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ORIGINAL RESEARCH

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The efficacy and safety of *Nigella sativa* in the management of osteoarthritis: A systematic review

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Abstract

Background and Aims: Osteoarthritis (OA) is one of the most common debilitating diseases among the aging population. *Nigella sativa* is one potential treatment for OA. Here, we sought to evaluate the efficacy and safety of *Nigella sativa* for treating patients with OA.

Methods: PubMed, Scopus, Embase, and Web of Science were searched up to October 20, 2022. The primary outcome was changes in the pain score after receiving *Nigella sativa* or control agents based on the results of randomized controlled trials (RCTs). The secondary outcome was set as the frequency of adverse events reported during the follow-up period.

Results: Six RCTs involving a total of 370 patients with knee OA were included in the present systematic review. Among the four screened studies, the topical administration of

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Nigella sativa oil was found to be more effective than the placebo in relieving pain in three trials. Additionally, the oral use of *Nigella sativa* oil was assessed in two trials, and an improvement in pain score relative to placebo was documented in only one of the studies. Also, the trial that evaluated the effectiveness of *Nigella sativa* oral capsules did not demonstrate any difference in pain reduction between the intervention and placebo groups. Overall, either topical or oral administration of *Nigella sativa* was well tolerated, and no serious adverse events were reported.

Conclusion: *Nigella sativa* is generally safe, but conflicting findings from low-quality studies hinder the ability to make clinical recommendations for or against treating OA. Robust trials are needed for informed decisions.

KEYWORDS

Nigella sativa, osteoarthritis, systematic review, WOMAC

1 | INTRODUCTION

Osteoarthritis (OA) is one of the most common debilitating diseases among the aging population and is characterized by articular cartilage damage, subchondral bone remodeling, and osteophyte formation.[1,2] Symptoms present as persistent and progressively worsening pain in older adults or middle-aged adults associated with intensive mechanical stress, eventually leading to a loss of function and a decrease in the quality of life.[3] More than 300 million individuals are affected by OA worldwide, [4] and it was estimated to cost an incredible 303 billion dollars in 2013, in terms of medical bills and lost earnings.[5]

Historically OA was thought to be a simple wear-and-tear disease, which was primarily caused by chronic overload and impaired biomechanics on the joint(s). Over the past decade, research has improved our understanding of the development of OA, which involves a complex pathology that includes mechanical loadings and biological effects. During the course of OA, the chondrocyte function is markedly altered and the cartilage is damaged as a result of mechanical forces and other factors. The results of this destruction and the proinflammatory mediators produced by chondrocyte activity act in a paracrine and autocrine manner to further increase the production of proinflammatory and catabolic products.[6] These products are also released into the synovial fluid, where they stimulate an inflammatory response in the synovium. Synovitis, a common feature of OA, is associated with an increased risk of progression for OA, as well as joint symptoms. Among the various chemokines and cytokines involved in the pathogenesis of OA, interleukin (IL)-1β, IL-6, and tumor necrosis (TNF)-α factor seem to be the main proinflammatory mediators in the disease process, and they facilitate the catabolic processes in the chondrocytes, as well as in the recruitment and activation of the immune cells.[7-9] Evidence from in vivo and in vitro studies has shown that blocking IL-1β and TNF-α production could be a valuable therapeutic strategy.[9] Furthermore, many of the chondrocytes in the involved joints show increased production of reactive oxygen species and nitric oxide, among other proinflammatory meditators.[10]

Despite the evolving understanding of its pathology, the options available for the treatment of OA remain limited to relieving symptoms, physical therapy, intra-articular injections, and surgical interventions.[3] There are currently no FDA-approved disease-modifying drugs for OA, and nonsteroidal anti-inflammatory drugs (NSAIDs) remain the first-line therapy in the management of OA.[11] While NSAIDs are moderately effective in reducing pain, they have the potential to increase the destruction of cartilage by inhibiting cartilage matrix production.[12] The use of these medications is further complicated in older individuals due to gastrointestinal, renal, and cardiovascular complications.[13] With this in mind, the need for safe and effective treatment options that also address the inflammatory nature of the disease has shifted toward alternative and herbal medicine options. *Nigella sativa*, also called black cumin, is one such herbal medicine with the potential to treat OA.

Nigella sativa is native to vast areas of northern Africa, the eastern Mediterranean, the Indian subcontinent, and southwest Asia. *Nigella sativa* is cultivated in many countries, including Egypt, Greece, India, Saudi Arabia, and Pakistan.[14] Aside from its culinary uses, *Nigella sativa*, in the form of essential oil, extract, powder, and paste, has been used in many traditional medicines as a miracle herb for treating asthma, rheumatism, headache, back pain, eczema, and amenorrhea.[15] In modern literature, *Nigella sativa* has been broadly studied for its antioxidant, anti-inflammatory, antidiabetic, anti-hypertensive, and antimicrobial properties.[16] The main active components of *Nigella sativa*, that are thought to be responsible for these therapeutic properties, are

thymoquinone, thymohydroquinone, thymol, carvacrol, nigellidine, and alpha-hederin.[17] The promising research results have led the medical community to consider *Nigella sativa* as a treatment option for OA, and several randomized controlled trials (RCTs) have been conducted in recent years to investigate the effects of this remedy on reducing the symptoms or reversing the pathological processes of OA. The present study conducted a systematic review to assess the efficacy and safety of *Nigella sativa* in managing patients with OA.

