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The effect of grape seed procyanidins extract on cognitive function in elderly people with mild cognitive impairment: A randomized, double-blind, placebo-controlled clinical trial

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ABSTRACT

Background: Procyanidins have antioxidative properties that may protect against age-related brain oxidative stress. Previous studies indicated that procyanidin-rich foods could improve cognitive function and prevent neurodegenerative diseases. This study hypothesized that grape seed procyanidins extract (GSPE) would have a favorable effect on cognitive function in elderly people with mild cognitive impairment (MCI).

Methods: A community-based, randomized, double-blind, placebo-controlled trial was conducted. Participants aged 60 years or older with MCI were randomly assigned into the GSPE group (n = 35, 320 mg/d) or placebo group (n = 36), and received capsules for 6 months. Cognitive function was assessed using the Montreal Cognitive Assessment Scale (MoCA). The change in MoCA scores between groups were tested by the time × treatment interaction in mixed-design ANOVA.

Results: After 6 months of intervention, the MoCA score was higher than the baseline both in the intervention group and placebo control group, while the there was no significant difference for mean change in MoCA score from baseline between the intervention group and the placebo group (2.35 ± 3.20 vs. 1.28 ± 2.93, $P = 0.192$).

Conclusions: Present study showed that 6-month supplementation with GSPE did not significantly improve cognitive function in subjects with MCI. Further investigations regarding the longer-term intervention effect of procyanidins extract on mild or moderate cognitive disorders are needed.

1. Introduction

Mild cognitive impairment (MCI) refers to an intermediate state between normal aging and dementia, manifested in memory loss which is incompatible with age but not yet reached the diagnosis standard of dementia [1,2]. Around the world, it is estimated that 15.8% of individuals aged 60 or older have MCI in the general population. MCI is well known as an intermediate phenotype for

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Nomenclature

Abbreviations

GSPE	grape seed procyanidins extract
MCI	mild cognitive impairment
MoCA	Montreal Cognitive Assessment Scale
AD	Alzheimer's disease
CDR	Clinical Dementia Rating
ADL:	Activities of Daily Living
GDS	Geriatric Depression Scale
RCT	randomized controlled trial

clinically overt dementia, of whom 14.9% will progress to Alzheimer's disease (AD) or other types of dementia in two years [3]. According to the World Alzheimer report 2018 [4], there are approximately 50 million people with dementia, with the involved cost adding up to a trillion US dollars per year. Therefore, it is of great significance to delay the progression from MCI to dementia.

A recent cohort study showed that polyphenol intake was associated with a lower risk of dementia and AD [5]. Procyanidins are a major group of antioxidant substances in polyphenols and consist of flavan-3-ol units and various oligomers with a degree ranging from 2 to 10 [6]. Procyanidins have antioxidative and anti-inflammatory properties that may protect brain health against neurodegenerative diseases [7–9]. Animal studies show that procyanidins extract reduced the generation of toxic peptides and significantly improved cognitive performance in aged rats [10]. Although several interventional studies for 6–16 weeks found the beneficial role of procyanidin-rich foods (*e.g.* cocoa diet, grape juice) on cognitive function in adults with intact cognition and MCI, the results were inconsistent [11–17]. More importantly, it remains unclear whether the observed effects in those studies are attributed to procyanidins or other components in the foods, the effect of procyanidins extract on cognitive function in humans remains unknown.

Therefore, we hypothesized that grape seed procyanidins extract (GSPE) would have a favorable effect on cognitive function in elderly people with MCI. A randomized controlled trial (RCT) was conducted to assess the effect of daily consumption of GSPE supplements for 6 months on cognitive performance in elderly people with MCI.

2. Methods

2.1. Study population

Participants were recruited from a previous cognitive screening study to identify subjects with MCI among the elderly in communities of Huangshi City, Hubei Province, China [18]. Briefly, 4327 community-dwelling adults aged 60 years or older were invited for cognitive assessment by two physicians, and among them, 1148 were willing to participate in the assessment through household interviews. Among them, 296 were diagnosed as MCI following Petersen's criteria [19]: reported memory complaints by the patient himself, family members, or insiders; objective cognitive impairment (scoring 1.5 standard deviations below the age-appropriate mean); absence of dementia [the overall decline in the scale of Clinical Dementia Rating (CDR) in 0.5 points or less]; intact daily functioning. The inclusion criteria and exclusion criteria are shown in Box 1for details. The flow diagram for participant inclusion in the cognitive screening and in this clinical trial is depicted in Figure 1.

