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Review

The pleiotropic neuroprotective effects of resveratrol in cognitive decline and Alzheimer's disease pathology: From antioxidant to epigenetic therapy

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ABSTRACT

While the elderly segment of the population continues growing in importance, neurodegenerative diseases increase exponentially. Lifestyle factors such as nutrition, exercise, and education, among others, influence ageing progression, throughout life. Notably, the Central Nervous System (CNS) can benefit from nutritional strategies and dietary interventions that prevent signs of senescence, such as cognitive decline or neurodegenerative diseases such as Alzheimer's disease and Parkinson's Disease. The dietary polyphenol Resveratrol (RV) possesses antioxidant and cytoprotective effects, producing neuroprotection in several organisms. The oxidative stress (OS) occurs because of Reactive oxygen species (ROS) accumulation that has been proposed to explain the cause of the ageing. One of the most harmful effects of ROS in the cell is DNA damage. Nevertheless, there is also evidence demonstrating that OS can produce other molecular changes such as mitochondrial dysfunction, inflammation, apoptosis, and epigenetic modifications, among others. Interestingly, the dietary polyphenol RV is a potent antioxidant and possesses pleiotropic actions, exerting its activity through various molecular pathways. In addition, recent evidence has shown that RV mediates epigenetic changes involved in ageing and the function of the CNS that persists across generations. Furthermore, it has been demonstrated that RV interacts with gut microbiota, showing modifications in bacterial composition associated with beneficial effects. In this review, we give a comprehensive overview of the main mechanisms of action of RV in different experimental models, including clinical trials and discuss how the interconnection of these molecular events could explain the neuroprotective effects induced by RV.

1. Introduction

According to 2015 United Nations report on the ageing of the world population, it is expected that the number of people aged 60 and over worldwide will double in the next 35 years, reaching almost 2.1 billion people. Ageing is an inevitable and irreversible process characterized by the progressive functional decline of organisms at the molecular, cellular and physiological level (Sen et al., 2016; López-Otín et al.,

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2013a). Despite these improvements in life expectancy, the incidence of common age-related chronic diseases as Alzheimer's Disease (AD) and other neurodegenerative diseases is expected to be increased.

During the last decade, a plethora of research demonstrated that ageing and neurodegeneration are closely related (Hung et al., 2010). Hence, several pathological mechanisms, such as the increase in oxidative stress (OS), mitochondrial dysfunction, inflammatory response, and reduction in gut microbiota composition have been linked to accelerate ageing (Petersen and Smith, 2016). Especially, OS has been established significant in the aetiology of a variety of age-related neurodegenerative diseases. Older adults are susceptible to OS due to impairment in their endogenous antioxidant systems. Indeed, most theories of ageing proposed that the accumulative OS leads to mitochondrial dysfunction, oxidative damage and inflammation.

Nutrition and supplementation are a crucial factor in the efficient clinical care of people with age-related cognitive-decline, particularly in those with dementia and AD (Shah, 2013; Shea and Remington, 2015; Hu et al., 2013; Bailey and Arab, 2012; Smith and Blumenthal, 2016; Dominguez and Barbagallo, 2018). Several reviews have described that nutrition affects brain structure and function throughout life (Vauzour, 2017; Spencer et al., 2017; Georgieff et al., 2018; Gomez-Pinilla and Gomez, 2011). Accordingly, studies have proved significant beneficial effects of the administration of antioxidant molecules, even promoting the lifespan extension of multiple model organisms (Banerjee and Ghosh, 2016). In particular, polyphenols with antioxidant and anti-inflammatory properties were proposed to be a useful strategy to contribute to the prevention of age-related diseases (Yang et al., 2015). Several studies attributed a multitude of health benefits to polyphenols, such as the reduction in OS and inflammatory agents and the maintenance of mitochondrial integrity (Pandey and Rizvi, 2009) as well as improvements in synaptic plasticity (Wang et al., 2013a; Li et al., 2009; Dias et al., 2016; Caracci et al., 2019) and changes in endoplasmic reticulum (ER) stress (Gaballah et al., 2016a; Wang et al., 2018a).

Natural polyphenols are divided into phenolic acids, flavonoids, stilbenes, and lignans (Tresserra-Rimbau et al., 2018). p-Coumaric, caffeic, ferulic and synaptic acids are the principal phenolic acids available in human nutritional food. Quercetin, myricetin and catechin are the main flavonoids found in food, whereas resveratrol (RV) is the most studied stilbene structure. Polyphenols are responsible for several health benefits of consuming fresh fruits and vegetables and are the attractive focus to face health challenges in several illnesses (Fernandes et al., 2017a; Sarubbo et al., 2017). Among many polyphenolic compounds, here we focus on RV, which is found in common dietary sources such as grapes, berries, peanuts, red wine, and in some herbal remedies, has been postulated as a potent antioxidant, among other properties. Indeed, research has described several beneficial activities of this compound, which help it to play essential roles in treatment against cardiovascular diseases and cancers (Oomen et al., 2009; Saiko et al., 2008), as well as degenerative disorders in the brain, including AD (Choi et al., 2012).

Moreover, increasing evidence demonstrates that changes in the epigenome during ageing leads to transcriptional alterations and genomic instability, mainly, contributing to the appearance of age-related diseases, such as cancer and neurodegenerative diseases (Sen et al., 2016; Guillaumet-Adkins et al., 2017). Therefore, nutritional epigenetics has reached a milestone in the last decade being one of the most exciting fields to explain the mechanisms linking gene and diet; so far, its development can elucidate the known beneficial role of nutrition in ageing and age-related disease. There is a general consensus based on evidence from animal models and human supporting the idea that the development of the idiopathic neurodegenerative disease is strongly associated with the quality of lifestyle starting from prenatal age (Gabbianelli and Damiani, 2018). Overall, most of the natural antioxidants have been described as neuroprotective compounds through different mechanisms. Nevertheless, its capability to modify epigenetic marks is becom ing a point of great interest in the latest published works in several systems and organisms (Sen et al., 2016; Guillaumet-Adkins et al., 2017). It is opening new avenues of research to explain the beneficial effects of polyphenols in ageing and age-related diseases.

In this review, we focus on the pleiotropic effects of RV such as OS, inflammation, apoptosis, mitochondrial function, proteostasis,gut microbiota diversity and lifespan. Furthermore, we focus on the epigenetic changes and transgenerational epigenetic inheritance effects modulated by RV, with potential to reduce ageing, and age-related cognitive impairment.

2. Oxidative stress, on the road to neurodegenerative diseases

The accumulation of free radical damage over time leads to increased inflammation within the brain. Thus, stress can also disrupt the homeostatic balance between anti- and pro-inflammatory cytokines inducing neurodegeneration. A recent study suggested that individuals with lower antioxidant mechanisms are more vulnerable to OS. The increase in OS biomarkers was correlated with raised levels of inflammatory cytokines; both were associated with decreased cognitive function, leading to a reduced lifespan (Baierle et al., 2015).

The pathogenesis of the primary neurodegenerative diseases remains unclear. However, growing evidence suggests that OS may play a critical role in the brain of patients with neurodegenerative disorders, such as AD (Tönnies and Trushina, 2017). Under physiological conditions, antioxidants enzymes maintain at relatively low levels ROS. Likewise, the redox balance can be disturbed by inflammation or mitochondrial dysfunction. On the one side, the neuropathogenesis of AD and Parkinson's disease (PD) is associated with the accumulation of misfolded proteins, which can induce the release of ROS through an inflammatory response. On the other side, aberrant mitochondrial function, which often accompanies aberrant ROS production, is closely related to neurodegenerative disorders, such as Huntington's disease (HD) (for revision see (Liu et al., 2017a)).

The high consumption of oxygen added to elevated polyunsaturated fatty acid content in cell membranes, as well as weak antioxidant mechanisms, renders the brain more vulnerable to OS (Kim et al., 2015). Significant biological markers related to OS have been found in the brain of individuals affected by neurodegenerative diseases. Likewise, some biomarkers of OS have also been found in peripheral tissues (Table 1). Therefore, there is evidence of increased OS in both brain and peripheral tissues of individuals affected by neurodegenerative diseases (Mancuso et al., 2006).

In the same way, studies have shown lower antioxidant defence markers, such as the activity of enzymes of the antioxidant defence (SOD, GPX and CAT) the state of components of blood glutathione (GSH) system and oxidative changes of plasma proteins, in patients samples compared to controls (Franco et al., 2007; Bennett et al., 2009).

Considering the crucial role played by OS in ageing and neurodegenerative diseases (Fig. 1), a reduction in oxidative damage should lead to a delay in the development of the pathology. Hence, studies have suggested the antioxidant therapeutics could potentially mimic the physiological actions of the natural antioxidant defence system, resulting in slower ageing and prolongation of lifespan.

3. Antioxidant nutrients as novel neuroprotective agents

As previously mentioned, OS could be a key factor that leads to the development of neurodegenerative disorders. In this context, there was a strong scientific focus on the application of antioxidants therapies, with a particular emphasis for neuroprotection. Antioxidants compounds are capable of averting or removing oxidative damage-related diseases and revert the harmful effects of ROS/RNS. Among them, RV, a natural polyphenolic compound, is able to neutralize either directly ROS/RNS or indirectly through the upregulation of the expression of cellular defensive genes. Moreover, it also enhances the expression of various

Table 1
Summary of molecular changes in different tissues promoted by OS and presented by several neurodegenerative diseases. (For original references see (Mancuso et al. (2006); Migliore et al., 2005; Liguori et al., 2018; Niedzielska et al., 2016)).

		Brain	Blood	CSF	Urine
Lipid peroxidation	AD	HNE, MDA, Acrolein, TBARS, F2-IsoP, F4-NP	HNE, MDA, TBARS, F2-IsoP	HNE, MDA, F2-IsoP	F2-IsoP
	PD	HNE, MDA, Acrolein, TBARS, F2-IsoP	HNE, MDA, TBARS, F2-IsoPs	HNE, MDA	
	ALS	HNE, MDA	HNE, MDA, TBARS		
	HD	MDA, TBARS	HNE	HNE, F2-IsoP	
Protein oxidation and nitration	AD	PC, 3 N T	3 N T		
	PD	PC, 3 N T			
	ALS	PC, 3 N T	AOPP		
	HD	3 N T			
Carbohydrates oxidation	AD	AGEs	AGEs		
	PD	AGEs			
	ALS	AGEs	AGEs		
	HD				
DNA/RNA oxidation	AD	8-OHG, 8-OHdG, NPrG, 8-oxoGua	8-OHG, 8-OHdG	8-OHG,8-OHd, 8-oxoGua	
	PD	8-OHG, 8-OHdG, 8-oxodG	8-OHdG	8-OHdG	
	ALS	8-OHG, 8-OHdG	8-OHdG	8-OHG, 8-OHdG	8-OHG, 8-OHdG
	HD	8-OHG, 8-OHdG			

Abbreviations: HNE 4-hydroxynonenal; MDA malondialdehyde; TBARS Thiobarbituric acid reactive substances; ; F2-IsoP F2-isoprostanes; ; F4-NP F4-neuroprostane; ; CML N-carboxymethyl-lysine; PC Protein carbonyl; NT nitrotyrosine; AOPP AGEs glycation end products; ; 8−OHG 8-Hydroxyguanine; 8−OHdG 8-Hydroxy-2′-deoxyguanosine; 8-oxoGua 8-oxo-7,8-dihydro-guanine; CFS cerebrospinal fluid; AML Amyotrophic Lateral Sclerosis.

antioxidant enzymes for maintaining the cellular redox balance (for revision see (Truong et al., 2017)).

3.1. Resveratrol

RV (3,5,4′-trihydroxystilbene) is a polyphenol present in black grapes and its derivatives. However, its primary dietary sources include also blackberries, peanuts, and peanut products. Currently, RV has gained extensive attention due to its therapeutic potential. Numerous health effects have been related to its intake, including antioxidant, anti-inflammation, neuroprotective, anti-cancer, and anti-ageing activity (Baur and Sinclair, 2006; Malhotra et al., 2015; Jardim et al., 2018; Cosín-Tomàs et al., 2019). A meta-analysis of randomised controlled trials suggests that RV may be therapeutic for humans (Marx et al., 2018). Until now, scientific research had shown that RV could prevent or slow the progression of a wide variety of illnesses (Fernandes et al., 2017a). In addition to neurodegenerative diseases, RV can prevent cardiovascular diseases, including cancer, some hepatic (*e.g.* cholestasis) (Farghali et al., 2009; Wu et al., 2005; Ara et al., 2005) and ischemic injuries, insulin resistance, fat accumulation and inflammation associated with obesity, improvement of cognitive decline (Jeon et al., 2012) as well as enhance stress resistance (Palomera-Ávalos et al., 2017) and extend the lifespan from yeast to vertebrates (Porquet et al., 2014).

3.1.1. Pharmacokinetic profile

Regarding the pharmacokinetic (PK) perspective, RV has a low oral bioavailability (<1 %) because it is metabolised in the liver and rapidly eliminated. This may be the principal reason for the discrepancies between *in vitro* and *in vivo* studies, which can be attributed to the rapid conjugation to glucuronic acid and/or sulphates, forming glucuronides and sulphate conjugates. These conjugates are accumulated in plasma and excreted in urine (Walle, 2011). RV limited bioavailability is due to poor water solubility, limited chemical stability, and high metabolism, among other factors (Amri et al., 2012). However, considering its molecular weight of 228 Da and its lipid-soluble properties, RV could easily cross the blood-brain barrier (BBB), in fact, several animal studies have shown that it is able to cross the BBB (Fig. 2) (Amri et al., 2012; Virgili and Contestabile, 2000; Sinha et al., 2002; Wang et al., 2002).

