

# Exploring Brain Health with Resveratrol

A Fresh Look into the Latest Scientific Evidence

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## Introduction

Aging is a natural process of any living organism; however, the rate depends on many factors, including genetic and environmental. The World Health Organization (WHO) estimates that the number of people above 60 years of age will be 1.2 billion by 2025

**The number of people above 60 years of age will be 1.2 billion by 2025 and two billion by 2050.<sup>1</sup>**

and two billion by 2050.<sup>1</sup> Along with the increase in age of the general population, the percent of individuals with age-related challenges is also rapidly growing. Among these challenges, cognitive decline is considered one of the most devastating age-related conditions.

As our brains age, there is a loss of cortical neurons, reduced number of synapses, and glucose metabolism that all lead to alterations in cognitive functions such as learning and memory processing. In addition, age-related cerebral vascular diseases lead to hypoperfusion and brain ischemia, thereby exacerbating cognitive deficits.<sup>2</sup> Moreover, oxidative stress and inflammation have been identified as the major causes of cognitive decline.

*Trans-resveratrol* (herein mentioned as resveratrol) is a polyphenolic compound naturally found in numerous foods such as grapes, wines, peanuts, blueberries and some other berries. Resveratrol is a secondary

metabolite and phytoalexin which is synthesized in plants generally in response to external stress such as infection and UV radiation.<sup>3</sup>

Beyond its protective role in plants, resveratrol has been extensively investigated for its beneficial effects on human health. There are more than 12,000 scientific publications, including 200 human clinical studies demonstrating the effects of resveratrol

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supplementation in several benefits such as cardiovascular health, diabetes, neurodegenerative diseases and cognitive health. In the context of brain health, resveratrol has been found to improve brain functionality through SIRT1 activation and inflammation modulation, prevention of oxidative stress and via regulation of some signaling pathways, such as Nuclear Factor- $\kappa$ B (NF- $\kappa$ B).<sup>4</sup>

The objective of this review is to provide the latest science-based evidence for resveratrol supplementation on cognitive health. First, insights into the potential mechanisms of action involved in the cognitive process and the role of resveratrol are outlined. Then a critical analysis of 13 clinical studies is presented. Along with

# Exploring Brain Health with Resveratrol

A Fresh Look into the Latest Scientific Evidence

the analysis, several factors of the study design are investigated, such as sample size, resveratrol dose, follow-up duration, as well as the participants' age, health status and sex. Two meta-analyses are then discussed, as well as the newly published outcomes of a highly respected clinical study with Evolva's Veri-te™ resveratrol. Lastly, the next steps in cognitive health research are highlighted along with the conclusion that outlines the positive results on cerebral blood flow and cognitive tasks that support the importance of resveratrol supplementation.

## Resveratrol functions on six levels to protect cognition

Resveratrol is considered an instrumental ingredient for healthy living, mainly due to its well documented free radical scavenging and anti-inflammatory properties.<sup>5</sup> At the molecular level, resveratrol has been reported as targeting:

- Sirtuins (particularly SIRT1)
- Adenosine Monophosphate Kinase (AMPK)
- NF-κB (nuclear factor "Kappa-light-chain-enhancer" of activated B cells)
- Inflammatory Cytokines
- Antioxidant Enzymes (such as catalase – CAT and superoxide dismutase – SOD).

Additionally, resveratrol can target cellular processes such as mitochondrial biogenesis.<sup>3</sup>

In general, mechanisms of action may include antioxidative, anti-inflammatory, anti-apoptotic processes and autophagy regulation, as well as increases in cerebral blood flow (CBF) and improvements in the plasticity of synaptic pathways, all important features in counteracting cognitive decline.<sup>6</sup> Below are the six main mechanisms involved in the protective effects of resveratrol in cognitive health (summary in **Figure 1**).

### 1. Resveratrol Crosses the Blood Brain Barrier (BBB) and Restores Functionality

The BBB consists of a specialized system of microvascular endothelial cells whose main function

is to protect the brain by selectively limiting the entry of potentially toxic compounds to the brain, while simultaneously permitting the entry of nutrients.<sup>7</sup>

There has been growing evidence that BBB disruption is associated with brain inflammatory conditions and decreased Central Nervous System (CNS) protection.<sup>8</sup> Recent studies have suggested that the breakdown or disruption of the BBB is an early biomarker of human cognitive dysfunction.<sup>9</sup> Rom *et al.*<sup>10</sup> report that the BBB permeability and memory loss are associated with the diminution of tight junctions in brain endothelium and inflammation in cerebral microvessels and brain tissue.

