The Impact of Nigella sativa on Oral Health: A Scoping Review

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***Abstract*—Introduction: Nigella sativa (NS) has been shown to improve periodontal health by reducing alveolar bone resorption and lowering periodontal indices and subgingival bacterial counts. However, public health and safety concerns are emerging, and there have been a few reported adverse effects associated with the use of NS. Thus, the current study aims to review clinical studies on the effectiveness NS for oral health conditions.**

Methods: The databases PubMed and Google Scholar were used to search the literature; the year of publication was not restricted in the search. Studies conducted in animal models in laboratories, as well as those involving an intervention of NS in combination with other herbs, were excluded.

Results: A total of thirteen human clinical studies that used NS as an intervention for treating different types of oral health conditions were included in this review. Improvement in clinical parameters was reported in all the included studies, although the statistical significance varied.

Conclusion: Although the studies show that NS is beneficial in the treatment and management of oral health conditions, there is still a need for more rigorous research in this area, particularly in the application of NS in real-world clinical settings.

***Index Terms*—Nigella sativa, Oral Health, Periodontal**

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I. INTRODUCTION

Worldwide, approximately 3.5 billion individuals suffer from oral diseases such as dental caries, periodontal disease, and oral cancers, which have profound implications on their health and quality of life (1, 2). Oral diseases are closely related to socioeconomic status, with a disproportionate impact observed among the poor and marginalised groups (2). Moreover, the current model of dentistry, which is high-technology and treatment-oriented, is unaffordable in many low- and middle-income countries (3).

The World Health Organization estimates that nearly 88% of all countries rely on different forms of traditional medicine, including herbal medicine, for the treatment of various ailments (4). The rise in popularity of herbal medicine is driven largely by its affordability, consonance with the patient's beliefs, and fewer side effects compared with modern synthetic medicines (5). Among the most commonly used herbal medicines globally is Nigella sativa (NS), a member of the Ranunculaceae family that grows annually in southwest Asia (6). This plant is also known as black cumin, black seed, and Habbatul- Barakah (7).

The Unani and Ayurvedic systems of medicine utilise this ancient herb extensively to treat an array of ailments, including headaches, nasal congestion, intestinal worms, conjunctivitis, and asthma (8, 9). The seeds are composed of 28-36% fixed oils, proteins, alkaloids, and saponins, and 0.4-2.5% essential oils (10). The key active ingredient of NS is thymoquinone (TQ), which promotes the action of CD8 T cells and displays a variety of biological effects such as anti-diabetic, anti-hypertensive, anticancer, antioxidant, hepatoprotective, neuroprotec, gastroprotective, immunomodulator, antimicrobial, anti-inflammatory, analgesic, and spasmolytic activities (11-13).

Specific to oral health, the application of TQ to oral tissues was found to control dental caries, retard the expansion of oral ulcers, induce bone formation in sockets of extracted teeth, promote apoptosis in human cancer cells, maintain pulp vitality, and stimulate healing and periodontal regeneration (10). Concerning the effect of NS on periodontal health, it has been shown to lessen alveolar bone resorption, and lower periodontal indices and sub-gingival bacterial counts (10).

Notwithstanding the benefits of herbal medicines, public health issues and safety concerns are also becoming evident in this regard (14), and there have been some reported adverse effects related to the use of NS. For instance, functional dyspeptic patients have reported nausea, bloating, and a burning sensation after taking NS oil, as well as a slight increase in liver and kidney enzyme markers after its consumption (15). This warrants the need for stringent clinical trials to assess the efficacy and safety of herbal medicinal products (16). Moreover, it is imperative to note that most of the studies related to the effects of NS on oral health have been conducted in animal models (17, 18). Recently, efforts have been made to study the effect of NS on human subjects; thus, the present study aims to review the clinical studies related to the effectiveness of using NS for oral health conditions.

II. MATERIALS AND METHODS

The literature was searched using the PubMed and Google Scholar databases based on PICO clinical questions. There was no restriction on the year of publication. The search terms used were “oral health”, “dental health”, “Nigella sativa”, “thymoquinone”, “gingivitis”, “periodontitis”, “caries”, and “pulp treatment”.

All human clinical studies published in the English language that assessed the effects of NS or TQ, in any form, on oral health conditions were included. Review articles, studies conducted in laboratories in animal models, and those that consisted of an intervention of NS in combination with other herbs were excluded. Articles without a full text were also excluded.

A total of 1372 articles were found. After eliminating duplication, titles and abstracts were screened following the study’s inclusion and exclusion criteria. Finally, 13 studies were included in this review. The complete process is outlined in the PRISMA flow diagram (**Figure 1**).

III. RESULTS

A total of 13 clinical studies were identified that used NS as an intervention to treat various oral health conditions (19-31). **Table 1** provides an overview of all these studies. The oral health conditions that were aimed to be treated included chronic periodontitis (22, 25-30), gingivitis (19, 23, 24), osseointegration of delayed implant (21), alveolar osteitis (31), and chemotherapy-induced oral mucositis (20).

