-type and Sir2 mutant populations. Pearson et al. (2008) also reported that resveratrol treatment had a range of beneficial effects in mice but did not increase the longevity of ad libitum-fed animals when started midlife. In addition, some studies have concluded that resveratrol is not a direct activator of sirtuins and even the increased longevity mediated by caloric restriction may be, at least partially, independent of Sir2 in yeast and, perhaps, higher eukaryotes (Jiang et al., 2002; Kaeberlein et al., 2004, 2005, 2006). Nevertheless, some evidence documented the beneficial effects of the compound on healthspan and showed protection against a large variety of diseases (Ingram and Roth, 2015). Analyzing these possible beneficial properties of this polyphenol, in mammalian cells resveratrol produces SIRT1-dependent effects that are consistent with improved cellular function and organismal health (Picard et al., 2004; Chen et al., 2005a; Frescas et al., 2005; Kolthur-Seetharam et al., 2006). *In vitro*, resveratrol reduced adipogenesis in fat-producing cells, consistent with SIRT1 antagonism of PPAR-γ (Picard et al., 2004). Other studies with resveratrol also have shown favorable effects on glucose metabolism (Pollack and Crandall, 2013). Resveratrol enhanced insulin-stimulated glucose uptake in skeletal muscle, hepatocytes, and adipocytes by activation of SIRT1 (Sun et al., 2007; Breen et al., 2008). In mice, resveratrol caused an activation of SIRT1, and its target PGC1-α, which leads to changes in mitochondrial number and function (Lagouge et al., 2006). Resveratrol intervention also resulted in increased levels of SIRT1, PGC-1α, and mtDNA copy number, and there was an improvement in high-fat diet-induced insulin resistance (Haohao et al., 2015). Recently it was reported that resveratrol can act as an anti-diabetic agent, due to the repression of the FOXO1 (an important player in insulin signaling) by activation of SIRT1 deacetylase (Sin et al., 2015). Furthermore, other studies observed an increase in mitochondrial biogenesis and oxidative phosphorylation in skeletal muscle, brown fat, and the liver after resveratrol treatments, potentially mediated by activation of SIRT1 and its down-stream targets, PGC1-α and AMPK (Lagouge et al., 2006; Breen et al., 2008; Um et al., 2010; Baur et al., 2012; Price et al., 2012). However, RNA interference experiments showed that the inhibitory effects of resveratrol on insulin signaling pathways, a hallmark of caloric restriction and longevity, are not weakened in rat hepatocytes cells with reduced expression of SIRT1 (Zhang, 2006). These observations raise the possibility that resveratrol may additionally modulate lifespan through inhibition of insulin signaling pathway, independently of SIRT1 (Zhang, 2006). In obese men treated with high doses of resveratrol, Poulsen et al. (2013) demonstrated no significant variations in either glucoregulatory functions or insulin sensitivity.

Studies *in vitro* and in animal models have suggested that resveratrol may have beneficial effects on lipids by modulation of genes involved in lipid metabolism (Ahn et al., 2008). In this, the hepatic expression of SIRT1 was increased by resveratrol treatment. Compared with mice fed the atherogenic diet, the addition of resveratrol significantly increased the expression of SIRT1, which was decreased by the atherogenic diet. Regarding cardiovascular aspects, activation of SIRT1 by resveratrol in rats improved cardiac contractility, as well as left ventricular function, in trauma-hemorrhage (Jian et al., 2012). In addition, resveratrol-mediated activation (Do et al., 2008) of SIRT1 reduces plaque formation in mice. In another study, resveratrol treatment augmented the cardioprotective effect of exercise training in aging rat hearts, activating SIRT1 that may block FOXO3 accumulation in the nucleus and inhibit cell death (Lin et al., 2014). Resveratrol, likely *via* a SIRT1-dependent mechanism, abrogated the adverse vascular effects of cigarette smoke in rats by attenuating smoke-induced oxidative stress and preventing proinflammatory phenotypic alterations in vascular tissues (Csiszar et al., 2008). However, in human studies, there was no change in blood pressure after resveratrol treatment in man (Pollack and Crandall, 2013; Poulsen et al., 2013) and the use of resveratrol in human cardiovascular diseases needs more preclinical information (Tang et al., 2014).

