A Double-Blinded, Placebo-Controlled, Randomized Trial of the Neuropsychologic Efficacy of Cranberry Juice in a Sample of Cognitively Intact Older Adults: Pilot Study Findings

W. DAVID CREWS, JR., Ph.D., 1,2 DAVID W. HARRISON, Ph.D., 1 MELANIE L. GRIFFIN, B.S., 1 KATHERINE ADDISON, B.S., 1 ALYSSA M. YOUNT, B.S., 1 MARIA A. GIOVENCO, B.S., 3 and JESSICA HAZELL, B.S. 1

ABSTRACT

Objectives: The aim of this research was to conduct the first known clinical trial of the short-term (i.e., 6 weeks) efficacy of cranberry juice on the neuropsychologic functioning of cognitively intact older adults.

Participants: Fifty (50) community-dwelling, cognitively intact volunteers, ≥60 years old, who reported no history of dementia or significant neurocognitive impairments, participated in this study.

Design: A 6-week, double-blind, placebo-controlled, randomized, parallel-group, clinical trial was utilized. Participants were randomly assigned to receive either 32 ounces/day of a beverage containing 27% cranberry juice per volume (n = 25) or placebo (n = 25) for 6 weeks, and administered a series of neuropsychologic tests at both pretreatment baseline and again after 6 weeks of either cranberry juice or placebo treatment to assess treatment-related changes.

Outcome measures: Efficacy measures consisted of participants’ raw scores on the following standardized neuropsychologic tests: Selective Reminding Test, Wechsler Memory Scale-III Faces I and Faces II subtests, Trail Making Test (Parts A and B), Stroop Color and Word Test, and the Wechsler Adult Intelligence Scale-III Digit Symbol-Coding subtest. A subjective Follow-up Self-report Questionnaire was also administered to participants at the conclusion of the end-of-treatment phase assessments.

Results: Two-factor, mixed analyses of variance (ANOVA) revealed no significant group (cranberry juice and placebo) by trial (pretreatment baseline and end-of-treatment assessments) interactions across all of the neuropsychologic tests and measures utilized in this study when a Bonferroni corrected alpha level was used to correct for multiple comparisons (i.e., .05/17 group by trial comparisons = .003). Pearson Chi-Square analyses of the groups’ self-reported changes over the 6-week treatment phase in their abilities to remember, thinking processes, moods, energy levels, and overall health on the Follow-up Self-report Questionnaire revealed no significant relationships. However, a nonsignificant trend (χ²(1) = 2.373, p = 0.123) was noted for participants’ self-reported overall abilities to remember from pretreatment baseline to the end-of-treatment assessment. Specifically, more than twice as many participants in the cranberry group (n = 9, 37.5%) rated their overall abilities to remember by treatment end as “improved” as compared to placebo controls (n = 4, 17.4%).

Conclusions: Taken together, no significant interactions were found between the cranberry and placebo groups and their pretreatment baseline and end-of-treatment phase (after 6 weeks) standardized neuropsychologic assessments. A nonsignificant trend was noted, however, on a subjective, self-report questionnaire where twice as many participants in the cranberry group rated their overall abilities to remember by treatment end as “improved” compared to placebo controls.

1Virginia Polytechnic Institute and State University, Blacksburg, Virginia.
3Radford University, Radford, Virginia.
INTRODUCTION

In recent years, studies have demonstrated the potential efficacy of dietary and herbal supplements that are high in antioxidant activity or phytochemicals on the neuronal and neuropsychologic processes of laboratory animals and humans (Bickford et al., 2000; Joseph et al., 1998; 1999; Mix and Crews, 2000; Mix and Crews, 2002). For example, Joseph and colleagues (1999) found that supplements of strawberry, spinach, or blueberry extract fed to aged rats for 8 weeks were effective in reversing age-related deficits in a number of neuronal (e.g., carbachol-stimulated GTPase activity) and behavioral (e.g., rod walking) indices; however, the blueberry supplement reportedly proved most effective in reversing declines.

