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REVIEW

# The effects of grape seed extract on glycemic control, serum lipoproteins, inflammation, and body weight: A systematic review and meta-analysis of randomized controlled trials

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The aim of this systematic review and meta-analysis was to analyze the effects of grape seed extract (GSE) on glycemic control and serum lipoproteins, inflammation and body weight. Two independent authors systematically searched online databases including EMBASE, Scopus, PubMed, Cochrane Library, and Web of Science from inception until May 30, 2019. Cochrane Collaboration risk of bias tool was applied to assess the methodological quality of included trials. The heterogeneity among the included studies was assessed using Cochrane's Q test and I-square ($I^2$) statistic. Data were pooled using a random-effects model and weighted mean difference (WMD) was considered as the overall effect size. Fifty trials were included in this meta-analysis. Pooling effect sizes from studies demonstrated a significant decrease in fasting plasma glucose (FPG) (WMD): −2.01; 95% confidence interval (CI): −3.14, −0.86), total cholesterol (TC; WMD: −6.03; 95% CI: −9.71, −2.35), low-density lipoprotein (LDL) cholesterol (WMD: −4.97; 95% CI: −8.37, −1.57), triglycerides (WMD: −6.55; 95% CI: −9.28, −3.83), and C-reactive protein (CRP) concentrations (WMD: −0.81; 95% CI: −1.25, −0.38) following GSE therapy. Grape seed did not influence HbA1c, HDL cholesterol levels, and anthropometric measurements. This meta-analysis demonstrated that GSE intake significantly reduced FPG, TC, LDL cholesterol, triglycerides, and CRP levels.

**KEYWORDS**
grape seed extract, inflammation, insulin resistance, LDL cholesterol, meta-analysis, triglycerides

## 1 | INTRODUCTION

Dyslipidemia, particularly elevated plasma low-density lipoprotein (LDL) cholesterol levels, is the most important risk factor for cardiovascular disease (CVD) (Catapano et al., 2016). Apart from smoking and arterial hypertension, another important risk factors for CVD is metabolic syndrome (MetS). This syndrome is clustering of metabolic disorders, including abdominal type of obesity, glucose, hypertension, intolerance/hyperglycemia, and atherogenic dyslipidemia (decreased high-density lipoprotein (HDL) cholesterol and increased triglyceride levels with normal or moderately elevated LDL cholesterol) (Alberti, Zimmet, & Shaw, 2006; Chapman et al., 2011; Ferrari et al., 2016; Fruchart et al., 2008; Grundy et al., 2005). LDL particles in atherogenic dyslipidemia are small and dense and are considered to be more atherogenic than large buoyant LDL particles (Reiner, 2017). Approximately, 20–25% of adults in the world, both in developed and

**Abbreviations:** BMI, body mass index; CRP, C-reactive protein; FPG, fasting plasma glucose; GSE, grape seed extract; HbA1C, hemoglobin A1C; HDL-C, high density lipoprotein cholesterol; LssDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

developing countries are affected by this syndrome which is characterized by abdominal obesity as a phenotypic manifestation. The most important etiopathogenic mechanism of MetS is insulin resistance causing mobilization of fatty acids, while other possible mechanisms include increased biomarkers of oxidative stress and low-grade chronic inflammation (Cameron, Shaw, & Zimmet, 2004). As a result, MetS is strongly associated with CVD and Type 2 diabetes mellitus (T2DM). Therefore, a twofold increase in cardiovascular outcomes and a 1.5-fold increase in all causes of death as well as an increased incidence of T2DM are associated with this syndrome (Grundy et al., 2005; Mottillo et al., 2010). On the other hand, atherogenic dyslipidemia is not only predictor of macrovascular atherosclerotic disease and CVD events but it is also a risk factor for microvascular disease in T2DM (Sacks et al., 2014). Several studies have shown that MetS is associated with many other metabolic diseases such as nonalcoholic fatty liver disease, obstructive sleep apnoea, systemic lupus erythematosus, polycystic ovary syndrome, and vascular dementia (Cornier et al., 2008; Mok, Mok, Dixon, Armstrong, & Shaw, 1982; Uzunlulu, Caklili, & Oguz, 2016).

Grape seed has high flavonoid content. Its beneficial effects on health have been evaluated in many studies. These studies have reported that grape seed polyphenols had a beneficial effect on metabolic abnormalities in patients with and without MetS. Some of these studies have shown that an extract of grape seed, which is rich in flavanols, has antioxidant properties (Puiggròs et al., 2005), improves lipoprotein metabolism (Del Bas et al., 2005), restricts adipogenesis (Pinent et al., 2005), mimics insulin action (Pinent et al., 2004), and reduces inflammation (Terra et al., 2011). Results of a meta-analysis published in 2011, in which nine RCTs were included, showed that grape seed extract (GSE) administration did not have any effect on total cholesterol (TC), LDL cholesterol, HDL cholesterol, triglycerides and C-reactive protein (CRP) levels (Feringa, Laskey, Dickson, & Coleman, 2011). A study by Argani et al. (2016) showed that taking GSE for 8 weeks by patients with mild to moderate hyperlipidemia led to a significant decrease in TC, triglycerides, and LDL cholesterol levels. However, administration of GSE for 8 weeks in T2DM patients did not affect serum lipids (Abedini, Pourghassem, Babaei, Aliasgarzadeh, & Pourabdollahi, 2013).

Since the results of these studies were not conclusive, this meta-analysis was performed to evaluate the effect of GSE administration on glycemic control, serum lipoproteins, CRP levels, and obesity as defined by anthropometric parameters.

## 2 | MATERIALS AND METHODS

### 2.1 | Search and studies selection strategies

Scientific international databases, including EMBASE, Cochrane Library, Web of Science, and PubMed were searched for relevant studies published from incent until May 30, 2019. A search strategy was developed using the following MeSH and text keywords; intervention "GSE" OR "grape seed powder (GSE)" OR "GSE beverages" AND "supplementation" OR "intake" OR "administration" OR "consumption," AND outcomes parameters "fasting glucose" OR "fasting plasma glucose (FPG)" OR "HbA1c" OR "TC" "triglycerides (TG)" OR "LDL cholesterol" OR "LDL-C" OR "HDL cholesterol" OR "HDL-C" OR "CRP" OR "body weight" OR "body mass index (BMI)."

### 2.2 | Inclusion and exclusion criteria

RCTs complying with the following criteria were included in meta-analysis: human trials with either crossover design or parallel, trials with data on the effects of GSE on glycemic control, serum lipoproteins, CRP and anthropometric measurements (including mean changes of FPG, HbA1c, serum lipoproteins, CRP, body weight and BMI with *SD* and related 95% confidence interval (CI) for the both intervention and placebo groups). Other studies such as animal experiments, in vitro studies, case reports, observational studies, trials without a control group, and studies that did not achieve the least quality score were excluded from this meta-analysis.

### 2.3 | Data extraction and quality assessment

Two independent authors (OA and BN) screened the articles based on the eligibility criteria. As the first step, the title and abstract of studies were reviewed. Then, the full text of relevant studies was assessed to ascertain the suitability of a study for the meta-analysis. Any disagreement was resolved by the judgment of the third author (Z.A.).

Following data were taken from selected studies: the first authors' name, study location, year of publication, sample size, age, study design, dosage of GSE, duration of study, type of disease, the mean and *SD* for FPG, HbA1c, serum lipoproteins, CRP, body weight, and BMI in each intervention group. The quality of the selected RCTs was independently assessed by the same authors using 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, and selective outcome reporting, and other sources of bias."

### 2.4 | Data synthesis and statistical analysis

The effects of GSE consumption on the changes of the following parameters were calculated: (a) FPG, (b) HbA1c, (c) triglycerides, (d) TC, (e) LDL cholesterol, (f) HDL cholesterol, (g) CRP, (h) body weight, and (i) BMI. Weighted mean difference (WMD) with 95% CI was used for pooling data to determine effect sizes. The change score approach was used to calculate the effect size of GSE intake on the identified outcome. The random-effect model was used to report the pooled effect sizes using 95% CI.

