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Original Research

Queen garnet plum juice supplementation does not provide additional cognitive benefits over a group-based memory program in older adults with mild cognitive impairment: A randomized clinical trial

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ABSTRACT

Research suggests a role for inflammation and oxidative stress in mild cognitive impairment (MCI) and its progression. Evidence suggests anthocyanin-rich foods may reduce inflammation and oxidative stress and improve cognition but benefits in MCI are unclear. Therefore, it was hypothesized that daily consumption of anthocyanin-rich Queen Garnet Plum (QGP) juice would improve cognition, mood and blood pressure in people with MCI. Partic-

Abbreviations: ABP, Ambulatory Blood Pressure; AD, Alzheimer's disease; aMCI, Amnestic mild cognitive impairment; ANOVA, Analysis of Variance; BMI, Body mass index; C3G, Cyanidin-3-glucoside; CAPM-other, Comprehensive Assessment of Prospective Memory other-report; CAPM-self, Comprehensive Assessment of Prospective Memory self-report; CFT, Complex Figure Test; CONSORT, Consolidated Standards of Reporting Trials; DAF, Department of Agriculture and Fisheries; DASS-21, 21-item Depression Anxiety and Stress Scale; DBP, Diastolic blood pressure; EMQ, Everyday Memory Questionnaire; HEPA, Health-enhancing physical activity; HPLC, High Pressure Liquid Chromatography; IPAQ, International Physical Activity Questionnaire; MCI, Mild cognitive impairment; MMSE, Mini-Mental State Examination; naMCI, Non-amnestic mild cognitive impairment; PKH, Port Kembla Hospital; QGP, Queen Garnet Plum; QLD, Queensland; RAVLT, Rey Auditory Verbal Learning Test; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; RPA-ProMem, Royal Prince Alfred-Prospective Memory Test; SBP, Systolic blood pressure; SD, Standard deviation; TEA, Test of Everyday Attention; TMT, Trail Making Test; TOPF, Test of Premorbid Functioning; UOW, University of Wollongong; WAIS-IV, Wechsler Adult Intelligence Scale Fourth Edition.

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ipants diagnosed with MCI ($N = 42$) participated in a double-blind, randomized controlled trial. Participants were administered either QGP juice or apricot juice (comparator) daily for 8-weeks and participated in a 6-week group-based memory program. Cognitive function was assessed using a battery of cognitive tests, including the Rey Auditory Verbal Learning Test (RAVLT), Complex Figure Test (CFT), Royal Prince Alfred-Prospective Memory Test (RPA-ProMem), and Comprehensive Assessment of Prospective Memory self-report (CAPM-self). Mood and blood pressure were also measured pre- and post-intervention. There was a significant effect of TIME for total RAVLT ($P = .028$, $\eta^2 = .12$), CFT-recall ($P = .036$, $\eta^2 = .11$), RPA-ProMem ($P < .001$, $\eta^2 = .28$), and CAPM-self ($P = .007$, $\eta^2 = .22$) scores. There was a non-significant trend towards an interaction for CFT-recall ($p = .063$, $\eta^2 = .09$), where Bonferroni adjusted pairwise comparisons showed that the QGP group, but not comparators, had significantly improved CFT-recall scores (QGP: +13.93%, $P = .007$; comparators: +0.84%, $P = .855$). Overall, QGP consumption during a group-based memory rehabilitation program did not result in additional cognitive benefits in older adults with MCI. This trial was registered at the Australian New Zealand Clinical Trials Registry as ACTRN12618001184268.

1. Introduction

Mild cognitive impairment (MCI) is a neurocognitive condition that involves cognitive deficits beyond normal ageing but minimal impairment to daily living activities [1]. MCI can be categorized as non-amnestic MCI (naMCI), or amnestic (aMCI) where memory loss is predominant and the risk of progression to Alzheimer's Disease (AD) is higher [2]. Furthermore, MCI is a heterogeneous disorder that can either be a transitional condition that precedes AD and other dementias, a state where cognitive deficits remain stable, or a temporary state where normal cognitive function restores over time [1]. Age is the primary risk factor for MCI [3], as well as vascular risk factors (i.e. diabetes mellitus, hypertension, cerebrovascular disease and hyperlipidemia) [4].

There is currently no standard pharmacological treatment for MCI [1,5]; however, evidence suggests that cognitive training may improve cognition and assist symptom management [6–9]. For example, a meta-analysis ($N = 1059$) that employed computerized cognitive training interventions (including exercises in attention, visual processing, sensory integration, and recollection) found a small yet significant increase in global cognitive function compared to controls [10]. Moreover, group-based memory training programs delivered face-to-face by qualified clinicians may provide additional benefits in some populations. For example, previous research demonstrates improved auditory anterograde memory (Rey Auditory Verbal Learning Test; RAVLT), self-reported prospective memory (Comprehensive Assessment of Prospective Memory; CAPM), and compensatory memory strategy use in individuals with various neurological conditions involving memory complaints [11], epilepsy [12], and stroke [13] following a group-based memory program. Others reported improved Mini-Mental State Examination (MMSE), Clinical Dementia Rating Scale, Boston Naming Test, block design, matrix reasoning, and semantic fluency task scores following a group-based program in people with MCI [14]. Overall, these results show promise for the use of group-based memory programs to improve cognition; however, further research is needed to understand the efficacy of this approach in people with MCI given its heterogeneity.

The neuropathology of MCI and factors that determine progression to AD remain unclear [15]. Neuronal loss and synaptic dysfunction have been reported in both AD and MCI, in brain regions critical for memory and cognition, such as the hippocampus [16]. Neuroinflammation and oxidative stress have been reported in AD and MCI that can contribute to neuronal injury, synaptic damage and neurodegeneration [17,18]. For example, a meta-analysis found significantly elevated inflammatory markers in individuals with AD and MCI compared to controls [19]. Additionally, increased inflammation in both the brain [20] and periphery [19] in individuals with MCI may be associated with an increased risk of progression to AD. Furthermore, oxidative stress has been demonstrated in MCI through decreased serum concentration of endogenous antioxidant enzymes, and increased markers of oxidative damage [21] and lipid peroxidation in cerebrospinal fluid, plasma, and urine [22]. Overall, the existing evidence demonstrates the presence of oxidative stress and inflammation in MCI. Therefore, compounds that can reduce oxidative damage and neuroinflammation are of interest as novel therapeutics.

