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Effects of 90 Days of Resveratrol Supplementation on Cognitive Function in Elders: A Pilot Study

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Abstract

Objective: The purpose of this trial was to study the effects of chronic resveratrol use on cognitive function in humans.

Design: The authors conducted a double-blind, Phase IIa randomized, placebo-controlled trial to obtain preliminary estimates of the effects of resveratrol supplementation on cognitive function over a 90-day period in older adults.

Location: University of Florida in Gainesville, FL.

Subjects: Sedentary, overweight older adults ($N = 32$; age range: 65–93 years, M age = 73.34 years, SD age = 7.02 years).

Intervention: Participants were randomized to one of three treatment groups (placebo, 300 mg/day resveratrol, 1000 mg/day resveratrol) for 90 days.

Outcome measures: Cognitive function was assessed before and after treatment using a well-characterized test battery: Trail Making, Digits Forward and Backward, Erikson-Flanker, Controlled Oral Word Association, Hopkins Verbal Learning Test-Revised, and Task Switching.

Results: Psychomotor speed improved on the Trail Making Test part A in participants taking 1000 mg/day of resveratrol compared with participants in both the 300 mg/day condition and the placebo condition ($p = 0.02$).

Conclusion: This pilot study suggests that 90 days of resveratrol supplementation at a dose of 1000/mg per day selectively improves psychomotor speed but does not significantly affect other domains of cognitive function in older adults. These findings provide modest support to further study the effects of resveratrol on cognitive function in older adults.

Keywords: brain, polyphenol, aging, performance, botanical, nutrient, processing speed

Introduction

Aging is associated with a decline in memory, executive functioning, attentional capacities, and processing speed.[1,2] The etiology of these age-associated losses is complex and multifactorial, but at least one set of factors seems related to cardiovascular function.[3] Cardiovascular risk factors (i.e., hypertension, dyslipidemia, diabetes, and obesity among others) have been associated with cognitive decline and dementia risk[4] by possibly promoting microvascular disease[5] and contributing

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to neuronal degeneration and hypoperfusion.[6] Another set of factors related to cognitive aging appears to be oxidative stress in neuronal cells. Higher levels of oxidative stress have been observed in overweight adults.[7,8] As such, overweight and obese older adults represent a population at higher risk for cognitive decline due to the adverse effects of excess body weight on oxidative stress,[9] inflammation,[10] and vascular function.[11]

Few therapies have been identified to treat cognitive decline or improve cognitive performance in older adults. The older adult segment of the population is steadily increasing in the United States and other industrialized nations.[12] This demographic change brings with it a growing number of individuals at risk for cognitive decline than at any time in history. Thus, new therapies are urgently needed to preserve cognitive function and reduce risk of cognitive decline in older adults, particularly among adults 65 years and older. Resveratrol, a natural polyphenol found mainly in red wine and dark-skinned grape cultivars, has potent antioxidant activity[13,14] and accumulating evidence indicates that resveratrol may have neuroprotective effects.[15,16] In particular, resveratrol has been found to attenuate hippocampal cell death, reduce intracellular reactive oxygen species,[17] and protect against excitotoxic brain damage; all of which contribute to the accelerated declines in cognitive function.[16] Resveratrol has also been shown to protect neurons against accumulation of a neurotoxic peptide that appears to play a critical role in the neuropathology of Alzheimer's disease (AD), amyloid β-peptide (Aβ).[18]

The effects of resveratrol on cognition in humans are currently not well understood, but there is emerging evidence that it could have direct effects on brain physiology. In an acute study, resveratrol at doses of 250 mg and 500 mg was found to increase cerebral blood flow to the frontal cortex in healthy young men during task performance on a variety of cognitive tests in a dose-dependent manner.[19] However, these physiologic changes were not reflected in changes in cognitive task performance. More recently, a study by Wong et al. found that a single dose of either 75 mg or 300 mg of resveratrol enhanced performance on a multitasking test battery in participants with type 2 diabetes.[20]

