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Systematic Review

The Effect of Grape-Seed Extract on Glycemic Control And Insulin Sensitivity: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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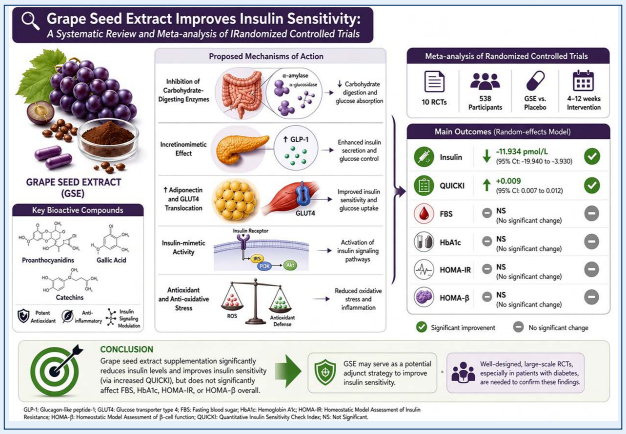
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Abstract

Introduction: Grape seed extract (GSE) supplementation has promising effects on the management of diabetes mellitus. Therefore, the present meta-analysis aimed to assess the effects of GSE on glycemic parameters systematically.



Methods: A comprehensive search was conducted in PubMed, Scopus, Web of Science, and Google Scholar for relevant English-language articles published through January 2025. The Cochrane Collaboration's tool was used to assess the risk of bias in the included studies. Data analysis was performed using STATA 17 with a random-effects model. Heterogeneity among studies was assessed using the I^2 statistic, and subgroup and sensitivity analyses were conducted.

Results: Ten randomized controlled trials (RCTs) were included in the meta-analysis. A significant reduction in insulin levels (WMD = -11.93, 95% CI: -19.94, -3.93; $P = 0.003$) and an increase in the Quicki index (WMD: 0.009, 95% CI: 0.007, 0.012; $P = 0.000$) were observed following GSE supplementation. However, no significant effects were found on fasting blood sugar (FBS), HOMA-IR, HOMA-β, or HbA1c levels ($P > 0.05$). In subgroup analyses, HOMA-IR was reduced in studies with durations < 8 weeks and doses < 400 mg/day.

Conclusion: Improved insulin sensitivity, as reflected by lower insulin levels and an improved Quicki index, may be achieved through GSE intake. These effects could be mediated through inhibition of intestinal α-glucosidase and pancreatic α-amylase activity, increased glucagon-like peptide-1 (GLP-1) release, and insulin-mimetic activity. However, additional large-scale RCTs are required to confirm these findings.

Trial registration: The study protocol was registered in the PROSPERO database (CRD42024596397)

Introduction

The rising trend of diabetes mellitus (DM) and abnormal glycemic markers is emerging as a significant public health challenge around the world.[1] According to the latest data from the International Diabetes Federation (2023), the global prevalence of diabetes is expected to reach 783 million by 2045.[2] Insulin resistance (IR) refers to a reduced ability of specific tissues to respond to insulin. It plays a pivotal role in the pathogenesis of numerous metabolic disorders, including hyperglycemia, type 2 diabetes (T2DM), dyslipidemia, and hypertension.[3] Some essential strategies for managing insulin resistance and hyperglycemia include various pharmacological medications, dietary and lifestyle interventions, and the

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use of medicinal plants as functional foods.[4,5] Grape seed is an economically valuable byproduct of the grape (Vitis vinifera) and is used as a food supplement. It consists of approximately (w/w) 40% fiber, 16% essential oil, 11% protein, and 7% complex phenolic compounds, including epicatechin, catechin, and epicatechin-3-O-gallate, called proanthocyanidins (PAs).[4,6] The phenolic compounds of grape seeds exhibit powerful antioxidant properties, which are reported to be approximately 20 times more than vitamin C and 50 times more than vitamin E.[7]

Studies have elucidated various pharmacological activities of GSE, including antioxidant and anti-inflammatory effects, as well as anticancer and cardioprotective properties.[8-11] Moreover, some recent studies suggest that supplementation with GSE can significantly decrease fasting blood sugar (FBS) and improve other glycemic markers.[12-14] Most recently, the results of Zaeemzadeh et al. demonstrated that supplementation with GSE has the potential to effectively manage blood pressure and FBS levels in patients with T2DM.[15] Ghanbari et al. reported a significant decrease in serum insulin level and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) after supplementation with GSE in patients with non-alcoholic fatty liver (NAFLD).[10] However, the results of a meta-analysis on the hypoglycemic effects of different grape products did not show any changes in hemoglobin A1c (HbA1C), FBS, or insulin levels.[16]