Despite research that has indicated that, like blueberries, cranberries are rich in antioxidants such as flavonoids, phenols, and vitamin C (Hakkinen et al., 1999; Kahkonen et al., 2001; Vinson et al., 2001) and may inhibit low density lipoprotein oxidation (Wilson et al., 1998), there is an absence of studies that have examined the neuropsychologic efficacy of cranberry juice in cognitively intact (CI) older adults. Thus, the purpose of this study was to conduct the first-known study of the short-term efficacy of cranberry juice on the neuropsychologic functioning of CI older adults. A 6-week trial was utilized, in light of our previous studies (Mix and Crews, 2000; Mix and Crews, 2002) involving antioxidant-rich Ginkgo biloba, which found improvements in the neurocognitive functioning of CI older adults after only 6 weeks of treatment.

METHODS AND MATERIALS

Participants

Fifty (50) community-dwelling participants, aged ≥60 years, who reported no history of dementia or significant neurocognitive impairment, were randomized in this study. To be included in the trial and considered CI, participants were required to obtain a total score of 24 out of 30 or greater on the Mini-Mental State Examination (Folstein et al., 1975). Participants’ histories were unremarkable for active or clinically significant medical, psychiatric, or substance abuse disorders, significant head injuries (i.e., loss of consciousness >5 minutes), episodes of anoxia/hypoxia, learning disabilities, color blindness, or current psychotropic medications. Consumption of any cranberry products was terminated prior to participants’ pretreatment assessments. Medication for pre-existing conditions was not discontinued, although changes or additions during the study would have resulted in participant exclusion. Furthermore, participants’ histories were unremarkable for conditions (such as uncorrected vision) that could have precluded their compliance with the neuropsychologic procedures.

Experimental design and procedures

A 6-week, double-blind, fixed-dose, placebo-controlled, randomized, parallel-group experimental design was used. Individuals meeting inclusionary criteria were randomly assigned to either the cranberry juice (n = 25) or placebo (n = 25) group. The study involved a low-calorie cranberry juice product, containing 27% juice/volume and sweetened with sucralose, and a matching placebo (similar appearance, smell, taste, and vitamin C content). Both beverages were furnished by the manufacturer, Ocean Spray Cranberries, Inc. Computerized randomization of the products was conducted by an independent researcher. Cases of beverages (and their randomization numbers, 1–50) were issued to participants in an ascending/sequential order as they entered the study. The cranberry juice or placebo (16 ounces/dose) was taken orally twice daily (i.e., 32 ounces/day).

Enrolled participants were administered the following series of standardized neuropsychological tests during pretreatment baseline evaluations, and again, after 6 weeks of treatment, to assess treatment-related performance changes: Selective Reminding Test (Buschke and Fuld, 1974); Wechsler Memory Scale-III Faces I and Faces II subtests (Wechsler, 1997a); Trail Making Test Parts A and B (Reitan, 1992; Reitan and Wolfson, 1993); Stroop Color and Word Test (Golden, 1978; Stroop, 1935); and the Wechsler Adult Intelligence Scale-III Digit Symbol-Coding subtest (Wechsler, 1997b). A Follow-up Self-report Questionnaire (FSRQ) (Mix and Crews, 2002) was also administered during the end-of-treatment assessment to assess participants’ perceptions of changes over the 6 weeks in the following variables: overall abilities to remember, thinking abilities/processes, moods, energy levels, and overall health.

Regarding treatment compliance, a deviation of ≥20% from the optimum treatment regimen was defined as non-compliant. Adverse events were assessed at the end-of-treatment phase and on an as-needed basis.

RESULTS

A trial flow diagram for the study is provided in Figure 1. Since only baseline and end-of-treatment assessments were conducted, the per-protocol data set was utilized in the analyses. Of the 50 randomized participants, 21 males and 26 females completed the trial’s protocol and were available for the efficacy analyses. Three participants were excluded due to treatment regimen noncompliance. No serious adverse events were reported.

Separate ANOVAs were conducted on the descriptive/criterion measures cited in Table 1. No significant group dif-
ferences were found for any of these measures. A Phi coefficient revealed no significant relationship ($\phi = 0.109, p = 0.454$) between the number of males and females who comprised the treatment groups.

For the neuropsychologic measures, mixed ANOVAs were conducted to examine possible interaction effects using the fixed factor of group and repeated measures of trial (i.e., pretreatment and end-of-treatment assessments). When a Bonferroni corrected alpha level (Winer, 1971) was utilized to correct for multiple comparisons (i.e., $0.05/17$ group by trial comparisons = $0.003$), none of these interactions were significant. Table 2 provides a summary of the groups’ neuropsychologic mean test scores, standard deviations, and group by trial interaction $p$ values.