2 | METHODS

The present systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[18]

2.1 | Literature search and study selection

PubMed, Scopus, Embase, and the Web of Science databases were searched up to October 20, 2022, with no time, language, or study type restrictions. To find all relevant studies, the top 50 pages of the Google Scholar search engine were also manually searched. In addition, backward and forward citation screening of the included studies was performed to find any additional publications. All key terms related to OA and *Nigella sativa* (e.g., "*Nigella sativa*" OR "black cumin") AND ("osteoarthritis" OR "degenerative arthritis") were searched, and the detailed search strategy is provided in Supporting Information S1: Table S1.

SEM and HM screened the title and abstract of each publication independently, for compliance with the inclusion criteria. SR and MN then examined the full texts of the retained publications, with any disagreements being resolved by discussion. The inclusion criteria were that the studies were RCTs investigating the efficacy of *Nigella sativa* among OA patients, regardless of the site of involvement, compared to a placebo or the best supportive care in the control arm. In contrast, the exclusion criteria included the following: (1) non-RCT studies, (2) studies enrolling patients with combined musculoskeletal disorders, and (3) using *Nigella sativa* in combination with other herbal medicines.

2.2 | Data collection and extraction

SR and MN, using a standard data extraction sheet in Microsoft Office Excel, independently extracted data, and any disagreements were resolved by discussion. The following items were extracted from each article: first author's name, study title, year of publication, country of study, phase of RCT, sample size, age range of participants, sex ratio of participants, follow-up duration, site of the affected joints, OA diagnosis criteria, dosage and administration route for *Nigella sativa* and the control agents, pain measurement tool, and effect sizes for the pain scores (mean ± standard deviation [SD]) in both the experimental and control arms.

2.3 | Quality assessment

The risk of bias was independently assessed by AF and SEM, using the revised Cochrane risk-of-bias tool (RoB2) [19] for randomized control trials, and any disagreements were resolved by discussion. In summary, this scale evaluates the quality of parallel-group trials across seven bias categories: bias arising from the randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported results. The tool for crossover trials has an additional domain: bias arising from period and carryover effects. Studies are graded as having a risk of bias that was either "low," "high," or there was "some concern".[19] The detailed RoB2 method has been described in a previous paper.[19]

2.4 | Data synthesis

Our primary outcome focused on changes in pain scores after receiving *Nigella sativa* or control agents. The secondary outcome was set as the frequency of adverse events reported during the follow-up period. Due to variations in the type of treatments and study outcomes, conducting a meta-analysis of the retrieved data was not feasible; thus, the findings were reviewed systematically.

