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Effects of Low-Level Gallium-Aluminum-Arsenide Laser Therapy on Human Dermal Fibroblast Proliferation, ATP, and ROS Levels

Sameerah Hasan Abdullah[1], Manijhe Mokhtari-Dizaji[1*], Zeinab Hormozi-Moghaddam[2], Mohsen Bakhshandeh[3], Mohammad Ali Nilforoshzadeh[4]

[1]Department of Medical Physics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[2]Radiation Biology Research Center and Department of Radiation Sciences, Allied Medicine Faculty, Iran University of Medical Sciences (IUMS), Tehran, Iran
[3]Department of Radiology Technology, Allied Medical Faculty, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Skin and Stem Cells Research Center, Tehran University of Medical Science, Tehran, Iran

***Correspondence to**
Manijhe Mokhtari-Dizaji,
Email: mokhtarm@modares.ac.ir

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Abstract

Introduction: Fibroblasts, the primary cells of connective tissue, play a crucial role in the healing process of tissues and organs. The study aimed to evaluate the effect of continuous gallium-aluminum-arsenide (Ga-Al-As) laser at a wavelength of 830 nm and output powers of 10 mW and 27 mW on adenosine triphosphate (ATP), reactive oxygen species (ROS) production, and fibroblast cell proliferation in culture.

Methods: Human fibroblast cells were cultured in a 96-well plate and exposed to continuous radiation from a Ga-Al-As laser at 830 nm, utilizing two different output powers of 10 and 27 mW and various energy densities. After 24 hours of laser exposure, fibroblast cell proliferation was assessed using the MTT assay. ROS production was measured with a microplate reader, and ATP levels were quantified.

Results: The most significant increase in cell proliferation was observed in the 10 mW group at an energy density of 3.78 J/cm² (0.79 ± 0.07) compared to the control group (0.51 ± 0.05). In contrast, the 27 mW group at 10 J/cm² exhibited lower cell proliferation (0.51 ± 0.05) during 90 s. ATP production significantly increased in the 10 mW group at 3.78 J/cm² (15,404 ± 819), compared to the control group (115 ± 51). Additionally, the groups had no significant difference in ROS levels.

Conclusion: The results suggest that low-level laser therapy (LLLT) using a Ga-Al-As laser at 830 nm with an output power of 10 mW for 3.78 J/cm² significantly affected fibroblast cell proliferation and ATP synthesis.

Keywords: Photobiomodulation, Human dermal fibroblast, Cell proliferation, ATP synthesis, Reactive oxygen species, Wound healing

Introduction

The complex process of wound healing involves several biological activities, including blood coagulation, inflammation, tissue regeneration, and remodeling. This process requires the collaboration of various cell types, such as immune cells, endothelial cells, fibroblasts, and keratinocytes.[1,2] Among these, the migration and proliferation of fibroblasts are crucial for the formation of granulation tissue and the overall healing of wounds. The coordination of intercellular and intracellular pathways during fibroblast migration and proliferation highlights their essential role in the wound-healing process.[3]

Low-level laser therapy (LLLT) is a form of photomodulation that alters biological activity using photons.[4,5] The biochemical reactions stimulated by LLLT play a vital role in cellular repair and its overall effectiveness. It is important to select the appropriate wavelength and power density (W/cm²) and to deliver the necessary dose (J/cm²) consistently to achieve optimal photochemical interactions and desirable treatment outcomes. Laser-generated photons can accelerate the healing process of both acute and chronic wounds, especially those that are healing slowly.[6,7] LLLT also causes changes in the distribution of organelles within cells. While photon absorption is the primary mechanism in photobiomodulation, it is theoretically possible for photons to penetrate cells and induce changes even if they are not fully absorbed.[8] Different materials absorb light at different wavelengths; for example, injured skin cells are more sensitive to light than intact tissue. The accelerated healing of wounds results from biochemical processes that begin when the target cells absorb the photons.[9]

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Laser therapy involves multiple processes that target cellular mechanisms. When a laser probe emits photons, these photons are absorbed by the mitochondria and cell membranes of the target cells. This absorbed energy is then integrated into cellular molecules, leading to changes in their physical or chemical properties. It can also activate or deactivate enzymes and increase kinetic energy. One significant outcome of this process is the increased production of adenosine triphosphate (ATP), which serves as the primary energy source for cellular activities and protein synthesis. Additionally, laser therapy promotes cell proliferation and alters cell membrane permeability, enhancing calcium uptake. Together, these factors contribute to a growth factor response within cells and tissues. As a result, a series of metabolic effects occurs, leading to various physiological changes. These changes ultimately improve tissue repair, accelerate the resolution of inflammation, and help reduce pain.[10,11]

