

Effects of *Nigella sativa* supplementation on blood parameters and anthropometric indices in adults: A systematic review on clinical trials

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Background: *Nigella sativa* (*N. sativa*) has been used in traditional medicine and several studies have been performed in the last decades to reveal the effects of it on different medical disorders such as diabetes, dyslipidemia, hypertension, and obesity. We evaluated the effects of *N. sativa* supplementation on lipid profiles, glycemic control, blood pressure (BP), and some anthropometric indices in humans.

Materials and Methods: A search on published studies was done by using databases including PubMed, Google Scholar, Thomas Reuters Web of Science, and Cochrane. Medical subject headings (MeSH) terms searched included "*N. sativa*," "Black seed," "Black cumin," "kalonji," and "Triglycerides," "Cholesterol," "Lipoproteins," "LDL," "Lipoproteins," "HDL," "Blood glucose," "Hemoglobin A," "Glycosylated," "Blood pressure," "Body mass index," "Waist circumference". Initially 515 articles were extracted. Four hundred ninety-two papers that were unrelated, reviews, animal studies, and combined and duplicated studies were excluded, 23 articles were eligible for this review.

Results: After analyzing 23 articles including 1531 participants, these results were achieved: In 4 trials, *N. sativa* reduced BP, but in 5 trials it could not. Fasting blood sugar (FBS) was reduced significantly in 13 studies. In addition, *N. sativa* reduced levels of glycosylated hemoglobin (HbA1c). Although weight and waist circumference (WC) in 2 articles were reduced significantly, in 6 articles they were not. Fluctuation in lipid profile in the articles was very controversial, being significant in many of them but not in others. **Conclusion:** Our systematic review revealed that *N. sativa* supplementation might be effective in glycemic control in humans.

Key words: Anthropometric indice, glycemic control, lipid profile, *Nigella sativa*

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INTRODUCTION

In the beginning of human life, plants were used as medicines.^[1] Nowadays there is much more attention paid to the use of plants as therapeutics because of lower adverse effects. *Nigella sativa* (black seed), which belongs to family of Ranunculaceae, has been used to improve health and cure diseases for centuries, especially in the Middle East and Southeast Asia.^[2] A great focus has been placed on several traditional uses and therapeutic properties of *N. sativa*.^[3]

The pharmacological properties of *N. sativa* is attributed to several component including proteins, amino

acids, carbohydrates, fibers, oils (combination of fatty acids, especially polyunsaturated fatty acids), volatile oil (frequently thymoquinone), mineral, alkaloids, flavonoids, saponins, and others.^[4]

Effects of *N. sativa* are reported in experimental models, including hypoglycemic,^[5] antihyperlipidemic,^[6] antihypertensive,^[7] antioxidant,^[8] and antiinflammatory^[9] properties. Several studies showed the different activities of *N. sativa* on the parameters of the metabolic syndrome, such as blood glucose, lipid profile, and blood pressure (BP).^[10]

N. sativa is a rich source of unsaturated fatty acids such as linoleic acid and oleic acid and it contains small

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amount of linolenic, arachidonic, and eicosenoic acid, which constitute 80–84% of fatty acids in this seed and may have roles in the hypolipidemic effect of this plant.^[11] However, there was no effect of black seed on lipid profiles in some animal studies.^[12]

It was also shown that *N. sativa* contains several chemicals (such as thymoquinone) that provide antioxidant activity and diuretic effect, which may play roles in reducing hypertension.^[13,14]

However, the cardiovascular properties of *N. sativa* are controversial because some studies show decrease in BP^[15,16] but others report no effect in animals^[17] or humans.^[18]

In the field of blood glucose-lowering effect of *N. sativa*, it has been proposed that activation of insulin secretion^[19] and antioxidant action^[20] of this seed may be the reason for this effect. However, it was reported to have no effect in some studies.^[21]

In some animal studies, it was reported that *N. sativa* has an antiobesity property. The reasons for this effect are not so clear, but factors such as reduction of appetite are proposed.^[22]

There are a few review articles^[23-25] that have surveyed the effect of *N. sativa* on some diseases. In these research projects, the role of this plant as a treatment factor is evaluated but only a section of parameters was investigated, such as lipid profile in diabetes,^[23] BP,^[24] or antioxidant activity.^[25] Therefore, we are going to review the effect of *N. sativa* supplementation on different clinical and biochemical parameters in humans, the majority of which exist in metabolic syndrome.