A growing body of evidence demonstrates the anti-inflammatory and antioxidant effects of anthocyanin-rich foods [23–27]. In clinical trials, berry-derived anthocyanins improved memory, psychomotor speed and executive function domains of cognition, as well as vascular function (see review by Ahles et al. [28]). Other studies have also demonstrated improved peripheral [27] and cerebral [29] vascular function, and the promotion of neurogenesis and increased synaptic connectivity in brain regions associated with memory and learning as a result of consumption of anthocyanin-rich foods [30,31]. The Queen Garnet plum (QGP; *Prunus salicina*) [25] has been bred to have higher levels of anthocyanins compared to conventional plums and has higher antioxidant [25] and anti-inflammatory capacity [26], and has been shown to improve vascular function in overweight older adults [27]. We have previously investigated the anthocyanin content of 12 plant-

based foods and supplements and identified that the QGP was significantly higher in anthocyanins (~200 mg C3G equivalents per 100 g) compared to other samples, followed by elderberry (~100 mg C3G equivalents per 100 g) [25]. Anthocyanin-rich foods are of interest for the treatment of MCI. Recent research suggests that elderberry consumption may benefit the visuospatial cognitive flexibility (trend increase in elderberry group) and inflammation in MCI [32], while another study found improvements to processing speed, visuospatial learning and global cognition after supplementation with a polyphenol-rich grape and blueberry extract [33]. However, the potential benefits of anthocyanin-rich dietary interventions requires further research and it is unknown whether supplementation with anthocyanin-rich QGP juice can improve cognition in people with MCI. In addition, combining QGP juice supplementation with a group-based memory program may provide additional benefits beyond the memory group alone. Therefore, it was hypothesized that daily consumption of QGP juice would improve memory, mood and blood pressure compared to a comparator (apricot juice) in people with MCI undergoing a group-based memory intervention program. This was tested by comparing results from baseline and post-testing for the QGP treatment group and comparator group. In addition, it was hypothesized that the group-based memory program would have an overall positive effect, tested by observing patient outcomes over time.

2. Methods and materials

This clinical trial was approved by the joint University of Wollongong and Local Health District Human Research Ethics Committee, NSW, Australia (HREC 2017/581), registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618001184268), conducted according to the Declaration of Helsinki and adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement [34]. Informed consent was obtained from all individual participants included in the study. This manuscript reports the primary aim of the clinical trial, i.e.: to evaluate the combined effect of a group-based memory rehabilitation program with intake of QGP juice (vs comparator) on cognition in older adults with MCI.

2.1. Study design and procedure

The study was a randomized, controlled, double-blind clinical trial conducted at the University of Wollongong (UOW) and Port Kembla Hospital (PKH), NSW, Australia. The study consisted of 8 weeks of daily juice intervention (Fig. 1). The week 8 endpoint was selected as our previous study examined cognition after 6 and 12 weeks and found no further improvements between the 6 and 12 week timepoints [35]. After 2 weeks of administration, all participants commenced a 6-week group-based memory rehabilitation program [36]. This is the first study to examine the combined effect of a food source of anthocyanins and a group-based memory program. The study design was employed to determine whether consumption of anthocyanin-rich QGP juice can enhance the cognitive outcomes of the group program.

Participants attended appointments at UOW and PKH before (baseline pre-testing) and after (post-testing) the 8-week intervention. For baseline testing (detailed in 2.5) demographic, anthropometric, 24-hour ambulatory blood pressure, habitual diet and other measures of general health data were collected. Participants also attended PKH for neuropsychological assessment conducted by Clinical Neuropsychologists, where cognitive and mood measures were taken (details Section 2.6). Additional cognitive measures were obtained at baseline to provide a broad overview of the cognitive status of the participants that did not form the outcome measures of the study (details in 2.5).

Block randomization was conducted by a researcher independent of the data collection and enrolment of participants, with groups of 6 participants randomly assigned to the 2 conditions to achieve a final ratio of 1:1 participants in each condition using a computer-generated randomization sequence. Based on these allocations participants then received either the anthocyanin-rich treatment (QGP juice) or comparator (apricot juice) daily for 8 weeks (details Section 2.3). After 2 weeks of daily juice intervention, all subjects participated in a 6-week 'Making the most of your memory' group program [36]. Post-testing was then conducted following the 8-week study period to assess cognition, mood and blood pressure following the intervention (Fig. 1).

2.2. Participants

Forty-two participants completed the study in total. Twenty-one participants completed the study between April 2018 and November 2019, after which the study was discontinued due to COVID-19 restrictions throughout 2020 and 2021 and recommenced with the remaining 21 participants completing the study between May 2022 and November 2022 (Fig. 2). Participants were recruited from MCI patients referred to the Illawarra Shoalhaven Local Health District (ISLHD) Geriatric Outpatient Services or Rehabilitation and Medical Psychology Department. The inclusion criteria were: 50+ years, English speaking, diagnosis of aMCI with memory complaints and intact Activities of Daily Living [37,38], MMSE score of 24-30, and an estimated premorbid IQ > 80 (estimated by combining educational history and performance in the Test of Premorbid Functioning (TOPF)). Clinical Neuropsychologists performed cognitive testing at baseline and post-testing to ensure that participants scores were within the study criteria. Exclusion criteria were: a diagnosis of dementia or neurodegenerative disease, significant neurological or psychiatric history, untreated hypertension or diabetes, allergy to stone fruits or food colorants, extensive and significant cognitive deficits not consistent with MCI diagnosis, and a change in medication within 3 months from commencement of the study or planned medication changes during the study period.

2.3. Dietary intervention

Juices were prepared and supplied to participants weekly. The treatment group received high-anthocyanin QGP juice, which was a blend of 220 g of frozen QGP fruit (Department of Agriculture and Fisheries (DAF), Queensland Government, QLD, Australia) pureed with 30 ml of water. The comparator

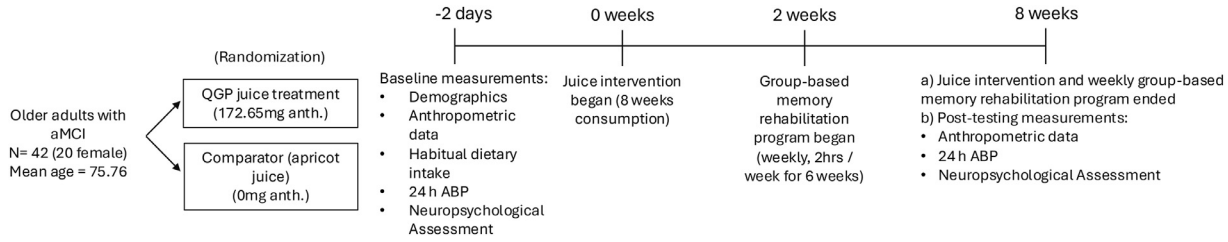

FIG. 1 – Study design and procedures for a double-blind randomized controlled trial examining the effect of daily consumption of QGP juice and a group-based memory program on cognition in older adults with MCI. ABP, Ambulatory Blood Pressure; MCI, mild cognitive impairment; PKH, Port Kembla Hospital; QGP, Queen Garnet Plum; UOW, University of Wollongong. Created with BioRender.com.

