

Therapeutic potential of thymoquinone gel in stage II grade A periodontitis: a prospective clinical and biochemical evaluation

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ABSTRACT

Background: Periodontitis is a chronic inflammatory oral disease influenced by microbial plaque and oxidative stress, affecting human health and wellbeing. Conventional therapy with scaling and root planing (SRP) may benefit from adjunctive medicine with antioxidant and anti-inflammatory properties. Thymoquinone, derived from *Nigella sativa*, has shown promise in modulating oxidative stress and inflammation. However, there is limited clinical evidence regarding its adjunctive use in non-surgical periodontal therapy.

Purpose: This clinical study aimed to evaluate the efficacy of 0.2% thymoquinone gel as an adjunct to SRP in treating stage II grade A periodontitis. **Methods:** Thirty patients diagnosed with stage II grade A periodontitis were randomly divided into two groups: Group 1 (Control), receiving SRP alone ($n = 15$), and Group 2 (Test), receiving SRP with 0.2% thymoquinone gel ($n = 15$). Clinical parameters, including the gingival index (GI), plaque index (PI), clinical attachment level (CAL), and probing pocket depth (PPD), were assessed. Additionally, oxidative stress index (OSI), total antioxidant capacity (TAOC), and total oxidant status (TOS) were measured in unstimulated saliva samples. Evaluations were conducted at baseline and three months post-treatment. Statistical analyses were employed to compare outcomes within and between groups. **Results:** Both groups demonstrated significant intragroup improvements ($p < 0.05$) in TOS, TAOC, CAL, PPD, GI, PI, and OSI from baseline to three months. However, intergroup comparisons revealed that Group 2 showed significantly greater improvement ($p < 0.05$) in all parameters except PI, which remained statistically insignificant ($p > 0.05$). **Conclusion:** The adjunctive use of 0.2% thymoquinone gel with SRP resulted in significantly greater improvements in clinical parameters (PPD, CAL, GI) and salivary oxidative stress markers (TOS, OSI, TAOC) compared with SRP alone. The study supports the potential role of thymoquinone as an adjunctive antioxidant agent in improving nonsurgical management of stage II grade A periodontitis.

Keywords: antioxidant; oxidative stress; periodontitis; scaling and root planing

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INTRODUCTION

Periodontitis is an inflammatory disorder characterized by the gradual destruction of the supporting structures of the teeth, culminating in eventual tooth loss. The disease begins with microbial plaque accumulation on the surface of the teeth, instigating an immune response, thereby leading to tissue destruction. A key factor in periodontitis progression is the imbalance between oxidative stress and antioxidant defenses, which promotes the release of pro-inflammatory cytokines like interleukin-1 β (IL-1 β), tumor necrosis

factor- α (TNF- α), and interleukin (IL-6), leading to tissue destruction and bone loss.^{1–3}

The cornerstone of periodontitis treatment lies in mechanical debridement, with scaling and root planing (SRP) serving as the gold standard approach. This process involves mechanical removal of plaque and calculus from the tooth surfaces and periodontal pockets. Nonetheless, its effectiveness can be limited in regions that are challenging to access with mechanical instruments. Bacterial plaque often remains in deep periodontal pockets, intrabody defects, or furcation areas. Furthermore, the success of

this approach relies heavily on the clinician's proficiency and various patient-specific factors.^{4,5} Therefore, systemic antibiotics have been employed to complement mechanical therapy, particularly in severe or refractory cases. These antibiotics help to reduce bacterial load throughout the body and provide better results in the management of periodontitis. However, they can lead to side effects such as gastrointestinal disturbances and contribute to the growing problem of antibiotic resistance.⁶

To overcome the limitations of systemic antibiotic therapy, such as low drug concentration at the infection site, systemic side effects, and risk of antimicrobial resistance, local drug delivery (LDD) systems have emerged as a superior alternative in periodontal therapy. LDD enables the direct placement of antimicrobial or therapeutic agents into periodontal pockets, ensuring sustained release and achieving drug concentrations up to multiple-fold higher than systemic administration, precisely wherever needed.^{7–10} These systems, including antiseptic and antibiotic gels, provide high concentrations of the drug directly to the periodontal pocket, minimizing systemic toxicity and enhancing treatment effectiveness. The substantivity of these local treatments, or their ability to remain in the site of action for extended periods, makes them particularly valuable in managing periodontitis.¹¹