MATERIALS AND METHODS

The protocol that was used in this study is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. A search of published studies was performed by using computer databases including PubMed, Google Scholar, Thomas Reuters Web of Science, and Cochrane.

Searching was done for articles in the English language until June 2014. Medical subject headings (MeSH) terms included: (“*Nigella sativa*” [MeSH] OR “blackseed” [tiab] OR “blackcumin” [tiab] OR “Kalonji” [tiab]) AND “Triglycerides” [MeSH] OR “Cholesterol” [Mesh] OR “Lipoproteins, LDL” [MeSH] OR “Lipoproteins, HDL” [MeSH] OR “Blood glucose” [MeSH] OR “Hemoglobin A, Glycosylated” [MeSH] OR “Blood pressure” [MeSH] OR “Body mass index” [MeSH] OR “Waist circumference” [MeSH]).

Primary outcome: Blood glucose
Secondary outcome: Nausea

Inclusion criteria

1. The effect of *N. sativa* on clinical or biochemical parameters.
2. Clinical trial.

Exclusion criteria

1. Animal studies.
2. Review studies.
3. The effect of *N. sativa* on unrelated blood or clinical parameters.
4. The effect of *N. sativa* in combination with other plants or exercise.
5. Duplicated studies.

Data extraction

The following data were extracted: Author, country of study, date of publication, study design, duration of study, aims, number and age of persons, dose of supplement, score of study, and effects of intervention.

Quality of studies

In scoring studies, the trials were stratified based on a scoring checklist as Down Quality Assessment scores.^[26] Trials were stratified in this checklist based on acquired scores [Appendix].

Study selection

Initially, 515 articles were extracted. After reviewing their titles and abstracts and removing unrelated, animal, and review studies, 28 articles were retrieved for further evaluation. Finally, 23 studies were considered eligible for our review [Table 1].

The eligible articles were published until June 2014. Five articles could not be included in this review as 3 of them evaluated the effect of *N. sativa* in combination with other plants or exercise. The other 2 were duplicated.

RESULTS

Characteristics of the included studies

All of the studies were clinical trials (of course 5 articles were quasi-experimental). These surveys have been done on different patients and subjects such as 5 studies^[27-31] on

Table 1: Process of study selection

Process	Selected studies
Initial search (based on MeSH terms)	515 papers
After exclusion of studies that were unrelated to our study, including effects of <i>N. sativa</i> on unrelated parameters and others	76 papers
After exclusion of animal studies	52 papers
After exclusion of review studies	28 papers
After exclusion of combined studies	25 papers
After exclusion of duplicated studies	23 papers

Appendix: Scoring of studies in the systematic review based on Downs Quality Assessment score

Item	Hoseini	Dehk- Hoseini	Hoseini	Qidwai	Mohta- shami	Datau	Sabzgh- abae	Bamosa	Kaatabi	Bilal	Ibrahim	Najmi	Najmi	Ibrahim	Najmi	Bamosa	Ibrahim	Shah	Bhatti	Eire- hany	Haque	Najmi	Ahmed	
	hf	ordi	ms	ms	shami	Datau	abae	2010	2010	rm	2012	2012	rm	Ibrahim	Najmi	2007	1997	da	Shah	Bhatti	Eire- hany	Haque	Najmi	Ahmed
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
5	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
6	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
7	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
8	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
9	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
11	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
12	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
13	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
14	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
15	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
16	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
17	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
18	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
19	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
20	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
21	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
22	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
24	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
26	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
27	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Total	24	24	24	24	23	22	21	19	19	18	17	17	17	16	16	16	16	16	16	16	15	15	14	14
score																								

diabetic patients, 7, trials^[32-38] on patients with metabolic syndrome, 4 studies^[39-42] on patients with hyperlipidemia, 2 articles^[43,44] in the field of hypertension and coronary disease, 1 study^[45] on obese men and others were investigated in healthy subjects.^[45-48]

With regard to the form of supplement, 2 studies^[31,43] have used extract of *N. sativa*, 8 articles^[28,30,32,37,38,44,46,48] used oil from the seed, and in the others, that is, 13 articles, powder of *N. sativa* was provided for subjects. The total number of subjects in the trials was 1531. The duration of the trials was between 2 weeks and 6 months. The dose of *N. sativa* supplements was between 200 mg and 5 g per day and was administered orally in all studies. The age range of the participants in trials was 18-65 years old.

