

# Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

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## ALSUntangled no. 49: resveratrol

### THE ALSUNTANGLED GROUP

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## RESEARCH ARTICLE

## ALSUntangled no. 49: resveratrol

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ALSUntangled reviews alternative and off-label therapies on behalf of persons with amyotrophic lateral sclerosis (PALS). Here, we review the use of resveratrol in PALS for which we have received over 550 votes (1).

**Overview**

Resveratrol is the common name for the chemical compound known as *trans*-3,5,4'-trihydroxystilbene. It can be naturally found in small quantities in wine, grapes, berries, and peanuts (2,3). Resveratrol has been studied in a myriad of human diseases including cancer, diabetes, obesity, and neurodegenerative diseases and is commonly thought to be a sirtuin activator (see “mechanisms”; 3–5). It is difficult to study *in vitro* and in cell culture due to its ability to interfere with some commonly used biochemical assays. This assay interference can potentially lead to results that falsely suggest therapeutic benefits (6,7). Therefore, we will primarily focus on evidence obtained from animal and human trials in this review.

**Mechanisms**

There are several ways resveratrol could potentially benefit PALS including modulating sirtuins, inhibiting protein aggregation, and altering the gut microbiome.

*Sirtuins*

Sirtuins are a family of enzymes we discussed in a previous ALSUntangled review (8). Sirtuin 1

(SIRT1), the best-known sirtuin deacetylates proteins, including histones, which directly regulate gene expression (9) and can consequently affect many downstream pathways that might be relevant in ALS including adenosine monophosphate kinase (AMPK), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), and heat shock factor 1 (HSF1). These pathways modulate oxidative stress (10,11), mitochondrial function (10,11) neuroinflammation (12), and protein folding (13). SIRT1 activation has been shown to be beneficial on survival in cell and animal models of one type of familial ALS (14–16). Six human trials have explored whether resveratrol can affect SIRT1 expression in blood or muscle. Four of these trials reported an increase in SIRT1 expression (17–20), but two did not (21,22). Theoretically, resveratrol would need to enter the central nervous system (CNS) to be therapeutic in ALS. Resveratrol’s chemical structure could plausibly cross the blood-brain barrier (23) and resveratrol was shown in a single human clinical trial to be detectable in the cerebrospinal fluid (CSF) following chronic oral supplementation (24,25). In the mutant SOD1 mouse model, resveratrol was shown to induce higher SIRT1 expression in the spinal cord motor neurons (26).

*Protein aggregation*

Misfolded protein aggregates, including some containing SOD1, are a well-described feature of ALS (27–29). One research group used a computer modeling program to predict that resveratrol would reduce SOD1 protein aggregates (30). Although

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Note: This paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

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this computational study is intriguing, this effect of resveratrol must be confirmed experimentally. Furthermore, even if resveratrol really does inhibit SOD1 aggregation, it is unknown if this mechanism would be clinically beneficial to PALS. Administration of a different SOD1 aggregation inhibitor succeeded in decreasing SOD1 aggregation, but this small molecule failed to produce any clinical benefit in a mouse model of familial ALS (31).

### *Gut microbiome*

It has been hypothesized that the gut microbiome may contribute to ALS pathophysiology through neurotoxins produced by cyanobacteria or clostridial species (32,33). In both a worm model and the mutant SOD1 mouse model of ALS, benefits were reported after modulation of the gut microbiome (34–36). Resveratrol has been shown to alter the fecal microbiome in rodents (37–39). It remains unclear whether resveratrol can do this in humans (40,41).

In summary, resveratrol is likely able to increase SIRT1 expression in the blood of humans and motor neurons of mice, theoretically inhibits SOD1 aggregation, and likely modulates the fecal microbiome in rodents. It is unknown if targeting any of these three mechanisms would lead to a beneficial therapeutic outcome in ALS, but all three of these discussed mechanisms are likely relevant to ALS pathophysiology. Based on the above evidence, ALSUntangled assigns resveratrol a “mechanisms” grade of B (Table 1).

### **Pre-clinical models**

Resveratrol has been studied in several cell models and the mutant SOD1 mouse model of ALS. In one study, primary cultures of rat cortical neurons were induced to express mutant SOD1. When resveratrol was applied to these cultured cells, cell survival increased from 50 to 75% of the survival of control cells (14). Another study used the motor neuron-neuroblastoma hybrid cell line known as VSC 4.1. Inducing these cells to express mutant SOD1 decreased survival to approximately 60% of the survival of control cells that did not express mutant SOD1. When resveratrol was applied to the mutant SOD1 cells, cell survival increased in a dose-dependent manner. At higher resveratrol concentrations, the cell survival rate was fully restored (42). The assay used in this study to determine cell survival may be subject to interference by resveratrol (43), which limits interpreting the results of this study. There have been several additional studies of cell culture “ALS models” that are not established pre-clinical models of ALS. We will not discuss these because it is not clear if they

Table 1. Table of evidence for resveratrol.

	Grade	Explanation
Mechanism B		In the mutant SOD1 mouse model of ALS, oral resveratrol was successful in increasing SIRT1 expression with expected changes in several downstream targets. This occurred in the motor neurons located in the lumbar spinal cord of the mice. Data from humans without neurodegenerative disease indicates resveratrol may raise SIRT1 expression, at least in the blood, but CNS-specific SIRT1 activation has not been studied.
Pre-clinical B		In several studies with the transgenic SOD1 (G93A mutation) mouse model of ALS, resveratrol was successful in slowing disease progression. There was only one study that found benefits with oral supplementation; this study was reasonably well-conducted.
Cases	C	We know of one PALS that experienced an “ALS reversal” in association with a multi-supplement cocktail that included resveratrol. We independently verified the ALS diagnosis and a substantial and sustained partial reversal of ALS disease, but it is unknown if resveratrol was a factor in this improvement.
Trials	U	There are no trials of resveratrol in ALS.
Risks	U	There is no data on resveratrol risk in PALS. Based on data from other patient populations, there is an increased risk of weight loss.

are relevant to the pathophysiology of PALS (44–47).

