Complementary Therapies in Medicine 90 (2025) 103174

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Effects of black seed (*Nigella sativa* L.) on cardiometabolic indices in type 2 diabetic patients: A systematic review and meta-analysis of RCTs

Mehdi Karimi [a,*,1], Samira Pirzad [b,2], Seyed Morteza Ali Pourfaraji [c,3], Fatemeh Maleki Sedgi [d,4], Bahar Darouei [e,5], Reza Amani-Beni [e,6], Kimia Kazemi [f], Reyhaneh Rabiee [g,*,7]

[a] Faculty of Medicine, Bogomolets National Medical University (NMU), Kyiv, Ukraine
[b] Faculty of Medicine, Islamic Azad University, Tehran Medical Sciences Branch (IAUTMU), Tehran, Iran
[c] Faculty of Medicine, Tehran University of Medical Science (TUMS), Tehran, Iran
[d] Department of Nutrition, Urmia University of Medical Sciences, Urmia, Iran
[e] Heart Failure Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
[f] Department of Food Science and Technology, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran
[g] Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

ARTICLE INFO

Keywords:
Black seed
Nigella sativa
Diabetes
Metabolism
Phytotherapy
Herbal medicine
Nutrition
Traditional Persian medicine

ABSTRACT

Background: Black seed is known for its health benefits in traditional medicine. While recent studies suggest it may improve cardiometabolic health, its impact on type 2 diabetes mellitus (T2DM) remains unclear. This study aims to meta-analysis randomized controlled trials (RCTs) to assess the effects of black seed supplementation on cardiometabolic indices in T2DM patients.

Methods: Following PRISMA guidelines, a comprehensive database search was conducted up to January 2025, and data were extracted from relevant RCTs. Mean differences (MD) and standard deviations (SD) were analyzed using a random-effects model, heterogeneity was assessed, and publication bias was evaluated.

Results: The pooled meta-analysis of 16 RCTs showed that black seed supplementation significantly reduced fasting blood glucose (FBG) (MD: −21.43 mg/dL; $p = 0.005$), hemoglobin A1c (HbA1c) (MD: −0.44; $p = 0.01$), total cholesterol (TC) (MD: −18.80 mg/dL; $p = 0.04$) and low-density lipoprotein (LDL) (MD: −19.53 mg/dL; $p = 0.003$). No significant effects were observed for 2-hour postprandial glucose (2-hpp), fasting insulin, homeostatic model assessment (HOMA), triglycerides (TG), high-density lipoprotein (HDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and body weight, or body mass index (BMI). Subgroup analyses revealed that black seed supplementation effectively reduced FBG for longer than 8 weeks; additionally, HbA1c, HOMA, and LDL in higher doses (>1 g/day), shorter durations (≤8 weeks), and use of the oil form.

Conclusion: Black seed supplementation appears to significantly improve FBG, HbA1c, TC, and LDL levels in patients with T2DM. However, no significant effects were observed on other metabolic parameters, including insulin, TG, liver enzymes, kidney function, or body weight. These findings suggest that black seed may be a

Abbreviations: RCT, Randomized Controlled Trial; T2DM, Type 2 Diabetes Mellitus; FBG, Fasting Blood Glucose; HbA1C, Hemoglobin A1c; 2-hpp, 2-Hour Postprandial Glucose Test; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HOMA-β, Homeostatic Model Assessment for Pancreatic Beta Cell; TG, Triglyceride; TC, Total Cholesterol; LDL-C, Low-density Lipoprotein Cholesterol; HDL-C, High-density Lipoprotein Cholesterol; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; BMI, Body Mass Index.

* Corresponding authors.
E-mail addresses: Karimi9010@gmail.com (M. Karimi), rabieer97@gmail.com (R. Rabiee).
[1] ORCID: (0009–0006-4388–0214)
[2] ORCID: (0009–0003-9220–3891)
[3] ORCID: (0009–0003-7712–9427)
[4] ORCID: (0000–0002-9187–0786)
[5] ORCID: (0000–0002-5269–0061)
[6] ORCID: (0000–0002-8383–6676)
[7] ORCID: (0009–0007-9292–8306)

https://doi.org/10.1016/j.ctim.2025.103174
Received 7 February 2025; Received in revised form 3 April 2025; Accepted 7 April 2025
Available online 8 April 2025

beneficial adjunct therapy for glycemic and lipid control in T2DM patients but require further research to confirm its broader metabolic effects.

1. Introduction

Type 2 diabetes mellitus (T2DM) represents one of the most widespread metabolic disorders around the world. In 2022, it was estimated that about 10 % of adults globally were affected by diabetes, totaling approximately 828 million people.[1] T2DM markedly increases the likelihood of various metabolic complications such as neuropathy, nephropathy, coronary heart disease, and dyslipidemia.[2] As a result, enhancing glycemic control and lipid levels is deemed a vital approach for managing complications related to diabetes. It is recommended that individuals with T2DM adopt dietary changes, utilize oral hypoglycemic medications, and engage in regular physical activity to improve metabolic results.[3] Due to concerns about the possible adverse effects of certain anti-diabetic medications and the tendency for individuals to resort to herbal remedies, the World Health Organization (WHO) has identified a significant lack of information necessary to investigate the efficacy and safety of herbs that may have healing properties.[4] Complementary and alternative medicine, including herbal products, plays a vital role in enhancing overall health outcomes, reflecting the growing interest in holistic approaches and their integration into modern healthcare practices.[5–7] Research has shown that herbal medicines may offer benefits in improving the metabolic profile of individuals with overweight and T2DM.[8–10]

Black Seed (*Nigella sativa* L.) is a member of the Ranunculaceae family and is recognized worldwide as a medicinal plant.[11] Traditionally, it has been utilized to treat various health issues, including rheumatoid arthritis, digestive problems, hypertension, imbalanced lipid levels, and deficiencies in the immune system.[12,13] The primary active components found in black seed include thymoquinone, thymohydroquinone, dithymoquinone, p-cymene, and carvacrol.[11]

Multiple studies have indicated that treatment with black seed improved glycemic control and diminished insulin resistance in individuals with T2DM.[14,15] Furthermore, previous clinical research has demonstrated that the use of black seed resulted in significant enhancements in lipid profiles.[16] Black seed has several properties that contribute to its antidiabetic, antihyperlipidemic, gastroprotective, hepato-protective, and antihypertensive effects. It improves insulin sensitivity, decreases intestinal glucose absorption, and inhibits enzymes responsible for carbohydrate breakdown.[17–19] Moreover, it influences glucose production in the liver as well as lipid metabolism.[20] Recent investigations have indicated that black seed elevates the levels of components related to glycemic control.[21] It may enhance hepatic protective effects by impacting liver enzymes.[22] Nevertheless, there are variable findings.[23,24] Another meta-analysis examined the effects of black seed supplementation on cardiometabolic parameters, but it was based on a limited number of studies and did not evaluate certain markers, such as liver enzymes.[25]

Due to the inconsistency in clinical trial results and the lack of large studies, a meta-analysis is required to fill the knowledge gap on black seed health outcomes. Hence, this review aims to meta-analyze the randomized controlled trials (RCTs) investigating the effects of black seed on cardiometabolic indices in participants with T2DM.

Table 1
The population, intervention, comparison, outcome (PICO) od study.

Domain	Selection Criteria
Participants	Adult patients with type 2 diabetes mellitus (T2DM)
Intervention	Oral supplementation with Black Seed (*Nigella sativa* L.)
Comparison	Placebo, Control
Outcomes	Cardiometabolic indices include: – Glycemic markers (FBG, 2-HPP, fasting insulin, HbA1c, HOMA-IR, HOMA-β) – Lipid profile (TC, TG, HDL, LDL) – Liver enzymes (AST, ALT) and Creatinine – Antropometric: BMI, body weight
Search Keywords	("Nigella sativa" OR "N. sativa" OR "Nigella" OR "black seed" OR "black caraway" OR "black cumin" OR "kalonji" OR "charnushka" OR "Roman coriander" OR "fennel flower") AND ("Diabetes" OR "Diabetes mellitus" OR "Type 2 Diabetes Mellitus" OR "Type II diabetes mellitus" OR "T2DM" OR "Diabetic" OR "noninsulin-dependent")

(**FBG**: fasting blood glucose, **HbA1c**: hemoglobin A1c, **2-hpp**: 2-hour postprandial blood glucose, **HOMA-IR**: homeostatic model assessment for insulin resistance, **HOMA-β**: homeostasis model assessment-beta cell, **BMI**: body mass index, **TG**: triglyceride, **TC**: total cholesterol, **LDL-C**: low-density-lipoproteins cholesterol, **HDL-C**: high-density-lipoproteins cholesterol, **AST**: aspartate aminotransferase, **ALT**: alanine aminotransferase).

2. Methods

2.1. Study protocol and registration

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring clarity, transparency, and comprehensive reporting.[26] To enhance methodological rigor and reproducibility, the research protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under registration number **CRD42024572908**.

2.2. Search strategy

A comprehensive, advanced search across major scientific databases, including PubMed, Web of Science, Scopus, and Embase, covering all records up to January 2025, to identify RCTs investigating the impact of Black seed supplementation on cardiometabolic indices in individuals with T2DM. The search strategy employed a combination of relevant Medical Subject Headings (MeSH) terms and non-MeSH keywords, using Boolean operators (AND, OR) within [Title/Abstract] fields, with no time restrictions applied. Only articles published in English were considered. Furthermore, reference lists of all identified articles were manually screened to capture additional eligible studies, including grey literature, that might have been overlooked in the database search. The specific keywords used in the search strategy are detailed in Table 1.

The research question was constructed carefully using the Patient, Intervention, Comparison, and Outcome (PICO) framework, ensuring a clear and systematic approach to the study's objectives, as detailed in Table 1.

2.3. Inclusion and exclusion criteria

This review included original RCTs that assessed the effects of Black Seed supplementation on cardiometabolic health in individuals with T2DM. Studies were required to involve adult participants aged 18 years or older, follow a randomized design, and incorporate a placebo or control group to ensure methodological reliability. Only trials that reported relevant cardiometabolic outcomes, such as blood glucose levels, lipid profiles, blood pressure, or insulin resistance, were considered. Additionally, studies published in peer-reviewed journals and written in English were included to maintain consistency and accessibility of the findings.

