Received: 10 September 2022 | Revised: 4 April 2023 | Accepted: 9 May 2023

DOI: 10.1002/ptr.7891

REVIEW

WILEY

Antihypertensive effects of *Nigella sativa* supplementation: An updated systematic review and meta-analysis of randomized controlled trials

Zeynab Kavyani[1,2] | Vali Musazadeh[1,2] | Ehsan Safaei[1] | Mina Mohammadi Asmaroud[3] | Fatemeh Khashakichafi[3] | Sana Sedgh Ahrabi[1] | Parvin Dehghan[4]

[1]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

[2]School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

[3]Department of Pharmacy, Xi'an Jiaotong University of Medical Sciences, Xi'an, China

[4]Nutrition Research Center, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran

Correspondence
Parvin Dehghan, Nutrition Research Center, Faculty of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran.
Email: dehghan.nut@gmail.com

Vali Musazadeh, School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.
Email: musazadehv@tbzmed.ac.ir

Funding information
Tabriz University of Medical Sciences Student Research Committee, Grant/Award Number: 71664

Abstract

Clinical studies have suggested that *Nigella Sativa* (*N. sativa*) supplementation may effectively reduce blood pressure, but the findings are controversial. Therefore, this study aimed to examine the effects of *N. sativa* on blood pressure in adults. PubMed, Cochrane Library, Web of Science, Scopus, Embase databases, and Google Scholar were searched till August 2022. To analyze weighted mean differences (WMDs), a random-effects model was utilized. Nonlinear dose–response analysis and a meta-regression were conducted. *N. sativa* supplementation was effective in reducing both systolic (WMD: −3.06 mmHg; 95% CI: −3.89 to −2.22, $p < 0.001$; $I^2 = 84.7\%$, $p < 0.001$) and diastolic blood pressure (WMD = −2.69 mmHg; 95% CI: −3.72, −1.66, $p < 0.001$; $I^2 = 97.3\%$, $p < 0.001$). The current meta-analysis suggests that *N. sativa* supplementation can improve blood pressure and claims that *N. sativa* could be used as an effective approach to blood pressure management.

KEYWORDS
blood pressure, hypertension, meta-analysis, *nigella sativa*, systematic review

1 | INTRODUCTION

High blood pressure, also known as hypertension (HTN), is defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg (Nugroho et al., 2022). HTN is an established risk factor for stroke, ischemic heart disease (Burnier & Egan, 2019), and renal dysfunction (Hall et al., 2019). HTN is one of the main causes of cardiovascular mortality and morbidity worldwide, it is preventable and affects over one billion adults, and the most common reason for medical consultation (Valente Silva et al., 2022). Diet and lifestyle modification can regulate BP to control HTN or its associated outcomes (Carey, Whelton, & Committee, 2018). Although various antihypertensive drugs are available, there has been a spreading interest and need for non-pharmacological interventions like medical plants which have a critical role in BP reduction (Mahmood et al., 2019).

Nigella sativa L. (*N. sativa*), as black cumin, has been used for centuries, especially in the Middle East, India, and Northern Africa. This plant flowers every year and have black seeds which are the most precious part with important health effects. *N. sativa* is a natural remedy that is recommended for health conditions such as diabetes, cancer, hypercholesterolemia, inflammation, arterial HTN, and gastrointestinal disorders. *N. sativa*'s BP-lowering effect has been reported in animals (Ahmed & El-Mottaleb, 2013; Jaarin et al., 2015) and human studies (Amin et al., 2015; Bin Sayeed et al., 2013; Datau et al., 2010;

Zeynab Kavyani and Vali Musazadeh have contributed equally to this work and share first authorship.

Dehkordi & Kamkhah, 2008; Fallah Huseini et al., 2013; Ibrahim et al., 2014; Latiff et al., 2014; Mahdavi et al., 2015; Najmi et al., 2013; Qidwai et al., 2009; Sayeed et al., 2014).

Numerous randomized controlled trials (RCTs) have shown that *N. sativa* can lower BP. Despite growing study on *N. sativa*, there is inconsistency among trials examining the effects of *N. sativa* on BP, with some demonstrating favorable effects and others not. A previous meta-analysis published in 2016 assessed the antihypertensive effects of *N. sativa* on BP in adults using 11 studies, although some did not examine changes in BP in detail (Sahebkar et al., 2016). We have further researched *N. sativa* effects on BP in adults due to the contradictory results of these studies and the lack of a thorough meta-analysis. Thus, we performed a meta-analysis of RCTs, as studies with the highest quality of evidence, to better quantify the effect of *N. sativa* on BP.

2 | METHODS

This study was performed based on the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (Moher et al., 2009). Moreover, the protocol of this study is registered in PROSPERO under the number CRD42022347964.

2.1 | Search strategy

We conducted a detailed literature search using online databases including PubMed, Cochrane Library, Scopus, Web of Science, Embase, and Google Scholar until August 20, 2022 without restriction time to discover related articles on the impact of *N. Sativa* supplementation on BP in adults. In the search strategy (Table S1), the following Medical Subject Headings (MeSH) and subject terms or keywords were used.

References from all relevant peer-reviewed research were consulted and cross-referenced through databases to make sure that no articles were missed. Duplicates were excluded from consideration and following citations were included in the Endnote screening software.

2.2 | Inclusion and exclusion criteria

The considered criteria for this meta-analysis were: (i) parallel or cross-over designed RCTs, (ii) examination of the effectiveness of *N. sativa* on BP, (iii) providing baseline and end-of-trial values of BP in both groups of intervention and control, and (iv) supplementing (with *N. sativa*) period of at least 2 weeks. Experimental studies, case reports, animal studies, observational studies, in vitro studies were excluded from the meta-analysis.

2.3 | Quality assessment and certainty assessment

The risk of bias assessment in the selected studies was evaluated using the Cochrane Collaboration's risk of bias tool (Higgins et al., 2011). The quality of the studies was assessed by two independent authors (ZK and SSA) based on the following criteria: random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias, and other potential sources of bias. Therefore, each domain of study bias was categorized under terms such as "low," "moderate," and "unclear." A corresponding author evaluated and found differentiations in study bias between two reviewers in each domain (VM). We assessed the overall certainty of evidence in studies according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines working group (gradeworkinggroup.org) (Guyatt et al., 2008). Quality of evidence was divided into four categories considering the evaluation criteria and categorized as high, moderate, low, and very low.

2.4 | Study selection and data extraction

Each of the qualified studies was screened and two independent investigators (ZK and ES) extracted the data. Name of the first author, publication year, country of origin, study design, sample group size (placebo/control and intervention), participant demographics (mean ± standard deviation [SD], gender, mean age, and the baseline of body mass index [BMI]), *N. sativa* dosage, intervention duration, mean± SD of BP (SBP and DBP) changes for both groups (intervention and control), and type of *N. sativa* supplement and control were contained in data extracted. For conducting data analysis, whenever possible, dataset values were transformed to the most common units of expression.

2.5 | Quantitative data synthesis

To examine the effect size for markers of BP, mean differences and SD for control and intervention groups were collected. Additionally, random-effects models were used to estimate weighted mean differences (WMDs) with 95% confidence intervals (CIs) (DerSimonian & Laird, 1986). In studies reporting standard errors (SEs), 95% CIs, and interquartile ranges (IQRs), the means + SD values were calculated. All BP units were collected in mmHg. Cochran's Q test and an *I*-square (I^2) statistic was utilized to determine the heterogeneity between studies where $I^2 > 50.5\%$ or $p < 0.1$ was considered as having high heterogeneity between studies. To find potential sources of heterogeneity, we conducted a subgroup analysis in conformity with the baseline BMI, duration of the study, intervention dosage, health condition, mean age, type of *N. sativa* product, study quality, gender, and sample size. To determine the effect of individual studies on the overall estimation, a sensitivity analysis was carried out. Egger's regression asymmetry test and Begg's adjusted rank correlation were conducted to analyze small study effects (Begg & Mazumdar, 1994; Egger et al., 1997). Using funnel plots, the publication bias assessment was carried out. In order to impute potentially missing studies in case of finding publication bias, we used the "trim and fill" method. A meta-regression analysis was conducted to investigate probable association between alterations in BP corresponding to *N. sativa* supplementation

and relevant moderator factors such as *N. sativa* dosage, duration of the intervention, and sample size. Performed fractional polynomial modeling also was utilized to explore nonlinear potential effects of *N. sativa* dosage (g/day) and intervention duration (weeks). For statistical analysis STATA software, version 16 (Stata Corp, College Station, TX), was used. $p < 0.05$ were considered statistically significant for all analyses.