The hypoglycemic effect of GSE may be mediated through several mechanisms, including inhibition of intestinal α-glucosidase and pancreatic α-amylase activity, increased glucagon-like peptide-1 (GLP-1) release, significant elevation in adiponectin levels, and insulin-mimetic activity.[17,18] Moreover, Polyphenols in GSE can counteract oxidative stress-induced insulin resistance by improving the redox balance, increasing insulin efficacy,[19] and enhancing the expression of glucose transporter type 4 (GLUT4).[20]

Considering the inconsistent findings and the limited scope of the previous meta-analysis by Asbaghi et al, which focused only on FBS and HbA1c,[21] the present meta-analysis was conducted to provide a more comprehensive evaluation of grape seed extract by examining a wider range of glycemic indices, including FBS, insulin, HOMA-IR, Homeostasis Model Assessment of β-Cell Function (HOMA-β), quantitative insulin sensitivity check index (QUICKI), and HbA1c. Additionally, studies examining other forms of grape seed products or multi-component interventions were excluded to ensure that the observed effects were attributable solely to grape seed extract. Moreover, the present study incorporates four newly published randomized controlled trials,[4,10,15,22] that were not available at the previous meta-analysis.[21] Including these updated data enhances the robustness and contemporary relevance of the present review.

Methods

The present meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary file 1, Table S1).[23] The review has been registered at PROSPERO (www.crd.york.ac.uk/prospero/) with the registration number CRD42024596397.

Literature Search Strategies

International scientific databases, including PubMed, Scopus, and Web of Science, were searched for relevant studies published until January 2025. The search strategy is presented in Supplementary file 1, Table S2. Moreover, we hand-searched the reference lists of included articles and related reviews and meta-analyses. All articles were managed using EndNote software (version 21.5; Clarivate Analytics).

Study Selection, Inclusion, and Exclusion Criteria

The PICO criteria that guided inclusion and exclusion in our research included adults as the population, grape seed extract as the intervention, and glycemic markers as outcomes. Articles were considered for data extraction if they met the following criteria: RCT studies (parallel or crossover design) that examined just the effects of GSE (not in combination with other interventions like other herbs), performed on adults aged at least 18 years or more, and provided sufficient information, including 95% confidence interval (CI), standard error (SE), or standard deviation (SD) of data set at baseline and at the end of the trial in both treatment (grape seed) and control groups for the targeted outcomes including, FBS, HbA1c, insulin level, HOMA-IR, HOMA-β, and QUICKI. Irrelevant studies, including trials without an appropriately controlled design, experimental studies, observational studies, reviews, case reports, and case series, were excluded from the study. A total of 10 RCTs involving 538 participants (287 in the intervention group, 251 in the control group) were included. Studies were published between 2007 and 2024, primarily conducted in Iran, with participants aged 18–62 years. Sample sizes varied from 12 to 90. Grape seed extract doses ranged from 69.37 to 2000 mg/day, and intervention durations ranged from 30 days to 25 weeks. Most trials had a parallel design, and one used a crossover design. Participants included healthy individuals and patients with T2DM, NAFLD, CKD, PCOS, and hypertension.

Data Extraction

Two reviewers independently screened titles and abstracts using predefined selection criteria. Disagreements were resolved through discussion or consultation with a third reviewer.

The following data were taken from selected studies: the first authors' names, study location, year of publication, sample size, mean age, study design, dosage of GSE, duration of the study, type of disease, the mean and SD for FBS, HbA1c, insulin level, HOMA-IR, HOMA-β, and QUICKI in each intervention and control group. Moreover, if a study had reported the effects of two

different doses of GSE, each dosage arm was considered an independent study.

Quantitative Data Synthesis and Statistical Analysis

The effect size, weighted mean difference (WMD), was calculated using the change-from-baseline method, in which the mean difference between the final and initial values for each group was used to determine the mean change in each group. The random-effect inverse-variance model was used to pool the results of the included studies, and WMD with 95% CI were presented as the effect size. The mean change in glycemic-related parameters, including FBS, HbA1c, insulin level, HOMA-IR, HOMA-β, and QUICKI, was calculated by subtracting the baseline value from the final follow-up value. The SD of the mean change was calculated using the following formula: SD = square root [(SD pretreatment)^2+(SD posttreatment)^2-(2R × SD pretreatment × SD posttreatment)], in which a correlation coefficient (R) of 0.8 was assumed.[24,25] In studies that reported SE instead of SD, the following formula was used to calculate the SD, where N is the number of subjects: SD = SE × square root of N. The methods, as published by Hozo et al,[24] were used to estimate the mean and SD when outcomes of interest were reported as median and range.