Improvement in clinical parameters was reported in all the included studies, although the statistical significance varied. The majority of the articles identified dealt with periodontitis (n=7). Elamrousy (28) evaluated the clinical, immunological, and microbiological effectiveness of the local application of TQ gel in subjects with grade C periodontitis and found that at 8 weeks postoperative period, the treatment group showed a significant reduction in probing pocket depth, relative attachment level (RAL), matrix metallo-proteniease-8 (MMP-8) concentration in gingival crevicular fluid, and Aggregatibacter actinomycetemcomitans count in subgingival plaque samples when compared with the placebo group (all $p<0.05$). Al-Bayaty et al. (26) investigated the effectiveness of a periodontal chip containing TQ in a chitosan base for the management of chronic periodontitis and reported a statistically significant improvement in plaque index (PI) and bleeding on probing (BOP) in both the TQ group and the group receiving the plain chitosan chip ($p<0.05$). A significant decrease in periodontal pockets compared with baseline was observed in all three groups (TQ, chitosan, control). Regarding clinical attachment levels, the TQ group showed significantly greater improvement than the other groups ($p<0.05$). A study by Khalil and Alaaeldin (27) examined the effect of TQ gel on clinical periodontal parameters (PI, gingival index (GI), probing depth, and clinical attachment level) and reported a statistically significant improvement, compared with the baseline, in both group I,

