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

Naghsh, N., Moridpour, A. H., Kavyani, Z., Musazadeh, V., Jafarzadeh, J., Safaei, E., Clark, C. C. T. & Faghfouri, A. H.

DOI 10.1016/j.jff.2023.105565
ISSN 1756-4646
ESSN 2214-9414

Publisher: Elsevier

Journal of Functional Foods 105 (2023) 105565

Contents lists available at ScienceDirect

Journal of Functional Foods

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

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

Navid Naghsh [a], Amir Hossein Moridpour [b,c], Zeynab Kavyani [b,c], Vali Musazadeh [b,c,*], Jaber Jafarzadeh [b,c], Ehsan Safaei [b], Cain C.T. Clark [d], Amir Hossein Faghfouri [e,*]

[a] Department of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[b] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[c] School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Centre for Intelligent Healthcare, Coventry University, Coventry CV1 5FB, UK
[e] Maternal and Childhood Obesity Research Center, Urmia University of Medical Sciences, Urmia, Iran

ARTICLE INFO

Keywords:
Nigella sativa
Body composition
Obesity
Body mass index
Meta-analysis

ABSTRACT

Many studies have suggested that *Nigella Sativa* supplementation may exert a beneficial effect on anthropometric indices; however, the findings are inconclusive. Therefore, this study was conducted to obtain an updated finding in this regard. Systematic search was conducted in PubMed, Cochrane Library, Web of Science, Scopus, Embase databases, and Google Scholar, up to August 2022. *N. sativa* supplementation significantly reduced BW (WMD = −1.46 kg; 95 % CI: −2.53, −0.39) and BMI (WMD: −0.58 kg/m^2, 95 % CI: −0.86, −0.29) compared to placebo group. However, no significant reductions were found in WC (WMD: −2.54 cm, 95 % CI: −6.27, 1.19), HC (WMD: −1.92 cm; 95 % CI: −4.38 to 0.54), and WHR (WMD = −0.03; 95 % CI: −0.07, 0.01). The current meta-analysis revealed that *N. sativa* supplementation in adults led to a significant decrease in body weight and BMI, but not WC, HC, and WHR. Thus, according to our findings, *N. sativa* supplementation can be recommended as an adjunctive intervention in obesity management.

1. Introduction

Obesity is a growing concern in both developed and developing nations (Lim, Xue, & Wang, 2020). According to WHO reports, >1.9 billion people are overweight and 600 million are obese (Musazadeh, Zarezadeh, Ghalichi, Kalajahi, & Ghoreishi, 2022), whilst obesity-related illnesses including cardiovascular diseases, stroke, type 2 diabetes, and certain forms of cancer represent the biggest avoidable causes of mortality (Lafia, Ketounou, Honfoga, Bonou, & Zimé, 2022). Effective weight management is crucial as it can lead to reductions in cardiovascular risk factors, such as blood pressure, glucose, lipid profile, insulin, and inflammatory markers (Barazzoni, Gortan Cappellari, Ragni, & Nisoli, 2018; Clifton & Keogh, 2018; Harsha & Bray, 2008; Hasegawa et al., 2019; López-Domènech et al., 2019). Various approaches have been proposed to facilitate weight loss. For instance, herbal remedies are more widely available, less expensive, and have fewer side effects than synthetic medications (Payab et al., 2020).

Nigella sativa (*N. sativa*) is a medicinal plant of the Ranunculaceae family, also called "black seed" (Phulwaria, Kaushal, Sharma, Mishra, & Soni, 2018). *N. sativa* is primarily cultivated in the countries of the Middle East and Southwest Asia (Kizi & Kizi, 2022). The positive effects of *N. sativa* include its anti-inflammatory, anti-carcinogenic, anti-antioxidant, and anti-diabetic properties (Hamdan, Haji Idrus, & Mokhtar, 2019; Korak, Ergül, & Sazci, 2020); however, contradictory

Abbreviations: BMI, body mass index; BW, body weight; CI, confidence intervals; HC, hip circumference; IQRs, interquartile ranges; *N. sativa*, *Nigella sativa*; NAFLD, non-alcoholic fatty liver disease; NSSP, Nigella sativa seed polysaccharides; PPAR-γ2, peroxisome proliferator-activated receptor-γ2; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, protocol to the international prospective register of systematic reviews; RCTs, randomized controlled trials; SD, standard deviation; SEs, standard errors; T2DM, type 2 diabetes mellitus; TQ, Thymoquinone; WC, waist circumference; WHR, waist-to-hip ratio; WMDs, weighted mean differences; UCP1, Uncoupling protein 1.

* Corresponding authors at: Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran. Tel.: +989145632011 (V. Musazadeh).
E-mail addresses: Musazadehv@tbzmed.ac.ir (V. Musazadeh), Amir.nut89@gmail.com (A.H. Faghfouri).

https://doi.org/10.1016/j.jff.2023.105565
Received 10 January 2023; Received in revised form 27 March 2023; Accepted 27 April 2023
Available online 17 May 2023

results have been found by studies investigating how *N. sativa* affects weight control (Hadi et al., 2021; Maideen, 2022; Mostafa, Hegazy, Elnaidany, Shehabeldin, & Sawan, 2021). Also, the anti-obesity properties of *N. sativa* are mainly related to thymoquinone (TQ), which constitutes 30 to 48 % of *N. sativa* oil, and other components of *N. sativa*, including thymol, thymohydroquinone, dithymoquinone, nigellone, alpha-hederin, flavonoids, and fatty acids (linoleic acid, oleic acid, and others) (Daryabeygi-Khotbehsara, Golzarand, Ghaffari, & Djafarian, 2017). Furthermore, no serious side effects or toxicological effects were revealed in humans (Heshmati & Namazi, 2015; Mahdavi, Alizadeh, Namazi, & Farajnia, 2016) or animal models (Zaoui et al., 2002).

The effect of *N. sativa* supplementation on obesity indices was assessed by two meta-analyses published in 2018 (Mousavi et al., 2018; Namazi, Larijani, Ayati, & Abdollahi, 2018), although some did not examine changes in obesity indices in detail. Due to the conflicting findings of these studies, and the absence of a comprehensive meta-analysis, we conducted the current updated systematic review and meta-analysis to obtain a conclusive finding on the effect of *N. sativa* supplementation on body composition indices including body mass index (BMI), body weight (BW), waist circumference (WC), hip circumference (HC), and waist-to-hip ratio (WHR).

2. Methods

We utilized the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria to conduct a systematic review and meta-analysis of RCTs exploring the effect of *N. sativa* supplementation on obesity indices in adults (Moher, Liberati, Tetzlaff, Altman, & The, 2009). Furthermore, we registered our study protocol to the international prospective register of systematic reviews (PROSPERO) (**CRD42022358471**).

2.1. Search strategy

We searched PubMed, Web of sciences, Embase, Cochrane Library, SCOPUS, and Google Scholar databases with the following keywords to identify relevant researches published from database's inception to August 2022: "*Nigella sativa*" OR "Cuminum" OR "black cumin" OR "black caraway" OR "thymoquinone" OR "TQ" OR "kalonji" OR "Black seed" **AND** "body weight" OR "body weight changes" OR "body mass index" OR "weight loss" OR "obesity" OR "body weight" OR "body mass index" OR "BMI" OR "waist circumference" OR "WC" OR "hip circumference" OR "HC" OR "waist-to-hip ratio" OR "WHR". In Supplementary Table 1, additional information on the search technique and keywords is presented. The sensitivity of the search strategy was improved by using the wild-card phrase "*". Only studies in English were considered. We also reviewed the reference lists of review and original articles to ensure that no publication was overlooked.

2.2. Inclusion and exclusion criteria

We followed these PICO criteria: Population/Patients (P: adults aged 18 >), Intervention (I: treated with *N. sativa*), Comparison (C: control group), Outcome (O: body composition indices (BMI, BW,WC, HC, and WHR), and Study (S: randomized controlled trials (RCTs). The following exclusion criteria were considered: (i) in-*vivo* and *in-vitro* studies, case reports, and reviews; (ii) observational studies; (iii) co-supplementation with another ingredient; and (iv) lack of relevant information on the baseline or end-of-trial anthropometric indices. Finally, this report included all RCTs that met the criteria listed below: 1) Parallel or crossover original RCTs that explored the effects of *N. sativa* supplementing on anthropometric parameters, 2) RCTs involving adults (aged 18 or older), 3) Trials that provided accurate data on the mean [standard deviation (SD) or 95 % confidence intervals (CI)] changes in anthropometric measurements, namely BMI, weight, WC, HC, and WHR at before intervention (baseline), and at the end of the study (*N. sativa* consumption) for participants in both groups (experimental vs. control).

2.3. Data extraction

Following meeting the criteria for inclusion, two different researchers (AHM, and ZK) extracted the data. From each of the included trials, the following details were extracted: first author's name, publication date, duration of the study, design of the study, study location, characteristics of participants, sample size, and dosages of *N. sativa,* form (powder, oil) were used in the intervention and control groups and the key results. Any disagreements were discussed and settled by a third reviewer (VM).

2.4. Risk of bias assessment, and certainty of the evidence

We assessed the methodological quality of each study using the risk of bias tool developed by Cochrane Collaboration: a) Random sequence generation, b) Allocation.

concealment, c) Selective reporting, d) Other sources of bias, e) Blinding (participants and personnel), f) Blinding (outcome assessment), and g) Incomplete outcome data. In order to categorize each research bias domain, words like "High", "Low", and "Unclear" were used. For each domain, a corresponding author assessed and resolved variations in research bias across independent reviewers (Higgins et al., 2011).

We evaluated the general level of evidence certainty across studies in accordance with the GRADE recommendations working group (gradeworkinggroup.org). The quality of the evidence was divided into four scores based on the assessment criteria: high, moderate, low, and critically low (Guyatt et al., 2008).