Three research groups have reported that resveratrol extends the lifespan of the mutant SOD1 mouse model of ALS (mice<sub>G93A</sub>) when the resveratrol was given by an intraperitoneal injection (i.e., into the abdominal cavity). This survival benefit appeared to correlate with decreased motor neuron death in the spinal cord (48–50); however, one of these studies (50) is difficult to evaluate because the resveratrol was given in combination with another experimental drug (entinostat). A fourth research group gave resveratrol by mouth to mice<sub>G93A</sub> at a similar dosage to the studies that injected resveratrol into mice<sub>G93A</sub>. They reported that this oral dose of resveratrol was not beneficial in the mutant SOD1 mouse model (51). A subsequent well-conducted study by another research group tested an oral dose that was six-times higher than the prior studies. When this higher dose was administered to mice<sub>G93A</sub>, there was a survival benefit with an associated preservation of motor neurons in the spinal cord compared with mice<sub>G93A</sub> that did not receive resveratrol (26,52). Based on the above evidence, ALSUntangled assigns a TOE “pre-clinical models” grade of B (Table 1).

## Cases

On the online community PatientsLikeMe, 21 PALS report taking resveratrol, of which, eight PALS rated their perceived efficacy. One reported “no efficacy,” two reported “moderate efficacy,” and five reported “can’t tell”. All eight PALS reported no side effects (53). We did not have records to verify the diagnosis or efficacy for these eight PALS. We do know of one PALS that had an “ALS reversal” on a multi-supplement cocktail that included resveratrol. For this case of an “ALS reversal,” we independently verified the diagnosis and a “sustained and substantial improvement” (54). It is unknown if resveratrol contributed to these benefits. Based on the above evidence, ALSUntangled assigns a TOE “cases” grade of C (Table 1).

## Trials

We found no past or on-going trials of resveratrol in patients with ALS. Therefore, ALSUntangled assigns a TOE “trials” grade of U (Table 1).

Recently, there was an ALS pilot trial of an experimental drug (EH301) that has the same two ingredients as Elysium’s “Basis,” which we previously reviewed (8). These ingredients are a chemically modified form of resveratrol (pterostilbene) and a form of B3 (nicotinamide riboside). It is thought that this combination may also activate SIRT1 cellular pathways. After four months of treatment, the PALS taking EH301 had statistically significant improvements in ALS functional rating scale – revised (ALSFRS-R) scores, forced vital capacity (FVC) respiratory testing, and manual muscle testing relative to PALS taking a placebo (55). Interpretation of these results is limited by the small sample size, short duration, imbalances between treated and control groups after randomization, lack of intention-to-treat analyses, and authorship by members of the company that owns the product (56,57).

Of potential interest, there has been a 12-patient pilot trial of resveratrol in hereditary spastic paraplegia type 5 (HSP; a genetic disease that affects the axons of upper motor neurons). There was no observed benefit of resveratrol; however, the only outcome measure was an HSP biomarker (58). There have also been three double-blind randomized placebo-controlled trials of resveratrol in Alzheimer’s disease (a type of dementia). Two of these trials (24,25,59) suggested that resveratrol might help preserve cognition but the third was inconclusive (60).

## Risks

As mentioned above, there is little available data on resveratrol in PALS. In other populations,

clinical trials using doses under 500 mg per day report very few adverse events. Trials using doses above 500 mg per day report mild- to moderate-severity gastrointestinal side effects including diarrhea, nausea, and weight loss in 30–75% of participants (24,61,62). A trial in patients with multiple myeloma reported the serious adverse event of renal toxicity (i.e. kidney injury) in more than 10% of treated participants (63). It is unclear how these data will translate to PALS; weight loss could accelerate ALS disease progression (64). Based on the lack of data in PALS, ALSUntangled assigns a TOE “risks” grade of U (Table 1).

## Dosing and costs

Resveratrol supplements are widely available as capsules to be taken by mouth. They are manufactured in a variety of doses, typically 200–500 mg per capsule. Some manufacturers claim that combining resveratrol with the natural flavanol called quercetin may increase resveratrol’s bioavailability; however, data from a pharmacokinetic study in humans indicated that quercetin has no substantial effect on resveratrol blood levels (62).

There has not been any resveratrol dosing regimen studied in PALS. One of the AD trials described above utilized 1000 mg twice daily (2000 mg total daily dose). CSF taken from the patients in this trial contained detectable resveratrol (24,25). This is the only clinical trial we could find that assayed the levels of resveratrol in the CSF; therefore, it is unknown if lower dosages would lead to detectable levels of resveratrol in the CNS. If taking 1000 mg twice daily, the cost would be approximately \$15 per month on Amazon.com.

## Conclusions

Resveratrol is a dietary supplement that likely activates SIRT1 cellular pathways and may alter the gut microbiome. These are interesting mechanisms that may potentially alter the progression of ALS and do confer benefit in animal models of one type of familial ALS; however, to-date, there have been no trials of resveratrol in PALS. Some trials in other populations show frequent gastrointestinal adverse events, including weight loss, and one trial showed a high risk of serious renal toxicity. Given the unknown benefit of resveratrol in PALS and the possible risks, we cannot recommend resveratrol as an ALS treatment at this time. We hope to see well-designed clinical trials of resveratrol and other SIRT1 modulators in the near future.

**Declaration of interest**

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