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REVIEW ARTICLE

Biological Responses of Stem Cells to Photobiomodulation Therapy

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Abstract: ***Background:*** Stem cells have attracted the researchers interest, due to their applications in regenerative medicine. Their self-renewal capacity for multipotent differentiation, and immunomodulatory properties make them unique to significantly contribute to tissue repair and regeneration applications. Recently, stem cells have shown increased proliferation when irradiated with low-level laser therapy or Photobiomodulation Therapy (PBMT), which induces the activation of intracellular and extracellular chromophores and the initiation of cellular signaling. The purpose of this study was to evaluate this phenomenon in the literature.

Methods: The literature investigated the articles written in English in four electronic databases of PubMed, Scopus, Google Scholar and Cochrane up to April 2019. Stem cell was searched by combining the search keyword of "low-level laser therapy" OR "low power laser therapy" OR "low-intensity laser therapy" OR "photobiomodulation therapy" OR "photo biostimulation therapy" OR "LED". In total, 46 articles were eligible for evaluation.

Results: Studies demonstrated that red to near-infrared light is absorbed by the mitochondrial respiratory chain. Mitochondria are significant sources of reactive oxygen species (ROS). Mitochondria play an important role in metabolism, energy generation, and are also involved in mediating the effects induced by PBMT. PBMT may result in the increased production of (ROS), nitric oxide (NO), adenosine triphosphate (ATP), and cyclic adenosine monophosphate (cAMP). These changes, in turn, initiate cell proliferation and induce the signal cascade effect.

Conclusion: The findings of this review suggest that PBMT-based regenerative medicine could be a useful tool for future advances in tissue engineering and cell therapy.

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1. INTRODUCTION

Mesenchymal stem cells (MSC) have been used in regenerative medicine and tissue engineering in order to replace the conventional therapeutic modalities. These cells have the ability to differentiate into one of many different specialized cell types and have self-renewing properties under controlled *in vitro* conditions. Sources of stem cells include bone marrow [1], adipose tissue, dental pulp and umbilical cord [2]. Recent applications of stem cell therapy include not only bone marrow transplants for leukemia treatment, but also include the treatment of spinal cord injuries, Parkinson's disease, heart disease, multiple sclerosis and cancer [3].

Laser therapy has been used as a therapeutic modality to treat pathological tissue conditions such as different wounds to control inflammatory processes, and also to promote tissue healing [4]. It has been indicated that cellular proliferation and viability could be induced under laser irradiation. The molecular mechanism can be described by intensifying the formation of a transmembrane electromechanical proton gradient in mitochondria. Subsequently, more calcium is released into the cytoplasm from the mitochondria [5]. At low laser doses, this additional calcium transported into the cytoplasm triggers mitosis and enhances cell proliferation. It is well known that photobiomodulation increases ATP production, which activates Na, K-ATPase, and other ion carriers. Moreover, the synthesis of DNA and RNA, production of reactive oxygen species (ROS), nitric oxide (NO) release, cytochrome c oxidase activation, and expression of stress

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proteins are other cellular signaling cascades, which are generated by low power laser irradiation [6].

It has been indicated that low-level laser irradiation induces stem cell activity by increasing the proliferation, migration, viability of activated protein expression, and inducing differentiation in progenitor cells [7].

Regenerative medicine has the ability to transform the treatment of human diseases by introducing combined, innovative new therapies such as stem cell and LLLT that offer faster, complete recovery and reduce the risks of donor organ transplantation rejection through autologous grafts.

Studies in this area are few and contradictory. The present study reviewed the articles to develop an understanding of the effect of PBM on MSCs, to help design more accurate studies in the field of PBM.

2. STEM CELL CLASSIFICATION

Stem cells are non-specialized cells in the human body. They can be differentiated in each cell of an organism, and also have the ability to renew themselves. Stem cells are present in both the embryos and adult cells (Fig. **1**) [8]. Embryonic stem cells (ESCs) are involved in whole-body development. They are derived from the inner cell mass of preimplantation embryos. Moreover, they can be differentiated into pluripotent, totipotent, multipotent, and unipotent cells [9]. Pluripotent stem cells (PSCs) form the cells of all germ layers, but not extraembryonic structures, such as the placenta. Accordingly, another example is induced pluripotent stem cells (iPSCs) derived from the epiblast layer of implanted embryos [10]. Totipotent stem cells can be divided and differentiated into the total cells of the organism. Totipotency has the highest potential for differentiation and allows cells to form embryonic and extra-embryonic structures. One example of a totipotent cell is a zygote, which is formed after a sperm fertilizes an egg [11]. Multipotent stem cells have a narrower spectrum of differentiation in comparison with PSCs, however, they can be specialized in discrete cells of specific cell lineages. One example is a haematopoietic stem cell, which can be developed into several types of blood cells. After differentiation, a haematopoietic stem cell becomes an oligopotent cell. Oligopotent stem cells can be differentiated into several cell types. A myeloid stem cell is an example that can be divided into white blood cells, not in red blood cells. Unipotent stem cells are characterized by the narrowest differentiation capabilities and special property of repeatedly dividing, which make them able to be used in therapeutic applications such as regenerative medicine. Unipotent stem cells are able to form one cell type, such as dermatocytes. Somatic or adult stem cells are undifferentiated and found among differentiated cells in the whole body after development. Among many types, mesenchymal stem cells are present in many tissues. In bone marrow, these cells are mainly differentiated into the bone, cartilage, and fat cells. As stem cells, they are exceptions, because they act pluripotently and can be specialized in the cells of any germ layer [12].

