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Diabetology & Metabolic Syndrome

REVIEW

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Effects of Ginkgo biloba extract on glycemic control, inflammatory markers, lipid profile, anthropometric indices, and safety parameters in patients with metabolic syndrome and type 2 diabetes: a meta-analysis

Fatemeh Zali[1], Mahboobeh Sadat Hosseini[2], Mina Alimohammadi[3,4], Seyedeh Mahdieh Khoshnazar[5], Mohammad Jafar Keshavarzi[1], Fatemeh Hashemi[1] and Kiavash Hushmandi[6*]

Abstract

Background Ginkgo biloba extract (GBE) is widely used as adjunct therapy in metabolic syndrome (MetS) and type 2 diabetes (T2D), yet its effects on glycemic control, lipid profiles, inflammatory markers, and safety remain incompletely characterized.

Methods This systematic review and meta-analysis of eight randomized controlled trials, including 1,507 subjects, evaluated the impact of GBE supplementation on glycemic profile, lipid parameters, inflammatory biomarkers, anthropometric indices, and safety outcomes.

Results Compared with controls, GBE significantly reduced FBG (WMD – 13.88 mg/dL; 95% CI -24.61 to -3.15; $p = 0.01$) and improved insulin resistance (HOMA-IR; WMD – 3.64; 95% CI -5.71 to -1.56; $p < 0.01$) but did not significantly alter HbA1c or insulin levels. GBE also decreased anthropometric measures, including BMI (WMD – 0.85 kg/m^2; 95% CI -1.53 to -0.18; $p = 0.01$), waist circumference (WMD – 2.67 cm; 95% CI -4.97 to -0.37; $p = 0.02$), and visceral adiposity index (WMD – 48.09; 95% CI -66.74 to -29.44; $p = 0.01$). Effects on lipid profiles were mixed, with no significant changes in total cholesterol, triglycerides, LDL, or HDL cholesterol. Inflammatory markers CRP (WMD – 1.16 mg/L), TNF-α (WMD – 58.3 pg/mL), and IL-6 (WMD – 14.53 pg/mL) were significantly reduced (all $p < 0.05$). The safety study showed minor but statistically significant elevations in ALT and AST. However, the therapeutic value of these findings is questionable due to short trial durations and lack of threshold-level data. There was no clinical hepatotoxicity episodes reported. Subgroup analysis suggested that higher doses (≥ 120 mg/day) and short intervention duration (≤

*Correspondence:
Kiavash Hushmandi
houshmandi.kia7@ut.ac.ir

Full list of author information is available at the end of the article

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90 days) yielded greater improvements. Furthermore, Evidence of publication bias was detected for FBG, TG, CRP, WC, TNF-α, and BUN (Egger's test $p < 0.05$).

Conclusions GBE is associated with moderate but statistically significant improvements in short-term glycemic control, insulin sensitivity, inflammatory state, and obesity indices in MetS and T2D patients. Given the small effect sizes, substantial heterogeneity, lack of HbA1c improvement, and the possibility that publication bias will inflate estimates for numerous outcomes, these data should be viewed as preliminary and hypothesis-generating; they do not support the use of GBE as a standalone or first-line therapy. While lipid profile improvements were inconclusive, the extract appeared safe with manageable liver enzyme elevations. Although there were no side effects in these short-term trials, the minor elevations in liver enzymes should be interpreted with caution. Long-term hepatic safety has not been shown, thus periodic monitoring of liver function is recommended for extended use. These results are preliminary due to significant heterogeneity and a short trial period. Larger, patient-centered trials are needed to determine the therapeutic importance of these biochemical alterations.

Keywords Ginkgo biloba extract (GBE), Metabolic syndrome (MetS), Type 2 diabetes (T2D), Glycemic control, Inflammatory markers, Anthropometric indices, lipid profile

Introduction

Metabolic syndrome (MetS), also referred to as X syndrome or insulin resistance syndrome, is defined by the World Health Organization as a pathological condition marked by a cluster of metabolic abnormalities [1]. These include elevated triglyceride levels, reduced high-density lipoprotein cholesterol (HDL), hypertension, impaired glucose regulation, abdominal obesity, and insulin resistance [1, 2]. Therefore, these disturbances provoke a chronic inflammatory state that accelerates the development of atherosclerotic cardiovascular disease, Type 2 diabetes (T2D), hyperuricemia with resultant gout, chronic kidney disease, and obstructive sleep apnea [3].

Current therapeutic strategies primarily target individual components such as hypertension, hyperglycemia, and dyslipidemia, often complemented by lifestyle interventions like dietary modification and increased physical activity [3]. Pharmacological treatments include metformin for blood glucose control, sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists that also promote weight loss, statins for dyslipidemia management, and renin-angiotensin system blockers for hypertension [4].

Among adjunct therapies, Ginkgo biloba extract (GBE), one of the oldest extant plant species, stands out as a promising candidate. GBE has a longstanding role in traditional Chinese medicine, historically used to address respiratory and digestive conditions [5]. The plant's leaves and seeds are rich in antioxidants and anti-inflammatory compounds, which may help mitigate oxidative stress and systemic inflammation—key drivers of metabolic dysfunction. Emerging evidence supports the potential of GBE to improve vital metabolic parameters. Studies indicate its capacity to lower blood glucose, reduce insulin resistance, and decrease body mass index (BMI) [6, 7]. Moreover, there is an indication that GBE might enhance the efficacy of established treatments such as metformin, further attenuating BMI and inflammatory markers [6, 8].

Mechanistic studies reveal that GBE exerts anti-inflammatory effects by downregulating pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α. Additionally, the flavonoid compounds in GBE act as potent pancreatic lipase inhibitors, potentially reducing dietary fat absorption and contributing to weight loss [9]. Proteomic and oxidative stress analyses in adipose tissue highlight GBE's ability to modulate biological pathways associated with obesity and metabolic diseases [5]. Furthermore, this phytochemical modulates responses to bacterial components, lipids, and hormones, lowering inflammatory proteins such as IL-6 [8].

Given these promising biological and clinical effects, rigorous evaluation of GBE in patients with MetS and T2D is warranted. This systematic review and meta-analysis aim to comprehensively assess the impact of GBE on glycemic control (HbA1c, FBG, HOMA-IR, serum insulin), lipid profiles (TG, TC, LDL, and HDL cholesterol), inflammatory biomarkers (CRP, IL-6, TNF-α), renal and liver function parameters, and anthropometric measures in this patient population.

Method

Search strategy

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The protocol for this systematic review and meta-analysis was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD420251180652. This study aimed at investigating the efficacy of GBE in patients with Metabolic syndrome and T2D. A comprehensive literature search was performed across multiple electronic databases, including PubMed,

Web of Science, Cochrane, Embase, Scopus, and Google Scholar from database inception through March 31, 2025. The search strategy combined terms related to: ["metabolic syndrome" OR "MetS" OR "type 2 diabetes" OR "T2D" OR "insulin resistance"] AND ["Ginkgo biloba" OR "Ginkgo biloba extract" OR "GBE" OR "EGb 761" OR "maidenhair tree"] AND ["glycemic control" OR "fasting blood glucose" OR "FBG" OR "HbA1c" OR "HOMA-IR" OR "insulin" OR "lipid profile" OR "triglycerides" OR "cholesterol" OR "HDL" OR "LDL" OR "inflammatory markers" OR "CRP" OR "TNF-α" OR "IL-6" OR "anthropometric" OR "BMI" OR "waist circumference" OR "visceral adiposity index" OR "liver enzymes" OR "ALT" OR "AST" OR "renal function" OR "creatinine" OR "BUN"]. The full electronic search strategy for each database is provided in **Supplementary Table S1**. The reference lists of the included studies and related review papers were additionally hand searched for any additional eligible trials.

Eligibility criteria

Studies were included if they met the following criteria: [1] Randomized controlled trials (RCTs) with either a placebo or active comparator control group; [2] Adult patients (≥ 18 years) diagnosed with MetS (according to recognized criteria such as NCEP-ATP III or IDF) **or** T2D, including those with established T2D-related complications (e.g., diabetic nephropathy, erectile dysfunction); [3] Oral supplementation with GBE at any dose or formulation, administered either as monotherapy or as an adjunct to standard antidiabetic care (including metformin, lifestyle modification, or other oral agents). Trials evaluating GBE as part of a fixed-dose combination herbal formulation were included only if the GBE component was clearly specified and constituted a major active ingredient; [4] Studies reporting baseline and post-intervention data (or change scores) for at least one of the following outcome domains: glycemic control (FBG, HbA1c, serum insulin, HOMA-IR), lipid profile (TC, TG, LDL, HDL), inflammatory biomarkers (CRP, IL-6, TNF-α), anthropometric indices (BMI, waist circumference, visceral adiposity index), or safety parameters (liver enzymes ALT, AST, ALP; renal function tests BUN, creatinine); [5] Full-text articles published in English.

Studies were excluded if they were: [1] animal or in vitro studies; [2] trials lacking a control group or placebo comparator; [3] conference abstracts, case reports, or review articles.

Data extraction

The initial screening and data extraction from all available RCTs were conducted independently by F.Z. and MJ.K. Finally, any disagreements were resolved through consensus with a third author (M.A.). Extracted information included study characteristics (author, year, country, sample size), participant demographics (age, gender, baseline BMI), intervention details (dose, duration), outcome measures changes in FBG, HbA1c, HOMA-IR, insulin, inflammatory markers (CRP, IL-6, TNF-α), and anthropometric indices (BMI, WC, VAI), lipid profiles (HDL, LDL, TC, TG) and safety parameters (liver enzymes ALT, AST, ALP; renal function tests BUN, Cr) at baseline and end of treatment, compared to standard treatment or placebo.

Quality assessment

The methodological quality of included RCTs was assessed independently by two authors (F.Z. and M.A.) using the Cochrane Collaboration's Risk of Bias tool. The following six domains were evaluated: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Each domain was rated as having "low risk," "high risk," or "unclear risk" of bias according to the standardized criteria. Any disagreements were resolved through discussion or consultation with a third author (K.H.).

