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Short Communication

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Exploring the Neurocognitive Potential of a Sustainable Grape Seed Extract: Results from a 4-week Pilot Study

Simonetta Papa[1], Luca Giacomelli[1*], Roberto Eggenhoffner[2], Massimo Ronchi[3], Giovanna Petrangolini[4]

Abstract

Background: Polyphenolic compounds, including grape seed-derived oligomeric procyanidins, have demonstrated antioxidant and vascular benefits, yet human data on their neurocognitive and mood effects remain limited. Enovita™ is a standardized oligomeric procyanidin-rich extract derived from *Vitis vinifera* seeds, previously shown to support microvascular health.

Objective: To evaluate the acute and chronic effects of grape seed extract supplementation on cognitive performance and mood states in healthy adults.

Methods: In this randomized, double-blind, placebo-controlled pilot trial, 32 healthy participants ages 25–55 years were randomized to receive twice daily either 150 mg of standardized grape seed extract (Enovita™, 300 mg/day) or placebo for 4 weeks. Mood was assessed using the abbreviated profile of mood states, and cognitive performance was measured with the 4-part continuous performance test at baseline, 60 mins, 180 mins post-dose, and after 4 weeks. Trial Registration: NCT06309914.

Results: Grape seed extract was well tolerated with high compliance and no serious adverse events. After 4 weeks, all mood subscales showed directional improvement in the grape seed extract group compared to placebo, with the greatest deltas observed for anger (−1.19 vs. +0.62) and depression (−0.62 vs. +1.31). A significant group-by-time interaction was found in working memory performance at 4 weeks (p=0.050), with reduced errors in the grape seed extract group (−1.19) compared to increased errors in the placebo (+1.06).

Conclusion: Daily supplementation with a sustainable standardized Grape seed extract may support mood balance and working memory in healthy adults. These preliminary results warrant confirmation in larger, longer-term trials including mechanistic assessments.

Keywords: Cognitive performance; Dietary polyphenols; Enovita™; Grape seed extract; Mood states; Oligomeric Procyanidins; Randomized controlled trial

Introduction

Low mood and cognitive impairments are prevalent and complex conditions that significantly affect quality of life. These disturbances are often linked to multifactorial etiologies, including oxidative stress, neurotransmitter imbalances, neuroinflammation, and impaired neuroplasticity. Although pharmacological agents such as antidepressants and cognitive enhancers are widely used, they are often limited by adverse effects, suboptimal

Affiliation:

