Research Square

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Comparative Study of Spirulina Gel and Spirulina Nanoparticles Gel in the Treatment of Stage II Grade B Periodontitis: Randomized Controlled Study with Radiological and Biochemical Assessment

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Abstract

Objectives

Periodontitis stage II grade B represents moderate periodontal disease with a predictable, moderate rate of progression. It disrupts microbial-host balance, leading to attachment loss, deepened pockets, and gingival inflammation and bleeding. While scaling and root planing remain the gold standard, they face limitations in accessing deep periodontal pockets. Spirulina was recently introduced as a local delivery system for periodontal treatment therapy. The objectives of the present study were to evaluate the effects of locally delivered spirulina nanoparticle gel and spirulina gel with scaling and root planing (SRP) in treating periodontitis stage II, grade B.

Materials and Methods

In a randomized controlled trial, 60 patients with periodontitis stage II, grade B were enrolled. Each was assigned to one of three groups: Group I (spirulina nanogel + SRP), Group II (spirulina gel + SRP), or Group III (placebo gel + SRP). Clinical parameters (plaque index, gingival index, probing pocket depth, clinical attachment level) were recorded at baseline, 3, and 6 months. Gingival crevicular fluid samples were taken to assess superoxide dismutase (SOD) levels, and radiographic bone density was evaluated with ImageJ software.

Results

All groups showed significant improvements over time. The spirulina nanogel group had significantly greater reductions in periodontal parameters and a greater gain in clinical attachment level compared to the other groups ($p < 0.05$). SOD levels and radiographic bone density increased significantly across all groups, with the nanogel group showing the highest increase.

Conclusion

Combining spirulina nanogel with SRP resulted in better clinical, biochemical, and radiographic outcomes. Further long-term studies are needed to confirm these effects.

Registration

ClinicalTrials.gov with # ID NCT06699654

Date of registration: 16th, November, 2024

Introduction

Periodontitis is a chronic, multifactorial inflammatory disease that leads to the progressive destruction of the supporting tissues of the teeth, ultimately affecting patients' quality of life. It disrupts the equilibrium between the commensurate host response and microbial virulence factors [1, 2]. Periodontitis

is diagnosed based on the clinical attachment loss (CAL), alveolar bone loss, and pocket depth (PD). It may be associated with suppuration, pain, as well as gingival swelling that jeopardizes the long-term survival of the affected teeth [3] .

Periodontitis stage II grade B is characterized by a 15% to 33% radiographic alveolar bone loss that is mostly a horizontal pattern, CAL between 3–4 mm, PD ≤ 5 mm with a moderate rate of progression (Grade B: < 2 mm bone loss over the past 5 years) [4]. It often presents in systemically healthy individuals, with the disease presenting in a limited number of sites. This reflects a biofilm-driven process rather than a risk-modifier driven disease [5].

Superoxide dismutase (SOD) is a crucial antioxidant enzyme that converts superoxide radicals into hydrogen peroxide and oxygen, reducing oxidative tissue damage [6,7]. In a healthy periodontal state, antioxidant defenses manage reactive oxygen species (ROS) production, and effective periodontal therapy can restore antioxidant capacity in gingival crevicular fluid [8]. In periodontal inflammation, oxidative stress rises, depleting antioxidant mechanisms. Although there's no established reference for SOD levels in gingival crevicular fluid, changes in SOD activity can indicate shifts in oxidative balance. An increase in SOD post-treatment may suggest enhanced antioxidant capacity and improved redox homeostasis in the periodontal environment.

The objective of the current periodontal therapy is to restore symbiosis, inhibit inflammation of the periodontium, and enhance CAL. Both surgical and nonsurgical periodontal therapy aimed to eradicate periodontal pathogens and shift the human immune system toward shutdown of inflammation and stimulation of healing

Non-surgical periodontal management, primarily involving scaling and root planing (SRP), is essential despite challenges like accessing deep furcation areas and eliminating microbial pathogens within dentinal tubules [9,10]. Adjunctive local drug delivery (LDD) enhances treatment outcomes by delivering antimicrobial agents directly into periodontal pockets to target residual biofilm.