Data analysis

Meta-analyses were conducted using random-effects models to calculate weighted mean differences (WMD) with 95% confidence intervals (CI) for continuous outcomes. The random-effects model was chosen a priori because of the expected clinical and methodological heterogeneity among trials, depending on population characteristics, GBE formulations, and concurrent therapies. Statistical heterogeneity was assessed using the I^2 statistic, with values above 50% indicative of substantial heterogeneity. For outcomes with $I^2 > 90\%$, the pooled estimate should be considered with caution. It is provided to explain the direction and approximate the effect size across the existing data, instead of as a definitive treatment effect. The decision to include these outcomes in the meta-analysis was made according to the clinical significance of the endpoints and the consistency of effect direction across the majority of the trials, as represented in forest plots. Subgroup analyses were performed according to underlying disease (T2D vs. MetS), treatment type (GBE mono- vs. combination therapy), intervention dosage (≥120 or < 120 mg/day), and intervention duration (≤ 90 or > 90 days). The dosage cut-off of 120 mg/day was set because it corresponds to the typical daily intake of the well-investigated EGb 761 formulations (e.g., 120 mg once or twice daily), which has established bioavailability and clinical efficacy in other indications. The period cut-off of 90 days was chosen as

a clinically appropriate interval to distinguish between short-term and medium-term metabolic impacts. For outcomes with substantial heterogeneity, leave-one-out analyses were performed to assess if any single research disproportionately influences the pooled estimate or I^2 statistic. Publication bias was assessed qualitatively through funnel plots and Egger's and Begg's test. $P < 0.05$ was statistically significant. All statistical analyses were conducted using Stata version 17.0.

Result

Search strategy and study selection

The literature search identified 4,101 records, of which 485 duplicates were removed. The 3,616 records remained for screening based on title and abstract. The remaining 342 articles underwent abstract review, from which 296 were excluded due to being unrelated to the topic or not meeting the inclusion criteria. A total of 46 full-text articles were assessed for eligibility. Of these, 38 studies were excluded for reasons including lack of metabolic parameter reporting, non-randomized designs, animal or in vitro studies, or populations with significant comorbidities complicating interpretation. Ultimately, eight RCTs were included in the meta-analysis (Fig. 1).

Studies were published between 2006 and 2022 and included predominantly double-blind, placebo-controlled multicenter trials. A total of 1,507 subjects with MetS and T2D were included, varying from 10 to 600

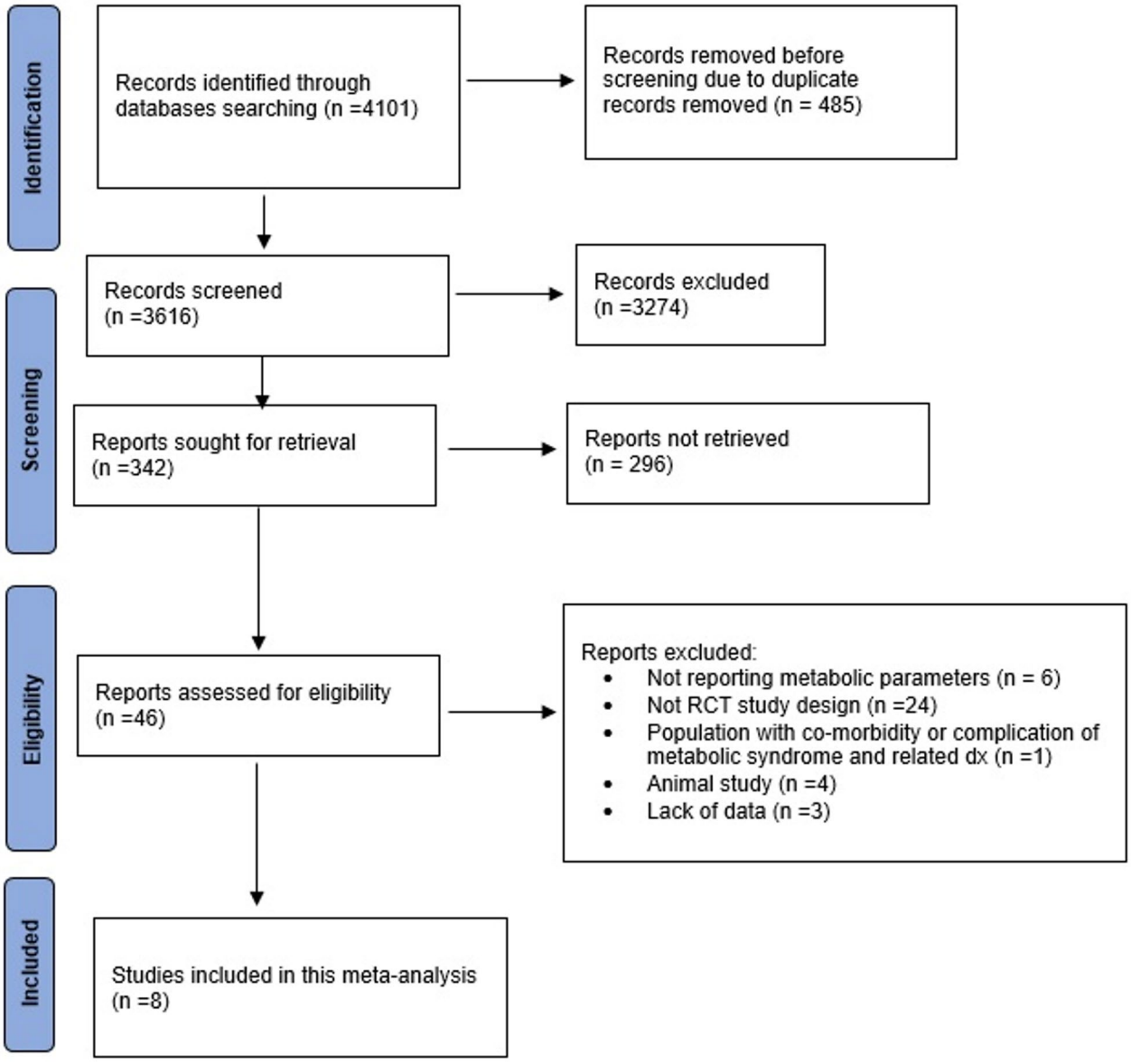


Fig. 1 Flowchart of the selection of studies presented in the study

per study. Participant demographics ranged from 44 to 62 years in age, with baseline BMI values between 23.8 and 36.3 kg/m². Interventions primarily involved standardized GBEs administered at ≥120 to <120 mg/day, with treatment durations varying from 3 to 24 months. Of the eight included RCTs, five utilized standardized GBE (EGb 761 or equivalent) at a dose of 120 mg/day [6, 7, 11–13]. The remaining trials employed a lower-dose GBE tablet (24 mg/day) in combination with Liuwei dihuang pills [14]; a proprietary nutraceutical blend containing GBE with alpha lipoic acid and *Vitis* vinifera [15]; or ginkgo leaf tablets containing flavonoids glycol glycosides and terpenoid lactones [16]. This heterogeneity in GBE formulations represents a potential source of variability in both efficacy and safety outcomes. Key outcomes included glycemic control markers (HbA1c, FBG, HOMA-IR, insulin), lipid profiles (TC, TG, HDL, LDL), and inflammatory biomarkers (CRP, IL-6, TNF-α), liver (AST, ALT, ALP), and renal function (Cr, BUN). A detailed summary of study designs, interventions, and outcome measures is presented in Table 1.

Main outcomes

Effect of GBE on glycemic Control

Meta-analysis demonstrated a significant reduction in FBG (WMD: -13.88 mg/dL; 95% CI: -24.61 to -3.15;$p = 0.01$) levels among patients receiving GBE compared to controls. Substantial statistical heterogeneity was observed (I^2 = 99.35%; p for heterogeneity < 0.001; τ^2 = 227.16). Insulin resistance, assessed by HOMA-IR, showed significant improvement following GBE treatment (WMD: -3.64; 95% CI: -5.71 to -1.56; I^2=82.49, $p < 0.001$). However, no statistically significant effect was observed on the levels of HbA1c (WMD: -0.17; 95% CI: -0.46 to 0.11; I^2=96.31%, $p < 0.001$) and insulin (WMD: -2.80; 95% CI: -5.99 to 0.39; I^2=98.72%, $p < 0.001$) (Fig. 2).

Table 1 Characteristics of included studies in this meta-analysis

Author, year	Research study design	Type of diabetes	Type of supplementation	NO. of subjects (*n*)	Mean age (control) (years)	Mean age (intervention) (years)	Mean BMI (control) (kg/m2)	Mean BMI (intervention) (kg/m2)	*Biomarkers
Aziz, 2018 [11]	DB	T2D	GBE (120 mg/capsule)	60	48.2 ± 10.3	48.7 ± 9.6	34.2 ± 6.2	33.0 ± 6.0	VAI, BMI, WC, HbA1c, FBG, serum insulin, HOMA-IR, AST, ALT, ALP, Cr, BUN
Hussain, 2022 [12]	MC, DB-PCT	T2D	GBE (120 mg/capsule)	60	48.2 ± 10.3	48.7 ± 9.6	34.2 ± 6.2	33.0 ± 6.0	TC, TG, HDL, LDL, CRP, TNF-α, IL-6
Aziz, 2021 [7]	RCT, DB, pilot	MetS	GBE (120 mg/capsule)	50	44.15 ± 9.5	45.7 ± 7.8	32.8 ± 7	31.5 ± 2.2	BMI, WC, VAI, HbA1c, TC, TG, HDL, LDL, AST, ALT, ALP, CRP, TNF-α, IL-6, Cr, BUN
Aziz, 2018 [6]	DB	MetS	GBE (120 mg/capsule)	60	47.3 ± 10.8	50.7 ± 7.8	34.2 ± 5.6	36.3 ± 4.9	BMI, WC, HbA1c, FBG, insulin, HOMA-IR, VAI, TC, TG, HDL, LDL, CRP, TNF-α, IL-6
Shi, 2019 [14]	MC, DB-PCT	T2D	Liuwei dihuang pills (1.5 g daily), GBE tablet 24 mg daily	600	60.45 ± 6.19	60.81 ± 6.36	23.99 ± 2.73	23.82 ± 2.76	HbA1c, TC, TG, HDL, LDL, BMI
Kudolo, 2006 [13]	DB-PC Crossover	T2D	GBE EGb 761, 120 mg/day	20	51.7 ± 14	51.7 ± 14	34.0 ± 5.7	34.0 ± 5.1	fasting insulin, HbA1c, TC, TG, HDL, LDL, AST, ALT, ALP, Cr
Derosa, 2022 [15]	DB-PCT	T2D	nutraceutical combination of alpha lipoic acid, Vitis vinifera L. and GBE (Blunorm forte®)	60	61.3 ± 7.4	60.8 ± 7.2	28.1 ± 2	28.6 ± 2.4	FBG, HbA1c, TC, TG, HDL, LDL, CRP, WC, BMI, HOMA-IR
Zhao, 2016 [16]	DB, DS-PCT	T2D	9.6 mg of flavonoids glycol glycosides and 2.4 mg of terpenoid lactones	140	60.7 ± 6.5	62.2 ± 6.4	24.0 ± 2.6	24.1 ± 3.0	FBG, HbA1c, TC, TG, HDL, LDL

*For C-reactive protein (CRP), both standard and high-sensitivity (hsCRP) assays were included and pooled under the common outcome 'CRP.' DB: Double-blind; PCT: Placebo-controlled trial; MC: Multicenter; RCT: Randomized controlled trial; PC: Placebo-controlled; DS: Double-simulated (both active and placebo interventions simulated); Metabolic syndrome (MetS); Type 2 diabetes (T2D)

