Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Resveratrol

Evidence Summary

A highly controversial molecule that has had minimal effects in clinical trials. If the mechanisms of action are correct, other chemicals with better bioavailability would likely be more effective.

Neuroprotective Benefit: Unlikely to reach the brain at high levels and there is little certainty that it would have positive effects.

Aging and related health concerns: Obese or diabetic individuals may experience minor metabolic benefits, but no clear benefits have been found in other populations.

Safety: High-dose use would likely be necessary for any potential benefit, but high doses are associated with gastrointestinal events, and it has not been studied for chronic use.

What is it? Resveratrol is a naturally occurring compound found in various foods such as grapes, berries, chocolate and peanuts. In plants, it helps protect against bacterial and fungal infections (Hain et al., 1990). It is often thought of as an activator of the Sirtuin proteins that could help to treat some aspects of aging biology (Hubbard et al., 2013; Sinclair & Guarente 2014) but it can affect other pathways as well (Hsieh 2016).

Amongst researchers, resveratrol is a controversial molecule. It is rapidly metabolized and excreted from the body (Neves 2012), suggesting that other therapies might have a greater chance at success. Extensive resources have gone into laboratory research but these studies have been broadly criticized by various experts, for example with an editorial entitled "the resveratrol fiasco" (Visioli 2014). The arguments are that the animal studies have used artificially high doses, the *in vitro* studies are unreliable because resveratrol is a pan-assay interference compound that interferes with the accuracy of many *in vitro* assays (Baell & Walters 2014), and the entire premise of resveratrol has been driven by inaccurate perceptions of a French paradox (Visioli 2014). However, other researchers continue to defend the work (e.g. Cottart 2015).

Neuroprotective Benefit: Unlikely to reach the brain at high levels and there is little persuasive evidence to predict that it would have positive effects.

Types of evidence: (bullet points)

- *0 meta-analyses or systematic reviews*
- *1 RCT in Alzheimer's patients; 5 RCTs (2 unpublished) on cognition in non-demented adults*
- *1 observational cohort on future cognitive impairment*
- *Numerous laboratory studies but some concerns over reliability*

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? Based on small clinical trials, it is unlikely that resveratrol can promote cognitive function in most healthy adults (Wightman 2014, Kennedy 2010). It might promote memory in overweight adults (Witte 2014) but the results are not yet either conclusive or confirmed to be sufficiently robust to be clinically meaningful. For long-term cognitive decline, one cohort study reported that Italians with the highest levels of resveratrol metabolites in their urine had a lower incidence of cognitive impairment 9 years later but the researchers concluded that, overall, resveratrol levels had no substantial association with long-term health (Semba 2014). The lack of meaningful effect is not surprising given that dietary

sources of resveratrol are extremely low. A clinical trial in Alzheimer's patient tested a high-dose supplement for one year but the results suggest that either benefit or harm is possible (see below).

Human research to suggest benefits to patients with dementia or cognitive aging. A phase 2 clinical trial reported mixed and modest results of high-dose resveratrol treatment of patients with mild to moderate Alzheimer's disease (Turner 2015). The treatment was well-tolerated, with a dose starting at 500 mg/d but escalated over time to 2000 mg/d. No benefits were seen to the patients in several measures of cognition and function (e.g. MMSE, CDR-SOB, ADAS-cog, or NPI) but a slight benefit was seen on a measure of activities of daily living (ADCS-ADL). The trial evaluated numerous biomarkers related to Alzheimer's disease with mixed results. On the positive side, patients treated with resveratrol showed a slower progression in one marker of Alzheimer's pathology: declining Aβ40 levels in the CSF and similar but non-significant trends were seen in CSF and plasma for Aβ42. On the negative side, structural imaging suggested accelerated brain volume loss with resveratrol treatment. While that could indicate a reduction in brain swelling, brain volume loss is usually interpreted as an indication of neurodegeneration. Moreover, there was a strong trend, albeit insignificant, for an increase in a marker of damage to the brain (increased phosphorylated tau in the CSF, $p = 0.08$). Overall, the trial indicates that high-dose resveratrol might have biological effects that should be further researched but the results are not persuasive for a benefit to Alzheimer's patients (Turner 2015). Another trial is underway in MCI patients with expected completion in December 2016 (Floel NCT01219244).

Mechanisms of action for neuroprotection identified from laboratory and clinical research

The relevance of most laboratory studies on resveratrol to humans has been questioned (see introduction). Nevertheless, *in vitro* evidence suggests that resveratrol may protect against dementia, Parkinson's disease, and other disorders in which oxidative stress plays a role in neuronal degeneration due to its antioxidant and anti-inflammatory properties (Sun et al., 2010). For example, one hallmark of Alzheimer's is the accumulation of Aβ plaques and tau protein tangles throughout the brain, causing inflammation and subsequent neurodegeneration associated with the disease. Using a mouse model of Alzheimer's disease, one study found that feeding resveratrol to mice reduced brain levels of Aβ plaques (Karuppagounder et al., 2009), an effect that some believe is regulated through increased Sirt1 activation (Donmez et al., 2010). Indeed, patients with Alzheimer's disease were found to have lower cortical Sirt1 levels, which indirectly correlated with greater levels of Aβ plaques and tau protein tangles (Julien et al., 2009;Theendakara et al., 2013). Interestingly, patients with mild cognitive impairment did not show reduced cortical Sirt1 levels (Julien et al., 2009), suggesting that preventing Sirt1 decreases at this early stage may help delay or prevent the progression to dementia. However, there is no evidence yet that resveratrol treatment in humans can increase Sirt1 in the brain.

