Avicenna Journal of Phytomedicine (AJP)

Review Article

Therapeutic potential of *Nigella sativa* for oral lesions: A systematic review of clinical trials across diverse pathogenesis

Lina Dezhampour[1], Farshad Javadzadeh[2], Vahideh Toopchizadeh[3], Soraya Babaie[4], Maryam Hosseinpour Sarmadi[2,*], Azizeh Farshbaf-Khalili[3,*]

[1]*Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran*
[2]*Department of Oral & Maxillofacial Medicine, Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran*
[3]*Physical Medicine and Rehabilitation Research Center, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran*
[4]*Physical Medicine and Rehabilitation Research Center, Tabriz University of Medical Sciences, Tabriz, Iran*

Article history:
Received: Jun 07, 2026
Received in revised form: Oct 04, 2026
Accepted: Oct 27, 2026
Epub ahead of print

**** Corresponding Authors:***
m.sarmadi91@gmail.com
afarshbafkhalili@gmail.com

Keywords:
Oral ulcer
Nigella sativa
Clinical trials
Systematic review

Abstract

Objective: This systematic review evaluated the clinical efficacy of *Nigella sativa* (NS) in oral lesions of differing pathogenesis: oral submucous fibrosis (OSMF), dry socket, gingivitis, periodontitis, recurrent aphthous stomatitis (RAS), Behçet's disease (BD), oral mucositis (OM), and oral lichen planus (OLP).

Materials and Methods: Following PRISMA guidelines, PubMed/MEDLINE, Embase, Cochrane Library, Scopus, Web of Science, ProQuest, and ClinicalTrials.gov were searched up to 3 October 2025. Eighteen studies (16 randomized controlled trials and 2 quasi-experimental studies; N=821 participants) were included. Risk of bias was assessed with RoB 2 and ROBINS-I tools. Findings were synthesized narratively for each condition.

Results: NS was comparable to active comparators in OSMF (turmeric–black pepper, steroids), gingivitis (chlorhexidine), and OLP (corticosteroids), and was inferior to scaling and root planing (SRP) in gingivitis. It was superior to the comparators in OM, RAS, and, in most trials, dry socket. NS did not improve inflammatory biomarkers in periodontitis, and oral NS did not alter systemic BD activity, whereas topical NS improved BD mucosal ulcers in one small trial. Certainty of evidence was low or very low for all outcomes, and adverse-event reporting was inconsistent.

Conclusion: The available clinical evidence suggests condition-specific potential for NS, but certainty is limited by small samples, methodological limitations, heterogeneous interventions and outcomes, and inconsistent reporting. NS should therefore be considered investigational rather than established therapy, and larger, well-designed trials with standardized preparations and prespecified outcomes are needed.

Please cite this paper as:
Dezhampour L, Javadzadeh F, Toopchizadeh V, Babaie S, Hosseinpour Sarmadi M, Farshbaf-Khalili A. Therapeutic potential of Nigella sativa for oral lesions: A systematic review of clinical trials across diverse pathogenesis. Avicenna J Phytomed, 2026

Introduction

Oral lesions are abnormal changes or injuries of oral tissues that present as ulcers,

white or red patches, swelling, or irregularities. They cause pain, impaired chewing, swallowing, and speech, halitosis, and dry mouth, and substantially reduce quality of life (Triantos 2005). Their causes include infections (periodontitis, and gingivitis), mechanical trauma, hypersensitivity, immune dysregulation (Behçet's disease [BD], and oral lichen planus [OLP]), micronutrient deficiency (recurrent aphthous stomatitis [RAS]), and potentially malignant states such as oral submucous fibrosis (OSMF). Treatment ranges from topical to systemic drugs chosen according to lesion type, severity, and patient factors, but side effects and limited drug availability in some regions restrict their use (Shaikh and Qazi 2025). Herbal agents are therefore increasingly considered adjuncts or alternatives because of their anti-inflammatory, antimicrobial, and regenerative actions, low cost, and cultural acceptability (Nishad et al. 2025; Sneha et al. 2021).

Nigella sativa (NS; black seed or black cumin), a member of the Ranunculaceae family (Amin and Hosseinzadeh 2016), has long been used in traditional medicine (Al Dhaheri et al. 2022; Belgaumi et al. 2020; Yimer et al. 2019). It is cultivated across South Asia, the Middle East, an Southern Europe (Ahmad et al. 2013; Chu et al. 2014), and its seeds are consumed as food and used for conditions such as diabetes, hypertension, rheumatoid arthritis, and skin disorders (Yimer et al. 2019). Its main bioactive constituent, thymoquinone (TQ), has anti-inflammatory, antioxidant, antimicrobial, and anticancer properties (Mamun and Absar 2018) and promotes granulation tissue formation, epithelialization, and fibroblast activity, which supports a role in mucosal wound healing (Mekhemar et al. 2020; Sallehuddin et al. 2020).

These properties provide a plausible rationale in several oral conditions: antifibrotic and antioxidant effects in OSMF, a chronic disorder driven by submucosal inflammation and fibrosis (Nordin et al. 2019; Passi et al. 2017); protection of the mucosa against inflammation and oxidative stress during cancer therapy (oral mucositis [OM]; Kadarullah et al. 2024); antibacterial activity against periodontal pathogens, with encouraging results for TQ-containing periodontal chips (Al-Bayaty et al. 2013; Mekhemar et al. 2020); and cytokine modulation and free-radical scavenging relevant to OLP.

However, the clinical literature is fragmented across conditions and limited by small samples and variable NS preparations (oils, extracts, powders, and TQ chips), which reduces its reliability and generalizability. This review therefore aimed to synthesize clinical trials of NS in oral lesions, with clinical indices as primary outcomes and inflammatory biomarkers as secondary outcomes, and to identify gaps that should guide standardized future trials. Because pathogenesis, clinical course, and standard treatment differ substantially between these conditions, the review was designed to be intervention-centered rather than disease-centered: findings are reported and interpreted separately for each condition, and no data were pooled across diagnoses.

Materials and Methods

This review followed the Cochrane Handbook for Systematic Reviews of Interventions (Workentin et al. 2022) and the PRISMA guidelines (Moher et al. 2015; Page et al. 2021). The protocol was prospectively registered in PROSPERO (CRD420251148737; 28 September 2025) and approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.DENTISTRY.REC.1404.024). The review question was structured according to the PICOS framework.

Participants (P): Individuals with oral lesions, including RAS, periodontitis, gingivitis, OM, OLP, dry socket, OSMF, and BD. Intervention (I): Topical or

systemic NS. Comparison (C): Placebo, no intervention, or alternative therapies.

Outcomes (O): Primary outcomes were prespecified, condition-specific clinical indices: Oral Clinical Manifestation Index (OCMI) for RAS; plaque index (PI) and gingival index (GI) for gingivitis and periodontitis; swallowing function for OM; pain for OLP and dry socket; interincisal mouth opening for OSMF; and ulcer healing for BD. Secondary outcomes were inflammatory biomarkers, lesion severity, symptom scores, and adverse events.

Eligibility criteria

Original interventional trials of NS (any dose, route, or duration; alone or combined with other agents) in participants of any age or sex with any oral lesion, published in English or Persian, were eligible. Reviews, observational studies, case reports, editorials, conference abstracts, animal studies, study protocols, and publications in other languages were excluded.

Search strategy

After a scoping search in August 2025, two researchers (L.D. and S.B.) searched PubMed/MEDLINE, Embase, Cochrane Library, Scopus, Web of Science, ProQuest, and ClinicalTrials.gov on 3 October 2025, combining controlled vocabulary and free-text terms for the oral conditions with terms for NS, black cumin, black seed, and Kalonji (Appendix 1). Reference lists of eligible studies and reviews were screened, and gray literature was searched through Google Scholar.

Study selection and data extraction

After duplicate removal in EndNote X8, two reviewers (L.D. and V.T.) independently screened titles, abstracts, and full texts; disagreements were resolved by discussion or by a third reviewer (M.H.S.). Two reviewers (L.D. and M.H.S.) independently extracted data with a standardized form covering study characteristics, participants, intervention, comparator, outcomes and time points, findings, and adverse events. Explicit reports of no adverse events were distinguished from outcomes for which adverse events were not assessed.