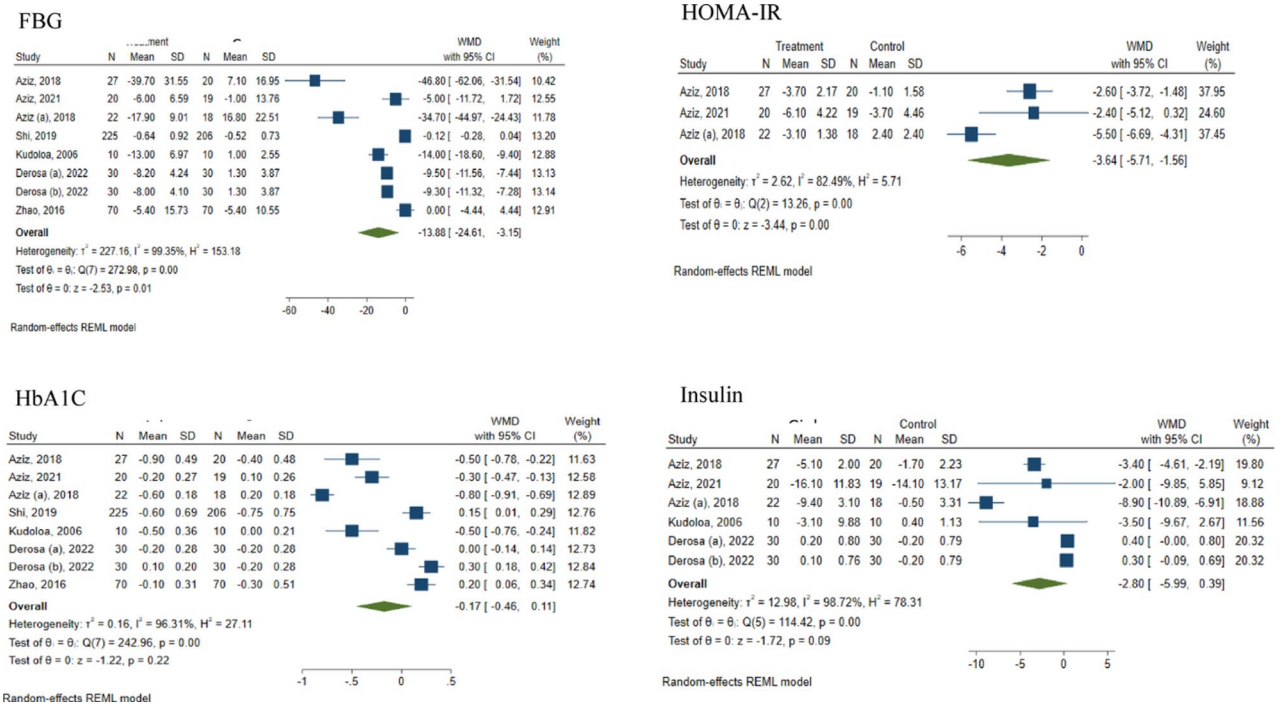


Fig. 2 Effects of GBE versus control on glycemic parameters. Forest plots display WMD with 95% CIs. The p-value beneath each pooled estimate tests the null hypothesis that WMD = 0. Heterogeneity statistics (I^2 and p-value from Cochran's Q test) are shown in the lower left corner of each panel. FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, glycated hemoglobin

Effect of GBE on anthropometric measures

GBE supplementation was associated with significant improvements in anthropometric indices, including reduced BMI (WMD, -0.85 kg/m^2; 95% CI, -1.53 to -0.18; I^2=93.63%, $p<0.001$), WC (WMD, -2.67 cm; 95% CI, -4.97 to -0.37; I^2=99.25%, $p<0.001$), and VAI (WMD, -48.09; 95% CI, -66.74 to -29.44; I^2=75.54%, $p=0.02$) (Fig. 3).

Effect of GBE on lipid profile

Analysis of lipid parameters indicated no significant difference in HDL cholesterol (WMD, 2.13 mg/dL; 95% CI, -0.02 to 4.28; I^2=96.48%, $p<0.001$), TC (WMD, -4.33 mg/dL; 95% CI, -12.93 to 4.27; I^2=95.76%, $p<0.001$), TG (WMD, -0.05 mg/dL; 95% CI, -15.37 to 15.27; I^2=98.19%, $p<0.001$), and LDL (WMD, -6.39 mg/dL; 95% CI, -15.72 to 2.95; I^2=97.35%, $p<0.001$) levels in patients receiving GBE supplementation compared to the control (Fig. 4).

Effect of GBE on inflammatory factors

Pooling data from five studies revealed a significant reduction in CRP levels among treatment groups compared to controls (WMD: -1.16 mg/L; 95% CI, -1.94 to -0.38; I^2=98.51%, $p<0.001$). In three studies, TNF-α levels were substantially decreased (WMD: -58.30 pg/mL; 95% CI, -72.70 to -43.91; $p<0.001$; I^2=70.80%, $p=0.02$), as were IL-6 concentrations (WMD: -14.53 pg/mL; 95% CI, -25.00 to -4.07; I^2=90.04%, $p<0.001$) (Fig. 5).

Effect of GBE on safety outcomes

Liver enzyme analysis indicated modest but statistically significant elevations in ALT (WMD: 1.42 U/L; 95% CI, 0.66 to 2.18; I^2=0.00%, $p=0.64$) and AST (WMD: 1.95 U/L; 95% CI, 1.07 to 2.82; I^2=0.00%, $p=0.25$), whereas ALP remained unchanged (WMD, 1.09 U/L; 95% CI, -4.03 to 6.21; I^2=85.60%, $p<0.001$). It is critical to highlight that these mean rises, while consistent, were frequently maintained within the normal reference ranges and were not related to reported cases of hepatotoxicity (e.g., jaundice, liver failure) in the included trials. Renal function markers showed a significant reduction in serum Cr (WMD, -0.12 mg/dL; 95% CI, -0.20 to -0.04; I^2=94.75%, $p<0.001$), with no significant effect on BUN (WMD, -3.24 mg/dL; 95% CI, -7.98 to 1.50; I^2=96.84%, $p<0.001$) (Fig. 6).

Subgroup analyses

Subgroup analyses were conducted to explore potential sources of heterogeneity and examine the effects of GBE on key outcomes stratified by underlying condition (T2D vs. MetS), treatment type (mono-therapy with GBE vs. combination therapy), intervention dose (< 120 mg/day vs. ≥120 mg/day), and treatment duration (≤ 90 days vs. > 90 days). In Table 2, P het is the p value from Cochran's Q test for heterogeneity within the subgroup, while P effect is the p value for the test of the pooled WMD against the null hypothesis of no effect. A non-significant P effect

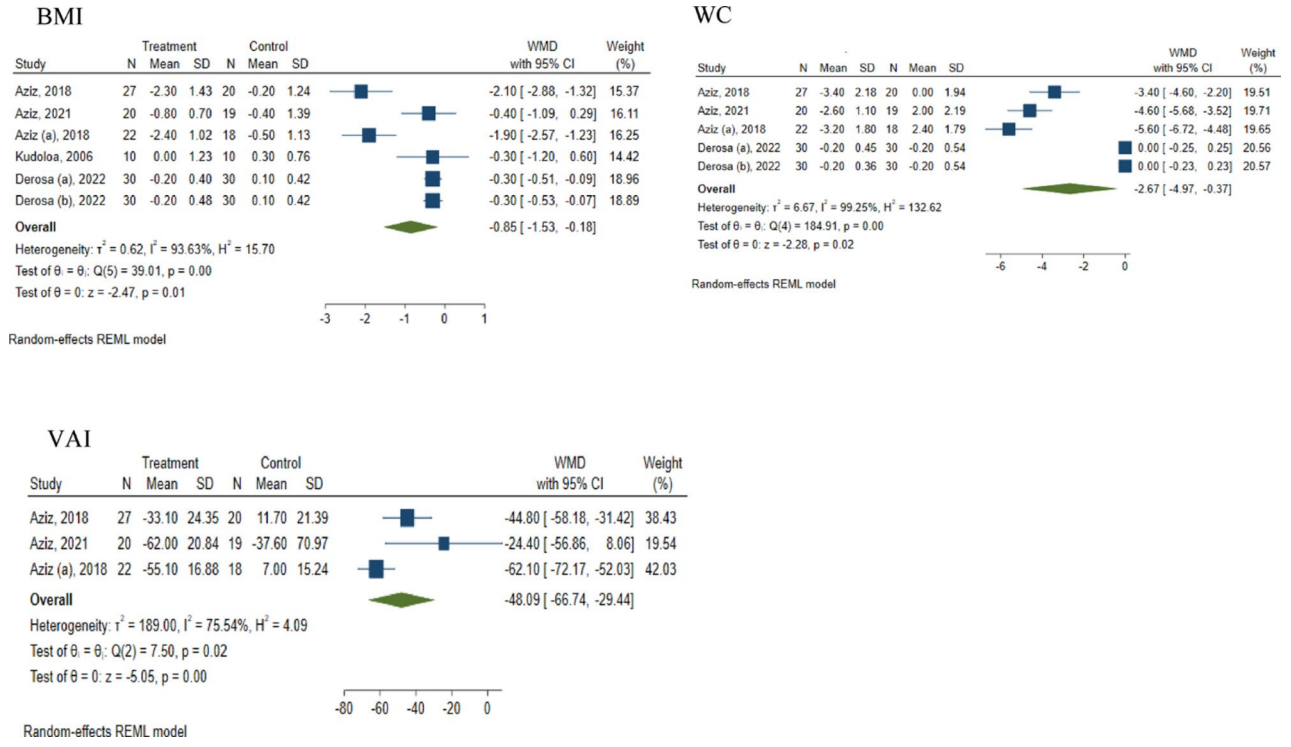


Fig. 3 Effects of GBE versus control on anthropometric indices.Forest plots display WMD with 95% CIs. For each pooled estimate, the p-value beneath the diamond tests the null hypothesis that WMD = 0. Heterogeneity statistics (I^2 and the p-value from Cochran's Q test) are shown in the lower left corner of each panel. BMI, body mass index; WC, waist circumference; VAI, visceral adiposity index