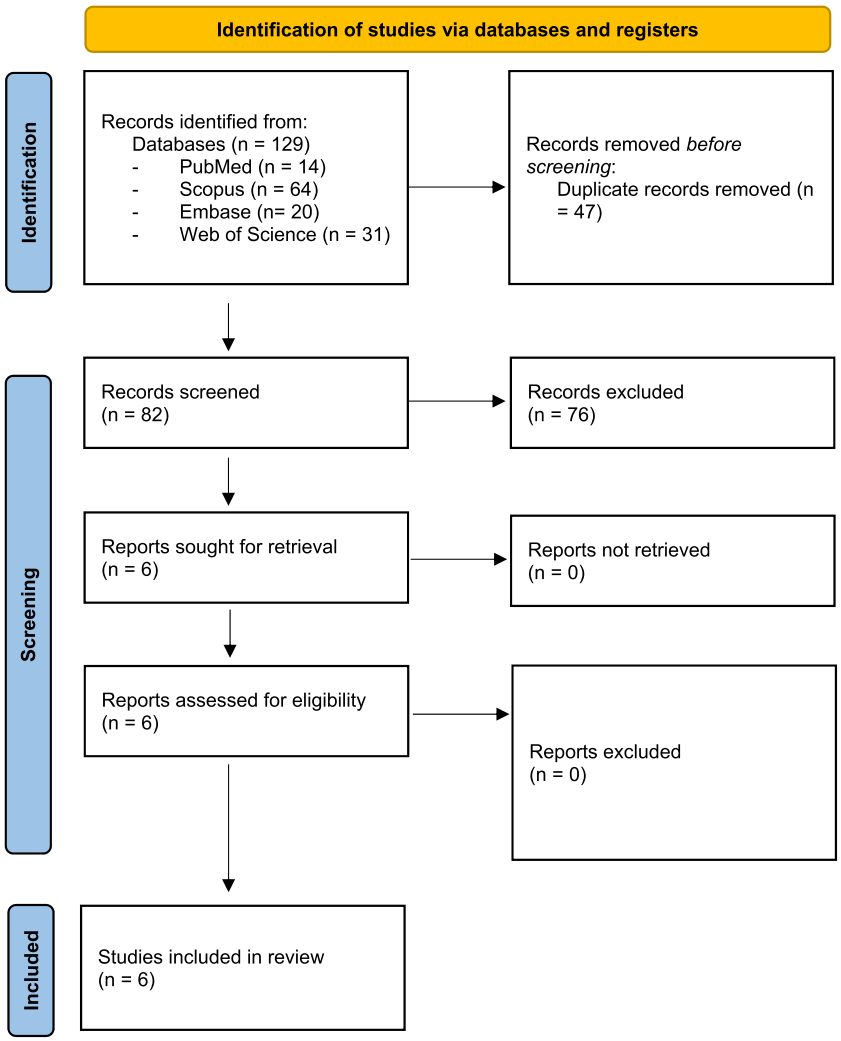
3 | RESULTS

3.1 | Study selection

A total of 129 references were identified through initial database screening. After removing 47 duplicated results, 82 articles remained for reviewing the title and abstracts. Of these, 76 records were excluded, resulting in six potential publications to be assessed by full texts. Consequently, no article was excluded in full-text reviewing, and all six RCTs were included in the present analysis [20–25] (Figure 1).

3.2 | Study characteristics

All eligible trials were published between 2016 and 2022. All RCTs had a parallel design, except for one study, which was a crossover-controlled trial.[23] Five studies were conducted in Iran,[20-24] and one in Turkey.[25] All included studies evaluated knee OA. The American College of Rheumatology Criteria was used as a criteria



FIIGURE 1 Study selection process.

for OA diagnosis in five trials, [20-24] and one study did not report the criteria for OA diagnosis.[25] A total of 370 participants were recruited across these studies. The mean age of patients was 63.05 ± 6.76 years and 26.76% of them were male.

Five studies used oral/topical *Nigella sativa* oil [20-23,25] and one trial used oral capsules.[24] Three studies also allowed the use of NSAIDs for participants if needed.[21,22,24] The control medications included: corn starch,[24] acetaminophen,[23] placebo syrup,[22] mineral oil,[21] diclofenac sodium gel,[20] and patients' routine prescriptions.[25] The pain was measured using the Visual Analogue Scale (VAS) in five studies,[21-23,25] while it was measured by the Knee Injury and Osteoarthritis Outcome Score (KOOS) in two studies.[20,24] Furthermore, the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) score was only reported in two RCTs [21,22] (Table 1).

3.3 | Efficacy of *Nigella sativa* on pain management

In the trial conducted by Azizi and colleagues, the efficacy of *Nigella sativa* oil (1 mL oil, twice a day) was compared with topically administered diclofenac gel 1% (60 g gel, twice daily) for 21 days. Measuring the pain score at baseline using the KOOS questionnaire showed no difference between the two groups. On day 10 the difference in pain scores was not statistically significant. At the end of the trial on day 21, the pain score decreased more in the intervention group relative to the control group, documenting a significant difference in final scores ($p = 0.04$).[20]

Similarly, Kooshki et al. assessed the efficacy of *Nigella sativa* oil (1 mL oil, three times a day) with acetaminophen tablets during a 3-week period. They found the reduction in pain score, using the VAS measurement tool, was significantly higher in the intervention group compared to the placebo group.[23]

The efficacy of topically using *Nigella sativa* oil, administered at a dosage of a dessert spoon three times a week, was also compared with the standard prescriptions of OA patients in a trial performed by Tuna et al. Over the course of four weeks, the administration of the oil resulted in a notable improvement in pain scores, as measured by the VAS, compared to the baseline score ($p < 0.001$). However, no significant difference was observed in the change of VAS values between the intervention and placebo groups.[25]

In another trial by Hussaini et al. the oral administration of *Nigella sativa* oil (5 mL oil, three times a day) was compared with a placebo oil. The baseline pain scores were comparable between the intervention and placebo group across all measurement scales. After 1 month of treatment, the *Nigella sativa* oil significantly reduced VAS scores ($p < 0.001$) as well as WOMAC total ($p < 0.001$), pain ($p = 0.007$), stiffness ($p < 0.001$), and physical function ($p < 0.001$), compared to the placebo. Furthermore, patients in the *Nigella sativa* group used fewer acetaminophen tablets ($p = 0.001$) and reported higher satisfaction with their treatment ($p < 0.001$) during the trial compared to the placebo group.[22]

