Revitalizing Resveratrol for Healthy Aging

A Closer Look at Cognition

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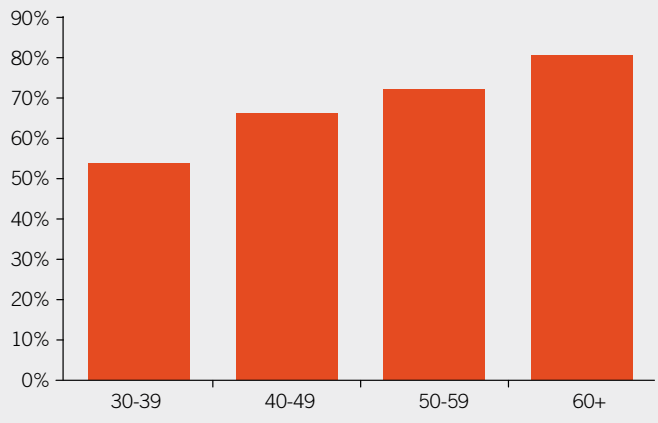
Resveratrol, an Ingredient Supporting Healthy Aging

Resveratrol (a.k.a. *trans*-resveratrol or 3, 4', 5-trihydroxystilbene) is a natural phytoalexin compound, found in red grape skin, Japanese knotweed, peanuts, blueberries, and some other berries.[1] It is a powerful antioxidant produced by some plants in response to stress, injury, infection or ultraviolet (UV)-irradiation.[1]

In the mid-1990s, resveratrol was brought into the spotlight as the main polyphenol in red wine, in the context of the French paradox (*i.e.*, the apparent contradiction between the French having a low rate of cardiovascular diseases despite having a diet rich in saturated fats, including the consumption of large amounts of alcohol, and cigarette smoking). It was hypothesized that the benefits for the French were due to their consumption of moderate amounts of red wine that contained 1 to 2 mg of resveratrol per 8 ounces.[1,2] Since then, scientific interest for this polyphenol has increased exponentially. By 1996, there were 46 scientific papers on resveratrol, increasing to over 1,300 by 2006 and to more than 9,800 by August 2017.[3] Now, resveratrol is recognized for its beneficial effects on, among others, cardiovascular health,[4] blood glucose control,[5] skin health,[6] bone health[7,8] and memory.[9] Resveratrol is therefore widely used as a key ingredient to promote healthy aging.

The mechanisms by which resveratrol achieves such a wide range of benefits is still being debated.[10] However, it has been shown that resveratrol, as with most polyphenols, is rapidly metabolized in the intestine and liver after oral intake to its glucuronide or sulfate derivatives, leading to relatively low plasma concentrations of free resveratrol.[11] Repeated or chronic dosing might result in saturation of the metabolism, leading to higher plasma and tissue levels of resveratrol.[11] Nevertheless, a low dose of 25 mg seems enough to yield a plasma concentration of total resveratrol (including its metabolites) of about 2 µM after 60 minutes.[12] Moreover, certain resveratrol metabolites seem to serve as an intracellular pool for resveratrol regeneration, possibly

Percentage of Consumers Using Supplements by Age Group



Source: *Nutrition Business Journal* consumer survey of 241 core natural consumers, August 2015. Question: Are you currently using any of the following to help manage the aging process? Answer reflects percentage choosing "supplements."

Figure 1.

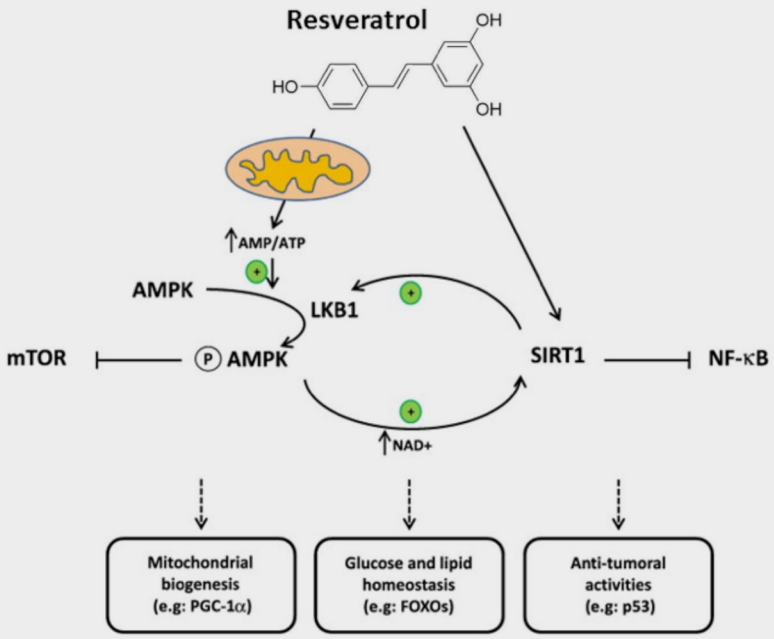


Figure 1. Resveratrol and the complex relationship between AMPK and SIRT1. AMPK and SIRT1 constitute two key targets of resveratrol. Resveratrol inhibits mitochondrial ATP production, leading to a higher AMP/ATP ratio and an LKB1-dependent activation of AMPK. Then, AMPK enhances NAD+ availability, which would overcome the rate-limitation that this cofactor exerts on SIRT1 enzymatic activity. In turn, SIRT1, as a possible direct target of resveratrol, can deacetylate LKB1, facilitating the formation of an active kinase complex. This way, SIRT1 could also positively control AMPK activity. Together, AMPK and SIRT1 create a positive feed-forward loop to amplify the adaptation response to nutrient scarcity. Through the modulation of diverse transcriptional regulators, the actions of AMPK and SIRT1 can explain many of the beneficial effects of resveratrol against metabolic and age-related complications. In addition, AMPK activation by resveratrol would lead to the inhibition of mTOR signaling, while SIRT1 activity would repress NF-κB activity, two key paths by which resveratrol modulates cellular growth, autophagy and immune responses.

