

Resveratrol: new avenues for a natural compound in neuroprotection

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ABSTRACT

This review summarizes the effects of resveratrol in neurodegenerative diseases and speculates on the direction the field will take in the immediate future. In particular, we emphasize studies on the effects of resveratrol on new pathways related to neurodegenerative diseases such as inflammatory processes, mitochondrial biogenesis and its control through gamma coactivator 1- α (PGC1 α), and the role of the tandem sirtuin 1 (SIRT1) and AMP-activated protein kinase (AMPK) in neurodegeneration and in neurohormesis. While not all reported results are free from controversy, the demographic shift toward an older population makes compounds with this broad spectrum of potential clinical applications particularly interesting.

Keywords: Resveratrol, polyphenols, sirtuin 1, aging, neurodegeneration, inflammation, autophagy.

Introduction

Resveratrol is a natural polyphenol that has been extensively investigated and has been proposed to protect Low-density lipoproteins (LDL) against oxidation, to have cancer chemopreventive activity, to modulate the hepatic synthesis of triglyceride and cholesterol and to inhibit platelet clotting [1]. Moreover, it has recently been discovered to play an important role in neuroprotection [2]. At present, many studies on resveratrol are available; these address its effects on cancer and heart disease, its neuroprotective activity, and its effects on longevity, inflammation, obesity and metabolism [3].

Up until now, many studies have shown that resveratrol extends the maximum or median life span and improves age-related markers in several species such as yeast [4], worms and flies [5], fish [6] and mice [7,8].

In spite of these findings, it remains to be clarified whether the effects of resveratrol on health and aging are strictly sirtuin 1 -dependent or modify other sirtuin 1-independent molecular pathways related to the aging process.

What is resveratrol? Where is it found?

Resveratrol (3,5,4'-trihydroxystilbene) is a non-flavonoid polyphenolic compound consisting of two aromatic rings attached by a methylene bridge [9]. With respect to its physical-chemical properties, resveratrol is a whitish solid powder with molecular formula $C_{14}H_{12}O_3$, a molecular weight of 228.25 g/mol and a melting point of 253-255°C. It is a soluble compound in lipids, ethanol and dimethyl sulfoxide, but practically insoluble in water. However, it is highly permeable and therefore considered as a Biopharmaceutics Classification System (BCS) class II compound, characterized high permeability and low solubility predicting a high the intestinal absorption. It exists as two isomers: *trans*-, which is more active biologically, and *cis*-, which is more unstable and not commercialized.

It is a natural phenol produced by 72 different plant species, including grapevines, pines and legumes. It is also found in high concentrations in peanuts, soybeans and pomegranates. When grapes are infected with *Botrytis cinerea*, it leads to the exclusive synthesis of resveratrol in the leaf epidermis and grape skins. During white wine production, grape skins are not fermented, so only red wine contains noticeable amounts of resveratrol [9]. Resveratrol also accumulates in plants in response to other exogenous factors such as injury or UV irradiation, in addition to other fungal infections.

Many compounds have been identified in red wine, including flavonols such as myricetin, kaempferol and the predominant quercetin, the flavan-3-ol monomers catechin and epicatechin, oligomeric and polymeric flavan-3-ols, proanthocyanidins, anthocyanins, phenolic acids such as gallic acid, caftaric acid, caffeic acid and *p*-coumaric acid, and the stilbene resveratrol. Thus, red wine appears to be the richest source of resveratrol through the skins, seeds, and stems of the grapes, where it is produced [9].