Plant materials, such as spirulina (Arthrospira), have been used for managing periodontitis due to their antibacterial, antioxidant, and anti-inflammatory properties [11]. Spirulina is a nutrient-rich cyanobacterium known for its high protein content, vitamins, and minerals, originally recognized for its use by NASA [12]. It activates antioxidant enzymes, inhibits lipid peroxidation, scavenges free radicals, and can modulate immune responses [13].

A controlled trial evaluated the effectiveness of spirulina peptide gel as a wound healing agent after periodontal flap surgery. The spirulina group showed significant reductions in plaque and bleeding indices at weeks 4 and 8, along with less gingival redness and lower pain scores at week 1 compared to the control group. Additionally, there was a decrease in pain medication use, indicating that spirulina gel enhances wound healing, reduces inflammation, and alleviates post-surgical pain [14].

Spirulina has demonstrated anti-inflammatory and antioxidant effects when applied as a gel for stage II grade B periodontitis [1, 15] but its effectiveness may be limited by challenges in penetrating and retaining within periodontal pockets.

While conventional spirulina gel is biocompatible and anti-inflammatory, nanoparticle gel may improve penetration and retention in deep periodontal defects, leading to better bioavailability and clinical outcomes, although formulation complexity and costs are higher [16].

The present study was conducted to evaluate the nanoparticle formulation clinically and biologically by comparing it with the conventional gel when used adjunctively with scaling and root panning (SRP) to address this evidence gap and guide future adjunctive periodontal therapies.

Materials and Methods

The experiment followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study design and methodology were conducted was conducted in accordance with the Helsinki Declaration as revised in 2013. The study was approved by the Research Ethics Committee (REC), Faculty of Oral and Dental Medicine, Kafrelsheikh University, Egypt (#KFSIRB200-68) and was registered in ClinicalTrials.gov with # ID: NCT06699654.

A total of 60 patients diagnosed with periodontitis stage II, grade B (clinical attachment loss of 3–4 mm, PPD of ≤ 5 mm of the lower posterior teeth of the mandible) had been recruited in the Department of Oral Medicine and Periodontology, Faculty of Dentistry, Kafrelskiekh University, to the trial.

Inclusion criteria

Participants with good oral hygiene, aged between 30 and 60 years.

Exclusion criteria

Any systemic illness influencing the periodontium, postmenopausal or pregnant females, individuals who have taken anti-inflammatory medications, vitamins, or antibiotics in the previous 3 months, regular users of mouthwashes, and participation in other clinical studies.

All participants received full written and verbal information about the research and signed the informed consent before the trial.

Sample size calculation:

The sample size (n) has been determined according to Cochran's formula, where zc is the selected critical value (zc = 1.96) of the desired significance level (α = 0.05), σ^2 is the estimated variance of the variable (σ^2 = 0.039), and e is the margin of error (e = 0.05). So the proposed sample size equals 60 sites (20 in each group).

Randomization: This double-blind randomized controlled study allocated 60 periodontal sites equally (20 per group) using a computer-generated randomization process. An independent investigator, not involved in patient recruitment or treatment, created a concealed allocation sequence with block randomization (1:1:1). After baseline measurements and SRP, participants received one of the three treatments based on the sequence: Group I received spirulina nanogel, Group II received spirulina gel, and Group III received a placebo gel (methylcellulose). Both patients and assessors were blinded to the treatment allocation. All participants gave their informed consent prior to their inclusion in the study.

Materials

Pure spirulina algae powder was sourced (Emtenan Health Shop, 2019©, Egypt). The preparation of spirulina forms and placebo gel took place at Kafrelsheikh University, Institute of Nanoscience and Nanotechnology (Suppl. File, Suppl. Figure 1).

