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Review Article

Effect of *Nigella sativa* Supplementation on Lipid Profile in Type 2 Diabetes: A Systematic Review and Meta-analysis of Randomized Ccontrolled Trials

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ABSTRACT

Objectives: Type 2 diabetes has become a global health burden, especially in developing nations, and is frequently linked to dyslipidemia. While various medications are available, there is a growing interest in herbal remedies such as Nigella sativa (N. sativa) as alternative treatments for type 2 diabetes. In this systematic review and meta-analysis, the objective was to assess the impact of N. sativa on the lipid profile of patients with type 2 diabetes.

Methods: Online databases, including Web of Science, Scopus, PubMed, and EMBASE, were searched. Changes in lipid profile parameters were reported as weighted mean differences, along with a 95% confidence interval. Sensitivity analysis, quality assessment, subgroup analysis, and publication bias were evaluated in the eligible studies.

Results: The study was performed on eight randomized controlled trials (RCTs) involving 1030 participants. According to the findings, supplementation of N. sativa in the form of seed powder or oil significantly reduced total cholesterol and LDL-cholesterol levels, while increasing HDL-cholesterol levels in patients with type 2 diabetes. The funnel plot exhibited visual symmetry for the studies included in the meta-analysis.

Conclusion: The findings indicate that N sativa may be beneficial as an adjunctive treatment alongside standard medications for managing dyslipidemia in individuals with type 2 diabetes.

Keywords: Diabetes mellitus, Dyslipidemia, Nigella sativa, Meta-analysis

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Introduction

Diabetes is a prevalent metabolic disorder that affects individuals of all genders, ages, and races worldwide. It has been estimated that the global prevalence of diabetes could reach 643 million cases by 2030 and 700 million by 2045 (1, 2). Diabetes is characterized by hyperglycemia resulting from dysfunction of beta cells and/or insulin resistance (3-6). Dyslipidemia is a common complication of diabetes characterized by elevated levels of cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and reduced levels of high-density lipoprotein

cholesterol (HDL-C) (7, 8). This imbalance in lipid metabolism can lead to various health problems, including atherosclerosis, coronary heart disease, and stroke (9-12). Conventional therapies, which include medications and lifestyle modifications, are often recommended to manage dyslipidemia in diabetic patients. However, these approaches may have side effects and are not always effective in controlling lipid levels (1, 13-15). Over the past three decades, there has been a significant increase in the use of herbal medicine or supplements as an alternative approach to treating diabetes (16-21). Black seed (also known as black cumin or kalonji), a traditional herbal remedy that has been used for centuries to treat various ailments, has recently garnered attention as a potential natural remedy for diabetes and its associated complications. Black seed, also known as Nigella sativa, is a plant native to Southwest Asia and the Middle East (22, 23). The chemical composition of black seed includes fixed oil (35-40%), volatile oil (0.5-1%), protein (23%), carbohydrates (33%), various amino acids, vitamins, minerals, and other substances. Substances such as thymol, thymoquinone, and di-thymoquinone are obtained from the volatile oil of black seed. Thymoquinone is one of the compounds that contributes to the significant medicinal effects of black seed (24) (Fig. 1).

N. Sativa has traditionally been used as a bronchodilator, appetite stimulant, antibacterial, diuretic, liver tonic, and analgesic. N. sativa also exerts therapeutic effects on various conditions, including hypertension, cardiovascular disease, diabetes, cancer, rheumatic disorders, gastrointestinal disorders, diarrhea, skin disorders, infections, and asthma (25-27). The plant seeds contain thymoquinone, which is a bioactive compound with anti-inflammatory, antioxidant, and lipid-lowering effects (26, 28, 29). The potential effects of N. sativa on dyslipidemia include the following: hepatic upregulation of LDL receptors, activation of peroxisome proliferator-activated receptor gamma (PPAR-γ), reduction in the absorption of nutritional LDL cholesterol, suppression of Denovo LDL cholesterol synthesis, and prevention of lipid peroxidation (30-35). Some studies have reported that supplementation with N. sativa had been related to reduced levels of serum triglycerides, total cholesterol, and elevated HDL-C concentrations. Although a few randomized controlled trials (RCTs) have been conducted, the results of these clinical studies have been controversial(32, 36-38). The team conducted a systematic review and meta-analysis of RCTs to evaluate the effect of N. sativa supplements on lipid profiles in patients with type 2 diabetes.

