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Resveratrol as a Potential Therapeutic Candidate for the Treatment and Management of Alzheimer's Disease

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Abstract: Resveratrol (3,4',5-trihydroxystilbene) is a naturally occurring phytochemical present in red wine, grapes, berries, chocolate and peanuts. Clinically, resveratrol has exhibited significant antioxidant, anti-inflammatory, anti-viral, and anti-cancer properties. Although resveratrol was first isolated in 1940, it was not until the last decade that it was recognised for its potential therapeutic role in reducing the risk of neurodegeneration, and Alzheimer's disease (AD) in particular. AD is the primary cause of progressive dementia. Resveratrol has demonstrated neuroprotective effects in several *in vitro* and *in vivo* models of AD. Apart from its potent antioxidant and anti-inflammatory roles, evidence suggests that resveratrol also facilitates non-amyloidogenic breakdown of the amyloid precursor protein (APP), and promotes removal of neurotoxic amyloid beta (Aβ) peptides, a critical step in preventing and slowing down AD pathology. Resveratrol also reduces damage to neuronal cells via a variety of additional mechanisms, most notably is the activation of NAD^+-dependent histone deacetylases enzymes, termed sirtuins. However in spite of the considerable advances in clarifying the mechanism of action of resveratrol, it is unlikely to be effective as monotherapy in AD due to its poor bioavailability, biotransformation, and requisite synergism with other dietary factors. This review summarizes the relevance of resveratrol in the pathophysiology of AD. It also highlights why resveratrol alone may not be an effective single therapy, and how resveratrol coupled to other compounds might yet prove an effective therapy with multiple targets.

Keywords: Resveratrol, Alzheimer's disease, Aβ pathology, oxidative stress, antioxidants.

INTRODUCTION

Alzheimer's disease (AD) is the major cause of dementia in the elderly. The aetiology and pathogenesis of AD remains unclear. However, AD appears to be a multifaceted age-related degenerative disorder with more still needing to be known in order to identify the most accurate therapeutic targets. Histopathologically, AD is characterised by the progressive loss of cholinergic neurons in the basal forebrain (septum, diagonal band of Broca, basal nucleus of Meynert) [1-3]. The loss of acetylcholine (Ach) directly correlates with a decline in memory function. The two main pathological hallmarks of AD include extracellular neuritic senile plaques (SP), and intracellular neurofibrillary tangles (NFTs)[4-6]. SPs contain aggregated deposits of amyloid-beta (Aβ) protein in close proximity to dystrophic neurons, and activated astrocytes and microglia, and other inflammatory cells [7-9]. NFTs are formed by irregular deposits of hyperphosphorylated tau proteins [10, 11]. AD presents a significant challenge to global health care systems, due to the growing costs of care for patients with the disease. Extensive research has failed to identify any therapeutic agents that successfully treat and alleviate cognitive dysfunction. Moreover, no currently available compounds have been able to slow down or prevent disease progression [12].

Several pharmacological strategies have been, and are being, developed to attenuate both the debilitating symptoms of AD and pathologies associated with AD [12]. Despite extensive research in the past decades, the exact molecular events leading to AD remain to be elucidated, and an effective therapeutic for AD is yet to be discovered. Cholinesterase inhibitors, such as Donepezil (Aricept) and Rivastigmine (Exelon) have been prescribed for the management of cognitive (memory and learning) deficits of dementia. These drugs inhibit the activity of the acetylcholinesterase enzyme, which is responsible for catabolising the essential neurotransmitter, Ach. The modest symptomatic benefits of these drugs are attributed to the role of acetylcholine in cognition in the central nervous system (CNS). However, while these drugs are generally well tolerated, they do produce significant adverse side effects with limited evidence of any bene-

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ficial effect in mild AD [13, 14]. Tacrine, another cholinesterase inhibitor, has restricted use in the treatment of AD due to its poor oral bioavailability and severe hepatotoxicity[15].

Another drug, Memantine (Axura, Akatinol, Namenda, Abixa, and Memox) has been used for the management of AD symptoms targeting the glutaminergic system by antagonising the N-methyl-D-aspartate- (NMDA-) type glutamate receptor [16, 17]. These drugs selectively reduce brain activity by agonising NMDA receptors on neuronal cells, thereby inhibiting activity of the excitatory effects of the neurotransmitter glutamate, at its binding sites. Under physiological conditions, glutamate serves an important role in memory and learning. However, under pathophysiological conditions, increased levels of glutamate overstimulate neuronal cells, leading to excitotoxicity and oxidative stress culminating in cell death via energy restriction and apoptosis [18, 19]. Only limited positive effects on cognition, mood, behaviour, and the ability to perform habits of daily living have been observed following the administration of Memantine in patients with moderate to severe AD [16, 17]. Memantine has been reported to be less efficacious clinically than the cholinesterase inhibitors [16, 17]. Owing to the heterogeneity of AD, pharmacotherapies which target multiple levels of AD pathology are needed.