We employed a random-effects model to account for potential heterogeneity in study designs. Heterogeneity between studies was examined using the I-squared (I^2) index. If the I^2 The test exhibited a value greater than 50%, indicating heterogeneity between the included trials. A sensitivity analysis was performed using the leave-one-out method to evaluate the effect of every single trial on the estimated effect size. Subgroup analyses were conducted for supplementation dose, intervention duration, and sample size to investigate potential sources of heterogeneity. Publication bias was evaluated using funnel plot asymmetry and Begg's rank correlation test in combination with Egger's weighted regression test. The trim-and-fill method was used to compensate for publication bias. All analyses were performed using Stata 17.0 (StataCorp, College Station, TX), and $P < 0.05$ was considered statistically significant.

Results

Search Results and Trial Flow

The study's flowchart is shown in Figure 1. The initial comprehensive search through databases identified 1038 articles. Removing duplicates yielded 737 articles. Then, 698 irrelevant studies were excluded, and thirty-nine papers were retrieved and reviewed based on their full texts. Among the full-text articles evaluated, 29 studies were excluded for the following reasons: not randomized placebo-controlled studies (n = 7), did not report glycemic indices (n = 10), use of GSE in combination with other components (n = 4), not provide sufficient data (n = 3), duplicate data (n = 1), and using different forms of grape seed (flour, powder or oil) (n = 4). Finally, 10 articles were identified as eligible and qualified for the final meta-analysis. The PRISMA flow diagram outlines the results of the study selection process for this systematic review and meta-analysis (Figure 1).

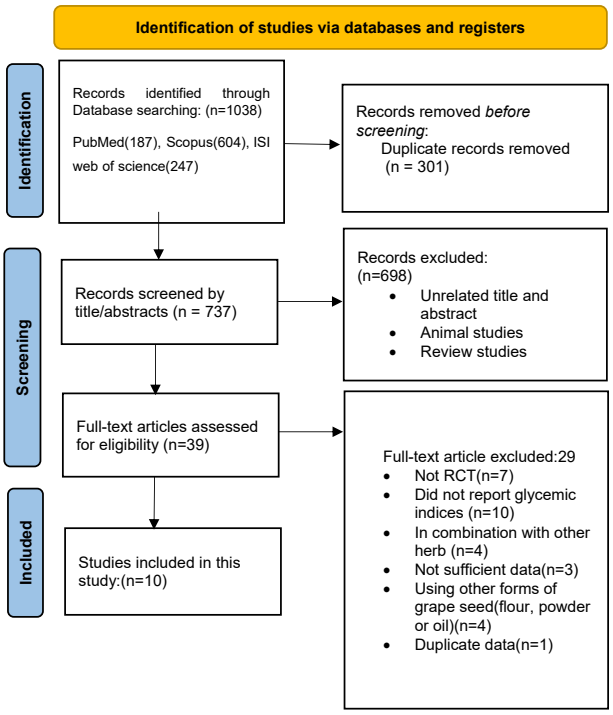


Figure 1. Literature search and the screening processes

Study Characteristics

The main characteristics of the included articles are given in Table 1. Overall, 538 participants were enrolled (intervention = 287 and control = 251). The included studies were published between 2007 and 2024, with the majority conducted in Iran.[4,10,15,20,22,26] Other studies were conducted in Japan,[27] the UK,[28] the USA,[29] and Tunisia.[30] The age range of the participants varied from 18 to 62 years. One trial included only women,[22] while the remaining trials included both men and women. The sample sizes ranged from 12 to 90. The dosage of grape seed extract varied from 69.37 mg/d to 2000 mg/d. Intervention periods ranged from 30 days[15] to 25 weeks.[30] Most included studies employed a parallel design, whereas one adopted a crossover design.[28] For the crossover trial, treatment effects were analyzed using a paired-design approach in accordance with Cochrane recommendations. The effect estimate was calculated from the within-participant difference between the intervention and control periods. The included crossover trial incorporated a washout period between treatment phases, which was considered sufficient to minimize potential carryover effects. Participants' health status varied across studies; two studies were conducted on healthy subject,[20,27] three were performed on subjects with T2DM,[15,26,28] and other studies included participants with NAFLD,[4,10] CKD,[30] PCOS,[22] and HTN.[29]