Materials and methods

Strategy search for the study

The present systematic review and meta-analysis were based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement guiding(39,40), which provides guidelines for conducting such studies. Two investigators independently searched electronic databases (SCOPUS, PubMed, Embase, and Web of Science) up to December 2023 to find relevant articles. We conducted a search in the databases using the following keywords: intervention ("*N. Sativa*" OR "*Sativa, Nigella*" OR "*Black Cumin*" OR "cumin" OR "*kalonjus*" OR "*kalonji*"), patients ("diabetes" OR "T2D" OR "type 2 diabetes"), and outcomes ("Low-Density Lipoprotein Cholesterol" OR "Triacylglycerol" OR "Triglycerides" OR "High-Density Lipoproteins" OR "Cholesterol" OR "total cholesterol" OR "TC" OR "LDL" OR "HDL" OR "TG"). The third researcher was used to resolve any disagreements regarding the extracted data. The wildcard "*" was used in this meta-analysis to increase the sensitivity of the search strategy. In addition, references in relevant articles were checked to find additional studies.

Inclusion and exclusion criteria for the study

This meta-analysis used the PICOS (Population, Intervention, Comparator, Outcome, Study types) approach as inclusion criteria. Population: subjects with type 2 diabetes; Intervention: N. Sativa usage (seed powder or oil); Comparator: placebo group; Outcome: measuring lipid parameters including total cholesterol, triglycerides, HDL-C, and LDL-C concentrations; and study design: RCTs (parallel or cross-over type). The following studies were excluded: (i) reviews, case reports, observational studies, cell, and animal experiments; (ii) subjects without diabetes but with impaired glucose tolerance; (iii) studies with a treatment duration of less than one week; (iv) studies without a control group; (v) and studies with unclear data.

Extraction of data and quality assessment for the study

Two researchers reviewed the eligible studies separately (H.H. and M.A.). Disagreements on data extraction were resolved through further clarification by the third researcher, F.GH. These data were listed: first author; year of publication; country of study; study design; sample size of intervention and placebo groups; participants' BMI (body mass index) and age; treatment duration; *N. sativa* dose; levels of total cholesterol, HDL-C, LDL-C, and triglycerides. Studies analyzing *N. sativa* with different intervention times or doses were analyzed as separate studies. This meta-analysis utilized the Cochrane Collaboration's tool for quality assessment in the included RCTs (41). The quality assessment evaluated the following items: (1) random sequence generation, (2) allocation concealment, (3) blinding of outcome assessment, (4) blinding of participants and

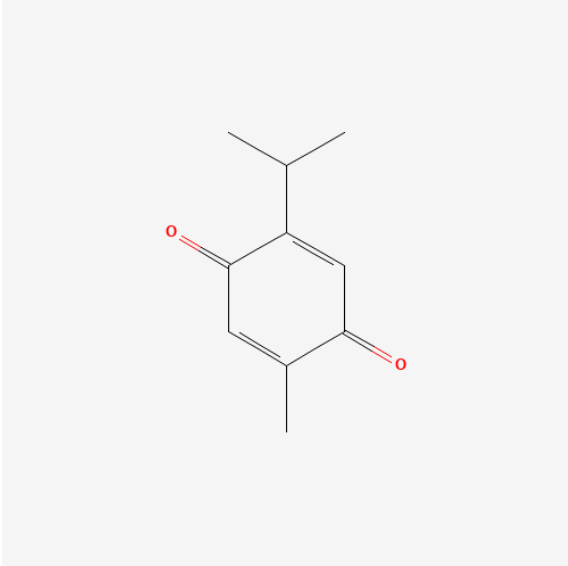

Figure 1: Chemical structure of thymoquinone. Obtained from PubChem.

operators, (5) selective outcome reporting, (6) and other potential sources of bias. A "yes" judgment indicates a minimum risk, "no" demonstrates a high risk, while marking "unclear" shows an undetermined risk of bias.