Studies that did not align with these criteria were excluded. This included animal studies, ecological studies, and observational research such as cross-sectional, case-control, and cohort studies. Trials that involved participants under 18 years old or those without diabetes were

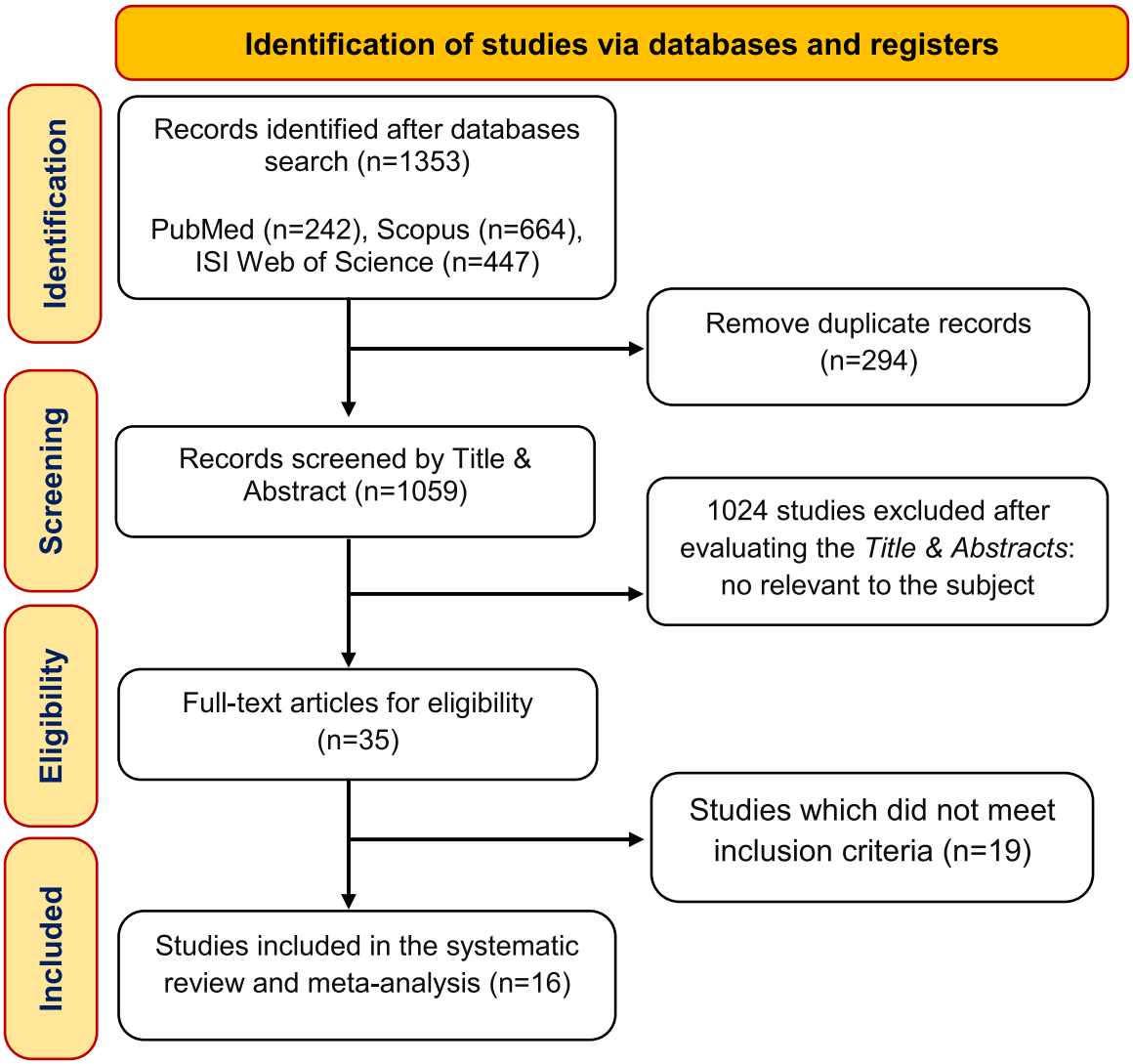

Fig. 1. PRISMA Flow chart of study selection for inclusion trials in the systematic review.

also omitted. Furthermore, studies that lacked randomization, a placebo, or a control group were not considered. Non-human research, including in vitro and in vivo studies, as well as reviews, abstracts, letters to the editor, and articles published in languages other than English, were also excluded to ensure clarity and relevance in the review.

2.4. Data extraction

The data from the included studies were meticulously screened and independently extracted by three reviewers (S.P. & B.D. & R.A.B) in accordance with the predefined inclusion criteria outlined above. Any discrepancies or disagreements encountered during the data extraction process were resolved through thorough discussion with a project supervisor (M.K.) to ensure accuracy and consistency. The extracted data encompassed several key variables, including the name of the first author, year of publication, study design, characteristics of participants (mean age, gender), sample sizes, country setting, and the mean ± standard deviation (SD) of changes observed in cardiometabolic indices. These indices included fasting blood glucose (FBG), 2-hour postprandial glucose (2-hpp), insulin levels, hemoglobin A1C (HbA1c), homeostasis model assessment (HOMA-IR), homeostasis model assessment of pancreatic beta cell function (HOMA-β), triglyceride (TG), total cholesterol (TC), low-density lipoproteins cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), body weight, and body mass index (BMI) were extracted for both intervention and control groups. This comprehensive data collection approach was critical to enable a robust analysis of the studies.

2.5. Quality assessment

Three researchers (S.P., B.D., and R.A.B.) evaluated the methodological quality of the included studies using the Revised Cochrane Risk-of-Bias Tool for RCTs (RoB-2). Discrepancies were resolved through discussion, with a fourth reviewer (M.K.) providing final decisions when needed. The RoB-2 tool assesses multiple bias domains, including randomization, intervention deviations, missing data, outcome measurement, and result selection, ensuring the reliability and validity of the studies.

2.6. Statistical analyses

The difference between the mean values of the baseline and endpoint variables in each arm was extracted, and the mean difference (MD) along with the standard deviation (SD) of the difference between the two arms was selected as the effect size.[27] If the difference between baseline and endpoint values was not directly reported in the study, the change in mean and related SD was calculated using the following formula: SD

Table 2
General characteristics of included studies in the meta-analysis.

Study	Country	Study design	Participants	Sample size (Int. / Cont.)	Gender (male/ female)	Age (Int./ Cont.)	Type of Nigella	Dose (gr/ day)	Duration
Ghods et al. 2024	Iran	RCT, DB	T2DM	79 (39 / 40)	M: 34 / F: 35	57 / 58	Oil	2	12
Rahmani et al. 2022	Iran	RCT, DB	T2DM, Diabetic Hemodialysis	41 (20 / 21)	M: 23 / F: 18	49 / 48	Oil	2	12
Assaad-Khalil et al. 2022	Egypt	RCT, DB	T2DM	198 (65 +69 [134] / 64)	M: 32 / F: 23	50 / 49	Powder	1 & 1.25	12
Hadi et al. 2021	Iran	RCT, DB	T2DM	43 (23 / 20)	M: 20 / F: 23	51 / 56	Oil	1	8
Jangjo-Borazjani et al. 2021	Iran	RCT, DB	T2DM	20 (10 / 10)	M: 0 / F: 20	44 / 42 43 / 44	Crushed seed	2	8
Kooshki et al. 2020	Iran	RCT, DB	T2DM	50 (27 / 23)	M: 16 / F: 34	52 / 55	Oil	1	8
Moustafa et al. 2019	Egypt	RCT, DB	T2DM	44 (21 / 23)	NR	NR	Oil	1.35	12
Alam et al. 2019	India	RCT, DB	T2DM, Diabetic Nephropathy	62 (30 / 32)	M: 29 / F: 33	47 / 47	Oil	2.5	12
Ansari et al. 2017	India	RCT, DB	T2DM	63 (32 / 31)	NR	53 / 48	Oil	2.5	12
Kaatabi et al. 2015	Saudi Arabia.	RCT, SB	T2DM	114 (57 / 57)	M: 63 / F: 51	46 / 46	Powder	2	48
Heshmati et al. 2015	Iran	RCT, DB	T2DM	72 (36 / 36)	M: 33 / F: 39	45 / 47	Oil	3	12
Bamosa et al. 2015	Saudi Arabia.	RCT, SB	T2DM	60 (30 / 30)	NR	46 / 47	Powder	2	48
Hosseini et al. 2013	Iran	RCT, DB	T2DM	70 (35 / 35)	M: 30 / F: 40	48 / 50	Oil	5	12
Najmi et al. 2012	Iran	RCT, DB	T2DM	80 (40 / 40)	M: 42 / F: 38	NR	Powder	0.5	8
Memon et al. 2012	Pakistan	RCT, DB	T2DM, MetS (HbA1C >7 %)	100 (50 / 50)	M: 50 / F: 50	48 / 51	Powder	0.5–1	12
Memon et al. 2010	Pakistan	RCT, DB	T2DM	100 (50 / 50)	M: 50 / F: 50	48 / 51	Powder	0.5–1	12

(**Ref.**: references, **RCT**: randomized clinical trial, **SB**: Single-blind, **DB**: Double-blind; **Int**: Intervention; **Cont**: Control; **T2DM**: type 2 diabetes mellitus, **MetS**: metabolic syndrome, **NR**: not reported).

change = square root [(SD baseline^2 + SD final^2) - (2 × 0.5 × SD baseline × SD final)].[28] The MDs were pooled using the random-effects model with restricted maximum likelihood estimation. Heterogeneity across the articles was evaluated using Cochrane's Q statistic and Hedges' I^2 estimation.[29] The observed between-study heterogeneity was classified based on the I^2 estimation into low (I^2 less than 40 %), moderate (I^2 between 40 % and 60 %), substantial (60–80 %), and high (I^2 more than 80 %) heterogeneity. Subgroup analysis was performed based on black seed form, intervention duration, and dosage to identify potential sources of heterogeneity.

The risk of publication bias was assessed visually through funnel plots and statistically using Begg's[30] and Egger's[31] tests. If a high probability of publication bias was detected, the trim-and-fill method was applied to address potential bias and missing studies.[32] Meta-regression analysis was conducted to examine the impact of the year of publication, sample size, dosage, and duration of treatment on the pooled effect sizes. Statistical tests with a p-value of less than 0.05 were considered significant. All analyses were performed using R Statistical Software with the "meta" package (v4.4.2; R Core Team 2023).