Risk of Bias Assessment of the Studies

The quality of the selected RCTs was independently

Table 1. Characteristics of included studies

Author, year	Study location	Study design	Study Duration (Week)	Study population (final sample size)/Health condition	Mean age ± SD (years)	BMI ± SD (kg/m²)	Control	GSE Intervention
Sano et al.[27](2007)	Japan	randomized Single-blind	2 Weeks pre observation+ 12 Weeks +2 -Weeks follow-up	Healthy subjects	I1:51 ± 2.4 I2:52.9 ± 2 P:53.2 ± 2.1	I1:24.2 ± 0.66 I2:24.1 ± 0.62 P:24.4 ± 0.59	Placebo tablet (0 mg Proanthocyanidin)	200 (Calculated as Proanthocyanidin)/ GSE:69.375mg/d 400(Calculated as Proanthocyanidin)/ GSE:138.750mg/d
Kar et al.[28](2009)	London, UK	double-blinded crossover	8+ 2 Week washout period	32 (16 M,16F) T2DM	61.8 ± 6.36	30.2 ± 5.92	NR	600mg/d GSE
Abedini et al.[26] (2013)	Iran	Triple Blind	8	48 (6 M,42 F) T2D	I:52 ± 9 P:51 ± 10	I:30.82 ± 5.67 P:29.69 ± 3.58	NR	200 mg/d GSE
Taghizadeh et al.[20] (2016)	Iran	Randomized, Double-Blind, Placebo-Controlled Clinical Trial	8	40 female volleyball players	I:19.8 ± 5.0 P:21.6 ± 7.0	I:21.6 ± 3.6 P:21.2 ± 1.5	placebo pearls	600 mg/d GSE
Park et al.[29](2016)	USA	randomized, two-arm, double-blinded, placebo-controlled/ parallel	6+ 4w follow-up phase	28 (15 M,13 F) pre-hypertension	I:44 ± 10 P:42 ± 10	I:34 ± 7 P:31 ± 9	Juice(40Kcal) containing 0 mg/d GSE	Juice(40Kcal) containing 300mg/d GSE
Turki et al.[30] (2016)	Tunisia	randomized double-blind, placebo-control pilot study	25	33 (19 M, 14 F) CKD	I:62.3 ± 9.1/ P:62.7 ± 7.5	NR	Starch	six capsules of GSE, each capsule containing 350 mg of grape seed powder:2 g GSE/ day
Sedighi et al.[22](2020)	Iran	double-blind, randomized, controlled clinical trial	8	50/pcos	I:37.8 ± 6.1 P:33.6 ± 8.8	I:25.4 ± 3.9 P:28.4 ± 1.8	NR	400 mg/d of GSE
Mojiri Forushani et al.[4](2021)	Iran	randomized, double-blind clinical trial	8	90(52M, 38F) NAFLD	I:37.71 ± 9.39 P:36.04 ± 9.40	I:28.08 ± 2.50 P:28.36 ± 1.75	Starch	400mg/d GSE
Ghanbari et al.[10] (2024)	Iran	Randomized, double-blind, placebo-controlled study	8	50(24 M, 26 F) NAFLD	I:43.52 ± 8.12 P:44.88 ± 10.14	I:31.52 ± 3.58 P:31.42 ± 3.63	cellulose, silicon dioxide, magnesium stearate, and starch	520 mg/d GSE
Zaeemzadeh et al.[15] (2024)	Iran	Randomized, Double-Blind, Placebo-Controlled Clinical Trial	30 Days	74(32M,42F) T2D	I:52.89 ± 10.01 P:53.36 ± 10.63	I:28.22 ± 4.04 P:28.09 ± 3.85	NR	526.4 mg/d GSE

Abbreviations: BMI, body mass index; F, female; M, male; NR, not reported

evaluated by the same authors utilizing the Cochrane Collaboration risk of bias tool based on the following criteria: "randomization generation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Accordingly," Low risk," "High risk," or "Unclear risk" terms were applied to describe each domain. The assessments indicated that most of the included studies had a low risk of bias in the random sequence generation, allocation concealment, blinding of participants and personnel, and incomplete outcome data domains. However, some of the included RCTs had a high risk of bias for the selective outcome reporting and blinding of outcome assessor's domains. Details of the risk-of-bias assessment are provided in Supplementary file 1, Table S3.

Effects of Grape Seed Extract on Fasting Blood Sugar (FBS)

We found nine articles in this area. Pooled results from 8 trials with nine treatment arms (271 cases and 214 controls) showed that FBS levels did not significantly differ in grape seed extract consumers compared with the control group (Effect size (WMD): 0.355, 95% CI: -2.188,2.899, $P=0.784$), with significant heterogeneity being detected ($I^2=68.1$ %, $P=0.001$) (Figure 2A).

When studies were categorized by sample size, a significant FBS-reducing effect was observed in studies with a sample size of ≤ 40 (Effect size (WMD): -2.176 mg/l; 95% CI: -4.302, -0.050; $P=0.045$), but not in studies with more than 40 participants. Subgroup analyses based on duration and dose did not reveal significant associations (Supplementary file 1, Table S4).