Data synthesis and statistical analysis

Meta-analysis was conducted using Comprehensive Meta-Analysis software (Biostat, NJ) (42). The lipid parameters (total cholesterol, HDL-C, LDL-C, and triglycerides) were considered as continuous variables. The effect size was expressed as a weighted mean difference (WMD) along with a 95% confidence interval (CI). This meta-analysis utilized Cochrane's Q test and I-squared (I2) statistics to assess heterogeneity among the studies. Significant heterogeneity was defined as p-value levels less than 0.10 (Q value < 0.1) or an I-squared statistic greater than 50% (I2 > 50%). If the heterogeneity was significant, a DerSimonian and Laird random-effects model (43, 44) was employed. A sensitivity assessment was performed using the leave-one-out approach, where each study was removed one at a time to evaluate its effect on the overall effect size.

Subgroup analyses and publication bias

Subgroup analyses were conducted to identify the potential causes of heterogeneity. Subgroup analyses were conducted based on the following moderator variables: the dosage of N. Sativa (≥2000 mg/d or <2000 mg/d), intervention duration (≤12 weeks or >12 weeks), and the type of N. Sativa intervention (seed powder or seed oil). Additionally, these analyses were performed in the present study. Funnel plots were used to assess the publication bias using Begg's rank correlation (45) and Eggar's weighted regression tests (46).

Results

By searching all databases, 245 studies were retrieved. 154 articles were excluded because they were duplicates. In the screening stage, 51 studies were excluded after reviewing the titles and abstracts, and 27 were selected for full-text reading. In the eligibility stage, after considering the inclusion and exclusion criteria, 17 articles were excluded. Three articles were excluded because they used multi-ingredient supplementation, two articles were excluded because they did not have a control group, and thirteen articles were excluded because they did not provide a goal marker for the outcome. Therefore, this meta-analysis was conducted on 8 RCTs with a total of sixteen effect sizes. In the studies conducted by Badar et al. (47) and Kaatabi et al. (48), the effect of N. sativa was investigated at various doses and durations. Therefore, each dose and duration was treated as a separate effect size during the evaluation. Fig. 2 shows additional details of the identification and selection process in the study. All eligible RCTs were conducted using a parallel design (47, 49-55). Five RCTs were conducted in Iran (49, 51-54), two in Saudia Arabia (47, 55), and one in Egypt (50). In the included articles, three RCTs (47, 49, 55) used seed powder, and five (50-54) used N. sativa oil to investigate the effects on lipid profiles. Among the included studies, the dosage of N. sativa varied from 1000 mg/day to 3000 mg/day, and the intervention period ranged from 8 weeks to 52 weeks. A total of 1030 individuals were included, with 529 diabetic patients in the intervention group and 511 diabetic patients in the placebo group. In addition, the ages of the participants ranged between 16 and 60

