Alzheimer's
Drug Discovery
Foundation

Resveratrol

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Resveratrol is a naturally occurring compound found in foods such as grapes, berries, chocolate, and peanuts. It is also available as a concentrated supplement. Resveratrol may be able to activate sirtuins, a family of proteins involved in aging biology (1), as well as other cellular pathways (2). In clinical trials, however, resveratrol has led to disappointingly few benefits for healthy people, although some small clinical trials suggest that it may help patients with diabetes or obesity. Resveratrol supplements are regarded as safe although long-term use has not been sufficiently studied.

Among researchers, resveratrol is a controversial molecule. It is rapidly metabolized and excreted from the body (3), suggesting that other therapies might have a stronger chance at success. Extensive resources have gone into laboratory research, but these studies have been broadly criticized (4). Critics argue 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 (5), and the entire premise of resveratrol has been driven by inaccurate perceptions of the French paradox regarding coronary heart disease (4). Other researchers continue to defend the work (6).

EVIDENCE AND POTENTIAL BENEFIT FOR BRAIN HEALTH
Rated 1/4 based on 2/4 evidence

Randomized controlled trials: Based on small clinical trials, it is unlikely that resveratrol can promote cognitive function for most healthy adults (7; 8). It might increase blood flow to the brain, although the relevance of this to long-term brain health is not yet clear [7]. High-dose resveratrol appeared to have some effects on the brains of Alzheimer's patients in one trial, but whether those effects were positive or negative is unclear (see For Dementia Patients section).

Resveratrol was originally thought to improve metabolic and cardiovascular health and protect from aging, all of which might lead to better long-term brain health. However, meta-analyses of small trials suggest that resveratrol has no meaningful benefit on cardiovascular risk factors (9; 10). The evidence for cancer is highly inconsistent (11) and one trial reported that resveratrol reduced the benefits of exercise in a group of healthy older men (12). Dietary intake of resveratrol has been less studied than high-dose supplements but had no substantial relationship with long-term health or mortality over nine years in elderly Italians (13).

If resveratrol has health benefits, they are most likely to occur in adults with diabetes or obesity. Some minor benefits in patients with diabetes were concluded by meta-analyses (14; 15) and a pilot clinical trial with overweight, but otherwise healthy, older adults suggested that a six-month daily regimen of 200 mg of resveratrol supplements may improve short-term memory and the functioning of the hippocampus (the part of the brain most responsible for memory) [8]. However, these results are either inconclusive or not yet confirmed as clinically meaningful.

Biology: Preclinical resveratrol studies have come under heavy criticism on the grounds that they have used artificially high doses. There are additional concerns that the *in vitro* studies are unreliable because resveratrol is a pan-assay interference compound that affects the accuracy of many assays (5). And, the premise of resveratrol's benefit may have been driven by inaccurate perceptions of the French paradox (4).

Resveratrol has been reported in preclinical studies to have antioxidant, anti-inflammatory, anti-viral, and anti-cancer properties. Much of resveratrol's purported benefit has been related to its ability to activate a family of proteins called sirtuins (1). In rodents, high levels of certain sirtuins have been connected to a lower occurrence of cancer, improved general health, enhanced metabolism, and longer lifespan, possibly by mimicking the effects of caloric restriction (16). Patients with Alzheimer's disease were found to have lower cortical levels of sirtuin1 (Sirt1), which indirectly correlated with greater levels of Aβ plaques and tau protein tangles (17; 18). Patients with mild cognitive impairment did not show reduced cortical Sirt1 levels (17), weakly suggesting that preventing Sirt1 decreases at this early stage may help delay or prevent the progression to dementia. However, there is no evidence that resveratrol treatment in humans can increase Sirt1 in the brain. Using a mouse model of Alzheimer's disease, one study found that feeding resveratrol to mice reduced brain levels of Aβ plaques (19). Preclinical studies also suggest that resveratrol may delay age-related cognitive decline. For example, old mice on daily resveratrol supplementation performed better on spatial learning (20) and working memory tests (21).

