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Review Article

The Effect of *Nigella Sativa* on Lipid Profile, Fasting Blood Sugar and Blood Pressure of Patients: A Meta-Analysis Systematic Review

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ABSTRACT

Background: The impact of *Nigella sativa* on various health markers have been studied before. The present systematic review and meta-analysis reveals the effect of *N. sativa* on lipid profile, fasting blood sugar (FBS) and blood pressure.

Methods: Relevant studies published up to April 21, 2024 were searched through the PubMed, SCOPUS and google scholar databases to collect all randomized clinical trials that evaluated the effect of *N. sativa* on FBS, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with different conditions. We conducted our study according to the 2020 PRISMA guidelines. Only English language publications were included. Pooled meta-analysis was measured by a random-effect model and were reported as the weighted mean difference (WMD) and 95% confidnce interval (95%CI).

Results: Fifteen articles were included in this systematic review and meta-analysis. Our pooled meta-analysis indicated a significant reduction in TG, TC, LDL, SBP, DBP and FBS after administration of *N. sativa*. Also, a significant increase in HDL was noticed after administration of *N. sativa*.

Conclusion: This meta-analysis demonstrated the decreased effect of *N. sativa* on FBS, HDL, LDL, TG, TC, SBP and DBP. Further large random clinical trials are required to shed light on this issue.

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Introduction

Metabolic syndrome (MetS), which includes obesity, diabetes and hyperlipidemia has been a significant clinical concern by World Health Organization (WHO) (1, 2). WHO has identified MetS as a major issue due to its association with chronic inflammations and blood clotting abnormalities. It was shown that the prevalence of MetS ranges from 37.6% to 44% in different populations (3). Risk factors such as imbalances in fatty acids and insulin resistance can play an important role in development of MetS. Additionally, low-

grade inflammations and oxidative stresses may contribute to the onset of MetS (4-7). Findings from various researches have revealed that MetS is linked to a greater than two-fold increase in cardiovascular disease risk factors and more than 1.5 times increase in overall mortality rates (4, 8, 9). There have been findings indicating a connection between MetS and various health conditions such as polycystic ovary syndrome, nonalcoholic fatty liver disease, hepatic steatosis, systemic lupus erythematosus, obstructive sleep apnea, and vascular dementia (10-12).

Numerous chemical medications have been utilized to treat MetS, however, some studies have highlighted the adverse effects associated with such treatments (13, 14). A combination of healthy eating habits, regular exercise, and supplementary treatments are considered effective in managing MetS (15). The utilization of herbs in the management of MetS is currently being researched (16). *N. sativa*, popularly known as one of the most powerful medicinal herbs, is renowned for its miraculous healing properties in treating various disorders. It boasts a deep-rooted historical and religious significance, making it a truly remarkable herb with multifaceted benefits (17). *N. sativa* therapeutic benefits and biological properties have been evaluated before (17). Black seed essential oil has been commonly utilized in a variety of foods, including breads and pickles, as a flavoring agent due to its low level of toxicity (18). In 2021, Tang *et al.* conducted a comprehensive review and analysis of previous studies examining the impact of *N. sativa* on various health markers including total cholesterol (TC), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglyceride (TG), insulin, fasting blood sugar (FBS), and the severity of fatty liver (19). The research findings suggested no link between taking *N. sativa* supplements and levels of TC, LDL-cholesterol (LDL-C), TG, insulin, and TNF-α. Nevertheless, use of *N. sativa* supplements did lead to any improvement in levels of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), FBS, HDL, high sensitivity C-reactive protein (hs-CRP), and the severity of fatty liver in comparison to a placebo (19).

In addition, a study conducted in 2020 examined the impact of *N. sativa* on control of FBS, lipid profiles, and markers of inflammation and oxidative stress. This meta-analysis included fifty studies and found that supplementation with *N.* sativa had a significant lowering effect on TC, TG, and LDL-C. The results also showed positive effects on FBS, HbA1c, TG, TC, Very Low-Density Lipoprotein (VLDL), and LDL levels (20). A recent study from 2019 revealed that black seed had notable effects on various laboratory parameters related to high blood sugar levels and diabetes management including a significant reduction in FBS levels, as well as post-meal blood glucose levels, glycosylated hemoglobin, and insulin resistance. Additionally, treatment with black seed resulted in an increase in serum insulin levels. These findings indicate that black seed may be beneficial in managing components of MetS (21). Given the conflicting findings on the impact of *N. sativa* supplementation on various health markers such as blood pressure, cholesterol levels, and blood sugar, it is essential to review the existing data. Previous reviews have only focused on a few metabolic parameters, so our goal is to conduct a comprehensive analysis of earlier randomized clinical trials (RCTs) to evaluate the effects of *N. sativa* supplementation on metabolic health.

Materials and Methods

Search Strategy

We performed a systematic review and meta-analysis of RCTs to assess the effect of *N. sativa* supplementation on metabolic components among subjects using 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Relevant studies published up to April 21, 2024 were searched through PubMed, SCOPUS and google scholar databases using the keywords of ((“*Nigella sativa*” [tiab] OR “*Nigella sativa*” [MESH] OR “black seed” [tiab] OR “black cumin” [tiab] OR “black seed oil” [tiab] OR “thymoquinone” [tiab] OR “thymoquinone” [MESH]) AND (“Diabetes Mellitus, Type 2” [MESH] OR “Diabetes Mellitus, Type 2” [tiab] OR “Diabet” [tiab] OR “T2DM” [tiab] OR “hyperglycemi” [tiab] OR “hyperglycaemi” [tiab] OR “hypoglycemia” [tiab] OR “blood glucose” [MESH] OR “blood glucose” [tiab] OR “FBS” [tiab] OR “FBG” [tiab] OR “Glycated Hemoglobin A” [MESH] OR “Glycated Hemoglobin A” [tiab] OR “Hb A1c” [tiab] OR “dyslipidemia” [tiab] OR “Dyslipidemias” [MESH] OR “dyslipoproteinemia” [tiab] OR “hyperlipoproteinemia” [tiab] OR “hyperlipidemia” [tiab] OR “hypercholesterolemia” [tiab] OR “cholesterol” [tiab] OR “triglyceride” [tiab] OR “TG” [tiab] OR “high density lipoprotein” [tiab] OR “HDL” [tiab] or “low density lipoprotein” [tiab] OR “LDL” [tiab] or “total cholesterol” [tiab] OR “TC” [tiab] OR “hHypertension” [tiab] OR “hypertension” [MESH] OR “blood pressure” [tiab] OR “blood pressure” [MESH] OR “SBP” [tiab] OR “systolic blood pressure” [tiab] OR “DBP” [tiab] OR “diastolic blood pressure” [tiab])). We included only studies in English language. In order to ensure all data to be accounted for, the reference lists of pertinent prior research were thoroughly reviewed.

Inclusion Criteria

All RCTs about the effect of *N. sativa* or its derivatives on DBP, SBP, FBS, HDL, LDL, TC and TG were included.

Exclusion Criteria

We excluded any studies with the criteria of (i) studies done on animals; (ii) studies that had measured metabolic components immediately after *N. sativa* supplementation; (iii) *in vitro* studies; (iv) studies done on pregnant or lactating women; (v) observational studies or case reports; (vi) studies done an children and (vii) grey literature, including dissertations and congress abstracts.