Given all its limitations, researchers have focused on enhancing the PK parameters of RV, including the co-administration of inhibitors of trans-RV metabolism (Johnson et al., 2011) and the search for analogues (He and Yan, 2013). Most trans-RV metabolites were found to be derived by glucuronidation or sulphatation. For instance, after co-treatment between piperine and RV, an improvement in its bioavailability was observed *in vivo* (Johnson et al., 2011). Likewise, the combination of RV with other polyphenolic compounds can increase the *in vivo* efficacy (Singh et al., 2013). Furthermore, several drug delivery systems are designed to improve these inherent biologic limitations, such as nanoformulations (Amri et al., 2012; Summerlin et al., 2015).

3.1.2. Mechanism of action of resveratrol

RV is an effective drug which was named as a “promiscuous molecule” because of seems to act on many different molecular pathways and binding partners (Britton et al., 2015). Nevertheless, this variety of pathways might also explain the diverse range of effects in which RV appears to be beneficial for health, ageing and neurodegenerative diseases. The following sections contain a summary of the RV mechanisms to explain its actions (Fig. 3).

3.1.2.1. Anti-oxidative effects. The antioxidant activity of RV consists of its ability to scavenge free radicals and metals, like ion copper, aluminium and zinc (Leonard et al., 2003). In this regard, its antioxidant effect is involved in the mechanisms described below, which were reported in several *in vitro* and *in vivo* studies (Sönmez et al., 2007; Venturini et al., 2010). It has been demonstrated that RV reduces OS and improves the expression of several memory-related proteins (Rege et al., 2015). RV has an antioxidant action because it reduces the formation of ROS by inhibiting genes that encode pro-oxidant proteins such as Nicotinamide adenine dinucleotide phosphate oxidase ($NADPH^{+}$) and myeloperoxidase, inducing the expression of genes that code for several antioxidant enzymes such as SOD, CAT, thioredoxin (TRX) and GPX (Carrizzo et al., 2013; Liu et al., 2017b). In the same manner, RV decreases the activity of the enzymes involved in the development of OS, directly reducing the production of free radicals in tissues. As well, RV downregulates the expression of proteins that induce OS, such as Glycogen synthase kinase 3β (GSK-3β) (Simão et al., 2012). Moreover, RV acts to improve glial, oxidative and inflammatory responses by increasing the expression of Heme oxygenase-1 (HO1) and the extracellular GPX content in C6 cells induced by H_2O_2. Likewise, RV was also shown to upregulate the expression of HO1 by activating Nuclear factor erythroid 2-related factor 2 (NRF2) (Chen et al., 2005a). Besides, some authors observed that RV protected PC12 cells against amyloid-β (Aβ)-induced cytotoxicity, cell death and accumulation of intracellular ROS and inhibited the activation of Nuclear Factor Kappa B (NF-κβ) induced by Aβ in PC12 cells (Seo et al., 2018). Furthermore, RV decreased the lipid peroxide levels in cells exposed to Aβ (Rege et al., 2015) and inhibited membrane lipid peroxidation, decreasing the toxic effects produced by ROS. Additional antioxidant mechanisms of RV were also described and include sirtuin 1 (SIRT1) and

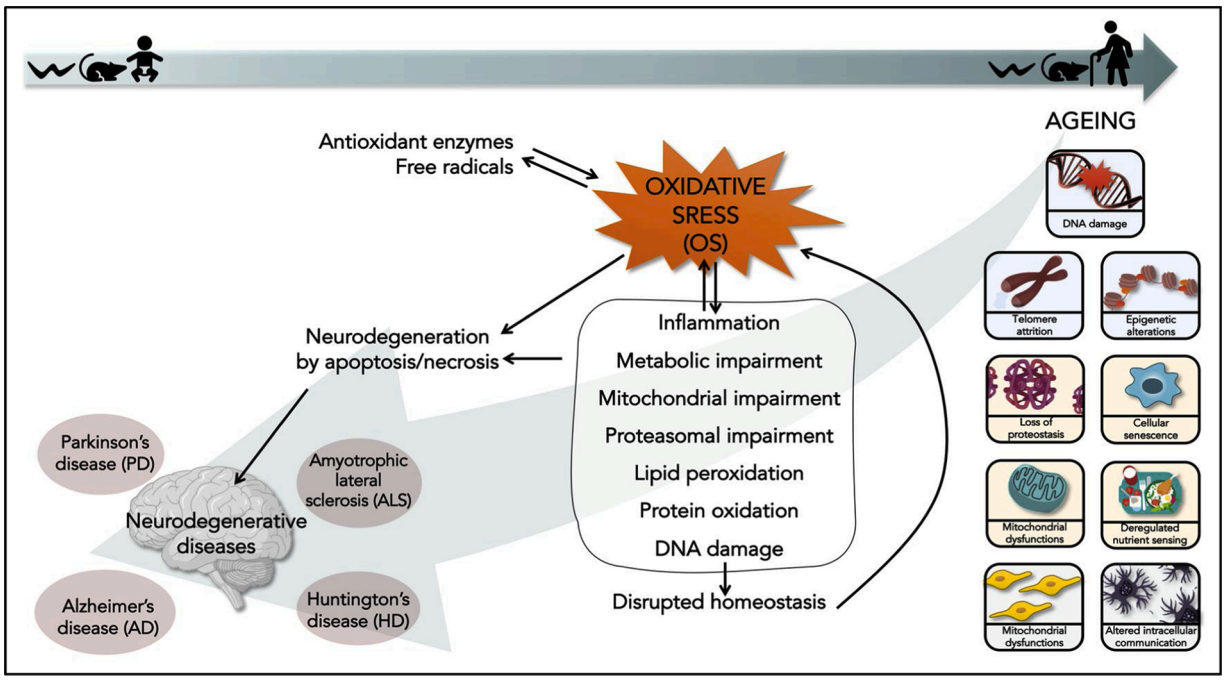

Fig. 1. Overview of the interplay between ageing hallmarks, molecular changes associated to OS triggering neurodegeneration and promoting neurodegenerative diseases such as AD, ALS, HD and PD.

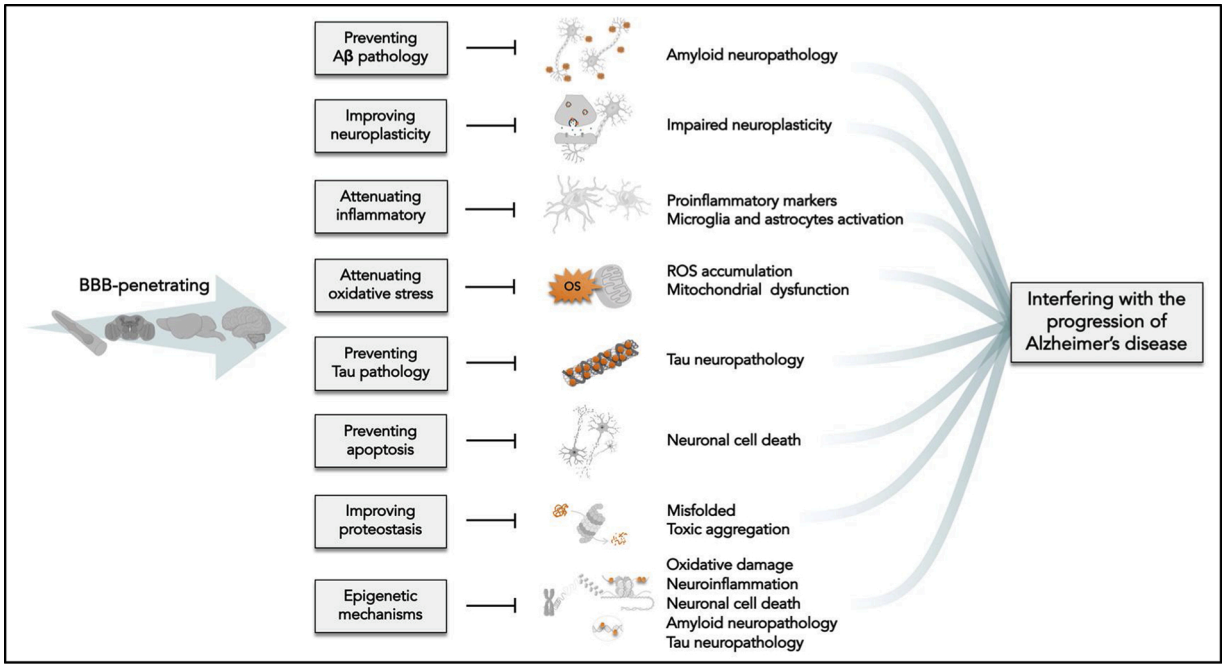

Fig. 2. Brain-penetrating polyphenols may attenuate AD pathology through blocking different key molecular events implicated in neurodegeneration. (Adapted from (Pasinetti et al., 2015)).

peroxisome-proliferator-activated receptor-g coactivator-1α (PGC-1α) activation, recovering the mitochondria dysfunction (Lagouge et al., 2006). As well, it has shown that RV protects neocortical neurons cultured from the senescence-accelerated mouse strain (SAMP8) against increased susceptibility to oxidative damage *via* SIRT1 activation (Cristòfol et al., 2012). As aforementioned, it has been established the interplay between the free radical production and the cognitive impairment observed in AD. Studies showed that RV ameliorates cognitive impairment, increasing GSH levels, which is an intracellular free radical scavenger (Kumar et al., 2007). Also, RV reduces the high levels of MDA and 3 N T observed in AD rats (Kumar et al., 2007). Likewise, ROS increase Aβ production and accumulation, inducing OS, and as a consequence, accelerate the progression of neurodegeneration (Kim et al., 2010). Hence, it has been shown that RV protects against Aβ-induced neurotoxicity. Finally, RV is also useful in suppressing inducible nitric oxide synthase (iNOS) production, which is involved in lipid peroxidation induced by Aβ and negative regulation of HO1 in a rat model of AD (Huang et al., 2011).

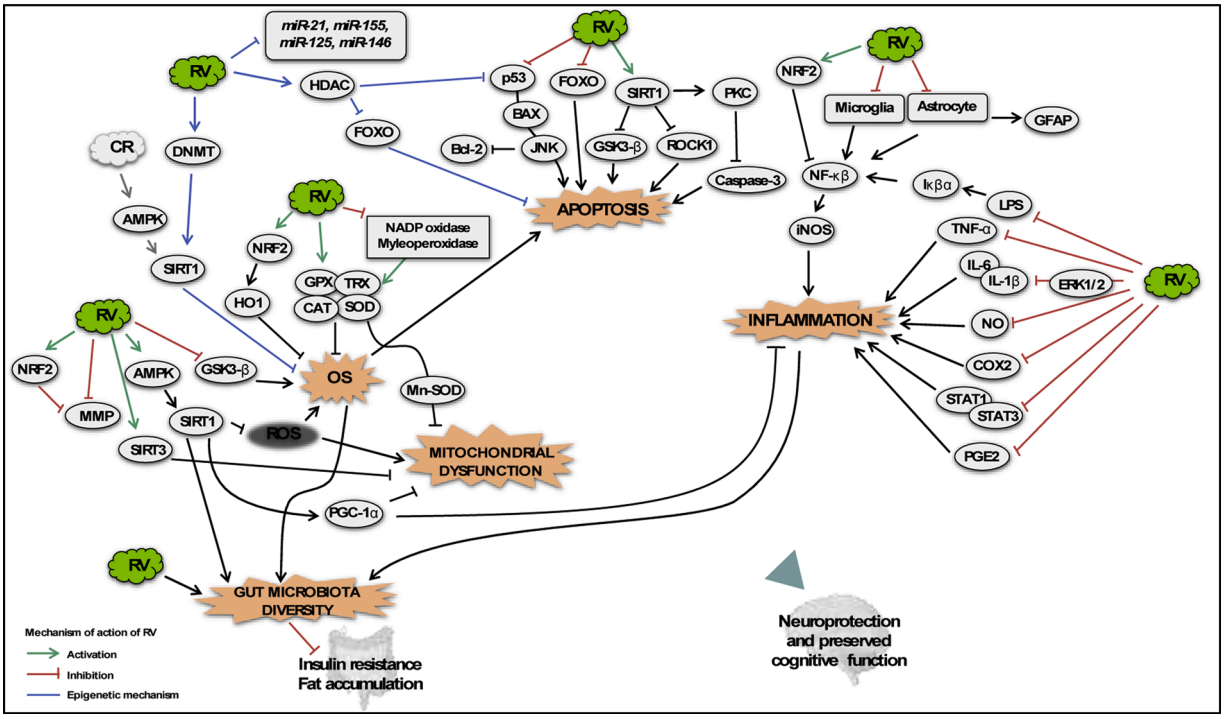

Fig. 3. Scheme of the putative mechanisms of action of RV on different processes (epigenetics, OS, mitochondrial dysfunction, inflammation, apoptosis, and gut microbiota) that mediate neuroprotection and preserve the cognitive function.

