The effects of quercetin supplementation on cognitive functioning in a community sample: a randomized, placebo-controlled trial

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Abstract:
Background: The purpose of the present study was to examine the effects of quercetin supplementation on neurocognitive functioning.
Methods: A large community sample (n = 941) completed a 12-week supplementation protocol, and participants were randomly assigned to receive 500 mg/day or 1000 mg/day quercetin, or placebo.
Results: Results failed to indicate significant effects of quercetin on memory, psychomotor speed, reaction time, attention, or cognitive flexibility, despite large increases in plasma quercetin levels among the quercetin treatment groups.
Discussion: Consistent with recent research, this study raises concerns regarding the generalizability of positive findings of *in vitro* and animal quercetin research, and provides evidence that quercetin may not have an ergogenic effect on neurocognitive functioning in humans.

Keywords: attention, cognition, ergogenic, memory, performance, quercetin

Introduction

In recent years, there has been a proliferation of research aimed at examining the potential physical and psychological benefits of specific natural food substances and nutritional supplements. One focus of this research has been on the health-enhancing properties of flavonoids, a class of secondary metabolites of plants found in many fruits and vegetables. Flavonoids have been shown to possess numerous health-enhancing properties in laboratory animals, including vasodilation, anticarcinogenic, anti-inflammatory, immune-stimulating, and antiallergic effects [e.g. Comalada *et al.* 2005; Davis *et al.* 2008; Harwood *et al.* 2007; Neuhouser, 2004].

Much of the research examining the positive effects of flavonoids has focused on quercetin, which is widely distributed in fruits and vegetables [Manach *et al.* 2005]. Quercetin has been shown in several *in vitro* studies to be a potent antioxidant, capable of scavenging free radicals and protecting neuronal cells from neurotoxicity caused by oxidative stress [e.g. Cho *et al.* 2006; Heo and Lee, 2004]. Quercetin is also an adenosine A1 receptor antagonist *in vitro* [Alexander, 2006], suggesting that it may reduce physical and mental fatigue. Indeed, animal research has suggested that quercetin may enhance spatial memory [Priprem *et al.* 2008] and even reverse cognitive deficits in aged and ethanol-intoxicated mice [Singh *et al.* 2003]. In addition, mice administered quercetin supplements have been shown to exhibit increased learning and memory functioning in comparison to nontreated mice [e.g. Liu *et al.* 2006; Lu *et al.* 2006]. Thus, taken together, *in vitro* and animal research appears to suggest that quercetin may possess neuroprotective properties and enhance cognitive functioning.

Despite the promising results of *in vitro* and animal studies of quercetin, research on the potential neuroprotective and cognitive-enhancing properties of quercetin in human samples is largely absent. In an unpublished study (The effects of quercetin supplementation on reaction time after intense prolonged exercise, Rocheleau, Penwell, Huelsman and Nieman), 36 trained cyclists who received either 3 weeks of quercetin supplementation (1000 mg) or placebo completed a 3 h cycling protocol (~57% W) over 3 consecutive days. Participants completed a

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Psychomotor Vigilance Task prior to and following cycling each day. The results indicated that participants who received placebo demonstrated a slowing of reaction times from pre to post cycling on day 2 ($p = 0.08$) and day 3 ($p = 0.04$), whereas the quercetin supplementation group did not demonstrate such slowing. These findings provide qualified support for a neuroprotective effect of quercetin in a human sample.

In the only published study to examine the effects of quercetin supplementation on human cognitive functioning, Olson and colleagues compared the immediate effects of 2000 mg of quercetin on vigilance and mood with those produced by 200 mg of caffeine or placebo [Olson *et al*. 2010]. One hour after ingestion of their relative treatment, 57 participants completed a 45 min vigilance task. The results indicated that participants ingesting caffeine outperformed those receiving placebo on the vigilance task. Although analyses failed to detect a significant effect of quercetin on vigilance, the authors noted a trend with participants that had consumed quercetin performed somewhat (though not statistically significant) better than participants who received placebo. Based on these findings, the authors concluded that quercetin is unlikely to generate significant effects on cognitive functioning when ingested in quantities typically found in human diets or dietary supplements. However, the long-term effects of quercetin supplementation were not investigated and remain unknown.

The purpose of the present research was to extend previous research by examining the effects of 12 weeks of quercetin supplementation on several cognitive performance tasks in a large community sample of adults. In addition, based on previous animal research suggesting that quercetin can reverse cognitive deficits in aged mice [Singh *et al*. 2003], separate analyses were conducted to examine the effects of quercetin supplementation on participants over the age of 60. Based on previous research, it was predicted that participants who ingested large doses of quercetin would demonstrate enhanced performance on cognitive tasks.