Resveratrol was first isolated from the root of *Polygonum cuspidatum*, a plant used in traditional Chinese and Japanese medicine [2], and was initially characterized as a phytoalexin [10]. In the 1990s, resveratrol was postulated to explain some of the positive effects of red wine. The term “the French paradox”

was coined in 1992 when it was observed that French people presented a low incidence of coronary heart disease despite having a diet rich in saturated fats. This led researchers to reflect on a possible reason and to propose that the high percentage of wine consumed in France was the cause of the apparent discrepancy. It was suggested that a reduction in platelet aggregation may be the main factor behind the effect on coronary heart disease. Several studies have been carried out that show a correlation between a low-to-moderate wine intake and lower mortality from cardiovascular and cerebrovascular diseases. It is also significant that heavy consumption of alcohol, including wine, increases the prevalence of myocardial infarction, cardiomyopathy, cardiac arrhythmias, hypertension, hemorrhagic shock and sudden death, which confirms that such consumption is harmful to the cardiovascular system [9]. Since these initial findings, many studies have shown that resveratrol can prevent or slow the progression of cancers, cardiovascular diseases and ischemic injuries. Moreover, it has been observed to enhance stress resistance and life span, not only in minor species such as the worm or fly [11], but also in mammals [8].

In terms of toxicity and safety, current information available on resveratrol is limited. Oral administration of a 20-mg/kg dose of resveratrol in rats showed harmful effects on growth, hematology, biochemistry and histopathology. On the other hand, a dose of 18,000 mg/kg led to death in most of the animals. In humans, single doses up to 10 g of resveratrol were well tolerated [12].

An important limitation of resveratrol is its low bioavailability due to its rapid metabolism into glucuronated and sulfonated conjugated forms [2, 13]. It has been observed that 46% of the drug is absorbed and results in conjugated forms [14]. An important aspect here is the presence of efflux proteins such as Multidrug resistance-associated protein 2 (MRP2) and breakpoint cluster region protein (BCR), which secrete conjugated forms to the intestinal lumen. This could restrict absorption [15]. Nevertheless, other studies have shown that hepatic metabolism is the main factor that affects the bioavailability of resveratrol. A study in humans revealed that after one hour of intravenous administration, only glucuronated and sulfonated forms were found in plasma [16]. Therefore, it is thought that metabolites could be partly responsible for the biological effects of resveratrol. Nonetheless, high doses of the compound

would be required to approach the active concentration described in animal models.

A noteworthy feature of resveratrol is its capacity to cross the blood-brain barrier in animal models. When intraperitoneally administered, resveratrol increased the activity of antioxidant enzymes in the brains of healthy rats [17]. Furthermore, a study in gerbils demonstrated that resveratrol reaches a concentration peak in the brain four hours after intraperitoneal administration [18].

Antioxidant properties of resveratrol: a major neuroprotective role?

Brain oxidative stress caused by a redox imbalance forms the basis of a number of diseases, including most age-related neurodegenerative diseases. The brain is the most metabolically active organ in the body, whereas it has a relatively low antioxidant defense and a high content of membrane lipids susceptible to oxidation. Therefore, brain tissue maintains a fragile redox homeostasis and neurons are particularly vulnerable to free radical damage. In such scenery, the neuroprotective potential of an antioxidant compound like resveratrol, which is accessible to the brain through diet, may be enormous.

Neurohormesis is a response to a moderate level of stress that enhances the nervous system's resistance to more severe stress that might be lethal or cause dysfunction or disease [19]. Neurohormetic phytochemicals such as resveratrol, sulforaphane, curcumin and catechins protect neurons against injury and disease.

It has long been known that *trans*-resveratrol, and with less potency the isomer *cis*-resveratrol, are effective antioxidants [20]. Their stilbene structure with two phenol rings means that it scavenges a variety of free radicals, including lipid peroxy and carbon-centered radicals, and reactive oxygen species. The neuroprotective effects of resveratrol, resulting from its antioxidant activity, have been widely reported. For instance, resveratrol treatment decreases markers of oxidative damage in *in vivo* and *in vitro* hypoxia-ischemia models, which have a high level of free radical formation. Resveratrol protected cultured neurons from senescence-accelerated mouse strain SAMP8 against their increased vulnerability to oxidative damage [21], and against amyloid beta oxidative

