المجلة العراقية للبحوث الإنسانية والإجتماعية والعلمية
Iraqi Journal of Humanitarian, Social and Scientific Research
Print ISSN 2710-0952 Electronic ISSN 2790-1254
العـــدد 17 أيـار 2025
No.17 May 2025

الية وتطبيقات العلاج بالليزر منخفض الطاقة (LLLT) على الخلايا الجذعية المكونة للدم: مراجعة علمية

ا. م. ميسم طارق صادق العبيدي
الجامعة المستنصرية – كلية العلوم
Kuldeep Mohanty
[1]Maysam1000@uomustansiriyah.edu.iq

الملخص

الهدف: تقيم هذه المراجعة او المقلة العلمية العلاج بالليزر واطئ الطاقه (LLLT) كطريقة لتعزيز تكاثر الخلايا الجذعية، مع التركيز على آليات التحفيز الضوئي والتأثيرات التجريبية. **الخلفية:** يعد العلاج بالليزر منخفض الطاقة واعدًا لتحفيز تكاثر الخلايا الجذعية وتمايزها في المختبر وفي الجسم الحي. حيث تواجه زراعة الخلايا الجذعية تحديات بسبب معدلات النمو البطيئة، مما يجعل العلاج بالليزر منخفض الطاقة استراتيجية مقنعة، وخاصة للخلايا الجذعية المكونة للدم (HSCs) في الطب التجديدي. و قد أظهرت الدراسات زيادة في تخليق ATP وDNA وRNA في الخلايا الجذعية بعد العلاج بالليزر منخفض الطاقة. تستكشف الدراسة او المقالة العلمية آليات التحفيز الضوئي (Photo-Stimulation) للعلاج بالليزر منخفض الطاقة، بما في ذلك الاختلافات في الطول الموجي ومصادر الليزر. ويناقش النتائج التجريبية حول تأثيرات العلاج بهذا النوع من الليزرات على التكاثر والتمايز عبر أنواع الخلايا الجذعية. **الاستنتاج:** تم في هذه المقالة تسليط الضوء على إمكانات العلاج بالليزر منخفض الطاقة لتعزيز تكاثر الخلايا الجذعية، من خلال التحقيق في نتائج العلاج بالليزر منخفض الطاقة على الخلايا المزروعة، وخاصة الخلايا الجذعية المكونة للدم، لوحظ أن التعرض للعلاج بالليزر منخفض المستوى يسبب امتصاص الفوتونات بواسطة الكروموفور داخل الميتوكوندريا في الخلايا الجذعية المكونة للدم. ثم يزيد من معدل تخليق ATP وDNA وRNA في الخلايا الجذعية المكونة للدم، مما يوفر رؤى حول تطبيقه في الطب التحفيزي للتكاثر وهو بمثابة مورد أساسي لمزيد من البحث في العلاجات القائمة على الخلايا الجذعية.

الكلمات المفتاحية: العلاج بالليزر واطئ الطاقة، الخلايا الجذعية، الخلايا الجذعية المكونة للدم (HSCs)، الطب التجديدي (الطب التحفيزي لتكاثر الخلايا)، التحفيز الضوئي.

Mechanism and Application of Low-Level Laser Therapy on Hematopoietic Stem Cells: A Review.

Maysam T. Al-obaidi[1], Kuldeep Mohanty[2]
[1]Maysam1000@uomustansiriyah.edu.iq
[2]kuldeep.mohanty@reseapro.com
[1]Department of Physics, College of Science, Mustansiriyah University, Baghdad, Iraq
[2]Senior Associate Editor, Reseapro ManuscriptEdit Pvt Ltd, Bhubaneswar, Odisha, India
Corresponding author
Maysam_1000@uomustansiriyah.edu.iq kuldeep.mohanty@reseapro.com

Abstract

Objective: This review evaluates Low-Level Laser Therapy (LLLT) as a method to enhance stem cell proliferation, focusing on photo-stimulatory mechanisms and experimental impacts.***Background:*** LLLT is promising for stimulating proliferation and differentiation of stem cells in vitro and in vivo.

