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Review

Roles of resveratrol and other grape-derived polyphenols in Alzheimer's disease prevention and treatment☆

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ABSTRACT

Alzheimer's disease (AD) is a devastating disorder that strikes 1 in 10 Americans over the age of 65, and almost half of all Americans over 85 years old. The odds of an individual developing AD double every five years after the age of 65. While it has become increasingly common to meet heart attack or cancer survivors, there are no AD survivors. There is mounting evidence that dietary polyphenols, including resveratrol, may beneficially influence AD. Based on this consideration, several studies reported in the last few years were designed to validate sensitive and reliable translational tools to mechanistically characterize brain bioavailable polyphenols as disease-modifying agents to help prevent the onset of AD dementia and other neurodegenerative disorders. Several research groups worldwide with expertise in AD, plant biology, nutritional sciences, and botanical sciences have reported very high quality studies that ultimately provided the necessary information showing that polyphenols and their metabolites, which come from several dietary sources, including grapes, cocoa *etc.*, are capable of preventing AD. The ultimate goal of these studies was to provide novel strategies to prevent the disease even before the onset of clinical symptoms. The studies discussed in this review article provide support that the information gathered in the last few years of research will have a major impact on AD prevention by providing vital knowledge on the protective roles of polyphenols, including resveratrol. This article is part of a Special Issue entitled: Resveratrol: Challenges in translating pre-clinical findings to improved patient outcomes.

1. Polyphenols as novel "natural drug" agents in the prevention and possible therapy of Alzheimer's disease

A notable example of one of the first achievements from ongoing investigations on the role of polyphenols in Alzheimer's disease (AD) is the demonstration that polyphenols from select red wines, including resveratrol, may help attenuate AD dementia by modulating β-amyloid (Aβ) neuropathology through the inhibition of both Aβ generation and abnormal Aβ oligomerization and through the promotion of Aβ clearance, and by modulating tau neuropathology through the inhibition of abnormal tau phosphorylation and tau aggregation [29,30,32,33,43,45,46,66,71,73–76]. All of these Aβ and tau mechanisms are key therapeutic targets for AD. While polyphenols from certain red wines inhibit Aβ aggregation, others do not [29,32]. These studies were conducted a few years ago, and provided, for the first time, the basis for subfractionation of complex grape-derived polyphenol preparations into increasingly less complex isolates for use in bioactivity studies, *in vitro* and *in vivo* [30,70]. Recent fractionation studies have also revealed that a grape seed polyphenolic extract (GSPE) is capable of significantly attenuating AD-type phenotypes in transgenic AD mice, primarily due to its ability to increase the bioavailability of flavan-3-ol molecules (*e.g.*, catechin, epicatechin, *etc.*) in the brains [22,70,73]. Interestingly, it was also reported that quercetin-3-O-glucuronide, from red wines and Concord grape juice, is capable of reaching the brain and contributes to protection against AD by modulating multiple mechanisms, including by: reducing Aβ generation, reducing Aβ oligomerization, and promoting neuroplasticity processes [30]. Notably, other studies revealed that resveratrol may promote intracellular Aβ

Abbreviations: AMPK, 5′ adenosine monophosphate-activated protein kinase; AD, Alzheimer's disease; ALS, Amyotrophic lateral sclerosis; BDPP, Bioactive dietary polyphenol preparation; BAT, Brown adipose tissue; CaMKKβ, Ca^{2+}/CaM-dependent protein kinase kinase β; CREB, cAMP response element-binding protein; CVD, Cardiovascular disease; CHO, Chinese hamster ovary; UCP-1, Uncoupling protein-1; cAMP, Cyclic adenosine monophosphate; HD, Huntington's disease; LKB1, Liver kinase B1; MCI, Mild cognitive impairment; NRF-1, Nuclear respiratory factor-1; PD, Parkinson's disease; PGC-1α, Proliferator-activated receptor γ co-activator-1α; mTOR, Protein kinase mechanistic target of rapamycin; SIRT1, Sirtuin 1; T2D, Type 2 diabetes; Aβ, β-Amyloid

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clearance, in part by activating autophagy and AMPK signaling *in vivo* [64]. Overall, outcomes from these studies support the notion that autophagy and inflammation work in concert with respect to the anti-amyloidogenic effect of resveratrol. Moreover, recent studies suggest that polyphenols may also reduce abnormal tau hyperphosphorylation and tau aggregation [29,32,71,75,76]. A major achievement in the search for the role of polyphenols in AD prevention and therapies is the finding that multiple polyphenol metabolites, derived from dietary polyphenols, are able to cross the blood–brain barrier (BBB) and to penetrate and accumulate in the brain at pharmacologically relevant sub-μM to μM concentration [22,30,77]. Moreover, we found that certain brain-penetrating polyphenols are capable of modulating AD neuropathogenic mechanisms. For example, we found that one of the brain-penetrating polyphenol metabolites, quercetin-3-O-glucoside, is capable of modulating Aβ neuropathogenic mechanisms [30]. Moreover, we found that another brain-penetrating polyphenol metabolite, 3′-O-methyl-epicatechin-5-O-β-glucuronide, is capable of directly modulating synaptic plasticity by promoting cAMP response element-binding protein (CREB) signal transduction, which is involved in mechanisms associated with learning and memory functions [30,70]. Based on these findings, we proposed that the dietary polyphenol preparations that we studied are able to modulate AD through the activities of their brain-penetrating polyphenol preparations, which modulate multiple pathogenic processes such as Aβ and tau neuropathogenic mechanisms, neuroplasticity, and inflammation (see Fig. 1).