### 2.5 | Heterogeneity and publication bias

Heterogeneity of included studies was assessed using Cochrane's Q test (with significant $p$-value <0.1) and I-square test ($I^2$ greater than 50% showing significant heterogeneity). The funnel plot, as well as the Begg's and Egger's regression tests was used to determine the publication bias. Both STATA 11.0 (Stata Corp., College Station, TX) and Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) were applied for data analysis.

## 3 | RESULTS

### 3.1 | Characteristics of studies

After screening 724 studies, 15 (Abedini et al., 2013; Alirezaei et al., 2017; Argani et al., 2016; Clifton, 2004; Kar, Laight, Rooprai, Shaw, & Cummings, 2009; Mellen, Daniel, Brosnihan, Hansen, & Herrington, 2010; Park, Edirisinghe, Choy, Waterhouse, & Burton-Freeman, 2016; Pourghassem-Gargari, Abedini, Babaei, Aliasgarzadeh, & Pourabdollahi, 2011; Sano et al., 2007; Sivaprakasapillai, Edirisinghe, Randolph, Steinberg, & Kappagoda, 2009; Taghizadeh, Malekian, Memarzadeh, Mohammadi, & Asemi, 2016; Terauchi et al., 2014; Turki et al., 2016; Vigna et al., 2003; Ward et al., 2005) of them were eligible to be included in this meta-analysis. These studies were detected by a process that is shown in Figure 1. General characteristics of eligible studies are summarized in Table 1. The studies were conducted in Italy (Vigna et al., 2003), Australia (Clifton, 2004; Ward et al., 2005), Japan (Sano et al., 2007; Terauchi et al., 2014), United Kingdom (Kar et al., 2009), United States (Mellen et al., 2010; Park et al., 2016; Sivaprakasapillai et al., 2009), Iran (Abedini et al., 2013; Alirezaei et al., 2017; Argani et al., 2016; Pourghassem-Gargari et al., 2011; Taghizadeh et al., 2016), and Tunisia (Turki et al., 2016). Studies were published between 2003 and 2017. Ten studies (Abedini et al., 2013; Argani et al., 2016; Park et al., 2016; Pourghassem-

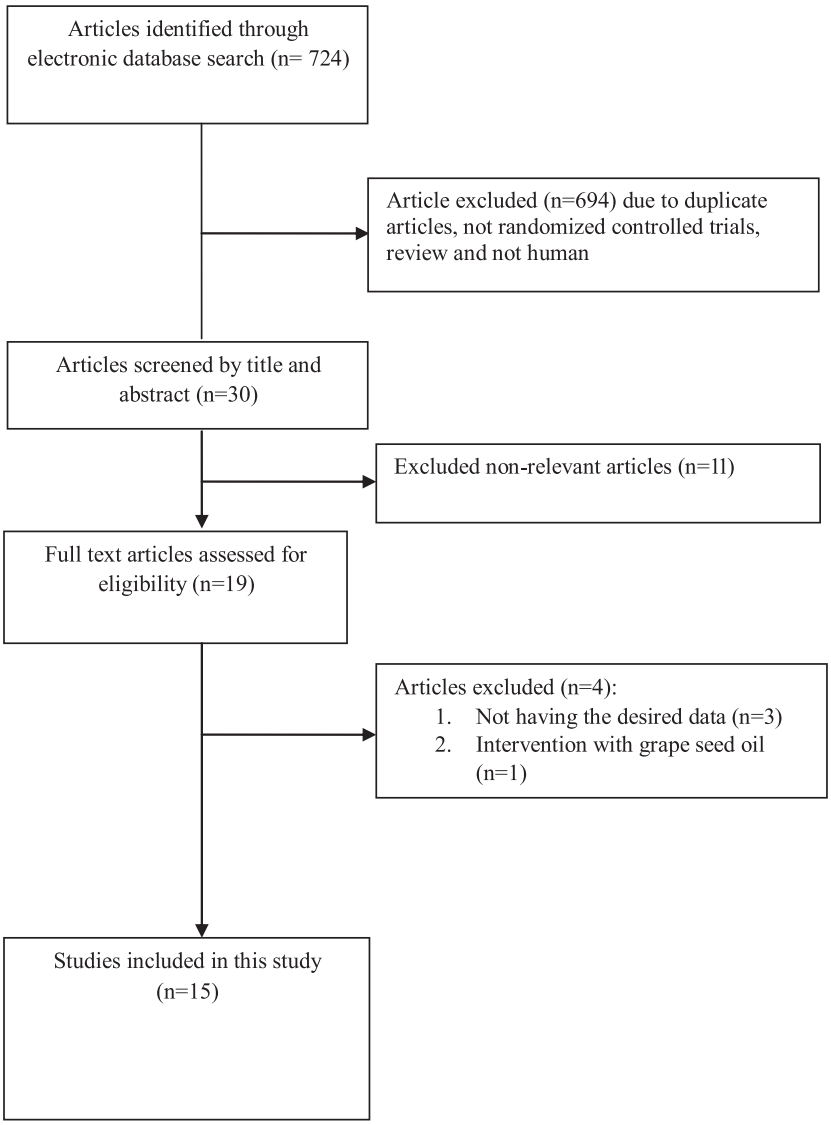



**FIGURE 1** Flowchart of number of studies identified and included into the meta-analysis

**TABLE 1** Characteristics of included studies

| References (publication year) | Country | Sample size (control/intervention) | Duration (week) | Age (years) (control/intervention) | Intervention/control (type and dosage) |
|---|---|---|---|---|---|
| Vigna et al. (2003) | Italy | 24/24 | 4 | 54 ± 3/54 ± 3 | 300 mg grape procyanidin extracts and soy phosphatidylcholine Placebo: Lactose and soy phosphatidylcholine |
| Clifton (2004) | Australia | 36/36 | 4 | 58 ± 9/58 ± 9 | 2000 mg GSE + yoghurt Control: Yoghurt |
| Ward et al. (2005) | Australia | 18/16 | 6 | 63.6 ± 8.2/61.3 ± 6.3 | 1000 mg grape-seed polyphenols Placebo: Matched placebo tablets |
| Sano et al. (2007) | Japan | 20/21 20/20 | 12 | 53.2 ± 2.1/51 ± 2.4 53.2 ± 2.1/52.9 ± 2 | 200 mg GSE 400 mg GSE Placebo: Proanthocyanidin |
| Kar et al. (2009) | United Kingdom | 32/32 | 4 | 61.8 ± 6.36/61.8 ± 6.36 | 600 mg GSE Placebo: NR |
| Sivaprakasapillai et al. (2009) | United States | 9/9 9/9 | 4 | 46 ± 3/45 ± 3 46 ± 3/47 ± 4 | 150 mg GSE 300 mg GSE Placebo: NR |
| Mellen et al. (2010) | United States | 50/50 | 4 | 52.1 ± 8.1/52.1 ± 8.1 | 1300 mg muscadine grape seed Placebo: Methylcellulose USP powder |
| Pourghassem-Gargari et al. (2011) | Iran | 22/26 | 8.6 | 30–65/30–65 | 200 mg GSE Placebo: NR |
| Abedini et al., 2013 | Iran | 22/26 | 8 | 51 ± 10/52 ± 9 | 200 mg GSE Placebo: NR |
| Terauchi et al. (2014) | Japan | 29/32 29/30 | 8 | 49.8 ± 5.2/49.2 ± 5.3 49.8 ± 5.2/49.8 ± 4.7 | 100 mg grape seed proanthocyanidin extract 200 mg grape seed proanthocyanidin extract Placebo: NR |
| Argani et al. (2016) | Iran | 35/35 | 8 | 46.6 ± 8.4/47.3 ± 9.3 | 200 mg red GSE Placebo: starch and cellulose |
| Park et al. (2016) | United States | 17/12 | 6 | 42 ± 10/44 ± 10 | 300 mg GSE beverages Placebo: Beverages contained 0 g GSE |
| Taghizadeh et al. (2016) | Iran | 20/20 | 8 | 21.6 ± 7/19.8 ± 5 | 300 mg GSE Placebo: NR |
| Turki et al. (2016) | Tunisia | 10/23 | 25 | 62.7 ± 7.5/62.3 ± 9.1 | 2000 mg GSE Placebo: starch |
| Alirezaei et al. (2017) | Iran | 30/30 | 4 | 58.5 ± 10.5/58.5 ± 10.5 | 200 mg red GSE Placebo: Starch |