Stem cell culture faces challenges due to slow growth rates, making LLLT a compelling strategy, especially for hematopoietic stem cells (HSCs) in regenerative medicine. Studies have shown increased ATP, DNA, and RNA synthesis in stem cells post-LLLT. The review explores LLLT's photo-stimulatory mechanisms, including variations in wavelength and laser sources. It discusses experimental findings on LLLT's effects on proliferation and differentiation across stem cell types.***Conclusion:*** This review highlights LLLT's potential to enhance stem cell proliferation, particularly HSCs, offering insights into its application in regenerative medicine. It serves as a foundational resource for further research in stem cell-based therapies.
Keywords: low-level laser therapy, stem cells, hematopoietic stem cells, regenerative medicine, photo stimulation

Introduction

There are numerous possible applications of stem cells in research and medicine. Immunomodulatory properties and multipotent differentiation with their self-renewal capacity are the unique properties that give an advantage for tissue repair and regeneration applications.[1] Furthermore, in vitro cell culture is one of the most basic methods used in cellular and molecular biology to study the biology, biochemistry, and metabolism of normal and diseased cells and is most helpful in the study of virology and oncology. Even though several mammalian cell lines can be cultured in vitro, their slow growth rate and susceptibility to contamination are major challenges in maintaining the cell lines for a prolonged period [2,3] Various techniques to improve the selective proliferation of the cell lines have been studied. The application of low-level laser is known to enhance in vitro cell proliferation.[4] Recent research has also shown increased proliferation of in vivo stem cells when illuminated with low-level laser therapy (LLLT). This leads to intracellular and extracellular chromophore activation and initiation of cellular signaling.[5,6] The current review is aimed to assess the application of LLLT in stem cell proliferation and differentiation.

Low-level laser therapy (LLLT) refers to the irradiation of low power lasers or light-emitting diodes (LEDs) to induce cell proliferation. Unlike high power lasers, which induce a thermal response and damage cellular components, low-power lasers are based on non-ionizing radiation that induces photophysical and photobiological events in cells through endogenous chromophores. However, its cell-stimulating effects are limited to specific wavelengths only and are not effective below a recommended dose.[7]

Mechanism of LLLT

The first law of photobiology states that, low power light can alter biochemical reactions in the biological system once the photons are captured by the cells. Photochemical reactions are well-established in biological research. LLLT acts

through the Grotthuss-Draper law, which states that light must be first absorbed by a chemical entity for a photochemical change. In LLLT, the chemical entity is represented by cytochrome c oxidase (Cox), present in the mitochondrial electron transport chain (ETC).[8-10] The photons cause the excitation of photoreceptors, which trigger a further chain of reactions. LLL irradiation favors cell proliferation through three main mechanisms, which have been discussed further.[11-14] A schematic representation of LLLT mechanism is shown in (Fig. 1.).

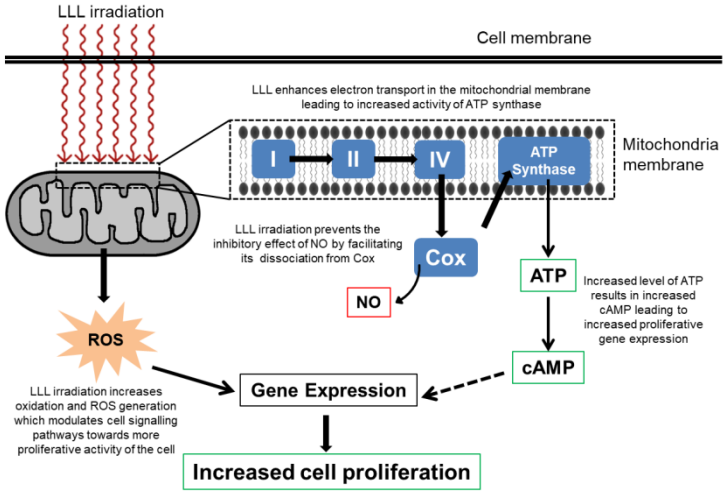

Fig. 1. Schematic representation of LLLT action on stem cells through different modes

By increasing mitochondrial Cox and ATP activity

Radiation pertaining to red and near-infrared (NIR) regions (600-1100 nm) potentially stimulates the cells through the photoreceptors of the mitochondria. Cox, through its multiple components, such as binuclear copper and heme centers, transfers electrons from water to oxygen. Cox is the terminal enzyme of the ETC and acts as an essential component in cellular energetics. Cox photo-stimulation leads to more efficient electron transportation and increased ATP production. [15,16] As ATP concentration increases in the cell, the activity of ATP-driven ion channels and antiporters such as Na^+/K^+, Ca^{2+} pump, ATPase Na^+/H^+, and Ca^{2+}/Na^+ also increases. Since ATP is the substrate for adenylcyclase, its concentration directly controls the level of cAMP. All the ATP-dependent activities are consequently dependent on the activity of terminal enzymes like Cox, and thus, it acts as a significant component in LLLT application.