damage [22]. The antioxidant potency of resveratrol is also due to its capacity to induce the expression of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase in SAMP8 mice [23] and heme oxygenase-1 in a rat model of Alzheimer's disease [24]. Recent studies have revealed that resveratrol modulates genes related to redox pathways. It induced the transcriptional coactivator peroxisome proliferator-activated receptor PGC-1 α , which is a master regulator of oxidative stress and mitochondrial metabolism, in a mouse model of Parkinson's disease [25] and upregulated the expression of the transcription factor erythroid 2-related factor 2 (Nrf2) in an ischemia rat model [26]. The Nrf2-signaling pathway activates the transcription of many genes that are crucial for protection against oxidative stress. Resveratrol treatment increased the expression and nuclear translocation of forkhead transcription factors of the FOXO3a class in dopaminergic cells [27]. FOXO genes mediate the first line of defense against oxidative stress. Neuroprotection against oxidative stress by resveratrol is at least partially-mediated through the activation of the SIRT1 pathway.

Cellular oxidative stress resulting from mitochondrial dysfunction is central to the aging process and neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Oxidative stress also occurs in strokes and cerebrovascular conditions, which are more common with advancing age and increase the risk of dementia. Resveratrol alleviates the oxidative stress that leads to neurodegeneration. Consequently, this aspect of resveratrol's pleiotropic activity may help increase health span.

Resveratrol and aging: key role in SIRT1 pathway

Mammals express up to seven sirtuins (SIRT1–7). Sirtuins are a family of deacetylases dependent on NAD⁺ with a conserved catalytic core domain, but different protein sequences flanking their catalytic core domain and different subcellular localization. In particular, SIRT1 can translocate from cytoplasm to the nucleus, where it deacetylates nucleosomal histones at specific residues and contributes to telomere maintenance [28]. This may partly explain their capacity to extend life span. On the other hand, SIRT1 deacetylates other non-histone substrates, including components of DNA repair machinery such as

Ku70 [29] and Poly (ADP-ribose) polymerase (PARP) [30], and many transcription factors related to energetic metabolism such as PGC1- α [31], Hypoxia-inducible factor 1 α (HIF-1 α) [32] and Peroxisome proliferator-activated receptor α (PPAR- α) [33], as well as other transcription factors such as p53 [34,35] Forkhead box (FOXO) family transcription factors [36] and nuclear factor kappa B (NF κ B) [37], which are involved in apoptosis, oxidative stress and inflammation, respectively.

It is known that caloric restriction (CR) has beneficial effects on mammalian health, extends life span and delays the onset of age-associated diseases such as cancer, diabetes and cardiovascular diseases in non-human primates [38]. Recent studies have shown similar effects of CR on the health of monkeys, although an increase in life span was not observed in this particular study [39], authors concluded that a separation between health effects, morbidity and mortality, study design, husbandry and diet composition may strongly affect the life-prolonging effect of CR, to explain discrepancies with others reports where showed increases in life span in monkeys under CR was showed [38].

Resveratrol mimics several aspects of calorie restriction [40, 41], and CR effects appear to be, in part, dependent on SIRT1 [29]. Similar effects are produced by other small SIRT1 activators, among others SRT501 and SRT1720, that replicate signaling pathways triggered by CR [42, 43]. Furthermore, SIRT1 transgenic mice have phenotypes resembling CR [44]. These SIRT1 transgenic mice are leaner than littermate controls; are more metabolically active; display reductions in blood cholesterol, adipokines, insulin and fasted glucose; and are more glucose tolerant. Furthermore, transgenic mice perform better on a rotarod challenge and also show a delay in reproduction.

Several studies have indicated that resveratrol activates SIRT1 directly [45, 46] through a fluorescence assay known as Fluor de Lys, but other studies have questioned this finding and shown that measuring SIRT1 activity by fluorescent substrate assay could lead to false results [47], since resveratrol only activates SIRT1 if the substrate is attached to a fluorophore.