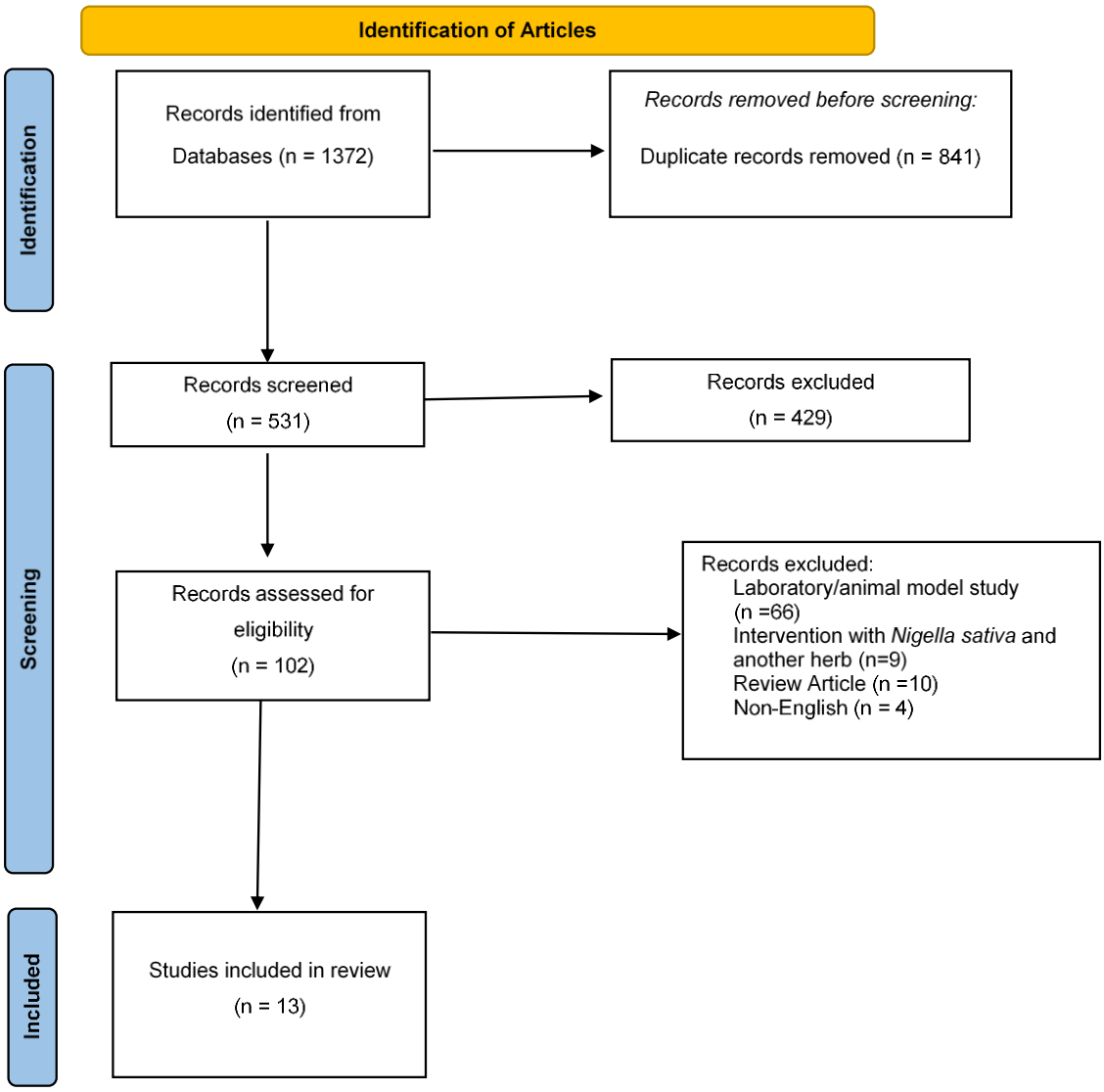

Figure. 1. PRISMA flow chart of included studies

(scaling and root planing (SRP) and TQ) and group II (SRP only) after weeks 4 and 12 ($p<0.0001$). Although group I showed more clinical improvement than group II, the difference was not statistically significant. Regarding biochemical parameters, significant improvement in group I was identified after 4 weeks compared with group II. Hassan and coworkers published three studies on this subject (22, 29, 30). The first examined the level of salivary MMP-8, and reported that the mean concentration of salivary MMP-8 in the NS treatment group decreased from 199.37 ± 300.75 ng/l to 114.17 ±129.21 ng/l, although the reduction was statistically non-significant (22). The second article aimed to determine the change in salivary interleukin-1 β and found no significant change in the levels after the use of NS oil (30). The third study examined the effect of NS oil-based mouth-wash on clinical periodontal parameters such as periodontal pocket depth (PPD), clinical attachment loss (CAL), PI, and BOP, and reported a statistically significant difference in all the parameters, both in the NS oil mouthwash group and the control group, although the difference in improvement between the groups was not significant (29). Kapil et al. (25) reported a comparison between the treatment group that received 0.2% TQ along with SRP and the control group (SRP only). The former showed a significant reduction in PPD ($p=0.018$), GCF-ALP levels ($p=0.048$), and a rise in RAL ($p=0.018$) but no statistically significant differences were observed in PI and GI at 6 weeks.

Concerning the treatment of gingivitis, Singh et al. (19) Demonstrated that topically applied ethanolic solution of NS in the ratio of 3:1 significantly reduced GI ($p<0.001$; F value 153.75) and PI ($p<0.001$, F value 30.40). Treatment at a ratio of 1:3 and 1:1 did not show a significant reduction. Rahman et al. (23) reported that both NS oil and the gold standard chlorhexidine (CHX) significantly reduced GI and PI scores ($p<0.0001$), as well as significantly decreasing colony-forming units ($p<0.0001$). However, compared with CHX, NS is better at lowering gingival IL-6 ($p =0.0076$ vs $p=0.145$), while neither NS ($p=0.284$) nor CHX ($p=0.418$) reduced IL-18 levels. Similarly, Khan and Ahmad (24) also confirmed the clinical efficacy of a thymoquinone gel to significantly reduce PI in comparison to CHX ($p<0.001$) during the 0–14th day and 0–28th day, as well as to significantly lower GI ($p=0.005$) during the 0–14th day and the 0–28th day ($p<0.001$) as compared with CHX gel.

The impact of NS gel on the osseointegration of delayed dental implants was evaluated by Ahmed et al. (21), who reported that in both treatment and control groups, there was a non-significant difference in the modified gingival index and probing depth at 3 and 6 months follow up. However, the treatment group showed a highly significant increase in bone density after 6 months in comparison with the control group.

One study, carried out by Khan et al. (31), conducted a comparative evaluation of a NS powder and oil mixture with Alvogyl in the treatment of alveolar osteitis, or dry sockets, in patients who had undergone tooth extraction and reported that the NS treatment group showed a significant difference in pain relief compared with the Alvogyl group ($p=0.031$) and the control group that was given a normal saline rinse ($p=0.001$).

The effect of NS on chemotherapy-induced oral mucositis (OM) was studied by Hussain et al. (20) who reported that, compared with the control formula, NS oil mouth rinse significantly decreased erythema and ulceration scores (AUC of total OMAS=11.4 vs. 85.9, $p<0.001$). Moreover, it significantly reduced salivary IL-6 (AUC=7376 vs. 16599, $p<0.001$), while the changes in TNF-α levels were not significant (AUC=676.9 vs. 885.2, $p>0.05$).

All the included studies were limited in being short-term (ranging between 7 days to 6 months) and having small sample sizes (ranging between 12-60 participants). Double blinding was reported in only six studies (22, 23, 28-31), and only one study was multi-sited (25). One of the studies included only female participants (23) and another only male (26). Three studies reported a high loss of follow-up (22).

IV. DISCUSSION

The current review explored the potential impact of NS on oral health. Thirteen clinical studies involving human subjects were included. Generally speaking, all studies indicated a potentially beneficial effect of NS in reducing symptoms related to the different oral health conditions under investigation; however, the statistical significance of the effect varied.

A significant decrease in the gingival index and plaque index was reported in two studies related to the treatment of gingivitis (19, 23) and two studies related to the treatment of periodontitis (26, 27). However, one study reported no significant difference in PI and GI on treatment with TQ in patients with periodontitis (25). Thus, further clinical studies are required to examine the role of NS in reducing PI and GI.