2.2. Study procedure

The present study was a randomized, double-blind, parallel-group, placebo-controlled, 6-month trial conducted between June 2016 and December 2016, CONSORT 2010 checklist was uploaded as **Supplementary file 1**. The study has been registered online and approved at the China Clinical Registration Center (registration number: ChiCTR-IPR-16008164). The study protocol was also approved by the Medical Ethics Committee of Medical College, Wuhan University of Science and Technology (Approved number of the ethic committee: WUSTMC-201550). Written informed consent was obtained from all participants.

The intervention substance is extracted from grape seeds rich in procyanidins and formed into grape seed extraction capsules after a series of extraction processing. In similar studies, we did a summary of intervention studies on older adults, and found that procyanidins dosage in most of the studies were in the range of 100–900 mg/day [11,20–25], and the daily intake of the population was in the range of 100–150 mg/day [26,27]. Meanwhile, the safety has been confirmed in clinical trial [28]. Given the daily intake and safety of procyanidins, we selected 320 mg/day as the dosage in this study. We refer to published articles on procyanidins [11,20–25] or blueberry intervention [29,30], and many studies had a short duration than six months. Thus, six-months duration is enough longer to observe the benefits, and could also avoid the potential loss to follow-up due to the longer interventional period.

Among the individuals who were diagnosed with MCI in previous cross-sectional study, 71 participants met the eligibility criteria of this trial, entered the present study, and completed the risk factor questionnaire and the relevant scales, such as Activities of Daily Living (ADL), CDR, and Geriatric Depression Scale (GDS). The process of simple randomization was based on a computer-generated allocation sequence. First, the GSPE group and placebo group were randomly blinded to group A and group B. Each participant was randomly assigned to group A or group B. Only research designer performed the process of allocation concealment, enrolling

participants, and assigning participants to interventions. Participants, interviewers, and statistics experts were blinded to the treatment allocation. Participants (28 females, 43males) were randomized into the GSPE intervention group and the placebo control group, who received either GSPE (320 mg/d) or placebo capsule once daily through 6 months, respectively. The GSPE capsule was consisted of procyanidins, soybean oil, beeswax, phospholipids, gelatin, purified water, glycerin, titanium dioxide. The placebo capsule has the similar composition to GSPE capsule, except procyanidins content. The appearance, taste, quality, and composition of both capsules are shown in Table 1. We provided subjects and caregivers with instructions and contact details and told them that any adverse events such as gastrointestinal symptoms over the treatment period should be reported to the investigators.

During the intervention study period, all subjects were asked not to take other dietary supplements (deep-sea fish oil, vitamin C/E, etc.) or drink alcohol. Besides, we remind the subjects to take the capsules on time through telephone interviews and text messages twice a week. At the end of this trial, the investigators reassessed cognitive function.

2.3. Outcome assessment

The primary outcome was the change in cognitive function over the 6-month intervention period. In intervention studies on cognitive function, the 6-month duration is acceptable to repeat the cognitive test, and widely used in many researches [29,30]. The Montreal Cognitive Assessment Scale (MoCA) was employed to assess cognitive function. MoCA, originally from Canada, has been widely accepted and revised to a variety of versions across the world. The Chinese Changsha version of the MoCA scale used in the present study has been validated [31,32]. It takes 10–20 min to complete and has 30 points, including seven cognitive domains as follows: visual space and executive function, name, attention, language, abstract, delayed recall, and orientation. Higher scores indicate better cognitive performance.

2.4. Statistical analysis

A sample size of 71 participants provided 81% power to detect 0.6 SD in MoCA scores with 70% correlation between two measurements, assuming a 20% loss of follow-up and an α of 0.05. We evaluated the cognitive performance based on the intention-to-treat principle. Descriptive statistics were calculated for all demographics of the study subjects. The change in MoCA scores between groups were tested by time × treatment interaction in mixed-design ANOVA. Continuous variables have been checked for the normal distribution. Differences within groups were tested by paired t-tests or Wilcoxon matched pair rank test (continuous variables) and chi-square test (categorical variables). Within-group differences were tested by paired sample *t*-test. All data analyses were performed using SPSS16.0 (SPSS Inc., Chicago, IL). Two-tailed P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Participants

The flow diagram was shown in Figure 1. Of the 71 participants, 58 subjects completed the whole study. The loss of follow-up rates of the GSPE group and placebo group was 25.71% and 11.11%, respectively. There was no significant difference between the two groups ($|^2 = 2.53$, $P > 0.05$). No difference was observed in baseline characteristics of participants between the two groups (Table 2).