Risk of bias assessment

Two reviewers (S.B. and A.F.Kh) independently assessed risk of bias, with disagreements resolved by a third reviewer (F.J.). RCTs were assessed with the Cochrane RoB 2 tool (randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result), and each study was rated as low risk, some concerns, or high risk (Sterne et al. 2019). The two non-randomized studies were assessed with ROBINS-I (Sterne et al. 2016). Judgments were used when interpreting findings and grading the certainty of evidence.

Data synthesis and analysis

Meta-analysis was not performed because of clinical and methodological heterogeneity in lesion type, NS preparation, route, dose, duration, comparator, outcome definition, and follow-up, and because most outcomes came from one or two studies. Findings were synthesized narratively for each condition, considering the direction of effect, statistical significance, comparison with control, and consistency across studies. Findings from a single study were considered preliminary.

The characteristics and key findings of each study are presented in Table 1 using arrows, adapted from a previously published systematic review (Gholamnezhad et al. 2022).

Table 1. Characteristics and key findings of the included studies

Study (country)	Condition	Design; participants	NS intervention	Comparator	Outcomes (1° primary; 2° secondary)	Main findings	Adverse events
Pipalia et al. (2016) India	OSMF	RCT, double-blind n=40 (20/20) Age ~28 y; 100% male	NS capsules 500 mg × 2, TID, 3 mo	TBP: turmeric 400 mg + black pepper 100 mg × 2, TID, 3 mo	1°: MO, BS (VAS) 2°: tongue protrusion, cheek flexibility, SOD	NS: MO ↑; BS ↓; tongue protrusion ↑; cheek flexibility ↑; SOD ↑ (not normalized) vs. TBP: all ↔	None
Batool et al. (2022) Pakistan	OSMF	RCT n=39 (30 analyzed) Age ~35 y; 93% male	NS oil 1 mL buccal, BID, 3 mo + physiotherapy	Betamethasone 0.1% lotion 1 mL, BID, 3 mo + physiotherapy	1°: pain/BS (VAS), IIMO 2°: AE	NS: pain ↓; IIMO ↑ vs. steroid: pain ↔; IIMO ↔	None
Al-Niaimi et al. (2022) Iraq	Dry socket	RCT n=52 (26/26) Age ~28–38 y; both sexes	Miswak powder + NS oil, single application	Alvogyl	1°: pain (VAS), days 1–3	NS: pain ↓ vs. Alvogyl: pain ↔	NR
Alabdullah et al. (2023) Syria	Dry socket	Comparative randomized trial n=40 sockets (20/20) Age 20–50 y	NS oil 100% on gelfoam	Eugenol 100% on gelfoam	1°: healthy granulation tissue score 2°: inflammation score T0, day 3, day 7	NS: granulation score ↓; inflammation score ↓ vs. eugenol: day 3 ↔; day 7 scores ↓ (favors NS)	NR
Khan et al. (2022) Saudi Arabia	Dry socket	RCT, double-blind n=60 (20/20/20) Age >18 y (mean 42–53); both sexes	NS powder + oil in socket, repeated until pain subsided	Alvogyl; saline rinse	1°: pain (VAS) to day 7 2°: healing time, no. of sessions, AE	NS: pain ↓ (from 30 min) vs. Alvogyl/saline: pain ↓; sessions ↓ (favors NS)	NR
Singh et al. (2019) India	Gingivitis	Split-mouth RCT n=24 Age 25–45 y	Ethanolic NS extract (3 ratios: 1:3, 1:1, 3:1) sulcular irrigation, 3 days; follow-up to day 28	SRP (split-mouth control)	1°: PI, GI (baseline, day 14, day 28)	NS: PI ↓; GI ↓ (3:1 greatest) vs. SRP: PI ↑; GI ↑ (favors SRP)	NR
Rahman et al. (2023) Saudi Arabia	Gingivitis	RCT, double-blind n=40 (37 analyzed) Age 20–40 y; 100% female	50% NS oil mouthwash 10 mL, BID, 15 d	2% CHX mouthwash 10 mL, BID, 15 d	1°: GI, PI 2°: GCF IL-6, IL-18; CFU	NS: GI ↓; PI ↓; IL-6 ↓; IL-18 ↔; CFU ↓ vs. CHX: GI ↔; PI ↔; IL-6 ↔; IL-18 ↔; CFU ↑ (favors CHX)	NR
Ilangovan & Rajasekar (2021) India	Gingivitis	RCT, double-blind n=30 (15/15) Age 18–28 y	20% aqueous NS mouthwash 10 mL, BID, 1 wk	0.12% CHX mouthwash	1°: PI, GI	NS: PI ↓; GI ↓ (pre–post) vs. CHX: PI ↔; GI ↔	NR
Hassan et al. (2020a) Pakistan	Periodontitis	Parallel RCT n=40 (20/20) Age ~37 y; 55% male	NS oil mouthwash (Kalonji), BID, 2 wk	Normal saline mouthwash	1°: salivary MMP-8 2°: optical density	NS: MMP-8 ↔ vs. saline: MMP-8 ↔	NR
Hassan et al. (2020b) Pakistan	Periodontitis	Parallel, triple-blind placebo RCT n=40 (20/20) Age ~37 y; 55% male	NS oil 5 mL (55 drops) topical on gingiva, BID, 2 wk	Normal saline, same regimen	1°: salivary IL-1β 2°: PPD, CAL, PI, BOP	NS: IL-1β ↔ vs. saline: IL-1β ↔	NR

Table 1. Continued

Samara et al. (2006) Iraq	RAS	Placebo-controlled, non-randomized n=40 (20/20) 57.5% male	NS fixed oil, TID, 4 d	Glycerin, TID, 4 d	1°: healing rate (OCMI) Baseline, day 4, day 8	NS: OCMI ↓ vs. glycerin: OCMI ↓ (favors NS)	NR
Abdali (2009) Iraq	BD (orogenital ulcers)	RCT, double-blind n=40 (20/20) 68% male	Topical NS oil 10% in glycerin, TID, 8 d	Glycerin, TID, 8 d	1°: oral and genital ulcer healing (day 4, day 8) 2°: pain relief	NS: oral ulcer healing ↑; genital ulcer healing ↑; pain ↓ (immediate) vs. glycerin: healing ↑; pain ↓ (favors NS)	Not assessed
Kavandi et al. (2018) Iran	BD	RCT, double-blind n=71 (NS 37, PL 34) Age >16 y	NS oil 1000 mg/d (soft gel), 12 mo	Placebo	1°: IBDDAM, TIAI, BDCAF (every 2 mo)	NS: activity scores ↓ (both arms) vs. PL: IBDDAM ↔; TIAI ↔; BDCAF ↔	Mild; dyspepsia → withdrawal (NS 2, PL 1); cough (NS 1)
Amizadeh et al. (2020) Iran	BD	RCT, double-blind n=96 (49/47) Age >16 y	NS oil 1000 mg/d (soft gel), 8 wk	Placebo	MDA, TAC, TNF-α, IL-10, hs-CRP	NS: MDA ↓; TAC ↑; TNF-α ↔; IL-10 ↔; hs-CRP ↔ vs. PL: all markers ↔	NR
Ameen et al. (2019a, 2019b) Iraq	OM (HNC, RT/CRT)	Open-label pilot RCT n=40 (20/20) Age ~55 y; 70% male	NS oil mouthwash 10 mL, every 6 h, 6–7 wk	Magic mouthwash 10 mL, every 6 h	1°: RTOG grade 2°: dysphagia, diet, pain, OM duration, salivary IL-6, TNF-α	vs. magic mouthwash: RTOG grade ↓ (wk 4–7); severe dysphagia ↓; severe pain ↓; normal diet ↑; OM duration ↔; IL-6 ↓ (AUC); TNF-α ↓ (AUC) (favors NS)	NR
Hussain et al. (2019) Iraq	OM (AML, chemotherapy)	Open-label RCT n=52 (27/25) Age ~35 y; both sexes	NS oil rinse 10 mL, every 6 h, day 1–28	Magic mouthwash 10 mL, every 6 h	1°: WHO, NCI, OMAS, pain (VAS) 2°: salivary IL-6, TNF-α	vs. magic mouthwash: WHO ↓; NCI ↓ (day 4 only); OMAS ↓; pain ↓; IL-6 ↓; TNF-α ↔ (favors NS)	NR
Kumar et al. (2024) India	OLP	RCT, double-blind n=49 analyzed (25/24) Age ≥18 y (mean 44–49)	NS cream 75% v/v, 1 g, BID, 45 d	Clobetasol 0.05% gel, 1 g, BID, 45 d	1°: BS (NRS), lesion size 2°: AE	NS: BS ↓; lesion size ↓ vs. clobetasol: BS ↔; lesion size ↔ (comparable)	NS: none Clobetasol: candidiasis (n=3)
Pakfetrat et al. (2024) Iran	OLP (erosive-atrophic)	Non-randomized pilot n=20 (10/10) Age ~53 y; 65% female	NS 10% mucoadhesive patch, TID, 4 wk (+ nystatin)	Triamcinolone 0.1% patch, TID, 4 wk (+ nystatin)	1°: pain (VAS), lesion severity (Thongprasom) 2°: AE, satisfaction	NS: pain ↓; severity ↓ vs. triamcinolone: pain ↓ (wk 2); severity ↓ (wk 3) (favors NS)	No serious AE; bitter taste (NS); mild burning, patch adherence (both)