Interleukin (IL)-6 levels were found to be significantly lowered in study participants with gingivitis (23) and chemotherapy-induced oral mucositis (20) on treatment with NS. This finding aligns with previous studies that established the anti-inflammatory property of TQ in hindering the production of IL 6 (32). Concerning IL-18, NS oil produced no significant reduction in gingival crevicular IL-18 levels in the clinical study by Rahman et al. (23). Since IL- 18 is known to have chemotactic, pro-inflammatory, and angiogenic properties, it may play a role in inflammation progression (33). Moreover, persistent gingival inflammation may be linked to IL- 18 accumulation in periodontal tissues (34). With regard to IL-1 β levels among patients with chronic periodontitis, no significant change in the levels of salivary IL-1 β in either the NS treatment group or the placebo group was reported by Hassan et al. (30). In contrast, Khalil and Alaaeldin (27) reported a significant reduction in IL-1 β levels from baseline to 4 weeks post-treatment (230.49± 24.73 (pg/µl) vs 153.26 ± 27.31 (pg/µl), respectively).

The use of NS oil for lowering chemotherapy-induced side effects such as oral mucositis in cancer patients has shown a significant reduction in erythema and ulceration scores ($p<0.001$) (20). This was confirmed earlier in an animal-model study that examined the effect of NS on cis-diamminedichloroplatinum (Cis) induced oral mucositis in rats (35). It was found that, compared with rats given only Cis (Group 1), rats fed Cis plus NS oil (Group 2) had less inflammatory cell infiltration, vascular dilatation, superficial erosion, and exudates. Additionally, Group 2 had similar results to the control groups (Groups 3 and 4). It was speculated that the anti-inflammatory, antioxidant and cytoprotective actions may be the mechanism by which NS oil prevents oral mucositis due to cisplatin-induced pro-inflammatory cytokines (35). Taken together, these findings underpin the potentially potent role of NS in preventing painful symptoms of chemotherapy-induced oral mucositis. Several recent studies have suggested a correlation between periodontitis and chronic systemic diseases such as type 2 diabetes mellitus and cardiovascular disease (36). Most of the clinical studies included in this review consisted of systemically healthy participants. Thus, the exact effect of NS in the treatment of periodontitis among patients with chronic conditions such as diabetes and cardiovascular disease remains unclear.

It is worth mentioning that all the clinical studies included in this review were generally short-duration studies and had small sample sizes. It is recommended that future studies in this direction include robust methodology in terms of long-term follow-up, large sample size, and double blinding.

In conclusion, this review summarises the currently available research regarding the effect of NS on oral health. Although, in general, the studies indicate the beneficial role of NS in the treatment and management of oral health conditions such as gingivitis, periodontitis, osseointegration of delayed implants, alveolar osteitis, and chemotherapy-induced oral mucositis, there remains a need for further vigorous studies in this area, particularly in relation to the application of NS in real-world clinical settings.

V. REFERENCES

1. Peres MA, Macpherson LMD, Weyant RJ, Daly B, Venturelli R, Mathur MR, et al. Oral diseases: a global public health challenge. The Lancet. 2019;394(10194):249-60.

2. Oral Health: Key Facts: World Health Organization [updated 15 March 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/oral-health.

3. Yee R, Sheiham A. The burden of restorative dental treatment for children in Third World countries. Int Dent J. 2002;52(1):1-9.

4. WHO Global Centre for Traditional Medicine. World Health Organization. [Available from: https://www.who.int/initiatives/who-global-centre-for-traditional-medicine.

5. Benzie IFF, Wachtel-Galor S, editors. Herbal

Medicine: Biomolecular and Clinical Aspects. 2nd ed. Boca Raton (FL): CRC Press/Taylor & Francis; 2011.

6. Kooti W, Hasanzadeh-Noohi Z, Sharafi-Ahvazi N, Asadi-Samani M, Ashtary-Larky D. Phytochemistry, pharmacology, and therapeutic uses of black seed (Nigella sativa). Chin J Nat Med. 2016;14(10):732-45.

7. Firenzuoli F, Gori L. Herbal medicine today: clinical and research issues. Evid Based Complement Alternat Med. 2007;4(Suppl 1):37-40.

8. Gaur S, Srivastava B, Gaur S, Bhardwaj R, Khanchandani R. Medicinal and therapeutically potential of Nigella sativa. International Journal of Medical and Biomedical Studies. 2017;1(5).

9. Boskabady MH, Mohsenpoor N, Takaloo L. Antiasthmatic effect of Nigella sativa in airways of asthmatic patients. Phytomedicine. 2010;17(10):707-13.

10. Al-Attass SA, Zahran FM, Turkistany SA. Nigella sativa and its active constituent thymoquinone in oral health. Saudi Med J. 2016;37(3):235-44.

11. Salem ML, Alenzi FQ, Attia WY. Thymoquinone, the active ingredient of Nigella sativa seeds, enhances survival and activity of antigen-specific CD8-positive T cells in vitro. Br J Biomed Sci. 2011;68(3):131-7.