Study Population

The sample consisted of 60 patients with one periodontal site each, allocated into three groups (n = 20). All received oral hygiene instructions and underwent full mouth SRP. Patients meeting the inclusion criteria were randomly assigned to treatments. After drying the surrounding tissues, a sterile syringe was used to inject 1 cc of gel twice a week for three weeks into the deepest periodontal pocket (Fig. 1). Participants were advised not to brush or floss around the gel for ten days.

- - Group I: Patients received injection of spirulina nanoparticles
- - Group II: Patients received injection of spirulina
- - Group III: Patients received placebo injection

Clinical measurements:

Prior to the study, the examiner underwent calibration for measuring PPD and CAL on 10 patients not included in the study, ensuring intra-examiner reproducibility with an intraclass correlation coefficients (ICC) of of 0.91 for PPD and 0.89 for CAL.

The primary outcome was the change in PPD at 1, 3 and 6 months post- treatment.

Secondary outcomes included:

PI, GI, CAL documented at baseline and at 1, 3, and 6 months after treatment.

Radiographic assessment:

Standardized digital periapical radiographs were taken at baseline and at 6 months post- treatment using the long-cone paralleling technique. A positioning device was utilized to ensure accuracy and

reproducibility. The exposure parameters (kVp, mA, exposure time) were kept constant for all participants, and the images were saved in TIFF format without compression to maintain image quality.

Radiographic bone density was analyzed using ImageJ software (National Institutes of Health, Bethesda, MD, USA) focusing on a standardized rectangular region of interest (ROI) at the interproximal alveolar bone adjacent to the study site. This region extended from 1 mm apical to the cemento-enamel junction to the crest of the alveolar bone.

Mean gray-scale values within the ROI (0-255 scale) were calculated as an indirect measure of bone density. Density change was calculated as the difference between baseline and 6-month mean gray values, with higher gray-scale values indicating increased radiographic density. Intra-examiner reproducibility was assessed by repeating measurements on 20% of randomly selected radiographs two weeks apart, and reliability was evaluated using intraclass correlation coefficients (ICC) that demonstrated high reliability (ICC > 0.90).

Biochemical analysis

Extracellular superoxide dismutase (SOD) levels were evaluated as a biomarker of oxidative stress at baseline and at 1, 3, and 6 months after treatment. Gingival crevicular fluid (GCF) samples were collected from sites that met the inclusion criteria using sterile paper points. Samples that were contaminated with blood were discarded. The collected paper points were placed in 0.2 mL of phosphate-buffered saline (PBS) and allowed to elute for 15 minutes before centrifugation. Afterwards, the paper points were removed, and the supernatant was stored at − 20°C until analysis. SOD concentrations were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (BT Laboratory, Zhejiang, China), following the manufacturer's instructions.

Statistical analysis:

Statistical analyses were performed using SPSS software, applying non-parametric tests for clinical parameters due to non-normal data distribution: Kruskal-Wallis H-test for intergroup comparisons at baseline, 1, 3, and 6 months, followed by Dunn's post-hoc test for pairwise differences, and Friedman test for intragroup changes with Nemenyi adjustments (significance at $p \leq 0.05$). For the parametric biochemical outcome (SOD levels), one-way ANOVA and Friedman tests for within-group trends were used, ensuring accurate handling of variances across demographic variables (independent t-tests or chi-square for age/sex). Each participant contributed data from only one periodontal site, maintaining the independence of observations.

Radiographic bone density values, measured with ImageJ, were first tested for normality using the Shapiro–Wilk test. After confirming normal distribution, one-way ANOVA was applied for intergroup comparisons, along with post-hoc analysis. For intragroup comparisons from baseline to 6 months,

paired t-tests were conducted, setting statistical significance at α = 0.05. All analyses were performed at the patient level to ensure independence of observations.

