



Clinical Efficacy of *Nigella sativa*-Containing Interventions for Urolithiasis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract. Introduction: Urolithiasis is common, and reviews suggest benefits of *N. sativa*, although evidence remains limited. This review evaluated efficacy and safety of *N. sativa*-based interventions in adults with urinary stones. Method: The protocol was registered in PROSPERO (CRD420261470368). PubMed, Scopus, ScienceDirect, and Google Scholar were searched to 3 August 2026. Randomized controlled trials of *N. sativa*-based interventions were eligible, with risk of bias assessed using the Cochrane Risk of Bias 2 tool. Result: Four trials involving 262 participants were included. Compared with tamsulosin, *N. sativa*-containing interventions increased complete stone passage (RR = 2.12, 95% CI: 1.31–3.43; $p = 0.002$; $I^2 = 0\%$). Compared with control or placebo, *N. sativa*-based interventions increased stone passage (RR = 2.47, 95% CI: 1.50–4.08; $p = 0.0004$; $I^2 = 0\%$). Stone size reduction favored *N. sativa*-based interventions (MD = -2.32 mm, 95% CI: -3.07 to -1.57 ; $p < 0.00001$; $I^2 = 0\%$). Each meta-analysis included only two trials. One study had low risk of bias and three had some concerns. Safety data were limited. Conclusion: *N. sativa*-based interventions may improve stone passage and reduce stone size, but evidence is limited by few trials, heterogeneous interventions, and safety reporting. Larger trials using standardized preparations are needed.

Keywords: Kidney Stones; Medical Expulsive Therapy; *Nigella Sativa*; Stone Passage; Urolithiasis.

1. INTRODUCTION

Urolithiasis is a common urological disorder that can cause pain, obstruction, infection, hydronephrosis, and renal impairment. Its prevalence ranges from 1–15%, with an overall estimate of about 5% (Shakeri et al., 2022). Recurrence remains a major long-term concern (Abdehvand et al., 2019). Repeated disease and treatment have increased interest in pharmacological and herbal approaches (Mehrabi et al., 2025).

Higher ambient temperatures are associated with more urolithiasis-related events, possibly through increased urinary calcium excretion and supersaturation (Villanueva-Congote et al., 2026). Management depends on stone size, location, symptoms, and complications, and some stones pass spontaneously (Wróblewski et al., 2026). Metabolic evaluation helps identify risk factors and guide recurrence prevention (Skolarikos et al., 2024).

Nigella sativa L., or black seed, has long been used for urinary disorders and stone passage. Persian sources described its use for kidney stones, while preclinical studies suggested effects on stone formation and calcium oxalate deposition (Ardakani Movaghati et al., 2019). Its major constituents include thymoquinone, dithymoquinone, thymohydroquinone, and thymol (Shakeri et al., 2022). A systematic review of 64 clinical and preclinical studies found that several plant-derived therapies may reduce urinary stone formation, size, and number (Allam & Sabra, 2024). However, results are not uniformly positive. A 2024 meta-analysis of

three randomized controlled trials found no significant effect of *N. sativa* on ICAM-1 or VCAM-1, with substantial heterogeneity (Ali et al., 2024). Previous evidence syntheses suggest possible benefits across several outcomes, but certainty remains low or very low (Li et al., 2023).

Evidence specific to urolithiasis remains limited. Abdehvand et al. (2019) found greater stone expulsion with *N. sativa* plus honey than with no pharmacological treatment in patients with stones <6 mm. Ardakani Movaghati et al. (2019) similarly found higher complete stone excretion and greater stone-size reduction with *N. sativa* capsules than with placebo. In contrast, Shakeri et al. (2022) found that both *N. sativa* and tamsulosin reduced stone size and number without significant between-group differences, although stone-passage efficacy and pain reduction favored *N. sativa*. Mehrabi et al. (2025) evaluated a combination of *N. sativa*, *Urtica dioica*, and *Peganum harmala* and reported reductions in pain, stone number, and stone size compared with tamsulosin.

Only a few randomized trials have examined *N. sativa* in urolithiasis, with substantial differences in formulation, dose, comparator, stone characteristics, follow-up, and outcome definitions. The magnitude and safety of its effects therefore remain uncertain.