By preventing competitive inhibition of Cox by NO

Coincidentally, Cox is competitively inhibited by nitric oxide (NO). NO binds to Cox through a coordinate bond, which can be dissociated using LLL.[17] This dissociation favors the mitochondrial respiration and ATP production. Thus LLLT can protect the cells from NO-induced cell senescence.[18]

By generation of ROS and gene expression

LLLT shifts the cellular redox potential and increases oxidation and ROS generation, which, in turn, modulate the intracellular signaling pathways, including the synthesis of proteins and nucleic acids, enzyme activation, and cell cycle. This leads to transcriptional changes through transcription factors responsible for gene expression, such as redox factor-1 (Ref-1)-dependent activator protein-1 (AP-1), nuclear factor B (NF-B), hypoxia-inducible factor (HIF)-1, and p53. [19,20] Upon LLL irradiation, genes responsible for cell proliferation, energy metabolism, and respiratory chain are up-regulated, whereas those responsible for cell degenerating pathways such as apoptosis are down-regulated.[21]

Types of LLLT

LLLT can be differentiated based on the wavelength of light used and the type of laser source used. LLL of different wavelengths have been used to study their effect on cells in vitro as well as in vivo. While visible, infrared, and ultraviolet light have been used in LLLT, the most effective results have been obtained from the light of 600-700 nm.[22] In fact, the light of different wavelengths imparts different effects on the cells. For example, monochromatic light of 860 nm wavelength stimulates cell proliferation while that of 812 nm increases nucleic acid synthesis, 660 nm light increases the production of fibroblasts, and 632.8 nm wavelength light causes differentiation of fibroblasts to myofibroblasts.[23] The 632.8 nm monochromatic laser light is reportedly one of the most effective lights in LLLT. It reportedly boosts keratinocyte proliferation, increases cellular motility, and enhances growth factor secretion from macrophages.

Based on the laser source, LLLT can be categorized into two main classes. The helium-neon (He-Ne) laser transmits (red light) at 632 nm wavelength, while the gallium-aluminium-arsenide (Ga-Al-As) laser transmits infrared light at 830 nm.[24] Other laser sources for administering LLLT include Krypton (521-647 nm) and Ga-As (904 nm).[25]

Dose-dependent activity of LLLT

Reports have shown that LLLT is effective only when administered at particular doses. Low doses yield better cellular response than high doses of the same wavelength.[26] This typical phenomenon is termed as “biphasic dose response” and is based on the Arndt-Schulz Law which implies that weak stimuli accelerate vital biological activities only up to a certain threshold. As the stimuli get stronger beyond that, a negative response is observed. The biphasic curve helps in determining energy levels for effective biostimulation.[27] In LLLT, an energy density range of 0.5 to 4.0 J/cm^2 of light between 600-700 nm is reported to improve proliferation rates of different in vitro cell lines.[23]

Depth of Penetration of LLL

Depth of penetration measures how deep laser or light penetrates into a substance, including the biological tissues. It is the depth at which the radiation's internal intensity decreases to 1/e (or around 37%) of its initial value. LLL light is in the limited range of 600-1000 nm in the biological window that can penetrate and spread into each cell of the tissues. Wavelengths of less than 600nm or more than 1000nm do not form the biological window as the blood cells, hair follicles, skin pigments, and water molecules obstruct the light.[28] LLL light falling 600-700 nm penetrates the skin to 1-2 cm. The 800-900 nm wavelength penetrates more into the tissue, reaching about 3-4 cm. A wavelength of 810 nm can aid the red blood cells to carry oxygen more efficiently from the lungs to different parts of the body. Hemoglobin specifically binds oxygen at 810 nm, which causes rapid binding activity.[29]

Effect of LLLT on stem cells

Multicellular organisms have partially differentiated or undifferentiated cells, which can proliferate into different kinds of cells indefinitely and divide into more stem cells of the same type. Seen in the embryonic stages and adult forms, these are the initial cells in a cell lineage, with each having a few distinct properties. Stem cells are unlike progenitor cells that do not have indefinite division, and precursor or blast cells have a commitment or differentiate into a particular cell type.[30,31] Hematopoietic stem cells (HSCs) produce blood cells in a process known as hematopoiesis.[32] In vertebrates, an event called endothelial-to-hematopoietic transition gives rise to the initial HSCs that first occur at the ventral endothelial wall of the embryonic aorta, specifically in the aorta-gonad-mesonephros region during mid-gestation.[33,34] In adults, hematopoiesis occurs at the core of bones, known as red bone marrow. Mesoderm gives rise to the red bone marrow.[35] HSCs give rise to two different lineages known as myeloid and lymphoid progenitor cells, which form different types of blood cells.[36] HSCs remain in a dormant condition or reversible growth arrest like all adult stem cells. Dormant HSCs have altered metabolism, which helps the cells survive for a long duration in the bone marrow in a hypoxic environment.[5] HSCs tend to end dormancy and divide again actively when triggered by cell damage or death. The transition from the quiescent stage to the dividing stage is regulated by specific pathways. Deregulation of the above may cause the exhaustion of stem cells or gradual loss of active HSCs in the blood system.[37,38] HSCs can move between the bone marrow of different bones because they possess a stronger potential compared to other immature blood cells in crossing the bone marrow. The liver or spleen may also become the site of development for these stem cells. As a result, this will make it possible to extract HSCs directly from blood.[38]