[1]Polistudium srl, Milan, Italy

[2]Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genova, Genova, Italy

[3]Formulation Development, Indena SpA, Viale Ortles, 12 – 20139, Milan, Italy

[4]Medical Department, Indena SpA, Viale Ortles, 12 – 20139, Milan, Italy

***Corresponding author:**

Luca Giacomelli, Polistudium srl, Milan, Italy

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efficacy, and poor long-term tolerability [1]. This has fueled growing interest in safer, natural alternatives with potential neuroprotective and mood-enhancing properties. Among such alternatives, plant-derived polyphenolic compounds - particularly anthocyanins, flavonoids, and procyanidins – have attracted attention for their potential in modulating mood and cognitive function [2]. These phytochemicals can interact with key molecular pathways in the brain, including the modulation of gamma-aminobutyric acid metabolism, inhibition of monoamine oxidase, and regulation of acetylcholine levels. In addition, they exhibit potent antioxidant activity, which may help counteract oxidative stress, a major contributor to neurodegenerative and mood-related disorders [3]. Preliminary clinical evidence supports these mechanisms by demonstrating beneficial effects of specific standardized extracts, such as *Vaccinium myrtillus* (Mirtoselect™), in improving mood states and selected aspects of cognition in healthy individuals [4]. GSEe, and specifically Enovita™, a standardized and sustainable extract rich in oligomeric procyanidins (OPCs) obtained from *Vitis vinifera* seeds, have been extensively investigated for their vascular, antioxidant, and anti-inflammatory properties [5-8]. GSEe is phytochemically characterized by a high content of low-molecular-weight procyanidins, which have demonstrated relatively high bioavailability and mechanistic activities relevant to vascular function and oxidative balance. These include inhibition of angiotensin-converting enzyme, modulation of endothelial nitric oxide availability, and free radical scavenging capacity, all of which have been implicated in the maintenance of healthy blood pressure and microvascular tone [9,10]. Beyond cardiovascular endpoints, preclinical and early clinical evidence have suggested that GSEs may also exert anxiolytic and mood-stabilizing effects, potentially through neuromodulatory actions involving catecholamine regulation, stress axis modulation, and protection against neuroinflammation. Indeed, grape-derived polyphenols can modulate hippocampal signaling, attenuate corticosterone release, and reduce markers of oxidative and inflammatory stress in brain tissue [6]. These findings support the hypothesis that OPC-rich GSEe, such as GSEe, may influence psychological and cognitive states, particularly in populations exposed to mild mental stress or age-related decline in cognitive performance. Despite growing interest in grape seed-derived procyanidins for cardiovascular and general health, no clinical data are currently available regarding the effects of GSEe on cognitive performance or mood states in healthy individuals. While prior work has established its cardiovascular benefits, its potential neuromodulatory and psychotropic actions remain unexplored in human studies. The present pilot, randomized, double-blind, placebo-controlled study was therefore designed to provide preliminary evidence on the effects of daily supplementation with GSEe over a 4-week period in healthy adults. The primary aim was to evaluate changes in cognitive function and mood states, both acutely (following a single dose) and chronically (after 4 weeks), using standardized neuropsychological testing and mood assessment scales. This investigation represents the first preliminary clinical step toward characterizing the neurocognitive profile of GSEe and informing the design of future, larger-scale trials.

Methods

Study Design and Participants

This was a randomized, double-blind, placebo-controlled, parallel-group pilot trial designed to assess the effects of GSEe on cognitive function and mood states in healthy adults. The trial was part of a broader investigation involving four arms: Enovita™, Mirtoselect™, Virtiva™ Plus, and placebo [4]. Only data from the GSEs and placebo arms are presented in this report. GSEe, Enovita™ is a proprietary OPC-rich extract, derived exclusively from recovered grape seeds from white wine production. With water as the extraction solvent, without the use of other less environmentally friendly solvents, GSEe production process meets sustainability criteria. GSEe is produced under HACCP conditions in a GMP- and ISO 14001-certified facility that is also equipped with photovoltaic panels, which allow for conscious and sustainable energy use. All this ensures full traceability from grape harvest to the finished product and a strong commitment to fighting climate change. The extract is standardized to provide ≥95.0% of OPCs by spectrophotometry and a relatively low amount of flavane monomers (5.0–15.0% catechin and epicatechin, by HPLC) [8–10].

The study was conducted at the Applied Science and Performance Institute (ASPI Labs, Florida, USA), in accordance with the Declaration of Helsinki, ICH-GCP guidelines (E6-R2), and all relevant regulatory requirements. The protocol received ethical approval from an external Institutional Review Board (Advarra IRB, ID: Pro00074459, September 2023) and was registered at ClinicalTrials.gov (Identifier: NCT06309914).

Healthy adults aged 25-55 years were eligible to participate. Screening was performed via an online questionnaire followed by an on-site baseline assessment. Individuals with cognitive impairment, significant cardiovascular, neurological, gastrointestinal, or metabolic conditions, active malignancy, psychiatric disorders, pregnancy or lactation, recent use of psychoactive substances, or medications affecting mood or cognition were excluded.

Randomization, Blinding and Intervention

Participants were randomized in a 1:1 ratio to receive either GSEe or a placebo. The randomization sequence was computer-generated, and allocation concealment was maintained by an independent third party. Blinding was upheld for participants, investigators, and outcome assessors.