↑ significant increase; ↓ significant decrease; ↔ no significant change or difference. "NS:" = change within the NS arm (vs. baseline); "vs. [comparator]:" = direction of the outcome in the NS arm relative to the comparator (e.g., pain ↓ = lower pain with NS; "favors" = interpretation). AE, adverse events; AML, acute myeloid leukemia; AUC, area under the curve; BD, Behçet's disease; BDCAF, Behçet's Disease Current Activity Form; BID, twice daily; BOP, bleeding on probing; BS, burning sensation; CAL, clinical attachment loss; CFU, colony-forming units; CHX, chlorhexidine; CRT, chemoradiotherapy; GCF, gingival crevicular fluid; GI, gingival index; HNC, head and neck cancer; IBDDAM, Iranian Behçet's Disease Dynamic Activity Measure; IIMO, interincisal mouth opening; MDA, malondialdehyde; MMP-8, matrix metalloproteinase-8; MO, mouth opening; NR, not reported; NRS, numeric rating scale; NS, Nigella sativa; OCMI, Oral Clinical Manifestation Index; OLP, oral lichen planus; OM, oral mucositis; OMAS, Oral Mucositis Assessment Scale; OSMF, oral submucous fibrosis; PI, plaque index; PL, placebo; PPD, probing pocket depth; RAS, recurrent aphthous stomatitis; RCT, randomized controlled trial; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SOD, superoxide dismutase; SRP, scaling and root planing; TAC, total antioxidant capacity; TBP, turmeric–black pepper; TIAI, Total Inflammatory Activity Index; TID, three times daily.

Results

Literature search and study selection

After the removal of duplicates and screening of titles and abstracts, the full texts of the remaining candidates were assessed, and 18 trials were included (Figure 1; the reasons for exclusion are given in the flow diagram).

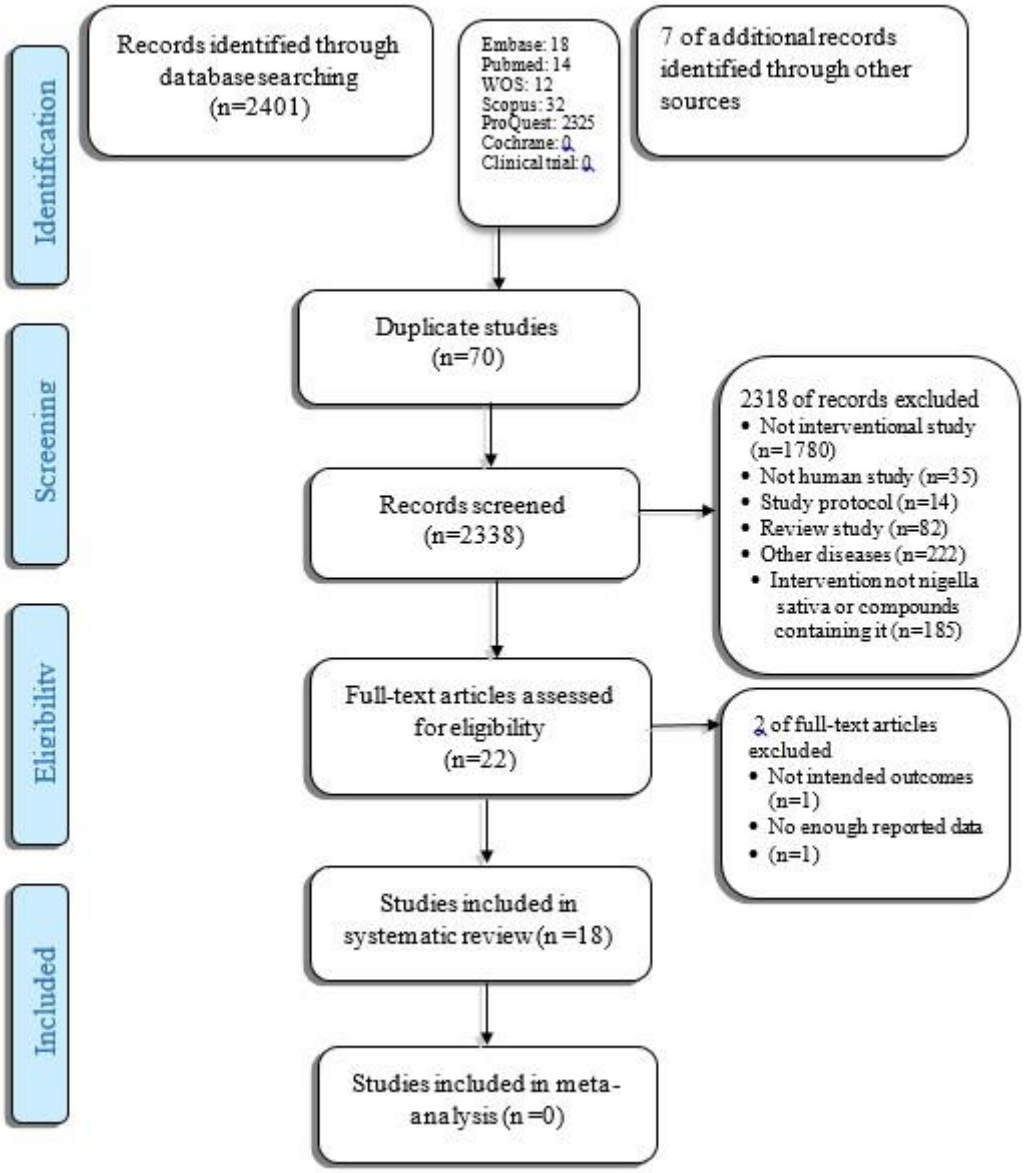


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart

Study characteristics

The included trials were published between 2006 and 2024 and were conducted in Iraq, India, Iran, Pakistan, Saudi Arabia, and Syria (Table 1), mainly in regions with a tradition of NS use, which may shape participants' expectations for subjective outcomes. They addressed OSMF (2 trials), dry socket (3), gingivitis (3), periodontitis (2), RAS (1), BD (3), OM (2 trials; 3 reports, because Ameen et al. [2019a and 2019b] describe the same trial), and OLP (2). Sixteen trials were randomized and two (Pakfetrat et al. 2024; Samara et al. 2006) were not. NS was administered as oil (mouthwash, topical, or capsule), powder, extract, cream, or mucoadhesive patch, alone or combined with other agents, and comparators were either inert (placebo, vehicle, or saline) or

active (turmeric–black pepper, steroids, chlorhexidine (CHX), Alvogyl, eugenol, scaling and root planing (SRP), or magic mouthwash). Treatment lasted from a single application or a few days (dry socket, RAS) to several weeks (gingivitis, OM, and OLP) and up to 3–12 months (OSMF and BD). Several trials enrolled a single sex (Pipalia et al. 2016; Rahman et al. 2023), which limits generalizability.