Numerous topically administered antimicrobial therapies have been investigated for their potential in managing periodontitis, either as a stand-alone therapy or as a supplement to traditional SRP.¹² Additionally, an effective use of antioxidant gels has gained research interest for the management of periodontitis by creating an oxidant-antioxidant imbalance, which requires further clinical trials to emphasize its significance.¹³ Local drug delivery using herbal formulations enhances periodontitis management by harnessing their natural antimicrobial, anti-inflammatory, and antioxidant properties to reduce bacterial load, inflammation, and oxidative stress, while their sustained-release forms—such as gels, rinses, or chips—ensure targeted action within periodontal pockets, minimize systemic side effects, lower the risk of antibiotic resistance, and promote safe, biocompatible healing compared with conventional therapies.^{14,15}

Nigella sativa (*N. sativa*), traditionally used in Middle Eastern and Asian medicine, has been employed to manage a range of conditions, including rheumatoid arthritis, hypertension, and asthma. Its therapeutic potential is primarily attributed to thymoquinone (2-isopropyl-5-methyl-1,4-benzoquinone), a bioactive monoterpenoid. Thymoquinone has been shown to modulate the immune response by regulating interleukin production and suppressing oxidative stress through inhibition of reactive oxygen species.¹⁶ These anti-inflammatory and antioxidant properties are of particular interest in periodontal disease pathogenesis, where dysregulated host responses and oxidative stress contribute considerably to tissue destruction. Consequently, thymoquinone may offer therapeutic potential as an adjunct in

periodontal treatment by modulating these pathological mechanisms.¹⁷

Although the anti-inflammatory and antioxidant properties of thymoquinone have been extensively demonstrated in preclinical and in vitro models, there remains a considerable gap in clinical evidence supporting its use in periodontal therapy. To date, few studies have explored its therapeutic efficacy in vivo within periodontal settings. This study seeks to address this gap by providing clinical data on the adjunctive benefits of thymoquinone in improving periodontal outcomes and modulating oxidative stress. Hence, this prospective clinical study aimed to assess the effectiveness of 0.2% thymoquinone gel as an adjunct to SRP in the treatment of stage II grade A periodontitis.

MATERIALS AND METHODS

A 99% pure thymoquinone extract (Product No. 274666 from Sigma Aldrich Company) was obtained in crystal form and finely ground using a pestle and mortar. The materials were precisely weighed, and a total of 500 grams of gel was prepared. To create the gel base, 14 grams of Carbopol was dissolved in 485 ml of hot water heated to 80–90°C and stirred for 30 minutes to ensure proper hydration. One gram of thymoquinone was then added to achieve a 0.2% concentration in the gel, and the mixture was stirred until fully homogenized. The gel's pH was adjusted to 7.0 using 1N sodium hydroxide, and the mixture was subsequently cooled to room temperature (approximately 35°C).¹⁸

A prospective clinical study was conducted from March to August 2024, involving 30 patients diagnosed with stage II grade A periodontitis. These individuals, aged between 20 and 55 years, were selected from outpatients visiting the Department of Periodontology at Saveetha University. The diagnosis of periodontitis was established according to the 2017 guidelines of the American Academy of Periodontology. Patients were categorized into: Group 1 (Control), treated with SRP alone (n = 15), and Group 2 (Test), treated with SRP combined with an antioxidant gel (thymoquinone gel) (n = 15). Approval for the study was secured from the Ethics Committee of Saveetha University. (IHEC/SDC/PERIO-2203/24/065), and all participants provided written consent. The sample size was determined to be 30 using G*Power software version 3.1.9.4 (Heinrich Heine University Düsseldorf, Düsseldorf, Germany), with an 80% statistical power and a 95% confidence interval, based on data from a previous study.¹⁹ Accordingly, 30 participants were enrolled in the study.