3. Results

3.1. Study selection

The initial electronic search yielded 1353 articles, of which 294 were excluded due to duplicate titles. Then, 1024 of the 1059 studies were excluded because of unrelated topics. The remaining 35 studies were retrieved for further full-text evaluations, and 19 were excluded, mainly due to insufficient or missing data. Finally, 16 RCTs were selected for the systematic review, all used in the final meta-analysis. The details regarding the literature search and study selection process are presented in Fig. 1.

3.2. Basic characteristics

The characteristics of the included RCTs are presented in Table 2. Data were collected from 16 eligible studies involving 18 effect sizes. In total, there were 1215 participants (579 in the intervention group and 636 in the control group), with a range age of 18–60 years. All articles employed a parallel design and included participants of both genders. These RCTs were conducted in Iran,[14,21,33–38], Egypt,[39,40] India,[41–43] and Saudi Arabia[15,44] and were published between 2010 and 2024. The dosage of black seed supplementation varied from 0.5 to 5 (gr/day or ml/day), with intervention trial durations ranging from 8 to 48 weeks, administered the supplement in oil form, while others utilized black seed powder.

3.3. Quality assessment

The quality assessment of the included studies reveals that most trials exhibited a low risk of bias across the evaluated domains, indicating high methodological rigor. However, a few studies, such as Bamosa et al. (2015),[15] had a high risk of bias in domains related to the randomization process (D1) and selection of the reported result (D5). Overall, the majority of studies demonstrated robust quality, supporting the reliability of the meta-analysis findings (Fig. 2).

4. Meta-analysis of black seed on cardiometabolic indices in patients with T2DM

4.1. Effect of black seed on glycemic markers

The pooled analysis, conducted using a random-effects model, demonstrated that black seed supplementation significantly reduced FBG (MD: −21.43 mg/dL; 95 % CI: −35.28, −7.57; $p = 0.005$; I^2 = 93.5 %)[21,33–45] and HbA1c (MD: −0.44; 95 % CI: −0.80, −0.08; $p = 0.01$; $I^2 = 69.6$ %) levels.[15,21,33,34,36,37,39–41,44] However, no significant differences were found in the 2-hpp (MD: −4.15 mg/dL; 95 % CI: −33.75, 25.43; $p = 0.73$; $I^2 = 76.2$ %),[33,39–43] fasting insulin (MD: 0.16; 95 % CI: −5.08, 5.41; $p = 0.93$; I^2 = 90.8 %),[21,34,36,38,39] HOMA-IR (MD: −0.39 mg/dL; 95 % CI: −1.74, 0.95; $p = 0.50$; $I^2 = 80.1$ %),[34,36,38–40,44] and HOMA-β (MD: 1.07 mg/dL; 95 % CI: −11.93, 14.09; $p = 0.82$; I^2 = 49.8 %)[38–40,44] among the intervention and control groups (Fig. 3).

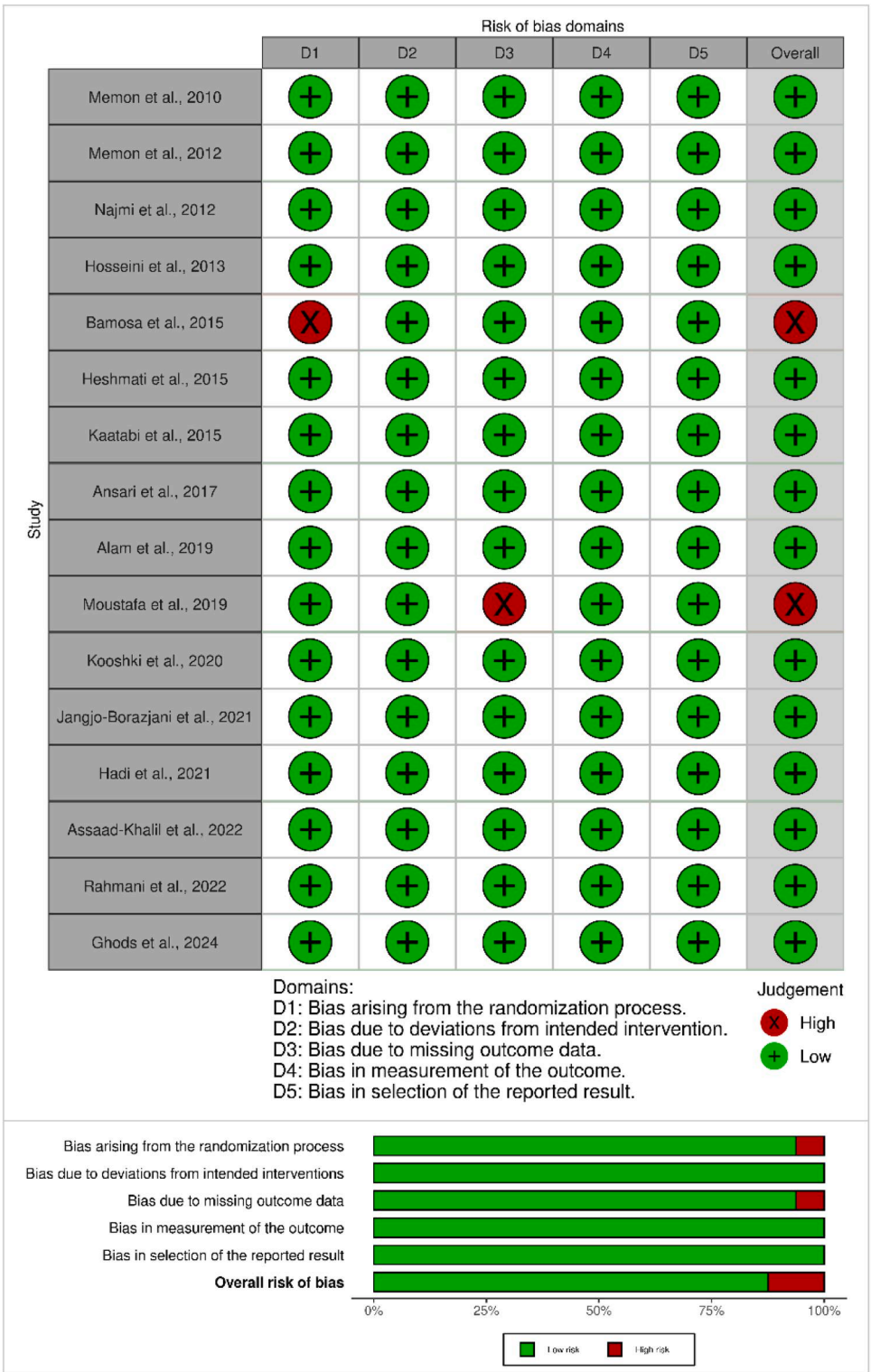

Fig. 2. Quality assessment of studies according to Cochrane risk-of-bias 2 (RoB-2).

Subgroup analyses revealed that black seed supplementation effectively lowered FBG when administered for more than 8 weeks, at a dosage exceeding 1 gr/day, and in oil form. Additionally, a significant reduction in HbA1c was observed when the black seed dosage was greater than 1 gr/day. Moreover, a notable decrease in HOMA-IR was evident when the duration of intervention was 8 weeks or less (Table 3, Supplementary Figure).

4.2. *Effect of black seed supplementation on lipid profile*

Overall pooled analysis reported a significant effect of black seed supplementation on TC (MD: −18.80 mg/dL; 95 % CI: −37.09, −0.51; $p = 0.04$; $I^2 = 73.5$ %)[33–36,38,39] and LDL-C (MD: −19.53 mg/dL; 95 % CI: −30.41, −8.66; $p = 0.003$; $I^2 = 67.5$ %)[33–36,38,39,41] in patients with T2DM. However, there was no significant difference in TG (MD: −13.88 mg/dL; 95 % CI: −39.56, 11.79; $p = 0.24$; $I^2 = 85.2$ %)[33–36,38,

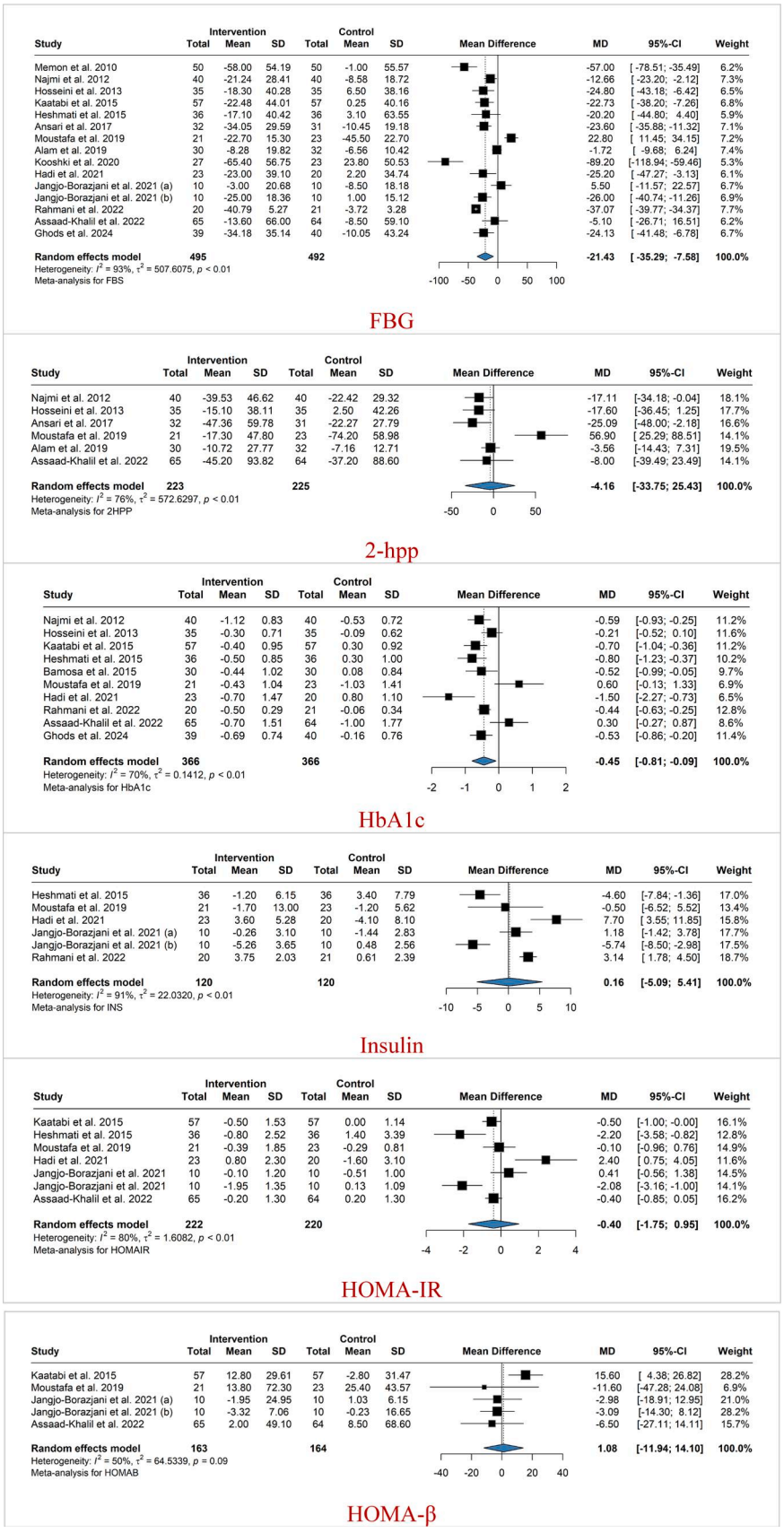

Fig. 3. Forest plot demonstrating the mean difference (MD) with 95 % confidence intervals (CIs) for the effects of black seed supplementation on glycemic markers, including fasting blood glucose (FBG), 2-hour postprandial glucose test (2-hpp), Hemoglobin A1c (HbA1c), Insulin, Homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of pancreatic beta cell function (HOMA-β).