APOE4 interactions: No evidence for an interaction

Aging and related health concerns: Obese or diabetic individuals may experience minor metabolic benefits, but no clear benefits have been found in other populations.

Types of evidence:

- *3 meta-analyses and 1 systematic review*
- *1 prospective cohort over 9 years*

Dietary intake of resveratrol was reported to have no substantial effect on long-term health or mortality over 9 years in elderly Italians (Semba 2014). Many small trials have tested higher dose supplements in clinical trials. Meta-analyses of these trials suggest that resveratrol has no meaningful benefit on cardiovascular risk factors (e.g. Sahebkar 2015, Liu 2015). One study even found that resveratrol reduced the beneficial effects of exercise in a group of healthy older men (Gliemann et al., 2013). The evidence for cancer is highly inconsistent (e.g. Carter 2014). Meta-analyses suggest that it might offer minor benefits in patients with diabetes (e.g. Hausenblas 2015, Liu 2014).

Laboratory studies on aging and related health in mammals have similarly reported that resveratrol has little effect on metabolism or lifespan in healthy animals (Baur et al., 2006;Miller et al., 2007;da Luz et al., 2012;Marchal et al., 2013, see da Luz et al., 2012 for an exception) but it may alleviate aspects of metabolic syndrome to extend healthy lifespan in metabolically-challenged groups (Baur et al., 2006). Likewise, studies in obese rhesus monkeys found that daily resveratrol supplementation for two years protected from the loss of pancreatic β-cells (the cells that make and store insulin) and preserved insulin sensitivity (Fiori et al., 2013), as well as increased Sirt1 expression and improved metabolism (Jimenez-Gomez et al., 2013).

Immune system: Resveratrol has also been shown to slow down replication and inhibit infectivity of viruses such as influenza (Palamara et al., 2005), HIV-1 (Clouser et al., 2012), and herpes simplex virus (Faith et al., 2006). Interestingly, one study in immuno-deficient mice showed that a 12.5% resveratrol cream was able to suppress herpes lesion formation when applied up to 6 hours after infection, and reapplied every three hours for 5 days (Docherty et al., 2004). Whether benefits will occur in humans is uncertain.

Safety: High-dose use would likely be necessary for any potential benefit, but high doses are associated with gastrointestinal events, and it has not been studied for chronic use.

Types of evidence:

- Several meta-analyses on short-term trials. 1 recommendation from a 2010 working group

Many small clinical trials on resveratrol have been performed but there is no reliable information on the safety of chronic high-dose use (e.g. Vang 2011). Diarrhea or gastrointestinal discomfort is common at high doses above 1 gram/day (Vang 2011, La Porte 2010). One trial did report moderately serious side effects from 1 gram/day in postmenopausal women including liver enzyme changes and severe (grade 3) skin rash (Chow 2014) and another trial reported serious concerns of kidney failure with resveratrol plus standard medical treatment of multiple myeloma (cancer) patients (Popat 2013). Because resveratrol has been shown to have blood thinning capabilities (Wu et al., 2001;Wang et al., 2002), patients at risk of bleeding from surgery or from anti-platelet or anti-coagulant medications should avoid resveratrol supplements. Resveratrol may also act on estrogen receptors which may be risky for some conditions including hormone-sensitive breast cancer.

Sources and dosing: Resveratrol can be found naturally in some foods such as peanuts, blueberries and even cocoa, but the highest concentration is found in the skin of red grapes. One 5-ounce glass of red wine contains around 200 µg of resveratrol; thus, it would take around 20 bottles of red wine a day to equal the level of resveratrol used in even the lowest-dose clinical trials. Purified resveratrol supplements are available in capsule form and typically contain between 200-350 mg, derived from the skin of red grapes, or more commonly, Japanese knotweed. Doses between 20 mg to 5000 mg per day have been used in clinical trials, with gastrointestinal side effects more common above 1000 mg/day (Vang 2011, La Porte 2010). Micronized resveratrol are sold on the market but these formulations may not overcome the known problems with bioavailability of resveratrol (Smoliga & Blanchard 2014).

Research underway: A Phase 4 clinical trial is comparing the effects of resveratrol to omega-3 fatty acids, calorie restriction or placebo) in MCI patients, with results expected in December 2016 (NCT01219244). A Phase 2 clinical trial is underway in Florida to look for improvements in vigor and vitality in elders taking 1000-1500 mg/d resveratrol for 90 days (NCT02123121, results expected 2018). Various formulations are being pursued to improve the bioavailability of resveratrol (Neves 2016 and many others). Other molecules with related properties are also being pursued for sirtuin activation including natural products and small molecules (Kasiotis 2013, Sinclair & Guarente 2014).

Search terms:

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- resveratrol filtered by meta-analysis & syst review
- resveratrol with cancer, aging, cognitive, brain, Alzheimer, micronized

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