With regard to the quality of the research based on Down Quality Assessment scores,^[26] 5 studies^[30,39,43,46,49] showed double blinding of intervention and 13 trials^[30,34-39,41-43,46,48,49] demonstrated appropriate randomization, but in the other studies randomization or blinding was unclear.

The characteristics of 18 included clinical trials are shown in Table 2.

Five articles^[27-29,40,47] had no control group and were quasi-experimental studies [Table 3].

In 9 studies,^[27,29,30,39,41,43,46-48] there were similar baseline characteristics between groups.

Eight trials^[27-29,39,41,43,45,49] reported the rate of dropouts, but in all of them the rate was more than 10%, as in 1 article^[28] it was 42%, which naturally affected the results of the study.

In 6 studies,^[28,34,35,42,47,49] sample sizes were 10-41 and in the others were 55-161 subjects.

Effects of *N. sativa* on different clinical and biochemical parameters

Effect on lipid profiles

1. Triglyceride (TG)

The influence of *N. sativa* in lowering TG was effective in 7 trials.^[29,31,34,40-42,44]

This effect in 10 studies was not significant.^[30,32,33,35,37,39,43,45,47,49]

2. Total cholesterol (TC)

In 10 studies *N. sativa* reduced TC significantly.^[29,30-32,34,40,41,42,44,45]

This effect was not found in 4 trials.^[33,37,39,47]

3. Low-density lipoprotein (LDL)

Reduction of LDL was reported significantly in 11 studies.^[29,31-35,37,40-42,44]

This reduction was not significant in 3 articles.^[30,39,47]

4. High-density lipoprotein (HDL)

N. sativa increased HDL in 6 trials.^[29,31,33,37,40,44]

The elevation of this parameter was not significant in 10 studies.^[30,32,34,35,39,41-43,47,49]

Effect on glycemic control

1. Fasting blood sugar (FBS)

FBS was affected by *N. sativa* and reduced notably in 13 studies.^[27,28,30-35,37,42,45,47,48]

In 3 articles this effect was not significant.^[39,41,49]

2. Glycosylated hemoglobin (HbA1c)

This parameter reveals the condition of the blood glucose level from several weeks ago (6-8 weeks) and is a part of the glucose in serum that is combined with hemoglobin. In normal circumstances this parameter should be <6%. In all of the trials that evaluated this factor,^[27,30,35,48] *N. sativa* could reduce the level of this factor significantly. This reduction was accompanied by the lowering of the FBS level.

Effect on blood pressure (BP)

One of the most important factors in cardiovascular disease and metabolic syndrome is BP. In 4 studies, *N. sativa* could reduce this factor.^[36,43,44,46]

However, this effect was not shown in 5 trials.^[33,37,39,42,49]

Effect on some anthropometric parameters

Weight and body mass index (BMI)

These parameters were evaluated in 8 studies. Two trials^[30,49] have demonstrated the effect of *N. sativa* in lowering weight and BMI significantly, but in the other articles this effect was not seen.^[33,34,37,38,39,43]

Overweight and obesity, especially central obesity, is associated with metabolic disturbances such as diabetes and dyslipidemia.

Waist circumference (WC)

WC plays an important role in the detection of metabolic syndrome. From these studies, 6 trials evaluated this parameter and of them only 1 article^[49] showed the reduction of WC, and in 5 articles this was not significant.^[32,33,37-39]

In 1 study, lowering of WC was accompanied by the reduction of weight.^[49]

Toxicity

Attention to the adverse effect of *N. sativa* supplement is reported in 10 trials.^[27,30,35,36,39,41,43,46,48,49]

Only in 2 studies,^[30,46] did a few participants who received *N. sativa* oil at the dose of 5 mL per day experience mild nausea,

Table 2: Characteristics of included studies (clinical trials) (listed based on acquired score)