2.5. Statistical analysis

Mean differences and standard deviations for experimental and control groups were calculated to investigate the effect size for body composition. Also, weighted mean differences (WMDs), with 95 % CIs, were estimated using a random-effect model (DerSimonian & Laird, 1986). Means ± SD were calculated in studies where data were given as standard errors (SEs), interquartile ranges (IQRs), and 95 % CIs. Cochran's Q test was used to measure the between-study heterogeneity, and assessed using the *I*-square (I^2) statistic. I^2 values>50.5 %, or p values lower than 0.1, were regarded to indicate significant between-study heterogeneity. In order to identify potential sources of heterogeneity, we conducted a subgroup analysis based on baseline BMI, duration of intervention, health condition, study location, study quality, mean age, type of experimental intervention, type of control intervention, sample size, and gender. By conducting a sensitivity analysis, we assessed the impact of various studies on the overall estimate. To investigate the effects of small studies, Egger's regression asymmetry test and Begg's adjusted rank correlation were also used (Begg & Mazumdar, 1994; Egger, Smith, Schneider, & Minder, 1997). We assessed publication bias by analyzing funnel plots. Due to publication bias, we carried out the "trim and fill" procedure to impute studies that may have been missed when bias in publication was detected. To determine the relationship between the dosage of *N. sativa* (mg/day), and observed effect size, a non-linear dose-response analysis was conducted. Regarding non-linear response analysis, in the first stage, the fitting of limited cubic lines with three nodes and models with linear and quadratic trends was performed. In the subsequent step, a Wald-type test was performed, which was used to detect deviation from a linear model. Following this, restricted maximum likelihood estimation was used in a one-step dose–response meta-analysis (Crippa & Orsini, 2016). In the dose–response analysis, $P < 0.05$ was considered statistically significant. This method estimates the study-specific slopes and combines them to obtain an overall average slope in a single stage, and is a more precise, flexible, and efficient method than the traditional two-stage method. The significance for non-linearity was calculated by null hypothesis

testing, in which the coefficient of the second spline was considered equal to zero. Statistical analysis was performed using version 16 of the STATA program (Stata Corp, College Station, TX). For all analyses, P-values<0.05 were regarded as statistically significant.

3. Results

3.1. Selection and characteristics of studies

Fig. 1 shows the flowchart for the literature search procedure. Through the initial search of electronic databases, 2,125 articles were found, of which 1,142 were duplicates. The titles and abstracts of 983 studies were examined, and 962 articles were excluded. Finally, 21 RCTs published between 2008 and 2021 were eligible for inclusion in the meta-analysis. Table 1 lists the specific characteristics of the included RCTs in more detail. The mean age of 1,454 participants in this study ranged from 24 to 56 years and the duration of the interventions varied between 3 and 16 weeks. There were 14 studies conducted in Iran (Darand et al., 2019; Dehkordi & Kamkhah, 2008; Fallah Huseini et al., 2013; Farhangi, Dehghan, Tajmiri, & Abbasi, 2016; Hadi et al., 2021; Heshmati, Namazi, Memarzadeh, Taghizadeh, & Kolahdooz, 2015; Hozoori, Fallah Hoseini, Kolahdooz, Nasri, & Zadeh Modarress, 2016; Khonche et al., 2019; Mahdavi, Namazi, Alizadeh, & Farajnia, 2015; Naeimi, Hajimehdipoor, & Saber, 2020; Rashidmayvan, Mohammadshahi, Seyedian, & Haghighizadeh, 2019; Safi et al., 2021; Shirazi, Khodakarami, Feizabad, & Ghaemi, 2020; Tavakoli-Rouzbehani, Abbasnezhad, Kheirouri, & Alizadeh, 2021), three in Pakistan (Amin, Islam, Anila, & Gilani, 2015; Hussain, Tunio, Arain, & Shaikh, 2017; Qidwai, Hamza, Qureshi, & Gilani, 2009), two in Indonesia (Datau, Surachmanto, Pandelaki, & Langi, 2010; Rachman & Darmawan, 2017), one in Bangladesh (Bin Sayeed et al., 2013), and one in Malaysia (Ibrahim et al., 2014).

3.2. Risk of bias assessment and grading of-evidence

The results of the quality assessment of RCTs are shown in Table 2. The GRADE assessment revealed moderate quality for body weight, BMI, and WC due to serious limitations of imprecision, but HC and WHR had high quality of evidence (Table 3).

3.3. Effect of N. Sativa supplementation on BW

In total, 15 eligible studies with 16 treatment arms, including a total of 995participants (case = 524, control = 471), examined the effect of *N. sativa* intake on body weight. Based on a random-effect model, we found that *N. sativa* supplementation decreased body weight significantly (WMD = -1.46 kg; 95 % CI: −2.53, −0.39, p = 0.008) (Fig. 2). The between-study heterogeneity was considerable (I^2 = 94.6 %, p < 0.001). Accordingly, the mean age, health status, duration of intervention, type of intervention and control, and baseline BMI of the included studies could explain the heterogeneity. *N. sativa* oil supplementation, in durations of > 8-weeks, among subjects with type 2 diabetes mellitus (T2DM) and metabolic syndrome, and in RCTs that used sunflower oil as control, and a mean participant age ≥ 45 years, contributed to a greater decrease in body weight in both males and females, respectively (Table 4). A sensitivity analysis revealed no significant difference with any single study excluded (**Fig.S1**).

3.4. Effect of N. Sativa supplementation on BMI

Overall, 17 trials, with 19 treatment arms and 1,167subjects (case = 618, control = 549), reported the effect of *N. sativa* consumption on BMI. Pooled results of the random-effect model showed that *N. sativa* administration significantly reduced BMI (WMD: −0.58 kg/m^2, 95 % CI: −0.86, −0.29, p < 0.001) with a high degree of study heterogeneity (I^2 = 87.1 %, p < 0.001) (Fig. 3) which was reduced by subgroup analysis

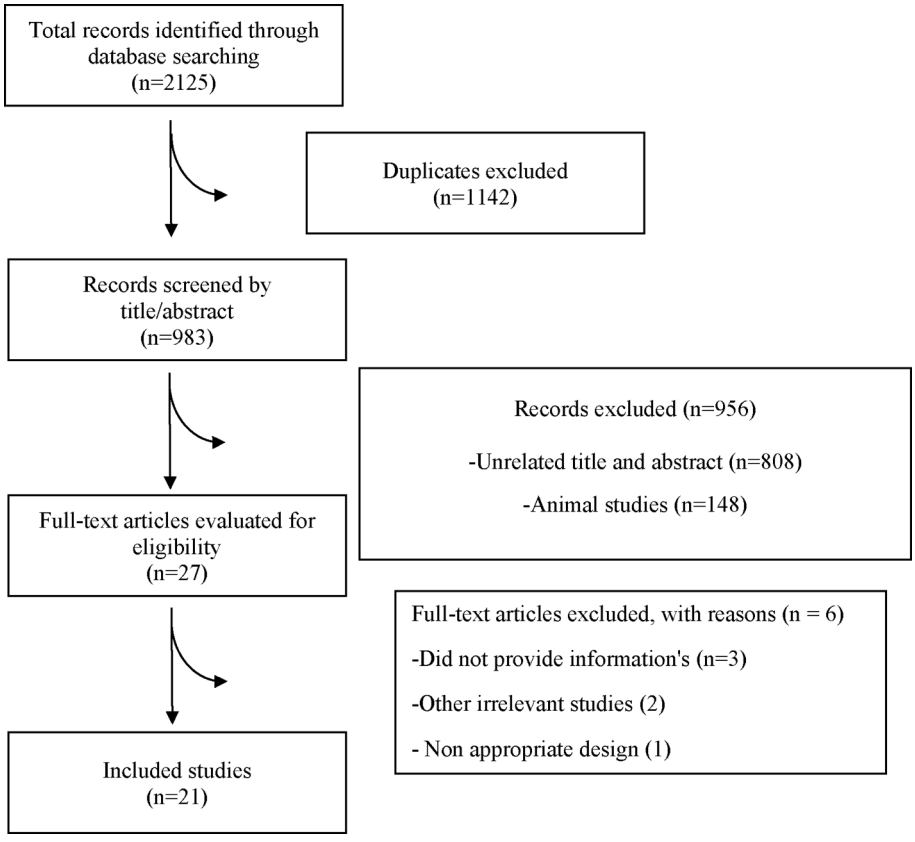

Fig. 1. Flow diagram of study selection.

Table 1
Study characteristics of included studies.