For the FSRQ, Pearson Chi-Square analyses were conducted using the treatment groups’ self-report data (Table 3). Frequency data for each question was summarized into three categories: “worse” (“much worse” and “somewhat worse” categories), “no change,” and “improved” (“somewhat improved” and “much improved” categories). Although no significant relationships were found among the questionnaire’s 5 questions, a nonsignificant trend ($\chi^2(1) = 2.373, p = 0.123$) was noted for the question concerning changes in participants’ overall abilities to remember from pretreatment to the end-of-treatment assessment. Specifically, more than twice as many participants in the cranberry group ($n = 9, 37.5\%$) rated their overall abilities to remem-

**DISCUSSION**

Despite this pilot study’s a priori hypothesis of enhanced neurocognitive performance by treatment end in the group of CI participants who consumed cranberry juice versus a placebo, when a Bonferroni corrected alpha level was utilized to correct for multiple comparisons, none of the group by trial interactions for the neuropsychologic test data were significant.

Although cranberry juice may actually have no significant effects on the neuropsychologic processes of CI older adults, this statement is contrary to the growing body of evidence (Bickford et al., 2000; Joseph et al., 1998; Joseph et al., 1999; Mix and Crews, 2000; Mix and Crews, 2002) concerning the potential benefits of dietary/herbal products, such as cranberry juice, that are high in antioxidant activity (proposed to decrease cellular and neuronal damage due to oxidative stress) and past research (Joseph et al., 1999) that has demonstrated the efficacy of another *Vaccinium* product (blueberry extract) on several neuronal/behavioral indices of aged rats.

In light of this previous research, it seems plausible that a diversity of factors may have contributed to the overall null findings in this pilot trial. For one, the relatively small sample size of the current study likely decreased the power of the statistical measures to find any significant differences between the groups, especially subtle or modest ones that possibly existed.

The relatively short duration (6 weeks) of the treatment phase and notably lower quantity/concentration of *Vaccinium* product consumed in the present trial (32 ounces/day of a beverage containing 27% cranberry juice by volume), as compared to the Joseph et al. (1999) study, may have also contributed to the overall null findings. Specifically, the aged rats in the Joseph et al. (1999) study received notably greater quantities/concentrations of blueberry extract (18.6 gm of dried aqueous extract per kilogram of diet) over a relatively longer time period (8 weeks). This combination of increased *Vaccinium* product consumption over a relatively longer duration (especially in relation to the life spans of rats) may have interacted to produce more potent antioxi-

| Table 1. Group Means and Standard Deviations for the Descriptive and Criterion Measures |
|----------------------------------|------------------|------------------|
| Cranberry group                 | Placebo group    |
| Age (in years)                  | 69.17 ± 7.11     | 69.39 ± 5.80     |
| Education level (in years)      | 16.88 ± 3.00     | 15.48 ± 2.47     |
| Mini-Mental State Examination (total scores) | 29.17 ± 0.76 | 29.13 ± 1.01     |
| Treatment regimen compliance (%) | 98.34 ± 2.59     | 98.76 ± 2.38     |
Wechsler Adult Intelligence Scale-III

Overall health 1.980 0.372
Energy 1.099 0.577
Mood 0.006 0.940
Memory 2.373 0.123