These scientific achievements are indicators of the widespread success of research in polyphenols in AD. Most excitingly, for the first time, these studies provided the basis for translational investigations into clinical studies exploring the feasibility of developing select polyphenols for preventative strategies in AD. As discussed further below, this increasing interest in the field of polyphenols is reflected by 85 currently listed clinical trials in the NIH clinicaltrials.gov registry exploring the role of resveratrol in several conditions, including 5 studies in AD and 29 on the role of type 2 diabetes (T2D) in cognitive functions associated with aging. This evidence strongly supports the widespread mounting interest in the role of polyphenols, including the use of resveratrol for prevention and treatment of AD and age-related cognitive deterioration.

2. Resveratrol, inflammation, and type 2 diabetes: implications in metabolic disturbances associated with the onset and progression of AD

A large body of literature has shown that resveratrol, a naturally occurring polyphenol (*trans*-3,4′,5-trihydroxystilbene), exerts beneficial effects on AD, an age-related neurodegenerative condition that in some cases is also comorbid with certain metabolic disorders, such as type 2 diabetes and obesity [6,38]. Resveratrol mimics caloric restriction by extending the lifespan of several small organisms [7,25], and by delaying specific age-related phenotypes, *e.g.*, abnormal glucose metabolism [51]. Resveratrol is also thought to beneficially influence cognitive deterioration [2,54]. Clinical studies are underway to explore the benefits of resveratrol for treating individuals with dementia, particularly those characterized by mild cognitive impairment (MCI), a clinical condition that eventually progresses to AD.

The direct molecular targets of resveratrol, *in vitro* and *in vivo*, are unknown. The compound has been suggested to modulate cellular processes by activating key metabolic sensor/effector proteins, including AMP-activated protein kinase (AMPK), sirtuin 1 (SIRT1), and peroxisome proliferator-activated receptor γ co-activator-1α (PGC-1α) [11,12,62,63,64]. It was initially proposed that resveratrol binds *in vitro* to SIRT1 and activates the deacetylase activity of this enzyme [34]. However, recent studies have challenged these data by showing that the reported direct interaction between resveratrol and SIRT1 *in vitro* was likely an artificial observation, implying that resveratrol might act *in vivo* by targeting other proteins [9,48]. Nevertheless, SIRT1 appears to be required for resveratrol metabolic functions *in vivo* by contributing to an energy sensing network involving AMPK and PGC-1α [11,12,59].

Resveratrol has been shown to have beneficial effects in *in vitro* models of epilepsy, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and nerve injury [58]. AMPK, SIRT1, and PGC-1α were all thought to be involved in the etiology of these neurological disorders. Based on evidence that resveratrol modulates these proteins, it was proposed that resveratrol has therapeutic potential in the above-mentioned neurodegenerative diseases. The therapeutic potential of resveratrol in

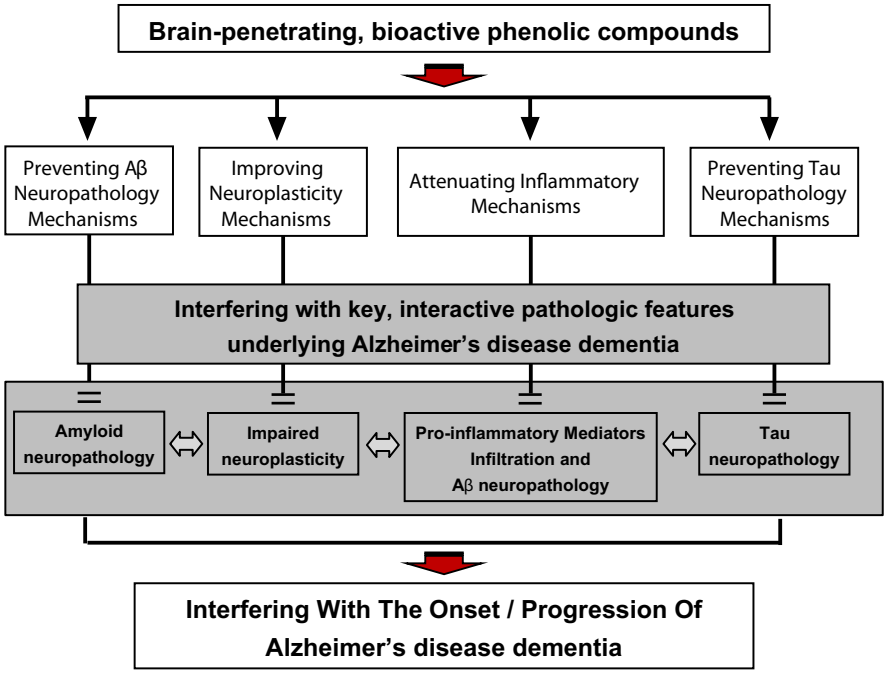

Fig. 1. Brain-penetrating polyphenol metabolites derived from certain bioactive dietary polyphenol preparation may attenuate AD dementia by modulating Aβ and tau neuropathogenic mechanisms, neuroplasticity, and inflammatory mechanisms.