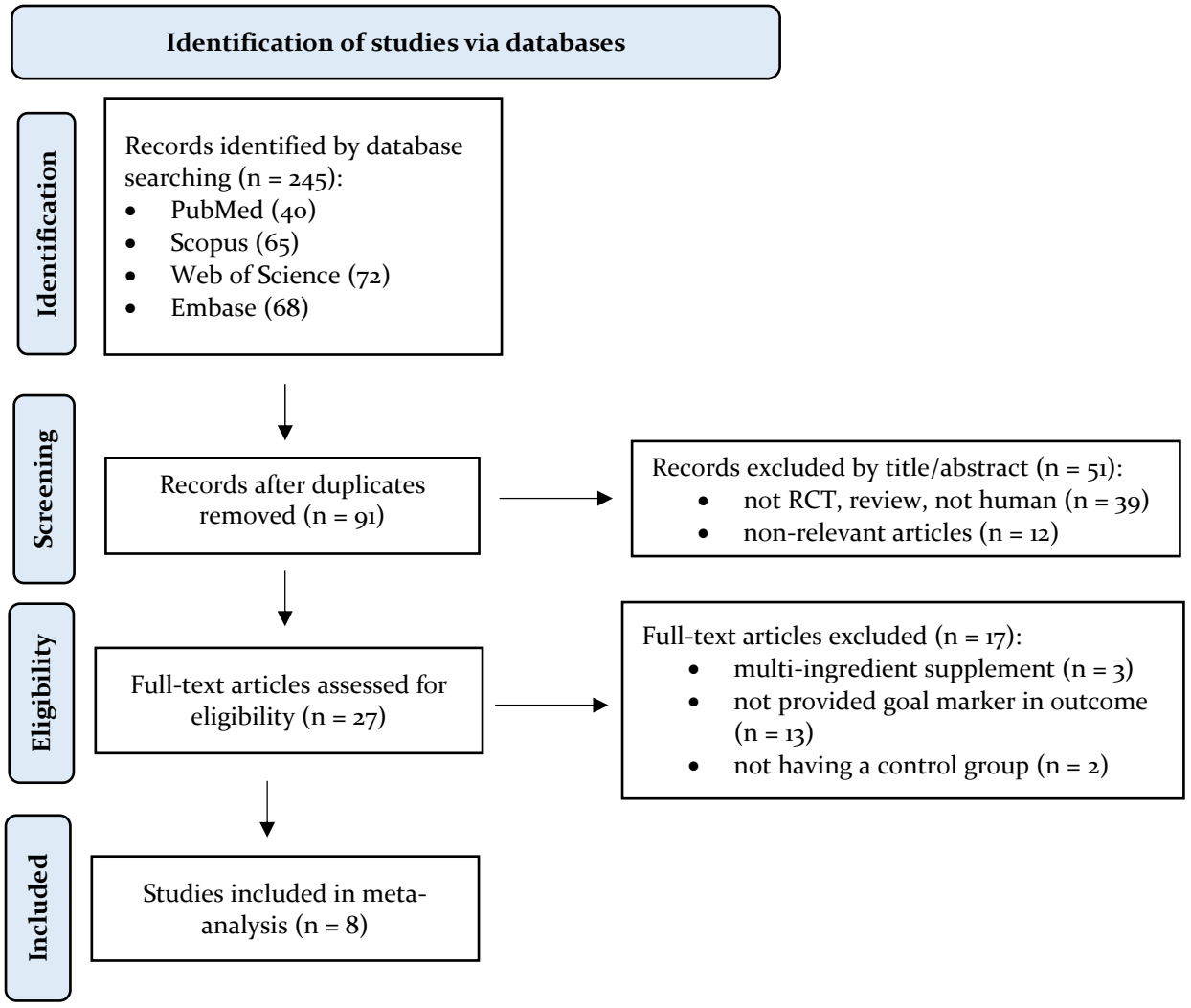

Figure 2: Flow diagram of the study selection procedure.

years. The lipid parameters were reported as outcomes in 8 RCTs following consumption of N. sativa. All data regarding the study is shown in Table 1.

Effect of N. sativa supplementation on lipid profile

Fig. 3 illustrates the association between *N. sativa* supplementation and lipid concentrations. Based on the random-effects model, the overall effect size revealed the following changes after the usage of *N. sativa* (seed powder and oil together): a significant reduction in total cholesterol (WMD: −14.35 mg/dl; 95% CI, −22.49 to -6.21; P = 0.00), LDL-cholesterol (WMD: −14.84 mg/dl; 95% CI, -21.39 to -8.29; P = 0.00), and increased levels of HDL-cholesterol (WMD: 1.61 mg/dl, 95% CI: 0.13, 3.01; P = 0.02). In contrast, no significant effect was observed on triglyceride concentrations after consuming *N. sativa* (WMD: −9.75 mg/dl; 95% CI, -24.4 to 4.03; P = 0.19).