Adapted from Kulkarni *et. al.*[17]

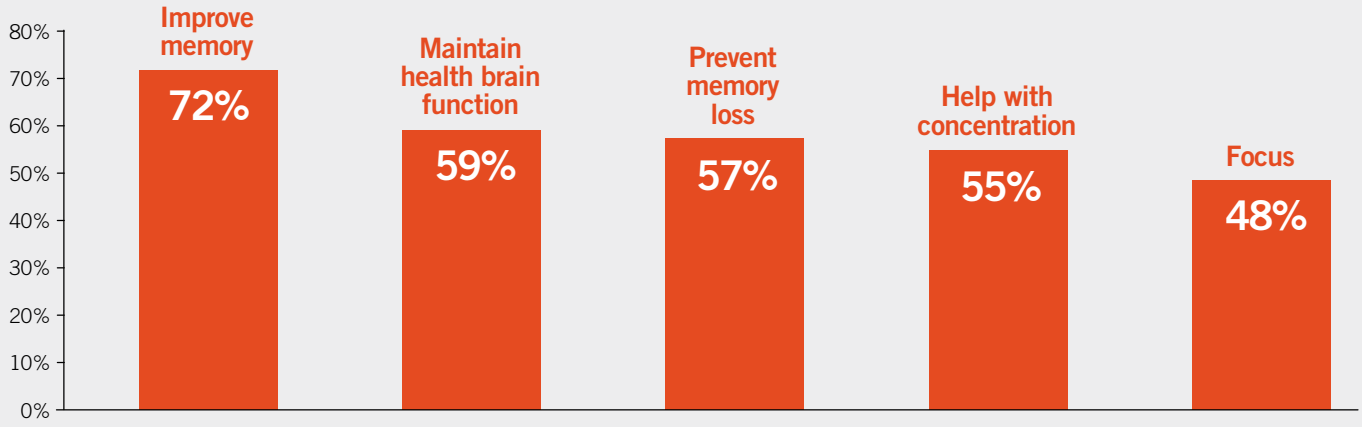
allowing higher local concentrations and leading to positive cellular effects.[13] As a result, resveratrol and its metabolites appear to be present in all tissues, even crossing the blood-brain barrier, having potential beneficial effects on the central nervous system (CNS).[14,15]

In order to contribute to the understanding of the mechanisms through which resveratrol exerts its biological effects, Britton, Kovoor and Brown[16] recently reviewed the direct molecular targets of resveratrol. These targets include enzymes involved in inflammation, adipogenesis, apoptosis, DNA repair, autophagy, regulation of cellular energy, regulation of gene expression, and stress response at the cellular level.[16]

Importantly, several of the molecular targets of resveratrol seem to interact and trigger a cellular response similar to calorie restriction[17] (see Figure 1). Calorie restriction has been shown to have a lengthening effect on the lifespan of a number of species ranging from yeast[18] to dogs[19] to primates [20,21] and to ameliorate multiple age-related diseases such as type 2 diabetes, cardiovascular diseases, and cancer.[22] Many of the effects of calorie restriction are mediated by the activation of a histone deacetylase enzyme called SIRT1[23] and through the so called AMP-activated protein kinase (AMPK) pathway and its role on maintaining a proper mitochondrial function[17].

Relevant to the potential benefits of resveratrol is how different foods/supplements affect the gut biota, especially those promoting increased growth of favorable microbes in the gut. Resveratrol and other polyphenols have been suggested to inhibit pathogenic bacteria while stimulating the growth of beneficial bacteria, exerting prebiotic-like effects.[24–26] Importantly, recent publications show that some of the effects of resveratrol including reduced atherosclerosis[27] and improved glucose homeostasis[28] occur via gut microbiota remodeling. This opens the door to the possibility that other health benefits attributed to the oral intake of resveratrol could also be mediated by gut microbiota remodeling and provides a new possible explanation for the so-called resveratrol paradox conundrum (*i.e.* low bioavailability but high bioactivity).[29]

The brain health space is now a $2.7 billion global market



BENEFITS MOST SOUGHT IN COGNITIVE-RELATED SUPPLEMENTS

Source: Euromonitor

In any case, and whatever mode of action is actually involved, the health benefits of resveratrol in humans are supported by over 200 clinical studies[3] published to date. The present document is a review of the published and ongoing clinical studies that investigate the health benefits of the oral intake/supplementation of resveratrol in neuro-cognitive health. Thirteen clinical studies investigated the benefits of resveratrol supplementation on neurocognitive health. Results indicated that resveratrol supplementation optimized circulatory function in the brain, increased cerebral blood flow, and modulated neuro-inflammation. Resveratrol supplementation was associated with enhanced performance on cognitive tests in some clinical studies. Resveratrol was well tolerated without any reported adverse events.

As we age, decreased blood flow to the brain, increased inflammation and other normal neurobiological changes, together with diet and lifestyle play a role in the cognitive aging process.[30] In addition to physical and mental exercise helping to preserve cognitive performance,[31] current aging populations are seeking specialized nutritional strategies to support memory and cognition.[32,33] Among these, the inclusion of resveratrol and other polyphenols in the diet has been suggested as an effective way to tackle some of the age-related conditions that have been associated with a decline in cerebral function.[34–36] It has been suggested that the antiaging effects of resveratrol in the brain could be due to several related mechanisms, among which are the prevention of oxidative stress, SIRT1 activation and inflammation modulation, all via regulation of some signaling pathways, such as NF-κB.[37,38]

In clinical research, randomized controlled trials (RCTs) are considered the best way to study the safety and efficacy of new treatments. Most of the articles described in this review are randomized, double-blind, placebo-controlled human clinical trials, the "gold-standard" for clinical research.* In some cases, the studies are defined as randomized "crossover" trials, indicating that the subjects receive a sequence of different treatments (*e.g.* treatment and placebo) in a random order, allowing comparison of the results with the same individual as well as between individuals and treatments and thus reducing the influence of confounding covariates.