Author, year	Design	Participants, n	Health condition	Age, year	Intervention		Duration (week)
					Treatment group	Control group	
Dehkordi and Kamkhah (2008)	RA/DB/ parallel	M: 108 Int1: 36, Int2: 39 Con: 33	Mild Hypertension	Int: 44.6, Con: 43.1 Int: 43.7, Con: 43.1	200 mg/d *Nigella sativa* (capsule) 400 mg/d *Nigella sativa* (capsule)	Placebo: Placebo	8
Qidwai et al. (2009)	RA/DB/ parallel	M/F: 73 Int: 39, Con: 34	Hypercholesterolemia	Int: 45.58, Con: 46.86	1000 mg/d *Nigella sativa* (capsule)	Placebo: Calcium Lactate Powder	6
Datau et al. (2010)	RA/DB/ parallel	M: 39 Int: 20, Con: 19	Obese	30–45	3000 mg/d *Nigella sativa* (capsule)	Placebo: Wheat Flour	12
Fallah Huseini et al. (2013)	RA/DB/ parallel	M/F: 70 Int: 35, Con: 35	Healthy	Int: 47.3, Con: 45.4	5 ml/d *Nigella sativa* (oil)	Placebo: Mineral Oil	8
Bin Sayeed et al. (2013)	RA/SB/ parallel	M: 40 Int: 20, Con: 20	Healthy	Int: 55.8, Con: 55.9	1000 mg/d *Nigella sativa* (capsule)	Placebo: Psyllium Seed Husk	9
Ibrahim et al. (2014)	RA/ crossover	F: 35 Int: 18, Con: 17	Menopausal Women	41.5	1000 mg/d *Nigella sativa* (capsule)	Placebo: Placebo	4
Amin et al. (2015)	RA/DB/ parallel	M: 125 Int: 62, Con: 63	Metabolic syndrome	Int: 45.1, Con: 41.57	1500 mg/d *Nigella sativa* (capsule)	Placebo Ispaghula	8
Heshmati and Namazi (2015)	RA/DB/ parallel	M/F: 72 Int: 36, Con: 36	T2DM	Int: 45.3, Con: 47.5	3000 mg/d *Nigella sativa* (oil)	Placebo: Sunflower Soft Gel	12
Mahdavi et al. (2015)	RA/DB/ parallel	F: 84 Int: 43, Con: 41	Obese	Int: 41.5, Con: 39.3	3000 mg/d *Nigella sativa* (oil)	Placebo: Sunflower Oil	8
Hozoori et al. (2016)	RA/DB/ parallel	M: 67 Int: 37, Con: 30	Overweight	Int: 31.6, Con: 32.1	2.5 ml/d *Nigella sativa* (oil)	Placebo: Paraffin Oil	8
Farhangi et al. (2016)	RA/DB/ parallel	M/F: 40 Int: 20, Con: 20	Hashimoto's thyroiditis	Int: 35.7, Con: 33.95	2000 mg/d *Nigella sativa* powder (capsule)	Placebo: Starch	8
Hussain et al. (2017)	RA/parallel	M/F: 70 Int: 35, Con: 35	NAFLD	Int: 38, Con: 36	2000 mg/d *Nigella sativa* (capsule)	Placebo: Micro Crystalline Cellulose	12
Rachman and Darmawan (2017)	RA/SB/ parallel	M/F: 99 Int1: 33, Int2:33, Con: 33	Metabolic Syndrome	50	1500 mg/d *black seed oil* (soft gel capsule) 3000 mg/d *black seed oil* (soft gel capsule)	Placebo: Placebo	3
Rashidmayvan et al. (2019)	RA/DB/ parallel	M/F: 44 Int: 22, Con: 22	NAFLD	Int: 39, Con: 42.22	1000 mg/d *Nigella sativa* (oil)	Placebo: Paraffin Oil	8
Darand et al. (2019)	RA/DB/ parallel	M/F: 43 Int: 22, Con: 21	NAFLD	Int: 48.9, Con: 46.2	2000 mg/d *Nigella sativa* (capsule) + lifestyle modification	Placebo: Rice Starch	12
Naeimi et al. (2020)	RA/DB/ parallel	F: 55 Int: 32, Con: 23	PCOS	Int: 24, Con: 24	1000 mg/d *Nigella sativa oil* (soft gel capsule)	Placebo: sunflower oil	16
Khonche et al. (2019)	RA/DB/ parallel	M/F: 120 Int: 60, Con: 60	NAFLD	Int: 47.9, Con: 45.9	5 ml/d *Nigella sativa* (oil)	Placebo: Placebo	12
Hadi et al. (2021)	RA/DB/ parallel	M/F: 42 Int: 23, Con: 19	T2DM	Int: 51.4, Con: 56	1000 mg/d *Nigella sativa* (oil)	Placebo: Sunflower Oil	8
Safi et al. (2021)	RA/DB/ crossover	F: 39 Int: 19, Con: 20	Overweight and Obese	Int: 38.3, Con: 33.55	2000 mg/d *Nigella sativa* (capsule)	Placebo: Paraffin Oil	8
Shirazi et al. (2020)	RA/DB/ parallel	F: 140 Int: 70, Con: 70	Metabolic Syndrome	Int: 50.6, Con: 50.5	500 mg/d *Nigella sativa* (capsule)	Placebo: Starch	8
Tavakoli-Rouzbehani et al. (2021)	RA/DB/ parallel	M/F: 49 Int: 25, Con: 24	Coronary Artery Disease	Int: 55.92, Con: 54.25	2000 mg/d *Nigella sativa* (oil)	Placebo: Sunflower Oil	8

Abbreviations: RA; Randomized, DB; Double-blinded, M; Male, F; Female, Int; Intervention, Con; Control, SB; Single-blinded, T2DM; Type 2 diabetes mellitus, NAFLD; Non-alcoholic fatty liver disease, PCOS; Polycystic ovary syndrome.

based on gender, health status, duration of intervention, sample size, control type of intervention, and quality of the study. Subgroup analysis revealed that *N. sativa* supplementation, duration > 8 weeks, in subjects with T2DM and hypertension, with BMI 25–30 kg/m^2 and mean age < 45 years, in trials that used sunflower oil as control, contributed to a greater reduction in BMI levels (Table 4). According to the sensitivity analysis (**Fig.S2**), no single study had a significant effect on the total effect size of studies.

3.5. Effect of N. sativa supplementation on WC

A meta-analysis of 12 studies, with 785 participants (case = 402,

Table 2
Results of risk of bias assessment for randomized clinical trials included in the current meta-analysis on the effects of *N. sativa* supplementation on body composition.

Study	Random Sequence Generation	Allocation concealment	Reporting bias	Other sources of bias	Performance bias	Detection bias	Attrition bias
Dehkordi and Kamkhah (2008)	L	U	L	H	L	L	L
Qidwai et al. (2009)	L	L	L	H	L	L	L
Datau et al. (2010)	L	U	L	H	L	L	L
Fallah Huseini et al. (2013)	L	L	H	H	L	L	H
Bin Sayeed et al. (2013)	L	L	H	H	L	H	L
Ibrahim et al. (2014)	L	L	H	H	U	U	H
Amin et al. (2015)	L	L	L	L	L	L	L
Heshmati and Namazi (2015)	L	L	L	L	L	L	L
Mahdavi et al. (2015)	L	L	L	L	L	L	L
Hozoori et al. (2016)	L	L	L	H	L	L	L
Farhangi et al. (2016)	L	L	L	L	L	L	L
Rachman and Darmawan (2017)	L	L	H	H	L	H	L
Hussain et al. (2017)	L	L	L	H	U	U	H
Rashidmayvan et al. (2019)	L	U	L	H	L	L	H
Darand et al. (2019)	L	L	L	L	L	L	L
Khonche et al. (2019)	L	L	H	H	L	L	L
Naeimi et al. (2020)	L	L	H	L	L	L	L
Hadi et al. (2021)	L	L	L	L	L	L	L
Safi et al. (2021)	L	L	L	L	L	L	L
Shirazi et al. (2020)	L	L	L	H	L	L	L
Tavakoli-Rouzbehani et al. (2021)	L	L	L	L	L	L	L

Each study was assessed for risk of bias using the Cochrane Risk of Bias Assessment tool. Domains of assessment were included random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias and other sources of bias. Each domain was scored as "high risk" if it contained methodological flaws that may have affected the results, "low risk" if the flaw was deemed inconsequential, and "unclear risk" if information was insufficient to determine. If a study got "low risk" for all domains, it considered as a high quality study with totally low risk of bias.

Table 3
Summary of findings and quality of evidence assessment using the GRADE approach.

Outcome measure	Summary of findings		Quality of evidence assessment (GRADE)					
	No of patients (Trials)	WMD (95 % CI)	Risk of bias [a]	Inconsistency [b]	Indirectness [c]	Imprecision [d]	Publication bias [e]	Quality of evidence [f]
Anthropometric measures								
BMI (kg/m^2)	1,200 (17)	−0.58 (−0.86, −0.29)	Not Serious	Not Serious	Not Serious	Serious	Not Serious	Moderate
Body weight (kg)	1,028 (15)	−1.46 (−2.53, −0.39)	Not Serious	Not Serious	Not Serious	Serious	Not Serious	Moderate
WC (cm)	785 (12)	−2.54 (−6.27, 1.19)	Not Serious	Not Serious	Not Serious	Serious	Not Serious	Moderate
HC	453 (7)	−1.92 (−4.38, 0.54)	Not Serious	Not Serious	Not Serious	Not Serious	Not Serious	High
WHR	354 (7)	−0.03 (−0.07, 0.01)	Not Serious	Not Serious	Not Serious	Not Serious	Not Serious	High

BMI = Body mass index; WC = Waist circumference, HC = Hip circumference, WHR = Waist-to-hip ratio, WMD = weighted mean difference.
[a] Risk of bias based on the Cochrane risk-of-bias.
[b] Downgraded if there was a substantial unexplained heterogeneity ($I^2 > 50$ %, $P < 0.10$) that was unexplained by meta-regression or subgroup analyses.
[c] Downgraded if there were factors present relating to the participants, interventions, or outcomes that limited the generalizability of the results.
[d] Downgraded if the 95 % confidence interval (95 % CI) crossed the minimally important difference (MID) for benefit or harm. MIDs used for each outcome were: 0.2 kg/m^2 for BMI, and 2 cm for WC, 5–10 % for body weight (Viguiliouk et al., 2019).
[e] Downgraded if there was an evidence of publication bias using funnel plot.
[f] Since all included studies were randomized clinical trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded based on prespecified criteria. Quality was graded as high, moderate, low, very low.

control = 383), showed that *N. sativa* supplementation had no significant effect on WC compared with placebo (WMD: −2.54 cm, 95 % CI: −6.27, 1.19, p = 0.183) (Fig. 4). However, significant heterogeneity was detected between included trials (I^2 = 99.4 %, p < 0.001). Study population, control intervention type, and BMI were the possible sources of it. Conducting subgroup analysis indicated that the effects of *N. sativa oil* on WC in patients with T2DM, in durations of ≤ 8-weeks, in RCTs that used placebo as control, and subjects with a mean age ≥ 45 years in women were more robust than the overall result (Table 4). Moreover, the overall effects of *N. sativa* on WC changed to substantially meaningful after removing a study by Datau et al. (Datau et al., 2010) using sensitivity analysis (WMD: −1.49 cm, 95 % CI: −2.34, −0.64, p < 0.05) (**Fig. S3**).

3.6. Effect of N. sativa supplementation on HC

A pooled analysis on seven studies, including 230 cases and 223 controls, revealed that *N. sativa* had no significant effect on HC (WMD: −1.92 cm; 95 % CI: −4.38 to 0.54, p = 0.125; I^2 = 97.3 %, p < 0.001) (Fig. 5). High level of heterogeneity was reduced by intervention type. *N. sativa* oil supplementation, and in both sex contributed to a greater reduction in HC levels (Table 4). Sensitivity analysis for HC indicated that the pooled effect was influenced by the removal of a study conducted by Safi *et al.* (Safi et al., 2021) (WMD: −2.69 cm, 95 % CI: −5.26, −0.13, p < 0.05) (**Fig.S4**).