2.1. Mesenchymal Stem Cells and Regenerative Medicine

Mesenchymal stem cells (MSCs), discovered by Friedenstein in 1976, are adult stem cells found in the whole body, which could share a fixed set of characteristics. Their own characteristics are preserved, which means that they remain multipotent and undifferentiated, with the capability of self-renewal and differentiation into multiple cell lines, including osteogenic, chondrogenic, adipogenic, and myogenic lineages, under specific *in vitro* conditions [13].

The unique regenerative abilities of stem cells offer new potential for treating some diseases like diabetes and heart disease. However, many studies and investigations remain to be done, to understand how to use these cells for cell-based therapies to treat disease [8]. Differentiation is the process whereby unspecialized stem cells change into specialized cells. Differentiation is a multi-step process where the differentiating cells become more specialized with each step. Understanding the effects of inside and outside cell signals is the main interest of research, which can clarify the differentiation process. The stimulus for MSCs differentiation must be efficient, resulting in viable and functional cells that produce extracellular matrix. This functionality is highly important for cellular characterization and applications in regenerative medicine [14]. These are internal and external inducers promoting cell proliferation and differentiation to regenerate the new tissue. The internal signals are controlled by a cell's genes. The external signals for cell differentiation include chemicals and materials released by surrounding cells, physical contact with neighboring cells, certain molecules in the microenvironment and physicochemical stimulants on stem cells, such as electromagnetic fields [15-18] or low light level laser stimulation/photobiomodulation [19, 20].

3. LASER THERAPY

Laser (Light Amplification by Stimulated Emission of Radiation) can be used as a therapeutic device, which produces monochromatic (one specific wavelength), coherent

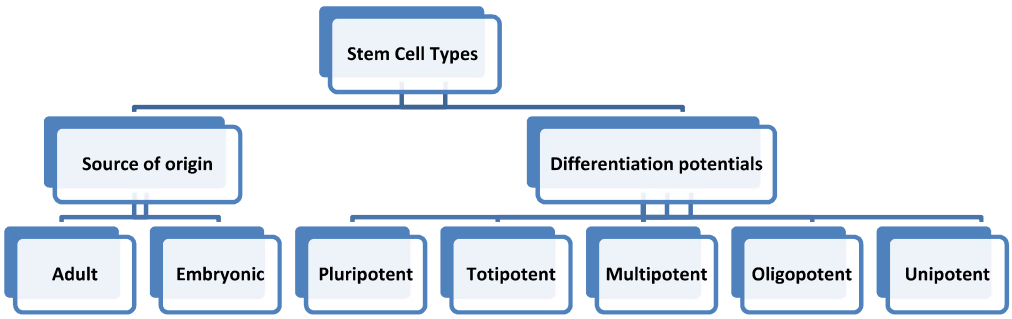

Fig. (1). Stem cell classification.

(constant phase) and polarized (directional) light. Lasers are divided into several classes, based on their power and wavelengths. Therapeutic lasers are low-level lasers for therapy with power less than 500 mW, and High-Intensity Laser with power 500 mW and more [5].

3.1. Low-level Laser Therapy (LLLT)

The most usual Low-Level Laser Therapy (LLLT) procedures are carried out by irradiation of low-level or low-powered lasers to sites of injury in order to speed up the cellular processes resulting in better healing and decreased inflammation and pain [21]. Almost all LLLT treatments refer to the use of red-beam or near infra-red lasers (600-1100 nm), with an output power of 1-1000 mW. This type of radiation is a continuous wave or pulsed light, which consists of a constant beam of relatively low energy density (0.04-50 J/cm2). LLLT procedures are non-invasive, non-thermal and allowing light to penetrate tissue, in order to reach the target tissue, which deals with photochemical effects, and this means that the light is absorbed by biological systems and causes biophysical chemical changes in organs [6, 22]. Schneede *et al*., also reported a temperature increase of less than 0.065°C, with laser irradiation of 40 mW/cm^2, using a micro thermal probe in a monolayer of cells [23]. A number of different laser light sources, including helium-neon, ruby, and gallium aluminum- arsenide, have been used to deliver LLLT in different treatments and on different schedules.

3.2. High-intensity Laser Therapy (HILT)

High-intensity Laser Therapy technology is based on the well-known principle of low-level laser therapy (LLLT). High power and choice of the right wavelength allow deep tissue penetration. HIL offers a powerful and non-addictive form of pain management. Through a natural process of energy transfer (biostimulation and photomechanical effect), it could speed up the healing and regeneration process. HIL is particularly effective in the treatment of sports related injuries, *e.g*. muscle strain or joint distortion, and back pain caused by *e.g*. herniated disc or disorders in the cervical region, which lead to neck pain [24].