Resveratrol is not only able to cross the BBB but also can help restore the BBB functionality and integrity. Wang *et al.*<sup>11</sup> demonstrated in an animal model that resveratrol exerted protective effects on the tight junction proteins to improve the BBB integrity mainly by its anti-inflammatory and antioxidant properties.

### 2. Resveratrol Activates SIRT-1

Sirtuins are of crucial relevance when referring to cognitive processes. It is well reported that calorie restriction and caloric restriction mimetics, such as resveratrol, are all capable of upregulating sirtuin isoforms.<sup>12</sup> Sirtuin-1 is a protein encoded by the SIRT1 gene in humans, which is popularly referred to as the "Longevity Gene." SIRT 1 activation is known for protecting against several metabolic and age-related diseases such as type 2 diabetes, cardiovascular and neurodegenerative diseases, and cognitive decline.<sup>13,14</sup>

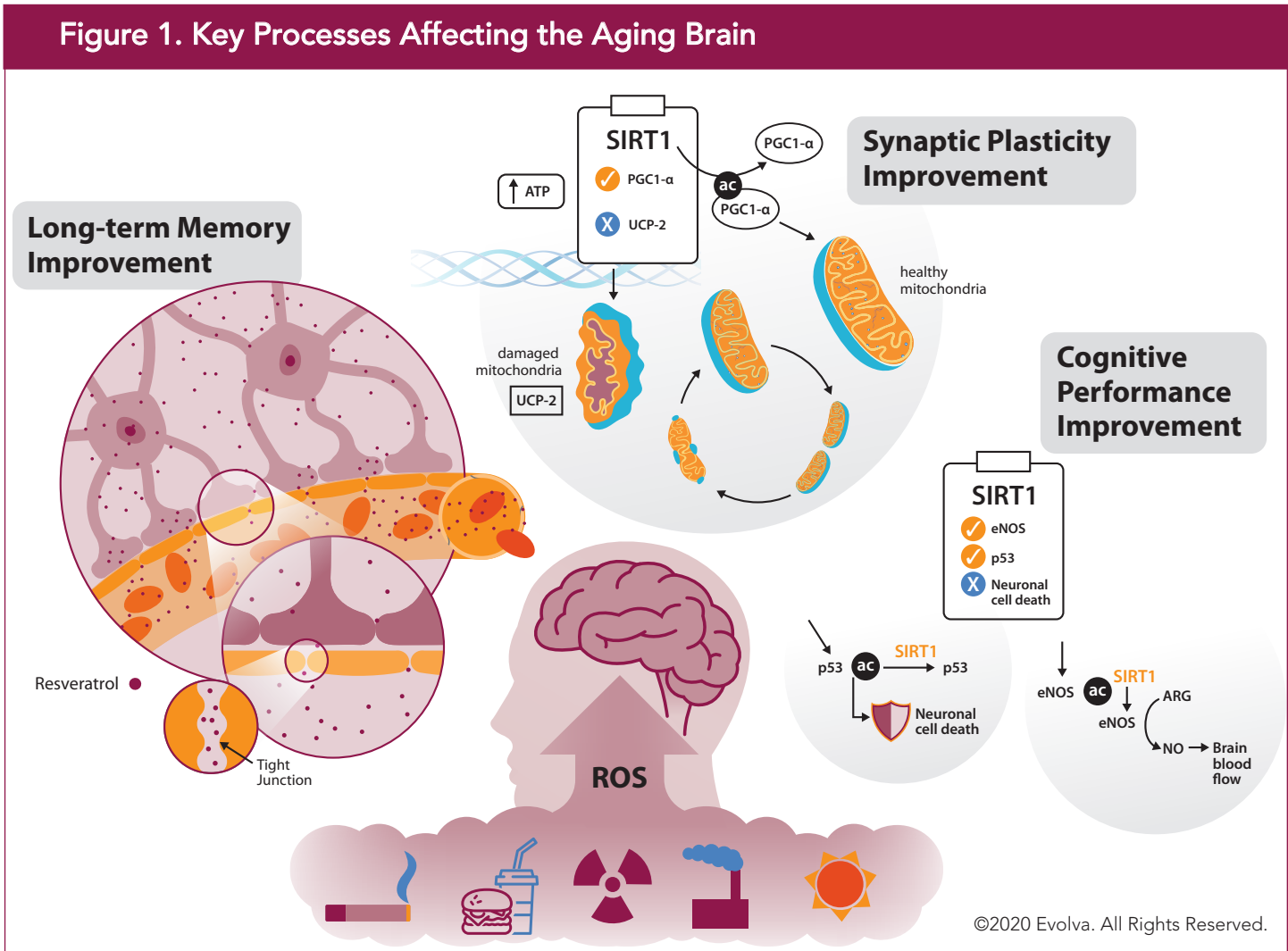
Several phytochemicals have been identified as Sirtuin Activating Compounds (STACs), and among those, resveratrol is considered to be the most potent dietary SIRT1 activator identified to date.<sup>14,15</sup> Additionally, some authors have reported that optimal SIRT1 activation is the most crucial step in the neuroprotection provided by resveratrol against cognitive impairment.<sup>6</sup>