Data Extraction

MKh and AE independently screened studies for eligibility and extracted the data of the name of first author, year of publication, country, participants' gender, participants' age, study design, *N. sativa* dosage, study duration, outcomes of interest, outcome assessment methods, the mean and SD for outcomes at baseline and end of treatment or their changes throughout the study, and any other interventions and type of disease.

Data Synthesis and Statistical Analysis

We used mean changes and 95% confidence interval (CI) of metabolic components in the intervention and control groups to measure the overall weighted mean difference (WMD) and 95% CI by the random effects model. The Cochrane's Q test and I-square statistics were used to evaluate between-study heterogeneity (I2 greater than 50% was considered as significant heterogeneity). To find possible route of heterogeneity, subgroup analyses was conducted. We used the fixed effect analysis for all subgroups analyses. STATA (version 11.0) was utilized to undertake all statistical analyses. A $p<0.05$ was considered statistically significant.

Results

Characteristics of Included Studies

A flowchart for study selection was shown in Figure 1 revealing 690 studies to be identified by searching Pubmed, Scopus and Google Scholar. Totally, 120 articles remained for detailed assesment after removing duplicates, animal studies and screening by title/abstract. A total of 15 articles with 15 effect sizes were included in this systematic review (Table 1).

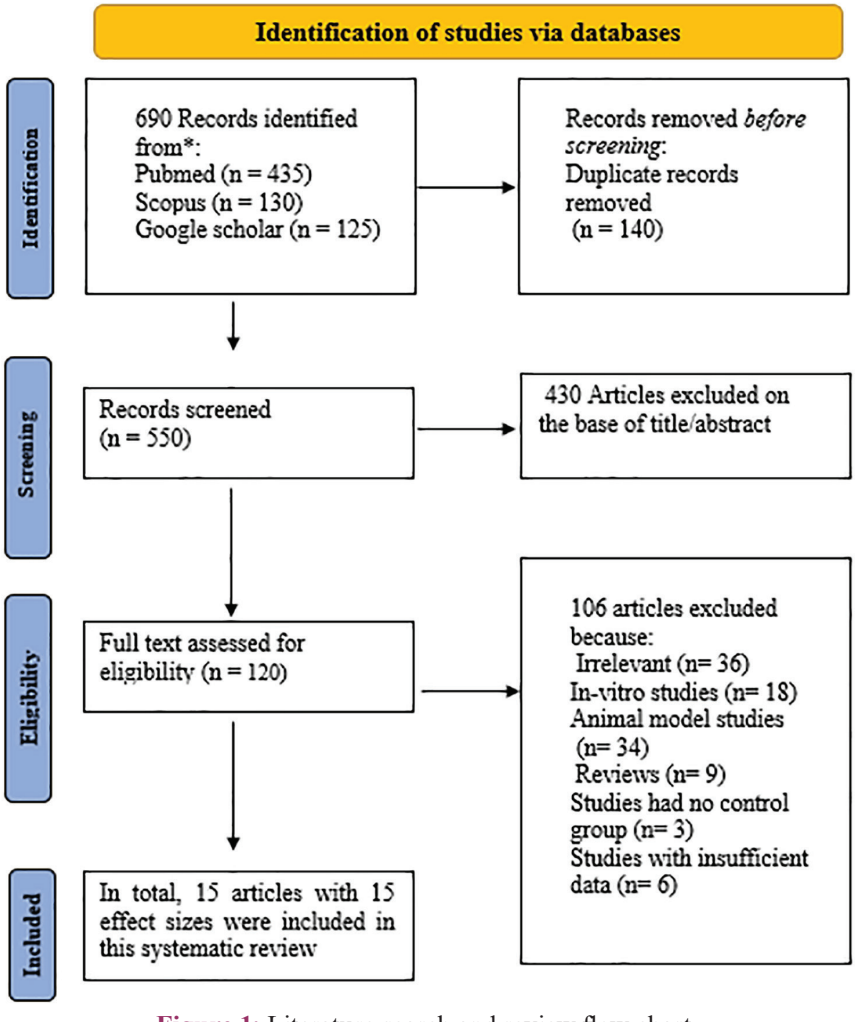

Figure 1: Literature search and review flow chart.

Table 1: General characteristics of included studies.

Code/ Author (year)	Country	Subjects and gender	Age range and mean	Desi gn	Nigella dosage/ day	Dura-tion (week)	Outcomes	Outcome		Control group	Disease
								Intervention (Int) mean±SD and number	Control (Con) mean±SD and number		
Amin and *et al.*, 2015 (35)	Pakistan	Int: 62 Con: 63 Total: 125	Int: 45.1±11.7 Con: 41.57±12.8	Paralel	1.5 g	8	SBP (mmHg) DBP (mmHg) FBG (mg/dL) LDL (mg/dL) HDL (mg/dL) TC (mg/dL) TG (mg/dL)	SBP B 131.8±20.2 A 126.5±18.4 DBP B 82.5±12.1 A 78.8±11.4 FBG B 121.9±14.1 A 111.9±33.6 LDL B 110.2±28.0 A 103.3±29.9 HDL B 34.3±7.8 A 35.4±6.9 TC B 184.3±33.6 A 162.8±39.1 TG B 169.5±44.3 A 141.8±64.3	SBP B 125.5±16.7 A 125.5±14.7 DBP B 76.8±1.5 A 78.8±10.4 FBG B 119.1±15.3 A 116.1±24.5 LDL B 119.5±27.3 A 138.9±13.2 HDL B 33.7±7.4 A 33.4±7.7 TC B 180.8±23.3 A 179.2±28.9 TG B 163.6±42.7 A 162.3±32.2	Turmeric	Metabolic Disease
Ansari and *et al.*, 2017 (36)	India	Int: 32 Con: 31 Total: 63	Int: 53.27 Con: 48.09	Paralel	2.5 mL	12	FBG (mg/dL)	FBG B 138.14±33.13 A 104.09±9.30	FBG B 114.27±22.00 A 103.82±13.18	Received conservative management of diabetic nephropathy	Diabetic Nephropathy

Code/ Author (year)	Country	Subjects and gender	Age range and mean	Desi gn	Nigella dosage/ day	Dura- tion (week)	Outcomes	Outcome		Control group	Disease
								Intervention (Int) mean±SD and number	Control (Con) mean±SD and number		
Badar and *et al.*, 2017 (37)	Saudi Arabia	Int: 57 Male: 33 Con: 57 Male: 30 Total: 114	Int: 46.82 (8.63) Con: 46.12 (6.41)	Paralel	2 g	48	TG (mg/dL) TC (mg/dL) LDL-C (mg/ dL) HDL-C (mg/ dL) SBP (mmHg) DBP (mmHg)	TG B 170.87 (102.19) A 169.62 (102.60) TC B 194.19 (40.58) A 180.66 (41.91) LDL-C B 126.49 (33.91) A 114.25 (34.62) HDL-C B 42.54 (43.01) A 44.02 (10.45) SBP B 139.03 (15.68) A 129.37 (17.43) DBP B 80.17 (8.34) A 76.66 (7.80)	TG B 180.82 (124.14) A 189.72 (114.99) TC B 195.63 (46.30) A 199.27 (39.29) LDL-C B 122.98 (33.12) A 120.72 (26.96) HDL-C B 42.45 (10.05) A 43.79 (9.81) SBP B 133.77 (14.37) A 134.37 (15.32) DBP B 78.59 (7.60) A 79.89 (7.88)	The placebo was an activated charcoal capsule (260 mg)	Type-2 diabetic
Darand *et al.*, 2019 (38)	Iran	Int: 22 Male: 50% Con: 21 Male: 47% Total: 43	Int: 48.9±12.7 Con: 46.2±11.0	Paralel	2 g	12	TG (mg/dL) HDL-C (mg/ dL) LDL-C (mg/dL) TC (mg/dL)	TG (mg/dL) B 140.81±52.16 A 136.95±65.92 HDL-C (mg/dL) B 37.25±4.43 A 38.70±9.13 LDL-C (mg/dL) B 80.10±17.72 A 79.85±23.82 TC (mg/dL) B 151.13±32.42 A 153±27.74	TG (mg/dL) B 160.06±76.36 A 152.86±32.77 HDL-C (mg/dL) B 34.89±5.01 A 34.42±4.66 LDL-C (mg/dL) B 86.46±1.52 A 84.57±17.55 TC (mg/dL) B 160.73±30.59 A 157.20±36.96	Lifestyle modification alone	Metabolic Disease