4. BIOLOGICAL RESPONSE IN STEM CELLS AFTER LOW-LEVEL LASER IRRADIATION/PHOTOBIOMODULATION

Low-level laser irradiation can stimulate a number of biological processes, including cell growth, proliferation [25], and differentiation [26]. The effects of low level laser irradiation on cell proliferation *in vitro* have been investigated on different cell types including fibroblasts [27, 28], endothelial cells [29], skeletal cells [30, 31], keratinocytes [32], myoblasts [33], and other cell types [34-37]. Generally, it is accepted that low-level laser irradiation (especially red and near-infrared light) promotes proliferation mainly through activating the mitochondrial respiratory chain, and the initiation of cellular signaling [38, 39]. The laser energy absorbed by intracellular chromophores triggers the dissociation of NO from cytochrome c oxidase, resulting in a cascade of responses, including an increase in cytochrome c oxidase enzyme activity, electron transportation, oxidative respiration, mitochondria-related RNA and protein synthesis, oxygen consumption, membrane potential [5, 6, 36], and ATP production, leading to increased reactive oxygen species (ROS), and cytokines, and also expressions of growth factors [40, 41]. ATP acts via multiple P2 nucleotide receptor subtypes to increase the concentration of intracellular calcium (Ca^{2+}) [42, 43]. Simultaneously, the ATP regulates protein synthesis and DNA synthesis, which consequently improve cellular oxygenation, nutrition, and regeneration (Fig. **2**) [44-46].

The biological response of cells to these changes results in the activation of transcription factors, which can induce many gene transcript products. The concentration of induced ROS can switch the secondary biological response of live cells. Low dose ROS can stimulate cellular proliferation by switching various cell signaling pathways; however high concentration of ROS reduces the cell viability and inhibits proliferation [47]. Low-level laser irradiation can affect the ligand-binding mitochondrial macromolecules such as redox enzymes in the respiratory chain [48, 49]; for example, NOx dissociation from binding sites on the redox enzyme, reactivation of these enzymes in the respiratory chain, and increase of the ATP production in cells [50].

The extracellular signal-regulated kinase (ERK) cascade plays an important role in the cellular proliferation of many cells [51]. ATP-induced activation of ERK1/ ERK2 is dependent on the dual-specificity kinase mitogen-activated protein kinase/ERK kinase (*i.e*., MEK), but independent from the phosphatidylinositol 3-kinase (PI3K) activity [52]. PI3K is a lipid kinase, which promotes diverse biological functions, including cellular proliferation, survival, and motility. The PI3K pathway is an important driver of cell proliferation and cell survival [53], whereas the ERK pathway is a major regulator of cell proliferation [54]. It has been reported that LLLT specifically activates MAPK (mitogen-activated protein kinase)/ERK pathway, and consequently induces cell proliferation [55]. In another study, it was shown that LLLT specifically activates RTK/PKCs signaling pathway to promote cell proliferation [56], and results in significant activation of ROS/Src pathway [57]. Furthermore, Akt can be activated either by Src or by PKCs protein kinase [58, 59]. Therefore, it is probable that Akt is involved in LLLT-induced cell proliferation [60]. Since the LLLT treatment can increase the level of intracellular ROS generation [61], the increased intracellular oxidants can mediate the activation of Akt [62]. Many Reports suggested the existence of the ROS/Akt signaling pathway during LLLT induced proliferation [6] (Fig. **3**).

Different lasers were used in different studies, which have different parameters, including wavelength, power density, fluency, and application time. LLLT can prevent cell apoptosis and enhance cell proliferation, migration, and adhesion at a low dose compared to high does [63]. The effect of LLLT on cell proliferation has been confirmed in several types of cells [64].

Boulton and Marshall revealed that laser irradiated cultures exhibit a significant increase in the number of human skin fibroblasts, which grow on the plastic substrates compared to their respective non-irradiated controls after 24 and 48 h [65]. The effects of LLLT on cell cultures have been studied generally by Karu *et al.* [66]. It was also described

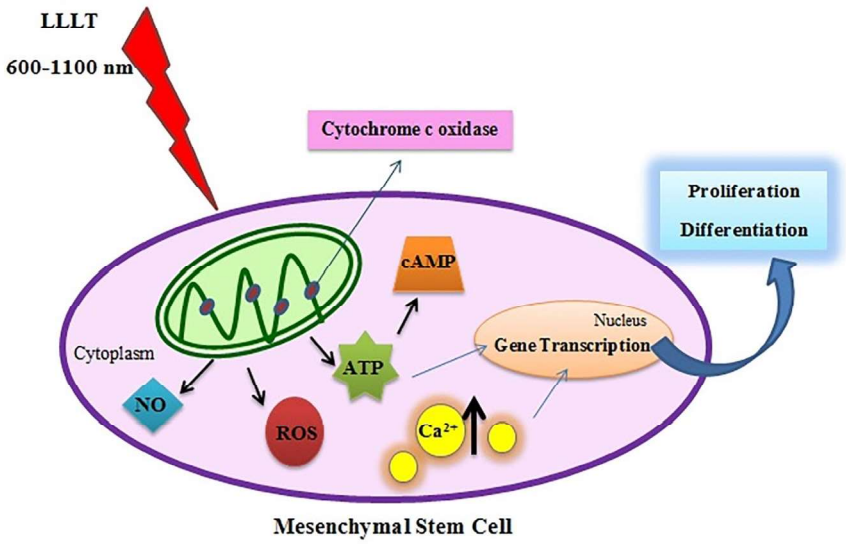

Fig. (2). Cellular response in mesenchymal stem cells after low-level laser irradiation/ photobiomodulation.

that the stimulation of cellular proliferation depends on the dose of laser irradiation, as lower doses increase the cell proliferation rate and other cellular functions, while higher doses of LLLT have negative and inhibitory effects [63].