Numerous studies have shown that naturally occurring phytochemicals may represent important therapeutics for AD [20-24]. This is supported by evidence from several epidemiological reports suggesting that diet and lifestyle factors may influence the development and progression of AD and other neurodegenerative disorders [25-28]. In particular, a strong correlation has been identified between diets rich in polyphenolics, and a lower incidence of AD [20-24]. While these findings represent associations only. An intense effort is directed at identifying compounds with neuroprotective effects. Naturally occurring polyphenols have become a subject of growing scientific interest due to their potential neuroprotective effects, both *in vitro* and *in vivo*.

Polyphenols are produced as secondary metabolites in plants. They are almost always associated with maintaining defence against irradiation from ultraviolet or pathogenic insult [29]. Owing to their high antioxidative nature, their consumption may exert therapeutic benefits in neurodegenerative disorders. One study has shown that consumption of 3-4 glasses of wine per day may lower the risk of dementia and AD [30]. Similarly, diets rich in fruit and vegetable juices, containing large amounts of polyphenols, appear to play a protective role in slowing the onset of AD [31]. Polyphenols derived from fruits and vegetables are invaluable for mediating neuroprotection due to their favourable antioxidant and anti-inflammatory properties, and their effects on signal transduction, cellular proliferation, apoptosis, and cellular differentiation [32].

Among the wide variety of naturally occurring polyphenols and related phenolic compounds, resveratrol has received considerable interest due it its apparent anti-AD properties, its possible role as an anti-amyloidogenic, its antioxidative, and anti-inflammatory potential, and its effect on numerous other molecular targets that play a critical role in neuroprotection in AD [33-37]. Subsequent studies have reported that resveratrol, the main active polyphenol in red wine, has several important biological activities, including anti-inflammatory, antioxidant, vasorelaxing, phytoestrogenic, and possibly anticarcinogenic effects. Resveratrol has therefore been touted as a potential adjunct in treatments against cancers and vascular diseases, as well as complex brain degenerative disorders such as AD [38]. The neuroprotective effects of resveratrol for the treatment of AD have been investigated in various *in vitro* and *in vivo* models of AD. In spite of the current focus, research on resveratrol and AD is still developing, and data following chronic supplementation with the phytonutrient in human patients and age-matched controls are still missing in the current literature.

ALZHEIMER'S DISEASE – A COMPLEX MULTI-FACETED DISORDER

In spite of significant improvements in our knowledge of the pathogenesis of AD over recent decades, the precise mechanisms leading to AD development remain elusive. Over the years, several different hypotheses have been postulated to address the pathological lesions observed in AD. Indeed, oxidative stress has been consistently observed as an underlying biochemical anomaly in several neurodegenerative diseases including AD. However, whether oxidative stress presents a causal role or is secondary to AD pathogenesis remains unclear [39]. Markers for oxidative stress have been reported during early development of the disease and in patients with mild cognitive impairment well before the onset of SPs and NFTs [40].The brain is highly vulnerable to the cytotoxic effects of reactive oxygen species (ROS), and is susceptible to oxidative damage due to inherent low antioxidant defences and high levels of polyunsaturated fatty acids. Oxidatively damaged mitochondria will also produce significant quantities of ROS due to induction of nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). These ROS can induce damage to lipids, proteins and nucleic acids, often resulting in compromised cellular integrity due to excessive lipid peroxidation, protein oxidation and DNA damage[41]. ROS can also promote Aβ production which facilitate oxidative stress formation, thus the negative circle between ROS production and accumulation of Aβ , likely enhance AD progression and further facilitate cognitive dysfunction [42]. Polyphenolic compounds with potent antioxidant properties have been reported to protect against Aβ-induced neurotoxicity both *in vitro* and *in vivo* [41].

Neuroinflammation also appears to be seminal in the pathobiology of AD. Activated microglial cells, the resident inflammatory cells of the brain are present in the AD brain, particularly within amyloid deposits. Activated astrocytes and astrogliosis are also commonly reported in the AD brain [43]. Aggregation of Aβ has been shown to induce the activation of astrocytes and microglia in cell culture models and animal studies, leading to increased production of several proinflammatory mediators, including cytokines, ROS, and reactive nitrogen species (RNS) such as nitric oxide (NO), all of which are capable of enhancing the generation of the insoluble neurotoxic form of Aβ [43-45]. Aβ can interact with redox active metals, stimulating the production of yet more ROS and the inflammatory cytokine, tumor necrosis factor alpha (TNF-α), which further aggravate Aβ deposition

promoting neuronal dysfunction and eventual cell death [46]. Overwhelming evidence for the involvement of neuroinflammation in the pathogenesis of AD has prompted the consideration of anti-inflammatory agents as potential treatment strategies [47].