### 3. Resveratrol Promotes Nitric Oxide (NO) Synthesis and Increases Blood Flow to the Brain

NO, a free gaseous signaling molecule involved in the regulation of the cardiovascular, nervous and immune system, is produced by three isoforms of NO synthase (NOS): the neuronal (nNOS), the inducible (iNOS) and

# Exploring Brain Health with Resveratrol

A Fresh Look into the Latest Scientific Evidence



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**Figure 1.** Resveratrol has been reported as acting in several key processes affecting the aging brain. **Long-term Memory Improvement:** Crossing and restoring the integrity of the Blood Brain Barrier. **Synaptic Plasticity Improvement:** Promoting mitochondrial biogenesis and neurogenesis. **Cognitive Performance Improvement:** Activating SIRT1 to prevent neuronal cell death, activating Nitric Oxide Synthase (NOS), and increasing blood flow.

the endothelial (eNOS).<sup>16</sup> A considerable number of publications have demonstrated the importance of nNOS in a variety of synaptic signaling events and the implication in modulating physiological functions such as learning, memory, and neurogenesis.<sup>17</sup>

In this context, resveratrol stimulates NO production via several mechanisms, including upregulation of NOS expression, stimulation of NOS enzymatic activity and reversal of eNOS uncoupling. By reducing oxidative stress, resveratrol prevents oxidative NO inactivation

by superoxide, thereby enhancing NO bioavailability. Molecular pathways underlying these effects of resveratrol involve SIRT1, AMPK, Nrf2 and estrogen receptors.<sup>16</sup>

#### 4. Resveratrol Supports Mitochondrial Biogenesis

Mitochondria are “the powerhouse” of the cell, playing a vital role in generating energy for the intricate functions of the cells mainly through the process of oxidative phosphorylation. Though this process is



# Exploring Brain Health with Resveratrol

A Fresh Look into the Latest Scientific Evidence

essential for the functioning of cells, it also generates Reactive Oxygen Species (ROS), which can cause damage to cells when in excess.<sup>18</sup>

Mitochondrial fission/fusion and biogenesis are key processes in regulating mitochondrial homeostasis.<sup>19</sup> Although impairment of mitochondrial biogenesis can naturally happen as we age, it is also impacted by diabetes, and neurodegenerative diseases.<sup>20</sup>

Resveratrol has been reported as promoting a mitochondrial protective effect due to the induction of mitochondrial antioxidant systems and by reducing mitochondrial ROS production in the cells.<sup>20</sup> Additionally, activation of SIRT1 by resveratrol can promote deacetylation and activation of peroxisome proliferator activator gamma coactivator 1 alpha (PGC-1 $\alpha$ ), a key regulator of mitochondrial biogenesis.<sup>20</sup>

**Resveratrol presents a multifaceted mechanistic approach to improving cognitive health in different conditions; therefore, it is a key adjunct for counteracting age-related cognitive decline.**

## 5. Resveratrol Scavenges ROS as a Powerful Antioxidant

The hippocampus, the region of the brain responsible for certain aspects of learning and memory, is particularly susceptible to damage by circulating toxins, metabolic disturbances and ROS.<sup>7</sup> Neurons in the hippocampus rely heavily both on oxidative phosphorylation and mitochondria for energy, and abnormalities in either of these mechanisms compromise hippocampal integrity.<sup>7</sup>

Resveratrol has been extensively investigated and reported as a potent antioxidant. In general, resveratrol protects against excessive ROS production or oxidative stress by reducing ROS generation, directly scavenging free radicals, promoting endogenous antioxidant enzymes (SOD and CAT), and mitochondrial biogenesis, mainly through AMPK, SIRT1 and Nrf2.<sup>21</sup> Therefore, resveratrol has the potential ability to act as a direct antioxidant and an indirect cellular antioxidant system inducer through modulation of several cellular antioxidant pathways.<sup>22</sup>

## 6. Resveratrol Promotes Neurogenesis

Adult hippocampal neurogenesis is a complex process by which stem cells in the hippocampal brain region differentiate and proliferate into new neurons.<sup>23</sup> As expected, neurogenesis plays a vital role in neural plasticity and brain homeostasis, in addition to preserving the cognitive function affected by aging. This process is known to be affected by many intrinsic and extrinsic factors, including diet (e.g., high fat and high sugar), aging, neuroinflammation and oxidative stress.<sup>23</sup>

