Journal of Lasers in Medical Sciences

J Lasers Med Sci 2026;17:e50924

Original Article

http://journals.sbmu.ac.ir/jlms

doi:10.34172/jlms.50924

Enhancing Proliferation and Pluripotency in Human Dental Pulp Stem Cells through 980-nm Laser Irradiation: Implications for Regenerative Dentistry

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Received: November 20, 2025
Accepted: May 25, 2026
ePublished: August 8, 2026

Abstract

Introduction: Dental pulp stem cells (DPSCs) possess remarkable proliferative ability and multilineage differentiation potential, and they are known as immunomodulatory cells. Identifying factors that enhance DPSC proliferation is crucial, as accelerated expansion is necessary for tissue engineering applications, while maintaining pluripotency gene expression is essential to preserve their proliferative and differentiation potential. Low-level laser irradiation (LLLI) has increasingly been recognized as a promising non-invasive approach to accelerate proliferation and enhance tissue regeneration. Within this framework, the current study was designed to evaluate the influence of laser irradiation on proliferation, pluripotency, and angiogenesis in DPSCs.

Methods: The DPSCs were purchased from the Iranian Biological Resources Center and cultured under standard conditions. The experimental protocol involved exposing DPSCs to a 980 nm diode laser with an output power of 50 mW for a duration of 20 seconds, corresponding to an energy density of 1 J/cm^2. Following a 24-hour incubation period post-irradiation, cell viability was quantitatively measured using the MTT colorimetric assay. Subsequently, the expression levels of Sox2, Nanog, VEGF, TGF-β, PCNA, and Cyclin D1 were assessed through quantitative reverse transcription-polymerase chain reaction (qRT-PCR), while the protein expression of Sox2, TGF-β, and Cyclin D1 was determined using western blot analysis.

Results: The results showed that laser irradiation at 980 nm for 20 seconds increased the expression of Sox2, TGF-β, and Cyclin D1 at the RNA expression level ($P<0.05$). Moreover, Sox2 and Cyclin D1 protein levels were increased compared to the control group.

Conclusion: Our findings suggest that irradiation with a 980-nm laser at an energy density of 1 J/cm^2 significantly enhances the proliferative capacity and upregulates pluripotency marker expression in DPSCs, supporting its potential as a therapeutic approach in regenerative medicine.

Keywords: Dental pulp stem cells, Laser irradiation, Proliferation, Pluripotency, Angiogenesis

Introduction

Dental mesenchymal stem cells (DMSCs) are typically isolated from various dentoalveolar tissues and include some different cell types, such as human dental pulp stem cells (DPSCs), stem cells originating from the apical papilla (SCAPs), periodontal ligament stem cells (PDLSCs), and stem cells from human exfoliated deciduous teeth (SHED).[1-6] These cell populations are characterized by robust expansion capacity and multilineage differentiation potential, with reported commitment toward osteogenic, adipogenic, neurogenic, and chondrogenic phenotypes.[3,6]

Dental-derived mesenchymal stem cells, particularly DPSCs and SHED, also possess notable immunomodulatory properties. These features support their potential use in allogeneic settings and make them attractive candidates as alternatives to bone marrow-derived mesenchymal stem cells in regenerative applications.[6-10]

In this context, identifying factors that can effectively enhance DPSC proliferation is crucial. Since DMSCs proliferation is a time-consuming process, recognizing

Please cite this article as follows: Soheilifar MH, Hemmati P, Ghahremani-Nasab M, Shirkavand A, Keshmiri Neghab H, Nobari S, et al. Enhancing proliferation and pluripotency in human dental pulp stem cells through 980-nm laser irradiation: implications for regenerative dentistry. J Lasers Med Sci 2026;17:e50924. doi:10.34172/jlms.50924

