Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment

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Concord grape juice contains polyphenol compounds, which have antioxidant and anti-inflammatory properties and influence neuronal signalling. Concord grape juice supplementation has been shown to reduce inflammation, blood pressure and vascular pathology in individuals with CVD, and consumption of such flavonoid-containing foods is associated with a reduced risk for dementia. In addition, preliminary animal data have indicated improvement in memory and motor function with grape juice supplementation, suggesting potential for cognitive benefit in ageing humans. In this initial investigation of neurocognitive effects, we enrolled twelve older adults with memory decline but not dementia in a randomised, placebo-controlled, double-blind trial with Concord grape juice supplementation for 12 weeks. We observed significant improvement in a measure of verbal learning and non-significant enhancement of verbal and spatial recall. There was no appreciable effect of the intervention on depressive symptoms and no effect on weight or waist circumference. A small increase in fasting insulin was observed for those consuming grape juice. These preliminary findings suggest that supplementation with Concord grape juice may enhance cognitive function for older adults with early memory decline and establish a basis for more comprehensive investigations to evaluate potential benefit and assess mechanisms of action.

Memory: Cognitive impairment: Elderly: Grape juice: Polyphenols

Worldwide dementia prevalence is almost 25 million cases and is projected to reach more than 81 million cases by the year 2040¹. Alzheimer’s disease comprises 60 to 80 % of cases of dementia². The construct mild cognitive impairment³ identifies individuals with elevated risk for dementia⁴, and progression from mild cognitive impairment to Alzheimer’s disease can be as high as 10 % per year⁵. Further, there are indications that even age-associated memory impairment, originally conceptualised as benign forgetfulness⁶,⁷, can reflect very early neurodegeneration. Older adult samples with subjective memory complaints who meet criteria for age-associated memory impairment show degradation in the medial temporal lobe that is similar, albeit not as extensive, as that observed in subjects with mild cognitive impairment and Alzheimer’s disease⁸, and longitudinal investigation has shown a trebling of risk for those categorised as having age-associated memory impairment⁹,¹⁰. Such findings imply that memory complaints and associated manifestations in everyday functioning can be meaningful indicators of neurodegeneration. Preventive interventions initiated when early memory decline is evident have the potential to forestall progression, most likely at the final stage when such treatment might be effective¹¹.

Regulation of inflammation generally is reduced with ageing¹², and accelerated inflammation is implicated in neurodegenerative disorders such as Alzheimer’s disease¹³. Berry fruits contain polyphenol compounds, which have anti-inflammatory and antioxidant properties¹⁴. Polyphenols also induce neuroprotective effects and influence neuronal signalling involved in memory function¹⁴–¹⁶, and specific constituents of grape juice have exhibited neuroprotective effects¹⁷. Concord grape juice contains a variety of flavonoids and antioxidants, among them anthocyanins and proanthocyanidins¹⁸–¹⁹ and comparatively high levels of total phenolics²⁰. Information concerning flavonoid transport into the central nervous system and absorption into brain tissue is emerging. A number of recent studies have indicated that certain of these compounds, in particular anthocyanins, cross the blood–brain barrier, although specific mechanisms have not been established²¹–²³. In addition, anthocyanins have been identified in brain regions that mediate cognition, including the medial temporal lobe and cortex²⁴, and hippocampal distribution has been associated with behavioural enhancement in animal supplementation studies²⁴,²⁵. Human trials have shown that short- and moderate-term supplementation with grape juice produces benefit in individuals with CVD, including increased serum antioxidant capacity and reduced LDL oxidation²⁶, improved endothelial function²⁶ and reduced platelet aggregation²⁷. Such findings are pertinent with respect to age-related cognitive decline because of the strong relationship between CVD and neurodegeneration²⁸–³¹. Epidemiological studies indicate that consumption of fruits and vegetables is associated with lower risk of neurodegenerative disorders and better cognitive performance in the elderly³²–³⁴, and these effects have been

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attributed to the intake of a variety of flavonoid compounds with antioxidant and anti-inflammatory properties. Recently, a preliminary animal study demonstrated that ingestion of Concord grape juice for 6–8 weeks induced enhancement of cognitive performance in aged rodents. We sought to assess the effect of supplementation with Concord grape juice on memory performance in older adults with early age-related memory decline in a controlled trial as an initial assessment of potential benefit in an at-risk sample. We also obtained data on mood, anthropometrics and metabolic parameters.