Resveratrol also induces autophagy, reducing the activity of the mammalian target of rapamycin, protein kinase related to inflammation and to oxidative stress processes. This effect may involve SIRT1-dependent actions (Ghosh et al., 2010); however, other authors have indicated that actions of resveratrol on mTOR occur in a SIRT-1-independent manner (Liu et al., 2010). In addition, when aged mice consumed a diet supplemented with resveratrol, it reduced infection-related neuroinflammation and deficits in working memory (Abraham and Johnson, 2009). The anti-inflammatory effects of resveratrol in aged mice could be linked to its ability to inhibit factors involved in gene transcription such as mitogen-activated protein kinase (MAPK), activator protein-1, and NF-κB (Manna et al., 2000). How this occurs is not clear; however, it may be that resveratrol activates SIRT1, which deacetylates NF-κB, thereby inactivating the transcription factor (Howitz et al., 2003; Yeung et al., 2004).

Several studies have demonstrated that resveratrol has neuroprotective effects and the ability to limit pathological states.

Supplementation with a resveratrol analog improved spatial working memory without any effect on spatial reference memory in old rats (Joseph et al., 2008). Resveratrol also enhanced the spatial memory skills tested in a Barnes-like maze in non-human primates (Dal-Pan et al., 2011). In human studies, resveratrol treatment has exhibited efficacy in improving memory performance in older subjects (Witte et al., 2014). Resveratrol has been shown to cross the blood-brain barrier in animal models; hence, when resveratrol was intraperitoneally administered, there was an increase of antioxidant enzyme activities in the brains of healthy rats (Mokni et al., 2007). Although resveratrol is known to exhibit neuroprotection by an antioxidant effect, there are reports of its indirect neuroprotective effect *via* activation of sirtuin pathways (Raval et al., 2006, 2008). The positive effects of enhanced SIRT1 activation by resveratrol may also be important in mitigating the pathogenesis of neurodegenerative diseases (Rocha-González et al., 2008). In an *in vitro* Wallerian degeneration model, the axonal degeneration was reduced after treatment with resveratrol through a SIRT1-dependent mechanism (Araki et al., 2004), providing new therapeutic opportunities for the treatment of diseases involving axonopathy and neurodegeneration. *In vivo*, resveratrol also ameliorated cognitive decline and brain damage in senescence-accelerated mice, mediated, at least in part, by SIRT1 activation (Cristòfol et al., 2012). Resveratrol-induced SIRT1 also protected neurons against polyglutamine toxicity (Parker et al., 2005). Other investigators also showed that resveratrol improved the impaired learning and memory in neurodegenerative conditions such as that in Alzheimer's disease rodent models. For example, SIRT1 activation by resveratrol also deacetylates PGC-1α and p53 proteins improving the learning capability in Alzheimer's transgenic mice (Kim et al., 2007). Overexpression of SIRT1 and the addition of resveratrol markedly reduced NF-κB signaling stimulated by amyloid-β and had strong neuroprotective effects in Alzheimer disease (Chen et al., 2005b). Nevertheless, in a study performed by Chang et al. (2012) dietary supplementation of pterostilbene showed significant cognitive improvement over resveratrol in the senescence-accelerated prone 8 (SAMP8) mice. Furthermore, pterostilbene was a more potent effector in activating protective signaling cascades and downregulating stress cascades at doses the same as those of resveratrol, events independent of SIRT1 regulation. It has been observed that resveratrol reduces mutant superoxide dismutase-induced neurotoxicity in transfected neurons of mice by SIRT-1 protein activation (Kim et al., 2007). In another study, resveratrol significantly improved memory formation and synaptic plasticity compared with control 8–9 month-old mice treated with vehicle; this effect was SIRT1-dependent and involved the microRNA-CREB-BDNF pathway (Zhao et al., 2013). *In vivo* resveratrol pre-treatment also protected rat brain from cerebral ischemic damage *via* a SIRT1 - UCP2 pathway (Della-Morte et al., 2009). Employing an *in vitro* model of cerebral ischemia, the organotypic hippocampal slice culture, resveratrol pre-treatment mimics ischemic preconditioning *via* the SIRT1 pathway. Blockade of SIRT1 activation by sirtinol after ischemic preconditioning or resveratrol pre-treatment abolished this neuroprotection (Raval et al., 2006, 2008).