To our knowledge, no previous systematic review and meta-analysis has specifically synthesized randomized controlled trials evaluating *N. sativa*-based interventions for urolithiasis. Previous reviews have assessed plant-based therapies for urolithiasis broadly or *N. sativa* across multiple health outcomes rather than focusing specifically on urolithiasis-specific randomized evidence.

This review evaluated the efficacy and safety of *N. sativa*-based interventions in adults with urolithiasis, focusing on stone passage, stone burden, pain, biochemical outcomes, and adverse events.

2. METHODS

Study Design

This systematic review included randomized controlled trials evaluating *N. sativa*-based interventions in adults with urolithiasis. The protocol was registered prospectively in PROSPERO (CRD420261470368). Eligible participants were adults aged ≥ 18 years with confirmed kidney and/or ureteral stones. Interventions included *N. sativa* alone or in combination with other herbal or natural substances. Studies were classified as isolated *N. sativa* or *N. sativa*-containing combination interventions. Comparators included placebo, no treatment, standard therapy, or active treatment such as tamsulosin. Studies had to report stone

passage or expulsion, stone-size or burden reduction, urinary or biochemical outcomes, pain, or adverse events. Only peer-reviewed randomized controlled trials published in English and available in full text were included. Translation of non-English studies was not feasible within the available resources.

Animal, *in vitro*, laboratory, non-urolithiasis, and non-clinical studies were excluded, as were reviews, case reports, case series, editorials, letters, commentaries, abstracts, duplicates, overlapping datasets, and studies with insufficient information. Non-English studies were also excluded.

Literature Search Strategy

Table 1. Search Strategies.

Database	Search strategy	Search limits	Records identified
PubMed	#1: ("Nigella sativa"[Title/Abstract] OR "black seed"[Title/Abstract] OR "black cumin"[Title/Abstract]); #2: ("Kidney Calculi"[MeSH Terms] OR nephrolithiasis[Title/Abstract] OR urolithiasis[Title/Abstract] OR "kidney stone"[Title/Abstract] OR "renal stone"[Title/Abstract] OR "stone passage"[Title/Abstract]); #3: #1 AND #2	Not specified	10
Scopus	TITLE-ABS-KEY(("Nigella sativa" OR "black seed" OR "black cumin") AND (nephrolithiasis OR urolithiasis OR "kidney stone" OR "renal stone" OR "stone passage"))	Not specified	50
ScienceDirect	"Nigella sativa" AND ("kidney stone" OR "stone passage")	Article type: Research articles	163
Google Scholar	"Nigella sativa" ("kidney stone" OR "stone passage")	726 results retrieved; first 200 screened manually by title and, where necessary, abstract, in default relevance-ranked order on 3 August 2026.	726 results retrieved; first 200 screened manually

PubMed, Scopus, ScienceDirect, and Google Scholar were searched from inception to 3 August 2026 without publication-year restrictions. Search terms combined *Nigella sativa* with urinary stone-related terms. Results were combined, duplicates removed, and the remaining records screened. For Google Scholar, 726 results were retrieved on 3 August 2026, and the first 200 results were screened manually by title and, when necessary, abstract, in the default relevance-ranked order.