Nowadays, investigation of the use of low-level lasers in health, medicine and biology is one of the interesting fields in biomedical research. These studies and findings will lead to greater credit of low-level laser therapy in the mainstream medicine and may also result in using LLLT for more complicated diseases such as stroke [5], heart attack and degenerative brain diseases [67]. The effect of low-level laser on changing the cell membrane potential and reducing pain is one of the well-known effects of LLLT [68]. The ability to control the cell membrane potential can help researchers control drug delivery in the cells for therapeutic purposes [69, 70].

PubMed, Scopus and Google scholar electronic databases were searched for finding the articles about the effect of low-level laser irradiation on the biological response of stem cells. The used keywords were "low-level laser therapy" OR "low power laser therapy" OR "low-intensity laser therapy" OR "soft laser" OR "photobiomodulation therapy" OR "photo biostimulation therapy" OR "LED and stem cells". The retrieved articles were limited to the English language and were taken from the period of 2009 to April 2019. Data extraction involved cell origin, laser parameters, and final results. The selected articles were characterized as *in vitro or in vivo* experimental studies and clinical trials, which evaluated the effects of irradiation from LLLs and LEDs on MSCs. The initial selection included a review of articles; those that did not reflect the purpose, were excluded. Also, we included all articles that evaluated all lasers types except other light sources such as Xenon flash lamps. Those articles which assessed the phototherapeutic effect on other stem cell types, such as dental follicle stem cells, were excluded. This article only focused on the photo stimulatory effects such as proliferation and differentiation of stem cells. The abstracts of other studies were analyzed. At the end of the selection process, after reading the full texts, articles that met the inclusion criteria were reviewed. Finally, 46 articles were used to compile this review (Table **1**).

Irradiation of cells at certain wavelengths can activate the specific biochemical reactions as well as altering the whole cellular metabolism [49]. Karu stated that the laser effect depends on the radiation, wavelength, dose, and intensity as well as on other cell culture conditions [66], although many types of LLLT have been used to deliver irradiation to different cell lines, in order to achieve the maximum proliferation rate (Table **1**). Also, two types of LLLT were mainly used for *in vitro* studies. Helium-neon (He-Ne) lasers were used at a wavelength of 632 nm that transmit red visible light, while the second type used gallium-aluminum arsenide (Ga-Al-As) with a wavelength of 830 nm, which is in the near-infrared region of the spectrum. Most *in vitro* studies have been carried out with the He-Ne laser [71].

In most studies, the visible spectrum (600-700nm) was effective for a cellular response (proliferation or differentiation) of stem cells [19, 72-75]. De Villiers *et al*., found an increase in cellular viability and proliferation on human adipose-derived MSCs (hADSCs) using a diode laser [76] (Table **1**). Giannelli M *et al*., reported that the proliferation of mouse MSC increased after irradiation with the 635 nm diode laser [77]. Mvula *et al*., suggested that the proliferation of ADSCs significantly increased after exposure to a diode laser at 636 nm wavelength (5 J/cm^2) [78].

The reviewed studies used laser energy densities between 0.2-9 J/cm^2. The power density used for visible light was 30-170mW/cm^2, and it was also 50-700mW/cm^2 for infrared light.

Amid *et al*., in 2014 [79] and a systematic review by Ginani *et al*., [80] supported the stimulatory effect of Red and IR lasers confirming both proliferation and osteogenic differentiation of stem cells. Bloise *et al*., reported that 659 nm diode laser with a power output 10mW and energy density of 1, 3 J/cm^2 could induce the proliferation and differen-