Calorie restriction, physical exercise and dietary components such as resveratrol have been shown to induce neurogenesis in adult brains.<sup>23</sup> For instance, Kodali *et al.*<sup>24</sup> reported the efficacy of resveratrol in counteracting age-related memory and mood impairments and the associated detrimental changes in the hippocampus in a rat model. Resveratrol-treated animals had increased net neurogenesis and microvasculature. Moreover, Dias *et al.*<sup>25</sup> reviewed the evidence implicating resveratrol in regulating hippocampal neural plasticity and in mitigating the effects of various disorders and diseases. These authors highlighted that resveratrol has the potential of improving cognition and mood and enhance hippocampal plasticity and neurogenesis.

In light of this analysis, resveratrol presents a multifaceted mechanistic approach to improving cognitive health in different conditions; therefore, it is a key adjunct for counteracting age-related cognitive decline.

## Clinical studies on cognitive health following resveratrol supplementation: A critical analysis

In order to assess the current science-based evidence for the benefits of resveratrol supplementation on cognitive health, a systematic search on the primary scientific databases (Cochrane Library, Pubmed/Medline and Google Scholar) was performed. The studies were compiled and included in the analysis based on set criteria:

# Exploring Brain Health with Resveratrol

## A Fresh Look into the Latest Scientific Evidence

- **Source of resveratrol:** only studies administering resveratrol in its pure form (*trans*-resveratrol) were included in order to correlate the observed effect to resveratrol. Studies administering wine or grape powder extracts were excluded as other biologically active compounds are also present, such as flavonoids and proanthocyanidins. Exceptions were two studies where resveratrol was administered in combination with other compounds with the purpose of enhancement of bioavailability;
- **Study design:** only randomized, placebo-controlled trials were included;
- **Population:** only studies recruiting healthy participants were included. Studies recruiting patients with neurodegenerative diseases such as Parkinson's and Alzheimer's diseases were excluded.

Based on these criteria, a total of 13 clinical studies were retrieved, and the details of each study are presented in **Table 1**. The main findings are summarized in the table and represented as favorable (resveratrol supplementation supports the benefit) or null (resveratrol supplementation does not promote a statistically significant change compared to placebo).

The analysis indicates that resveratrol supports improvement of cerebral blood flow (CBF) in young and elderly populations. However, the effects in cognition vary depending on several factors, including population (young vs. elderly), the timing for assessment after supplementation (45 minutes to 75 minutes), and the co-administration of resveratrol with other compounds.

### Population: Age

Participants were between 18 to 80 years old. Young or older participants seemed to benefit from resveratrol supplementation with respect to an increase in CBF even at single doses of resveratrol. However, for cognitive performance, it seems that older populations would benefit more than younger populations following the settings of these published studies. Very recently, Wightman *et al.*<sup>26</sup> performed an assessment by combining the individual cohorts from six individual

trials to create one larger, more powerful, sample size to assess a variety of cognitive outcomes. These authors concluded that administering single doses of up to 500 mg resveratrol does not provide any short-term effect in a wide range of cognition measurements in a healthy and young population (18 - 35 year old).

Although a significant effect on brain blood flow has been observed for young and older populations, there is no correlation with cognitive response improvement. This same lack of correlation has been reported by Catchlove *et al.*<sup>27</sup> who assessed age-related contribution of regional Cerebrovascular reactivity (CVR) to cognitive performance. These authors observed that when analyzing age groups separately, CVR contributed significantly to improve memory score in the older group and was also related to subjective memory complaints. However, no associations between CVR and cognition were observed in younger adults.

### Assessment of cognitive performance: Timing after supplementation

For some studies, researchers assessed participants' performance in cognitive tasks 45 minutes after the intake of supplementation while others did after 75 minutes. From the findings on the clinical studies, 45 minutes after supplementation seems to be sufficient to promote an increase in CBF but not for improving cognitive task performance. For instance, Kennedy *et al.*<sup>28</sup>, Wightman *et al.*<sup>29</sup> and Eschle *et al.*<sup>30</sup> performed the measurement 40 – 45 minutes after supplementation and no effect was observed for cognitive performance. However, Wong *et al.*<sup>31</sup> assessed participants after 75 minutes of supplementation and observed significant improvement not only for CBF but also in cognitive performance. All these studies administered single doses of resveratrol to the participants although doses of resveratrol varied from 75 mg to 500 mg. Interestingly, Wong *et al.*<sup>31</sup> administered the lowest dose for participants, 75 mg, and observed significant effects.

