

Original Article

Clinical efficacy evaluation of Nd:YAG laser combined with Kangfuxin solution in the treatment of oral lichen planus

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Abstract: Objective: To evaluate the clinical efficacy, as well as the cytoprotective and osteoprotective effects, of Nd:YAG laser therapy combined with Kangfuxin Liquid in the management of oral lichen planus (OLP) via a retrospective clinical study and basic experiments. Methods: This retrospective study reviewed the medical records of 50 OLP patients with periodontitis (25 EOLP cases and 25 NEOLP cases) and 25 healthy controls. The patients received Nd:YAG laser therapy combined with Kangfuxin solution, whereas the healthy controls received no intervention. Clinical evaluation comprised the RAE score, VAS score, GI-Avg, and serum inflammatory factors (measured via ELISA). Additionally, basic experiments were conducted to evaluate the effects of the combined treatment on cell viability, DNA damage, cell migration, mitochondrial ultrastructure, cell senescence, and alveolar bone microstructure, using an LPS-induced human oral keratinocyte inflammation model and an OLP-like mouse model. Results: Combined treatment significantly reduced RAE, VAS, and GI-Avg, and also significantly lowered serum TNF- α , IL-6, and IL-17 levels to values approaching those of healthy controls. The 24-week recurrence rate was 12% in the EOLP group and 8% in the NEOLP group. In vitro and in vivo experiments showed that the combined treatment was significantly more effective than either monotherapy in enhancing cell viability and migration, reducing DNA damage and senescence, protecting mitochondrial structure, and reducing alveolar bone loss. Conclusion: Nd:YAG laser therapy combined with Kangfuxin solution demonstrates effectiveness and safety in the treatment of OLP, offering multifaceted cytoprotective and bone-protective effects. This provides a valuable hormone-free treatment strategy for clinical practice; however, its efficacy needs to be further verified through randomized controlled trials.

Keywords: Nd:YAG laser, Kangfuxin solution, oral lichen planus, combined therapy, mitochondrial ultrastructure, micro-CT

Introduction

Oral lichen planus (OLP) is a chronic, immune-mediated inflammatory disorder affecting the oral mucosa, characterized by bilateral white striations (Wickham's striae), erythema, erosions, and ulcerations [1, 2]. With a global prevalence of approximately 0.5-2% and a higher incidence among middle-aged women, OLP significantly impairs patients' quality of life due to pain, dysphagia, and the potential risk of malignant transformation into oral squamous cell carcinoma (OSCC), which occurs in approximately 1-3% of cases [3, 4]. The pathogenesis of OLP involves a dysregulated T-cell-mediated

immune response, in which CD8⁺ cytotoxic lymphocytes target basal keratinocytes, triggering apoptosis, basement membrane degradation, and persistent inflammation [5, 6]. Additional factors, including stress, genetic predisposition, and autoimmune comorbidities, may further complicate disease management [7]. Current first-line therapies, including topical corticosteroids, calcineurin inhibitors, and systemic immunosuppressants, primarily provide symptomatic relief but are limited by frequent relapse, corticosteroid resistance, and adverse effects like mucosal atrophy and oral candidiasis [8-10]. These limitations underscore the urgent need for innovative, minimally invasive

therapies that can simultaneously regulate inflammatory responses and promote tissue repair while preserving mucosal integrity.

In recent years, laser-based technologies have emerged as a promising adjunctive approach for the management of oral mucosal disorders, owing to their precision, reduced healing time, and antimicrobial benefits [11, 12]. Among various laser modalities, the neodymium-doped yttrium aluminum garnet (Nd:YAG) laser has gained increasing attention in dentistry and dermatology for its deep tissue penetration, hemostatic properties, and ability to modulate cellular activity through photobiomodulation (PBM) [13]. Unlike ablative laser systems, Nd:YAG laser therapy operates in a non-thermal or sub-ablative mode, stimulating mitochondrial cytochrome c oxidase to enhance adenosine triphosphate production, reduce pro-inflammatory cytokines, and promote fibroblast proliferation and collagen synthesis [14, 15]. A previous clinical study has demonstrated its efficacy in alleviating pain and reducing lesion size in OLP patients, with therapeutic effects lasting up to 6 weeks [16]. However, Nd:YAG laser monotherapy may not fully address the multifactorial nature of OLP, particularly in cases with extensive ulceration or superimposed microbial infections, necessitating complementary therapeutic agents to optimize clinical outcomes.

Kangfuxin Solution, a traditional Chinese medicine (TCM) derived from the ethanol extract of *Periplaneta americana*, has demonstrated remarkable wound-healing and anti-inflammatory properties [17-19]. Its bioactive components - including amino acids, peptides, and polysaccharides - exert multimodal biological effects by promoting epithelial cell migration, enhancing growth factor expression, and inhibiting NF- κ B signaling to reduce the production of inflammatory mediators [20, 21]. Clinically, Kangfuxin Solution has been applied in the treatment of oral aphthous ulcers, chemotherapy-induced oral mucositis, and chronic gastritis, with trials highlighting its ability to accelerate mucosal repair and reduce pain [22, 23]. However, its therapeutic potential in immune-mediated conditions like OLP remains underexplored, and its viscous formulation may limit penetration into deeper epithelial layers affected by lichenoid inflammatory infiltration. Combining Kangfuxin with laser therapy may

overcome these limitations by leveraging laser-induced microstructural alterations to enhance drug penetration while simultaneously targeting inflammation and tissue regeneration.

This study aims to evaluate the clinical efficacy, safety, and underlying mechanisms of Nd:YAG laser combined with Kangfuxin Solution for the treatment of OLP. We reviewed clinical outcomes, including lesion resolution, pain relief, inflammatory biomarker changes, and histological evidence of epithelial regeneration. In addition, *in vitro* experiments using inflamed human oral keratinocytes (including transmission electron microscopy (TEM)-based evaluation of mitochondrial ultrastructure) and an *in vivo* mouse model assessed by maxillofacial micro-computed tomography (CT) were conducted to further elucidate the cellular and bone-protective mechanisms of this combined therapy. By integrating clinical, molecular, and structural findings, this study provides preliminary evidence on the potential mechanisms by which this combination therapy may modulate the immune dysregulation-tissue damage cycle in OLP.

Methods and materials

Study design and ethical approval

This retrospective study included patients who were treated at the Department of Stomatology, Suqian Hospital, affiliated with Nanjing Drum Tower Hospital Group. The study protocol was approved by the Institutional Ethics Committee of Suqian Hospital. All procedures were performed in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design of the study, the requirement of written informed consent was waived by the institution.