Since 1992, the Aβ hypothesis has been the focus of AD research. According to the Aβ hypothesis, deposition of Aβ is the elementary cause of AD, and all other pathological features of AD, including NFTs and brain atrophy are downstream effects of the Aβ cascade [4, 48]. Raised extracellular levels of Aβ have been reported in the cortex and hippocampus of AD brains. Aβ is formed following the abnormal cleavage of the Amyloid precursor protein (APP) by β- and γ-secretases, but not α-secretase. This accumulation of Aβ is thought to be a primary cause of the progressive loss of neurons, disruption of neuronal circuits, and final cognitive decline characteristic in AD [49]. Under normal conditions, APP is cleaved by α-secretase into soluble amyloid precursor α (sAPPα). This reduces the formation of Aβ and protects neurons. Therefore, inhibition of β- and γ-secretases represent additional targets for the development AD therapies [50, 51].

Since Aβ deposition in SPs appears to be a late, non-specific event in the development of AD, more recent research suggests that hyperphosphorylation of tau and Aβ aggregation may represent the early common pathway in AD. Tau is a highly soluble microtubule-associated protein (MAP) which stabilises microtubules and maintains the neuronal cytoskeleton [11, 52]. Phosphorylation of tau is mediated by several kinases, and leads to microtubule disassembly and the formation of neurofibrillary tangle aggregates (NFTs), a key feature of AD pathology. Once NFTs develop, the tau loses its ability to connect to tubulin and the microtubule assembly. Considering the evidence for the pathological role of hyperphosphorylated tau in AD, inhibition of tau aggregation may represent a potential therapeutic approach for AD and other tauopathies[10, 53].

Loss of neuronal synaptic density appears to be dominant feature of AD, and is possibly the direct cause for the incidence and progression of clinical dementia. Importantly synaptic dysfunction occurs early in AD, while actual loss of synapses does not appear until much later in the disease. The loss of synaptic density leads to inhibition of the excitatory transmission in both the hippocampus and cerebral cortex, leading to significant memory loss [54, 55]. Although Aβ deposition and tau phosphorylation may induce neuronal loss, the predominant mechanism accounting for-synaptic thinning is more likely progressive neuronal apoptosis. Several factors have been shown to stimulate apoptosis in various models of AD, including, impaired glucose metabolism, excitotoxicity and mitochondrial dysfunction. Additionally, factors, such as tumor suppressor protein p53, forkhead box protein (FOXO), and ROS, can mediate apoptosis in AD [56, 57]. Thus, new treatment strategies aimed at developing molecules that downregulate apoptosis are currently a primary focus.

Recent findings provide support for the role of resveratrol as a potential neuroprotective agent for AD due to its diverse pleiotropic effects. The beneficial metabolic effects of resveratrol have been widely reported in a number of models, both *in vitro* and *in vivo* [58, 59]. More recently, resveratrol has been shown to activate enzymes known as sirtuins [60]. Gene silencing by this class of enzymes has been shown to prolong lifespan in various lower organisms and improve metabolic function in murine models of ageing[61]. Studies so far support a role for resveratrol in the clearance of Aβ (Fig. **3**), attenuation of oxidative stress, reduction in inflammation, amelioration of platelet aggregation, inhibition of the activation of astrocytes and microglial cells, and overall reduction in neuron cell death [38].

Over 120 different studies published in the last 5 years have investigated the effect of resveratrol on health outcomes in the treatment and management of AD. This review summarises the potential beneficial anti-AD properties of resveratrol.

CHEMISTRY OF RESVERATROL

Resveratrol (3, 5, 4′-trihydroxy-trans-stilbene) is phytochemical produced in plants, especially grape skin and seeds. In lower organisms such as bacteria or fungi, resveratrol acts as a phytoalexin with potent antimicrobial activity against these pathogens [62]. One epidemiological study reported a positive association between low to moderate red wine consumption and a reduced incidence of cardiovascular disease. This phenomenon is known as the "French Paradox" [63, 64]. Resveratrol is naturally found in both cis- and trans-isomers (Fig. **1**). The trans- isomer is the most common and highly active form. Resveratrol is highly vulnerable to isomerisation due to UV. With at least 80% of trans-resveratrol being transformed to cis-resveratrol after exposure to just 1 hour of ordinary light [65].

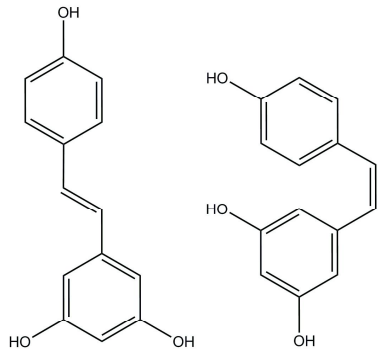

Fig. (1). Stoichemistry of resveratrol isomers.