These observations underscore the importance of the timing for assessment when designing a clinical study. It is well documented that resveratrol is metabolized into conjugates (mainly sulfates and glucuronides), as well as microbial metabolites. All these metabolites can enter

# Exploring Brain Health with Resveratrol

A Fresh Look into the Latest Scientific Evidence

**Table 1. Human Clinical Studies Evaluating the Potential Benefits of *trans*-Resveratrol Supplementation for Cognitive Health**

Reference	Population	Study Design	Sample Size	Dose & Duration	Biomarkers	Main Findings
Thaung Zaw <i>et al.</i> , 2020 <sup>36</sup>	<b>Postmenopausal women</b> (45-85 yo)	R, DB, PC, P	N= 129	2 x 75 mg <b>Veri-te™</b> daily Morning and evening <b>12 months</b>	Cognition CBF, Cerebrovascular responsiveness (CVR) Cardiometabolic markers	Interim results from the parallel analysis (12 months): <b>Favorable:</b> • Improved overall cognitive performance • Attenuated the decline in CVR to cognitive stimuli
Eschle <i>et al.</i> , 2019 <sup>30</sup>	<b>Healthy</b> (mean age 22 yo)	DB, PC Acute	N= 27	1 x 250-mg or 2 x 250 mg <b>1 day for each arm</b>	Cognitive tasks (45 min and at 2 and 3 hours)	<b>Null:</b> • Acute administration was unable to modulate energy expenditure or cognitive performance
Huhn <i>et al.</i> , 2018 <sup>33</sup>	<b>Elderly</b> (60 - 79 yo) BMI 21 - 37	R, DB, PC	N= 60	200 mg <b>Veri-te™</b> combined with quercetin (2 capsules/day) <b>26 weeks</b>	Verbal memory (Before and after intervention)	<b>Null:</b> • No significant improvements in verbal memory
Anton <i>et al.</i> , 2018 <sup>37</sup>	<b>Healthy Elderly</b> (79 ± 14 yo) <b>Overweight</b> (BMI 25 - 34.9)	R, DB, PC Pilot study	N= 32	Low dose: 300mg/d High dose: 1000mg/d <b>90 days</b>	Cognitive function (Assessments: day 0 and 90 days)	<b>Favorable:</b> • Dose of 1000/mg/day improved psychomotor speed
Kobe <i>et al.</i> , 2017 <sup>32</sup>	<b>Acute Patients</b> with mild cognitive impairment (50 - 80 yo)	R, DB	N= 40	200mg combined with 350mg quercetin (1x d) <b>26 weeks</b>	Levels of glucose, glycated hemoglobin A1c and insulin Memory function (Assessments: day 0 and 26 weeks)	<b>Null:</b> • No significant differences in memory performance <b>However:</b> • Reduced glycated hemoglobin A1c, preserved hippocampus volume
Evans <i>et al.</i> , 2017 <sup>38</sup>	<b>Postmenopausal women</b> (45 - 85 yo)	R, DB, PC, P	N= 80	75 mg (2 x daily) <b>14 weeks</b>	Cerebrovascular function Cognition & Mood (Assessments: day 0 and 14 weeks)	<b>Favorable:</b> • Enhancement of cerebrovascular function and cognition
Evans <i>et al.</i> , 2016 <sup>39</sup>	<b>Postmenopausal women</b> (45 - 85 yo)	R, DB, PC, P	N= 80	75 mg (2 x daily) <b>14 weeks</b>	Cognition CVR to cognitive tasks Overall well-being (Assessments: day 0 and 14weeks)	<b>Favorable:</b> • Enhancement of circulatory function in the brain as well as mood and cognition
Wong <i>et al.</i> , 2016a <sup>31</sup>	<b>T2DM Adults</b> (40 - 80 yo)	R, DB, PC Acute	N= 36	doses: 0, 75, 150 and 300 mg <b>1-week interval</b>	Changes in BFV during a cognitive test battery (75 min post-supplementation)	<b>Favorable:</b> • Single 75 mg dose of resveratrol was able to improve neurovascular coupling and cognitive performance
Wong <i>et al.</i> , 2016b <sup>40</sup>	<b>Dementia-free Non-insulin dependent T2DM</b> (49 - 78 yo)	R, DB, PC, CO, B	N= 36	single doses 0, 75, 150 and 300 mg <b>1-week interval</b>	Cerebrovascular reactivity (CVR) to hypercapnic stimulus (Before and 45 min post-supplementation)	<b>Favorable:</b> • Acute enhancement of vasodilator responsiveness in cerebral vessels; • Maximum improvement was observed with the lowest dose (75 mg)
Wightman <i>et al.</i> , 2015 <sup>34</sup>	<b>Healthy</b> (18 - 30 yo)	R, DB, PC, P	N= 60	500mg (containing 10mg of piperine/capsule) <b>1x day, with breakfast 28 days</b>	Cognitive tasks & Mood CBF (Assessments on days 0 and 28)	<b>Favorable:</b> • Single dose: modulate CBF pattern consistent with increased blood flow and reduced fatigue <b>Null:</b> • No clear improvements in cognitive function.
Wightman <i>et al.</i> , 2014 <sup>29</sup>	<b>Healthy</b> (19 - 34 yo)	R, DB, PC, (within-subjects comparison) Acute	N= 23	250 mg <i>trans</i> -resveratrol and 250mg <i>trans</i> -resveratrol with 20mg piperine <b>Consumed with 1-week interval</b>	Cognitive tasks CBF (40-min post supplementation)	<b>Favorable:</b> • Co-supplementation with piperine enhanced the bioefficacy of resveratrol with regard to CBF <b>Null:</b> • No effect on cognitive performance
Witte <i>et al.</i> , 2014 <sup>41</sup>	<b>Healthy</b> (50 - 75 yo) <b>Overweight</b> (BMI 25 - 30)	R, PC, P, (Pairwise comparison)	N= 46	2 x 2 capsules per day (total 200 mg of resveratrol and 320 mg of quercetin) Before meals <b>26 weeks</b>	Memory performance (Before and after intervention)	<b>Favorable:</b> • Significant effect of resveratrol on retention of words after 30 min • Significant increases in hippocampal functional connectivity (FC) • Improvement of memory performance
Kennedy <i>et al.</i> , 2010 <sup>28</sup>	<b>Healthy</b> (21 - 29 yo)	R, DB, PC, CO	N= 22	250 mg and 500 mg of <i>trans</i> -resveratrol <b>1-week interval 1 day</b>	Cognitive tasks CBF (45-min post supplementation)	<b>Favorable:</b> • Single doses of orally administered resveratrol can modulate CBF <b>Null:</b> • Cognitive function was not affected