The neuroprotective effects of resveratrol were also evaluated in an *in vitro* model of Parkinson's disease using rat cerebellar granule neurons (CGNs). The loss of cell viability and the induction of apoptosis in CGNs were prevented by the addition of resveratrol. However, these neuroprotective actions were not mediated by the activation of SIRT1 (Alvira et al., 2007). Furthermore, one study reported that resveratrol-stimulated AMPK activity in neuron cultures, affecting neuronal energy homeostasis, and requiring the upstream regulator kinase LKB1; however, this effect was completely independent of SIRT1 (Dasgupta and Milbrandt, 2007). Another report claimed that the neuroprotective action of resveratrol depended on the presence of LKB1, and this LKB1-dependent mitochondrial protection resulted from resveratrol's poly(ADP-ribose) polymerase activation, but not SIRT1 activation (Shin et al., 2009). Vingtdeux et al. (2010), using cultured cells, showed that resveratrol activated AMPK by increasing intracellular calcium levels and also found that the inhibition of AMPK counteracted the effect of resveratrol on Aβ levels. This effect was also obtained *in vivo* since the peripheral administration of resveratrol activated AMPK and reduced cerebral Aβ accumulation in the mouse cerebral cortex, likely *via* an SIRT-independent pathway. Thus, it remains to be seen whether resveratrol activation of AMPK is mediated by sirtuin or whether resveratrol activation of sirtuins and AMPK are parallel and fully independent. Tang (2010) hypothesize that resveratrol is neuroprotective in a variety of experimental paradigms not because it activates SIRT1 directly, but rather because it does not activate SIRT1 during the acute phase of neuronal cell demise. Related with this, SIRT1 inhibition has also been shown to be neuroprotective agent, particularly when acute neuronal death is concerned. While resveratrol may be generally beneficial, specific SIRT1 activators may not be, particularly in acute brain injuries and ischemia (Tang, 2010; Ng and Tang, 2013).

It has been noted that resveratrol may also exert its effects through other multiple pathways, independent of its activation of SIRT1. Resveratrol does have other cellular targets including other sirtuins, cyclooxygenases, lipooxygenases, kinases, ribonucleotide reductase, adenylyl cyclase, aromatase and DNA polymerases (Pirola and Fröjdö, 2008; Pacholec et al., 2010; Tang, 2010; Chung et al., 2012; Morris, 2013); this pathways may work in parallel to SIRT1 (Allard et al., 2009). One possible explanation is the 'hormesis hypothesis', which is discussed above; regarding the concept of hormesis, it has been hypothesized that sensing stress responses, such as resveratrol accumulation, in a food source might induce a hormetic response in animals eating that food (Howitz et al., 2003; Lamming et al., 2004; Menendez et al., 2013). Whether resveratrol can activate endogenous pathways to promote health (such as those that are active during caloric restriction) or whether this polyphenol acts through fortuitous interactions are important points to address (Baur and Sinclair, 2006). Experimental evidence suggests that different doses may elicit distinct biological effects, with lower doses activating SIRT1-dependent pathways and higher doses acting in an SIRT1-independent mechanism (Price et al., 2012).

The use of resveratrol supplements to promote health has become increasingly popular (Mercken et al., 2012). Nevertheless, results obtained from clinical trials in humans evaluating the potential effects of resveratrol have generated considerable controversy, and in some cases the findings of these trials are not consistent with results from animal models (Yoshino et al., 2012; Smoliga et al., 2013). However, disparity in dosing protocols and clinical paradigms may cause conflicting findings. Only long-term epidemiological studies and meta-analysis can clarify the use of resveratrol as a therapy to reduce the physiological decline and age-related diseases (Smoliga et al., 2013).