3 | RESULTS

3.1 | Study selection

The initial search yielded 2231 studies; however, 368 of those were removed due to duplication. Another 1834 studies due to unrelated titles and abstracts ($n = 1315$) and animal studies ($n = 519$) were excluded. In the end, 29 relevant studies were left to be reviewed in full text. As a result of the did not provide sufficient information, and in-appropriate design, seven studies were excluded. Finally, 22 studies were included in the current meta-analysis (Figure 1).

3.2 | Characteristics of the studies

A summary of the characteristics of the included studies is provided in Table 1. Totally, 1527 subjects were included, and the dates of publications were between 2008 and 2022. Among the 22 studies, 19 were parallel studies (Amin et al., 2015; Bin Sayeed et al., 2013; Datau et al., 2010; Dehkordi & Kamkhah, 2008; Fallah Huseini et al., 2013; Hadi et al., 2021; Ibrahim et al., 2014; Mahdavi et al., 2015; Naeimi et al., 2020; Qidwai et al., 2009; Rachman & Darmawan, 2017; Rashidmayvan et al., 2019; Rashidmayvan et al., 2022; Rizka et al., 2018; Salem et al., 2021; Sayeed et al., 2014; Shoaei-Hagh et al., 2021; Siddiqui et al., 2022; Tavakoli-Rouzbehani et al., 2021), and three were crossover (Latiff et al., 2014; Mohtashami, 2019; Razmpoosh et al., 2021). The sample size ranged from 32 to 200 participants and the duration of the study ranged from 4 to 16 weeks. The baseline BMI varied between 21.8 and 32.4 kg/m^2. Studies were conducted in the following countries: Iran (Dehkordi & Kamkhah, 2008; Fallah Huseini et al., 2013; Hadi et al., 2021; Mahdavi et al., 2015; Mohtashami, 2019; Naeimi et al., 2020; Rashidmayvan et al., 2019; Rashidmayvan et al., 2022; Razmpoosh et al., 2021; Shoaei-Hagh et al., 2021; Tavakoli-Rouzbehani et al., 2021), Saudi Arabia (Badar et al., 2017; Salem et al., 2021), Indonesia (Datau et al., 2010; Rachman & Darmawan, 2017; Rizka et al., 2018), Pakistan (Amin et al., 2015; Qidwai et al., 2009; Siddiqui et al., 2022), Malaysia (Ibrahim et al., 2014; Latiff et al., 2014), and Bangladesh (Bin Sayeed et al., 2013; Sayeed et al., 2014). *N. sativa* in forms of powder (doses from 0.5 to 3 g/day) and oil (doses from 0.1 to 4.2 g/day) were used in the studies.

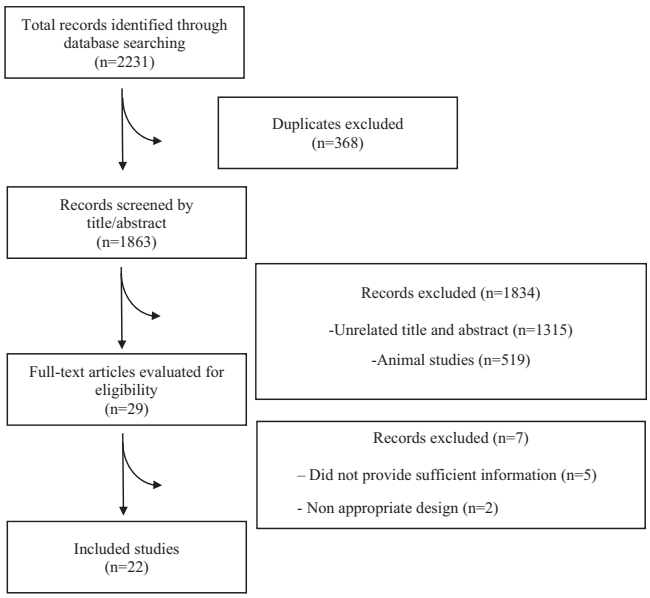

FIGURE 1 Flow diagram of study selection.

3.3 | Risk of bias and grade assessment

The risk of bias assessment of the included studies using Cochrane criteria is shown in Table 2. Using the GRADE approach, both outcomes were rated moderate for evidence quality (Table 3).

3.4 | Effect of *N. sativa* supplementation on SBP

The overall estimate that was carried out on 22 studies with 29 arms revealed that *N. sativa* had a significant effect on SBP (WMD: −3.06 mmHg; 95% CI: −3.89 to −2.22; $I^2 = 84.7\%$, $p < 0.001$) (Figure 2). From these analyses, we found a significant decreasing effect of *N. sativa* oil supplementation on SBP in RCTs with prescribed ≥2 g/day of *N. sativa*, mean age ≥50 years old, sample size of ≤60 participants, and duration of intervention ≤8 weeks in both sexes (Table 4).

3.5 | Effect of *N. sativa* supplementation on DBP

The results of our analysis of 22 studies with 29 arms indicated that *N. sativa* supplementation substantially reduced DBP (WMD = −2.69 mmHg; 95% CI: −3.72, −1.66, $p < 0.001$; $I^2 = 97.3\%$, $p < 0.001$) (Figure 3). *N. sativa* powder supplementation resulted in a significant decrease in DBP at the dosage of ≤1.5 g/day, in RCTs with a sample size of ≤60, and those trials that were conducted on patients with HTN and healthy subjects with a BMI of 25–30 kg/m^2, and mean age over 50 years old in duration of intervention ≤8 weeks (Table 4).

TABLE 1 Study characteristics of included studies.

Citation (first author et al., year)	Target population	Duration	Gender	*n*	Study groups	Age (year)	BMI (kg/m^2)	SBP (mmHg)		DBP (mmHg)	
								Baseline	End of study	Baseline	End of study
Dehkordi & Kamkhah, (2008)	Mild HTN	8 weeks	M	36	0.1 g/day NS oil	44.6 ± 1.3	23.9 ± 0.8	151.2 ± 7.8	NR	93.2 ± 3	NR
				39	0.2 g/day NS oil	43.7 ± 1.3	24.1 ± 0.8	149.5 ± 8.12	NR	95.1 ± 5.0	NR
				33	Placebo	43.1 ± 1.4	24.5 ± 0.7	148.20 ± 6.89	NR	94.50 ± 4.60	NR
Qidwai et al., (2009)	HC	6 weeks	M/F	39	2 g/day NS powder	45.58 ± 10.86	27.13 ± 3.88	128.90 ± 18.37	115.39 ± 12.65	81.82 ± 11.24	80.87 ± 11.39
				34	Placebo	46.86 ± 11.00	28.26 ± 6.75	122.30 ± 17.76	116.97 ± 13.58	80.45 ± 11.48	79.12 ± 8.57
Datau et al., (2010)	Obese	12 weeks	M	19	1.5 g/day NS powder	ND	ND	130.53 ± 13.11	121.58 ± 7.65	80.53 ± 13.93	79.47 ± 4.05
				20	Placebo	ND	ND	123.50 ± 12.68	126 ± 11.43	80.00 ± 7.96	82 ± 6.16
Bin Sayeed et al., (2013)	Healthy	9 weeks	M	20	1 g/day NS powder	55.8 ± 0.57	24.77 ± 0.34	119.50 ± 3.35	119.35 ± 0.63	80.95 ± 3.13	78.95 ± 0.70
				20	Placebo	55.9 ± 0.65	24.55 ± 0.18	120.55 ± 2.45	120.75 ± 0.84	79.15 ± 3.26	79.75 ± 0.78
Fallah Huseini et al., (2013)	Healthy	8 weeks	M/F	35	4.2 g/day NS oil	47.3 8.6	21.8 3.4	129.7 ± 11.9	119.1 ± 7.0	77.0 ± 8.0	67.4 ± 4.4
				35	Placebo	45.4 10.3	20.9 3.4	127.3 ± 12.8	126.9 ± 11.8	75.20 ± 6.70	73.9 ± 7.9
Sayeed et al., (2014)	Healthy adolescent	4 weeks	M	24	0.5 g/day NS powder	14–17	22.69	134.08 ± 2.60	134.48 ± 2.90	84.17 ± 1.16	83.79 ± 0.85
				24	Placebo		22.57	133.7 ± 2.62	134.04 ± 2.25	84.5 ± 1.06	84.29 ± 0.85
Ibrahim et al., (2014)	Menopausal	8 weeks	F	19	1 g/day NS powder	53.22 ± 2.16	27.18 ± 4.34	129.33 ± 15.44	124.53 ± 13.31	77.13 ± 9.16	75.53 ± 9.56
				18	Placebo	53.71 ± 3.57	27.75 ± 4.38	138.4 ± 18.9	140.71 ± 11.85	83.93 ± 15.73	89.00 ± 12.53
Latiff et al., (2014)	Perimenopausal	12 weeks	F	69	1.6 g/day NS powder	50.1 ± 7.6	26.31 ± 4.89	122.32 ± 15.25	117.63 ± 14.65	79.07 ± 7.76	73.96 ± 9.48
				69	Placebo		26.03 ± 4.66	121.42 ± 14.89	118.18 ± 15.4	78.42 ± 8.48	74.5 ± 9.30
Amin et al., (2015)	Mets	8 weeks	M	61	1.5 g/day NS powder	45.1 ± 11.7	27.4 ± 3.1	131.80 ± 20.2	127.3 ± 18.0	82.5 ± 12.1	80.0 ± 10.7
				63	Placebo	41.57 ± 12.8	27.5 ± 4.12	125.5 ± 16.7	127.6 ± 14.9	76.8 ± 11.5	78.7 ± 10.3
Mahdavi et al., (2015)	Obese	8 weeks	F	43	3 g/day NS oil	41.5 ± 11.7	32.4 ± 1.5	120.5 ± 10.3	120.4 ± 9.0	7.7 ± 0.7	7.5 ± 0.7
				41	Placebo	39.3 ± 9.9	31.6 ± 1.5	120.4 ± 10.4	120.3 ± 7.0	7.9 ± 0.6	7.7 ± 0.9
Hadi et al., (2021)	T2DM	8 weeks	M/F	23	1 g/day NS seeds (capsule)	51.4 ± 9.2	28.4 ± 4.4	132 ± 14.1	124 ± 31.1	82.1 ± 7.7	77.7 ± 8.2
				20	Placebo	56.00 ± 3.4	28.8 ± 8.1	132 ± 17.8	131 ± 14.8	85.4 ± 10.5	86.3 ± 9.1
Rashidmayvan et al., (2019)	NAFLD	8 weeks	M/F	22	1 g/day NS oil	39 ± 5.37	27.59 ± 2.83	121.4 ± 17.61	121.22 ± 17.36	80.54 ± 11.53	81.04 ± 11.10
				22	Placebo	42.22 ± 8.85	27.67 ± 4.37	125.45 ± 18.18	127.77 ± 18.68	79.45 ± 10.22	77.59 ± 13.28
Razmpoosh et al., (2021)	Overweight and obese	8 weeks	F	19	2 g/day NS seeds (capsule)	38 ± 10.6	31 ± 5	118 ± 10	113 ± 6	75 ± 6	70 ± 5
				20	Placebo	34 ± 9.4	32 ± 5.5	116 ± 14	114 ± 7	75 ± 7	74 ± 4
Rizka et al., (2018)	HTN in Elderly	3 weeks	M/F	38	0.6 g/day NS seed extract (capsule)	72 ± 5.9	24.5 ± 3.5	160.4 ± 15.7	145.8 ± 19.8	78.3 ± 11.9	74.4 ± 8.2
				38	Placebo	73.8 ± 6.8	24.2 ± 5.2	160.9 ± 16.3	147.53 ± 22.0	79.0 ± 12.4	78.2 ± 8.9