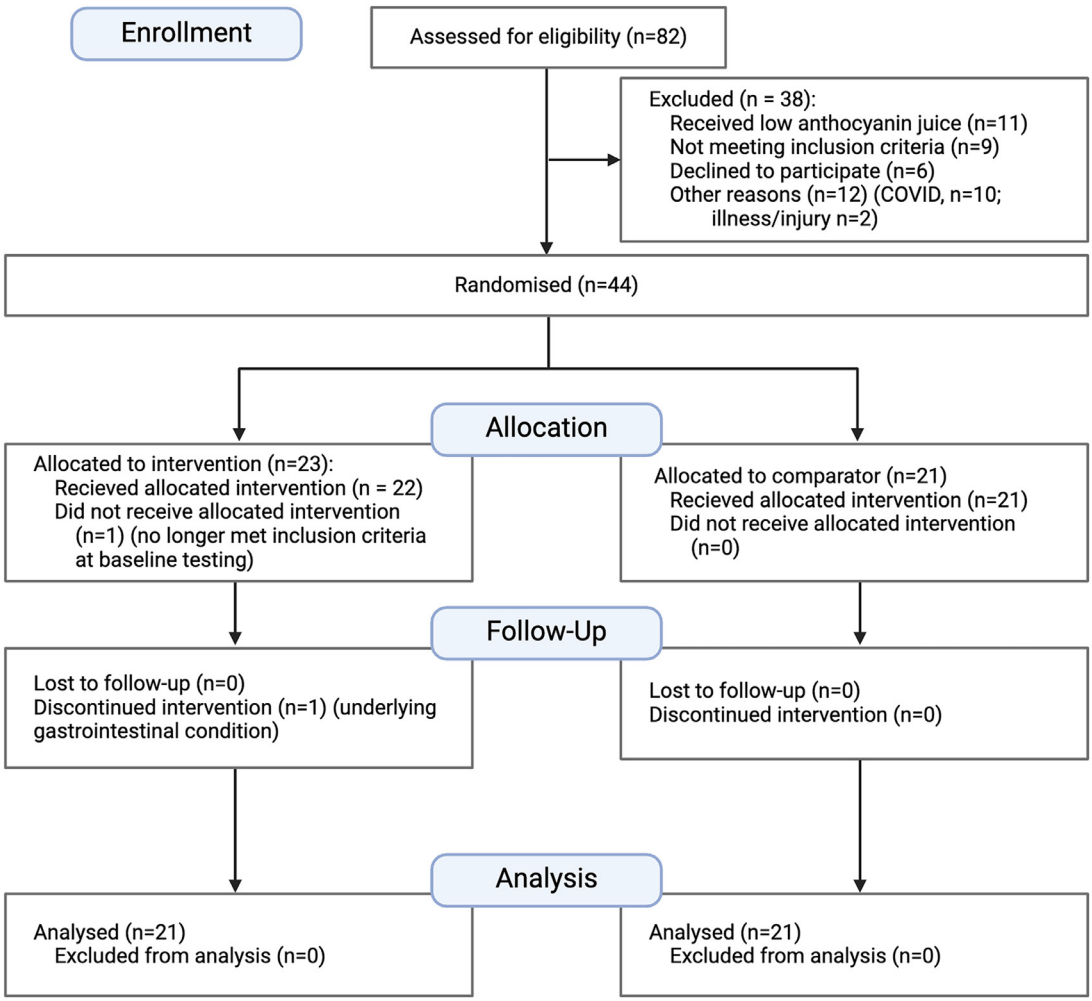

FIG. 2 – CONSORT flow diagram of the progress through the phases (i.e., enrolment, intervention allocation, follow-up, and data analysis) of a double-blind randomized controlled trial examining the effect of daily consumption of Queen Garnet plum juice and a group-based memory program on cognition in older adults with mild cognitive impairment. Created with BioRender.com.

group received apricot juice (Tropico Fruits Pty Ltd, QLD, Australia) that had a similar consistency, color (using food dyes) and nutritional content to the QGP juice, but without anthocyanins. The anthocyanin content of both juices was analyzed by Queensland Department of Agriculture and Fisheries (DAF, QLD, Australia) by a fully validated High Pressure Liquid Chromatography (HPLC) method [39] (details in S1). Due to delays in the trial resulting from COVID-19 restrictions, 2 batches of QGP fruit from different growing seasons were received containing 200.8 mg and 144.5 mg (average 172.65 mg) cyanidin-3-glucoside equivalents (C3G eq.) / 250 ml bottle for the first and second batch of plums, respectively (see Table 1). This

Table 1 – Nutrition information of the dietary intervention (QGP) and comparator (apricot juice control) fruit juices (250 mL) consumed daily for 8 weeks in a study of older adults with MCI

	QGP juice	Apricot juice
Energy (kcal)	98	96
Protein (g)	0.6	0.7
Fat – total (g)	<0.1	<0.1
Saturated fat (g)	<0.1	<0.1
Carbohydrates (g)	22.2	22.2
Dietary fibre (g)	4.4	4.0
Sodium (mg)	6	2
Vitamin C (mg)	0.3	1.2
Anthocyanins[1] (mg)	200.8 (batch 1) 144.5 (batch 2)	0

g, grams; kcal, kilocalorie; MCI, mild cognitive impairment; mg, milligram; QGP, Queen Garnet plum. [1]High Performance Liquid Chromatography; Remaining values were obtained from the Australian Food Composition Database 2019 [1].

dosage was selected based on previous evidence examining the dose-response of adults to anthocyanins, where 80 mg per day (mg/d) was found to be an effective dose for reduction of inflammation in healthy adults [40] and our previous study where 138 mg/d was effective at improving aspects of cognition in older adults with mild-moderate dementia [35]. No anthocyanins were detected in the apricot juice (comparator) (details Table 1 and Table S3).

2.4. *Group-based memory rehabilitation intervention*

The group-based memory rehabilitation intervention was an age-appropriate adapted version of 'Making the Most of your Memory: An Everyday Memory Skills Program' [36]. The group program involved 6 weekly 2-hour face-to-face sessions. Each session involved education about memory and the factors influencing optimal memory function, and training in the use of compensatory strategies, including both internal/mental strategies and external memory aids. Group exercises were adapted from the manualized version to tasks that were applicable to older adults, and homework tasks were set to encourage practice and generalization of strategy use between sessions. There were approximately 6 participants and 2 blinded facilitators per group, including an experienced Clinical Neuropsychologist (ZF). This program was selected based on evidence of improved memory functioning across a range of neurological conditions (epilepsy [12], stroke [13] and mixed neurological conditions [11]). However, it was unknown whether the modified program would be beneficial for a population of individuals with MCI.

2.5. *Baseline measures*

2.5.1. *Demographic data*

Participant age, sex, level of education, and years of education were collected at baseline.

2.5.2. *Measures of general health*

Measures including alcohol consumption (drinking status), and recent exercise history were collected. Exercise was measured by the International Physical Activity Questionnaire – Short Form (IPAQ) [41], which categorizes participants as inactive, minimally active, or HEPA active (health-enhancing physical activity; highly active category) [42]. Handgrip strength (kg) was taken as a measure of maximal upper body strength, where participants were instructed to exert maximal force once using each hand to a hand dynamometer (Jamar Plus, Sammsons Preston Rolyan, Bolingbrook, IL, USA) whilst seated, arm adducted, and elbow at a 90° angle [43]. A 30-second sit-to-stand test (number of stands completed) was performed as a measure of lower extremity performance, where participants were instructed to perform as many chair stands, with arms folded across their chest, as possible in a 30-second period [44]. Anthropometric measures, including waist and hip circumference (cm) were obtained using a tape measure (SECA 201 1 mm graduation) and waist-to-hip ratio was calculated as a measure of adiposity by dividing waist circumference by hip circumference. Height was measured using a stadiometer (SECA 217 1 mm graduation) and weight using a floor scale (SECA 874 þ/- 100 g). Body mass index (BMI) was then calculated using the standard formula: $weight\ (kg)/height\ (m)^2$.

2.5.3. *Habitual diet*

Habitual diet was assessed at baseline using a 3-day food record and analyzed for daily nutrient intake using Foodworks (Version 10, Xyris Software, Australia), which references the Australian Food Composition Database [45]. Anthocyanin intake was calculated by cross-referencing the dietary data with the 'PhenolExplorer' polyphenol food composition database [46]. Participants were instructed to maintain their usual diet throughout the course of the study.