Study population

A total of 50 patients diagnosed with OLP and concurrent chronic periodontitis were retrospectively enrolled. Based on their clinical manifestations, patients were classified into two subgroups: the erosive OLP (EOLP) group (n = 25) and the non-erosive OLP (NEOLP) group (n = 25). Additionally, 25 healthy individuals with intact oral mucosa and periodontal tissues, who underwent routine physical examinations at the health screening center of our hospital during the same period, were selected

as the healthy control group (control group); this group did not receive any treatment.

Inclusion criteria: (1) OLP diagnosis confirmed by clinical and histopathological examinations; (2) Presence of chronic periodontitis, defined as probing depth ≥ 4 mm accompanied by clinical attachment loss; (3) Age between 30 and 75 years.

Exclusion criteria: (1) History of malignancy or precancerous lesions other than OLP; (2) Systemic diseases affecting immune function (e.g., HIV, uncontrolled diabetes); (3) Pregnancy or lactation; (4) Use of immunosuppressive drugs or corticosteroids within the previous three months.

Treatment protocol

All OLP patients received a combination therapy of Nd:YAG laser irradiation and topical application of Kangfuxin Solution. The healthy control group received no intervention.

Nd:YAG Laser Application: An Nd:YAG laser system (operating at a wavelength of 1064 nm) was used for treatment. The laser was applied in a pulsed mode with the following parameters: power, 2.0 W; frequency, 20 Hz; pulse duration, 150 μ s; and energy density, 80 J/cm². The fiber tip was maintained in a non-contact position approximately 2-3 mm above the lesion surface and moved in a painting motion pattern until a whitish coagulation layer formed on the erosive lesions. Laser treatment was repeated every 2 weeks for a total of 4 sessions.

Kangfuxin Solution Application: Immediately following laser irradiation, Kangfuxin Solution was applied topically to the lesions using cotton swabs. During the treatment period, patients were instructed to apply the solution three times daily for 4 weeks and retain it in the oral cavity for at least 5 min before swallowing or expectorating.

Clinical assessment

Clinical evaluations were performed at baseline (pre-treatment) and at 2, 4, 6, and 24 weeks after treatment.

OLP severity assessment: Disease severity was quantified using the Reticular, Atrophic, and

Erosive (RAE) scoring system. The oral mucosa was divided into 10 anatomical regions, and each region was scored according to the predominant lesion type: reticular lesions (1 point), atrophic lesions (2 points), and erosive lesions (3 points). The total RAE score was calculated as the sum of the scores from all affected sites.

Pain assessment: Subjective pain intensity was assessed using a 100-mm Visual Analogue Scale (VAS), ranging from 0 ("no pain") to 100 ("worst imaginable pain").

Periodontal status assessment: Gingival inflammation was evaluated using the Gingival Index (GI). Scores ranged from 0 (normal gingiva) to 3 (severe inflammation with ulceration). The average GI (GI-Avg) was calculated for each patient.

ELISA

Peripheral blood samples from all OLP patients were collected at baseline and at 24 weeks post-treatment. For the healthy control group, peripheral blood samples were collected only at the time of their routine physical examination. Serum levels of pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-17 (IL-17), were quantified using Enzyme-Linked Immunosorbent Assay (ELISA) kits according to the manufacturer's protocols.

In vitro cell experiments

To elucidate the cytoprotective mechanisms underlying the combined treatment, human oral keratinocytes (HOKs) were stimulated with lipopolysaccharide (LPS, 1 μ g/mL) for 24 h to establish an *in vitro* inflammatory model. The experiment comprised five groups: (1) Control (untreated HOKs); (2) Model (LPS stimulation alone); (3) Laser (LPS stimulation + Nd:YAG laser irradiation); (4) KFX (LPS stimulation + Kangfuxin solution at a final concentration of 100 μ g/mL for 24 hours); and (5) Laser + KFX (LPS stimulation + Nd:YAG laser irradiation combined with Kangfuxin solution).

After treatment, the following parameters were assessed: (1) Cell viability: determined using the CCK-8 assay by measuring absorbance at 450 nm; (2) DNA damage: evaluated using the alkaline comet assay. After electrophoresis,

samples were stained with SYBR Green, and the tail moment was analyzed using Comet-Score software; (3) Pro-inflammatory cytokine secretion: cell culture supernatants were collected, and the concentrations of TNF- α , IL-6, and IL-17 were measured by ELISA; (4) Cell migration: assessed using a Transwell chamber (8- μ m pore size). The lower chambers were filled with medium containing 10% FBS, and cells were seeded into the upper chambers and incubated for 12 h. After crystal violet staining, the number of migrated cells in five randomly selected microscopic fields was counted under a light microscope; (5) Mitochondrial ultrastructure: cell pellets were collected, fixed with glutaraldehyde, post-fixed with osmium tetroxide, embed in epoxy resin, and sectioned into 70-nm ultrathin sections. Mitochondrial morphology was then observed using transmission electron microscopy (TEM) at 120 kV; and (6) Cell senescence: Cells were stained using an SA- β -gal staining kit and incubated overnight at 37°C; the percentage of SA- β -gal-positive (blue) cells was subsequently determined under a light microscope.

In vivo animal experiments

To evaluate the effects of combination treatment on alveolar bone, an OLP-like mouse model was established using an adoptive transfer approach. Fifty specific pathogen-free (SPF) female C57BL/6 mice (aged 6-8 weeks, weighing 18-22 g) were randomly assigned to five groups: control, model, laser, KFX, and Las + KFX ($n = 10$ per group). Mice were housed in an SPF animal facility under controlled temperature and humidity conditions with a 12-h light/dark cycle.

Donor mice were primed subcutaneously at the tail base with OVA emulsified in complete Freund's adjuvant (CFA). Seven days after priming, splenocytes were collected and stimulated ex vivo with OVA for 72 h, followed by purification using a CD8⁺ T cell isolation kit (yielding > 95% purity). Following anesthesia, 5×10^6 OVA-specific CD8⁺ T cells suspended in 50 μ L of PBS were injected into the bilateral buccal submucosa of recipient mice, followed by local application of OVA (100 μ g per dose) for three consecutive days to provide local antigenic stimulation. On day 7, the presence of white striae and erosions on the buccal mucosa was considered indicative of successful model establishment.