Author	Date of publication	Study design	Duration of study	Aims	N (case/ control)	Age of subject (years)	Dose of NS	Score	No of refs	Results
Hoseini, HF (Iran)	2013	DB ¹ -RCT ²	8 weeks	Effect of NS ³ oil on BP in healthy adults	70 (35/35)	34-63	5 mL/day	24	47	Sig ⁴ reduction ($P<0.001$) in SBP ⁵ and DBP ⁶
Dehkordi (Iran)	2008	DB-RCT	8 weeks	Effect of NS on BP in patients with mild hypertension	108 (36, 39/33)	35-50	200 mg/day and 400 mg/day (extract of NS)	24	43	Sig reduction ($P<0.05$) in SBP and DBP. Nonsig. change ($P>0.05$) in weight, TG, ⁷ and HDL ⁸
Hoseini, MS (Iran)	2013	DB-RCT	3 month	Effect of NS oil in Type 2 diabetic Patients	70 (35/35)	34-63	5 ml/day	24	30	Sig reduction ($P<0.05$) in FBS ⁹ , 2 h PPBG ¹⁰ , HbA1c, ¹¹ BMI, ¹² and TC. ¹³
Qidwai (Pakistan)	2009	DB-RCT	6 weeks	Effect of NS on some blood parameters and body weight	73 (39/34)	≥18	1 g/day	24	39	Nonsig. change ($P>0.05$) in TG, LDL, ¹⁴ and HDL
Mohtashami (Iran)	2011	RCT	2 months	Effect of NS oil on blood glucose in healthy adults	70 (35/35)	25-60	5 mL/day	23	49	Nonsig. change ($P>0.05$) in Lipid profile, FBS, BMI, BP, and WC ¹⁵
Datau (Indonesia)	2010	DB-RCT	3 month	Effect of NS on some blood parameters and weight in obese men	39 (19/20)	30-45	1.5 g/day	22	45	Sig. reduction ($P<0.001$) in weight and WC
Sabzghabae (Iran)	2012	RCT	4 weeks	Effect of NS in treatment of hyperlipidemia	74 (37/37)	≥18	2 g/day	21	41	Nonsig. change ($P>0.05$) in BP, FBS, TG, and HDL
Ibrahim R.M. (Malaysia)	2014	RCT	2 months	Effect of NS on some blood parameters in menopausal women	37 (19/18)	50-55	1 g/day	18	42	Sig. reduction ($P<0.05$) in TC, LDL, and FBS.
Najmi (North India)	2012	RCT	8 weeks	Effect of NS on some blood parameters in patients with poor glycaemic control	80 (40/40)	40-60	500 mg/day	17	35	Sig. reduction ($P<0.001$) in FBS 2 h PPBG, HbA1c, and LDL.
Najmi (North India)	2013	RCT	8 weeks	Effect of NS on BP in metabolic syndrome	90 (45/45)	40-60	500 mg/day	17	36	Nonsig. change ($P>0.05$) in TG and HDL
Ibrahim R.M. (Malaysia)	2014	RCT	2 months	Effect of NS on metabolic syndrome in menopausal women	35 (18/17)	45-60	1 g/day	17	34	Sig. reduction ($P<0.05$) in TC, LDL, TG, and HDL
Najmi (North India)	2007	RCT	6 weeks	Effect of NS oil on parameters of metabolic syndrome	161 (81/80)	40-60	5 mL/day	16	37	Sig. change ($P<0.05$) in LDL, FBS, and HDL
Bamosa (Saudi Arabia)	1997	CT ¹⁶	2 weeks	Effect of NS on some blood parameters	16 (9/7)	Second year male medical students	2 g/day	16	46	Nonsig. reduction ($P>0.05$) in weight, BP, TC, TG, and WC
Shah (Pakistan)	2012	CT	6 weeks	Effect of NS on metabolic syndrome	159 (80/79)	40-60	500 mg/day	16	33	Sig. reduction ($P<0.05$) in FBS, LDL, and HDL
Eirehany (Egypt)	2012	CT	8 weeks	Effect of NS oil on patients with coronary artery disease and dyslipidemia	55 (40/15)	35-65	900 mg/day	15	44	Nonsig. reduction ($P>0.05$) in TC, weight, TG, BP, and WC
Haque (North India)	2011	RCT	6 weeks	Effect of NS oil as antiobesity therapy in metabolic syndrome	60 (30/30)	40-60	5 mL/day	15	38	Sig. change ($P<0.001$) in BP, TC, LDL, TG, and HDL
Najmi (North India)	2008	CT	6 weeks	Effect of NS oil on various parameters in metabolic syndrome	60 (30/30)	?	5 mL/day	14	32	Nonsig. change ($P=?$) in weight and WC
Ahmed (Egypt)	2012	CT	6 months	Effect of NS tea on glycaemic control and lipid profile in type 2 diabetic patients	66 (41/25)	?	5 g/day (Extract of <i>N. sativa</i>)	14	31	Sig. reduction ($P<0.05$) in TC, LDL, and FBS. Nonsig. change ($P>0.05$) in TG, HDL, and WC