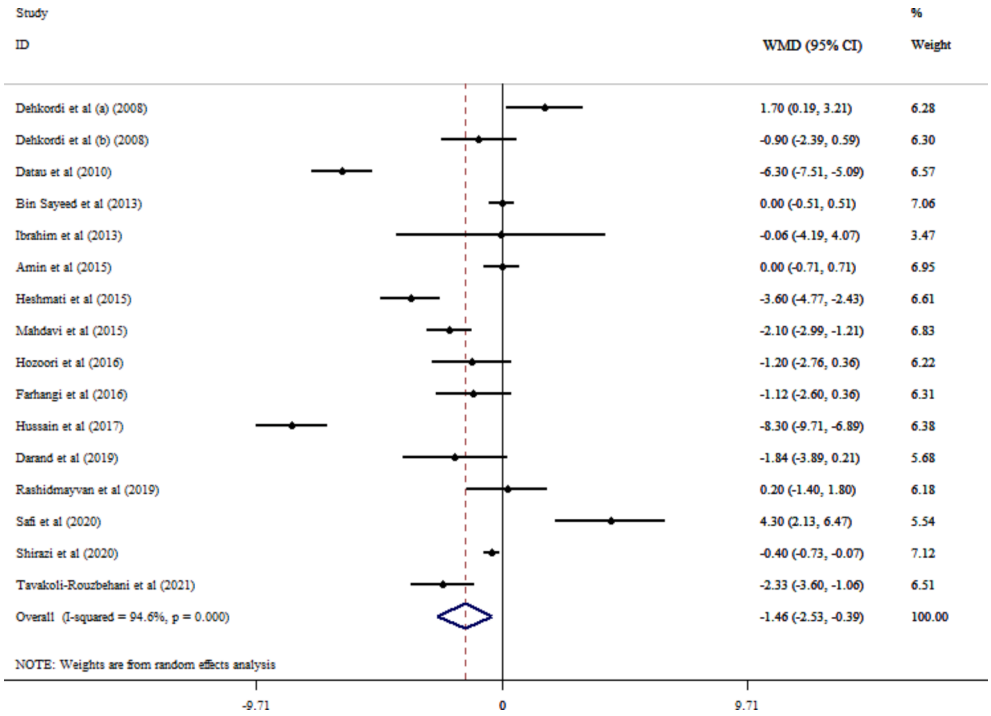

Fig. 2. Forest plot (A) detailing mean difference and 95 % confidence intervals (CIs) the effects of *N. sativa* supplementation on body weight levels.

3.7. Effect of N. sativa supplementation on WHR

The results of our analysis of seven studies, including 183 cases and 171 controls, indicated that *N. sativa* supplementation did not substantially reduce WHR (WMD = -0.03; 95 % CI: −0.07, 0.01, p = 0.145; I^2 = 98.9 %, p < 0.001) (Fig. 6). Baseline BMI, mean age, and intervention type were found to be possible sources of heterogeneity in subgroup analysis (Table 4). Sensitivity analysis for WHR did not show evidence of sensitivity (**Fig.S5**).

3.8. Publication bias

Using Egger's and Begg's tests, no small-study effects were detected for body weight, BMI, and WC (p > 0.05). Due to the funnel plot assessment's findings that suggested an uneven distribution of studies across body weight, BMI, and WC (**Fig.S6-8**), we carried out the trim and fill test. Consequently, trim and fill analysis for BW and WC revealed that the addition of five imputed studies increased the significance of the results (WMD: −2.64 kg, 95 %CI: −3.88, −1.40; p < 0.05), and (WMD: −4.44 cm, 95 % CI: −7.29, −1.59, p < 0.05). However, after trim and fill analysis (no imputed study), BMI results remained unchanged. Begg's tests revealed no publication bias for HC, and WHR (p = 0.999 and 0.548, respectively).

3.9. Non-linear dose–response relationships between doses of supplemental N. sativa and body composition indices

We conducted a non-linear dose–response analysis to examine the association between dose of *N. sativa* and effect sizes attributed to BW, BMI, and WC. Accordingly, our analysis suggested *N. sativa* supplementation did not significantly alter BW (**P-non-linear: 0.08**), BMI (**P-non-linear: 0.65**), and WC levels based on dose (**P-non-linear: 0.35**) (**Fig.S9-11**).

4. Discussion

Different healthy effects have been proposed for *N. sativa* including antimicrobial, cardioprotective, gastroprotective, neuroprotective, anticancer, anti-diabetic, anti-oxidant, anti-dyslipidemic, anti-obesity, immunomodulatory, anti-histaminic, anthelmintic, anti-infertility, anti-inflammatory, mucositis healing, nephroprotective, and anti-arthritic activities (Ahmad et al., 2021). This current updated meta-analysis of 21 controlled clinical trial studies evaluated the effects of *N. sativa* supplementation on body composition indices. We demonstrated that the effects of *N. sativa* on BW and BMI were significant, but not for WC, HC, and WHR. This indicates that anti-obesity effect of *N. sativa* is greater on general obesity than on abdominal obesity. Subgroup analysis revealed that participants with metabolic syndrome, hypertension, coronary artery disease, and T2DM in both genders, yielded greater benefits from *N. sativa* supplementation. Moreover, >8 weeks of *N. sativa* supplementation elicited a more beneficial effect on BW and BMI. However, ≤8 weeks of *N. sativa* supplementation led to a significant decrease in WC. *N. sativa* in oil form has a better improving effect on anthropometric indices than its capsule form especially as compared with sunflower oil or placebo.

A systematic review and meta-analysis by Namazi et al. (Namazi et al., 2018) in 2018 containing 11 clinical trials reported that *N. sativa* supplementation could moderately reduce BW, BMI, and WC. Similar to our results, Mousavi et al. (Mousavi et al., 2018) in 2018 reported that *N. sativa* reduced BW and BMI, while this effect was not significant regarding WC. However, the aforementioned study did not evaluate some anthropometric indicators, including HC and WHR, and evidence as not evaluated according to the GRADE approach. As a result, the quality of the results may be questioned. Moreover, the associated protocol was not prospectively registered in databases for systematic reviews, such as PROSPERO or the Cochrane database.

However, due to the high heterogeneity, this finding should be interpreted with caution. Therefore, we performed a comprehensive subgroup analysis based on the age, intervention duration, the dosage of *N. sativa*, study population, type of intervention and placebo, sample size, BMI, study quality, and gender of participants to investigate the source of heterogeneity. Subgroup analysis revealed that dosage of *N. sativa*, study population, control intervention type, gender, intervention type, and BMI can alter homogeneity of results, because they

Table 4
Subgroup analyses for the effects of *N. sativa* supplementation on body composition.

	No	WMD (95 % CI)[1]	P-within[2]	I^2 (%)[3]	P-heterogeneity[4]
***N. sativa* supplementation on body weight**					
Overall	16	−1.46 (−2.53, −0.39)	0.008	94.6	<0.001
Age(year)					
<45	10	−1.46 (−3.63, 0.71)	0.189	95.3	<0.001
≥45	6	−1.17 (−2.05, −0.29)	0.009	88.2	<0.001
Gender					
Women	4	0.20 (−1.68, 2.08)	0.833	90.5	<0.001
Men	5	−1.10 (−3.20, 1.00)	0.304	96.1	<0.001
Both	7	−2.62 (−4.69, −0.55)	0.013	92.9	<0.001
Intervention duration (week)					
≤8	11	−0.36 (−1.13, 0.41)	0.357	80.8	<0.001
>8	5	−4.00 (−7.42, −0.59)	0.022	97.9	<0.001
Intervention type					
N. sativa (capsule)	11	−1.26 (−2.66, 0.13)	0.076	95.8	<0.001
N. sativa oil	5	−1.90 (−3.01, −0.79)	<0.001	74.5	0.004
Study population					
NAFLD	3	−3.33 (−8.87, 2.21)	0.238	97	<0.001
Overweight and obese	4	−1.42 (−4.87, 2.02)	0.419	96.2	<0.001
Metabolic syndrome	2	−0.33 (−0.63, −0.03)	0.031	0.3	0.317
Menopausal Women	1	−0.06 (−4.19, 4.07)	0.977	0.0	<0.001
Hypertension	2	0.40 (−2.15, 2.94)	0.761	82.7	0.016
T2DM	1	−3.60 (−4.77, −2.43)	<0.001	–	–
Hashimoto's thyroiditis	1	−1.12 (−2.60, 0.36)	0.138	–	–
Healthy	1	0.00 (−0.51, 0.51)	0.999	–	–
Coronary artery disease	1	−2.33 (−3.60, −1.06)	<0.001	–	–
Control intervention type					
Sunflower oil	3	−2.64 (−3.56, −1.72)	<0.001	52.2	0.123
Placebo	13	−1.15 (−3.29, 0.09)	0.489	95.0	<0.001
Sample size					
≤50	8	−0.99 (−2.97, 0.99)	0326	94.1	<0.001
>50	8	−1.83 (−3.36, −0.30)	0.019	95.6	<0.001
BMI					
≤ 25	3	0.21 (−0.95, 1.38)	0.759	67.6	0.046
25–30	6	−2.12 (−4.56, 0.32)	0.088	95.6	<0.001
> 30	4	−0.95 (−3.53, 1.63)	0.471	92.4	<0.001
NR	3	−2.40 (−7.07, 2.28)	0.315	97.7	<0.001
Study quality					
Low	4	−2.12 (−6.49, 2.25)	0.342	97.5	<0.001
High	12	−1.23 (−2.35, −0.11)	0.032	93.1	<0.001
***N. sativa* supplementation on BMI**					
Overall	19	−0.58 (−0.86, −0.29)	<0.001	87.1	<0.001
Age(year)					
<45	10	−0.66 (−1.12, −0.21)	0.004	85.3	<0.001
≥45	9	−0.49 (−0.87, −0.10)	0.014	88.6	<0.001
Gender					
Women	3	0.19 (−0.47, 0.86)	0.565	16.0	0.304
Men	4	−0.60 (−1.21, −0.00)	0.049	88.5	<0.001
Both	12	−0.68 (−1.05, −0.31)	<0.001	89.3	<0.001
Intervention duration (week)					
≤8	14	−0.39 (−0.71, −0.06)	0.021	85.0	<0.001
>8	5	−1.20 (−1.96, −0.45)	0.002	90.4	<0.001
Intervention type					
N. sativa (capsule)	8	−0.64 (−1.21, −0.08)	0.025	88.2	<0.001
N. sativa oil	11	−0.53 (−0.89, −0.17)	0.003	87.5	<0.001
Study population					
NAFLD	4	−0.81 (−1.56, −0.05)	0.036	90.6	<0.001
Overweight and obese	3	−0.03 (−0.49, 0.55)	0.643	38.4	0.197

(*continued on next page*)

Table 4 (*continued*)