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Subjects in the GSEe group received two capsules per day, each containing 150 mg of GSEe, administered once in the morning and once in the evening with meals, for a total daily dose of 300 mg. The placebo group received matching capsules identical in appearance, containing only inert excipients (rice flour and magnesium stearate). Both GSEe and placebo capsules were manufactured by Nature's Value (Coram, NY, US).

Outcome Measures and Testing Procedures

Study assessments were conducted at baseline (in the fasted state), and at 60 minutes, 180 minutes, and after 4 weeks of supplementation. These time points were selected to capture both acute (single-dose) and chronic (4-week) effects.

Mood state was evaluated using the abbreviated profile of mood states (POMS). This 40-item psychometric questionnaire provides subscale scores for tension, depression, anger, vigor, fatigue, and confusion, as well as a composite Total Mood Disturbance score.

Cognitive performance was assessed via the 4-part continuous performance test (4CPT), a component of the CNS Vital Signs computerized neuropsychological battery (Morrisville, NC, USA).

All cognitive testing was performed in a controlled environment using standardized equipment and instructions. Test administrators were trained to ensure procedural consistency. Participants were instructed to avoid alcohol, caffeine, and intense physical activity for at least 24 hours before each testing session.

Safety and Compliance

Participants were instructed to maintain daily records of capsule intake and return any unused product at the final visit. Compliance was assessed through capsule count and self-report. Adverse events were monitored throughout the study and were documented and classified according to severity and potential relationship to the intervention.

Statistical Analysis

This study was designed as a pilot, with sample size determined pragmatically. Data were analyzed using generalized linear mixed models, with time (baseline, 60 minutes, 180 minutes, and 4 weeks) as a repeated within-subject factor and treatment group (Enovita™ or placebo) as a between-subject factor. Pairwise comparisons of marginal means were adjusted using the Bonferroni correction to account for multiple testing. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, version 20 (IBM Corp., Armonk, NY, USA).

Result

Baseline characteristics

A total of 32 healthy adults were evenly randomized to receive either GSEe (n = 16) or placebo (n = 16). Baseline characteristics were comparable across groups (Table 1).

Table 1: Baseline characteristics

Characteristic	GSEe (n=16)	Placebo (n=16)
Demographics		
Age (years), mean ± SD	39.2 ± 7.5	38.6 ± 7.6
Sex, n (%)		
· Male	8 (50.0)	7 (43.8)
· Female	8 (50.0)	9 (56.2)
Race, n (%)		
· White/Caucasian	15 (93.8)	14 (87.5)
· Black/African–American	0 (0.0)	0 (0.0)
· Other/not reported	1 (6.2)	2 (12.5)
Ethnicity, n (%)		
· Hispanic/Latino	0 (0.0)	0 (0.0)
· Not Hispanic/Latino	16 (100.0)	16 (100.0)

Age is expressed as mean ± standard deviation. The number of subjects and gender is count and the percentage of the sample size. GSEe: grape seed extract.

Mood Assessment (POMS)

After 4 weeks of supplementation, participants in the GSEe group showed directional improvements across several POMS subscales compared to placebo (Table 2). While no significant group-by-time interactions were observed for any POMS variable, the most notable directional changes were seen in fatigue (−0.50 vs. +2.50), tension (−0.06 vs. +1.12), and depression (−0.62 vs. +1.31). Anger scores decreased substantially in the GSEe group while increasing in the placebo (−1.19 vs. +0.62). Vigor scores improved in the GSEe group (+0.69) while declining in the placebo group (−0.69). Confusion decreased in both groups, but more so with GSEe (−0.50 vs. +0.44). Although these directional changes consistently favored GSEe across all mood domains, the differences did not reach statistical significance.

Statistics were performed for groups by time interaction vs placebo, using pairwise comparisons, with Bonferroni correction for multiple comparisons. Mean Δ ± SD: Mean delta change (from baseline) ± standard deviation. GSEe = grape seed extract; POMS = Profile of Mood States.