It has been reported the effects of SIRT1 deficiency and overexpression on mouse learning and memory as well as on synaptic plasticity, and it was demonstrated that the absence of SIRT1 impaired cognitive abilities, associated with defects in synaptic plasticity. In contrast, brain overexpression of SIRT1 develops normal synaptic plasticity and memory [48]. Authors conclude the key role of SIRT1 in learning, memory and synaptic plasticity in mice. However, resveratrol have other beneficial effects apart from SIRT1 activation that renders it active in absence of SIRT1. For example, several studies showed that resveratrol is a potent activator of AMPK in neuronal cell lines, primary neurons, and the brain [49] but these resveratrol-mediated AMPK activation during were independent of SIRT1. Furthermore, many of the actions of resveratrol, including mitochondrial biogenesis and neurite outgrowth, depended on the presence of a functional AMPK complex and its upstream regulator LKB1. Moreover, recent studies have found that resveratrol inhibits PDE4 increasing cAMP levels that increases AMPK activity, which leads to an increase in the NAD⁺/NADH ratio and in the activation of SIRT1 [50].

Resveratrol extends life in numerous species, although some discrepancies between laboratories remain unexplained [4]. In mice, resveratrol prevents the early mortality associated with obesity [7], and recently it was demonstrated to prolong life in lean, healthy animals [8]. The deaths that have been prevented in obese mice seem to have resulted primarily from vascular complications, which are not a significant cause of mortality in lean mice, but are associated with morbidity and mortality in humans. Therefore, the mouse studies provide good rationale for studying the effects of resveratrol on human health. However, the influence of factors such as interspecies differences in metabolism, genetic variation, diet, physical activity, disease and mental health should not be underestimated when extrapolating from rodent models. Further experimental evidence is needed to clarify the importance of SIRT1 and other potential mechanisms in the effects of resveratrol.

Neuronal survival and autophagy: role for resveratrol.

Autophagy is an intracellular catabolic process involved in protein and organelle degradation via the lysosomal pathway [51]. In animals, autophagy works as a central process in cellular quality control by removing waste or excess proteins and organelles. Impaired autophagy and the age-related decline of this pathway favor the pathogenesis of many diseases that occur primarily in old age such as neurodegenerative diseases and cancer. The functional efficiency of the autophagic–lysosomal system clearly declines during aging, which compromises the maintenance of a healthy cell and can lead to certain proteinopathies and neurodegeneration typical of aging [52]. Several studies have also demonstrated that enhancing autophagic degradation, for example with rapamycin, has therapeutic potential in experimental models of protein aggregation diseases such as Huntington's [53] and Parkinson's diseases [53]. The signaling pathways regulating autophagy and the aging process are linked to each other at the molecular level. In particular, the repressive effects of the mammalian target of rapamycin (mTOR), an evolutionarily conserved protein kinase for modulating autophagy, the role of Beclin-1, a repressor or activator of autophagy, and the activator LC3B have been described [51, 52]. Interestingly, recent studies have revealed that different stress resistance and longevity signaling pathways such as p53 [54] and SIRT1 [55] are also potent regulators of autophagic degradation. Recent studies demonstrate that the advantages of consuming polyphenols such as resveratrol, catechin, quercetin, silibinin and curcumin may also be connected to autophagy induction. This is associated with the negative regulation of SIRT1 on mTOR [556]. Resveratrol reduces the activity of mTOR in a SIRT1-dependent manner [57]. Sirtuin 1 interacts with and deacetylates pro-autophagic proteins Atg5, Atg7, and Atg8 [55]. Furthermore, SIRT1 is shown to deacetylate the major AMPK kinase LKB1, thereby increasing its activity and capacity to activate AMPK [57]. Thus, the SIRT1/LKB1/AMPK pathway may be involved in regulating autophagy. In addition to activating SIRT1, resveratrol has also been shown to inhibit p70 S6 kinase, thereby suppressing autophagy [58]. It seems that multiple target molecules are involved in the regulation of the effects of polyphenols on autophagy. Investigations of these molecular pathways would identify the molecular target(s) in regulation of autophagy in chronic inflammatory diseases such as chronic obstructive pulmonary disease and diabetes, where autophagy

is deregulated [59-62] and, as mentioned above, major neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease [2, 53, 54].