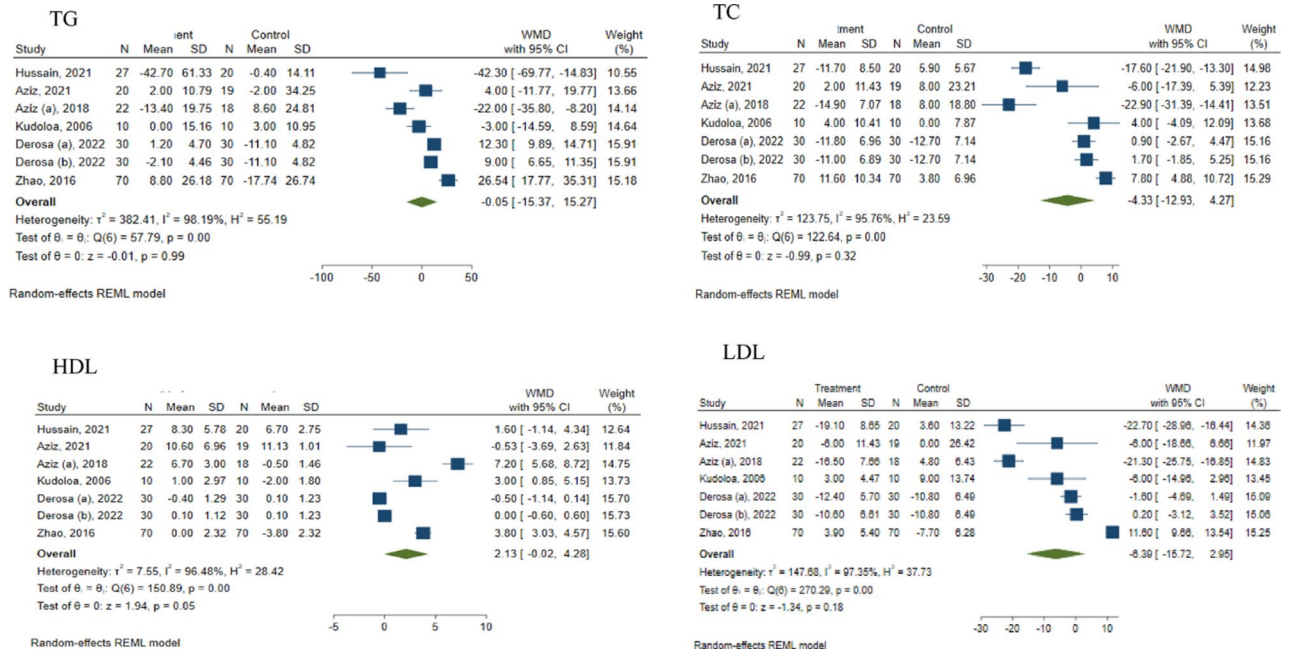


Fig. 4 Effects of GBE versus control on lipid profile parameters. Forest plots display WMD with 95% CIs. For each pooled estimate, the p-value beneath the diamond tests the null hypothesis that WMD = 0. Heterogeneity statistics (I^2 and the p-value from Cochran's Q test) are shown in the lower left corner of each panel. HDL, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein cholesterol

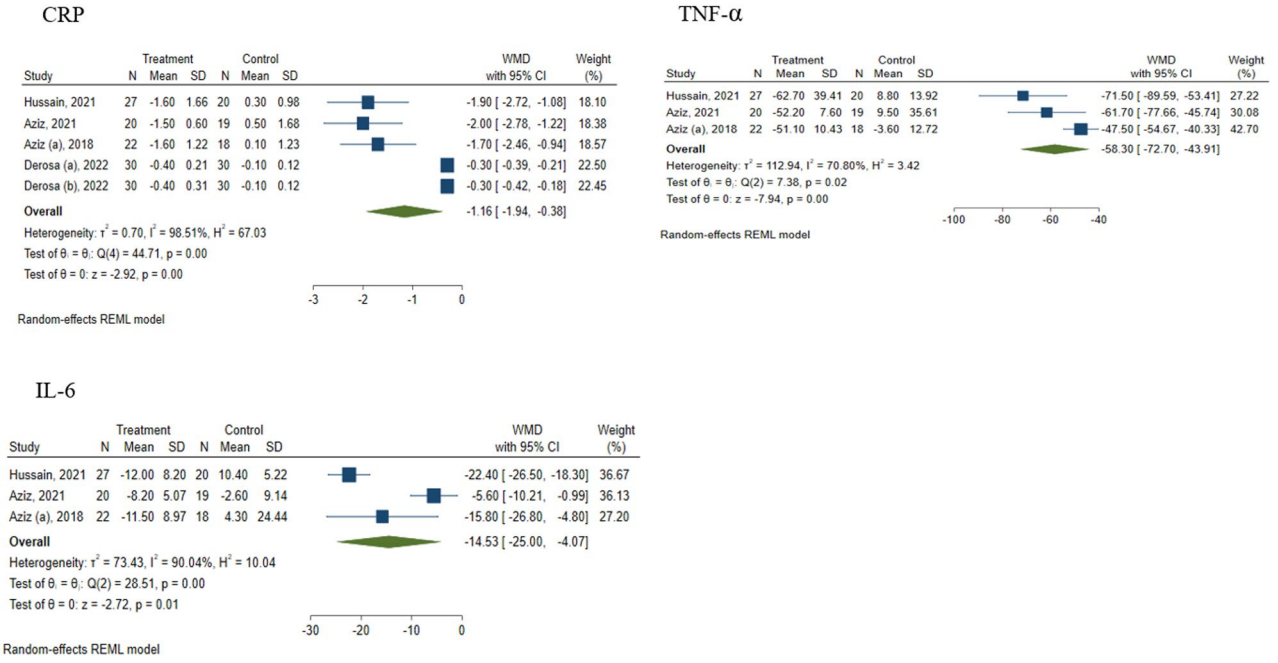


Fig. 5 Effects of GBE versus control on inflammatory biomarkers. Forest plots display WMD with 95% CIs. For each pooled estimate, the p-value beneath the diamond tests the null hypothesis that WMD = 0. Heterogeneity statistics (I^2 and the p-value from Cochran's Q test) are shown in the lower left corner of each panel. CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha

(e.g., > 0.05) indicates that the observed difference is not statistically distinguishable from zero, while a significant P het (e.g., < 0.05) indicates that the studies within that subgroup are more variable than expected by chance alone. The results showed that GBE significantly reduced those with MetS with a significant decrease in insulin (WMD = − 6.54; 95% CI: − 12.95 to − 0.12; $p = 0.09$; I^2 = 64.13%), CRP (WMD = -1.85; 95% CI: -2.39 to -1.30; $p = 0.59$; I^2 = 0.00%) and TNF-α (WMD = − 52.74; 95% CI: − 66.16 to − 39.31; $p = 0.11$; I^2 = 60.46%), and WC (WMD = -5.09 (95% CI: − 6.07 to -4.11; $p = 0.21$; I^2 =37.22%) levels. Monotherapy trials showed more pronounced reductions in HbA1c (WMD = − 0.37; 95% CI: − 0.56 to − 0.18; $p = 0.20$; I^2 = 37.89%) compared to combination therapy. In addition, combination therapy was associated with a significant reduction in HOMA-IR (WMD = − 4.04; 95% CI: − 6.89 to − 1.20; $p > 0.001$; I^2 = 91.73%), BUN , VAI and BMI (95% CI: -2.05 to -0.13, $p > 0.001$; I^2 = 96.77%) and a significant increase in ALT (WMD = 1.54; 95% CI: 0.75 to 2.33; $p = 0.47$; I^2 = 0.00%) and AST (WMD = 2.82; 95% CI: 0.82 to 4.81; $p = 0.20$; I^2 = 39.89%). Both monotherapy and combination therapy demonstrated significant reduction in FBG and CRP, IL-6, TNF-α, and Cr. Dose stratification demonstrated that doses ≥ 120 mg/day were associated with greater improvements in glycemic and anthropometric outcomes than doses < 120 mg/day. Furthermore, Shorter duration interventions (≤ 90 days) yielded significant benefits on FBG.

Risk of Bias assessment

The risk of bias of the included studies was evaluated using the Cochrane Risk of Bias tool across six domains (Fig. 7). Across studies, overall risk assessments varied from low risk to high risk or unclear. Only two of the eight studies had a low overall risk of bias, while one study had a high risk of bias. The remaining studies were judged as having unclear (supplementary Table S2 for study-level ratings). In terms of specific outcomes, the significant improvements in FBG and HOMA IR were largely due to studies with low risk of bias for random sequence generation and blinding, whereas inconsistent findings for lipid parameters and HbA1c were linked to studies with a higher proportion of unclear risks in key domains. Trials with a low risk of bias demonstrated significant decreases in inflammatory markers (CRP, TNF-α, IL 6). The considerable heterogeneity is most likely caused by clinical variation rather than methodological differences. The constant finding of small increases in liver enzymes (ALT, AST) was gathered from trials with a low risk of bias for outcome assessment, confirming the validity of this safety signal.

Publication bias assessment

All primary outcomes were evaluated for the possibility of publication bias. Given that statistical tests for funnel plot asymmetry have limited power when the number of studies is small, our interpretation was based on a combination of visual inspection and quantitative Egger's and