Table 3
Meta-analysis findings for the effects of black seeds supplementation on cardiometabolic indices in individuals with type 2 diabetes.

Group	No. of effect size	Mean difference	95 % CI (Lower – Upper limits)	P value[1]	Heterogeneity (I^2)	P value[2]
FBG (mg/dl)						
Overall	15	−21.43	(−35.28 – −7.57)	**0.005** *	93.5 %	< 0.01
Oil	11	−20.75	(−38.92 – −2.57)	**0.03** *	94.8 %	< 0.01
Powder	4	−23.73	(−59.01 – 11.54)	0.12	80.2 %	< 0.01
> 8 weeks	10	−18.85	(−34.23 – −3.47)	**0.02** *	94.8 %	< 0.01
≤ 8 weeks	5	−27.86	(−70.70 – 14.96)	0.15	87.4 %	< 0.01
> 1 gr	11	−20.54	(−38.61 – −2.47)	**0.03** *	94.8 %	< 0.01
≤ 1 gr	4	−24.37	(−60.26 – 11.51)	0.12	80.3 %	< 0.01
HbA1c (%)						
Overall	10	−0.44	(−0.80 – −0.08)	**0.01** *	69.6 %	< 0.01
Oil	6	−0.47	(−1.12 – 0.17)	0.14	67.4 %	< 0.01
Powder	4	−0.42	(−1.10 – 0.26)	0.12	75.2 %	< 0.01
> 8 weeks	8	−0.35	(−0.71 – 0.01)	0.06	67.7 %	< 0.01
≤ 8 weeks	2	−0.97	(−6.69 – 4.73)	0.27	77.7 %	< 0.01
> 1 gr	7	−0.44	(−0.77 – −0.11)	0.02	60.4 %	< 0.01
≤ 1 gr	3	−0.57	(−2.75 – 1.61)	0.38	86.1 %	< 0.01
2-hpp (mg/dl)						
Overall	6	−4.15	(−33.75 – 25.43)	0.73	76.2 %	< 0.01
Oil	4	1.07	(−55.98 – 58.13)	0.96	84.6 %	< 0.01
Powder	2	−15.04	(−63.53 – 33.45)	0.16	0.0 %	0.58
> 8 weeks	5	−0.95	(−39.76 – 37.86)	0.95	79.5 %	< 0.01
≤ 8 weeks	1					
> 1 gr	4	1.078	(−55.98 – 58.13)	0.96	84.6 %	< 0.01
≤ 1 gr	2	−15.04	(−63.53 – 33.45)	0.16	0.0 %	< 0.01
HOMA-IR						
Overall	7	−0.39	(−1.74 – 0.95)	**0.50**	80.1 %	< 0.01
Oil	5	−0.35	(−2.66 – 1.96)	0.70	86.7 %	< 0.01
Powder	2	−0.44	(−1.07 – 0.18)	0.07	0.0 %	0.63
> 8 weeks	4	−0.48	(−1.22 – 0.25)	0.13	56.2 %	< 0.01
≤ 8 weeks	3	0.18	(−5.34 – 5.71)	0.90	91.2 %	< 0.01
> 1 gr	5	−0.81	(−2.24 – 0.60)	0.19	77.9 %	< 0.01
≤ 1 gr	2	0.88	(−16.84 – 18.60)	0.64	90.3 %	< 0.01
Overall	5	1.07	(−11.93 – 14.09)	0.82	49.8 %	0.04
Oil	3	−3.58	(−9.85 – 2.68)	0.13	0.0 %	0.78
Powder	2	6.31	(−132.29 – 144.91)	0.67	70.6 %	< 0.01
> 8 weeks	3	3.253	(−33.44 – 39.95)	0.74	58.2 %	< 0.01
≤ 8 weeks	2	−3.05	(−3.71 – −2.39)	**0.01** *	0.0 %	0.49
> 1 gr	4	2.34	(−15.27 – 19.96)	0.70	57.8 %	< 0.01
≤ 1 gr	1					
Fasting Insulin						
Overall	6	0.16	(−5.08 – 5.41)	0.93	90.8 %	< 0.01
Oil	6	0.16	(−5.08 – 5.41)	0.93	90.8 %	< 0.01
Powder	0					
> 8 weeks	3	−0.47	(−10.62 – 9.66)	0.86	89.6 %	< 0.01
≤ 8 weeks	3	0.92	(−15.68 – 17.52)	0.83	93.4 %	< 0.01
> 1 gr	5	−1.22	(−6.09 – 3.64)	0.52	90.9 %	< 0.01
≤ 1 gr	1					
TG (mg/dl)						
Overall	9	−13.88	(−39.56 – 11.79)	0.24	85.2 %	< 0.01
Oil	7	−22.12	(−51.62 – 7.38)	0.12	82.6 %	< 0.01
Powder	2	13.45	(−247.67 – 274.57)	0.63	83.6 %	< 0.01
> 8 weeks	4	−2.77	(−34.03 – 28.47)	0.80	62.7 %	< 0.01
≤ 8 weeks	5	−22.68	(−75.11 – 29.74)	0.30	90.8 %	< 0.01
> 1 gr	6	−20.17	(−56.46 – 16.10)	0.21	84.5 %	< 0.01
≤ 1 gr	3	−2.32	(−87.05 – 82.40)	0.92	88.9 %	< 0.01
TC (mg/dl)						
Overall	7	−18.80	(−37.09 – −0.51)	**0.04** *	73.5 %	< 0.01
Oil	7	−18.80	(−37.09 – −0.51)	**0.04** *	73.5 %	< 0.01
Powder	0					
> 8 weeks	3	−10.82	(−55.62 – 33.96)	0.41	75.0 %	< 0.01
≤ 8 weeks	4	−25.37	(−59.54 – 8.80)	0.10	74.7 %	< 0.01
> 1 gr	6	−19.23	(−42.21 – 3.73)	0.08	77.6 %	< 0.01
≤ 1 gr	1					
LDL-C (mg/dl)						
Overall	8	−19.53	(−30.41 – −8.66)	**0.003** *	67.5 %	< 0.01
Oil	7	−16.39	(−27.25 – −5.53)	**0.01** *	48.7 %	0.19
Powder	1					
> 8 weeks	3	−13.64	(−54.63 – 27.34)	0.29	56.5 %	< 0.01
≤ 8 weeks	5	−22.07	(−36.87 – −7.27)	**0.01** *	71.8 %	< 0.01
> 1 gr	6	−14.93	(−28.65 – −1.21)	**0.04** *	48.9 %	0.29
≤ 1 gr	2	−28.28	(−109.98 – 53.41)	0.14	69.7 %	< 0.01
HDL-C (mg/dl)						
Overall	9	1.97	(−1.14 – 5.09)	0.18	71.1 %	< 0.01

(*continued on next page*)

Table 3 (*continued*)

Group	No. of effect size	Mean difference	95 % CI (Lower – Upper limits)	P value[1]	Heterogeneity (I^2)	P value[2]
Oil	7	2.39	(−2.06 – 6.85)	0.24	76.4 %	< 0.01
Powder	2	1.26	(−10.33 – 12.87)	0.40	11.3 %	0.42
> 8 weeks	5	2.57	(−2.68 – 7.83)	0.22	68.5 %	< 0.01
≤ 8 weeks	4	1.66	(−4.55 – 7.88)	0.50	73.5 %	< 0.01
> 1 gr	6	2.93	(−2.47 – 8.34)	0.22	78.2 %	< 0.01
≤ 1 gr	3	1.04	(−2.02 – 4.11)	0.28	0.0 %	0.42
AST (mg/dl)						
Overall	4	0.52	(−2.34 – 3.39)	0.59	17.9 %	0.66
Oil	4	0.52	(−2.34 – 3.39)	0.59	17.9 %	0.66
Powder	0					
> 8 weeks	2	0.52	(−4.35 – 5.39)	0.40	0.0 %	0.79
≤ 8 weeks	2	0.23	(−25.22 – 25.6)	0.93	71.6 %	< 0.01
> 1 gr	4	0.52	(−2.34 – 3.39)	0.59	17.9 %	0.66
≤ 1 gr	0					
ALT (mg/dl)						
Overall	4	−3.28	(−9.81 – 3.25)	0.20	71.6 %	< 0.01
Oil	4	−3.28	(−9.81 – 3.25)	0.20	71.6 %	< 0.01
Powder	0					
> 8 weeks	2	−0.33	(−7.11 – 6.44)	0.64	0.0 %	0.70
≤ 8 weeks	2	−6.58	(−28.61 – 15.44)	0.16	8.1 %	0.69
> 1 gr	4	−3.28	(−9.81 – 3.25)	0.20	71.6 %	< 0.01
≤ 1 gr	0					
Creatinine (mg/dl)						
Overall	5	−0.07	(−0.18 – 0.03)	0.12	56.9 %	< 0.01
Oil	4	−0.09	(−0.20 – 0.01)	0.07	50.8 %	< 0.01
Powder	1					
> 8 weeks	5	−0.07	(−0.18 – 0.03)	0.12	56.9 %	< 0.01
≤ 8 weeks	0					
> 1 gr	4	−0.09	(−0.20 – 0.01)	0.07	50.8 %	< 0.01
≤ 1 gr	1					
Weight (Kg)						
Overall	5	−0.25	(−3.64 – 3.14)	0.84	48.1 %	0.10
Oil	4	−1.03	(−7.84 – 5.78)	0.66	60.8 %	< 0.01
Powder	1					
> 8 weeks	3	−0.02	(−5.17 – 5.12)	0.96	53.4 %	< 0.01
≤ 8 weeks	2	−2.89	(−67.14 – 61.36)	0.67	69.2 %	< 0.01
> 1 gr	4	−1.03	(−7.84 – 5.78)	0.66	60.8 %	< 0.01
≤ 1 gr	1					
BMI (Kg/m^2)						
Overall	8	−0.60	(−1.51 – 0.30)	0.16	0.0 %	0.45
Oil	6	−1.20	(−2.42 – 0.02)	**0.05**	0.0 %	0.49
Powder	2	0.10	(−0.63 – 0.84)	0.32	0.0 %	0.55
> 8 weeks	5	−0.51	(−1.67 – 0.64)	0.29	0.0 %	0.43
≤ 8 weeks	3	−1.26	(−6.33 – 3.79)	0.39	20.9 %	0.19
> 1 gr	7	−0.56	(−1.59 – 0.45)	0.23	7.7 %	0.40
≤ 1 gr	1					

