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Cardiometabolic Health Benefits of a Sustainable Grape Seed Extract supplementation on Elevated Blood Pressure and Stage 1 Hypertension: Results from a Multicenter, Double-Blind, Placebo-Controlled Randomized Clinical Trial

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Abstract

Background: Elevated blood pressure (BP) and Stage 1 hypertension represent early stages of cardiovascular risk where non-pharmacological interventions are recommended. Grape, a polyphenolic antioxidant, has shown potential BP-lowering and cardiometabolic benefits, but controlled clinical evidence remains limited.

Objective: Aim of the study was modulation of BP, lipid profile, systemic inflammation, psychological well-being, lipid, after grape supplementation vs placebo for 8 weeks in individuals at an early stage of BP dysregulation.

Methods: In this multicenter, randomized, double-blind, placebo-controlled clinical trial, 80 adults with elevated BP or Stage 1 hypertension were randomized to receive either a sustainable oral grape seed extract (GSEe) supplement, 2x150 mg daily, or placebo for 8 weeks. Primary outcomes were changes in systolic and diastolic BP. Secondary outcomes included lipid profile, high-sensitivity C-reactive protein (hs-CRP), and psychological well-being assessed by the Positive and Negative Affect Schedule (PANAS), perceived stress (PSQ-30), and health-related quality of life (QoL) questionnaires.

Results: GSEe supplementation resulted in significant between-group differences versus placebo ($p < 0.01$), and progressive reductions in systolic (−7.8 mmHg) and diastolic BP (−10.1 mmHg) at 8 weeks compared with baseline. Favorable effects on cardiometabolic parameters were observed, including reductions in LDL cholesterol and attenuation of non-HDL cholesterol progression. Systemic inflammation (hs-CRP) decreased in the GSEe group. Psychological outcomes showed improvements in affective status, alongside in QoL domains and reductions in PSQ-30.

Conclusion: Supplementation with a sustainable GSEe improved blood pressure, lipid profile, inflammatory status, and psychological well-being, in adults at an early stage of BP dysregulation, supporting GSEe benefits in early cardiovascular risk management.

Keywords: Oligomeric proanthocyanidins; Antioxidants; Grape seed extract; Oxidative stress; Cardiometabolic health; Blood pressure; Lipid modulation; Enovita™.

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Introduction

Hypertension is one of the leading risk factors for cardiovascular morbidity and mortality worldwide [1,2]. It is commonly defined as a systolic blood pressure (SBP) of ≥140 mmHg or a diastolic blood pressure (DBP) of ≥90 mmHg, according to contemporary clinical guidelines [3]. Even modest elevations below this threshold are clinically relevant. Individuals with elevated BP (SBP 120–129 mmHg and DBP <80 mmHg) and those with Stage 1 hypertension (SBP 130–139 mmHg or DBP 80–89 mmHg) carry a significantly increased long-term risk of cardiovascular disease and progression to overt hypertension [4]. These early stages therefore represent a critical window in which preventive measures may reduce long-term cardiovascular risk and slow progression toward established hypertension. As pharmacological therapy is typically not indicated at this point under most clinical guidelines, the primary emphasis is placed on lifestyle modification, where practical and accessible strategies - such as diet, physical activity, stress reduction, and targeted nutritional support - can help maintain vascular health and prevent BP from rising into the hypertensive range. This has driven growing interest in nutritional and lifestyle-based approaches that may support physiological BP regulation and reduce the future burden of hypertension [5-8].

Oxidative stress and low-grade inflammation are key contributors to early BP dysregulation and cardiometabolic risk [9-12]. Dietary and fruit-derived polyphenolic antioxidants have been shown to modulate redox balance, endothelial function, and inflammatory processes, supporting their potential role in non-pharmacological cardiovascular prevention strategies [13-15].

Grape seed extract (GSE), particularly standardized formulations rich in oligomeric proanthocyanidins (OPCs), has emerged as a promising nutritional approach for early BP management [5-8,16-23]. Grape seed extract is a concentrated source of OPCs, a well-characterized class of polyphenolic antioxidants, which have been shown in preclinical and human studies to exert antioxidant and vasoprotective effects and to modulate cardiometabolic risk factors [13-15,17]. OPCs in GSEs are primarily composed of flavan-3-ol subunits, including (+)-catechin and (−)-epicatechin monomers, as well as B-type procyanidin dimers, trimers, and higher oligomers. Proanthocyanidins demonstrate antioxidant and vascular-supporting properties, which may help counteract mechanisms contributing to early BP elevation, such as oxidative stress, reduced nitric oxide bioavailability, and endothelial dysfunction [7,20,22-24]. Several clinical trials have reported that supplementation with standardized GSE can lead to clinically meaningful improvements in systolic and diastolic BP, especially among individuals with elevated BP or Stage 1 hypertension [5-8,16-23]. These findings suggest that GSE may offer a safe and accessible nutritional strategy to support vascular health during the early stages of BP dysregulation and may play a role in reducing the long-term risk of cardiovascular complications associated with progressing hypertension.

Psychological stress and emotional well-being influence physiological pathways - such as autonomic regulation, oxidative balance, and inflammation - that are closely linked to BP control. Chronic stress and sympathetic overactivation can elevate BP and contribute to its progression over time. Evidence suggests that GSE may affect several of these mechanisms, supporting endothelial function and modulating oxidative and inflammatory processes that also relate to mood and stress responses [13,14,16-18,20,23]. Assessing both cardiovascular and psychological outcomes is therefore relevant when exploring the preventive potential of GSE in individuals with early-stage BP elevations.

Despite growing clinical interest in the potential cardiometabolic and psychological health benefits of GSE, controlled clinical evidence in individuals with elevated BP or Stage 1 hypertension remains limited. Few studies have assessed BP together with biochemical and psychological measures, even though factors such as lipid status, inflammation, and stress physiology may interact with BP regulation. This underscores the need for well-designed trials that evaluate the broader beneficial potential of GSE in early BP dysregulation. To address this need, we conducted a double-blind, placebo-controlled randomized clinical trial to evaluate the potential health effects of a sustainable and standardized GSE (hereafter GSEe) in adults with elevated BP or Stage 1 hypertension. The study examined changes in participants BP, emotional well-being, alongside lipid profile and systemic inflammation, over an 8-week supplementation period. By integrating cardiovascular, biochemical, and psychological outcomes, this trial aimed to provide comprehensive evidence on the potential preventive role of GSE supplementation in individuals at an early stage of BP dysregulation.

Materials and Methods

Study Design

This study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, prospective clinical trial conducted to evaluate the efficacy and safety of a sustainable and standardized grape seed extract as a supportive nutritional approach in the management of elevated BP, and its secondary effect on improving emotional well-being. Participants were recruited from outpatient clinics at Lady Reading Hospital, Peshawar, Mayo Hospital, Lahore, and the Punjab Institute of Cardiology, Lahore, Pakistan.

The study was conducted between July 2025 and November 2025, in accordance with the principles of the

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Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all participants prior to enrolment. The study was approved by the institutional ethics committees of Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro (Approval No.: LUMHS/REC/734), and Lady Reading Hospital, Peshawar (Ref. No.: 465/LRH/MTI), Pakistan, and registered at ClinicalTrials.gov (NCT06982365).