*Note that the statistical significance and the clinical relevance of a study does not always correlate. The concept of power of a clinical trial refers to the probability of detecting a difference between study groups when a true difference exists.[39] An underpowered study may lack sufficient statistical significance due to an inadequate experimental design, including use of inaccurate measurement methods, loose stratification of the participants or simply a too small sample size. When sufficient research is available and to minimize the chance of disregarding statistically relevant differences when a treatment does have a real effect, systematic reviews and meta-analyses of several RCTs have the potential advantage to provide higher levels of evidence to support clinical interventions.[40]

Clinical Studies on Resveratrol for Neurocognitive Health

Thirteen published RCTs investigated the benefits of resveratrol supplementation on neurocognitive health. Daily doses of resveratrol ranged from 75 mg to 2,000 mg/day for up to 52 weeks. The studies included healthy subjects and those with Alzheimer's disease (AD), Mild cognitive Impairment (MCI), schizophrenia (SZ), and type 2 diabetes (T2DM). The endpoints are indicated in Table 1.

Ref.	Study Design	Resveratrol Preparation and Dose	Duration	Subjects *n* Age Disorder/ Status	Mean age / age range	Purpose/ Outcome Measures	Main Results
Evans *et al.*, 2017	R, DB, PC	150 mg resveratrol	14 weeks	80 healthy post-menopausal women	Range 45-85 yrs	Test if resveratrol enhances cerebrovascular function	Resveratrol optimized circulatory function in the brain
Kennedy *et al.*, 2010	R, DB, PC, CO	250 and 500 mg resveratrol	45 mins after administration	22 healthy adults	Mean age 20.17 yrs, range 18-25 yrs	Effects of oral resveratrol on cognitive performance and localized cerebral blood flow variables in healthy human adults	Resveratrol increased cerebral blood flow (dose-dependent) during task performance. Also increased deoxy-hemoglobin, suggesting enhanced oxygen extraction. Cognitive function was not affected.
Köbe *et al.*, 2017	R, DB, PC	200 mg resveratrol	26 weeks	40 subjects with mild cognitive impairment	Range 50-80 yrs	Learning, memory, hippocam-pus volume, microstructure and RSFC, serum levels of glucose, HbA1c and insulin	Resveratrol reduced HbA1c, preserved hippocampus volume and improved RSFC
Lee *et al.*, 2016	R, DB, PC	72 g grape powder containing resveratrol and other polyphe-nols (total polyphenols 495 mg/100 g)	6 months	10 older subjects with mild decline in cognition	Mean age 72.2 ± 4.7 yrs	Cognitive performance and changes in brain metabolism	Grape powder prevented decline in brain metabolism
Moussa *et al.*, 2017	R, DB, PC	500 mg resveratrol + 500 mg every 13 weeks. Max. = 2000 mg resveratrol	52 weeks	38 subjects with mild to moderate Alzheimer's disease and levels of CSF Aβ42 <600 ng/ml	Not described	Markers of neurodegenerative disease and metalloproteinases	Resveratrol decreased CSF MMP9, modulated neuro-inflammation, and induced adaptive immunity
Scholey *et al.*, 2014	R, DB, B	100 ml red wine + 200 mg resveratrol	Single administration	16 subjects	Mean age of 70.44 yrs, range 65-78	Acute mood and cognitive effects of resveratrol-enriched wine	Resveratrol-enriched wine enhanced performance in some of the cognitive tests performed
Turner *et al.*, 2015	R, DB, PC	500 mg resveratrol + 500 mg increments every 13 weeks. Max = 2000 mg resveratrol	52 weeks	119 subjects with mild to moderate Alzheimer's disease	Mean age 70 ± 7 yrs	Effects on tolerability, safety and Alzheimer biomarkers	High-dose resveratrol is safe and well-tolerated. It penetrated the blood-brain barrier
Wightman *et al.*, 2014	R, DB, PC	250 mg resveratrol ± 20 mg piperine on separate days	28 days	23 healthy adults	Mean age 21 yrs, range 19-34 yrs	Test if piperine affects resveratrol's bioavailability and its CBF effects	Piperine and resveratrol augmented CBF compared to placebo and resveratrol alone
Wightman *et al.*, 2015	R, DB, PC	500 mg resveratrol	28 days	60 young subjects	Mean: 20 yrs, range 18- 30 yrs	Evaluation of performance of cognitively demanding tasks	Resveratrol had acute cerebral blood flow effects
Witte *et al.*, 2014	R, PC	200 mg resveratrol	26 weeks	46 healthy overweight older subjects	Mean age 64.8 ± 6.8, range 51–75 yrs	Test memory performance in older adults	Resveratrol improved memory performance and increases hippocampal FC
Wong *et al.*, 2016a	R, DB, CO, PC	0, 75, 150 and 300 mg single dose resveratrol at weekly intervals	4 weeks	36 dementia-free older subjects with, non-insulin dependent type 2 diabetes	Range 49-78 yrs	Determine resveratrol dose to improve cerebral vasodilation in T2DM	Resveratrol caused acute enhancement of vasodilation in cerebral vessels
Wong *et al.*, 2016b	R, DB, PC	0, 75, 150 and 300 mg single dose resveratrol at weekly intervals	4 weeks	36 dementia-free older subjects with, non-insulin dependent type 2 diabetes	Mean 68.5 yrs	Effect of resveratrol on neuro-vascular coupling, cognitive performance, ...	Resveratrol improved neurovascular coupling and cognitive results in T2DM
Zortea *et al.*, 2016	R, DB, PC	200 mg resveratrol	1 month	19 adult men with Schizophrenia	Range 18-65 yrs	Cognitive tests including neuropsychology performance and psychopathology severity	Resveratrol did not significantly improve cognitive parameters

Table 1. Studies on Resveratrol for Neurocognitive Health. R, randomized; DB, double blind; PC, placebo controlled; CO, crossover; B, balanced; RES, Resveratrol; FC, Functional Connectivity; T2DM, Type 2 Diabetes Mellitus; CSF, Cerebrospinal Fluid; CBF, cerebral blood flow; HbA1c, glycated hemoglobin; RSFC, resting-state functional connectivity; MMP-9, Matrix metallopeptidase 9.