Code/ Author (year)	Country	Subjects and gender	Age range and mean	Desi gn	Nigella dosage/ day	Dura-tion (week)	Outcomes	Outcome		Control group	Disease
								Intervention (Int) mean±SD and number	Control (Con) mean±SD and number		
Fallah Huseini *et al.*, 2013 (39)	Iran	Int: 35 Male: 17 Con: 35 Male: 16 Total: 70	Int: 47.3±8.6 Con: 45.4±10.3	Paralel	5 mL	8	SBP (mmHg) DBP (mmHg)	SBP B 129.7 (11.9) A 119.1 (7.0) DBP B 77.0 (8.0) A 67.4 (4.4)	SBP B 127.3 (12.8) A 126.9 (11.8) DBP B 75.2 (6.7) A 73.9 (7.9)	Turmeric	Healthy Volunteers
Hadi and *et al.*, 2021(40)	Iran	Int: 23 Female: 56.5% Con: 20 Female: 50% Total: 43	Int: 51.4±9.2 Con: 56.00±3.4	Paralel	1000mg	8	FBS (mg/dL) TC (mg/dL) TG (mg/dL) LDL-C (mg/dL) HDL-c (mg/dL) SBP (mmHg) DBP (mmHg)	FBS B190±71.5 A 167±51.02 TC B 189±48.2 A 173±38.3 TG B 156±73.9 A 139±62.7 LDL-c B 114±38.2 A 98.1±30.5 HDL-C B 48.07±7.5 A 47.3±8.2 SBP B 132±14.1 A 124±31.1 DBP B 82.1±7.7 A 77.7±8.2	FBS B154.2±35.7 A 156.4±33.7 TC B 175±41.7 A 178±43.5 TG B142±61.8 A 159±55.8 LDL-c B 102±39.6 A 108±28.07 HDL-c B 48.2±10.5 A 47.7±11.08 SBP B 132±17.8 A 131±14.8 DBP B 85.4±10.5 A 86.3±9.1	Received two identical placebo soft gel capsules containing sunflower oil	Type 2 diabetes

Code/ Author (year)	Country	Subjects and gender	Age range and mean	Desi gn	Nigella dosage/ day	Dura- tion (week)	Outcomes	Outcome		Control group	Disease
								Intervention (Int) mean±SD and number	Control (Con) mean±SD and number		
Ibrahim *et al.*, 2014 (41)	Malaysia	Int: 19 Con: 18 Total: 37 Total= Female	Int: 53.22±2.16 Con: 53.71±3.57	Paralel	1 g	8	FBG (mg/dL) SBP (mmHg) DBP (mmHg)	FBG B 114.7±11 A 90.5±9.2 SBP B 129.33±15.44 A 124.53±13.31 DBP B 77.13±9.16 A 75.53±9.56	FBG B 106.92±7.92 A 103.1±13.5 SBP (mmHg) B 138.40±18.90 A 140.71±11.85 DBP (mmHg) B 83.93±15.73 A 89.00±12.53	Wheat germ	Menopausal women
Mahdavi *et al.*, 2015 (42)	Iran	Int: 43 Con: 41 Total: 84	Int: 41.5±11.7 Con: 39.3±9.9	Paralel	3 g	8	SBP (mmHg) DBP (mmHg) TC (mg/dL) TG (mg/dL) LDL-C (mg/ dL) HDL-C (mg/ dL)	SBP B 120.5±10.3 A 120.4±9.0 DBP B 7.7±0.7 A7.5±0.7 TC B 203.1±42.2 A 192.2±35.8 TG B 130.2±65.9 A 114.0±55.9 LDL-C B 129.1±32.3 A 119.5±111.8 HDL-C B 48.8±11.6 A 49.8±9.9	SBP B 120.4±10.4 A 120.3±7.0 DBP B 7.9±0.6 A 7.7±0.9 TC B 191.7±41.1 A 188.2±45.8 TG B 115.5±64.7 A 106.8±55.9 LDL-C B 119.2±33.0 A 111.8±40.9 HDL-C B 49.3±13.4 A 46.8±11.9	Sunflower oil	Obese women

Code/ Author (year)	Country	Subjects and gender	Age range and mean	Desi gn	Nigella dosage/ day	Dura-tion (week)	Outcomes	Outcome		Control group	Disease
								Intervention (Int) mean±SD and number	Control (Con) mean±SD and number		
Qidwai *et al.*, 2009 (25)	Pakistan	Int: 39 Con: 34	Int: 45.58±10.86 Con: 46.86±11	Paralel	1 g	6	TC (mg/dL) TG (mg/dL) HDL (mg/dL) LDL (mg/dL) FBS (mg/dL) SBP (mmHg) DBP (mmHg)	TC B 209.07±28.63 A 188.95±20.37 LDL B 145.76±23.30 A 128.03±18.02 HDL B 40.53±8.52 A 35.87±8.48 TG B 163.14±71.43 A 140.24±58.09 FBS B 95.76±16.79 A 86.01±13.36 DBP B 81.82±11.24 A 80.87±11.39 SBP B 128.90±18.37 A 115.39±12.65	TC B 217.11±27.72 A 199.64±27.30 LDL B 144.43±24.00 A 133.21±20.90 HDL B 41.74±10.63 A 36.07±9.13 TG B 157.12±84.53 A 157.76±90.71 FBS B 98.37±12.37 A 90.27±23.78 DBP B 80.45±11.48 A 79.12±8.57 SBP B 122.30±17.76 A 116.97±13.58	Calcium lactate powder	Metabolic Disease
Razmpoosh *et al.*, 2021 (43)	Iran	Int: 19 women Con: 20 Women Total: 39	Int: 3810.6 Con: 349.4	Paralel	2000mg	8	TG (mg/dL) LDL-C (mg/dL) HDL-C (mg/dL) SBP (mmHg) DBP (mmHg)	TG (mg/dL) B: 133±48 A:115.5±26 LDL-C (mg/dL) B:101±28 A:98±19.5 HDL-C (mg/dL) B:41±4 A:44±3.5 SBP (mmHg) B: 118±10 A: 113±6 DBP (mmHg) B:75±6 A:70±5	TG (mg/dL) B:121±60 A:125.5±30 LDL-C (mg/dL) B:106±26 A:103±16.5 HDL-C (mg/dL) B:41±5 A:42±3 SBP (mmHg) B:116±14 A:114±7 DBP (mmHg) B:75±7 A:74±4	Paraffin oil	Obese and overweight women