Only a few studies have looked at the effects of chronic resveratrol supplementation on cognitive performance. A study by Witte et al. demonstrated that a dietary supplement containing resveratrol (200 mg/day) combined with quercetin (320 mg/day) resulted in a significant improvement in word retention over a 26-week period in healthy older adults, using a quasi-experimental (i.e., pairwise matched), double-blind, and placebo-controlled design.[21] In addition, resting-state functional connectivity between the hippocampus, a region critical for memory functions, and other brain regions was also significantly increased in the resveratrol group (compared to the placebo group) and was correlated with improvements in word retention scores.[21] Wightman et al. found that supplementation with 500 mg of resveratrol over a 28-day period in young adults significantly improved performance on the N-Back test; other domains of cognitive function, however, did not improve.[22] More recently, Lee et al.[23] found that a grape formulation, but not placebo, protected against longitudinal changes in cerebral metabolism over a 6-month period in a small sample of older participants experiencing mild cognitive decline. In addition, Kobe et al.[24] found that resveratrol supplementation (200 mg/day) was effective in improving hippocampal resting-state functional connectivity and preserving hippocampal volume in patients with mild cognitive impairment. No significant changes in memory, however, were observed.

The present study provides experimental data from a pilot randomized controlled trial on the effects of short-term (i.e., 90 days) resveratrol administration on cognitive outcomes in sedentary, overweight older adults (age ≥65 years). Based on preclinical findings,[25,26] the authors hypothesized that resveratrol supplementation, compared with a placebo, would enhance cognitive performance in this population, and that higher doses of resveratrol (i.e., 1000 mg/day) would enhance cognitive performance to a greater degree than lower doses (i.e., 300 mg/day).[27]

Materials and Methods

Participants

A total of 32 healthy, community-dwelling, overweight older adults (79 ± 14 years) participated in this study. Eligible participants were sedentary (less than 120 min of moderate intensity physical activity per week),[28] nonsmokers, with a self-reported ability to walk one mile, and a body mass index (BMI) between 25 and 34.9 kg/m^2. To be eligible, participants needed to score above 24 on the Mini-Mental Status Examination (MMSE) to ensure a cognitively intact sample. Table 1 provides detailed information on study eligibility criteria and Table 2 summarizes participant demographic and health information by treatment group.

Participants were randomized to one of three treatment groups (placebo: $n = 10$, low-dose resveratrol (300 mg/day): $n = 12$, high-dose resveratrol (1000 mg/day): $n = 10$), with equal numbers of women and men assigned to each treatment group. Detailed study procedures, including the participant flow diagram, have been described previously.[29]

Study design and procedure

This study was approved by the University of Florida's Institutional Review Board. Participants were recruited from September 2006 through December 2008. After obtaining informed consent, data were collected at the University of Florida's Aging & Rehabilitation Research Center.

The study was a double-blind, Phase IIa randomized, placebo-controlled trial designed to determine the efficacy of resveratrol supplementation on various components of cognitive functioning in older adults. Eligible participants were randomly assigned to one of the three treatment groups, with a randomized block design by gender for a period of 90 days. Participants were instructed to orally consume one capsule of resveratrol or placebo twice a day with their morning and evening meal (total daily dose = 300 mg or 1000 mg). The study product was provided by Reserveage Organics and contained naturally derived resveratrol from grapes and wild Japanese Knotweed (*Polygonum cuspidatum*). Microcrystalline cellulose was used for the placebo. Adherence to the intervention was determined based on pill counts at monthly study visits.

Cognitive measures were assessed at baseline and post-treatment (~90 days). Study visits occurred in the mornings typically between the hours of 9–11 am at the University of Florida's Institute on Aging and Rehabilitation's Research

Table 1. Participant Inclusion/Exclusion Criteria

Inclusion criteria	*Exclusion criteria*
Age 65–100 years old	Active treatment for cancer, stroke (<6 months), peripheral vascular disease, coronary artery disease (myocardial infarction <6 months), stage III, IV CHF, valvular heart disease, severe anemia, liver or renal disease, diabetes, severe osteoarthritis, fracture in extremity ≤6 months, extremity amputation
BMI 25–35	CBC values and CMP values not cleared by physician
Report of ability to walk one mile	Anabolic medications or Anticholinesterase inhibitor; Anticoagulant therapy (aspirin use permitted); Statin use
MMSE >24	History of significant head injury; Vision or hearing impairment
C-reactive protein levels ≥1.0 mg/L	Dementing illness, major psychiatric disease, Parkinson's Disease
Nonsmoker	Excessive alcohol use (>2 drinks/day) or >1 glass of red wine or purple grape juice/week
	Blood pressure >180/100 mmHg; Resting heart rate >120 bpm
Sedentary lifestyle (<120 min of aerobic activity/week)	Aerobic physical activity (i.e., running, bicycling, etc.) >120 min per week
Willing and able to participate in all aspects of the study	Failure to give consent
Willing to be randomized to either treatment group	Consumption of any dietary supplements containing resveratrol, quercetin, grape seed extract, ginko biloba, or *P. cuspidatum* in the previous 90 days
	Participation in another clinical trial or intake of an investigational product ≤30 days before screening/enrollment
	CES-D >20; Current use of an antidepressant
	Contraindications to MRI (e.g., cardiac pacemaker, implanted cardiac defibrillator, aneurysm clip, claustrophobia, etc.)