Participants aged 20–55 years who met the following conditions: absence of systemic diseases, no periodontal therapy within 6 months prior to enrollment, no use of any medications in the preceding 3 months, non-smokers, no alcohol consumption, presence of >18 teeth, and normal salivary flow without hypo- or hyper-salivation were included in the study. However, patients with systemic illnesses, pregnancy, smoking, and the use of any

medications or dietary supplements within six months prior to the study were excluded.

SRP was performed for patients in both groups using sterile curettes (Hu-Friedy®, Chicago, IL, USA). In the test group, SRP was followed by a one-time application of the prepared thymoquinone gel, which was administered into the periodontal pockets using a 26-gauge insulin syringe based on feasibility and prior evidence supporting the effectiveness of one-time local drug delivery in periodontal therapy. All clinical procedures were carried out by a single calibrated operator (NN). The assessment was carried out by a trained periodontist (AR).

A volume of 5 mL of unstimulated saliva was collected from each participant through the spitting method. Samples were immediately centrifuged at 5000g for 20 minutes at 4°C, and the supernatant was carefully separated for biochemical analysis. To prevent oxidative degradation, an antioxidant solution comprising 10 µL of 0.5 M butylated hydroxytoluene (BHT) per 1 mL of saliva was added to each sample. The processed saliva samples were then stored at –80°C until analysis. All samples were analyzed within 120 days of collection to ensure sample stability and reliability of oxidative stress marker measurements.²⁰

Clinical parameters, including plaque index (PI), gingival index (GI), probing pocket depth (PPD), and clinical attachment level (CAL), were assessed. The Löe²¹ method was utilized to record plaque scores from four surfaces of each tooth, with the average score calculated. Similarly, the Löe²¹ method was employed to measure gingival scores from the same four surfaces, and the average was determined. For PPD and CAL, measurements were taken using a UNC-15 periodontal probe at six sites per tooth, and the average values were calculated.

Biochemical parameters, including total oxidant status (TOS), total antioxidant capacity (TAOC), and oxidative stress index (OSI), were evaluated. On the day of the assays, saliva samples were slowly thawed at 4°C.

TOS was measured using a colorimetric technique. In this method, oxidants present in the sample facilitated the conversion of Fe²⁺ ions into Fe³⁺ ions. Subsequently, xylenol orange was employed to identify Fe³⁺ ions. The TOS concentration was estimated using the hydrogen peroxide calibration curve. TOS was determined in triplicate. The values were reported as µmol H₂O₂ Equiv./L.²²

TAOC was assessed using a colorimetric method. This technique evaluates the sample's ability to neutralize the 2,2-azino-bis (3-ethylbenzothiazoline-6-sulfonate) cationic radical (ABTS). The absorbance of the ABTS solution was measured at 660 nm. For TAOC determination, 5 µL of each sample was mixed with 200 µL of 0.4 M acetate buffer at pH 5.8. Subsequently, 20 µL of ABTS solution was added, prepared in 30 mM acetate buffer at pH 3.6. After incubation, the absorbance was recorded at 660 nm. TAOC concentrations were calculated using a Trolox (6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid) standard curve and expressed as µM Trolox/mg of total protein. Each measurement was performed in triplicate.²³

OSI was calculated by determining the ratio of TOS to TAOC and was expressed as a percentage.²² At baseline and 3 months after SRP, sample collection was done, and clinical parameters were evaluated. This was performed by a single examiner (AR) at baseline and at the third month. SPSS (IBM Corp., Armonk, NY, USA, Version 20.0) was utilized for statistics. Paired t-test was employed for intra-group comparisons, while an independent t-test was applied for inter-group comparisons. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Intragroup analysis after 3 months in the control group showed significant improvements from baseline in Group 1. PI decreased from 1.76 ± 0.26 to 0.19 ± 0.07 , GI reduced from 1.45 ± 0.10 to 0.77 ± 0.10 , and PPD dropped from 4.55 ± 0.21 to 2.78 ± 0.25 . Additionally, a gain in CAL was noted, improving from 5.35 ± 0.39 to 2.81 ± 0.48 . TOS reduced from 7.11 ± 0.79 to 3.57 ± 0.48 , while TAOC increased from 1.46 ± 0.26 to 2.51 ± 0.31 . OSI changed from 0.64 ± 0.10 to 0.13 ± 0.03 . All changes were statistically significant ($p < 0.05$) (Table 1).