LLLT uses red or near-infrared lasers with wavelengths between 600 and 1100 nm and power levels ranging from 1 to 500 mW. The power directed at the tissue or cell monolayer is measured in milliwatts (mW). This type of radiation can be delivered in a continuous wave or as pulsed light, maintaining a steady beam with a relatively low energy density of 0.04 to 50 J/cm^2.[12] Various laser light sources, including gallium-aluminum-arsenide (Ga-Al-As), helium-neon, and ruby, are employed in different LLLT treatments, often according to specific protocols. One key characteristic of LLLT is that it does not generate heat or vibrations, as it transmits energy at low levels. Consequently, the temperature of the tissue exposed to the laser radiation does not significantly increase, and the responses are nonthermal. Research has shown that after exposure to LLLT, the initial rise in temperature of the target tissue is negligible, approximately ± 1 °C.[13] Numerous researchers confirmed that during LLLT radiation, the temperature of fibroblast suspensions did not alter.[14] Schneede et al also found a temperature rise of less than 0.065 °C under 40 mW/cm^2 of laser light by employing a micro-thermal probe in a monolayer of cells.[15]

ATP is crucial for cell proliferation because it is the primary energy currency of the cell. ATP plays a critical role in supporting biosynthesis, cell cycle progression, maintenance of ion gradients and pH, as well as regulating shifts between mitochondrial and glycolytic energy production pathways. ATP increase is essential for every step in the proliferation process. If ATP levels are insufficient, the cell may produce a stress response or halt the cell cycle.[16]

Reactive oxygen species (ROS) are molecules that contain one or more unpaired electrons alongside at least one oxygen atom, which allows them to exist independently. These reactive species, including oxygen, are primarily produced in three cellular locations: peroxisomes, the endoplasmic reticulum (ER), and mitochondria. The electron transport chain (ETC) within the mitochondria generates free radicals, commonly referred to as ROS and singlet oxygen. The balance between the levels of antioxidants in cells and the rate of oxidant generation helps maintain a constant level of ROS within them.[17]

ROS play a dual role in biological systems, acting as essential signaling molecules in physiological processes and contributing to cellular damage when their levels become excessive. The stability and balance of ROS are critical for maintaining cellular homeostasis, and disruptions in this balance can have significant clinical implications. An imbalance favoring excessive ROS production leads to oxidative stress, which can damage cellular components like lipids, proteins, and DNA. Maintaining ROS stability is vital for preventing and managing various diseases.[18]

A decline in ATP synthesis and uncontrolled release of ROS can occur if mitochondrial function is impaired. The physiological effects of ROS depend on their concentration; while high levels can directly induce cell death during cancer treatment, lower levels may promote cell migration and proliferation.[17]

The dermis of the skin contains cells called dermal fibroblasts, which play a crucial role in producing connective tissue and facilitating healing after skin injuries.[19] Fibroblast growth factor (FGF) can stimulate the proliferation of these dermal fibroblasts, which are somewhat specialized or differentiated cells.[20] In the context of wound healing, metabolically active cells are essential for managing the extracellular matrix (ECM), intracellular fluid volume, and pressure.[21] Given the significance of these factors, the study aimed to evaluate the effects of continuous Ga-Al-As laser treatment at a wavelength of 830 nm and output powers of 10 mW and 27 mW on ATP levels, ROS production, and fibroblast cell proliferation in vitro. While previous studies have explored the impact of LLLT on fibroblast proliferation, limited research exists on the comparative effects of varying power outputs on ATP and ROS production.