Light crosses the tissue interior (including the blood or HSCs) in two ways for interaction: absorption and scattering. Absorption is the interaction between a photon and an atom or molecule, resulting in the transfer of the entire energy to

the atom or molecule. Both the direction and energy of each photon may change, which results in inelastic scattering, or just the direction of the photon may change, resulting in elastic scattering.[39] Elastic scattering may occur in HSCs when there is an interaction of the light or LLL with the biological tissues. [39,40] Irradiation with visible and infrared light is known to cause physiological stimulation of stem cells. Many studies have reported effective treatment of various diseases and conditions using LLLT, especially in regenerative medicine. LLLT is shown to positively affect cell growth, proliferation, and differentiation of stem cells.

Factors affecting stem cell-LLL interaction

Size, shape, the refraction index of the biological tissue core, and the wavelength used by the laser all affect the scattering and interaction of the light with the cell. Since absorption and scattering are affected by anatomy, biochemistry, and wavelength, determining the penetration and depth of light inside the biological tissues is an extreme problem. The effectiveness of the LLL is mainly related to the amount of light that reaches the target biological tissue. LLLT procedures require the determination of each irradiation and dose parameters in the output of the laser device according to the type of biological medium. Irradiation parameters include wavelength (nm), power (W), beam area (cm^2), and laser pulse structure. While dose parameters include energy J, energy density J/cm2, treatment chronology, and irradiation pulse times. All these parameters, in addition to patient-specific conditions, make utilizing low-level laser therapy and its dosimetry a pitfall in many research and clinical approaches.[41] Wavelength in the range of 800-905nm has an effective role in the irradiation of HSCs because it essentially contributes to stem cell activity, communication, and the process of proliferation.[29]

Effect of LLLT on hematopoietic stem cell growth and proliferation

LLLT is reported to increase stem cell proliferation. The physiological state of the cells is an important parameter that determines the effect of LLLT. If the cells are in a poor growing state, LLLT has the maximum stimulatory effect on them. However, fully functional cells do not respond well to LLLT, and no therapeutic benefit has been observed.[42] A pilot study conducted by Soto et al. (2015) studied the administration of LLLT as a preventative measure against oral mucositis in patients receiving HSC transplantation.[43] Twelve children undergoing transplantation were treated with a combination of intraoral and extraoral laser therapy using red light (685 nm). A substantial decrease in oral mucositis was noticed at the end of the treatment.[43] It has been found that LLL stimulated stem cell proliferation at 685 nm. It generates higher ATP, DNA, and RNA synthesis rates in stem cells and other cell lines with no cytotoxic effects. The growth and differentiation potential of long-term (about three years) cryopreserved human peripheral blood progenitors (PBPs) can be restored by LLLT.[44,45] In another study, Santinoni et al (2020) explored the

combinatorial effect of coagulated bone marrow aspirate and LLLT on bone healing.[46] They found that the application of LLLT resulted in a positive influence on bone regeneration mediated by stimulation of endothelial progenitors and HSCs, promotion of higher vasculogenesis, and heightened secretion of chemical mediators at the wound site.[46] Hou et al. (2008) demonstrated the use of laser with 635 nm wavelength to significantly improve the proliferation of bone marrow-derived mesenchymal stem cells.[47] Similar results were obtained by another study where apical papilla stem cells were irradiated with 650 nm wavelength LLLT, and proliferative enhancement of the cells was observed. An increased production of growth factors such as VEGF and TGFβ2 was observed along with higher osteogenic activity.