Intragroup analysis after 3 months in the test group showed significant improvements from baseline in Group 2. PI decreased from 1.67 ± 0.14 to 0.18 ± 0.07 , GI reduced from 1.50 ± 0.69 to 0.19 ± 0.07 , and PPD dropped from 4.62 ± 0.12 to 2.10 ± 0.42 . Additionally, a gain in CAL was observed, improving from 4.70 ± 0.26 to 2.52 ± 0.57 . TOS decreased from 7.54 ± 0.35 to 3.10 ± 0.33 , while

Table 1. Comparison of clinical and biochemical parameters in Group 1 (control) from baseline to 3 months

Variable	Pre-operative	Post-operative	p value
PI	1.76 ± 0.26	0.19 ± 0.07	0.023*
GI	1.45 ± 0.10	0.77 ± 0.10	0.012*
PPD	4.55 ± 0.21	2.78 ± 0.25	0.023*
CAL	5.35 ± 0.39	2.81 ± 0.48	0.011*
TOS	7.11 ± 0.79	3.57 ± 0.48	0.026*
TAOC	1.46 ± 0.26	2.51 ± 0.31	0.032*
OSI	0.64 ± 0.10	0.13 ± 0.03	0.017*

*Statistically significant

Table 2. Comparison of clinical and biochemical parameters in Group 2 (test) from baseline to 3 months

Variable	Pre-operative	Post-operative	p value
PI	1.67 ± 0.14	0.18 ± 0.07	0.013*
GI	1.50 ± 0.69	0.19 ± 0.07	0.011*
PPD	4.62 ± 0.12	2.10 ± 0.42	0.023*
CAL	4.70 ± 0.26	2.52 ± 0.57	0.017*
TOS	7.54 ± 0.35	3.10 ± 0.33	0.045*
TAOC	1.29 ± 0.31	3.01 ± 0.98	0.023*
OSI	0.25 ± 0.07	0.05 ± 0.03	0.029*

*Statistically significant

Table 3. Inter-group comparison of clinical and biochemical parameters at 3 months

Variable	Group 1 (control)	Group 2 (test)	p value
PI	0.19 ± 0.07	0.18 ± 0.07	0.06
GI	0.77 ± 0.10	0.19 ± 0.07	0.03*
PPD	2.78 ± 0.25	2.10 ± 0.71	0.04*
CAL	2.81 ± 0.48	2.52 ± 0.57	0.03*
TOS	3.57 ± 0.48	3.10 ± 0.33	0.02*
TAOC	2.51 ± 0.31	3.01 ± 0.98	0.03*
OSI	0.13 ± 0.03	0.05 ± 0.03	0.03*

*Statistically significant

TAOC increased from 1.29 ± 0.31 to 3.01 ± 0.98. OSI changed from 0.25 ± 0.07 to 0.05 ± 0.03. All changes were statistically significant ($p < 0.05$) (Table 2).

Inter-group comparison at the 3-month mark revealed statistically significant differences between the groups ($p < 0.05$) across all parameters except for PI ($p > 0.05$), which was 0.19 ± 0.07 in Group 1 and 0.18 ± 0.07 in Group 2. There was a drop in GI scores with 0.77 ± 0.10 in Group 1 and 0.19 ± 0.07 in Group 2. CAL gain was 2.81 ± 0.48 in Group 1 and 2.52 ± 0.57 in Group 2. PPD reduction of 2.78 ± 0.25 in Group 1 and 2.10 ± 0.42 in Group 2. Reduction in TOS was observed in Group 2 compared with Group 1, with 3.57 ± 0.48 in Group 1 and 3.10 ± 0.33 in Group 2. OSI levels lowered to 0.13 ± 0.03 in Group 1 and 0.05 ± 0.03 in Group 2, and TAOC improved in Group 2 (3.01 ± 0.98) compared with Group 1 (2.51 ± 0.31) (Table 3).