BMI, body mass index; CBC, complete blood count; CMP, complete metabolic panel; MMSE, Mini-Mental Status Examination.

Center. Participants were instructed to consume the study product with a glass of water 30 min before arriving at the Research Center for all visits. Following a fasting blood draw, participants were provided with a snack before completing the cognitive test battery. This test battery (detailed in the Cognitive test battery section below) took ~1 h to complete and was used to assess cognitive performance across various cognitive domains, including visual attention, working memory, verbal fluency, semantic memory, and processing speed.

Cognitive test battery

Controlled oral word association. This task measures verbal fluency. Participants were asked to generate as many

Table 2. Baseline Demographic Variables and Cognitive Measures

Demographic variables	*Placebo M (SD)*	*Low-dose M (SD)*	*High-dose M (SD)*	p-*Value*
Age (years)	73.30 (2.06)	73.17 (2.08)	73.60 (2.53)	0.97
Caucasian (*n*,%)	9 (90)	12 (100)	10 (100)	0.32
Females (*n*,%)	5 (50)	6 (50)	5 (50)	1.00
BMI (kg/m^2)	29.74 (0.62)	29.84 (0.60)	29.03 (1.00)	0.88
Cognitive measures				
Controlled oral word association (words generated)	33.90 (10.87)	35.92 (12.89)	36.30 (9.12)	0.87
Digits forward and backward (total score)	15.67 (4.77)	15.08 (3.67)	17.30 (2.49)	0.38
DSST(number correct)	44.90 (6.89)	41.00 (14.52)	49.40 (10.81)	0.25
Eriksen Flanker task (incongruent RT–congruent RT)[a]	61.25 (29.55)	52.94 (49.51)	61.75 (42.71)	0.95
HVLT–Recall (number correct)	37.40 (8.50)	35.25 (13.86)	39.10 (12.96)	0.76
HVLT–Discrimination index (number correct minus number incorrect)	18.60 (4.06)	20.42 (2.81)	18.70 (4.35)	0.44
Task switching	115.8 (4.61)	118.30 (1.57)	109.50 (20.63)	0.27
Accuracy reaction time–No Switch (in ms)[a]	871.98 (545.32)	1340.85 (1593.53)	466.83 (182.6)	0.16
Reaction time–Yes Switch (in ms)[a]	1108.34 (539.21)	1630.0 (1651.27)	676.32 (249.7)	0.13
Trail making test A (s)	44.70 (15.46)	39.62 (17.36)	45.92 (14.37)	0.61
Trail making test B (s)	76.58 (22.41)	120.13 (86.55)	77.94 (13.82)	0.13
MMSE (number correct)	27.70 (0.47)	27.67 (0.63)	28.80 (0.29)	0.17
CES-D (total score)	6.60 (2.04)	7.33 (1.33)	6.80 (2.02)	0.75

[a]Median was reported.
MMSE, Mini-Mental Status Examination.

words as possible beginning with the specific letters F, A, and S within 60 sec each. The authors calculated the total number of words generated across letters as a measure of verbal fluency.[30]

Digits forward and backward. This task from the Wechsler Adult Intelligence Scale-IV WAIS-IV[31] measures immediate auditory attention (forward) and working memory (backward). Participants were orally presented with a series of numbers, which they were asked to repeat in the same (forward) or in reverse (backward) order as presented. The number correct for both digits forward and backward combined was used as the outcome measure.

Digit symbol substitution test. This measure of attention and processing speed from the WAIS-IV[31] required participants to match symbols and numbers as fast as possible, within 90 sec through a written response. The outcome measure was the total number of correct matches made.