Resveratrol is naturally anabolised by the catalytic activity of stilbene synthase (STS). This enzyme is rapidly activated in response to exogenous and environmental stress factors, including physical injury, UV irradiation, and chemical modulators in response to pathogenic insult. It has been previously shown that peak levels of resveratrol occur within 24 hours following exposure to stress, and declines 42-72 hours later, in response to the activity of stilbene oxidase [65]. The stoichemistry for resveratrol synthesis involves three condensation reactions between coumaroyl-coenzyme A (CoA) and malonyl-CoA. STS also catalyses the removal of the terminal carboxyl group resulting in the generation of resveratrol [66].

BENEFICIAL EFFECTS OF RESVERATROL IN NEURONAL CELL CULTURE SYSTEMS

The beneficial effects of resveratrol have been documented in several murine and human cellular models (Fig. **2**, Table **1**). Using hippocampal slices removed from 10-day-old Sprague-Dawley rat pups, resveratrol was shown to down-regulate extracellular signal-regulated kinase (ERK) activation due to excitotoxic concentrations of glutamate. Resveratrol also reduced the expression of monocyte chemoattractant protein-1 (MCP-1) expression, and interleukin-1β (IL-1β) in a dose-dependent manner [67]. Similarly, resveratrol reduced peroxisome proliferator-activated receptor-gamma coactivator- (PGC-) 1α in rat cortical neurons. Resveratrol has also been shown to protect against the neurotoxic effects of protein p25 or mutant superoxide dismutase (SOD1). Resveratrols' neuroprotective effects appear to be mediated through the deacetylation of p53, and the subsequent reduction of p53 levels, a major apoptotic mediator [68, 69].

Resveratrol also protected against NMDA-induced neuronal death in rat cortical neurons by reducing intracellular calcium transients and NMDA-mediated ROS production[70]. Exposure of cells with A β_{25-35}, and other forms of Aβ, has been shown to induce neurotoxicity *in vitro*. Resveratrol (15–40μM) attenuated $A\beta_{25-35}$-induced apoptosis in hippocampal neurons in a dose-dependent manner. Most favourable effect was observed at a 25μM dosage. Resveratrol also prevented the cleavage of the DNA nick sensor, poly(ADP-ribose) polymerase (PARP), ameliorated the reduction in Bcl-XL expression, inhibited pro-apoptotic Bax protein expression, and blocked JNK phosphorylation [71]. All of which indicates that when available to the cell at micromolar concentrations, resveratrol can attenuate Aβ pathology via numerous linked pathways

Resveratrol has also been shown to inhibit both the expression of iNOS and NO production in response to Aβ. Aβ can also induce translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). This effect was prevented following pre-treatment with resveratrol [72]. NF-κB signalling also regulates the expression of iNOS and cathepsin B, which can trigger apoptosis. Resveratrol induced protein kinase C (PKC) phosphorylation dose-dependently, with maximal effects seen at 20–30 μM. The PKC pathway is a significant mediator in the neuroprotective effects of resveratrol against the cytotoxic effects of Aβ in hippocampal neurons [73].Though resveratrol decreased the phosphorylation of PKC-d slightly, it displayed no effect on PKC-α/βII, PKC-μ (Ser916), and PKC-θ (Thr538) phosphorylation, suggesting that PKC-δ (Thr505) likely played a role in the neuroprotective effects of resveratrol.

Resveratrol and other polyphenolic compounds have been shown to ameliorate nitric oxide (NO) cytotoxicity to hippocampal cells, potentially through its demonstrated antioxidant and anti-inflammatory capacity. In glial/neuronal hippocampal cultured cells, resveratrol (5 - 25 μM) treatment increased cell survival following treatment with the NO donor SNP (100μM). Another study showed that resveratrol