### 3.2. Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine, Fig. 3) is a highly and widely distributed molecule found throughout of plant and animal kingdoms and it likely exists in every living organism (Dubbels et al., 1995; Manchester et al., 1995; Tan et al., 2007; Byeon et al., 2013; Park et al., 2013; Reiter et al., 2013). This indoleamine is synthesized from the essential amino acid L-tryptophan by the action of four enzymes: tryptophan hydroxylase, L-aromatic amino acid decarboxylase, *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase (also known as acetylserotonin methyltransferase) (Stehle et al., 2011; García et al., 2014).

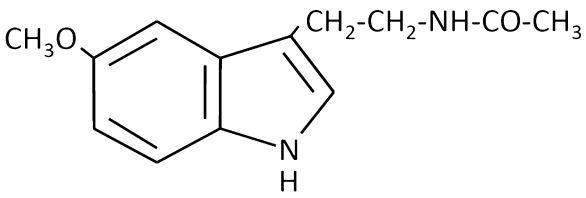


**Fig. 3.** Chemical structure of the indoleamine melatonin.

In vertebrates, melatonin is best known as a secretory product of the pineal gland, but it as well as the enzymes that produce it are present in numerous other tissues including retina, skin, immune system, gastrointestinal tract and reproductive tract (Reiter, 1991; Huether et al., 1992; Tan et al., 1999; Stefulj et al., 2001; Slominski et al., 2002; Kleszczynski and Fischer, 2012; Lanoix et al., 2012; Acuña-Castroviejo et al., 2014).

Although the concentrations of melatonin vary in subcellular compartments, the highest levels are found within membranes and mitochondria, where it interacts with lipids, stabilizes all cellular membranes (Martín et al., 2000; Paradies et al., 2010) and reduces lipid peroxidation (García et al., 2014). These effects are reflected in the ability of melatonin to improve ETC activity in the inner mitochondrial membrane and to enhance ATP production (Acuña-Castroviejo et al., 2001). Due to its antioxidant and free radical scavenging capacity, melatonin can protect proteins of the ETC and mtDNA from oxidative stress (Karbownik et al., 2000).

Melatonin has the capability of penetrating all morphophysiological barriers and entering all subcellular compartments due to its amphiphilic nature (Menendez-Pelaez and Reiter, 1993; Costa et al., 1995; Reiter, 2000; Reiter et al., 2013). Because of this, it is in a position to modulate a diverse number of physiological processes *via* different mechanisms (León et al., 2005). Melatonin acts by binding to membrane receptors and possibly to nuclear binding sites (Acuña-Castroviejo et al., 1994; Witt-Enderby et al., 2003; Dubocovich and Markowska, 2005) and also by interacting with cytosolic proteins such as calmodulin (Benítez-King, 2006). Melatonin is an endogenous molecule that, through both receptor-dependent and receptor-independent signaling pathways, activates a broad spectrum of molecular pathways, including activation of sirtuins such as SIRT1.

In addition, melatonin is a powerful direct free radical scavenger (Tan et al., 1993) and the resulting metabolites also have the ability to efficiently scavenge ROS and reactive nitrogen species (RNS) (Allegra et al., 2003; Galano et al., 2013; Tan et al., 2014). Melatonin also increases the activity of endogenous antioxidant enzymes (Rodriguez et al., 2004; Fischer et al., 2013; García et al., 2014). Its high efficacy as a scavenger may be explained by the unique cascade of reactions of melatonin and its metabolites with toxic free radicals and reactive oxygen intermediates (Tan et al., 2014). For example, related with this potent antioxidant capacity, melatonin can counteract or modulate the skin stressors produced by solar UV irradiation, a major environmental skin stressor that produces the aging of the skin. Thus, endogenous intracutaneous melatonin together with topically applied exogenous melatonin or its metabolites may be expected to represent one of the most potent antioxidative defense systems against UV-induced skin aging and photocarcinogenesis (Fischer et al., 2008, 2013; Kleszczynski and Fischer, 2012; Janjetovic et al., 2014).