Participants Eligibility Criteria

Adults aged 30-80 years were screened for eligibility during routine outpatient visits at Lady Reading Hospital, Peshawar, Mayo Hospital, Lahore, and the Punjab Institute of Cardiology, Lahore, Pakistan. Participants were eligible if they met the diagnostic criteria for either elevated BP (systolic 120-129 mmHg and diastolic <80 mmHg) or Stage 1 hypertension (systolic 130-139 mmHg or diastolic 80–89 mmHg), according to American Heart Association guidelines [3]. Additional inclusion criteria required participants to have no use of antihypertensive medication within the preceding 3 months, willingness to comply with study procedures and follow-up visits, and the ability to provide written informed consent.

Participants were excluded if they presented with Stage 2 hypertension (systolic ≥140 mmHg or diastolic ≥90 mmHg) at screening, or if they had known chronic kidney disease, diabetes mellitus, or had experienced a cardiovascular event (myocardial infarction or stroke). Additional exclusion criteria included allergy to grape products, current use of polyphenol-containing supplements, pregnancy or breastfeeding, and participation in another clinical study within the past 30 days.

Randomization and Blinding

Participants meeting eligibility criteria were randomly assigned in a 1:1 ratio to receive either GSEe or placebo. A 6-block randomization was carried out using a computer-generated sequence prepared by an independent statistician, and treatment allocation was concealed using sequentially coded, identical study products. Allocation concealment was maintained through identical, sequentially numbered, opaque containers. A double-blind design was maintained throughout the study: participants, investigators, study coordinators, and outcome assessors remained unaware of group assignments.

Study Product and Dosing

GSEe, as Enovita™ (Indena S.p.A, Milan, Italy) is a food-grade sustainable OPCs rich extract made exclusively with grape seeds from white wine production and with only water as extraction solvent. GSEe is standardized to contain ≥95.0% OPCs (by spectrophotometry) and 5.0–15.0% flavane monomers (catechin and epicatechin, by HPLC) [16-18].

Participants in the active supplementation arm received 150 mg of GSEe tablet twice daily, administered orally after a meal, for a total of 8 weeks. The placebo group received matching tablets containing the same inert excipients of GSEe tablets, administered in the same manner and frequency as the grape supplement. GSEe and placebo tablets were identical in appearance, size, color, and packaging to ensure blinding integrity.

All participants were instructed to maintain their usual diet and physical activity routines and to refrain from initiating any new pharmacotherapy, antioxidant supplements, or herbal products during the study period.

Study Outcome Assessment

The study primary objective was to evaluate the potential beneficial effect of 8 weeks of GSEe supplementation on systolic and diastolic BP compared with placebo; the tolerability and safety of the supplementation through adherence monitoring and documentation of side effects or adverse events were also assessed.

Secondary objectives were to evaluate the broader psychological and physiological effects of grape seed extract (GSEe) supplementation over the 8-week study period. These included assessing changes in emotional well-being using validated self-reported instruments: the Positive and Negative Affect Schedule (PANAS) and the Perceived Stress Questionnaire (PSQ-30). Quality of life (QoL) was evaluated using the self-reported SF-36 Health Survey. In addition, lipid profile parameters, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and non-HDL-C, were measured, using the standard laboratory techniques, to explore potential effects on cardiometabolic health. Systemic inflammation was assessed by measuring high-sensitivity C-reactive protein (hs-CRP) levels.

Schedule of Assessments

Participants were evaluated at baseline (week 0), week 4, and week 8 (end of study). At each visit, vital signs, including BP, were recorded using standardized procedures. Measures of emotional well-being, and QoL were assessed at all three visits. Blood samples for biochemical analyses were collected at baseline and week 8.

Safety Monitoring

Safety and tolerability were assessed throughout the study. Participants were advised to report any symptoms, side effects, or health-related concerns to the study team at any time during the study period. Any serious adverse events were to be promptly brought to the attention of the study investigators and documented appropriately.

Adherence to the study product was assessed at each follow-up visit through tablets counts and participant confirmation of daily intake.

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Sample size

A total of 80 participants were enrolled in this exploratory pragmatic randomized controlled study, with 40 participants allocated to each group. The sample size was considered adequate to detect meaningful changes in systolic and diastolic BP based on effect sizes reported in previous clinical studies evaluating grape seed extract and GSEe in individuals with elevated BP or Stage 1 hypertension [5-8,16,17,19-23,25]. Previous trials have demonstrated reductions of approximately 5-10 mmHg in systolic BP with grape seed extract supplementation over comparable durations. Assuming a moderate effect size in this range, a sample of 80 participants (40 per group) was expected to provide sufficient precision to evaluate between-group differences and to allow for anticipated attrition during follow-up. The sample size was therefore deemed appropriate for achieving the primary objective of assessing BP changes over the 8-week study period.

Statistical analysis

All statistical analyses were performed using R software (v.4.5.0). Longitudinal changes in blood pressure, blood biochemical parameters, and questionnaire-derived outcomes were analyzed using two-way repeated-measures analysis of variance (RM-ANOVA) with Group (Placebo vs. GSEe) as the between-subject factor and Timepoint as the within-subject factor. The assumption of normality for RM-ANOVA was assessed on model residuals using both Shapiro–Wilk tests and visual inspection of histograms and Q–Q plots. Although the Shapiro–Wilk test indicated statistical deviations from normality, visual inspection showed that residuals were approximately normally distributed, with only minor deviations in the distribution tails and no evidence of substantial skewness or non-normal structure. When significant effects were detected, Sidak-adjusted post hoc comparisons based on estimated marginal means were performed to assess between-group differences at each timepoint and within-group changes over time. Potential sex-related differences in blood pressure response were explored using three-way RM-ANOVA, including Group, Timepoint, and Gender as factors. Multivariate patterns of affective status were further explored using principal component analysis (PCA) based on the PANAS positive affect (PAS) and negative affect (NAS) scores. Group differences in this multivariate space were evaluated using MANOVA to assess the overall affective profile. Similarly, multivariate patterns of health-related quality of life were explored using PCA based on the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, and group differences were evaluated using MANOVA to assess the overall QoL profile. Assumptions underlying MANOVA were evaluated by inspecting residual distributions, assessing approximate multivariate normality, and checking for the absence of extreme outliers. To further assess the adequacy of the selected sample size for the primary blood pressure outcomes, post hoc sensitivity analyses were performed on the change in systolic and diastolic blood pressure from baseline to week 8. These analyses used the observed pooled standard deviations of the change scores, a two-sided α of 0.05, and 80% power to estimate the minimum detectable between-group differences. All statistical tests were two-sided, statistical significance was set at $P < 0.05$.

Results

Baseline characteristics

Baseline demographic and clinical characteristics of the study population are summarized in table 1. A total of 173 individuals were screened for eligibility, of whom 80 participants were enrolled and randomized in a 1:1 ratio to receive GSEe or placebo (Figure 1). The study population comprised 42 men and 38 women (52% male), with a comparable sex distribution between the placebo and GSEe groups. Mean age was similar between groups. Anthropometric measures, including body weight, and body mass index (BMI), were well balanced across the two study arms, as well as the baseline cardiovascular parameters, including BP, heart rate, and respiratory rate. In addition, baseline serum CRP concentrations and lipid profile parameters were similar in the placebo and GSEe groups. Overall, no clinically relevant differences in baseline demographic or clinical characteristics were observed between the two groups, supporting the adequacy of the randomization process. All randomized participants completed the 8-week study (no dropouts were observed) and were included in the final analysis.

Table 1: Baseline demographic and clinical characteristics of the study population.