Question Chi-square p
memory 308

TABLE 2. NEUROPSYCHOLOGICAL TEST SCORES EXPRESSED AS MEANS ± STANDARD DEVIATIONS, AND P VALUES

<table>
<thead>
<tr>
<th>Test/variable</th>
<th>Baseline</th>
<th>End of treatment</th>
<th>Group x trial interaction p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cranberry group</td>
<td>Placebo group</td>
<td>Cranberry group</td>
</tr>
<tr>
<td>Selective Reminding Test (raw scores)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate free recall</td>
<td>108.77 ± 15.82</td>
<td>104.23 ± 17.20</td>
<td>111.91 ± 16.13</td>
</tr>
<tr>
<td>Long-term storage</td>
<td>102.32 ± 19.74</td>
<td>91.64 ± 29.70</td>
<td>103.95 ± 23.21</td>
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<tr>
<td>Short-term recall</td>
<td>14.32 ± 7.27</td>
<td>21.00 ± 14.51</td>
<td>14.59 ± 9.85</td>
</tr>
<tr>
<td>Long-term retrieval</td>
<td>94.45 ± 21.72</td>
<td>83.23 ± 30.97</td>
<td>97.32 ± 24.79</td>
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<tr>
<td>Consistent long-term retrieval</td>
<td>72.00 ± 27.30</td>
<td>58.59 ± 33.93</td>
<td>78.50 ± 32.07</td>
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<td>Random long-term retrieval</td>
<td>22.45 ± 12.29</td>
<td>24.64 ± 13.01</td>
<td>18.82 ± 15.03</td>
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<tr>
<td>Cued recall</td>
<td>9.68 ± 1.49</td>
<td>9.27 ± 1.55</td>
<td>10.32 ± 1.13</td>
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<tr>
<td>Delayed free recall</td>
<td>9.41 ± 2.40</td>
<td>8.55 ± 2.84</td>
<td>9.64 ± 2.08</td>
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<tr>
<td>Delayed recognition</td>
<td>11.86 ± 0.35</td>
<td>11.91 ± 0.29</td>
<td>11.82 ± 0.40</td>
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<tr>
<td>Wechsler Memory Scale-III (raw scores)</td>
<td></td>
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<tr>
<td>Faces I</td>
<td>36.29 ± 4.79</td>
<td>36.04 ± 5.17</td>
<td>39.17 ± 4.84</td>
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<td>Faces II</td>
<td>38.25 ± 4.18</td>
<td>38.17 ± 4.32</td>
<td>40.71 ± 4.15</td>
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<tr>
<td>Wechsler Adult Intelligence Scale-III (raw scores)</td>
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<td></td>
<td></td>
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<tr>
<td>Digit Symbol</td>
<td>67.46 ± 14.70</td>
<td>65.61 ± 15.25</td>
<td>74.58 ± 13.68</td>
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<tr>
<td>Trail Making Test (total time)</td>
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<tr>
<td>Part A</td>
<td>30.75 ± 11.48</td>
<td>31.87 ± 8.73</td>
<td>27.67 ± 13.48</td>
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<tr>
<td>Part B</td>
<td>74.58 ± 34.95</td>
<td>71.13 ± 27.61</td>
<td>69.08 ± 31.03</td>
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<td>Stroop Color-Word Test (raw scores)</td>
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<tr>
<td>Word page</td>
<td>96.46 ± 16.75</td>
<td>95.74 ± 11.65</td>
<td>100.33 ± 15.76</td>
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<tr>
<td>Color page</td>
<td>70.17 ± 13.21</td>
<td>66.48 ± 11.25</td>
<td>71.71 ± 12.79</td>
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<tr>
<td>Color-word page</td>
<td>37.71 ± 10.60</td>
<td>36.30 ± 6.82</td>
<td>38.71 ± 10.05</td>
</tr>
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</table>

No values were significant when a Bonferroni corrected α level was used to correct for multiple comparisons (i.e., 0.05/17 comparisons = .003).

dant effects and the noted reversals of the animals’ age-related declines.

Furthermore, participants’ relatively high mean levels of educational achievement may have negatively impacted the current results. In particular, higher versus lower levels of education have been associated with enhanced performance on neuropsychologic tests (Lezak, 1995). Persons with higher levels of educational attainment typically also have notably more test-taking experience than individuals with less education. These factors, along with the fact that participants appeared to be CI at the onset of this study, may have enabled them to optimize their test performances to such a degree that precluded the identification of any subtle or modest group differences.

Additionally, a nonsignificant trend was noted on the FSRQ for the summarized frequency data from a question concerning participants’ overall abilities to remember from baseline to the end-of-treatment. Specifically, more than twice as many participants in the cranberry group (n = 9) rated their overall ability to remember by treatment end as “improved,” as compared to controls (n = 4). Thus, the cranberry juice may have enhanced aspects of some participants’ memory processes that were perceptible to them by treatment end, but that were not of sufficient magnitude to be observed on the neuropsychologic measures in such a small, educated sample of CI older adults.

Future research is required that examines the neuropsychologic efficacy of cranberry juice in large, heterogeneous, samples of CI persons. Longitudinal studies are also needed that more closely parallel the previous research involving Vaccinium products and aged laboratory animals.

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REFERENCES


Address reprint requests to:
W. David Crews, Jr., Ph.D.
Virginia Neuropsychology Associates, Inc.
P.O. Box 11754
Lynchburg, VA 24506

E-mail: wdcrewsjr@aol.com