

Clinical Uses of *Nigella Sativa* in Pediatrics: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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OBJECTIVE *Nigella sativa* (NS) has been widely used and investigated in several pediatric studies; however, its safety and efficacy in pediatrics are yet to be evaluated. This systematic review evaluates the clinical uses, safety, and efficacy of NS in pediatrics.

METHODS The search was conducted across 4 databases, including PubMed, Web of Science, Scopus, and Cochrane, up to September 6, 2023, and included clinical trials using NS in pediatrics. A methodological quality assessment was performed using the Cochrane risk of bias tool for randomized trials (Rob 2). A meta-analysis was conducted to evaluate safety. The systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

RESULTS Two hundred sixty-five studies were screened for eligibility, including 125 papers from Scopus, 31 from PubMed, 37 from Cochrane, and 72 from the Web of Science. Sixty-eight duplicate papers were eliminated, and 185 studies were excluded. Three studies were added from snowballing. Fifteen clinical trial studies were included in this review. Limited studies have been conducted on NS in pediatrics. Based on the meta-analysis, no statistically significant side effects have occurred. Different doses and forms of NS were used, and most studies have reported improvements in the outcomes.

CONCLUSION More high-quality studies are needed to establish the efficacy of using NS in different diseases, along with its effective dose and form. The studies in this review report no severe adverse effects and no statistically significant occurrence of side effects. However, further studies are needed to fully understand the safety of using NS in pediatrics.

ABBREVIATIONS NS, *Nigella sativa*; NSO, *Nigella sativa* oil; RCT, randomized control trial

KEYWORDS *Nigella sativa*; black seeds; children; pediatrics; systematic review; meta-analysis

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Introduction

The benefits of *Nigella sativa* (NS) have attracted considerable research attention due to its immunomodulatory, anti-inflammatory, and antioxidant properties. NS use has been widespread in traditional medicine throughout history, especially in Prophetic Medicine (Tibb-e-Nabwi), Unani, Siddha, and Ayurveda. The oil and seeds of this plant have been used in folklore as medicines and foods; it is considered one of the most effective healing methods in Islamic literature.¹ *Nigella sativa* is a medicinal herb belonging to the Ranunculaceae family and widely referred to as blackseed, also called black cumin or kalonji. The seeds and oils of NS contain various bioactive components, such as thymoquinone, thymohydroquinone, and carvacrol.² Thymoquinone is a major bioactive component of NS, identified as a potential antimicrobial, anti-inflammatory, and chemoprotective agent.¹

Nigella sativa is native to several regions, including Southwest Asia, the Eastern Mediterranean, North Africa, and Asia, and has been used in numerous food cultures as a flavoring agent and adjuvant.³ *Nigella sativa* comprises 38% to 45% lipids, 32% carbohydrate, and 21% protein; primary amino acids found in it are glutamic acid, aspartic acid, arginine, leucine, and glycine. It contains high levels of unsaturated fatty acids (57.71% linoleic acid and 24.46% oleic acid), mainly in *Nigella sativa* oil (NSO). The oil in NS seeds is rich in essential fatty acids, tocopherols, phytosterols, and polyphenols, making it a valuable ingredient in traditional medicine and the food industry.⁴ The seeds of NS are rich in calcium, magnesium, sodium, potassium, phosphorus, manganese, iron, zinc, and copper.⁵ Research has examined the plant's potential benefits for diabetes mellitus, skin cancer, acne vulgaris, and wound healing.² Furthermore, the plant has been shown to benefit the

reproductive, pulmonary, and immune system.¹Gholamnezhad et al⁶ reviewed numerous studies showing that NS and its main active compound, thymoquinone, have anti-inflammatory, antioxidant, antimicrobial, antitumor, antidiabetic, and antiepileptic properties that could benefit children. *Nigella sativa* and thymoquinone have glucose-lowering effects that could help manage diabetes in children and hepatoprotective effects that could prevent damage to liver tissue in children exposed to toxic substances.⁷ In addition, NS and thymoquinone have been found to possess immunomodulatory effects that could strengthen the immune system. Additionally, it has a bronchodilator effect that could benefit children with asthma and allergies.^{6,8} However, the safety of using NS in the pediatric population is unclear. Mashayekhi et al⁹ investigated the toxicological profile of NS and reported that it is generally considered safe, but more detailed studies are needed to draw a definitive conclusion. The side effects of this medicinal herb did not cause serious adverse events, and it can be used in clinical trials because of its major effects that have been shown to be beneficial.¹⁰ To our knowledge, no systematic review has been conducted to evaluate the efficacy, safety, and clinical uses of NS in pediatrics. Therefore, this systematic review aims to assess the safety, effectiveness, and clinical uses of NS in the pediatric population.