The laser and Laser + KFX groups received Nd:YAG laser irradiation once every two weeks for a total of four sessions. The KFX and Laser + KFX groups received topical Kangfuxin solution (100 μ L) three times daily for four weeks. The control and model groups received PBS as a vehicle control; in addition, the model group underwent sham laser irradiation to control for procedure-related effects.

The following parameters were assessed after treatment: (1) Serum inflammatory factors: blood was collected from the orbit venous plexus, and levels of TNF- α , IL-6, and IL-17 were measured by ELISA; (2) Alveolar bone parameters: the maxillae were excised and analyzed using micro-CT (SkyScan 1176) to determine bone mineral density (BMD) and trabecular number (Tb.N).

Statistical analysis

Statistical analyses were performed using GraphPad Prism 6.0. Continuous variables are presented as mean $\pm$ standard deviation (SD). Comparisons among multiple groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's honestly significant difference (HSD) test for post hoc pairwise comparisons. For intra-group comparisons of clinical parameters (RAE score, GI-Avg, and VAS score) between baseline and each follow-up time point (2, 4, 6, and 24 weeks), paired Student's t-tests were used. Independent Student's t-tests were used to compare continuous variables between the EOLP and NEOLP groups at baseline. Categorical variables, including sex and lesion sites, were analyzed using the chi-square (χ^2) test. All statistical tests were two-tailed, and a p -value of < 0.05 was considered statistically significant.

Results

Baseline demographics and clinical characteristics

Statistical analysis revealed no significant differences in age ($P = 0.905$) or sex distribution ($P = 0.782$) between the EOLP and NEOLP groups. However, baseline disease severity differed significantly between the two subtypes, with the EOLP group exhibiting significantly higher RAE scores than the NEOLP group ($P < 0.001$) (Table 1).

Table 1. Comparison of baseline demographics and clinical characteristics among groups

Variable	Healthy controls (n = 25)	EOLP group (n = 25)	NEOLP group (n = 25)	Test Statistics	P-value
Age (years)	57 ± 11	58 ± 12	58 ± 12	t(48) = 0.121	0.905
Female, n (%)	14 (56)	14 (56)	14 (56)	χ ² (1) = 0.082	0.782
Lesion site, n (%)					
Tongue	-	8 (32)	9 (36)	χ ² (2) = 0.342	0.845
Gingiva	-	8 (32)	8 (32)	χ ² (2) = 0.002	1.000
Buccal mucosa	-	7 (28)	6 (24)	χ ² (2) = 0.152	0.927
Other	-	2 (8)	2 (8)	χ ² (2) = 0.002	1.000
Baseline RAE score	-	8.2 ± 1.5	4.5 ± 1.1	t(48) = 9.831	< 0.001

EOLP, erosive oral lichen planus; NEOLP, non-erosive oral lichen planus; RAE, reticular, atrophic, and erosive.

Serological analysis demonstrated significant reductions in systemic immunomodulatory cytokine levels following combination therapy. At the 24-week follow-up, serum levels of the pro-inflammatory cytokines (TNF-α, IL-6, and IL-17) were significantly decreased compared with baseline levels. Specifically, in the EOLP group, TNF-α decreased from 45.2 ± 8.6 pg/mL to 18.4 ± 4.2 pg/mL (t(24) = 14.32, P < 0.001), IL-6 from 32.8 ± 6.4 pg/mL to 12.1 ± 3.5 pg/mL (t(24) = 13.67, P < 0.001), and IL-17 from 28.5 ± 5.9 pg/mL to 10.3 ± 2.8 pg/mL (t(24) = 13.05, P < 0.001). Similar reductions were observed in the NEOLP group, with all post-treatment levels approaching those in healthy controls (**Figure 1A**). One-way ANOVA comparisons among the three groups (healthy, EOLP-post, NEOLP-post) showed no significant differences in TNF-α (F(2, 72) = 1.85, P = 0.164), IL-6 (F(2, 72) = 2.12, P = 0.127), or IL-17 (F(2, 72) = 1.56, P = 0.218) (**Figure 1A-C**).

Clinical efficacy

Combination therapy with Nd:YAG laser and Kangfuxin Solution induced rapid and sustained improvement in OLP lesions in both subgroups (**Figure 2**).

Clinical photographs demonstrated restoration of the oral mucosa, characterized by reductions in white striae and erythema, and recovery of a more normal mucosal texture (**Figure 2A**).

EOLP Group: Patients exhibited a dramatic reduction in disease activity over time (**Figure 2B**). The mean RAE score decreased from 8.2 ± 1.5 at baseline to 1.3 ± 0.6 at the 24-week follow-up (paired t-test, t(24) = 18.64,

P < 0.001). The reduction was already evident at 2 weeks (6.5 ± 1.3, t(24) = 8.72, P < 0.001) and continued progressively through 4 weeks (4.1 ± 0.9, t(24) = 14.28, P < 0.001) and 6 weeks (2.8 ± 0.8, t(24) = 15.93, P < 0.001). Notably, complete epithelialization of erosive lesions was achieved in 92% (23/25) of patients by week 24.

NEOLP Group: Patients in this group also showed significant clinical improvement (**Figure 2B**), with the mean RAE score declining from 4.5 ± 1.1 at baseline to 0.8 ± 0.4 at 24 weeks (paired t-test, t(24) = 16.21, P < 0.001). Within the first month of treatment, 88% (22/25) of patients achieved an asymptomatic state accompanied by resolution of atrophic and reticular lesions.

The therapeutic regimen was also associated with significant improvement in periodontal health. The mean Gingival Index (GI Avg) for the entire cohort decreased progressively from 2.8 ± 0.7 at baseline to 0.9 ± 0.3 at 24 weeks (P < 0.001), with similar trends observed in the EOLP and NEOLP subgroups (**Figure 2C**), indicating a marked reduction in gingival inflammation.