Risk of bias

Only one trial was judged to be at low risk of bias (Hassan et al. 2020a); the others raised some concerns or were at high risk, mainly because of problems in the randomization process and the lack of blinded outcome assessment (Figure 2). Both non-randomized studies (Pakfetrat et al. 2024; Samara et al. 2006) were judged to have an overall serious risk of bias, mainly due to confounding and outcome measurement. Both studies had low risk of bias in participant selection and intervention classification, but concerns remained regarding lack of blinding, deviations from intended interventions, and selective reporting. Overall, these methodological limitations should be considered when interpreting the findings (Table 2).

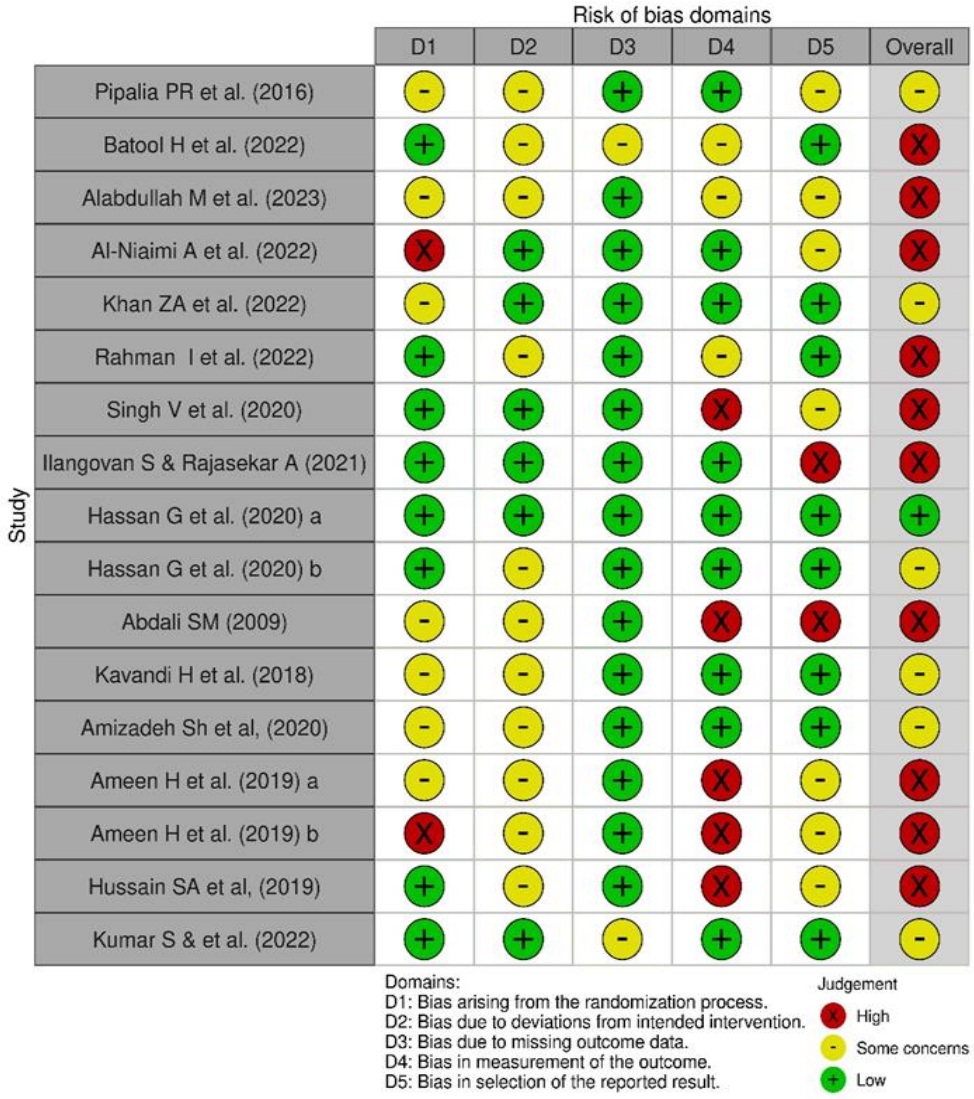


Figure 2. Risk of bias according to RoB-2 (The trial by Ameen et al. (2019a and 2019b) represents a single clinical trial reported across two separate publications; because the two papers reported different outcomes, they were entered into the RoB 2 assessment as two distinct records).

Table 2 - Risk of bias in the non-randomized studies based on ROBINS-I

Domain	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Judgment	Serious	Low	Low	Moderate	Moderate	Serious	Moderate	Serious
Samara et al., 2006	Method of allocation to the two groups not described (no randomization or matching reported); age/sex distribution reported only for the whole sample, not by group	All 40 patients underwent clinical assessment and specialist consultation to confirm eligibility before intervention allocation	Interventions (10% NS oil in glycerin vs. glycerin alone) are clearly and fixedly defined from baseline	No mention of blinding of patients/providers, adherence monitoring, or co-interventions; the oil's strong odor likely made patients aware of their allocation	No participant flow, dropouts, or losses to follow-up reported; all 40 patients assumed to have completed both assessments (day 4 and day 8)	OCMI includes relatively subjective components; no blinding of outcome assessors reported; blinding seems unlikely given the oil's distinctive odor	No registered or pre-specified protocol mentioned; selective reporting cannot be ruled out	Serious concerns in the Confounding and Measurement of outcomes domains
Judgment	Serious	Low	Low	Moderate	Low	Serious	Moderate	Serious
Pakfetrat et al., 2024	Allocation method not described for this nonrandomized 1:1 design; baseline pain imbalanced (mean VAS 6.5 NS vs. 4.4 triamcinolone; more patients with OLP >1 yr in NS arm), and only age and gender were adjusted for, so larger NS improvement may partly reflect regression to the mean	Eligibility criteria clearly defined; 22 patients assessed and 2 excluded for pregnancy and severe dysplasia; participants began treatment at the start of follow-up	Interventions clearly defined (bilayer mucoadhesive patch with 10% NS extract vs. 0.1% triamcinolone, TID for 4 wk)	No blinding of patients or providers; the bitter taste of NS patches likely revealed allocation; adherence not monitored; nystatin given to both arms (balanced co-intervention)	CONSORT diagram shows no loss to follow-up or discontinuation; all 20 patients analyzed	VAS is patient-reported and Thongprasom scoring was done by the same clinician without reported blinding; the authors acknowledge the absence of blinding	No registered protocol reported; the stated primary measure (proportion of patients improving) was not reported, and many time-point comparisons were made without correction	Serious concerns in the Confounding and Measurement of outcomes domains

NS in oral submucous fibrosis (OSMF)

Pipalia et al. (2016) found that NS capsules improved mouth opening and burning sensation as well as turmeric–black pepper, and raised serum superoxide dismutase (SOD) without restoring it to healthy levels. Batool et al. (2022) similarly found topical NS oil equivalent to a topical steroid for pain and mouth opening. Both groups of authors concluded that NS is as effective as standard OSMF therapy. In our appraisal, this conclusion is weaker than it appears: neither trial had a placebo or no-treatment arm, the study populations were small and predominantly male, the routes differed (oral vs. topical), and

physiotherapy was a co-intervention in one trial. The incomplete normalization of SOD suggests that the antioxidant effect of NS is partial. No trial examined disease progression or malignant transformation, which are the main concerns in OSMF.