Effect on stem cell differentiation

Stem cell trans-differentiation to various types of cells is a pre-requisite for regeneration of injured tissue. Many experiments have also demonstrated enhanced cell differentiation upon LLL exposure. One study has reported ex vivo exposure of murine bone marrow cells to LLL increases their differentiation potential into myeloid progenitors.[48] Bone marrow-derived mesenchymal stem cells have the potential to differentiate into osteoblasts, fibroblasts, adipocytes, myoblasts, and other kinds of functional cells in a suitable environment. LLLT has been shown to stimulate bone nodule formation in osteoblasts. Irradiated stem cells showed an increased production of osteoblast differentiating factors upon laser treatment.[49] In another study, mesenchymal stem cells irradiated with 810 nm laser showed neuronal features.[50] In a comparative study, Wang et al (2016) showed that osteoblast differentiation occurred better at laser lights of wavelength 420 and 540 nm compared to that of 660 nm and 810 nm.[51] This was confirmed by biochemical analysis of calcium levels of the cells irradiated with different wavelength lights. LLLT has also been reported to have epigenetic effects in modulating DNA methylation and subsequent differentiation of stem cells.[52] Significant results have shown that the implementation of specific wavelengths of light in the near-infrared region (808, 890, 905, and 1064 nm) displayed consequential outcomes in bone formation and wound healing.[1,45,53] Table 1 summarizes the types of equipment, wavelengths, and their energy densities applied in the experiment. These results reveal the ability of LLLT to enhance HSC differentiation and proliferation in humans and mice, provided the right laser parameters are adopted.

Table 1. Human bone marrow stem cells (hematopoietic stem cells) associated with LLL application.[34]

Types of Light device	Wavelengths in nm	Energy density in J/cm^2	Related study fields	Criteria	References

Red diode laser	630 and 660	1	*In vitro*, osteogenesis	Osteogenic differentiation	Fekrazad et al. 2020[1]
NIR laser	808 and 905	0.93-6.27	*In vitro*, wound	Proliferation	Pasternak-Mnich et al. 2019[54]
LED, diode laser, and NIR diode laser	405, 635, and 808	0.4	*In vitro*, bone	Proliferation, osteogenic differentiation at 635 nm	Tani et al. 2018[55]
NIR laser	890	0.2	*In vivo*, DM wound healing	Proliferation shortened the inflammatory phase	Amini et al. 2018[53]
NIR laser	890	0.2, 6 days a week for 15 days	*In vivo*, DM wound	Induced anti-inflammatory and angiogenic activities	Fridoni et al. 2019[56]
NIR diode laser	808	0.5, 1, 2, 3, and 4	*In vitro, in vivo*, gingival wound	Gingival migration at 1 J/cm^2 in nonproliferation	Feng et al. 2020[57]
Collimated laser to IR light	1064	8.8, 17.6, and 26.4	*In vitro*, adipocyte	Adipogenic differentiation	McColloch et al. 2021[58]
InGaAlP red laser	660	2.5, 5.0, and 7.5	*In vitro*, osteogenesis	Osteogenetic proliferation	Vale et al. 2017[59]

Conclusions

By investigating the outcome of LLLT on cultured cells, particularly HSCs, it has been observed that exposure to LLL causes photon absorption by the chromophore inside the mitochondria of HSCs. It then increases the ATP, DNA, and RNA synthesis rate in stem cells, indicating that more stem cells have been generated. In other words, a proliferation process is achieved. LLL is also applied to enhance other mitochondrial products like NADH, protein, and oxygen-consuming, reactive oxygen species. Remarkable results can be obtained by utilizing a wavelength laser in near-infrared (IR) region (600-1100) nm

applied for bone marrow, including HSCs. However, it is essential to supply more scientific evidence favoring the application of LLLT in cutting-edge stem cell techniques to achieve reliable clinical applications.

List of abbreviations

LLLT: Low-level laser therapy
HSCs: Hematopoietic stem cells
LLL: Low-level laser
LEDs: light-emitting diodes
ATP: Adenosine triphosphate
DNA: Deoxyribonucleic acid
RNA: Ribonucleic acid
HIF: Hypoxia-inducible factor
VEGF: Vascular endothelial growth factor
TGF-β: Transforming growth factor-β
IR: Infrared radiation

Acknowledgements

We want to acknowledge the Department of physics, College of science, Mustansiriyah University, Baghdad, Iraq for the assistance in conducting the study.