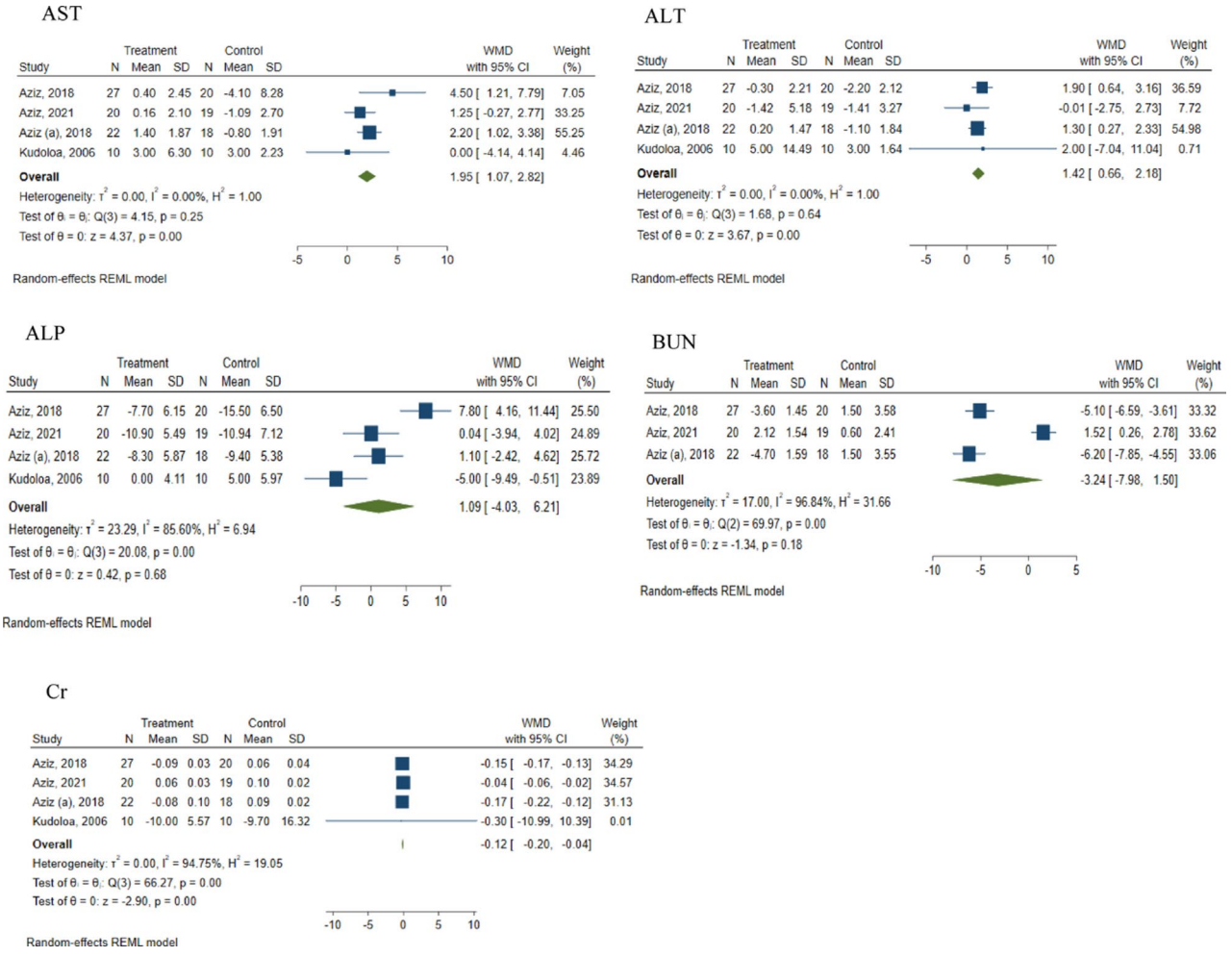


Fig. 6 Effects of GBE versus control on safety parameters.Forest plots display weighted mean differences (WMD) with 95% confidence intervals. For each pooled estimate, the p-value beneath the diamond tests the null hypothesis that WMD = 0. Heterogeneity statistics (I^2 and the p-value from Cochran's Q test) are shown in the lower left corner of each panel. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cr, creatinine

Begg's tests (Table 3). Significant asymmetry was found for FBG, TG, CRP, WC, TNF-α, and BUN (Egger's test $p < 0.05$). For outcomes with fewer than 5 contributing studies (e.g., HOMA-IR, VAI, IL-6, TNF-α), the tests are underpowered, and results should be regarded with caution. The funnel plots are included in the supplementary materials (Supplementary Figure S1). The leave-one-out analysis demonstrated that the meta-analytic estimations are not spuriously affected by outlying or methodologically weak research. The Shi [14] and Derosa [15] investigations, which used lower-dose or combination formulations, contribute to the observed the high heterogeneity in FBG and lipid outcomes. However, their removal did not change the direction of the effect. The findings of the Leave-one-out sensitivity analysis are provided in Supplementary Figure S2.

Discussion

This systematic review and meta-analysis synthesized evidence from 8 RCTs involving 1,507 participants with MetS and related conditions, including T2D. The findings provide important insights into the potential metabolic benefits of GBE supplementation, although the evidence is characterized by considerable heterogeneity and some inconsistencies across outcomes. The most consistent outcome was a statistically significant decrease in FBG found in patients receiving GBE (WMD: -13.88 mg/dL; 95% CI: -24.61 to -3.15). Although this reduction is modest in absolute magnitude, it was detected over relatively short intervention durations (typically ≤ 90 days) and in individuals already receiving routine background treatments, including metformin. The effect was seen in both monotherapy and combination therapy categories. Exploratory analyses suggest that higher doses (≥ 120 mg/day) and shorter treatment durations (< 90 days) were

Table 2 Effects of GBE on T2D and MetS

Variables	Trials, *n*	I^2 (%)	*P*-het	WMD (95% CI)	*P*-effect
FBG					
Total	8	99.35%	< 0.001	-13.88 [-24.61, -3.15]	0.01
Underlying disease					
T2D	6	99.49%	< 0.001	-12.07 [-24.16, 0.02]	0.05
MetS	2	95.56%	< 0.001	-19.59 [-48.69, 9.51]	0.19
Treatment type					
Mono therapy	2	78.69%	< 0.001	-9.85 [-18.64, -1.05]	0.03
Combination therapy	6	99.63%	< 0.001	-15.72 [-30.47, -0.98]	0.04
Dose of treatment					
< 120 mg/d	2	0	0.96	-0.12 [-0.28, 0.04]	0.96
≥ 120 mg/d	6	98.41%	< 0.001	-18.76 [-31.24, -6.28]	< 0.001
Treatment duration					
≤ 90 days	6	98.41%	< 0.001	-18.76 [-31.24, -6.28]	< 0.001
> 90 days	2	0	0.96	-0.12 [-0.28, 0.04]	0.14
HbA1C					
Total	8	96.31%	< 0.001	-0.17 [-0.46, 0.11]	0.22
Underlying disease					
T2D	6	94.25%	< 0.001	-0.04 [-0.32, 0.23]	0.77
MetS	2	95.81%	< 0.001	-0.55 [-1.04, -0.06]	0.03
Treatment type					
Mono therapy	2	37.89%	0.20	-0.37 [-0.56, -0.18]	< 0.001
Combination therapy	6	97.34%	< 0.001	-0.10 [-0.46, 0.25]	0.56
Dose of treatment					
< 120 mg/d	2	0.01%	0.62	0.17 [0.08, 0.27]	< 0.001
≥ 120 mg/d	6	95.98%	< 0.001	-0.29 [-0.62, 0.03]	0.07
Treatment duration					
≤ 90 days	6	95.98%	< 0.001	-0.29 [-0.62, 0.03]	0.07
> 90 days	2	0.01%	0.62	0.17 [0.08, 0.27]	< 0.001
HOMA-IR					
Total	3	82.49%	< 0.001	-3.64 [-5.71, -1.56]	< 0.001
Underlying disease					
T2D	1	-	-	-2.60 [-3.72, -1.48]	< 0.001
MetS	2	76.09%	< 0.001	-4.20 [-7.20, -1.20]	0.01
Treatment type					
Mono therapy	1	-	-	-2.40 [-5.12, 0.32]	0.08
Combination therapy	2	91.73%	< 0.001	-4.04 [-6.89, -1.20]	0.01
Insulin					
Total	6	98.72%	< 0.001	-2.80 [-5.99, 0.39]	0.09
Underlying disease					
T2D	4	97.38%	< 0.001	-1.07 [-3.25, 1.11]	0.34
MetS	2	64.13%	< 0.001	-6.54 [-12.95, -0.12]	0.05
Treatment type					
Mono therapy	2	0%	0.77	-2.93 [-7.78, 1.92]	0.24
Combination therapy	4	99.44%	< 0.001	-2.82 [-7.04, 1.40]	0.19
HDL					
Total	7	96.48%	< 0.001	2.13 [-0.02, 4.28]	0.05
Underlying disease					
T2D	5	94.43%	< 0.001	1.50 [-0.28, 3.27]	0.10
MetS	2	94.64%	< 0.001	3.46 [-4.11, 11.04]	0.37
Treatment type					
Mono therapy	2	69.43%	< 0.001	1.43 [-2.00, 4.87]	0.41
Combination therapy	5	98.00%	< 0.001	-2.40 [-0.40, 5.20]	0.09
Dose of treatment					

Table 2 (continued)

Variables	Trials, *n*	I^2 (%)	*P*-het	WMD (95% CI)	*P*-effect
< 120 mg/d	1	-	-	3.80 [3.03, 4.57]	< 0.001
≥ 120 mg/d	6	96.19%	< 0.001	1.82 [-0.65, 4.29]	0.15
Treatment duration					
≤ 90 days	6	96.19%	< 0.001	1.82 [-0.65, 4.29]	0.15
> 90 days	1	-	-	3.80 [3.03, 4.57]	< 0.001
TC					
Total	7	95.76%	< 0.001	-4.33 [-12.93, 4.27]	0.32
Underlying disease					
T2D	5	95.87%	< 0.001	-0.69 [-9.41, 8.04]	0.88
MetS	2	81.61%	< 0.001	-14.89 [-31.43, 1.64]	0.08
Treatment type					
Mono therapy	2	49.20%	0.16	-0.16 [-9.82, 9.50]	0.97
Combination therapy	5	97.64%	< 0.001	-5.70 [-17.25, 5.85]	0.33
Dose of treatment					
< 120 mg/d	1	-	-	7.80 [4.88, 10.72]	< 0.001
≥ 120 mg/d	6	94.16%	< 0.001	-6.51 [-15.49, 2.48]	0.16
Treatment duration					
≤ 90 days	6	94.16%	< 0.001	-6.51 [-15.49, 2.48]	0.16
> 90 days	1	-	-	7.80 [4.88, 10.72]	< 0.001
TG					
Total	7	98.19%	< 0.001	-0.05 [-15.37, 15.27]	0.99
Underlying disease					
T2D	5	98.91%	< 0.001	3.13 [-16.41, 22.66]	0.75
MetS	2	83.09%	< 0.001	-9.29 [-34.76, 16.18]	0.47
Treatment type					
Mono therapy	2	0.00%	0.48	-0.54 [-9.88, 8.79]	0.91
Combination therapy	5	99.21%	< 0.001	-1.24 [-24.16, 21.69]	0.92
Dose of treatment					
< 120 mg/d	1	-	-	26.54 [17.77, 35.31]	< 0.001
≥ 120 mg/d	6	97.83%	< 0.001	-4.31 [-19.01, 10.39]	0.57
Treatment duration					
≤ 90 days	6	97.83%	< 0.001	-4.31 [-19.01, 10.39]	0.57
> 90 days	1	-	-	26.54 [17.77, 35.31]	< 0.001
LDL					
Total	7	97.35%	< 0.001	-6.39 [-15.72, 2.95]	0.18
Underlying disease					
T2D	5	97.85%	< 0.001	-3.43[-14.39, 7.53]	0.54
MetS	2	79.98%	< 0.001	-14.85 [-29.66, -0.04]	0.05
Treatment type					
Mono therapy	2	0.0%	1.00	-6.00 [-13.31, 1.31]	0.11
Combination therapy	5	98.68%	< 0.001	-6.39 [-15.72, 2.95]	0.32
Dose of treatment					
< 120 mg/d	1	-	-	11.60 [9.66, 13.54]	< 0.001
≥ 120 mg/d	6	94.08%	< 0.001	-9.63 [-18.01, -1.25]	0.02
Treatment duration					
≤ 90 days	1	-	-	11.60 [9.66, 13.54]	0.02
> 90 days	6	94.08%	< 0.001	-9.63 [-18.01, -1.25]	< 0.001
CRP					
Total	5	98.51%	< 0.001	-1.16 [-1.94, -0.38]	< 0.001
Underlying disease					
T2D	3	99.17%	< 0.001	0.76 [-1.72, 021]	0.12
MetS	2	0.00%	0.59	-1.85 [-2.39, -1.30]	< 0.001
Treatment type					