Periodontal outcomes, safety, and long-term prognosis

VAS assessment demonstrated significant symptomatic relief following treatment (**Figure 3A, 3B**). In the EOLP group, the mean VAS score dropped from 7.5 ± 1.2 at baseline to 2.1 ± 0.9 at 2 weeks post-treatment (P < 0.001), with a further gradual decrease to 1.8 ± 0.7 at 24 weeks (P < 0.001). Similarly, the NEOLP group reported a marked reduction in

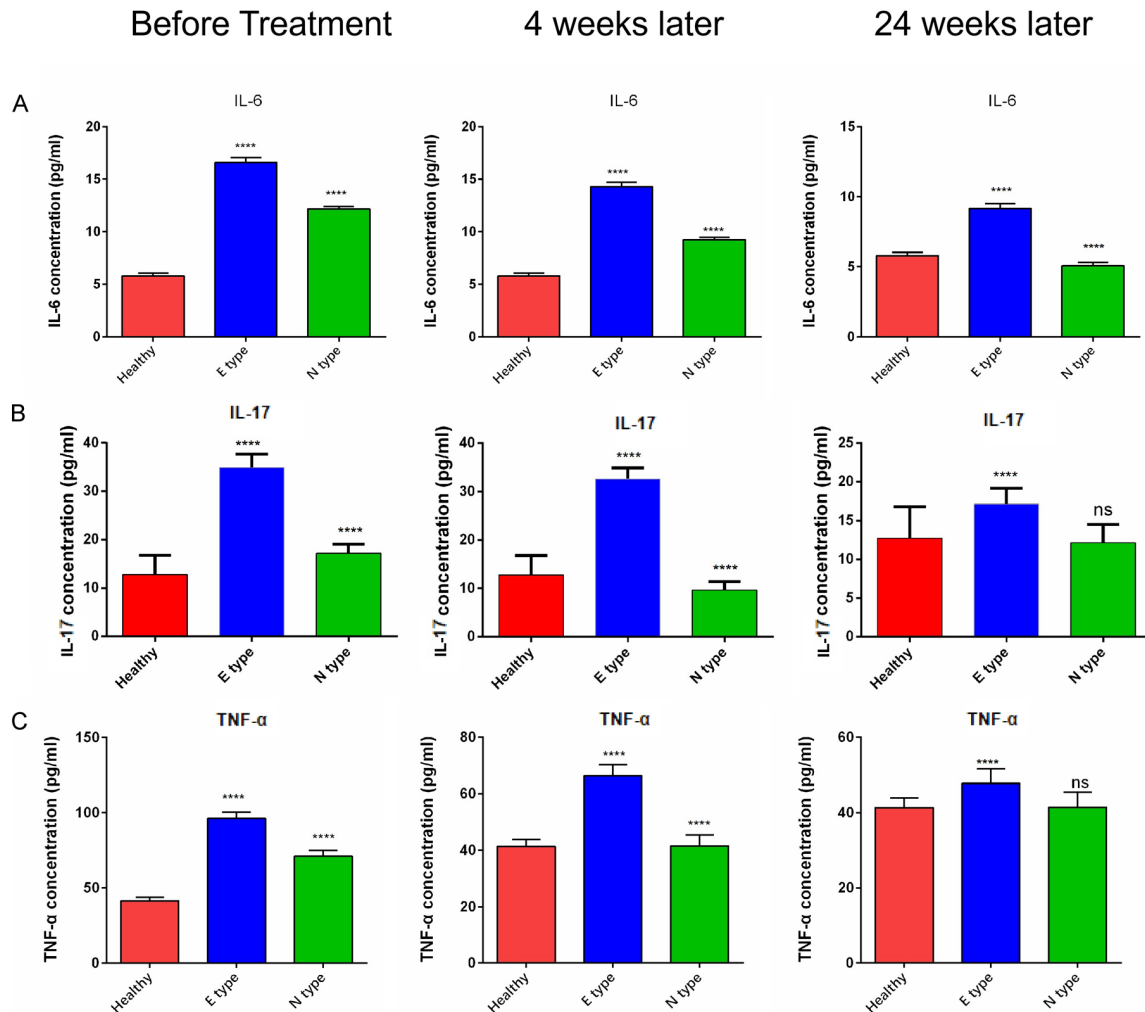


Figure 1. Serum levels of inflammatory cytokines in healthy controls, EOLP, and NEOLP groups before and after combined intervention. A. Serum IL-6 levels; B. Serum IL-17 levels; C. Serum TNF- α levels. Notes: EOLP, erosive oral lichen planus; NEOLP, non-erosive oral lichen planus. **** $P < 0.0001$. ns, not significant.

discomfort, with the mean VAS score decreasing from 3.4 ± 1.0 at baseline to 0.8 ± 0.5 at 2 weeks ($P < 0.001$) and remaining low at 24 weeks (0.5 ± 0.3) ($P < 0.001$). At 2 weeks, the VAS scores remained significantly higher in the EOLP group than in the NEOLP group ($P < 0.001$).

During the 24-week follow-up period, the cumulative recurrence rate was 12% (3/25) in the EOLP group and 8% (2/25) in the NEOLP group. All recurrent cases were mild and were successfully managed with an additional cycle of therapy. No malignant transformation was observed during the study period. The treatment was well tolerated; transient mild pain immediately after irradiation was reported by 16% (8/50) of patients and resolved without

intervention. No adverse events related to mucosal atrophy, candidiasis, or systemic toxicity were recorded.

Cytoprotective, mitochondrial and skeletal benefits of Nd:YAG laser plus Kangfuxin solution

To further elucidate the biological mechanisms underlying the observed clinical efficacy, complementary *in vitro* and *in vivo* experiments were performed. In LPS-stimulated HOKs, the combined treatment significantly enhanced cell viability compared to the Model group ($62.3 \pm 5.1\%$ vs. $35.6 \pm 4.8\%$, $P < 0.001$; **Figure 4A**). The combined treatment also markedly attenuated DNA damage, as indicated by a significantly lower tail moment in the comet assay (Model group: 8.7 ± 1.2 ; Combination