Subgroup analyses for the study

Due to the high degree of heterogeneity, subgroup analyses were conducted based on the following variables: the dosage of *N. Sativa* (≥2000 mg/d or <2000 mg/d), intervention duration (≤12 weeks or >12 weeks), and the form of *N. Sativa* (seed powder or oil). The results of the subgroup analysis showed that higher doses of *N. Sativa* (≥2000 mg/day) significantly reduced total cholesterol and increased HDL-C concentrations. In contrast, lower doses of *N. Sativa* (<2000 mg/day) did not have a significant impact on type 2 diabetes-associated dyslipidemia. The results show that consuming *N. Sativa* for up to 12 weeks significantly decreases triglyceride levels, whereas treatment for more than 12 weeks does not affect triglyceride concentrations. However, the change in treatment duration did not affect the results regarding other lipid parameters. In both greater than 12 and less than or equal to 12 weeks, *N. Sativa* improved

Table 1: Demographic characteristics of the RCTs included in the systematic review and meta-analysis

Author-Year	Country	Duration (day)	Type of N. sativa	Dose (mg/day or ml/day)	Age Placebo	Age Intervention	BMI Placebo	BMI Intervention
Kooshki-2020	Iran	8	Oil	1000 mg/day	52.30	55.91	29.01	28.06
Moustafa-2019	Egypt	13	Oil	1350 mg/day	16-60	16-60	33.30	34.40
Badar-2017	Saudi Arabia	12	Powder	2000 mg/day	46.82	46.12	30.76	32.15
Heshmati-2015	Iran	12	Oil	3000 mg/day	45.30	47.50	29.50	28.60
Kaatabi-2012	Saudi Arabia	8	Powder	1000 mg/day	44.91	47.80	30.48	31.83
Hadi-2015	Iran	8	Oil	1000 mg/day	51.4	56	28.40	28.80
Hosseni-2013	Iran	12	Oil	5 ml/day	50.72	48.74	30.81	30.92
Najmi-2012	Iran	8	Powder	500 mg/day	20-60	20-60	--	--