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Table 2: POMS Outcomes at 4 Weeks (Change from Baseline).

Subscale	GSEe (n=16), Mean Δ ± SD	Placebo (n=16), Mean Δ ± SD	Group × Time (Interaction p-value)	Direction Favors
Tension	−0.06 ± 0.94	+1.12 ± 0.37	0.549	GSEe
Depression	−0.62 ± 0.71	+1.31 ± 1.22	0.118	GSEe
Anger	−1.19 ± 1.81	+0.62 ± 1.02	0.072	GSEe
Vigor	+0.69 ± 0.38	−0.69 ± 0.06	0.448	GSEe
Fatigue	−0.50 ± 1.07	+2.50 ± 1.75	0.294	GSEe
Confusion	−0.50 ± 1.54	+0.44 ± 0.31	0.631	GSEe
Total mood disturbance	−3.56 ± 7.97	+6.44 ± 2.66	0.336	GSEe

Cognitive Performance (4CPT – Working Memory Errors)

On Part 4 of the 4-Part Continuous Performance Test, a significant group-by-time interaction was detected for incorrect responses (p = 0.050) (Figure 1), indicating that the pre-to-post change differed significantly between groups (Table 3). The GSEe group showed a reduction in working memory errors (−1.19 errors, effect size g = −0.282), while the placebo group showed an increase (+1.06 errors, effect size g = 0.385). This represents a statistically significant improvement in sustained attention and working memory performance with GSEe supplementation.

Safety

The GSEe supplementation was well tolerated by all participants. No serious adverse events or discontinuations due to adverse events were reported in either group throughout the 4-week supplementation period. Compliance with the supplementation regimen was high, exceeding 90% in both groups, as confirmed by capsule count and participant diaries. There were no protocol deviations related to product administration or safety monitoring.

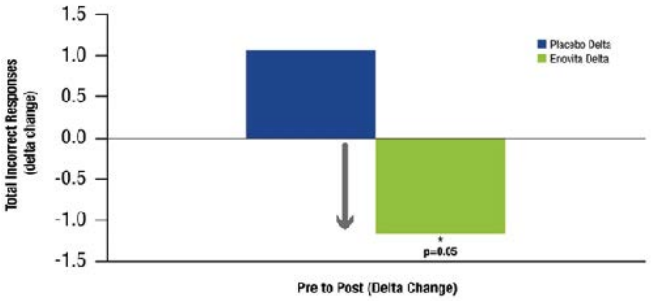

Figure 1: Effects of 4-week supplementation on working memory and reducing errors, as measured by a four-part continuous task.

Discussion

The role of polyphenolic compounds in supporting emotional balance and neurocognitive performance has become increasingly prominent, driven by growing interest in nutritional strategies that complement traditional pharmacotherapy. Among these compounds, OPCs extracted from grape seeds have shown vascular and antioxidant properties, but their potential to impact mood and cognitive performance has remained underexplored in human populations [6]. The present findings, though preliminary, offer new insight into the psychobiological potential of a sustainable standardized GSEe and add to the evolving evidence supporting the use of botanical agents in psychological health. From a neurobiological standpoint, the observed trends toward reduced depressive and anger symptoms in participants receiving GSEe are consistent with preclinical studies showing that this GSEe and OPCs modulate oxidative stress, neuroinflammation, and neurotransmitter systems [8]. Moreover, the attenuation of stress-induced behavioral responses in animal models has been associated with suppression of NF-κB signaling and upregulation of BDNF expression, suggesting a molecular cascade through which polyphenols could influence mood states [2]. These effects may be potentiated by peripheral anti-inflammatory actions that reduce systemic cytokine burden, indirectly supporting central nervous system homeostasis. This mechanism has also been hypothesized for other polyphenol-rich extracts such as bilberry and green tea [11].

Table 3: 4CPT Working Memory Errors (Incorrect Responses).