12. Ahmad MF, Ahmad FA, Ashraf SA, Saad HH, Wahab S, Khan MI, et al. An updated knowledge of Black Seed (Nigella sativa Linn.): Review of phytochemical constituents and pharmacological properties. J Herb Med. 2021;25:100404.

13. Al Mofleh IA, Alhaider AA, Mossa JS, Al-Sohaibani MO, Al-Yahya MA, Rafatullah S, et al. Gastroprotective effect of an aqueous suspension of black cumin Nigella sativa on necrotising agents-induced gastric injury in experimental animals. Saudi J Gastroenterol. 2008;14(3):128-34.

14. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014;4:177.

15. Tavakkoli A, Mahdian V, Razavi BM, Hosseinzadeh H. Review on Clinical Trials of Black Seed (Nigella sativa) and Its Active Constituent, Thymoquinone. J Pharmacopuncture. 2017;20(3):179-93.

16. Parveen A, Parveen B, Parveen R, Ahmad S. Challenges and guidelines for clinical trial of herbal drugs. J Pharm Bioallied Sci. 2015;7(4):329-33.

17. Omar OM, Khattab NM, Khater DS. Nigella sativa oil as a pulp medicament for pulpotomized teeth: a histopathological evaluation. J Clin Pediatr Dent. 2012;36(4):335-41.

18. Setiawatie EM, Gani MA, Rahayu RP, Ulfah N, Kurnia S, Augustina EF, et al. Nigella sativa toothpaste promotes anti-inflammatory and anti-destructive effects in a rat model of periodontitis. Arch Oral Biol. 2022;137:105396.

19. Singh V, Gupta A, Verma UP, Mishra T, Pal M. 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. 2019;40(3):152-8.

20. Hussain SA, Mohammed Ameen HA, Mohammed MO, Ahmed KM, Hama-Gareb Ali R, Safar BM, et al. Nigella sativa Oil Mouth Rinse Improves Chemotherapy-Induced Oral Mucositis in Patients with Acute Myeloid Leukemia. BioMed Research International. 2019;2019:3619357.

21. Ahmed ZM, Attia MS, Mahmoud AM, Shoreibah EA. Evaluation of Topical Application of Nigella Sativa (Black Seeds) on Delayed Dental Implant. Al-Azhar Dental Journal for Girls. 2020;7(2- B):255-61.

22. Hassan G, Ghafoor S, Chaudhry S, Khan ZA. Effect of Nigella sativa (Kalonji) oil-based mouthwash on salivary matrix metalloproteinase-8 levels in patients with chronic periodontitis. A randomised controlled trial. Biomedica. 2020;36(3):285-90.

23. Rahman I, Mohammed A, AlShiddi M, Algazlan A, Alwably A, Hebbal M, et al. The Assessment of Nigella Sativa oil as a Therapeutic Aid for Gingivitis: A Randomised Clinical Trial. Research Square; 2022.

24. Khan SY, Ahmad I. Clinical Efficacy of a Novel Lipid-based Thymoquinone Gel: A Two-arm, Single-blinded, and Randomised Study. J Int Soc Prev Community Dent. 2021;11(4):376-81.

25. Kapil H, Suresh DK, Bathla SC, Arora KS. Assessment of clinical efficacy of locally delivered 0.2% Thymoquinone gel in the treatment of periodontitis. The Saudi Dental Journal. 2018;30(4):348-54.

26. Al-Bayaty FH, Kamaruddin AA, Ismail MA, Abdulla MA. Formulation and Evaluation of a New Biodegradable Periodontal Chip Containing Thymoquinone in a Chitosan Base for the Management of Chronic Periodontitis. Journal of Nanomaterials. 2013;2013:397308.

27. Khalil AA, Alaaeldin E. Clinical and Biochemical Evaluation of Thymoquinone Gel in the Treatment of Chronic Periodontitis. International Journal of Advanced Research. 2019;7(4):83-93.

28. Elamrousy W. Effect of locally delivered 0.2% Thymoquinone gel in subjects with Grade C Periodontitis: Clinical, Immunological and Microbiological Assessment. European Journal of Molecular & Clinical Medicine. 2018;5(1):89-101.

29. Hassan G, Ghafoor BS, Atif S, Chaudhry S. 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. 2021;30(02).

30. Hassan G, Ghafoor S, Chaudhry S, Khan ZA. Salivary Interleukin-1 Levels in Chronic Periodontitis Patients after use of Nigella Sativa (Kalonji) Oil. Journal of the Pakistan Dental Association. 2020;29(4).

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

32. Hossen MJ, Yang WS, Kim D, Aravinthan A, Kim JH, Cho JY. Thymoquinone: An IRAK1 inhibitor with in vivo and in vitro anti-inflammatory activities. Sci Rep. 2017;7:42995.

33. Johnson RB, Serio FG. Interleukin-18 concentrations and the pathogenesis of periodontal disease. J Periodontol. 2005;76(5):785-90.

34. Nair V, Bandyopadhyay P, Kundu D, Das S. Estimation of interleukin-18 in the gingival crevicular fluid and serum of Bengali population with periodontal health and disease. J Indian Soc Periodontol. 2016;20(3):260-4.