NS in dry socket

Al-Niaimi et al. (2022) reported that a miswak–NS mixture reduced pain as effectively as Alvogyl, and interpreted this as support for the mixture as an alternative dressing. However, a single application cannot separate pain relief from the natural course of dry socket, and the contribution of NS within the mixture cannot be isolated. Alabdullah et al. (2023) found that NS oil on gelfoam produced better soft-tissue healing and lower inflammation than eugenol only at the later assessment, which the authors attributed to the anti-inflammatory and wound-healing activity of NS. Khan et al. (2022) found that an NS powder–oil mixture gave faster pain relief and required fewer dressing changes than Alvogyl or saline, and proposed an analgesic and anti-inflammatory mechanism. The benefit therefore appeared in the two trials in which NS was the sole active agent, but the trials differed in comparator, formulation, and outcome (pain vs. tissue healing), and the examiner-rated healing indices are susceptible to detection bias. Overall, NS is a promising local dressing, but the evidence is inconsistent.

NS in gingivitis

Singh et al. (2019) found that sulcular irrigation with an ethanolic NS extract improved plaque and gingival indices at all extract ratios, with the greatest gingival improvement at the highest NS ratio, which suggests a dose-response relationship; SRP, however, was clearly superior. This was a split-mouth design with only brief NS exposure, so carry-over between sites and the handling of paired data are concerns. Rahman et al. (2023) and Ilangovan and Rajasekar (2021) found that NS mouthwashes performed similarly to CHX. In Rahman et al., NS lowered gingival crevicular interleukin-6 (IL-6) while CHX was more effective against bacterial counts, which led the authors to propose that NS acts mainly through anti-inflammatory rather than antimicrobial mechanisms. Ilangovan and Rajasekar reported internally inconsistent statistics, which limits the weight of their conclusion that NS is a CHX alternative. In none of the trials was NS superior to the active comparator, and two lacked a placebo or no-treatment control, so the improvement may partly reflect oral hygiene instruction and the Hawthorne effect rather than NS itself. NS mouthwash is thus at best a CHX alternative for short-term use, and cannot replace mechanical debridement.

NS in periodontitis

Hassan et al. (2020a and 2020b) reported that NS oil mouthwash did not reduce salivary matrix metalloproteinase-8 (MMP-8) or IL-1β more than saline, and concluded that NS has limited anti-inflammatory value in periodontal therapy. Our appraisal supports a null finding but not a definitive one. The rinse was used for only two weeks and is unlikely to reach the subgingival biofilm, salivary biomarkers are highly variable, the trials were small, and the two reports appear to derive from the same participants. The accompanying clinical improvement was attributed to non-surgical periodontal therapy rather than to NS (Hassan et al. 2021). If NS is to be tested in periodontitis, local sustained-release delivery (such as TQ chips) is more rational than a mouthwash.

NS in recurrent aphthous stomatitis (RAS)

Samara et al. (2006) reported that 10% NS oil in glycerin healed aphthous ulcers faster than glycerin alone and described NS as a potent natural treatment with possible prophylactic value. This is the only RAS study, and it was non-randomized with serious risk of bias, unblinded (the odor of

the oil makes concealment unlikely), assessed with a partly subjective index, and followed for only 8 days. The vehicle-only control does not show superiority over corticosteroids, and recurrence, the defining feature of RAS, was not measured, so the proposed prophylactic effect remains untested.

NS in Behçet's disease (BD)

The effect of NS in BD depended on the route of administration. Abdali (2009) found that topical NS oil accelerated healing of oral and genital ulcers and provided immediate pain relief, which the author attributed to a local anti-inflammatory action. This trial was older, short, and vehicle-controlled, without a standard-treatment comparator. In contrast, Kavandi et al. (2018) found that oral NS for 12 months did not change disease activity beyond placebo, and Amizadeh et al. (2020) found that oral NS shifted oxidative markers within the NS group but not relative to placebo, with no change in inflammatory markers. Both groups of authors concluded that oral NS at this dose is ineffective. Possible explanations are insufficient systemic exposure at 1000 mg/day, background immunosuppressive therapy masking small additive effects, and the heterogeneity of BD. The evidence for a topical benefit rests on a single trial and needs confirmation.

NS in oral mucositis (OM)

Ameen et al. (2019a and 2019b) found that NS oil mouthwash was superior to magic mouthwash in head and neck cancer patients receiving radiotherapy or chemoradiotherapy, with lower mucositis grades, less pain and dysphagia, better dietary tolerance, and attenuated salivary IL-6 and TNF-α. The authors interpreted this as an anti-inflammatory mechanism that prevents or reduces mucositis. Hussain et al. (2019) found a similar benefit in acute myeloid leukemia patients receiving chemotherapy, with lower IL-6 but no difference in TNF-α. The discordant TNF-α findings suggest that the cytokine data are not robust. These trials originated from the same research group and setting, used the same comparator, and were open-label, so they cannot be regarded as independent replications, and the patient-reported outcomes are exposed to performance and detection bias. Magic mouthwash is widely used empirically but has no well-established efficacy, so the apparent superiority of NS may partly reflect a weak control. Even so, OM showed the most consistent direction of effect across outcomes and settings.

NS in oral lichen planus

Kumar et al. (2024) found that 75% NS cream was comparable to clobetasol gel for burning sensation and lesion size, and Pakfetrat et al. (2024) found that a 10% NS mucoadhesive patch was at least as effective as a triamcinolone patch, with NS better at isolated time points. Both groups of authors suggested NS as an effective alternative to corticosteroids, possibly with fewer local complications, since candidiasis occurred only in the clobetasol arm of the former trial. This interpretation needs caution. The comparisons were against active drugs without a placebo arm, the pilot study was very small, the between-arm differences at isolated time points were not corrected for multiple testing, nystatin was given to both arms in the pilot study (which may mask any difference in candidiasis), the formulations and concentrations were very different, and neither trial reported recurrence, a central issue in a relapsing disease.

Safety

Safety reporting was inconsistent. Some trials explicitly reported no adverse events, while others did not assess them, and the absence of reported events was therefore not interpreted as evidence of safety. Reported events were mild and similar between arms: bitter taste, oral burning, dyspepsia, cough, and difficulties with patch adherence. In the 12-month BD trial

(Kavandi et al. 2018), dyspepsia led to discontinuation in both arms. Candidiasis occurred only with clobetasol in one OLP trial (Kumar et al. 2024). No trial systematically examined allergic reactions, organ toxicity, or herb–drug interactions (Table 1).

Discussion

Main findings and strength of evidence

In 18 trials covering eight oral conditions, the clinical signal for NS depended more on the lesion type and the mode of delivery than on the plant itself. Topical NS in short-course, self-limiting inflammatory or ulcerative lesions (OM, RAS, dry socket, and OLP) was superior or non-inferior to the comparators in most trials. In OSMF and gingivitis it was only equivalent to active controls, and in periodontitis, and as an oral supplement in systemic BD, it showed no added benefit. "Comparable to standard therapy" was the commonest finding, but without placebo arms, prespecified non-inferiority margins, and adequate power, this does not show that NS works; it is equally compatible with all treatments being similarly ineffective beyond natural healing. The low or very low certainty of evidence therefore does not support recommending NS as established therapy for any of the conditions reviewed.

Mechanistic plausibility versus clinical evidence

The pharmacology of NS gives a coherent rationale. TQ inhibits pro-inflammatory mediators and cytokines (Shaterzadeh-Yazdi et al. 2018), reduces reactive oxygen species (Alberts et al. 2024), exerts analgesic effects through nitric oxide and K+ATP-channel pathways independent of opioid receptors (Ghannadi et al. 2005), is active against periodontal pathogens such as *Porphyromonas gingivalis in vitro* (Waris et al. 2017), and limits fibrosis by regulating epithelial-to-mesenchymal transition (Nordin et al. 2019). The trial data support these mechanisms only partly. The fall in IL-6 in OM and gingivitis agrees with an anti-inflammatory action, and the early pain relief in dry socket, OM, and OLP fits the analgesic profile. By contrast, TNF-α was discordant between mucositis trials, IL-1β and MMP-8 did not change in periodontitis, antioxidant markers in BD did not differ from placebo, and SOD did not normalize in OSMF. Furthermore, the superior antibacterial effect of CHX despite similar clinical indices in gingivitis suggests that any benefit of NS is more likely anti-inflammatory and analgesic than antimicrobial. These observations are hypothesis-generating, because biomarkers were secondary outcomes, were measured in saliva or crevicular fluid with different assays, and were often underpowered.