TABLE 1 (Continued)

Citation (first author et al., year)	Target population	Duration	Gender	*n*	Study groups	Age (year)	BMI (kg/m^2)	SBP (mmHg)		DBP (mmHg)	
								Baseline	End of study	Baseline	End of study
Shoaei-Hagh et al., (2021)	HTN	3 weeks 6 weeks 8 weeks	M/F	26	4.2 g/day NS seeds oil	58.04 ± 10.35	27.16 ± 3.11	142.50 ± 10.33	136.81 ± 10.08	87.47 ± 7.15	82.50 ± 6.04
				29	Placebo	59.92 ± 11.30	25.96 ± 2.90	142.44 ± 11.39	134.65 ± 10.40	87.09 ± 7.96	78.90 ± 7.12
									134.13 ± 12.037		78.93 ± 8.15
									141.70 ± 12.46		86.11 ± 7.26
									138.88 ± 16.86		85.78 ± 8.46
									139.58 ± 15.08		85.98 ± 7.93
Tavakoli-Rouzbehani et al., (2021)	CAD	8 weeks	M/F	25	2 g/day NS oil	55.92 ± 1.34	29.28 ± 3.89	126.88 ± 14.05	116.19 ± 12.03	82.08 ± 10.2	73.48 ± 8.17
				24	Placebo	54.25 ± 1.55	28.61 ± 3.77	120.22 ± 7.75	119.05 ± 10.07	77.17 ± 8.5	76.67 ± 6.95
Mohtashami, (2019)	Mets	8 weeks	M/F	27	3 g/day NS powder	47.5 ± 5.7	29.9 ± 3.8	117.658 ± 10.68	114.53 ± 11.13	72.78 ± 8.09	69.518 ± 9.01
				24	Placebo			118.73 ± 10.2	115.82 ± 11.13	73.17 ± 7.78	70.63 ± 7.98
Rashidmayvan et al., (2019)	NAFLD	8 weeks	M/F	22	1 g/day NS oil (soft gel)	39 ± 5.37	27.59 ± 2.83	121.4 ± 17.61	121.22 ± 17.36	80.54 ± 11.53	81.04 ± 11.10
				22	Placebo	42.22 ± 8.85	27.67 ± 4.37	125.45 ± 18.18	127.77 ± 18.68	79.45 ± 10.22	77.59 ± 13.28
Salem et al., (2021)	Healthy	4 weeks	M/F	26	0.5 g/day NS seeds (capsule)	22.25	27.94	130.15 ± 13.42	119.69 ± 12.83	72.46 ± 10.45	69.23 ± 11.85
				34	1 g/day NS seeds (capsule)\	22.35	28.71	128.73 ± 8.87	125.36 ± 8.42	79.09 ± 7.46	66.09 ± 10.08
				22	2 g/day NS seeds (capsule)	20.89	22.83	124.5 ± 12.52	123.1 ± 0.08	67.5 ± 9.68	71.9 ± 10.81
				12	Placebo	21.53	25.26	107.17 ± 53.55	122 ± 9.88	59.17 ± 30.57	69.83 ± 6.08
Siddiqui et al., (2022)	HTN	6 weeks 12 weeks	M/F	100 100	1.5 g/day NS seeds Placebo	45.16 + 10.54 41.61 + 10.97	NR	139.49 ± 6.337 139.07 ± 6.307	137.87 ± 5.829 132.66 ± 5.887 138.93 ± 6.961 133.37 ± 5.836	102.32 ± 6.135 102.85 ± 5.844	100.58 ± 6.081 95.26 ± 6.594 102.75 ± 5.518 95.64 ± 6.850
Naeimi et al., (2020)	PCOS	16 weeks	M/F	32	1 g/day NS oil (soft gel)	24 ± 5.9	27 ± 5	106 ± 8.6	104 ± 2.88	70.2 ± 77.9	70 ± 14.57
				23	Placebo	24 ± 5.3	26 ± 5	104. ± 8.9	105 ± 6.11	70 ± 8.1	70.1 ± 12.84
Rachman & Darmawan, (2017)	Mets	3 weeks	M/F	33	1.5 g/day NS oil	>18	23.76 ± 4.34	141.73 ± 16.84	136.10 ± 15.946	80.52 ± 9.138	79.52 ± 17.160
				33	3 g/day NS oil		24.53 ± 3.8	143.64 ± 18.63	139.81 ± 17.662	81.09 ± 9.531	80.87 ± 9.804
				33	Placebo		24.15 ± 4.10	142.48 ± 16.42	138.66 ± 13.170	79.76 ± 7.005	75.31 ± 8.476

Abbreviations: NR, Not reported; T2DM, type 2 diabetes mellitus; NAFLD, Nonalcoholic fatty liver; MetS, metabolic syndrome; HTN, Hypertension; RCT, Randomized Control Trial; DB, Double Blind; HC, Hypercholesterolemia.

3.6 | Sensitivity analysis, meta-regression, and publication bias

Based on sensitivity analysis, the exclusion of any individual study did not affect the pooled estimate of the impact of *N. sativa* supplementation on SBP and DBP. Meta-regression analysis did not reveal a linear relationship between dosage, sample size, duration, and absolute change in outcomes.

Egger's ($p < 0.05$) but not Begg's ($p > 0.05$) tests revealed a significant small-study effect for SBP and DBP. Since the results of the visual inspection of the funnel plot (Figure S1, S2) assessment demonstrated an unequal distribution of studies, thus, we performed the trim and fill method, no imputed studies were added.

3.7 | Nonlinear dose–responses between dosage, and duration of *N. sativa* supplementation and BP

Dose–response analysis indicated that *N. sativa* supplementation did not change SBP and DBP based on dose and duration (P-nonlinear: 0>05) (Figures 4, 5 and S3, S4).