Methods

Participants

A large community sample of 1002 (60% women) residents from western North Carolina were recruited to participate in this study by mass advertising. Of the 1002 recruited, 941 completed full study requirements, which included cognitive testing at baseline and post treatment. Participants ranged in age from 18 to 85 [mean = 45.96; standard deviation (SD) = 16.27] and were stratified by age during recruitment to ensure representation from various age ranges: 40% were young adults (18–40), 40% were middle age (41–65), and 20% were older age (66–85) adults. Participants were also stratified by body mass index (BMI) to include 33% normal BMI (18.5–24.9), 33% overweight (25–29.9), and 33% obese (30 or more). Women who were pregnant or lactating were excluded from the study. The majority of participants had completed a high-school education (97.7%), and approximately half had earned a college degree (56%). Racial and ethnic backgrounds represented included 95% white, 1.8% African American, and 3.2% other. Participants agreed not to consume any other supplements containing quercetin during the 12-week study. No other restrictions were placed on diet or medication/supplement usage. This study complied with all relevant American Psychiatric Association ethical standards for the treatment of human subjects, and the informed consent process and research design received approval from the Institutional Review Board at Appalachian State University.

Instruments

Central Nervous System Vital Signs. Central Nervous System (CNS) Vital Signs is a computerized test battery that is composed of seven tests that are widely used in psychological assessment and have demonstrable reliability and validity (see Gaultieri and Johnson [2006] for a review). Subtests include verbal and visual memory, finger tapping, digit-symbol coding, the Stroop test, a shifting attention test, and a continuous performance test. The seven tests are used to derive five domain scores representing: memory, psychomotor speed, reaction time, complex attention, and cognitive flexibility. Research suggests that the reliability and concurrent/discriminant validity of CNS Vital Signs tests are comparable to the traditional tests upon which they are based [Gaultieri and Johnson, 2006].

Procedure

Participants were randomly assigned to one of three supplement conditions: 500 mg of quercetin per day, 1000 mg of quercetin per day, or

placebo. Two weeks prior to their first lab visit, participants completed online demographic and psychological questionnaires via Surveymonkey.com. At baseline assessment, participants reported to the laboratory session between 7 and 9 a.m., and height and body composition measurements were taken. Blood samples were taken from participants, who were required to have completed overnight fasting. Participants then reported to a computer lab (containing 34 computers) to complete computerized cognitive testing via the CNS Vital Signs program. Laboratory access was limited to the research study during the testing periods, and research staff (at least one of the first two authors and at least two assistants) were present at all times to aid the participants as needed. Participants were seated in front of a computer and instructed that they would be completing a series of seven brief subtests. Participants were informed that the directions were different for each subtest, and they should pay close attention to the directions for each. Participants were also informed that a research assistant would be available to respond to questions or clarify tasks, and that if they had questions, they should ask prior to beginning the subtest because once the subtest began it could not be paused and assistance would be unavailable during the test. Participants were generally able to complete the CNS Vital Signs battery within 30 min. Following completion of baseline cognitive testing, participants were provided with their supplements. Supplements (quercetin or placebo) were administered under double-blind conditions, and participants were directed to ingest two soft chews on awakening and two chews between 2 p.m. and dinner for 12 weeks. Supplements were prepared by Nutravail Technologies (Chantilly, VA, USA) with Quercegen Pharma (Newton, MA, USA).

Participants were monitored at monthly intervals during the study to ensure compliance with their supplement regimen. Each month, participants completed a series of questionnaires via an online survey tool, including items that evaluated the extent to which they had completed the study protocol as directed.

Following the 12-week supplementation regimen, participants were re-evaluated using a protocol identical to baseline assessment, including completing physiological measures, having blood samples taken following overnight fasting, and completion of the CNS Vital Signs test battery. Following completion of CNS Vital Signs testing at post treatment, participants were dismissed from the study.