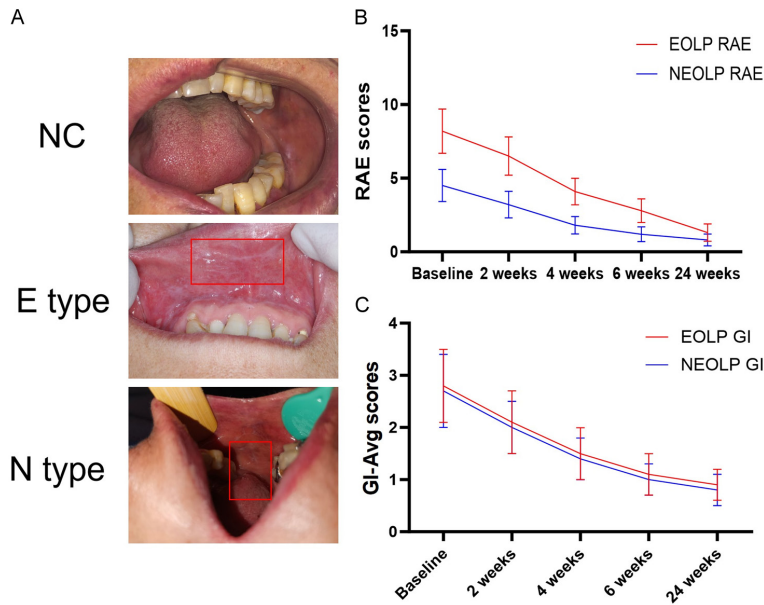


Figure 2. Clinical manifestations and changes in RAE and GI-Avg scores following combined treatment. A. Representative clinical photographs showing oral mucosal manifestations; B. Changes in RAE scores in the EOLP and NEOLP groups from baseline to 24 weeks after treatment; C. Changes in GI-Avg scores from baseline to 24 weeks after treatment. Notes: EOLP, erosive oral lichen planus; NEOLP, non-erosive oral lichen planus; RAE score, reticular, atrophic, and erosive score; GI-Avg, mean Gingival Index.

group: 2.1 ± 0.6 ; $t(18) = 15.42$, $P < 0.001$; **Figure 4B**). Furthermore, secretion of pro-inflammatory cytokines was significantly reduced in the combination group compared with the Model group (TNF- α : 142.5 ± 18.6 pg/mL vs. 312.4 ± 24.3 pg/mL, $t(18) = 13.87$, $P < 0.001$; IL-6: 85.3 ± 10.2 pg/mL vs. 208.6 ± 16.8 pg/mL, $t(18) = 11.93$, $P < 0.001$; IL-17: 62.4 ± 8.5 pg/mL vs. 156.2 ± 14.1 pg/mL, $t(18) = 10.86$, $P < 0.001$; **Figure 4C**).

The combined treatment significantly enhanced cell migration in Transwell assays compared to the Model group (128.6 ± 15.3 cells/field vs. 52.4 ± 8.7 cells/field, independent t test, $t(18) = 14.51$, $P < 0.001$; **Figure 5A**). TEM revealed that the combined treatment preserved mitochondrial ultrastructure in HOKs, with reduced mitochondrial swelling and cristae disruption compared with the Model group (**Figure 5B**). Moreover, premature cellular senescence, as assessed by SA- β -gal staining, was significantly attenuated by the combined treatment compared with the Model group ($12.4 \pm 3.1\%$ vs. $45.6 \pm 5.2\%$ senescent cells, $t(18) = 11.76$, $P < 0.001$; **Figure 5C**).

In the OLP-like mouse model, the combined treatment exerted significant anti-inflammatory effects, as evidenced by reduced serum levels of TNF- α , IL-6, and IL-17 compared with the Model group (one-way ANOVA, $F(3, 36) = 28.45$ for TNF- α , $F(3, 36) = 22.37$ for IL-6, $F(3, 36) = 19.82$ for IL-17; all $P < 0.001$; Tukey's post-hoc tests for Combination vs. Model, all $P < 0.001$; **Figure 6A**). **Figure 6B** presents representative micro-CT (micro-computed tomography) images displaying the three-dimensional structure of the maxilla in mice. These images visually demonstrate the three-dimensional reconstructed alveolar bone structures of each group of mice (Control, Model, Laser, KFX, Laser + KFX). Through the images, one can directly compare the morphology and bone mass of the alveolar

bone across groups. It can be observed that in the Model group (disease model group), there is significant bone resorption and destruction in the alveolar bone, with a marked reduction in bone mass and sparse trabeculae. In contrast, the alveolar bone structure in the Laser + KFX group (combined therapy group) is closer to that of the Control group, with significantly reduced bone resorption and better preservation of bone mass. Micro-CT analysis demonstrated marked amelioration of alveolar bone loss. BMD was significantly higher in the Combination group than in the Model group (0.85 ± 0.08 g/cm³ vs. 0.52 ± 0.06 g/cm³; one-way ANOVA, $F(3, 36) = 31.26$; Tukey's post hoc test, $P < 0.001$; **Figure 6C**). Trabecular number (Tb.N) was also significantly higher in the Combination group than in the Model group (1.85 ± 0.22 mm⁻¹ vs. 1.12 ± 0.18 mm⁻¹; $F(3, 36) = 24.53$; Tukey's post hoc test, $P < 0.001$; **Figure 6D**). Collectively, these findings indicate that Nd:YAG laser combined with Kangfuxin Solution exerts multi-level protective effects, including enhancement of cell migration, preservation of mitochondrial integrity, attenuation of cellular senescence and inflammation, and

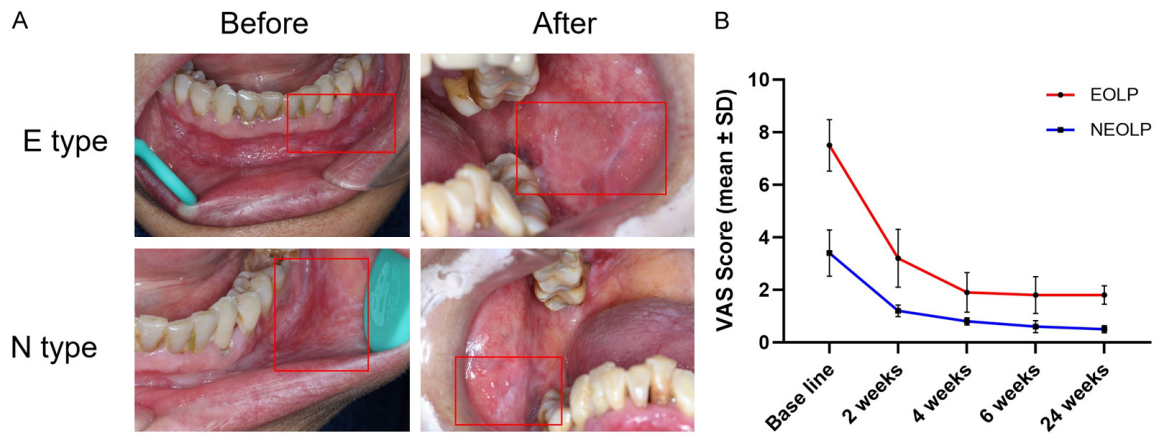


Figure 3. Changes in pain severity following combined intervention in patients with different subtypes of OLP. A. Representative clinical photographs showing oral mucosal manifestations; B. Changes in VAS scores in the EOLP and NEOLP groups from baseline to 24 weeks after treatment. Notes: EOLP, erosive oral lichen planus; NEOLP, non-erosive oral lichen planus; VAS, visual analog scale.

protection against alveolar bone loss, thereby providing a biological basis for the clinical benefits observed in patients.