Melatonin possesses marked anti-inflammatory properties (Dugo et al., 2001; Sener et al., 2005; Yavuz et al., 2007; Wu et al., 2008; Lowes et al., 2011; Agil et al., 2013; Mauriz et al., 2013). This action of melatonin contributes to its ability to attenuate tissue damage under a variety of conditions including neurodegenerative diseases where inflammatory responses are frequently a serious component of these conditions. Some of the anti-inflammatory properties are related with SIRT1-activation. For example, in a study based on hydrogen peroxide ($H_2O_2$)-stimulated human chondrocytes in rabbit osteoarthritis (OA) model, melatonin exerted cytoprotective and anti-inflammatory effects. The authors also showed that downregulating SIRT1 expression through transfection of SIRT1 siRNA and blockade of SIRT1 activity through treatment with sirtinol, reversed the effects of melatonin on $H_2O_2$-mediated induction of pro-inflammatory cytokines and the expression of inflammatory mediators. Melatonin also interfered with $H_2O_2$-induced phosphorylation of PI3K/Akt p38 and MAPK, as well as activation of NF-κB, which was reversed by sirtinol and SIRT1 siRNA. These findings are consistent with the idea that the cytoprotective and anti-inflammatory properties of melatonin involve the dynamic action of the SIRT1 pathway (Lim et al., 2012). In addition, in cadmium-induced hepatotoxicity, melatonin exerts positive effects, which are associated with enhanced mitochondrial biogenesis through a SIRT1-dependent PGC-1α pathway. This effect appeared to be mediated partially through the binding of melatonin to its MT1 recepor, which activates signaling to mitochondria (Guo et al., 2014).

In apolipoprotein E-deficient mice, melatonin reduced the impairment of endothelial damage and limited loss of SIRT1 and endothelial nitric oxide synthase, and decreased p53 and endothelin-1 expression. In particular, RETARD melatonin, formulated to release a low dose of melatonin rapidly and a higher dose over a longer period of time, was a more appropriate option for overcoming the vascular dysfunctions linked to aging, than was FAST melatonin, an immediate release melatonin formulation (Rodella et al., 2013). Melatonin confered cardioprotective effect against myocardial ischemia reperfusion injury by reducing oxidative stress damage *via* activation of SIRT1 signaling in a receptor-dependent manner (Yu et al., 2014). Melatonin treatment also attenuated cerebral ischemia-reperfusion injury in mice by reducing ischemia reperfusion-induced mitochondrial dysfunction through the activation of SIRT1 signaling and the attenuation of mitochondrial oxidative damage (Yang et al., 2015).

The major regulator of circadian melatonin synthesis in the vertebrate pineal gland is the light–dark cycle. During darkness the suprachiasmatic nucleus, through a multisynaptic sympathetic pathway, promotes the production of melatonin in the pineal gland (Stehle et al., 2011). The chronobiotic actions of this indoleamine on organismal activity, including endocrine and non-endocrine rhythms, are a consequence of its circadian production and release from the pineal (Hardeland et al., 2012; Acuña-Castroviejo et al., 2014). Whereas the 24 h rhythm of melatonin production is robust in young animals including humans, the cycle deteriorates during aging, suggesting a potential association between the loss of melatonin and the signs of aging (Reiter et al., 1980, 1981; Pang et al., 1984; Nair et al., 1986; Reiter, 1992; Poeggeler et al., 1993; Pierpaoli and Regelson, 1994). The rhythm of melatonin can be substantially preserved during aging by restricting food intake of experimental animals (Reiter, 1992). Stokkan et al. (1991) proposed that food restriction could mediate some of its beneficial physiological effects through its ability to sustain pineal activity in old age. Fisher 344 rats given 60% of the food eaten by control animals retained a melatonin rhythm at 29 months of age that was equivalent to those of much younger animals. Food restriction presumably conserves the melatonin rhythm in part because it prevents the reduction in pineal β-adrenergic receptors normally reported in old rats (Henden et al., 1992). The loss of melatonin in the elderly may lead to disorders of circadian rhythms, referred to as chronodisruption (Erren and Reiter, 2009), causing a desynchronization of the various genes resulting in a decrease in overall health (Karasek, 2007; Jung-Hynes et al., 2010).