Code/ Author (year)	Country	Subjects and gender	Age range and mean	Desi gn	Nigella dosage/ day	Dura-tion (week)	Outcomes	Outcome		Control group	Disease
								Intervention (Int) mean±SD and number	Control (Con) mean±SD and number		
Rizka *et al*., 2017 (44)	Indonesia	Int: 38 Male:13 Con: 38 Male:8 Total: 76	Int: 72±5.9 Con: 73.8±6.8	Paralel	600 mg	4	SBP (mmHg) DBP (mmHg)	SBP B 160.4±15.7 A 145.8±19.8 DBP B 78.3±11.9 A 74.4±8.2	SBP B 160.9±16.3 A 147.53±22.0 DBP B 79.0±12.4 A 78.2±8.9	Received capsules of similar color, weight, and smell containing flour	Elderly with hypertension
Sa-bzghabaee *et al*., 2012 (45)	Iran	Int: 37 Male: 54.1% Con: 37 Male: 56.8% Total: 74	Int: 40.38 Con: 38.4	Paralel	2 g	4	TC (mg/dL) TG (mg/dL) HDL (mg/dL) LDL (mg/dL) FBS (mg/dL)	TC B 235.24±28.29 A 224.00±32.39 TG B 173.91±69.35 A 144.94±68.30 HDL B 51.48±15.45 A 52.76±14.33 LDL B 144.58±19.06 A 133.51±21.78 FBS B 86.62±11.95 A 86.12±11.66	TC B 233.39±26.24 A 231.31±25.73 TG B 173.88±47.92 A 181.16±43.96 HDL B 48.03±8.70 A 47.65±7.15 LDL B 138.36±19.05 A 135.81±20.37 FBS B 83.58±9.70 A 85.35±9.70	Capsules the matching INT group	Hypercho-lesterolemia
Sadeghza-deh d *et al*., 2023 (46)	Iran	Int: 28 Con: 29 Total: 57	Int: 57.2±3.7 Con: 58.4±3.4	Paralel	1 g	24	FBS (mg/dL) TG (mg/dL) HDL (mg/dL) LDL (mg/dL) Total Chol (mg/dL)	FBS (mg/dL) B: 113.11±19.05 A: 94.68±31.32 TG (mg/dL) B: 130.18±30.57 A:105.11±17.23 HDL (mg/dL) B: 42.66±5.81 A:46.90±6.39 LDL (mg/dL) B: 121.70±36.14 A:117.46±33.14 TC (mg/dL) B: 190.40±37.65 A:164.11±19.79	FBS (mg/dL) B: 110.95±20.35 A: 106.85±26.07 TG (mg/dL) B: 116.6±25.7 A: 102.5±19.0 HDL (mg/dL) B: 42.23±6.45 A: 47.40±11.23 LDL (mg/dL) B: 117.94±58.42 A: 112.77±55.03 TC (mg/dL) B: 183.51±55.41 A: 171.50±32.32	Curcumin	Postmeno-pausal Women

Code/ Author (year)	Country	Subjects and gender	Age range and mean	Desi gn	Nigella dosage/ day	Dura-tion (week)	Outcomes	Outcome		Control group	Disease
								Intervention (Int) mean±SD and number	Control (Con) mean±SD and number		
Shoaei-Hagh and et al. 2021(47)	Iran	Int : 26 Male: 11 Con : 29 Male: 9 Total : 55	Int : 58.04±2.03 Con: 59.92±2.10	Paralel	5 ml	8	SBP (mmHg) DBP (mmHg) FBS(mg/dl) TG(mg/dl) HDL(mg/dl) LDL(mg/dl) Total Cholesterol(mg/dl)	SBP B 142.50±10.33 A 134.13±12.037 DBP B 87.47±7.15 A 78.93±8.15 FBS B 104.00 A 97.50 TG B 129.42±50.40 A 129.23±46.61 HDL B 44.30±12.98 A 45.63±13.23 LDL B 109.04±38.00 A 95.15±35.62 TC B 176.12±44.81 A 167.42±45.63	SBP B 142.44±11.39 A 139.58±15.08 DBP B 87.09±7.96 A 85.98±7.93 FBS B 99.00 A 103.00 TG B 129.79±49.49 A 131.10±45.08 HDL B 46.03±10.95 A 45.72±10.20 LDL B 106.07±39.29 A 109.76±38.08 TC B 172.31±42.80 A 176.03±41.33	Sunflower oil	Hypertensive

Code/ Author (year)	Country	Subjects and gender	Age range and mean	Desi gn	Nigella dosage/ day	Dura-tion (week)	Outcomes	Outcome		Control group	Disease
								Intervention (Int) mean±SD and number	Control (Con) mean±SD and number		
Tavakoli-Rouzbehani *et al.*, 2021 (48)	Iran	Int: 25 Male: 68% Con: 24 Male: 75% Total: 49	Con: 54.25±1.55 Int: 55.92±1.34	Paralel	2 g	8	FBS (mg/dL) TG (mg/dL) TC (mg/dL) LDL-C (mg/dL) HDL C (mg/dL)	FBS B 97.4±17.84 A 93.08±13.58 TG B 161.61±52.25 A 154.09±35.04 TC B 156.60±33.19 A 163.68±28.51 LDL C B 83.5±26.69 A 90.58±20.34 HDL C B 43.16±8.65 A 47.28±9.05 SBP B 126.88±14.05 A 116.19±12.03 DBP B 82.08±10.2 A 73.48±8.17	FBS B 89.52±9.32 A 93.35±9.95 TG B 169.45±63.73 A 181.32±87.86 TC B 158.52±24.38 A 165.70±24.78 LDL C B 80.77±16.54 A 83.32±12.84 HDL C B 46.35±11.32 A 48.82±12.37 SBP B 120.22±7.75 A119.05±10.07 DBP B 77.17±8.5 A 76.67±6.95	Sunflower oil	Coronary artery disease

DBP: Diastolic Blood Pressure, FBS: Fasting Blood Sugar, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, NR: Not-Respond, TC: Total Cholesterol, TG: Triglyceride, SBP: Systolic Blood Pressure

Studies published between 2009 to 2024 showe 1002 male and female patients, 505 in intervention and 497 in the placebo group, with a mean age ranging from 38 to 72 years were included. Various types of *N. sativa*, including powdered and oil form were used as intervention group in all included studies. *N. sativa* was administered with doses ranging from 600 to 3000 mg. The intervention duration ranged from 4 to 48 weeks.

Findings for the Effect of N. Sativa on TG Level

The pooled meta-analysis indicated that *N. sativa* supplementation in doses of 1000-3000 mg/day over a period of 4-48 weeks was correlated with a reduction in TG level in comparison to the control group among 10 studies with 10 effect sizes (WMD: −17.11; 95%CI: −25.20, −9.03, I2=72.7%, Figure 2). Subgroup analyses by the participants' age and *N. sativa* dosage showed significant changes in TG level. Also, significant influence of *N. sativa* supplementation was seen among studeis with shorter duartion (≤8 weeks). However, no significant effect was found in studies with higher duartion (>8 weeks, Table 2). Egger regression analysis showed no significant evidence for publicarion bias (p=0.94). Moreover, step by step removal of each individual showed that no study had a great influence on overall TG level.