	No	WMD (95 % CI)[1]	P-within[2]	I^2 (%)[3]	P-heterogeneity[4]
Hypertension	2	−1.09 (−1.68, −0.51)	<0.001	66.2	0.086
T2DM	2	−1.52 (−1.88, −1.16)	<0.001	0.0	0.829
metabolic syndrome	3	0.08 (−0.19, 0.35)	0.565	39.9	0.189
Healthy	1	−1.10 (−1.43, −0.77)	<0.001	–	–
Hashimoto's thyroiditis	1	−0.49 (−1.03, 0.05)	0.074	–	–
Hypercholesterolemia	1	0.18 (−0.44, 0.80)	0.570	–	–
Coronary artery disease	1	−0.86 (−1.30, −0.42)	<0.001	–	–
PCOS	1	−1.00 (−2.66, 0.66)	0.238	–	–
Control intervention type					
Sunflower oil	5	−0.94 (−1.59, −0.29)	0.005	78.8	<0.001
Placebo	12	−0.46 (−0.78, −0.14)	0.005	86.2	<0.001
Others	2	−0.49 (−1.74, 0.76)	0.445	86.2	<0.001
Sample size					
≤50	6	−0.53 (−1.03, −0.03)	0.039	74.2	0.002
>50	13	−0.60 (−0.96, −0.24)	<0.001	90.0	<0.001
BMI					
≤ 25	5	−0.60 (−1.25, 0.04)	0.065	91.6	<0.001
25–30	10	−0.59 (−0.94, −0.24)	<0.001	84.4	<0.001
> 30	4	−0.39 (−1.46, −0.68)	0.479	88.1	<0.001
Study quality					
Low	5	−0.59 (−1.37, 0.20)	0.142	94.0	<0.001
High	14	−0.59 (−0.89, −0.29)	<0.001	82.1	<0.001
***N. sativa* supplementation on serum WC**					
Overall	12	−2.54 (−6.27, 1.19)	0.183	99.4	<0.001
Age(year)					
<45	6	−3.43 (−10.35, 3.49)	0.332	99.6	<0.001
≥45	6	−1.58 (−2.82, −0.33)	0.013	89.8	<0.001
Gender					
Women	3	−1.99 (−3.65, −0.34)	0.018	81.4	0.005
Men	3	−5.97 (−17.52, 5.59)	0.311	99.8	<0.001
Both	6	−1.54 (−2.95, −0.14)	0.032	88.9	<0.001
Intervention duration (week)					
≤8	10	−1.24 (−2.04, −0.45)	<0.001	81.4	<0.001
>8	2	−10.06 (−22.11, 1.99)	0.102	99.7	<0.001
Intervention type					
N. sativa (capsule)	7	−2.84 (−8.77, 3.10)	0.349	99.7	<0.001
N. sativa oil	5	−2.09 (−2.98, −1.20)	<0.001	67.1	0.016
Study population					
NAFLD	2	−2.34 (−5.43, 0.74)	0.137	92.0	<0.001
Metabolic syndrome	2	−0.92 (−1.91, 0.07)	0.069	73.6	0.051
Overweight or obese	4	−4.80 (−13.84, 4.25)	0.299	99.6	<0.001
Hashimoto's thyroiditis	1	−0.72 (−1.63, 0.19)	0.120	–	–
Hypercholesterolemia	1	1.25 (−0.02, 2.52)	0.053	–	–
Coronary artery disease	1	−2.05 (−3.00, −1.10)	<0.001	–	–
T2DM	1	−3.10 (−4.59, −1.61)	<0.001	–	–
Control intervention type					
Sunflower oil	3	−2.70 (−3.43, −1.97)	<0.001	30.3	0.238
Placebo	8	−2.91 (−3.43, −1.97)	0.017	99.6	<0.001
Others	1	−5.12 (−17.23, 6.99)	0.407	–	–
Sample size					
≤50	7	−3.62 (−9.73, 2.50)	0.246	99.6	<0.001
>50	5	−1.03 (−2.27, 0.21)	0.103	89.2	<0.001
BMI					
25–30	7	−0.98 (−1.86, −0.10)	0.029	78.0	<0.001
> 30	3	−3.31 (−4.47, −2.15)	<0.001	47.3	0.150
NR	2	−8.80 (−23.30, 5.70)	0.234	99.9	<0.001
Study quality					

(*continued on next page*)

Table 4 (*continued*)

	No	WMD (95 % CI)[1]	P-within[2]	I^2 (%)[3]	P-heterogeneity[4]
Low	2	−8.49 (−23.63, 6.65)	0.272	99.8	<0.001
High	10	−1.56 (−2.48, −0.65)	<0.001	86.4	<0.001
***N. sativa* supplementation on serum HC**					
Overall	7	−1.92 (−4.38, 0.54)	0.125	97.3	<0.001
Age(year)					
<45	3	0.33 (−1.97, 2.63)	0.778	94.1	<0.001
≥45	4	−3.71 (−8.15, 0.72)	0.101	98.2	<0.001
Gender					
Women	2	1.05 (−2.18, 4.28)	0.524	95.0	<0.001
Men	1	0.65 (−0.67, 1.97)	0.335	–	–
Both	4	−4.11 (−7.89, −0.32)	0.034	98.1	<0.001
Intervention duration (week)					
≤8	6	−2.12 (−5.02, 0.79)	0.153	97.8	<0.001
>8	1	−0.87 (−1.97, 0.23)	0.120	–	–
Intervention type					
N. sativa (capsule)	5	−2.40 (−6.26, 1.46)	0.223	98.2	<0.001
N. sativa oil	2	−0.95 (−1.59, −0.31)	0.003	0.0	0.394
Sample size					
≤50	4	−0.12 (−1.87, 1.64)	0.896	92.9	<0.001
>50	3	−4.53 (−11.74, 2.68)	0.218	98.8	<0.001
BMI					
25–30	4	−3.75 (−7.85, 0.35)	0.073	98.2	<0.001
> 30	3	0.42 (−1.86, 2.69)	0.721	93.0	<0.001
***N. sativa* supplementation on serum WHR**					
Overall	7	−0.03 (−0.07, 0.01)	0.145	98.9	<0.001
Age(year)					
<45	5	−0.04 (−0.11, 0.04)	0.324	99.2	<0.001
≥45	2	−0.02 (−0.04, −0.00)	0.050	92.1	<0.001
Intervention type					
N. sativa (capsule)	3	−0.03 (−0.04, −0.02)	<0.001	0.0	0.880
N. sativa oil	4	−0.03 (−0.08, 0.02)	0.276	99.5	<0.001
BMI					
≤30	4	−0.00 (−0.01, 0.00)	0.228	49.8	0.113
> 30	3	−0.07 (−0.13, −0.00)	0.048	98.5	<0.001

Abbreviation: WMD: weighted mean difference, CI: confidence interval NR; Not reported, T2DM; Type 2 diabetes mellitus, NAFLD; Non-alcoholic fatty liver disease, PCOS: Polycystic ovary syndrome.

[1] Obtained from the Random-effects model, [2]Refers to the mean (95 % CI, [3]Inconsistency, percentage of variation across studies due to heterogeneity, [4]Obtained from the Q-test.

can affect the overall effect size of the results. As a result, the interpretation of subgroup results can give a better picture of *N. sativa*'s effect on anthropometric indicators.

The analysis of subgroups showed that the effect of *N. sativa* on anthropometric indices is more dependent on the form of the supplement, the duration of the supplementation and the quality of the studies, rather than depending on age and gender. Thymoquinone (TQ), as a fat-soluble compound, is the main component of *N. sativa* oil, which is considered to be the main responsible for its biological function (Tavakkoli, Mahdian, Razavi, & Hosseinzadeh, 2017). The high concentration of TQ in its oil form compared to its powder form can explain the more positive anti-obesity effect of *N. sativa* oil (Razavi & Hosseinzadeh, 2014). The more improving effect of *N. sativa* on weight and BMI in>8 weeks indicates that the overload of *N. sativa* 's active components leads to the greater anti-obesity outcomes. Performed clinical trials have reported that the side effects of *N. sativa* appear not to be serious (Tavakkoli et al., 2017). The reducing effect of *N. sativa* on WC in ≤ 8 weeks can be due to the larger sample size (>50) in most of these studies compared to trials supplemented for > 8 weeks. As a basic principle in epidemiologic studies, the greater sample size can lead to a higher probability of statistically significant differences between groups (Andrade, 2020).

If only high-quality studies are considered, *N. sativa* can be considered as an agent for improving general and abdominal obesity by reducing weight, BMI, and WC. The presence of bias and improper randomization and blinding principles can departure of results from the truth (Lewis & Warlow, 2004). To determine the risk of bias, important sources of bias such as random sequence generation, allocation concealment, reporting bias, other sources of bias, performance bias, detection bias, and attrition bias were investigated in all studies. Results of risk of bias assessment of 21 RCTs included in the current meta-analysis showed that there were 11 high quality studies (Badar et al., 2017; Bin Sayeed et al., 2013; Fallah Huseini et al., 2013; Hussain et al., 2017; Ibrahim et al., 2014), and that the source of bias in most of them was related to reporting and unknown factors. The other 10 studies had high quality and a low risk of bias. Quality of evidence assessment using the GRADE approach revealed that quality of evidence for BW, BMI, and WC was moderate and for HC and WHR was high.Our results showed that BW, BMI, and WC reduction were greater when the control intervention was sunflower oil. Carotenoid, chlorophyll, and total polyphenols contents of black seed oil are greater than sunflower oil (Mazaheri, Torbati, Azadmard-Damirchi, & Savage, 2019). Therefore, robust anti-obesity effect of black seed oil compared to sunflower oil can be related to these higher contents.