35. Eğilmez OK, Kökten N, Kalcıoğlu MT, Ekici AID, Şerifler S, Yeşilada E. Investigation of the Protective Effect of Nigella Sativa Oil in Cisplatin Induced Oral Mucositis: An Experimental Study. Turk Arch Otorhinolaryngol. 2020;58(1):10-5.

36. Seitz MW, Listl S, Bartols A, Schubert I, Blaschke K, Haux C, et al. Current Knowledge on Correlations Between Highly Prevalent Dental Conditions and Chronic Diseases: An Umbrella Review. Prev Chronic Dis. 2019;16:E132.

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Table 1. Human-based studies related to the impact of *Nigella sativa* on oral health

Author, Year	Study Design & Setting	Duration of Study	Patient Group	Aim/Outcome Measure	Methods	Key Findings	Clinical Significance
Elamrousy, 2018 (28)	Clinical study Kafrelsheikh, Egypt	8 weeks	26 subjects with grade C periodontitis	To evaluate the efficacy of local application of TQ gel. The parameters investigated included: probing pocket depth (PPD), relative attachment level (RAL), matrix metallo-proteinase-8 (MMP8) concentration in gingival crevicular fluid (GCF), and Aggregatibacter actinomycetemcomitans (A.a) count in subgingival plaque.	Random assignment of the involved sites to either the TQ group (30 sites) or the placebo group (30 sites). In the TQ group, sites were treated with SRP followed by 0.2% TQ topical (intra-pocket) gel, while in the placebo group sites were treated with SRP followed by a placebo topical (intra-pocket) gel.	At the 8-week evaluation point, the TQ group showed a significant decrease in PPD, RAL, MMP-8 levels in GCF, and A.a count in subgingival plaque samples when compared with the placebo group (all p values <0.05).	TQ gel shows favourable outcomes when used as an adjunct to nonsurgical periodontal therapy in subjects with grade C periodontitis.
Al-Bayaty et al., 2013 (26)	Randomised single-blind split-mouth study Shah Alam, Selangor, Malaysia	2 months	12 male patients with chronic periodontitis	To evaluate the effectiveness of a biodegradable periodontal chip containing TQ for managing chronic periodontitis. Clinical parameters recorded on day 0 and day 60 were: plaque index (PI), bleeding on probing (BOP), clinical probing pocket depth (PPD) and clinical attachment level (CAL).	At day 0, all patients were treated with full-mouth scaling and root planing (SRP). Periodontal pockets were divided into three groups: Group I consisted of 60 sites and received SRP alone (control group). Group II: 60 sites; received plain chitosan chips. Group III: 60 sites; received chips containing TQ.	Significant improvement in PI and BOP and a reduction in periodontal pockets from baseline were observed in all three groups ($p<0.05$). Gains in CAL were significantly higher ($p<0.005$) in the group receiving TQ chips compared with other groups.	Periodontal chips containing TQ can be used as an adjunct to conventional SRP in the management of chronic periodontitis.
Khalil and Alaaeldin, 2019 (27)	Clinical study Minia, Egypt	12 weeks	68 subjects (including 48 with	To investigate the effect of TQ gel on PI, GI, probing depth (PD), and	Group I (24 patients) received non-surgical periodontal therapy and	When compared with the baseline, a statistically significant improvement in	Adjunctive use of TQ gel showed significant improvement in biochemical parameters after 4

			moderate to severe chronic periodontitis)	clinical attachment level (CAL), as well as the level of IL-1β and total antioxidant capacity levels in the gingival crevicular fluid.	TQ gel (0.1 % w/w). Group II (24 patients) received only non-surgical periodontal therapy. Group III were 20 healthy subjects (control group). The clinical parameters were recorded at baseline (before treatment) and at weeks 4 and 12 after treatment.	clinical parameters was found in both Group I and Group II after weeks 4 and 12 ($p<0.0001$). Although Group I showed more clinical improvement than Group II, the difference was not statistically significant. Regarding biochemical parameters, significant improvement in Group I was noted at 4 weeks as compared with group II.	weeks of treatment compared with single non-surgical periodontal therapy.
Hassan et al., 2020 (22)	Randomised controlled trial Lahore, Pakistan	2 weeks	40 patients with chronic periodontitis	To explore salivary matrix metalloproteinase-8 (MMP-8) levels after NS oil-based mouthwash compared with placebo (normal saline) after non-surgical periodontal therapy.	The treatment group received NS oil and the control group received simple normal saline. Salivary samples for MMP-8 levels were collected once before non-surgical periodontal therapy and again after 2 weeks of rinsing.	The mean concentration of salivary MMP-8 in the NS group decreased from 199.37 ± 300.75 ng/l to 114.17 ± 129.21 ng/l, while in the normal saline group, it decreased from 195.29 ± 175.89 ng/l to 147.35 ± 144.9 ng/l. This reduction was statistically non-significant both within and between the study groups.	MMP-8 levels in patients with chronic periodontitis were slightly decreased with NS oil-based mouthwash after non-surgical periodontal therapy, but this decrease was not statistically significant.
Hassan et al., 2020 (30)	Parallel-arm triple-blind placebo-based randomised clinical trial Lahore, Pakistan	2 weeks	40 patients with chronic periodontitis	To determine the change in salivary interleukin (IL)-1β levels after the use of NS oil.	Patients in the control group were given normal saline (placebo), while those in the intervention group received NS oil. All participants underwent scaling and root planing before the start of the trial. Salivary samples were collected on day 0 and day 15 and IL-1β levels were examined using ELISA.	No statistically significant change was found in the salivary IL-1β levels, either in the control or the treatment group.	Treatment with NS oil in chronic periodontitis patients following scaling and root planing showed no significant change in before and after IL-1β levels.
Hassan et al., 2021 (29)	Parallel-arm randomised controlled trial Lahore,	2 weeks	40 patients with chronic periodontitis	To analyse the effects of NS oil mouthwash after non-surgical therapy. The parameters evaluated include: periodontal	Both the control group and the treatment group underwent scaling and root planing, and were given a mouthwash of	A statistically significant difference was found in the pre-treatment and post-treatment values of PI, CAL, PPD and BOP, in both the groups. The	PI, CAL, PPD and BOP parameters improved following non-surgical periodontal therapy in both the group using NS oil-based mouthwash and that using