Note: T2DM= type 2 diabetes mellitus; CBF (Cerebral Blood Flow); BFV (Blood Flow Velocity); R (Randomized); DB (Double Blind); PC (Placebo controlled); CO (Crossover); B (Balanced); P (Parallel)



# Exploring Brain Health with Resveratrol

## A Fresh Look into the Latest Scientific Evidence

the enterohepatic circulation and potentially contribute to the beneficial effects of resveratrol. Not taking these metabolites into account could explain why earlier reporting of measurements does not see an effect on cognitive performance.

### Co-administration of resveratrol with other compounds: Bioavailability

A few authors have administered resveratrol in combination with other compounds in an attempt to enhance resveratrol's bioavailability. The strategy of combining resveratrol with quercetin (a flavonoid compound) was used by Köbe *et al.*<sup>32</sup> and Huhn *et al.*<sup>33</sup> The rationale for this combination is that quercetin can inhibit SULT1A1, which is a sulfotransferase enzyme involved in conjugation of compounds with sulfate groups. Therefore, resveratrol is not conjugated to sulfate, and the levels of free resveratrol are expected to be higher in the plasma.

Another strategy to enhance resveratrol's bioavailability is the combination with piperine (an alkaloid).<sup>29,34</sup> Piperine inhibits glucuronidation of resveratrol, once again aiming to increase the levels of free resveratrol in the plasma.

Although both approaches were expected to achieve better efficacy by increasing the levels of free resveratrol in plasma, no effect was observed in cognitive performance. This may prove the hypothesis that all resveratrol conjugates can contribute to the beneficial effects observed despite the so-called "low bioavailability." It is probable that the observed benefits of resveratrol supplementation are a result of the sum of resveratrol plus conjugates and not only from free resveratrol found in plasma.

This hypothesis has also been reported for other polyphenolic compounds. For instance, Zhao *et al.*<sup>35</sup> evaluated if polyphenols and their conjugates could potentially affect the attenuation of sleep deprivation-induced cognitive impairment. The authors reported that quercetin, quercetin-3-O-glucuronide (a quercetin conjugate), and malvidin-3-O-glucoside significantly attenuated sleep deprivation-induced

cognitive impairment in a mouse model of acute sleep deprivation.

In summary, the findings from the different clinical studies are often inconsistent, because their validity depends on many factors like the study design, sample size, resveratrol dose, follow-up duration, as well as the participants' age, health status and sex. Nevertheless, the positive results on CBF and cognitive tasks support further exploration of resveratrol supplementation.