3.1.2.2. Anti-inflammatory effects. Various reports have shown that neuroinflammation is an important contributor to the pathogenesis of age-related neurodegenerative diseases (Chen et al., 2016; Guzman--martinez et al., 2019). The anti-inflammatory properties of RV are mainly associated with SIRT1 activation (Ohtsu et al., 2017), and the following down-regulation of the pro-inflammatory factor NF-κβ (Yi et al., 2011). Moreover, inflammatory responses include the activation of microglia, astrocytes, lymphocytes, and macrophages that trigger numerous pro-inflammatory mediators and neurotransmitters (Scuderi et al., 2014; Moore and O'Banion, 2002). Among them, microglia activation is considered as the hallmark of brain neuroinflammation, which releases highly pro-inflammatory cytokines, ROS, and NO what leads to protein oxidation, lipid peroxidation, DNA fragmentation, neuronal inflammation, and cell death (Bellaver et al., 2014; Zhang et al., 2010). Several studies have shown that RV mediates the downregulation of several pro-inflammatory markers such as Tumor Necrosis Factor-α (TNF-α), Cyclooxygenase-2 (COX2), iNOS, and interleukins (IL) (Yao et al., 2015; Huang et al., 2012; Lu et al., 2010). Hence, the activities of RV against neuroinflammation appear to target activated microglia and result in the downregulation of pro-inflammatory factors (Tomé-Carneiro et al., 2013; Bastianetto et al., 2015). For instance, the anti-inflammatory effect of RV is mainly attributed to a suppression of TNF-α (Shi et al., 2017) and IL-6 (Ohtsu et al., 2017) production. Likewise, RV treatment inhibits extracellular-signal-regulated kinase (ERK) 1/2 pathway and thus decreases the resulting IL-1β levels, depicting anti-inflammatory properties (Lee et al., 2010). RV acts as a direct inhibitor of COX2 and also inhibits the generation of NO, the protein levels of iNOS in the cytosol and of macrophages activated with lipopolysaccharide (LPS) (Farghali et al., 2009; Bi et al., 2005). Likewise, chronic administration of RV reversed the cognitive deficits and inhibited the production of inflammatory cytokines (Pinheiro et al., 2019). Other authors have also shown that RV inhibits the translocation of p65 to the nucleus and blocks the pro-inflammatory action of the NF-κβ pathway or acts as an inhibitor of signal transducer and activator of transcription (STAT) 1 and STAT3 activation induced by Aβ (Jeon et al., 2012) and microglial activation (Capiralla et al., 2012). On the other hand, Aβ peptides interact with various Toll-like receptors (TLR) such as TLR4 and can cause microglial activation (Capiralla et al., 2012). In addition, one of the significant pathways seems to involve SIRT1 activation, which promotes T helper (Th2) responses by increasing anti-inflammatory cytokine expression and upregulating PGC-1α (Nimmagadda et al., 2013; Yang et al., 2017). Regarding AD, neuroinflammation induced by treatment of Aβ1–42 in astrocytes and N9 microglial cell lines was dose-dependently inhibited by RV treatment by regulating NF-κβ translocation and *p-inhibitor of kappaβ* (*Iκβ*) expression (Zhao et al., 2015). Given that signalling of NF-κβ is involved in cell death induced by Aβ, another link between AD and the neuroprotective action of RV is its potential to decrease the expression of iNOS, Prostaglandin E2 (PGE2), cathepsin and NO modulated by NF-κβ (Kim et al., 2007). Moreover, it has been shown that RV reduces the levels of Glial fibrillary acidic protein (GFAP) and TNF-α, leading astrocyte inactivation in AD rats (Cheng et al., 2015).

3.1.2.3. Anti-apoptotic effects. It has also been demonstrated that RV exhibits a potent anti-apoptotic action. Although its role is mainly described in cancer (Lin et al., 2011; Jang et al., 1997), RV has also shown a neuroprotective effect through the prevention of neuronal cell death. RV prevent apoptosis-inducing factor and caspase-3 activity by both caspase-dependent and caspase-independent pathways (Bastianetto et al., 2011). Moreover, its partial inhibition of Aβ fibril formation also prevents neuronal cell death (Bastianetto et al., 2000) and modulates cell survival/death signalling pathway by interacting with Protein Kinase C (PKC). This modulation increases the level of PKC, improving synaptic plasticity (Menard et al., 2013). Besides, RV also improves synaptic plasticity, neuronal structures and function by the activation of the protein kinase A (PKA) and cAMP-responsive element-binding protein (CREB), as demonstrated in Chronic cerebral hypoperfusion (CCH) (Li et al., 2016). In addition, RV blocks the activation of c-Jun N-terminal kinases (JNK) and the downregulation of B-cell lymphoma 2 (Bcl-2), protecting cell viability (Kang et al., 2009). Regarding the SIRT1 pathway, RV protected PC12 cells and inhibited Aβ-induced cell apoptosis due to the upregulation of SIRT 1 expression and

downregulation of Rho-associated kinase 1 (ROCK1) (Feng et al., 2013). Likewise, its overexpression by RV effectively suppresses the apoptotic activities of p53, NF-κβ and Forkhead Box O (FOXO) and confers neuronal protection in AD (Pasinetti et al., 2015).

3.1.2.4. Mitochondrial effects. ROS production results in oxidative damage to mitochondria, causing a reduction of mitochondrial energy production (Wu et al., 2018a; Reddy and Beal, 2005). Mitochondrial dysfunction is a molecular marker of ageing that establishes a connection between ageing and AD (Cadonic et al., 2016; Huang et al., 2016). Mitochondrial dysfunction in neuronal and glial cells has been viewed as an essential component of neurodegeneration (Arun et al., 2015). Studies observed deficiencies of mitochondrial complexes in AD pathology (García-Mesa et al., 2012), which elevated levels of oxidative lesions and alterations of antioxidant enzymes (Garciá-Mesa et al., 2015). RV may modulate the mitochondria-related redox biology by a mechanism associated with the upregulation of manganese (Mn)-SOD (Sheu et al., 2013). Mitochondrial dysfunction can be ameliorated by inducing PGC-1α (Palomera-Ávalos et al., 2017; Rodgers et al., 2005; Corpas et al., 2019) *via* RV mediated modulation of AMPK/SIRT1 pathway (Chen et al., 2013a; Banerjee et al., 2015), resulting in beneficial effects in the mitochondrial function (Lagouge et al., 2006; Cantó and Auwerx, 2009a; Valenti et al., 2016; Tang, 2016). RV decreased the modifications observed in mitochondrial membranes through the inhibition of ROS accumulation in PC12 cells (Wang et al., 2018b). RV also suppressed the loss of mitochondrial membrane potential (MMP) induced by different challenges in several experimental models (Quincozes-Santos et al., 2014).

Taking into account these findings, RV displays antioxidant, anti-inflammatory, and anti-apoptotic activities, in such a way that induces beneficial changes in mitochondrial being a candidate for the development of adjuvant therapies for AD (Molino et al., 2016; Rege et al., 2014; Sawda et al., 2017).

3.1.2.5. Lifespan effects. Natural antioxidant compounds can extend the lifespan of multiple organisms. RV, among the most potent of these, has shown its ability to extend the lifespan (Table 2), protecting against age-related diseases such as AD, cancer and diabetes in mammals (for review see (Bhullar and Hubbard, 2015)). A meta-analytic study characterized the effect of RV on invertebrate and fish lifespan from published data. On the other hand, due to significant variability between studies, the results for nematodes and flies resulted in unclear evidence of the positive lifespan effects by RV. Instead, the lifespan of the turquoise killifish was positively affected by RV (Hector et al., 2012).

Table 2
Summary of the lifespan-extension effects of RV in different species. (Table adapted from (Bhullar and Hubbard, 2015; Howitz et al., 2003)).

Species	Effect on lifespan	Reference
S. cerevisiae	Extension	(Howitz et al., 2003)
	Marginal effect	(Viswanathan et al., 2005)
C. elegans	Extension	(Bass et al., 2007; Gruber et al., 2007; Greer and Brunet, 2009; Zarse et al., 2010; Wood et al., 2004)
	Robust extension	(Bauer et al., 2004)
	No effect	(Bass et al., 2007)
D. melanogaster	Extension	(Bauer et al., 2004; Wang et al., 2013b)
	Extension (only in females)	(Zou et al., 2009)
A. ludens	No effect	(Rascón et al., 2012)
A. mellifera	Extension	(Valenzano et al., 2006)
N. fuzeri	Extension	(Yu and Li, 2012)
N. guentheri	Extension	(Genade and Lang, 2013; Baur et al., 2006)
M. musculus	No effect	(Pearson et al., 2008; Strong et al., 2013; Stuart and Robb, 2013)
	Extension	(Pearson et al., 2008)

Abbreviations: *S. cerevisiae: Saccharomyces cerevisiae; C. elegans: Caenorhabditis elegans; D. melanogaster: Drosophila melanogaster; A. ludens: Anastrepha ludens; A. mellifera: Apis mellifera; N. fuzeri: Nothobranchius fuzeri; N. guentheri: Nothobranchius guentheri; M. musculus: Mus musculus.*

3.1.2.6. Gut microbiota effects. In the past decades, evidence suggests that gut microbiota might be a link between diet *"lifestyle"* and cognitive function (see (Dickerson et al., 2017) for review). Furthermore, various studies link gut microbiota dysbiosis and development of psychiatric disorders such as depression, autism, anxiety, as well as neurodegenerative diseases such as AD (Sampson et al., 2016; Zhang et al., 2018). In this sense, alteration in gut microbiota diversity that takes place with ageing, is associated with an increase in microglial activation (Bastiaanssen et al., 2019). Consistently, altered gut microbiome increases the risk of AD (Kowalski and Mulak, 2019). Therefore, in recent years, targeting gut microbiota has emerged as a potential therapy for neurodegenerative diseases (Santoro et al., 2018; Franceschi et al., 2018).

As aforementioned, RV is poorly bioavailable, but the persistence in the intestine (24 h) after ingestion could demonstrate that gut is a key tissue to modulate the effects of RV. Therefore, it has been hypothesized that RV induces changes on the gut microbiota composition through direct modulation of the bacterial diversity, promoting a healthy outcome, or through the modulation of the typical pathways in which RV produces its beneficial effects, including energy regulation. Thus, RV studies revealed by several human, animal models with *in vitro* studies the modulation of gut microbiota for RV (Ozdal et al., 2016).

3.1.3. αKlotho and resveratrol

αKlotho (KL) is a protein mainly expressed in the kidneys and the brain choroid plexus. It is present in the plasmatic membrane (m-KL), and it can also be found in biological fluids (Kuro-o et al., 1997). This circulating isoform can be generated by proteolytic processing of m-KL (p-KL) by membrane metalloproteinases, or from alternative splicing of the *KL* gene that generates a shorter protein (s-KL) lacking the transmembrane domain (Shiraki-Iida et al., 1998).

KL has a wide range of functions, acting both as a transmembrane protein and as a humoral factor. In the kidney, the principal function of m-KL is to act as a co-receptor of Fibroblast growth factor 23 (FGF23), mainly in the convoluted tubules. This is essential for phosphate and vitamin D regulation, which has a strong impact on healthy ageing and longevity (Tsujikawa et al., 2003). Interestingly, vitamin D in turns upregulates KL transcription after the activation of the vitamin D receptor (VDR) (Haussler et al., 2016). Similarly to RV, KL presents high antioxidant properties, mainly mediated by the activation of the transcription factor FOXO3a (Foster et al., 2011). Secreted KL can also inhibit Wingless-type integration site family (Wnt) pathway downstream signalling, coffering antitumor resistance and protecting the kidneys from fibrotic stress (Yamamoto et al., 2005). Besides, it can inhibit insulin and Insulin-like growth factor 1 (IGF1) signalling pathways, what has been directly correlated with an increase in mammal's lifespan (Satoh et al., 2012). It also presents strong anti-inflammatory and neuroprotective properties, making this protein a key factor for health and longevity.

Several studies have reported the impact of RV on the transcription levels of KL. In an *in vitro* model for studying vascular calcification stress, RV increased KL expression both in control and significantly in the stressor-treated group. The treatment with RV was able to rescue the pathologic phenotype generated on the vascular smooth muscle cells, increasing mitochondrial integrity and decreasing ROS production (Kurosu et al., 2005). Another study used rats with ROS-induced damage to the circulatory system *via* the chronic administration of D-galactose. KL levels in serum significantly increased when this rat model was treated with a combination of an active form of vitamin D and RV. This experimental group also presented a significant increase in SOD and CAT enzymes expression and activity, conferring protection from ROS stress (Zhang et al., 2016).

Other authors have also reported that intraperitoneal injection in

mice of RV for one week, increased both mRNA and protein levels of KL in the kidneys. This increase was also observed *in vitro*, in a temporal and dose-dependent manner. This effect was due to the transcription factors c-Jun and Activating transcription factor 3 (ATF3), which present union sites in the promoter region of *KL* gene. These proteins were transcriptionally upregulated and activated after RV treatment, which allowed its heterodimerization and direct activation of *KL* expression (Dehghani et al., 2019).