Results

The study included 60 periodontal sites from systemically healthy patients with stage II grade B periodontitis, randomized into three groups (n = 20 each): Group I (spirulina nanogel with SRP), Group II (spirulina gel with SRP), and Group III (placebo gel with SRP).

Demographic characteristics showed no significant differences (Suppl.Table 1). All groups were comparable at baseline for GI, PI, PPD, CAL ($p > 0.05$), SOD ($p = 0.13$), and radiographic density ($p = 0.69$).

GI and PI decreased across all groups over time. No significant differences were found for GI at 1 month ($p = 0.175$) or PPD ($p = 0.538$), but PI had significant intergroup differences at 1 month ($p = 0.0007$), persisting at 3 and 6 months ($p < 0.001$) in Group I. At 3 months, Group I had a significantly lower GI compared to Group III ($p = 0.042$), with significant differences in PPD and CAL ($p < 0.001$). By 6 months, Group I had the lowest mean GI (0.20 ± 0.41), significantly lower PPD (2.43 ± 0.37 mm), and the greatest CAL gain (1.45 ± 0.39 mm) compared to the other groups (Tables 1–4).

Significant increases in alveolar bone density were observed in all groups, with the largest change in Group I ($t = 14.021$, $p < 0.001$). At 6 months, Group I had the highest mean bone density (109.64 ± 12.13), followed by Group II and Group III (Table 5). SOD levels were significantly different among the groups at 1, 3, and 6 months ($p < 0.001$), with Group I having the highest level (384.54 ± 23.61) at 6 months (Table 6).

Discussion

Periodontitis is a chronic disease characterized by interactions between bacteria and the host immune response, influenced by genetic and environmental factors [17]. Periodontitis stage II, grade B is marked by CAL of 3–4 mm and PPD ≤ 5 mm, indicating active inflammation without extensive tissue destruction. This stage allows for assessing the impact of nonsurgical interventions that can enhance disease resolution and tissue healing alongside standard SRP [4, 18]. Local drug delivery systems effectively target residual subgingival biofilm and modulate the local immune response.

Arthrospira, or "spirulina," is a blue-green micro-algae found in warm or alkaline waters, known for its pigments like phycocyanin, which have biomedical applications [19].

The selection of spirulina as a locally delivered adjunctive therapy for patients with stage II, grade B periodontitis in this study was based on its documented anti-inflammatory, antioxidant, and antimicrobial properties. These attributes are highly relevant to the pathophysiology of periodontitis, a condition characterized by excessive inflammatory responses from the host and oxidative stress caused by dysbiotic biofilm, that ultimately leads to the breakdown of connective tissue and loss of alveolar bone.

Spirulina contains several bioactive compounds, including phycocyanin, phenolic acids, γ-linolenic acid, and tocopherols, that can inhibit pro-inflammatory cytokines, scavenge reactive oxygen species, and enhance the activity of endogenous antioxidant enzymes such as superoxide dismutase and catalase [13, 20].

Spirulina has demonstrated therapeutic effects in chronic inflammatory conditions, such as arthritis, metabolic syndrome, and inflammatory skin disorders. Its immunomodulatory and antioxidant properties contribute to tissue protection and enhance the healing process [12, 21].

In periodontal therapy, spirulina has shown promising results when used as an adjunct to SRP. Previous clinical trials have reported significant reductions in PPD and GI, as well as improvements in CAL when spirulina is combined with SRP, compared to SRP alone [1,3, 22].

The rationale for delivering spirulina directly into the periodontal pocket is to achieve high concentrations of its bioactive agents at the site of the disease, while reducing systemic exposure and minimizing potential side effects, as spirulina is known for its biological effectiveness. Additionally, nano-based delivery systems are recognized for providing sustained and controlled release of bioactive compounds within confined environments, such as periodontal pockets, thereby prolonging therapeutic exposure [23].

In this study, 60 periodontal sites from systemically healthy patients with stage II grade B periodontitis were randomly assigned to three groups: group I (spirulina nanogel with SRP therapy), group II (spirulina gel with SRP therapy), and group III (placebo with SRP therapy). Baseline demographic and clinical parameters were statistically insignificant across the groups, ensuring homogeneity.

