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Determination of the effect of *Nigella sativa* on blood pressure; a systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Introduction: Hypertension is considered a significant and highly prevalent public health problem. Due to the wide application of the medicinal herb *Nigella sativa* in managing this condition, the present study aims to evaluate the effect of *N. sativa* consumption on reducing blood pressure (BP) levels using a systematic review and meta-analysis approach.

Materials and Methods: Multiple online databases, including PubMed, Scopus, Cochrane, Web of Science, and the Google Scholar search engine, were searched using standard keywords to identify relevant articles up to May 9, 2022. Data were analyzed using STATA 14 software, and the significance level was taken as $P<0.05$ for all tests.

Results: From the total of 12 reviewed studies with a sample size of 854, the consumption of *N. sativa* powder (SMD: -0.46; 95% CI: -0.63, -0.30) and *N. sativa* oil (SMD: -2.04; 95% CI: -2.75, -1.34) lowered the systolic BP (SBP) levels. The consumption of *N. sativa* powder (SMD: -0.45; 95% CI: -0.63, -0.28) and *N. sativa* oil (SMD: -2.31; 95% CI: -3.05, -1.57) altered the diastolic BP (DBP) level. Then, the standard effect sizes of *N. sativa* consumption on triglyceride (SMD: -0.14; 95% CI: -0.29, 0), LDL-C (SMD: -0.35; 95% CI: -0.54, -0.17), HDL-C (SMD: 0.01; 95% CI: -0.14, 0.16) and FBS (SMD: -0.36; 95% CI: -0.58, -0.15) levels were measured.

Conclusion: *Nigella sativa* consumption showed a higher impact on reducing SBP than DBP levels. In addition, the consumption of *N. sativa* oil was more effective in lowering BP levels than *N. sativa* powder. Hence, further research is suggested to evaluate and compare the effectiveness of *N. sativa* oil and powder.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42022336951).

Implication for health policy/practice/research/medical education:
In this systematic review and meta-analysis, we found that *N. sativa* consumption showed a higher impact on reducing systolic than diastolic blood pressure levels. In addition, *N. sativa* oil was more effective in lowering blood pressure levels than *N. sativa* powder. Furthermore, the effect of black seed decreased FBS, cholesterol, and LDL-C. However, it did not reduce TG and HDL-C.

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Meta-analysis

Introduction

The most recent definition describes hypertension as blood pressure that is persistently higher than 130/80 mm Hg (1). Twenty-five percent of the adult population worldwide have hypertension, and this value is projected to rise to 29% by 2025 (2). This condition is associated with various factors, including advanced age, race, stress, environmental and dietary factors, obesity,

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diabetes, cardiovascular diseases, smoking, and alcohol consumption (3).

Hypertension can elevate the risk of heart attack, renal problems, blood vessel damage, stroke, and eventually death (4,5). Different classes of anti-hypertensive drugs are available to minimize the consequences of high blood pressure (6). Today, the use of herbal remedies with lower adverse effects has sparked great attention. *Nigella sativa*, or black cumin, which belongs to the Ranunculaceae family, has been used for centuries for disease treatment and health improvement, particularly in the Middle East and South East Asia (7). Several studies have demonstrated the various activities of *N. sativa* on metabolic syndrome parameters, including blood sugar, lipid profile, and blood pressure (BP) (8). Given the inconsistency in the results of the previous studies, the current study aims to explore the effect of *N. sativa* consumption on systolic BP (SBP) and diastolic BP (SBP) using a systematic review and meta-analysis approach.

Materials and Methods

Study design

The current study is written based on the PRISMA checklist (9), specifically designed for systematic review and meta-analysis studies. The protocol of this study is registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (CRD42022336951).

Studied outcomes

Primary outcome: Determination of the effect of *N. sativa* consumption on systolic and diastolic BP levels.

Secondary outcomes: Determination of the effect of *N. sativa* consumption on cholesterol, triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and fasting blood sugar (FBS).

Search strategy

In this meta-analysis databases, PubMed, Scopus, Cochrane, Web of Science, and the Google Scholar search engine, were searched without any time or language restrictions. The literature search was carried out using standard keywords, including "blood pressure," "diastolic pressure," "systolic pressure," "black cumin," and "*N. sativa*," and their MeSH terms up to May 9, 2022. Databases were also queried for keyword combinations using Boolean operators "AND" and "OR." Moreover, a manual search of the reference lists of all initially retrieved articles was conducted. The search strategy in some databases is presented in Table S1 as an example.