Findings for the Effects of N. Sativa on TC Level

Pooled analysis of 10 effect sizes from 10 articles indicated *N. sativa* supplementation in doses of 1000-3000 mg/day over a period of 4-48 weeks to be significantly linked with decrease on TC level in comparison with the control group (WMD: -9.51; 95%CI: -14.91, -4.11, I2=79.2%, Figure 3). All subgroups analyses by *N. sativa* dosage and duration as well as participants' age demonstrated significant changes in TC level (Table 2). No significant evidence for publicarion bias (p=0.79) or the great impact of each study on overall results were seen.

Findings for the Effect of N. Sativa on HDL Level

Pooling 10 effect sizes, a significant increase in HDL level was found after administration of *N. sativa* (WMD: 1.29; 95%CI: 0.59, 2.00, I2=1.30%, Figure 4). Also, our sub-group analysis by dose of ≥1.5 g indicated the same findings. However, no significant influence for *N. sativa* on older participants during a longer duration (<8 week and >8 weeks, Table 2) was illustrated. No evidences were found for publicarion bias (p=0.76) or sensitivity of analyses on a single study.

Findings for the Effect of N. Sativa on LDL Level

Pooling 10 effect sizes, the analysis showed a significant reduction in LDL level after administration of *N. sativa* (WMD: -8.97; 95%CI: -15.60, -2.34, I2=89.3%, Figure 5). The same results for most sub-group analysis were observed too. However, No significant effect for *N. sativa* on LDL level was seen among older participants (≥47 years, Table 2). No significant publicarion bias (p=0.88) or influence of each study on overall results were found.

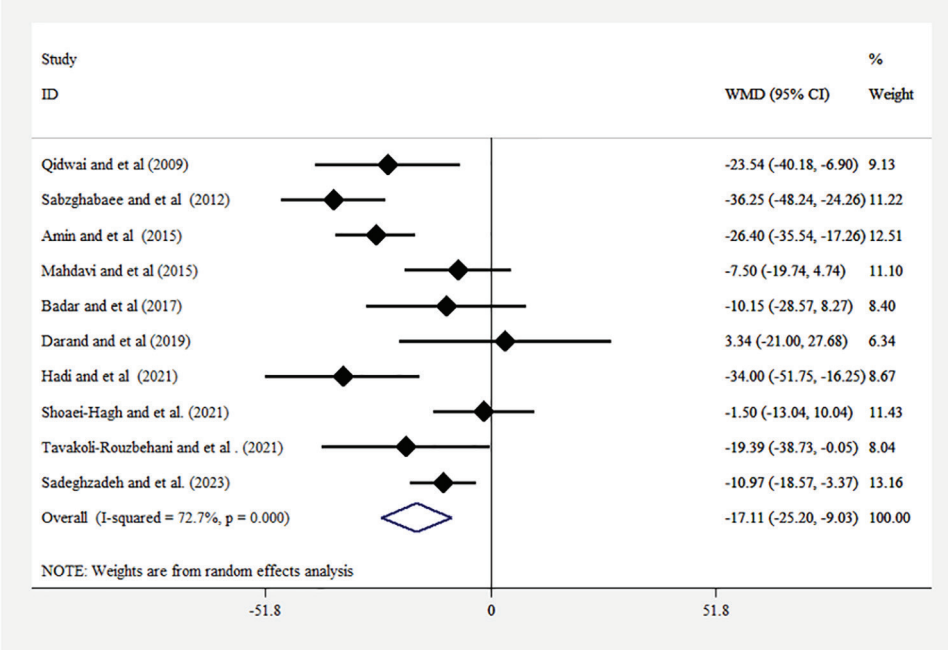

Figure 2: Forest plot for the effect of *Nigella sativa* on serum TG level; expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CI. Diamonds represent pooled estimates from random-effects analysis. CI: Confidence Interval, TG: Triglycerides, WMD: Weighted Mean Difference.

Table 2: Subgroup analyses for the effects of Nigella sativa supplementation on metabolic profile.

Variable		Subgroups	Number of effect sizes	Pooled WMD	95%CI	I^2 (%)	Between-study I^2 (%)
DBP	Age	<47 years	5	-0.14	(-0.31,0.02)	96.1	96.7
		≥47 years	6	-6.84	(-7.79,-5.90)	62	
	Dosage	≤1.5 g	5	-4.02	(-5.10,-2.94)	79.7	95.5
		>1.5 g	4	-0.14	(-0.30,-0.02)	97.3	
	Duration	<8 weeks	2	-1.20	(-2.97,0.56)	73.1	96.7
		8 weeks	8	-0.26	(-0.42,-0.10)	97.2	
		>8 weeks	1	-4.81	(-6.12,-3.50)	0	
FBS	Age	<47 years	3	-2.63	(-4.56,-0.70)	5.3	85.5
		≥47 years	5	-11.51	(-13.84,-9.19)	69	
	Dosage	≤1.5 g	5	-9.29	(-11.78,-6.80)	75.6	85.5
		>1.5 g	2	-3.85	(-5.73,-1.96)	86.4	
	Duration	<8 weeks	2	-2.18	(-4.20,-0.15)	0	85.5
		8 weeks	5	-10.28	(-12.52,-8.04)	47.9	
		>8 weeks	1	-23.60	(-33.21,13.99)	0	
HDL	Age	<47 years	5	1.63	(0.76,2.50)	0	1.3
		≥47 years	5	0.69	(-0.47,1.85)	9.5	
	Dosage	≤1.5 g	4	0.79	(-0.09,1.68)	24.4	1.3
		>1.5 g	5	2.20	(0.97,3.43)	0	
	Duration	<8 weeks	2	1.26	(-0.29,2.81)	0	1.3
		8 weeks	6	1.24	(0.42,2.07)	42.1	
		>8 weeks	2	1.79	(-0.60,4.18)	0	
LDL	Age	<47 years	5	-12.09	(-14.51,-9.66)	89.4	89.1
		≥47 years	5	-3.08	(-6.76,0.57)	86.8	
	Dosage	≤1.5 g	4	-14.81	(-18.07,-11.59)	92.4	89.1
		>1.5 g	5	-4.74	(-7.44,-2.03)	79.2	
	Duration	<8 weeks	2	-7.66	(-10.83,-4.49)	0	89.1
		8 weeks	6	-12.41	(-15.59,-9.23)	93.1	
		>8 weeks	2	-6.43	(-11.03,-1.83)	80.8	
SBP	Age	<47 years	5	-4.56	(-5.83,-3.29)	90.2	84.5
		≥47 years	6	-7.53	(-9.05,-6.01)	66.4	
	Dosage	≤1.5 g	5	-5.48	(-7.34,-3.63)	34.1	85.1
		>1.5 g	4	-4.95	(-6.31,-3.59)	93.7	
	Duration	<8 weeks	2	-5.04	(-7.93,-2.15)	81.8	84.5
		8 weeks	8	-5.07	(-6.19,-3.94)	84.8	
		>8 weeks	1	-10.26	(-12.89,-7.63)	0	
TC	Age	<47 years	5	-11.88	(-14.69,--9.07)	80.8	79.2
		≥47 years	5	-4.92	(-9.28,-0.57)	74.1	
	Dosage	≤1.5 g	4	-13.22	(-16.85,-9.59)	87.1	79.2
		>1.5 g	5	-6.86	(-10.12,-3.61)	78.8	
	Duration	<8 weeks	2	-6.24	(-10.43,-2.05)	47.2	79.2
		8 weeks	6	-12.50	(-15.82,-9.19)	76.7	
		>8 weeks	2	-8.66	(-14.29,-3.03)	93.1	
TG	Age	<47 years	5	-22.79	(-28.37,-17.22)	69.8	72.7
		≥47 years	5	-10.98	(-16.54,-5.42)	64	
	Dosage	≤1.5 g	4	-19.37	(-24.64,-14.11)	69.4	72.7
		>1.5 g	5	-18.06	(-24.97,-11.15)	74	
	Duration	<8 weeks	2	-31.90	(-41.63,-22.18)	32.2	72.7
		8 weeks	6	-14.74	(-19.24,-10.24)	72.7	
		>8 weeks	2	-5.24	(-19.92,9.45)	0	