To observe the impact of every study on the pooled effect size (WMD), we conducted a leave-one-out sensitivity analysis. The estimated effect size (WMD) for the effect of grape-seed extract on FBS was robust (Supplementary file 1, Figure S1A). Funnel plots revealed asymmetry in the

meta-analyses of the effects of grape-seed extract on FBS. Using the 'trim and fill' method to adjust for publication bias, two potentially missing studies were imputed for the meta-analysis of FBS (Effect size (WMD): 2.039 mg/l; 95% CI: -1.915, 2.994) (Supplementary file 1, Figure S1B), which did not influence the obtained results.

Effects of Grape Seed Extract on Insulin

Four effect sizes (82 cases and 86 controls) reported insulin. The overall pooled estimate of the effect (WMD) on insulin was -11.934 Pmol/L (95% CI: -19.938, -3.930), $P=0.003$, which revealed a substantial reduction in insulin. Statistical heterogeneity was observed ($I^2=68.8$ %, $P=0.022$) (Figure 2B).

Sensitivity analysis was performed by sequentially excluding each study to assess the robustness of the pooled results. The overall effect estimate (Effect size (WMD) = -11.93, 95% CI: -19.94 to 3.93) remained statistically significant in most scenarios, though certain studies notably influenced its magnitude. The exclusion of Sedighi et al.[22] strengthened the effect (Effect size (WMD) = -13.88, 95% CI: -18.43 to -9.34), suggesting that this study's neutral findings had been attenuating the overall effect. When Taghizadeh et al,[20] the study with the most significant weight (39.27%), was removed, the effect became borderline non-significant (Effect size (WMD) = -13.06, 95% CI: -27.95 to 1.83). The results demonstrated relative stability when other studies were excluded (Supplementary file 1, Figure S2A). The evaluation of potential publication bias yielded mixed results. Begg's rank correlation test showed no significant small-study effects (Kendall's Score = -2, z = -0.68, $P=0.497$). However, the trim-and-fill analysis suggested one potentially missing study on the right side of the funnel plot. When incorporating this imputed study, the adjusted effect size (WMD) attenuated from -12.17 (95% CI: -20.99 to 3.36) to -9.80 (95% CI: -18.74 to -0.86), representing a 19.5% reduction in effect magnitude (Supplementary file 1, Figure S2B). Because of the small number of included studies, the publication-bias tests and trim-and-fill are considered exploratory and not fully reliable.

Effects of Grape Seed Extract on HOMA-IR

Five publications, overall 232 patients (114 interventions and 118 controls), reported HOMA-IR data. Figure 3A shows the pooled results from the random-effects model combining the WMD for the effect of grape-seed extract supplementation on HOMA-IR in the study population, which did not reveal a significant reduction in the GSE

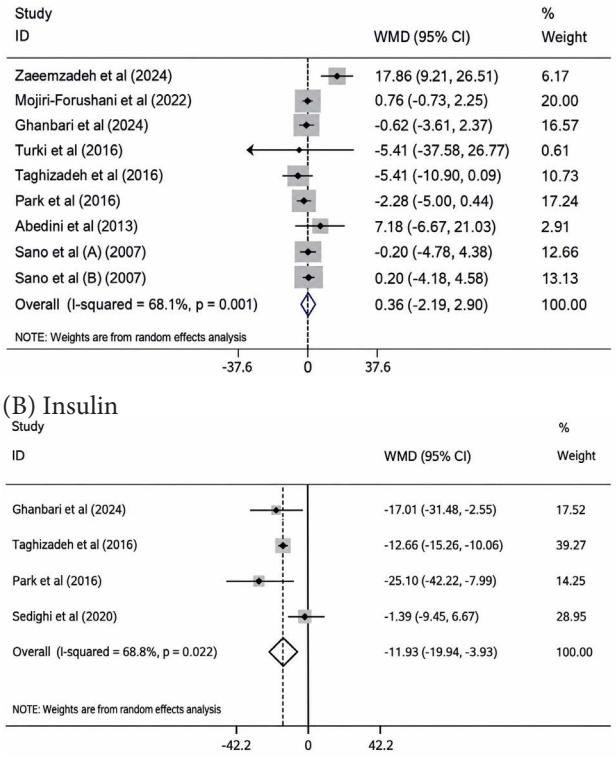


Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of grape seed extract supplementation on FBS (A) and Insulin (B)