Materials and Methods

Search Strategies. This systematic review follows the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. It is registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42023475329). A search was conducted across 4 databases for studies published until September 6, 2023. PubMed, Cochrane, Web of Science, and Scopus (Elsevier) databases were systematically searched for relevant English-language studies published in the literature. Search terms used were “Nigella Sativa” OR “black seed” OR “black cumini” OR “kalonji” AND “pediatric” OR “child” OR “adolescent” (Table 1). No filter was used in the Web of Science and Scopus databases. The clinical trials filter was used in PubMed and Cochrane. The search was peer-reviewed by another independent reviewer. No date limits were applied. The criteria included clinical trials, studies on children/pediatric populations, and studies in the English language. Exclusion criteria included review papers, case studies, non-English language studies, studies on adults, irrelevant studies, studies that did not use NS, and studies published without full articles. Randomized control trials (RCTs) were considered eligible if they answered the following questions of the P-I-C-O-S model:

- P: Participants: pediatric patients.
- I: Intervention: using NS.

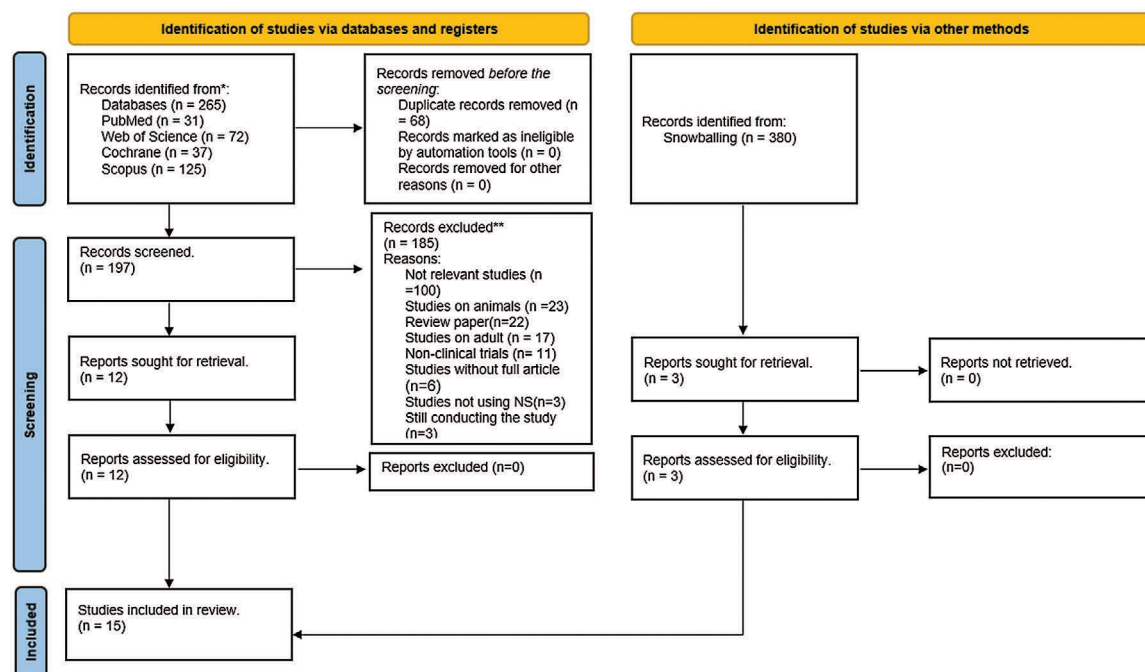
- C: Comparator: compared with standard treatment or others.
- O: Outcomes: outcomes measured by the study (no specific outcome).
- S: Study design: RCT.

Data Collection and Data Extraction. Results were uploaded to the Rayyan website, and duplicates were removed based on title, date, author, and volume fields. After the duplicates were removed, titles and abstracts were screened for relevance. Two independent reviewers screened the studies based on the inclusion criteria and the PICOS model. The titles and abstracts of the studies were reviewed as the first step, followed by the complete articles of the relevant studies. Forward and backward citation (snowballing) searching was conducted for the included studies using Citationchaser.¹¹

The RCTs were synthesized to describe the extracted data. Data were collected from studies by 2 independent reviewers. The data included the study author, year and country, population and sample size, study design, intervention, dose and duration of intervention, study outcome, reported side effects, and efficacy of using *Nigella*.

Data Synthesis and Statistical Analysis. A meta-analysis was conducted using the Meta-Mar online

Table 1. Search Strategy	
Database	Searched Terms
PubMed	(“Nigella sativa”[MeSH Terms] OR (“nigella”[All Fields] AND “sativa”[All Fields]) OR “nigella sativa”[All Fields] OR (“black”[All Fields] AND “seed”[All Fields]) OR “black seed”[All Fields] OR (“black”[All Fields] AND “cumin”[All Fields]) OR “black cumini”[All Fields] OR “kalonji”[All Fields]) AND (“pediatrics”[MeSH Terms] OR “pediatrics” [All Fields] OR “pediatric”[All Fields] OR (“child”[MeSH Terms] OR “child”[All Fields]) OR (“adolescent”[MeSH Terms] OR “adolescent”[All Fields]))
Cochrane	(“Nigella Sativa” OR “black seed” OR “black cumini” OR “kalonji”) AND (“pediatric” OR “child” OR “adolescent”)
Web of Science	(“Nigella Sativa” OR “black seed” OR “black cumini” OR “kalonji”) AND TS= (“pediatric” OR “child” OR “adolescent”)
Scopus	TITLE-ABS-KEY (“Nigella Sativa” OR “black seed” OR “black cumini” OR “kalonji”) AND TITLE-ABS-KEY (“pediatric” OR “child” OR “adolescent”)

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the search and study selection process.

software to assess the safety of using NS in pediatrics based on the presence of side effects among treated patients versus a placebo group. For the efficacy of using NS in pediatrics, it was only conducted in the treatment of epilepsy. Odds ratio and 95% CI were used. The p value threshold of 0.05 was used to determine statistical significance in both meta-analyses, as displayed in forest plots. Funnel graphs were used to detect the risk of publication bias in both meta-analyses.