## What is the science-based evidence? Resveratrol improves brain blood flow and certain cognitive domains

It is well-reported that improving cerebrovascular function is a key mechanism in protecting against cognitive decline besides living a healthy lifestyle, eating a healthy diet combined with physical activity. Among these healthy habits, long-term exercise training has been reported as a promising approach to improve cerebrovascular function, and as it increases blood flow to the brain, it may also contribute to the beneficial effects on cognitive functioning observed following exercise.<sup>42</sup> In this context, long-term resveratrol supplementation has been shown to increase CBF in populations at increased risk of accelerated cognitive decline (elderly) and young, which is demonstrated in **Table 1** in several clinical studies assessing resveratrol supplementation.

Meta-analyses of randomized controlled trials are considered the gold standard for scientific evidence of a certain treatment and health condition. Although no meta-analysis on the improvement of blood flow to the brain following resveratrol supplementation has been published to date, the outcomes shown in **Table 1** suggest that resveratrol can benefit young and older populations.

On the other hand, regarding cognitive health, two meta-analyses have been published on the effects of

# Exploring Brain Health with Resveratrol

A Fresh Look into the Latest Scientific Evidence

resveratrol supplementation related to the assessment of cognitive performance:

- Farzaei *et al.*<sup>43</sup>: included results obtained from 226 individuals from four randomized clinical trials evaluating the effects of resveratrol supplementation on cognition, memory performance and mood. The key finding from this meta-analysis is that resveratrol supplementation has the potential to enhance mood and significantly decrease fatigue.
- Marx *et al.*<sup>44</sup>: included ten studies among which three studies found that resveratrol supplementation significantly improved some measures of cognitive performance, two reported mixed findings, and five found no effect. When data were pooled, resveratrol supplementation had a significant effect on delayed recognition and negative mood.

The results of these two meta-analyses strengthen the scientific evidence on the benefits of resveratrol supplementation for cognitive health.

## RESHAW (Resveratrol Supporting Healthy Aging in Women): Sustained Effect on Cognitive Health

RESHAW study is considered the largest and longest clinical study evaluating the effects of resveratrol supplementation in postmenopausal women. Cognitive health, bone health and quality of life are among the biomarkers assessed during a 24-month follow up treatment with Veri-te™ resveratrol (see **Figure 2**).

This randomized, placebo-controlled trial was conducted by Dr. Rachel Wong, Jay Jay Thaug Zaw and Professor Peter Howe at the University of Newcastle, Australia. The study was completed in 2019, and 4 reports are expected to be published as a result of this long-term study's outcomes.

In fact, the interim results of the 12-month follow up have been recently peer-reviewed and published.<sup>36</sup> The authors reported that *"this long-term study confirms that regular consumption of resveratrol can enhance cognitive and cerebrovascular functions in postmenopausal women, with the potential to slow cognitive decline due to ageing and menopause."*

*"this long-term study confirms that regular consumption of resveratrol can enhance cognitive and cerebrovascular functions in postmenopausal women, with the potential to slow cognitive decline due to ageing and menopause"*

Moreover, other important conclusions were drawn from this study:

### Figure 2: RESHAW Study Design

Prof. Peter Howe, Dr. Rachel Wong, and Jay Jay Thaug Zaw

University of Newcastle, Australia

- Bone health: formation and risk of fracture
- Brain health: memory and cognition
- Menopausal symptoms: mood, sleep quality & pain perception

<https://www.anzctr.org.au/Trial/Registration/Trial-Review.aspx?id=370696>



125 postmenopausal women, 65 yrs. avg., 15 yrs. postmenopausal



24 months



2 x 75 mg Veri-te™ or placebo daily



Cognitive health, mood, perception of pain, bone health



First peer-reviewed publication indicates that Veri-te resveratrol can help counteract menopause-related cognitive decline. Additional interim data indicates: improvement in mood, perception of pain, glucose metabolism, bone loss and the risk of bone fracture. Awaiting 3 additional publications in 2020.



# Exploring Brain Health with Resveratrol

A Fresh Look into the Latest Scientific Evidence

- Statistically significant improvement in overall cognitive performance with resveratrol that is hypothesized to optimize executive function in healthy older adults and thought to delay subsequent impairment;
- Improved resting Blood Flow Velocity (BFV), stiffness in the cerebral vessels or Pulsatility Index (PI) and attenuation of decline in neurovascular coupling. Improvements in resting BFV and PI with resveratrol highlights the ability of regular resveratrol supplementation to sustain cerebrovascular function;
- Greater improvements in overall cognitive performance by resveratrol were observed when there was a lower cognitive function at baseline. Therefore,

resveratrol supplementation may be more beneficial for improving cognitive function in adults with a higher level of cognitive impairments;

- Benefits in cognition are not short-lived and can be sustained with an ongoing low-level of resveratrol supplementation for at least 12 months.<sup>36</sup>

RESHAW study has without a doubt strengthened the rationale for resveratrol supplementation in supporting a healthy aging brain.