Gargari et al., 2011; Sano et al., 2007; Sivaprakasapillai et al., 2009; Taghizadeh et al., 2016; Terauchi et al., 2014; Turki et al., 2016; Ward et al., 2005) had parallel design and other (Alirezaei et al., 2017; Clifton, 2004; Kar et al., 2009; Mellen et al., 2010; Vigna et al., 2003) had crossover design. One study was performed on men (Vigna et al., 2003), two studies (Taghizadeh et al., 2016; Terauchi et al., 2014) on women, and other studies (Abedini et al., 2013; Alirezaei et al., 2017; Argani et al., 2016; Clifton, 2004; Kar et al., 2009; Mellen et al., 2010; Park et al., 2016; Pourghassem-Gargari et al., 2011; Sano et al., 2007; Sivaprakasapillai et al., 2009; Turki et al., 2016; Ward et al., 2005) on both sexes. Totally, 825 subjects (451 in intervention and 374 in control group) were enrolled in these studies (Abedini et al., 2013; Alirezaei et al., 2017; Argani et al., 2016; Clifton, 2004; Kar et al., 2009; Mellen et al., 2010; Park et al., 2016; Pourghassem-Gargari et al., 2011; Sano et al., 2007; Sivaprakasapillai et al., 2009; Taghizadeh et al., 2016; Terauchi et al., 2014; Turki et al., 2016; Vigna et al., 2003; Ward et al., 2005). Mean age of the participants was between 19.8 (Taghizadeh et al., 2016) and 63.6 (Ward et al., 2005) years, and their mean BMI was between 21.3 ( Terauchi et al., 2014) and 37 (Sivaprakasapillai et al., 2009) kg/m$^2$. Trial duration ranged between 4 (Alirezaei et al., 2017; Clifton, 2004; Kar et al., 2009; Mellen et al., 2010; Sivaprakasapillai et al., 2009; Vigna et al., 2003) and 25 (Turki et al., 2016) weeks. Dosage of GSE in these studies varied between 100 ( Terauchi et al., 2014) and 2,000 mg/day (Turki et al., 2016). Four studies (Sano et al., 2007; Taghizadeh et al., 2016; Terauchi et al., 2014; Vigna et al., 2003) were made on healthy subjects, and other studies were performed on subjects with elevated cholesterol (Clifton, 2004), hypertension (Ward et al., 2005), T2DM (Abedini et al., 2013; Kar et al., 2009; Pourghassem-Gargari et al., 2011), MetS (Sivaprakasapillai et al., 2009), CVD (Mellen et al., 2010), hyperlipidemia (Argani et al., 2016), prehypertension (Park et al., 2016), chronic kidney disease (Turki et al., 2016), and subjects on hemodialysis (Alirezaei et al., 2017). Studies of Sano et al. (2007), Sivaprakasapillai et al. (2009), and Terauchi et al. (2014), each have two effect sizes due to having two intervention groups with two different doses of supplementation.

## 3.2 | The effects of GSE on glycemic control

Combining eight effect sizes from seven studies (Abedini et al., 2013; Mellen et al., 2010; Park et al., 2016; Pourghassem-Gargari et al., 2011; Sano et al., 2007; Taghizadeh et al., 2016; Turki et al., 2016), we found a significant decrease in FPG concentrations following GSE intake (WMD: −2.01; 95% CI: −3.14, −0.87) (Table 2 and Figure 2a). This finding remained unchanged in some subgroups, except for studies on subjects with baseline FPG <100 mg/dl (WMD: −1.24; 95% CI: −5.56, 3.08), trials with duration >6 weeks (WMD: −0.96; 95% CI: −4.94, 3.02), GSE dosages <300 mg/day (WMD: 1.18; 95% CI: −5.24, 7.62), studies performed on healthy subjects (WMD: −1.24; 95% CI: −5.56, 3.08), crossover design studies (WMD: −0.10; 95% CI: −7.01, 6.81), and studies performed on individuals with normal BMI (WMD: −1.24; 95% CI: −5.56, 3.08) (Table 3).

Pooling data from three studies (Abedini et al., 2013; Pourghassem-Gargari et al., 2011; Sano et al., 2007) with four effect sizes, no significant effect of GSE on HbA1c levels was found (WMD: −0.05; 95% CI: −0.21, 0.11) (Table 2 and Figure 2b). Due to the small number of effect sizes, we did not perform the subgroups analysis.

## 3.3 | The effects of GSE on serum lipoproteins

The pooled analysis of data from 13 studies (Abedini et al., 2013; Alirezaei et al., 2017; Argani et al., 2016; Clifton, 2004; Kar et al., 2009; Mellen et al., 2010; Park et al., 2016; Pourghassem-Gargari et al., 2011; Sano et al., 2007; Sivaprakasapillai et al., 2009; Taghizadeh et al., 2016; Turki et al., 2016; Vigna et al., 2003) with 15 effect sizes showed a significant reduction in TC concentrations after the intake of GSE (WMD: −6.03; 95% CI: −9.71, −2.35) (Table 2 and Figure 2c). However, subgroup analysis showed conflicting findings between studies on subjects with TC levels <200 mg/dl (WMD: −3.78; 95% CI: −8.72, 1.16), trials with duration ≤6 weeks (WMD: −2.09; 95% CI: −7.10, 2.90), GSE dosages ≥300 mg/day (WMD: −0.86; 95% CI: −6.36, 4.63), studies performed on healthy subjects (WMD: −1.94; 95% CI: −10.20, 6.32), crossover design studies (WMD: −0.77; 95%

**TABLE 2** The effects of grape seed extract on glycemic control, serum lipids, inflammation, and anthropometric measurements

| | | | | | Heterogeneity | |
|---|---|---|---|---|---|---|
| Variables | Number of effect sizes | Weighted mean difference | CI 95% | *p*-Value | $I^2$ (%) | *p*-Value heterogeneity |
| FPG | 8 | −2.00 | −3.14, −0.86 | .001 | 0.0 | .862 |
| HbA1C | 4 | −0.05 | −0.21, 0.11 | .545 | 0.0 | .559 |
| TC | 15 | −6.03 | −9.71, −2.35 | .001 | 23.3 | .195 |
| LDL-C | 13 | −4.97 | −8.37, −1.56 | .004 | 28.6 | .157 |
| TG | 15 | −6.55 | −9.28, −3.83 | <.001 | 34.5 | .092 |
| HDL-C | 13 | −0.71 | −1.89, 0.38 | .202 | 21.3 | .228 |
| CRP | 6 | −0.81 | −1.25, −0.38 | <.001 | 0.0 | .432 |
| Body weight | 7 | 0.41 | −1.48, 2.29 | .673 | 0.0 | .998 |
| BMI | 5 | −0.02 | −0.95, 0.90 | .961 | 0.0 | .982 |

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FPG, fasting plasma glucose; HbA1C: hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