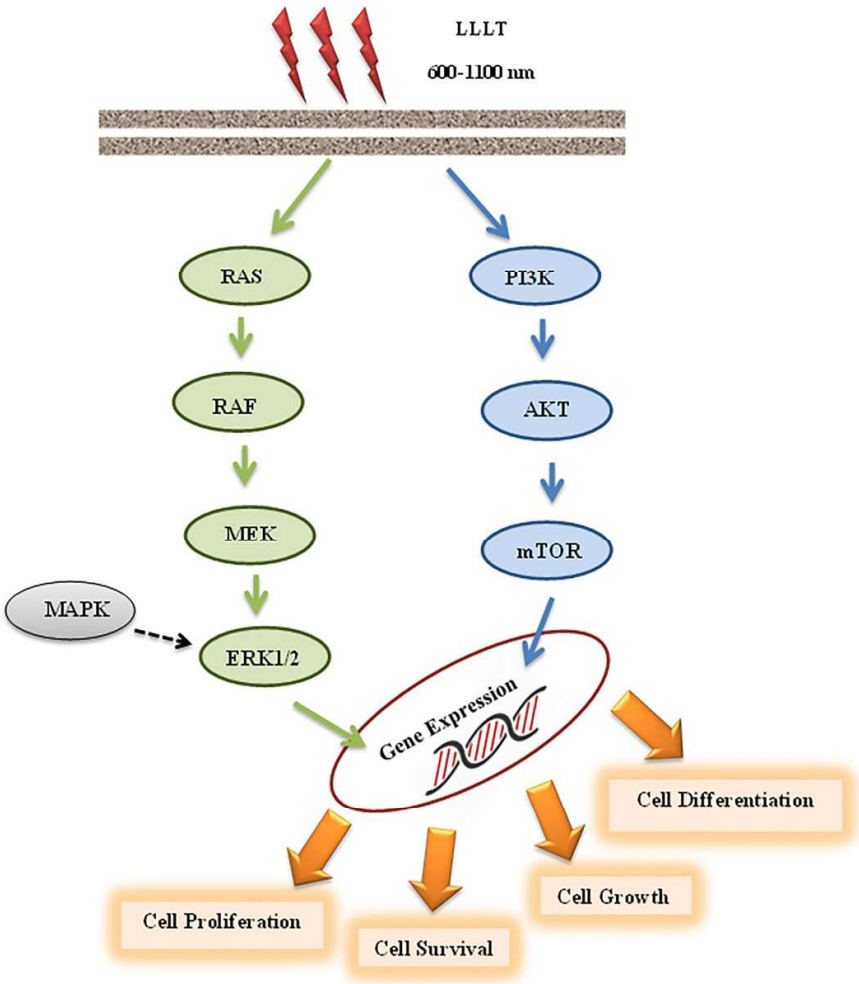

Fig. (3). The signaling pathways involved in the photobiomodulation treated Mesenchymal stem cells.

tiation in a human osteoblast-like cell line (Saos-2 cell) [81]. Ginani *et al*., presented the proliferation of murine bone marrow cells 72 h after irradiation with 635 nm laser using an energy density of 0.3 J/cm^2 and power 89 mW [77]. Fekrazad *et al*., indicated that using 810 nm diode laser with Power: 30 mW fluence 8.5 J/cm2 with 20 s irradiation per day for 3-week resulted in better healing of artificial osteochondral defects in comparison with BMSCs alone, with higher bone formation than cartilage formation [19, 82] (Table **1**). Jawad *et al*., indicated that the 940 nm laser diode with 100 and 200 mW powers significantly promoted cell differentiation; however, 300 mW stimulated the osteoblast proliferation in human fetal osteoblast cell lines [83].

There are a few reports on the use of a combination of different laser wavelengths for inducing proliferation or differentiation on stem cells. A combination of different laser wavelengths on MSCs proliferation and differentiation either on chondrocytes or on osteoblasts *in vitro* has been utilized by fekrazad *et al*. [84]. They found that the most effective laser wavelength for inducing both proliferation and differentiation of MSCs was of IR laser closely followed by red (R) laser. Moreover, they reported that the green (G) laser could suppress cellular proliferation and osteogenic differentiation; however, it could promote chondrogenic differentiation. A combination of IR-R suppressed the collagenous differentiation, while IR alone can stimulate it. Although R-G combination stimulated cartilage formation, G laser alone had a better effect compared to combined therapy. Each R and IR laser alone stimulated osteogenic differentiation, however, IR-R combination suppressed it [84]. Generally, using LLLT under the described experimental conditions for a period of 3 weeks, could be significantly effective in improving bone regeneration. However, applying MSCs alone or in addition to LLLT may not make a significant difference in bone formation over a short period of time in rabbits. This study conclusively indicated no synergistic effect of MSC and LLLT under earlier described conditions [84].

However, in a recent experimental study, Choi *et al*., reported significantly higher amounts of bone formation just after 2 weeks using adipose-derived mesenchymal stem cell-seeded ADM on 4 mm calvarial defects in mice [85]. Choi *et al*., reported a significant positive effect of using HeNe laser in conjunction with MSCs on the bone generation of mice [85].

Soleimani *et al*. [86], analyzed the action of LLLT on the proliferation rate of human bone marrow stem cells cultured

Table 1. Review of PBM and LLT effect on stem cells (2009-2019)-Energy density or Fluency (J/cm^2), Power density (mW/cm$^{2)}$, Energy (J), Power mW.

References	Wavelength (nm)	Irradiation Parameters	Cell Type	Biological Response	Results
Pasternak-Mnich *et al.* 2019 [90]	808 and 905	195, 230, and 318 mW/cm^2, 3, 10, and 20 J; 0.93-6.27 J/cm^2	Human bone marrow mesenchymal stem cells	Increases in cell viability and proliferation	Irradiation with the MLS M1 system can be used *in vitro* to modulate MSCs in preparation for therapeutic applications
Rafael *et al.* 2019 [91]	660	Output power: 30 mW; laser beam: 0.028 cm^2; irradiation: 1.07 mW/cm^2	Rat adipose tissue-derived MSCs	Significantly increased apoptosis as well as oxidative stress in the MSCs.	Future application of LLLI as a protective approach against DOX-induced toxicity in MSCs, particularly cell death
Babaee *et al.* 2019 [92]	625	Red LED 1.9 J/cm^2	Human Wharton's jelly-derived mesenchymal (hWJM) cells	Differentiated the cells into germ lineage	Photobiomodulation may be applied for gametogenic differentiation in-vitro
Kyuchang *et al.* 2019 [93]	633	Light-emitting diode array, 1.65-7.12 mW/cm^2, Fluence	Human umbilical cord blood-derived MSCs	Cell proliferation	PBM enhances the angiogenic potential of MSCs, leading to improved therapeutic efficacy for the treatment of radiation-induced enteropathy
Han *et al* 2019 [94]	655 and 635	Dual model device emitted florida 6 laser other parameters is not available	hAMSCs	Growth factor regulatory by MSCs	*In vitro* LLLT applied to AMSCs boosts its secretion of paracrine factors, thereby enhancing AMSCs potential as a treatment for KFs and HSFs via downregulation of Notch1 and TGF-β1
Ferreira *et al.* 2019 [95]	660	InGaAlP 20 mW, 0.028 cm^2	Human exfoliated deciduous teeth (SHEDs)	Cell growth was significantly higher	PBMT increases the number of stem cells with no interference in the undifferentiated state of the irradiated cells
Chen *et al.* 2019 [96]	635 and 808	Energy densities from 0 to 10 J/cm2	Human umbilical cord mesenchymal stem cells (hUC-MSCs)	635-nm laser increased cell proliferation, high positive expression of GFAP in the 808 nm	808 nm laser irradiation could help CSF to induce neuronal differentiation of hUC-MSCs in early-stage and tend to change to neuron rather than glial cells
Tani *et al.* 2018 [97]	405, 635 and 808	Diode lasers and LED: continuous wave with a 0.4 J/cm² energy density	Human osteoblast and mesenchymal stromal cell (hMSC)	Osteoblast responses to red light were mediated by Akt signaling activation, which seems to positively modulate reactive oxygen species levels. Violet-blue light-irradiated cells behaved essentially as untreated ones and NIR irradiated ones displayed modifications of cytoskeleton assembly, Runx-2 expression and mineralization pattern.	PBM with 635 nm laser as a potential, effective option for promoting/improving bone regeneration
Priglinger *et al.* 2018 [98]	475, 516 and 635	LEDs Energy info. NA	Human adipose tissue-derived stromal vascular fraction cells	Vascularization potential and proliferation capacity	Beneficial effects after LLLT on the vascularization potential and proliferation capacity of SVF cells
Amaroli *et al.* 2018 [99]	808	Irradiation (1 W, continuous-wave) fluency (64 J/cm^2)	Bone marrow stromal cells (BMSCs)	Cell differentiation	LLLI can modulate BMSCs differentiation in enhancing osteogenesis
Stancker *et al.* 2018 [100]	808	Power: 50 mW, energy: 42 J, energy density: 71.2 J/cm^2, spot size: 0.028	Adipose-derived stem/stromal cells (ADSCs) (Fischer 344 rats)	Downregulation of pro-inflammatory cytokines and MMPs	Downregulation of pro-inflammatory cytokines and MMPs