N. sativa improves metabolism by reducing insulin resistance and modulating thyroid hormones (Avci, Ulutas, Ozdemir, Kivrak, & Bulbul, 2022; Mekkawy, Ahmed, & El-Sakhawy, 2020; Najmi, Nasiruddin,

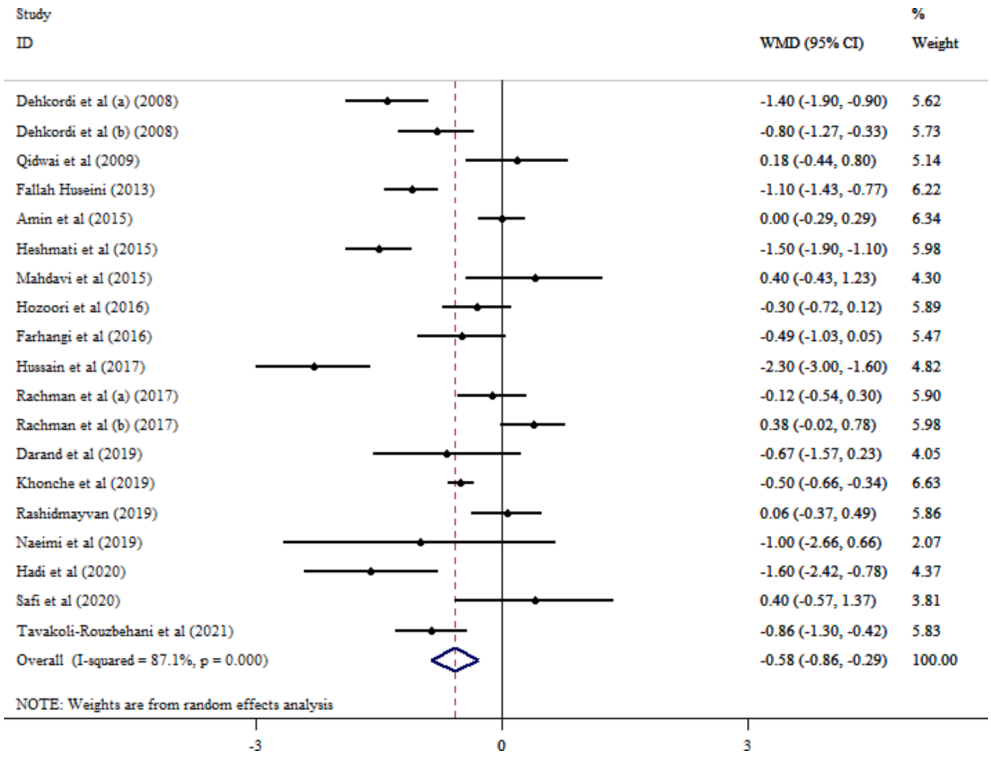

Fig. 3. Forest plot (A) detailing mean difference and 95 % confidence intervals (CIs) the effects of *N. sativa* supplementation on BMI levels.

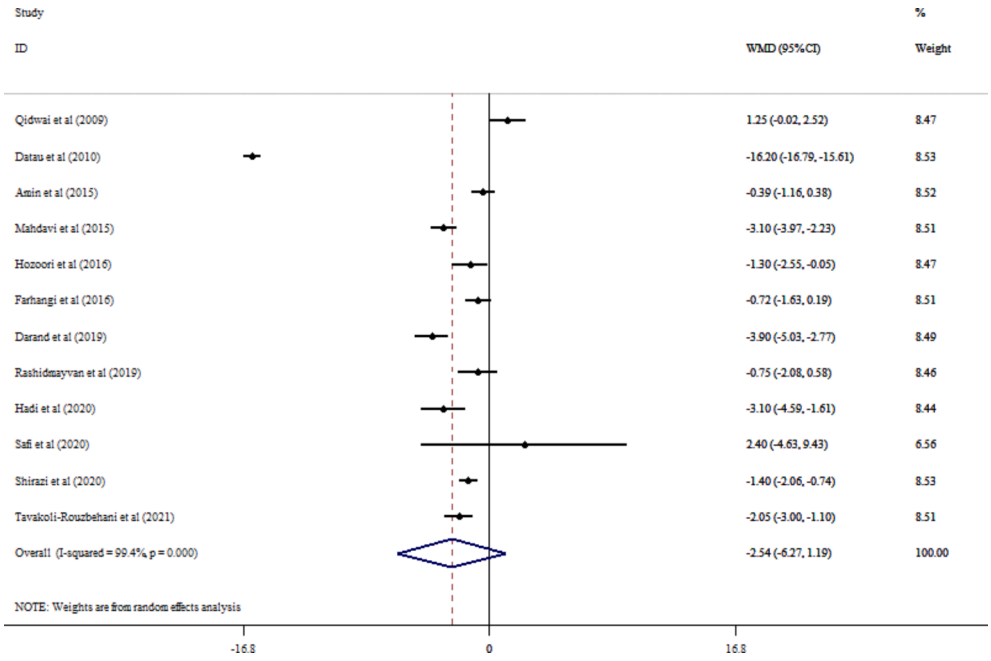

Fig. 4. Forest plot (A) detailing mean difference and 95 % confidence intervals (CIs) the effects of *N. sativa* supplementation on WC levels.

Khan, & Haque, 2008). TQ is one of the most abundant active natural substances in *N. sativa* seeds, which can help weight loss through a decrease in food intake, an improvement in lipid peroxidation, insulin sensitivity, and liver function (Kesen, 2021; Pari & Sankaranarayanan, 2009). Thymol, as another bioactive component of *N. sativa* seed, is an inhibitor of lipase and a lowering agent for unsaturated fatty acids that are involved in reducing BW (Abdollahzade Fard et al., 2021; Datau et al., 2010). *N. sativa* seed polysaccharides (NSSP) in high dosage interventions improve gut microbiome and increase unclassified Muribaculaceae and Bacteroides (Dong et al., 2020; Randhawa, Alenazy, Alrowaili, & Basha, 2017). Recent studies have determined the relationship between gut microbiota, body weight, and waist circumference (Gérard, 2016; Han et al., 2015; Osborne et al., 2020). In a study on mice, it was reported that hydroalcoholic and hexane extract of *N. sativa* can induce weight loss by positively affecting uncoupling protein 1 (UCP1) at the gene and protein level (Mahmoudi, Ghatreh Samani, Farrokhi, & Heidarian, 2018). Indeed, some studies have suggested that *N. sativa* suppresses appetite (Safi et al., 2021). Additionally,

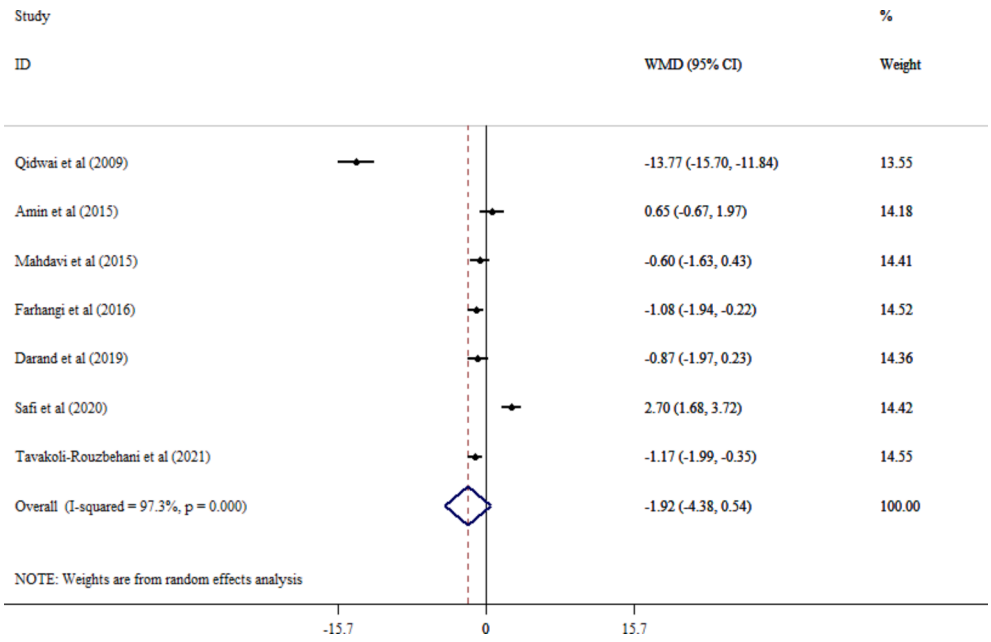

Fig. 5. Forest plot (A) detailing mean difference and 95 % confidence intervals (CIs) the effects of *N. sativa* supplementation on HC levels.

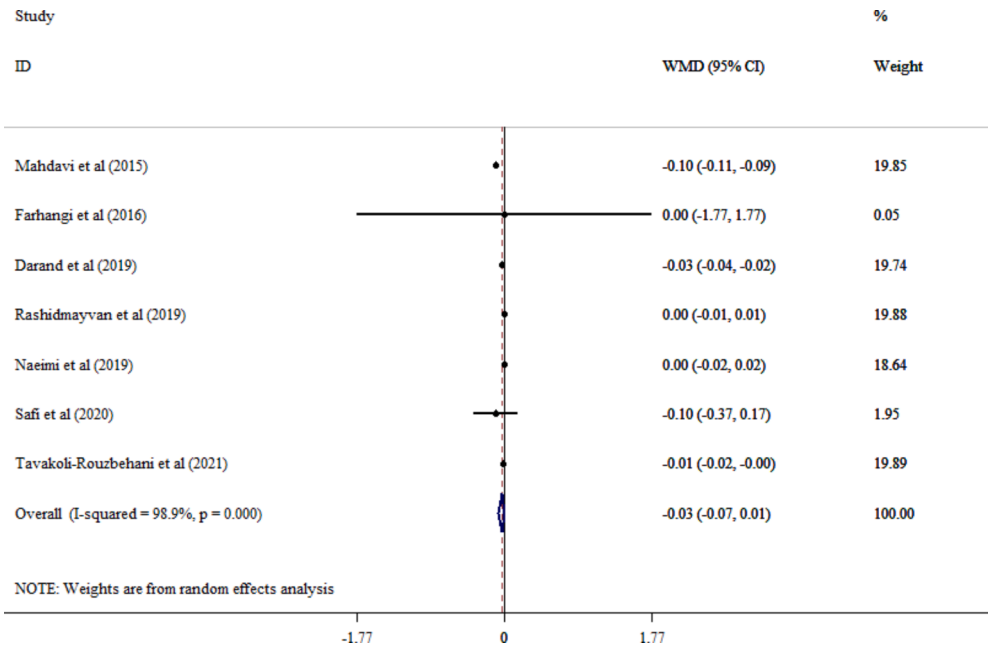

Fig. 6. Forest plot (A) detailing mean difference and 95 % confidence intervals (CIs) the effects of *N. sativa* supplementation on WHR levels.

N. sativa can act as an agonist of peroxisome proliferator-activated receptor-γ2 (PPAR-γ2) and stimulate the PPAR-γ2 receptors (Mahmoudi et al., 2018). PPAR-γ2 affects energy homeostasis and increases the expression of lipogenic genes and the differentiation of adipocytes in adipose tissues (Ryan et al., 2011). The major sterols of seeds are β-sitosterol, campesterol, stigmasterol, and 5-avenasterol, which are known to lower cholesterol levels (Aydin & Kart, 2021).