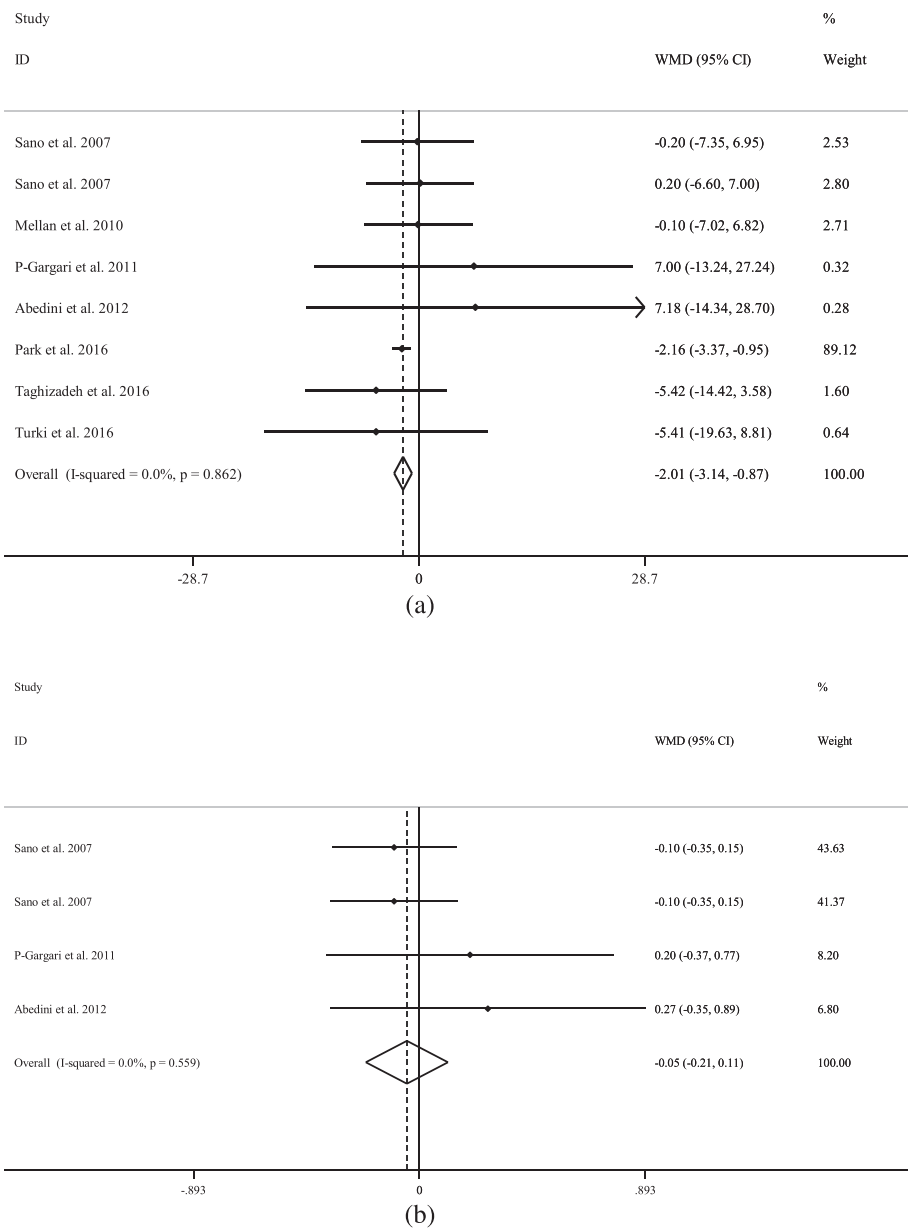
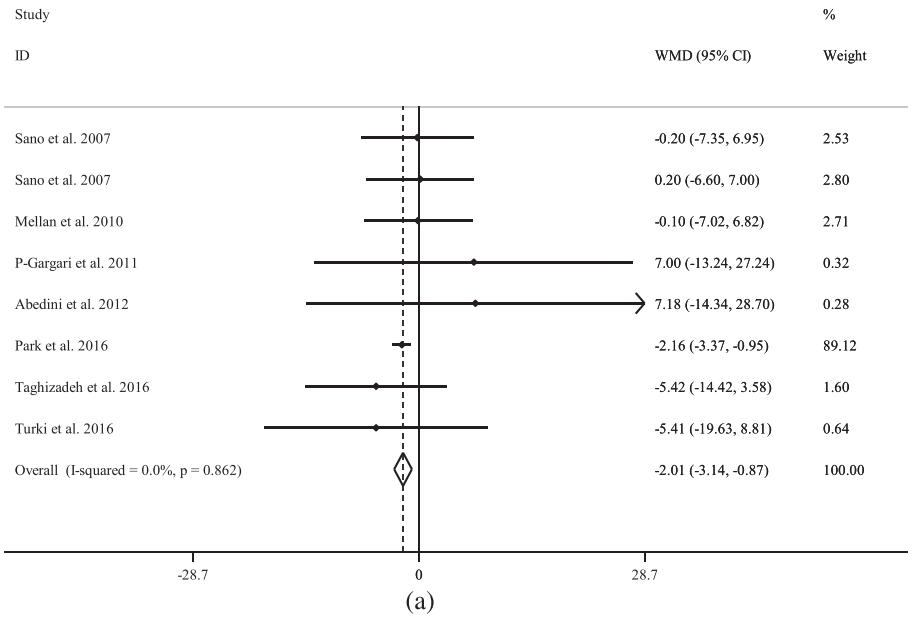



**FIGURE 2** (a–j) Meta-analysis metabolic profiles and anthropometric measurements weighted mean difference estimates for (a) FPG, (b) HbA1c, (c) TC, (d) LDL cholesterol, (e) triglycerides, (f) HDL cholesterol, (g) CRP, (h) body weight, and (j) BMI in the GSE and placebo groups (CI = 95%)

CI: −8.31, 6.77), studies made on individuals with normal BMI (WMD: −3.72; 95% CI: −12.74, 5.29), as well as studies on overweight (WMD: 3.05; 95% CI: −10.67, 16.78) and obese subjects (WMD: −4.55; 95% CI: −9.68, 0.57) (Table 3).

GSE administration had significant lowering effect on LDL cholesterol concentrations according to meta-analysis of 11 studies (Abedini et al., 2013; Alirezaei et al., 2017; Argani et al., 2016; Clifton, 2004; Mellen et al., 2010; Park et al., 2016; Pourghassem-Gargari et al., 2011; Sano et al., 2007; Sivaprakasapillai et al., 2009; Taghizadeh et al., 2016; Vigna et al., 2003) with 13 effect sizes (WMD: −4.97; 95% CI: −8.37, −1.56) (Table 2 and Figure 2d). Although this effect was also found in some subgroup analyses, GSE intake had no significant effect on LDL cholesterol concentrations in studies on subjects with LDL cholesterol levels <100 mg/dl (WMD: −5.46; 95% CI: −11.85, 0.92), trials with duration ≤6 weeks (WMD: −2.87; 95% CI: −7.24, 1.48), GSE dosages ≥300 mg/day (WMD: −0.59; 95% CI: −5.26, 4.08), studies performed on healthy subjects (WMD: −2.54; 95% CI: −9.10, 4.01), crossover design studies (WMD: 1.89; 95% CI: −5.27, 9.06), studies performed on individuals with normal BMI (WMD: −3.43; 95% CI: −10.41, 3.54) and overweight subjects (WMD: 1.42; 95% CI: −11.27, 14.13) (Table 3).