Condition-specific interpretation

Dry socket, RAS, OM, OLP, and BD ulcers are painful, short-lived or relapsing inflammatory lesions in which a topical agent stays in contact with the lesion and pain relief is a principal endpoint, which is probably why NS appeared most promising there. The same features, however, favor bias: pain and ulcer scores are subjective, ulcers heal spontaneously, and the characteristic odor and taste of NS oil probably compromised blinding even in trials described as blinded. In dry socket, which is a frequent complication of third-molar extraction (Dryla et al. 2022), a low-cost analgesic dressing is clinically attractive, but its benefit over eugenol- or Alvogyl-type dressings, and over standard chlorhexidine irrigation, requires blinded confirmation. The OM trials show the most consistent benefit (Freitas et al. 2012; Sardaro et al. 2019), but the lack of independence among them and the weak comparator limit this finding.

In OLP, a chronic T-cell-mediated disease with a relapsing course (Lavanya et al. 2011; Gururaj et al. 2021), similar performance to potent corticosteroids is clinically relevant, and the immunomodulatory activity of NS

(Darakhshan et al. 2015; Ciesielska-Figlon et al. 2023) offers biological plausibility. Isolated time-point differences in a small pilot and the absence of recurrence data do not, however, allow claims of superiority or a steroid-sparing effect. In RAS, in which oxidative stress is implicated (Estornut et al. 2024), the only study is non-randomized and cannot support conclusions. In OSMF, improvements in mouth opening and symptoms over 3 months say little about disease progression or malignant transformation, and the co-intervention of physiotherapy and the different routes of administration weaken inference.

In periodontitis, the null findings are biologically plausible because a rinse barely penetrates periodontal pockets, and the same patients improved after non-surgical therapy regardless of the rinse; the antibacterial activity of NS (Waris et al. 2017; Ismail et al. 2022) and the encouraging results with TQ chips (Al-Bayaty et al. 2013) suggest that sustained local delivery would be a better strategy. In BD, a multisystem vasculitis (Marshall 2004), oral NS at 1000 mg/day did not affect disease activity or biomarkers, whereas topical NS accelerated ulcer healing in a single trial. This divergence suggests that local concentration, rather than systemic exposure, drives any benefit, and that oral NS should not be expected to replace standard systemic therapy.

Heterogeneity of NS preparations

Preparations ranged from cold-pressed oil, aqueous and ethanolic extracts, and powder to capsules, creams, and mucoadhesive patches, at concentrations from 10% to 100%, and for durations from a single application to 12 months. TQ content, seed origin, extraction method, and stability were not reported, and only one trial compared more than one concentration. Without standardization, results cannot be compared across trials, and negative trials cannot be distinguished from under-dosed preparations.

Methodological limitations of the evidence base

Most trials had small arms, no formal sample-size calculation, and active comparators. Statistical handling was often inadequate: within-group tests were presented as evidence of effect, paired (split-mouth) and repeated measurements were not appropriately modeled, and multiple time points were tested without correction. Several trials came from the same research groups, regions, and local journals, and some reports overlapped. Publication bias is probable because small positive trials predominate, although it could not be tested, and cultural expectations of NS may inflate subjective outcomes in settings where it is traditionally used.

Safety

The available data do not allow the conclusion that NS is safe. Adverse-event reporting was inconsistent, follow-up rarely exceeded a few weeks, and allergic reactions, organ toxicity, and herb–drug interactions were not systematically assessed. The reported events were mild and balanced between arms, and the absence of candidiasis with NS in OLP is a potential advantage over corticosteroids that should be evaluated deliberately.

Implications and future research

At present, NS can be regarded as an investigational, low-cost adjunct for short-term topical symptom relief in dry socket, OM, and OLP, to be used within trials or under supervision rather than as a substitute for standard therapy; it should not be used for periodontitis or to control systemic BD. Future research should prioritize (i) multicenter, placebo- or vehicle-controlled, adequately powered trials with allocation concealment and blinded assessors (including masking of taste and odor); (ii) standardized, TQ-quantified preparations and dose-finding; (iii) prespecified non-inferiority margins when NS is benchmarked against corticosteroids or

CHX; (iv) core outcome sets that include patient-reported pain, function, quality of life, recurrence, and long-term follow-up; (v) validated biomarker panels analyzed according to prespecified plans; and (vi) trial registration and systematic adverse-event reporting.

Strengths and limitations of this review

The strengths of this review are prospective registration, a multi-database search, independent duplicate screening, extraction, and risk-of-bias assessment. Its limitations are the narrative synthesis without meta-analysis, restriction to English and Persian publications, the small number of trials per condition, possible overlap of participants across reports, and the grouping of eight conditions within one intervention-centered review. Conclusions therefore apply to each condition separately and should not be generalized to "oral lesions" as a single clinical entity.

The current evidence suggests that NS may have condition-specific therapeutic potential, most consistently as a topical agent for symptom relief in dry socket, OM, and OLP, with equivalence to active comparators in OSMF and gingivitis and tentative support in RAS. No benefit was shown in periodontitis or for oral NS in systemic BD. However, the evidence derives from small trials with methodological limitations and heterogeneous interventions and outcomes, and NS should not be described as established, universally effective, or safer than conventional therapies. Future trials should use standardized NS preparations, placebo or clinically relevant comparators, adequate sample sizes, appropriate handling of paired and repeated measurements, transparent adverse-event assessment, and prespecified protocols.

Acknowledgment

The researchers hereby appreciate the assistance and financial support provided by the Research Department of Tabriz University of Medical Sciences**.**

Conflicts of interest

The authors declare no conflicts of interest.

Funding

This article was financially supported by the Vice Chancellor for Research and Technology, (Grant no: 75812). We would like to appreciate their financial support.

Ethical Considerations

This study was approved by the regional Ethics Committee (IR.TBZMED.DENTISTRY.REC.1404.024). The protocol of the study was recorded in the PROSPERO (CRD420251148737).

Code of Ethics

IR.TBZMED.DENTISTRY.REC.1404.024

Authors' Contributions

M.H.S and L.D contributed to the conceptualization, formal analysis, methodology, project administration, resources, and manuscript writing. F.J and V.T contributed to the conceptualization, Data curation, visualization, supervision, and revising of the manuscript. S.B contributed to the conceptualization, data curation, investigation, and manuscript writing. A.F.Kh contributed to conceptualization, formal analysis, validation, and manuscript revision. All authors approved the final draft of the article.

Abbreviations

AE, adverse events; AML, acute myeloid leukemia; AUC, area under the curve; BD, Behçet's disease; BDCAF, Behçet's Disease Current Activity Form; BID, twice daily; BOP, bleeding on probing; BS, burning sensation; CAL, clinical attachment loss; CFU, colony-forming units; CHX, chlorhexidine; CRT, chemoradiotherapy; GI, gingival index; GCF, gingival

crevicular fluid; HNC, head and neck cancer; hs-CRP, high-sensitivity C-reactive protein; IBDDAM, Iranian Behçet's Disease Dynamic Activity Measure; IL, interleukin; IIMO, interincisal mouth opening; MDA, malondialdehyde; MMP-8, matrix metalloproteinase-8; MO, mouth opening; NCI, National Cancer Institute; NR, not reported; NRS, numeric rating scale; NS, Nigella sativa; OCMI, Oral Clinical Manifestation Index; OLP, oral lichen planus; OM, oral mucositis; OMAS, Oral Mucositis Assessment Scale; OSMF, oral submucous fibrosis; PI, plaque index; PICOS, Population, Intervention, Comparison, Outcomes, and Study design; PL, placebo; PPD, probing pocket depth; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RAS, recurrent aphthous stomatitis; RCT, randomized controlled trial; ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions; RoB 2, Risk of Bias 2; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SOD, superoxide dismutase; SRP, scaling and root planing; TAC, total antioxidant capacity; TBP, turmeric–black pepper; TIAI, Total Inflammatory Activity Index; TID, three times daily; TNF-α, tumor necrosis factor-alpha; TQ, thymoquinone; VAS, visual analog scale; WHO, World Health Organization.