(**FBG**: fasting blood glucose, **HbA1c**: hemoglobin A1c, **2-hpp**: 2-hour postprandial blood glucose, **HOMA-IR**: homeostatic model assessment for insulin resistance, **HOMA-β**: homeostasis model assessment-beta cell, **BMI**: body mass index, **TG**: triglyceride, **TC**: total cholesterol, **LDL-C**: low-density-lipoproteins cholesterol, **HDL-C**: high-density-lipoproteins cholesterol, **AST**: aspartate aminotransferase, **ALT**: alanine aminotransferase)
1 p-value of MD between surgical and non-surgical treatments of variables based on the random effect model
2 p-value of heterogeneity based on Cochran's Q

[39,41,46] and HDL-C (MD: 1.97 mg/dL; 95 % CI: −1.14, 5.09; P = 0.18; P-heterogeneity < 0.01, I^2 = 71.1 %)[33–36,38,39,41,46] levels between the intervention and control groups (Fig. 4).

The results of the subgroup analyses indicated that LDL-C reduction significantly in those who intervened with the oil form of the black seed and ≤ 8 weeks (Table 3, Supplementary Figure).

4.3. Effect of black seed supplementation on AST, ALT, and creatinine

The findings from the random-effect model revealed that AST (MD: 0.52 mg/dL; 95 % CI: −2.34, 3.39; $p = 0.59$; I^2 = 17.9 %),[33,38,39] ALT (MD: −3.28 mg/dL; 95 % CI: −9.81, 3.25; $p = 0.20$; I^2 = 71.6 %)[33,38,39] and creatinine (MD: −0.07 mg/dL; 95 % CI: −0.18, 0.03; $p = 0.12$; I^2 = 56.9 %)[33,39,42,43,46] didn't change after black seed supplementation (Fig. 5). In addition, no significant change was seen after subgroup analyses (Table 3, Supplementary Figure).

4.4. Effect of black seed supplementation on body weight and BMI

No significant effect of black seed was revealed on body weight (MD: −0.25 mg/dL; 95 % CI: −3.46, 3.14; $p = 0.84$; I^2 = 48.1 %)[34,38–40] BMI (MD: −0.60 kg/m^2; 95 % CI: −1.51, 0.30; $p = 0.16$; I^2 = 0 %)[15,33,34,36,38,39] (Fig. 6). Furthermore, we observed no significant changes between groups on subgroup analyses (Table 3, Supplementary Figure).

4.5. Sensitive analysis

Sensitive analysis for 2-hpp and HOMA-β indicated that the overall effect size was changed by excluding studies performed by Moustafa et al.[39] (MD: −12.40; 95 % CI: −23.40, −1.32) and Kaatabi et al.[44] (MD: −4.04; 95 % CI: −8.02, −0.05) respectively. In addition, the overall effect size of TC was influenced by removing Hosseini et al.[33] (MD: −20.02; 95 % CI: −43.04; 3.01) Heshmati et al.[34] (MD: −17.59; 95 % CI: −39.77; 4.59), Kooshki et al.[35] (MD: −13.03; 95 % CI: −26.92, 0.87), Hadi et al.[36] (MD: −19.24; 95 % CI: −42.22, 3.74) Jangjo-Borazjani

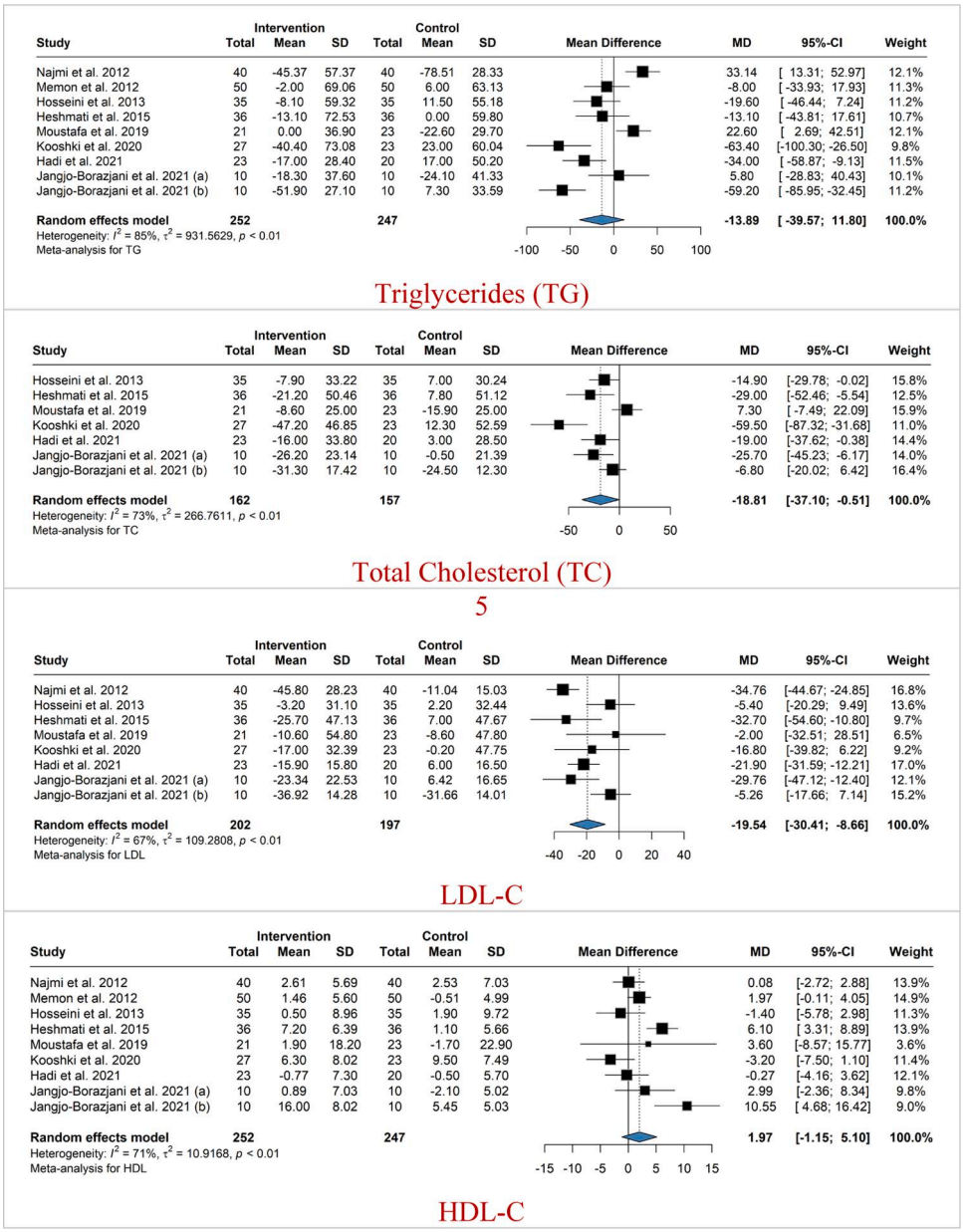

Fig. 4. Forest plot demonstrating the mean difference (MD) with 95 % confidence intervals (CIs) for the effects of black seed supplementation on lipid profile, including triglycerides (TG), total cholesterol (TC), low-density lipoproteins cholesterol (LDL-C), high-density lipoproteins cholesterol (HDL-C).

et al.[38] (MD: −17.59; 95 % CI: −43.04, 3.01), studies. However, the overall effect size didn't alter after sensitive analysis for FBG, HbA1c, insulin, HOMA-IR, TG, LDL-C, HDL, AST, ALT, creatinine, BMI, and weight (Fig. 7).

4.6. Publication bias

The funnel plot exhibited asymmetry for FBG and HbA1c (Supplementary Figure). Although, the results from Egger's and Begg's tests did not indicate publication bias (Fig. 8).

4.7. Meta-regression analysis

The meta-regression finding indicated no significant association between the year of publication, sample size, age, FBG, and HbA1c levels (Supplementary Table).