The combined meta-analysis of 15 effect sizes derived from 13 studies (Abedini et al., 2013; Alirezaei et al., 2017; Argani et al., 2016; Clifton, 2004; Kar et al., 2009; Mellen et al., 2010; Park et al., 2016; Pourghassem-Gargari et al., 2011; Sano et al., 2007; Sivaprakasapillai et al., 2009; Taghizadeh et al., 2016; Turki et al., 2016; Vigna et al., 2003) demonstrated a significant reduction in triglycerides concentrations following administration of GSE (WMD: −6.55; 95% CI: −9.28, −3.83) (Table 2 and Figure 2e). This finding did not change in most subgroups, except for studies on subjects with triglycerides levels <150 mg/dl (WMD: −5.03; 95% CI: −15.75, 5.68), studies performed on healthy subjects (WMD: −10.34; 95% CI: −24.03, 3.34), and studies performed on overweight (WMD: 10.52; 95% CI: −15.64, 36.68) and obese subjects (WMD: −0.74; 95% CI: −9.84, 8.35) (Table 3).



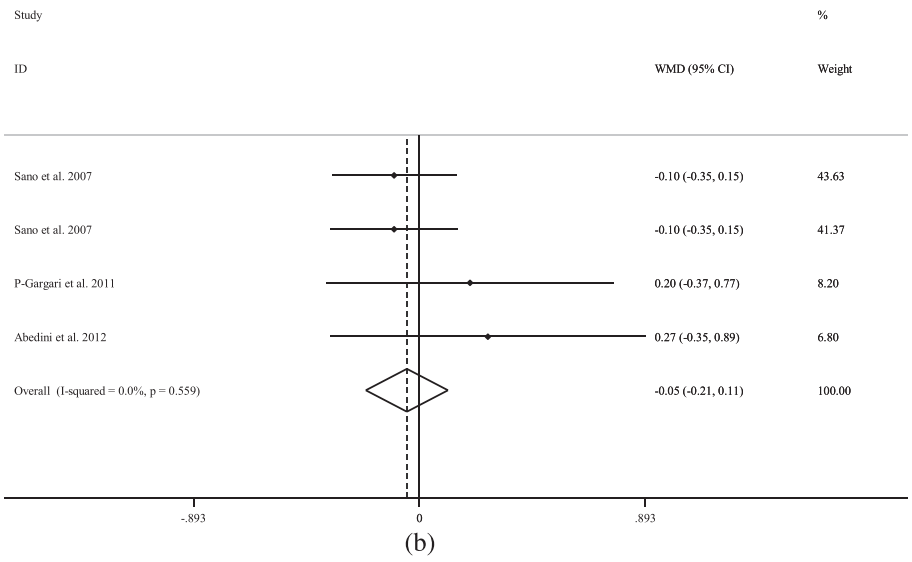




**FIGURE 2** (Continued)

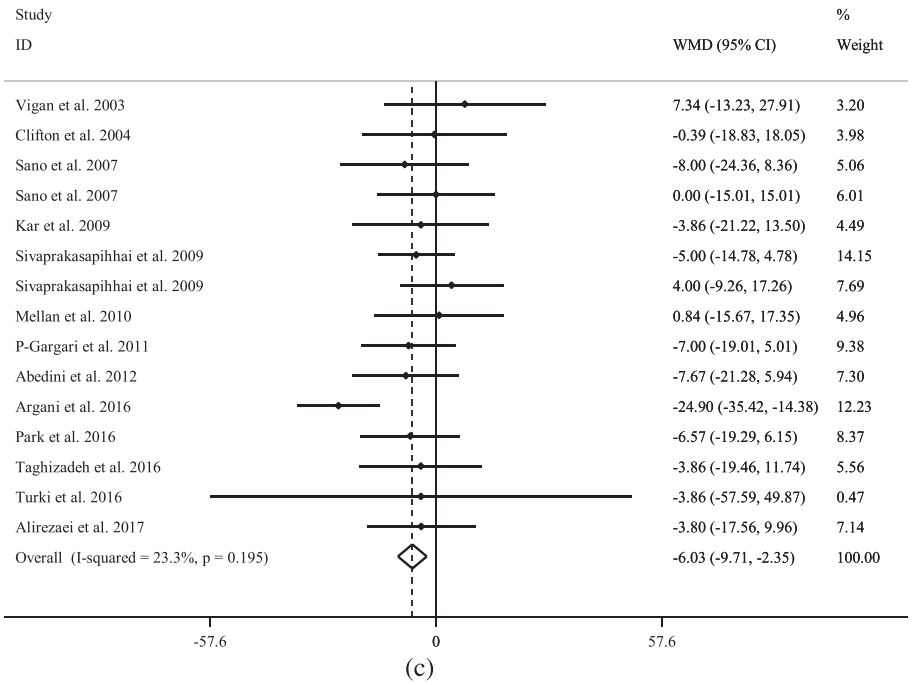
When we combined data from 11 studies (Abedini et al., 2013; Alirezaei et al., 2017; Argani et al., 2016; Clifton, 2004; Kar et al., 2009; Mellen et al., 2010; Park et al., 2016; Sano et al., 2007; Sivaprakasapillai et al., 2009; Taghizadeh et al., 2016; Vigna et al., 2003) consisting of 13 effect sizes, no significant effect was found on HDL cholesterol levels after the intake of GSE (WMD: −0.71; 95% CI: −1.80, 0.38) (Table 2 and Figure 2f). The same finding was also seen in all subgroups (Table 3).

## 3.4 | The effects of GSE on CRP levels

The pooled analysis of data from six studies (Alirezaei et al., 2017; Clifton, 2004; Kar et al., 2009; Mellen et al., 2010; Turki et al., 2016; Ward et al., 2005) showed a significant reduction CRP concentrations after the intake of GSE (WMD: −0.81; 95% CI: −1.25, −0.38) (Table 2 and Figure 2g). Due to the limited number of available studies, we were unable to perform any subgroup analysis.

## 3.5 | The effects of GSE on anthropometric measurements

Our meta-analysis on five studies (Abedini et al., 2013; Pourghassem-Gargari et al., 2011; Sano et al., 2007; Taghizadeh et al., 2016; Terauchi et al., 2014) with 7 effect sizes, showed no significant effect on body weight after the treatment with GSE (WMD: 0.41; 95% CI: −1.48, 2.29) (Table 2 and Figure 2h), Due to only few available data, analysis of subgroups was not performed. (Table 3).