Data analysis

The effects of quercetin on cognitive functioning were assessed using separate group by assessment session (3 × 2) mixed model analyses of variance (ANOVAs). If violations of the sphericity assumption were detected, significance tests were also conducted using the Greenhouse–Geisser correction method. Corrected and uncorrected analyses produced the same pattern of significant and nonsignificant effects. Therefore, to simplify data presentation, uncorrected *df*s are reported. Because multiple omnibus ANOVAs were conducted, Bonferroni corrected p values were used ($p = 0.01$) to assess main effects and interaction terms. Significant interactions were analyzed by examining within-group simple effects, also corrected for number of analyses performed, followed by *post hoc* mean comparisons using Tukey's honestly significant difference (HSD) procedure. Effect sizes were reported using partial eta squared (η_p^2), which represents effect size as a function of the total variance accounted for by the independent variable. All analyses were conducted with and without outliers (i.e. participants earning a scaled score below 50 on any of the domains). The significance of results did not differ based on whether outliers were included. Thus, to ease interpretation, all analyses presented were conducted on the full sample.

Results

Preliminary analyses

Independent t tests and chi-square analyses indicated that the three groups were comparable at baseline on all demographic variables (all p values > 0.10; see Table 1). Independent sample t tests revealed that the three groups were comparable at baseline on all CNS Vital Signs domain scores (all p values > 0.05; Table 2). Pearson-product moment correlations calculated on the neurocognitive domains assessed by the CNS Vital Signs at baseline indicated that all domains were strongly correlated with the Neurocognitive Index (NCI) total score and each other domain score (all p values < 0.001).

Manipulation check

A group by time (3 × 2) mixed-model ANOVA was conducted to determine whether quercetin

Table 1. Demographic characteristics by group.

Variable		Q-1000 (n = 319)			Q-500 (n = 309)			Placebo (n = 313)		
		%	Mean	SD	%	Mean	SD	%	Mean	SD
Age			46.09	16.50		46.44	16.60		45.35	15.72
Gender										
	Men	37.0			41.7			40.3		
	Women	63.0			58.3			59.7		
Race										
	White	93.4			95.5			93.9		
	African-American	2.5			1.0			1.9		
	Other	4.1			3.5			4.2		
Education	(years)		15.57	2.72		15.63	2.96		15.51	2.76
BMI			26.73	5.41		26.47	5.49		27.03	5.67

The groups did not significantly differ on any demographic characteristics.
BMI, body mass index; Q-1000, quercetin 1000 mg/day; Q-500, quercetin 500 mg/day; SD, standard deviation.

Table 2. Group means (and standard deviations) on Central Nervous System Vital Signs measures for the full sample.

Measure		Q-1000	Q-500	Placebo
NCI*	Pre	96.95 (16.53)	95.83 (17.16)	95.98 (14.99)
	Post	100.70 (19.16)	98.84 (20.92)	99.60 (16.52)
Memory	Pre	98.57 (8.84)	97.50 (9.20)	96.30 (9.65)
	Post	98.37 (9.87)	97.72 (9.63)	97.52 (9.52)
Psychomotor speed*	Pre	164.89 (31.85)	164.32 (27.75)	163.78 (25.35)
	Post	172.78(28.22)	169.94 (27.07)	169.39 (26.43)
Reaction time*	Pre	656.90 (119.67)	651.57 (108.32)	657.92 (96.96)
	Post	636.87 (101.72)	637.36 (104.47)	637.55 (96.01)
Attention	Pre	12.94 (20.77)	14.20 (21.37)	10.86 (13.56)
	Post	11.73 (25.15)	14.04 (30.12)	10.76 (20.77)
Cognitive flexibility*	Pre	39.59 (19.46)	38.03 (19.30)	40.50 (17.75)
	Post	46.57 (16.47)	44.88 (18.24)	46.84 (15.60)

*Significant change in scores from pre to post treatment. No significant group differences were indicated.
NCI, Neurocognition Index; Q-1000, quercetin 1000 mg/day; Q-500, quercetin 500 mg/day.

supplements effected mean plasma quercetin levels in the predicted manner. The results revealed a significant group by time interaction effect, $F(2, 985) = 100.25$, $p < 0.001$, $\eta_p^2 = 0.17$. Although the groups did not differ in plasma quercetin levels at baseline, the conditions demonstrated increases in plasma quercetin in a dose–response manner, with Q-1000 plasma levels (mean = 678.51, SD = 520.95) being significantly higher post treatment than Q-500 levels (mean = 490.00, SD = 345.10), which were significantly higher than placebo levels (mean = 288.40, SD = 223.62).

CNS Vital Signs

Neurocognition Index. A 3 × 2 mixed-model ANOVA was performed on mean NCI total scores. The results indicated a significant main effect for time, $F(1, 938) = 46.89$, $p < 0.001$, $\eta^2 = 0.05$, with NCI scores improving from baseline (mean = 96.26, SD = 16.24) to post treatment

Table 3. Group means (and standard deviations) on Central Nervous System vital Signs measures among older age participants.