DBP: Diastolic Blood Pressure, FBS: Fasting Blood Sugar, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, TC: Total Cholesterol, TG: Triglycerides, SBP: Systolic Blood Pressure, WMD: Weighted Mean Difference

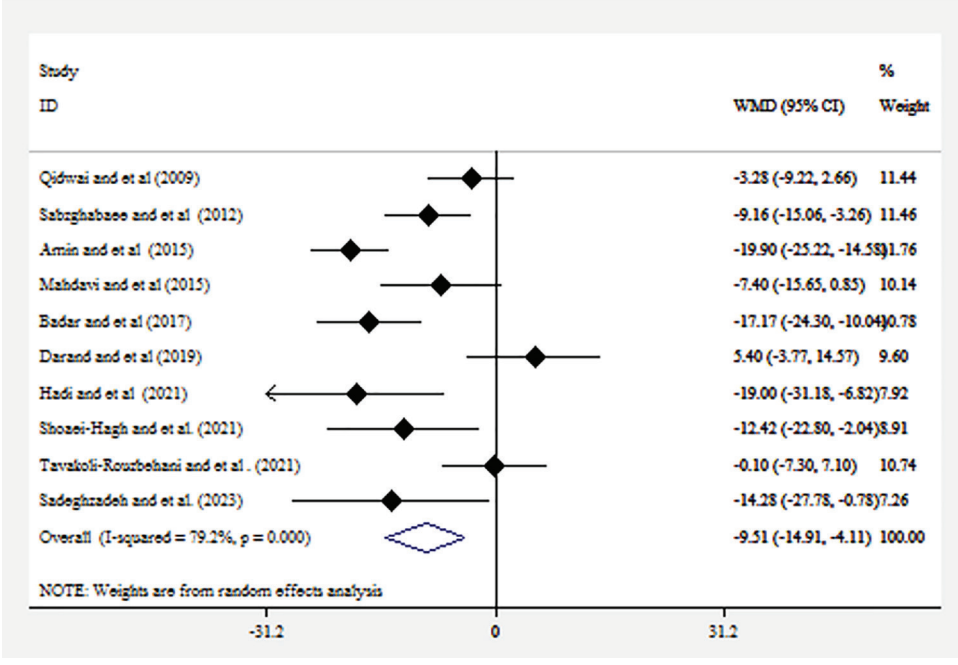

Figure 3: Forest plot for the effect of *Nigella sativa* on serum TC concentration; expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CI. Diamonds represent pooled estimates from random-effects analysis. CI: Confidence Interval, TC: Total Cholesterol, WMD: Weighted Mean Difference.

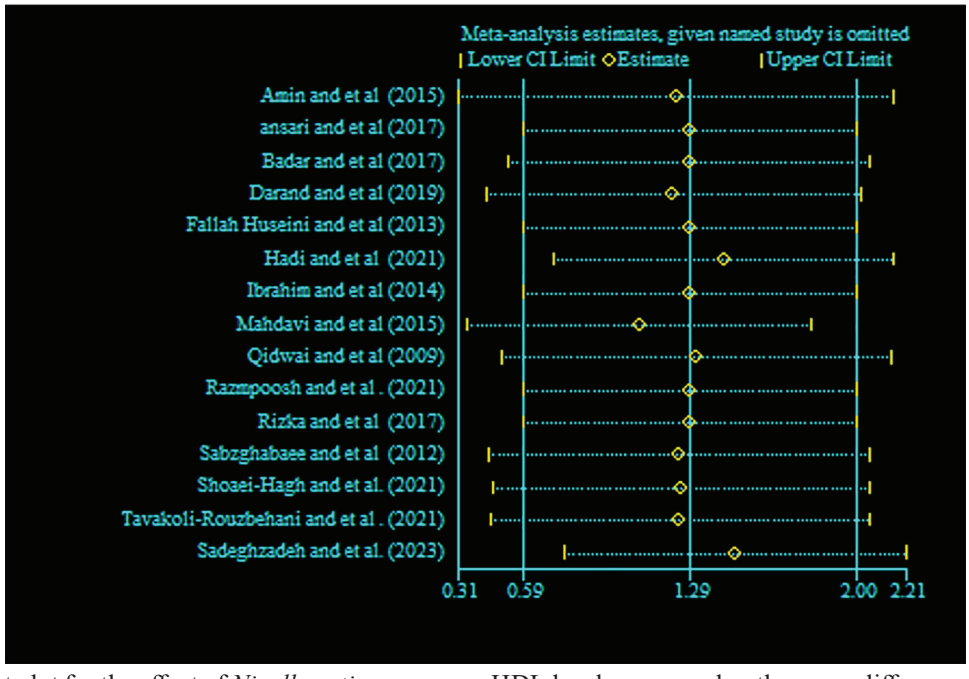

Figure 4: Forest plot for the effect of *Nigella sativa* on serum HDL level; expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CI. Diamonds represent pooled estimates from random-effects analysis. CI: Confidence Interval, HDL: High-Density Lipoprotein, WMD: Weighted Mean Difference.

Findings for the Effect of N. Sativa on SBP

Overall pooled analysis indicated that *N. sativa* supplementation was linked with a significant reduction in SBP (WMD: -6.11; 95%CI: -8.71,-3.51, I2=84.5%, Figure 6). This finding remained unchanged in all subgroups analyses (Table 2).

Findings for the Effect of N. Sativa on DBP

We pooled data from 11 available studies for *N. sativa* effect on DBP among metabolic components. Our pooled meta-analysis indicated that *N. sativa* supplementation had a significant association with DBP (WMD: -4.79; 95%CI: -7.26, -2.31, I2=96.7%, Figure 7). This finding was also seen in different dosages. But, there was no significant finding for studies on younger patients (<47 years) and also studies with shorter duration (<8 weeks, Table 2).