Although we provide a novel addition to the literature, there were some limitations in our study that warrant consideration. First, different types of *N. sativa* supplements in various doses were used in the included studies, potentially making it difficult to identify the most efficacious form of supplement. Second, body composition indices were measured by using different methods in these studies, which can harm comparability. Third, some of the included studies had a small sample sizes, reducing the statistical power in such studies. Fourth, participants in these clinical trials had different health statuses, which were not entirely accounted for individual studies. However, our study's strengths included registering the protocol in PROSPERO, conducting comprehensive, pre-defined, subgroup analyses, having a low risk of publication bias, determining the sources of significant heterogeneity, and performing a non-linear dose–response analysis.

5. Conclusion

The present meta-analysis confirms the potential benefits of *N. sativa* supplementation in reducing body composition indices including BW and BMI. The beneficial effects of *N. sativa* supplementation on WC and HC were shown after sensitivity analysis. It could be suggested as an

advantageous dietary component in managing obesity and related disorders. Moreover, it is suggested to supplement for a treatment period of ≥ 8 weeks. Overall, supplementation with *N. sativa* as a complementary treatment for weight management is supported by the results of this study.

6. Ethical consideration

The following study was carried out and reported based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) with attention to its main guiding principles. The protocols used for performing the present study can be found under registration in the following website; PROSPERO website, www.crd.york.ac.uk/PROSPERO (PROSPERO registration number = C RD42022358471).

7. Authors' contributions

NN and VM designed research; VM and AHM conducted research; VM performed statistical analysis; and ZK, NN, ES, CC and JJ wrote paper. VM and AHF had primary responsibility for final content. All authors have read and approved the final manuscript.

Funding

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

The Tabriz University of Medical Sciences Student Research Committee accepted and supported the research protocol (Registration code: 71125).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jff.2023.105565.

References

Abdollahzade Fard, A., Saboory, E., Tahmazi, Y., Rasmi, Y., Dindarian, S., & Parsamanesh, N. (2021). Effect of orally-administrated thymoquinone during pregnancy on litter size, pentylenetetrazol-induced seizure, and body weight in rat offspring. *Iran J Basic Med Sci, 24*(1), 30-37. 10.22038/ijbms.2020.47479.10930.

Ahmad, M. F., Ahmad, F. A., Ashraf, S. A., Saad, H. H., Wahab, S., Khan, M. I., … Athar, M. T. (2021). An updated knowledge of Black seed (Nigella sativa Linn.): Review of phytochemical constituents and pharmacological properties. *Journal of Herbal Medicine, 25*, Article 100404. https://doi.org/10.1016/j.hermed.2020.100404

Amin, F., Islam, N., Anila, N., & Gilani, A. (2015). Clinical efficacy of the co-administration of Turmeric and Black seeds (Kalongi) in metabolic syndrome–A double blind randomized controlled trial–TAK-MetS trial. *Complementary Therapies in Medicine, 23*(2), 165–174.

Andrade, C. (2020). Sample Size and its Importance in Research. *Indian Journal of Psychological Medicine, 42*(1), 102–103. https://doi.org/10.4103/ijpsym.Ijpsym_504_19

Avci, G., Ulutas, E., Ozdemir, V., Kivrak, I., & Bulbul, A. (2022). The positive effect of black seed (Nigella sativa L.) essential oil on thyroid hormones in rats with hypothyroidism and hyperthyroidism. *Journal of Food Biochemistry, 46*(4), e13801.

Aydin, E., & Kart, A. (2021). Health Promoting Activities of Nigella sativa Seeds. *Black cumin (Nigella sativa) seeds: Chemistry, Technology, Functionality, and Applications*, 153-177.

Badar, A., Kaatabi, H., Bamosa, A., Al-Elq, A., Abou-Hozaifa, B., Lebda, F., … Al-Almaie, S. (2017). 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. *Annals of Saudi medicine, 37*(1), 56–63.

Barazzoni, R., Gortan Cappellari, G., Ragni, M., & Nisoli, E. (2018). Insulin resistance in obesity: An overview of fundamental alterations. *Eating and Weight disorders-studies on Anorexia, Bulimia and Obesity, 23*(2), 149–157.

Begg, C. B., & Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, 1088–1101.

Bin Sayeed, M. S., Asaduzzaman, M., Morshed, H., Hossain, M., Kadir, M. F., & Rahman, M. (2013). The effect of Nigella sativa Linn. seed on memory, attention and cognition in healthy human volunteers.

Clifton, P. M., & Keogh, J. B. (2018). Effects of different weight loss approaches on CVD risk. *Current Atherosclerosis Reports, 20*(6), 1–8.

Crippa, A., & Orsini, N. (2016). Dose-response meta-analysis of differences in means. *BMC medical research methodology, 16*(1), 1–10.

Darand, M., Darabi, Z., Yari, Z., Hedayati, M., Shahrbaf, M. A., Khoncheh, A., … Hekmatdoost, A. (2019). The effects of black seed supplementation on cardiovascular risk factors in patients with nonalcoholic fatty liver disease: A randomized, double-blind, placebo-controlled clinical trial. *Phytotherapy Research, 33*(9), 2369–2377.

Daryabeygi-Khotbehsara, R., Golzarand, M., Ghaffari, M. P., & Djafarian, K. (2017). Nigella sativa improves glucose homeostasis and serum lipids in type 2 diabetes: A systematic review and meta-analysis. *Complementary Therapies in Medicine, 35*, 6–13.

Datau, E., Surachmanto, E. E., Pandelaki, K., & Langi, J. (2010). Efficacy of Nigella sativa on serum free testosterone and metabolic disturbances in central obese male. *Acta Medica Indonesiana, 42*(3), 130–134.

Dehkordi, F. R., & Kamkhah, A. F. (2008). Antihypertensive effect of Nigella sativa seed extract in patients with mild hypertension. *Fundamental & Clinical Pharmacology, 22*(4), 447–452.

DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials, 7*(3), 177–188.

Dong, J., Liang, Q., Niu, Y., Jiang, S., Zhou, L., Wang, J., … Kang, W. (2020). Effects of Nigella sativa seed polysaccharides on type 2 diabetic mice and gut microbiota. *International Journal of Biological Macromolecules, 159*, 725–738. https://doi.org/10.1016/j.ijbiomac.2020.05.042

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ, 315*(7109), 629–634.

Fallah Huseini, H., Amini, M., Mohtashami, R., Ghamarchehre, M., Sadeqhi, Z., Kianbakht, S., & Fallah Huseini, A. (2013). Blood pressure lowering effect of Nigella sativa L. seed oil in healthy volunteers: A randomized, double-blind, placebo-controlled clinical trial. *Phytotherapy Research, 27*(12), 1849–1853.

Farhangi, M. A., Dehghan, P., Tajmiri, S., & Abbasi, M. M. (2016). The effects of Nigella sativa on thyroid function, serum Vascular Endothelial Growth Factor (VEGF)–1, Nesfatin-1 and anthropometric features in patients with Hashimoto's thyroiditis: A randomized controlled trial. *BMC Complementary and Alternative Medicine, 16*(1), 1–9.

Gérard, P. (2016). Gut microbiota and obesity. *Cellular and Molecular Life Sciences, 73*(1), 147–162.

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., & Schünemann, H. J. (2008). GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ, 336*(7650), 924–926.

Hadi, S., Daryabeygi-Khotbehsara, R., Mirmiran, P., McVicar, J., Hadi, V., Soleimani, D., & Askari, G. (2021). Effect of Nigella sativa oil extract on cardiometabolic risk factors in type 2 diabetes: A randomized, double-blind, placebo-controlled clinical trial. *Phytotherapy Research, 35*(7), 3747–3755.

Hamdan, A., Haji Idrus, R., & Mokhtar, M. H. (2019). Effects of Nigella sativa on type-2 diabetes mellitus: A systematic review. *International journal of environmental research and public health, 16*(24), 4911.

Han, K., Bose, S., Kim, Y.-M., Chin, Y.-W., Kim, B.-S., Wang, J.-H., … Kim, H. (2015). Rehmannia glutinosa reduced waist circumferences of Korean obese women possibly through modulation of gut microbiota. *Food & Function, 6*(8), 2684–2692.

Harsha, D. W., & Bray, G. A. (2008). Weight loss and blood pressure control (Pro). *Hypertension, 51*(6), 1420–1425.

Hasegawa, Y., Nakagami, T., Oya, J., Takahashi, K., Isago, C., Kurita, M., … Uchigata, Y. (2019). Body weight reduction of 5 improved blood pressure and lipid profiles in obese men and blood glucose in obese women: A four-year follow-up observational study. *Metabolic Syndrome and Related Disorders, 17*(5), 250–258.

Heshmati, J., & Namazi, N. (2015). Effects of black seed (Nigella sativa) on metabolic parameters in diabetes mellitus: A systematic review. *Complementary Therapies in Medicine, 23*(2), 275–282.

Heshmati, J., Namazi, N., Memarzadeh, M.-R., Taghizadeh, M., & Kolahdooz, F. (2015). Nigella sativa oil affects glucose metabolism and lipid concentrations in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *Food Research International, 70*, 87–93.

Higgins, J. P. T., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., … Sterne, J. A. C. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ, 343*, Article d5928. https://doi.org/10.1136/bmj.d5928

Hozoori, M., Fallah Hoseini, H., Kolahdooz, M., Nasri, S., & Zadeh Modarress, S. (2016). The effects of Nigella sativa L. seed oil on BMI, WC and FBS in overweight men: A randomized controlled clinical trial. *Advanced Herbal Medicine, 2*(4), 35–41.

Hussain, M., Tunio, A. G., Arain, L. A., & Shaikh, G. S. (2017). Effects of Nigella sativa on various parameters in patients of non-alcoholic fatty liver disease. *Journal of Ayub Medical College Abbottabad, 29*(3), 403–407.

Ibrahim, R. M., Hamdan, N. S., Ismail, M., Saini, S. M., Abd Rashid, S. N., Abd Latiff, L., … Mahmud, R. (2014). Protective effects of Nigella sativa on metabolic syndrome in menopausal women. *Advanced Pharmaceutical Bulletin, 4*(1), 29.

Kesen, S. (2021). Composition and functionality of Nigella sativa seed extracts *Black cumin (Nigella sativa) seeds: Chemistry, Technology, Functionality, and Applications* (pp. 481-499): Springer.