The oral capsule format of *Nigella sativa* (2 g/day, four times a day) was compared with corn starch placebo capsules in the study performed by Salimzadeh and colleagues. After a 12-week follow-up period, the KOOS pain ($p < 0.05$), activities of daily living ($p < 0.05$), and function in sport and recreation ($p < 0.05$) were significantly decreased relative to the baseline scores. Nevertheless, there was no difference in the changes in KOOS scores between the *Nigella sativa* and placebo groups at the final endpoint. Also, the number of acetaminophen tablets used, together with global patient and physician satisfaction with the treatment, was comparable between the two groups.[24]

Dolatkhah et al. evaluated the efficacy of both topical and oral application of *Nigella sativa* oil among OA patients, using VAS and WOMAC scores. After 6 weeks, consuming and rubbing 2.5 mL of *Nigella sativa* oil three times a day both resulted in reduced the pain scores on the VAS ($p = 0.05$ and $p < 0.001$, respectively), as well as the WOMAC total ($p = 0.001$ and $p < 0.001$, respectively), pain ($p = 0.002$ and $p = 0.001$, respectively), and physical function subscales ($p = 0.001$ and $p < 0.001$, respectively) relative to the baseline pain scores. Compared to the placebo group, the final pain scores were significantly lower in the topical *Nigella sativa* group when measured by the VAS ($p = 0.005$), as well as the WOMAC total ($p = 0.002$), pain ($p = 0.015$), and physical function ($p = 0.001$) subscales, while no difference was detected between the oral *Nigella sativa* and placebo groups in any of the other pain scales. Additionally, the final pain scores in the WOMAC total and physical function were substantially lower in the topical use of *Nigella sativa* relative to the oral use ($p = 0.005$ and $p = 0.003$, respectively).[21]

3.4 | Safety of *Nigella sativa*

Three of the six studies reported adverse events related to the study treatment.[21,22,24] Overall, either topical or oral administration of *Nigella sativa* was well tolerated, and no serious adverse events were reported. One study documented contact dermatitis in 7.1% and 13.4% of OA patients who were administrated topical and oral *Nigella sativa* oil, respectively.[21] Moreover, it was reported that oral use of *Nigella sativa* capsules was associated with a higher risk of increased appetite compared to the placebo ($p = 0.02$).[24] In addition, there were no substantial changes in the complete blood count and serum biochemical parameters across the study.[22,24]

3.5 | Quality assessment

Overall, the methodological quality across the parallel group trials was low in one study,[22] had some concerns in two studies,[20,21] and was high in two studies.[24,25] In addition, the crossover trial was rated as a high-risk study.[23] The major component resulting in reducing the quality of studies was bias due to deviation from the intended intervention, and the item that had no bias was the selection of the reported results (Figure 2 and Supporting Information S1:Tables S2 and S3).

4 | DISCUSSION

In our systematic review, which included six RCTs and 370 participants, we found that *Nigella sativa* relieved pain and improved the physical functioning of patients with OA. Also, no serious adverse events were reported. However, these results should be interpreted with some degree of caution, as the quality of the included studies was low and had a small sample size. Furthermore, the interventions in these trials were tested over a relatively short period of time (3–6 weeks), which is insufficient for judging the clinical significance of these outcomes.

Although OA commonly affects knee, hip, first metatarsophalangeal, cervical and lumbar spine,[26] all of the trials in this study evaluated knee OA. Thus it is unclear whether the administration of NS would exhibit similar results in other joints affected by OA. Structural and symptomatic knee OA disproportionately affects women, and the difference in sex-specific prevalence becomes more prominent with advancing age.[27] This is reflected in the study population of these trials in which close to 75% of the participants were women, and the mean age of patients was over 60 years old. Several risk factors have been shown to affect the risk of knee OA and progression. Obesity, physical activity, and female sex are among some of the well-studied factors. 28

Obesity is a well established risk factor for the progression of knee OA.[29] Unsurprisingly, weight management is also one of the main strategies to slow down the progression of OA.[30] However, the included trials failled to adopt a stratification or statistical strategy that would take into account the effects of obesity and weight management among patients. As little as a 1% change in body weight can significantly alter the rate of knee cartilage loss.[31] The findings from several clinical studies suggest that *Nigella sativa* could also act as an antiobesity agent.[32] In this review, the trials did not focus on this property of *Nigella sativa* and were also of insufficient duration to show the possible weight-lowering effects of *Nigella sativa* on OA symptoms. Therefore, additional studies are needed to fully uncover the clinical significance of *Nigella sativa* for improving OA in the long term.

While guidelines recommend against a sedentary lifestyle in OA patients,[11] the trial designs did not consider differences in the level of physical activity between participants that could alter the course of the disease and pain symptoms. One important but often overlooked

TABLE 1 Characteristics of included trials.