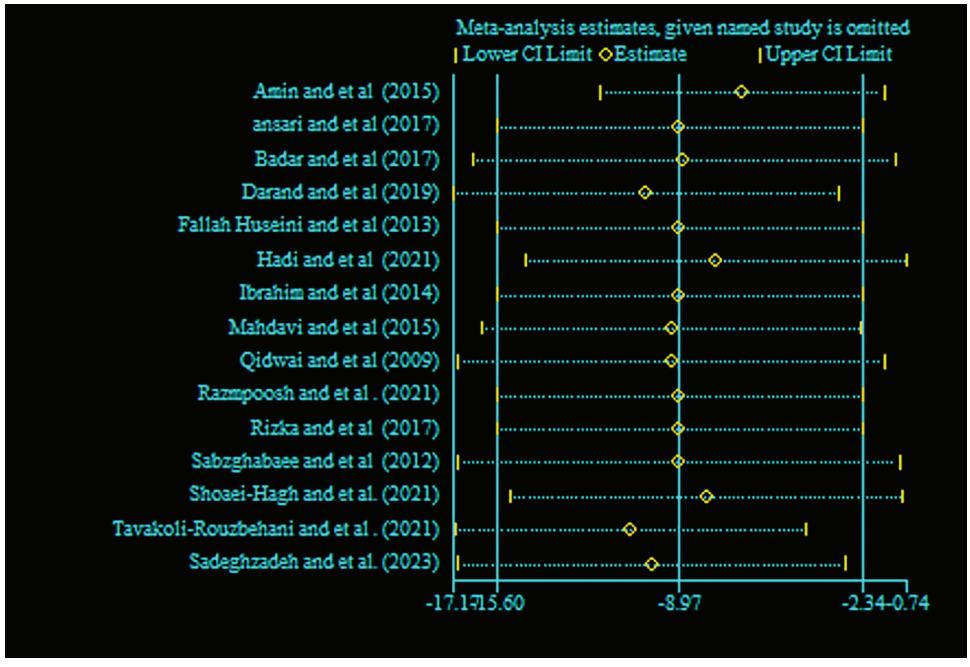

Figure 5: Forest plot for the effect of *Nigella sativa* on serum LDL concentration; expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CI. Diamonds represent pooled estimates from random-effects analysis. CI: Confidence Interval, LDL: Low-Density Lipoprotein, WMD: Weighted Mean Difference.

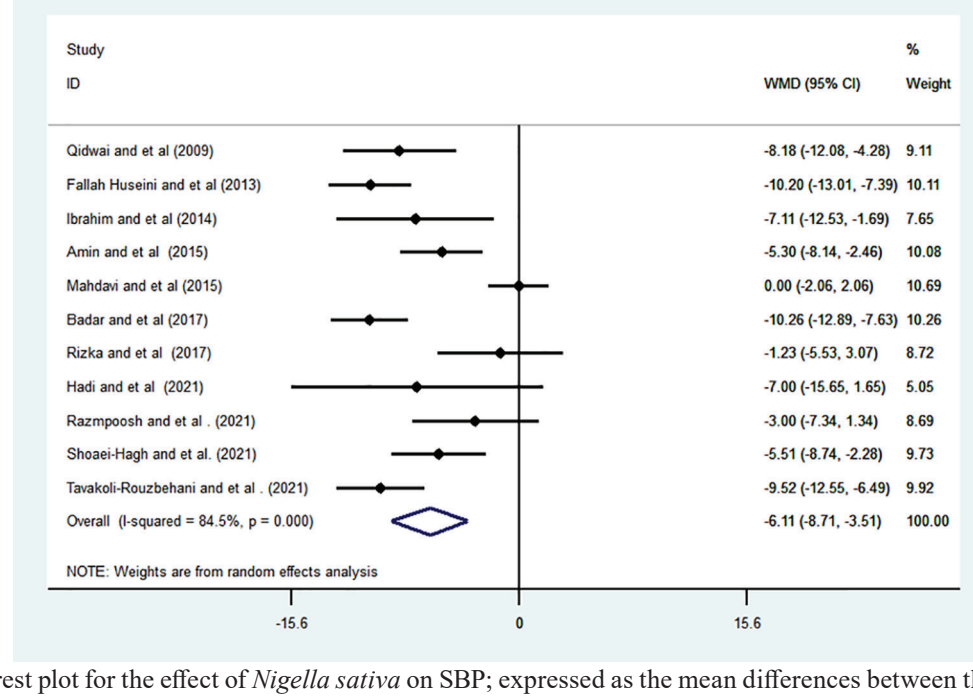

Figure 6: Forest plot for the effect of *Nigella sativa* on SBP; expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CI. Diamonds represent pooled estimates from random-effects analysis. CI: Confidence Interval, SBP: Systolic Blood Pressure, WMD: Weighted Mean Difference.

Findings for the Effect of N. Sativa on FBS Level

Overall pooled analysis indicated that *N. sativa* was associated with less FBS (WMD: -9.89; 95%CI: -14.47, -5.31, I2=85.5%, Figure 8). Our sub-group analysis by age of participants dosage and duration of supplementation reached the same findings (Table 2).

Discussion

The current research involved analyses of fifteen pertinent studies. *N. sativa* was found to have a significant impact on reducing TG, TC, SBP, DBP, FBS, and LDL levels. Additionally, a notable positive correlation was observed between *N. sativa* and HDL. We found a significant reduction in lipid profile after *N. sativa* administration. In line with our study, another meta-analysis showed strong beneficial effects of *N. sativa* on TG, TC, VLDL and LDL (20). Furthermore, A systematic

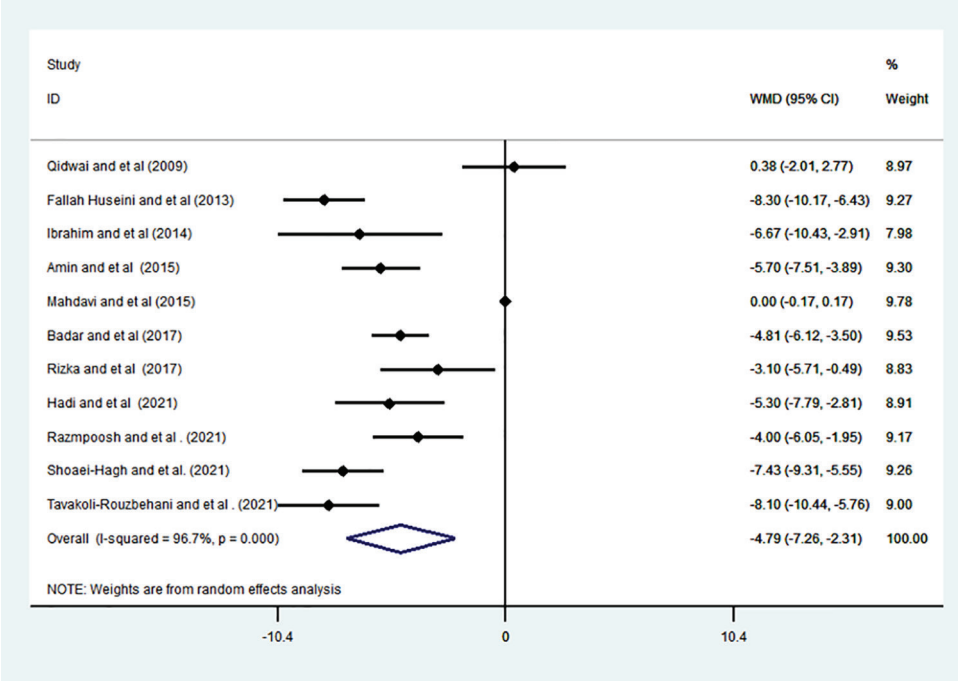

Figure 7: Forest plot for the effect of *Nigella sativa* on DBP; expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CI. Diamonds represent pooled estimates from random-effects analysis. CI: Confidence Interval, DBP: Diastolic blood Pressure, WMD: Weighted Mean Difference.