PRISMA 2020 Flow Summary

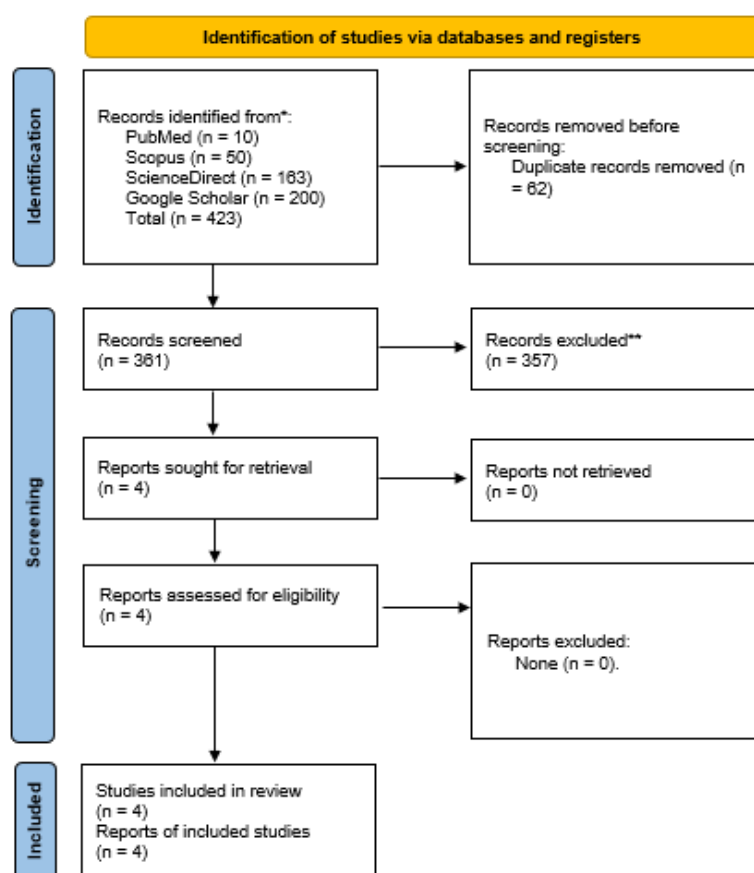


Fig 1. Flow Summary.

Study Selection

A total of 423 records were included in the screening set, comprising PubMed (n = 10), Scopus (n = 50), ScienceDirect (n = 163), and the first 200 of 726 Google Scholar results. After import into Rayyan, 62 duplicates were removed, leaving 361 unique records.

Title and abstract screening excluded 357 records. Four full-text reports were retrieved and assessed against the predefined eligibility criteria, and none was excluded at this stage. All four reports were therefore included in the review. Study selection was independently performed by two reviewers using blinded screening, with disagreements resolved through discussion and consensus.

Data Collection Process

Two reviewers independently extracted study characteristics, participant characteristics, intervention and comparator details, sample size, follow-up, stone characteristics, clinical outcomes, adverse events, and risk-of-bias information using a standardized extraction form. Disagreements were resolved through discussion and consensus.

Table 2. Traffic-Light Summary.

Study	D1. Bias arising from the randomization process	D2. Bias due to deviations from intended interventions	D3. Bias due to missing outcome data	D4. Bias in measurement of the outcome	D5. Bias in selection of the reported result	Overall risk of bias
Ardakani Movaghati et al. (2019)	 Low risk	 Low risk	 Low risk	 Low risk	 Low risk	 Low risk
Shakeri et al. (2022)	 Some concerns	 Some concerns	 Low risk	 Some concerns	 Low risk	 Some concerns
Mehrabi et al. (2025)	 Some concerns	 Low risk	 Low risk	 Some concerns	 Low risk	 Some concerns
Abdehvand et al. (2019)	 Some concerns	 Low risk	 Low risk	 Some concerns	 Low risk	 Some concerns

Legend:  Low risk;  Some concerns;  High risk.

Risk of Bias Assessment

Risk of bias was independently assessed by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool. Because RoB 2 judgments are outcome-specific, the assessments in this review were anchored to the principal clinical efficacy outcomes reported by each study, particularly complete stone passage and, where applicable, stone-size reduction. The overall judgments therefore refer to the specific efficacy results extracted for synthesis rather than representing a generic judgment for the study as a whole. Pain outcomes were considered separately because their measurement is more subjective and may have different susceptibility to measurement bias.

For Ardakani Movaghati et al. (2019), the RoB 2 assessment for the principal stone-related outcomes indicated low risk across all five domains. Shakeri et al. (2022) had some concerns, mainly related to limited reporting of the randomization process, deviations from intended interventions, and outcome measurement for the relevant clinical efficacy outcomes. Mehrabi et al. (2025) had some concerns because of limited reporting of randomization and allocation procedures and uncertainty regarding outcome measurement. Abdehvand et al. (2019) also had some concerns, particularly because of limited reporting of randomization and allocation procedures and aspects of outcome measurement.

