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File: ■ Resveratrol
■ Autophagy
■ Alzheimer's Disease

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RE: Autophagy-stimulating Activities of Resveratrol Might Contribute to Mitigation of Alzheimer's Disease

Kou X, Chen N. Resveratrol as a natural autophagy regulator for prevention and treatment of Alzheimer's disease. *Nutrients*. 2017;9(9):927. doi: 10.3390/nu9090927.

Resveratrol is a polyphenol best known for its occurrence in grape (*Vitis vinifera*, Vitaceae) skin and seeds. Research shows that it may be useful to prevent and treat degenerative brain disorders such as Alzheimer's disease (AD). The purpose of this report is to review the molecular mechanisms of resveratrol in regulating autophagy and microRNAs (miRNAs) during AD. The report begins with an extensive review of the molecular mechanisms of AD as currently understood to enhance readers' understanding of how resveratrol may play a role in preventing/treating AD.

Autophagy in AD
The primary pathological markers of AD are accumulations of misfolded proteins, including amyloid-β (Aβ) plaques and neurofibrillary tangles formed of highly phosphorylated Tau protein, in the brain. The autophagy-lysosome system digests long-lived and abnormal protein complexes and organelles. Hence, autophagy is needed for healthy neural function; however, it decreases in aging. Declining autophagy leads to increased reactive oxygen species (ROS), cell death, and neurodegeneration. Abnormal accumulation of autophagic vacuoles is apparent in neurons in some neurodegenerative diseases and in a mouse model of AD. The level of autophagy-related Beclin1 is significantly reduced in brain tissue of patients with AD. In a mouse model of AD, lower Beclin1 levels lead to Aβ accumulation and neurodegeneration. Autophagy is regulated by multiple signal pathways; for example, the mammalian target of rapamycin (mTOR) pathway negatively regulates autophagy, so substances inhibiting mTOR can increase autophagy in neurons. Upregulating autophagy may provide a protective effect and is a target for AD treatment.

MicroRNAs in AD
miRNAs are small, non-coding RNAs that can reduce messenger RNA (mRNA) stability and protein expression by targeting specific mRNAs. They are involved in neurodevelopment and synaptic plasticity. miRNAs also have a role in the production of

pro-inflammatory cytokines in AD, while reduced production of some miRNAs can increase the production of Aβ. Aβ peptide aggregation results from imbalanced Aβ production and disordered Aβ clearance. It may be involved in the development and progression of AD. [Note: It remains controversial whether Aβ plaque accumulation is a cause or a consequence of AD.] There is also some limited evidence that decline in miRNAs may increase production of phosphorylated Tau protein. Autophagy-related miRNAs are thought to be involved in the early stage of AD, while others may be involved in the late stage of AD and other degenerative diseases.

Resveratrol and AD

In vitro, resveratrol can reduce Aβ-induced cytotoxicity and cell apoptosis. Several in vivo studies suggest that resveratrol may be beneficial in preventing/treating AD. In a mouse model of AD, resveratrol treatment prevented neurodegeneration and cognitive decline. In a rat model of AD, resveratrol improved memory, putatively by increasing antioxidant activity. In amyloid precursor protein (APP)-transgenic mice, resveratrol decreased Aβ levels and brain amyloid deposition. In humans, consumption of red wine, rich in resveratrol, reduced symptoms of dementia. Resveratrol has some of the same effects as caloric restriction, which in rodent models may mitigate AD by improving glucose metabolism.

The mechanisms of action of resveratrol are multifold, including increasing autophagic and lysosomal clearance of Aβ. Specifically, resveratrol can activate autophagy via its effects on both sirtuin 1 (SIRT1)-mediated transcriptional regulation and mTOR-dependent signaling pathways. Resveratrol can scavenge free radicals and suppress glial activation. For example, nuclear factor kappa-B (NF-κB) induces inflammatory responses, and its activity is increased with aging. Resveratrol treatment can suppress Aβ-induced activation of NF-κB in vitro. Also, resveratrol decreases lipopolysaccharide (LPS)-induced production of inflammatory cytokines and increases release of anti-inflammatory interleukin-10. Resveratrol can also modulate miRNAs. Resveratrol can reduce LPS-induced upregulation of pro-inflammatory miR-155 and upregulate anti-inflammatory miR-663.

The authors briefly describe three clinical publications, relating to two human trials, which evaluated resveratrol treatment for AD. It is not clear how these articles were chosen or whether they are the only articles available. One trial evaluated 119 patients with mild to moderate AD who were treated with escalating doses of 500-2000 mg/day resveratrol or placebo for 52 weeks. The primary publication from this trial reported that resveratrol reduced Aβ in the plasma and cerebral spinal fluid compared with placebo, indicating that resveratrol can cross the blood-brain barrier; however, decline in brain volume was quicker in the resveratrol group. A second publication regarding a subset of the participants in that study [incorrectly cited in this review] reported reduced markers of neurodegeneration and reduced decline in cognitive tests in the resveratrol group. The third study evaluated 18 patients with mild cognitive impairment who were treated with 150 mg resveratrol for 48 weeks and concluded that resveratrol improved cognition and innate immune function. No significant adverse effects were reported.

The authors conclude that resveratrol may be able to prevent/treat AD by improving autophagic activity, thereby reducing Tau hyperphosphorylation (which leads to neurofibrillary tangles), neuroinflammation, and Aβ accumulation. However, the exact molecular mechanisms are unknown.

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—Heather S. Oliff, PhD

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