References

Abdali SM (2009) Topical Nigella Sativa in the treatment of oro-genital ulceration in Behcet's disease. Mustansiria Dent. J. 6:366–370.

Ahmad A, Husain A, Mujeeb M, Khan SA, Najmi AK, Siddique NA, Damanhouri ZA, Anwar F (2013) A review on therapeutic potential of Nigella sativa: A miracle herb. Asian Pac. J. Trop. Biomed. 3:337–352.

Al-Bayaty FH, Kamaruddin AA, Ismail MA, Abdulla MA (2013) Formulation and evaluation of a new biodegradable periodontal chip containing thymoquinone in a chitosan base for the management of chronic periodontitis. J. Nanomater. 2013:397308.

Al-Mayahy MH, Marlow M, Scurr DJ (2019) The Complementary Role of ToF-SIMS in the Assessment of Imiquimod Permeated into the Skin from a Microemulsion Dosage Form. Al Mustansiriyah J. Pharm. Sci. 19:196–210.

Al-Niaimi AI, Sulaiman NA, Salim HA, Al-Taee FGA (2022) The validity of Salvadoria persica and Nigella sativa in the treatment of dry socket. Rev. Esp. Cir. Oral Maxilofac. 44:100–104.

Al Dhaheri Y, Wali AF, Akbar I, Rasool S, Razmpoor M, Jabnoun S, Rashid S (2022) Nigella sativa, a cure for every disease: Phytochemistry, biological activities, and clinical trials, Black Seeds (Nigella Sativa). Elsevier, pp. 63–90.

Alabdullah M, Beit ZZK, Shehada A (2023) Comparative clinical study of the effect of Nigella sativa oil on soft tissue healing and inflammation reduction compared to Eugenol in the context of dry socket. Cureus 15.

Alberts A, Moldoveanu, E-T, Niculescu, A-G, Grumezescu AM (2024) Nigella sativa: A comprehensive review of its therapeutic potential, pharmacological properties, and clinical applications. Int. J. Mol. Sci. 25:13410.

Almuhayawi M (2023) Efficacy of Nigella sativa in Wound Healing. Indian J. Pharm. Sci. 85.

Ameen H, Mohammed MO, Ahmed KM, Ali R, Saeed KA, Hussain SA (2019) Anti-inflammatory effect of Nigella sativa oil on chemoradiation-induced oral mucositis in patients with head and neck cancers. Int. J. Curr. Pharm. Res. 11:58–64. a

Ameen HA, Mohammed MO, Ali RH, Ahmed KM, Hussain SA (2019) Nigella sativa oil for oral mucositis. Al Mustansiriyah J. Pharm. Sci. 19:54–67. b

Amin B, Hosseinzadeh H (2016) Black cumin (Nigella sativa) and its active constituent, thymoquinone: an overview on the analgesic and anti-inflammatory effects. Planta Med. 82:8–16.

Amizadeh S, Rashtchizadeh N, Khabbazi A, Ghorbanihaghjo A, Ebrahimi, A-A, Vatankhah, A-M, Mahdavi AM, Taghizadeh M (2020) Effect of Nigella sativa oil extracts on inflammatory and oxidative stress markers in Behcet's disease: A randomized, double-blind, placebo-controlled clinical trial. Avicenna J. Phytomed. 10:181.

Anil S, Al-Ghamdi HS (2006) The impact of periodontal infections on systemic diseases. Saudi Med. J. 27:767–776.

Batool H, Hosein M, Butt SA, Roghay SS, Ali A, Abidi F (2022) Nigella sativa in Comparison to Steroids in Managing Oral Submucous Fibrosis. Pak. J. Med. Dent. 11:44–49.

Belgaumi UI, Patil S, Gandhi JM, Shete AS (2020) The many therapeutic applications of Nigella sativa—a review of literature. J. Evol. Med. Dent. Sci. 9:2151–2158.

Chaimani A, Caldwell DM, Li T, Higgins JP, Salanti G (2019) Undertaking network meta-analyses. Cochrane handbook for systematic reviews of interventions, 285–320.

Chaimani A, Caldwell DM, Li T, Higgins JP, Salanti G (2019) Undertaking network meta-analyses. In: Cochrane handbook for systematic reviews of interventions. Wiley, pp 285–320.

Chu, S-C, Hsieh, Y-S, Yu, C-C, Lai, Y-Y, Chen, P-N (2014) Thymoquinone induces cell death in human squamous carcinoma cells via caspase activation-dependent apoptosis and LC3-II activation-dependent autophagy. PLoS One 9:e101579.

Ciesielska-Figlon K, Wojciechowicz K, Wardowska A, Lisowska KA (2023) The immunomodulatory effect of Nigella sativa. Antioxidants 12:1340.

CJ S, Shastry SP, Patil K, Doggalli N, Kumar N, Sharma S (2021) Herbal Therapy in Oral Submucous Fibrosis: A Short Review. Indian J. Forensic Med. Toxicol. 15.

Darakhshan S, Pour AB, Colagar AH, Sisakhtnezhad S (2015) Thymoquinone and its therapeutic potentials. Pharmacol. Res. 95:138–158.

Dryla A, Szymoniuk M, Rogatko K, Piecewicz-Szczęsna H (2022) Alveolar osteitis: the current state of knowledge. J. Educ. Health Sport 12:204–216.

Estornut C, Rinaldi G, Carceller MC, Estornut S, Pérez-Leal M (2024) Systemic and local effect of oxidative stress on recurrent aphthous stomatitis: systematic review. J. Mol. Med. 102:453–463.

Freitas APF, Bitencourt FS, Brito GAC, de Alencar NMN, Ribeiro RA, Lima-Júnior RCP, Ramos MV, Vale ML (2012) Protein fraction of Calotropis procera latex protects against 5-fluorouracil-induced oral mucositis associated with downregulation of pivotal pro-inflammatory mediators. Naunyn Schmiedebergs Arch. Pharmacol. 385:981–990.

Ghannadi A, Hajhashemi V, Jafarabadi H (2005) An investigation of the analgesic and anti-inflammatory effects of Nigella sativa seed polyphenols. J. Med. Food 8:488–493.

Gholamnezhad Z, Safarian B, Esparham A, Mirzaei M, Esmaeilzadeh M, Boskabady MH (2022) The modulatory effects of exercise on lipopolysaccharide-induced lung inflammation and injury: A systemic review. Life Sci. 293:120306. https://doi.org/10.1016/j.lfs.2022.120306.

Gururaj N, Hasinidevi P, Janani V, Divynadaniel T (2021) Diagnosis and management of oral lichen planus–Review. J. Oral Maxillofac. Pathol. 25:383–393.

Hassan G, Ghafoor BS, Atif S, Chaudhry S (2021) Non-Surgical Periodontal Therapy Improves Clinical Outcomes in Patients with Chronic Periodontitis Independent of the Use of Nigella Sativa Oil or Normal Saline Mouthwash; Randomized Controlled Trial. JPDA 30.

Hassan G, Ghafoor S, Chaudhry S, Khan ZA (2020a) Effect of Nigella Sativa (Kalonji) Oil Based Mouth Wash on Salivary Matrix Metalloproteinase-8 Levels in Patients with Chronic Periodontitis. A Randomized Controlled Trial. Biomedica 36.

Hassan G, Ghafoor S, Chaudhry S, Khan ZA (2020b) Salivary Interleukin-1 Levels in Chronic Periodontitis Patients after use of Nigella Sativa (Kalonji) Oil. J. Pak. Dent. Assoc. 29.

Higgins JP, Morgan RL, Rooney AA, Taylor KW, Thayer KA, Silva RA, Lemeris C, Akl EA, Bateson TF, Berkman ND (2024) A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). Environ. Int. 186:108602.