2.5.4. *Baseline measures of cognition*

Cognitive measures additional to the outcome measures were obtained at baseline to provide a broad overview of the cognitive status of participants prior to the study, including the Mini-Mental State Examination (MMSE), estimated IQ from the Test of Premorbid Functioning (TOPF) [47], Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) Digit Span Subtest [48], Trail Making Test (TMT) A and B [49] (normed Tombaugh, 2004 [50]), and the Test of Everyday Attention telephone search subtest (TEA) [51]. Methods for the cognitive tests forming the

post-intervention outcomes of this study are detailed in the main Methods section 2.6.

2.6. Outcome Measures

2.6.1. Cognitive Outcome Measures

The cognitive outcomes were standardized neuropsychological tests and questionnaires administered and scored by registered Clinical Neuropsychologists. Alternative versions of each test were used at different visits to minimize practice effects.

2.6.1.1. Objective Cognitive measures The RAVLT was used to measure auditory anterograde memory function [52]. Total learning and 20-minute delayed recall scores were examined. Normative values for the calculation of z-scores were determined using values previously reported [53]. The Complex Figure Test (CFT-recall) [54] was used to measure anterograde visual memory. T-scores were calculated for the 3-minute Delayed Recall scores based on norms for the Rey CFT-recall [55]. Total score from The Royal Prince Alfred Prospective Memory Test (RPA-ProMem) [56] was used as an objective measure of prospective memory function.

2.6.1.2. Subjective Cognitive Measures Subjective memory was assessed using the Comprehensive Assessment of Prospective Memory (CAPM) using the total score from both self-reported measures (CAPM-self) and measures provided from the perspective of an individual in daily contact with the participant (CAPM-other) [57]. The Everyday Memory Questionnaire (EMQ) self-rating scale was used to assess subjective memory concerns in everyday life [58].

2.6.2. Mood outcome measures

Participants completed the 21-item Depression Anxiety Stress Scale (DASS-21) [59], where self-reported depression, anxiety and stress ratings were obtained.

2.6.3. 24-hour ambulatory blood pressure outcome measures

The 24-h ambulatory blood pressure was measured using an automated ambulatory blood pressure monitor (7100; Welch Allyn, NSW, Australia). Participants were fitted with the device and provided with appropriate instructions for its use. Measurements were considered errors and excluded if SBP $\leq$70 mmHg or $\geq$250 mmHg, and DBP $\leq$30 mmHg or $\geq$130 mmHg. 24-hour blood pressure measurements were divided into daytime (defined as 09-21 h) and night-time (defined as 23-05 h) measurements and a "dipping" pattern was calculated using a ratio of night-time/daytime blood pressure in order to identify abnormal blood pressure variation which can indicate increased cardiovascular risk that is undetected using single timepoint measurements [60].

2.7. Statistical analyses

All statistical analyses were conducted using SPSS Statistics (v29; SPSS Inc., IL, USA) and PRISM (v9; GraphPad Software Inc., CA, USA). Shapiro-Wilk statistics and visual inspection of data distribution were conducted to assess normality. Differences in baseline demographic, health and anthropometric measures, dietary intake, and cognition between the QGP treatment group and comparator group were analyzed by independent sample t-test, Mann-Whitney U, or chi-squared tests depending on data distribution. Outcome measures were analyzed using a mixed model factorial ANOVA with TIME as the within-subjects factor and TREATMENT as the between-subjects factor. Eta-squared (η^2) values were provided as an indication of effect size. G*Power (Version 3.1.9.2; Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany; http://www.gpower.hhu.de/) [61] was used to calculate power for the critical interaction between TREATMENT and TIME on RAVLT (the primary outcome measure). Using previously published data [35] to determine the parameters, the calculation revealed that to detect a small to medium effect (F =.15) on RAVLT, 72 participants were required to achieve a power of 0.8. However, due to COVID-19 and subsequent unexpected resource constraints, 42 participants completed the study. A post-hoc power calculation revealed that with the sample size obtained the study was underpowered at 76% compared to the accepted 80% for clinical trials [62]. Due to the limited sample size, and following consultation with qualified statisticians, further exploratory post hoc analyses using Bonferroni corrected pairwise comparisons were examined to explore any significant changes over time for each group (comparators: pre vs post, QGP: pre vs post) and between groups at each timepoint (QGP vs comparator). Data were presented as mean and standard deviation (SD) unless otherwise stated. Significance was accepted at alpha $P < .05$, and $P = .050 - .090$ was considered a non-significant trend.

3. Results

3.1. Baseline comparisons

There were no significant differences between the groups for demographic, anthropometric or other general health measures at baseline (details Table 2). There were no significant differences between the groups at baseline for habitual dietary measures, including anthocyanin intake; however, a non-significant trend towards higher habitual vitamin A consumption in the comparator group at baseline was identified ($P = .070$) (details Table S4). There were also no significant differences between the groups at baseline for the additional baseline measures of cognition (details Table 3).

3.2. Cognitive outcomes

For RAVLT total, there was a significant main effect of TIME ($F(1, 39) = 5.22$, $P = .028$, $\eta^2 = .12$) showing that auditory anterograde memory function significantly improved between baseline (mean = −.97 (SD = .72)), and post-testing (−.74 (.98)). There was no main effect of TREATMENT ($P = .816$) nor a significant TIME x TREATMENT interaction ($P = .722$); however further exploratory pairwise comparisons showed a nonsignificant trend in the difference from baseline to post-testing for the QGP treatment group (mean change +28.04%, $P = .073$) but not the comparator group (mean change +19.97%, $P = .176$) (Fig. 3**A**). For RAVLT long delay there was no significant main effect of TIME ($P = .436$) or TREATMENT ($P = .585$), no signifi-

Table 2 – Baseline demographic, general health and anthropometric measures of older adults with MCI that participated in a double-blind randomized controlled trial examining the effect of daily consumption of a high-anthocyanin plum juice and a group-based memory program on cognition

	All	Comparator	Treatment	*P*-value
Age (years)	75.60 (6.78)	76.29 (6.99)	74.90 (6.66)	.516
Sex (%)				.121
Male	22 (52.4%)	14 (66.7%)	8 (38.1%)	
Female	20 (47.6%)	7 (33.3%)	13 (61.9%)	
Education level (%)				.277
Primary	5 (11.9%)	2 (9.5%)	3 (14.3%)	
Secondary	16 (38.1%)	6 (28.6%)	10 (47.6%)	
TAFE/diploma/vocational	9 (21.4%)	6 (28.6%)	3 (14.3%)	
Undergraduate	9 (21.4%)	4 (19.0%)	5 (23.8%)	
Post-graduate	3 (7.1%)	3 (14.3%)	0 (0.0%)	
Years of Education	12 (IQR 5)	12 (IQR 4.5)	10 (IQR 5)	.468
Drinking status (%)				.691
Non-drinker	12 (28.6%)	7 (33.3%)	5 (23.1%)	
<1 per day	16 (38.1%)	8 (38.1%)	8 (38.1%)	
1-2 per day	14 (33.3%)	6 (28.6%)	8 (38.1%)	
Exercise (%)				.852
Inactive	14 (33.3%)	6 (28.6%)	8 (38.1%)	
Minimally active	19 (45.2%)	10 (47.6%)	9 (42.9%)	
HEPA active	9 (21.4%)	5 (23.8%)	4 (19.0%)	
Hand-grip strength (kg)	22.22 (8.17)	23.77 (8.56)	20.68 (7.64)	.224
Sit-to-stand test	12 (IQR 5)	12 (IQR 6.5)	12 (IQR 3)	.861
Waist-to-hip ratio	0.94 (0.09)	0.96 (0.09)	0.92 (0.09)	.220
BMI (kg/m^2)	26.23 (3.86)	25.93 (2.85)	26.53 (4.73)	.624
Day SBP (mmHg)	128.33 (17.35)	131.52 (22.18)	125.97 (12.89)	.295
Day DBP (mmHg)	78.29 (10.53)	79.58 (9.45)	77.34 (11.42)	.520
SBP night/day ratio	0.94 (0.10)	0.90 (0.12)	0.96 (0.07)	.095
DBP night/day ratio	0.91 (0.12)	0.90 (0.10)	0.92 (0.13)	.600