Materials and Methods

Cell Culture

A human dermal fibroblast cell (HDFC) line was purchased from the Iranian Biological Resource Center (IBRC, Tehran, Iran). HDFCs were cultured in the DMEM/F12 medium (Bio Idea Co., Tehran, Iran) containing 10% FBS (Bio Idea Co., Tehran, Iran) and 0.5-1% streptomycin (Bio Idea Co., Tehran, Iran). They were maintained in an incubator with 5% CO_2 and 95% humidity at 37 °C until passage.[4]

Laser Irradiation Parameters

Human dermal fibroblast cells (5000 cells) were seeded in 200 µL of DMEM/F-12 supplemented with 10% FBS in sterile 96-well culture plates. The cells were divided into nine groups, each containing three samples. HDFCs were

irradiated using an LLLT device (Ga-Al-As, Uni-Laser 201, ASAH Medico Co., Japan) operating at a wavelength of 830 nm in continuous mode. The maximum output powers used were 10 mW and 27 mW at room temperature. The laser source had a spot diameter of 5.50 mm, which matched the diameter of the wells in the culture plates. There was no distance between the laser source and the cell plate. The device operated in continuous wave mode, with each group exposed to different output powers of 10 mW and 27 mW for various radiation times: 90 s, 3, 6, 9, 12, 15, 18, 20, and 30 minutes. Throughout all studies, the temperature was monitored continuously. Temperature variations at the two power levels were measured for 20 minutes using a digital thermocouple. The temperature was monitored every second during irradiation using a portable digital thermometer equipped with K-type thermocouples (TP-01, Lutron Electronic Enterprise Co., Taiwan). This thermometer was connected to a computer via an RS-232 port. Thermocouple data were recorded every second with the thermometer software (Multilogger, Thermometer, CHY502A, Taiwan). The energy density (J/cm^2) for each combination of output power (W), radiation time (s) and beam size (cm^2) was calculated:

$$Energy\ Density\left(\frac{J}{cm^2}\right)=\frac{\text{Power}(\text{W})\times\text{Time}(\text{s})}{\text{Beam size}(\text{cm2})}$$

The energy density provides a precise measure of the energy delivered per unit area for each treatment condition. For delivery of 10 mW, the energy densities recorded were 3.78, 7.56, 15.12, 22.68, 30.24, 37.8, 45.36, 52.92, and 75.60 J/cm^2. For 27 mW, the energy densities were 10, 20, 40, 60, 80, 100, 120, 140, and 205 J/cm^2. The control group plates were not exposed to any laser. The sham group was placed in the irradiated environment but without laser exposure. After LLLT, the cells were incubated at 37 °C for 24 hours, and cell proliferation was measured for each group. All tests were repeated three times.

Cell Proliferation Assay (MTT)

The proliferation rate of HDFCs following laser exposure was assessed using the MTT assay (3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide) from Bio Idea Co. in Tehran, Iran. After 24 hours, the MTT assay procedure was conducted to evaluate the survival of 5,000 cultured HDFC cells, which were placed in 96-well plates for all experimental groups following laser treatment. The proliferation rate was calculated using the MTT results obtained after 48 hours. This rate was determined as the ratio of the optical density (OD) of the treated cells to the OD of the corresponding group on a standard curve, with the control group consisting of the maximum number of cells (80 000). An ELISA instrument (DANA, Model DA3200, Iran) was utilized to measure the absorbance of the cell groups at a wavelength of 570 nm.

The MTT standard curve was plotted to estimate the cell number for the optical density obtained from the MTT assay. For a standard curve of fibroblast cells, a different density of 1000–80 000 cells was seeded in the third passage, and MTT[22] was added the following day. The standard curve extracted the proliferation index of experimental groups.

ATP and ROS Measurements

The luciferase enzyme was used to quantify ATP, indicating the presence of metabolically active or live cells. To stabilize the luminescent signal, the contents were left to incubate at room temperature for ten minutes, after which the luminescence.[23] was measured (BioTek Cytation 3 Cell Imaging Multi-Mode Reader, USA). The blank group was examined for background detection.

The production of free radicals was studied by low-level laser exposure at various power outputs and exposure times using the probe 2',7'-Dichlorodihydrofluorescin diacetate (DCFH-DA). MCF7 cells were incubated at 37 °C for 30 minutes before the treatment with DCFH-DA (10 µM). After the internalization of cells, DCFH-DA is converted to DCFH, which is non-fluorescent. However, when DCFH reacts with ROS, it forms the fluorescent compound DCF, which is released from the cell and is fluorescent. ROS concentration was determined relative to the fluorescence intensity of the negative control group (MFC-7 cells without treatment and H_2O_2). In addition, MCF7 cells were treated with 100 nM hydrogen peroxide (H_2O_2) as a positive control group to induce ROS and confirm the kit's performance. Fluorescence intensity was measured at 485 nm for excitation and 530 nm for emission using a fluorescence spectrophotometer (BioTek Cytation 3 Cell Imaging Multi-Mode Reader, USA).