Eriksen flanker task. This task measures response inhibition as a facet of executive function. Participants were presented with a target arrow facing either right or left and were asked to press a key indicating the direction of the arrow. The displays on each trial were either neutral (no flankers), congruent (flanker arrows pointing in the same direction as the target arrow), or incongruent (flanker arrows pointing in the opposite direction as target arrow). The outcome (response inhibition) measure was calculated as incongruent response time (RT in ms) minus congruent RT (i.e., response inhibition RT = incongruent RT–congruent RT).[32]

Hopkins verbal learning test-revised. This test assesses verbal learning, recognition memory, and recall. The test required recall of a series of 24 words over three learning trials, free recall after a 20 min delay, and a recognition trial. The word lists were presented orally to participants at a rate of one word every 2 sec. During the recognition trial, a list of 48 words was presented to participants, including all of the learned words and 24 false-positive words; half of which were semantically related to the learned words and half of which were not semantically related. The main outcome was the number of correctly recalled words over the first three learning trials and following delay. The authors also calculated a recognition discrimination index by subtracting the total number of false positives from the number of accurate positive responses.[33]

Task switching. This task measures attentional flexibility, more specifically, processes of preparation and interference control. The paradigm involved the performance of two simple tasks: deciding whether a letter was a vowel or a consonant or deciding whether a number was odd or even. In one condition (i.e., nonswitch trials), the same task was repeated a number of times. In a second condition (i.e., switch trials), participants were asked to switch between the two tasks. The outcome measures included both accuracy and RT, which was calculated as the extra time (in ms) required to perform switch trials compared to nonswitch trials (i.e., switch cost RT = switch trial RT - nonswitch trial RT), independent of task accuracy.[34,35]

Trail making test. This test measures psychomotor speed/sequencing (Trails A) and visual seeking and cognitive alternation or switching abilities (Trails B). Thus, these tests were treated as two independent outcomes. In the Trails A task, participants were asked to connect numbers in sequential order as fast as possible. In the Trails B task, participants were asked to connect numbers and letters in sequential order in an alternating pattern (1-A-2-B-3-C, etc.) as fast as possible. Task duration in seconds was monitored as the central outcome measures, respectively, for Trails A and B tasks.[36]

Statistical methods

The authors used intention to treat analyses, such that participants' outcomes were compared based on their randomized groups regardless of their compliance to the intervention. Change from baseline was defined as the value at time *t* (posttreatment; 90 days) minus the value observed at baseline for all response measures. Analysis of covariance was used to test if performance on each cognitive measure varied as a function of the two different treatment conditions (active (300 or 1000 mg/day of resveratrol vs. placebo). Change from baseline (90-day score minus baseline score) was the dependent variable and baseline scores on each measure, as well as age, gender, and BMI were covariates. *Post hoc* analyses of means were conducted. All analyses were carried out using SPSS version 22 software package.

Results

Participants did not differ on demographic or most health-related variables, although there was a trend for participants assigned to the high-dose group to have a lower prevalence of hypertension compared with participants in the placebo and low-dose groups. Participants' baseline demographic and health information have been previously reported by Anton et al.[29]

Participants in all conditions had high adherence rate (93% in each condition), as measured by pill counts at monthly visits. Rates of adverse events did not differ by condition.[29] Treatment groups did not differ at baseline on any demographic measure or performance on the cognitive measures (all *p-values* > 0.05; Table 2). A significant treatment group effect for psychomotor speed as measured in the Trail Making Test A was observed, with greater performance improvement in the high-dose group than the low-dose and the placebo group (Fig. 1). However, there were no significant differences in performance on tests of visual attention, working memory, verbal fluency, and semantic memory across treatment groups (Table 3).

Discussion

This study examined the effects of resveratrol supplementation at both a 300 mg and 1000 mg daily dose, compared with placebo administration, over a 90-day period on various cognitive ability measures in an overweight, older adult population. The key finding of this pilot study was that resveratrol supplementation at a dose of 1000 mg/day compared with low-dose (i.e., 300 mg/day) and placebo conditions selectively increased psychomotor processing speed from baseline to 90 days posttreatment. Other domains of cognitive