Inclusion criteria

The randomized clinical trials (RCTs) which investigated the effectiveness of *N. sativa* consumption on BP level entered this meta-analysis. The eligible studies reported the means and standard deviations of the SBP and DBP pre- and post-intervention.

Exclusion criteria

The case-report studies; studies lacking the required information for data analysis; articles that studied the effect of *N. sativa* and another medicinal herb concurrently; articles with full text unavailable; studies that qualitatively described the effect of *N. sativa* consumption on BP level; low-quality studies.

PICO components

Population: The individuals with high or normal BP that used *N. sativa* to lower BP levels; *Intervention: N. sativa* (in oil or powder forms); *Comparison:* Individuals that received standard treatment or placebo; *Outcome:* The standard effect size of the impact of *N. sativa* on BP level.

Qualitative assessment

To evaluate the quality of studies, two researchers independently applied Cochrane's quality assessment checklist for clinical trial studies (10). This checklist consists of seven items, each assessing one of the dimensions or types of major biases in clinical trials. Each item has three choices: high risk of bias, low risk of bias, and unclear. After completion of bias risk assessment in all studies, the differences were resolved by the two evaluators reaching a consensus on one single choice.

Data extraction

Two independent investigators extracted data from articles to minimize reporting bias and data collection errors. They entered the extracted data into a checklist containing the researcher's name, the year of study, the location of study, age group, the type of *N. sativa* preparation (oil or gel), duration of *N. sativa* consumption, the dosage of *N. sativa* consumption, the total sample size, the number of males and females, standardized mean difference (SMD) between *N. sativa* consumption and BP and its upper and lower limits, means and standard deviations of HDL, LDL, TG, cholesterol, FBS, SBP, and DBP levels, pre- and post-intervention. A third investigator examined the data extracted by the two previous researchers to resolve any discrepancy if one exists.

Statistical analysis

Given the quantitative nature of the primary outcome, the effect size of the intervention was measured, allowing the calculation of the within-group mean difference. If close to zero, this measure (SMD) indicates a weaker association, and if close to one and even higher, it indicates a stronger association. If the confidence interval of SMD intersects

zero, then the relationship is not statistically significant and vice versa.

The reviewed articles were pooled based on the sample size, mean and standard deviation. The heterogeneity of the studies was evaluated using the Q Cochrane test and I^2 index. Based on the I^2 index, heterogeneity is categorized into three levels, including low (less than 25%), moderate (between 25% and 75%), and high (above 75%) (11). Due to the moderate heterogeneity of the present study, the random-effects model was applied in this meta-analysis. Data analysis was executed in SATA 14 software, and the significance level of the tests was considered $P<0.05$.

Results

Initially, 401 articles were retrieved by searching the mentioned databases. Based on the titles of these studies, 191 duplicate articles were identified and removed. The remaining 210 articles were screened by abstracts, from which another 11 papers were excluded due to full-text unavailability. Of the remaining 199 articles, 187 met other exclusion criteria and were removed. Eventually, 12 papers entered the quality assessment step, which showed desirable quality and eligibility for the meta-analysis process (Figure 1).

The 12 reviewed articles, published from 2009 to 2022, had a sample size of 854, with an average age ranging from 14 to 72 years. The powder form of *N. sativa* was given in eleven studies, while one studies used the *N. sativa* oil. Regarding the distribution of the publications by country, three from Pakistan, two from Malaysia, two from Bangladesh, two from Indonesia, one from Iraq, one from India, and one from Saudi Arabia. Table 1 provides the information of the reviewed studies.

The consumption of *N. sativa* powder (SMD: -0.46; 95% CI: -0.63, -0.30) and *N. sativa* oil (SMD: -2.04; 95% CI: -2.75, -1.34) lowered the SBP levels. Overall, the consumption of *N. sativa* in all reviewed studies caused a reduction in SBP levels (SMD: -0.53; 95% CI: -0.72, -0.33) (Figure 2).