4 | DISCUSSION

The current systematic review and meta-analysis of 22 available RCTs investigated available evidence on the BP-lowering effect of *N. sativa* supplementation in adults. The pooled analysis revealed a significant effect of *N. sativa* in lowering DBP and SBP when compared with placebo/control. This favorable effect was more discernible when excluding studies with a high risk of bias. The subgroup analysis demonstrated that *N. sativa* supplementation for ≤8 weeks in ≥50-year subjects with a BMI 25–30 kg/m^2 led to more favorable effects regarding both components of BP.

Functional foods and nutraceuticals have recently been identified as promising adjunctive therapy for the treatment of cardiovascular risk factors (Sosnowska et al., 2017). Nutraceuticals, the foods or dietary components that have medicinal or therapeutic advantages, are considered variables in the management of chronic illnesses, glycemic and lipid metabolic disorders, and elements of metabolic syndrome (Cicero et al., 2017; Patti et al., 2018). Recently, the role of *N. sativa* as a nutraceutical in the management of BP is the subject of intense controversy. Our results were in accordance with a systematic review and meta-analysis by Sahebkar et.al in 2016. However, the subgroup analysis in their study was performed only based on intervention type (Sahebkar et al., 2016). Besides, our results build upon another previously published meta-analysis regarding the BP-lowering effects of *N. sativa*. Despite obtaining similar results, our study might better illustrate statistical differences due to the inclusion of six studies and increasing sample sizes by 36% (Golpour-Hamedani et al., 2022). Further, based on the GRADE system, they suggested that the quality of evidence of the included studies was high, while in our study, a moderate quality of evidence was documented due to serious limitations in inconsistency (Table 3).

The potential mechanism explaining the BP-lowering impact of *N. sativa* is so far unknown, and deeper research is required. However, several studies have postulated a variety of biological pathways that may play a role in the antihypertensive activities of *N. sativa*. Accumulating data indicates that oxidative stress plays a crucial role in the pathophysiology of HTN (Griendling et al., 2021) *N. sativa*'s robust antioxidant capacity, which can be linked to the presence of thymoquinone (TQ), flavonoids, nigellicine, transanethole, and limonene, reduces BP via enhancing endothelial function (Doménech et al., 2014; Fallah Huseini et al., 2013). BP-lowering benefits of *N. sativa* are also attributable to its polyphenol concentration (Kart & Aydın, 2021). Furthermore, it has been shown that flavonoids exert an inhibitory effect on the angiotensin-converting enzyme (ACE), which may improve normal endothelial function and hence reduce BP (Muchtaridi et al., 2020). A significant amount of unsaturated fatty acids, notably linoleic and oleic acids, also contributes to *N. sativa*'s antihypertensive properties (Shoaei-Hagh et al., 2021).

Previous investigations have revealed the beneficial association between dietary linoleic and oleic acid intake and BP (Kaikkonen et al., 2021). Thymol, another active component of *N. sativa*, has been demonstrated to reduce BP via modifying Ca^{2+} ion channels. It is possible that inhibition of Ca^{2+} release from the sarcoplasmic reticulum, reduced Ca^{2+} sensitivity of the contractile system, and inhibition of Ca^{2+} influx across the smooth muscle cell membrane, all contribute to *N. sativa*-induced endothelial relaxation (Peixoto-Neves et al., 2010). One of the other hypothesized mechanisms is *N. sativa*'s diuretic activity via an increase in electrolyte and urea excretion, followed by a decrease in electrolytes, water, and blood volume, hence a decrease in cardiac output and BP (Zaoui et al., 2000). In a separate investigation, the *N. sativa* oil-induced decline in BP was associated with plasma nitric oxide loss inhibition, enhanced heme oxygenase activity, and diminished malondialdehyde and ACE activity (Jaarin et al., 2015). Figure 6 displays the mechanism of action of *N. sativa* on BP.

Based on subgroup analysis, our results indicated that *N. sativa* supplementation for ≤8 weeks in ≥50-year subjects with a BMI 25–30 kg/m^2 led to a more significant decrease in SBP and DBP. The more desirable effects of *N. sativa* supplementation in the elderly might be due to functional and structural alterations to the vasculature, which is responsible for the high prevalence of HTN in the elderly (Denker & Cohen, 2013). Moreover, aging is associated with increased risk for low consumption of vitamins and antioxidants. At the same time, high levels of oxidative stress in older adults are involved in several health conditions such as cardiovascular diseases. Therefore, use of antioxidant supplements in the elderly compared to young people might have a more positive effect on chronic diseases like HTN. We also found supplementation with *N. sativa* had more significant effects on SBP in hypertensive adults compared with other patients. In terms of SBP, supplementing with *N. sativa* had more significant effects in healthy population. This might be explained by

TABLE 2 Results of risk of bias assessment for randomized clinical trials included in the current meta-analysis on the effects of *N. sativa* on blood pressure.

Study	Random sequence generation	Allocation concealment	Reporting bias	Other sources of bias	Performance bias	Detection bias	Attrition bias
Dehkordi & 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
Bin Sayeed et al., (2014)	L	L	L	L	L	L	L
Mahdavi et al., (2015)	L	L	L	L	L	L	L
Latiff et al., (2014)	H	H	L	H	H	H	L
Rashidmayvan et al., (2019)	L	U	L	H	L	L	H
Hadi et al., (2021)	L	L	L	L	L	L	L
Tavakoli-Rouzbehani et al., (2021)	L	L	L	L	L	L	L
Razmpoosh et al., (2021)	L	L	L	L	L	L	L
Rizka et al., (2018)	L	L	L	U	L	L	L
Shoaei-Hagh et al., (2021)	L	L	L	L	L	L	L
Mohtashami, (2019)	L	U	H	H	L	L	L
Rashidmayvan et al., (2022)	L	U	L	U	L	U	U
Salem et al., (2021)	L	L	L	L	L	U	L
Siddiqui et al., (2022)	U	U	L	H	U	U	U
Naeimi et al., (2020)	L	L	L	U	U	L	L
Rachman & Darmawan, (2017)	L	U	L	U	U	L	U

Note: 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 is considered as a high-quality study with totally low risk of bias.

higher sample size or high number of the included studies in these subgroups, which provided increased statistical power to detect significant effects. Overall, more studies are needed to investigate the effect of *N. sativa* on BP in other patients.

Besides, observing less significant effects in longer intervention duration might be due to the body's adaptation and compensatory mechanisms that could take place over time. Moreover, low adherence to study intervention in long-term trials could be another explanation for these findings. In subgroup analyses, we could not clarify which various forms of *N. sativa* (powder, oil) are better. However, a significant difference in SBP and DBP reduction between *N. sativa* versus control groups could be seen for *N. sativa* powder supplementation in a dosage of ≤1.5 g/day. Also, *N. sativa* oil supplements in a dosage of ≥2 g/day reduced SBP and DBP compared to a control, with the difference being that the effect of the *N. sativa* oil on DBP was not significant. In oil, TQ is a solvent, so its pharmacological properties are more clearly observable than in powders. Considering the studies in which powder and oil products were directly compared, we can suggest that only *N. sativa* powder may have a beneficial effect on SBP and DBP changes compared to the control treatment, while the evidence for *N. sativa* oil is not solid enough to draw any conclusion. However, this finding should be interpreted with caution since of the limited statistical power of subgroup analyses. More desirable effects were also obtained from high-quality studies regarding both components of BP. The quality of obtained evidence for both SBP and DBP was

TABLE 3 The results of 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]
Blood pressure								
SBP (mmHg)	1527 (22)	−3.06 (−3.89, −2.22)	Not serious	Serious	Not serious	Not serious	Not serious	Moderate
DBP (mmHg)	1527 (22)	−2.69 (−3.72, −1.66)	Not serious	Serious	Not serious	Not serious	Not serious	Moderate

Abbreviations: DBP, Diastolic blood pressure; SBP, Systolic blood pressure.

[a]Risk of bias based on the Cochrane of risk 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]optimal information size was not met, or the 95% CI include the null value lower and upper bounds of the 95% CI were <0.95 and >1.05, respectively.

[e]Downgraded if there was an evidence of publication bias using funnel plot.

[f]Since all included studies were RCTs, 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, and very low.