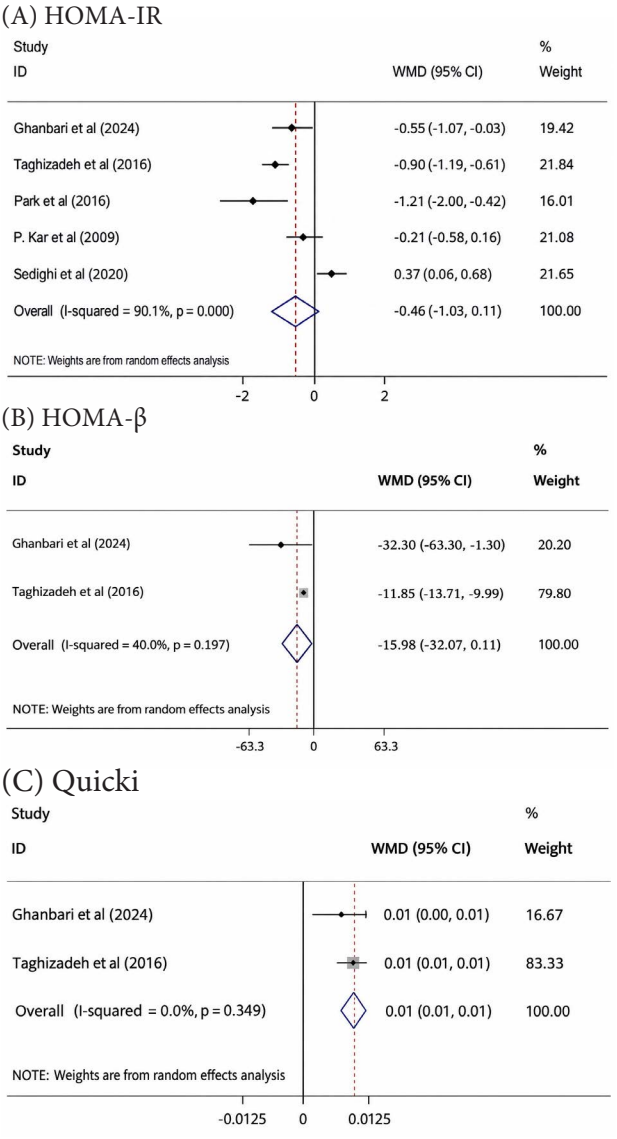


Figure 3. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of grape seed extract supplementation on HOMA-IR (A), HOMA-β (B) and Quicki (c)

treatment groups compared with the control groups (Effect size (WMD): -0.461, 95% CI: -1.031, 0.109, $P=0.113$), with substantial heterogeneity among the studies ($I^2=90.1\%$, $P=0.000$), but when we divided studies based on dose and duration, significant reduction was found for subsets of studies using GSE doses < 400 mg/ d (Effect size (WMD): -1.207, 95% CI: -1.998, -0.416, $P=0.003$) and less than 8 weeks supplementation (Effect size (WMD): -1.207, 95% CI: -1.998, -0.416, $P=0.003$) (Supplementary file 1, Table S4). Sensitivity analysis confirms that no single study dominates the findings; however, the overall effect is fragile and non-significant (Supplementary file 1, Figure S3A).

Begg's rank correlation test ($P=0.624$) and Trim-and-Fill analysis (with zero imputed studies) indicated no significant small-study effects or publication bias, and there was no asymmetry in the funnel plot. However, the limited number of studies reduces confidence in these assessments. The pooled effect remained non-significant after bias adjustment (Effect size (WMD) = -0.456, 95% CI: -0.989 to 0.077) (Supplementary file 1, Figure S3B).

Effects of Grape Seed Extract on HOMA-β and Quicki

Combining the results of two studies (45 cases and 45 controls) did not reveal a substantial reduction in HOMA-β (Effect size (WMD):-15.981, 95% CI: -32.073, 0.111, $P=0.052$) following grape seed extract supplementation. No statistical heterogeneity was observed ($I^2=40.0$ %, $P=0.197$) (Figure 3B). The results for Quicki were presented in two comparisons involving 90 participants. Overall, interventions with grape-seed extract significantly increased Quicki (Effect size (WMD): 0.009, 95% CI: 0.007, 0.012, $P=0.000$), with no significant heterogeneity among the studies ($I^2=0.0\%$, $P=0.349$) (Figure 3C).

Effects of Grape Seed Extract on HbA1c

Three studies involving four effect sizes and 220 participants (133 in the intervention group and 87 in the control group) reported HbA1c as an outcome measure. Combined results through the random-effects model showed that grape seed extract intake did not have a significant effect on Hb1Ac (Effect size (WMD): -0.053, 95% CI: -0.155, 0.049, $P=0.311$) without substantial heterogeneity across the studies ($I^2=11.7\%$, $P=0.334$) (Figure 4).