While no significant reduction in GI was observed at one month, significant intergroup differences emerged at three months, and were highly significant by six months, with the spirulina nanogel group demonstrating the most sustained improvement, followed by the spirulina gel group, and the placebo group showing the least change. These results suggest that spirulina, especially in a nanogel form, can effectively control gingival inflammation over time.

Supporting studies, including those by Kaipa et al., 2022, and Altabrizy et al., 2023, also reported significant reductions in GI at later follow-ups for spirulina groups compared to placebo [1, 16]. A reduction in plaque accumulation was noted at one month, with the spirulina nanogel group showing the most substantial decrease [15, 24].

Modest early reductions in PPD and CAL gains were seen at one month, but significant improvements were observed at three and six months, especially in the spirulina nanogel group. These findings align with earlier research by Mahendra et al., 2013, highlighting the efficacy of spirulina as an adjunctive therapy [22].

A radiographic evaluation was conducted at six months, a commonly used time frame in nonsurgical periodontal clinical trials to observe early changes in bone density and mineralization. While complete

structural bone regeneration typically requires longer observation periods, short- to medium-term radiographic changes may indicate alterations in mineral content linked to the resolution of inflammation and improved periodontal stability [25, 26]. Consequently, the current findings should be regarded as early increase in radiographic density, rather than definitive proof of new bone regeneration.

Alveolar bone density at 6th month follow-up, showed a significant higher bone density in group I compared with the other two groups, indicating enhanced alveolar bone by spirulina- nanogel. It may promote favorable bone remodeling events and stability of periodontal structures.

GCF is a specific inflammatory exudate that reflects the interactions between the host and microorganisms occurring within the periodontal pocket. Due to its content of inflammatory mediators, enzymes, oxidative stress markers, and byproducts of tissue breakdown, GCF is widely regarded as a reliable diagnostic and monitoring tool for assessing periodontal disease activity [27, 28].

SOD levels in GCF, that serve as a surrogate marker of the local oxidative stress–antioxidant balance within the periodontal pocket, were comparable at baseline, while after the treatment, they were higher in all groups, with the most notable increase in the spirulina groups. At 6 months, the SOD levels in the spirulina nanogel group were higher than the levels in the spirulina gel group or the placebo group, which implies a higher response in antioxidants. The marked increase in SOD may suggest enhanced local antioxidant defense and improved redox homeostasis, particularly in sites treated with spirulina-nanogel, thereby supporting tissue healing and limiting oxidative tissue damage. These findings should be viewed in the context of improved clinical parameters.

The biochemical observations in the current investigation are strongly supported by existing literature demonstrating spirulina’s antioxidant and anti-inflammatory properties [1, 29].

Since oxidative stress and pro-inflammatory cytokines directly contribute to osteoclast activation and alveolar bone resorption, reducing these pathways may create a microenvironment that is more supportive of periodontal tissue repair and bone stabilization. This biological mechanism may help explain the significantly greater increase in bone density observed in the spirulina nanogel group after 6 months.

Improvements in periodontal outcomes observed after using nano-spirulina can be partly attributed to its physicochemical properties. HR-TEM analysis confirmed the presence of well-dispersed nanoscale particles, primarily in rod and sheet-like shapes, which may enhance their contact with the periodontal pocket environment (Suppl. Figure 2a, b, c). The nanoscale size, supported by DLS measurements, is expected to improve penetration into the biofilm matrix and increase the available surface area- to-volume relation for biological interaction when compared to traditional spirulina gel formulations (Suppl. Figure 2- d). Additionally, a negative zeta potential of -25.20 mV suggests good colloidal stability, which may aid in the prolonged retention of the formulation within the periodontal pocket and minimize particle aggregation (Figure Suppl. 2- e). FTIR analysis showed that the major functional groups associated with proteins, lipids, and polysaccharides were preserved after the formation of nanoparticles, indicating that