The consumption of *N. sativa* powder (SMD: -0.45;

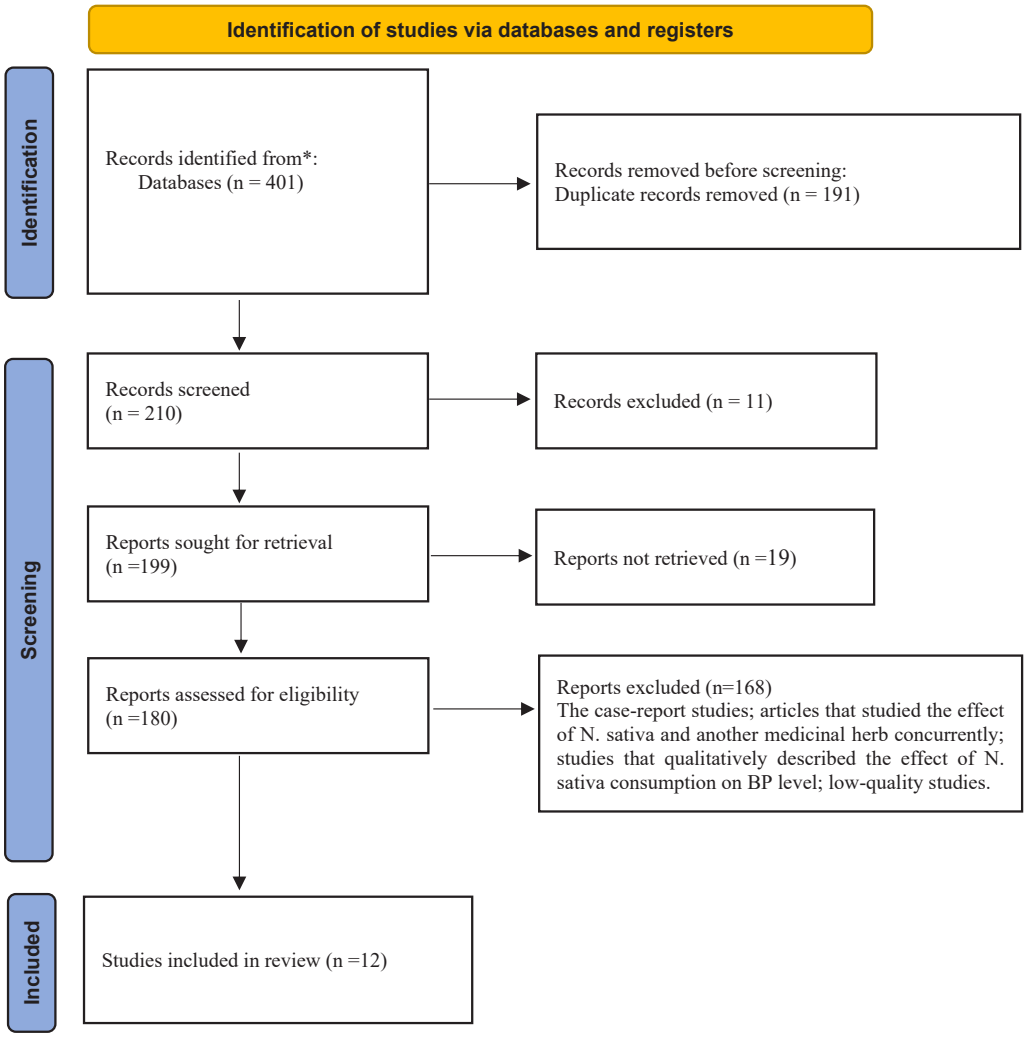

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. The information of the reviewed articles

First Author	Population	Powder/Oil	Country	Sample size	No. of female in cases	No. of male in cases	Age (y)	Dosage (mg/dL)	Duration (wk)
Siddiqui (12)	Hypertensive	Powder	Pakistan	200	33	67	18-60	1500	6
Siddiqui (12)	Hypertensive	Powder	Pakistan	200	33	67	18-60	1500	12
Al-Jawad (13)	Hypertensive	Oil	Iraq	24	15	9	31-65	1000	4
Badar (14)	T2D	Powder	Saudi Arabia	114	24	33	46.82	2000	12
Badar (14)	T2D	Powder	Saudi Arabia	114	24	33	46.82	2000	24
Badar (14)	T2D	Powder	Saudi Arabia	114	24	33	46.82	2000	36
Badar (14)	T2D	Powder	Saudi Arabia	114	24	33	46.82	2000	48
Rizka (15)	Elderly	Powder	Indonesia	76	25	13	72	600	4
Amin (16)	Metabolic syndrome	Powder	Pakistan	124	-	-	44	2500	4
Amin (16)	Metabolic syndrome	Powder	Pakistan	124	-	-	44	2500	8
Ibrahim (17)	Menopausal women	Powder	Malaysia	37	19	-	53.22	1000	4
Ibrahim (17)	Menopausal women	Powder	Malaysia	37	19	-	53.22	1000	8
Latiff (18)	Perimenopausal women	Powder	Malaysia	136	55	-	50.1	1600	12
Bin Sayeed (19)	Healthy adolescent	Powder	Bangladesh	48	-	24	14-17	500	4
Bin Sayeed (20)	Healthy human	Powder	Bangladesh	40	-	-	55.8	1000	9
Najmi (21)	Metabolic syndrome	Powder	India	80	-	-	40-60	500	8
Datau (22)	Men with central obesity	Powder	Indonesia	39	-	-	30-45	1500	12
Qidwai (23)	Adults	Powder	Pakistan	73	-	-	45.58	2000	6