DISCUSSION

The main etiologic component for periodontitis is the pathogenic bacteria that reside in the subgingival region.²⁴ As such, due to a lack of precise oxidative stress indicators, it is difficult to investigate the relationship between oxidant-antioxidant imbalance and disease, and detecting individual antioxidants may give an incomplete picture because antioxidants collaborate via chain-breaking events. Therefore, TOS and TAOC analysis help in understanding the precise status of the disease.²⁵ It is important to remember that lower antioxidant capacity could signify either an underlying weakness in basal antioxidant defense

or a rise in oxidative stress. Periodontitis may be linked to a weakened local antioxidant defense, creating an imbalance in the oxidant-antioxidant. The gold standard technique for periodontitis management is mechanical debridement. However, to overcome the limitations of conventional or standard SRP therapy, local delivery of antimicrobial drugs has been investigated. The use of sustained release formulations to directly deliver the antimicrobial agents at the site of infection within periodontal pockets, such as tetracycline fibers, metronidazole gel, and chlorhexidine chips, has recently emerged as a successful therapy and can improve the state, condition, and health of the periodontium.²⁶ However, there is not much clinical evidence for thymoquinone gel as a local drug. Thus, this study is the first of its kind to use thymoquinone as local drug delivery for the management of periodontitis, evaluating its effects on both clinical and biochemical parameters.

In the present study, the adjunct use of thymoquinone gel along with mechanical debridement showed statistically significant improvement in TOS, TAOC, CAL, PPD, GI, and OSI. This might be due to the molecular mechanisms of thymoquinone. Thymoquinone has been shown to inhibit the activity of matrix metalloproteinase (MMP), an enzyme involved in the degradation of the extracellular matrix (ECM) and periodontal tissue destruction. By downregulating MMP activity, thymoquinone may contribute to the preservation of periodontal structures and promote tissue regeneration.²⁷ Based on existing literature, the antioxidant properties of thymoquinone are instrumental in alleviating oxidative stress, an important factor in the pathogenesis of periodontitis. Oxidative

stress arises from a disruption between the production of reactive oxygen species (ROS) and the body's antioxidant defenses, resulting in cellular injury and inflammation. Thymoquinone's ability to scavenge ROS and enhance endogenous antioxidant enzyme activity suggests that it could help restore redox balance and protect periodontal tissues from oxidative damage.²⁸ However, PI was not significant in this current study. This might be heavily influenced by patient compliance with home care rather than by local drug delivery alone, which may further explain the lack of a significant intergroup difference. The Hawthorne bias could have influenced both groups, as participants were aware they were part of a clinical study and may have improved their oral hygiene practices independently of the intervention.

Several studies have highlighted the therapeutic potential of thymoquinone in periodontal therapy due to its antibacterial and anti-inflammatory properties. Kouidhi et al.²⁹ proposed that thymoquinone acts as a promising natural compound with selective antibacterial activity against oral pathogens and potential to modulate antimicrobial resistance. Ulfah et al.³⁰ compared the antibacterial efficacy of 3% thymoquinone mouth rinse with 0.1% doxycycline against *Porphyromonas gingivalis*, reporting a larger zone of inhibition with thymoquinone, indicating superior antimicrobial activity. When compared with chlorhexidine, Khan et al.³¹ found that a 0.1% thymoquinone gel group showed significantly lower gingival index (GI) scores at one month compared with the chlorhexidine group, supporting its anti-inflammatory potential with fewer reported side effects.