First author	Year of publication	Country	Trial ID	No of participants			Mean age, years		No. of males		Intervention		
				Total	Intervention	Control	Intervention	Control	Intervention	Control	Processing method	Route of administration	Dose and schedule
Tuna et al.[25]	2018	Turkey	NA	60	30	30	67.9	68.0	7	7	Black cumin oil has been received in 30 mL sun-proof bottles.	Topically	A dessert spoon of oil, three times a week for 1 month
Salimzadeh et al.[24]	2017	Iran	IRC-T2013-11151-5408N1	77	37	40	55.0	55.8	13	6	*Nigella sativa* seeds were powdered and processed by soaking in vinegar for 24 h. They were dried in a dark place at room temperature. The dried product was powdered again and sieved in a sieve, mesh size 14. Powders were filled into two-piece red opaque hard gelatin capsules of size 'tall 0'.	Orally	2 g/day; two capsules, 20 min before breakfast and one capsule, 20 min before lunch and dinner
Kooshki et al.[23]	2016	Iran	TCT-R2016-01250-03	40	20	20	75.7[a]		18[a]		*Nigella sativa* oil used was owned by Barij-e-Kashan; for all subjects, it was maintained away from sunlight and at ambient temperature.	Topically	1 mL oil every 8 h for 3 weeks
Huseini et al.[22]	2022	Iran	IRC-T2008-09010-01157-N13	116	58	58	59.6	63.3	16	13	The *Nigella sativa* oil prepared by cold press method and was purchased from the Barij Essence Pharmaceutical Company.	Orally	5 mL oil every 8 h for 1 month

Control			
Type of control medication	**Dose and schedule**	**Measurement scale**	**Outcome**
Routine prescription	NA	VAS	**Intervention**: D1 versus D30: 7.50 ± 0.97 versus 6.30 ± 1.14 ($p < 0.001$) **Placebo**: D1 versus D30: 7.33 ± 0.47 versus 7.53 ± 0.81 (p = NS) **Changes in intervention versus placebo**: p = NS
Corn starch	2 g/day; two capsules, 20 min before breakfast and one capsule, 20 min before lunch and dinner	KOOS	**KOOS symptom** **intervention**: Change W12 versus W1: 1.61 ± 2.74 (p = NS) **Placebo**: Change W12 versus W1: 4.34 ± 2.00 ($p < 0.05$) **Changes in intervention versus placebo**: p = NS **KOOS pain** **intervention**: Change W12 versus W1: 6.67 ± 3.13 ($p < 0.05$) **Placebo**: Change W12 versus W1: 5.38 ± 2.35 ($p < 0.05$) **Changes in intervention versus placebo**: p = NS **KOOS ADL** **intervention**: Change W12 versus W1: 8.06 ± 2.92 ($p < 0.05$) **Placebo**: Change W12 versus W1: 2.97 ± 2.54 (p = NS) **Changes in intervention versus placebo**: p = NS **KOOS Sport/Rec** **intervention**: Change W12 versus W1: 5.85 ± 4.50 ($p < 0.05$) **Placebo**: Change W12 versus W1: 2.35 ± 3.53 (p = NS) **Changes in intervention versus placebo**: p = NS **KOOS QoL** **intervention**: Change W12 versus W1: 4.73 ± 2.63 (p = NS) **Placebo**: Change W12 versus W1: 3.33 ± 2.10 (p = NS) **Changes in intervention versus placebo**: p = NS
Acetaminophen	325 mg tablet every 8 h for 3 weeks	VAS	**Changes in intervention versus placebo**: W1 versus W3: 4.23 ± 0.31 versus 4.76 ± 0.31 ($p = 0.01$)
Placebo syrup	5 mL oil every 8 h for 1 month	WOMAC VAS	**WOMAC pain** **intervention versus placebo W1**: 14.90 ± 3.63 versus 15.10 ± 3.07 (p = NS) **Intervention versus placebo W3**: 11.52 ± 4.15 versus 14.47 ± 2.45 ($p = 0.003$) **Percent changes in intervention versus placebo**: 22.68 ± 16.21 versus 4.17 ± 3.21 ($p = 0.007$) **WOMAC stiffness** **intervention versus placebo W1**: 5.47 ± 1.78 versus 5.70 ± 1.45 (p = NS) **Intervention versus placebo W3**: 3.65 ± 1.7 versus 5.30 ± 1.11 ($p = 0.006$) **Percent changes in intervention versus placebo**:

(Continues)

TABLE 1 (Continued)