5. Discussion

This meta-analysis assessed the impact of black seed supplementation on cardiometabolic factors in individuals with T2DM. The results suggest that black seed supplementation may contribute to improved glycemic control, as evidenced by reductions in FBG and HbA1c levels. Additionally, beneficial effects on lipid metabolism were observed, with significant decreases in TC and LDL cholesterol. Interestingly, when the supplementation period was 8 weeks or less, an increase in HOMA-β was noted, indicating a potential short-term enhancement in pancreatic β-cell function. Despite these promising findings, no significant effects were detected on 2-hpp, triglycerides, HDL-C, liver enzymes, creatinine levels, body weight, or BMI. These results suggest that while black seed supplementation may support certain aspects of cardiometabolic health, its effects may be limited to specific biomarkers and dependent on the duration of use. Further research is needed to explore the long-term impact, optimal dosage, and mechanisms underlying these effects to better understand its potential role as a complementary therapy for

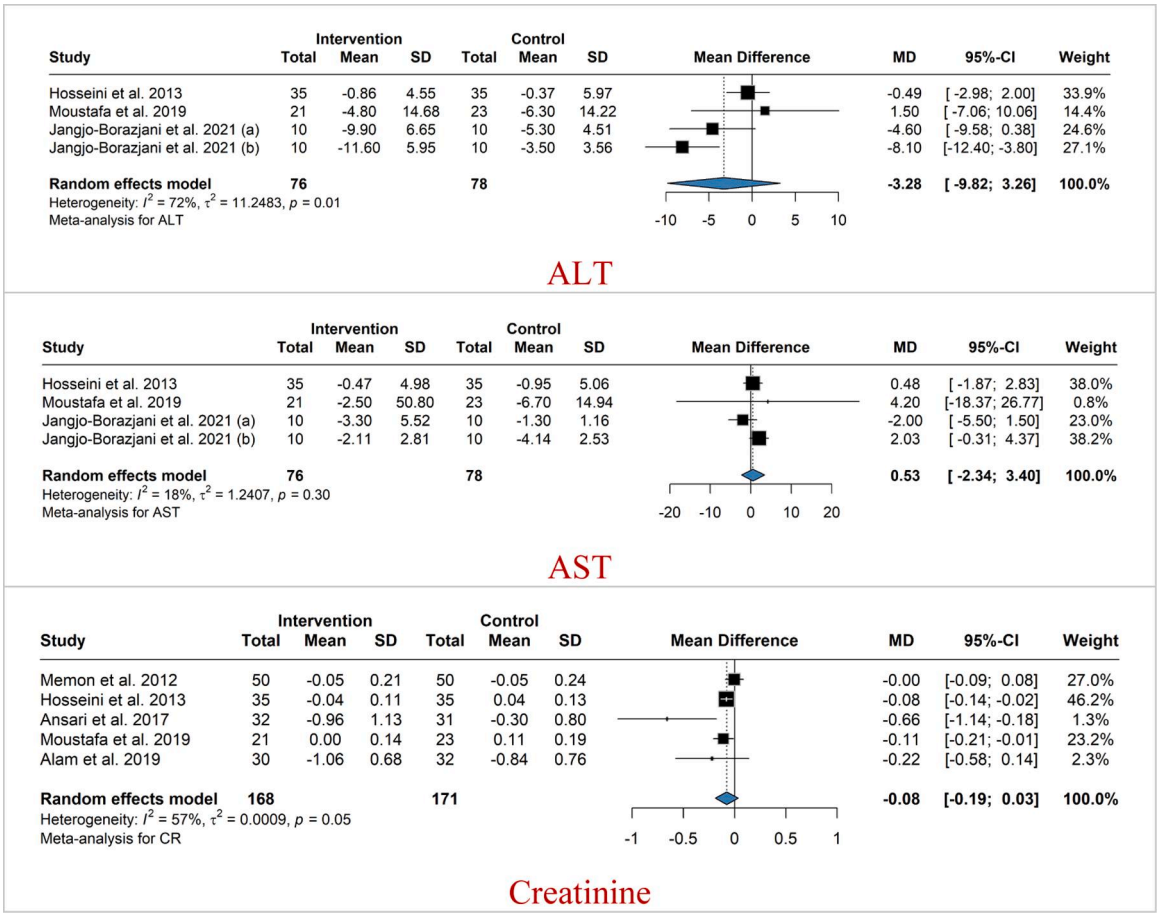

Fig. 5. Forest plot demonstrating the mean difference (MD) with 95 % confidence intervals (CIs) for the effects of black seed supplementation on aspartate aminotransferase (AST), alanine aminotransferase (ALT), and Creatinine.

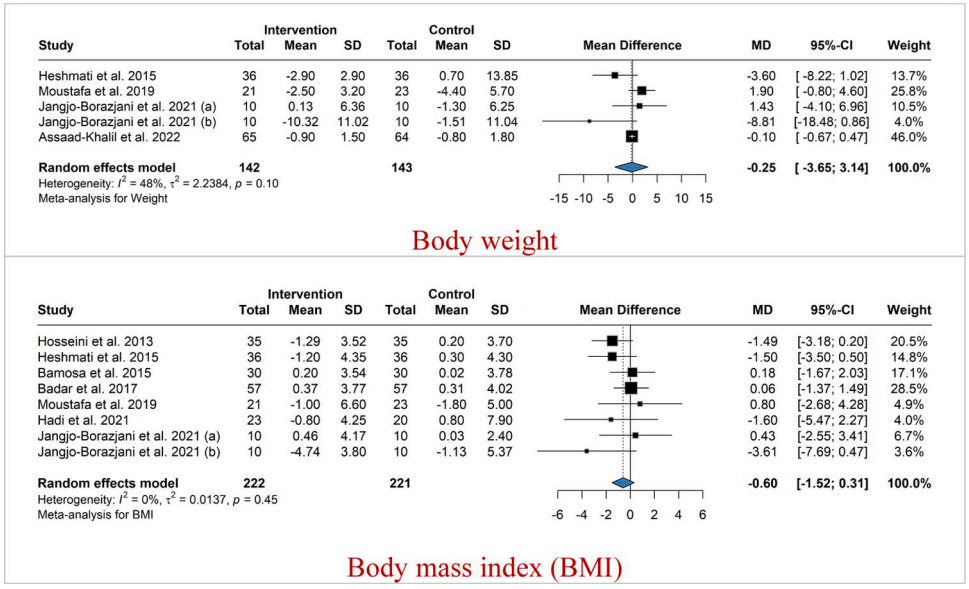

Fig. 6. Forest plot demonstrating the mean difference (MD) with 95 % confidence intervals (CIs) for the effects of black seed supplementation on body weight (BW) and body mass index (BMI).

T2DM management.

Our findings were consistent with previous studies, including the study conducted by Khotbehsara et al., which demonstrated the hypoglycemic effects of black seed.[47] and Saadati et al.[25]; black seed intervention led to a decrease in FBG and HbA1c levels in T2DM. Moreover, in another meta-analysis on diabetic and non-diabetic individuals, FBG and AbA1c declined after black seed supplementation.[48]

Literature has exhibited the significant anti-inflammatory and anti-

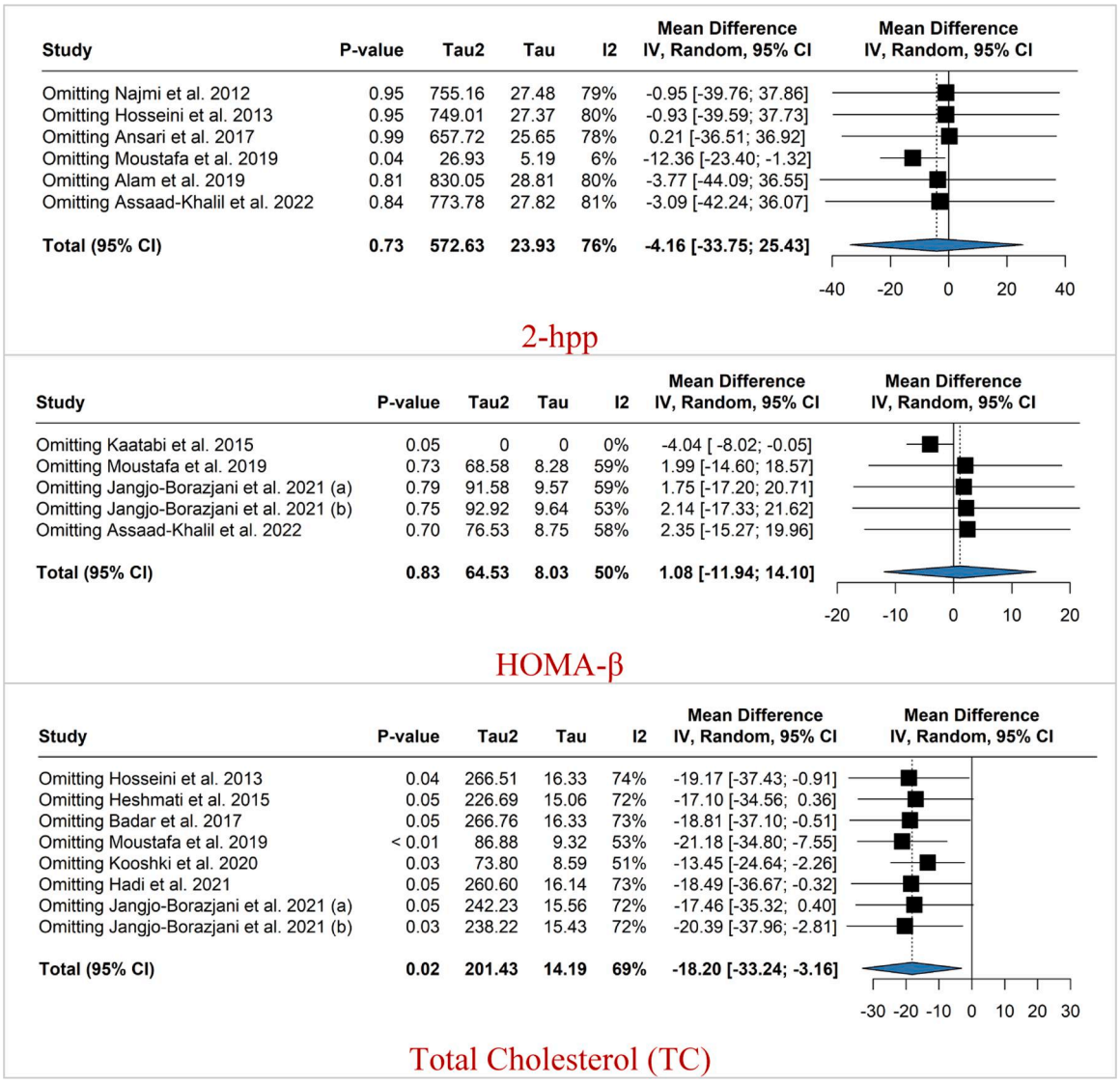

Fig. 7. Sensitive analysis of 2-hour postprandial glucose test (2-hpp), homeostasis model assessment of pancreatic β cell function (HOMA-β), and total cholesterol (TC).