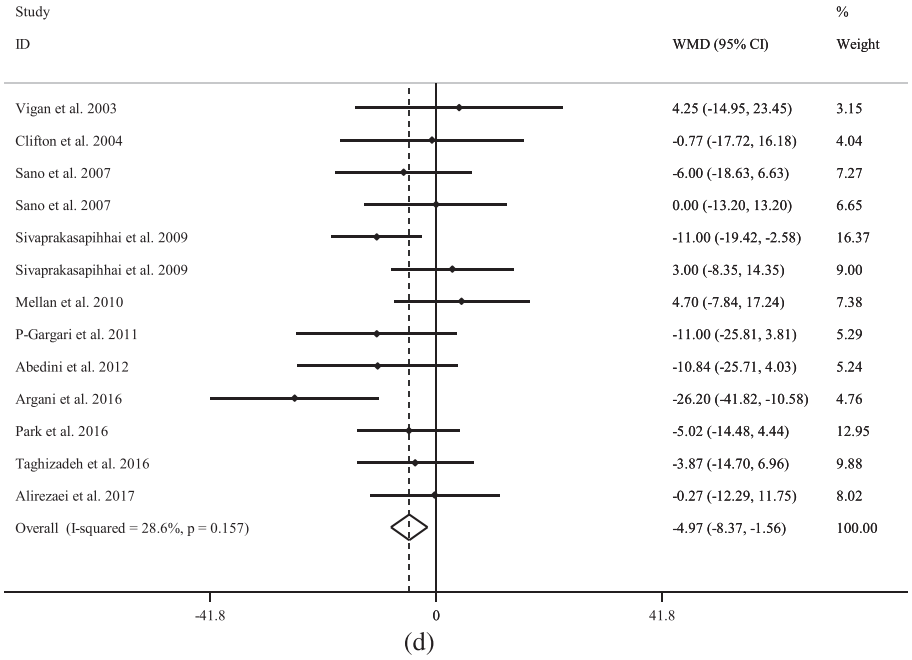




**FIGURE 2** (Continued)

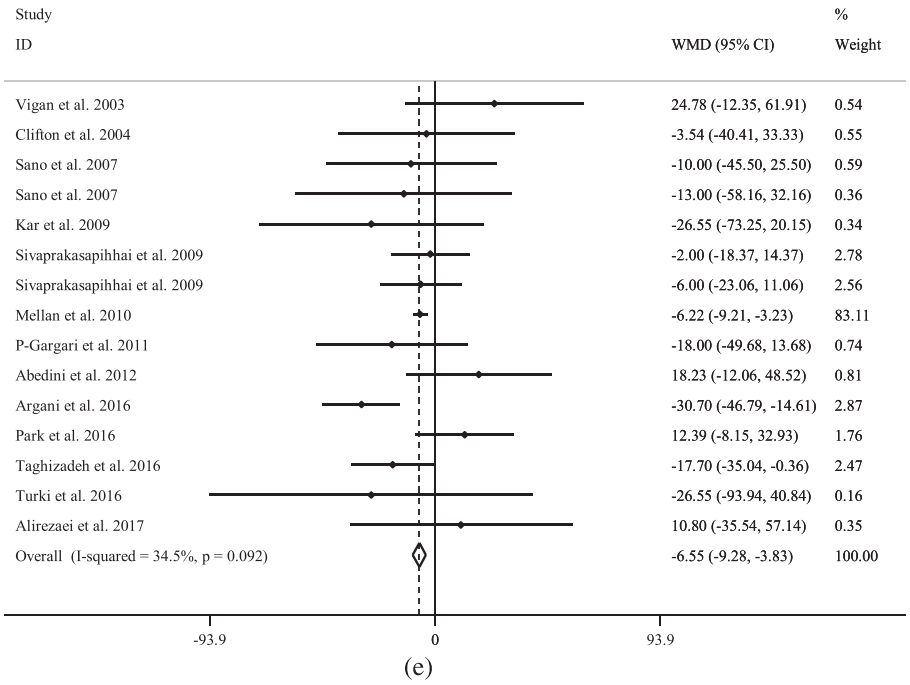
GSE supplementation had no significant effect on BMI according to meta-analysis of 4 studies (Abedini et al., 2013; Pourghassem-Gargari et al., 2011; Sano et al., 2007; Taghizadeh et al., 2016) five effect sizes (WMD: −0.02; 95% CI: −0.95, 0.90) (Table 2 & Figure 2j). Available data were not enough to perform the analysis of subgroups.

## 4 | DISCUSSION

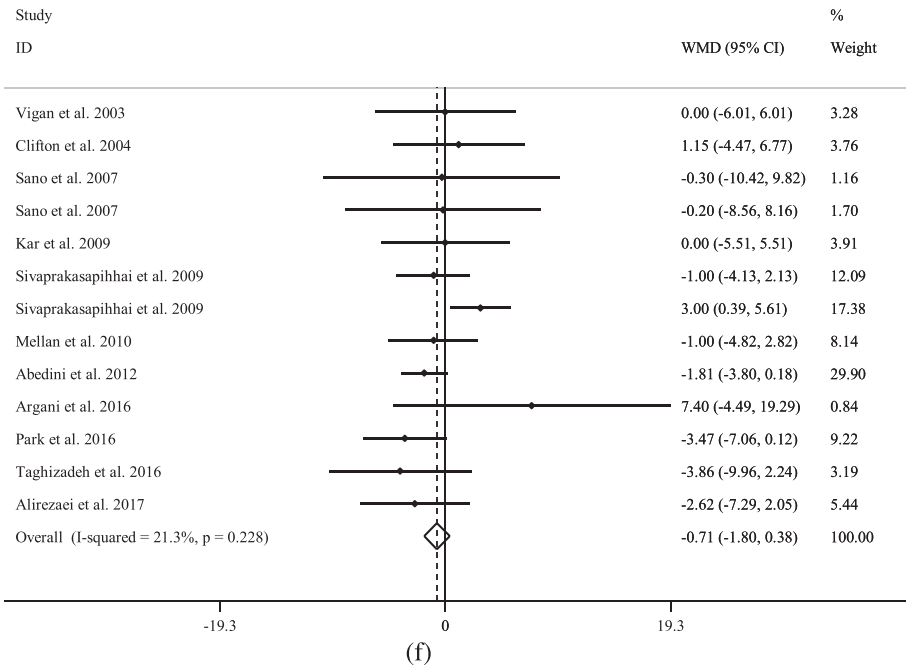
The current meta-analysis showed that GSE intake significantly reduced FPG, TC, LDL cholesterol, triglycerides, and CRP levels, but did not affect HbA1c, HDL cholesterol levels, and anthropometric measurements.

### 4.1 | Effects on glycemic control and serum lipoproteins

We found that GSE intake significantly reduced FPG, TC, LDL cholesterol, and triglycerides levels, but did not have any significant effect on HbA1c and HDL cholesterol levels. In animal models, it was



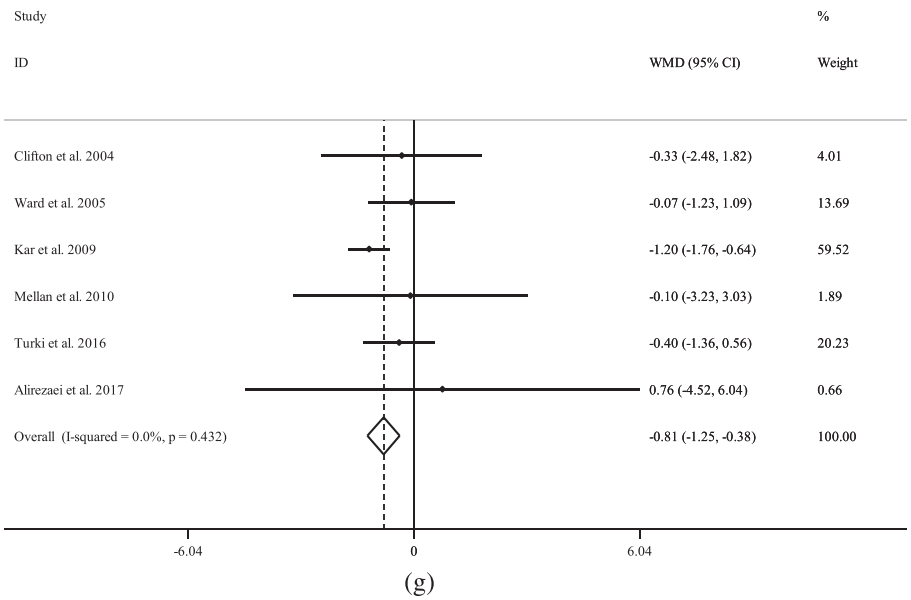

(e)