First author	Year of publication	Country	Trial ID	No of participants			Mean age, years		No. of males		Intervention		
				Total	Intervention	Control	Intervention	Control	Intervention	Control	Processing method	Route of administration	Dose and schedule
Dolatkhah et al.[21]	2022	Iran	IRC-T2008-10040-01292-N5	39	Group 1: 13 Group 2: 14	12	53.8 53.9	54.9	2 1	2	The *Nigella sativa* oil purchased from a local market in Tabriz, Iran and was prepared by cold press technique as specified in its catalogue.	Orally Topically	2.5 mL oil twice a day for 6 weeks 2.5 mL oil three times a day for 6 weeks
Azizi et al.[20]	2019	Iran	IRC-	52	26	26	66.4	67.0	7	8	*Nigella sativa* oil made by Ganjina	Topically	1 mL oil twice a day for 21 days

Control			
Type of control medication	**Dose and schedule**	**Measurement scale**	**Outcome**
			33.27 ± 20.12 versus 7.02 ± 12.05 ($p < 0.001$) **WOMAC function** **intervention versus placebo W1**: 44.12 ± 10.05 versus 44.67 ± 10.21 (p = NS) **Intervention versus placebo W3**: 30.96 ± 10.62 versus 44.80 ± 10.15 ($p = 0.003$) **Percent changes in intervention versus placebo**: 29.83 ± 19.23 versus 0.29 ± 1.08 ($p < 0.001$) **WOMAC total intervention versus placebo W1**:64.50 ± 14.31 versus 65.45 ± 12.94 (p = NS) **Intervention versus placebo W3**: 46.62 ± 15.34 versus 64.57 ± 13.31 ($p = 0.001$) **Percent changes in intervention versus placebo**: 27.72 ± 18.61 versus 1.34 ± 2.31 ($p < 0.001$) **VAS intervention versus placebo W1**: 5.33 ± 1.21 versus 5.10 ± 1.02 (p = NS) **Intervention versus placebo W3**: 3.52 ± 0.54 versus 4.63 ± 1.09 ($p = 0.005$) **Percent changes in intervention versus placebo**: 33.96 ± 17.04 versus 9.21 ± 0.32 ($p < 0.001$)
Mineral oil	2.5 mL oil three times a day for 6 weeks 2.5 mL oil twice a day for 6 weeks	WOMAC VAS	**WOMAC pain** **intervention (Oral)**: Change W6 versus W1: −2.41 ± 2.64 ($p = 0.02$) **Intervention (Topical)**: Change W6 versus W1: −3.03 ± 3.00 ($p = 0.02$) **Placebo**: Change W6 versus W1: −0.59 ± 2.09 ($p = 0.274$) **Changes in intervention (Oral) versus placebo**: $p = 0.217$ **Changes in intervention (Topical) versus placebo**: $p = 0.015$ **Changes in intervention (Oral) versus intervention (Topical)**: $p = 0.198$ **WOMAC stiffness** **intervention (Oral)**: Change W6 versus W1: −0.64 ± 1.83 ($p = 0.165$) **Intervention (Topical)**: Change W6 versus W1: −0.53 ± 1.76 ($p = 0.262$) **Placebo**: Change W6 versus W1: −0.18 ± 1.27 ($p = 0.566$) **Changes in intervention (Oral) versus placebo**: $p = 0.527$ **Changes in intervention (Topical) versus placebo**: $p = 0.347$ **Changes in intervention (Oral) versus intervention (Topical)**:$p = 0.955$ **WOMAC function intervention (Oral)**: Change W6 versus W1: −8.05 ± 8.18 ($p = 0.001$) **Intervention (Topical)**: Change W6 versus W1: −15.00 ± 10.33 ($p < 0.001$) **Placebo**: Change W6 versus W1: −1.81 ± 6.69 ($p = 0.296$) **Changes in intervention (Oral) versus placebo**: $p = 0.002$ **Changes in intervention (Topical) versus placebo**: $p = 0.569$ **Changes in intervention (Oral) versus intervention (Topical)**: $p = 0.001$ **WOMAC total intervention (Oral)**: Change W6 versus W1: −11.11 ± 10.68 ($p = 0.001$) **Intervention (Topical)**: Change W6 versus W1: −18.56 ± 13.98 ($p < 0.001$) **Placebo**: Change W6 versus W1: −2.56 ± 8.96 ($p = 0.265$) **Changes in intervention (Oral) versus placebo**: $p = 0.005$ **Changes in intervention (Topical) versus placebo**: $p = 0.516$ **Changes in intervention (Oral) versus intervention (Topical)**: $p = 0.002$ **VAS intervention (Oral)**: Change W6 versus W1: −1.11 ± 2.17 ($p = 0.050$) **Intervention (Topical)**: Change W6 versus W1: −2.06 ± 1.64 ($p < 0.001$) **Placebo**: Change W6 versus W1: −0.09 ± 1.08 ($p = 0.734$) **Changes in intervention (Oral) versus placebo**: $p = 0.019$ **Changes in intervention (Topical) versus placebo**: $p = 0.198$ **Changes in intervention (Oral) versus intervention (Topical)**: $p = 0.005$
Diclofenac sodium gel (1%)	60 g gel twice a day for 21 days	KOOS	**Intervention versus placebo D1**: 75.00 ± 16.29 versus 69.88 ± 18.24 ($p = 0.301$)

(Continues)

TABLE 1 (Continued)

First author	Year of publication	Country	Trial ID	No of participants			Mean age, years		No. of males		Intervention		
				Total	Intervention	Control	Intervention	Control	Intervention	Control	Processing method	Route of administration	Dose and schedule
			T2017-08083-5563N1								Osareh of Isfahan pharmaceutical company®.		