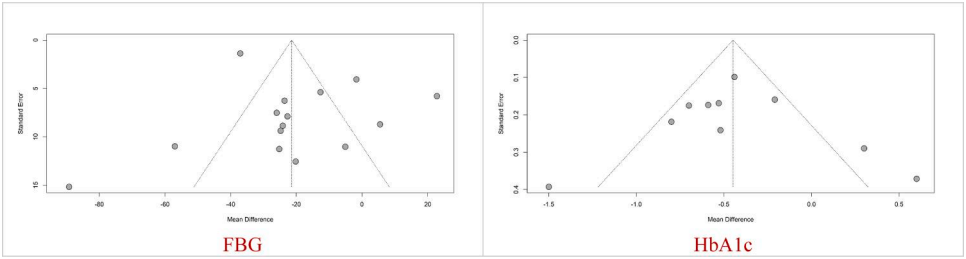

Fig. 8. Funnel plot of publication bias of fast blood glucose (FBG), hemoglobin A1c (HbA1c).

oxidative properties of black seed,[49,50] which may influence glycemic metabolism through several mechanisms. First, the antioxidant effects of thymoquinone, the bioactive compound found in black seed, improve pancreatic beta cells, leading to increased insulin secretion and enhanced glucose uptake by tissues.[51] Second, thymoquinone may reduce the expression of fructose 2,6-bisphosphatase and glucose 6-phosphatase, which helps decrease gluconeogenesis.[52] Third, it activates the AMP-activated protein kinase (AMPK) pathway, which improves insulin release.[53] Fourth, thymoquinone reduces glucose absorption by inhibiting sodium-glucose co-transporters and decreasing intestinal glucose absorption.[18] Notably, since thymoquinone is fat-soluble, black seed oil may be more effective than its aqueous extract.

It is suggested that individuals with T2DM are prone to developing dyslipidemia. However, the beneficial effect of black seed on dyslipidemia is controversial.[54–56] Our findings demonstrate a significant reduction in TC and LDL after black seed consumption. However, we found no significant changes in TG and HDL cholesterol. This is

consistent with recent meta-analyses which reported a significant effect of black seed on decreasing TC and LDL without affecting TG and HDL cholesterol levels.[25,47]

Contrary to our findings, previous meta-analyses on healthy and unhealthy individuals indicated a significant reduction in TG levels after black seed intervention.[48] An additional meta-analysis of 8 RCTs showed that black seed intervention decreased TC and LDL while increasing HDL cholesterol levels in patients with T2DM.[57] These discrepancies may be attributed to variations in the number of included articles and differences in the study populations. The lowering effect of black seed on lipid profile may be attributed to its ingredients. Polyunsaturated fatty acids (PUFAs) such as linoleic acid could inhibit the release of very low-density lipoproteins and hormone-sensitive lipase. It can also enhance fatty acid oxidation and destroy apo-B100.[58] Additionally, the ethanol extract of black seed can activate the PPAR-gamma gene,[59] which increases the expression of CD36 (a cellular scavenger receptor for atherogenic LDL)[60] and ATP-binding cassette transporter A1 (involved in cholesterol efflux from macrophages).[61] Black seed is also known to regulate insulin receptors in hepatocytes and improve LDL uptake.[62] Furthermore, the highly soluble fibers and sterols of black seed can reduce cholesterol absorption and increase bile production.[63,64] Flavonoids and thymoquinone in black seed decrease cholesterol by inhibiting the expression of the HMG-COAR gene.[65]

Inflammatory, oxidative stress, and insulin resistance are involved in diabetic complications that can lead to hepatic and renal dysfunction.[66,67] Elevated liver enzymes, such as ALT and AST, indicate liver damage.[68] Some studies have suggested that black seed may help reduce these enzymes.[22,38] An RCT found that consuming 2 g per day of black seed reduced inflammatory biomarkers in NAFLD patients.[50] However, previous meta-analyses of both healthy and unhealthy participants have not shown any effect of black seed intervention on ALT and AST[23,24]Our results agree with the previous meta-analysis. Differences among studies may be due to participant variations, black seed dosage, and duration of consumption.

Additionally, elevated creatinine levels have been associated with renal failure.[69] It has been suggested that thymoquinone, an active component of black seed, may prevent the development of renal dysfunction by reducing oxidative stress and preserving the activity of antioxidant enzymes.[70] However, our meta-analysis found that black seed supplementation didn't change creatinine levels. Similar results have been shown in previous studies.[33,39]

Available studies suggest that black seed supplementation may have an anti-obesity effect by suppressing appetite.[71,72] Two previous meta-analyses indicated that black seed supplementation in the general population decreased weight and BMI.[73,74] However, our findings did not demonstrate a beneficial effect on them, which was consistent with another meta-analysis conducted by Saadati et al.[25] which also did not show a reduction in BMI among patients with T2DM. The discrepancies in results may be attributed to differences in the populations studied and the measuring method. Furthermore, to obtain accurate results, it is advisable to assess calorie intake before and after the intervention.

In the current meta-analysis, we included 16 RCTs with various cardiometabolic factors. Moreover, subgroup analyses were conducted according to dose, duration, and form of blackseed supplementation. In addition, we evaluated publication bias by the results of Egger's test, and no evidence of publication bias was revealed, which caused more reliability in our results. However, some limitations should be acknowledged. Most of the studies were conducted in Asia, which may limit the generalizability of the results. Additionally, there was a high degree of heterogeneity among the studies; these variations could be attributed to differences in methodologies, sample sizes, the ages of participants, dosages, durations, and forms of black seed used. Furthermore, we could not consider some confounders, such as smoking status, types of medical treatment, and duration of diabetes, due to a lack of sufficient information.

6. Conclusion

In conclusion, this meta-analysis suggests that black seed supplementation can favorably affect some cardiometabolic factors. Black seed supplementation improved glycemic factors and lipid profiles by enhancing FBG, HbA1c, TC, and LDL in adults with T2DM. However, there were no significant changes in TG, HDL, liver enzymes, creatinine, and anthropometric factors after black seed supplementation. Further studies involving diverse populations are necessary to validate these findings.

Ethical approval

Not Applicable.

Funding

None.

CRediT authorship contribution statement

Rabiee Reyhaneh: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kazemi Kimia:** Writing – original draft, Validation, Supervision, Software, Resources, Investigation, Funding acquisition, Data curation, Conceptualization. **Pirzad Samira:** Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Karimi Mehdi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Amani-Beni Reza:** Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation. **Darouei Bahar:** Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation. **Maleki Sedgi Fatemeh:** Writing – original draft, Visualization, Validation, Supervision, Investigation, Funding acquisition, Conceptualization. **Pourfaraji Seyed Morteza Ali:** Visualization, Validation, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

None.

Acknowledgement

None.

Consent to Publish

Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ctim.2025.103174.

Data availability

The data supporting this study's findings are derived from publicly available randomized controlled trials and are reported in the articles and supplementary materials. For further inquiries, please contact the corresponding authors.