Evans *et al.*, 2017[41]

This RCT investigated the effects of resveratrol supplementation on mood and cognitive performance in postmenopausal women. The authors hypothesized that resveratrol supplementation may enhance cerebrovascular function and improve regional blood flow in response to cognitive demands. The following tests were performed: Rey Auditory Verbal Learning Test, Cambridge Semantic Memory Battery, the Double Span and the Trail Making Task. Also, cerebrovascular function was assessed simultaneously by monitoring blood flow velocity in the middle cerebral arteries using transcranial Doppler ultrasound. This trial demonstrated that resveratrol supplementation vs. placebo optimized circulatory function in the brain. The authors concluded that resveratrol may enhance mood and cognition and ameliorate the risk of developing dementia in postmenopausal women and in other at-risk populations.

	80 healthy postmenopausal women
	14 weeks
	150 mg/day resveratrol or placebo
	Cerebrovascular function
	Resveratrol optimized circulatory function in the brain

Kennedy *et al.*, 2010[42]

This crossover RCT assessed the effects of resveratrol supplementation on cognitive performance and localized cerebral blood flow variables in healthy human adults. Test subjects received placebo and 2 doses (250 and 500 mg) of resveratrol in counterbalanced order on separate days. Resveratrol administration resulted in dose-dependent increases in cerebral blood flow during task performance (45 minutes after administration a selection of cognitive tasks were performed for an additional 36 minutes), as indexed by total concentrations of hemoglobin vs. placebo. There was also an increase in deoxyhemoglobin after both doses of resveratrol, which suggested enhanced oxygen extraction. Cognitive function was not significantly affected.

	22 healthy adults
	45 minutes after administration
	2 doses: 250 and 500 mg/day resveratrol or placebo
	Cerebral blood flow and hemodynamics in the frontal cortex
	Resveratrol resulted in dose-dependent increase in cerebral blood flow

Köbe *et al.*, 2017[43]

The goal of this clinical trial was to investigate if the effects of resveratrol supplementation in long-term glucose control, resting-state functional connectivity (RSFC) of the hippocampus, and memory function extend to individuals at high-risk for dementia, *i.e.*, patients with mild cognitive impairment (MCI). Indeed, in comparison to the control group, resveratrol supplementation resulted in a lower glycated hemoglobin A1c concentration, higher RSFC, and led to a moderate preservation of left anterior hippocampus volume. However, no significant differences in memory performance emerged between groups.

	40 subjects with mild cognitive impairment (MCI)
	26 weeks
	200 mg/day resveratrol or placebo
	Memory, hippocampus RSFC, serum levels of glucose, glycated hemoglobin A1c (HbA1c), *etc.*
	Resveratrol lowered HbA1c and improved RSFC

Lee *et al.*, 2017[44]

The study presented by Lee and colleagues studied the effect of resveratrol-containing grapes on regional cerebral metabolism in older subjects with mild decline in cognition. Test subjects received daily a placebo or 72 g of a grape formulation (containing about 50.4 µg of resveratrol and 356.4 mg of total polyphenols). In contrast to participants taking the active grape formulation, who displayed no significant decline in metabolism, the placebo arm underwent significant metabolic decline in standardized volumes of interest and statistical parametric mapping, with stable brain metabolism in the active formulation arm. No significant differences were seen in scores on the neuropsychological battery of tests between the two groups but the metabolism in the right superior parietal cortex and the left inferior anterior temporal cortex was correlated with improvements in attention/working memory. According to the authors, these results suggest a protective effect of grapes against early pathologic metabolic decline.

	10 older subjects with mild decline in cognition
	6 months
	72 g/day grape powder containing resveratrol or placebo
	Cognitive performance and changes in brain metabolism
	Grape powder prevented decline in brain metabolism

Moussa *et al.*, 2017[45]

In this retrospective study, the authors examined banked cerebrospinal fluid (CSF) and plasma samples from a subset of Alzheimer disease subjects with CSF Aβ42 <600 ng/ml at baseline (38 subjects out of the total 119 subjects from Turner *et al.*, 2015) in which markers of neurodegenerative disease and metalloproteinases (MMPs) in CSF and plasma samples were measured. The results obtained showed that resveratrol supplementation vs. placebo markedly reduced CSF MMP9 and increased macrophage-derived chemokine, interleukin (IL)-4, and fibroblast growth factor (FGF)-2. In a subset analysis, resveratrol treatment attenuated declines in mini-mental status examination scores, changes in ADCS-ADL (Alzheimer's Disease Cooperative Study Activities of Daily Living Scale) scores, and CSF Aβ42 levels during the 52-week trial, but did not alter Tau protein levels. Collectively, these data suggested that resveratrol supplementation decreased CSF MMP9, modulated neuro-inflammation, and induced adaptive immunity.

	38 subjects with mild-moderate Alzheimer's disease
	52 weeks
	Start 500 mg resveratrol, increasing 500 mg every 13 weeks until 2000 mg daily
	Metalloproteinase levels and markers of neurodegenerative disease
	Resveratrol reduced MMP9 and modulated neuro-inflammation and immunity

Scholey *et al.*, 2014[46]

The objective of this RCT was to compare the acute mood and cognitive effects of resveratrol-enriched red wine with red wine alone during mentally effortful tasks in older individuals. Results showed that there were differential cognitive effects in the two treatment groups. Compared with red wine alone, resveratrol-enriched wine was associated with significantly enhanced performance in the Serial Sevens Test. Conversely, red wine alone resulted in better performance during the Serial Threes Test. These results may reflect increased blood flow associated with resveratrol and the documented stimulant effects of alcohol at low levels.