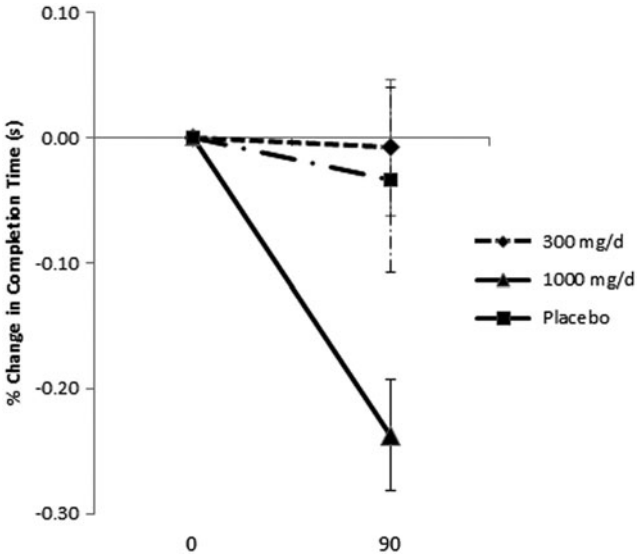

FIG. 1. Change in time to complete Trails Making Task A.

functioning, however, including attention, working memory, response inhibition, verbal fluency, and semantic memory were not significantly affected by the intervention across treatment groups. Word recall, as measured by the HVLT-R, did show a large improvement (30% increase), although not statistically significant, than in the low-dose (300 mg/day) condition. Thus, the findings of this pilot study suggest that resveratrol supplementation at a dose of 1000 mg/day may enhance psychomotor speed, but may not affect other aspects of cognitive function in an overweight, older adult population.

There is also growing body of evidence indicating that obesity and increased adiposity can have detrimental effects on cognitive function and brain health.[37] Older adults with obesity appear to be at particularly high risk of cognitive decline and memory conditions, including AD and other dementias.[38,39] Moreover, mild cognitive impairment and AD have been associated with impaired cerebrovascular responsiveness, ability of cerebral vessels to dilate during cognitive demands.[40]

The underlying mechanisms of action of resveratrol on cognitive function are not well understood yet in humans. In preclinical models, resveratrol has been found to activate a cascade of molecular events that impact vascular function, including vasodilation, and increased cerebral blood flow, which could have an effect on psychomotor processing speed.[41,42] In line with this work, acute resveratrol administration has been shown to increase cerebral blood flow in humans in a dose-dependent manner.[19] This evidence combined suggests that the effects of resveratrol on cognition may be, at least partially, mediated by putative increase in cerebral blood flow. Thus, an increase in cerebral blood flow may be one explanation for why in the present study the higher dose was more effective than the lower dose in increasing performance on the Trails A test, a measure of psychomotor processing speed. Further supporting this speculation, recent studies have shown that chronic resveratrol administration over a 14-week period significantly improved cerebrovascular responsiveness.[43] In addition, resveratrol's antioxidant activity may be linked to improved cognitive performance.[30,31]

Few therapies have been identified to treat cognitive decline or improve cognitive performance in older adults. Even fewer have been shown to specifically target

Table 3. Change in Performance (Baseline to 90 Days) on Cognitive Measures Between Groups

	Placebo M (SD)	*Low-dose M (SD)*	*Cohen's d (effect size)*	*High-dose M (SD)*	*Cohen's d (effect size)*	p-*Value*
Controlled oral word association (Words generated)	4.50 (5.28)	2.42 (7.43)	0.4 (0.2)	3.90 (7.09)	0.2 (0.1)	0.67
Digits forward and backward	1.56 (2.92)	0.08 (2.07)	0.58 (0.3)	–0.70 (2.79)	0.8 (0.4)	0.20
DSST correct	4.70 (2.67)	6.25 (10.14)	0.2 (0.1)	8.90 (8.13)	0.7 (0.3)	0.64
Eriksen flanker task (incongruent RT–congruent RT)[a]	–7.70 (25.93)	5.72 (61.6)	0.3 (0.1)	–9.83 (33.9)	0.07 (0.04)	0.48
HVLT–Recall (number correct)	2.10 (6.33)	8.33 (15.04)	0.5 (0.3)	1.80 (8.57)	0.04 (0.02)	0.46
HVLT–Discrimination index (number correct minus number incorrect)	1.50 (2.46)	–0.17 (2.08)	0.7 (0.3)	0.00 (2.54)	0.6 (0.3)	0.25
Task switching						
Accuracy	0.56 (6.06)	–1.60 (4.03)	0.42 (0.21)	8.22 (20.70)	–0.50 (–0.24)	0.77
Reaction time no switch (in ms)	–325.22 (320.31)	–328.00 (350.37)	0.01 (0.004)	5.72 (185.10)	–1.27 (–0.53)	0.13
Reaction time yes switch (in ms)	–463.22 (363.73)	–633.35 (333.46)	0.49 (0.24)	34.11 (682.48)	–0.91 (–0.41)	0.13
Trails A time (s)	–2.99 (10.87)	–1.19 (7.94)	0.1 (0.06)	–11.78 (8.64)	0.97 (0.4)	0.02
Trails B time (s)	1.29 (28.24)	4.76 (26.93)	0.1 (0.06)	6.31 (30.61)	0.2 (0.08)	0.77