References

1. Zhou B, et al. Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: a pooled analysis of 1108 population-representative studies with 141 million participants. *Lancet*. 2024;404(10467):2077–2093.
2. Fowler MJ. Microvascular and macrovascular complications of diabetes. *Clin Diabetes*. 2008;26(2):77–82.
3. Association, A.D. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014; 37(ement_1):S14–S80.
4. Organization, W.H., The WHO strategy for traditional medicine: Review of the global situation and strategy implementation in the Eastern Mediterranean Region, 2002.
5. Damavandi SA, Ashayeri N, Hesabi A. The use of complementary and alternative medicine among cancerous children: a survey at Ali Asghar Children's Hospital. *Tradit Integr Med*. 2025.
6. Meysami M, et al. Efficacy of short term topical Malva sylvestris l. cream in pediatric patients with atopic dermatitis: a randomized double-blind placebo-controlled clinical trial. *Endocr Metab Immune Disord Drug Targets*. 2021;21(9):1673–1678.
7. Drebka A, et al. Patient-reported therapeutic benefits of herbal medicinal products in the treatment of gynecological ailments. *BMC Complement Med Ther*. 2025;25(1): 99.
8. Karimi M, et al. Effect of boswellia (Boswellia serrata L.) supplementation on glycemic markers and lipid profile in type 2 diabetic patients: a systematic review and meta-analysis. *Front Clin Diabetes Health*. 2024;5:1466408.
9. Karimi M, et al. Effects of chia seed (Salvia hispanica L.) supplementation on cardiometabolic health in overweight subjects: a systematic review and meta-analysis of RCTs. *Nutr Metab (Lond)*. 2024;21(1):74.
10. Karim M, et al. Effects of saffron (Crocus sativus L.) supplementation on cardiometabolic Indices in diabetic and prediabetic overweight patients: a systematic review and meta-analysis of RCTs. *Diabetol Metab Syndr*. 2024;16(1):286.
11. Ahmad A, et al. A review on therapeutic potential of Nigella sativa: a miracle herb. *Asian Pac J Trop Biomed*. 2013;3(5):337–352.
12. Nikkhah-Bodaghi M, et al. The effects of Nigella sativa on quality of life, disease activity index, and some of inflammatory and oxidative stress factors in patients with ulcerative colitis. *Phytother Res*. 2019;33(4):1027–1032.
13. Liang Q, et al. Immunomodulatory effects of Nigella sativa seed polysaccharides by gut microbial and proteomic technologies. *Int J Biol Macromol*. 2021;184:483–496.
14. Heshmati J, Namazi N. Effects of black seed (Nigella sativa) on metabolic parameters in diabetes mellitus: a systematic review. *Complement Ther Med*. 2015;23 (2):275–282.
15. Bamosa A, et al. Nigella sativa: a potential natural protective agent against cardiac dysfunction in patients with type 2 diabetes mellitus. *J Fam Community Med*. 2015; 22(2):88–95.
16. Farzaneh E, et al. The effects of 8-week Nigella sativa supplementation and aerobic training on lipid profile and VO2 max in sedentary overweight females. *Int J Prev Med*. 2014;5(2):210.
17. Houstis N, Rosen ED, Lander ES. Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature*. 2006;440(7086):944–948.
18. Meddah B, et al. Nigella sativa inhibits intestinal glucose absorption and improves glucose tolerance in rats. *J Ethnopharmacol*. 2009;121(3):419–424.
19. Sobhi W, et al. Effect of lipid extracts of Nigella sativa L. seeds on the liver ATP reduction and alpha-glucosidase inhibition. *Pak J Pharm Sci*. 2016;29(1).
20. Fararh K, et al. Mechanisms of the hypoglycaemic and immunopotentiating effects of Nigella sativa L. oil in streptozotocin-induced diabetic hamsters. *Res Vet Sci*. 2004; 77(2):123–129.
21. Rahmani A, et al. Effect of Nigella sativa oil on oxidative stress, inflammatory, and glycemic control indices in diabetic hemodialysis patients: a randomized double-blind, controlled trial. *Evid-Based Complement Altern Med*. 2022;2022(1):2753294.
22. Abdel-Fattah A-FM, Matsumoto K, Watanabe H. Antinociceptive effects of Nigella sativa oil and its major component, thymoquinone, in mice. *Eur J Pharmacol*. 2000; 400(1):89–97.
23. Razmpoosh E, et al. The effect of Nigella sativa on the measures of liver and kidney parameters: a systematic review and meta-analysis of randomized-controlled trials. *Pharmacol Res*. 2020;156, 104767.
24. Azizi N, et al. The effects of Nigella sativa supplementation on liver enzymes levels: A systematic review and meta-analysis of randomized controlled trials. *Clin Nutr Res*. 2021;10(1):72.
25. Saadati S, et al. Nigella sativa supplementation improves cardiometabolic indicators in population with prediabetes and type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Front Nutr*. 2022;9, 977756.
26. Page MJ, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *bmj*. 2021;**372**.
27. Takeshima N, et al. Which is more generalizable, powerful and interpretable in meta-analyses, mean difference or standardized mean difference? *BMC Med Res Method*. 2014;14:30.
28. Borenstein M, et al. *Introduction to Meta-Analysis*. Wiley; 2011.
29. Higgins JP, et al. Measuring inconsistency in meta-analyses. *Bmj*. 2003;327(7414): 557–560.
30. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4), 1088-101.
31. Egger M, et al. Bias in meta-analysis detected by a simple, graphical test. *Bmj*. 1997; 315(7109):629–634.
32. Duval S. The Trim and Fill Method. *Publ Bias Meta-Anal*. 2005:127–144.
33. Hosseini, M., et al., Effects of Nigella sativa L. seed oil in type II diabetic Patients: A randomized, double-blind, placebo-controlled clinical trial, 2013..
34. Heshmati J, et al. Nigella sativa oil affects glucose metabolism and lipid concentrations in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *Food Res Int*. 2015;70:87–93.
35. Kooshki A, et al. Effect of Nigella sativa oil supplement on risk factors for cardiovascular diseases in patients with type 2 diabetes mellitus. *Phytother Res*. 2020;34(10):2706–2711.
36. Hadi S, et al. Effect of Nigella sativa oil extract on cardiometabolic risk factors in type 2 diabetes: a randomized, double-blind, placebo-controlled clinical trial. *Phytother Res*. 2021;35(7):3747–3755.
37. Ghods M, et al. Anti-diabetic effect of a combination of black seed (Nigella sativa) and cumin (Cuminum cyminum), a two-step study from bench to bed, 2767-3146, *Funct Food Sci-Online ISSN*. 2024;4(2):55–68.
38. Jangjo-Borazjani S, et al. Effects of resistance training and Nigella sativa on type 2 diabetes: implications for metabolic markers, low-grade inflammation and liver enzyme production. *Arch Physiol Biochem*. 2023;129(4):913–921.
39. Moustafa HAM, et al. Effect of Nigella sativa oil versus metformin on glycemic control and biochemical parameters of newly diagnosed type 2 diabetes mellitus patients. *Endocrine*. 2019;65:286–294.
40. Assaad-Khalil S, et al. A Phase II, Randomized, Double-Blind, Double-Dummy, Active-Controlled Clinical Trial to Investigate the Efficacy and Safety of NW Low-Glu® in Patients Newly Diagnosed with Type 2 Diabetes Mellitus. *Evid-Based Complement Altern Med*. 2022;2022(1):9176026.
41. Najmi A, et al. Therapeutic effect of Nigella sativa in patients of poor glycemic control. *Asian J Pharm Clin Res*. 2012;5(3):224–228.
42. Ansari ZM, et al. Protective role ofnigella sativain diabetic nephropathy: a randomized clinical trial. *Saudi J Kidney Dis Transplant*. 2017;28(1):9–14.
43. Alam Ma, et al. Nigella sativa oil as an add-on in the conservative management of diabetic nephropathy: a novel systematic approach. *Asian J Pharm Clin Res*. 2019;12 (10).
44. Kaatabi H, et al. Nigella sativa improves glycemic control and ameliorates oxidative stress in patients with type 2 diabetes mellitus: placebo controlled participant blinded clinical trial. *PloS One*. 2015;10(2), e0113486.
45. Memon AR, et al. Effect of combination of Nigella sativa and Trigonella foenum-graecum seeds with glibenclamide on blood sugar levels in type-2 diabetes mellitus patients. *ISRA Med J*. 2010;2:46–51.
46. Memon AR, et al. Effect of combination of Nigella sativa and Trigonella foenum-graecum with glibenclamide on serum triglyceride, HDL and creatinine levels in type-2 diabetes mellitus patients. *Pak J Pharm*. 2012;29:1–6.
47. Daryabeygi-Khotbehsara R, et al. Nigella sativa improves glucose homeostasis and serum lipids in type 2 diabetes: a systematic review and meta-analysis. *Complement Ther Med*. 2017;35:6–13.
48. Hallajzadeh J, et al. Effects of Nigella sativa on glycemic control, lipid profiles, and biomarkers of inflammatory and oxidative stress: a systematic review and meta-analysis of randomized controlled clinical trials. *Phytother Res*. 2020;34(10): 2586–2608.
49. Nikkhah-Bodaghi M, et al. The effects of Nigella sativa on quality of life, disease activity index, and some of inflammatory and oxidative stress factors in patients with ulcerative colitis. *Phytother Res*. 2019;33(4):1027–1032.
50. Darand M, et al. Nigella sativa and inflammatory biomarkers in patients with non-alcoholic fatty liver disease: results from a randomized, double-blind, placebo-controlled, clinical trial. *Complement Ther Med*. 2019;44:204–209.
51. Abdelrazek HM, et al. Black seed thymoquinone improved insulin secretion, hepatic glycogen storage, and oxidative stress in streptozotocin-induced diabetic male wistar rats. *Oxid Med Cell Longev*. 2018;2018(1):8104165.
52. Pari L, Sankaranarayanan C. Beneficial effects of thymoquinone on hepatic key enzymes in streptozotocin–nicotinamide induced diabetic rats. *Life Sci*. 2009;85(23-26):830–834.
53. Benhaddou-Andaloussi A, et al. The in vivo antidiabetic activity of Nigella sativa is mediated through activation of the AMPK pathway and increased muscle Glut4 content. *Evid-Based Complement Altern Med*. 2011;2011(1), 538671.
54. Latiff LA, et al. Alternative supplement for enhancement of reproductive health and metabolic profile among perimenopausal women: a novel role of Nigella sativa. *Iran J Basic Med Sci*. 2014;17(12):980.
55. Bilal A. Pir Mehr Ali Shah Arid Agriculture University Rawalpindi, Pakistan. *Eff Differ Prep Nigella sativa (ns) Glucose Lipid Metab Type II Diabet Patients*. 2008.
56. Badar A, et al. Effect of Nigella sativa supplementation over a one-year period on lipid levels, blood pressure and heart rate in type-2 diabetic patients receiving oral hypoglycemic agents: nonrandomized clinical trial. *Ann Saudi Med*. 2017;37(1): 56–63.
57. Aliyari M, et al. Effect of Nigella sativa supplementation on lipid profile in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Acta Biochim Iran*. 2024;1(4):166–175.
58. Calder PC. Mechanisms of action of (n-3) fatty acids. *J Nutr*. 2012;142(3): 592S–599S.
59. Benhaddou-Andaloussi A, et al. Multiple molecular targets underlie the antidiabetic effect of Nigella sativa seed extract in skeletal muscle, adipocyte and liver cells. *Diabetes, Obes Metab*. 2010;12(2):148–157.
60. Nagy L, et al. Oxidized LDL regulates macrophage gene expression through ligand activation of PPARγ. *Cell*. 1998;93(2):229–240.
61. Chawla A, et al. A PPARγ-LXR-ABCA1 pathway in macrophages is involved in cholesterol efflux and atherogenesis. *Mol Cell*. 2001;7(1):161–171.
62. Esser N, et al. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract*. 2014;105(2):141–150.
63. de Jong A, Plat J, Mensink RP. Metabolic effects of plant sterols and stanols. *J Nutr Biochem*. 2003;14(7):362–369.

64. Bilal A, et al. Effects of Nigella sativa oil on some blood parameters in type 2 diabetes mellitus patients. *Asian J Chem*. 2009;21(7):5373.
65. Al-Naqeep G, Ismail M, Yazan LS. Effects of thymoquinone rich fraction and thymoquinone on plasma lipoprotein levels and hepatic low density lipoprotein receptor and 3-hydroxy-3-methylglutaryl coenzyme A reductase genes expression. *J Funct Foods*. 2009;1(3):298–303.
66. Finelli C. and G. Tarantino, *What is the role of adiponectin in obesity related non-alcoholic fatty liver disease? World J Gastroenterol: WJG*. 2013;19(6):802.
67. Hojs R, et al. Markers of inflammation and oxidative stress in the development and progression of renal disease in diabetic patients. *Nephron*. 2016;133(3):159–162.
68. Lala V, Zubair M, Minter D. *Liver Function Tests*. StatPearls; 2023.
69. Brookes EM, Power DA. Elevated serum urea-to-creatinine ratio is associated with adverse inpatient clinical outcomes in non-end stage chronic kidney disease. *Sci Rep*. 2022;12(1):20827.
70. Sayed-Ahmed MM, Nagi MN. Thymoquinone supplementation prevents the development of gentamicin-induced acute renal toxicity in rats. *Clin Exp Pharmacol Physiol*. 2007;34(5-6):399–405.
71. Houcher Z, et al. Effects of methanolic extract and commercial oil of Nigella sativa L. on blood glucose and antioxidant capacity in alloxan-induced diabetic rats. *Pteridines*. 2007;18(1):8–18.
72. Tasawar Z, et al. The effects of Nigella sativa (Kalonji) on lipid profile in patients with stable coronary artery disease in Multan, Pakistan. *Pak J Nutr*. 2011;10(2):162–167.
73. Namazi N, et al. The effects of Nigella sativa L. on obesity: a systematic review and meta-analysis. *J Ethnopharmacol*. 2018;219:173–181.
74. Naghsh N, et al. The effect of Nigella sativa (black seed) supplementation on body weight and body composition: a GRADE-assessed systematic review and dose-response meta-analysis of randomized controlled trials. *J Funct Foods*. 2023;105,105565.