effective methods and factors to accelerate their expansion is essential prior to their application in tissue engineering. Additionally, studies have shown that commonly used *in vitro* culture methods may reduce the expression of pluripotency markers (Oct4, Sox2, and Stro1) in human dental stem cells. Therefore, maintaining the expression of pluripotency-related genes is critical for preserving the functional properties of DPSCs.[11-17] Several factors have been explored to promote DPSCs proliferation or differentiation, including insulin-like growth factor 1 (IGF-1), enamel matrix derivatives, and Trichostatin A (a histone deacetylase inhibitor) [6,18-23]; however, a major limitation of these factors is their high cost. Among the approaches investigated for promoting MSC expansion, low-level laser therapy (LLLT), also termed low-level laser irradiation (LLLI), has attracted considerable attention due to its potential stimulatory effects on cell growth.[6] Evidence indicates that LLLT increases cellular proliferation and regulates biological activity in various cell types, such as fibroblasts, keratinocytes, and osteoblasts. Additionally, it has shown effectiveness in wound healing, angiogenesis, reducing pain, and facilitating bone repair and remodeling.[6,24-26] LLLT has been reported to influence several cellular processes, including proliferation, differentiation, migration, and programmed cell death. It may also modulate the production of growth factors such as FGF and VEGF, thereby contributing to tissue repair and regeneration.[6,27,28] Multiple studies have demonstrated that LLLT exerts its effects via signaling pathways involving cytokines such as IGF-1, mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), and bone morphogenetic protein (BMP)/Smad. In addition, LLLT increases intracellular ATP production, regulates the activity of inducible nitric oxide synthase, and suppresses several proinflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8. It also regulates growth factors such as PDGF, IGF-1, NGF, and FGF-2.[29-32] Successful tissue engineering strategies rely heavily on angiogenesis, as the establishment of a functional vascular network is essential for tissue survival and regeneration. However, achieving adequate vascularization remains a major challenge in this field. DPSCs are very useful in tissue engineering due to their angiogenic properties.[33-35] DPSCs induce angiogenesis by releasing angiogenic factors into the conditioned medium (CM), and the supernatant profile of these cells shows the presence of VEGF and MCP-1, classical factors that induce angiogenesis.[35-39] In view of these observations, the present study was designed to evaluate the effects of LLLT, applied under defined laser parameters, on the expression of proliferation-related markers (PCNA and Cyclin D1) as well as pluripotency-associated genes (Oct4, Sox2, and Nanog) in DPSCs. In addition, the present study evaluated the effect of LLLT on the angiogenic potential of DPSCs by analyzing the secretion levels of angiogenesis-related markers, including VEGF and TGF-β.

Material and Methods

Dental pulp stem cell culture

DPSCs were purchased from the Iranian Biological Resource Center. The cells were maintained in the α-MEM medium (Sigma-Aldrich) supplemented with 10% fetal bovine serum (FBS; DNAbiotech) and 1% penicillin/streptomycin (DNAbiotech). Cultures were then incubated at 37°C in a humidified atmosphere containing 5% CO_2 for three days until reaching confluence.

Laser irradiation

DPSCs were seeded in 24-well plates and irradiated using a 980-nm, 50-mW near-infrared (NIR) Laser Diode Dot Module (spot size~2 mm in diameter at the aperture, continuous wave output; JTSF, Inc). The procedure was conducted under sterile conditions within a laminar flow hood. A fixed distance was maintained between the laser device and the surface of the cell layer in all experimental groups (Table 1). Each sample received a single irradiation session, and post-irradiation assessments were carried out 24 hours later to evaluate the effects.

Cell viability assay

Cell viability was evaluated using the MTT assay. Briefly, DPSCs were seeded in 96-well plates at a density of 10,000 cells per well and allowed to incubate for 24 hours. After exposing DPSCs to irradiation for 10, 20, 40, and 80 seconds, each well received 0.2 mL of MTT solution (0.5 mg/mL), which was then incubated for 4 hours at 37°C. Subsequently, the supernatant was removed, and 100 µL of DMSO (Sigma-Aldrich) was added to each well and then incubated for half an hour. Finally, the absorbance was measured by an ELISA reader at a wavelength range of 540 to 630 nm.

Quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) analysis

Gene expression levels of Sox2, Nanog, VEGF, TGF-β, PCNA, and Cyclin D1 were quantified via qRT-PCR using the primer sequences detailed in Table 2. Following a 24-hour incubation period in 6-well plates, DPSCs were subjected to 980-nm laser irradiation for 20 seconds. Total RNA was subsequently isolated using RNX-Plus™ solution (SinaClon) and quantified using a NanoDrop spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA). Subsequently, cDNA was then synthesized from the extracted RNA using a commercial kit (Parstous Biotechnology, Iran). Targeted gene expression was evaluated through qRT-PCR and analyzed via the $2^{-\Delta\Delta Ct}$ method, and β-actin was used as a reference

Table 1. Parameters of laser irradiation time and energy density applied to DPSCs.

Laser irradiation time	Energy density (J/cm²)
10 s	0.5
20 s	1
40 s	2
80 s	4

Table 2. Primer sequences of genes used for qRT-PCR

Gene	Primer sequence (5' to 3')	Product length (bp)
Sox2	Forward TACAACTCCATGACCAGCTCG Reverse ACTTGACCACCGAACCCATG	118
Nanog	Forward ATTCTTCCACCAGTCCCAAAGG Reverse AGCTGAGGTTCAGGATGTTGG	207
VEGF	Forward ATCTTCAAGCCATCCTGTGTGC Reverse TATGTGCTGGCCTTGGTGAGG	138
TGF-β	Forward AGGGATAACACACTGCAAGTGG Reverse AAGCAATAGTTGGTGTCCAGGG	176
PCNA	Forward AAGATGCCTTCTGGTGAATTTGC Reverse TGTCACCGTTGAAGAGAGTGG	267
Cyclin D1	Forward TTCGTGGCCTCTAAGATGAAGG Reverse TTGAGCTTGTTCACCAGGAGC	125
β-actin	Forward AGACGCAGGATGGCATGGG Reverse GAGACCTTCAACACCCCAGCC	161

gene.[40,41]

Western blotting

The expression of Sox2, TGF-β, and Cyclin D1 proteins with and without irradiation was measured by western blotting. To this end, DPSCs were cultured in 6-well plates for 24 hours. The cells were then irradiated with a 980-nm laser for 20 seconds. Cell lysates were prepared using a buffer supplemented with a protease inhibitor cocktail. Equal amounts of protein (20 µg per sample) were then separated by SDS-PAGE and transferred onto nitrocellulose membranes. To minimize non-specific antibody interactions, membranes were blocked using non-fat dry milk (NFDM). After blocking, the membranes were incubated overnight at 4°C with primary antibodies targeting Sox2, TGF-β, Cyclin D1, and β-actin. After thorough washing steps, membranes were incubated with goat anti-mouse HRP-conjugated secondary antibodies for 1 hour at room temperature. Finally, protein bands were detected using an enhanced chemiluminescence (ECL) detection system.[41]

Statistical analysis

Experiments were performed in triplicate. Data were reported as mean ± standard error of the mean (SEM). Statistical analyses were carried out in GraphPad Prism version 7 (GraphPad Software Inc., La Jolla, CA, USA). Comparisons between two independent groups were conducted using a two-tailed unpaired Student's t-test. Statistical significance was defined as $^{*}P<0.05$ and $^{**}P<0.01$.

Results

Short-duration laser irradiation enhances DPSCs viability

According to the MTT results (Figure 1), the cell viability of the group that was exposed to laser irradiation for 10 seconds was not statistically significant compared to the control group. In irradiation for 20 seconds, the cell viability increased significantly compared to the control group ($P<0.001$). In contrast, the effects of laser irradiation for 40 and 80 seconds on cell survival were not significant.