Haussler et al. postulated another mechanism for RV and KL interaction. As mentioned, RV increases *Sirt1* gene expression, which can upregulate both *KL* transcription and secretion. Sirt1-deacetylase activity modifies VDR to make it easier to activate by vitamin D, which will increase *KL* gene expression (Hsu et al., 2014). On the other hand, Sirt1 activates Disintegrin and Metalloproteinase 10 (ADAM10) expression, one of the metalloproteinases that process m-KL to its soluble form, increasing its dissemination throughout the body (Tsujikawa et al., 2003).

As can be seen in Table 3, RV and KL are both implied in ROS regulation, longevity, anti-diabetic and anti-cancer pathways, mitochondrial protection and have anti-inflammatory potential. Some of these properties are mediated through the same intermediates, but others are dependent on different pathways. Consequently, developing treatments with RV and KL, could combine the beneficial properties of these two molecules and may also lead to synergic effects increasing the beneficial characteristics they confer.

3.1.4. *Effects on proteostasis*

Maintaining a healthy proteome despite the ever-changing external and internal environment is a challenge every organism has to meet in order to succeed. For proteostasis maintenance, it is required that the cells be able not only to monitor and control the quality of the proteins produced but also to get rid of those that prove to be inefficient in performing their function or even harmful. Importantly, the proteostasis network is one of the foundations of neuronal organization, function and neurodegeneration (Newton et al., 2019; Klaips et al., 2018). RV has been shown to be involved in these processes in various ways through known or as yet unknown molecular mechanisms.

Molecular chaperones play a central role in the maintenance of a healthy proteome. They facilitate the folding and assembly of newly synthesized proteins, govern their transport, protect from misfolding, refold misfolded ensembles or target irreparable proteins to proteasomal and lysosomal degradation (Hartl et al., 2011). Hence, they emerge as crucial factors in neuronal biology (Ciechanover and Kwon, 2017). By regulating the expression of cytosolic chaperones or heat shock proteins, the Heat shock transcription factor-1 (HSF-1) is at the forefront of an adequate response to proteotoxic effects (Joutsen and Sistonen, 2019). RV treatment of both cell lines and human peripheral lymphocytes activates the HSF-1 promoter and elevated expression of the Hsp70 chaperone – comparable to moderate heat-stress, which conferred protection from lethal stresses (Putics et al., 2008). HSF-1 is regulated in a very intricate manner by various post-translational modifications and protein-protein interactions (Gomez-Pastor et al., 2018). As a potential mechanism of RV action, it has been shown that inhibitory acetylation of HSF-1 is removed by SIRT1, which leads to a longer DNA binding at the Hsp70 promoter (Westerheide et al., 2009). This was demonstrated to culminate in cytoprotection against mutant SOD1-induced neurotoxicity in motoneurons of mice (Han et al., 2012). Confirming this, RV also seems to protect against L-arginine-induced acute necrotizing pancreatitis (ANP) in mice, possibly through SIRT1-mediated deacetylation of p53 and HSF-1 (Wang et al., 2017). It is tempting to speculate that RV might influence other non-canonical but relevant HSF-1 functions (Barna et al., 2018). Both HSF-1, Hsp70 and SIRT1 overexpression also protected primate cells from the toxicity of misfolded proteins, although SIRT1 appeared to act *via* a non-catalytic manner (Arslan et al., 2012), which suggests other, RV-independent effects of SIRT1 on proteostasis. The SIRT1 regulated FOXO transcription factors, and their *C. elegans* DAF-16 orthologue are also major protective factors in proteostasis (Webb and Brunet, 2014) and neurodegeneration (McLaughlin and Broihier, 2018). Intriguingly, a well-known RV target, the NRF2 antioxidant and xenobiotic transcription factor is emerging as a key hub in proteostasis and neurodegeneration by regulating the endoplasmic reticulum proteostasis, proteasome and autophagy (Pajares et al., 2017). In nematodes, an age-associated decline observed in all HSF-1, DAF-16, and SKN-1/NRF2 activation and proteostasis (Ben-Zvi et al., 2009; Papp et al., 2012) might well respond to the multi-target effect of RV.

Various proteotoxic effects lead to the emergence of misfolded proteins with unstable conformations in other cellular compartments. The unfolded protein response (UPR) deals with these abnormal agents either in the endoplasmic reticulum (UPR^{ER}) or the mitochondria (UPR^{mt}). RV acts against ER stress by inducing the expression of heat-shock proteins and ER-associated degradation (ERAD) pathways (Lee et al., 2019). In addition, it was reported, that RV not only decreased the expression of UPR-related proteins and inflammatory mediators in the hippocampus but also attenuated postoperative learning and memory impairment in aged mice, accompanied by an elevated SIRT1 expression (Wang et al., 2018a). This was further supported the previous findings of a study showing that SIRT1 is a negative regulator of UPR in human type 2 diabetes (T2D) through inhibition of mTORC1 and ER stress,

Table 3
Different molecular pathways and actions modulated by RV and KL after their administration.

Properties	Resveratrol	Klotho	References
Antioxidant	The direct scavenge of some ROS molecules. It also directly regulates enzymes implied in ROS production.	Direct control of antioxidant enzymes expression.	(Forster et al., 2011)
	Indirect effect through SIRT1 activation of FOXO factors, and NRF2.	Indirect effect by activating FOXO factors.	(Foster et al., 2011)
Antitumor	The direct effect after conversion to piceatannol by Cytochrome P450 enzyme.	Modulation of the Wnt and IGF1 pathways.	(Satoh et al., 2012)
	Indirect through SIRT1 regulation of several genes implied in cell cycle and apoptosis.		
Anti-diabetic	Protection of pancreatic β-cells and increases sensitivity to insulin, mediated by SIRT1 and AMPK.	Regulates of insulin secretion modulating TRPV2 receptor.	(Zeldich et al., 2014)
	Reduction of glucose in the blood up-regulating the transporter GLUT4.	Protects pancreatic B-cell from apoptosis.	(Lin and Sun, 2012)
Anti-ageing	Through SIRT1 activation.	Inhibition of insulin and IGF1 signalling pathways.	(Satoh et al., 2012)
Mitochondria biogenesis	SIRT1-dependent deacetylation of PGC-1α that results in mitochondrial biogenesis.	Maintains integrity of the mitochondrial matrix, preventing mtDNA damage by ROS stress.	(Lin and Sun, 2015)
Anti-inflammatory	SIRT1-dependent deacetylation of NF-κβ.	Reduction of pro-inflammatory cytokines production.	(Sahu et al., 2018)
		Inhibition of NF-κβ.	(Hui et al., 2017)

Abbreviations: TRPV2: Transient receptor potential cation channel subfamily V member 2; GLUT4: Glucose transporter 4; mtDNA: mitochondrial DNA.

ameliorating systemic insulin-resistance and improving glucose homeostasis (Li et al., 2011). This image is further illuminated by the finding that in *C. elegans,* both UBL-5 and XBP-1 – which are involved in the UPR in the mitochondria and the ER, respectively – proved to be necessary for RV's action in the prevention of Aβ-toxicity (Regitz et al., 2016).

SIRT1 is often referred to in the context of another important regulator of energy homeostasis, the AMP-activated protein kinase (AMPK), which is also activated by RV. Interestingly, RV was demonstrated to increase the NAD-to-NADH ratio in an AMPK-dependent manner, which would explain an indirect SIRT1-activation by RV through AMPK (Um et al., 2010). In healthy mice and a mouse model of AD, it was shown that RV improved proteostasis by not only mitigating the secretion of Aβ but also by improving the capacity and activity for protein degradation through the proteasome system and by an upregulation of the AMPK/-SIRT1 pathway leading to improved neuronal resilience against misfolded proteins (Corpas et al., 2019). In accordance with these results, Solberg et al. (Solberg et al. (2014)) showed that RV reduces average amyloid-β plaque density by 2.3-fold in transgenic Aβ protein precursor/presenilin-1 (AbetaPP/PS1) (Alzheimer mutant) mice and also limits memory loss.

Through SIRT1 – probably its best-known interactor – RV has been shown to positively affect mitochondrial biogenesis in a mouse model of the peroxisomal neurometabolic disease X-linked adrenoleukodystrophy (X-ALD) (Morató et al., 2015). They found that overexpression of SIRT1 and RV treatment were both enough to help proteostasis *via* normalizing the redox homeostasis, mitochondrial respiration and bioenergetics failure in the axons of disease-affected neurons. In WI-38 fibroblasts, RV was able to attenuate senescence-induced alterations to cell morphology, senescence-associated β-galactosidase activity, and cell proliferation resulting from copper sulphate-induced premature senescence (CuSO4-SIPS) (Matos et al., 2017). This phenomenon relied on the improvement of cellular proteostasis by restoring copper-induced elevated protein levels, attenuating immunoglobulin-binding protein levels and reducing carbonylated and polyubiquitinated proteins through the induction of autophagy.

Besides ameliorating the effects of copper-induced early senescence partially through inducing autophagy, RV pretreatment is also capable of working against H_2O_2-induced cytotoxicity, morphological damage, oxidative stress and apoptosis (Wang et al., 2020). This might also act *via* the induction of autophagy, since not only did RV restore the levels of SIRT1 and autophagy-related proteins including LC3-II, Beclin-1 and p62, but autophagy inhibition by 3-methyladenine (3-MA) abolished the observed protective effects. Moreover, RV stimulated the clearance of misfolded proteins through increasing the expression of HSP72, restoring the chaperone activity of cluster in a SIRT1-dependent manner and increasing the activation of the autophagy and ERAD pathways during tunicamycin-induced ER stress (Lee et al., 2019). Another layer for the role of RV in autophagy regulation emerged when it was reported using mouse embryonic stem cells (ESCs) that it affects the activity of p53 in a complex way: negative regulation occurs through SIRT1 deacetylation and positive by AMPK phosphorylation (Suvorova et al., 2018). Interestingly, the resulting activation of p53 does not lead to apoptosis, but to stimulation of autophagy *via* upregulating the expression of the *dram1* (DNA-damage regulated autophagy modulator 1) gene. The resulting autophagy flux is beneficial in the maintenance of ESC pluripotency *in vitro*. The importance of autophagy in the mechanism of RV's action is demonstrated well by the fact that in an Alzheimer model of *C. elegans,* inhibition of macroautophagy, chaperone-mediated autophagy or proteasomal degradation prevented RV from reducing paralysis and amyloid-β-toxicity (Regitz et al., 2016).

From these findings, a multifaceted picture of RV emerges concerning its role in the maintenance of proteostasis. Simultaneously, ameliorating the harmful effects of proteotoxic agents by reducing the scope of damage through hindering the secretion of certain misfolded proteins and facilitating their removal by ERAD or autophagy.

3.1.5. Resveratrol in AD: anti-amyloidogenic and anti-tauopathy effects

AD is the main cause of dementia and is characterized by progressive cognitive and memory deficits. The pathological hallmarks of AD include the accumulation and deposition of Aβ in the senile plaques, and hyperphosphorylation Tau (p-Tau) protein, a microtubule assembly protein formation of neurofibrillary tangles (Grill and Cummings, 2010). OS plays a crucial role in the aetiology of AD (Tönnies and Trushina, 2017), as described above. Likewise, neuronal death (Ehrnhoefer et al., 2011) and synaptic abnormalities (Kashyap et al., 2019) also exhibit essential roles in AD. Furthermore, one of the molecular changes of ageing that might contribute to the development of AD is the deficiency in cellular control mechanisms that degrade aberrant proteins (Vilchez et al., 2014). The ubiquitin-proteasome system (UPS) is the primary proteolytic mechanism to aberrant clearance proteins, including Aβ and p-Tau (Ciechanover and Kwon, 2015; Xin et al., 2018). In this way, functional alterations of UPS and its molecular components indicate impairment of the proteasome function in AD brain (Keller et al., 2000; Tseng et al., 2008; Gadhave et al., 2016) and represent a clear link with the ageing process.

RV upregulates proteasome activity in AD models, suggesting a recovery of the UPS functionality (Corpas et al., 2019). Therefore, the activation of proteolysis systems by RV may be critical in both prevention and therapy against AD and neurodegenerative diseases characterized by the accumulation of aberrant proteins. RV is involved in the maintenance of quality control of proteins mediated by UPS, mainly by SIRT1 pathway activation (Corpas et al., 2017; Tomita et al., 2015). This polyphenol promotes Aβ clearance and a decrease in its production through stimulation of proteasomal proteolysis, as shown in cell lines expressing APP695 (Marambaud et al., 2005) and in a *C. elegans* model of AD (Regitz et al., 2016). It has been shown that when RV was incubated with Aβ can decrease the length and the number of fibrils (Ge et al., 2012) and Aβ plaques (Porquet et al., 2014). RV may decrease Aβ generation by favouring the non-amyloidogenic pathway of Aβ Precursor Protein (APP) degradation (Kelsey et al., 2010; Porquet et al., 2013). In this context, RV reduces the amyloidogenic pathway and increases the amyloid-degrading enzyme Neprilysin (NEP) levels in AD mouse models (Corpas et al., 2019)). Thus, RV reduces the activity of β-secretase (BACE) through the activation of SIRT1 (Porquet et al., 2014; Jeon et al., 2007). Likewise, a study, using neuronal and non-neuronal cells and mice models, showed that the anti-amyloidogenic activity of RV is also mediated by AMPK (Porquet et al., 2013; Vingtdeux et al., 2010), which then maintains mitochondrial integrity by regulating normal autophagy (Wu et al., 2011). Furthermore, RV administration reduces p-Tau levels in AD models, which occur mainly through the deacetylation of the tau protein by SIRT1 (Min et al., 2010), favouring p-Tau degradation by the proteasome-mediated pathway (Tan et al., 2008). Besides, other studies also showed the potential of RV attenuating Tau levels in rats (Patil et al., 2013) by the upregulation of BAG family molecular chaperone regulator 2 (BAG2) levels and inhibiting the hyperphosphorylation and aggregation of Tau (Pasinetti et al., 2015; He and Yan, 2013) by the inhibition of GSK-3β and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), and the activation of Protein phosphatase 2 (PP2A) (He and Yan, 2013; Schweiger et al., 2017). Interestingly, RV induces normalization of Heat Shock Protein (Hsp) 70 and the ubiquitinated proteins in agreement with SIRT1 regulation (Westerheide et al., 2009) (Fig. 4).