95% CI:-0.63, -0.28) and *N. sativa* oil (SMD: -2.31; 95% CI:-3.05, -1.57) altered the DBP levels. In all studies, *N. sativa* consumption had a lowering impact on DBP (SMD: -0.52; 95% CI: -0.73, -0.31) (Figure 3).

The effect of black seed consumption on BP, lipid and sugar profile of patients is shown in Table 2.

Discussion

The effect of black seed consumption on SBP and DBP was lower in the group that consumed black seed powder than

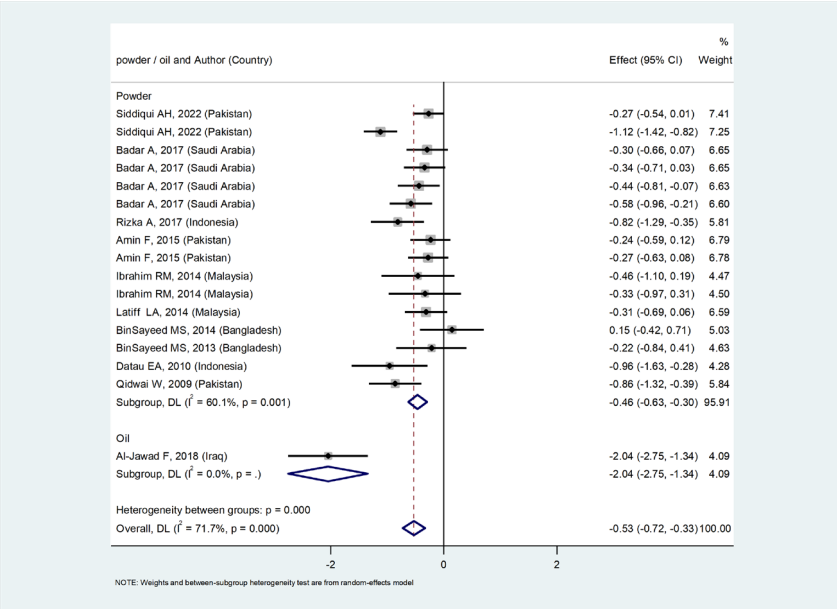

Figure 2. The standard effect size of the effect of *N. sativa* consumption on systolic blood pressure levels and its 95% confidence interval by the type of *N. sativa*.

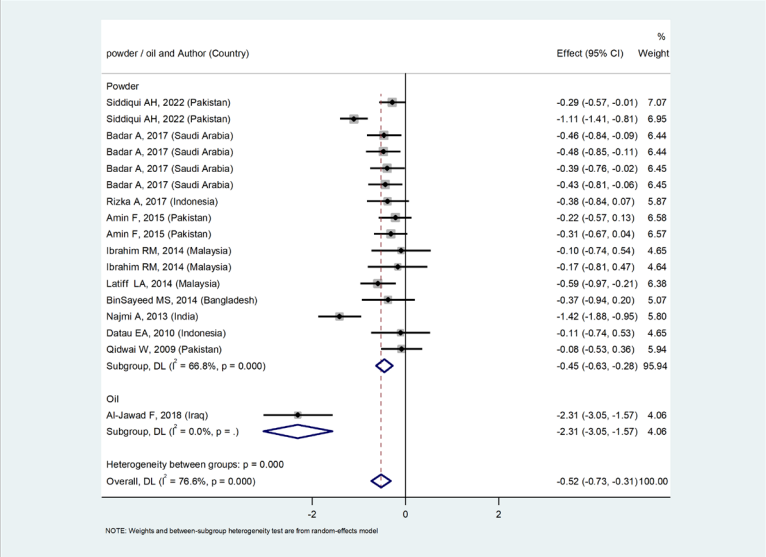

Figure 3. The standard effect size of the effect of *N. sativa* consumption on diastolic blood pressure levels and its 95% confidence interval by the type of *N. sativa*.

in the group that consumed black seed oil. By examining different age groups, we saw that the effect of black seed consumption on SBP is not statistically significant only in the age group of 10 to 19 years, and in other groups, black seed consumption causes a significant decrease in SBP.