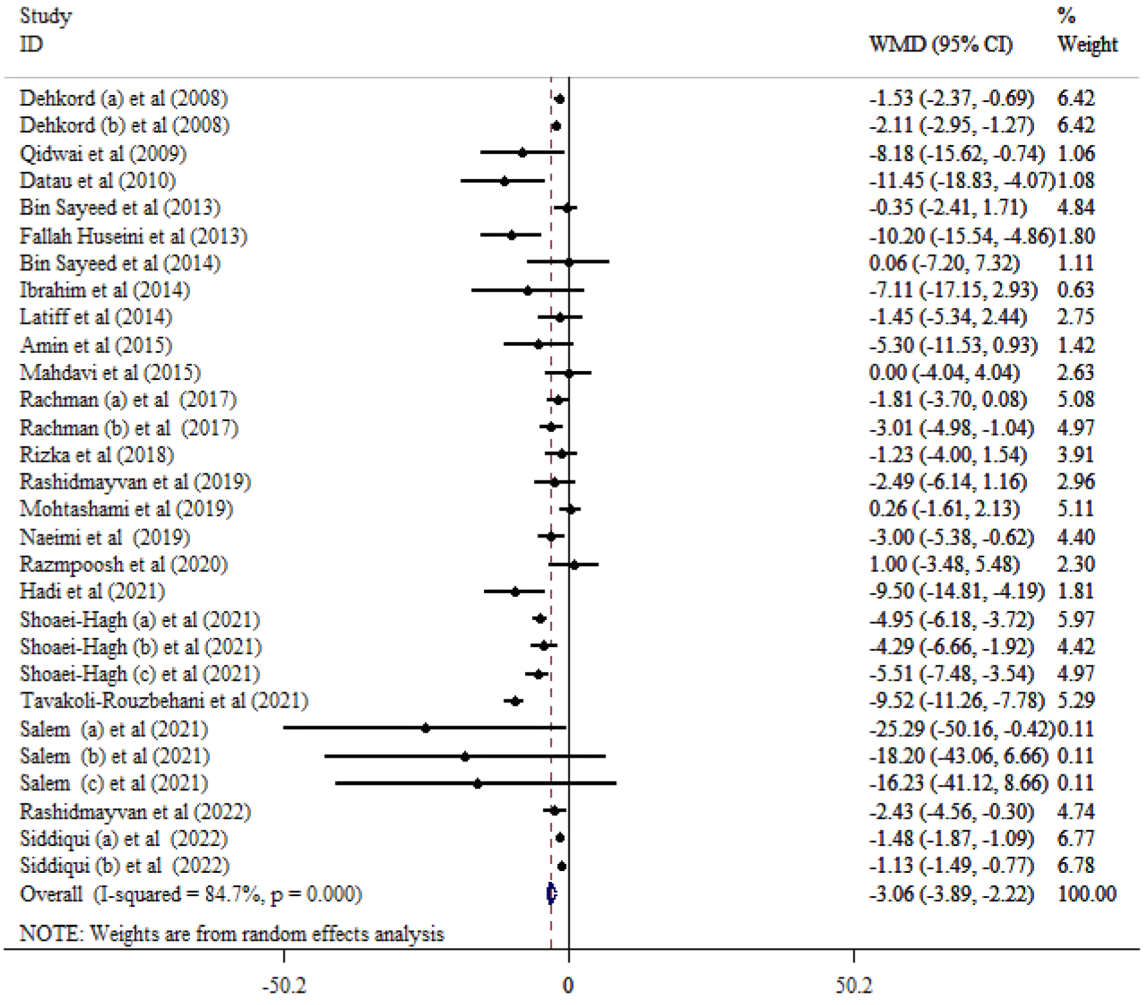

FIGURE 2 Forest plot detailing mean difference and 95% confidence intervals (CIs) the effects of *N. sativa* supplementation on SBP levels.

high. While there was a considerable risk of bias in some included studies, both high and low qualified studies confirmed the antihypertensive effects of *N. sativa*. This means that the presence of bias in some included studies could not change the real effects of *N. sativa* on BP components. Therefore, our interpretations were based on appropriate evidence.

This is not the first meta-analysis to examine the hypotensive effects of *N. sativa* supplementation, but it is the most extensive and

TABLE 4 Subgroup analyses for the effects of *N. sativa* supplementation on blood pressure.

	No	WMD (95% CI)[a]	P-within[b]	I^2 (%)[c]	P-heterogeneity[d]
N. sativa supplementation on SBP					
Overall	29	−3.06 (−3.89, −2.22)	<0.001	84.7	<0.001
Age (year)					
<50	18	−1.78 (−2.43, −1.13)	<0.001	59.3	<0.001
≥50	11	−4.13 (−5.99, −2.27)	<0.001	85.8	<0.001
Gender					
Men	6	−1.85 (−3.04, −0.65)	0.002	53.9	0.055
Women	4	−0.62 (−2.94, 1.69)	0.598	0.0	0.499
Both	19	−3.70 (−4.81, −2.60)	<0.001	89.4	<0.001
Intervention duration (week)					
≤8	24	−3.41 (−4.50, −2.33)	<0.001	85.1	<0.001
>8	5	−1.82 (−3.45, −0.20)	0.028	61.5	0.034
Intervention type					
Powder	17	−1.62 (−2.43, −0.81)	<0.001	57.4	<0.001
Dosage of *N. sativa* powder (g/day)					
≤1.5	11	−1.61 (−2.36, −0.85)	<0.001	54.3	0.016
>1.5	6	2.99 (−6.61, 0.63)	0.105	67.2	0.009
Oil	12	−3.84 (−5.31, −2.36)	<0.001	88.7	0.003
Dosage of *N. sativa* oil (g/day)					
<2	7	−3.90 (−6.07, −1.74)	<0.001	92.2	<0.001
≥2	5	−4.10 (−5.45, −2.75)	<0.001	52.8	0.076
Study population					
Hypertension	8	−2.53 (−3.37, −1.68)	<0.001	87.7	<0.001
Healthy	6	−6.30 (−12.85, 0.26)	0.061	72.3	0.003
Metabolic syndrome	4	−1.78 (−3.61, 0.05)	0.057	58.2	0.012
Obese and overweight	3	−2.73 (−8.87, 3.40)	0.382	76.9	0.013
Menopausal	2	−2.31 (−6.29, 1.67)	0.237	5.7	0.303
NAFLD	2	−2.45 (−4.29, −0.60)	0.009	0	0.978
Coronary artery disease	1	−9.52 (−11.26, −7.78)	<0.001	–	–
PCOS	1	−3.00 (−5.38, −0.62)	0.014	–	–
Hypercholesterolemia	1	−8.18 (−15.62, −0.74)	0.031	–	–
T2DM	1	−9.50 (−14.81, −4.19)	<0.001	–	–
Sample size					
≤60	17	−4.18 (−6.06, −2.29)	<0.001	83.7	<0.001
>60	12	−1.72 (−2.25, −1.19)	<0.001	53.1	0.015
BMI					
≤25	9	−1.97 (−2.89, −1.04)	<0.001	48.2	0.051
25–30	15	−4.66 (−6.49, −2.83)	<0.001	81.5	<0.001
> 30	2	0.45 (−2.55, 3.45)	0.770	0.0	0.745
NR	3	−1.40 (−2.14, −0.66)	<0.001	77.7	<0.001
Quality					
Low	11	−1.53 (−2.15, −0.90)	<0.001	54.0	0.016
High	18	−4.23 (−5.80, −2.65)	<0.001	84.9	<0.001
N. sativa supplementation on DBP					
Overall	29	−2.69 (−3.72, −1.66)	<0.001	97.3	<0.001

(Continues)

TABLE 4 (Continued)