Statistical Analysis

The cellular phase results, which included the proliferation rate, ATP, and ROS assay, were presented as the mean ± SD. Each cell group comprised a minimum of 5000 MCF7 cells in culture. This study compared treatment protocols across the cell groups, using three samples from each group as a reference. Statistical analysis was conducted using SPSS 20 software, employing one-way analysis of variance (ANOVA) with a confidence level of 95% and a significance threshold set at $P < 0.05$.

Results

Temperature Monitoring

Figure 1 shows the results of temperature change as a result of exposure time in 30-second intervals. The temperature changes in cells after 20 minutes of irradiation were 6.8 °C for 27 mW and 4.7 °C for 10 mW.

LLLT (Ga–Al–As) Stimulated HDFC Proliferation

After LLLT, no changes in morphology were observed, but changes in cell density were noted in groups with the highest

confluency. HDFCs were examined morphologically after LLLT (Ga-Al-As) and culture (Figure 2). The fibroblast cells were observed as flat cells adhering to the surface of the culture plate. The impact of increased exposure time and energy density on human dermal fibroblast cells (HDFCs) was assessed by comparing cell confluency across three groups: 90 s (3.78 J/cm²), 6 minutes (7.56 J/cm²), and a control group. Notably, an increase in cell numbers was observed in the group exposed for 90 s at an energy density of 3.78 J/cm².

After LLLT (Ga-Al-As), the proliferation index of HDFC was examined by the MTT assay method (Figure 3A). The standard MTT curve was designed to predict the cell number acquired from the MTT assay by optical density (Figure 3B). The highest significant increase in the cell proliferation index was observed in group 1 treated with 10 mW power at 90 seconds, 3 minutes, and 6 minutes. The corresponding proliferation values were 0.79 ± 0.07, 0.74 ± 0.07, and 0.67 ± 0.06, respectively, with energy densities of 3.78, 7.56, and 15.12 J/cm². These values were significantly higher than those of the control group (0.51 ± 0.05) and the sham group (0.42 ± 0.04), with a *P* value of 0.000 (Figure 3A). Also, the highest average in the cell proliferation of power 27 mW was seen in group 90 s (10 J/cm²) with 0.51 ± 0.05 (*P* = 0.000) (Figure 3B).

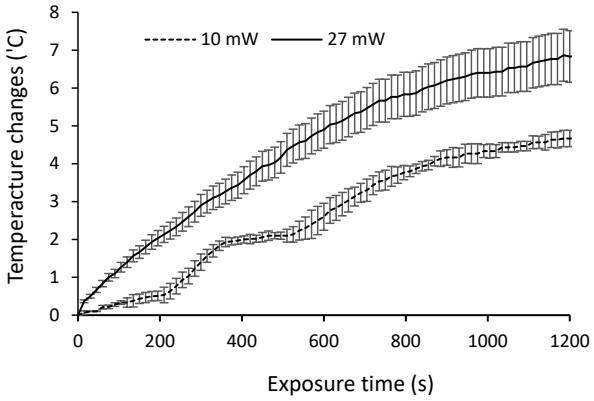

Figure 1. The Mean ± SD of Temperature Changes (°C) in Cells Versus Exposure Time (s) for the Effective Mode Used in Irradiation (3 Experiments)

LLLT (Ga–Al–As) Increased ATP Production

The ATP content of the fibroblasts, a key indicator of metabolic activity, was measured to assess the post-radiation effects. Intracellular ATP was measured by continuously monitoring ATP production through luminescence after LLLT radiation with 10 mW output power, corresponding to the highest proliferation index (Figure 4). This finding further solidifies our key observation of a significant increase in ATP production post-radiation. The precision of data is evident in the results, which show that ATP levels were significantly