	16 older subjects
	Single ingestion, tests performed 60 min. after resveratrol administration
	100 ml red wine ± 200 mg resveratrol
	Acute mood and cognitive parameters
	Resveratrol-enriched wine enhanced performance in some of the cognitive tests

Turner *et al.*, 2015[15]

This RCT was designed to determine the safety and tolerability of resveratrol and to examine its pharmacokinetics. The authors showed that resveratrol and its metabolites were well tolerated and crossed the blood–brain barrier, reduced the decline on Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL) scores and altered some Alzheimer's disease (AD) biomarker trajectories. Although the observed central nervous system effects cannot be extrapolated to a physiological benefit, the results observed are encouraging and justify a larger, more potent study to determine whether resveratrol could be a real candidate element for the prevention and/or treatment of AD.

	119 subjects with mild to moderate Alzheimer's Disease
	52 weeks
	500 mg/day - increased up to 2000 mg/day resveratrol
	Safety, tolerability and AD biomarkers
	High-dose resveratrol was well-tolerated and crossed the blood-brain barrier

Wightman *et al.*, 2014[47]

In this RCT the effect of piperine on resveratrol bio-efficacy in cerebral blood flow (CBF) and their combined cognitive effects were studied. The results indicated that when co-supplemented, piperine and resveratrol significantly augmented CBF during task performance in comparison with placebo and resveratrol alone. Cognitive function, mood and blood pressure were not affected. The plasma concentrations of resveratrol and its metabolites were not significantly different between treatment groups. This finding indicated that the co- supplementation of piperine with resveratrol enhanced the bio-efficacy of resveratrol with respect to CBF effects, but not cognitive performance, without altering resveratrol's bioavailability.

	23 adults
	28 days
	250 mg/day resveratrol with or without 20 mg piperine on separate days
	Resveratrol bioavailability and cerebral blood flow
	Piperine and resveratrol augmented CBF vs placebo and resveratrol alone

Wightman *et al.*, 2015[48]

The objective of this RCT was to evaluate whether resveratrol administration had an effect on the performance of cognitively demanding tasks. Blood pressure and measurements of cerebral blood flow (CBF) were also considered. The only significant cognitive finding on day 28 was a beneficial effect of resveratrol on the accuracy of the 3-Back task before resveratrol treatment vs. placebo. Subjective ratings of 'fatigue' were significantly lower across the entire 28 days in the resveratrol group. Resveratrol also resulted in modulation of CBF parameters on day 1. These results confirmed the acute CBF effects of resveratrol and the lack of some interpretable cognitive effects.

	60 adults between 18 and 30 years old
	28 days
	500 mg/day resveratrol
	Cerebral blood flow and performance in cognitively demanding tasks
	Resveratrol had acute cerebral blood flow effects

Witte, *et al.*, 2014[9]

The effect of resveratrol supplementation on memory performance and its mechanisms was explored in this placebo controlled study. Results showed a significant effect of resveratrol supplementation on retention of words over 30 minutes vs. placebo. In addition, resveratrol supplementation led to significant increases in hippocampal functional connectivity (FC), decreases in glycated hemoglobin (HbA1c) and body fat, and increases in leptin vs. placebo. This study provided initial evidence that supplementation with resveratrol improved memory performance in association with improved glucose metabolism and increased hippocampal FC in older adults.

	46 healthy overweight older subjects
	26 weeks
	200 mg/day resveratrol or placebo
	Memory performance tests
	Resveratrol improved memory performance and increased hippocampal FC

Wong *et al.*, 2016a[46]

Progressive microvascular dysfunction in type 2 diabetes mellitus (T2DM) may impair the ability of cerebral vessels to supply blood to brain regions during local metabolic demand, thereby increasing the risk of dementia. This crossover RCT was designed to determine the most efficacious dose of resveratrol needed to improve cerebral vasodilator responsiveness (CVR) in T2DM subjects. Results indicated that resveratrol supplementation increased CVR in the middle cerebral arteries. Maximum improvement was observed at the lowest dose used.

	36 older subjects with Type 2 Diabetes Mellitus
	4 weeks
	0, 75, 150 and 300 mg/day resveratrol at weekly intervals
	Cerebral circulation
	Acute enhancement of vasodilator responsiveness in cerebral vessels

Wong *et al.*, 2016b[49]

This RCT investigated the effects of resveratrol administration on neurovascular coupling capacity (cerebral vasodilator responsiveness to cognitive stimuli), cognitive performance and correlation to plasma resveratrol concentrations in type 2 diabetes subjects. Compared with placebo, 75 mg of resveratrol significantly improved neurovascular coupling capacity, which correlated with total plasma resveratrol levels. Enhanced performance on the multi-tasking test battery was also evident following 75 mg and 300 mg resveratrol administration.

	36 older, dementia-free subjects with non-insulin dependent T2DM
	4 weeks
	0, 75, 150 and 300 mg/day resveratrol at weekly intervals
	Cerebral vasodilation
	Resveratrol caused acute enhancement of vasodilation in cerebral vessels

Zortea *et al.*, 2016[50]

Schizophrenia (SZ) is associated with psychotic experiences and cognitive deficits. The objective of this RCT was to determine the efficacy of resveratrol supplementation on cognition in individuals with SZ. A series of cognitive tests determining neuropsychological performance were used to assess psychopathological severity. In this study, 1 month of a resveratrol supplementation (200 mg/day) did not improve significantly ($P > 0.05$) episodic memory, working memory, attention and concentration capacity, inhibitory control, interference measures, selective attention, and mental flexibility as compared with placebo in patients with SZ.