3.1.6. The neuroprotective potential of resveratrol: from in vitro studies to clinical trials

So far, none of the AD treatment turned out to be able to cure or reduce disease progression. Therefore, it is indispensable to find new therapeutic strategies. Hence, RV is considered a drug that can modify the underlying pathology of AD (Jardim et al., 2018; Porquet et al., 2014; Corpas et al., 2019; Rege et al., 2014; Sawda et al., 2017; Sun et al., 2010). As mentioned, several studies have described that RV may attenuate OS by scavenging free radicals, clearance of Aβ and inhibit its production and aggregation, decrease the production of

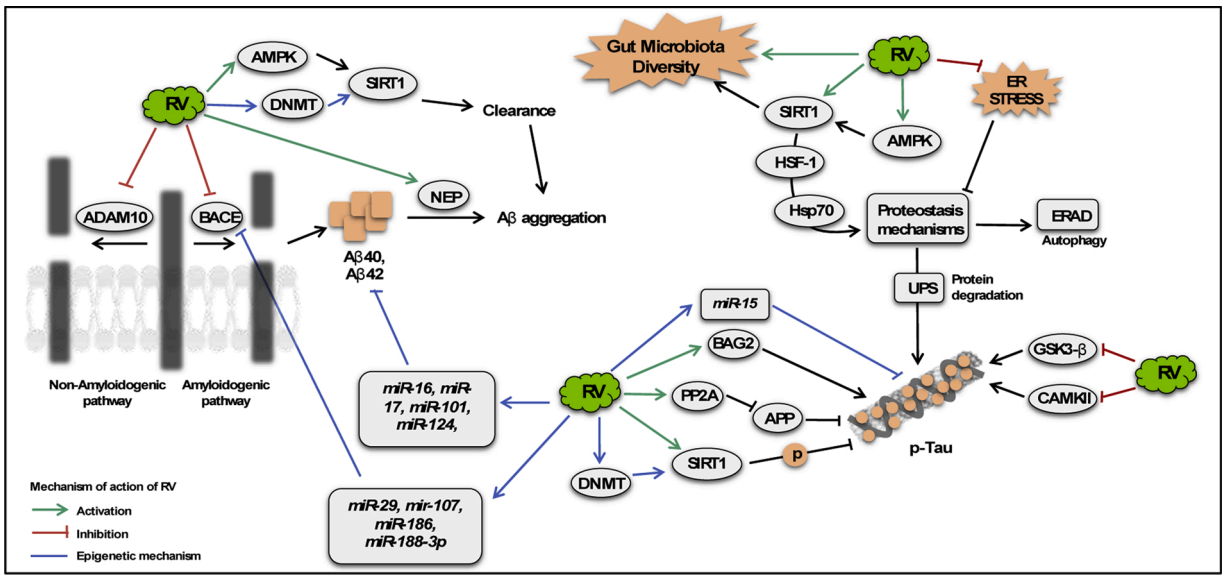

Fig. 4. Scheme of the specific molecular and cellular mechanisms, including epigenetics, that are activated or inhibited by RV and are implicated in neuropathological hallmarks of AD modification.

pro-inflammatory factors, suppress activation of astrocytes and microglia, and reduce neuron cell death (Ahmed et al., 2017). Both *in vitro* and *in vivo* studies (Baur and Sinclair, 2006; Ma et al., 2014), show that RV has a neuroprotective effect in several models and pathways (Tables 4,5 and 6).

3.1.6.1. Background: in vitro studies. Regarding the *in vitro* models, the neuroprotective effects of RV have been investigated in several cellular models, which are summarized in Table 4. For example, RV attenuated Aβ cytotoxicity, apoptosis pathways, and intracellular ROS accumulation through NF-κβ downregulation, an aspect suggesting the involvement of SIRT1, in cells (Bastianetto et al., 2000; Jang and Surh, 2003; Kim et al., 2006; Sun et al., 2001). Another unusual mechanism of the RV is the inhibition of Aβ fibril formation (Xia et al., 2019). According to those and the data present in Table 4, RV was positively considered a neuroprotective compound in the context of AD drug discovery.

However, *in vitro* approaches have the disadvantage that they fail to show all mechanisms involved in the effect of the RV or its toxicity, as well as the influence of metabolism on its biodisponibility and elimination. Therefore, *in vivo* results have become increasingly important in our attempts to understand how RV is effective in the treatment of AD pathology.

3.1.6.2. From C. elegans to clinical trials. In the current review, we highlighted the nematode *C. elegans,* as a model organism of age-related diseases. *C. elegans* is a suitable preclinical model for ageing, mainly due to its short lifespan under normal growth conditions (for revision see (Alexander et al., 2014; Chen et al., 2015)). Moreover, *C. elegans* has emerged as a powerful tool for neuroprotective compound screening owing to the highly conserved neurological pathways between mammals and invertebrates. For instance, the signal transduction pathways for OS, including insulin signalling pathway, autophagy pathway and target of rapamycin (TOR) signalling pathway, as well as SOD and CAT mechanisms all have worm orthologs (Moreno-Arriola et al., 2014). Hence, this experimental model has been used to study numerous nutritional natural compounds (for revision see (Liao, 2018)), such as RV.

On the other hand, increases in antioxidant enzymes have been found to increase worm lifespan (Folch et al., 2017; Rodríguez-Chávez et al., 2015) although other studies casted doubt on this (see (Gems and Partridge, 2013) for review). It has been found that dietary supplementation with RV extends lifespan in *C. elegans* through the SIRT1 orthologue SIR-2.1 activation (Pallas et al., 2009; Chen et al., 2013b). The following Table 5 compiled some effects of RV treatment in *C. elegans.*

Most genes and pathways involved in human diseases have orthologues in *C. elegans*. Nevertheless, there are also limitations that must be considered. There are aspects of pathologies that cannot easily be modelled in worms, such as neuroinflammation and microglial cell activation in several neurodegenerative diseases, notably AD (Chen et al., 2015; Amor et al., 2010). Hence, the extrapolation of results obtained in *C. elegans* to humans is not possible without validating these findings in further animal models, such as rodent models, among others (Folch et al., 2017). Taking into account all the advantages and disadvantages, this experimental model could be considered as a bridge between *in vitro* and the rest of *in vivo* approaches (Kaletta and Hengartner, 2006). Indeed, the neuroprotective effects of RV have also been widely described in other *in vivo* models (Table 6).

Despite abundant preclinical studies have been carried out *in vivo* and *in vitro* models, only a few clinical trials aimed at assessing the effect of RV on cognitive function or AD pathology have been completed. RV is considered a low-toxicity substance, as humans have used several RV-containing foods for a long time (Almeida et al., 2009; Juan et al., 2002). RV was found to be safe and well-tolerated in populations at risk for AD (Turner et al., 2015). Moreover, RV was under Phase III NCT00678431 to determine the effects in mild-to-moderate AD in combination with glucose and malate in NCT00678431 study. However, there is little clinical evidence on its beneficial neuroprotective effects (Table 7). Therefore, more studies on human subjects are necessary to reach a better awareness of the role of polyphenols on neurodegenerative diseases because caution is needed to extrapolate results obtained using animal models to humans (for revision see (Berman et al., 2017; Mazzanti and Di Giacomo, 2016; Drygalski et al., 2018)).

4. Epigenetic mechanisms in gene regulation

Over time the term epigenetics has changed from describing the different phenotypes from a particular genotype into the more concrete "a stably heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" as described by Berger et al. (Berger et al. (2009)). Finally, we can define epigenetics as heritable changes to the genome without changes to the DNA sequence itself. To

Table 4
Summary of the molecular changes of RV in different *in vitro* studies associated with neuroprotective effects.

Model	Effects		References
Primary cortical neurons	↑	SIRT1 activity.	(Kim et al., 2007)
	↓	Cognitive decline.	
	↓	Intracellular calcium.	(Ju et al., 2008)
	↓	ROS production.	
	↑	SIRT-1 expression.	(Cristòfol et al., 2012)
	↓	Oxidative damage.	
Primary hippocampal cells	↓	Aβ25–35 -induced cell death.	(Han et al., 2004)
	↓	Phosphorylation of PKC-δ.	
Glial and neuronal hippocampal cells	↑	Hippocampal cells against NO-induced toxicity.	(Bastianetto et al., 2000)
	↓	NO generation.	
	↓	iNOS in LPS-activated macrophages.	
Primary microglial cells	↓	PGE2 and free radical formation.	(Candelario-Jalil et al., 2007)
	↓	LPS and COX1.	
	↓	NO production and iNOS expression.	
Rat C6 glioma cells	↓	Accumulation of PGE2.	(Kim et al., 2006)
	↓	COX2 expression.	
	↓	Translocation of NF-κβ.	
RAW 264.7 cells	↓	Cytokines levels.	
BV-2, cells	↓	Phosphorylated Iκβα, and NF-κβ levels.	(Capiralla et al., 2012)
Ba/F3 cells	↓	STAT1 and STAT3 activation.	
	↓	iNOS and COX2 expression.	
PC12 cells	↓	Bcl-XL and Bax expression.	(Jang and Surh, 2003; Ladiwala et al., 2010)
	↓	JNK pathway.	
	↓	NF-κβ DNA binding.	
	↑	cell viability, p53 acetylation	(Feng et al., 2013)
	↓	Bax, caspase-3, Bcl-2	
	↑	Cell viability, mitophagy, CAT, T-SOD, ATP, Beclin-1, Parkin ND LC3II/LC3I.	(Wang et al., 2018b, c)
	↓	Caspase-3 and MDA.	
	↓	Apoptosis.	
	↓	IL-1β, IL-6, and TNF-α expression.	(Zhang et al., 2019)
		Inhibited LPS-induced inflammatory injury.	
	↑	HO1 levels by the activation of NRF2.	
	↓	Activation of ERK.	
	↓	ROS production.	
Murine HT22 hippocampal cells and primary hippocampal neuron cells	↑	GSH levels.	
		Attenuated neuronal cell death.	(Kwon et al., 2010)
		Co-treatment with melatonin exerted a synergistic effect.	
HUVEC-derived EA. hy926 cells	↑	SOD1 and GPX1 expression.	(Spanier et al., 2009)
		Suppressed the extension of amyloidogenic Aβ peptides.	
SH-SY5Y neuroblastoma cells	↓	Disaggregated Aβ42 fibrils.	(Feng et al., 2009; Granzotto and Zatta, 2011)
	↓	Cytotoxicity and apoptosis.	
		ROS production, APP, BACE, PSEN1, Aβ, SIRT1, p53 and Caspase-3/pro-caspase-3.	
	↓	Aβ accumulation, APP β-CTF, BACE1 activity	(Hu et al., 2015)
	↑	Bcl-2/bax	
	↓	ROS production, APP, BACE, PS1, Aβ, SIRT1, GRP78, p53, caspase-3/pro-caspase-3	(Ko et al., 2015)
SK-N-SH cells	↑	NEP and ACE activity	(Melzig and Escher, 2002)
	↓	PGE2 and PGD2 production by the inhibition of the COX2 activity.	(Wendeburg et al., 2009)
	↓	Cytotoxicity.	
	↓	ROS levels.	
	↑	SIRT1-dependent autophagy.	
APP-HEK293 and APP-N2a cell	↑	AMPK pathway.	(Albani et al., 2009; Cai et al., 2012)
N9 microglial cell	↑	Cell viability, SOCS1.	(Zhang et al., 2017a, b)
	↓	iNOS, TNF-α, IL-1β and NF-κβ.	
hNSCs cells	↑	Cell viability, SOD1, CAT, NRF2, GSH, GPX1, HO1 levels.	(Chiang et al., 2018)
	↓	TNF-α, IL-1β, IKK-α, IKK-β, NF-κβ, iNOS, COX2.	
Lymphocytes immortalized from AD patients	↓	ROS production after oxidative injury.	(Cosín-Tomàs et al., 2019)
	↑	Expression SIRT1, SIRT3 and antioxidant genes.	

Abbreviations: Bcl-XL: B-cell lymphoma-extra large; Bax: Bcl-2-associated X; T-SOD: Total-Superoxide dismutase; LC3: Light chain 3; PSEN1: Presenilin 1; PGD2: Prostaglandin 2; SOCS1: Suppressor of cytokine signalling 1; IKK: Iκβ kinase; LDH: Lactate dehydrogenase.

Table 5
Summary of protective effects promoted by RV supplementation in *C. elegans*.