Table 2 (continued)

Variables	Trials, *n*	I^2 (%)	*P*-het	WMD (95% CI)	*P*-effect
Mono therapy	1	-	-	-2.00 [-2.78, -1.22]	< 0.001
Combination therapy	4	98.78%	< 0.001	-0.97 [-1.81, -0.13]	0.02
IL6					
Total	3	90.04%	< 0.001	-14.53 [-25.00, -4.07]	0.01
Underlying disease					
T2D	1	-	-	-22.40 [-26.50, -18.30]	< 0.001
MetS	2	64.43%	< 0.001	-9.43 [-19.11, 0.25]	0.06
Treatment type					
Mono therapy	1	-	-	-5.60 [-10.21, -0.99]	0.02
Combination therapy	2	17.69%	< 0.001	-21.15 [-26.22, -16.09]	< 0.001
TNF-α					
Total	3	70.80%	< 0.001	-58.30 [-72.70, -43.91]	< 0.001
Underlying disease					
T2D	1	-	-	-71.50 [-89.59, -53.41]	< 0.001
MetS	2	60.46%	< 0.001	-52.74 [-66.16, -39.31]	< 0.001
Treatment type					
Mono therapy	1	-	-	-61.70 [-77.66, -45.74]	< 0.001
Combination therapy	2	82.88%	< 0.001	-58.00 [-81.34, -34.67]	< 0.001
BUN					
Total	3	96.84%	< 0.001	-3.24 [-7.98, 1.50]	0.18
Underlying disease					
T2D	1	-	-	-5.10 [-6.59, -3.61]	< 0.001
MetS	2	98.11%	< 0.001	-2.32 [-9.89, 5.24]	0.55
Treatment type					
Mono therapy	1	-	-	1.52 [0.26, 2.78]	0.02
Combination therapy	2	0.00%	0.33	-5.59 [-6.70, -4.49]	< 0.001
Cr					
Total	4	94.75%	< 0.001	-0.12 [-0.20, -0.04]	< 0.001
Underlying disease					
T2D	2	0.00%	0.98	-0.15 [-0.17, -0.13]	< 0.001
MetS	2	95.8%	< 0.001	-0.10 [-0.23, 0.02]	0.11
Treatment type					
Mono therapy	2	0.00%	0.96	-0.04 [-0.06, -0.02]	< 0.001
Combination therapy	2	0.05%	0.46	-0.15 [-0.17, -0.13]	< 0.001
ALP					
Total	4	85.60%	< 0.001	1.09 [-4.03, 6.21]	0.68
Underlying disease					
T2D	2	94.68%	< 0.001	1.47 [-11.07, 14.01]	0.82
MetS	2	0.00%	0.7	0.63 [-2.00, 3.27]	0.64
Treatment type					
Mono therapy	2	63.10%	0.1	-2.37 [-7.30, 2.57]	0.35
Combination therapy	2	85.10%	0.01	4.43 [-2.13, 11.00]	0.19
ALT					
Total	4	0.00%	0.64	1.42 [0.66, 2.18]	< 0.001
Underlying disease					
T2D	2	0.00%	0.98	1.90 [0.66, 3.15]	< 0.001
MetS	2	0.00%	0.38	1.14 [0.18, 2.10]	0.02
Treatment type					
Mono therapy	2	0.00%	0.68	0.16 [-2.46, 2.78]	0.91
Combination therapy	2	0.00%	0.47	1.54 [0.75, 2.33]	< 0.001
AST					
Total	4	0.00%	0.80	1.95 [1.07, 2.82]	< 0.001
Underlying disease					

Table 2 (continued)

Variables	Trials, *n*	I^2 (%)	*P*-het	WMD (95% CI)	*P*-effect
T2D	2	64.05%	0.1	2.43 [-1.96, 6.83]	0.28
MetS	2	0.00%	0.33	1.84 [0.91, 2.77]	< 0.001
Treatment type					
Mono therapy	2	0.00%	0.58	1.10 [-0.32, 2.53]	0.13
Combination therapy	2	39.89%	0.20	2.82 [0.82, 4.81]	0.01
BMI					
Total	6	93.63%	< 0.001	-0.85 [-1.53, -0.18]	0.01
Underlying disease					
T2D	4	95.28%	< 0.001	-0.71 [-1.54, 0.12]	0.09
MetS	2	89.38%	< 0.001	-1.15 [-2.62, 0.32]	0.12
Treatment type					
Mono therapy	2	0.00%	0.86	-0.36 [-0.91, 0.18]	0.19
Combination therapy	4	96.77%	< 0.001	-1.09 [-2.05, -0.13]	0.03
VAI					
Total	3	75.54%	< 0.001	-48.09 [-66.74, -29.44]	< 0.001
Underlying disease					
T2D	1	-	-	-44.80 [-58.18, -31.42]	< 0.001
MetS	2	78.84%	< 0.001	-46.54 [-82.92, -10.16]	0.01
Treatment type					
Mono therapy	1	-	-	-24.40 [-56.86, 8.06]	0.14
Combination therapy	2	75.60%	< 0.001	-54.03[-70.95, -37.12]	< 0.001
WC					
Total	5	99.25%	< 0.001	-2.67 [-4.97, -0.37]	0.02
Underlying disease					
T2D	3	99.18%	< 0.001	-1.06 [-3.21, 1.09]	0.33
MetS	2	37.22%	0.21	-5.09 [-6.07, -4.11]	< 0.001
Treatment type					
Mono therapy	1	-	-	-4.60 [-5.68, -3.52]	< 0.001
Combination therapy	4	99.45%	< 0.001	-2.20 [-4.89, 0.49]	0.11

*P-het: p-value for heterogeneity (Cochran's Q test); P-effect: p-value for the overall effect estimate (test of WMD = 0)

associated with bigger decreases. These findings should not be taken as evidence that GBE is equivalent to or a replacement for existing glucose-lowering medicines. Rather, they imply that when combined with standard therapy, GBE may provide a small, supplementary advantage in terms of fasting glycemia and insulin sensitivity. The lack of a comparable significant reduction in HbA1c emphasizes the preliminary nature of these findings and the need for longer-term trials to determine if these short-term gains are sustained or translate into clinically useful glycemic management.

The considerable pooled advantages for measures such as FBG, HOMA-IR, and inflammatory markers were primarily driven by studies in which GBE was added to existing therapies, such as metformin. Regarding insulin resistance, the pooled analysis revealed that GBE significantly improved HOMA-IR values, suggesting a potential role in enhancing insulin sensitivity among patients with MetS and related disorders. The observed decrease in FBG of around 14 mg/dL (0.78 mmol/L) is statistically significant, but it is less than the standard minimal clinically relevant difference (MCID) indicated for diabetic therapies, which typically cut-off of ≥ 126 mg/dL (≥ 0.7 mmol/L) for fasting glucose [17]. The absence of a significant reduction in HbA1c, a key metric for assessing long-term glycemic control and predicting microvascular complication risk, suggests that the short-term FBG improvement observed in these trials may not result in lasting or clinically significant glycemic benefits. The American Diabetes Association (ADA) recommends a HbA1c reduction of ≥ 0.5% for clinically significant improvement [18]. However, our pooled estimate of -0.17% (95% CI -0.46 to 0.11) is inadequate of this standard. This disparity implies that GBE may have short- to medium-term impacts on insulin resistance and fasting glucose, without necessarily affecting the underlying physiological mechanisms to the point where HbA1c levels improve over the trial durations investigated. Longer-term trials (≥ 6–12 months) are needed to evaluate if short-term improvements may be sustained and result in long-term glycemic benefits.

These results are consistent with individual clinical trials that have investigated the role of GBE in managing T2D. For example, a randomized, placebo-controlled

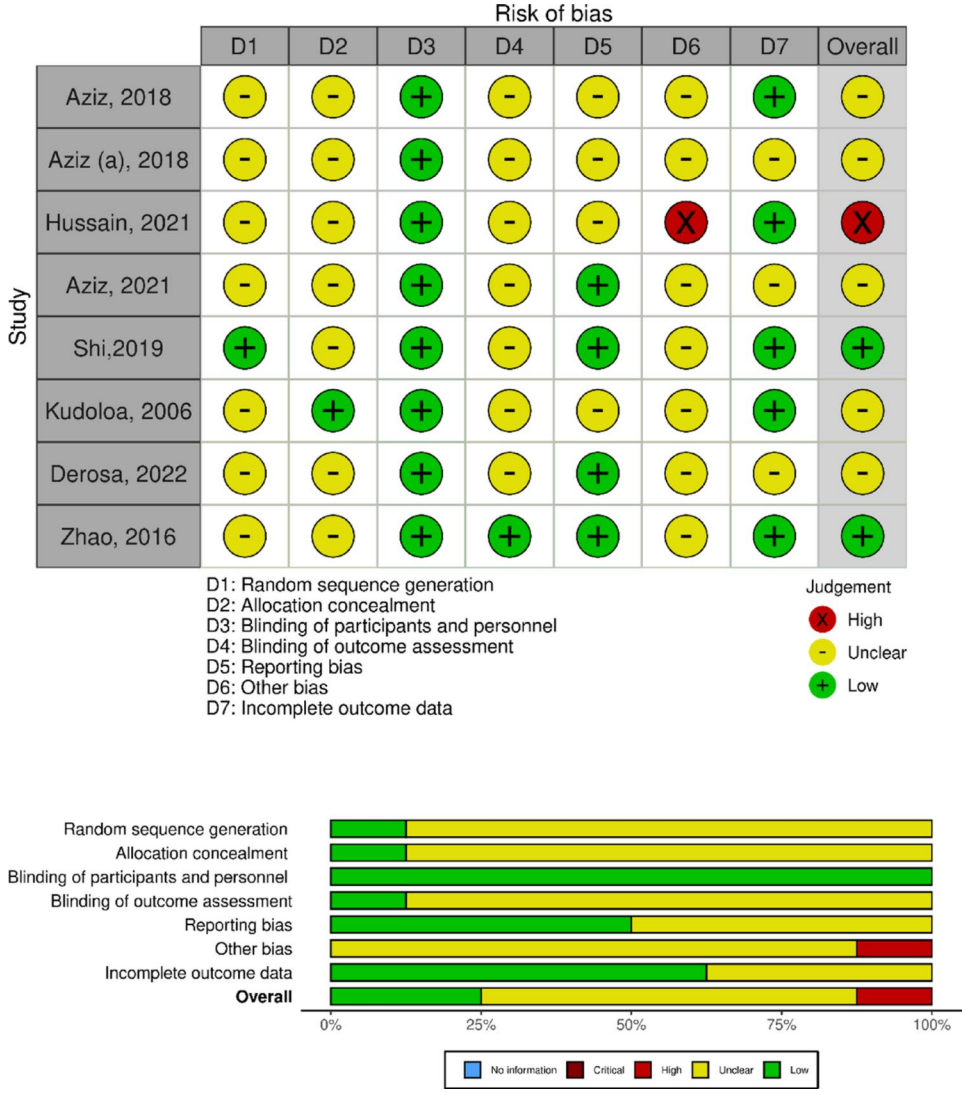


Fig. 7 Cochrane risk of bias summary for included studies. Risk of bias judgments (low, unclear, high) for each domain across all included RCTs