## What is next? Gut-brain axis and systemic inflammation

### Figure 3: Gut-Brain Axis and Systemic Inflammation Study Design

Dr. Emma Wightman and Ellen Smith (PhD candidate)  
Northumbria University, UK

#### Study 1: The Effects of Resveratrol Supplementation on Cognition, Cerebral Blood Flow, Microbiota and Systemic Inflammation Design

- Gut microbiome: gut/brain axis, intestinal/systemic inflammation
- Brain health: memory, attention and mood






<https://clinicaltrials.gov/ct2/show/NCT03448094>

#### Study 2: The Effects of Resveratrol Supplementation on Cognition and Systemic Inflammation

- Brain health: memory, attention and mood
- Anti-inflammation
- Anti-oxidative stress

<https://clinicaltrials.gov/ct2/show/NCT04314739>

	110 overweight adults, 35 - 60 yrs., Body Mass Index (BMI) 25 - 42
	12 weeks
	2 x 250 mg Veri-te or placebo daily
	Cognitive assessment, cerebral blood flow, systematic inflammation, gut microbiota, metabolomics
	Completed and awaiting publication in 2020

	100 participants, 18 - 55 yrs., 4 BMI groups 18.5 - 42
	4 weeks
	2 x 250 mg Veri-te or placebo daily
	Cognitive assessment, cerebral blood flow, systematic inflammation, and dietary information
	Completion and publication expected in 2020

# Exploring Brain Health with Resveratrol

A Fresh Look into the Latest Scientific Evidence

The association between systemic inflammation and cognitive impairment has been well-documented in the literature. For instance, Lin *et al.*<sup>45</sup> investigated the extent to which systemic inflammation levels mediated age-related cognitive decline in a human clinical study. The authors observed that the levels of pro-inflammatory cytokines, IL-6 and TNF- $\alpha$ , were elevated with age in addition to cognitive measures showing age-related deficits.<sup>45</sup> Research has shown that obesity is also a significant risk factor for cognitive decline and neurodegenerative diseases. For example, strong positive correlations exist between body mass index (BMI) and Alzheimer's Disease (AD) development across various age groups.<sup>7</sup>

In this context, one of the ongoing clinical studies with Veri-te™ resveratrol is being conducted at Northumbria University (UK). The lead investigator, Dr. Emma Wightman and her PhD student, Ellen Smith, investigate the effects of resveratrol supplementation on systemic inflammation and the gut microbiota, and their effect on cognitive health (see **Figure 3**). The researchers also look into BMI and diet as factors influencing cognitive health.

This cutting-edge research will bring new insights into how resveratrol can be a key ingredient for a healthy gut and brain when combined with a balanced diet and lifestyle.

## Conclusions

Resveratrol is one of the most investigated compounds with more than 12,000 scientific publications, including 200 human clinical studies reporting benefits in several areas. Among the mechanisms of action, resveratrol is well-known for its antioxidant properties. However, it is now known that beyond its antioxidant properties, resveratrol acts as an activator of critical pathways such as SIRT-1, AMPK and mitochondrial biogenesis. These pathways are of particular interest when considering cognitive health, as discussed throughout this review.

A total of 13 human clinical studies falling within the criteria set here have evaluated the benefits of resveratrol on cognitive health. The published studies demonstrate that independent of sex or dose,

resveratrol improved the blood flow to the brain and highlighted the importance of this ingredient as a potent vasoactive molecule for young and older populations.

When considering cognitive health, there are key parameters such as age and timing of assessment that led some studies to not show significant effects. For instance, studies where young participants were recruited, did not show any significant improvement in cognitive domains. Similarly, studies that performed assessments at approximately 45 minutes after supplementation, may not have had enough time to allow the metabolites to be considered and that timing played an important role in the outcomes.

**It can be concluded that resveratrol supplementation has the potential to enhance mood and significantly decrease fatigue.**

In light of this and after a careful review of the two meta-analyses, it can be concluded that resveratrol supplementation has the potential to enhance mood and significantly decrease fatigue. Additionally, the latest research with 12 months of a low-dose of Veri-te resveratrol supplementation indicates that regular consumption can enhance cognitive and cerebrovascular functions, thereby slowing the cognitive decline due to aging and menopause. This study also provides evidence that executive function in healthy older adults can be optimized with resveratrol, as well as the delay of subsequent impairment. More importantly, these benefits are not short-lived, given the length of this study.

**More importantly, these benefits are not short-lived, given the length of this study.**

**In summary, resveratrol supplementation should be considered an essential component in supporting brain health when combined with adequate diet and exercise.**

# Exploring Brain Health with Resveratrol

## A Fresh Look into the Latest Scientific Evidence

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# Exploring Brain Health with Resveratrol

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