Resveratrol has been touted as a treatment to slow aging biology, which could delay age-related diseases including dementia to extend healthy lifespan. Although resveratrol significantly extended lifespan in yeast, worms, and fruit flies (22; 23), most studies report no effect on lifespan in mammals (24; 25; 26) with the possible exception of mice with obesity caused by diet or genetic engineering (24).

For Dementia Patients

Randomized controlled trials: A Phase 2 clinical trial reported mixed and modest results of a high-dosage of resveratrol for patients with mild to moderate Alzheimer's disease (27). The treatment was well-tolerated, with a daily dose starting at 500 mg that was gradually escalated to 2 g. The study was not optimized to detect a benefit to patient function or

cognition (such trials usually require very large numbers of patients). Also, the patients treated with placebo had, on average, been diagnosed with dementia for longer, which might interfere with accuracy. Nevertheless, researchers observed a slight benefit related to activities of daily living but no effect on other measures of cognition and function (27).

The trial evaluated numerous biological markers 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 Aβ 40 levels in the CSF and similar but non-significant trends seen in CSF and plasma Aβ 42. But structural imaging suggested that resveratrol treatment accelerated brain volume loss. While that could theoretically indicate reduced brain swelling, brain volume loss is usually interpreted as an indication of neurodegeneration. There was a trend, albeit insignificant (p=0.08), for increased phosphorylated tau 181 in the CSF, which could indicate damage (27). More research is needed to interpret these results. Another trial, expected to finish in December 2016, is underway in patients with mild cognitive impairment (28).

SAFETY

Rated 3/4

A number of small clinical trials reported no adverse side effects for daily doses of resveratrol between 20 mg and 2 g (29). In a clinical trial of Alzheimer's patients, one year of use starting at 500 mg and going up to 2 g per day was reported to be safe and well-tolerated (27). However, there is no reliable information on the safety of longer-term high-dosage use (29). Diarrhea or gastrointestinal discomfort can be common at doses above 1 g per day (29; 30). One trial reported moderately serious side effects from 1 g per day in postmenopausal women, including liver enzyme changes and severe skin rash (31). Yet another trial reported serious risk of kidney failure with resveratrol plus standard medical treatment for multiple myeloma (cancer) patients (32), though again most small clinical trials have not reported serious adverse effects (9). Resveratrol might interact dangerously with common drugs, including but not limited to blood thinners, anti-inflammatory drugs, and anti-hypertensive drugs. It may, for example, impair the normal clearance of those drugs from the body (33).

HOW TO USE

Resveratrol is found in a variety of foods, including peanuts, blueberries, and cocoa. The highest concentration, though, is found in the skin of red grapes used to make red wine. However, these naturally occurring sources contain relatively small amounts of the compound. For example, you would have to drink about 20 bottles of red wine to consume the equivalent amount of resveratrol found in a 200 mg supplement. Resveratrol in supplements is derived from the skin of red grapes or, more commonly, from Japanese knotweed. Doses of 20 mg to 2 g per day have been used in clinical trials. Micronized

resveratrol is available, but these formulations may not overcome resveratrol's known bioavailability problems (34).

WHAT'S THE FUTURE?

A Phase 4 clinical trial is comparing the effects of resveratrol to omega-3 fatty acids, calorie restriction, or placebo in patients with mild cognitive impairment (MCI) and results are expected in December 2016 (28). A Phase 2 clinical trial is underway in Florida to look for improvements in vigor and vitality in elderly patients taking 1,000 to 1,500 mg resveratrol per day for 90 days. Results are expected in 2018 (35). Various formulations are being pursued to improve the bioavailability of resveratrol (e.g., 36 and many others). Other molecules with related properties are also being pursued for sirtuin activation including natural products and small molecules (37; 38).

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