Risk of Bias and Quality Assessment. To evaluate the evidence of quality included in this review, the Cochrane risk of bias tool for RCTs version 2 (Rob 2) was used to assess the risk of bias. Three independent reviewers conducted the assessment, and the review team only evaluated the published paper in the journal, aiming to adhere to the intervention (the per-protocol effect) based on the following 5 risks of bias domains: Domain 1: randomization process; domain 2: deviations from the intended interventions; domain 3: missing outcome data; domain 4: outcome measurement; and domain 5: selection of the reported result.

Results

Literature Search and Study Characteristics. Two hundred sixty-five studies were screened for eligibility; 125 papers from Scopus, 31 from PubMed, 37 from Cochrane, and 72 from the Web of Science. Sixty-eight duplicate papers were eliminated, and 185 studies were excluded. Reasons for excluding records

were review papers (n = 22), studies on adults (n = 17), animal studies (n = 23), irrelevant studies (n = 100), nonclinical trials (n = 11), studies without full articles (n = 6), not using NS (n = 3), still conducting the study (n = 3). Studies that might meet the inclusion criteria but were excluded because of the study design.¹⁰ Three studies were identified from 383 papers obtained through backward and forward (snowballing) citations. Fifteen clinical trial studies were included in this review, as depicted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram in Figure 1. The summary of the included studies is displayed in Table 2. All studies were published between 2008 and 2020. Four studies were conducted in Egypt, 4 in Iran, 2 in Iraq, 2 in Indonesia, 1 in India, 1 in Pakistan, and 1 in Bangladesh.

Diseases That Used Nigella Sativa. Three studies were conducted on children with epilepsy,^{12–14} 3 on leukemia,^{15–17} 1 on brain tumors,¹⁸ 2 on asthma,¹⁹ 1 on wheeze associated with lower respiratory tract illness,²⁰ 2 on children and adolescents with acne vulgaris,^{21,22} 1 on allergic rhinitis,²³ 1 on neonates with staphylococcal skin infection,²⁴ and 1 on healthy adolescents.²⁵

NS Forms, Doses, and Side Effects. Different forms of NS have been used to treat various diseases in children, such as natural seeds, aqueous extract, powdered form, oil, topical lotion, and nasal drops. Doses included oral powdered NS at a dose of 500 mg/day for 4 weeks up to 2 g/day for 3 months or based on

Table 2. Summary of Included Studies

Author, Publication Year, and Country of Origin	Objective of Study	Population and Sample Size	Study Design	Intervention	Study Findings
Akhondian, 2007, Iran ¹²	To assess the efficacy of black cumin seed extract in reducing the frequency of seizures in children with refractory epilepsy	20 children, 13 mo to 13 yr old, with refractory epilepsy	RCT, double-blinded crossover clinical trial	Aqueous extract of black seed (40 mg/kg/8hr), placebo for 4 wk	The frequency of seizures significantly decreased, the water extract of NS has an antiepileptic effect, and may alter monoamine levels in the central nervous system in children with refractory seizures
Shawki, 2013, Egypt ¹⁴	To evaluate the effects of black seed oil on oxidative stress markers, seizure frequency, and severity	22 children, aged 2–16 yr, with intractable seizures	Prospective, randomized, single-blinded, controlled, crossover pilot study	Black seed oil (40–80 mg/kg/day) for 4 wk	Black seed oil as an add-on therapy did not alter oxidative stress markers, seizure frequency, or severity in intractable epileptic patients
Ahmad, 2010, India ²⁰	To study the role of NSO in children with wheeze-associated lower respiratory tract illness	84 Children aged 6–15 yr with wheeze	RCT, prospective, open study	NSO in a dose of 0.1 mL/kg/day for 14 days, the control group received standard treatment	NSO has a beneficial effect in decreasing the pulmonary index and increasing the peak expiratory flow rate
Barlianto, 2017, Indonesia ²⁶	To investigate the potential antiasthmatic effect of NSO on Th1/Th2 cells, IFN γ /IL-4 cytokines, and asthma control	82 children aged 6–15 years with asthma	RCT, single-blind	NSO 15–30 mg/kg/day with standard treatment guidelines for asthma for 8 wk	Supplementation with NSO improves children's IFN γ /IL-4 balance and asthma control. There is no significant correlation between Th1/Th2 cells and ACT scores
Barlianto, 2018, Indonesia ¹⁹	To investigate the effects of NSO on TH17/Treg and the improvement of asthma control in asthmatic children	28 children aged 4–14 yr with asthma	RCT, single-blind	NSO, 15–30 mg/kg/day for 8 weeks with standard treatment of asthma	NSO supplementation improves Th17/Treg balance and clinical symptoms in asthmatic children
Hagag, 2020, Egypt ¹⁶	To evaluate the protective role of black seed oil against doxorubicin-induced cardiotoxicity in children with ALL	40 children aged 2–16 yr with ALL	RCT	Black seed oil 80 mg/kg/day, divided into three doses with doxorubicin therapy for 1 wk after each dose, placebo intervention in group 2	Black seed oil improves some cardiac side effects of doxorubicin, as shown by better systolic functions in children with acute lymphoblastic leukaemia

(Table cont. on page 584)

Table 2. Summary of Included Studies (cont.)