Regarding the dose of black seed, a group of people who used doses of 500, 1000, 1600 and 2500 mg/dL, black seed consumption had no effect on their SBP. However, the people who used black seed with doses of 600, 1500 and 2000 mg/dL, the consumption of black seed caused a significant decrease in their SBP. We can see that among these three doses, the greatest effect of black seed on SBP was at the dose of 600 mg/dL. People who used black seed for 4, 12, 36 or 48 weeks, their SBP was significantly reduced. However, people who had consumed black seeds for 6, 8, 9 or 24 weeks, consumption of black seeds had no effect on reducing their SBP.

In the subgroup analysis, we saw that the effect of black seed consumption on DBP of people whose age group was between 10 to 19 years and 70 to 79 years was not statistically significant. However, black seed consumption by people aged 40 to 49 and 50 to 59 years caused a significant decrease in their DBP.

In terms of dosage, people who consumed 1500 mg/dL or less of black seed, their DBP did not decrease. On the other hand, people who had used a dose of 1600 mg/dL and above, their DBP had decreased significantly. By examining the duration of consumption, we came to the conclusion that those who had consumed black seeds for 6 or 8 weeks, their DBP did not decrease. But those who had consumed black seeds for 4, 12, 24, 36, 48 weeks, their DBP had decreased.

In a review study conducted in 2013. Researchers stated that black seed is widely used as anti-hypertensive, liver tonic, diuretic, anti-diarrhea, appetite stimulant, analgesic, antibacterial. Also, in the studies reviewed in this research, the researchers pointed out the medicinal uses of this natural product, such as: anti-diabetic, anti-cancer, immune modulator, pain reliever, antimicrobial, anti-inflammatory, liver and kidney protector (8). In another study, it was stated that the published original research articles on the effects of *N. sativa* and its ingredients strongly indicate its medicinal potential in the field of skin (24).

A meta-analysis conducted in 2022 on 4 RCT studies showed that *N. sativa* supplementation was beneficial for the treatment of nonalcoholic fatty liver disease without side effects (25). A total of 1393 research articles were potentially related to the effect of black seed and its bioactive compound, thymoquinone, on type 2 epithelial to mesenchymal transition. After screening, 22 research articles met the inclusion criteria and were included in this review. Most studies reported accelerated wound healing or significant prevention of tissue inflammation and organ fibrosis following black seed or thymoquinone treatments. In terms of wound healing, studies included the development of pathological changes associated with epithelial to mesenchymal transition after treatment with nigella or thymoquinone. Alternatively, in terms of fibrosis and inflammation, studies included reversal of epithelial to mesenchymal transition (EMT)-related pathological changes after treatment with nigella or thymoquinone (26). As it is clear from the above studies, black seed consumption has favorable therapeutic effects on various

Table 2. The standard effect size of the effect of *Nigella sativa* on blood pressure, blood sugar, and lipid levels