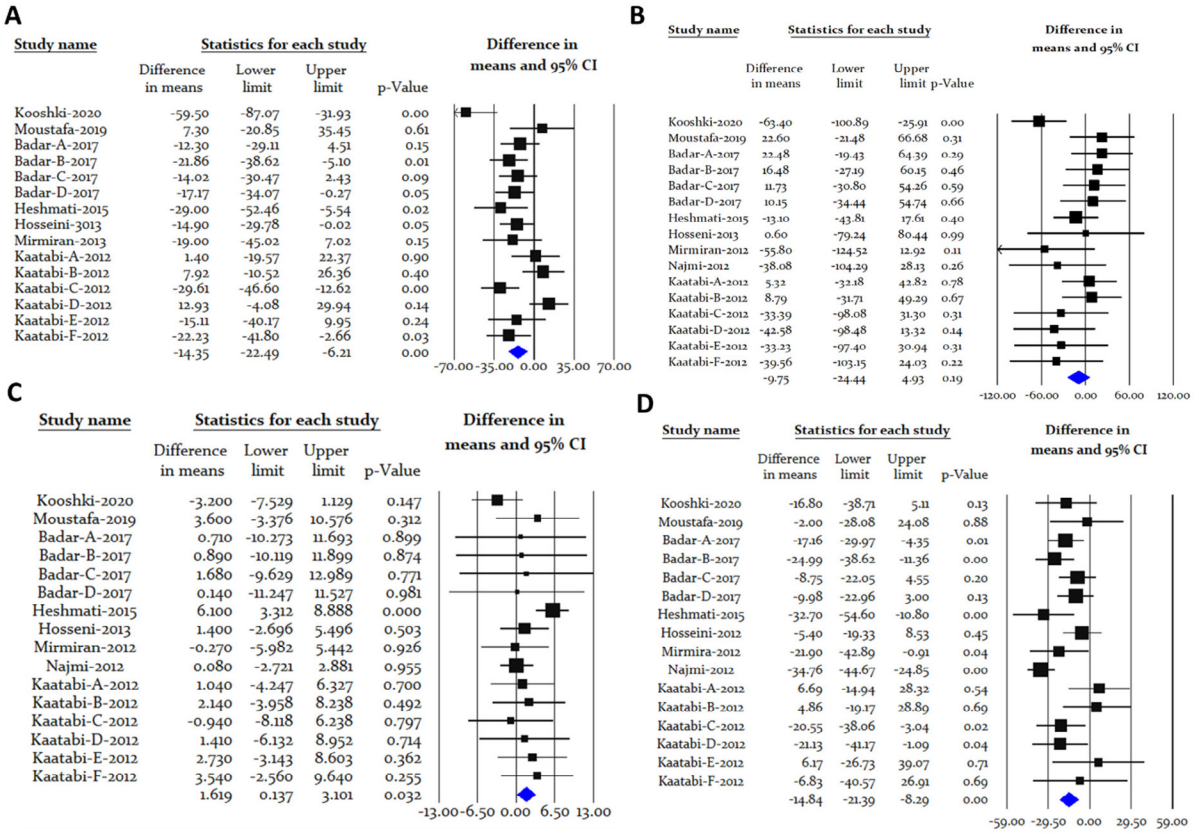

Figure 3: The weighted mean difference (WMD) results for the effects of the intake of Nigella sativa on the lipid profile concentration. (A) Total cholesterol, (B) triglyceride, (C) HDL-C, and (D) LDL-C.

lipid parameters. No significant differences were found between the effects of *N. Sativa* powder and oil on lipid profiles in diabetic patients. Table 2 displays the pertinent data.

Publication bias and sensitivity analysis

The funnel plot displayed visual symmetry for the studies included in the systematic review and meta-analysis, indicating no publication bias in reporting the levels of lipid parameters in diabetic patients (Fig. 4). In addition, there was no indication of publication bias for total cholesterol (two-tailed Begg's test p-value = 0.55, two-tailed Egger's test p-value = 0.29), LDL-C (two-tailed Begg's test p-value = 0.43, two-tailed Egger's test p-value = 0.04), HDL-C (two-tailed Begg's

Table 2: Subgroup analysis to assess the effects of *Nigella sativa* consumption on the lipid profile.

Items	Study Number		SMD	p-Value	I2	P-heterogeneity
Total cholesterol						
Dose	<2000	5	-10.39	0.16	73.07	0.02
	≥2000	10	-15.77	0.00	39.43	0.09
Duration	≤12	4	-26.84	0.01	80.61	0.01
	>12	11	-10.63	0.01	48.92	0.02
Type of *N. sativa*	Powder	4	-22.58	0.02	68.01	0.01
	Oil	11	-10.81	0.00	49.11	0.02
Triglycerides						
Dose	<2000	6	-17.39	0.28	62.07	0.01
	≥2000	10	-4.58	0.55	0.00	0.50
Duration	≤12	3	-56.84	0.01	0.00	0.80
	>12	13	-0.09	0.99	0.00	0.62
Type of *N. sativa*	Powder	5	-22.08	0.20	60.01	0.03
	Oil	11	-1.26	0.87	0.00	0.49
HDL						
Dose	<2000	6	0.00	1.00	0.00	0.58
	≥2000	10	3.43	0.00	0.00	0.62
Duration	≤12	4	26.84	0.01	81.61	0.00
	>12	12	10.63	0.01	0.00	1.00
Type of *N. sativa*	Powder	5	22.58	0.02	72.01	0.00
	Oil	11	10.81	0.00	0.00	0.99
LDL						
Dose	<2000	5	-0.34	0.00	84.07	0.00
	≥2000	10	-0.40	0.00	68.43	0.00
Duration	≤12	3	-0.97	0.01	82.61	0.01
	>12	12	-0.25	0.00	36.92	0.10
Type of *N. sativa*	Powder	4	-0.39	0.00	8.61	0.35
	Oil	11	-0.38	0.00	81.7	0.02