References

1. Fekrazad R, Asefi S, Allahdadi M, Kalhori KA. Effect of photobiomodulation on mesenchymal stem cells. Photomed Laser Surg 2016;34(11):533-542. doi:10.1089/pho.2015.4029.
2. Paul J. Cell and tissue culture 1970. 4th edition.
3. Alubaidi GT, Hasan SM. Stem cells: Biology, types, polarity, and asymmetric cell division: A review. Med J Babylon 2022;19(3):318-323. doi:10.4103/mjbl.mjbl_34_22.
4. Bai J, Li L, Kou N, et al. Low level laser therapy promotes bone regeneration by coupling angiogenesis and osteogenesis. Stem Cell Res Ther 2021; 12:1-8. doi:10.1186/s13287-021-02493-5
5. Miranda JM, de Arruda JA, Moreno LM, et al. Photobiomodulation therapy in the proliferation and differentiation of human umbilical cord mesenchymal stem cells: an *in vitro* study. J Lasers Med Sci 2020;11(4):469-474. doi:10.34172/jlms.2020.73.
6. Khorsandi K, Hosseinzadeh R, Abrahamse H, et al. Biological responses of stem cells to photobiomodulation therapy. Curr Stem Cell Res Ther 2020;15(5):400-413. doi:10.2174/1574888X15666200204123722.
7. Zein R, Selting W, Hamblin MR. Review of light parameters and photobiomodulation efficacy: dive into complexity. J Biomed Opt 2018;23(12):120901-120917. doi:10.1117/1.JBO.23.12.120901
8. Lyu K, Liu X, Jiang L, et al. The functions and mechanisms of low-level laser therapy in tendon repair. Front Physiol 2022;13:808374. doi:10.3389/fphys.2022.808374

9. Hamblin MR. Mechanisms and mitochondrial redox signaling in photobiomodulation. Photochem Photobiol 2018;94(2):199-212. doi:10.1111/php.12864
10. Sommer AP, Schemmer P, Pavláth AE, et al. Quantum biology in low level light therapy: death of a dogma. Ann Transl Med 2020;8(7):440. doi:10.21037%2Fatm.2020.03.159
11. Berni M, Brancato AM, Torriani C, et al. The role of low-level laser therapy in bone healing: systematic review. Int J Mol Sci 2023;24(8):7094. doi:10.3390/ijms24087094
12. Garzón J, Baldion PA, Grajales M, et al. Response of osteoblastic cells to low-level laser treatment: a systematic review. Lasers Med Sci 2022;37(8):3031-3049. doi:10.1007/s10103-022-03587-z
13. Kao YC, Lin GY, Cheng JY, et al. Neurite growth induced by red light-caused intracellular reactive oxygen species production through cytochrome c oxidase activation. J Photochem Photobiol B 2023;241:112681. doi:10.1016/j.jphotobiol.2023.112681
14. Tam SY, Tam VC, Ramkumar S, et al. Review on the cellular mechanisms of low-level laser therapy use in oncology. Front Oncol 2020;10:1255. doi:10.3389/fonc.2020.01255
15. Glass GE. Photobiomodulation: A review of the molecular evidence for low level light therapy. J Plastic Reconstr Aesthet Surg 2021;74(5):1050-1060. doi:10.1016/j.bjps.2020.12.059
16. Yu W, Naim JO, McGowan M, et al. Photomodulation of oxidative metabolism and electron chain enzymes in rat liver mitochondria. Photochem Photobiol 1997;66(6):866-871. doi:10.1111/j.1751-1097.1997.tb03239.x.
17. Quirk BJ, Whelan HT. What lies at the heart of photobiomodulation: light, cytochrome C oxidase, and nitric oxide—review of the evidence. Photobiomodul Photomed Laser Surg 2020;38(9):527-530. doi:10.1089/photob.2020.4905
18. Maldaner DR, Azzolin VF, Barbisan F, et al. *In vitro* effect of low-level laser therapy on the proliferative, apoptosis modulation, and oxi-inflammatory markers of premature-senescent hydrogen peroxide-induced dermal fibroblasts. Lasers Med Sci 2019;34:1333-1343. doi:10.1007/s10103-019-02728-1
19. Ganipineni VD, Gutlapalli SD, Kumar IA, et al. Exploring the potential of energy-based therapeutics (photobiomodulation/low-level laser light therapy) in cardiovascular disorders: A review and perspective. Cureus 2023;15(4): e37880. doi:10.7759/cureus.37880
20. Soluki M, Abdolmaleki A, Mahmoudi F, et al. Effect of low-level laser therapy on neurorehabilitation: A narrative review. J Laser Appl 2022;34(1):011201. doi:10.2351/7.0000577