Resveratrol implication in the inflammation process and neurodegeneration.

The inflammatory trigger could be a variety of stimuli, including tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), T-cell activation signals, reactive oxygen intermediates, etc., which promote the activation of NF κ B, the central regulator of inflammation [63-65]. A number of studies have demonstrated that resveratrol mediates the down-regulation of various inflammatory biomarkers such as TNF- α , cyclooxygenase-2 (COX2), inducible nitric oxide synthase (iNOS) and interleukins [66-69]. This activity seems to depend on some structural features of resveratrol such as the number and position of hydroxyl groups and also the action of resveratrol on SIRT1.

Gentilli *et al.* [70] demonstrated that resveratrol exerts an inhibitory action on COX2, acting as an aryl hydrocarbon receptor antagonist and a direct inhibitor. Resveratrol also inhibits nitric oxide (NO) generation, cytosolic iNOS protein levels and lipopolysaccharide (LPS)-activated macrophages. Moreover, several studies have indicated that the phytoalexin inhibits the translocation of p65 to the nucleus, thereby blocking the proinflammatory action of NF κ B pathways in several tissues. Several studies have reported the suppression of the pro-inflammatory kinases c-Jun N-terminal kinase-1 (JNK-1) and I κ B kinase β .

(IKK β), the intra-nuclear binding of NF κ B, a reduction in the expression of TNF α and IL-6 in mononuclear cells, and TNF α and C reactive protein plasma concentrations after treatment in humans with an enriched resveratrol extract of *Polygonum cuspidatum* [71].

As mentioned above, resveratrol has been linked to an increase in PGC1- α , and this transcription factor is enriched in tissues with higher oxidative stress. On the other hand, the role of PGC1- α in the inflammatory process has been widely addressed in the literature, mainly in metabolic diseases, but also in the brain.

So resveratrol exerts part of its anti-inflammatory activity through the activation of the transcriptional role of PGC1- α on well-known mediators of inflammatory processes such as several cytokines.

Therefore, the involvement of multiple intracellular resveratrol targets in neuroinflammation seems to be clear, although more studies on the structure/activity relationships are required in order to analyze the exact role of this effect on the beneficial activity of resveratrol in the treatment and prevention of neurodegenerative processes [72].

Several toxic paradigms, both *in vitro* and *in vivo*, of neuroinflammation have been tested with resveratrol. For instance, resveratrol averts neuronal loss in several animal models in which neurons are exposed to toxic agents. Rats with cognitive loss induced by streptozocin, that induces a decrease in the central metabolism of glucose jointly with a excitotoxic mechanism of neurotoxicity, had improved memory and learning (tested by means of maze negotiation and avoidance of foot shocks) after being given resveratrol [73]. In another murine model, in which rats were injected with colchicine (which disrupts microtubules and interferes with axonal and dendritic transport), resveratrol again alleviated the cognitive function deficit, measured by the water maze test [74]. Moreover, in newborn rats, resveratrol reduced neuronal loss after traumatic brain injury. Elderly rats fed pterostilbene, another polyphenol found in grapes and blueberries, performed better in the water maze test than those fed a control substance, and pterostilbene provided even greater *in vitro* protection in a chemical-induced neurotoxicity model than resveratrol, as well as in a murine model of senescence (SAMP8) [75].

The neuroprotective role of polyphenols has also been gated with the inhibition of microglial function, for example resveratrol exerts anti-inflammatory effects in microglia and astrocytes by inhibiting different proinflammatory cytokines and key signaling molecules, as NF κ B and the activator protein 1 (AP-1) [76, 77].

Conclusions

Much evidence shows that hormetic phytochemicals are an important resource for the development of novel neuroprotectants [19,78]. Hormetic

phytochemicals activate several transcription factors (NFκB, Nrf2 and CREB) and modulate the adaptive stress response to various stimuli [19]. The autophagy process also has a key role in neuroprotection and has been related to the pleiotropic action of resveratrol [79] (Fig. 1).