BMI, body mass index; DBP, diastolic blood pressure; HEPA, health enhancing physical activity; kg, kilogram; kg/m^2, kilogram per square meter; MCI, mild cognitive impairment; mmHg, millimeters of mercury; SBP, systolic blood pressure. Data presented as mean (SD), median (IQR), or frequency (%); *p*-value for independent samples *t*-test, Mann-Whitney *U* or chi-square test between treatment ($n = 21$) and control ($n = 21$) groups at baseline.
*$P < .05$; $N = 33$-42.

Table 3 – Mean standardized scores for cognitive tests in older adults with MCI who participated in a double-blind randomized controlled trial examining the effect of daily consumption of QGP juice (vs comparator) and a group-based memory program on cognition (RAVLT total, RAVLT long delay, CFT-recall, RPA-ProMem, CAPM self-report, CAPM other-report, and EMQ)

Parameter	Group	n	Baseline	Post-testing	TIME	TREATMENT	TIME x TREATMENT
RAVLT total	Comparator	21	−0.98 (0.78)	−0.78 (1.07)	.028	.816	$F(1, 39) = .13$,
	Treatment	20	−0.96 (0.67)	−0.69 (0.89)			$P = .722$, $\eta^2 = .003$
RAVLT long delay	Comparator	21	−1.10 (1.13)	−1.06 (1.15)	.436	.585	$F(1, 39) = .19$,
	Treatment	20	−0.97 (1.00)	−0.84 (1.12)			$P = .667$, $\eta^2 = .005$
CFT-recall	Comparator	21	51.24 (17.85)	51.67 (16.23)	.036	.876	$F(1, 39) = 3.65$,
	Treatment	20	48.80 (15.17)	55.60 (14.95)			$P = .063$, $\eta^2 = .086$
RPA-ProMem	Comparator	17	4.76 (3.65)	6.82 (4.75)	< .001	.280	$F(1, 35) = .022$,
	Treatment	20	6.05 (3.63)	7.95 (2.67)			$P = .883$, $\eta^2 = .001$
CAPM-self	Comparator	16	1.80 (0.54)	1.57 (0.36)	.007	.311	$F(1, 30) = .005$,
	Treatment	16	1.96 (0.63)	1.74 (0.50)			$P = .942$, $\eta^2 = .000$
CAPM-other	Comparator	14	2.07 (0.83)	2.10 (0.83)	.768	.131	$F(1, 25) = .006$,
	Treatment	13	1.68 (0.28)	1.70 (0.62)			$P = .939$, $\eta^2 = .000$
EMQ	Comparator	15	1.71 (0.45)	1.61 (0.43)	.280	.462	$F(1, 29) = .000$,
	Treatment	16	1.84 (0.65)	1.73 (0.54)			$P = .983$, $\eta^2 = .000$

CAPM, Comprehensive Assessment of Prospective Memory; CFT, Complex Figure Test; EMQ, Everyday Memory Questionnaire; MCI, mild cognitive impairment; QGP, Queen Garnet plum; RAVLT, Rey Auditory Verbal Learning Test; RPA-ProMem, Royal Prince Alfred Prospective Memory Test. Measurements were conducted at baseline and at the end of the 8-week study (post-testing). Data presented as mean (SD), *p*-values for 2 × 2 mixed model factorial ANOVA; $N = 28$-42.

