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**File: ■ Grapes (*Vitis* spp.)**
**■ Red Wine Polyphenols**
**■ Alzheimer's Disease**

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**RE: Review of the Potential Therapeutic Value of Red Wine Polyphenols in Alzheimer's Disease Prevention and/or Therapy**

Pasinetti GM. Novel role of red wine-derived polyphenols in the prevention of Alzheimer's disease dementia and brain pathology: experimental approaches and clinical implications. *Planta Med*. 2012;78(15):1614-1619.

Alzheimer's disease (AD) is a form of dementia that currently affects 5 million people in the United States and is a major financial burden to the healthcare system, as well as to many families. AD is associated with memory loss, language problems, depression, delusions, as well as numerous other cognitive problems. With no cure for, or anything to delay the progression of, AD, and with only a few agents that minimally affect the clinical symptoms of this disease, there is a huge need for novel therapeutics.

AD is a neuropathological condition that is associated with abnormal aggregation and deposition of two major toxic peptide fragments in the brain – β-amyloid (Aβ) peptides and tau proteins. Extracellular neuritic plaques (NPs) develop from Aβ peptides, whereas intracellular neurofibrillary tangles (NFTs) result from aggregates of tau proteins. Neither NPs nor NFTs appear to directly induce the neuropathology of AD. Rather, the high-molecular-weight oligomeric Aβ peptides contribute to spatial memory deficits, and the abnormally phosphorylated tau species is associated with microtubule instability, leading to neurotoxicity.

The amyloid precursor protein (APP) creates Aβ peptides by amyloidogenic processing with β and γ secretases, which can develop into oligomeric Aβ peptides. Mutations in 3 major genes associated with early-onset AD (APP, presenilin 1, and presenilin 2) have been shown to cause accelerated Aβ deposition, as well as cognitive problems in animal models. Although it has been speculated that Aβ neuropathology is a major cause of AD, tau neuropathology has been shown to be better correlated with progressive cognitive decline and neuron and synapse loss.

Based on this information, researchers have suggested that reducing the accumulation of oligomeric Aβ peptides and tau species is a good approach for AD therapy. Nongenetic factors in AD are starting to receive more attention, especially for the more

common late-onset sporadic AD cases. As a result, dietary approaches are also being investigated for treatment or prevention of AD. Polyphenolic compounds found in many plants, including grapes (*Vitis* spp.) used for making wine, have been found to have potential therapeutic effects on AD. Although polyphenolic content varies in different types of grapes and wines, some of the major polyphenols identified include flavonoids (anthocyanins, flavanols, flavonols, flavones, flavanones, isoflavones, and proanthocyanidins), as well as lignans, stilbenes, and coumestans.

Most studies that have investigated the role of polyphenols for treatment of AD have been in vitro. However, these studies do not take into account that the polyphenols that reach the brain may not be found in the food source but rather have gone through phase II xenobiotic metabolism. The bioavailability of these compounds varies based on food composition, dose, and other factors. Moreover, only specific metabolically derived forms of polyphenols accumulate in the brain. Epicatechin glucuronide derivatives are one example that penetrate the brain and may affect the course of AD by promoting neuroplasticity processes.

In addition to epidemiological evidence that suggests grape polyphenols protect against AD, several preclinical trials have substantiated these claims. Grape seed polyphenolic extracts (GSPEs), as well as polyphenolic components from both red Muscadine wine (from muscadine grapes [*Vitis rotundifolia*]) and Cabernet Sauvignon red wine (from *Vitis vinifera*), prevented AD phenotypes in a transgenic AD mouse model (Tg2576) by decreasing Aβ neuropathology and cognitive dysfunction. A potential mechanism associated with the effects of grape polyphenols against AD involves the reduction of Aβ-peptide generation from APP or disruption of the assembly of Aβ peptides into larger neurotoxic aggregates of Aβ peptides.

Interestingly, Cabernet Sauvignon wine polyphenols have reduced the generation of Aβ peptides whereas Muscadine wine polyphenols have only attenuated Aβ aggregation. By fractionating polyphenols from Cabernet Sauvignon wine and assessing their AD-modifying activities, it was found that the Aβ-lowering effects could be attributed to anthocyanins. Additionally, resveratrol is also found in red wine and enhances Aβ clearance; however, the concentration of this polyphenol was too low in Cabernet Sauvignon to cause any significant effects. Moreover, GSPEs are reported to have effects on Aβ neuropathology and to prevent the abnormal aggregation of tau species. Studies with GSPEs in mutant tau mouse models (TMHT and JNPL3) that overexpress the human TAU441 gene also prevented abnormal tau aggregation and brain neuropathology. As a result, more studies are being conducted to investigate the role of other grape-derived products for their effects on tau neuropathology.

Overall, this review suggests that dietary supplementation with red wine polyphenols (equivalent to modest dietary consumption) may be preventative or therapeutic for people with AD by reducing the development of Aβ-mediated neuropathology, as well as by modulating tau neuropathology. However, more studies are needed to identify the bioactive polyphenols in red wine and their effects on AD. Ultimately, clinical trials are warranted to assess the cognitive benefits of red wine polyphenols for patients with AD.

*—Laura M. Bystrom, PhD*

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