Abbreviations: VAS, visual analogous scale; KOOS, Knee injury and osteoarthritis outcome score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis index; ADL, activities of daily living; Sport/Rec, function in sport and recreation; QoL, quality of life; W, Week; D, Day; NS, not significant; NA, not available.

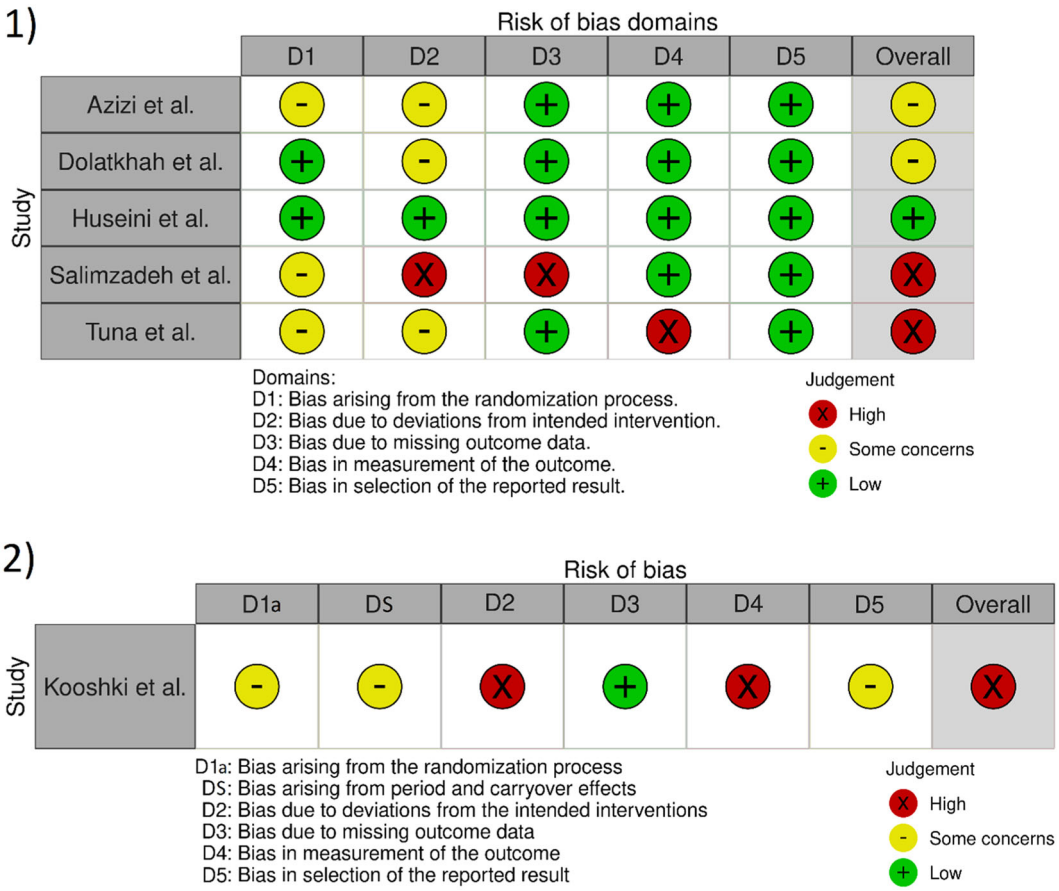


FIGURE 2 Summary of risk of bias assessment for the included studies based on Cochrane Collaboration's risk of bias assessment tool 2 (RoB 2); (1) parallel group trials, (2) crossover trials.

factor in OA RCTs is the proportional contextual effect (PCE) in relation to pain outcomes.[33,34] None of the studies included in our review assessed the contribution of PCE to reported outcomes and how it could impact the clinical translation of results. A higher proportion of women is also correlated with increased PCE.[34] Furthermore, RCTs with patient-reported outcomes tend to show higher PCE.[34]

The oral administration of *Nigella sativa* did not show statistically significant results in terms of pain relief. It should be noted that the improvements found in the topical administration studies could be hampered by the failure to use massage in the control groups, which would have ensured that the observed outcomes were only attributable to *Nigella sativa*. None of the trials that used the KOOS as the pain measurement tool showed any remarkable changes in the pain score, which is in contrast to the trials using the VAS. These results could at least be partially explained by the higher assay sensitivity of the VAS compared to the KOOS.[35] Furthermore, evidence from the five studies that recruited participants according