For objective outcomes such as stone passage and stone size, the potential for measurement bias was considered lower when outcomes were assessed by imaging or documented stone expulsion. In contrast, pain outcomes were considered more susceptible to measurement-related bias because they relied on subjective patient reporting. Lack of blinding alone was not considered sufficient to indicate bias due to deviations from intended

interventions, particularly for objective stone-related outcomes. Overall, one study (25%) had low risk of bias and three (75%) had some concerns for the assessed principal efficacy outcomes. No study had a high overall risk of bias.

Effect Measures

The primary outcome was complete stone passage. Dichotomous outcomes were expressed as RRs with 95% CIs, and continuous outcomes on the same scale as MDs with 95% CIs.

Quantitative Synthesis

(Shakeri et al., 2022) and (Mehrabi et al., 2025) contributed to the pooled analysis of complete stone passage versus tamsulosin. Both tested interventions containing *N. sativa*, but (Shakeri et al., 2022) evaluated *N. sativa* alone whereas (Mehrabi et al., 2025) used a combination of *N. sativa*, *Urtica dioica*, and *Peganum harmala*. Therefore, the pooled estimate represents *N. sativa*-containing interventions rather than isolated *N. sativa*.

(Abdehvand et al., 2019) and (Ardakani Movaghati et al., 2019) were not included in this comparison because their comparators were no treatment and placebo, respectively. Outcomes were pooled only when numerical data and definitions were sufficiently comparable. Other outcomes were synthesized narratively.

Data Preparation and Statistical Analysis

R Rs were calculated from event counts and group totals. MDs were used for continuous outcomes measured on the same scale. No imputation was performed for incomplete numerical data.

Analyses were conducted in RevMan 5.4.1 using random-effects models, with Mantel–Haenszel methods for dichotomous outcomes and inverse variance for continuous outcomes. Heterogeneity was assessed using Cochran’s Q and I^2 . Subgroup and sensitivity analyses separating isolated and combination interventions were not performed because each pooled analysis contained only two studies.

Meta-analytic Model

A random-effects model was selected because of expected clinical and methodological differences in formulations, regimens, populations, stone characteristics, and outcome assessment. $RR > 1$ indicated greater treatment success with *N. sativa*-based interventions.

Assessment of Reporting Bias

Funnel plots and formal tests for small-study effects were not performed because each quantitative synthesis included only two studies. Potential missing results were considered qualitatively.

Interpretation of the Meta-analysis

Pooled estimates were interpreted as the relative probability of complete stone passage compared with the relevant comparator. Statistical significance was assessed using the 95% CI and p-value. Because each synthesis included only two trials, the findings were considered exploratory.

Certainty of Evidence Assessment

The certainty of evidence was assessed using the GRADE approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias for the key pooled outcomes. Randomized trials were initially rated as high-certainty evidence and downgraded when important concerns were identified.

Table 3. GRADE Summary of Findings.

Outcome	Studies	GRADE domains	Effect estimate	Certainty
Complete stone passage vs tamsulosin	2 RCTs	RoB: Serious; Inconsistency: not serious; Indirectness: not serious; Imprecision: Serious; Publication bias: not assessable	RR 2.12 (1.31–3.43)	⊕⊕○○ Low
Complete stone passage vs control/placebo	2 RCTs	RoB: Serious; Inconsistency: not serious; Indirectness: not serious; Imprecision: Serious; Publication bias: not assessable	RR 2.47 (1.50–4.08)	⊕⊕○○ Low
Stone-size reduction vs control/placebo	2 RCTs	RoB: Serious; Inconsistency: not serious; Indirectness: Serious; Imprecision: not serious; Publication bias: not assessable	MD –2.32 mm (–3.07 to –1.57)	⊕⊕○○ Low

Notes: RCTs were initially rated as high-certainty evidence and downgraded according to GRADE domains.

Publication bias was not formally assessed because only two studies contributed to each meta-analysis.