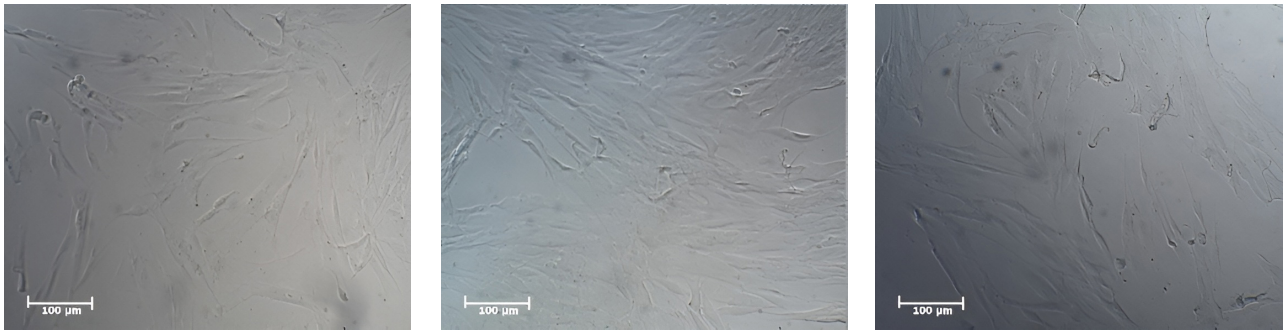

Figure 2. Effects of LLLT on Human Dermal Fibroblast Cells (HDFCs) in the Control Group and Compared to Groups Exposed to 90 s at 3.78 J/cm² and 6 min at 7.56 J/cm² with a 10 mW laser (10X Invert Microscope, Nikon Co., USA)

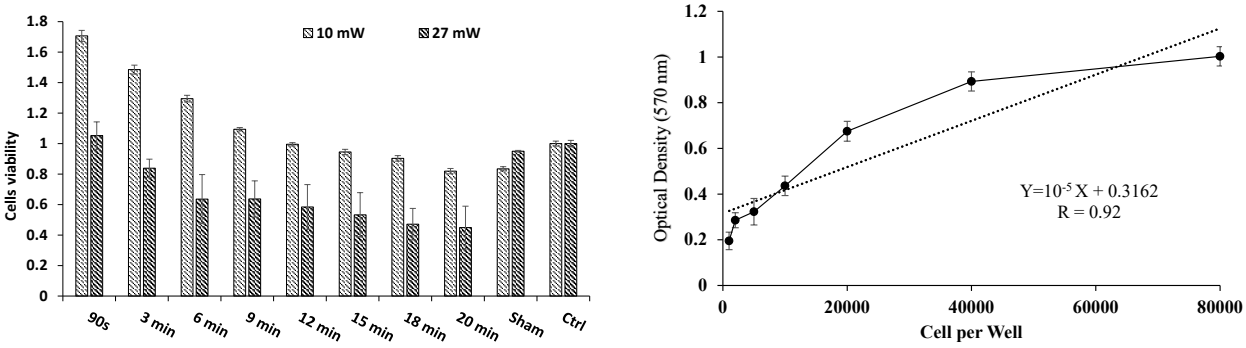

Figure 3. Effect of Low-Level Laser Therapy at Various Output Powers (10 mW, 27 mW) and Times on HDFCs Proliferation: A) Cell Proliferation Index; B) Standard Curve for HDFCs

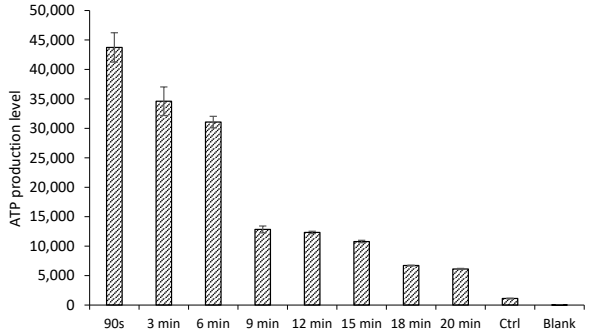

Figure 4. The Impact of low-Level Laser Therapy Using Ga-Al-As at 10 mW on ATP Production Levels Over Various Times and Energy Densities

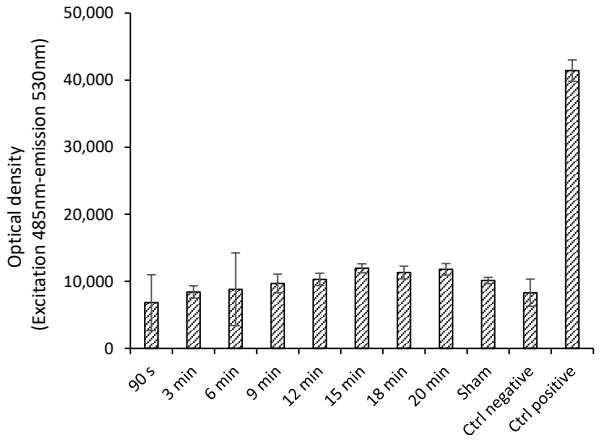

Figure 5. The Low-Level Laser Therapy Using Ga-Al-As at 10 mW on the Levels of Reactive Oxygen Species Concentration at Various Times and Energy Densities