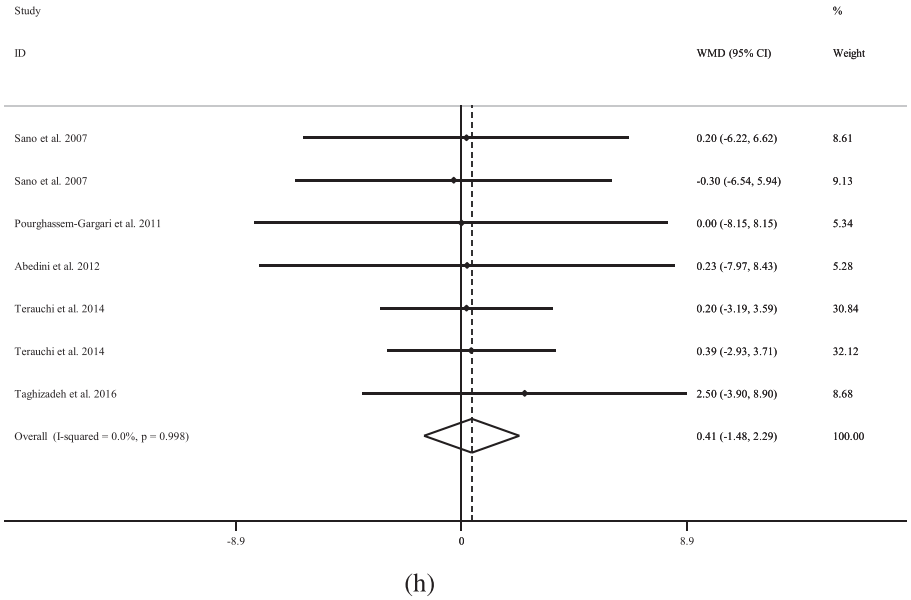

(f)

**FIGURE 2** (Continued)

reported that dietary grape seed intake significantly increased fecal excretion of cholesterol by approximately twofold and these animals had lower TC, LDL cholesterol, VLDL cholesterol, triglycerides and higher HDL cholesterol (Tebib, Besancon, & Rouanet, 1994). In a meta-analysis by Feringa et al. (2011), which included results of nine RCTs, no significant effect of grape seed on serum TC, LDL cholesterol, HDL cholesterol, triglycerides, and diastolic blood pressure could be shown. Grape seed administration at a dosage of 200 mg/day to patients with mild hyperlipidemia during 8 weeks decreased TC, LDL cholesterol, and oxidized LDL cholesterol (Razavi et al., 2013). In another study on hypercholesterolemic patients, combined administration of niacin-bound chromium and GSE for 2 months significantly decreased TC and LDL cholesterol levels while HDL cholesterol did not change (Preuss et al., 2000). The administration of grape seed at a dosage of 300 mg twice a day to female volleyball players for 8 weeks had no significant effects on FPG and serum lipids (Taghizadeh et al., 2016). Earlier studies have shown that phenolic compounds in grape seed may improve FPG and insulin function by increasing expression and plasma adiponectin concentrations (Maeda et al., 2001; Olholm, Paulsen, Cullberg, Richelsen, & Pedersen, 2010).




(g)




(h)

**FIGURE 2** (Continued)

Enhanced expression of insulin signaling pathway-related proteins, including Akt and glucose transporter Type 4, mRNA expression of adiponectin, adiponectin receptor R1, and AMP-activated protein kinase-α together with increased mRNA levels of glycogen synthase and suppressed mRNA expression of. These mechanisms may explain beneficial effects of grape seed on FPG and serum lipids (Meeprom, Sompong, Suwannaphet, Yibchok-anun, & Adisakwattana, 2011). In addition, it seems the beneficial effects of grape seed on TC and LDL cholesterol levels may be due to inhibiting intestinal cholesterol absorption. However, it is most likely that the primary beneficial effect of grape seed occurs due to mechanisms other than just decrease of plasma lipoproteins concentrations, including scavenging of hydroxyl and peroxyl radicals, antioxidant activities, and suppressing of the oxidation of LDL. Therefore, it seems that the antioxidant properties of grape seed polyphenols are central to their mechanism(s) of action, which also include cellular signaling mechanisms and interactions at the genomic level (Leifert & Abeywardena, 2008).

## 4.2 | Effects on inflammatory markers and anthropometric measurements

This meta-analysis showed that GSE intake significantly reduced CRP levels, but did not influence anthropometric measurements, that is, obesity. It has been reported that grape seed has anti-inflammatory and antioxidative properties. in vitro studies demonstrated that flavonoid-rich food products suppress lipoxygenase pathways, which

**TABLE 3** Subgroup analyses of grape seed extract on FPG and lipid profiles

| | NO | WMD (95% CI) | *p* Within group | *p* Heterogeneity | $I^2$ (%) | Between-study $I^2$ (%) |
|---|---|---|---|---|---|---|
| *Subgroup analyses of GSE supplementation on FPG levels* | | | | | | |
| Baseline serum FPG (mg/dl) | | | | | | |
| <100 | 3 | −1.24 (−5.56, 3.08) | .573 | .582 | 0.0 | 0.719 |
| >100 | 5 | −2.06 (−3.24, −0.88) | .001 | .731 | 0.0 | |
| Trial duration (week) | | | | | | |
| ≤6 | 2 | −2.09 (−3.28, −0.91) | .001 | .565 | 0.0 | 0.592 |
| >6 | 6 | −0.96 (−4.94, 3.02) | .636 | .759 | 0.0 | |
| GSE dosage | | | | | | |
| ≥300 | 5 | −2.10 (−3.26, −0.95) | <.001 | .826 | 0.0 | 0.323 |
| <300 | 3 | 1.18 (−5.24, 7.62) | .718 | .684 | 0.0 | |
| Health status | | | | | | |
| Healthy | 3 | −1.24 (−5.56, 3.08) | .573 | .582 | 0.0 | 0.719 |
| Unhealthy | 5 | −2.06 (−3.24, −0.88) | .001 | .731 | 0.0 | |
| Study design | | | | | | |
| Crossover | 1 | −0.10 (−7.01, 6.81) | .977 | — | — | 0.584 |
| Parallel | 7 | −2.05 (−3.21, −0.90) | <.001 | .817 | 0.0 | |
| BMI | | | | | | |
| Normal | 3 | −1.24 (−5.56, 3.08) | .573 | .582 | 0.0 | 0.895 |
| Obese | 3 | −2.09 (−3.30, −0.89) | .001 | .472 | 0.0 | |
| *Subgroup analyses of GSE supplementation on TC levels* | | | | | | |
| Baseline serum TC (mg/dl) | | | | | | |
| <200 | 9 | −3.78 (−8.72, 1.16) | .134 | .966 | 0.0 | 0.182 |
| >200 | 6 | −8.82 (−14.33, −3.31) | .002 | .015 | 64.5 | |
| Trial duration (week) | | | | | | |
| ≤6 | 8 | −2.09 (−7.10, 2.90) | .411 | .912 | 0.0 | 0.023 |
| >6 | 7 | −10.64 (−16.07, −5.22) | <.001 | .108 | 42.4 | |
| GSE dosage | | | | | | |
| ≥300 | 9 | −0.86 (−6.36, 4.63) | .758 | .973 | 0.0 | 0.013 |
| <300 | 6 | −10.21 (−15.16, −5.26) | <.001 | .078 | 49.5 | |
| Health status | | | | | | |
| Healthy | 4 | −1.94 (−10.20, 6.32) | .645 | .698 | 0.0 | 0.278 |
| Unhealthy | 11 | −7.04 (−11.15, −2.93) | .001 | .110 | 36.1 | |
| Study design | | | | | | |
| Crossover | 5 | −0.77 (−8.31, 6.77) | .841 | .918 | 0.0 | 0.118 |
| Parallel | 10 | −7.67 (−11.88, −3.46) | <.001 | .095 | 39.4 | |
| BMI | | | | | | |
| Normal | 3 | −3.72 (−12.74, 5.29) | .418 | .779 | 0.0 | 0.114 |
| Overweight | 2 | 3.05 (−10.67, 16.78) | .663 | .583 | 0.0 | |
| Obese | 6 | −4.55 (−9.68, 0.57) | .082 | .839 | 0.0 | |
| *Subgroup analyses of GSE supplementation on LDL-C levels* | | | | | | |
| Baseline serum LDL-C (mg/dl) | | | | | | |
| <100 | 4 | −5.46 (−11.85, 0.92) | .094 | .607 | 0.0 | 0.857 |
| >100 | 9 | −4.77 (−8.79, −0.74) | .020 | .060 | 46.4 | |
| Trial duration (week) | | | | | | |
| ≤6 | 7 | −2.87 (−7.24, 1.48) | .196 | .323 | 14.0 | 0.133 |
| >6 | 6 | −8.22 (−13.66, −2.77) | .003 | .181 | 34.0 | |