Khonche, A., Huseini, H. F., Gholamian, M., Mohtashami, R., Nabati, F., & Kianbakht, S. (2019). Standardized Nigella sativa seed oil ameliorates hepatic steatosis, aminotransferase and lipid levels in non-alcoholic fatty liver disease: A randomized, double-blind and placebo-controlled clinical trial. *Journal of Ethnopharmacology, 234*, 106–111.

Kizi, K. S. A., & Kizi, A. B. J. (2022). THERAPEUTIC POTENTIAL OF NIGELLA SATIVA: A MIRACLE HERB. *European International Journal of Multidisciplinary Research and Management Studies, 2*(04), 259–262.

Korak, T., Ergül, E., & Sazci, A. (2020). Nigella sativa and cancer: A review focusing on breast cancer, inhibition of metastasis and enhancement of natural killer cell cytotoxicity. *Current Pharmaceutical Biotechnology, 21*(12), 1176–1185.

Lafia, A. T., Ketounou, T. R., Honfoga, J. N. B., Bonou, S. I., & Zimé, A. K. B. (2022). Dietary habits, prevalence of obesity and overweight in developed and developing countries. *Research, Society and Development, 11*(10).

Lewis, S. C., & Warlow, C. P. (2004). How to spot bias and other potential problems in randomised controlled trials. *Journal of Neurology, Neurosurgery & Psychiatry, 75*(2), 181–187. https://doi.org/10.1136/jnnp.2003.025833

Lim, H. J., Xue, H., & Wang, Y. (2020). Global trends in obesity. *Handbook of Eating and Drinking: Interdisciplinary Perspectives*, 1217-1235.

López-Domènech, S., Martínez-Herrera, M., Abad-Jiménez, Z., Morillas, C., Escribano-López, I., Díaz-Morales, N., … Rocha, M. (2019). Dietary weight loss intervention improves subclinical atherosclerosis and oxidative stress markers in leukocytes of obese humans. *International Journal of Obesity, 43*(11), 2200–2209.

Mahdavi, R., Alizadeh, M., Namazi, N., & Farajnia, S. (2016). Changes of body composition and circulating adipokines in response to Nigella sativa oil with a calorie restricted diet in obese women. *Journal of Herbal Medicine, 6*(2), 67–72.

Mahdavi, R., Namazi, N., Alizadeh, M., & Farajnia, S. (2015). Effects of Nigella sativa oil with a low-calorie diet on cardiometabolic risk factors in obese women: A randomized controlled clinical trial. *Food & Function, 6*(6), 2041–2048.

Mahmoudi, A., Ghatreh Samani, K., Farrokhi, E., & Heidarian, E. (2018). Effects of Nigella sativa Extracts on the Lipid Profile and Uncoupling Protein-1 Gene Expression in Brown Adipose Tissue of Mice. *Advanced Biomedical Research, 7*, 121. https://doi.org/10.4103/abr.abr_91_18

Maideen, N. M. (2022). Nigella Sativa (Black seeds)–Potential Herb to Help Weight Loss. *Current Traditional Medicine, 8*(4), 1–7.

Mazaheri, Y., Torbati, M., Azadmard-Damirchi, S., & Savage, G. P. (2019). Oil extraction from blends of sunflower and black cumin seeds by cold press and evaluation of its physicochemical properties. *Journal of Food Processing and Preservation, 43*(10), e14154.

Mekkawy, A. M., Ahmed, Y. H., & El-Sakhawy, M. A. (2020). Ameliorative effect of Nigella sativa oil and vitamin C on the thyroid gland and cerebellum of adult male albino rats exposed to Monosodium glutamate (histological, immunohistochemical and biochemical studies). *Tissue and Cell, 66*, Article 101391.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The, P. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine, 6*(7), e1000097.

Mostafa, T. M., Hegazy, S. K., Elnaidany, S. S., Shehabeldin, W. A., & Sawan, E. S. (2021). Nigella sativa as a promising intervention for metabolic and inflammatory disorders in obese prediabetic subjects: A comparative study of Nigella sativa versus both lifestyle modification and metformin. *Journal of Diabetes and its Complications, 35*(7), Article 107947.

Mousavi, S. M., Sheikhi, A., Varkaneh, H. K., Zarezadeh, M., Rahmani, J., & Milajerdi, A. (2018). Effect of Nigella sativa supplementation on obesity indices: A systematic review and meta-analysis of randomized controlled trials. *Complementary Therapies in Medicine, 38*, 48–57.

Musazadeh, V., Zarezadeh, M., Ghalichi, F., Kalajahi, F., & Ghoreishi, Z. (2022). Vitamin D supplementation positively affects anthropometric indices: Evidence obtained from an umbrella meta-analysis. *Frontiers in Nutrition, 9*.

Naeimi, S. A., Hajimehdipoor, H., & Saber, S. (2020). Comparing the effect of Nigella sativa oil soft gel and placebo on oligomenorrhea, amenorrhea and laboratory characteristics in patients with polycystic ovarian syndrome, a randomized clinical trial. *Research Journal of Pharmacognosy, 7*(1), 49–59.

Najmi, A., Nasiruddin, M., Khan, R. A., & Haque, S. F. (2008). Effect of Nigella sativa oil on various clinical and biochemical parameters of insulin resistance syndrome. *International Journal of Diabetes in Developing countries, 28*(1), 11.

Namazi, N., Larijani, B., Ayati, M. H., & Abdollahi, M. (2018). The effects of Nigella sativa L. on obesity: A systematic review and meta-analysis. *Journal of Ethnopharmacology, 219*, 173–181.

Osborne, G., Wu, F., Yang, L., Kelly, D., Hu, J., Li, H., … Shaheen, I. (2020). The association between gut microbiome and anthropometric measurements in Bangladesh. *Gut Microbes, 11*(1), 63–76.

Pari, L., & Sankaranarayanan, C. (2009). Beneficial effects of thymoquinone on hepatic key enzymes in streptozotocin–nicotinamide induced diabetic rats. *Life Sciences, 85*(23), 830–834. https://doi.org/10.1016/j.lfs.2009.10.021

Payab, M., Hasani-Ranjbar, S., Shahbal, N., Qorbani, M., Aletaha, A., Haghi-Aminjan, H., … Hassani, S. (2020). Effect of the herbal medicines in obesity and metabolic syndrome: A systematic review and meta-analysis of clinical trials. *Phytotherapy Research, 34*(3), 526–545.

Phulwaria, R., Kaushal, K., Sharma, A. K., Mishra, R. C., & Soni, P. (2018). A review on folklore uses and therapeutic indications of Nigella sativa-a miracle herb. *World Journal of Pharmaceutical Research, 7*, 1369–1379.

Qidwai, W., Hamza, H. B., Qureshi, R., & Gilani, A. (2009). Effectiveness, safety, and tolerability of powdered Nigella sativa (kalonji) seed in capsules on serum lipid levels, blood sugar, blood pressure, and body weight in adults: Results of a randomized, double-blind controlled trial. *The Journal of Alternative and Complementary Medicine, 15*(6), 639–644.

Rachman, P., & Darmawan, E. (2017). *The efficacy of black cumin seed (Nigella sativa) oil and hypoglycemic drug combination to reduce HbA1c level in patients with* metabolic *syndrome risk*. Paper presented at the IOP Conference Series: Materials Science and Engineering.

Randhawa, M. A., Alenazy, A. K., Alrowaili, M. G., & Basha, J. (2017). An active principle of Nigella sativa L., thymoquinone, showing significant antimicrobial activity against anaerobic bacteria. *Journal of Intercultural Ethnopharmacology, 6*(1), 97–101. https://doi.org/10.5455/jice.20161018021238

Rashidmayvan, M., Mohammadshahi, M., Seyedian, S. S., & Haghighizadeh, M. H. (2019). The effect of Nigella sativa oil on serum levels of inflammatory markers, liver enzymes, lipid profile, insulin and fasting blood sugar in patients with non-alcoholic fatty liver. *Journal of Diabetes & Metabolic Disorders, 18*(2), 453–459.

Razavi, B., & Hosseinzadeh, H. (2014). A review of the effects of Nigella sativa L. and its constituent, thymoquinone, in metabolic syndrome. *Journal of Endocrinological Investigation, 37*, 1031–1040.

Ryan, K. K., Li, B., Grayson, B. E., Matter, E. K., Woods, S. C., & Seeley, R. J. (2011). A role for central nervous system PPAR-γ in the regulation of energy balance. *Nature Medicine, 17*(5), 623–626.

Safi, S., Razmpoosh, E., Fallahzadeh, H., Mazaheri, M., Abdollahi, N., Nazari, M., … Salehi-Abargouei, A. (2021). The effect of Nigella sativa on appetite, anthropometric and body composition indices among overweight and obese women: A crossover, double-blind, placebo-controlled, randomized clinical trial. *Complementary Therapies in Medicine, 57*, Article 102653.

Shirazi, M., Khodakarami, F., Feizabad, E., & Ghaemi, M. (2020). The effects of nigella sativa on anthropometric and biochemical indices in postmenopausal women with metabolic syndrome. *Endocrine, 69*(1), 49–52.

Tavakkoli, A., Mahdian, V., Razavi, B. M., & Hosseinzadeh, H. (2017). Review on Clinical Trials of Black Seed (Nigella sativa) and Its Active Constituent, Thymoquinone. *Journal of Pharmacopuncture, 20*(3), 179–193. https://doi.org/10.3831/kpi.2017.20.021

Tavakoli-Rouzbehani, O. M., Abbasnezhad, M., Kheirouri, S., & Alizadeh, M. (2021). Effects of Nigella sativa oil supplementation on selected metabolic parameters and anthropometric indices in patients with coronary artery disease: A randomized, double-blind, placebo-controlled clinical trial. *Phytotherapy Research, 35*(7), 3988–3999.

Viguiliouk, E., Kendall, C. W. C., Kahleová, H., Rahelić, D., Salas-Salvadó, J., Choo, V. L., … Sievenpiper, J. L. (2019). Effect of vegetarian dietary patterns on cardiometabolic risk factors in diabetes: A systematic review and meta-analysis of randomized controlled trials. *Clinical Nutrition, 38*(3), 1133–1145. https://doi.org/10.1016/j.clnu.2018.05.032

Zaoui, A., Cherrah, Y., Mahassini, N., Alaoui, K., Amarouch, H., & Hassar, M. (2002). Acute and chronic toxicity of Nigella sativa fixed oil. *Phytomedicine, 9*(1), 69–74.