Characteristic	Mean	Placebo	GSEe
Subjects, *n*	80	40	40
Men / Women, *n* (men frequency %)	42/38 (52)	18/22 (45)	24/16 (60)
Age (years)	38.5 ± 0.9	38.6 ± 1.3	38.5 ± 1.3
Weight (Kg)	74.7 ± 1.5	73.4 ± 2.0	76.0 ± 2.2
BMI (kg/m²)	27.3 ± 0.6	26.9 ± 0.7	27.6 ± 0.9
Systolic blood pressure (SBP) (mm Hg)	129.7 ± 0.7	128.8 ± 0.9	130.6 ± 1.0
Diastolic blood pressure (DBP) (mm Hg)	84.0 ± 0.9	82.1 ± 1.2	85.9 ± 1.2
Heart rate (BPM)	82.2 ± 1.1	82.4 ± 1.8	82.0 ± 1.4
Respiratory rate (BPM)	15.0 ± 0.2	14.8 ± 0.2	15.3 ± 0.3
Serum CRP (mg/L)	4.5 ± 0.8	4.6 ± 1.5	4.4 ± 0.8
Total Cholesterol (mg/dL)	182.7 ± 4.5	178.1 ± 5.3	187.7 ± 7.3
LDL-cholesterol (mg/dL)	129.4 ± 4.7	121.1 ± 5.7	138.2 ± 7.3
HDL cholesterol (mg/dL)	44.0 ± 1.4	45.7 ± 2.3	42.3 ± 1.4
Non-HDL cholesterol (mg/dL)	138.7 ± 4.3	132.4 ± 5.3	145.4 ± 6.9

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Values are expressed as Mean ±Standard Error of the Mean (SEM). BMI: Body mass index; CRP: C-Reactive Protein; LDL: low-density lipoprotein, HDL: High Density Lipoprotein; GSEe: sustainable grape seed extract.

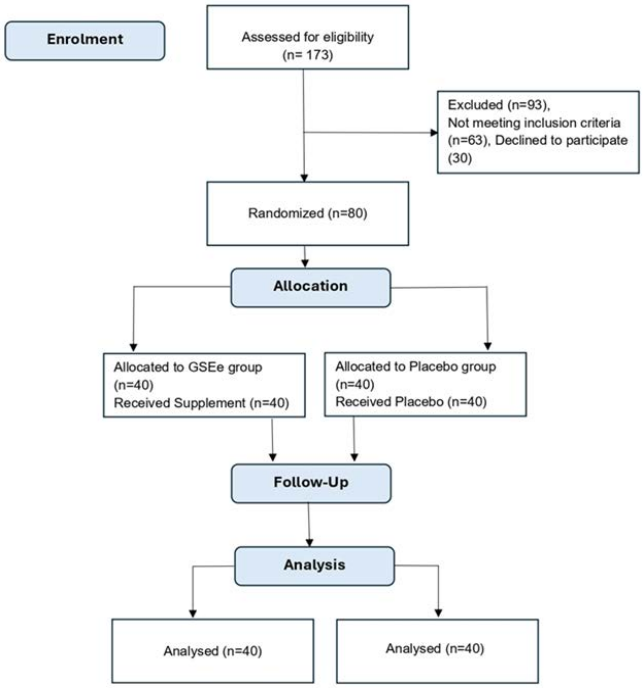

Figure 1: Study CONSORT flow diagram.

Supplementation effects on primary outcome measure

Effect on blood pressure

As shown in figure 2, GSEe supplementation was associated with a distinct time-dependent pattern of SBP and DBP compared with placebo. For SBP, a significant Group × Timepoint interaction was observed ($F = 19.65$, $p < 0.0001$), indicating that SBP changed differently over time between the two study arms. Sidak-adjusted post hoc between-group comparisons showed no significant difference between GSEe and placebo at week 4 (mean difference: −1.60 mmHg; 95% CI: −4.88 to 1.68; $p = 0.34$), whereas at week 8 SBP was significantly lower in the GSEe group compared with placebo (−8.15 mmHg; 95% CI: −11.43 to −4.87; $p < 0.001$; Figure 2A and 2C).

Consistent with this between-group effect, within-group comparisons showed a progressive reduction in SBP in the GSEe group, with decreases already evident at week 4 (−4.05 mmHg; 95% CI: −6.80 to −1.30; $p = 0.0015$) and more pronounced at week 8 (−7.80 mmHg; 95% CI: −10.55 to −5.05; $p < 0.0001$) compared with baseline (Figure 2A and 2E). In contrast, no comparable reduction was observed in the placebo group, although a modest increase was detected between week 4 and week 8 (+2.80 mmHg; $p = 0.045$).

A similar pattern was observed for DBP, with a significant Group × Timepoint interaction ($F = 11.20$, $p < 0.0001$). At baseline, DBP was higher in the GSEe group than in the placebo group (+3.80 mmHg; 95% CI: 0.24 to 7.36; $p = 0.037$). This difference was no longer present at week 4 (−0.13 mmHg; 95% CI: −3.69 to 3.44; $p = 0.945$), and by week 8 DBP was significantly lower in the GSEe group compared with placebo (−4.85 mmHg; 95% CI: −8.41 to −1.29; $p = 0.008$; Figure 2B and 2D).

Within-group analyses further supported this trajectory (Figure 2A and 2F), showing significant DBP reductions in the GSEe group at both week 4 (−4.88 mmHg; 95% CI: −8.00 to −1.75; $p < 0.001$) and week 8 (−10.05 mmHg; 95% CI: −13.17 to −6.93; $p < 0.0001$) compared with baseline, whereas no significant longitudinal reduction was observed in the placebo group.

Overall, these findings indicate that GSEe supplementation resulted in statistically significant between-group reductions in both SBP and DBP after 8 weeks. The within-group trajectories provide supportive longitudinal information, showing a progressive BP reduction in the GSEe arm, while the primary interpretation is based on the significant Group × Timepoint interactions and the corresponding between-group effect estimates.

The effects of GSEe supplementation on systolic and diastolic BP were further evaluated using a three-way RM-ANOVA with treatment, time, and gender as factors (data not shown). No significant Group × Timepoint × Gender interaction was observed for either systolic BP ($F = 1.32$, $p = 0.2714$) or diastolic BP ($F = 1.09$, $p = 0.3399$), indicating that the BP response to GSEe supplementation did not significantly differ between women and men.

Tolerability and safety assessment

GSEe supplementation was generally well tolerated throughout the study. Two participants in the GSEe group and four participants in the placebo group reported mild, transient gastrointestinal symptoms, which resolved spontaneously without any intervention. No participants discontinued the study due to adverse events, and no serious adverse events were reported during the intervention period.

Overall adherence to the study intervention was high. Compliance with supplementation, assessed by tablet counts and participant reporting, exceeded 95% in both the GSEe and placebo groups. No clinically relevant differences in adherence were observed between treatment arms, and all participants completed the 8-week intervention.