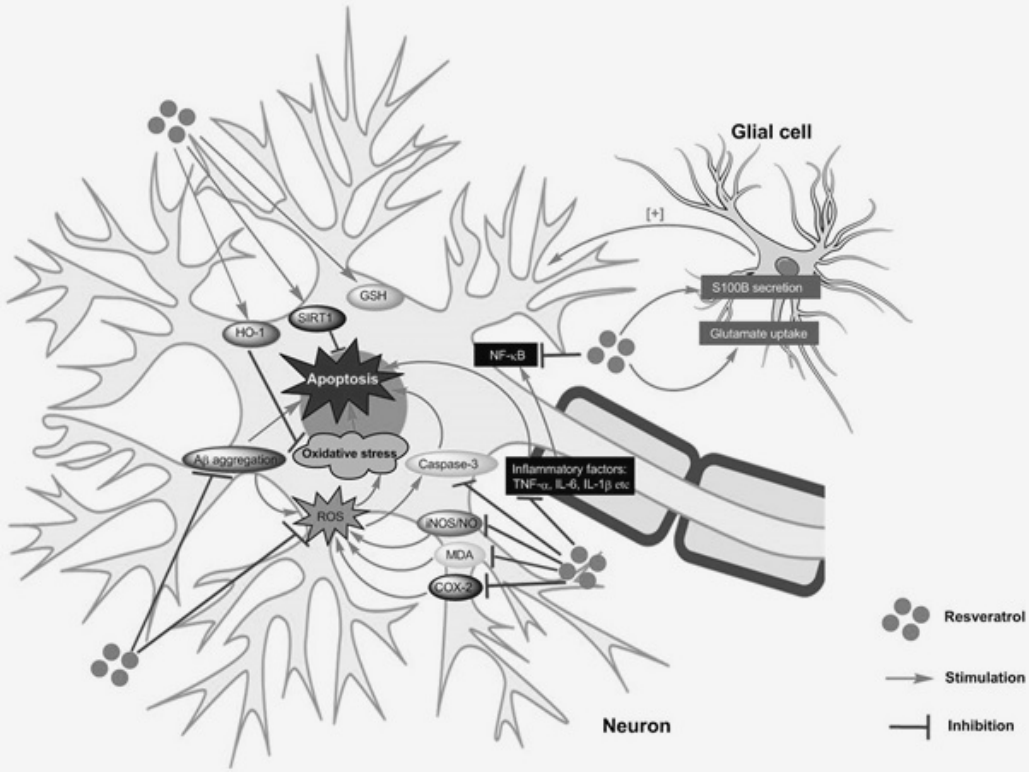

Fig. (2). Neuroprotective effects of resveratrol in AD pathogenesis. Resveratrol can potentially protect neurons by decreasing the levels of Aβ, activating and up-regulating the levels of SIRT1 and endogenous antioxidant enzymes, preventing oxidative stress and apoptosis, inhibiting the activation ofNF-κB, modulating the release of inflammatory factors, and promoting the release of S100B and glutamate uptake by glial cells.

Table 1. Summary of the neuroprotective effects of resveratrol *in vitro* and *in vivo*.

Experimental Model	Exposure	Beneficial Effect of resveratrol	Reference
Hippocampal slices	Treatment with glutamate	Downregulated ERK activation, MCP-1, and IL-1β expression.	[67]
Primary cortical neurons	Treatment with NMDA	Inhibited Increased intracellular calcium influx and NMDA-mediated production of ROS.	[70]
Primary hippocampal cells	Aβ induced	Prevented the cleavage of PARP), the decrease of Bcl-XL expression, inhibited the expression of the pro-apoptotic Bax protein, blocked activation of JNK via phosphorylation. Reduced cell death, decreased the phosphorylation of PKC.	[71]
Mixed (glial/neuronal) hippocampal cell cultures	Treatment with SNP	Rescued hippocampal cells against NO-induced toxicity, Inhibited NO generation, Suppressed iNOS in LPS-activated macrophages.	[74]
Primary microglial cells	Stimulated with LPS	Inhibit PGE2, ROS generation, and expression of mPGES-1 and COX-1.	[75]
RAW 264.7, BV-2, and Ba/F3 cells	Stimulated with LPS	Reduced the levels of several cytokines, and phosphorylation of IKKα, IκB, and NF-κB, inhibited STAT1 and STAT3 activation, and reduced the expression of iNOS and COX-2.	[76]
HUVEC-derived EA.hy926 cells	DMNQ-induced	Reduced Nox4 expression, increased SOD1 and GPx1 expression.	[77]
SH-SY5Y neuroblastoma cells	Treatment with Aβ complexes	Reduced formation of Aβ-Fe, Aβ-Cu, and Aβ-Zn and thus reduced their toxicity.	[78]
SK-N-BE cells	Treatment with TAT-α-syn (A30P) and $A\beta_4$	Prevented toxicity.	[79]
APP-HEK293 and APP-N2a cell	Treatment with Aβ	Activation of AMPK independent of SIRT1 pathway.	[80]
Tg2576 mice	Fed with GPSE	Reduced oligomerization of Aβ peptide and attenuated cognitive impairments.	[84]
APP/PS1 mice	Fed with resveratrol	Lowered the number of activated microglia	[76]
C67BL/6J mice	Fed with resveratrol in a high-fat diet	Ameliorated neuroinflammation and oxidative stress	[85]
C57BL/6J mice	Fed with resveratrol	Increased microvascular density, lowered number of vacuolar abnormalities. Improvements in spatial orientation and memory.	[86]
Wistar rats, ICV injection of STZ	ICV injection of resveratrol	Increased retention latencies and shorter transfer latencies.	[88]
Inducible p25 transgenic mice	ICV injection of resveratrol	Reduces hippocampal neurodegeneration, prevents cognitive decline.	[94]