study evaluated the effect of GBE as an adjunct to metformin in patients with poorly controlled diabetes who had been on stable metformin therapy for at least six months, with baseline HbA1c levels ≥ 7.5%. Over a 90-day intervention, the addition of GBE improved FBG, circulating insulin, and HbA1c compared with baseline values, although the between-group differences versus placebo were less pronounced [11]. The authors proposed that the beneficial effects may be explained by mechanisms such as preservation of pancreatic β-cell function, reduction of insulin resistance, and enhanced glucose transport in peripheral tissues [19–21]. Preclinical data also suggest that GBE improves insulin sensitivity by increasing transcription of insulin receptor substrate 2 and reducing negative regulators of the insulin signaling pathway [22]. These findings suggest that GBE may offer complementary benefits when combined with standard antidiabetic therapy, particularly in patients who are insufficiently controlled with metformin alone.

With respect to lipid metabolism, the overall evidence regarding the effects of GBE remains inconsistent. A modest improvement in HDL levels has been observed; however, the statistical significance was borderline, and substantial heterogeneity (I^2 = 96.48%) undermines the robustness of this finding. In contrast, pooled analyses revealed no significant effects on TC or TG levels, both of which were also accompanied by considerable heterogeneity across trials. These discrepancies may reflect differences in baseline lipid status, concomitant therapies, or variations in the duration and dosage of GBE supplementation.

Experimental studies further support the potential lipid-modulatory effects of GBE. For example, GBE has been shown to inhibit adipogenesis and regulate lipid metabolism in mice, leading to reductions in body

Table 3 Publication bias assessment used by Egger's and Begg's tests

Biomarkers	Egger's test (*P*-value)	Begg's test (*P*-value)
FBG	0.0001	0.7105
HbA1c	0.2673	0.2655
Insulin	0.6687	0.7071
HOMA-IR	0.5934	1.0000
TG	0.0111	0.3675
HDL	0.9504	1.0000
LDL	0.445	0.763
TC	0.3797	0.1331
BMI	0.2847	0.4524
VAI	0.0562	0.2963
CRP	< 0.0001	0.0864
IL-6	0.9648	1.0000
TNF-α	0.0074	0.2963
WC	< 0.0001	0.2207
AST	0.8787	1.0000
ALT	0.7046	1.0000
ALP	0.0849	0.3082
BUN	0.0014	0.2963
Cr	0.8452	1.0000

weight, food intake, and visceral adiposity, while significantly enhancing HDL levels [22]. In models of non-alcoholic fatty liver disease, GBE corrected dyslipidemia, potentially through mechanisms such as increased total lipase activity, reduced hepatic free fatty acid content, and diminished triglyceride synthesis [23].

In line with these preclinical findings, a study demonstrated that GBE significantly increased HDL in patients with MetS, while metformin also improved HDL levels compared with baseline [24]. Moreover, adjunctive use of GBE with metformin did not significantly alter serum TGs, a result consistent with earlier observations [25]. Interestingly, GBE was also reported to reduce the adiposity index, which may underlie concurrent decreases in LDL-c and TC [6].

Nevertheless, not all studies have corroborated these benefits. Several investigations failed to detect significant differences between intervention and control groups with respect to HDL, LDL, TC, TG, or microalbuminuria [15, 26, 27], suggesting that the lipid-modulating potential of GBE may not be universal. These inconsistencies highlight the likelihood that patient characteristics, concomitant medications, and baseline metabolic status strongly influence treatment outcomes.

Taken together, the available evidence suggests that GBE holds promise in improving selected aspects of the lipid profile, particularly HDL and indices linked to adiposity. However, its effects on LDL, TC, and TG remain inconclusive, underscoring the need for high-quality, large-scale RCTs with standardized intervention protocols to better define its role in the management of dyslipidemia and MetS.

In this systematic review and meta-analysis, our pooled results demonstrated that GBE exerts a significant anti-inflammatory effect. The reductions in CRP (-1.16 mg/L), TNF-α (-58.3 pg/mL), and IL-6 (-14.5 pg/mL) are proportionally bigger than the baseline values reported in the included trials. However, it is unclear if these biochemical changes will lead to a decrease in cardiovascular or diabetes-related complications. Although low-grade inflammation has been linked to insulin resistance and atherogenesis, the MCID for inflammatory biomarkers in MetS remains unclear. Additionally, no trials included in this meta-analysis were designed or powered to assess incident cardiovascular events, progression to diabetes, or mortality. The therapeutic significance of these changes, however, must be balanced against the fact that GBE did not result in significant reductions in the atherogenic lipid profile (LDL-C, TG), which are important determinants of cardiovascular risk in this group.

Another study further indicated that GBE effectively reduces inflammatory mediators, particularly TNF-α, with significant differences compared to placebo. This outcome has been attributed to the modulatory effects of GBE constituents on inflammatory gene expression [28]. Since TNF-α plays a central role in stimulating reactive oxygen species, inducing other pro-inflammatory mediators, activating leukocytes, and amplifying inflammatory cascades, its suppression by GBE may represent a key mechanism of action [29]. Supporting this, in vitro experiments confirmed that GBE suppresses cytokine production, including TNF-α, via downregulation of the JNK-AP-1 signaling pathway [30].

Aziz et al. showed that GBE monotherapy in patients with MetS improved certain components of metabolic inflammation [24]. Several other studies have confirmed the ability of GBE to attenuate inflammatory responses [31, 32]. Because oxidative stress and pro-inflammatory mediators are central to the pathogenesis of insulin resistance, reducing inflammation may help prevent its progression [33]. Consistent with this, studies reported marked decreases in TNF-α and IL-6 compared with both baseline and metformin groups. These anti-inflammatory effects may result from GBE's ability to regulate inflammatory gene expression, reduce nitric oxide and prostaglandin E2 formation, downregulate pro-inflammatory cytokines, and modulate NF-κB activity [29, 34]. The association between IL-6, CRP, and insulin resistance is well established as a major contributor to comorbidities in MetS [35]. Beyond MetS, T2D itself is linked to multiple inflammatory pathways, including AGE accumulation, leukocyte infiltration, cytokine release, and adhesion molecule expression, which contribute to renal impairment [36, 37]. GBE improved platelet function, modified platelet–vessel wall interactions, and reduced malondialdehyde levels in patients with T2D [38]. A study revealed how GBE phytochemicals can protect

against age-associated and diabetic ocular diseases via antioxidant, anti-apoptotic, and anti-angiogenic mechanisms [39]. In addition, a recent experimental investigation found that GBE reduced diabetic retinopathy development in a rat model via modifying TP53 ubiquitination, a critical regulator of cellular stress and death [40].

Additional evidence supports these findings in MetS. A pilot clinical study involving 11 patients demonstrated that 2 months of GBE supplementation reduced CRP and IL-6, along with improvements in arteriosclerotic, inflammatory, and oxidative stress biomarkers. According to data from larger trials, which highlight the link between insulin resistance, low-grade inflammation, cardiovascular disease, and mortality, these results suggest potential reductions in CVD risk and overall mortality [35]. Furthermore, a study showed that Blunorm forte, a formulation containing GBE, decreases high-sensitivity CRP [41]. These findings imply that the systemic benefits in inflammation and glycemic stability seen in our study may be part of a larger positive profile that could include lowering the risk or progression of diabetes complications.

Lifestyle interventions and approved weight control pharmacotherapies, such as GLP-1 receptor agonists and orlistat, can reduce BMI and WC over time [42]. Beyond its immunomodulatory actions, GBE has also been shown to improve metabolic parameters. While reductions in anthropometric indices were statistically significant, the overall size was small. These improvements, while beneficial, are insufficient as a stand-alone weight-loss strategy. GBE alone may not significantly reduce obesity-related comorbidities or cardiovascular risk profiles. They may, however, act as surrogate indications of positive changes in visceral adiposity and body composition, which could supplement other therapeutic regimes. This observation is in line with clinical evidence showing that VAI decreased significantly in the GBE-treated group, demonstrating the extract's ability to attenuate visceral adiposity, stimulate insulin signaling in skeletal muscle, and improve insulin sensitivity [22, 43–46]. Aziz et al. reported that in patients with poorly controlled T2D, GBE improved glycemic status, insulin resistance, BMI, and VAI [25]. Furthermore, Hussain's study suggested leptin as another potential target of GBE [47]. Leptin, secreted by adipose tissue, regulates appetite and energy expenditure via hypothalamic nuclei [48]. Impaired leptin signaling due to mutations in leptin or its receptor leads to increased food intake and reduced energy expenditure, even in obese individuals [49]. Interestingly, a 90-day treatment with GBE was suggested to exert anti-inflammatory effects on the hypothalamus by reducing orexigenic peptides and/or enhancing anorexigenic peptides, thereby promoting weight loss through appetite suppression [31]. Experimental evidence in animal models also supports these effects, where GBE inhibited adipogenesis, modulated lipid metabolism, reduced food intake, and increased HDL levels [45]. These findings suggest that the beneficial impact of GBE on BMI, WC, and VAI may be mediated through multiple mechanisms, including inhibition of lipid absorption, stimulation of lipolysis, and improvement of insulin sensitivity. Importantly, these effects were achieved without serious or clinically significant adverse reactions, underscoring the therapeutic potential of GBE as an adjunct in the management of obesity and related metabolic complications.

Our analysis also evaluated the effects of GBE on kidney function tests and liver activity markers. Pooled data indicated that GBE did not significantly affect BUN levels compared to control groups ($p = 0.18$, $I^2 = 96.84\%$). However, Cr levels were significantly reduced in patients receiving GBE ($p = 0.00$, $I^2 = 94.75\%$), suggesting a modest but statistically meaningful benefit in Cr metabolism. Individual studies provide additional insights. In one study, serum urea levels decreased significantly in GBE-treated patients but rose non-significantly in placebo recipients. Similarly, Cr levels significantly reduced in the GBE-plus-metformin group, while the placebo group experienced significant increases [25]. Other trials confirmed consistent reductions in ALP and urea with GBE supplementation, whereas Cr rose only in the placebo groups [6, 24]. Interestingly, a study administering 120 mg of EGb 761 daily for 3 months found no significant changes in renal function, complete blood count, or metabolic panel in subjects with either normal glucose tolerance (NGT) or T2D. These discrepancies may be explained by differences in study design, patient populations, treatment duration, and GBE dosage [13]. A 2025 meta-analysis of 41 RCTs ($n = 3,269$) assessing GBE as an adjuvant to ACEI/ARB for diabetic renal disease revealed no significant difference in adverse events between GBE and control groups, and reported significant improvements in blood Cr and BUN [50].