1 = Double blind; 2 = Randomized clinical trial; 3 = *Nigella sativa*; 4 = Significant; 5 = Systolic blood pressure; 6 = Diastolic blood pressure; 7 = Triglyceride; 8 = High-density lipoprotein; 9 = Fasting blood sugar; 10 = 2-hour Post Prandial Blood Glucose; 11 = Glucosylated hemoglobin; 12 = Body mass index; 13 = Cholesterol; 14 = Low-density lipoprotein; 15 = Waist circumference; 16 = Clinical trial

Table 3: Characteristics of included studies (quasi-experimental) (listed based on acquired score)

Author	Date of publication	Study design	Duration of study	Aims	N (case/control)	Age of subject (years)	Dose of NS	Score	No. of refs	Results
Bamosa (Saudi Arabia)	2010	CT (Noncontrol)	3 months	Effect of NS on glycemic control in patients with type 2 diabetes	68 (23 case, 26 control, 19)	18-60	1 2 3 g/day	19	27	Nonsig. change ($P>0.05$) in group with 1 g/day. Sig. reduction ($P<0.05$) in FBS, 2h PPBG, HbA1c in group with 2.3 g/day
Kaatabi (Saudi Arabia)	2012	CT (Non control)	3 months	Effect of NS on lipid profile in type 2 diabetic patients	71 (23 case, 26 control, 22)	18-60	1 2 3 g/day	19	29	Nonsig. change ($P>0.05$) in group with 1 g/day. Sig. change ($P<0.05$) in TC, TG, LDL, and HDL in group 2.3 g/day
Bilal (Pakistan)	2009	CT (Noncontrol) (40-day NS 40-day placebo)	40 days	Effect of NS oil on some blood parameters in type 2 diabetic patients	41	30-60	0.7 g/day	18	28	Sig. reduction ($P<0.001$) in FBS
Ibrahim D.A (Yemen)	2011	CT (Noncontrol) 2 weeks NS 2 weeks washout 2 weeks oil fish	2 weeks	Effect of NS (in comparison fish oil) on blood glucose and lipid profile	18	23-31	500 mg/day	16	48	Sig. reduction ($P<0.05$) in FBS. Nonsig. change ($P>0.05$) in lipid profile
Bhatti (Pakistan)	2009	CT (Noncontrol)	2 months	Effect of NS on lipid profile in hyperlipidemic Patients	10	50-55	1 g/day	16	40	Sig. change ($P<0.05$) in TC, TG, LDL, and HDL

at the beginning of study, and the nausea disappeared at the second week of intervention.

In the other 8 trials, no notable liver or kidney side effects were observed. This was evidenced by laboratory tests done for liver and kidney functions.

Other articles (13 trials) did not detect any adverse effects of this plant.

DISCUSSION

In this systematic review we have tried to evaluate the effects of *N. sativa* supplementation on lipid profiles, glycemic factors, BP, and some of anthropometric indices (weight, BMI, and WC), of which a few are parameters of metabolic syndrome.

In many studies *N. sativa* could effectively change parameters in different patients and subjects, but in several trials these changes were not significant [refer to Table 2].

Lipid profiles constitute one of the most important factors that can be changed in many diseases and are used to evaluate conditions of the patients and subjects. In our review, changes in lipid profiles were different as in many trials *N. sativa* supplement could change these parameters significantly, but in some studies it could not. However, in 4 articles^[29,31,40,44] all of parameters (TG, TC, LDL, and HDL) were affected significantly by *N. sativa*.

Several mechanisms are proposed to explain the hypolipidemic effect of *N. sativa*, including:

- Increase in cholesterol metabolism due to a rich source of polyunsaturated fatty acids.^[50]
- Inhibition of lipid peroxidation and reduction in cholesterol synthesis in the liver by antioxidant factors such as phytosterols and flavonoids.^[51]
- Reduction insulin resistance and dyslipidemia throughout antioxidative action of thymoquinone.^[52]
- Increase in the secretion of cholesterol in the bile and hence excretion in feces.^[53]
- Reduction of serum TG due to presence of nigellamin that act like a clofibrate.^[54]
- Regulation of cholesterol synthesis through effect on key enzyme HMG-COA reductase (Hydroxy Methyl Glutaryl – COA).^[55]