Effects	References
↑ lifespan under normal and acute stress conditions.	(Rascón et al., 2012; Valenzano et al., 2006; Yu and Li, 2012; Genade and Lang, 2013)
Via the induction of a subset of ER-resident protein genes.	(Zou et al., 2009)
Via SIR-2.1, and AMPK pathway-dependent manner.	(Lee et al., 2016)
Via FOXO/DAF-16-independent manner.	
Protective effects, depending on the duration and order of administration.	(Soares et al., 2018)
↓ Aβ aggregation.	
↓ Aβ-induced toxicity.	
↑ degradation of aged proteins by autophagy induction and proteasomal degradation.	(Regitz et al., 2016)
Rescued early neuronal dysfunction phenotypes induced by mutant polyglutamines.	(Parker et al., 2005)
ROS-scavenging activity and minimized mitochondrial dysfunctions.	(Ye et al., 2010)
↑ autophagy by the activation of SIR-2.1.	(Morselli et al., 2010, 2009)

date, more than twenty different epigenetic marks have been identified consisting mainly of processes that can directly modify DNA, such as DNA methylation (5-mC) or post-translational modifications (PMTs) of nucleosomal histones (Tessarz and Kouzarides, 2014; Bird, 2002). These modifications can induce changes in gene expression by altering chromatin structure or recruiting histone modifier enzymes. By last, microRNAs (miRNAs) are non-coding RNAs that post-transcriptionally control gene expression, acting as a regulator of their mRNA targets *via* degradation and/or translational repression (Valinezhad Orang et al., 2014). As a consequence, changes to the epigenome might have consequences for the molecular pathways of cells, tissues and organs, modifying the risk of developing diseases. Thus, the epigenome is not fixed, and environmental exposure, including nutrition, can influence the epigenetic marks. So, epigenetics provides a mechanism through which nutrition modulates health and wellbeing throughout life (Malcomson

Table 6
Summary of behavioural, cognitive and molecular changes promoted by RV supplementation described by using different *in vivo* models of neurodegeneration.

Model	Effects	References
D. melanogaster	↓ Behavioural deficits and brain histopathology. ↑ Survival rate and lifespan. ↓ H_2O_2 and NO. GST and CAT. ↑	(Abolaji et al., 2018)
Tg2567 mice	↑ Lifespan, locomotor activity, and muscle ATP production. ↓ Mitochondrial aggregates. ↑ Autophagy and mitophagy. ↓ Aβ neuropathology. ↓ Spatial memory deterioration.	(Wu et al., 2018b) (Wang et al., 2006)
Tg199589 mice	↓ Oligomerization of Aβ peptide. ↓ Cognitive impairment. ↓ Aβ plaque deposits in the medial cortex, striatum and hypothalamus.	(Wang et al., 2008) (Karuppagounder et al., 2009)
3xTg-AD	↑ Protected learning and memory impairment. ↓ Aβ and tau pathology. ↑ Improved proteostasis mechanisms. ↑ SIRT1 pathway.	(Corpas et al., 2019)
APP/PS1 mice	↓ Aβ-mediated activated microglia, IL-6, TNF-α, p-STAT1, p-STAT3, p-IκBα. ↑ p-AMKP/AMPK, LC3-II/LC3-I. ↑ Absence of decrease plaque burden in these mice. p-GSK3-β. ↓ Memory impairment. ↓ Aβ burden. ↑ Mitochondrial complex IV protein levels. ↑ SIRT1 and AMPK pathways. ↑ IL-1β and TNF gene expression. ↑ Mitochondrial function.	(Capiralla et al., 2012; Vingtdeux et al., 2010) (Varamini et al., 2014) (Porquet et al., 2014)
C67BL/6 J mice	↑ Aerobic capacity. ↑ Sensorimotor function. ↓ Serum TNF-α. ↑ Cognitive function. ↑ Improved in spatial orientation and memory performance. ↓ p62 levels. ↑ SIRT1 and autophagy.	(Lagouge et al., 2006) (Jeon et al., 2012) (Oomen et al., 2009) (Guo et al., 2016)
C57BL/6 J mice	↓ Gene expression of pro-inflammatory cytokines. ↑ AMPK-PGC-1α axis. Cognition impairment. ↓ Correlation with the effects of mitochondrial functioning and the diminution of NeuroD6 gene expression in old animals. ↑ Antioxidant status. ↓ Lipid peroxidation.	(Palomera-Ávalos et al., 2017)
SAMP8 mice	↓ Mitochondrial deletion. ↑ Learning and memory impairment. ↑ Lifespan ↓ Cognitive impairment.	(Liu et al., 2012)
Inducible p25 transgenic mice	↑ SIRT1, p-AMPK and p-GSK/GSK in the cortex, AMPK in the hippocampus. ↓ Aβ deposition. ↑ Non-amyloidogenic pathway in the hippocampus. ↓ p-Tau. ↓ Neurodegeneration in the hippocampus. ↓ Cognitive decline. ↓ Acetylation of SIRT1 substrates, PGC-1α, and p53.	(Porquet et al., 2013) (Kim et al., 2007)
Wistar rats	↓ Memory impairment,	(Ma et al., 2013)

Table 6 (*continued*)

Model	Effects	References
	↓ MDA levels. ↑ Superoxide dismutase activity and glutathione levels. ↓ Insoluble Aβ levels in the hippocampus. ↓ RAGE expression in the hippocampus. ↓ MMP-9 expression. ↓ ER stress markers genes expression. ↓ Caspase-3 activity, IL-1β levels. ↑ GPX and Nrf2 signalling pathway.	(Zhao et al., 2015) (Gaballah et al., 2016b)
Rats, ICV administration of colchicine	↑ Attenuated OS. ↓ Cognitive dysfunction, ↓ MDA and nitrite levels ↑ GSH and Ache activity. ↓ COX2 and TNF-α levels. ↑ BDNF expression. ↓ Aβ accumulation.	(Lin et al., 2018) (Kumar et al., 2007) (Jin et al., 2008) (Rahvar et al., 2011)
Sprague-Dawley rat	Aβ-induced spatial memory. ↑ Reversed Aβ induced iNOS expression. ↑ HO1 expression. ↓ Lipid peroxidation. ↑ PSEN1 expression.	(Huang et al., 2011) (Torres et al., 2011)

Abbreviations: GST: Glutathione-S-transferases; NeuroD6: Neuronal Differentiation 6; AchE: Acetylcholinesterase; BDNF: Brain-derived neurotrophic factor.

and Mathers, 2017).

DNA methylation is the epigenetic mechanism that occurs by the addition of a methyl group (−CH3) to the cytosine modifying the DNA directly (Bird, 2002). These methylated cytosines occur almost exclusively in the cytosine residue followed by a guanine residue (called CpG dimers). The CpG dimers are distributed unevenly in the genome, concentrating in areas called CpG islands, very close to the regulatory regions of the genes (Deaton and Bird, 2011; Jang et al., 2017; Blackledge and Klose, 2011). The enzymes involved in the methylation process of the 5′carbon of the cytosine giving rise to the 5′-methyl-cytosine are the family of methyltransferases (DNMTs). We can divide the DNMTs in maintenance (DNMT1) and *de novo* (DNMT3A and DNMT3B) methyltransferases (Li et al., 1993; Hermann et al., 2004; Bestor, 2000; Hata et al., 2002; Takeshita et al., 2011). In general, 5-mC is related to gene silencing; it is a dynamic process, where methylation and demethylation of some areas of DNA can mediate transcriptional repression of repeated regions. The dynamic control of the methylation-demethylation process implies that the changes produced are not permanent and depend on the homeostatic factors of the cells and their environment. OS is one of the essential modulators in this balance.

In addition to 5-mC, another process that directly affects DNA is the 5-hydroxymethyl-cytosine (5-hmC), which seems to be an intermediate stage before demethylation of the cytosine. Hydroxylases of the DNA called "Ten-Eleven Translocation family" (TETs) are involved in this modification, specifically TET1, TET2, and TET3. The degree of 5-hmC of DNA depends on the tissue, but the nervous system is one of those with the highest level of 5-hmC (Li et al., 2015; Ficz et al., 2011; Tahiliani et al., 2009; Gu et al., 2011; Huang et al., 2014).

On the other hand, histones are critical protein structures in transcription processes and are also susceptible to PMTs, including acetylation, methylation, phosphorylation, ubiquitination, sumoylation, ADP-ribosylation (Wen et al., 2016). Among all possible PMTs acetylation of lysine residues is one of the key regulatory mechanisms in all-eukaryotic organisms. The lysine acetylation process is dynamic and regulated by enzymes that add acetyl groups, histones acetyltransferases family (HATs) or that remove, histone Deacetylases family (HDACs) are

Table 7
Synthesis of clinical trials with RV and its beneficial effects presented in the site of www.clinicaltrials.gov.

Reference (and trial number)	Status	Results
(National Institutes of Health, 2021a) NCT00743743	Withdrawn	–
(Zhu et al., 2018; National Institutes of Health, 2021b) NCT00678431	Published	Low-dose oral administration was safe and well-tolerated.
(National Institutes of Health, 2021c) NCT00996229	Unknown	Not available.
(National Institutes of Health, 2021d) NCT01126229	Completed in 2012	Not available.
(Kennedy et al., 2010)	Published	Cognitive function not affected. Increased in CBF.
(National Institutes of Health, 2021e) NCT01794351	Completed in 2012	Not available.
(Wong et al., 2013) ACTRN12611000060943	Published	Increased circulatory function. No effects on BP, arterial compliance, and cognitive function.
(National Institutes of Health, 2021f) NCT01716637	Completed in 2016	Not available.
(Turner et al., 2015; National Institutes of Health, 2021g; Moussa et al., 2017) NCT01504854	Published	Safe and well-tolerated. Altered AD biomarker trajectories. Preserved BBB integrity. Modulated the CNS immune response. Reduced CSF MMP-9, increase IL-4, attenuated decline in Aβ42 and Aβ40. No significant effect on cognitive score.
(Veronica Witte et al., 2014)	Published	Improved memory performance. Increased hippocampal functional connectivity. Improved glucose metabolism.
(Wightman et al., 2014) NCT01331382	Published	Co-treatment with piperine improved the effect of RV on CBF but not on cognitive performance and bioavailability.
(National Institutes of Health, 2021h) NCT02502253	Recruiting	–
(Wightman et al., 2015)	Published	Reduced fatigue and higher diastolic BP. No modulation on sleep and CBF.
(Wong et al., 2016) ACTRN12614000891628	Published	Increased cerebrovascular responsiveness. Reduced glycosylated HbA1c.
(Köbe et al., 2017) NCT01219244	Published	Preserved the volume of the hippocampus and improved the hippocampus resting-state functional connectivity in patients at risk of dementia.
(Evans et al., 2017) ANZCTR12616000679482	Published	Improved cerebrovascular function Improved cognition

Abbreviations: CBF: Cerebral blood flow; BP: Blood pressure; CNS: Central Nervous System; HbA1c: Hemoglobin A1c.

involved. These enzymes act through multiprotein complexes, regulated by coactivators and corepressors. Apart from the acetylation, histone can suffer methylation which is catalysed by histone methyltransferase family (HMTs), and it is a much more stable brand than acetylation, mainly affecting lysine and arginine residues (for revision see (Griñán-Ferré et al., 2018)). Likewise, when the histone PTMs are completed, their actions to control DNA transcription are accomplished by proteins called "readers" such as methyl CpG binding protein 2 (MeCP2), histone-lysine N-methyltransferase 2 (G9a) and histone-lysine methyltransferase 1 (GLP) (Griñán-Ferré et al., 2018). The main function of these proteins is act as effectors, compacting the chromatin, among others.

By last, only 1.5 % of the genome is transcribed to mRNA, and the rest is mainly considered functional non-protein-coding DNA sequences, most of them are transcribed into RNA. Among them, the ones that have generated most interest are miRNAs that are between 18 and 25 nucleotides long, and to which gene repression is associated, that is, the blockage of transcription. Furthermore, miRNAs are critical to determining cellular fate because they regulate development, maturation, differentiation and apoptosis of the cell, cell signalling, cellular interactions, and homeostasis (Ranganathan and Sivasankar, 2014). Likewise, miRNAs play a central role of several pathological conditions such as cancer (Sundarbose et al., 2013; Peng and Croce, 2016; Di Leva et al., 2014), cardiovascular disease (Barwari et al., 2016; Romaine et al., 2015; Zhou et al., 2018), diabetes (Kameswaran et al., 2014; Ciccacci et al., 2013; Feng et al., 2016), including neurodegenerative diseases (Maciotta Rolandin et al., 2013; Junn and Mouradian, 2012; Femminella et al., 2015; Tan et al., 2015; Eacker et al., 2009; Van den Hove et al., 2014; Nelson et al., 2008) and age-related cognitive decline (Harman and Martín, 2019; Cosín-Tomás et al., 2018; Kosik et al., 2012; Barter and Foster, 2018; Siedlecki-Wullich et al., 2019). Besides, complex interactions between epigenetic mechanisms occur, providing an explanation for the wide range of effects and different phenotypes in both physiological and pathological conditions (Romanowska and Joshi, 2019).