Originally linked to longevity in yeast sirtuins, and more specifically SIRT1, have been implicated in numerous biological processes

having both protective and/or detrimental effects. SIRT1 appears to play a critical role in the process of carcinogenesis, especially in age-related neoplasms (Jung-Hynes et al., 2010). The first indication of a positive relationship between sirtuins and melatonin was obtained in the senescence-accelerated SAMP8 mice, in which melatonin was reported to upregulate SIRT1 (Gutierrez-Cuesta et al., 2008). In this study, the authors suggested that melatonin controls certain clock genes, and also points toward a possible scenario that melatonin may be controlling circadian rhythms *via* SIRT1, which may be the mechanism connecting melatonin with aging and cancer susceptibility. The authors also assessed the effect of melatonin on the cellular pathways regulated by SIRT1. They found that melatonin increased protein levels of SIRT1 and subsequently reduced the levels of acetylated p53 and acetylated NF-κB in SAMP8 mice, but not in the senescence-accelerated-resistant 1 (SAMR1) animals. Nevertheless, contrasting findings were obtained in cancer and in inflammatory responses induced by oxidative stress (Hardeland, 2013). The results obtained by Jung-Hynes et al. (2011) identified melatonin as a novel inhibitor of SIRT1 in prostate cancer (PCa), which overexpress SIRT1, and suggest that melatonin may inhibit PCa growth *via* SIRT1 inhibition. Melatonin also inhibited SIRT1 in human osteosarcoma cells, thereby reducing proliferation, cell vitality, adhesion, and migration; in this study melatonin also increased ROS formation and apoptosis, accounting for its antitumor activity (Cheng et al., 2013). Thus, the age-dependent decline in melatonin secretion and increased susceptibility to cancer led to the hypothesis that melatonin may downregulate SIRT1 in cancer cells. Unraveling the molecular mechanisms connecting aging and cancer with a specific focus on SIRT1, melatonin and circadian rhythms is an important goal of subsequent research (Jung-Hynes and Ahmad, 2009; Jung-Hynes et al., 2010).

Focusing on neuroprotective effects in aging, in neuronal cultures from cerebellum, melatonin also enhanced the deacetylation of various SIRT1 substrates, such as PGC-1α, FOXO1, NF-κB and p53, effects which were largely reversed by the SIRT1 inhibitor sirtinol (Tajes et al., 2009). This suggests that pretreatment with melatonin partially prevents neuronal disturbances associated with aging. The authors proposed that anti-aging effect of melatonin can be a result of strengthening of the SIRT1 downstream pathway, in addition to the widely-known antioxidant properties of melatonin and its metabolites (Tajes et al., 2009). The melatonin-induced effects *via* SIRT1, PGC-1α and PPAR-γ also suggest the indoleamine may maintain mitochondrial capacity during aging (Hardeland et al., 2011; Hardeland, 2013). Melatonin treatment also increased the expression of SIRT1 in dentate gyrus of aged rats (Kireev et al., 2013), suggesting a neuroprotective role of melatonin through the SIRT1 pathway during aging. Chang et al. (2009) showed that melatonin treatment effectively preserved the relative protein levels of SIRT1 in the hippocampus of total sleep-deprived rats and also prevented the memory deficits, possibly by preserving the metabolic function and neuronal plasticity engaged in maintaining cognitive activity. Melatonin, like resveratrol, enhanced SIRT1 expression in SAMR1 and SAMP8 mice (Cristòfol et al., 2012; Cuesta et al., 2013). A deficiency of the SIRT1 pathway may contribute to the early age-related brain damage in these mice; thus, the therapeutic use of SIRT1-enhancing agents may protect against age-related nerve cell dysfunction and brain frailty during aging (Cristòfol et al., 2012). In addition, the expression of SIRT1 gene was significantly upregulated after melatonin replacement therapy in the dentate gyrus of ovariectomized females rats (Kireev et al., 2014).

Although the experimental basis for a relationship between melatonin and SIRT1 is still rather limited, such an association, if verified, would have the potential to become a field with numerous implications for circadian rhythmicity, aging, neuroprotection and cancer (Hill et al., 2009; Jung-Hynes et al., 2010). The question resulting from the divergent findings of SIRT1 and melatonin requires clarification. Countless publications have documented the cytoprotective and antiapoptotic effects of melatonin in normal cells related *via* sirtuin-pathways, whereas it behaves an oncostatic and proapoptotic various cancer cell lines (Bizzarri et al., 2013). Related with this, melatonin significantly reduces SIRT1 levels to about half the control values in MCF7 breast cancer cells, thereby possibly mediating its an anti-cancer actions (Proietti et al., 2014). The solution for understanding the antagonistic effects can be found in the dynamics of the cyclicity and the importance of circadian oscillators to lifespan and healthy aging (Hardeland, 2013).