21.Chu YH, Chen SY, Hsieh YL, et al. Low-level laser therapy prevents endothelial cells from TNF-α/cycloheximide-induced apoptosis. Lasers Med Sci 2018;33:279-286. doi:10.1007/s10103-017-2364-x
22.Motlagh KH, Azizi A, Ghadim NM. *In Vitro* Effect of 445 nm blue laser and 660 nm low-level laser on the quantity and quality of human gingival fibroblasts. Photochem Photobio 2023;99(3):920-928. doi:10.1111/php.13716
23.Ma H, Yang JP, Tan RK, et al. Effect of low-level laser therapy on proliferation and collagen synthesis of human fibroblasts *in vitro*. J Wound Manag Res 2018;14(1):1-6. doi:10.22467/jwmr.2018.00283
24. Luke AM, Mathew S, Altawash MM, et al. Lasers: A review with their applications in oral medicine. J Lasers Med Sci 2019;10(4):324. doi:10.15171%2Fjlms.2019.52
25. Das N. A Biostimulation Therapy in Periodontics: An Evidence-Based. Perio J 2022;6(1):1-11. doi:10.26810/perioj.2022.a1
26. Heiskanen V, Hamblin MR. Photobiomodulation: lasers vs. light emitting diodes?. Photochem Photobiol Sci 2018;17(8):1003-1017. doi:10.1039/C8PP00176F
27. Jodynis-Liebert J, Kujawska M. Biphasic dose-response induced by phytochemicals: experimental evidence. J Clin Med 2020;9(3):718. doi:10.3390/jcm9030718
28. Ash C, Dubec M, Donne K, et al. Effect of wavelength and beam width on penetration in light-tissue interaction using computational methods. Lasers Med Sci 2017;32:1909-1918. doi:10.1007/s10103-017-2317-4.
29. Wang P, Sun J, Meng L, et al. Therapeutic effect of forearm low level light treatment on blood flow, oxygenation, and oxygen consumption. Proc SPIE Mech of Photobiomodulation Ther XIII 2018;10477:12-17. doi:10.1117/12.2287750
30. Zakrzewski W, Dobrzyński M, Szymonowicz M, et al. Stem cells: past, present, and future. Stem Cell Res Ther 2019;10(1):1-22. doi:10.1186/s13287-019-1165-5
31.De Luca M, Aiuti A, Cossu G, et al. Advances in stem cell research and therapeutic development. Nat Cell Biol 2019;21(7):801-811. doi:10.1038/s41556-019-0344-z
32.Dzierzak E, Bigas A. Blood development: hematopoietic stem cell dependence and independence. Cell stem cell 2018;22(5):639-651. https://doi.org/10.1016/j.stem.2018.04.015
33. De Freitas LF, Hamblin MR. Proposed mechanisms of photobiomodulation or low-level light therapy. IEEE J Sel Top Quantum Electron 2016;22(3):348-364. doi:10.1109/jstqe.2016.2561201
34.Aragon JW, Hirschi KK. Endothelial cell differentiation and hemogenic specification. Cold Spring Harb Perspect Med 2022:a041164. https://doi.org/10.1101/cshperspect.a041164

35. Monga I, Kaur K, Dhanda SK. Revisiting hematopoiesis: applications of the bulk and single-cell transcriptomics dissecting transcriptional heterogeneity in hematopoietic stem cells. Brief Funct Genom 2022;21(3):159-176. doi:10.1093/bfgp/elac002
36. Mann Z, Sengar M, Verma YK, et al. Hematopoietic stem cell factors: their functional role in self-renewal and clinical aspects. Front Cell Dev Biol 2022;10: 664261. doi:10.3389/fcell.2022.664261
37. Ottersbach K. Endothelial-to-haematopoietic transition: an update on the process of making blood. Biochem Soc Trans 2019;47(2):591-601. doi:10.1042/BST20180320
38. Baumgartner C, Toifl S, Farlik M, et al. An ERK-dependent feedback mechanism prevents hematopoietic stem cell exhaustion. Cell Stem Cell 2018;22(6):879-892. doi:10.1042/BST20180320
39. Tuchin VV. Tissue optics and photonics: light-tissue interaction. J Biomed Photonics Eng 2015;1(1):3-21. doi:10.18287/jbpe-2015-1-1-3
40. Sousa H, Hamblin MR, de Sousa MV, Agrawal T. Handbook of low-level laser therapy. Jenny Stanford Publishing 2016:1170. doi:10.1201/9781315364827
41. Karu T. Primary and secondary mechanisms of action of visible to near-IR radiation on cells. J Photochem Photobiol B 1999;49(1):1-17. doi;10.1016/S1011-1344(98)00219-X
42. Oshiro T. Progress in laser therapy: Selected papers from the October 1990 ILTA Congress. Wiley, New York 1991.
43. Soto M, Lalla RV, Gouveia RV, et al. Pilot study on the efficacy of combined intraoral and extraoral low-level laser therapy for prevention of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation. Photomed Laser Surg 2015;33(11):540-546. doi:10.1089/pho.2015.3954
44. Siedlecka N, Mecinska-Jundzill K, Fierek E, et al. Biostimulative effect of laser on growth of mesenchymal stem/stromal cells *in vitro*. Postepy Dermatol Alergol 2020;37(5):771-780. doi:10.5114/ada.2020.100487
45. Nascimento RX, Callera F. Low-level laser therapy at different energy densities (0.1–2.0 J/cm2) and its effects on the capacity of human long-term cryopreserved peripheral blood progenitor cells for the growth of colony-forming units. Photomed Laser Surg 2006;24(5):601-604. doi:10.1089/pho.2006.24.601
46. Santinoni CS, Neves AP, Almeida BF, et al. Bone marrow coagulated and low-level laser therapy accelerate bone healing by enhancing angiogenesis, cell proliferation, osteoblast differentiation, and mineralization. J Biomed Mater Res A 2020;109(6):849-858. doi:10.1002/jbm.a.37076
47. Hou JF, Zhang H, Yuan X, et al. *In vitro* effects of low-level laser irradiation for bone marrow mesenchymal stem cells: Proliferation,