	No	WMD (95% CI)[a]	P-within[b]	I^2 (%)[c]	P-heterogeneity[d]
Age (year)					
<50	18	−1.37 (−2.14, −0.60)	<0.001	91.5	<0.001
≥50	11	−4.16 (−7.06, −1.27)	0.005	97.9	<0.001
Gender					
Men	6	−1.74 (−2.48, −1.00)	<0.001	19.2	0.228
Women	4	−4.64 (−8.64, −0.64)	0.023	95.9	<0.001
Both	19	−2.64 (−4.31, −0.96)	0.002	97.5	<0.001
Intervention duration (week)					
≤8	24	−3.06 (−4.32, −1.81)	<0.001	97.8	<0.001
>8	5	−0.93 (−2.35, 0.50)	0.203	53.6	0.072
Intervention type					
Powder	17	−2.67 (−3.77, −1.57)	<0.001	87.9	<0.001
Dosage of *N. sativa* powder (g/day)					
≤1.5	11	−3.17 (−4.60, −1.74)	<0.001	91.4	<0.001
>1.5	6	−1.90 (−3.74, −0.06)	0.043	63.7	0.017
Oil	12	−2.25 (−4.41, −0.09)	0.041	98.7	<0.001
Dosage of *N. sativa* oil (g/day)					
<2	7	−1.77 (−4.54, 1.00)	0.211	95.6	<0.001
≥2	5	−2.89 (−6.68, 0.90)	0.135	99.4	<0.001
Study population					
Hypertension	8	−3.29 (−5.13, −1.44)	<0.001	98.4	<0.001
Healthy	6	−6.09 (−10.49, −1.69)	0.007	83.0	<0.001
Metabolic syndrome	4	0.59 (−3.04, 4.22)	0.750	95.3	<0.001
Obese and overweight	3	−2.12 (−5.57, 1.34)	0.230	92.5	<0.001
NAFLD	2	2.36 (0.67, 4.05)	0.006	0.0	1.00
Menopausal	2	−8.48 (−22.97, 6.01)	0.251	96.7	<0.001
Hypercholesterolemia	1	0.38 (−4.59, 5.35)	0.881	–	–
Coronary artery disease	1	−8.10 (−9.48, −6.72)	<0.001	–	–
PCOS	1	−0.30 (−3.51, 2.91)	0.855	–	–
T2DM	1	−5.25 (−8.95, −1.55)	0.005	–	–
Sample size					
≤60	17	−4.30 (−6.19, −2.40)	<0.001	94.4	<0.001
>60	12	−0.91 (−1.82, 0.00)	0.052	95.7	<0.001
BMI					
≤25	9	−1.29 (−3.64, 1.06)	0.281	94.8	<0.001
25–30	15	−4.41 (−6.49, −2.34)	<0.001	95.0	<0.001
>30	2	−1.92 (−5.84, 1.99)	0.336	96.1	<0.001
NR	3	−0.89 (−2.57, 0.80)	0.301	95.5	0.952
Quality					
Low	11	−1.07 (−2.58, 0.44)	0.163	95.5	<0.001
High	18	−3.99 (−5.90, −2.08)	<0.001	98	<0.001

Abbreviations: CI, confidence interval; NAFLD, Nonalcoholic fatty liver disease; PCOS, Polycystic ovary syndrome; T2DM, Type 2 diabetes mellitus; WMD, Weighted mean difference.

[a]Obtained from the random-effects model.

[b]Refers to the mean (95% CI).

[c]Inconsistency, percentage of variation across studies due to heterogeneity.

[d]Obtained from the Q-test.

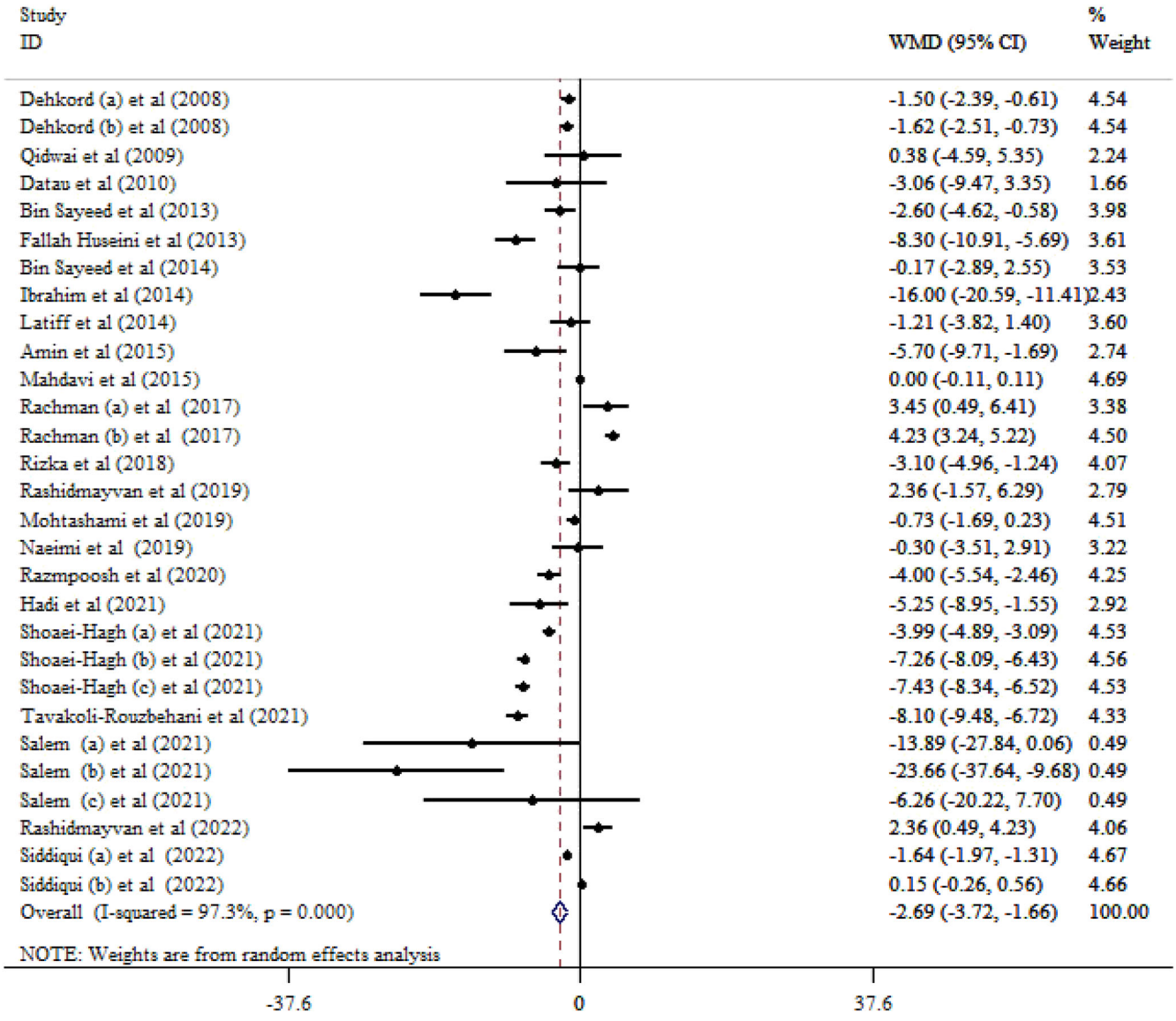

FIGURE 3 Forest plot detailing mean difference and 95% confidence intervals (CIs) the effects of *N. sativa* supplementation on DBP levels.

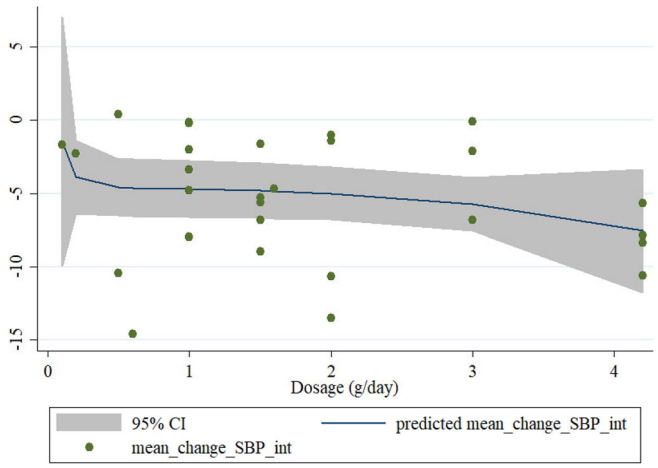

FIGURE 4 Nonlinear dose–response relations between dose of *N. sativa* supplementation (g/day) and absolute mean differences in SBP.

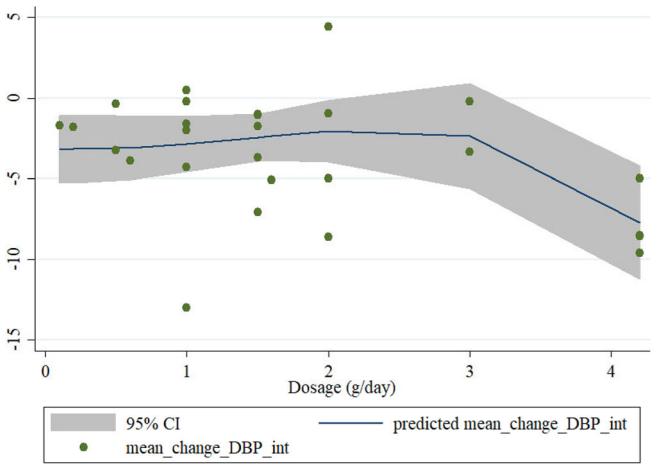

FIGURE 5 Nonlinear dose–response relations between dose of *N. sativa* supplementation (g/day) and absolute mean differences in DBP.