3. RESULTS AND DISCUSSION

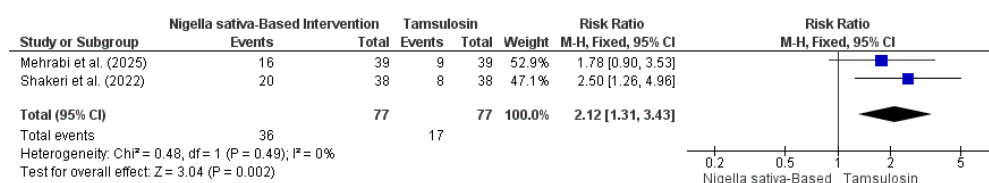


Figure 2. *N. sativa*-Containing Interventions Versus Tamsulosin.

Two trials showed a higher probability of complete stone passage with *N. sativa*-containing interventions than with tamsulosin (RR = 2.12, 95% CI: 1.31–3.43; Z = 3.04; p = 0.002). Statistical heterogeneity was not detected (Chi² = 0.48, df = 1, p = 0.49; I² = 0%). However, with only two studies, the heterogeneity statistic had limited power. The pooled result suggests a potential benefit of *N. sativa*-containing treatment, but not definitive superiority over tamsulosin.

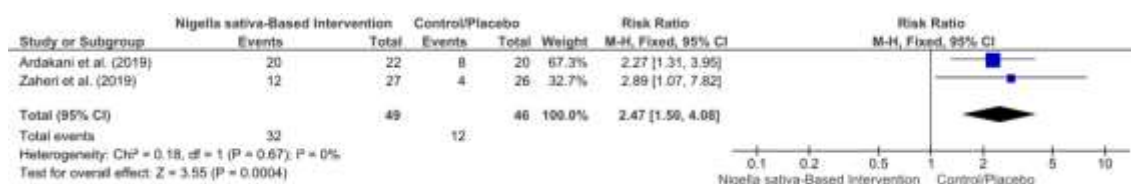


Figure 3. *N. sativa*-Containing Interventions Versus Control/Placebo.

Two trials demonstrated greater complete stone passage with *N. sativa*-based interventions than with control or placebo (RR = 2.47, 95% CI: 1.50–4.08; $Z = 3.55$; $p = 0.0004$). No statistical heterogeneity was detected ($\chi^2 = 0.18$, $df = 1$, $p = 0.67$; $I^2 = 0\%$). The result indicates a favorable signal but remains based on only two studies.

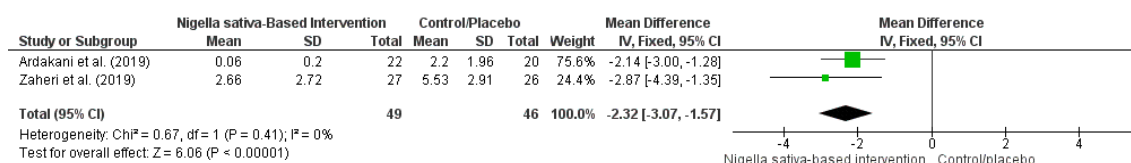


Figure 4. Stone Size.

Two studies reported stone-size outcomes and demonstrated a greater reduction with *N. sativa*-based interventions compared with control/placebo (MD = -2.32 mm, 95% CI: -3.07 to -1.57; $Z = 6.06$; $p < 0.00001$). No statistical heterogeneity was detected ($Q = 0.67$, $df = 1$, $p = 0.41$; $I^2 = 0\%$). The combined sample size was 95 participants. Because ultrasonographic measurement and short follow-up may influence observed dimensions, this finding should not be interpreted as definitive evidence of stone dissolution.

Reporting Bias

Formal assessment of reporting bias was not performed because only two studies contributed to each quantitative synthesis.

Table 4. Characteristics and findings of included studies.