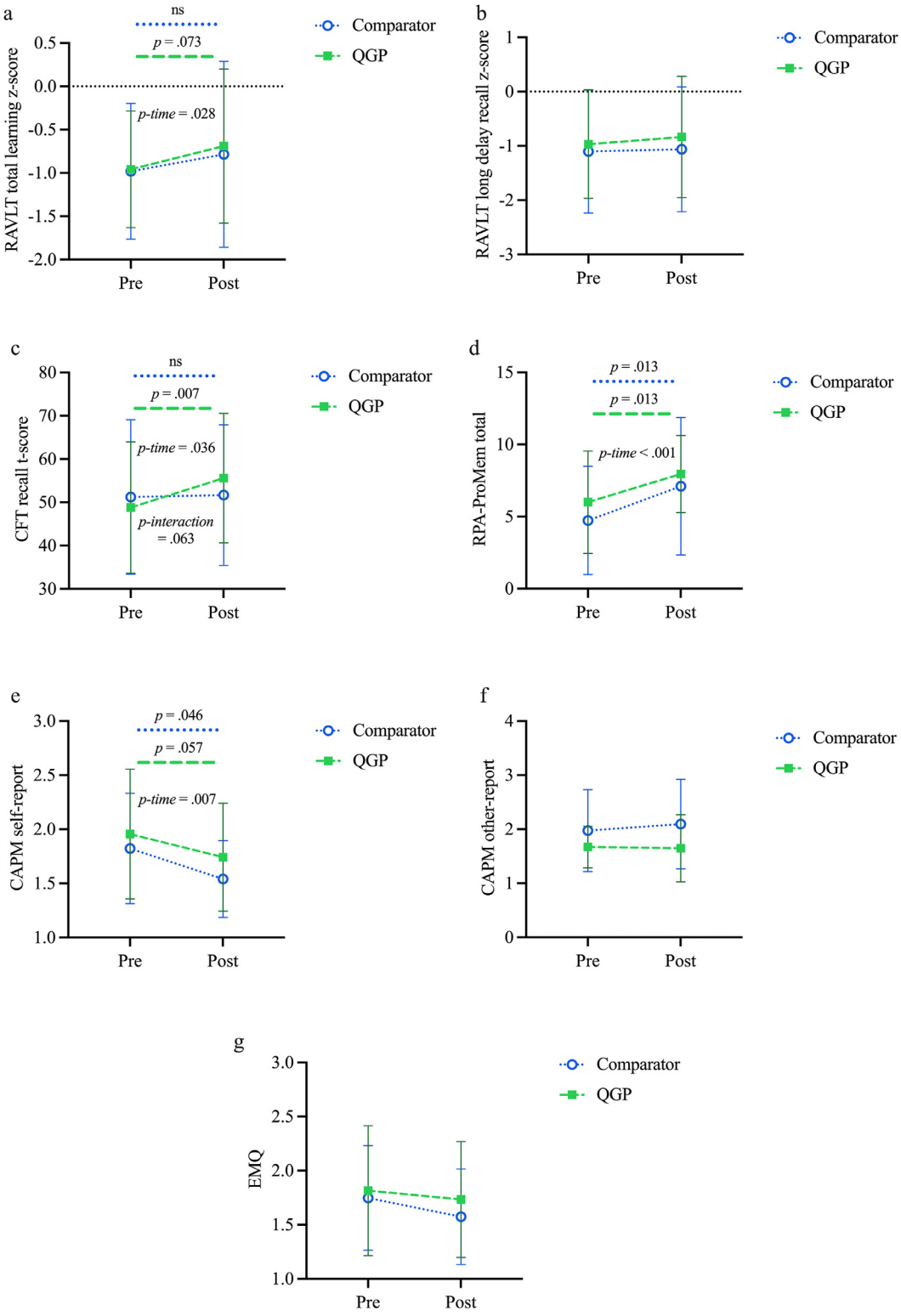

FIG. 3 – Mean standardized scores for cognitive tests in older adults with MCI who participated in a double-blind randomized controlled trial examining the effect of daily consumption of a QGP juice (vs comparator) and a group-based memory program on cognition: (A) RAVLT total, (B) RAVLT long delay, (C) CFT-recall, (D) RPA-ProMem, (E) CAPM self-report, (F) CAPM other-report, and (G) EMQ. Measurements were conducted at baseline (pre) and at the end of the 8-week study (post). Data presented as mean ± standard deviation; *p-time*, main effect of TIME; *p-interaction*, TIME x TREATMENT interaction; blue dotted line *p:* comparator pre vs post (*n* = 14-21); green dashed line *p:* QGP pre vs post (*n* = 14-21); N = 28-42. CAPM, Comprehensive Assessment of Prospective Memory; CFT, Complex Fig. Test; EMQ, Everyday Memory Questionnaire; MCI, mild cognitive impairment; QGP, Queen Garnet Plum; RAVLT, Rey Auditory Verbal Learning Test; RPA-ProMem, Royal Prince Alfred Prospective Memory Test.

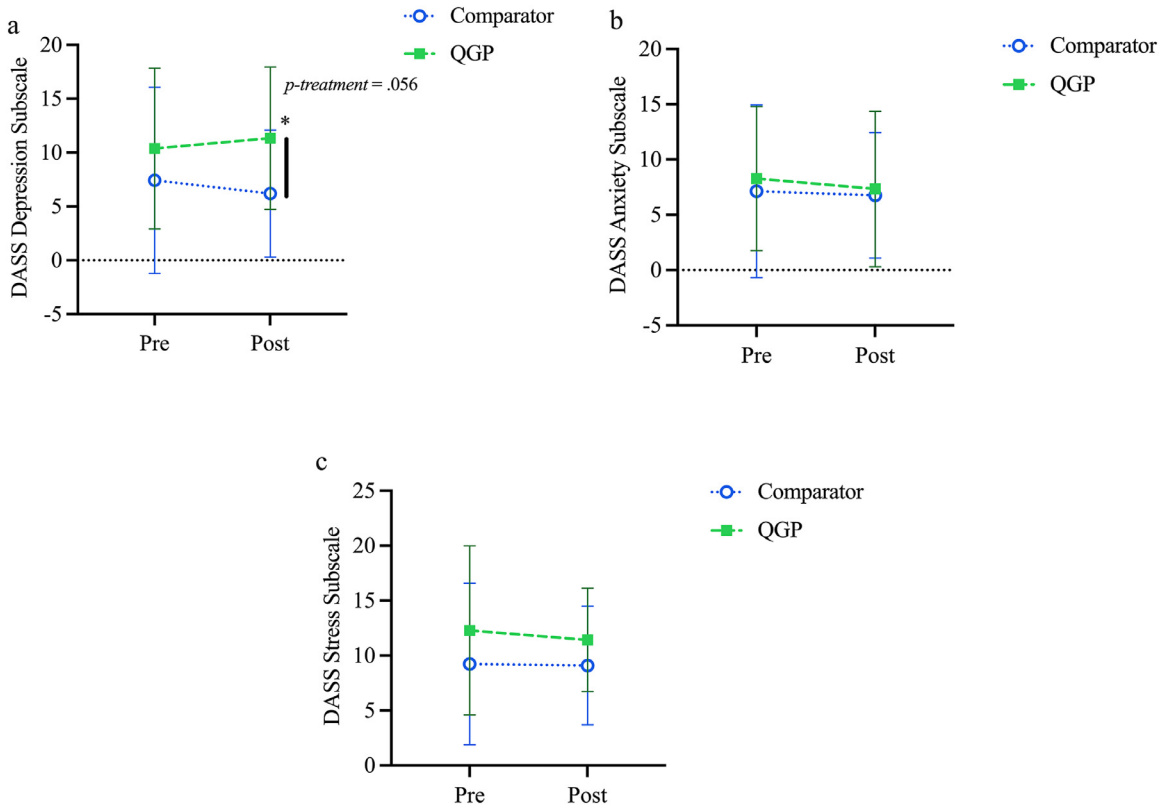

FIG. 4 – Mean DASS-21 scores for older adults with MCI that participated in a double-blind randomized controlled trial examining the effect of daily consumption of a QGP juice (vs comparator) and a group-based memory program on: (A) depression, (B) anxiety, and (C) stress subscales of the DASS-21. Measurements were conducted at baseline (pre) and at the end of the 8-week study (post). Data presented as mean ± standard deviation; *p-treatment:* QGP vs comparator; *P < .05 QGP vs comparator at post-testing; *n* = 21; *N* = 42. DASS-21, Depression Anxiety and Stress Scale 21; MCI, mild cognitive impairment; QGP, Queen Garnet Plum.

cant TIME x TREATMENT interaction ($P = .667$), and no further differences observed (Fig. 3**B**).

Total recall scores for visual anterograde memory also improved, with a significant main effect of TIME on CFT-recall ($F(1, 39) = 4.70$, $P = .036$, $\eta^2 = .11$), showing increased scores for the combined groups at post-testing (53.59 (15.55)) compared to baseline (50.05 (16.44)). There was no significant main effect of TREATMENT ($P = .876$); however, a non-significant trend towards a TIME x TREATMENT interaction was observed ($F(1, 39) = 3.65$, $P = .063$, $\eta^2 = .09$). Examination of the means indicated that the QGP treatment group showed a greater improvement from baseline (48.80 (15.17)) to post-testing (55.60 (14.95)) than the comparator group (baseline 51.24 (17.85), post-testing 51.67 (16.23)). Indeed, pairwise comparisons showed that the change from baseline to post-testing was significant for the QGP treatment group (mean change +13.93%, $P = .007$) but not the comparator group (mean change +0.84%, $P = .855$) (Fig. 3**C**).

There was a significant main effect of TIME for prospective memory ($F(1, 35) = 13.74$, $P < .001$, $\eta^2 = .28$) whereby RPA-ProMem scores were higher at post-testing (7.43 (3.75)) compared to baseline (5.46(3.65)) (Fig. 3**D**); however, there was no main effect of TREATMENT ($P = .280$), or TIME x TREATMENT interaction ($P = .883$). Further exploration of the data revealed that the significant changes over time were apparent for both the QGP (+31.40%, $P = .013$) and comparator groups (+43.21%, $P = .013$) (Fig. 3**D**).