Time Point	Enovita™ (n=16), Mean Δ from Baseline	Placebo (n=16), Mean Δ from Baseline	Group × Time (p-value)
60 minutes	−0.56	0.56	NS
180 minutes	0	0.18	NS
4 weeks	−1.19	1.06	0.050*

Mean Δ: Mean delta change; 4CPT: 4-part continuous performance test. Statistics were performed for the group by time vs placebo, using pairwise comparisons, with Bonferroni correction for multiple comparisons. *Statistically significant group × time interaction

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The cognitive benefits observed – particularly the reduction in working memory errors - are similarly aligned with mechanistic hypotheses linking OPCs to improved neurovascular coupling. Endothelium-dependent vasodilation and increased nitric oxide bioavailability, both documented effects of GSEe, may enhance perfusion to prefrontal cortical areas involved in attention and executive function [9]. The acute onset of cognitive improvements seen in this trial also corresponds to the known pharmacokinetics of OPCs, which reach peak plasma concentrations within two hours of ingestion. This temporal alignment strengthens the plausibility that direct neurovascular effects may underlie the early cognitive improvements observed in the GSEe group. These results are also noteworthy in light of broader discussions on personalizing non-pharmacological supports in mental health. As noted by Pillinger and colleagues [1], the increasing complexity of psychiatric prescribing necessitates individualized approaches that consider both benefit and burden, particularly in preventive or subclinical contexts. In this regard, botanical supplements, such as GSEe with favorable tolerability and preliminary efficacy, may represent a compelling adjunct in holistic strategies for mental performance enhancement and emotional regulation, especially among individuals not eligible for pharmacologic intervention or those seeking lifestyle-based solutions. It is worth noting that the psychotropic relevance of polyphenols may extend beyond their biochemical properties. The gut-brain axis, increasingly recognized as a conduit for dietary influences on mental health, may also play a role. Polyphenols can modulate gut microbiota composition and activity, with downstream effects on neuroactive metabolite production and systemic inflammation [2]. Although such mechanisms remain speculative in the absence of microbiota data from this trial, they add a layer of biological plausibility to the findings and merit investigation in future studies. This was an exploratory, short-duration study with a modest sample size, which limits the statistical power and generalizability of findings. In addition, the study focused only on healthy volunteers with no baseline cognitive impairment, which may have created a ceiling effect, limiting the ability to detect larger changes. Future studies should consider enrolling individuals with subjective cognitive decline or elevated stress levels, using longer supplementation periods and broader cognitive batteries.

Additionally, the mechanistic underpinnings of the observed benefits remain speculative. While the antioxidant, vascular, and neurochemical actions of OPCs are plausible mediators, no biomarker data were collected in this trial to confirm these pathways.

Conclusion

This pilot, double-blind, placebo-controlled study provides the first clinical indication that Enovita™, a standardized GSEe rich in oligomeric procyanidins, may positively influence mood regulation and working memory in healthy adults. While the findings are preliminary, the favorable direction of changes in key psychological and cognitive outcomes, along with excellent tolerability, support further investigation of this sustainable standardized GSEe as a safe, botanical option for supporting neurocognitive health. Larger and longer-term studies, ideally incorporating mechanistic endpoints, are warranted to confirm and expand upon these results.

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Data availability statement

Data is available from the corresponding author upon reasonable request.

Author contributions

All authors made substantial contributions to the study conception and design, interpretation of data, drafting and critical revision of the manuscript, and approved the final version for submission.

Ethics

The protocol received ethical approval from an external Institutional Review Board (Advarra IRB, ID: Pro00074459, September 2023) and was registered at ClinicalTrials.gov (Identifier: NCT06309914).

Consent to publish

All participants provided informed consent for publication.

Conflict of interest

M.R. and G.P. are employees of Indena SpA.; L.G. and S.P. are collaborators of Polistudium srl. R. E. declares no commercial or financial relationships that could be construed as potential conflicts of interest.

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