Author, Publication Year, and Country of Origin	Objective of Study	Population and Sample Size	Study Design	Intervention	Study Findings
Hagag, 2013, Egypt ¹⁷	To evaluate the protective role of black seed oil against hepatotoxicity induced by methotrexate therapy in children with ALL	40 children with ALL, ages ranged from 4–13 yr	RCT	Oral NSO in capsule 450 mg (80 mg/kg/day) on 3 divided doses for 1 wk after each methotrexate dose	NSO can prevent hepatotoxicity from methotrexate therapy and improve overall survival in children with ALL
Dogar, 2009, Pakistan ¹⁵	Assessing the efficacy of Nigella sativa seeds in children with ALL, and evaluating the efficacy of the 3 test treatments	48 children, ages between 2 and 18 yr with ALL	RCT	Powdered NS seeds (40 mg/kg orally in 2 equally divided doses) with conventional therapy for 3 mo	Nigella sativa seeds, in combination with cytotoxic drugs, could help treat children with ALL and improve treatment outcomes
Alsamarai, 2014, Iraq ²³	To evaluate the therapeutic efficacy of the NS extract as a treatment approach for allergic rhinitis	68 children, adolescents, and adults, aged 6–45 yr	RCT	Topical NSO (nasal drops) about 15 mL, 2 drops (one in each nostril) 3×/day for 6 wk	Topical NSO was influential in treating allergic rhinitis and improving symptoms
Mousa, 2017, Egypt ¹⁸	To evaluate the effect of black seeds on the prevention of febrile neutropenia and length of hospital stay in children with brain tumors	80 children, aged 2–18 yr	RCT, randomized pretest-posttest control group study	Whole natural black seeds 5 g/day for 3–9 mo, the control group received no intervention (nothing)	Black seeds decrease febrile neutropenia and length of hospital stay in children with brain tumors
Momen, 2019, Iran ¹³	To assess the efficacy of a mixture of NS and <i>Thymus vulgaris</i> extracts (Epistop) on seizure frequency and duration	22 children with refractory epilepsy aged between 2 and 18 yr	RCT, double-masked placebo-controlled cross-over design	A mixture of NS and <i>Thymus vulgaris</i> extracts (Epistop) for 4 wk vs placebo group	No improvement was seen in the frequency and duration of seizures. Only a minority of highly selected children experienced a reduction in seizure frequency
Soleymani, 2020, Iran ²¹	To assess the effect of topical Nigella sativa gel on acne vulgaris	60 patients, aged 15–35 yr	RCT, double-blind	Topical Nigella sativa hydrogel twice daily for 60 days, placebo hydrogel	NS hydrogel improved the symptoms of acne vulgaris and significantly decreased the count of acne lesions and reduced the mean number of pustules observed

(Table cont. on page 585)

Table 2. Summary of Included Studies (cont.)					
Author, Publication Year, and Country of Origin	Objective of Study	Population and Sample Size	Study Design	Intervention	Study Findings
Bin Sayeed, 2014, Bangladesh ²⁵	To examine the effect of NS on anxiety, mood, and cognition in adolescents	48 healthy adolescents aged between 14 and 17 yr	RCT	500 mg/day of Nigella sativa once daily for 4 wk	Nigella sativa improves mood and cognition and decreases anxiety
Rafati, 2014, Iran ²⁴	To explore the antimicrobial effect of black seed extract on skin pustule infection	40 neonates with pustular infection aged between 6 and 11 days	Clinical trial	Black seed extract drops, were applied topically, 3×/day for 4 days, on the skin lesions	Black seeds extract is effective, like the standard drug (mupirocin), in treating localized infection and has antimicrobial activity. There was no significant difference in recovery time compared with traditional medicines
Nasir & Hadi, 2010, Iraq ²²	To evaluate the use of NSO lotion as a natural remedy for the treatment of acne vulgaris	81 adolescents and adults with acne vulgaris, ages ranging from 13–23 yr	RCT	10% of Nigella sativa oil lotion twice daily for 8 wk	Nigella sativa oil lotion was effective as a topical treatment for acne vulgaris, safe and well-tolerated topical treatment for moderate acne vulgaris

ACT, asthma control test; ALL, acute lymphoblastic leukemia; IFN, interferon; IL-4, interleukin-4; NS, Nigella sativa; NSO, Nigella sativa oil; RCT, randomized control trial; Th1, T-helper cell type 1; Th2, T-helper cell type 2; TH17, T-helper cell 17

body weight at a dose of 40 mg/kg in 2 equally divided doses for 3 months, with no side effects reported in those studies. One study used whole natural NS seeds at a dose of 5 g/day for 3 to 9 months with no side effects or adverse events reported.¹⁸ Oil of NS was used at a dose of 15 to 30 mL/kg/day for 8 weeks, with no side effects reported, and at a dose up to 40 to 80 mg/kg/day for 4 weeks.^{19,26} Nausea and vomiting were reported in 1 patient, and 2 patients had an exacerbation of seizures after receiving NS oil.⁷ Topical NS in the form of skin lotion or hydrogel has been used to treat pustule infection and acne,^{21–23} or as nasal drops at approximately 15 mL, 2 drops (1 in each nostril) administered 3 times/day for 6 weeks to treat allergic rhinitis.²³ A summary of the doses, forms, and side effects reported by each study has been described in Tables 3 and 4. None of the studies reported a severe adverse event, and a few reported mild side effects.