Study	Design	n	Intervention vs Comparator	Main Results
Mehrabi et al. (2025)	Non-blinded randomized parallel-group trial	80	Herbal combination containing <i>N. sativa</i> 150 mg + <i>U. dioica</i> 300 mg + <i>P. harmala</i> 150 mg/day vs tamsulosin 0.4 mg/day	Herbal combination reduced pain, stone number, and stone size, and increased successful stone passage (52.63% vs 21.10%; $p = 0.01$).
Abdehvand et al. (2019)	Randomized controlled trial	42	<i>N. sativa</i> + honey 8 g/day vs no pharmacological treatment	Stone expulsion was higher with <i>N. sativa</i> + honey (90.9% vs 40.0%; $p = 0.0001$).
Ardakani Movaghati et al. (2019)	Triple-blind randomized placebo-controlled trial	60 randomized; 53 analyzed	<i>N. sativa</i> 500 mg BID vs placebo	Complete stone passage was higher with <i>N. sativa</i> (44.4% vs 15.3%; $p = 0.035$), with greater reduction in stone size ($p < 0.05$).
Shakeri et al. (2022)	Randomized clinical trial	80; 78 analyzed	<i>N. sativa</i> seeds 1 g q12h vs tamsulosin 0.4 mg nightly	Stone passage/treatment efficacy was higher with <i>N.</i>

Study	Design	n	Intervention vs Comparator	Main Results
				<i>sativa</i> (78.5% vs 61.6%; $p = 0.005$), with greater pain reduction ($p = 0.001$).

This review found generally favorable effects of *N. sativa*-based interventions on stone passage, stone burden, and pain across four randomized trials. (Abdehvand et al., 2019) reported greater stone expulsion with *N. sativa* plus honey than with no pharmacological treatment (90.9% vs. 40.0%; $p = 0.0001$), while (Ardakani Movaghathi et al., 2019) reported complete stone passage in 44.4% versus 15.3% with placebo ($p = 0.035$). (Shakeri et al., 2022) found reductions in stone size and number with both *N. sativa* and tamsulosin, although treatment efficacy and pain reduction favored *N. sativa*. (Mehrabi et al., 2025) reported lower pain, fewer and smaller stones, and higher successful passage with a combination containing *N. sativa*, *Urtica dioica*, and *Peganum harmala* than with tamsulosin. These findings suggest potential benefit, but differences among interventions and study designs limit direct comparison.

The pooled analyses also favored *N. sativa*-based interventions. Compared with tamsulosin, complete stone passage was higher (RR = 2.12, 95% CI: 1.31–3.43; $p = 0.002$). Compared with control or placebo, stone passage was also higher (RR = 2.47, 95% CI: 1.50–4.08; $p = 0.0004$). Stone-size reduction also favored *N. sativa* (MD = -2.32 mm, 95% CI: -3.07 to -1.57 ; $p < 0.00001$).

However, each pooled analysis included only two studies, limiting the power of Q and I^2 to detect heterogeneity. Clinical heterogeneity was also present in the formulations and doses of *N. sativa*-containing interventions, comparators, stone location and size, treatment duration, and definitions of complete stone passage. Therefore, the observed $I^2 = 0\%$ should not be interpreted as evidence of clinical homogeneity or consistency of treatment effects across studies.

The comparison with tamsulosin is relevant because tamsulosin is an established medical expulsive therapy for selected ureteral stones. However, these findings do not establish superiority of *N. sativa*. (Shakeri et al., 2022) evaluated *N. sativa* alone, whereas (Mehrabi et al., 2025) used a multi-herbal preparation containing *N. sativa*, *Urtica dioica*, and *Peganum harmala*. The observed effect therefore applies to *N. sativa*-containing interventions rather than isolated *N. sativa*. The pooled reduction in stone size provides a further signal of potential benefit, but the mean difference of approximately 2.3 mm should not be equated with stone dissolution. Changes may reflect reduced stone burden, fragment passage, or measurement

variability, especially with ultrasonography. Short follow-up also prevents conclusions about sustained clearance or recurrence prevention. The consistency of the pooled estimates must be considered alongside study quality.

Only one study had low overall risk of bias, while three had some concerns. Consistent with the GRADE assessment, the certainty of evidence for all three pooled outcomes was rated as low.

(Aghamirei et al., 2022) found that alcoholic *N. sativa* extract (100 mg twice daily for 12 weeks) reduced urinary oxalate compared with usual treatment, but not stone size. The study was published in Persian and was excluded because the protocol required English-language studies. (Mohammadi et al., 2025) reported fewer and smaller kidney stones with *N. sativa* and honey in a non-randomized trial, but the absence of randomization and a control group limits causal inference.