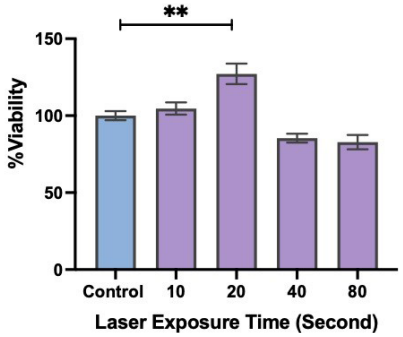

Figure 1. Histogram of the MTT assay on the effects of irradiation on the viability of DPSCs after exposure times of 10, 20, 40, and 80 seconds ($^{**}P<0.01$).

qRT-PCR reveals significant upregulation of proliferation and pluripotency genes following irradiation in DPSCs

qRT-PCR was performed to determine whether irradiation influenced genes associated with proliferation, pluripotency, and angiogenic signaling. Relative to control cells, irradiated DPSCs showed significant increases in Sox2, TGF-β, and Cyclin D1 expression, with fold changes of 2.76, 1.76, and 2.30, respectively ($P<0.05$). VEGF and PCNA expression increased modestly by 1.31- and 1.30-fold, whereas Nanog expression showed no statistically significant change (0.90-fold of control); none of these latter changes reached statistical significance (Figure 2).

Protein expression levels of Sox2, TGF-β, and Cyclin D1 in irradiated DPSCs

Western blot analysis was performed to assess the protein levels of Sox2, TGF-β, and Cyclin D1 following irradiation (Figure 3). These targets were selected based on the qRT-PCR findings. The results indicated that TGF-β protein expression remained unchanged between irradiated and control groups. In contrast, Cyclin D1 protein levels were elevated following laser exposure. Notably, Sox2 protein expression was markedly higher in irradiated DPSCs than in untreated controls.

Discussion

In the present study, we investigated the effects of 980-nm laser irradiation on the survival, proliferation, pluripotency, and potential angiogenic potential of DPSCs. Our MTT assay findings indicated that cell viability in the group exposed to 20 seconds of laser irradiation was higher than that in the control group. qRT-PCR analysis revealed significant increases in the expression levels of TGF-β, Cyclin D1, and Sox2 genes post-irradiation, while no significant changes were observed in PCNA, VEGF, and Nanog gene expression. Additionally, Western blotting demonstrated that Cyclin D1 and Sox2 protein levels significantly increased following 980-nm laser irradiation, whereas TGF-β protein expression remained

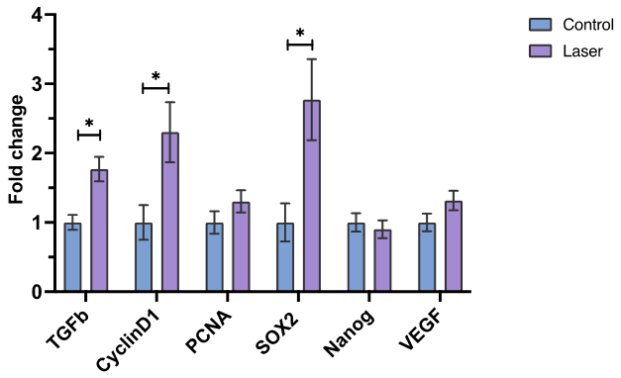

Figure 2. Histogram of the qRT-PCR of Sox2, Nanog, VEGF, TGF-β, PCNA, and Cyclin D1 genes expression after exposure to laser irradiation. The gene expression is expressed as fold change relative to the control (*$P<0.05$)

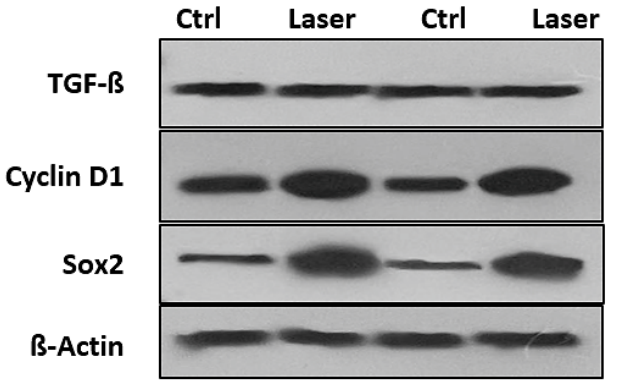

Figure 3. The expression level of TGF-β, Sox2, and Cyclin D1 proteins in DPSCs exposed to irradiation

unchanged.