(10μM) inhibited the production of NO and suppressed the expression of inducible nitric oxide synthase (iNOS) in macrophages activated by lipopolysaccharide- (LPS-)[74]. The generation and secretion of prostaglandin E_2 (PGE_2) and multiple cytokines, such as IL-6, TNF-α, M-CSF, and IL-1ra by activated microglial cells was also suppressed by resveratrol via regulation of the cyclooxygenase (COX)/PGE_2 pathway. Moreover, resveratrol can suppress microsomal prostaglandin E synthase-1 (mPGES-1) and COX-1 expression, but not COX-2 expression induced by LPS treatment [75]. Resveratrol also inhibited LPS-mediated expression of signal transducer and activator of transcription (STAT) 1 and STAT3 and fibrillary Aβ in the RAW264.7 murine microglial cell line, and lowered iNOS and COX-2 expression in a dose-dependent manner [76].

In addition to its own antioxidant activity, the gene expression of the anti-oxidative enzymes, SOD1 and glutathione peroxidase-1 (GPx1) have been shown to be increased by resveratrol treatment in human umbilical vein endothelial cells (HUVEC) [77]. Using SH-SY5Y neuroblastoma cells, it was shown that resveratrol can play a protective role in AD by reducing growth of amyloidogenic Aβ peptides and disrupting Aβ42 fibril aggregations without inhibiting Aβ42 oligomer formation [78]. Resveratrol also reduced the generation of Aβ ionic complexes (Aβ-Fe, Aβ-

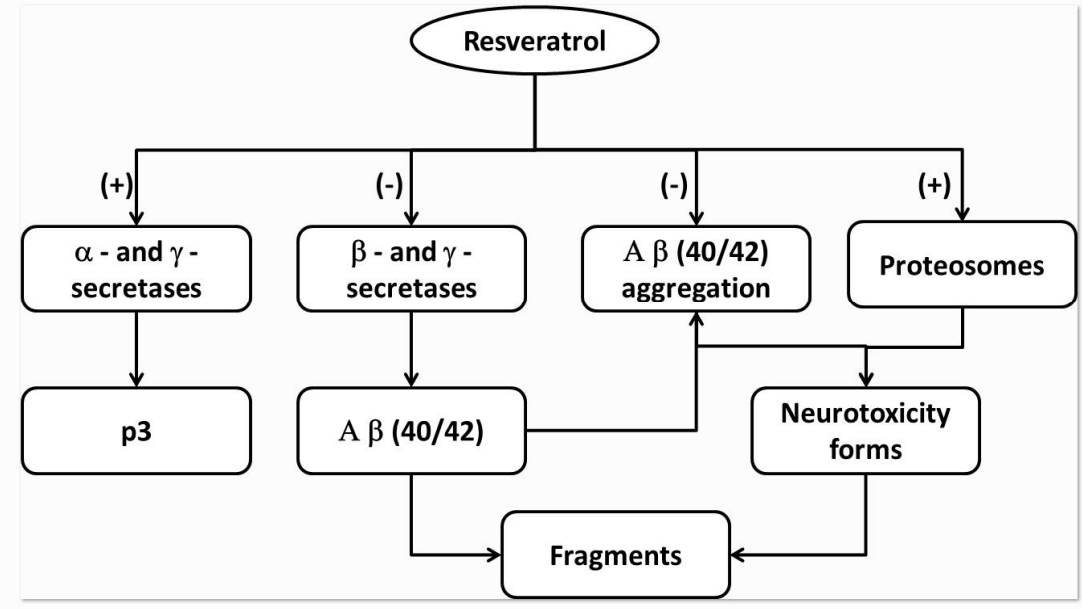

Fig. (3). Antiamyloidogenic effects of resveratrol. Resveratrol stimulates anti-amyloidogenic processing of APP and enhances the degradation of Aβ via proteasomes. Resveratrol can also inhibit the oligomerisation of Aβ and ameliorates Aβ-induced neurotoxicity.

Cu, and Aβ-Zn), thereby reducing their potential toxicity. Resveratrol has also shown antioxidant activity against hydrogen peroxide (H_2O_2) and 6-hydroxydopamine (6-OHDA). As the protective effects were sensitive to sirtinol, involvement of SIRT1 enzymatic activity is likely [78].