Table (1) contd….

References	Wavelength (nm)	Irradiation Parameters	Cell Type	Biological Response	Results
Peat *et al.* 2018 [101]	1064	Nd:YAG energy density of 9.77 J/cm^{2,} power of 13.0 W	Equine bone marrow-derived mesenchymal stem cell (MSC)	No difference in viability was detected, a significant increase in expression of interleukin (IL)-10 and vascular endothelial growth factor (VEGF)	Under these irradiation parameters, equine MSCs remained viable and expressed increased concentrations of IL-10 and VEGF. IL-10 has an anti-inflammatory action by inhibiting the synthesis of proinflammatory cytokines at the transcriptional level.
Fekrazad *et al.* 2016 [19]	810	Power: 30 mW Fluence 8.5 J/cm2	Rabbit BMSC	Healing of artificial osteochondral defects	There was better healing by LLLT compared with BMSCs alone, with higher bone formation rather than cartilage formation
Farfara *et al.* 2015 [102]	Not reported	Power: 400 mW Fluence: 1 J/cm2	MSCs of mouse with Alzheimer's disease (AD)	Activate a Beneficial immune response in progressive disease stages of AD mouse	Use of LLLT as a therapeutic application in progressive stages of AD and implying its role in mediating MSC therapy in brain amyloidogenic diseases
Fekrazad *et al.* 2016 [82]	810	Power: 200 mW Fluence 4 J/cm2	Rabbit BMSC	Healing of artificial calvarial defects	LLLT significantly increased new bone formation relative to control group but had no synergistic effect in conjunction with MSCs in bone formation.
de Oliveira *et al.* 2015 [103]	660	GaAlAs, Power: 30 mW Fluence 0.75-9 J/cm2	hMSCs And rMSCs	Cell adhesion and proliferation	LLLT on human and rat MSCs might upregulate VEGF messenger RNA (mRNA) expression and modulate cell adhesion and proliferation distinctively.
Huertas *et al.* 2014 [104]	940	Pulsed radiation Energy outputs: 1-5 J Intensities: 0.5, 1, 1.5 and 2 W/cm2	MG-63 cell	Proliferation	Pulsed low-level laser with low-energy density range appears to exert a biostimulatory effect on bone tissue.
Barboza *et al.* 2014 [72]	660	InGaAlP, Continuous mode, Power: 30 mW Fluence 0. 5-1 J/cm2	BMSCs and AMSCs of mice	Cell proliferation	Cell proliferation increased in a dose-dependent manner
Migliario *et al.* 2014 [105]	980	Continuous mode Power outputs	Murine preosteoblasts MC3T3 cells	Proliferation	LLLT increased proliferation significantly by 5-15 J energy output. While higher energies (25-50 J) had an inhibitory effect on the osteoblast proliferation
Bloise *et al.* 2013 [81]	659	Single transverse-mode Power output 10 mW Fluence 1, 3 J/cm2	Human osteoblast-like cell line (Saos-2 cell line)	Proliferation differentiation	LLLT enhanced Saos2 cells proliferation and maturation.
Choi *et al.* 2013 [85]	632.8	Continuous mode Energy out puts: 17.0 mW Intensities: 0, 1 and 3 J/cm2	Adipose-derived mesenchymal stem cell	Bone regeneration potential	Enhanced the proliferation and survival of ASCs at 14 days ASC-seeded grafts promote bone regeneration, and the application of LLLT on ASC seeded ADM results in rapid bone formation.
Jawad *et al.* 2013 [83]	940	Continuous mode Power outputs 100, 200, 300 mW	Human fetal osteoblast cell line	Proliferation differentiation	100 and 200 mW powers promoted cell differentiation significantly however 300 mW stimulated osteoblast proliferation
Wu *et al.* 2013 [106]	660	Energy out puts: 15 -17 mW.cm−2, Intensities: 1, 2 and 4 J/cm2	Human periodontal ligament cells (hPDL)	Cell proliferation and differentiation, gene expression, cytotoxicity	Potential for use in clinical applications
Giannelli *et al.* 2013 [77]	635	Single irradiation Power 89 mW Fluence 0.3 J/cm2	Murine bone marrow	Proliferation	Diode laser increased cell proliferation significantly at 72 h after irradiation

Table (1) contd….