higher in the 90 s, 3 minutes, and 6 minutes groups with 3.78, 7.56, and 15.12 J/cm^2 compared to all other groups ($P=0.000$). This result is statistically significant, demonstrating an increase in the level of ATP production in the radiated groups compared to the control and sham groups, as shown in Figure 3. Specifically, the ATP levels in the 10 mW (90 seconds) group increased by 13.21% compared to the control group ($P=0.000$).

LLLT (Ga–Al–As) Did Not Affect ROS Activity

The intracellular production of ROS was assessed after a 1-hour LLLT (Ga-Al-As) radiation period, and the ROS concentration was analyzed by using DCFH-DA. ROS concentration in all groups did not increase significantly at each change in exposure time compared with the control group (Figure 5). The results indicate that the 90 LLLT at 1.10 times the negative control resulted in the lowest level of ROS, suggesting minimal oxidative stress and cellular damage. In contrast, the groups exposed to longer radiation durations of 15, 18, and 20 minutes at 1.50 times the negative control showed increased ROS levels, indicating higher oxidative stress and potential cell damage. Figure 3 demonstrates that there was no significant difference between the groups, particularly between the 90 s therapy group and the negative control group ($P=0.9931$).

Discussion

Many studies have explored the use of high and low-energy lasers in therapy, with low-level lasers being particularly effective in wound repair and pain relief. These lasers have photochemical effects on various tissue cells, promoting the growth of fibroblast cells and enhancing wound healing. In this study, we used an 830 nm laser with 10 mW and 27 mW output power. The results showed significant changes in human fibroblast (HF) proliferation across all groups, with different mean proliferation rates corresponding to increasing time and energy density.

In our comparison of the groups, we found a significant increase ($P<0.001$) in cell proliferation rates of 0.79 ± 0.07, 0.74 ± 0.07, and 0.67 ± 0.06 for the groups exposed to radiation for 90 seconds, 3 minutes, and 6 minutes, respectively, at a power of 10 mW and energy doses of 3.78, 7.56, and 15.12 J/cm^2. These results were significantly higher compared to the control group (0.51 ± 0.05) and the sham group (0.42 ± 0.04). Additionally, the group treated with 27 mW LLLT for 90 seconds (10 J/cm^2) exhibited the highest average cell proliferation rate of 0.51 ± 0.05.

We found that shorter exposure times at 10 mW output power are more effective in promoting fibroblast proliferation. Studies indicated that after laser radiation, fibroblasts exhibited polarized behavior, forming bundles in different directions, which induces cellular activity and movement.[24] Also, LLLT stimulates fibroblast proliferation by releasing specific growth factors and producing platelet-derived growth factor (PDGF).[25] Ma et al found that dual-wavelength light (635 nm + 830 nm) was optimal for accelerating fibroblast proliferation and wound healing.[26]

Houreld and Abrahamse[27] compared low-level lasers operating at 830, 980, and 2940 nm and found that 830 nm had the most significant bio-stimulation impact on human skin fibroblasts. Phan et al[28] used various energy densities (2.5, 3, 3.5, 4, and 5 J/cm^2) to assess the effect of LLLT on fibroblast proliferation and found that 3 and 3.5 J/cm^2 had a significant effect compared to other energy levels. Cavalcanti et al[29] concluded the significant effect of LLLT at 2.5 J/cm^2 on fibroblast cell proliferation in each radiation at three consecutive days. Results showed high levels of ATP production in the group radiated for 90 seconds ($P<0.001$), while the group radiated for 20 minutes exhibited lower ATP levels compared to the control group. The ATP assay showed a reduction in levels with longer exposure times due to a decrease in metabolic activity and cellular stress or damage. According to Karu,[30] ATP synthesis is stimulated by the increased activity of cytochrome C oxidase (Cox), a photoreceptor and transducer of photo signals, through photon absorption during laser radiation; this interaction increases mitochondrial membrane potential, enhancing

ATP synthesis and fibroblast proliferation.[31]

Hawkins and Abrahamse[32] reported that injured fibroblasts responded positively to a single treatment of 5.0 J/cm² and multiple treatments at 2.5 J/cm². These levels of energy increased cell migration and proliferation without harming cell viability. However, a higher energy density of 16 J/cm² caused additional stress, which reduced cell migration, viability, ATP activity, and cell proliferation.