Regarding hepatic biomarkers, pooled results from four studies showed no significant impact on ALP, although heterogeneity was substantial ($I^2 = 85.60\%$). In contrast, four RCTs consistently found significant increases in ALT and AST following GBE administration, both without heterogeneity ($I^2 = 0.00\%$). According to the findings of this meta-analysis, GBE is generally well tolerated in the short to medium term. The constant signal of modest, asymptomatic transaminase increase is noteworthy, while its clinical value in these trials was minimal. It should be noted that none of the included trials provided individual participant-level data on the proportion of participants whose liver transaminases exceeded the upper limit of normal or other predetermined safety thresholds.

As a result, no quantitative assessment of clinically relevant enzyme increases was possible. Preclinical studies showed that GBE prevents drug-induced hepatotoxicity. In a rat model, GBE reduced methotrexate-induced ALT, AST, and ALP levels, as well as caspase-3 and TNF-α [51].

Although the lack of statistical heterogeneity confirms this finding, several drawbacks prevent definitive conclusions on the long-term hepatic safety of GBE in this population. The included trials were of relatively short duration (predominantly ≤ 90 days), making it unclear whether these minor enzyme elevations would stay, progress, or resolve with extended therapy. Second,individual participant data were not available; thus, we were unable to assess the proportion of patients whose liver enzymes surpassed the upper limit of normal or crossed preset safety thresholds. Third, several trials used GBE in conjunction with other nutraceuticals or varied baseline pharmacotherapies, which introduced possible confounding that could not be fully resolved. It is worth noting that no clinical hepatotoxicity events (such as jaundice, hepatitis, or liver failure) were reported in any of the studies examined, and the observed mean enzyme increases were within population reference ranges. Preclinical research suggests that GBE has hepatoprotective characteristics, reducing drug-induced (e.g., methotrexate) and cholestatic liver injury in animal models via antioxidant and anti-inflammatory mechanisms.

An ongoing Phase 2 trial (NCT03004508) is specifically assessing liver function and genetic markers of hepatocarcinogenesis in participants taking GBE (120 mg twice daily for 6 months), which may give more definite safety data once completed. Our findings of a significant reduction in serum Cr align with a recent large meta-analysis of 41 RCTs, which concluded that GBE combined with ACEI/ARB is associated with improved renal function in diabetic kidney disease, with no significant increase in adverse events compared to control [50]. Taken together, the available short-term data imply that GBE is generally well tolerated, although the data is insufficient to rule out unusual or long-term unfavorable liver consequences. Prudent clinical practice would involve periodic monitoring of liver enzymes during extended GBE supplementation, especially for patients receiving concurrent pharmaceuticals with hepatotoxic potential.

Limitations

Several limitations should be considered when interpreting the findings of this meta-analysis. First, although the overall sample size is substantial, numerous individual trials were small, thereby reducing their statistical power to detect actual effects, particularly for safety outcomes. Second, the safety analysis is hampered by several factors, including short follow-up periods (typically ≤ 90 days) that are insufficient to assess chronic hepatotoxicity or carcinogenicity, trials combining GBE with other nutraceutical ingredients (e.g., Blunorm forte® containing alpha lipoic acid and Vitis vinifera), making it difficult to attribute observed enzyme changes solely to GBE, and background heterogeneity. Third, the metabolic effects of GBE were compared to a variety of background drugs (e.g., metformin alone vs. different combinations), making it difficult to separate the pure effect of GBE and extrapolate findings to other treatment settings. Fourth, the short duration of most trials (≤ 90 days) makes it impossible to examine the long-term efficacy and safety of GBE supplementation. Fifth, the type and standardization of GBE formulations utilized in the trials differed significantly. Only four investigations used the well-characterized standardized extract EGb 761 (or equivalent) at a dose of 120 mg/day; the others used lower doses, mixed herbal products, or inadequately reported extracts. Because the phytochemical content of GBE products has a direct impact on their pharmacological activity and interaction potential, the results of this meta-analysis may not be applicable to all commercial GBE supplements. Future RCTs should only employ standardized, pharmaceutical-grade GBEs and openly state their specifications. Finally, there is evidence of publication bias for some key outcomes. This means that smaller studies with null or negative findings may be underrepresented in the published literature, thus overestimating real effect sizes for these outcomes. The pooled estimates for FBG, CRP, and anthropometric indices—some of the most positive findings in this analysis—should be considered with caution. While the consistency of effect direction across most individual studies is encouraging, the idea that the current data base offers an excessively optimistic picture of GBE's metabolic advantages cannot be dismissed. This emphasizes the vital importance of prospective trial registration and the publication of all completed trials, regardless of their conclusions, in order to provide more reliable assessments of GBE's real efficacy.

Conclusions and implications

The meta-analysis demonstrates a pattern of small, statistically significant improvements in particular short-term metabolic and inflammatory parameters, contrasted with no effect on recognized long-term indicators (HbA1c) and inconsistent effects on lipids. This profile shows that GBE may be more effective as an adjuvant therapy, potentially addressing components such as insulin resistance and inflammation in individuals already receiving standard care, rather than as a monotherapy with comprehensive metabolic control. As a result, the findings of this meta-analysis should not be interpreted as evidence for GBE as a standalone metabolic treatment. The data do not show that GBE monotherapy is sufficient to achieve

clinically relevant glycemic, dyslipidemic, or obese management in patients with MetS or T2D. Instead, the evidence indicates standardized GBE compounds could offer additional, modest beneficial effects when used in conjunction with traditional treatment, possibly targeting residual insulin resistance or inflammation in patients whose control is suboptimal with standard care alone. The difference is crucial for accurate clinical interpretation and the proper use of the findings.

In the context of this meta-analysis, the use of GBE alongside metformin in multiple trials is significant. GBE, specifically standardized EGb 761, has been shown to stimulate cytochrome P450 enzymes (most notably CYP2C19) and inhibit CYP3A4, as well as exert antiplatelet action via platelet-activating factor (PAF) receptor antagonism. While Kudolo et al. (2006) explicitly evaluated this interaction and discovered co-ingestion of standardized EGb 761 (120 mg/day) with metformin did not result in a significant change in metformin pharmacokinetics, the overall risk of altered drug metabolism warrants caution [13]. The interaction potential of GBE is known to be formulation-dependent. Standardized extracts, like EGb 761, fulfill strict standards (e.g., 0.036—1.87% flavonol glycosides, 0.11%–0.72% terpene trilactones, ≤ 5 ppm ginkgolic acids) [52]. In contrast, many commercially available GBE supplements are poorly defined and may differ significantly in phytochemical composition, potentially affecting their CYP450 modulatory effects. Unger et al. found that at recommended doses (≤ 240 mg/day), the standardized extract EGb 761 poses minimal clinically meaningful risk for pharmacokinetic herb drug interactions [53]. However, the interaction potential of non-standardized GBE products is unknown. Preclinical investigations have revealed that GBE slightly inhibits CYP3A4 and induces CYP2C19 at supratherapeutic levels, and its antiplatelet effects via PAF receptor antagonism are well recognized [54]. Patients with MetS or T2D should pay special attention to co-administered therapies with limited therapeutic indices or those metabolized by impaired CYP450 pathways (e.g., warfarin, certain statins, some antiplatelet drugs). The lack of observed bleeding events in these trials does not invalidate GBE's documented antiplatelet effect; patients undergoing surgery or receiving anticoagulant medication should be closely tracked. Physicians should assess GBE's pharmacologic profile, advise patients on potential interactions, and use caution when administering it in conjunction with drugs with sensitive metabolism or bleeding risk.

From a research perspective, these findings highlight the urgent need for large-scale, multicenter RCTs with standardized dosing protocols and longer follow-up durations. Future studies should stratify patient populations (e.g., poorly controlled diabetes versus MetS without diabetes) and investigate dose-response relationships. Mechanistic studies are also warranted to elucidate the pathways by which GBE modulates glucose metabolism, inflammation, and adiposity. The pooled effect estimates include I^2 values above 90% for FBG, HbA1c, and all lipid markers. Because of the significant heterogeneity—which is most likely due to changes in GBE formulations, background medication, baseline metabolic status, and trial duration—the pooled point estimate cannot be considered an accurate or universally applicable treatment effect. Furthermore, the small effect sizes, limited trial durations, and lack of change in HbA1c or lipid profiles suggest that the data do not support GBE's routine use as a primary or standalone intervention for MetS or T2D. GBE's prospective usefulness would most likely be as an addition to known therapy (e.g., metformin, lifestyle management) in individuals with residual insulin resistance or increased inflammatory markers. Indeed, these findings contribute to developing hypotheses regarding the situations under which GBE may be beneficial (for example, as a short-term supplementary therapy in patients with increased inflammatory markers) and suggest major sources of variability that should be addressed in future trials. As a result, clinicians should not use pooled WMD values to predict the benefit for an individual patient, but rather consider the overall pattern of directional change across metabolic, inflammatory, and anthropometric domains. They also should consider the short-term biochemical benefits observed in this meta-analysis against the absence of long-term safety and efficacy data, small but constant elevations in liver transaminases, and the potential for herb-drug interactions. Importantly, future research should systematically assess long-term safety outcomes, particularly hepatic and renal parameters, to establish the risk–benefit profile of GBE supplementation.

Supplementary Information

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Supplementary material 1.

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Author contributions
K.H: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. F.Z, MS.H, M.A, SM.K, MJ.K, F.H: Writing – original draft, Data Curation, Investigation, Software.

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Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval
This study protocol was reviewed and approved by the Nephrology and Urology Research Center, Clinical Sciences Institute, Baqiyatallah University of Medical Sciences, Tehran, the Islamic Republic of Iran, approval number [IR.BMSU.BAQ.REC.1404.008].

Consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

Author details
[1]Student Research Committee, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2]Health research center, life style institute, Baqiyatallah university of medical sciences, Tehran, Iran
[3]Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Research Center for Prevention of Oral and Dental Diseases, Baqiyatallah University of Medical Sciences, Tehran, Iran
[5]Clinical Research Development Unit, Shahid Bahonar Hospital, Kerman University of Medical Sciences, Kerman, Iran
[6]Nephrology and Urology Research Center, Clinical Sciences Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran

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