Polyphenols may induce epigenetic changes that are neuroprotective. Histone acetylation may be implicated in the pathogenesis of several dementing illnesses, including Alzheimer's disease and Parkinson's disease [80] (Fig. 2). As mentioned above, SIRT1, which may be a target of resveratrol action, also has histone deacetylase action, which leads to conformational changes in DNA-wrapped histones that prepare the DNA for transcription by RNA polymerases [81, 82]. Mice engineered with a defect in histone acetylation show greater memory deficits in old age [83], so the activity of resveratrol on the histone deacetylation role by activation of SIRT1 should not be underestimated.

In terms of the effectiveness of resveratrol or its derivatives in humans, several clinical trials on the use of resveratrol alone or in combination with other substances in the treatment of dementia are now under way [see 9 and 13, for revision].

In light of the evidence presented in this review and in the literature currently available, special attention should be given to the possibility of dietary countermeasures to fight against age-related neurodegenerative diseases.

Abbreviations: **AMPK:** AMP-activated protein kinase; **AP-1:** activator protein 1; **BCR:** breakpoint cluster region ; **cAMP:** Cyclic adenosine monophosphate; **COX- 2:** cyclooxygenase-2; **CR:** caloric restriction; **CREB:** cAMP response element-binding; **FOXO:** Forkhead box; **HIF-1α:** Hypoxia-inducible factor 1α; **IKKβ:** IκB kinase β; **IL-1,** interleukin-1; **iNOS:** inducible nitric oxide synthase; **JNK-1:** c-Jun N-terminal kinase-1; **LDL:** Low-density lipoproteins; **LPS:** lipopolysaccharide; **MRP2:** Multidrug resistance-associated protein 2; **mTOR:** mammalian target of rapamicyne; **NFκB:** nuclear factor kappa B; **NO:** Nitric

oxide; **Nrf2** : erythroid 2-related factor 2; **PARP**: Poly (ADP-ribose) polymerase; **PDE 4**: Phosphodiesterase 4; **PGC1- α** : Peroxisome proliferator-activated receptor- γ coactivator 1- α ; **PPAR- α** : Peroxisome proliferator-activated receptor- α ; **SIRT1**: Sirtuin 1; **TNF α** : tumor necrosis factor- α

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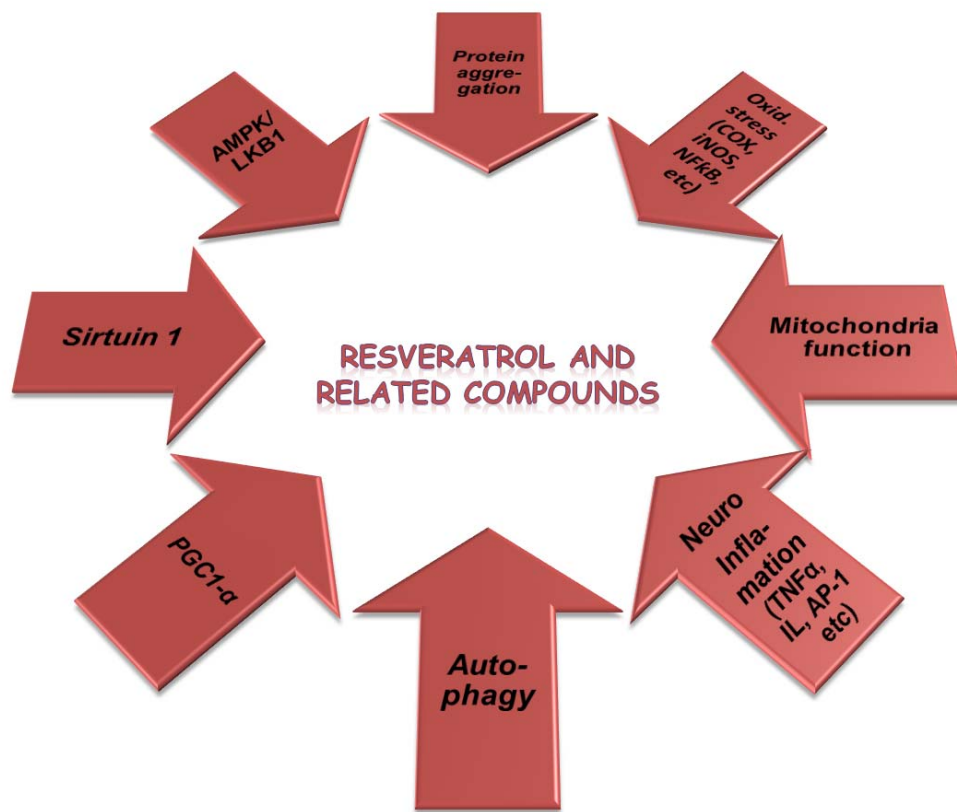