Quality Assessment and Risk of Bias. All included studies in the review were available in full text. The overall risk of bias across 15 studies was assessed; 4 had a low risk of bias, 1 had some concerns, and

the remaining 10 RCTs had a high risk of bias, as shown in Figure 2. Despite this, we reported a low risk of bias concerning the randomization process (73% low risk). Some studies did not clearly describe the type of randomization process. The domain of deviations from the intended intervention had a 50% high risk of bias due to the lack of double blinding in most of the studies or blinding not being mentioned in the study.

Furthermore, almost none of the included studies have evaluated adherence to the intervention. Low risk of bias was judged regarding the domain of missing outcome data for all studies. However, most of the included studies reported a high risk of bias in the domain of measuring the outcome, with only 40% of studies having a low risk of bias. Finally, only 13% have a high risk of bias in the domain of selecting reported results, and most of the studies included showed a low risk of bias in this domain.

Statistical Analysis. Meta-analysis of the pooled data is shown in Figure 3. Of the 114 participants in the NS group, 12 reported side effects, compared

Table 3. Summary of the Reported Side Effects From Using Oral *Nigella Sativa*

Study	Dose, Type, and Duration	Total Number of Participants	Number of Patients With the Presence of Side Effects	Number of Patients With the Absence of Side Effects	Side Effects Reported
Akhondian ¹²	Aqueous extract of black seed (40 mg/kg/8 h) for 4 wk	21	4	17	3 patients reported adverse events: 1 reported constipation in the NS group, 1 developed a maculopapular rash on the trunk, and 1 increased laughing at the time of seizure in the placebo group
Shawki ¹⁴	Black seed oil (40–80 mg/kg/day) for 4 wk	22	3	19	1 patient developed nausea and vomiting, and 2 patients had an exacerbation of seizures after receiving black seed oil
Momen ¹³	A mixture of NS and <i>Thymus vulgaris</i> extracts (Epistop) for 4 wk	22	2	19	Only 3 patients reported lethargy and diarrhea, 2 in the intervention group and 1 in the placebo group
Ahmad ²⁰	NSO 0.1 ml/kg/day for 14 days	84	1	83	1 patient developed diarrhea in the NSO group
Barlianto ^{19,26}	NSO 15–30 mg/kg/day for 8 wk	28	0	28	No side effects reported
Dogar ¹⁵	Oral powdered nigella sativa (40 mg/kg) in 2 equally divided doses for 3 mo	48	0	48	No side effects reported, NS seeds improved the outcome of treatment
Mousa ¹⁸	Whole natural black seeds 5 g/day for 3–9 mo	80	0	80	No side effects reported
Bin Sayeed ²⁵	500 mg/day of NS for 4 wk	48	0	48	No side effects reported

NS, *Nigella sativa*; NSO, *Nigella sativa* oil

with 102 participants in the placebo group, with only 3 experiencing side effects. Overall, the analysis shows that the reported side effects in the included studies are statistically not significant, as indicated by a p value > 0.05 . No heterogeneity exists between studies ($I^2 = 0\%$). For the efficacy of using NS in pediatrics, meta-analysis was applicable only to 3 studies conducted on children with epilepsy. The meta-analysis was pooled from 3 studies, which could generate the OR and CI to

evaluate the efficacy of using NS in epilepsy (seizure frequency). As shown in Figure 4, the effect of NS on seizure frequency was not significant (p value > 0.05). No heterogeneity exists among the 3 studies, with an I^2 value of 0%. The risk of bias summary is presented in Figures 5 and 6. The symmetrical distribution of the points and their scatter suggests that there is a publication bias in both meta-analyses, due to the small number of studies included in the meta-analyses.

Table 4. Summary of the Reported Side Effects From Using Topical <i>Nigella Sativa</i>					
Study	Dose, Type, and Duration	Total Number of Participants	Number of Patients With the Presence of Side Effects	Number of Patients With the Absence of Side Effects	Side Effects Reported
Nasir & Hadi ²²	10% of <i>Nigella sativa</i> oil lotion twice a day for 8 wk	81	0	81	No side effects reported
Alsamarai ²³	Topical <i>Nigella sativa</i> oil (nasal drops) about 15 mL, 2 drops (1 in each nostril) 3×/day for 6 wk	68	5	56	Nasal dryness was reported
Rafati ²⁴	Black seed extract drops were applied topically 3× daily for 4 days on the skin lesions	40	0	40	No side effects reported
Soleymani ²¹	Topical Nigella sativa hydrogel twice daily for 60 days	60	0	60	No side effects were reported

Figure 2. Risk of bias in the included studies.