Supplementation effects on secondary outcome measure

Effects on lipid profile and systemic inflammation

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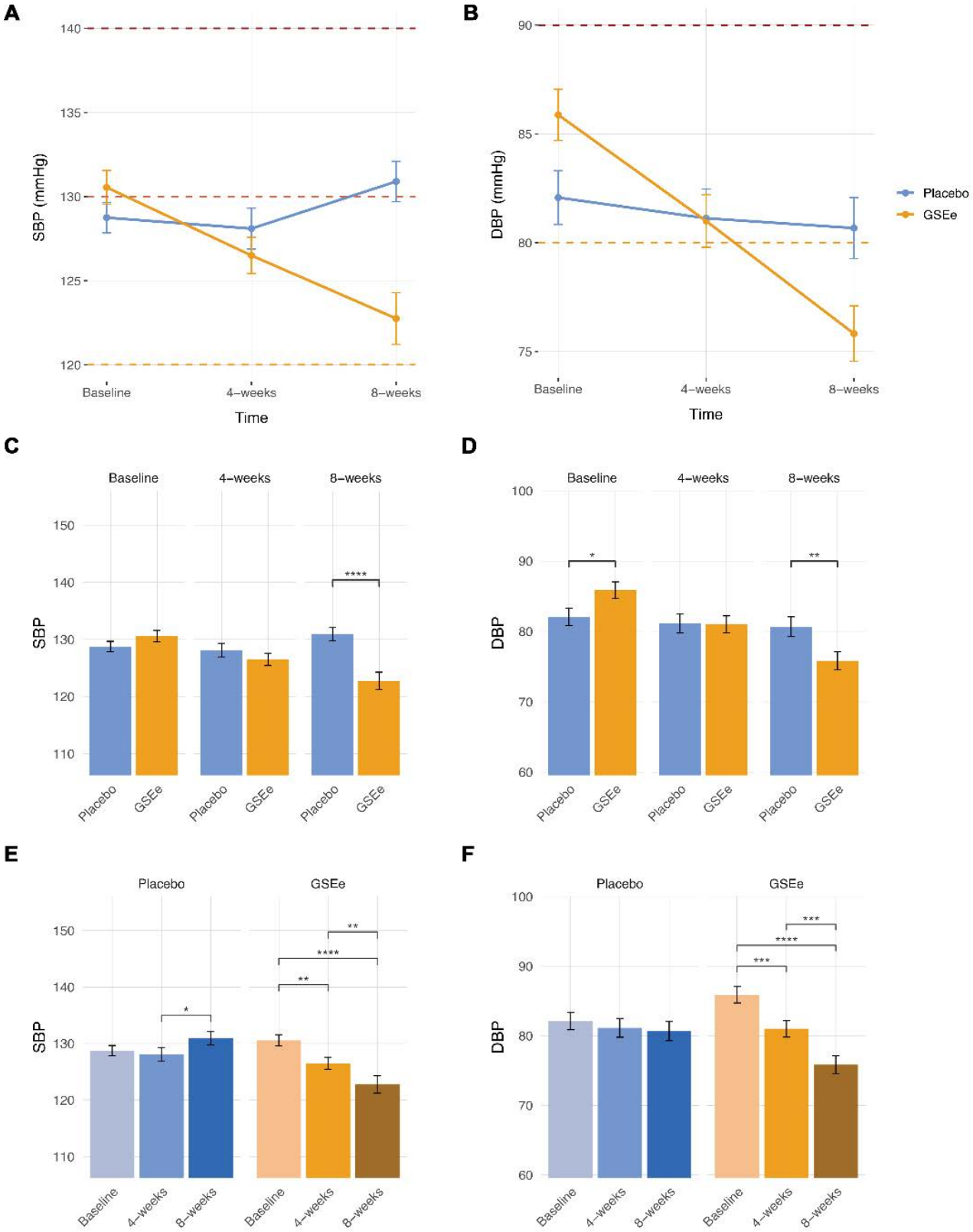

Figure 2: Effects of grape seed extract (GSEe) supplementation on systolic and diastolic blood pressure (SBP, DBP, respectively). (**A,B**) Longitudinal changes in SBP and DBP at baseline, week 4, and week 8 in the placebo and GSEe groups. (**C,D**) Between-group comparisons at each timepoint. (**E,F**) Within-group changes over time. Data are presented as mean ± SEM. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$; **** $p \leq 0.0001$.

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Circulatory lipid parameters and inflammatory markers including LDL-C, non-HDL-C, HDL-C, TC and CRP, were analyzed to evaluate the metabolic effects of GSEe supplementation from baseline to 8 weeks (Figure 3).

In the GSEe group, direct LDL-C (a major atherogenic lipid fraction) decreased markedly and significantly from 138.2 ± 7.3 mg/dL (mean ± SEM) at baseline to 111.4 ± 4.9 mg/dL at 8 weeks (−26.8 mg/dL; p = 0.0008), whereas only a modest not significant reduction was observed in the placebo group (121.1 ± 5.7 to 116.3 ± 6.3 mg/dL; −4.8 mg/dL, n.s.) (Figure 3A and 3B).

A complementary effect was observed for non-HDL-C. Non-HDL-C (that comprise all atherogenic, potentially harmful, cholesterol particles, including, LDL, VLDL, IDL (intermediate-density lipoprotein), Lipoprotein(a), Remnant lipoproteins) remained essentially stable in the GSEe group (145.4 ± 6.9 to 144.3 ± 6.5 mg/dL; −1.1 mg/dL), while a substantial increase was observed in the placebo group over the same period (132.3 ± 5.2 to 149.5 ± 6.8 mg/dL; +17.2 mg/dL; p = 0.029). HDL-C declined in both groups during the study period; however, the magnitude of reduction was smaller and not significant in the GSEe group (42.3 ± 1.4 to 39.2 ± 1.2 mg/dL; −3.1 mg/dL) compared with the placebo group (45.7 ± 2.3 to 38.8 ± 1.5 mg/dL; −6.9 mg/dL; p = 0.0018). Total Cholesterol (TC) (the sum of all circulating cholesterol fractions) showed minimal change in the GSEe group (187.6 ± 7.3 to 184.4 ± 6.6 mg/dL; −3.2 mg/dL), whereas an increase was observed in the placebo group (178.1 ± 5.3 to 188.2 ± 6.9 mg/dL; +10.1 mg/dL). Overall, none of the lipid parameters showed statistically significant between-group differences at baseline or after 8 weeks of intervention.

CRP (a marker of systemic inflammation) concentrations decreased in both groups over the intervention period, with an enhanced effect in the GSEe group (4.4 ± 0.8 to 2.8 ± 0.8 mg/L; −1.6 mg/L) compared with placebo (4.6 ± 1.5 to 3.9 ± 0.85 mg/L; −0.7 mg/L), indicating a more pronounced attenuation of systemic inflammatory status associated with GSEe supplementation. However, these differences did not reach statistical significance, and no significant between-group effect was detected.

Effects on Affective Status (PANAS)

Changes in positive and negative emotional states from baseline to week 8 were assessed using self-reported PANAS questionnaire [28]. For positive affective status (PAS), a significant Group × Timepoint interaction was observed (F = 10.03, p < 0.0001), indicating a different longitudinal pattern between the two study arms (Figure 4). Sidak-adjusted between-group comparisons showed no significant differences at baseline or after 4 weeks of intervention. After 8 weeks, a trend toward higher PAS values was observed in the GSEe group compared with placebo (mean difference = +3.46; p = 0.073; Figure 4A). Within-group analyses demonstrated a significant and progressive increase in PAS in the GSEe group, with improvements evident from baseline to 4 weeks (+2.92; p = 0.0004) and further ameliorated at 8 weeks (+6.59; p < 0.0001), as well as between 4 and 8