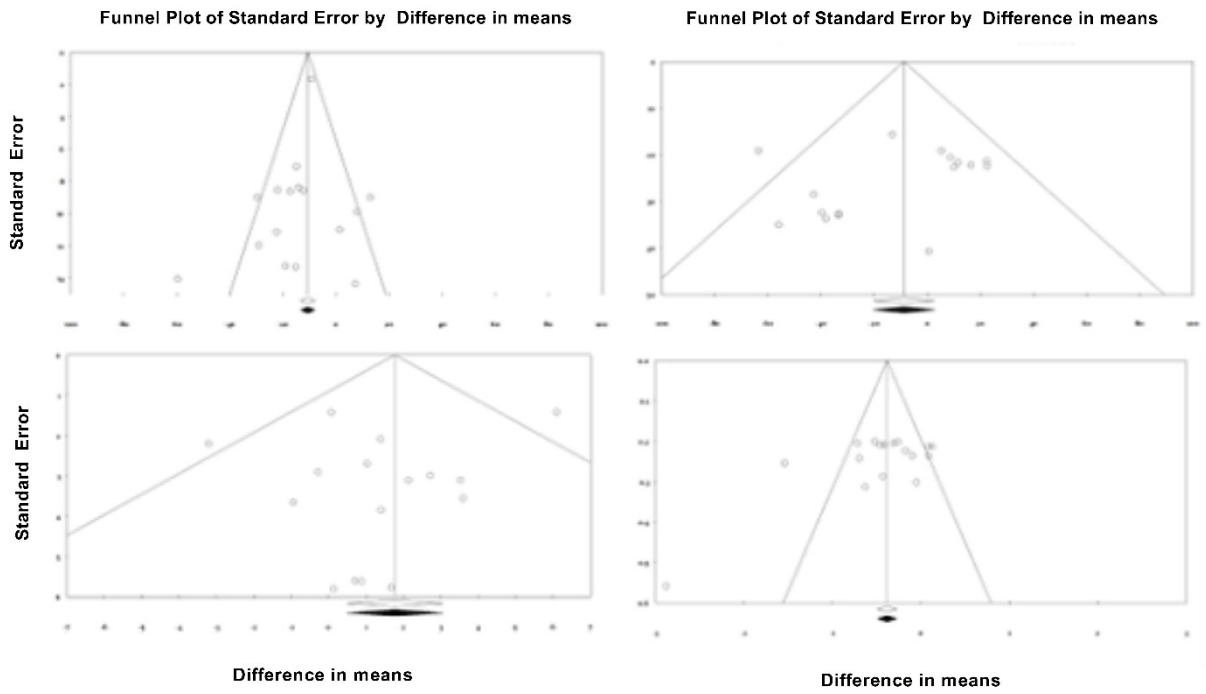

Figure 4: Funnel plot results in the RCTs studying the effects of Nigella sativa consumption on the lipid profile concentration. (A) Total cholesterol, (B) triglyceride, (C) HDL-C, and (D) LDL-C.

test p-value = 0.89, two-tailed Egger's test p-value = 0.43), and triglycerides (two-tailed Begg's test p-value = 0.33, two-tailed Egger's test p-value = 0.19) levels. Sensitivity analyses also indicated that excluding particular studies did not influence the overall effect size of *N. sativa* on total cholesterol, LDL-C, HDL-C, and triglycerides concentration. Related data is shown in Table 3.

Table 3: Quality assessment of studies selected for analysis.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Selective reporting	Other source
Kaatabi - 2015	yes	yes	yes	yes	yes	yes
Mostafa - 2019	yes	yes	unclear	unclear	yes	unclear
Kooshki - 2020	yes	yes	yes	unclear	unclear	yes
Hadi-2015	yes	yes	yes	yes	yes	yes
Badar-2017	yes	yes	yes	yes	yes	yes
Heshmati-2015	yes	yes	yes	yes	yes	unclear
Hosseini-2013	yes	yes	unclear	unclear	unclear	no
Najmi-2012	yes	yes	unclear	unclear	unclear	no