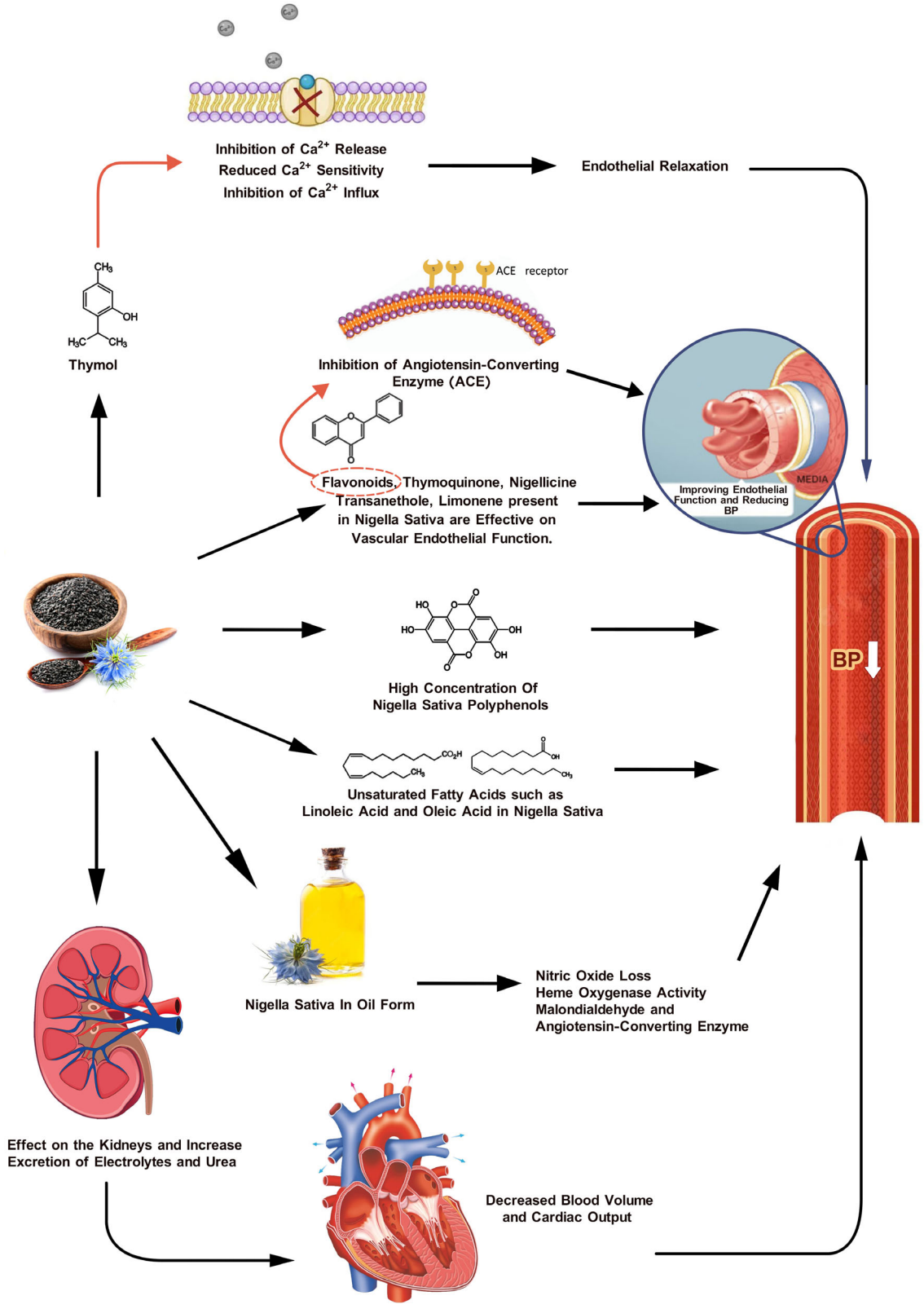

FIGURE 6 The mechanism of action of *N. sativa* on blood pressure.

up-to-date analysis in this field. Our meta-analysis included an adequate number of RCTs. We discovered considerable heterogeneity in our findings. As a result, the random-effects model was utilized to account for study heterogeneity. A visual inspection of the funnel plot also revealed publication bias. Consequently, we carried out trim and fill analysis with no imputed studies. Additionally, subgroup analysis

was employed to provide more precise results. Nevertheless, some limitations should also be viewed in light of our findings. First, the characteristics of the research participants were diverse (i.e., healthy people, patients with T2DM, metabolic syndrome, HTN, etc.). Second, the majority of the trials included were conducted on populations with normal BP. Therefore, the genuine normotensive impact of *N. sativa* on individuals with HTN could not be determined. There are several differences across trials, including the duration and stage of HTN, other health conditions of the participants, medication used, degree of adherence to study interventions, physical activity level, life habits, dietary intakes, and excess body weight. Lack of controlling for these confounding factors in the statistical analyses might affect the independent effect of *N. sativa* on BP and may result in large differences across trials.

5 | CONCLUSION

The present meta-analysis confirms the potential benefits of *N. sativa* supplementation in BP management and shows that *N. sativa* can be used for controlling high BP, especially in older ages (≥50 years), patients diagnosed with HTN with a BMI 25–30 kg/m^2, and interventions with duration ≤8 weeks. In addition, the use of *N. sativa* alongside antihypertensive medicinal agents as well as bioactive components with BP lowering effects requires high-quality clinical trials to clarify the possible beneficial use of *N. sativa* as a clinical approach.

AUTHOR CONTRIBUTIONS

zeynab kavyani: Conceptualization; data curation; writing – original draft. **Ehsan Safaei:** Data curation; investigation; methodology; writing – original draft. **Sana Sedgh Ahrabi:** Conceptualization; data curation; investigation; resources; writing – original draft. **Mina Mohammadi Asmaroud:** Conceptualization; data curation; investigation; methodology; writing – original draft. **Fatemeh Khashakichafi:** Conceptualization; formal analysis; investigation; writing – original draft. **vali musazadeh:** Conceptualization; data curation; formal analysis; investigation; formal analysis; software; supervision; writing – review and editing. **parvin dehghan:** Supervision; writing – original draft; writing – review and editing.

ACKNOWLEDGMENTS

Tabriz University of Medical Sciences Student Research Committee accepted and supported the research protocol (Registration code: 71664).

CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable.

ORCID

Vali Musazadeh https://orcid.org/0000-0002-4978-9474

REFERENCES

Ahmed, O. G., & El-Mottaleb, N. A. A. (2013). Renal function and arterial blood pressure alterations after exposure to acetaminophen with a potential role of Nigella sativa oil in adult male rats. *Journal of Physiology and Biochemistry*, *69*(1), 1–13.

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.

Badar, A., Kaatabi, H., Bamosa, A., Al-Elq, A., Abou-Hozaifa, B., Lebda, F., Alkhadra, A., & 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.

Begg, C. B., & Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, *50*, 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.

Burnier, M., & Egan, B. M. (2019). Adherence in hypertension: A review of prevalence, risk factors, impact, and management. *Circulation Research*, *124*(7), 1124–1140.

Carey, R. M., Whelton, P. K., & Committee, A. A. H. G. W. (2018). Prevention, detection, evaluation, and management of high blood pressure in adults: Synopsis of the 2017 American College of Cardiology/American Heart Association hypertension guideline. *Annals of Internal Medicine*, *168*(5), 351–358.

Cicero, A. F., Colletti, A., Bajraktari, G., Descamps, O., Djuric, D. M., Ezhov, M., Fras, Z., Katsiki, N., Langlois, M., Latkovskis, G., Panagiotakos, D. B., Paragh, G., Mikhailidis, D. P., Mitchenko, O., Paulweber, B., Pella, D., Pitsavos, C., Reiner, Z., Ray, K. K., … Banach, M. (2017). Lipid-lowering nutraceuticals in clinical practice: Position paper from an international lipid expert panel. *Nutrition Reviews*, *75*(9), 731–767.

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.

Denker, M. G., & Cohen, D. L. (2013). What is an appropriate blood pressure goal for the elderly: Review of recent studies and practical recommendations. *Clinical Interventions in Aging*, *8*, 1505–1517. https://doi.org/10.2147/cia.S33087

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

Doménech, M., Roman, P., Lapetra, J., García de la Corte, F. J., Sala-Vila, A., de la Torre, R., Corella, D., Salas-Salvadó, J., Ruiz-Gutiérrez, V., Lamuela-Raventós, R.-M., Toledo, E., Estruch, R., Coca, A., & Ros, E. (2014). Mediterranean diet reduces 24-hour ambulatory blood pressure, blood glucose, and lipids: One-year randomized, clinical trial. *Hypertension*, *64*(1), 69–76. https://doi.org/10.1161/hypertensionaha.113.03353

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.