Melatonin exerts a broad spectrum of effects on physiological functions of relevance to aging, such as metabolic sensing, mitochondrial modulation, antioxidative protection of biomolecules and subcellular structures, sirtuin activation as well as a coordinating role concerning central and peripheral circadian oscillators, which may contribute to the reduction of damage (Tajes et al., 2009; Hardeland, 2013). In addition, melatonin has an uncommonly low toxicity profile (Reiter et al., 1996), thus having great potential as a useful therapy. These known actions of this indoleamine may explain, at least in part, the protective ability of melatonin to delay the deleterious effects of aging and a variety of age-related diseases, such as Parkinson's disease, Alzheimer's disease, epilepsy, ischemia-reperfusion and sepsis (Martín et al., 2000; Acuña-Castroviejo et al., 2001; León et al., 2005).

### 3.3. Synergistic effects of melatonin and resveratrol

There are several studies that analyze the possible synergistic effects of melatonin and resveratrol, given their many similar beneficial properties. Kwon et al. (2010) noted that melatonin and resveratrol were beneficial for energy preservation and the prevention of neuronal cell death. In this study, co-administration of melatonin and resveratrol had neuroprotective properties against amyloid β1-42 peptide-induced cytotoxicity in HT22 hippocampal neuronal cells. Associated with the protective actions of these compounds, there was an attenuation of oxidative stress through the induction of other antioxidants, the inhibition of glycogen synthase kinase 3 β activity and the AMPK-dependent pathway. In addition, it was possible that a combination of melatonin and resveratrol may exert a synergistic effect on SIRT1 activity, and that this combination treatment could be more neuroprotective than each agent alone (Kwon et al., 2010). Melatonin has also been shown to potentiate the neuroprotective effect of resveratrol against oxidative injury by enhancing heme oxygenase-1 (HO-1) expression, and moreover, their combined use provided neuroprotection against oxidative stress in rat primary neurons and astrocytes, possibly *via* stability control of HO-1 protein through modulation of PI3K-Akt-GSK3β pathways. These results suggest that the combination of melatonin and resveratrol could be an effective way to control oxidative stress and neuroinflammatory processes in the brain, providing new means to treat neurodegenerative disorders (Kwon et al., 2011).

The combination of resveratrol and melatonin had protective effects on *N*-methyl-*N*-nitrosourea-induced rodent breast cancer. The treatment reduced tumor incidence, significantly decreased invasive and *in situ* carcinomas and prevented the food intake reduction resulting from carcinogen application in rats (Kisková et al., 2012). However, the reason for the superior effect of resveratrol/melatonin remains unknown.

For their many properties, the resveratrol-melatonin combination also was explored for the potential benefits in postmenopausal women. In ovariectomized and obesity rats with associated metabolic alterations, the combination of resveratrol-melatonin effectively normalized anthropometrical, biochemical, and histopathological parameters (Majumdar et al., 2014). The authors indicated that resveratrol and melatonin may act on dif-

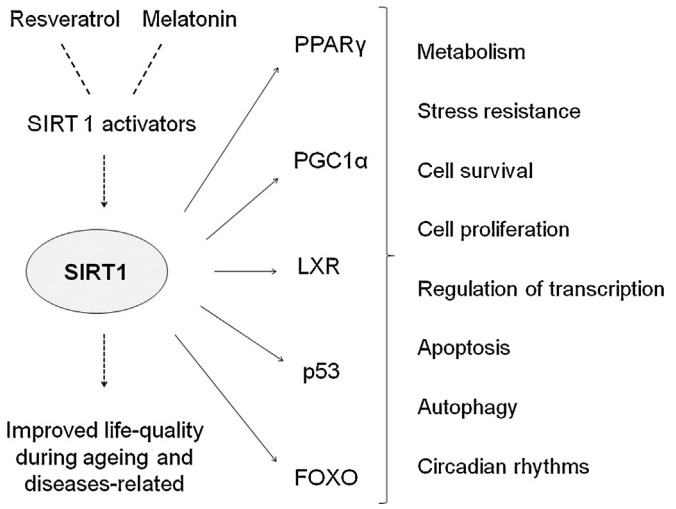


**Fig. 4.** Schematic interaction between sirtuin 1 (SIRT1) and some of its substrates in mammalian cells involved in different functions related with ageing.