3.2. Compliance with the (GSPE/placebo) supplementation

Based on calculating the pill counts by interview, compliance rates with the GSPE supplementation and placebo were 88.46% and 81.25%, respectively. There was no difference between the GSPE group and placebo group in compliance ($|^2 = 0.569$, $P > 0.05$). During the trial, one participant assigned to the GSPE group reported discomfort and then discontinued taking the capsule.

Table 1
The appearance, taste, quality and composition of both soft capsule[a].

Characteristics	GSPE capsule	Placebo capsule
Color	The capsule is opaque brown and the contents are red-brown	The capsule is opaque brown and the contents are red-brown
Taste scent	No taste and odorless	No taste and odorless
Appearance	Soft capsules, complete appearance, no rupture deformation	Soft capsules, complete appearance, no rupture deformation
Acid value, mg KOH/g	≤6.0	≤6.0
POV, g/100 g	≤0.25	≤0.25
Product specifications	1 g/tablet	1 g/tablet
Main ingredient	Soybean oil, beeswax, phospholipids, gelatin, purified water, glycerin, Titanium dioxide	Soybean oil, beeswax, phospholipids, gelatin, purified water, glycerin, Titanium dioxide
Procyanidins	320 mg	0 mg

aSimilarities and differences between the two soft capsules. POV, peroxide value; GSPE, grape seed procyanidins extract.

Table 2
Baseline characteristics of participants according to allocated treatment[a].

Characteristics	GSPE (n = 35)	Placebo (n = 36)	*P*
Age, y	68.91 ± 4.91	70.53 ± 5.34	0.190
Male, n (%)	24 (68.6)	19 (52.8)	0.173
Married[b], n (%)	29 (82.9)	29 (80.6)	0.802
Education			0.655
College or above, n (%)	3 (8.6)	5 (13.9)	
High school, n (%)	4 (11.4)	5 (13.9)	
Junior high school, n (%)	12 (34.3)	7 (19.4)	
Primary school, n (%)	9 (25.7)	9 (25.0)	
Illiteracy, n (%)	7 (20.0)	10 (27.8)	
Smoking, n (%)	2 (5.7)	3 (8.3)	0.666
Drinking, n (%)	3 (8.6)	5 (13.9)	0.479
Physical activity, n (%)	4 (11.4)	6 (16.7)	0.526
Dietary supplements, n (%)	10 (28.6)	6 (16.7)	0.230
BMI, kg/m^2	23.82 ± 3.26	22.68 ± 3.74	0.176
Hypertension, n (%)	14 (40.0)	19 (52.8)	0.280
Diabetes, n (%)	5 (14.3)	4 (11.1)	0.735
Stroke history, n (%)	10 (28.6)	10 (27.8)	0.941
History of head trauma, n (%)	2 (5.7)	4 (11.1)	0.674

aValues are Mean ± SDs; Comparison between the intervention group and placebo group; *P* values of continuous variables and categorical variables were determined with the use of independent *t*-test and chi-square test; GSPE, grape seed procyanidins extract.
bMarital status were categorized as married (married and living as married), widowed, divorced and single (never married and separated).

3.3. The effect of GSPE on cognitive function

As shown in Table 3, there was no difference at baseline between the two groups on scores from the total MoCA scale and each individual item. After the 6-month intervention, for the subjects assigned to the GSPE group, the total scores at the end were significantly higher than those at the baseline (mean change: 2.35 ± 3.20). Similarly, for the subjects assigned to the placebo group, the total scores at the end were significantly higher than those at the baseline (mean change: 1.28 ± 2.93). Although the subjects assigned to the GSPE group showed a greater mean change than subjects assigned to the placebo group, there was no significant difference ($P = 0.192$) in the change between the two groups.

For the seven individual items in MoCA, there was no significant difference in mean change for any of seven individual items in MoCA between the two groups. Nevertheless, as compared with the baseline, the score on language items in the GSPE group significantly (mean change: 0.50 ± 1.07) increased at the endpoint, while in the placebo group, no significant change from the baseline was observed (mean change: 0.06 ± 1.11). Similarly, as compared with the baseline, the score on the abstract item in the placebo group significantly (mean change: −0.04 ± 0.72) decreased, while the score in the GSPE group was not significantly different between the baseline and endpoint (mean change: −0.34 ± 0.65).

Table 3
Effects of GSPE on the cognitive performance in subjects with MCI[a].