The biological plausibility of these findings is supported by traditional use and experimental evidence suggesting reduced calcium oxalate deposition. However, clinical formulations varied substantially, making attribution to *N. sativa* alone uncertain. (Shakeri et al., 2022) also found no significant between-group difference in stone size or number versus tamsulosin despite better overall treatment efficacy and pain reduction with *N. sativa*. Its potential role as an adjunct to standard medical expulsive therapy remains a hypothesis that should be evaluated in future randomized trials.

Previous meta-analytic evidence also suggests that *N. sativa* has anti-inflammatory and antioxidant effects, including lower CRP, TNF- α , and MDA levels and higher total antioxidant capacity and SOD (Lan & Xia, 2025). *Nigella sativa* and thymoquinone may exert antioxidant and anti-inflammatory effects through Nrf2, NF- κ B, PI3K/AKT, and AMPK pathways (Sadeghi et al., 2023). Effects on VCAM-1 and ICAM-1 have also been reported, although findings remain inconsistent (Faghfoori et al., 2025). A 2025 meta-analysis found higher stone-expulsion rates with silodosin, tadalafil, and tadalafil plus tamsulosin than with tamsulosin alone, with broadly comparable safety (Ebrahimpour et al., 2025). A recent meta-analysis of 29 randomized controlled trials found that alpha-blockers increased ureteral stone expulsion and shortened expulsion time, particularly for distal stones measuring 5–10 mm, with generally infrequent adverse events (Almaghthawi et al., 2026).

The antiurolithiatic mechanism of *N. sativa* in humans remains unclear. Its seeds contain thymoquinone, dithymoquinone, thymohydroquinone, and thymol, and experimental studies suggest effects on calcium oxalate formation and renal deposition. In an animal study cited by (Ardakani Movaghati et al., 2019), *N. sativa* reduced renal calcium oxalate deposition.

Another study reported lower urinary calcium oxalate after ethanolic extract administration. In the clinical trial by (Ardakani Movaghati et al., 2019), changes in serum calcium and urinary pH were also observed, but these findings do not prove stone dissolution or a specific mechanism of expulsion. Safety findings were generally reassuring but incompletely reported. One participant receiving *N. sativa* developed hydronephrosis and elevated blood pressure and was excluded from analysis; causality could not be established (Ardakani Movaghati et al., 2019).

Overall, *N. sativa* showed potential benefits across stone passage, stone burden, and pain, but the evidence is not sufficient to establish clinical superiority. Whether *N. sativa* may provide additional benefit when used as an adjunct to standard medical expulsive therapy remains uncertain and should be evaluated in future randomized trials.

This is particularly relevant because the study by (Shakeri et al., 2022) excluded patients with indications for immediate intervention and severe pain. Further adequately powered trials using standardized *N. sativa* preparations and direct comparisons with established medical expulsive therapies are needed.

Strengths and Limitations

Strengths included restriction to randomized controlled trials, searches across multiple databases, independent study selection, and RoB 2 assessment. The English-language restriction may have introduced language bias and reduced the comprehensiveness of the evidence base. Limitations included the small number of trials, differences in interventions, comparators, stone characteristics, and outcome definitions, risk-of-bias concerns, limited safety reporting, short follow-up, and multi-herbal formulations that limit attribution to *N. sativa* alone. All studies were conducted in Iran, which may limit generalizability.

4. CONCLUSION

Nigella sativa-based interventions may improve stone passage and reduce stone size in adults with urolithiasis. Pooled analyses favored *N. sativa*-containing interventions over tamsulosin and control/placebo, with greater reduction in stone size. However, the certainty of evidence for the pooled outcomes was low, with each analysis including only two studies and substantial clinical and methodological differences. Combination preparations also limit attribution to *N. sativa* alone. Safety data were limited, and three of four studies had some risk-of-bias concerns. The clinical role of *N. sativa*-based interventions remains investigational, and adequately powered randomized trials using standardized preparations and comprehensive safety monitoring are needed before routine clinical use can be recommended.

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