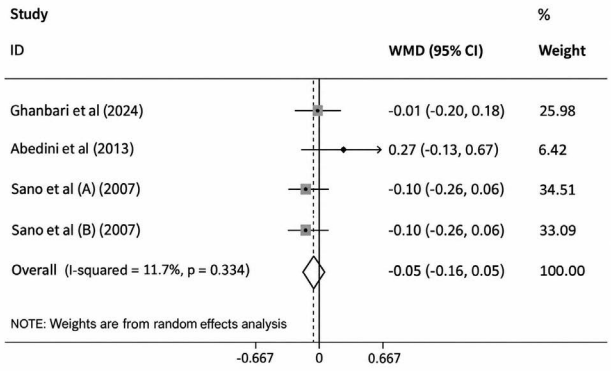


Figure 4. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of grape seed extract supplementation on HbA1c

The study's stratification did not reveal a significant effect on HbA1C reduction (Supplementary file 1, Table S4). The overall effect remained remarkably stable (WMD ≈ -0.05) regardless of which study was omitted (Figure Supplementary file 1, S4A). There was asymmetry in the funnel plot, and the trim-and-fill analysis, conducted under a random-effects model, imputed one additional study to address potential publication bias. The adjusted pooled estimate shifted slightly from −0.056 (95% CI: −0.151, 0.038) to −0.076 (95% CI: −0.168, 0.016). The trim-and-fill adjustment did not alter the meta-analytic inference, as the null effect persisted post-imputation (Supplementary file 1, Figure S4B).

Sensitivity Analyses of the Assumed Correlation Coefficient (r)

The assumed correlation coefficient was applied to the studies of FBS, insulin, HOMA-IR, and HbA1c, because the studies of HOMA-β and QUICKI reported SD change. Sensitivity analyses using correlation coefficients of 0.2, 0.5, and 0.8 yielded very similar pooled estimates. Therefore, the overall findings were robust to the assumed correlation coefficient used for imputing SD change.

Discussion

The current meta-analysis revealed that supplementation with grape-seed extract led to a -11.934 Pmol/L decrease in insulin levels and improved insulin sensitivity by increasing the Quicki index by 0.009. However, HbA1C, FBS, HOMA-IR, and HOMA-β levels were not influenced by GSE. Subgroup analyses revealed a reduction in HOMA-IR in studies lasting less than 8 weeks and doses lower than 400 mg.

Our findings showed some consistencies and discrepancies with the results of earlier systematic reviews. Moodi et al. (2021) reported no significant effects of all grape products on HbA1c and insulin levels but showed a significant effect on FBS and HOMA-IR.[16] While our results confirm the null effect on HbA1c, we observed a significant reduction in insulin levels, in contrast to their findings. In contrast, the meta-analysis by Asbaghi et al. found significant reductions in FBS but no effect on HbA1c after GSE supplementation; however, they did not examine insulin sensitivity indices, such as QUICKI or HOMA-IR.[21] This discrepancy may be attributed to the inclusion of results from recent high-quality randomized controlled trials in our meta-analysis, as well as differences in the type of interventions (GSE vs. various grape seed products).

Our results provide novel insights into the potential effects of GSE on insulin sensitivity, as measured by parameters including insulin levels, QUICKI, HOMA-IR, and HOMA-β. Similarly, the results of a recent RCT by Ghanbari et al. (2024) demonstrated that GSE supplementation led to a significant reduction in fasting

insulin levels and HOMA-IR. Additionally, a notable improvement in the QUICKI index (as a marker of insulin sensitivity) was observed. However, no significant effects were reported on FBS or HbA1c.[10] This finding is particularly noteworthy as it suggests GSE's potential role in addressing insulin signaling pathways and insulin resistance, a fundamental pathophysiological component of metabolic disorders.

Overall, some discrepancies in the effects of GSE on glycemic parameters across different clinical trials can be attributed to differences in ethnicity and socioeconomic status, variations in participants' health status, diverse phenolic concentrations of GSE depending on processing techniques, storage conditions, and study designs.

The most important active constituents of GSE are proanthocyanidins, Gallic acid, and Catechins.[4,28,31] According to Figure 5, it was proposed that the hypoglycemic effect of grape seed extract can be achieved through some default mechanisms, such as the inhibition of intestinal α-glucosidase and pancreatic α-amylase activity, with equal or even higher potency than acarbose.[32-34]

Moreover, it was reported that the procyanidins of GSE may have an incretinomimetic effect by inhibiting endothelial Dipeptidyl peptidase-4 (DPP-4) activity and increasing GLP-1 release.[35] The other mechanism of action is a significant elevation of adiponectin levels by GSE phenolic compounds. As adiponectin plays a crucial role in the translocation of GLUT4 to the plasma membrane,[10,36] it can enhance insulin sensitivity and glucose uptake in muscle cells.[37-39] Moreover, it has been reported that grape seed-derived procyanidins exhibit insulin-mimetic activity, which is associated with insulin signaling pathways.[40] Hyperglycemia is associated with increased oxidative stress, which can disrupt insulin signaling and reduce glucose uptake. However, polyphenols in GSE can break this vicious circle by regulating the cellular redox balance.[36,41,42]

The present meta-analysis takes a significant step toward elucidating the potential effect of GSE on insulin sensitivity, as measured by parameters including insulin levels, QUICKI, HOMA-IR, and HOMA-β. However, there are some limitations, including heterogeneity across study designs and participants' health status (research on different diseases), GSE dosage, and intervention duration. Further well-designed clinical trials exclusively on patients with diabetes can better conclude the hypoglycemic effects of GSE.