Measure		Q-1000 (n = 77)	Q-500 (n = 78)	Placebo (n = 62)
NCI*	Pre	94.36 (16.90)	93.45 (17.16)	94.81 (14.14)
	Post	100.25 (18.21)	97.05 (20.65)	100.24 (13.05)
Memory	Pre	94.52 (9.36)	92.53 (10.75)	92.71 (10.24)
	Post	94.86 (10.08)	92.21 (10.53)	93.69 (9.26)
Psychomotor speed*	Pre	135.23 (31.92)	137.22 (28.41)	135.89 (25.91)
	Post	144.99 (29.24)	144.12 (26.79)	140.44 (30.53)
Reaction time*	Pre	737.45 (146.42)	720.40 (144.97)	731.53 (106.11)
	Post	702.99 (136.05)	710.50 (126.05)	717.23 (115.96)
Attention	Pre	22.77 (32.90)	23.32 (28.11)	14.53 (14.97)
	Post	16.84 (32.81)	20.82 (38.68)	13.29 (15.76)
Cognitive flexibility*	Pre	25.83 (21.00)	24.13 (22.85)	28.61 (21.17)
	Post	35.52 (19.99)	32.00 (22.92)	36.05 (19.75)

*Significant change in scores from pre to post treatment. No significant group differences were indicated.
NCI, Neurocognition Index; Q-1000, quercetin 1000 mg/day; Q-500, quercetin 500 mg/day.

(mean = 99.72, SD = 18.94). The main effect for group (p = 0.48) and the interaction effect (p = 0.82) were nonsignificant.

Memory. A 3 × 2 mixed-model ANOVA was performed on mean memory domain scores. No significant effects emerged from these analyses.

Psychomotor speed. A 3 × 2 mixed-model ANOVA performed on mean psychomotor speed domain scores revealed a significant main effect for time, $F(1, 938) = 157.47$, $p < 0.001$, $\eta^2 = 0.14$. Psychomotor speed scores significantly increased from baseline (mean = 164.34, SD = 28.44) to post treatment (mean = 170.72, SD = 27.27). However, the main effect for group (p = 0.54) and the interaction effect (p = 0.11) were nonsignificant.

Reaction time. A 3 × 2 mixed-model ANOVA conducted on mean reaction time domain scores indicated a significant main effect for time, $F(1, 938) = 38.21$, $p < 0.001$, $\eta^2 = 0.04$. The results revealed that participants' reaction time scores were slower at baseline (mean = 655.49, SD = 108.70) than at post treatment (mean = 637.25, SD = 100.68). The main effect for group (p = 0.91) and the interaction effect (p = 0.63) were nonsignificant.

Attention. A 3 × 2 mixed-model ANOVA was performed on mean attention domain scores. No significant effects emerged from these analyses.

Cognitive flexibility. A 3 × 2 mixed-model ANOVA conducted on cognitive flexibility domain scores indicated a significant main effect for time, $F(1, 938) = 266.45$, $p < 0.001$, $\eta^2 = 0.22$. Analyses indicated that cognitive flexibility scores significantly increased from baseline (mean = 39.38, SD = 18.86) to post treatment (mean = 46.11, SD = 17.14). However, the main effect for group (p = 0.24) and the interaction effect (p = 0.80) were nonsignificant.

Older age population

Previous animal research has suggested that quercetin treatment can reverse cognitive deficits in aged mice [Singh *et al.* 2003]. To determine whether quercetin has comparable effects in aged humans, separate mixed-model ANOVAs were conducted on cognitive performance scores for participants who were 60 years and older (n = 217). The results failed to indicate any significant main effects for group or group by time interactions (all p values > 0.10). Similar to the full sample analyses, NCI, psychomotor speed, and cognitive flexibility scores significantly improved among the older age sample (p values < 0.05; see Table 3).

Discussion

The purpose of the present study was to examine the effects of a 12-week quercetin supplementation program on cognitive functioning. Although

the results indicated significant improvement in scores among all groups across several cognitive domains (i.e. reaction time, psychomotor speed, and cognitive flexibility), performance was not influenced by quercetin ingestion. Rather, participants who received moderate and large doses of quercetin performed comparably to those who received placebo. Thus, the results failed to support the hypothesis that quercetin supplementation would significantly enhance neurocognitive functioning in any of the domains assessed.