Discussion

The present study provides preliminary evidence that Nd:YAG laser combined with Kangfuxin Solution may represent an effective, safe, and steroid-sparing therapeutic strategy for patients with oral lichen planus (OLP) complicated by chronic periodontitis. Nevertheless, given the retrospective, single-arm study design, these findings should be interpreted with caution. Clinical improvement was maintained throughout the 24-week follow-up period and was accompanied by improvements in periodontal status, low recurrence rates, and no observed malignant transformation. In parallel, mechanistic experiments demonstrated cytoprotective, anti-inflammatory, and alveolar bone-protective effects of the combined treatment. These findings collectively suggest the potential clinical utility of this combined regimen in the management of OLP.

In the present cohort, combination treatment was associated with rapid and sustained improvement in mucosal lesions in both erosive and non-erosive OLP subtypes. The erosive OLP group exhibited a profound reduction in the mean RAE score from baseline to the end of follow-up, with the majority of patients achieving complete epithelialization of erosive lesions by week 24. Similarly, the non-erosive

OLP group showed significant clinical improvement, with a marked decrease in RAE scores and the majority of patients achieving an asymptomatic state within the first month of treatment initiation. Clinical photographs further demonstrated improvement in oral mucosal architecture, characterized by reductions white striae and erythema and restoration of a more normal mucosal texture. These observations indicate that the combined intervention may facilitate the resolution of OLP-associated mucosal inflammation and promote epithelial repair.

Concomitant with the improvement in mucosal lesions, rapid and significant symptomatic relief was observed. In the erosive OLP subgroup, VAS pain scores markedly decreased from baseline value to a mild level as early as the first follow-up assessment. In the non-erosive subgroup, VAS scores similarly decreased from a moderate baseline level to a minimal level. Such rapid reduction in symptom severity may represent a notable clinical benefit of the combined treatment. However, because no corticosteroid-treated control group was included, direct comparisons between this regimen and conventional corticosteroid therapy cannot be made.

In addition to local clinical improvement, significant changes in circulating inflammatory cytokines were observed after combination therapy. Serum concentrations of the pro-inflammatory cytokines TNF- α , IL-6, and IL-17

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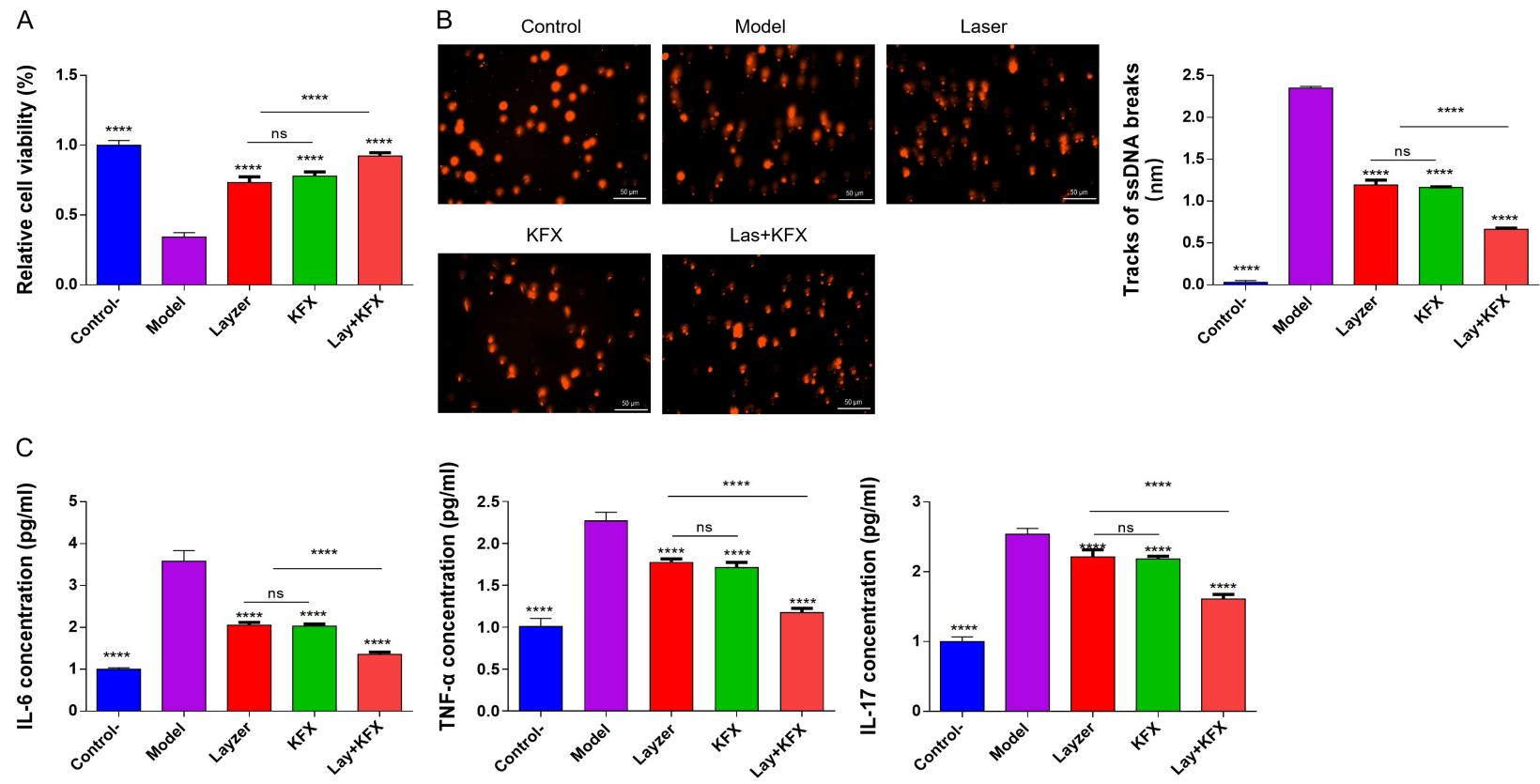


Figure 4. Effects of combined treatment on cell viability, DNA damage, and inflammatory cytokine secretion in LPS-stimulated HOKs. A. Cell viability assessed using the CCK-8 assay; B. DNA damage evaluated using the comet assay (with tail moment used as the quantitative parameter). Representative images are shown at $\times 100$ magnification (scale bar = 50 μm); C. Inflammatory cytokine levels measured by ELISA. Notes: Comparisons between the Model and Combination groups were performed using independent Student's t-tests. **** $P < 0.0001$, ns, not significant.