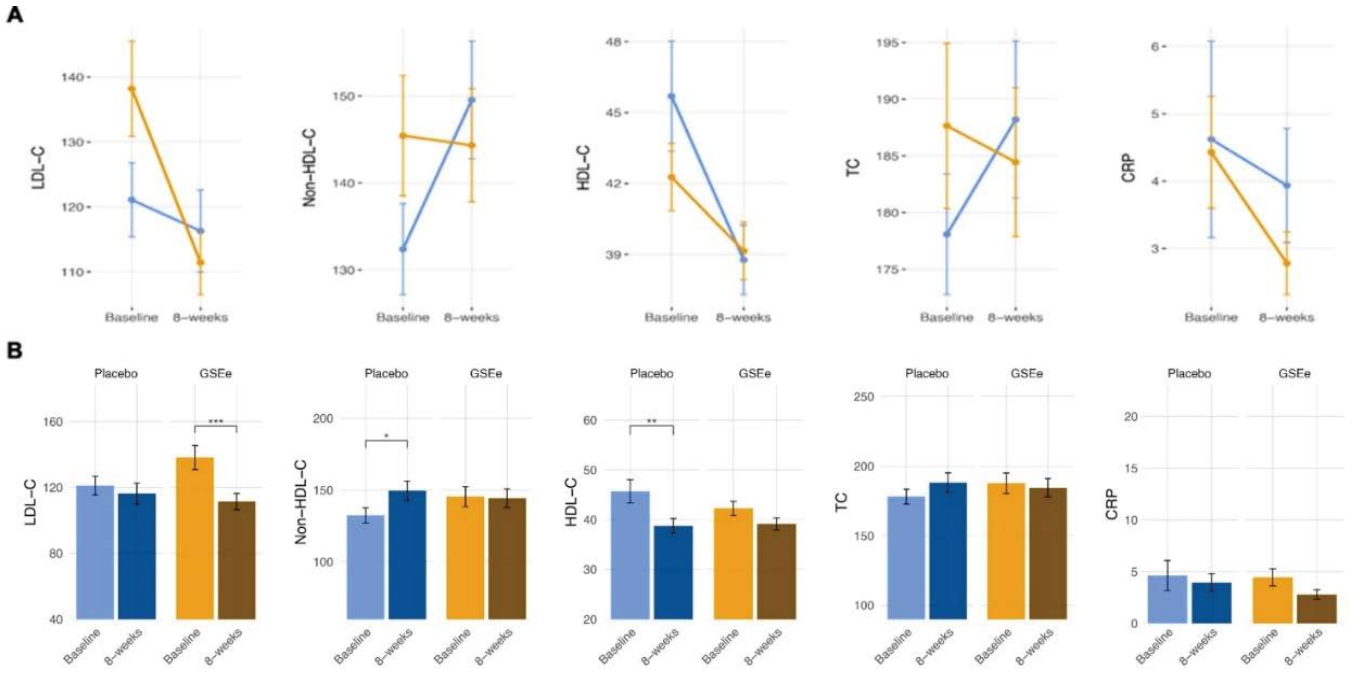

Figure 3: Effects of GSEe supplementation on circulating lipid parameters and inflammatory markers. (**A**) Longitudinal changes from baseline to week 8 for LDL-C, non-HDL-C, HDL-C, TC, and CRP in the placebo and GSEe groups. (**B**) Within-group changes from baseline to week 8 in the placebo and GSEe groups.

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weeks (+3.67; $p < 0.0001$; Figure 4A and 4C). In contrast, the placebo group exhibited only a modest increase in PAS from baseline to 8 weeks (+1.92; $p = 0.031$), with no significant changes detected at earlier timepoints.

For negative affective status (NAS), a significant Group × Timepoint interaction was also observed ($F = 4.65$, $p = 0.011$), supporting a different temporal pattern between groups (Figure 4). No significant between-group differences were detected at baseline or after 4 weeks; however, after 8 weeks, a trend toward lower NAS values was observed in the GSEe group compared with placebo (mean difference = −3.54; $p = 0.057$; Figure 4B). Within-group analyses revealed a marked reduction in NAS in the GSEe group from baseline to 8 weeks (−5.23; $p < 0.0001$), as well as between 4 and 8 weeks (−3.79; $p < 0.0001$; Figure 4B and 4D). In the placebo group, NAS showed a smaller reduction from baseline to 8 weeks (−1.90; $p = 0.048$), with a comparable change observed between 4 and 8 weeks.

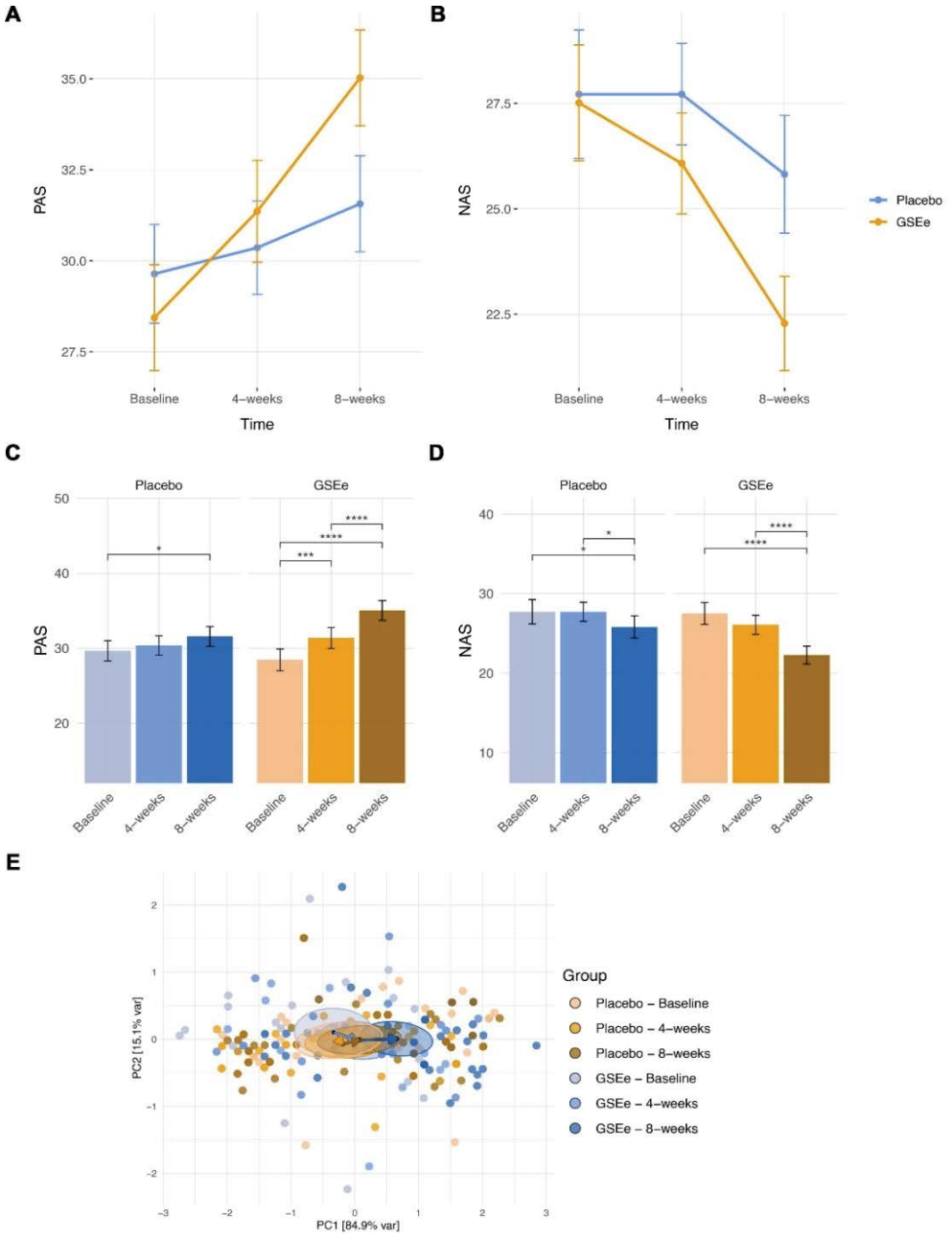

Figure 4: Effects of GSEe supplementation on affective status assessed by the Positive and Negative Affect Schedule (PANAS) questionnaire. (**A,B**) Longitudinal changes in Positive Affect Score (PAS) and Negative Affect Score (NAS) at baseline, week 4, and week 8 in the placebo and GSEe groups. (**C,D**) Within-group changes over time. (**E**) Principal component analysis (PCA) based on PAS and NAS scores showing group trajectories from baseline to week 8. Data are presented as mean ± SEM. *$p \leq 0.05$; ***$p \leq 0.001$; ****$p \leq 0.0001$.