4.1. Epigenetic modulation during ageing and disease: oxidative stress a key point

Increasing evidence demonstrated that global changes and imbalance of the epigenome during ageing leads to transcriptional alterations and genomic instability, mainly, contributing to the appearance of age-related diseases, such as cancer and neurodegenerative diseases (Sen et al., 2016; Guillaumet-Adkins et al., 2017). Likewise, the production of ROS increases during ageing and determines OS, which might be responsible for the alterations in the epigenetic state of the cell. There is a relationship between the effect of OS and the epigenetic landscape. Thus, ROS accumulation impairs the function of cells, determining histone modifications and its epigenetic machinery remodelling the chromatin structure (Guillaumet-Adkins et al., 2017; Kietzmann et al., 2017; Cencioni et al., 2013). Indeed, the activity of the epigenetic machinery since chromatin-modifying enzymes depend on intracellular levels of essential metabolites such as Acetyl-CoA, Fe, ketoglutarate, NAD^{+}, and S-adenosyl-methionine. Therefore, OS can modulate them, demonstrating that epigenetic changes are linked to global cellular metabolism and energy levels of the cell (Simpson et al., 2012).

Epigenetic modifications are one of the primary cause of ageing (López-Otín et al., 2013b). Indeed, older organisms present a different epigenome (Pal and Tyler, 2016). For instance, during senescence, several cells of mice and humans develop global hypo-methylation compared to young cells. In contrast, in mice and humans, the CpG islands near the promoters are typically hypermethylated with age. It is interesting to note that the genes affected or modulated by these changes in 5-mC are related to differentiation, development, apoptosis or senescence processes (Cencioni et al., 2013). Furthermore, ROS influences the methylome through the formation of oxidized DNA lesions formed by hydroxylation of pyrimidines and 5-mC, which can interfere due to structural similarities with epigenetic signals to 5-hmC (Lewandowska and Bartoszek, 2011).

A large body of literature shows that histone modifications occurring in an older epigenome are associated with the appearance of diseases (O'sullivan et al., 2010; Dang et al., 2009; Wang et al., 2018d; Guan et al., 2009; Sadri-Vakili et al., 2007; Lithner et al., 2013; Tohgi et al.,

1999; Peleg et al., 2010; Kontopoulos et al., 2006; Marques et al., 2012). Moreover, histone modifications have also been directly implicated in the ageing process due to an alteration of activating and repressive histone modifications, affecting the compaction of chromatin in ageing cells (Feser and Tyler, 2011) (Table 8). Of these, histone methylation (me) and acetylation (ac) are well-understood, and some general trends have been shown. Increased histone (H)4 lysine (K)16H4K16ac, H3K4me3, or H4K20me3, as well as decreased H3K9me or H3K27me3, were shown to be age-associated epigenetic marks (Han and Brunet, 2012; Fraga and Esteller, 2007). For example, depletion of the ASH-2, WDR-5, and the H3K4me3 methyltransferase SET-2 complex affects lifespan in *C. elegans* (Greer et al., 2010). Levels of H3K56ac decrease during yeast ageing, while H4K16ac levels increase (Dang et al., 2009). Similar changes in these two marks of histone acetylation levels were also shown during replicative ageing in human fibroblast samples (O'sullivan et al., 2010).

In addition to histone modifications, the correlation between changes in gene expression of encoding miRNAs during ageing and disease has also been shown to be associated with changes in life expectancy. An overall increase in the expression of miRNAs during ageing has been described, including specific ones that promote senescence (Cencioni et al., 2013) (Table 8). In contrast, it has been detected the sub-expression of various miRNAs that inhibit senescence, which together seems to be one of the causes of cellular senescence. Of note, *C. elegans* model is highly suitable for the miRNA impact on the ageing process. Ibañez-Ventoso et al. (Ibáñez-Ventoso et al., 2006) identified 34 of 114 miRNAs that exhibit significant changes in expression levels during nematode adulthood, suggesting the potential mechanisms of miRNAs to modulate the biology of ageing. Levels of most of these miRNAs decreased with age, such as miRNA *lin-4* and its target lin-4, which are one of the most relevant marks that regulates life span (Boehm and Slack, 2006, 2005). Other age-related miRNAs, including *let-7* and the muscle miRNA *miR-1*, have been downregulated, favouring age-related decline. In contrast, *miR-34* was found to be upregulated during ageing (Ibáñez-Ventoso et al., 2006). In the same way as *C. elegans*, changes in miRNA expression occur with ageing in other organism models (Table 8).

Table 8
Summary of the epigenetic dysregulated marks and mechanisms found during ageing and AD by different species.

Epigenetic modifications during ageing	Species	References
DNA hypomethylation.	Mouse	(Feser and Tyler, 2011)
↓ DNMT1.	Human	(Han and Brunet, 2012; Fraga and Esteller, 2007; Greer et al., 2010)
DNA hypermethylation.	BN rats, Human	(Ibáñez-Ventoso et al., 2006; Boehm and Slack, 2006, 2005; Barbot et al., 2002)
↑ DNMT3.	Human	(Han and Brunet, 2012; Casillas et al., 2003)
Alteration DNA methylation level of CpG sites.	C57BL/6 J mice	(Rampersaud et al., 2000)
↓ 5-mC.	SAMR1, Albino rats, Human	(Cosín-Tomás et al., 2018; Ciccarone et al., 2016; Oakes et al., 2003)
↑ 5-hmC.	C57BL/6 J mice	(Casillas et al., 2003; Choi et al., 1996)
↓ Tet1 and Tet2 gene expression.	SAMP8, C57BL/6 J mice	(Cosín-Tomás et al., 2018; Waki et al., 2003)
↓ SIRT1.	Albino rats	(Ciccarone et al., 2016)
Global histone loss.	*S. cerevisiae*, Human	(O'sullivan et al., 2010; Issa et al., 1994; Chouliaras et al., 2012)
Global hypoacetylation of H3 and H4.	*D. melanogaster*, C57BL/6 J mice	(Peleg et al., 2010; Lin et al., 2016; Vanyushin et al., 1973)
↓ H3K56Ac and increased of H4K16Ac.	*S. cerevisiae*	(Dang et al., 2009; Issa et al., 1994; Wilson and Jones, 1983; Szulwach et al., 2011)
↑ trimethylation marks on H3K4, H3K9, H3K27, and H3K36.	*C. elegans, D. melanogaster*, SAMP8	(Boehm and Slack, 2006; Jessop and Toledo-Rodriguez, 2018; Feser et al., 2010; Liu et al., 2013)
↑ H3K27ac, H3K4m1, H3K4m2, H3K4m3, and H3K9ac.	Human	(Steffan et al., 2001)
↑ H4 K20me3.	SAMP8, Rat, Human	(Liu et al., 2013; Ryu et al., 2011; Rohde and Cardenas, 2003)
Dephosphorylation of H1.4 and H1.5.	Human	(Chen et al., 2012)
↑ *miR-34*.	*C. elegans*	(Ibáñez-Ventoso et al., 2006; Pu et al., 2015; Wood et al., 2010; Wang et al., 2010; McClay et al., 2013)
↓ *miR-4*, *let-7* and *miR-71*.		
↑ *miR-34a*, *miR-93*, *miR-669c*, *miR-214*, and *miR-709*.	C57BL/6 J mice	(Sarg et al., 2002; Shumaker et al., 2006)
↑ *miR-29*.	ATM$^{-/-}$ and ATRs/s mice	(Happel et al., 2008)
↑ *miR-143* and *miR-200*.	Human	(Kato et al., 2011; Smith-Vikos and Slack, 2012)

4.2. Resveratrol, neuroprotection and epigenetics

Polyphenols, as RV, can produce several chemical modifications after oral administration such as oxidation, dehydroxylation, demethylation, among others. Thus, RV can act either directly by inhibiting epigenetic enzymes such as DNMTs, HDACs, or HATs or by altering the availability of substrate necessary for those enzymatic reactions. This, in turn, modifies the expression of critical genes and impact on our overall health and longevity (De Lencastre et al., 2010). Recently, it has been described that nutritional polyphenols involve multiple chromatin-modifier writer-reader-eraser proteins in cognitive improvement (Tiffon, 2018). Furthermore, several studies illustrate the epigenetic modulation by dietary consumption of polyphenols, namely for the modulation of pro-inflammatory and anti-inflammatory miRNAs (Tili and Michaille, 2016). In this context, Song et al. (Song et al. (2016)) described that RV was able to upregulate *miR-let7A* levels, with effects on TNF, IL-6, IL-10, BDNF and ASK1. Therefore, the putative role of RV on epigenetic changes as a key point underlying their benefits on ageing and neurodegenerative diseases such as AD, PD or neurological pathologies as depression has been addressed by different authors (Athanasopoulos et al., 2016) (Table 9).

4.2.1. Epigenetic mechanisms modulated by resveratrol

As mentioned, the pleiotropic mechanism of action of RV is not completely described. Recent evidence indicates that modification of

Table 9
Compilation of articles establishing the correlation between RV and epigenetic mechanisms in ageing and neurodegenerative diseases.

Study	Type of report	Conclusions
(Hubbard and Sinclair, 2014)	Review	RV enhances SIRT1 activity reducing neurodegenerative diseases pathologies.
(Schiaffino et al., 2018)	Original	The administration of RV to SOD1 (G93A) mice restored the normal RelA acetylation AMPK/SIRT1, delaying the disease onset, improving motor performance, and increasing lifespan.
(Isac et al., 2017)	Original	RV influences the expression of non-coding miRNAs *miR-124, miR-132, miR-134, miR-146* and *miR-15a* in the hippocampus of mice in response to perinatal asphyxia.
(Palomera-Ávalos et al., 2017)	Original	RV reverses oxidative stress and inflammatory processes by acting on SIRT1-AMPK-PGC-1α. Moreover, methylation and acetylation changes on DNA that are depending on OS were demonstrated.

epigenetic mechanisms could also be implicated in RV beneficial effects. In the last years, an increasing number of findings point out the key role of epigenetics in ageing and neurodegeneration and highlight several insights about the role of RV on epigenetics (Fernandes et al., 2017b).

One of the most studied mechanisms of neuroprotection by RV is its role as an activator of SIRT1, an HDAC type III member. In fact, this polyphenol is considered as a calorie restriction-mimetic (Barger et al., 2008); it is widely known that caloric restriction is related to SIRT1 activation and a strategy that extends lifespan in organisms ranging from yeast to mammals (Lin et al., 2004) and a strategy to protect brain function (Porquet et al., 2013; Barger et al., 2008). The most accepted mechanism indicates that RV mimics the antioxidant and anti-ageing effects of caloric restriction (Albani et al., 2009; Barger et al., 2008). RV binds to the SIRT1 at an allosteric site amino-terminal to the catalytic domain and increases the affinity for acetylated substrates, constituting an allosteric modification.

Moreover, RV enhances AMPK activity, which in turn increases NAD^+ concentration, resulting in the activation of the SIRT1 pathway (Cristòfol et al., 2012; Cantó et al., 2009; Price et al., 2012) due to its effect on cAMP signalling (Park et al., 2012). SIRT1 catalyses the deacetylation of histones and several transcription factors through the consumption of the substrate NAD^+ (Herskovits and Guarente, 2014; Johnson and Imai, 2018). Therefore, RV induces beneficial effects through the upregulation of the AMPK/SIRT1 pathway (Um et al., 2010; Hubbard and Sinclair, 2014). Chen et al. (Chen et al. (2005b)) shown that RV inhibits NF-κβ through SIRT1 activation, protecting Aβ-dependent neurodegeneration in mixed cortical cultures. Similar, the ability of RV treatment to decrease ROCK1 expression modulated by SIRT1 pathway have been demonstrated in AD (Qin et al., 2006; Tang, 2005). Another downstream target of SIRT1 is Akt, which can be modulated through deacetylation, promoting axonogenesis (Li et al., 2013), and neuron viability (Zhang et al., 2014). Besides, different studies revealed the role of SIRT1 in the neuroinflammatory process, showing that RV treatment regulated pro-inflammatory cytokines levels (Tsai et al., 2016). Pro-inflammatory changes may induce cognitive deficits (Tanaka et al., 2011), then RV treatment could ameliorate memory deficits (Chen et al., 2017).

Additionally, other effects on epigenetic machinery have been described for RV. A recent study, in retinal pigment epithelial cells, RV prevented the decrement in DNMT1, DNMT3A, DNMT3B, and SIRT1 expression induced by an oxidative or inflammatory stimuli (Maugeri et al., 2018); RV-induced changes in SIRT1 activity in T2D patients reduced OS and improves disease (Bo et al., 2018) and in animals models of T2D (Yonamine et al., 2019) has been also reported, among others.

Moreover, a key target of RV effects may be the regulation of miRNAs expression, which are involved in cell death, ageing, as well as neurodegenerative disorders, diabetes, cardiovascular, and other diseases (McCubrey et al., 2017). Notably, the levels of *miR-21*, *miR-125*, *miR-146*, and *miR-155* are upregulated in neurodegenerative diseases. Tili et al. (Tili et al. (2010)) showed that RV attenuates pro-inflammatory *miR-155* levels induced by LPS by upregulating *miR-663*. Likewise, RV downregulated *miR-124* and *miR-134* levels, promoting BDNF synthesis (Zhao et al., 2013a; Shen et al., 2018). However, a recent study RV treatment up regulates *miR-124* expression in T Cells in the Brain (Gandy et al., 2019). Other examples can be found in Table 10.