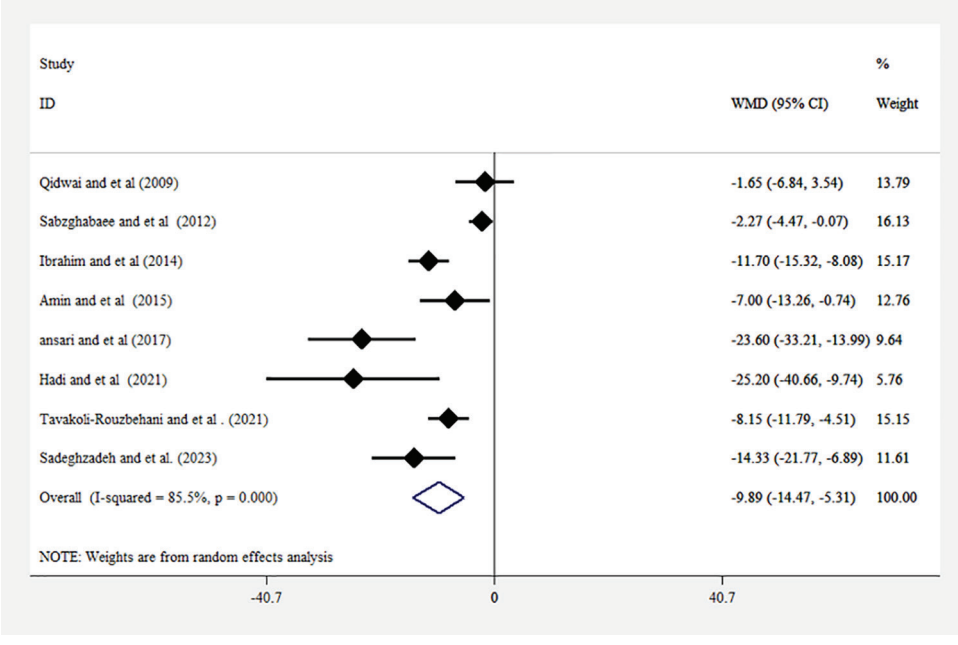

Figure 8: Forest plot for the effect of *Nigella sativa* on FBS; expressed as the mean differences between the intervention and the control groups. The area of each square is proportional to the inverse of the variance of the WMD. Horizontal lines represent 95% CI. Diamonds represent pooled estimates from random-effects analysis. CI: Confidence Interval, FBS: Fasting Blood Sugar, WMD: Weighted Mean Difference.

review and meta-analysis in 2017 revealed effective impact of *N. sativa* on serum lipid homeostasis. Their findings indicated that *N. sativa* was a proper therapy for management of patients with metabolic dysfunction (22).

In a meta-analysis, *N. sativa* after supplementation with 75-2000 mg/day for 8-24 weeks exhibited no beneficial effect on lipid profile of TC, LDL, and TG levels (19). Another systematic review illustrated the effect of *N. sativa* on lipid profile that was very controversial, because the researchers used articles that had been published until 2014 with a limited sample size (23). Our subgroup analysis showed better lipid lowering effect of *N. sativa* in higher dosages and durations. In addition, LDL declined and HDL increased significantly only among studies carried out on younger participants. Our meta-analysis indicated that *N. sativa* administration was

related to a reduction in FBS. In line with our study, other researchers demonstrated FBS to be improved after *N. sativa* supplementation at a dose of 75-2000 mg/day for 8-24 weeks in intervention group when compared to placebo (19).

Furthermore, a recent meta-analysis which was conducted in 2020 by Hallajzadeh *et al.* showed that *N. sativa* hasd strong beneficial effects on FBS and HbA1c (20). In another study, it was shown that *N. sativa* had significant reductive effect on FBS 2 hours after meals, and on HbA1c and insulin resistance (21). Furthermore, one sytemayic review and meta-analysis indicated that consumption of *N. sativa* had a significant reductive effect on FBS (24). Another meta-analysis which conducted in 2017 revealed the same results (22). However, Qidwai *et al.* in 2009 found no significant effect of *N. sativa* on FBS level (25). They did a 6-week random trial on 123 patients that received two capsules twice daily (1000 mg) of either *N. sativa* or placebo. Qidwai *et al*. used a limited sample size during a short period of time when compared to other studies (25). In addition, they used less *N. sativa* (1000 mg) that can be the reason not finding an association between *N. sativa* supplementation and change in FBS (25).

Our pooled analysis indicated that *N. sativa* had reductive effect on DBP and SBP. In line with our study, a meta-analysis showed that short-term treatment with *N. sativa* powder can significantly decrease SBP and DBP levels (26). Many studies indicated that *N. sativa* can lower blood pressure in adults (27-29). A systematic-review in 2017 indicated that *N. sativa* showed reductive effect on blood pressure in 4 trials, but in 5 trials, it could not afford. Also, many RCTs showed that *N. sativa* did not have significant effect on blood pressure (25, 30, 31). In one of them, the authors stated that small sample size and limited duration of the intervention can be the cause of this discerpency (25).

Reductive effect of *N. sativa* on FBS was shown to be correlated with its antioxidant features (32). Thymoquinone is an antioxidant ingredient of *N. sativa* which has antioxidant activity that can improve oxidatve stress (33) Also, It could promote the proliferation of pancreatic β-cells, so can improve insulin secretion (34). Furthermore, another relevant mechanism of hypoglysemic effect of *N. sativa* can be correlated with its ability to regulate intestinal glucose absorption and its downregulating effect on expression of gluconeogenic enzymes (22). *N. sativa* can activate adenosine monophosphate-activated protein kinase in muscles and the liver and inhibit gluconeogenesis too (21).

Furthermore, *N. sativa* has a key role to decrease the secretion of VLDL and hormone-sensitive lipase, degradation of apo-B100, increase in clearance of TG by an increase in the activity of endothelial lipoproteins, a reduction in cholesterol absorption, and an increase in bile production and loss via feces (20). Also, *N. sativa* can cause a reduction in cholesterol synthesis via inhibiting expression of HMG-COA reductase genes (20). Some reductive effects of *N. sativa* on blood pressure includes its diuretic effect, calcium channel blocking impact and heart-weakening influence. *N. sativa* can directly or indirectly reduce arterial and heart rate through mechanisms involved in serotonergic and muscarinic receptors too (26).

One of the strengths of the present systematic review and meta-analysis is summarizing the effect of *N. sativa* on various components of metabolic profile. However, few limitations of current study should be taken into account. Only english-language studies were included in our study. Besides that, all included studies utilized different dosages, type and duration of supplementation. Many studies have been conducted in Eastern countries, making it difficult to apply the results to Western populations. Additionally, the present study is limited by the small number of included participants. To address this limitation, we performed subgroup analyses based on factors such as *N. sativa* dosage, study duration, and participant age. Finally, participants of these studies were at different physiological status, and it was difficult to confer supplementation effect on a single health condition. Although our study included only a few relevant studies, further research is necessary to fully understand the effects of *N. sativa* supplementation on metabolic health.

Conclusion

This meta-analysis demonstrated the positive effect of *N. sativa* on FBS, HDL, LDL, TG, TC, SBP and DBP. However, no significant changes in TG was noticed after longer time and more dosages. Furthermore, there was no significant changes in DBP among younger patients and a shorter duration of therapy. HDL and LDL did not show any signs of improvement among older pateints too.

Aknowledgment

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Authors' Contribution

MKH wrote the main text of the article, did the initial screening and data extraction. AE and AM analyzed the data and re-checked the written text and SHM performed secondary screening and rechecking of data extraction.

Conflict of Interest

None declared.

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