[a]Median was reported.

psychomotor processing speed. One notable exception was the speed of processing intervention, which presented increasingly more complex information in successively shorter inspection times, tested in the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial.[44] The ACTIVE trial was specifically designed to examine the extent to which cognitive training interventions (memory, reasoning, and speed of information processing) could affect cognitively based measures of daily functioning. Ten years following these interventions, cognitive function for the majority of participants who received the speed-of-processing intervention, was at or above their baseline level for this cognitive ability but not for any of the other cognitive abilities.[45] This suggests that the effects of cognitive training interventions are specific to the cognitive ability trained. Other treatment modalities that enhance cerebral blood flow, such as exercise, may also improve psychomotor processing speed, but to date the empirical evidence from clinical trials supporting this effect is still limited.

The findings of the present study differed from the findings of Witte et al. who found significant effects on word retention following 26 weeks of resveratrol administration. It is noteworthy, however, that the low-dose condition (i.e., 300 mg/day), which was very similar to the dose of resveratrol tested in the Witte et al. study (i.e., 200 mg/day), did show a large (30% increase), although not statistically significant, improvement in word recall as measured by the HVLT-R. There are a number of potential reasons for why the authors did not observe statistically significant effects for word recall in their study. First, the small sample size of this pilot study may have limited their ability to detect statistical significance. Another possibility is that the effects on memory performance observed in the Witte et al. study were due, in part, to the quercetin contained in their study product, (200 mg/day of resveratrol and 320 mg/day of quercetin), which the authors' product did not contain. Differences in the age range of the participants across the two studies may have also contributed to the differences in findings. In Witte et al., the mean age of participants was $\sim$63 years. Participants in this study were, on average, 10 years older, with a mean age of 73 years.

The present study had some weaknesses that limit the generalizability and interpretation of the results. The sample size and the very homogenous composition of the sample in terms of race/ethnicity did not provide adequate power to examine differences in response to the intervention between men and women and/or as a function of race/ethnicity. This study only informs about the effects of 90-day resveratrol supplementation and thus does not inform about effects over a longer administration period. The selected participant sample limits the generalizability of the findings to sedentary, overweight older adults. This population was selected because obesity has been found to increase risk of functional decline during aging,[7,8] and findings from preclinical models suggest that resveratrol may have more pronounced effects in overweight animals.[46] In addition, the study product tested was a resveratrol-containing product, which was comprised primarily of resveratrol but also included grape polyphenols. Thus, the authors cannot rule out that the effects were due to resveratrol alone and not the other polyphenols in the blend, or perhaps the synergy of the ingredients.

The present study had a number of strengths. Few studies have tested the effects of resveratrol in an older adult population. Thus, the findings from this research contribute to the small but growing body of research on the effects of resveratrol on cognition. Importantly, this study provides preliminary evidence that high doses of resveratrol may improve select aspects of cognitive functioning in adults aged 65 years and older. The testing of two doses of resveratrol represents an important design feature, given that an optimal dose of resveratrol for specific populations is currently unknown. An additional strength of this study was the inclusion of equal numbers of men and women in each treatment condition, which allowed for examination of a more diverse sample.

Conclusions

The findings of this 90-day pilot study indicate that resveratrol supplementation at a dose of 1000 mg/day selectively increased psychomotor speed compared to both placebo and a resveratrol dose of 300 mg/day. The authors did not observe significant effects in other domains of cognitive function, however, in the sample of sedentary, overweight older adults. Overall, the findings of this study provide modest support and effect sizes needed for further study of the effects of resveratrol on specific aspects of cognitive function in older adults.

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Author Disclosure Statement

Dr. Anton previously served as a scientific advisor and as a consultant for Reserveage Organics, the provider of the resveratrol product used in this trial. All findings and views expressed in this article are those of the authors and do not necessarily reflect the views of the Company. All other authors declare no conflict of interest.

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