Table 10
Main examples of epigenetic marks modulated by RV in neurodegenerative diseases.

Resveratrol effects on epigenetic mechanisms	References
Inhibition of DNMT activity.	(Muñoz Fernández and Lima Ribeiro, 2018)
Activation of SIRT1.	(Cosín-Tomàs et al., 2019; Corpas et al., 2019; Chen et al., 2005b; Huber and Superti-Furga, 2011)
Regulation of acetylation of histones (H1, H3, H4) and non-histones chromatin protein (FOXO, p53, Ku70, PPAR, PGC-1α, NF-κβ).	(Vahid et al., 2015; Cantó and Auwerx, 2009b)
Regulation of HDAC and HAT activities.	(Vahid et al., 2015)
Modulation of miRNAs, such as the upregulation levels of *miR-15, miR-29, miR-34, miR-124* and *miR-214*, as well as, the downregulation of *miR-21* and *miR-155*.	(Zhao et al., 2013b; Wang et al., 2015; Kou and Chen, 2017)
Its analogue CAY10512 downregulates miR-146a, inhibiting expression of NF-κβ.	(Lukiw et al., 2008)

4.2.2. Epigenetic inheritance mediated by resveratrol

Experiences and different environmental factors like stress or diet during life can have significant effects on the successive generation (Atakan et al., 2019). Epigenetic inheritance refers to the transmission of several epigenetic marks to offspring, who inherit the phenotype in the absence of the external signal (van Otterdijk and Michels, 2016; Tian et al., 2017; Izquierdo et al., 2019). Furthermore, the interest in epigenetic mechanisms is growing; due to its capacities of transmission across generations and focused on the study of how multifactorial diseases appears. Because a potential discordance might be created between the maternally programmed behaviour of the offspring and the actual environment, contributing to the risk of chronic diseases later in life.

Moreover, an increasing number of studies in animal models have demonstrated that nutritional interventions might alter the phenotype of the organism through epigenetic mechanisms (Ideraabdullah and Zeisel, 2018) as well as these epigenetic modifications can be transmitted across generations (Rando and Simmons, 2015). For instance, the exposure of high glucose concentrations in the parental generation of *C. elegans* protects against cellular stress in the descendent progenies (Tauffenberger and Parker, 2014). Besides, experimental data in mice demonstrates that the diet of a pregnant female could affect not only her offspring but also subsequent generations (Morgan and Whitelaw, 2008; Cropley et al., 2006). Furthermore, paternal diet influences gene expression (Strakovsky et al., 2011) and 5-mC in the liver of the offspring (Cooney et al., 2002) as well as chronic high-fat diet (HFD) in fathers, led to glucose intolerance in female offspring and epigenetic changes in pancreatic cells (Ng et al., 2010). In humans, the transgenerational effect of diet on the epigenome has been associated with poor nutrition and reduced food supply. There is evidence of link the experience of famine in women in early gestation was associated with glucose intolerance and chronic disease in later life and obesity and cardiovascular disease after two generations (Lumey, 1992; Lumey et al., 2007), demonstrating the relevance of epigenetic inheritance in disease. Similar, a more recent study described the consequences for the offspring's later health induced by maternal obesity, suggesting the importance of early prevention of overweight and obesity in women of child-bearing age (Eriksson et al., 2014). An epidemiological study related to food supply in the grandparental generation to health outcomes in the grandchildren (Kaati et al., 2007). Regarding the beneficial effects of polyphenols across generations (for revision see (Silva et al., 2019)), a few studies have been done in rodents, which demonstrated improvement in different tissues and molecular pathways. RV protects rat offspring of maternal HFD and alleviates symptoms of metabolic syndrome (Sheen et al., 2018), prevents the formation of fatty livers in offspring after maternal exposure to HFD, regulating lipid metabolism, reducing OS and apoptosis (Tiao et al., 2018), and prevents the development of hypertension and the gut microbiota alteration by HFD in adult rats offspring (Tain et al., 2018). In this regard, it has been shown that maternal intervention with RV during pregnancy decreases maternal and offspring OS and the resultant damage in a sex-specific manner (Vega et al., 2016). Ros et al. (Ros et al. (2017)) also observed the metabolic protective effects by RV only in female offspring, and thus, these outcomes should be considered in the design of early-life interventions. Interestingly, maternal RV intake during lactation was

associated with a decrease of fatty acid synthesis in the livers of adult male rat offspring by hepatic activation of AMPK through SIRT1 upregulation (Tanaka et al., 2017). A recent study proposed the RV treatment as a reprogramming strategy to protect against hypertension programmed through combined maternal HFD and exposure to the food contaminant oestrogen-mimic Bisphenol A (Hsu et al., 2019).

In addition, nutrition and diet impact during the perinatal period are important factors of later life patterns in neurological diseases such as addiction, stress response, loss of memory and cognitive capacity (Lupu et al., 2012). Interestingly, a diet supplementation lacking in methyl donors during fetal development had a similar effect of increasing anxiety in the mature female rat offspring, but higher learning and memory in new environmental conditions (Konycheva et al., 2011). In contrast, Li et al. (Li et al. (2017)) shown that maternal and postnatal HFD caused metabolic syndrome and cognitive dysfunction in adult rat offspring. Little is known about the neuroprotective effects of parental dietary with polyphenols such as RV in offspring as well as which mechanisms underlie these effects, including epigenetics.

Recently, it has been described that parental diet supplemented with RV associated with the prevention of several symptoms and neurodegenerative diseases in offspring in mice. For instance, maternal RV supplementation in the SAMP8 for two months prior to mating produced changes in global 5-mC and 5-hmC as well as changes in their enzymatic machinery such as DNMT3A/B and TET2 in offspring (Cosín-Tomás et al., 2018). Moreover, methylation levels of NRF2 and NF-κβ genes promoter reduce OS and inflammation in the hippocampus of offspring. Finally, the two next generations exhibited a cognitive improvement, specifically in the hippocampal memory (Izquierdo et al., 2019). Another study in which rat mothers were fed with RV supplementation in perinatal asphyxia (PA), demonstrated neuroprotective effects in offspring through reduction of inflammatory markers such as IL-1β, TNF-α and S-100 Calcium Binding Protein B (S-100B) protein that were regulated by miRNAs *miR-124, miR-132, miR-134, miR-146* and *miR-15a* (Isac et al., 2017). Therefore, RV modulates different epigenetic mechanisms without changing the DNA sequence, changing 5-mC or 5-hmC, histone modification and miRNAs levels and prevents chronic diseases in offspring (Fig. 5). All of these studies indicate that RV diet could have an important role in early treatment to avoid chronic and neurodegenerative diseases, and it is an innovative strategy of preventing cognitive impairment through food intake supplementation.

5. Conclusions and future perspectives

To conclude, OS has a crucial role in ageing and neurodegenerative diseases. Indeed, it is well documented that a reduction in oxidative damage should lead to a delay in the development of diverse pathologies. Recently, nutrition has been proven to effective in the CNS models of ageing and dementia. In this manner, several antioxidants compounds have been investigated for their neuroprotective effects in order to propose them as potential candidate drugs. Among them, RV is thoroughly studied, and it has emerged as a suitable candidate owing to its antioxidant and anti-inflammatory properties. Hence, it prevents cognitive impairment and neurodegeneration.

Noteworthy, even though AD is the most common neurodegenerative disease, there are no effective therapies available. AD is considered multifactorial diseases due to the complexity of its aetiology and pathophysiology. Taking into account this consideration, new combined therapy treatments or multi-target approaches, which allow modifying several pathways that are involved in AD. As aforementioned, RV enhances the clearance of Aβ, showing anti-amyloidogenic properties. Also reduces inflammation, improves synaptic plasticity and UPS functionality, induces autophagy, ameliorates mitochondrial dysfunction,

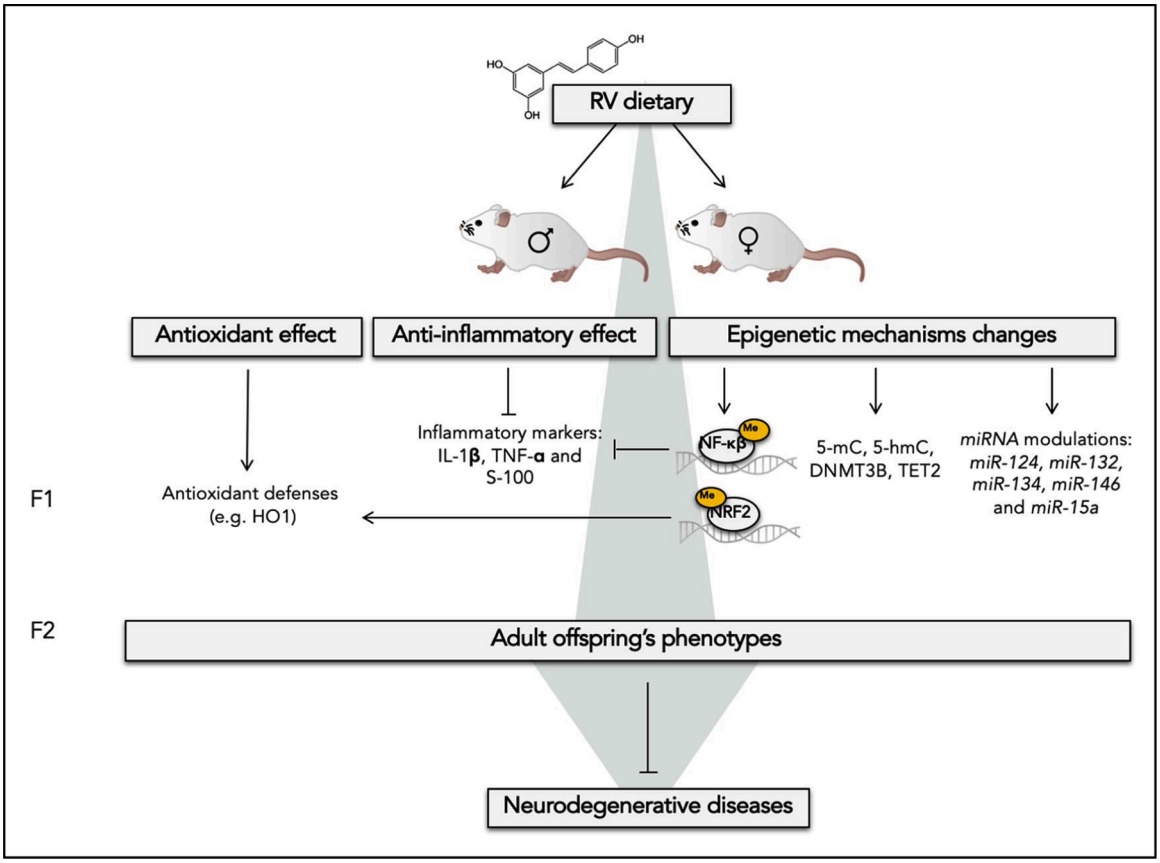

Fig. 5. Scheme of published results on paternal RV supplementation, which promotes beneficial effects through antioxidant, anti-inflammatory and epigenetic mark on neurodegeneration and over generations.

modifies gut microbiota composition, and reduces neuronal cell death. Therefore, it prevents cognitive impairment and neurodegeneration in age-related diseases. Herein, we discussed the main pathways involved in the neuroprotective effects of RV as well as the potential therapeutic effect of RV on age-related cognitive decline and AD pathology. Thus, several *in vivo* and *in vitro* studies suggested that RV might be of benefit in age-related cognitive decline treatment. Clinical trials indicated that RV has low toxicity and can penetrate BBB easily. However, the clinical outcomes of RV are ambiguous due to the low oral bioavailability of RV limited its efficacy. Therefore, novel approaches should be developed in order to improve the relationship between dose, bioavailability and efficacy in the human body, particularly in the brain (for revision see (Wahl et al., 2018)).

Moreover, this review also summarizes the epigenetic mechanisms related to RV action. Due to the regulation of epigenetic mechanisms plays a crucial role in neurological diseases, the relationship between polyphenols and epigenetic changes is being considered as a key point to understand its beneficial mechanisms on ageing and AD. In this context, RV has epigenetic effects that can contribute to improve cognitive impairment in mice and rats. Experimental data associated with epigenetics changes indicate that RV exhibits the capacity to modulate several neurodegenerative pathways, reducing the expression of genes crucial for age-related diseases. There are still some questions that must be answered to define the mechanisms of action of RV in humans. However, new studies are continually supporting the neuroprotective effects by RV through new mechanisms. Therefore, future research directions must lead us to a better definition of the use of antioxidants, including RV, as a potential therapy to prevent cognitive decline and AD.

CRediT authorship contribution statement

Christian Griñán-Ferré: Conceptualization, Investigation, Funding acquisition, Writing - original draft. **Aina Bellver-Sanchis:** Investigation, Writing - original draft. **Vanessa Izquierdo:** Writing - original draft. **Rubén Corpas:** Investigation, Writing - original draft. **Joan Roig-Soriano:** Investigation, Writing - original draft. **Miguel Chillón:** Writing - original draft. **Cristina Andres-Lacueva:** Writing - original draft. **Milán Somogyvári:** Writing - original draft. **Csaba Sőti:** Writing - original draft. **Coral Sanfeliu:** Writing - original draft. **Mercè Pallàs:** Funding acquisition, Writing - original draft.

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