	19 adult men with Schizophrenia
	1 month
	200 mg/day resveratrol or placebo
	Cognitive tests
	Resveratrol did not improve significantly cognitive parameters

Selection of Ongoing Studies with Resveratrol

Since resveratrol was put into the spotlight in the 1990s, in the context of the *French paradox*, the number of clinical studies using resveratrol has increased enormously. It is hard to keep up with the studies being carried out with resveratrol and often they only become known to the scientific community once they are published. Different registries of clinical trials exists in several countries. The World Health Organization (WHO) maintains an international registry portal at http://apps.who.int/trialsearch/ but researchers do not always register their trials or registration is only completed when the trials are close to publication. Among the country-specific registries, the oldest and most popular is ClinicalTrials.gov, in the United States, with more than 250,000 clinical studies registered to date. A list of registries for clinical trials can be found below:

- Australia and New Zealand's (ANZCTR) (http://www.anzctr.org.au)
- Brazilian Clinical Trials Registry (ReBec) (http://www.ensaiosclinicos.gov.br)
- Chinese Clinical Trial Registry (ChiCTR) (http://www.chictr.org.cn)
- Clinical Research Information Service (CRiS), Republic of Korea (http://cris.cdc.go.kr)
- Clinical Trials Registry - India (CTRI) (http://ctri.nic.in)
- Cuban Public Registry of Clinical Trials (RPCEC) (http://registroclinico.sld.cu)
- EU Clinical Trials Register (EU-CTR) (https://www.clinicaltrialsregister.eu/)
- German Clinical Trials Register (DRKS) (http://www.drks.de)
- Iranian Registry of Clinical Trials (IRCT) (http://www.irct.ir/)
- Japan's UMIN-CTR (http://umin.ac.jp)
- Thai Clinical Trials Registry (www.clinicaltrials.in.th)
- The Netherlands' Trialregister.nl (http://www.trialregister.nl)
- The United Kingdoms' ISRCTN registry (http://www.isrctn.com)
- The United States' ClinicalTrials.gov (https://www.clinicaltrials.gov)
- Pan African Clinical Trial Registry (PACTR) (http://www.pactr.org/)
- Sri Lanka Clinical Trials Registry (SLCTR) (http://www.slctr.lk/)

Therefore, an exhaustive list of ongoing clinical studies on the effects of resveratrol on cognitive function and/or neuroprotection does not exist. So here we list a selection of the most relevant ongoing trials.

Supporting healthy aging in women with resveratrol - RESHAW

This crossover RCT is conducted by the University of Newcastle, Australia and will study the effect of a 12-month daily resveratrol supplementation on brain and bone health in post-menopausal women. The active group will receive a 150 mg dose of Veri-te™ resveratrol (taken as two 75 mg capsules) per day. The primary outcome is a neuropsychological test battery, including the measurement of verbal memory, attentional and executive functions. Secondary outcomes include measurements of bone mineral density and bone formation biomarkers, cardiovascular and neurovascular parameters, mood and others. The study has already completed the recruitment process and is expected to be finish by mid-2019.

	ACTRN12616000679482
	160 women; 45-85 yrs.; postmenopausal
	12 months + 12 months
	150 mg Veri-te™ resveratrol per day or placebo
	Neuropsychological test, bone density and other parameters

Impact of resveratrol on brain function and structure

This RCT is conducted by the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig, Germany and will study the effects of Veri-te™ resveratrol (200 mg/day for 6 months) in the general brain structure and function of healthy older individuals. The primary outcome is a screening test for memory impairment (Verbal Learning Task). Secondary outcomes include other brain function tests, brain MRI images and plasma biomarkers. The study has recently concluded. The publication of the results is expected before the end of 2017.

	NCT02621554
	60 older individuals; 60+ yrs.
	6 months + 6 months
	75 mg Veri-te™ resveratrol per day or placebo
	Change from baseline Verbal Learning Task Scores

Effects of Resveratrol on mood and cognition in patients with type 2 diabetes

This RCT is conducted by the Institute of Endocrinology and Metabolism, Iran University of Medical Sciences and will study the effects of resveratrol (240 mg/day for 8 weeks) on mood, cognitive function and serum brain-derived neurotrophic factor (BDNF) in patients with type 2 diabetes. Mood and cognitive function will be evaluated via questionnaires while serum BDNF will be measured using the enzyme-linked immunosorbent assay (ELISA) method. The recruitment has been completed but there is no indication of the expected completion date. The results have not been published yet.

	IRCT201411112394N14
	60 individuals; 45-70 yrs.; with T2DM
	8 weeks
	240 mg resveratrol per day or placebo
	Mood, cognitive function, serum BDNF (brain-derived neurotrophic factor)

BDPP Treatment for mild cognitive impairment (MCI) and prediabetes

This RCT is conducted by the Johns Hopkins University, Maryland, USA and will study the effects of effects of the intake for 4 months of a Bioactive Dietary Polyphenol Preparation (BDPP, containing Concord grape juice, grape seed extract, and resveratrol in undisclosed proportions) on mood and cognitive function in patients with mild cognitive impairment and prediabetes. Mood and cognitive function will be evaluated via questionnaires. The trial is recruiting participants and there is no indication of the expected completion date.

	NCT02502253
	48 individuals; 55-85 yrs.; with MCI and Impaired Fasting Glucose (IFG)
	4 months
	Undisclosed low, moderate and high dose of a Bioactive Dietary Polyphenol Preparation (BDPP) containing resveratrol
	Mood and cognition tests

Resveratrol and Huntington's disease - REVHD

This triple-blind RCT is conducted by several public hospitals in Paris, France and will study the effects of 80 mg/day of resveratrol (taken as 2 capsules of 20 mg of resveratrol in the morning and in the evening) for 1 year on the caudate nucleus volume in subjects with Huntington's disease. The rate of caudate atrophy will be estimated by volumetric MRI. The decline in cognitive performance and the progression of disease will be estimated by different questionnaires and tests. The trial is recruiting participants and the estimated primary completion date is March 2018.