Methods

Participants

Participants were recruited from the general community with newspaper advertising soliciting older adults with early memory decline but not dementia for a dietary intervention study. We enrolled twelve participants (eight men, four women) with acquired memory changes such as forgetfulness and prospective memory lapses. The mean age of the entire sample was 78.2 (SD 5.0) years and the mean educational level was 14.1 (SD 2.9) years.

Procedure

Prospective participants were assessed with structured interview instruments to determine eligibility for study inclusion. The Academic and Medical History Questionnaire was used to obtain demographic information and information regarding academic attainment, current and past medical conditions, and medication and substance use. Those with diabetes, substance-abuse disorder, or diagnosed psychiatric or neurological condition were excluded. The level of memory impairment was determined with the Clinical Dementia Rating classifications indicating no impairment, mild decline, as well as cognitive–cerebral function in older adults, and there are indications in pre-clinical studies with other berry fruits that several weeks may be required for accumulation in brain regions. We instituted a dosing schedule determined by body weight to maintain daily consumption between 6 and 9 ml/kg, a range consistent with other human grape juice trials. Individuals weighing 54 to 64 kg were prescribed 444 ml/d, those weighing between 65 and 76 kg consumed 532 ml/d, and those weighing between 77 and 91 kg consumed 621 ml/d. Participants were instructed to take daily quantities in equal, divided dosages with the morning, midday and evening meals.

The primary outcomes were neurocognitive measures of memory function administered before and after the intervention. The California Verbal Learning Test was administered to assess verbal learning and retention, and the Spatial Paired Associate Learning Test was used to evaluate non-verbal memory. The California Verbal Learning Test is a list-learning and recall task, and the Spatial Paired Associate Learning Test assesses memory for visual-spatial information that is not amenable to verbal encoding. Both list-learning and paired associate tasks have been used in the context of cognitive ageing and dementia and are among the more sensitive measures of memory decline associated with neurodegeneration. We also assessed mood as a potential covariate of the cognitive measures with the Geriatric Depression Scale. We performed weight and waist circumference measures and obtained fasting blood samples for determination of serum glucose and insulin values.

Analyses of covariance were performed for each outcome factor to isolate effects of the intervention while controlling for individual differences. The outcome score from the final visit was the dependent measure and the corresponding baseline visit was the independent measure. We used eta squared values to derive Cohen’s effect size estimates, which are characterised as small (0–0.1), medium (0.2–0.4) and large (0.4–0.7).

Fig. 1. List acquisition performance assessing verbal learning on the California Verbal Learning Test. Values are adjusted means, with standard errors represented by vertical bars. Subjects consuming Concord grape juice demonstrated significant improvement ($F(1, 8) = 5.55; P = 0.04$; Cohen’s $f = 0.28$).
consumption and aversion to the taste of the juice or placebo that developed over time.

As shown in Fig. 1, analysis of covariance demonstrated a significant effect ($P=0.04$) for item acquisition across learning trials on the California Verbal Learning Test, indicating improvement for subjects in the Concord grape juice group relative to those receiving placebo. The effect size was moderate (Cohen’s $f=0.28$). Also, there were trends toward improved performances for the grape juice subjects with respect to delayed verbal recall ($P=0.10$; Cohen’s $f=0.33$) and spatial memory ($P=0.12$; Cohen’s $f=0.67$), although these were not statistically significant (Fig. 2).