References	Wavelength (nm)	Irradiation Parameters	Cell Type	Biological Response	Results
Pyo *et al.* 2013 [107]		Continuous mode Energy out puts: 1000 mW Intensities: 1.2, 2.4 and 3.6 J/cm2	Hypoxic cultured Human fetal osteoblast cells	1.Cell viability 2. Expression of hypoxia-inducible factor-1s (HIF-1s), bone morphogenic protein-2 (BMP-2), osteocalcin, type I collagen, transforming growth factor-β1 (TGF-β1), and Akt	Induces the expression of BMP-2, osteocalcin, and TGF-β1 in 1 % hypoxic-cultured human osteoblasts
Leonida *et al.* 2013 [108]	1064	Nd:YAG, pulsed mode, Power: 1.5-2.25 W Fluence: 0.326-3.81 J/cm2	BMSCs	Cell Proliferation	Proliferation significantly increased in scaffolds treated with laser after 7 days.
Ong *et al.* 2013 [108]	530	Light-emitting diode green LED	Human orbital fat stem cells (OFSCs)	OFSC migration, activation of extracellular signal-regulated kinases (ERK)/MAP kinase/p38 signaling pathway	Stem cells are sensitive to green LED irradiation-induced directional cell migration through activation of ERK signaling pathway via a wavelength-dependent phototransduction
Soares *et al.* 2013 [109]	660	Power: 30 mW Fluence: 0.5 and 1 J/cm2	Human periodontal ligament stem cells (hPDLSC)	Dose dependent cell proliferation	It can be concluded that LLLI using infrared light and an energy density of 1.0 J/cm² has a positive stimulatory effect on the proliferation of hPDLSC
Anwer *et al.* 2012 [110]	532	Nd:YAG, Power: 30 mW Fluence: 5-45 J/cm2	ADSCs	Proliferation rates of cells correlation with auto fluorescence intensity.	At longer exposures, there was a significant decrease in proliferation and autofluorescence. A strong correlation was observed between proliferation rates of cells and autofluorescence intensity.
Wu *et al.* 2012 [111]	660	Diode laser, Power: 38 mW Fluence: 1-4 J/cm2	Mouse BMSCs	Dose-dependent differentiation	Osteogenic differentiation was increased in a dose-dependent manner.
Pereira *et al.* 2012 [112]	660	Energy fluences (0.05, 0.30, 7 and 42 J/cm(2)	Human dental pulp stem cells (hDPSC)	No statistically significant differences were observed between the proliferation rates	The irradiation with low-level InGaAlP red low-level laser (660 nm) in four different energy fluences potentiated neither proliferation nor odonto-osteogenic differentiation of hDPSC isolated from patients with normal and inflamed pulps.
Kim *et al.* 2012 [113]	632.8	He-Ne, Power: 17 mW Fluence: 0-3 J/cm2	Canine ASCs	Wound healing, survival of ASCs	LLLT is an effective bio- stimulator of ASCs in wound healing that enhances the survival of ASCs and stimulates the secretion of growth factors in the wound bed.
Soleimani *et al* 2012 [86]	810	1, 3, and 5 days' after incubation Power 50 mW Fluence 2 and 4 J/cm2	Human bone marrow	Cell Proliferation Differentiation	Cell proliferation was enhanced by doses of 2, 3, and 4 J/cm2 but 6 J/cm2 gave no difference. ALP activity increased significantly by laser irradiation.
Wu *et al.* 2012 [114]	635	Single irradiation Power 60 mW Fluence 0.5 J/cm2	Murine bone marrow	Gene expression and Cell Proliferation	Bone marrow proliferation was increased significantly by laser at 2, 4, and 6 days later of irradiation
Wang *et al.* 2012 [115]	635	Single irradiation Power 60 mW Fluence 0.5 J/cm2	Murine bone marrow	Proliferation	Laser irradiation promotes proliferation processes 2 and 4 days' after exposure compares to control group.

Table (1) contd….