the bioactive components of spirulina were retained (Suppl. Figure 2- f). These characteristics may enhance local bioavailability and enhance the modulation of oxidative stress and inflammatory pathways, which is reflected in the significant increase in SOD levels. Improved redox balance and suppression of inflammatory mediators may create a microenvironment that is more conducive to the repair of periodontal tissue and stabilization of alveolar bone. This is consistent with the greater increase in bone density and anti-inflammatory effects seen in clinical settings in the nanogel group.

Additionally, the nano-formulation may provide a more sustained and controlled release of spirulina's bioactive compounds within the periodontal pocket, prolonging their local therapeutic effects.

However, while the improved physicochemical properties of the spirulina nanoparticles may optimize local delivery and interaction with periodontal tissues, clinical outcomes ultimately depend on the host's response and the severity of the disease. This underscores the need to integrate nano-based adjuncts with traditional periodontal therapy for better results. Spirulina's bioactive components with a nanogel delivery system may provide a synergistic effect that enhances periodontal tissue healing, reduces inflammation, and promotes antioxidant balance.

Limitations

This investigation has been limited by a small sample size, a relatively short monitoring period. Future multicenter randomized clinical trials with larger populations, and extended follow up times are recommended to validate these results and to investigate the molecular mechanisms underlying spirulina's therapeutic effects in periodontal health.

Conclusion

Within the limitations of the present study, adjunctive application of spirulina nanogel in conjunction with SRP demonstrated enhanced clinical and biochemical improvements compared with spirulina gel or placebo with SRP in treating periodontitis stage II grade B. These findings suggest potential effects of nanoparticle-based local delivery systems in optimizing adjunctive periodontal therapy.

Clinically, the use of spirulina nanogel may provide a biologically based host-modulatory strategy for cases of moderate periodontitis, especially when surgical intervention is not warranted. Spirulina nanogel could be used as an adjunct local delivery system in conjunction with mechanical debridement of periodontal pockets. This treatment option is safe, biocompatible, and cost-effective. Long-term trials are warranted to confirm the clinical relevance and lasting impact of these findings.

Declarations

Acknowledgment:

The authors extend their sincere gratitude to the Department of Oral Medicine and Periodontology, Faculty of Dentistry, Kafrelsheikh University, for providing the needed facilities and support during this research. Special thanks to the participants for their cooperation and commitment. We also acknowledge the technical assistance provided by the Central Laboratory Unit at Kafrelsheikh University in conducting the biochemical analyses.

The study was approved by the Research Ethics Committee (REC), Faculty of Oral and Dental Medicine, Kafrelsheikh University, Egypt (#KFSIRB200-68).

The experiment followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study design and methodology were conducted in accordance with the Helsinki Declaration as revised in 2013.

All participants gave their informed consent prior to their inclusion in the study.

Consent for publication: NA

Data Availability: The information presented in this research is accessible on request from the corresponding author. The information isn't publicly accessible because of privacy restrictions related to patient information.

Competing interests: All authors declare that this study does not have any conflict of interest

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Author contributions;

M A, A E: Conceptualization of the work

S E: Design Methodology, wrote the draft

O E, N H: Biological analysis, prepared figures

M Z, H A, D M, D S: Curation and analysis of Data, resources

E E: Design Methodology, supervision, clinical work

All authors reviewed the manuscript

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Tables

Tables are available in the Supplementary Files section.

Figures



Figure 1

Injection of 1 cc of spirulina nanogel into the deepest periodontal pocket

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx
- Suppl.Table1.docx
- Suppl.1Gelpreparation.docx
- Suppl.Figure1.jpeg
- Suppl.Figure2a.jpg
- Suppl.Figure2b.jpg
- Suppl.Figure2c.jpg
- Suppl.Figure2d.jpg
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- Supplegends.docx