The change in ROS concentration was evident across all groups with varying exposure times. High levels of ROS[33] increase oxidative stress, which causes free radicals to interact with cellular structures. This interaction can potentially damage mitochondrial function, alter protein structures, induce DNA damage, and trigger apoptosis, a mechanism often utilized in cancer treatment. Conversely, low levels of ROS can activate specific cellular gene expression profiles, increase mitochondrial membrane potential, and enhance ATP synthesis, which in turn promotes fibroblast proliferation.

The results showed high fibroblast proliferation in the group with a shorter exposure time (90 s) at 10 mW with 3.78 J/cm² output power. On the other hand, George et al[34] studied the effect of varying energy densities of a low-level laser (825 nm) on ROS levels in dermal fibroblasts and found increased ROS levels across all energy densities. Similarly, Naderi et al.[35] used a low-level laser at 660 nm with 50 mW/cm² output power and different energy densities (1, 5, and 10 J/cm²) to determine fibroblast proliferation. Their results indicated the highest significant cell proliferation ($P < 0.05$) at energy densities of 1 and 5 J/cm², with the highest ROS production at 10 J/cm².

We used 830 nm near-infrared light at low power outputs (10 and 27 mW) and exposure times of 1 to 20 minutes, fitting within the photobiomodulation range for beneficial effects like increased ATP without excessive ROS production.

Because the 830 nm light activates cytochrome c oxidase (COX), this wavelength is absorbed by COX in mitochondria, enhancing ATP production without causing bottlenecks or electron leaks that lead to ROS. The power levels (10 and 27 mW) remain within the "Therapeutic Window," stimulating mitochondrial function without phototoxicity. Any brief increase in ROS is quickly neutralized. Exposure times of 1-20 minutes allow for a range of responses. Longer durations may activate protective pathways. Light enhances efficient ATP production and reduces electron leakage and ROS generation. Fibroblasts can upregulate antioxidants and catalase in response to mild photobiomodulation, quickly neutralizing any transient ROS.[36]

However, in vitro conditions cannot fully represent in vivo environments and there is variability in cell line responses. These findings underscore the efficacy of LLLT (Ga-Al-As) in promoting cellular activities essential for wound healing and tissue regeneration and offer a promising non-invasive therapeutic approach. Future studies should focus on refining these parameters and exploring the underlying mechanisms to optimize LLLT applications in clinical settings.

Conclusion

This study highlights the effective use of low-level Ga-Al-As laser therapy (LLLT) in boosting ATP production, controlling ROS levels, and increasing the proliferation of HDFCs. The results show that using an 830 nm wavelength laser at 10 mW power for 90 seconds (with an energy dose of 3.78 J/cm²) significantly enhances fibroblast growth by increasing cellular energy (ATP) and balancing oxidative stress (ROS). These effects suggest a potential benefit in promoting wound healing and tissue repair. Future research should focus on optimizing these laser settings and exploring the underlying biological mechanisms, especially for treating radiodermatitis and skin wounds caused by chronic conditions.

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Authors' Contribution

Conceptualization: Sameerah Hasan Abdullah, Manijhe Mokhtari-Dizaji, Zeinab Hormozi-Moghaddam.
Data curation: All authors.
Formal analysis: Sameerah Hasan Abdullah, Manijhe Mokhtari-Dizaji, Zeinab Hormozi-Moghaddam.
Investigation: Sameerah Hasan Abdullah, Manijhe Mokhtari-Dizaji, Zeinab Hormozi-Moghaddam.
Methodology: All authors.
Project administration: Manijhe Mokhtari-Dizaji.
Supervision: Manijhe Mokhtari-Dizaji.
Visualization: All authors.
Writing–original draft: Sameerah Hasan Abdullah, Manijhe Mokhtari-Dizaji, Zeinab Hormozi-Moghaddam.
Writing–review & editing: All authors.

Competing Interests

None.

Ethical Approval

This study was approved by the ethics committee of Tarbiat Modares University (IR.MODARES.AEC.1402.007).

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