Subgroups			SMD	Low	Up	*P* value	I^2 (%)	Significant
SBP		Total	-0.53	-0.72	-0.33	<0.001	71.7	Yes
	Type of use	Powder	-0.46	-0.63	-0.30	0.001	60.1	Yes
		Oil	-2.04	-2.75	-1.34	-	0	Yes
	Age group	10-19 years	0.15	-0.42	0.71	-	0	No
		40-49 years	-0.41	-0.55	-0.26	0.380	6.3	Yes
		50-59 years	-0.32	-0.59	-0.06	0.963	0	Yes
		70-79 years	-0.82	-1.29	-0.35	-	0	Yes
	Dosage (mg/d)	500	0.15	-0.42	0.71	-	0	No
		600	-0.82	-1.29	-0.35	-	0	Yes
		1000	-0.75	-1.55	0.05	<0.001	83.5	No
		1500	-0.76	-1.40	-0.13	<0.001	88.5	Yes
		1600	-0.31	-0.69	0.06	-	0	No
		2000	-0.48	-0.66	-0.30	0.359	8.4	Yes
		2500	-0.25	-0.50	0	0.878	0	No
	Duration (wk)	4	-0.65	-1.27	-0.04	<0.001	85.4	Yes
		6	-0.53	-1.11	0.04	0.033	78.1	No
		8	-0.29	-0.60	0.02	0.875	0	No
		9	-0.22	-0.84	0.41	-	0	No
		12	-0.66	-1.13	-0.19	0.001	82.1	Yes
		24	-0.34	-0.71	0.03	-	0	No
		36	-0.44	-0.81	-0.07	-	0	Yes
		48	-0.58	-0.96	-0.21	-	0	Yes
DBP		Total	-0.52	-0.73	-0.31	<0.001	76.6	Yes
	Type of use	Powder	-0.45	-0.63	-0.28	<0.001	66.8	Yes
		Oil	-2.31	-3.05	-1.57	-	0	Yes
	Age group	10-19 years	-0.37	-0.94	0.20	-	0	No
		40-49 years	-0.35	-0.49	-0.21	0.808	0	Yes
		50-59 years	-0.38	-0.70	-0.06	0.318	12.8	Yes
		70-79 years	-0.38	-0.84	0.07	-	0	No
	Dosage (mg/dL)	500	-0.91	-1.93	0.12	0.005	87.1	No
		600	-0.38	-0.84	0.07	-	0	No
		1000	-0.85	-2.19	0.50	<0.001	91.8	No
		1500	-0.53	-1.17	0.11	<0.001	89.1	No
		1600	-0.59	-0.97	-0.21	-	0	Yes
		2000	-0.39	-0.56	-0.22	0.691	0	Yes
		2500	-0.27	-0.52	-0.02	0.707	0	Yes
	Duration (wk)	4	-0.63	-1.24	-0.02	<0.001	85.4	Yes
		6	-0.23	-0.47	0.01	0.449	0	No
		8	-0.64	-1.42	0.13	<0.001	87.6	No
		12	-0.62	-1.02	-0.21	0.006	75.7	Yes
		24	-0.48	-0.85	-0.11	-	0	Yes
		36	-0.39	-0.76	-0.02	-	0	Yes
		48	-0.43	-0.81	-0.06	-	0	Yes
Blood lipids		Cholesterol	-0.38	-0.54	-0.22	0.257	22.6	Yes
		TG	-0.14	-0.29	0	0.384	5.7	No
		LDL	-0.35	-0.54	-0.17	0.107	42.5	Yes
		HDL	0.01	-0.14	0.16	0.327	13.5	No
Blood sugar		FBS	-0.36	-0.58	-0.15	0.526	0	Yes

diseases such as skin problems, diabetes, wound healing, anti-inflammatory, etc. In the current meta-analysis, the consumption of black seed decreased the BP level and it was consistent with the results of previous studies.

Conclusion

In general, it can be concluded that the effect of black seed on reducing SBP is slightly more than that of DBP. The results of this meta-analysis suggested that the consumption of *N. sativa* oil more strongly affected the reduction of SBP and DBP levels than its powder form. Hence, future research is suggested to compare the effect of *N. sativa* powder and oil on BP levels to allow a more detailed discussion of their differing outcomes. Additionally, the effect of black seed decreased the level of fasting blood glucose, cholesterol and LDL-C. However, it had no effect on reducing TG and HDL-C.

Limitations of the study

The limitations of the present study are as follows: (a) unavailability of the full text of some studies; (b) since the reviewed studies failed to report the effect of *N. sativa* consumption on BP by gender, we could not compare the effect of *N. sativa* consumption on BP in males and females; (c) due to the non-uniform distribution of studies in different countries, there was no information available in many countries; (d) the reviewed studies did not mention the type of BP measurement device.

Authors' contribution

Conceptualization: Mahmood Moosazadeh, Mohammad Yousofpour, Alireza Fatahian and Moloud Fakhri.
Methodology: Moloud Fakhri, Mahmood Moosazadeh, Mohammad Azadbakht.
Formal analysis: Mahmood Moosazadeh and Moloud Fakhri.
Resources: Melina Ramezanpour.
Funding acquisition: Moloud Fakhri.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no conflict of interest regarding the contents of this article.

Ethical issues

This study was conducted in accordance with the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42022336951). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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Supplementary files

Supplementary file 1 contains Table S1.

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