For the self-reported CAPM scores, there was a significant main effect of TIME ($F(1, 30) = 8.28$, $P = .007$, $\eta^2 = .22$) with participants reporting significantly fewer memory lapses at the end of the study (1.66(.44)) compared to baseline (1.88(.58)), but no main effect of TREATMENT ($P = .311$), nor a significant TIME x TREATMENT interaction ($P = .942$) (Fig. 3**E**). However, further examination of the data via pairwise comparisons identified that there was a significant improvement from baseline to post-testing for the comparator group (−12.67%, $P = .046$) and a non-significant trend towards an improvement in the QGP treatment group (−11.03%, $P = .057$) (Fig. 3**E**). On the other hand, there was no significant main effect of TIME ($P = .768$), TREATMENT ($P = .131$), nor a significant TIME x TREATMENT interaction ($P = .939$) on CAPM provided from the informant perspective (CAPM-other) (Fig. 3**F**). The EMQ also showed no significant main effect of TIME ($P = .280$), TREATMENT ($P = .462$), nor a significant TIME x TREATMENT interaction ($P = .983$) and no other significant differences between groups (Fig. 3**G**).

Table 4 – 24-hour ambulatory SBP and DBP parameters in older adults with MCI that participated in a double-blind randomized controlled trial examining the effect of daily consumption of QGP juice (vs comparator) and a group-based memory program. Measurements were conducted at baseline and at the end of the 8-week study (post-testing)

Parameter	Group	n	Baseline	Post-testing	TIME	TREATMENT	TIME x TREATMENT
Day SBP (mmHg)	Comparator	17	132.44 (20.63)	126.85 (10.78)	.087	.274	$F(1, 35) = .144$, $P = .707$ $\eta^2 = .004$
	QGP	20	126.54 (12.79)	122.93 (16.58)			
Day DBP (mmHg)	Comparator	17	78.97 (9.03)	78.71 (8.26)	.360	.256	$F(1, 35) = .566$, $P = .457$, $\eta^2 = .016$
	QGP	20	76.74 (11.44)	74.26 (9.94)			
24 h SBP (mmHg)	Comparator	14	126.73 (17.49)	125.79 (9.08)	.473	.698	$F(1, 31) = .041$, $P = .842$, $\eta^2 = .001$
	QGP	19	125.27 (14.34)	123.60 (14.29)			
24 h DBP (mmHg)	Comparator	14	76.41 (8.54)	78.43 (8.26)	.776	.523	$F(1, 31) = 1.30$, $P = .263$, $\eta^2 = .040$
	QGP	19	76.00 (11.96)	74.79 (9.07)			
Nocturnal SBP (mmHg)	Comparator	14	116.61 (11.49)	118.37 (14.39)	.977	.576	$F(1, 31) = .727$, $P = .400$, $\eta^2 = .023$
	QGP	19	121.39 (18.38)	119.74 (18.71)			
Nocturnal DBP (mmHg)	Comparator	14	70.92 (9.66)	72.78 (13.47)	.742	.716	$F(1, 31) = .818$, $P = .373$, $\eta^2 = .026$
	QGP	19	70.76 (14.20)	69.90 (11.80)			
SBP night/day ratio	Comparator	14	.902 (.123)	.930 (.130)	.494	.184	$F(1, 31) = .288$, $P = .596$, $\eta^2 = .009$
	QGP	19	.961 (.072)	.965 (.136)			
DBP night/day ratio	Comparator	14	.895 (.097)	.905 (.122)	.724	.596	$F(1, 31) = .024$, $P = .878$, $\eta^2 = .001$
	QGP	19	.917 (.131)	.921 (.104)			

DBP, diastolic blood pressure; MCI, mild cognitive impairment; mmHg, millimeters of mercury; QGP, Queen Garnet Plum; SBP, systolic blood pressure. Data presented as mean (SD), *p*-values for 2 × 2 mixed model factorial ANOVA; $N = 33$-37.

3.3. *Mood outcomes*

3.3.1. *Depression, Anxiety and Stress Scales*

For the DASS-21 depression subscale there was no significant main effect of TIME ($P = .869$) and no significant TIME x TREATMENT interaction ($P = .210$); however, there was a non-significant trend towards a main effect of TREATMENT ($F(1, 40) = 3.86$, $P = .056$, $\eta^2 = .09$), with participants in the QGP treatment group (10.86 (1.46)) trending towards a higher mean score on the depression scale compared to the comparator group (6.81 (1.46)) (+37.29%) regardless of timepoint (Fig. 4**A**). Exploratory pairwise comparisons showed a significant difference between groups at post-testing ($P = .011$) with a significant difference between QGP and the comparator group that was not apparent at baseline ($P = .244$) (Fig. 4**A**). There was no significant main effect of TIME ($P = .484$) or TREATMENT ($P = .650$), nor a significant TIME x TREATMENT interaction ($P = .764$) observed when analyzing the anxiety scale data (Fig. 4**B**) and no significant main effect of TIME ($P = .584$) or TREATMENT ($P = .134$), nor a significant TIME x TREATMENT interaction ($P = .696$) on the stress scale (Fig. 4**C**).

3.4. *24-hour ambulatory blood pressure outcomes*

There were no significant TIME, TREATMENT, or TIME x TREATMENT interaction effects on the 24-hour ambulatory systolic and diastolic blood pressure parameters (daytime, nocturnal and 24-h, and dipping patterns; all $P > .05$). However, for daytime SBP blood pressure there was a non-significant trend towards a main effect of TIME ($F(1, 35) = 3.10$, $P = .087$ $\eta^2 = .081$) with participants' daytime SBP trending towards an improvement from baseline (129.25 (16.86)) to post-testing (124.73 (14.16)), results summarized in Table 4.

4. Discussion

The present study investigated the ability of fruit-based anthocyanin supplementation to improve cognition, mood and blood pressure in older adults with MCI undergoing a group-based memory rehabilitation program. Anterograde auditory (RAVLT total) and visuospatial (CFT-recall) learning and memory, and both objective and subjective prospective memory (RPA-ProMem and CAPM-self, respectively) significantly improved in both groups during the study, suggesting efficacy of the group-based memory rehabilitation program in improving aspects of learning and memory in older adults with MCI. This is the first study to investigate the efficacy of the 'Making the most of your memory' [36] group-based memory rehabilitation program in an MCI population and further research validating the efficacy of this program in MCI is required as the present study did not have a group who did not receive the memory program. To our knowledge, this is also the first study to examine the impact of combining an anthocyanin-rich food source with a group-based memory rehabilitation program. In contrast to our hypothesis, the group that received QGP supplementation did not have additional benefits, over and above the memory training intervention, for any of the outcomes investigated including the battery of cognitive tests, 24-hour blood pressure, depression, anxiety or stress.