growth factors secretion and myogenic differentiation. Lasers Surg Med 2008;40(10):726-733. doi:10.1002/lsm.20709

48. Roy S, Tripathy M, Mathur N, et al. Hypoxia improves expansion potential of human cord blood–derived hematopoietic stem cells and marrow repopulation efficiency. Eur J Haematol 2012;88(5):396-405. doi:10.1111/j.1600-0609.2012.01759.x
49. Abramovitch-Gottlib L, Gross T, Naveh D, et al. Low level laser irradiation stimulates osteogenic phenotype of mesenchymal stem cells seeded on a three-dimensional biomatrix. Lasers Med Sci 2005;20:138-146. doi:10.1007/s10103-005-0355-9
50. Soleimani M, Abbasnia E, Fathi M, et al. The effects of low-level laser irradiation on differentiation and proliferation of human bone marrow mesenchymal stem cells into neurons and osteoblasts—an in vitro study. Lasers Med Sci 2012;27:423-430. doi:10.1007/s10103-011-0930-1
51. Wang Y, Huang YY, Wang Y, et al. Photobiomodulation (blue and green light) encourages osteoblastic-differentiation of human adipose-derived stem cells: role of intracellular calcium and light-gated ion channels. Sci Rep 2016;6(1):33719. doi:10.1038/srep33719
52. Gomes MV, Manfredo MH, Toffoli LV, et al. Effects of the led therapy on the global DNA methylation and the expression of *Dnmt1* and *Dnmt3*a genes in a rat model of skin wound healing. Lasers Med Sci 2016;31:1521-1526. doi:10.1007/s10103-016-2007-7
53. Amini A, Pouriran R, Abdollahifar MA, et al. Stereological and molecular studies on the combined effects of photobiomodulation and human bone marrow mesenchymal stem cell conditioned medium on wound healing in diabetic rats. J Photochem Photobiol B 2018;182:42-51. doi:10.1016/j.jphotobiol.2018.03.010
54. Pasternak-Mnich K, Ziemba B, Szwed A, et al. Effect of photobiomodulation therapy on the increase of viability and proliferation of human mesenchymal stem cells. Lasers Surg Med 2019;51(9):824-833. doi:10.1002/lsm.23107
55. Tani A, Chellini F, Giannelli M, et al. Red (635 nm), near-infrared (808 nm) and violet-blue (405 nm) photobiomodulation potentiality on human osteoblasts and mesenchymal stromal cells: a morphological and molecular in vitro study. Int J Mol Sci 2018;19(7):1946. doi:10.3390/ijms19071946
56. Fridoni M, Kouhkheil R, Abdollhifar MA, et al. Improvement in infected wound healing in type 1 diabetic rat by the synergistic effect of photobiomodulation therapy and conditioned medium. J Cell Biochem 2019;120(6):9906-9916. doi:10.1002/jcb.28273
57. Feng J, Li X, Zhu S, et al. Photobiomodulation with 808-nm diode laser enhances gingival wound healing by promoting migration of human

gingival mesenchymal stem cells via ROS/JNK/NF-κB/MMP-1 pathway. Lasers Med Sci 2020;35:1831-1839. doi:10.1007/s10103-020-03040-z

58. McColloch A, Liebman C, Liu H, et al. Alterted adipogenesis of human mesenchymal stem cells by photobiomodulation using 1064 nm laser light. Lasers Surg Med 2021;53(2):263-274. doi;10.1002/lsm.23278
59. Vale KL, Maria DA, Picoli LC, et al. The effects of photobiomodulation delivered by light-emitting diode on stem cells from human exfoliated deciduous teeth: a study on the relevance to pluripotent stem cell viability and proliferation. Photomed Laser Surg 2017;35(12):659-665. doi:10.1089/pho.2017.4279