	Pakistan			pocket depth (PPD), clinical attachment loss (CAL), PI, BOP.	either normal saline solution or NS oil, respectively, to be used daily for 2 weeks.	difference in improvement between the treatment and control groups was not statistically significant.	normal saline-based mouthwash. Thus, both types of mouthwash showed a beneficial effect.
Kapil et al., 2019 (25)	Clinical study India	6 weeks	40 subjects with chronic periodontitis	To evaluate the benefit of local application of TQ gel as an adjunctive to scaling and root planing (SRP) in subjects with chronic periodontitis. Clinical parameters recorded were: plaque index (PI), gingival index (GI), probing pocket depth (PPD), and relative attachment level (RAL).	Subjects in Group I were administered with 0.2% TQ along with SRP, while the control (Group II) consisted of subjects who only received SRP.	There was a significantly high reduction in PI, GI, PPD, gain in RAL, and GCF ALP ($p=0.001$) in both the groups at 6 weeks from baseline. In a comparison between Group I and Group II, the former showed a significant reduction in PPD, GCF-ALP levels and rise in RAL, but no statistically significant differences were observed in PI and GI at 6 weeks.	Using 0.2% TQ intracrevicularly as an adjunct to SRP could be beneficial in treating chronic periodontitis.
Singh et al., 2019 (19)	Split-mouth clinical study Lucknow, India	28 days	24 patients with moderate to severe gingivitis	To explore the clinical efficacy of different ethanolic solutions of NS in moderate-to-severe gingivitis patients. The clinical parameters, i.e., gingival index (GI) and plaque index (PI), were recorded at baseline, 14 days, and 28 days in all the individuals.	Individuals were divided into group I_1, group II_1 and group III_1 (scaling and root planing; i.e., control) and group I_2, group II_2 and group III_2 (experimental). Three doses of solution 1 (1:3), solution 2 (1:1), and solution 3 (3:1) were administered to the experimental groups for 3 consecutive days.	Intergroup comparison of GI showed a significant difference on the 14th and 28th day from baseline between I_1 & I_2, at only the 28th day between II_1 & II_2, and a non-significant difference between III_1 & III_2 at all time intervals from baseline. On intragroup comparison, a significant reduction in GI was found in all groups from baseline until 28 days, but among the experimental groups, the best result was seen in group III_2 ($p<0.001$; F value 153.75). Regarding the PI, comparison between different groups showed significant differences from baseline to the 14th and 28th days between all groups; i.e, I_1 & I_2, II_1 & II_2, and III_1 & III_2. On intragroup comparison, a significant reduction in PI was noted in all	The NS extract showed better wound healing potential, and can be used in conjunction with scaling and root planing and during periodontal flap surgery procedures to speed up periodontal wound healing.