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Multivariate analysis of PAS and NAS scores provided additional exploratory support for a coordinated longitudinal change in affective status. While no significant multivariate differences between groups were detected at individual timepoints, within-group MANOVA demonstrated a strong and highly significant shift in the combined PAS/NAS profile in the GSEe group from baseline to 4 weeks ($p < 0.0001$), from baseline to 8 weeks ($p < 0.0001$), and between 4 and 8 weeks ($p = 0.0002$). These coordinated multivariate changes were reflected in the principal component analysis (PCA) score plot (Figure 4E), which showed a clear temporal displacement of GSEe-treated participants, consistent with a simultaneous increase in positive affect and reduction in negative affect over the intervention period. In contrast, multivariate changes in the placebo group were smaller, less consistent, and reached statistical significance only at later timepoints.

Overall, these findings suggest a longitudinal favorable modulation of affective status in the GSEe group, characterized by improved positive affect and reduced negative affect, with effects emerging after 4 weeks and becoming more pronounced after 8 weeks of supplementation.

Effects on perceived stress (PSQ Index)

Changes in the PSQ index, with lower scores indicating lower perceived stress, were analyzed to evaluate the effect of GSEe supplementation over time. A trend-level Group × Timepoint interaction was observed for PSQ index ($F = 2.37$, $p = 0.097$), suggesting a possible not significant difference in the longitudinal pattern between the two study arms (Figure 5A).

Within-group analyses, interpreted descriptively, showed a time-dependent reduction in PSQ index values in the GSEe group, with a significant decrease from baseline to week 8 (-0.083; $p < 0.0001$) and between week 4 and week 8 (-0.055; $p < 0.001$), while the change from baseline to week 4 did not reach statistical significance (-0.029; $p = 0.14$, Figure 5B). In the placebo group, a smaller reduction was observed from baseline to week 8 (-0.040; $p = 0.018$), whereas no significant differences were detected at earlier timepoints. Overall, these results indicate that perceived stress levels changed over time in both study arms, with a more pronounced longitudinal improvement observed in the GSEe group, particularly during the later phase of the intervention.

Effects on Health-Related Quality of Life

Health-related QoL was assessed using the SF-36 questionnaire, with the Physical and the Mental Component Summary scores (PCS and MCS, respectively) analyzed to evaluate the effects of GSEe or placebo supplementation over time.

For PCS, no significant between-group differences were observed at baseline or after 4 weeks of intervention (Figure 6A). In contrast, after 8 weeks, PCS values were significantly higher in the GSEe group compared with placebo (means difference = +4.02; $p = 0.030$). Within-group analyses demonstrated a marked improvement in PCS in the GSEe group, with a significant increase from baseline to 8 weeks (+8.65; $p < 0.0001$) and a further significant increase between 4 and 8 weeks (+7.36; $p < 0.0001$; Figure 6A and 6C). In the placebo group, a more modest but significant increase in PCS was observed from baseline to 8 weeks (+3.78; $p = 0.0002$), with a smaller improvement between 4 and 8 weeks (+2.34; $p = 0.036$), while no significant change was detected between baseline and 4 weeks.

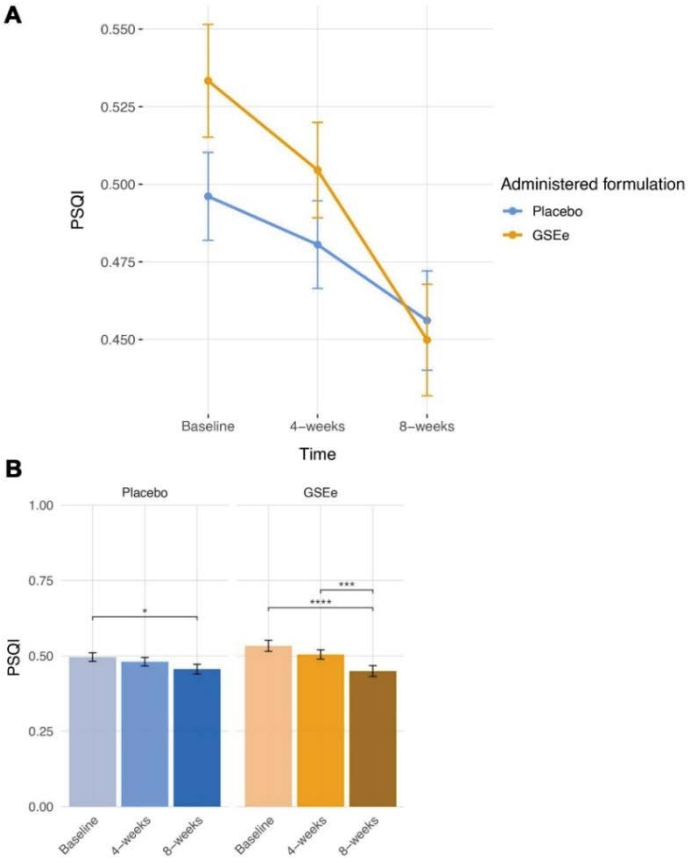

Figure 5: Effects of GSEe supplementation on perceived stress assessed by the perceived stress questionnaire index (PSQ Index). (**A**) Longitudinal changes in PSQ index (PSQI) at baseline, week 4, and week 8 in the placebo and GSEe groups. (**B**) Within-group changes in the placebo and GSEe groups. Data are mean ± SEM. *p ≤ 0.05; ***p ≤ 0.001; ****p ≤ 0.0001.

For MCS, no significant between-group differences were detected at any timepoint (Figure 6B). Within-group analyses revealed a significant improvement in MCS in the GSEe group from baseline to 8 weeks (+7.53; $p < 0.0001$), as well as between 4 and 8 weeks (+6.37; $p < 0.0001$; Figure 6B and 6D). In the placebo group, a smaller increase in MCS was observed from baseline to 8 weeks (+3.27; $p = 0.015$), while changes at earlier timepoints did not reach statistical significance.

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Multivariate analysis of PCS and MCS scores further supported a longitudinal effect of GSEe supplementation on overall quality of life. While no significant multivariate differences between groups were detected at baseline or after 4 weeks, a trend toward separation between the GSEe and placebo groups emerged at 8 weeks ($p = 0.104$). Within-group MANOVA demonstrated a marked and highly significant shift in the combined PCS/MCS profile in the GSEe group from baseline to 8 weeks ($p < 0.0001$) and between 4 and 8 weeks ($p < 0.0001$). These coordinated multivariate changes were reflected in the principal component analysis (PCA) score plot (Figure 6E), which showed a clear rightward displacement of GSEe-supplemented participants, indicating a global improvement in both physical and mental QoL dimensions. In contrast, although placebo-treated participants also exhibited multivariate changes over time, these shifts were less pronounced and less structured.

Overall, these findings indicate that GSEe supplementation was associated with a significant between-group improvement in the physical component of health-related QoL after 8 weeks. Changes in the mental component and in the combined PCS/MCS profile suggest a favorable longitudinal pattern, but these findings should be interpreted as supportive and exploratory because between-group differences for MCS did not reach statistical significance at individual timepoints.