Hussain SA, Mohammed Ameen HA, Mohammed MO, Ahmed KM, Hama-Gareb Ali R, Safar BM, Saeed KA (2019) Nigella sativa oil mouth rinse improves chemotherapy-induced oral mucositis in patients with acute myeloid leukemia. Biomed. Res. Int. 2019:3619357.

Ilangovan S, Rajasekar A (2021) Evaluation of Efficacy of 20% Nigella sativa on Gingival Health. environment 8:9.

Ismail NFA, Rostam MA, Jais MFM, Shafri MAM, Ismail AF, Arzmi MH (2022) exploring the potential of Nigella sativa for tooth mineralization and periodontitis treatment and its additive effect with doxycycline. IIUM J. Orofac. Health Sci. 3:136–146.

Kadarullah O, Tamtomo DG, Wasita B, Setiamika M, Prayitno A, Widyaningsih V, Soetrisno S (2024) Cisplatin-Induced Oral Mucositis Prevention: Nigella sativa's Anti-Inflammatory Role through NFκB Pathway. Trends Sci. 21:8105.

Kavandi H, Hajialilo M, Khabbazi A (2018) Efficacy of Nigella sativa seeds oil in patients with Behcet's disease: a double-blind randomized controlled trial. Avicenna J. Phytomed. 8:498.

Khan ZA, Prabhu N, Ahmed N, Lal A, Issrani R, Maqsood A, Vohra F, Alam MK (2022) A Comparative Study on Alvogyl and a Mixture of Black Seed Oil and Powder for Alveolar Osteitis: A Randomized Double-Blind Controlled Clinical Trial. Int. J. Clin. Pract. 2022:7756226.

Kohandel Z, Farkhondeh T, Aschner M, Samarghandian S (2021) Anti-inflammatory effects of thymoquinone and its protective effects against several diseases. Biomed. Pharmacother. 138:111492.

Kumar S L, Naik Z, Panwar A, M S, Keluskar V, Kumar RS (2024) Comparative evaluation of the efficacy of Nigella sativa (75% v/v) cream and clobetasol propionate (0.05% w/w) gel in oral lichen planus—a double-blinded randomized control trial. Oral Maxillofac. Surg. 28:225–234.

Lalla RV, Brennan MT, Gordon SM, Sonis ST, Rosenthal DI, Keefe DM (2019) Oral mucositis due to high-dose chemotherapy and/or head and neck radiation therapy. JNCI Monogr. 2019, lgz011.

Lavanya N, Jayanthi P, Rao UK, Ranganathan K (2011) Oral lichen planus: An update on pathogenesis and treatment. J. Oral Maxillofac. Pathol. 15:127–132.

Mamun M, Absar N (2018) Major nutritional compositions of black cumin seeds–cultivated in Bangladesh and the physicochemical characteristics of its oil. Int. Food Res. J. 25:2634–2639.

Marshall SE (2004) Behçet's disease. Best Pract. Res. Clin. Rheumatol. 18:291–311.

Mekhemar M, Hassan Y, Dörfer C (2020) Nigella sativa and thymoquinone: A natural blessing for periodontal therapy. Antioxidants 9:1260.

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group, P-P (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4:1.

Nishad SR, Narwade SS, Naik PR, Patil VP (2025) Nature's Shield for Oral Ulcer Management: A Comprehensive Review. Res. J. Pharmacogn. Phytochem. 17:49–55.

Nordin A, Kamal H, Yazid MD, Saim A, Idrus R (2019) Effect of Nigella sativa and its bioactive compound on type 2 epithelial to mesenchymal transition: A systematic review. BMC Complement. Altern. Med. 19:290.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372.

Pakfetrat A, Delavarian Z, Malakooti M, Bagheri H, Esmaily H, Ghorbani M, Saeedi P (2024) Comparing the efficacy of a novel mucoadhesive patch containing Nigella sativa 10% with triamcinolone 0.1% in patients with erosive-atrophic oral lichen planus: A pilot study. Clin. Exp. Dent. Res. 10:e886.

Passi D, Bhanot P, Kacker D, Chahal D, Atri M, Panwar Y (2017) Oral submucous fibrosis: Newer proposed classification with critical updates in pathogenesis and management strategies. Natl. J. Maxillofac. Surg. 8:89–94.

Pipalia PR, Annigeri RG, Mehta R (2016) Clinicobiochemical evaluation of turmeric with black pepper and nigella sativa in management of oral submucous fibrosis-a double-blind, randomized preliminary study. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 122:705–712.

Pipalia PR, Annigeri RG, Mehta R (2016) Clinicobiochemical evaluation of turmeric with black pepper and Nigella sativa in management of oral submucous fibrosis—a double-blind, randomized preliminary study. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 122:705–712.

Rahman I, Mohammed A, AlSheddi MA, Algazlan A, Alwably A, Hebbal M, Omar MG (2023) Nigella sativa oil as a treatment for gingivitis: A randomized active–control trial. Asian Pac. J. Trop. Med. 16:129–138.

Sallehuddin N, Nordin A, Bt Hj Idrus R, Fauzi MB (2020) Nigella sativa and its active compound, thymoquinone, accelerate wound healing in an in vivo animal model: a comprehensive review. Int. J. Environ. Res. Public Health 17:4160.

Samara MA, Hadi NA, Ali AF, Waiz MM, Hayani RK (2006) A placebo control study of the effect of Nigella sativa fixed oil on the healing rate of recurrent aphthous ulceration. J. Fac. Med. Baghdad 48:168–171

Sardaro N, Della Vella F, Incalza MA, Di Stasio D, Lucchese A, Contaldo M, Laudadio C, Petruzzi M (2019) Oxidative stress and oral mucosal diseases: An overview. In Vivo 33:289–296.

Shah R, Gayathri G, Mehta DS (2015) Application of herbal products in management of periodontal diseases: A mini review. Int. J. Oral Health Sci. 5:38–44.

Shaikh SH, Qazi MA (2025) The Environmental-Clinical Nexus: How Agricultural Fungicide Use is Driving the Antifungal Resistance Crisis and the Race for Novel Solutions. Precis. Med. Health J. 1:1–15.

Shaterzadeh-Yazdi H, Noorbakhsh, M-F, Hayati F, Samarghandian S, Farkhondeh T (2018) Immunomodulatory and anti-inflammatory effects of thymoquinone. Cardiovasc. Hematol. Disord. Drug Targets 18:52–60.

Singh V, Gupta A, Verma UP, Mishra T, Pal M (2019) An evaluation of the efficacy of ethanolic extract of Nigella sativa L.(Kalonji) on the clinical parameters of moderate-to-severe gingivitis: a split-mouth clinical study. AYU (Int. Q. J. Res. Ayurveda) 40:152–158.

Slots J (2002) Selection of antimicrobial agents in periodontal therapy. J. Periodontal Res. 37:389–398.

Sneha D, Magesh K, Sivachandran A, Sathya Kumar M (2021) Use of medicinal plants in oral lesions. Int. J. Curr. Res. Rev. 13:42–46.

Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ, 366.

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ, 355.

Talebi M, Talebi M, Farkhondeh T, Samarghandian S (2021) Biological and therapeutic activities of thymoquinone: Focus on the Nrf2 signaling pathway. Phytother. Res. 35:1739–1753.

Triantos D (2005) Intra-oral findings and general health conditions among institutionalized and non-institutionalized elderly in Greece. J. Oral Pathol. Med. 34:577–582.

Waris K, Saleem S, Arshad MU, Iqbal J (2017) A novel complementary alternative medicine: An In-Vitro evaluation of efficacy of Nigella sativa extract as an antibacterial agent against Porphyromonas gingivalis. Ann. Punjab Med. Coll. 11:247–251.

Workentin M, Castro Arteaga M, Alamgir A, Kupka CF (2022) PRISMA statement and Cochrane reviews: Striving to improve quality and validity of systematic reviews.

Yimer EM, Tuem KB, Karim A, Ur-Rehman N, Anwar F (2019) Nigella sativa L.(black cumin): a promising natural remedy for wide range of illnesses. Evid. Based Complement. Alternat. Med. 2019:1528635.