Discussion

Nigella sativa's immunomodulatory, anti-inflammatory, and antioxidant properties have been observed in many clinical trials. However, few studies have been conducted on the pediatric population. Three studies in this review have evaluated the efficacy of NS in children with epilepsy (Table 2).^{13,14,27} Shawki et al¹⁴ evaluated the efficacy of black seed oil at a dose

of 40 to 80 mg/kg/day for 4 weeks. They reported that black seed oil did not significantly affect seizure frequency or severity. In addition, the study reported an exacerbation of seizures after receiving black seed oil in 2 patients. However, a greater than 50% reduction in seizure frequency was seen in 6 patients. A greater than 50% reduction in the severity of seizures was seen in 2 patients after the administration of black seed oil

Figure 3. Forest plot of the included studies to evaluate the safety of using *Nigella sativa* in pediatrics.

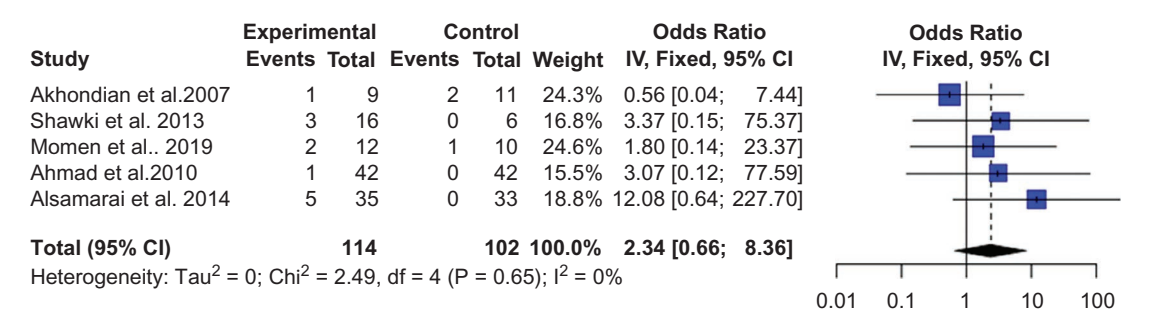


Figure 4. Forest plot to evaluate the efficacy of using *Nigella sativa* on epilepsy (seizure frequency) in 3 studies that used *N. sativa* with epilepsy.

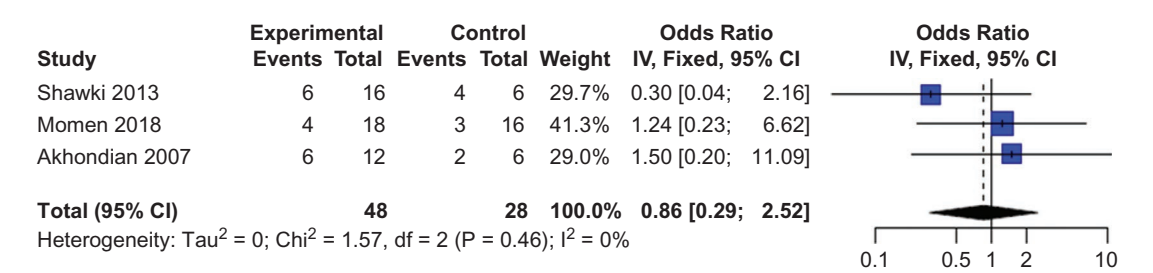


Figure 5. Funnel plot for publication bias in the included studies.

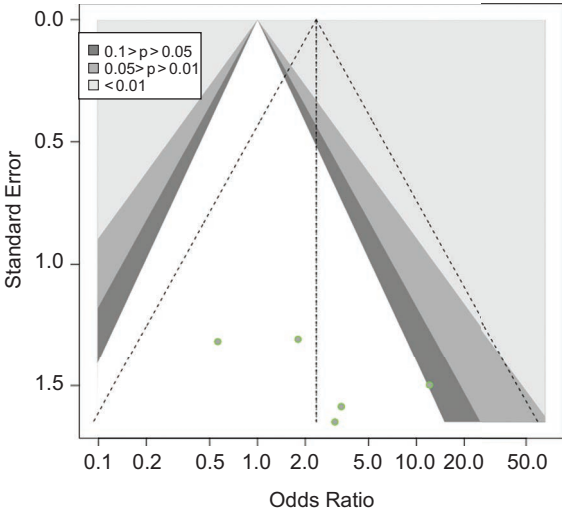


Figure 6. Funnel graph for publication bias in the included studies on *Nigella sativa* in epilepsy.