Resveratrol also inhibited the ROS mediated TAT-α-syn (A30P) and Aβ42 fibrillar induced toxicity. In addition, resveratrol, through SIRT1, reduced Aβ42-dependant ROS generation and subsequent toxicity, influenced Aβ42 fibril production and steadiness, and reduced intracellular Aβ42-dependent ROS generation [79]. In addition to its SIRT1 activator function, resveratrol can also play a neuroprotective role by activating 5' adenosine monophosphate-activated protein kinase (AMPK) independently of SIRT1. Resveratrol has also been shown to reduce A βaccumulation through direct activation of AMPK signalling in HEK293 and N2a cell lines and in primary neuronal cultures. Resveratrol treated cells also showed reduced Aβ aggregation through increased autophage activity and promotion of lysosomal degradation of Aβ [80].

POTENTIAL PROTECTIVE EFFECTS OF RESVERATROL IN RODENT MODELS FOR AD

In addition to the numerous *in vitro* data showing positive benefits for resveratrol as summarised above, resveratrol has also been shown to have significant benefit *in vivo* including amelioration of oxidative stress damage and improving motor and cognitive impairments in several animal models of AD (Table **1**) [81]. Recent studies have shown that extracellular accumulation of soluble Aβ oligomers do play a role in the pathophysiology of AD dementia and cognitive dysfunction [82, 83]. Grape seed polyphenolic extract (GPSE) containing resveratrol reduced Aβ oligomerization and improved cognitive function in Tg2576 mice overexpressing a mutant form of APP (isoform 695) bearing the Swedish mutation (KM670/671NL) [84]. Similarly, a reduced number of activated microglia was reported in resveratrol-treated APP/PS1 mice, independent of it effect on Aβ deposition. This suggests that resveratrol can reduce neuroinflammation independently of its anti-amyloidogenic properties [76]. Resveratrol treatment also ameliorated neuroinflammation and oxidative stress in the hippocampus, and improved cognitive function in C67BL/6J mice fed a high-fat diet [85]. In another study significant improvements in spatial orientation and memory performance were reported, parallel to increased hippocampal microvascular density and reduced vacuolar abnormalities in endothelial cells from both the hippocampus and cortical microvascular following treatment with resveratrol [86].

Treatment with resveratrol also improved memory and learning following intracerebroventricular (ICV) injection of streptozotocin (STZ) in rats. Streptozotocin induces diabetes in rats, and reduces choline acetyltransferase levels in the hippocampus due to impaired glucose and energy metabolism [87]. Chronic treatment with trans-resveratrol showed significantly increased retention latencies and shorter transfer latencies on the elevated plus maze, although no significant difference in the locomotor activity was observed [88].

As previously described, the sirtuin genes are thought to represent the main target for caloric restriction. SIRT1, the founding member of seven mammalian homologues of the sirtuin family of NAD^+-dependent deacetylases, regulates several signal transduction pathways which can promote longevity [61, 89-92]. Resveratrol has been shown to activate SIRT1 in some studies, however it is a commonly held view that resveratrol is not a direct activator [93]. In the inducible p25 transgenic mouse model of taupathies and AD, ICV injection of resveratrol resulted in a significant activation of SIRT1. Administration of resveratrol reduced apoptotic neurodegenerative changes in the CA1 and CA3 regions of the hippocampus as shown by reduced levels of caspase-3 and glial fibrillary acidic protein (GFAP), a marker of astro-

gliosis. Learning capability was also significantly improved following treatment with resveratrol for 3 weeks [94].

WHY RESVERATROL IS NOT LIKELY TO BE AN EFFECTIVE 'SINGLE' THERAPY FOR AD

Despite the high bioactivity of resveratrol in AD, results in *in vivo* animal models and human clinical trials are less convincing. In addition the anti-inflammatory properties of resveratrol remain to be fully elucidated. Due to its poor bioavailability the concentrations of resveratrol required to produce favourable biological effects in the brain and neuronal cells are insufficient to demonstrate efficacy in humans. Resveratrol demonstrates poor bioactivity due to its rapid and extensive first pass metabolism [95-98]. The half-life of resveratrol is 8–14 minutes. Resveratrol is metabolized into sulfate and glucuronide metabolites in the liver and intestinal epithelial cells [99]. Resveratrol has low bioavailability and poor aqueous solubility (<1mg/mL) [99]. Trans-resveratrol is also highly photosensitive, and is readily oxidized, and presents unfavourable pharmacokinetics [100]. Therefore, clinical use of resveratrol as a single 'take home' oral therapy alone presents a major challenge for the treatment of AD. Researchers have tried several approaches to increase the miscibility and bioavailability of resveratrol, including co-administration of trans-resveratrol metabolic inhibitors, synthesis of bioactive analogs and development of novel trans-resveratrol delivery systems [101]. However further development in the area is still required if even the modest benefits of resveratrol are to be accessible to the wider clinical population.