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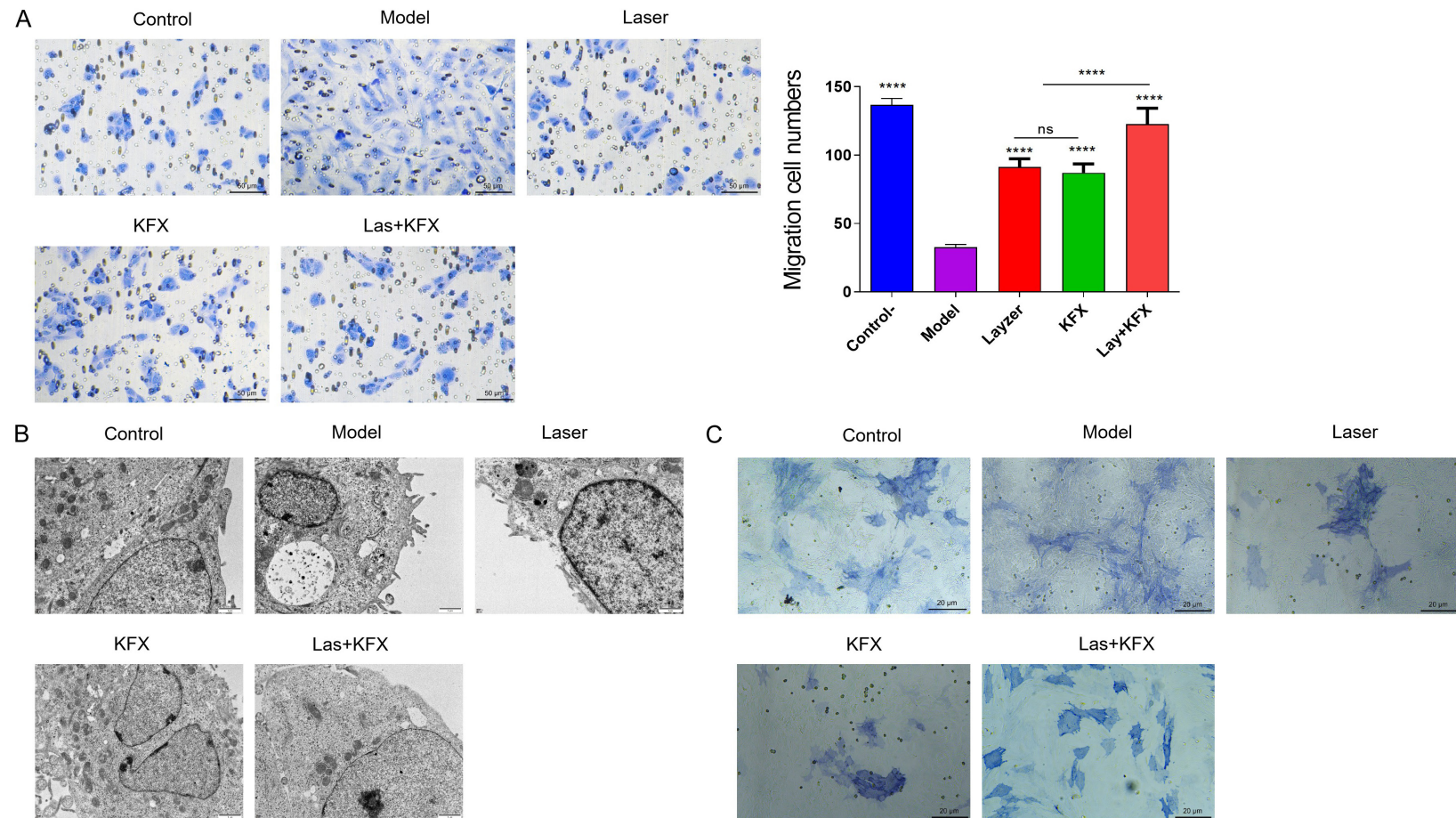


Figure 5. Effects of the combined treatment on cell migration, mitochondrial ultrastructure, and cellular senescence. A. Cell migration assessed using the Transwell migration assay; Representative images are shown at $\times 100$ magnification (scale bar = $50\ \mu\text{m}$); B. Mitochondrial ultrastructure examined by Transmission electron microscopy; Representative images are shown at $\times 1000$ magnification (scale bar = $1\ \mu\text{m}$); C. Cellular senescence assessed by senescence-associated β -gal staining; Representative images are shown at $\times 200$ magnification (scale bar = $20\ \mu\text{m}$). Notes: **** $P < 0.0001$, ns, not significant.