Yes: low risk of bias, No: high risk of bias, Unclear: unclear risk of bias

Discussion

In this systematic review and meta-analysis of RCTs, the impact of *N. sativa* supplementation on the lipid profile of patients with type 2 diabetes was evaluated. The results indicated that supplementation with *N. sativa* improved the lipid profile to some extent in patients with type 2 diabetes. A significant reduction in total cholesterol and LDL-C levels was observed, as well as a significant increase in HDL levels. However, no significant change was found in triglyceride concentration following consumption of N. sativa. Therefore, supplementation with N. sativa, as part of a medical treatment, can improve dyslipidemia in patients with type 2 diabetes. Several lines of evidence suggest that therapeutic mechanisms of N. sativa, such as antioxidant activity, acting as an agonist of PPAR-γ, reducing lipid peroxidation, enhancing hepatic LDL uptake, and inhibiting HMG-COA reductase, are effective in improving lipid profile (30, 56-58). A meta-analysis conducted by Sahebkar et al. evaluated the effects of *N. Sativa* on lipid levels in healthy individuals. Somewhat consistent with the results of this study, they reported significantly reduced levels of total cholesterol and LDL-C, with no change in HDL-C and triglyceride concentrations (59). Since the effects of *N. sativa* on metabolic factors, such as lipid profile and glycemic index, may vary depending on the type of disease, a meta-analysis was conducted to specifically evaluate the effect of *N. sativa* on type 2 diabetes. This approach differs from the study conducted by Sahebkar et al. Another meta-analysis by Khotbehsara et al. reported that consumption of *N. sativa* reduced total cholesterol and LDL-C. In contrast to the results of this study, they did not observe any significant effect on triglyceride and HDL-C levels. One possible reason could be the smaller number of studies included in this meta-analysis. Also, in this meta-analysis, different doses and intervention times were used in the studies conducted by Badar et al. and Kaatabi et al., which are considered separate studies.

The results of the subgroup analysis show that the changes in lipid parameters are associated with the dose of *N. sativa* consumption. Specifically, higher doses of *N. sativa* were found to significantly decrease total cholesterol and increase HDL-C in patients with type 2 diabetes. No significant changes were observed in triglyceride and LDL-C concentrations with higher doses of *N. sativa* intake. In addition, based on the results of subgroup analysis, there was no difference in the effect of seed powder or oil on lipid parameters in diabetic patients. Therefore, these studies were analyzed together in this study.

N. sativa supplementation can reduce LDL-C to a lesser extent than standard statin doses. Evidence suggests that lowering LDL-C after statin treatment reduces all-cause mortality by up to 9% in participants with diabetes. However, in addition to statins, *N. sativa* can help confirm its complementary benefits (60). In addition, some of the included studies involved diabetic patients who were using sugar-lowering drugs like metformin during the intervention (47, 49, 52-54). Therefore, using *N. sativa* supplements alongside conventional lipid-lowering drugs can help improve dyslipidemia in diabetic patients more effectively and with fewer side effects (60). In some included studies, diabetic patients have used sugar-lowering drugs such as metformin during the intervention (47, 49, 53, 61). In this regard, Mustafa et al. demonstrated that *N. sativa* has a lesser effect than metformin in reducing glucose and HbA1C levels. However, it is comparable to metformin in reducing weight, BMI, insulin resistance, ALT, and lipid parameters in patients with type 2 diabetes. *N. sativa* was found to be tolerable in patients with type 2 diabetes, with no reported side effects compared to metformin administration. The group that received metformin showed a significant increase in AST and creatinine levels, while the *N. sativa* group did not experience any adverse effects (61).

This systematic review and meta-analysis had both limitations and strengths. Limitations of the study included a high level of heterogeneity observed in the included RCTs, which was due to differences in the timing of intervention, doses of N. sativa, and characteristics of participants (including gender, genetic background, and geographic region). The dietary changes during the intervention were not controlled in most trials, which

may have affected the results. Additionally, only English search terms were utilized. Strengths of the study included: this meta-analysis is the first study to evaluate the effects of *N. sativa* consumption on lipid profiles in patients with type 2 diabetes. Although there was high heterogeneity, subgroup analyses were conducted based on the type of N. sativa, the dosage of N. sativa, and the duration of the intervention. The search was not limited to specific publication dates. Finally, the effects observed in the meta-analysis were robust in the sensitivity analysis, and no single study significantly determined the overall effect size estimate.

In conclusion, the results suggest that supplementation with *N. sativa* may be beneficial as a complementary therapy, in conjunction with other antidiabetic drugs, for managing diabetic dyslipidemia. The results of this study may pave the way for a new preventive and therapeutic strategy to decrease the risk of dyslipidemia in patients with type 2 diabetes. However, the present results must be interpreted with caution due to the limitations of the study. Finally, additional research is required to determine the ideal dosage and preparation of *N. sativa* in order to achieve maximum effectiveness in improving blood lipid levels.

Conflict of Interest

The authors have nothing to declare.

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