RESVERATROL 'COUPLED TO OTHER COMPOUNDS' MIGHT YET PROVE EFFICACIOUS FOR THE TREATMENT OF AD

As resveratrol targets are limited to modest antioxidant activity and transcriptional regulation, combination drug therapies with multiple targets may be more beneficial for the treatment of AD. As discussed previously, AD is characterised by an increase is inflammatory and oxidative activity which are closely linked to Aβ deposition and in appropriate tau phosphorylation. While the initial pathobiochemical causes are still to be defined the contribution of free redox active metals such as Fe^{2+} and Cu^{+} are well established. It is therefore likely that therapies targeting only one or two elements of the pathobiochemical processes will not produce significant clinical benefit.

We propose herein a novel combination therapy consisting of an agent for chelating redox-active metals (Fe^{2+}) and/or an antioxidant to reduce damage caused by residual oxygen free radicals, in addition to resveratrol, a modulator of AMPK and sirtuin pathways (nuclear transcription). Resveratrol may increase activity SIRT1 and promote improved DNA repair by enhancing PARP enzyme activity through increased production of their essential substrate NAD^{+}, and thus improve cell viability and longevity.

Each constituent should be administered in such a way that each of the desired biochemical effects, i.e. 1) effective chelation of free redox metals, 2) increased antioxidant capacity, 3) increased sirtuin activity are present at the same time. This may be accomplished by administering each bioactive component at various times, to produce the maximum desired effect, administered together in a single dosage unit.

A close association between brain metal dyshomeostasis and the onset and/or progression of Alzheimer's disease (AD) has been well documented in several *in vitro* and *in vivo* studies. Although the exact role of redox-active metals in the pathogenesis of AD still remains obscure, chelation therapy remains an attractive pharmacological option for the treatment of AD[102-104]. Chelating agents suitable for synergistic compositions include, but are not limited to, ethylenediaminetetraacetic acid (EDTA), Ethylenediaminetetraacetic acid (calcium disodium versante) (CaNa2-EDTA), Ethylene glycol tetraacetic 20 acid (EGTA), dimercaptosuccinic acid (DMSA), Alpha lipoic acid (ALA), 2,3-dimercapto-1-propanesulfonic acid (DMPS), Dimercaprol (BAL), Deferoxamine, D- penicillamine, dimercaprol, Aminophenoxyethane-tetraacetic acid (BAPTA) Defarasirox, Diethylene triaminepentaacetic acid (DTPA) 2-pyridinecarboxylic acid (picolinic acid), 2,3-pyridinedicarboxylic acid (quinolinic acid), 2-aminobenzoic acid (anthranilic acid), 25 kynurenic acid, xanthurenic acid and 8-hydroxyquinoline (and functional derivatives thereof)[105]. In general, the chelating agent will be capable of forming complexes with redox-active metals, thereby reducing hydroxyl radical production. Examples of redox-active metals that may be bound and complexed by chelating agents include, but are not limited to Fe^{2+}, Cu^{+}, Cr^{3+}, Mn^{2+}, Co^{2+},Ni^{2+}, Ag^{+}.

Antioxidants suitable for the synergistic compositions with resveratrol include, but are not limited to, melatonin, vitamin E, vitamin C, methionine, taurine, SOD, catalase (CAT), GPx1, L-ergothioneine. N-Acetyl Cysteine (NAC), vitamin A, beta-carotene, retinol, catechins, epicatechins, epigallocatechin-3-gallate, flavenoids, L-ergothioneine, idebenone and selenium. Other suitable antioxidants are described in US Patent No's. 2008015218 and 20110110913 A1. Their neuroprotective effects in AD have been previously reviewed [106].

CONCLUDING REMARKS

Despite an enormous increase in the elucidating the complex neurobiology of AD, the etiopathogenesis of this debilitating neurodegenerative disorder remains largely obscure. As yet, there are no effective drugs that can be prescribed to reverse or safely attenuate cognitive decline in affected patients. Compelling evidence suggests that the pathogenesis of AD is multifactorial, and potential drug candidates are required which function on multiple brain targets. The protective effects of resveratrol have been demonstrated in several cellular and mammalian models. However, caution should be taken when considering resveratrol as a single therapy alone, since its efficacy and utility in the clinic is questionable. Based on the above arguments, it is evident that combination therapy with multiple targets may play a significant role in the medical treatment of AD as they have the potential to attenuate multiple effects. A synergistic combination of a selected antioxidant substance,Fe^{2+}chelating agents and resveratrol (improved nuclear transcription) may be expected to provide a more clinically successful treatment.

CONFLICT OF INTEREST

The authors Braidy N and Grant R, acknowledge that they are co-authors of US patent # US 20110110913 A1Pharmaceutical formulations of resveratrol and methods of use thereof for treating cell disorders R. Grant is a Director of the company NAD+ Life, who owns the above patent.

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