In terms of clinical outcomes related to mechanical debridement, Kapil et al.¹⁸ reported a significant reduction in GI scores at 6 weeks when 0.2% thymoquinone gel was used adjunctively with scaling and root planing (SRP), compared with SRP alone. Microbiological analysis confirmed its efficacy against periodontal pathogens such as *Prevotella intermedia*, *Porphyromonas gingivalis*, and *Aggregatibacter actinomycetemcomitans*. Similarly, another study³² comparing 0.2% thymoquinone gel with a placebo gel, both in conjunction with SRP, demonstrated a statistically significant reduction in probing pocket depth (PPD) and gain in clinical attachment level (CAL) at 8 weeks in the test group ($p = 0.00$). Our findings are consistent with the above evidence, showing significant reductions in GI, PPD, and CAL with adjunctive thymoquinone therapy ($p < 0.05$), further validating its potential as an effective local agent in periodontal treatment.

In a study conducted by Almeshmadi et al.³³, which compared three groups that included SRP with thymoquinone gel 0.1% (Group I), SRP alone in periodontitis patients (Group II) and healthy individuals (Group III), the clinical parameters, including GI, PI, PPD and CAL, were assessed at 4 and 12 weeks, with a significant reduction observed across all measures in Group I (SRP + LDD) than Group II (SRP alone). IL-1 β levels and TAOC levels were also evaluated. The results demonstrated a significant reduction in IL-1 β after 4 weeks of treatment in Group I compared

with Group II, with a p -value of < 0.001 . AbdallahKhalil et al.³⁴ conducted a study to assess the impact of thymoquinone gel on clinical periodontal parameters, as well as the levels of IL-1 β and total antioxidant capacity in the gingival crevicular fluid of patients with chronic periodontitis. The clinical parameters, including PI, GI, PPD, and CAL, alongside IL-1 β levels and total antioxidant capacity in the gingival crevicular fluid, were measured at baseline (before treatment), and again at 4- and 12-week post-treatment. The results revealed significant improvements in both clinical and biochemical parameters in the group treated with 0.1% thymoquinone gel in conjunction with mechanical debridement, compared with the group receiving mechanical debridement alone, with a p -value of < 0.05 . Our results also showed that there was a marked reduction in TOS and OSI values and increased levels of TAOC in favor of the thymoquinone gel group, which is in alignment with the previous studies.

In conclusion, the current study indicates that thymoquinone gel, when used as a local drug alongside SRP, led to a more substantial reduction in GI scores, PPD, CAL, TOS and OSI, as well as a notable improvement in TAOC at the three-month follow-up, compared with SRP alone. These results suggest that the enhanced therapeutic efficacy of thymoquinone gel may be attributed to its active oxygen release or its potent bactericidal effects against gram-negative bacteria.

Nevertheless, further longitudinal studies are essential to thoroughly explore the therapeutic potential of thymoquinone in periodontitis management. This study is limited by its inability to determine key factors such as optimal dosage, application frequency, and bioavailability. Therefore, well-designed randomized controlled trials with larger, more diverse populations are necessary to confirm these initial findings. Also, a placebo gel (base formulation without thymoquinone) was not used in the control group. Although a placebo-controlled design could have enhanced internal validity by accounting for the potential effects of the gel vehicle, it was not implemented in this study due to logistical constraints. Additionally, a deeper understanding of the molecular mechanisms underlying the gel's action is needed. Future research should focus on optimizing formulations for clinical use and evaluating their in vivo efficacy to fully realize the potential of thymoquinone in treating periodontitis.

Thymoquinone gel demonstrates strong potential as an adjunctive therapy to SRP in the management of stage II grade A periodontitis. Over a three-month period, its local application resulted in statistically significant improvements in clinical parameters—gingival index ($p = 0.00$), probing pocket depth ($p = 0.00$), and clinical attachment level ($p = 0.03$)—as well as biochemical markers including total oxidant status ($p = 0.01$), oxidative stress index ($p = 0.00$), and total antioxidant capacity ($p = 0.02$), compared with SRP alone. These findings highlight its effectiveness in enhancing periodontal outcomes and support its potential integration into routine clinical practice.

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