						control groups; i.e, I_1, II_1 & III_1, but among the experimental groups, only group III_2 showed a significant reduction ($p<0.001$, F value 30.40).	
Rahman et al., 2022 *(Preprint)* (23)	Double-blind randomised clinical trial Riyadh, Saudi Arabia	2 weeks	40 systemically healthy participants, aged between 20 to 40 years, with chronic generalised gingivitis	To investigate the clinical anti-inflammatory and antimicrobial efficacy of NS oil compared with chlorhexidine (CHX) in patients with gingivitis. Primary outcomes were gingival and plaque indices and levels of gingival crevicular IL-6 and IL-18. Secondary outcomes were overall bacterial load and assessment of alpha-haemolytic plaque-causing bacteria.	Patients were randomly assigned to Group 1: NS oil (n = 18), or Group 2: CHX (n = 19).	Both CHX and NS reduced PI and GI scores ($p<0.0001$). NS was better than CHX ($p=0.145$) at reducing gingival IL-6 ($p= 0.0076$). Neither NS ($p=0.284$) nor CHX ($p=0.418$) reduced IL-18 levels. There was no difference in post-intervention PI and GI scores and inflammatory cytokine levels between treatments. Both NS and CHX caused a significant reduction in CFU ($p<0.0001$) and a reduction in pathogenic bacteria *S. mitis*, *S. oralis*, *S. sanguinis*, and *S. parasanguinis* in 50% of CHX patients ($p=0.1031$) and 20% of NS patients ($p= 0.7395$).	There were clinically comparable results between NS oil and CHX for reducing gingival and plaque indices and lowering antimicrobial resistance. Clinicians can consider NS oil as a natural antimicrobial and anti-inflammatory mouthwash alternative without artificial flavours, colours, or preservatives.
Khan and Ahmad, 2021 (24)	Randomised clinical trial Aligarh, India	28 days	60 children with gingivitis	To evaluate the clinical efficacy of topical 0.1% lipid-based thymoquinone (TQ) gel as an anti-plaque and anti-gingivitis agent. Clinical parameters recorded included the plaque index and the gingival index.	Group A (n=30) applied a peanut-sized amount of CHX gel, twice a day for 2 minutes. Group B (n=30) did the same, but with a 0.1% lipid-based TQ gel.	The TQ significantly reduced the PI as compared with CHX ($p<0.001$) from day 0–14 and day 0–28. Moreover, it produced a significant reduction in gingival index ($p=0.005$) from day 0–14 and day 0–28 ($p<0.001$), as compared with CHX gel.	It may be possible to consider TQ-based gels as alternatives to CHX gels.
Ahmed et al., 2020 (21)	Randomised clinical trial Cairo, Egypt	6 months	12 healthy patients with delayed implant insertion	To evaluate the effect of topically applied NS on osseointegration of delayed dental implants. Modified gingival index (MGI), probing depth (PD), and cone beam computed tomography	The test group applied topical NS gel after preparation of the osteotomy site and before implant placement, while the control group did not.	A non-statistically significant difference was recorded in clinical parameters (MGI, PD) after three and six months of follow-up in both groups. The test group showed a highly significant increase in bone density after six months in	In delayed dental implants, NS gel may improve bone quality around implants by increasing bone density, resulting in better osseointegration of the implants and thus a better long-term outcome.

				(CBCT) to record bone density were recorded for each patient at 3 months and 6 months after implant placement.		comparison with the control group.	
Khan et al., 2022 (31)	Comparative randomised double-blind controlled clinical trial Sakaka, Saudi Arabia	7 days	60 patients who underwent tooth extraction and were clinically diagnosed with dry socket or alveolar osteitis	To evaluate and compare the effects of Alvogyl and a mixture of NS powder and oil in the treatment of dry sockets. Pain scores were assessed on a visual analogue pain scale.	Patients were allocated randomly to one of three groups. Group 1 received Alvogyl; Group 2 received a mixture of NS powder and oil; Group 3 was the control and received normal saline rinse. Pain relief and socket healing were assessed.	The group given NS powder and oil showed a significant difference in pain relief compared with the Alvogyl group ($p=0.031$) and the control group ($p=0.001$). Moreover, the NS group required A mixture of NS powder and oil dressings than the Alvogyl group.	NS oil mixture can be used successfully in patients suffering from alveolar osteitis, since it demonstrated immediate pain relief and was shown to be more effective than Alvogyl or normal saline rinse.
Hussain et al., 2019 (20)	Randomised open-label controlled study Sulaimani City, Iraq	28 days	54 acute myeloid leukaemia (AML) patients receiving "3 + 7" chemotherapy protocol (3 days of 60-90mg/m^2 daunorubicin and 7 days of 100 - 200mg/m^2 cytarabine)	To evaluate the effects of NS oil as a mouth rinse against chemotherapy (CT)-induced oral mucositis (OM) in patients with AML. The primary outcome was the incidence and severity of CT-induced OM (erythema and ulcer). Secondary outcomes were pain severity score, swallowing function, and salivary concentrations of interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α).	Patients in the test group received NS oil mouth rinse during their 28-day CT, while the control group received a "magic mouthwash" formula.	NS oil mouth rinse attenuated the progression of CT-induced OM compared with the control formula (AUC=5.9 vs. 38.4, $p<0.05$) and significantly decreased the erythema and ulceration scores (AUC of total OMAS=11.4 vs. 85.9, $p<0.001$) compared with the magic mouthwash formula. It also reduced the pain score and enabled all the participants of this group to consume normal food during treatment. It significantly decreased salivary IL-6 (AUC =7376 vs. 16599, $p<0.001$), while the changes in TNF-α levels were not significant (AUC=676.9 vs. 885.2, $p>0.05$).	In AML patients suffering from CT-induced OM, NS oil mouth rinse reduces pain and improves swallowing function.