In this relatively small sample of individuals with MCI, additional exploratory post hoc analyses were conducted for pairwise, within-group (pre vs post) and between group (QGP vs comparator) comparisons. In those analyses, the QGP group showed improvements in anterograde visuospatial recall over time that were not evident in the comparator group. While the effects of anthocyanins on the anterograde visuospatial recall has not previously been reported, a

previous study has demonstrated a positive effect of anthocyanins (138 mg/d, for 6 weeks) on verbal/auditory memory measures (RAVLT and verbal fluency task) and blood pressure in individuals with mild-to-moderate AD [35]. Improved verbal memory was also observed in older adults with age-related memory decline after 12 weeks of daily consumption of concord grape juice [63] and blueberry juice [64]. Additionally, in healthy adults, consumption of freeze-dried wild blueberry powder (302 mg anthocyanins/d) had significant improvements in blood pressure, verbal learning and cognitive flexibility compared to the comparator group [65]. In contrast, a study utilizing purified anthocyanin capsules (320 mg/d) compared to placebo in individuals at increased risk for dementia, found no significant between-group differences [66]. The difference in results could potentially be attributed to several factors, including use of purified anthocyanin compared to the whole foods administered in other studies, processing of anthocyanins that can result in degradation [67], and cohort characteristics. The discrepancy between studies examining anthocyanin-rich food interventions and purified anthocyanin capsules could also indicate that there are other compounds within these anthocyanin-rich foods that are responsible for these beneficial effects. In addition, although in vitro studies demonstrate strong antioxidant effects of phenolic compounds, including anthocyanins [23,68–71], in vivo results are varied and negative findings could be attributed to the bioavailability of polyphenols, as low plasma concentrations have been reported after consumption in humans [72].

Several measures of cognition improved over time regardless of treatment group, indicating potential beneficial effects of participation in the group-based memory rehabilitation program. Improvements were found in anterograde auditory learning (RAVLT total) and self-reported prospective memory (CAPM-self), which coincides with previous research that utilized this program in populations of people with other neurological disorders [11–13]. Interestingly, the present study also found improvements in other areas of cognition, including visual memory (CFT-recall) and objective prospective memory (RPA-ProMem). Visuospatial aspects of learning and memory are primarily affected in early AD, as visuospatial deficits are indicative of medial and lateral parietal lobe dysfunction, which is uniquely affected in the early stages of AD [73,74]. Indeed, participants in the present study were selected based on the probable presence of aMCI, which has a high risk of progressing to AD [2]. In the present study, we also identified improved self-reported prospective memory, which was echoed in the RPA prospective memory test, but not in the CAPM other-report. This result was not entirely unexpected, as research indicates that self-, informant-, and performance-based measures of prospective memory may demonstrate varying aspects of prospective memory function [75]. The positive CFT-recall and RPA prospective memory test findings are important in the context of the existing literature as the previous studies that employed the group-based memory rehabilitation program for other indications did not identify improvements in these memory domains [11–13]. Therefore, we show for the first time that the modified memory training program utilized in the present study had unique benefits in an MCI population. Previous evidence suggests that the severity of impairment is an important predictor of training effects [11], which may explain why improvements to these domains were specific to MCI.

As behavioral disorders and psychological symptoms are often comorbid with MCI and affect its presentation and course [76], depression, anxiety, and stress scores were examined in participants in the present study. We did not identify any changes in anxiety or stress, however there was a trend towards higher depression scores in the treatment group. This was unexpected as participation in group activities reportedly has a protective effect against depression anxiety and stress in older adults [77] and a high anthocyanin intake has previously been associated with lower depression scores in people with and without major depressive disorder [78]. However, evidence suggests that the response of individuals to treatment is complex. For example, a recent study showed that a single acute dose of blueberry supplementation reduced Beck Depression Inventory-II (BDI-II) scores in self-reported depressed participants; however, after 6 weeks of treatment, the depression scores were significantly worse than the comparator group [79]. The authors suggested the presence of a biphasic response to anthocyanin administration. In the present study, we examined depression scores prior to the start, and at the end of the intervention period and further studies that examine depression over time are justified.

In the present study, there was also a lack of significant improvement in blood pressure following QGP treatment. While this was unexpected, this is the first study to examine the effect of anthocyanins on blood pressure in MCI and there is recent evidence of inconsistent findings in the literature, including a meta-analysis, which concluded that supplementation of anthocyanins had limited clinical efficacy in reducing blood pressure [80]. This may be due to the mounting confounding evidence about the effects of anthocyanins on blood pressure that are likely to be underpinned by methodological (e.g. dosage, duration of treatment) and cohort characteristics variability. For example, 1 study found that anthocyanin treatment could reduce blood pressure in a population who were hypertensive and overweight or obese [81], while other studies reported a change in blood pressure after 12 weeks of administration [35,65,81].

This study was conducted throughout the COVID-19 pandemic and was impacted by several lockdowns, which resulted in fewer participants than originally intended to achieve sufficient power. Our smaller sample size also limited our ability to conduct subgroup analyses and include covariates that would result in a further loss of power. In addition, both empirical evidence and published data show that the COVID-19 pandemic and lockdowns induced stress, isolation and uncertainty, particularly for older adults in the community [82], which may have impacted our results. Another consideration that is relevant for nutritional intervention studies is the selection of the control. As the aim of this study was to examine the efficacy of anthocyanins on memory and other health parameters in individuals undergoing a group-based memory program, the intervention was an anthocyanin-rich QGP juice compared to a nutritionally similar juice that lacked anthocyanins (comparator: apricot). It has been reported that apricots contain some polyphenols [83] that could have affected the results; however, the polyphenol family includes a broad range of compounds and the focus of this study was anthocyanins (a subclass of

phenols). In future research, additional analyses at the species level of bioactive compounds that nutritional interventions contain would be an important addition that would allow more precise interpretation, reproducibility and comparison of results across similar studies. Importantly, the results from our analysis showed an absence of anthocyanins in the apricot juice. In addition, the apricot juice was a commercially available pasteurized long-life juice and exposure to high temperatures during the pasteurization process, as well as long storage duration, has been shown to reduce the polyphenol content of various juices [84]. Therefore, it is unlikely that phenols were delivered in a sufficient dosage to drive benefits in the comparator group in the present study. As discussed in our previous publications [27], there are ongoing challenges and limitations researchers should consider in relation to selecting an appropriate control for dietary intervention studies. In addition, future studies would benefit from measuring plasma and urine concentration of anthocyanins and phenolic metabolites to understand bioavailability and inter-individual variation in metabolism of in participants. Another consideration of this study is that MCI does not necessarily translate to neurodegeneration and progression to AD in all individuals [1]. MCI is a heterogenous diagnostic category and although we included participants with aMCI, our sample likely contained both participants who may progress to an AD diagnosis and those with MCI related to different pathologies. The neuroprotective effects of anthocyanins may not be effective at improving cognition in people without neurodegeneration, which suggests that further research into specific subgroups of individuals with MCI may be of benefit. Importantly, there are no known negative effects of anthocyanin consumption [85]. Therefore, an increase in dietary anthocyanin consumption may offer a low-risk option for individuals seeking to protect or improve cognitive health; however, further research is needed. Despite demonstrating an overall positive effect of the group-based memory intervention in older adults with MCI in the present study, these benefits have been inferred based on time effects and further studies examining the efficacy of this program in individuals with MCI compared to patients who do not engage in the program (controls) are justified in this cohort. Additionally, the lack of another intervention arm that received the QGP juice but not the memory training program may have shed more light on the comparative benefits of both interventions, when implemented separately. We suggest that further adequately powered studies are needed to investigate this aspect and thus guide clinical advice offered to older adults with MCI.

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Author declarations

None.

Ethics approval

This clinical trial was approved by the joint University of Wollongong and Local Health District Human Research Ethics Committee, NSW, Australia (HREC 2017/581), registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618001184268), conducted according to the Declaration of Helsinki and adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement.

Consent to participate/publish

Informed consent was obtained from all individual participants included in the study.

Sponsor's role

The funding sources had no input into the design, methods, subject recruitment, data collection, analyses or preparation of the paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nutres.2025.04.006.

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