There was no appreciable effect of the intervention on depressive symptoms (adjusted Geriatric Depression Scale scores $5.0$ v. $7.2$; $F(1,8) = 2.56$; $P=0.14$) and no effect on weight ($77.5$ v. $77.8$ kg, adjusted values; $F(1, 8) = 0.31$; $P=0.58$) or waist circumference ($94.9$ v. $95.5$ cm, adjusted values; $F(1, 8) = 0.24$; $P=0.63$). Fasting glucose values were not affected by the intervention ($1011$ v. $975$ mg/dl, adjusted values; $F(1, 8) = 0.42$; $P=0.53$), but fasting insulin at 12 weeks was significantly elevated for the subjects consuming grape juice ($10.0$ v. $13.7$ µU/ml, adjusted values; $F(1, 8) = 6.07$; $P=0.03$). Table 1 contains the unadjusted mean scores for the outcome measures and shows the changes in absolute values from the baseline to final assessment.

### Results

At pre-intervention baseline there was a modest, non-significant difference for age between the groups ($80$ v. $75$ years; $t(10) = 1.8$; $P=0.10$). There was no group difference for educational level ($13.4$ v. $15.2$ years; $t(10) = 1.42$; $P=0.32$), index of functional impairment (Clinical Dementia Rating sum of boxes score $1.0$ v. $1.0$; $t(10) = 0.0$; $P=1.0$), weight ($74.3$ v. $79.4$ kg; $t(10) = 1.04$; $P=0.32$) and waist circumference ($92.7$ v. $96.7$ cm; $t(10) = 0.81$; $P=0.43$).

There was a group difference for level of depressive symptoms (Geriatric Depression Scale score $7.8$ v. $3.0$; $t(10) = 2.19$; $P=0.05$), with greater depressive symptomology among the placebo subjects. However, the symptom level was not clinically elevated for either group.

Both the juice and placebo beverage were generally well tolerated, and there was no consistently reported adverse effect. Discrete concerns included, for example, increased frequency of urination associated with greater fluid loss and fluid volume. Mechanisms would be primary considerations.

### Discussion

In this preliminary study we sought to assess the effect of moderate-term supplementation with $100\%$ Concord grape juice on cognition in older adults with early memory decline and found that memory function was improved with regular grape juice consumption. To our knowledge, this is the first controlled human trial examining neurocognitive response to this dietary intervention, and our findings are consistent with those of a recent animal study showing improvement in cognitive performance with grape juice supplementation in aged rodents. Our data do not provide information as to possible mechanisms leading to the beneficial effects. However, given the existing body of research concerning reductions of inflammatory and oxidative stress markers in human subjects with CVD and lower risk of age-related neurodegeneration with flavonoid consumption, these putative mechanisms would be primary considerations.

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### Table 1. Unadjusted mean values for memory, mood, anthropometric and metabolic measures by group*

<table>
<thead>
<tr>
<th></th>
<th>Placebo ($n=7$)</th>
<th>Concord grape juice ($n=5$)</th>
<th>Difference</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Final</td>
<td>Difference</td>
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<tr>
<td>CVLT learning</td>
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<tr>
<td>CVLT recall</td>
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<tr>
<td>S-PAL</td>
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<td>2.0</td>
<td>0.4</td>
</tr>
<tr>
<td>GDS</td>
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<td>7.2</td>
<td>0.6</td>
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<tr>
<td>Weight (kg)</td>
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<td>74.9</td>
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<td>Waist (cm)</td>
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<tr>
<td>Glucose (mg/dl)</td>
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<td>999</td>
<td>3</td>
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<tr>
<td>Insulin (µU/ml)</td>
<td>11.9</td>
<td>11.1</td>
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</tr>
</tbody>
</table>

CVLT, California Verbal Learning Test; S-PAL, Spatial Paired Associate Learning Test; GDS, Geriatric Depression Scale.

* Baseline refers to measures obtained at the pre-intervention assessment. Final refers to measures obtained during the final week of the intervention. Difference = final score less baseline score.
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R. K. conceived of the study and supervised the data collection, analyses, interpretation and manuscript preparation. T. A. N. and M. D. S. participated in data collection, interpretation and manuscript preparation. B. S.-H. and J. A. J. participated in manuscript preparation.

None of the authors has a financial interest in the supporting company or the outcome of the research activity.

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