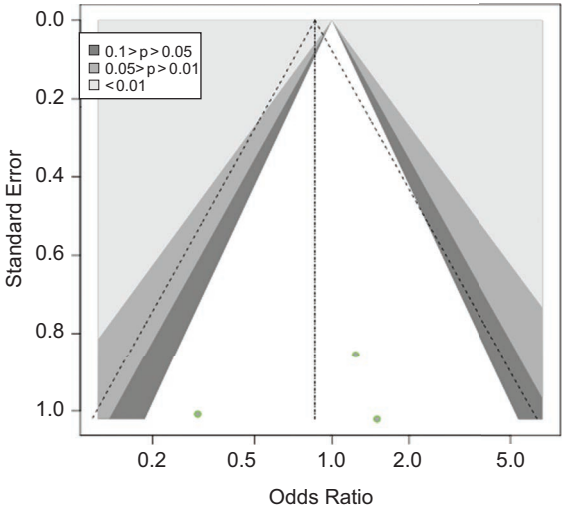


Table 5. Nigella Sativa and Children With Epilepsy							
Study	Age & Sample Size	Sex	NS Group	Control Group	Seizure Frequency Before Treatment	Seizure Frequency After Treatment (NS)	p value
Shawky ¹⁴	<18, 22	M = 10 F = 12	✓	✓	≥2 seizures/mo	6 patients showed >50% reductions in seizure frequency	0.552
Momen ¹³	<18, 22	M = 8 F = 14	✓	✓	Seizure frequency ranged between 2 and 140 events/wk. Median seizure frequency = 35 events/wk	In 4 patients, seizure frequency was reduced by >60 %	0.0528
Akhondian ¹²	<18, 20	M = 10 F = 10	✓	✓	≥1 seizure/mo	Improvement in seizure frequency was seen in 65 % of patients	≤0.001

F, female; M, male; NS, Nigella sativa

in the study by Noor et al.²⁸ Momen and colleagues¹³ showed that using a mixture of NS and *Thymus vulgaris* extracts (Epistop) for 8 weeks does not affect the duration and frequency of seizures. However, 4 children with refractory epilepsy showed a significant reduction in seizure frequency after administration of Epistop. The author's opinion was that the administration of the Epistop might be beneficial in children with refractory seizures with typical development, normal magnetic resonance imaging and electroencephalogram, and low seizure frequency of less than 10 events per week. Using the aqueous extract of NS seeds in a dose of 40 mg/kg/8hr for 4 weeks was effective and had an antiepileptic effect in children with refractory epilepsy.¹⁴ The benefits seen in epileptic patients included in those studies might be due to the thymoquinone presented in NS, which produces antinociceptive effects through indirect activation of the supraspinal mu (1)- and kappa-opioid receptor subtypes. Thymoquinone had anticonvulsant activity in rats, probably through an opioid receptor-mediated increase in GABAergic tone.²⁹ Almost all animal studies that have explored the effect of NS on seizure models have shown an anticonvulsive effect.^{29–33}

In the current review, 2 studies have investigated the anti-asthmatic effect of NSO in asthmatic children,^{19,26} and 1 study evaluates the role of NSO in wheeze-associated lower respiratory tract illness in children (Table 2).²⁰ Supplementation with NSO at a dose of 15 to 30 mg/kg/day with standard treatment for 8 weeks

was compelling and improved interferon-g/interleukin-4 balance, T-helper cell 17/Treg balance, asthma control score, and symptoms in asthmatic children. The chemical composition of NS has been studied in detail. One of the main active components appears to be mainly attributed to thymoquinone. The mechanism of action of NS enables it to act as an immunomodulator and regulate T helper/Treg balance.³⁴ Boskabady and Farhadi³⁵ have reported a beneficial effect of using the aqueous extract of NS as a prophylactic measure to improve the asthma severity. Another study has shown that NSO helps decrease pulmonary index and increase peak expiratory flow rate in children with wheeze-associated lower respiratory tract illness.²⁰ *Nigella sativa* is therapeutically beneficial in controlling asthma symptoms and relieving airway inflammation.³⁶

Three studies were conducted on children with leukemia and 1 on children with brain tumors. A review of NS and its anti-cancer properties *in vitro* and *in vivo* models found that this might be due to the high thymoquinone content in NS.³⁷ *Nigella sativa* has been shown to possess antineoplastic activity against tumors.³⁸ *Nigella sativa* exhibits an anti-cancer effect through different proposed mechanisms of action, including its effect on the activity of enzymes, usage of free radicals, intracellular glutathione changes, inhibiting cell proliferation, trapping the free radicals, and antioxidant activity.^{39,40} All 3 studies in this review were focused on reducing treatment or disease-related side effects.

Dogar et al¹⁵ reported that NS seeds, at a dose of 40 mg/kg/day in 2 equally divided doses for 3 months, in combination with a cytotoxic drug, could assist in the treatment of acute lymphoblastic leukemia. It significantly improved treatment outcomes and proved to be an excellent anticancer agent. The 2 studies from Hagag and colleagues^{16,17} reported an improvement in some cardiac side effects of doxorubicin in children with ALL (n = 40), exhibiting better systolic function, as well as decreased methotrexate hepatotoxicity, and improved overall survival. Mousa et al¹⁸ used whole natural black seeds at a dose of 5 g/day for 3 to 9 months to decrease the incidence of febrile neutropenia and length of hospital stay in children with brain tumors (n = 80).