Although some trials had not reported any significant change in lipid profiles caused by *N. sativa*, the researcher proposed several factors, such as increased dropouts and small sample size^[39] or different characteristic of patients.^[30]

In the other studies, the reasons for nonsignificant change in these parameters are not reported. However, it is speculated that the factors that are effective include:

- Different characteristic of patients in study.^[32,33,37,49]
- Small dose of supplement.^[33,43,47]
- Short duration of intervention.^[37,47]

Glycemic control involving factors such as FBS and HbA1c are useful parameters in the detection and control of diabetes and increased blood glucose in the subjects. Of course, HbA1c is used to evaluate blood sugar in the past several weeks. Our review revealed that these factors are affected in many trials and *N. sativa* could reduce glycemic factors significantly. However, in a few studies this effect was not seen.^[39,41,49]

It is proposed that reduction of FBS and HbA1c by *N. sativa* supplementation is related to the following:

- Reduction in oxidative stress and maintenance of the integrity of pancreatic b-cells that lead to increased blood insulin level.^[56,57]
- Presence of thymoquinone with antioxidant activity.^[58]
- Activation of insulin receptors and improvement in tissue sensitivity to insulin.^[59]
- Decreased gluconeogenesis in the liver.^[60]
- Reduction in glucose absorption from the intestine.^[61]

In 3 trials that did not demonstrate any hypoglycemic effect of *N. sativa*, some reasons were proposed, including: small sample size^[39] and short-term duration of intervention, and probably change in diet or exercise.^[41]

In 1 trial^[45] any reason was reported but it was speculated that small sample size and low dose of supplement were effective.

BP is one of the most important parameters that is evaluated in many studies (9 trials). In 4 studies,^[36,43,44,46] the antihypertensive effect of *N. sativa* was demonstrated. However, in 5 trials this effect was not significant.^[33,37,39,42,49]

The authors proposed several mechanisms for lowering BP using *N. sativa* supplementation, including the following:

- Antioxidant activity of thymoquinone, polyphenols, and flavonoids in *N. sativa* that cause nitric oxide production and vasodilator effect.^[62]
- Presence of linoleic acid that affects ionic fluxes across the vascular endothelial cells.^[63]
- Presence of oleic acid that regulates lipid structure in membrane and control G-protein.
- Mediated signaling that leads to lowering of BP.^[64]
- Calcium channel-blocking activity by *N. sativa*.^[65]
- Inhibition of angiotensin-converting enzyme by flavonoids.^[66]

In some trials that did not reveal any significant effect of *N. sativa* on BP, the researchers did not detect any obvious reasons.^[33,37,39,42,49] Only in 1 trial, the author reported a small sample size and limited duration of the intervention.^[39] It seems that in other studies there are different reasons, such as small sample size,^[42,49] low dose of supplement,^[33,42,49] and short duration of intervention.^[33,37]

With regard to anthropometric parameters (weight and WC), there are remarkable results. Only in 2 trials was the effect of *N. sativa* in reducing weight or WC statistically significant.^[30,49] However, in 7 studies, these effects were not found.^[32,33,34,37,38,39,43]

It has been proposed that the petroleum extract of *N. sativa* has a slight appetite-reducing property^[67] and also has antiobesity action because of the presence of lipase enzyme.^[68]

While these 7 studies had no significant effects, only 1 trial^[39] had reported a small sample size as a reason. It seems that in other studies (6 trials), several factors were effective, including low doses of the supplement^[33,34,39,43] and the short duration of intervention.^[33,37,38,39]

Limitation

The most important limitation in our systematic review was difficulty in finding the full texts of many published papers. Further, we included only English-language articles and clinical trials in this review and not other studies.

CONCLUSION

This systematic review on 23 studies demonstrated that *N. sativa* supplement in different doses and durations can change various clinical and biochemical parameters, including lipid profiles, glycemic factors, BP, and some anthropometric indices in humans. However, the effect of this supplement is more pronounced on levels of TC, LDL, FBS, and HbA1c than on TG, HDL, BP, weight, and WC.

Therefore, it is suggested that consumption of *N. sativa* supplementation be considered as a complementary treatment protocol for many diseases, especially metabolic disorders.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

AM contributed in the preparation of the work and conducting the study and MHE (as Corresponding author) contributed in the revising of the draft and approval of the final version of manuscript.

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