MoCA items	GSPE			Placebo			Mean difference (95%CI)	*P interaction*
	Week 0	Week 24	Mean change	Week 0	Week 24	Mean change		
Total scores	21.34 ± 2.15	23.69 ± 3.38	2.35 ± 3.20†	22.03 ± 2.21	23.31 ± 3.14	1.28 ± 2.93†	1.06 (−0.55, 2.68)	0.192
Visual space and executive function	2.88 ± 0.95	3.19 ± 1.06	0.31 ± 0.84	3.03 ± 1.20	3.25 ± 1.02	0.22 ± 1.18	0.09 (−0.46, 0.64)	0.748
Name	2.92 ± 0.27	2.96 ± 0.20	0.04 ± 0.20	2.97 ± 0.18	3.00 ± 0.00	0.03 ± 0.18	0.01 (−0.09, 0.11)	0.884
Attention	4.73 ± 0.92	5.00 ± 1.41	0.27 ± 1.48	4.69 ± 0.23	5.06 ± 1.11	0.38 ± 1.41	−0.11 (−0.87, 0.66)	0.782
Language	1.81 ± 0.80	2.31 ± 0.88	0.50 ± 1.07†	2.19 ± 0.82	2.25 ± 0.80	0.06 ± 1.11	0.44 (−0.14, 1.01)	0.134
Abstract	0.96 ± 0.66	0.92 ± 0.80	−0.04 ± 0.72	1.25 ± 0.72	0.91 ± 0.69	−0.34 ± 0.65†	0.31 (−0.06, 0.67)	0.096
Delayed recall	2.46 ± 1.27	3.50 ± 1.30	1.04 ± 1.46†	2.34 ± 1.45	3.06 ± 1.72	0.72 ± 1.99†	0.32 (−0.62, 1.26)	0.467
Orientation	5.58 ± 0.64	5.81 ± 0.49	0.23 ± 0.71	5.56 ± 0.67	5.78 ± 0.55	0.22 ± 0.55	0.01 (−0.32, 0.34)	0.943

aValues are Mean ± SDs; Differences within groups were analyzed by paired *t*-test; The *P* for time × treatment interactions were analyzed by mixed-design ANOVA; GSPE, grape seed procyanidins extract.
†$P < 0.05$.

4. Discussion

Our hypothesis was not supported by the findings, for the total scores and seven individual items of MoCA, there was no significant difference in mean change from the baseline between the two groups. In this randomized, double-blind, placebo-controlled clinical trial, we found that 6-months GSPE intervention did not significantly enhance cognitive function in elderly people with MCI.

To the best of our knowledge, this is the first clinical trial to investigate the effect of GSPE supplementation on the cognitive function of elderly people with MCI. Several previous studies explored the protective effect of procyanidin-rich foods, such as grape juice [11,12] and black chocolate and cocoa powder [13], on cognitive function. One interventional study reported that subjects with MCI (n = 5) taking the Concord grape juice (data not shown) for 12 weeks showed an improvement in memory function as compared with subjects in the placebo group (n = 7) [11]. However, the other interventional study with slightly larger samples got different results. After taking Concord grape juice for 16 weeks, there was no significant improvement in learning and retention performance between the intervention group (n = 10, 355–551 mg/d) and the placebo group (n = 11) [12]. Another interventional study found that cocoa drink intervention for 8 weeks, improved cognition in subjects with MCI, and showed better performance on Trail Making Test A and B in high (n = 30, 746 mg/d) and intermediate dose treatment groups (n = 30, 390 mg/d) when compared with low dose group (n = 30, 33 mg/d) [13]. In addition, some clinical trials also showed that consumption of procyanidin-rich foods was associated with enhanced cognitive performance in healthy subjects [14,15].

The discrepancy of the interventional effects between these reports and our study may be due to some reasons. First, foods contain complex ingredients. Some other nutrients or bioactive substances from the procyanidin-rich foods, rather than procyanidins themselves, may influence cognitive function [12,33]. It is also possible that there are synergistic effects between procyanidins and other nutrients or bioactive substances in procyanidin-rich foods. Second, procyanidins are comprised of catechin and epicatechin in monomeric, oligomeric, and polymeric forms. Results from animal studies showed that only monomeric form treatment, rather than oligomers and polymers form, resulted in the accumulation of bioactive metabolites in the brain that are capable of improving cognitive function in a mouse model of AD [34]. In the present study, a daily 320 mg oral procyanidins mixture may not be able to reach the effective concentration in the aging brain. Future studies exploring the effects of specific bioactive procyanidins form and their metabolites on cognitive function in the human study are warranted.