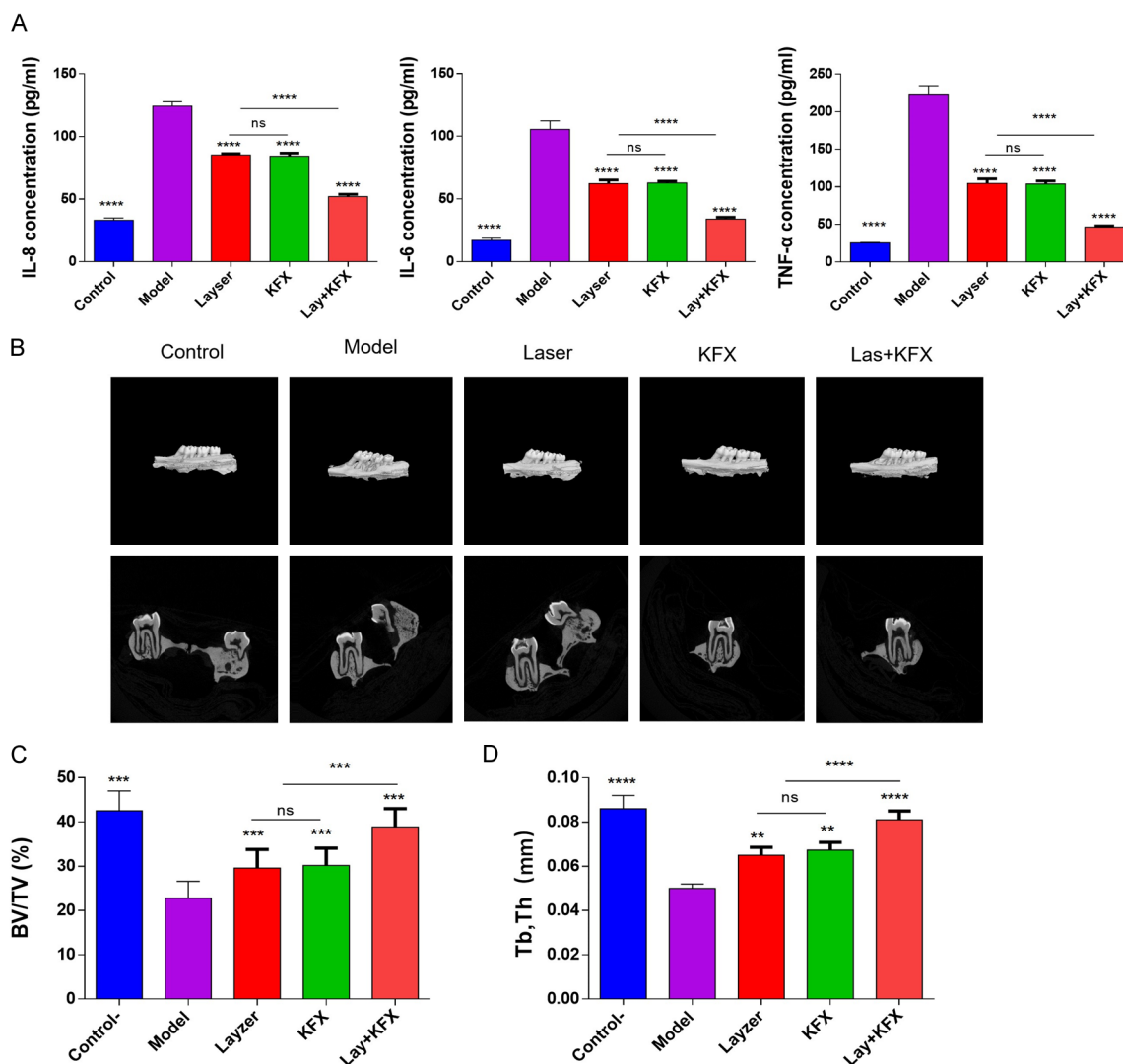


Figure 6. Micro-CT analysis of mouse maxillofacial region. A. Inflammatory cytokine levels (ELISA); B. Representative 3D reconstructions of maxilla; C. Bone mineral density (BMD) of alveolar bone; D. Quantification of Tb (alveolar bone loss). Data are mean $\pm$ SD. ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$, ns, not significant.

were significantly lower at the end of follow-up than at baseline and did not differ significantly from those observed in healthy controls. Given the established involvement of T-cell-mediated inflammatory responses and associated cytokine networks in OLP, reductions in these inflammatory mediators may be associated with the observed clinical improvement. However, whether these cytokine changes directly contribute to sustained remission or a reduced risk of recurrence requires further investigation.

The therapeutic protocol is also associated with significant improvements in periodontal health. The GI-Avg decreased progressively

from baseline to the end of follow-up, indicating a marked reduction in gingival inflammation. This outcome is clinically relevant given the coexistence of periodontitis in OLP patients and the potential for persistent oral inflammation to contribute to periodontal tissue destruction [24]. The antimicrobial and anti-inflammatory effects of Nd:YAG laser, coupled with the mucosal repair-promoting properties of Kangfuxin Solution, may contribute to a local microenvironment conducive to periodontal healing and reduce overall inflammatory burden within the oral cavity [25, 26].

Mechanistic investigations using inflamed human oral keratinocytes further supported the

biological effects of the combined treatment. Combination treatment significantly enhanced cell viability and migration, attenuated inflammation-induced DNA damage and premature cellular senescence, and reduced the secretion of TNF- α , IL-6, and IL-17. Transmission electron microscopy further demonstrated preservation of mitochondrial ultrastructure, with less mitochondrial swelling and cristae disruption. These cytoprotective, anti-senescent, and mitochondrial-stabilizing effects reduce keratinocyte apoptosis and preserve epithelial integrity, which are critical for sustained OLP remission.

In the mouse model of OLP-like mucosal inflammation, micro-CT analysis demonstrated that combination therapy significantly reduced alveolar bone loss and preserved BMD, with favorable effects on trabecular architecture and bone volume fraction. This bone-protective effect, consistent with clinical periodontal improvements, indicates that the combined regimen may have protective effects against inflammation-associated alveolar bone destruction.

Several limitations of this study should be acknowledged. First, this study employed a retrospective, single-arm design and lacked parallel control groups receiving laser monotherapy, Kangfuxin Solution monotherapy, standard corticosteroid therapy, or placebo treatment. Moreover, the healthy control group received no intervention and served as reference for inflammatory cytokine levels. Consequently, the observed clinical improvements cannot be definitively attribute to the combined regimen, and the relative contributions of Nd:YAG laser and Kangfuxin Solution cannot be determined. Second, the relatively small sample size ($n = 50$) limits the statistical power and generalizability of our findings. Third, the 24-week follow-up period was insufficient to assess long-term recurrence or sustained remission. Fourth, although our *in vitro* and *in vivo* experiments provide supportive mechanistic evidence and included monotherapy groups, these experimental findings cannot establish that the same mechanisms are responsible for the clinical effects observed in patients. Future prospective, randomized controlled trials with larger cohorts, appropriate comparator groups, and longer follow-up are

warranted to validate the efficacy and safety of this combination strategy and to clarify the individual and combined effects of Nd:YAG laser and Kangfuxin Solution.

Conclusion

Nd:YAG laser combined with Kangfuxin Solution can effectively suppress local and systemic inflammation, protect DNA and mitochondrial integrity, inhibit cellular senescence, promote epithelial migration and mucosal repair, and preserve alveolar bone. These effects were associated with rapid symptom relief, high rates of complete remission, low recurrence during the 24-week follow-up period, favorable safety, and concurrent improvement in periodontal status.

Despite the limitations, this steroid-free, minimally invasive combination shows promise as a potential therapeutic strategy for the clinical management of OLP, particularly in patients with comorbid periodontitis. Our preliminary findings warrant further investigation in rigorously designed randomized controlled trials to confirm its clinical efficacy, safety, and underlying mechanisms.

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Disclosure of conflict of interest

None.

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