(Continues)

**TABLE 3** (Continued)

| | NO | WMD (95% CI) | *p* Within group | *p* Heterogeneity | $I^2$ (%) | Between-study $I^2$ (%) |
|---|---|---|---|---|---|---|
| GSE dosage | | | | | | |
| ≥300 | 7 | −0.59 (−5.26, 4.08) | .805 | .867 | 0.0 | 0.007 |
| <300 | 6 | −9.91 (−14.88, −4.94) | <.001 | .212 | 29.7 | |
| Health status | | | | | | |
| Healthy | 4 | −2.54 (−9.10, 4.01) | .448 | .809 | 0.0 | 0.396 |
| Unhealthy | 9 | −5.86 (−9.84, −1.87) | .004 | .057 | 47.1 | |
| Study design | | | | | | |
| Crossover | 4 | 1.89 (−5.27, 9.06) | .604 | .926 | 0.0 | 0.033 |
| Parallel | 9 | −6.97 (−10.84, −3.09) | <.001 | .161 | 32.1 | |
| BMI | | | | | | |
| Normal | 3 | −3.43 (−10.41, 3.54) | .334 | .809 | 0.0 | 0.632 |
| Overweight | 2 | 1.42 (−11.27, 14.13) | .826 | .701 | 0.0 | |
| Obese | 5 | −6.81 (−11.69, −1.94) | .006 | .337 | 12.0 | |
| *Subgroup analyses of GSE supplementation on TG levels* | | | | | | |
| Baseline serum TG (mg/dl) | | | | | | |
| <150 | 6 | −5.03 (−15.75, 5.68) | .358 | .149 | 38.5 | 0.773 |
| >150 | 9 | −6.66 (−9.48, −3.83) | <.001 | .106 | 39.3 | |
| Trial duration (week) | | | | | | |
| ≤6 | 8 | −5.54 (−8.38, −2.69) | <.001 | .415 | 1.9 | 0.014 |
| >6 | 7 | −18.15 (−27.78, −8.52) | <.001 | .224 | 26.8 | |
| GSE dosage | | | | | | |
| ≥300 | 9 | −6.10 (−8.95, −3.26) | <.001 | .369 | 8.0 | 0.280 |
| <300 | 6 | −11.61 (−21.17, −2.04) | .017 | .042 | 56.6 | |
| Health status | | | | | | |
| Healthy | 4 | −10.34 (−24.03, 3.34) | .139 | .247 | 27.6 | 0.579 |
| Unhealthy | 11 | −6.39 (−9.18, −3.61) | <.001 | .076 | 40.9 | |
| Study design | | | | | | |
| Crossover | 5 | −6.01 (−8.97, −3.05) | <.001 | .416 | 0.0 | 0.361 |
| Parallel | 10 | −9.56 (−16.58, −2.55) | .008 | .055 | 45.9 | |
| BMI | | | | | | |
| Normal | 3 | −15.87 (−30.60, −1.14) | .035 | .922 | 0.0 | 0.184 |
| Overweight | 2 | 10.52 (−15.64, 36.68) | .431 | .289 | 11.1 | |
| Obese | 6 | −0.74 (−9.84, 8.35) | .873 | .328 | 13.5 | |
| *Subgroup analyses of GSE supplementation on HDL-C levels* | | | | | | |
| Baseline serum HDL-C (mg/dl) | | | | | | |
| <50 | 9 | −0.56 (−1.76, 0.64) | .362 | .079 | 43.3 | 0.568 |
| >50 | 4 | −1.38 (−3.94, 1.17) | .289 | .847 | 0.0 | |
| Trial duration (week) | | | | | | |
| ≤6 | 8 | −0.15 (−1.52, 1.21) | .821 | .156 | 34.1 | 0.194 |
| >6 | 5 | −1.65 (−3.45, 0.14) | .071 | .568 | 0.0 | |
| GSE dosage | | | | | | |
| ≥300 | 8 | 0.07 (−1.45, 1.60) | .926 | .157 | 34.0 | 0.155 |
| <300 | 5 | −1.50 (−3.05, 0.04) | .056 | .624 | 0.0 | |
| Health status | | | | | | |
| Healthy | 4 | −1.39 (−4.96, 2.17) | .444 | .812 | 0.0 | 0.693 |
| Unhealthy | 9 | −0.63 (−1.78, 0.50) | .274 | .078 | 43.4 | |

(Continues)

**TABLE 3** (Continued)

| | NO | WMD (95% CI) | *p* Within group | *p* Heterogeneity | $I^2$ (%) | Between-study $I^2$ (%) |
|---|---|---|---|---|---|---|
| Study design | | | | | | |
| Crossover | 5 | −0.73 (−2.93, 1.46) | .511 | .878 | 0.0 | 0.977 |
| Parallel | 8 | −0.70 (−1.95, 0.55) | .274 | .050 | 50.2 | |
| BMI | | | | | | |
| Normal | 3 | −2.15 (−6.58, 2.28) | .341 | .726 | 0.0 | 0.826 |
| Overweight | 2 | 0.61 (−3.49, 4.72) | .770 | .784 | 0.0 | |
| Obese | 5 | −0.63 (−1.91, 0.64) | .331 | .024 | 64.5 | |

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; GSE, grape seed extract; LDL-C, low-density lipoprotein cholesterol; TG; triglycerides, TC, total cholesterol, WMD, weighted mean differences.

increase pro-inflammatory leukotrienes (Schewe, Kuhn, & Sies, 2002). It has also been suggested that orally ingested GSE helps preventing imbalanced cytokine patterns (Terra et al., 2011). In a study by Irandoost, Ebrahimi-Mameghani, and Pirouzpanah (2013), grape seed consumption improved insulin resistance and inflammatory markers in overweight/obese women. Supplementation with 2 g/day grape seed during 6 months in patients with chronic kidney disease improved kidney function by its anti-inflammatory and antioxidant properties (Turki et al., 2016). Administration of 200 or 400 mg/day grape seed to healthy subjects during 8 and 12 weeks failed to show any significant effect on body weight and BMI (Sano et al., 2007). In another study, supplementation neither with low dose (100 mg/day) nor with high dose (200 mg/day) of grape seed to middle-aged women during 8 weeks did have any effect on body weight and BMI (Terauchi et al., 2014). The discrepancies between different studies might be explained by the different dosages of grape seed used, different durations of intervention, quality grape seed used, or the different characteristics of study participants. Polyphenols in GSE could be responsible for its anti-inflammatory effects in experimental studies. CRP is an acute-phase protein produced by the liver as a response to tissue damage or inflammation. Therefore, CRP can be used as a marker of acute inflammation, but it is also used to predict atherosclerotic cardiovascular events since atherosclerosis is characterized by a low-grade chronic inflammation (Danesh et al., 2004). Our finding that GSE reduces CRP levels might be an interesting additional explanation why GSE could have antiatherogenic effects. It is in accordance with findings of some other authors who have suggested that grape seed has anti-inflammatory effects.

## 5 | CONCLUSIONS

This meta-analysis demonstrated that GSE intake significantly reduced FPG, TC, LDL cholesterol, triglycerides, and CRP levels, but did not affect HbA1c, HDL cholesterol levels, and anthropometric measurements.

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### CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

### AUTHOR CONTRIBUTIONS

O.A. and Z.A. contributed in conception, design, statistical analysis, and drafting of the manuscript. O.A., B.N., Z.R., E.A., and F.K. contributed in data collection and manuscript drafting. All authors approved the final version for submission. Z.A. supervised the study.

### ETHICS STATEMENT

This study was considered exempt of ethical approval by the LUMS Institutional Review Board.

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