The efficacy of low-level laser therapy (LLLT) in modulating cell proliferation is highly contingent upon specific laser parameters. Consequently, defining the optimal configurations, including energy density, output power, and the distance between the source and target cells, is imperative to maximize the proliferative capacity of dental stem cells for clinical applications.[13,27,42,43] Research indicates that red and infrared wavelengths (600–1200 nm) elicit biological responses, with energy densities ranging from 0.05 to 10 J/cm² associated with biostimulatory effects [6,12,44-46]; however, doses exceeding 10 J/cm² may lead to inhibitory outcomes.[44] Low-power lasers (660, 810, or 980 nm) with energy densities of 0.1 to 3 J/cm² have been shown to promote DMSC proliferation, although further research is needed to refine optimal laser parameters.[6]

Consistent with these findings, the MTT assay results demonstrated that a 20-second exposure to a 980-nm laser at an energy density of 1 J/cm² enhanced the viability of DPSCs. Cyclin D1, a critical regulator of cell cycle progression, was significantly upregulated under laser irradiation, corroborating the findings of Sperandio et al., who reported increased Cyclin D1 expression in keratinocytes following low-level laser treatment.[47-49] Parallel to previous reports, our findings showed that Cyclin D1 expression significantly increased at both the gene and protein levels under the influence of laser irradiation. Based on these results, it can be stated that the stimulating effect of laser irradiation on cellular proliferation may be mediated, at least in part, through the upregulation of Cyclin D1.

In addition, DPSCs can promote tissue vascularization by secreting angiogenic factors that act on local endothelial cells or by differentiating into endothelial-like cells within the vasculature.[50,51] Since angiogenesis is critical for tissue regeneration and repair, DPSC-conditioned medium (DPSC-CM) is expected to contain factors that stimulate this process. The role of VEGF in regulating the migration and differentiation of endothelial cells (ECs) and in recruiting them for angiogenesis and endothelialization in injured tissue has been well-established. Analysis of the DPSCs-CM has shown the presence of VEGF and MCP-1, two classical factors that induce angiogenesis. In addition, DPSCs demonstrate angiogenic potential through the expression of endothelial differentiation markers.[35,52-55] Nawam et al.[14] investigated the angiogenic and odontogenic effects of low-level laser therapy (660 nm, 1 J/cm²) on the dentin-pulp complex *in vitro*. They reported that laser irradiation at these parameters significantly upregulated VEGF and VEGFR2 expression.[14]

In our study, qRT-PCR analysis revealed that VEGF gene expression showed a slight, non-significant increase 24 hours post-irradiation, which is generally consistent with previous reports, although the magnitude of the response was lower in the present study. This suggests that the cellular response to laser irradiation may depend on experimental conditions, including the laser dose and exposure duration.

A network of transcriptional regulators, including Sox2, Oct4, and Nanog, is essential for preserving the undifferentiated phenotype and self-renewing properties of stem cells.[56,57] Consistent with this role, Oct4 and Nanog expression has been documented in DPSCs expressing the stem cell-associated markers STRO-1$^+$ and CD146$^+$. The knockout of Oct4 and Nanog leads to a significant reduction in the proliferative capacity of human DPSCs as well as in the expression of STRO-1$^+$ and CD146$^+$ markers. These factors are critical for the functional properties of DPSCs, as loss of Oct4 and Nanog expression has been shown to significantly reduce both the proliferative and osteogenic potential of these cells. In addition, the upregulation of Oct4/Nanog increases the colony-forming ability and promotes osteogenic, chondrogenic, and adipogenic differentiation capacity of pulp stem cells.[58-60] Another study has shown that STAT3, Oct4, and Sox2 can play a key role in preserving the pluripotency of DPSCs and PDLCs by maintaining intercellular interactions.[61] However, *in vitro* culture methods may reduce the expression of pluripotency markers (Oct4, Sox2, and Stro-1) in DPSCs, PDLCs, and other MSCs.[62] A number of stimulating factors can be used to overcome this problem. In this context, studies have shown that laser irradiation can be a suitable option for both increasing the proliferation of stem cells and serving as a regenerative therapy.[11-17] In the present study, the expression of Sox2