	NCT02336633
	102 individuals; 18+ yrs.; with early Huntington's Disease
	1 year
	80 mg resveratrol per day or placebo
	Rate of caudate nucleus atrophy using volumetric MRI

Conclusions

Resveratrol is a natural compound found in several plants which has been shown to have powerful antioxidant properties. Antioxidants neutralize free radicals, which are believed to be associated with aging, cardiovascular disease, and other inflammatory medical conditions.

This review describes the benefits of resveratrol in cognitive function and neuroprotection. A total of 13 published and 5 ongoing RCTs have been considered. The published studies demonstrated that resveratrol supplementation with doses ranging from 75 mg to 2,000 mg for up to 52 weeks optimized circulatory function in the brain, increased cerebral blood flow, and modulated neuro-inflammation, while enhancing performance in some cognitive tests. In all studies considered, resveratrol was well tolerated. No serious adverse events were reported.

The described evidence that resveratrol, as an antioxidant, can protect against damage due to cardiovascular disease and other inflammatory conditions needs further study. The present research suggest that some of the effects of resveratrol in neurocognitive health could be mediated by its effects in improving cerebral perfusion and demonstrates that resveratrol represents a promising and safe therapeutic agent/dietary supplement for a variety of medical conditions including neurocognitive health.

Literature

1. Soleas, G. J., Diamandis, E. P. & Goldberg, D. M. Resveratrol: A molecule whose time has come? And gone? *Clinical Biochemistry* **30**, 91–113 (1997).
2. Constant, J. Alcohol, ischemic heart disease, and the French paradox. *Clin Cardiol* **20**, 420–424 (1997).
3. PubMed. National Institutes of Health. *Data from US Natl. Libr. Med.* at <https://www.ncbi.nlm.nih.gov/pubmed>
4. Liu, Y., Ma, W., Zhang, P., He, S. & Huang, D. Effect of resveratrol on blood pressure: A meta-analysis of randomized controlled trials. *Clin. Nutr.* **34**, 27–34 (2015).
5. Liu, K., Zhou, R., Wang, B. & Mi, M.-T. Effect of resveratrol on glucose control and insulin sensitivity: a meta-analysis of 11 randomized controlled trials. *Am. J. Clin. Nutr.* **99**, 1510–9 (2014).
6. Farris, P., Krutmann, J., Li, Y. H., McDaniel, D. & Krol, Y. Resveratrol: a unique antioxidant offering a multi-mechanistic approach for treating aging skin. *J Drugs Dermatol* **12**, 1389–1394 (2013).
7. Poulsen, M. M. *et al.* Short-term resveratrol supplementation stimulates serum levels of bone-specific alkaline phosphatase in obese non-diabetic men. *J. Funct. Foods* **6**, 305–310 (2014).
8. Ornstrup, M. J., Harsløf, T., Kjær, T. N., Langdahl, B. L. & Pedersen, S. B. Resveratrol Increases Bone Mineral Density and Bone Alkaline Phosphatase in Obese Men: A Randomized Placebo-Controlled Trial. *J. Clin. Endocrinol. Metab.* **99**, 4720–4729 (2014).
9. Witte, a V., Kerti, L., Margulies, D. S. & Flöel, A. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. *J. Neurosci.* **34**, 7862–70 (2014).
10. Pezzuto, J. M. The phenomenon of resveratrol: Redefining the virtues of promiscuity. *Ann. N. Y. Acad. Sci.* **1215**, 123–130 (2011).
11. Walle, T. Bioavailability of resveratrol. *Ann. N. Y. Acad. Sci.* **1215**, 9–15 (2011).
12. Walle, T., Hsieh, F., Delegge, M. H., Oatis, J. E. & Walle, U. K. High absortion but very low bioavaibility of oral resveratrol in humans. *Drug Metab. isposition* **32**, 1377–1382 (2004).
13. Patel, K. R. *et al.* Sulfate metabolites provide an intracellular pool for resveratrol generation and induce autophagy with senescence. *Sci. Transl. Med.* **5**, 205ra133 (2013).
14. Swomley, A. M. *et al.* Comparative proteomic analyses of the parietal lobe from rhesus monkeys fed a high-fat/sugar diet with and without resveratrol supplementation, relative to a healthy diet: Insights into the roles of unhealthy diets and resveratrol on function. *J. Nutr. Biochem.* **39**, 169–179 (2017).
15. Turner, R. S. *et al.* A randomized, double-blind, placebo-controlled trial of resveratrol for Alzheimer disease. *Neurology* **85**, 1383–1391 (2015).
16. Britton, R. G., Kovoor, C. & Brown, K. Direct molecular targets of resveratrol : identifying key interactions to unlock complex mechanisms. **1348**, 124–133 (2015).
17. Kulkarni, S. S. & Cantó, C. The molecular targets of resveratrol. *Biochim. Biophys. Acta - Mol. Basis Dis.* **1852**, 1114–1123 (2015).
18. Lin, S.-J., Defossez, P.-A. & Guarente, L. Requirement of NAD and SIR2 for Life-Span Extension by Calorie Restriction in Saccharomyces cerevisiae. *Science (80-.).* **289**, 2126 LP-2128 (2000).
19. Lawler, D. F. *et al.* Diet restriction and ageing in the dog: major observations over two decades. *Br. J. Nutr.* **99**, 793–805 (2008).
20. Ingram, D. K. *et al.* The potential for dietary restriction to increase longevity in humans: Extrapolation from monkey studies. *Biogerontology* **7**, 143–148 (2006).
21. Allard, J. S., Perez, E., Zou, S. & de Cabo, R. Dietary activators of Sirt1. *Mol. Cell. Endocrinol.* **299**, 58–63 (2009).