Over the years, increasing studies have indicated the potential mechanisms of procyanidins on cognitive function. Evidence from human studies reported that flavanol-rich cocoa consumption causes an increase in cerebral blood flow [35] and cardiovascular benefits [36] closely related to cognitive function, which may result from vasodilation by activation of the nitric oxide system [37]. Besides, the dietary intake of cocoa also causes an increase in capillary density in the hippocampal formation, subsequently increases cerebral blood volume, and improves cognition [15]. On the other hand, evidence from animal studies also shows that procyanidins can relieve the symptoms of cognitive impairment via preventing the pathological process of AD, including extracellular amyloid deposits and neurofibrillary tangles [38]. Furthermore, a growing body of animal experiments has shown that procyanidins could improve antioxidant capacity, scavenge reactive oxygen species, and prevent lipid peroxidation [7,8,39,40], which involved the regulation of cAMP response element binding (CREB), silent information regulator 1 (SIRT1), and an interplay of the two aspects, hence decreasing neuronal death and promoting neuronal survival and synaptic plasticity [9,38,41].

There are several strengths of this study. First, the present RCT is the first to evaluate the direct effect of procyanidins extract, rather than procyanidin-rich foods, on cognitive function. Previous studies using powder-made, procyanidin-rich beverages or juice inevitably introduced other compounds such as anthocyanin in grape juice and confounded the interpretation of the effects of procyanidins. Second, all subjects in the present study were recruited from the former community-based, cross-sectional study for cognitive assessment, as compared with patients derived from hospitals who may suffer from different diseases and use various medications that affect the outcomes. Lastly, the compliance of the participants in our study is high because of regular follow-up.

There are also several limitations to this study. First, the MoCA scale used in the present study is a neuropsychological test that mainly assesses visual space and executive function, name, attention, language, abstract, delayed recall, and orientation. Future studies are needed to assess multiple domains of cognitive performance using the battery of neuropsychological tests. Second, although the present study has a larger sample size and much longer treatment duration compared to previous studies on procyanidin-rich foods or beverages and cognitive function, an even larger sample size, and longer duration may be needed to identify the meaningful change in cognitive function. In particular, the subgroup analysis with larger sample size could provide the possibility to find the subgroups population who benefit more from GSPE. Third, the absence of diet survey at baseline limited the ability to exclude the participants with a flavonoids-rich diet. We did not know the exact amounts of flavones and other nutrients from the participants' diet that have a possibility of influencing cognition. Finally, although we have assessed compliance by counting the number of capsules, the results would be better if blood or urine markers are measured.

5. Conclusions

The current study demonstrated that 6-month GSPE supplementation did not significantly improve cognitive function in subjects with MCI. Further studies are warranted to clarify the effect of procyanidins with longer-term intervention on cognitive function in mild or moderate mnemonic-cognitive disorders.

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Ethical standards

The study protocol was approved by the Medical Ethics Committee of Medical College, Wuhan University of Science and Technology (Approved number of ethic committee: WUSTMC-201550). Study was conducted and followed the ethical standards of the committee and Helsinki Declaration of 1975, as revised in 2000. Written informed consent was obtained from all participants.

Author contributions

S. Rong: Conceived and designed the experiments; Wrote the paper.

J. Cheng, W. Li, Y. Yang, H. Zhu, B. Li, G. Cheng, Q. Dai, Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

S. Rong, W. Bao, B. Liu, Provided ongoing advice and support; Analyzed and interpreted the data; Wrote the paper.

All authors read and approved the final manuscript.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e16994.

BOX 1 Eligibility criteria of study population

Inclusion Criteria
■Meeting the MCI diagnostic criteria;
■60–85 years old;
■Informed consent (insiders who are often associated with the subject and aware of the intervention trial agree to supervise the subject to receive the intervention and accompany the subjects to accept the test);
■Not using medication for rheumatoid arthritis or psoriasis interfering with GSPE supplement;
■No history of alcohol abuse;
■Not currently living in a nursing home or on a waiting list for a nursing home.
Exclusion Criteria
■Severe physical disease;
■Mental disease;
■Neurological disorders (including AD, Parkinson's disease, vascular dementia, Huntington's disease, normal hydrocephalus, brain tumors, progressive supranuclear palsy, epilepsy, chronic subdural hematoma and multiple sclerosis, with severe head trauma history associated with persistent neurological deficits or known brain structural abnormalities);
■History of stroke within two months;
■History of drug abuse within two months;
■History of taking dietary supplements for vitamin and phytochemicals within two months;
■Hearing or language disorders and inability to communicate.

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