and Nanog was evaluated following a 20-second laser irradiation of DPSCs. Our qRT-PCR findings revealed that while LLLT failed to upregulate Nanog, it induced a significant increase in Sox2 transcript levels. This upregulation was further validated at the translational level, as Western blot analysis demonstrated a significant elevation in Sox2 protein expression in the irradiated groups. In conclusion, given that Sox2 is activated in response to physical or chemical stimuli, our findings indicate that laser irradiation may enhance pluripotency through the upregulation of Sox2 expression.

TGF-β is a cytokine with a critical role in biological processes and is secreted by cells, including endothelial cells, fibroblasts, macrophages, platelets, and immune cells.[63-65] MSCs can induce angiogenic processes through the TGF-β/SMAD pathway. Moreover, TGF-β expression is directly correlated with blood vessel density.[66] TGF-β is involved in the differentiation of SHED into vascular smooth muscle cells, which may have potential applications in vascular regenerative medicine.[63] As demonstrated by Arany et al. [67], low-level laser treatment facilitates the activation of latent TGF-β, which subsequently induces the *in vitro* differentiation of dental stem cells into odontoblasts and enhances *in vivo* dentin regeneration.[67]

Our findings revealed a significant increase in TGF-β gene expression following laser irradiation, whereas no significant changes were observed at the protein level compared with the control group. This discrepancy may result from mRNA instability and rapid degradation prior to translation, as well as potential epigenetic mechanisms, such as microRNAs inhibitory function, that may regulate TGF-β translation despite the presence of mRNA.

One limitation of the present study is that gene and protein expression were evaluated at a single time point (24 hours post-irradiation). Since cellular responses to low-level laser irradiation may vary over time, assessing multiple time points could provide a more comprehensive understanding of the temporal dynamics of proliferation and the expression of pluripotency markers. Future studies should investigate the temporal effects of 980-nm laser irradiation on DPSCs.

Conclusion

In conclusion, notwithstanding the inherent limitations of this study, our findings suggest that a 980-nm laser irradiation protocol (20 s, 1 J/cm^2) significantly enhances the viability, proliferative capacity, and pluripotency potential of DPSCs. Notably, the applied laser treatment successfully upregulated the expression of both Sox2 and Cyclin D1 at both the transcriptomic and translational levels, indicating a robust molecular response to irradiation. While TGF-β gene expression was elevated, no corresponding change in protein levels was observed, and laser irradiation did not affect VEGF gene expression. Given that no statistically significant changes were observed for VEGF or TGF-β under the experimental conditions, it is suggested that angiogenic effects may be context-dependent or require longer time points or additional stimuli. Overall, the results support the potential utility of laser irradiation as a practical and cost-efficient adjunct in regenerative dentistry. Further experimental and preclinical research is needed to substantiate these outcomes and to clarify the biological mechanisms responsible for the observed effects.

Acknowledgements

We acknowledge the Yara Institute of Wound and Tissue Repair Technologies for hosting the experimental work and for the technical assistance essential to the related assays. We utilized AI-powered tools to check grammar and enhance the academic quality of the text, which was primarily written by the authors. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the published article.

Authors' Contribution

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Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

All experimental protocols were approved by the Ethical Committee of Hamadan University of Medical Sciences (Ethics Approval Code: IR.UMSHA.REC.1400.677).

Funding

This work was funded by Hamadan University of Medical Sciences (Grant ID: 14010206687).

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