22. Trepanowski, J. F., Canale, R. E., Marshall, K. E., Kabir, M. M. & Bloomer, R. J. Impact of caloric and dietary restriction regimens on markers of health and longevity in humans and animals: a summary of available findings. *Nutr. J.* **10**, 107 (2011).
23. Most, J., Tosti, V., Redman, L. M. & Fontana, L. Calorie restriction in humans: An update. *Ageing Res. Rev.* (2016). doi:10.1016/j.arr.2016.08.005
24. Laparra, J. M. & Sanz, Y. Interactions of gut microbiota with functional food components and nutraceuticals. *Pharmacol. Res.* **61**, 219–225 (2010).
25. Conlon, M. A. & Bird, A. R. The impact of diet and lifestyle on gut microbiota and human health. *Nutrients* **7**, 17–44 (2015).
26. Qiao, Y. *et al.* Effects of resveratrol on gut microbiota and fat storage in a mouse model with high-fat-induced obesity. *Food Funct.* **5**, 1241–9 (2014).
27. Chen, M. L. *et al.* Resveratrol attenuates trimethylamine-N-oxide (TMAO)-induced atherosclerosis by regulating TMAO synthesis and bile acid metabolism via remodeling of the gut microbiota. *MBio* **7**, 1–14 (2016).
28. Sung, M. M. *et al.* Improved glucose homeostasis in obese mice treated with resveratrol is associated with alterations in the gut microbiome. *Diabetes* **66**, 418–425 (2017).
29. Tomé-Carneiro, J. *et al.* Resveratrol and clinical trials: the crossroad from in vitro studies to human evidence. *Curr. Pharm. Des.* **19**, 6064–93 (2013).
30. Deary, I. J. *et al.* Age-associated cognitive decline. *Br. Med. Bull.* **92**, 135–152 (2009).
31. Kirk-Sanchez, N. J. & McGough, E. L. Physical exercise and cognitive performance in the elderly: current perspectives. *Clin. Interv. Aging* **9**, 51–62 (2014).
32. Barclay, B. L. Cognition. **13**, 56 (2007).
33. Williams, K and Kemper, S. Exploring Interventions to Reduce Cognitive Decline in Aging. *J Psychosoc Nurs Ment Heal. Serv.* **48**, 42–51 (2010).
34. Mazzanti, G. & Di Giacomo, S. Curcumin and resveratrol in the management of cognitive disorders: What is the clinical evidence? *Molecules* **21**, 1–27 (2016).
35. Poulose, S. M., Thangthaeng, N., Miller, M. G. & Shukitt-Hale, B. Effects of pterostilbene and resveratrol on brain and behavior. *Neurochem.* Int. **89**, 227–233 (2015).
36. Wąsik, A. & Antkiewicz-Michaluk, L. The mechanism of neuroprotective action of natural compounds. *Pharmacol. Reports* **69**, 851–860 (2017).
37. Sarubbo, F., Esteban, S., Miralles, A. & Moranta, D. Effects of Resveratrol and Other Polyphenols on Sirt1: Relevance to Brain Function During Aging. *Curr. Neuropharmacol.* (2017).
38. Sarubbo, F., Moranta, D., Asensio, V. J., Miralles, A. & Esteban, S. Effects of Resveratrol and other Polyphenols on the most common Brain Age-Related Diseases. *Curr. Med. Chem.* (2017).
39. Bhardwaj SS, Camacho F, Derrow A, Fleischer AB Jr, F. S. Statistical significance and clinical relevance. *Arch Dermatol* **140**, 1520–3 (2004).
40. Sauerland, S. & Seiler, C. M. Role of systematic reviews and meta-analysis in evidence-based medicine. *World J. Surg.* **29**, 582–587 (2005).
41. Evans, H. M., Howe, P. R. C. & Wong, R. H. X. Effects of resveratrol on cognitive performance, mood and cerebrovascular function in post-menopausal women; a 14-week randomised placebo-controlled intervention trial. *Nutrients* **9**, (2017).
42. Kennedy, D. O. *et al.* Effects of resveratrol on cerebral blood flow variables and cognitive performance in humans : a double-blind , placebo-controlled , crossover. *Am. J. Clin. Nutr.* **91**, 1590–1597 (2010).
43. Köbe, T. *et al.* Impact of resveratrol on glucose control, hippocampal structure and connectivity, and memory performance in patients with mild cognitive impairment. *Front. Neurosci.* **11**, 1–11 (2017).
44. Lee, J., Torosyan, N. & Silverman, D. H. Examining the impact of grape consumption on brain metabolism and cognitive function in patients with mild decline in cognition: A double-blinded placebo controlled pilot study. *Exp. Gerontol.* **87**, 121–128 (2017).
45. Moussa, C. *et al.* Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. *J. Neuroinflammation* **14**, (2017).
46. Wong, R. H. X., Nealon, R. S., Scholey, A. & Howe, P. R. C. Low dose resveratrol improves cerebrovascular function in type 2 diabetes mellitus. *Nutr. Metab. Cardiovasc. Dis.* **26**, 393–399 (2016).
47. Wightman, E. L. *et al.* Effects of resveratrol alone or in combination with piperine on cerebral blood flow parameters and cognitive performance in human subjects: a randomised, double-blind, placebo-controlled, cross-over investigation. *Br. J. Nutr.* **112**, 203–213 (2014).
48. Wightman, E. L. *et al.* The effects of chronic trans-resveratrol supplementation on aspects of cognitive function, mood, sleep, health and cerebral blood flow in healthy, young humans. *Br. J. Nutr.* **114**, 1427–1437 (2015).
49. Wong, R. H. X., Raederstorff, D. & Howe, P. R. C. Acute resveratrol consumption improves neurovascular coupling capacity in adults with type 2 diabetes mellitus. *Nutrients* **8**, (2016).
50. Zortea, K., Franco, V. C., Guimarães, P. & Belmonte-de-Abreu, P. S. Resveratrol supplementation did not improve cognition in patients with schizophrenia: Results from a randomized clinical trial. *Front. Psychiatry* **7**, 1–5 (2016).