The current review also included 2 studies on acne vulgaris patients^{21,22} and 1 on newborns with a staphylococcal skin infection (Table 2).²⁴ A 10% NS oil lotion applied twice daily for 8 weeks was a safe and well-tolerated topical therapy for acne vulgaris.²² Thymoquinone, the active component in NS, has been shown to suppress leukotrienes, prostaglandins, and 5-lipoxygenases in numerous inflammatory models and can also decrease the production of IL-1 β , TNF- α , and monocyte chemoattractant protein.^{34,41} Nitric oxide production in macrophages and mixed-glial cells is reduced by the NS extract and thymoquinone lipopolysaccharide-induced inflammation.^{41,42} The aqueous extract of NS can suppress the expression of key inflammatory mediators, including nitric oxide, IL-6, and tumor necrosis factor.³⁷ *Nigella sativa* has anti-bacterial effects against many bacteria, and multidrug-resistant strains, such as *Staphylococcus aureus* and *Mycobacterium tuberculosis*. NS is active against several bacteria, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*. Alpha-pinene, one of the phytochemicals in NS, impacts *Propionibacterium acnes*.⁴³

Additionally, Soleymani et al²¹ showed that applying a topical NS hydrogel twice a day for 60 days reduced the symptoms of acne vulgaris when used topically 3 times a day for 4 days on skin lesions in newborns and infants aged 6 to 11 days.

Black seed extract drops were found to have antibacterial activity and to be as effective as the usual medication, mupirocin, in treating localized infections. *Nigella sativa* is thought to have potential as a medicinal plant for treating acne due to its immunomodulatory, anti-inflammatory, antioxidant, and antibacterial properties against *P. acne*. Other clinical uses of NS in pediatrics were used on children with beta-thalassemia major (n = 25); 2 g/day of powdered NS added to foods or drinks for 3 consecutive months was found to decrease iron overload-induced oxidative stress and hemolytic anemia. In addition, NS reduced the side effects of iron chelation therapy.⁴⁴ *Nigella sativa* was also used in patients suffering from allergic rhinitis as a topical oil (nasal drops) of approximately 15 mL, 2 drops (1 in

each nostril) 3 times/day for 6 weeks; it improved the symptoms and was effective in the treatment of allergic rhinitis, and only nasal dryness was reported as a side effect.²³ *Nigella sativa* was used on healthy adolescents (n = 48) to examine the efficacy of NS on anxiety, mood, and cognition in adolescents. *Nigella sativa* administered at 500 mg/day once daily for 4 weeks was effective in stabilizing mood, modulating anxiety positively, and decreasing anxiety.²⁵ This is because NS increases the level of hydroxytryptamine-5 and thus decreases anxiety. Also, NS and thymoquinone decrease NO, decrease brain gamma-aminobutyric acid, and provide an anxiolytic effect.³³

Regarding the safety of using NS in pediatrics, none of the included studies report a serious adverse event from using NS in pediatrics. Our analysis shows that the reported side effects in the included studies were not statistically significant. However, a few mild adverse events have been reported. Two patients experienced an exacerbation of seizures, which might raise concern when using NSO with epileptic children, and 1 patient developed nausea and vomiting after black seed oil administration.¹⁴

The gastrointestinal problems reported by Shawki et al¹⁴ were similar to those of Kalus et al,¹⁰ who reported a mild gastrointestinal problem after black seed oil administration on an empty stomach. In another study, 1 patient reported constipation with the use of black seed extract.²⁷ Momen et al¹³ did not report an adverse event from using a mixture of NS and *Thymus vulgaris* extracts, and none of the children discontinued the treatment. A topical form of NS was used for acne, skin infections, and allergic rhinitis. None of the studies that used the topical form of NS reported any serious side effects. Some nasal dryness was reported in 1 study when NSO was used as nasal drops.²⁵ The meta-analysis in our study shows that the occurrence of side effects was not statistically significant. *Nigella sativa* seeds are approved by the United States Food and Drug Administration and recognized to be safe as a flavoring agent or an adjuvant in food (21 CFR§182.20).⁴⁵ An overview of NS safety concluded that studies assessing the toxicity of NS have reported it as a safe medicinal plant.⁹ The extract of NS seeds, and its bioactive components, are considered chemicals with low toxicity^{3,10,29} and a wide safety margin.^{46,47} For thymoquinone and NS extracts, a high-quality clinical trial investigating the relationship of NS dose, form, and duration of use to clinical outcomes is needed.

Information about the bioavailability of NS constituents after human consumption is lacking, and additional information about the absorption, distribution, and disposition of NS bioactive constituents in humans is needed.³

For future studies, more detailed and high-quality studies are required to establish the safety and

efficacy of using NS in the pediatric population. None of the studies included in this review measures the participants' adherence to the intervention. Frequent supervision and follow-ups on compliance and adherence to the intervention are required in those studies conducted on pediatrics.

Limitations. The literature has some limitations. Limited studies have been conducted on NS use in pediatric diseases, and limited analyses were applicable. In addition, a high risk of bias was seen in the methodological quality assessment in most of the included studies in this review.

Conclusion. Limited studies have been conducted on NS in the pediatric population; more detailed studies are needed to establish the efficacy of using NS in different diseases, along with its effective dose and forms. Because there are limited studies on NS in pediatric populations, statistical analysis cannot be applied to a definitive conclusion on its efficacy. The studies in this review report no severe adverse effects, and the occurrence of side effects is statistically not significant. However, further high-quality studies are needed to fully understand uses, efficacy, and safety of NS in the pediatric population.

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