References	Wavelength (nm)	Irradiation Parameters	Cell Type	Biological Response	Results
Peng *et al.* 2012 [116]	Red light LED	Fluence: 0-4 J/cm(2)	MSCs	Cellular proliferation alkaline phosphatase activity and mineralized nodule formation	nonconherent red light can promote proliferation but cannot induce osteogenic differentiation of MSCs in normal media, while it enhances osteogenic differentiation and decreases proliferation of MSCs in media with osteogenic supplements.
Tuby *et al.* 2011 [117]	804	GaAlAs, Power: 400 mW Fluence:1 J/cm2	Bone marrow of exposed tibia and heart of rats' after myocardial infarction	Decreased infarct size	Application of LLLT decreased infarct size as compared with control. Irradiation to bone marrow was more effective than to heart to reduce infarct.
De Villiers *et al.* 2011 [76]	636	Diode laser, Power: 78 mW Fluence: 5 J/cm2	hADSCs	Cellular viability and proliferation	LLLI does not induce differentiation of isolated hADSCs, and increases cellular viability and proliferation.
Aleksic *et al.* 2010 [118]	2940	Pulsed radiation Energy/pulse output 30-350 mJ Fluence 0.7-17.2 J/cm2	Mouse-derived osteoblastic cell line MC3T3-E1	Cell proliferation	Er:YAG laser may be able to promote bone healing following periodontal and peri implant therapy.
Renno *et al.* 2010 [119]	830	Single exposure Power output 30 mW	Osteoblastic (MC3T3) cell line	Cell proliferation	Laser irradiation reduced osteoblast proliferation compared to control group.
Mvula *et al.* 2010 [78]	636	Diode laser, Power: 110 mW Fluence: 5 J/cm2	EGF on adult ADSCS	Extracellular calcification of MSCs	Irradiation was able to promote extracellular calcification of MSCs.
Li WT *et al.* 2010 [120]	630	LED array Power: 5-15 mW Fluence: 2-4 J/cm2	Rat bone marrow MSCs	Growth of MSCs was enhanced MSCs proliferation	LLLI led only to a short-term increase in MSCs proliferation, A maximal increase in cell proliferation was observed with multiple exposures of LLLI
Kushibiki and Awazu. 2009 [121]	405	Power: NA Fluence: 9-36 J/cm2	MSCs	Inhibition in cell growth at high doses	Bio-stimulation at lower doses at all time points evaluated and inhibition in cell growth after 48 h at higher doses.
Horvat-Karajz *et al* 2009 [122]	660	Power 60 mW Fluence 1.9 and 3.8 J/cm2	Murine bone marrow	Cell proliferation	Lower doses had bio-stimulatory effect in adverse cell proliferation was inhibited after 48 h at higher doses
Bouvet-Gerbettaz *et al.* 2009 [25]	808	Continuous mode Fluence 4 J/cm2	Murine bone marrow cell	Cell proliferation and differentiation	Infrared laser did not alter proliferation and differentiation compared to the control group
Kim *et al.* 2009 [123]	647	LED radiation energies of 0.093 J, 0.279 J and 0.836 J	Mouse mesenchymal stem cells (D1 cells)	Alkaline phosphatase (ALP) activity, mRNA expressions of osteocalcin and etc.	Osteogenic differentiation of mesenchymal stem cells (MSCs) in ODM is enhanced by LED light exposure
Liao *et al.* 2018 [87]	650-nm	GaAlAs laser irradiation	Human adipose-derived stem cells (ADSCs)	Cytokine secretion adipogenic differentiation thicknesses of the epidermis and dermis	In the mouse model of photoaged skin, ADSCs treated with GaAlAs laser irradiation had markedly decreased the epidermal thickness and increased the dermal thickness of photoaged mouse skin
Wang *et al.* 2018 [88]	660 nm	GaAlAs red laser	Human adipose-derived stem cells (hADSCs)	Critical sized calvarial defect in a rat model	combined treatment with ADSCs and LPLI could further enhance the bone healing process
D. Lucke *et al.* 2018 [89]	808 nm/infrared	Power 40 mW Fluence 50 J/cm2	Adipose-derived mesenchymal stem cells	Expression of *Dcn, Il1b*, *Timp2*, *Tgfb1*, *Lox*, *Mmp2*, *Mmp8 and Mmp9* and organization of collagen fibres	Transplanted ASCs migrated to the transected region, and all treatments altered the remodelling genes expression.

in medium supplemented with osteogenic and neurogenic inducing factors. The authors noticed a significant increase in the proliferation of irradiated cells, compared to the non-irradiated group, even with the cells cultured on differentiating media [86].

Along with *in vitro* studies, there are some *in vivo* studies on low-level laser irradiation effect on stem cells in an animal model. Liao *et al*., have shown that in the mouse model of photoaged skin, ADSCs treated with GaAlAs laser irradiation markedly decreased epidermal thickness and increased dermal thickness of photoaged mouse skin [87]. Wang *et al*., noticed that ADSC and Low power laser irradiation (LPLI) treatments improved fracture repair in critical-sized calvarial defects in rats. Importantly, the combined treatment of ADSCs and LPLI further enhances the bone healing process [88]. In a study by D. Lucke *et al*., it was noted that transplanted ASCs migrated to the transected region, and all treatments altered the remodelling genes expression. The LLL was the most effective in the collagen reorganization, followed by its combination with ASCs [89].

Since laser parameters such as wavelength and dose play such a crucial role in the effects observed in irradiated stem cells, it is essential to determine the best parameters for use during irradiation of stem cells. Due to the variation in the experimental design, comparing the experimental results of laser therapy in cell culture is difficult.

CONCLUSION

Regenerative medicine and stem cell therapy have the potential to provide diseases-free, functional tissues and organs, and improving the quality of life for patients. Stem cells frequently have a low yield and a reduced proliferative rate *in vitro*, which decrease their efficacy in clinical regenerative therapy. Therefore, combined innovative new therapies such as stem cell therapies and LLLT/photobiomodulation are necessary for regenerative medicine. The results of this review suggest that LLLT -based regenerative medicine could be a useful tool for future advances in tissue engineering and cell therapy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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