ferent targets, modulating different pathways involved in glucose and lipid metabolism.

Finally, the presence of both melatonin and resveratrol in some Mediterranean foods and beverages (Tan et al., 2012; Vitalini et al., 2013) adds a new factor to the hypothesis of health potential benefits associated with Mediterranean dietary patterns (Kwon et al., 2011; Iriti and Vitalini, 2012). In this view, it is interesting that both melatonin and resveratrol are present in red wine and in other constituents of the Mediterranean diet, and they would have synergistic preventive effects compared to the diets that contain only a single compound. This could contribute to optimization of physiological functions in humans (Kwon et al., 2011). Related to this, Lamont et al. (2011) found that resveratrol and melatonin, at concentrations found in red wine, significantly reduced infarct size compared with control hearts in wild-type mice *via* the powerful survivor activating factor enhancement pathway.

Further investigation is necessary to precise the exact mechanisms underlying the possible cooperative beneficial actions of melatonin and resveratrol. Furthermore, additional studies are required for identifying the clinical efficacy involved in nutritional therapies to reduce the risk of cancer, cardiovascular, and neurodegenerative diseases with combined melatonin plus resveratrol treatments.

## 4. Conclusions

Numerous studies indicate that the consumption of antioxidants is crucial to health and beneficial to lifespan, consistent with the free radical theory of aging. However, recent findings have revealed that ROS formation is likely not the main cause of aging (Hekimi et al., 2011) and while chronic high levels of ROS can produce cellular damage, contributing to the aged phenotype, low levels are implicated in cellular stress responses and survival mechanisms, which are highly regulated processes controlled by a complex network of intracellular signaling pathways (López-Otín et al., 2013). By sensing the intracellular nutrient and energy status, the functional state of mitochondria, and the concentration of ROS produced in mitochondria, the longevity network regulates lifespan across species by coordinating information flow along multiply diverse signaling pathways, including vitagenes which are genes involved in preserving cellular homeostasis during stressful conditions (Cornelius et al., 2013). Vitagenes encode for heat shock proteins Hsp32 and Hsp70, the thioredoxin and the sirtuin protein systems (Calabrese et al., 2008). Dietary antioxidants have recently been demonstrated to be protective through the activation of hormetic pathways, including vitagenes (Cornelius et al., 2013), such as both melatonin and resveratrol that promote SIRT1 protein expression (Fig. 4) (Allard et al., 2009; Tajes et al., 2009). Further research is required to explain the role of ROS in aging processes, as well as new investigations about compounds that activate the survival signaling pathways, such as that of SIRT1. This could provide a promising therapeutic strategy to protect against the deterioration of biological functions, thereby retarding or reducing the risk of many age-related diseases (Tajes et al., 2009; Cristòfol et al., 2012; Kireev et al., 2013). Accordingly, it is also important that subsequent studies identify the possible beneficial effects of antioxidants (in particular antioxidants presents in foods or nutritional supplements) in aging processes and several related-disorders, especially when there are elevated levels of ROS.

With regard to the most frequently observed age-dependent decline of nocturnal melatonin and its association with impaired circadian rhythmicity in elderly persons, a substitution therapy in aged individuals seems promising, at least to some degree (Hardeland, 2013). Melatonin can be proposed as a potential anti-aging strategy that offers both antioxidant and possibly SIRT1 activation effects for treating senescence processes (Tajes et al., 2009). In addition, the beneficial effects of melatonin on human health as a result of the consumption of this agent in the diet deserve more detailed analysis (Tan et al., 2012).

## Conflict of interest

The authors have no conflicts of interests.

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