Control			
Type of control medication	Dose and schedule	Measurement scale	Outcome
			Intervention versus placebo D10: 54.44 ± 17.31 versus 57.66 ± 19.66 ($p = 0.542$) **Intervention versus placebo D21**: 38.88 ± 27.88 versus 50.33 ± 27.88 ($p = 0.040$)

[a]The study only reported the overall values.

to the American College of Rheumatology Criteria may be applicable to current clinical practice. However, in one study the recruiting criteria were not described, resulting in an unclear risk of selection bias and a questionable use in clinical practice. The results of studies that used commercial products without adequately describing their contents are only attributable to those specific products and cannot be generalized to other medicinal products from this plant unless bioequivalence has been demonstrated.[36]

Our results are consistent with the findings of an earlier clinical trial, as well as in vivo and in vitro studies, which demonstrated the antioxidative, anti-inflammatory, and immunomodulatory effects of *Nigella sativa* and its active principal, thymoquinone.[32] The evidence regarding the pathogenesis of OA and thymoquinone's mechanism of action provides justification for using *Nigella sativa* products in the management of OA through the oral or topical route.

Thymoquinone, in particular, has been found to have important anti-inflammatory and immunomodulatory qualities that are of particular interest in OA.[37,38] Treatment of OA with thymoquinone has been demonstrated to upregulate the anti-inflammatory gene expression, downregulate matrix metalloproteinase activity in the chondrocytes and inhibit nitric oxide, IL-1β, IL-2, IL-6, TNF-α, and cyclooxygenase (COX)-2 in several human, in vivo and in vitro studies.[32,39–45] *Nigella sativa* also has a substantial antioxidant effect. In vivo and in vitro studies have shown the capability of thymoquinone to reduce reactive oxygen species and to upregulate the antioxidant enzymes in different tissues.[32] A meta-analysis of RCTs evaluating the effect of *Nigella sativa* supplementation on oxidative stress and antioxidant parameters found that treatment with *Nigella sativa* could improve the superoxide dismutase level but failed to show any significant effect on the malondialdehyde level and total antioxidant capacity.[46]

While in vitro studies suggest a possible role for *Nigella sativa* as a disease-modifying agent, RCTs have focused on symptomatic management of OA and the functional disability experienced by patients. There is a research gap in this area that needs to be addressed. There are two notable shortcomings in these trials. First, short duration of trials compared to the decade long nature of OA. Second, there are serious concerns regarding bias due to deviations from intended interventions, stemming from inadequate blinding in trials that compared oral and topical interventions.

To the best of our knowledge, this is the first systematic review to examine the efficacy of *Nigella sativa* for the management of OA. Although we addressed important gaps in the existing evidence regarding the use of this herbal medicine in the management of OA, we acknowledge that our review has several limitations. First, the number of trials included in our review was low and the number of participants in these studies was not enough to make a generalizable conclusion. Second, there was a high degree of clinical heterogeneity among the studies due to variations in the primary outcome, participants, and interventions. This diversity prevented the conduction of a meta-analysis and the formulation of a robust conclusion. Third, the overall quality of the included studies was unsatisfactory, and thus the results of our systematic review will be useful to help guide future trials to establish more robust evidence.

5 | CONCLUSION

The present systematic review found that *Nigella sativa* is a safe medication. However, the clinical heterogeneity and low-quality of the studies means that the findings are controversial. As a result, there is currently insufficient evidence to make clinical recommendations for or against using *Nigella sativa* to treat OA. For more informed clinical decision-making, there is a need for clinical trials of higher methodological quality and with adequate sample sizes. Also, future studies can evaluate other effects of *Nigella sativa* on OA in other parts of the body.

AUTHOR CONTRIBUTIONS

Seyed Ehsan Mousavi: Conceptualization; data curation; investigation; methodology; resources; writing—original draft; writing—review & editing. **Maryam Noori**: Conceptualization; methodology; project administration; writing—original draft; writing—review & editing. **Hanieh Marandi**: Data curation; writing—original draft; writing—review & editing. **Asra Fazlollahi**: Data curation; writing—original draft; writing—review & editing. **Seyed Aria Nejadghaderi**: Data curation; project administration; writing—original draft; writing—review & editing. **Shayan Rahmani**: Data curation; writing—original draft; writing—review & editing. **Mahdi Noordoost**: Writing—original draft; writing—review & editing. **Nahid Karamzad**: Writing—original

draft; writing—review & editing. **Mark J. M. Sullman**: Writing—original draft; writing—review & editing. **Ali-Asghar Kolahi**: Writing—original draft; writing—review & editing. **Saeid Safiri**: Writing—original draft; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

TRANSPARENCY STATEMENT

The lead authors Ali-Asghar Kolahi and Saeid Safiri affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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SUPPORTING INFORMATION

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

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