Multiple pathways have been proposed through which quercetin may affect cognitive functioning. For example, *in vitro* studies suggest that quercetin is a potent antioxidant and may protect neuronal cells from neurotoxicity associated with oxidative stress. *In vitro* research also suggests that quercetin is an adenosine antagonist, and thus may enhance cognitive functioning and reduce cognitive and physical fatigue through mechanisms similar to that of caffeine. Initial animal research appeared to support the notion that quercetin can enhance memory and learning [Priprem *et al*. 2008] and reduce cognitive deficits associated with age [Singh *et al*. 2003]. However, the results of the present research raise questions about the generalizability of these findings to human populations. Specifically, human participants who consumed moderate to large doses of quercetin daily for 12 weeks did not perform any better on tests of verbal or nonverbal memory than participants who ingested placebo. Furthermore, although one unpublished study with humans has provided some evidence that quercetin may moderate reaction time deficits in trained athletes following several days of intense physical exercise [Rocheleau *et al*. 2010], these findings should be interpreted with caution as multiple limitations associated with the study (e.g. small unique sample, absence of peer review, only one significant finding among many analyses) reduce confidence in the internal and external validity of the results. Although the present study did not involve intense exercise, no evidence of enhanced reaction time was uncovered after 12 weeks of quercetin supplementation. Finally, despite previous research suggesting that quercetin may improve cognitive functioning among aged mice, this study failed to find any significant effect of quercetin on neurocognitive performance among aged adult humans (age > 60).

The results of this research are consistent with a growing body of literature raising concerns about the generalizability of findings from *in vitro* and animal quercetin research to human populations. For example, animal research has suggested that quercetin supplementation may have an ergogenic effect, with results indicating that mice who received 1 week of quercetin demonstrated significant increases in muscle oxidative capacity and endurance [Davis *et al*. 2009]. However, research on the potential ergogenic effect of quercetin in human participants has generated largely inconsistent findings. Although some research has suggested that quercetin ingestion may be associated with small improvements in physical performance (e.g. 3%) among trained males [Nieman *et al.* 2010], other studies have failed to find any evidence of quercetin-induced performance enhancement among human samples [e.g. Cheuvront *et al.* 2009; Cureton *et al.* 2009; Nieman *et al.* 2007]. Similarly, recent research failed to detect immediate effects of 2000 mg of quercetin on vigilance among human samples. The results of the present study, though novel in that they pertain to the cognitive effects of long-term quercetin supplementation, are consistent with the null ergogenic findings of several prior quercetin trials, and suggest that quercetin may not be associated with enhanced cognitive or physical functioning. Thus, research to date appears to suggest that, at best, quercetin's ergogenic effects are far below that reported in mice. Additional research is needed to determine which, if any, physiological, cognitive, and psychological benefits of quercetin noted in animal and *in vitro* research extend to humans.

This research has many strengths that enhance confidence in the results obtained, including the use of a large community sample of adults ranging in age from 18 to 85 years, a placebo-controlled double-blind methodology, a full 12 weeks of supplementation, blood monitoring of quercetin levels at baseline and post treatment, and multiple assessments of a variety of cognitive functions. However, several limitations are worth noting as well. For example, although the cognitive tests participants completed were objective, standardized tests based on popular, well validated measures of neuropsychological functioning, several of the subtests on the CNS Vital Signs battery are relatively brief and may not be sensitive enough to detect very subtle changes in neuropsychological functioning. Future research may wish to include lengthier, more in-depth assessments of cognitive domains thought to be affected by quercetin. In addition, practice effects are a well documented concern with the repeated administration of many

cognitive tests [e.g. Dikmen *et al*. 2000]. Although the cognitive measures were administered 12 weeks apart, it is possible that improvements in performance due to practice effects may have obscured the ability to detect any direct effects of quercetin on cognitive functioning. Future studies using alternative research designs may help to clarify this concern. It is also worth noting that previous research demonstrating positive psychological effects of quercetin has generally focused on used unique subpopulations (e.g. physically stressed athletes, ethanol-treated mice). Thus, it is possible that under more extreme circumstances or in populations with more marked cognitive deterioration (e.g. people with Alzheimer's disease), the limited effects of quercetin may be more easily detected. Additional research is needed to clarify under which, if any, circumstances quercetin exerts an effect on cognitive functioning in human populations.

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Conflict of interest statement

D.C. Nieman is a board member of Quercegen Pharma. The other authors have no conflict of interest.

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