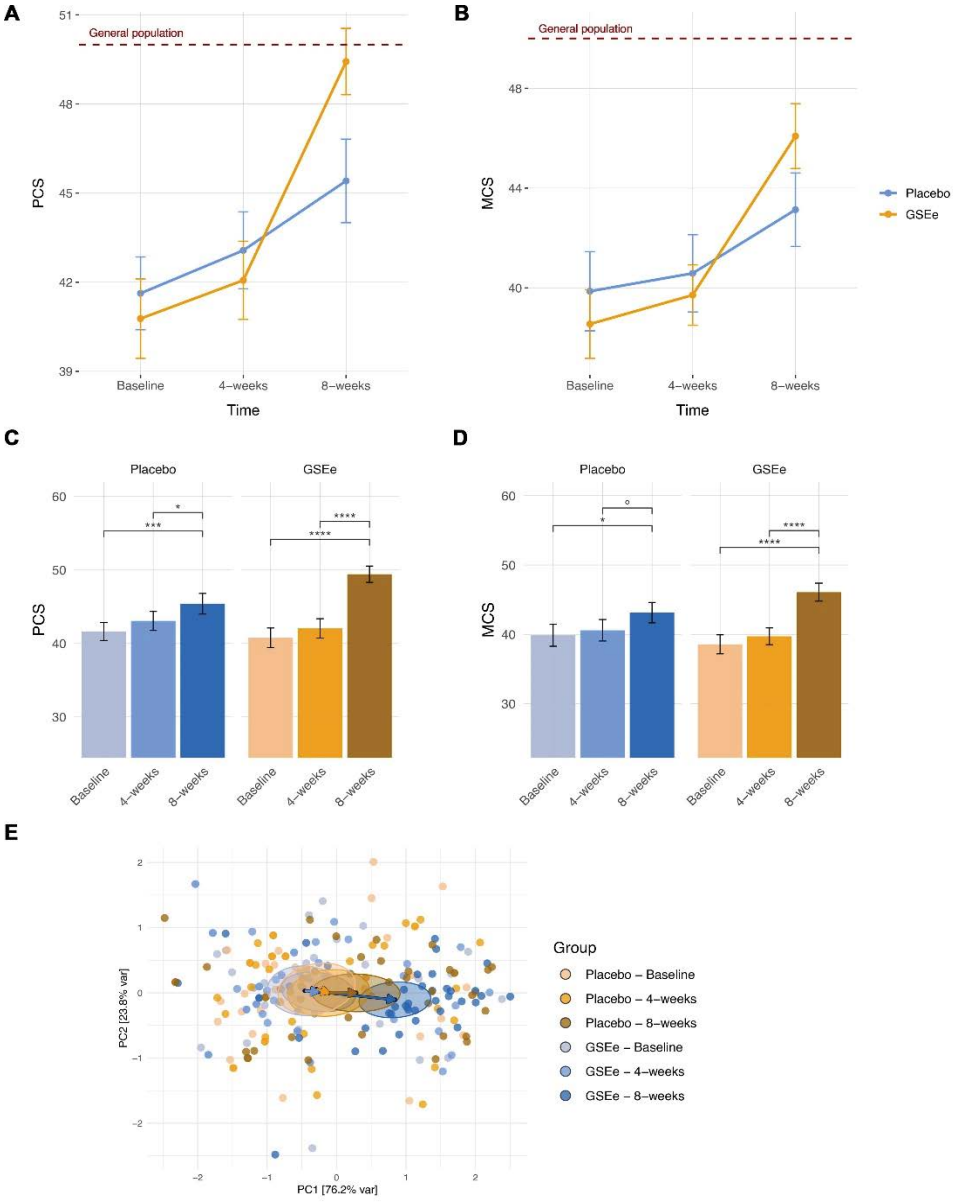

Figure 6: Effects of GSEe supplementation on health-related quality of life (QoL) assessed by QoL (SF-36) questionnaire. (**A,B**) Longitudinal changes in Physical Component Summary (PCS) and Mental Component Summary (MCS) scores at baseline, week 4, and week 8 in the placebo and GSEe groups. (**C,D**) Within-group changes over time. (**E**) Principal component analysis (PCA) based on PCS and MCS scores showing group trajectories from baseline to week 8. Data are presented as mean ± SEM. °$p \leq 0.1$; *$p \leq 0.05$; ***$p \leq 0.001$; ****$p \leq 0.0001$.

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Discussion

This randomized, double-blind, placebo-controlled clinical trial demonstrates that supplementation with a sustainable and standardized grape seed extract (GSEe) for 8 weeks results in clinically meaningful and coordinated benefits across cardiovascular, metabolic, inflammatory, and mental domains in adults with elevated blood pressure or Stage 1 hypertension. The supplementation was associated with significant reductions in systolic and diastolic BP, favorable modulation of lipid parameters, attenuation of systemic inflammation, and improvements in emotional affective status, perceived stress, and health-related quality of life. Taken together, these findings support the potential role of GSEe as a multifaceted nutritional strategy for early cardiovascular risk management. The observed improvements in BP and inflammatory markers are consistent with the well-established antioxidant and redox-modulating properties of OPCs reported in previous experimental and clinical studies.

The primary outcome of this study was BP modulation. GSEe supplementation resulted in a significant and time-dependent reduction in both systolic and diastolic BP, with effects becoming evident after 4 weeks and more pronounced at 8 weeks. In contrast, changes observed in the placebo group were modest and did not show a comparable progressive reduction over time, indicating a more pronounced BP-lowering response in participants receiving GSEe. The magnitude of BP reduction observed in this trial is clinically relevant and aligns well with previous randomized controlled trials, and meta-analyses of grape-derived polyphenols and grape seed extracts [5-8,15-17,19-24]. Systematic reviews have consistently reported modest but significant reductions in systolic and diastolic BP following grape product supplementation, particularly in individuals with elevated baseline BP or cardiometabolic risk factors [5,7,16]. Notably, the relative reductions observed in the present study fall within, and in some cases exceed, the range reported in these meta-analyses, supporting the efficacy of the standardized GSEe in early BP regulation.

The BP-lowering effects of GSEe are biologically plausible and supported by extensive mechanistic evidence. Grape seed proanthocyanidins have been shown to improve endothelial function through multiple complementary pathways, including enhancement of nitric oxide bioavailability, attenuation of oxidative stress, and inhibition of angiotensin-converting enzyme (ACE) activity [7,13,14,17]. Together, these effects reduce peripheral vascular resistance and improve arterial compliance, thereby contributing to reductions in both systolic and diastolic BP. In vitro and ex vivo studies with GSEe have further demonstrated endothelial-protective actions, including modulation of endothelin-1 release and adhesion molecule expression, providing direct support for a vascular mechanism of action [16,17]. Importantly, the present study extends existing evidence by demonstrating that the BP response to GSEe is consistent across sexes, with no evidence of gender-specific differences in the evaluated population. This finding supports the generalizability of the supplementation and is consistent with prior GSEe studies reporting comparable vascular responses in male and female participants [17]. Collectively, these results suggest that GSEe supplementation may represent a practical and well-tolerated nutritional strategy for supporting vascular health and BP control in individuals with elevated BP or Stage 1 hypertension.