Figure 1: Protective effects and mechanism of resveratrol in the nervous system

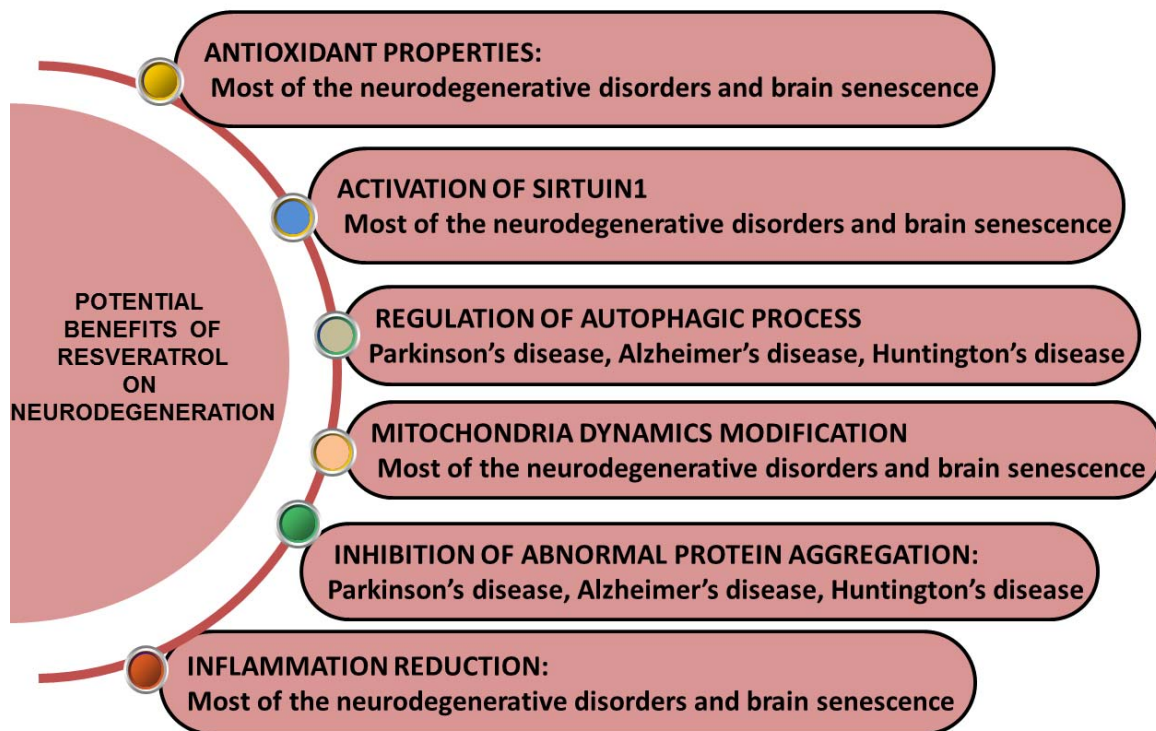


Figure 2: Non-exhaustive list of potential benefits of resveratrol on neurodegenerative diseases.