Golpour-Hamedani, S., Hadi, A., SafariMalekabadi, D., Najafgholizadeh, A., Askari, G., & Pourmasoumi, M. (2022). The effect of nigella

supplementation on blood pressure: A systematic review and dose-response meta-analysis. *Critical Reviews in Food Science and Nutrition*, 1–14.

Griendling, K. K., Camargo, L. L., Rios, F. J., Alves-Lopes, R., Montezano, A. C., & Touyz, R. M. (2021). Oxidative stress and hypertension. *Circulation Research*, *128*(7), 993–1020.

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.

Hall, J. E., do Carmo, J. M., da Silva, A. A., Wang, Z., & Hall, M. E. (2019). Obesity, kidney dysfunction and hypertension: Mechanistic links. *Nature Reviews Nephrology*, *15*(6), 367–385.

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

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), 29–33.

Jaarin, K., Foong, W. D., Yeoh, M. H., Kamarul, Z. Y., Qodriyah, H. M., Azman, A., Zuhair, J. S. F., Juliana, A. H., & Kamisah, Y. (2015). Mechanisms of the antihypertensive effects of Nigella sativa oil in L-NAME-induced hypertensive rats. *Clinics (São Paulo, Brazil)*, *70*(11), 751–757. https://doi.org/10.6061/clinics/2015(11)07

Kaikkonen, J. E., Jula, A., Viikari, J. S., Juonala, M., Hutri-Kähönen, N., Kähönen, M., Kähönen, M., Lehtimäki, T., & Raitakari, O. T. (2021). Associations of serum fatty acid proportions with obesity, insulin resistance, blood pressure, and fatty liver: The cardiovascular risk in young finns study. *The Journal of Nutrition*, *151*(4), 970–978.

Kart, A., & Aydın, E. (2021). Health promoting activities of Nigella sativa seed extracts. In *Black cumin (Nigella sativa) seeds: Chemistry, technology, functionality, and applications* (pp. 521–537). Springer.

Latiff, L. A., Parhizkar, S., Dollah, M. A., & Hassan, S. T. S. (2014). Alternative supplement for enhancement of reproductive health and metabolic profile among perimenopausal women: A novel role of Nigella sativa. *Iranian Journal of Basic Medical Sciences*, *17*(12), 980–985.

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.

Mahmood, S., Shah, K. U., Khan, T. M., Nawaz, S., Rashid, H., Baqar, S. W. A., & Kamran, S. (2019). Non-pharmacological management of hypertension: in the light of current research. *Irish Journal of Medical Science (1971)*, *188*, 437–452.

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. https://doi.org/10.1371/journal.pmed.1000097

Mohtashami, A. (2019). Effects of bread with Nigella sativa on blood glucose, blood pressure and anthropometric indices in patients with metabolic syndrome. *Clinical Nutrition Research*, *8*(2), 138–147.

Muchtaridi, M., Fauzi, M., Khairul Ikram, N. K., Mohd Gazzali, A., & Wahab, H. A. (2020). Natural flavonoids as potential angiotensin-converting enzyme 2 inhibitors for anti-SARS-CoV-2. *Molecules*, *25*(17), 3980.

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., & Haque, S. F. (2013). Indigenous herbal product Nigella sativa proved effective as an antihypertensive in metabolic syndrome. *Asian Journal of Pharmaceutical and Clinical Research*, *6*(1), 61–64.

Nugroho, P., Andrew, H., Kohar, K., Noor, C. A., & Sutranto, A. L. (2022). Comparison between the world health organization (WHO) and international society of hypertension (ISH) guidelines for hypertension. *Annals of Medicine*, *54*(1), 837–845. https://doi.org/10.1080/07853890.2022.2044510

Patti, A. M., Al-Rasadi, K., Giglio, R. V., Nikolic, D., Mannina, C., Castellino, G., Chianetta, R., Banach, M., Cicero, A. F. G., Lippi, G., Montalto, G., Rizzo, M., & Toth, P. P. (2018). Natural approaches in metabolic syndrome management. *Archives of Medical Science*, *14*(2), 422–441.

Peixoto-Neves, D., Silva-Alves, K. S., Gomes, M. D., Lima, F. C., Lahlou, S., Magalhães, P. J., Ceccatto, V. M., Coelho-de-Souza, A. N., & Leal-Cardoso, J. H. (2010). Vasorelaxant effects of the monoterpenic phenol isomers, carvacrol and thymol, on rat isolated aorta. *Fundamental & Clinical Pharmacology*, *24*(3), 341–350. https://doi.org/10.1111/j.1472-8206.2009.00768.x

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.

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.

Rashidmayvan, M., Vandyousefi, S., Barati, M., Salamat, S., Ghodrat, S., Khorasanchi, M., Jahan-Mihan, A., Nattagh-Eshtivani, E., & Mohammadshahi, M. (2022). The effect of nigella sativa supplementation on cardiometabolic outcomes in patients with non-alcoholic fatty liver: A randomized double-blind, placebo-controlled trial. *Complementary Therapies in Clinical Practice*, *48*, 101598.

Razmpoosh, E., Safi, S., Nadjarzadeh, A., Fallahzadeh, H., Abdollahi, N., Mazaheri, M., Nazari, M., & Salehi-Abargouei, A. (2021). The effect of Nigella sativa supplementation on cardiovascular risk factors in obese and overweight women: A crossover, double-blind, placebo-controlled randomized clinical trial. *European Journal of Nutrition*, *60*(4), 1863–1874.

Rizka, A., Setiati, S., Lydia, A., & Dewiasty, E. (2018). Effect of Nigella sativa seed extract for hypertension in elderly: A double-blind, randomized controlled trial. *Acta Medica Indonesiana*, *49*(4), 307.

Sahebkar, A., Soranna, D., Liu, X., Thomopoulos, C., Simental-Mendia, L. E., Derosa, G., Maffioli, P., & Parati, G. (2016). A systematic review and meta-analysis of randomized controlled trials investigating the effects of supplementation with Nigella sativa (black seed) on blood pressure. *Journal of Hypertension*, *34*(11), 2127–2135.

Salem, A., Bamosa, A., Alam, M., Alshuraim, S., Alyalak, H., Alagga, A., Tarabzouni, F., Alisa, O., Sabit, H., & Mohsin, A. (2021). Effect of Nigella sativa on general health and immune system in young healthy volunteers; a randomized, placebo-controlled, double-blinded clinical trial. *F1000Research*, *10*(1199), 1199.

Sayeed, M. S. B., Shams, T., Hossain, S. F., Rahman, M. R., Mostofa, A., Kadir, M. F., Mahmood, S., & Asaduzzaman, M. (2014). Nigella sativa L. seeds modulate mood, anxiety and cognition in healthy adolescent males. *Journal of Ethnopharmacology*, *152*(1), 156–162.

Shoaei-Hagh, P., Kamelan Kafi, F., Najafi, S., Zamanzadeh, M., Heidari Bakavoli, A., Ramezani, J., Soltanian, S., Asili, J., Hosseinzadeh, H., Eslami, S., & Taherzadeh, Z. (2021). A randomized, double-blind, placebo-controlled, clinical trial to evaluate the benefits of Nigella sativa seeds oil in reducing cardiovascular risks in hypertensive patients. *Phytotherapy Research*, *35*(8), 4388–4400.

Siddiqui, A. H., Khan, N., Naseer, S., Malkera, A., Khan, S. A., Ahsan, I., & Israr, M. (2022). Anti-hypertensive effect of nigella sativa seeds in patients with hypertension. *Pakistan Journal of Medical & Health Sciences*, *16*(2), 86–89.

Sosnowska, B., Penson, P., & Banach, M. (2017). The role of nutraceuticals in the prevention of cardiovascular disease. *Cardiovascular Diagnosis and Therapy*, *7*(Suppl 1), S21–S31.

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.

Valente Silva, B., Santos De Sousa, C. I., Caldeira, D., Abreu, A., & Pinto, F. J. (2022). Management of arterial hypertension: Challenges and opportunities. *Clinical Cardiology*, *45*, 1094–1099.

Zaoui, A., Cherrah, Y., Lacaille-Dubois, M. A., Settaf, A., Amarouch, H., & Hassar, M. (2000). Diuretic and hypotensive effects of Nigella sativa in the spontaneously hypertensive rat. *Thérapie*, *55*(3), 379–382.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kavyani, Z., Musazadeh, V., Safaei, E., Mohammadi Asmaroud, M., Khashakichafi, F., Ahrabi, S. S., & Dehghan, P. (2023). Antihypertensive effects of *Nigella sativa* supplementation: An updated systematic review and meta-analysis of randomized controlled trials. *Phytotherapy Research*, 1–15. https://doi.org/10.1002/ptr.7891