Conclusion

This meta-analysis demonstrated that GSE intake may improve glycemic indices and insulin sensitivity. These improvements may be achieved by some default mechanisms, including inhibition of intestinal α-glucosidase and pancreatic α-amylase activity, increased glucagon-like peptide-1 (GLP-1) release, significant elevation in adiponectin levels, and insulin-mimetic activity. However, future large-scale RCTs, especially in patients with diabetes, are required to confirm these results.

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Authors' Contribution

Conceptualization: Vahideh Ebrahimzadeh-Attari, Bita Meysami
Data Curation: Bita Meysami
Formal Analysis: Roghayeh Molani-Gol
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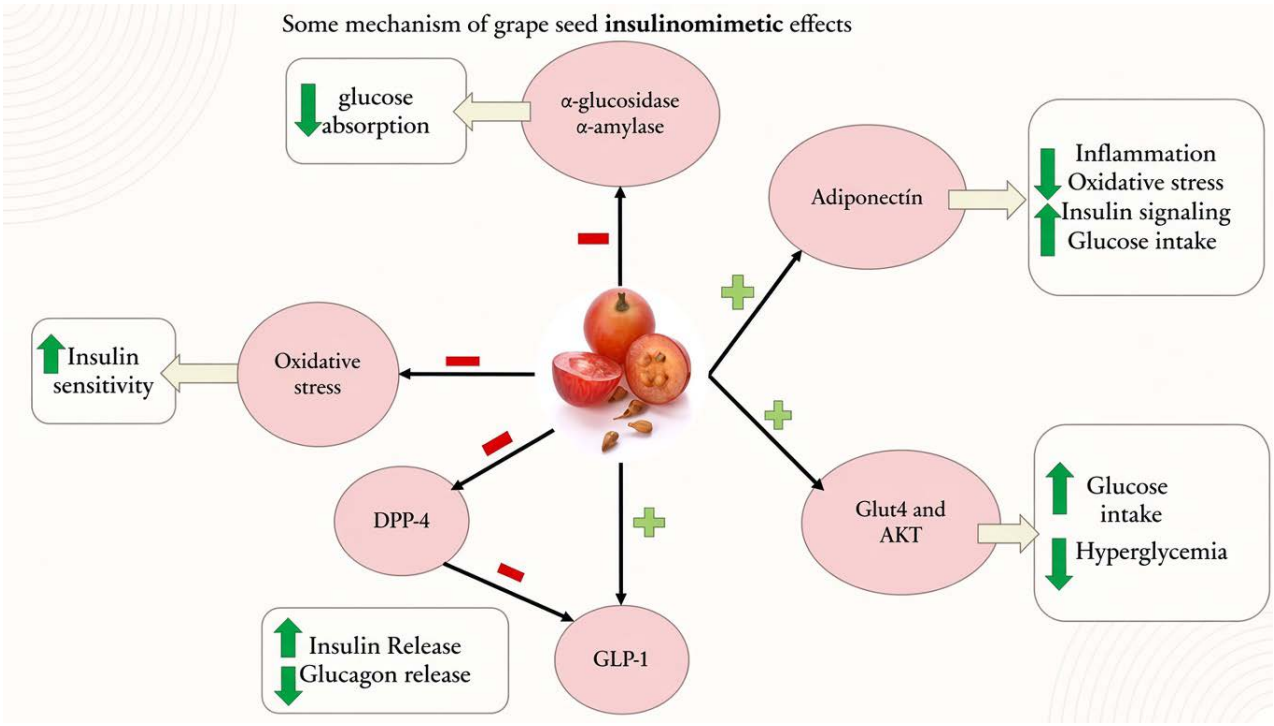


Figure 5. Possible mechanisms underlying how grape seed extract influences glycemic status

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Visualization: Vahideh Ebrahimzadeh-Attari, Bita Meysami
Writing–Original Draft: Bita Meysami
Writing–Review & Editing: Vahideh Ebrahimzadeh-Attari, Roghayeh Molani-Gol

Competing Interests
The authors declare that they have no conflicts of interest.

Data Availability
The information supporting the results of this review can be found in our supplementary documents.

Ethical Approval
Not applicable.

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Supplementary File
Supplementary file 1 contains Figures S1-S4.
Supplementary file 2 contains Table S1-S5.

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