Beyond BP, GSEe supplementation favorably influenced several lipid parameters relevant to cardiovascular risk. The most prominent effect was a marked reduction in LDL cholesterol, accompanied by stabilization of non-HDL cholesterol, whereas placebo treatment was associated with deterioration of atherogenic lipid fractions. Given that non-HDL cholesterol reflects the total burden of atherogenic lipoproteins, its stabilization in the GSEe group is particularly noteworthy and may have important implications for long-term cardiovascular risk reduction. The lipid-modulating effects of grape seed polyphenols have been reported previously, although results across studies have been heterogeneous [13,14,20]. Proposed mechanisms include reduced intestinal cholesterol absorption, modulation of hepatic lipid metabolism, inhibition of LDL oxidation, and improvement of antioxidant capacity. Proanthocyanidins have also been shown to interact with bile acid metabolism and lipid transport pathways, which may contribute to the observed LDL-lowering effect [13,14]. The present findings suggest that, in individuals with early BP dysregulation, GSEe supplementation may help prevent the progression of dyslipidemia alongside its vascular benefits. HDL cholesterol declined modestly in both groups, a pattern that appears largely time-related rather than treatment-specific. Importantly, the reduction was less pronounced in the GSEe group, and the overall lipid profile remained more favorable compared with placebo. Total cholesterol similarly remained stable with GSEe while increasing in the placebo group, reinforcing the concept of metabolic stabilization rather than isolated lipid lowering.

Systemic inflammation is increasingly recognized as a key contributor to both hypertension and cardiometabolic disease progression. In the present study, CRP levels decreased in both groups, with a more pronounced reduction observed in participants receiving GSEe. This finding is coherent with the well-documented anti-inflammatory properties of grape seed proanthocyanidins and supports the hypothesis that attenuation of low-grade inflammation may contribute to the cardiovascular benefits of GSEe [7,13,14,17,18]. Oxidative stress and inflammation are also tightly linked to neuropsychological stress pathways. Chronic activation of stress-related inflammatory signaling can exacerbate

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endothelial dysfunction, dyslipidemia, and BP elevation. The observed reduction in CRP therefore provides a potential mechanistic bridge between the cardiometabolic and psychological outcomes of the study.

A distinctive feature of this trial is the concurrent assessment of mental well-being alongside cardiovascular outcomes. PANAS analyses revealed a robust improvement in affective status, characterized by a significant increase in positive affect and a reduction in negative affect in the GSEe group. While between-group differences at individual timepoints approached but did not always reach statistical significance, within-group and multivariate analyses demonstrated a clear and coordinated shift in the affective profile of GSEe-supplemented participants. Principal component analysis further supported these findings by illustrating a distinct temporal trajectory consistent with improved emotional well-being. Perceived stress outcomes complemented these affective findings. GSEe supplementation was associated with a significant and progressive reduction in perceived stress, as measured by the PSQ-30, with effects becoming significant primarily during the second half of the intervention period. This temporal pattern mirrors the BP response and suggests that sustained supplementation may be required to elicit measurable psychophysiological benefits. Improvements in health-related QoL provide additional evidence of the broader impact of GSEe supplementation. The observed enhancements in both physical and mental dimensions of QoL are clinically meaningful and align with prior GSEe studies reporting benefits on perceived stress and mood in healthy and at-risk populations [17,18,26]. Together, these findings suggest that GSEe may support mental resilience and emotional balance. Recent mechanistic studies with GSEe have also demonstrated inhibition of monoamine oxidase-A, modulation of GABAergic signaling, and neuroprotective effects under oxidative stress conditions, providing a plausible biological basis for the observed improvements in mood and stress perception [14,17,18,26,27]. These neuropsychological effects may, in turn, contribute to improved autonomic regulation and BP control, highlighting the interconnected nature of cardiovascular and mental health.

Importantly, GSEe supplementation was well tolerated, with only a small number of participants, observed as doubled in the placebo group, reporting mild and transient gastrointestinal symptoms, which resolved spontaneously. No serious adverse events were reported, and adherence to supplementation exceeded 95% in both supplemented arms. These findings are consistent with previous clinical studies and support the favorable safety profile of this standardized GSEe when used in a preventive context [5-8,15-17,19-24]. The selected dosage in this exploratory study was the administration of 150 mg GSE twice daily (300 mg/day). Based on previous published studies examining the effects of GSE on cardiovascular and metabolic health, this dosage acted as a nutraceutical tool rather than an obtainable dose only with diet, aimed at modulating vascular endothelial function and improving cardiovascular risk, including potential reductions in BP and blood sugar [16,17]. Indeed, the 300 mg per day dose is considered a healthy supplement level, not one easily achievable through a standard diet. While grape seeds are rich in polyphenols, consuming that quantity of specific, standardized proanthocyanidins solely through diet (eating grapes or drinking juice) is considered unfeasible. The selected dosage is intended for supplements and their use in studies to ensure a consistent amount of active ingredients (proanthocyanidins) to achieve a "nutraceutical" effect, as for a dietary supplement [13,16,17,19-24]. Specifically, clinical trials have used this dosage to achieve measurable health benefits, including increased vascular flexibility and improved autonomic cardiac function [28,29]. This dosage showed increase in the production of nitric oxide (NO) via activation of endothelial nitric oxide synthase (eNOS), causing peripheral vasodilation and improved endothelial function, and enhanced the antioxidant capacity [17,30].

Overall, while the most robust evidence from this trial relates to the blood pressure–lowering effect of GSEe, secondary findings suggest potential broader cardiometabolic and psychological benefits that require confirmation in larger, adequately powered studies. From a clinical perspective, these findings are particularly relevant for individuals with elevated BP or Stage 1 hypertension, a population for whom pharmacological treatment is often deferred in favor of lifestyle and dietary supports. GSEe supplementation may represent a well-tolerated, and evidence-based nutritional option to boost vascular health, metabolic balance, and mental well-being during this critical preventive window. Strengths of the study include its multi-center, randomized, double-blind, placebo-controlled design, the use of the well-characterized, sustained, and standardized GSEe, and the comprehensive assessment of cardiovascular, biochemical, and psychological outcomes. The integration of univariate and multivariate analyses provides a nuanced understanding of both specific and global intervention effects. Limitations include the relatively short supplementation duration and the absence of long-term follow-up to assess persistence of effects. Additionally, while multiple outcomes were assessed, the study was not powered to detect small between-group differences across all secondary endpoints. Another limitation is the absence of objective biochemical verification of supplement intake (e.g., circulating polyphenol metabolites or biomarkers of antioxidant capacity), as compliance was assessed through tablet counts and participant self-report. Further studies with longer duration, larger sample sizes, and mechanistic biomarkers (e.g., endothelial function, oxidative stress markers, other inflammatory markers, polyphenol metabolites, autonomic measures) might confirm compliance and better elucidate the pathways underlying the observed benefits.

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Conclusion

This study provides comprehensive clinical evidence that supplementation with a sustainable standardized grape seed extract rich in OPCs improves blood pressure, lipid profile, and inflammatory status, with additional favorable effects on perceived stress, affective balance, and health-related QoL, in adults with elevated blood pressure or Stage 1 hypertension. These findings support the role of grape-derived OPCs, a class of fruit-derived polyphenolic antioxidants, as a promising nutritional strategy for early cardiovascular risk management and highlight the potential value of integrated approaches addressing both physiological and psychological dimensions of cardiometabolic health.

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Data availability statement

The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

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 the Institutional Ethics Committees of Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro (Approval No.: LUMHS/REC/734), and Lady Reading Hospital, Peshawar (Ref. No.: 465/LRH/MTI), Pakistan, and was registered at ClinicalTrials.gov (Identifier: NCT06982365).

Consent to publish

All participants provided informed consent for publication.

Conflicts of interest

G.P. is an employee of Indena S.p.A., Milan, Italy, which provided the grape seed extract used in this study, Enovita™ a registered trademark of Indena S.p.A. All remaining authors declare no commercial or financial relationships that could be construed as a potential conflict of interest.

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