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- 29 Photobiomodulation therapy for osteoarthritis: Mechanisms of action

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Photobiomodulation therapy for osteoarthritis: Mechanisms of action

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Abstract

Photobiomodulation (PBM) is a non-invasive therapeutic modality with demonstrated effects in many fields related to regenerative medicine. In the field of orthopedics, in particular, PBM at various wavelengths has demonstrated the capacity to trigger multiple biological effects associated with protective mechanisms in musculoskeletal tissues. The articles cited in this review show that devices operating close to or within the near infrared range at low intensities can provoke responses which favor the shift in the predominant catabolic microenvironment typically seen in degenerative joint diseases, especially osteoarthritis (OA). These responses include proliferation, differentiation and expression of proteins associated with stable cell cycles. Additionally, PBM can also modulate oxidative stress, inflammation and pain by exerting regulatory effects on immune cells and blocking the transmission of pain through sensory neuron fibers, without adverse events. Collectively, these effects are essential in order to control the progression of OA, which is in part attributed to exacerbated inflammation

and degradative enzymatic reactions which gradually contribute to the destruction of joint tissues. PBM may offer medical experts ease of application, financial viability, efficacy and lack of serious adverse events. Therefore, it may prove to be a suitable ally in the management of mild to moderate degrees of OA. This review explores and discusses the principal biological mechanisms of PBM and how the produced effects may contribute to the amelioration of osteoarthritic progression. Literature was reviewed using PubMed and Google Scholar in order to find studies describing the mechanisms of PBM. The investigation included a combination of nomenclature such as: “photobiomodulation”, “phototherapy”, “laser therapy”, “PBM”, “osteoarthritis”, “low level light therapy”, “inflammation” and “cartilage”. We considered only articles written in English, with access to the full text.

Key Words: Photobiomodulation; Low-level laser therapy; Osteoarthritis; Inflammation; Regenerative medicine

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Core Tip: Photobiomodulation (PBM) is a non-invasive therapeutic modality with demonstrated effects in regenerative medicine. In the field of orthopedics, in particular, PBM at various wavelengths has demonstrated the capacity to trigger multiple biological effects associated with protective mechanisms in musculoskeletal tissues. These responses include proliferation, differentiation and expression of proteins associated with stable cell cycles. Additionally, PBM can also modulate oxidative stress, inflammation and pain by exerting regulatory effects on immune cells and blocking the transmission of pain through sensory neuron fibers.

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INTRODUCTION

Photobiomodulation (PBM), often referred to as low-level laser (or light) therapy (LLLT), can be interpreted as a therapeutic modality which utilizes light to promote a wide variety of biological effects such as tissue repair, analgesia and reduced inflammation[1]. These effects can be attained *via* the use of a low-power light source, namely LASER (Light Amplification by the Stimulated Emission of Radiation) or LED (Light Emitting Diodes)[1]. Due to the standard low intensity, the treatment does not cause an expressive increase in the temperature of the target tissue. Additionally, for the same reason, the gross tissue structure is not significantly affected either[2]. One of the distinct features of PBM in comparison to other light-based treatments is that, since it operates within a low-intensity range, it does not provoke ablation. Instead, it is more likely attributed to a photochemical effect, where light is absorbed and chemical reactions in the cellular microenvironment are generated[3]. Furthermore, unlike photodynamic therapy, for instance, PBM does not require the application of photosensitizers. Once photosensitizing agents are activated by the corresponding wavelength, reactive oxygen species (ROS) are released. When ROS levels are not adequately regulated they end up triggering apoptosis and necrosis of target cells[4,5], which is the opposite effect of PBM. Another advantage of this therapeutic tool is that, in addition to being non-invasive, it has a broad range of applications. PBM can contribute in the treatment of various health conditions by playing significant roles in pain relief, promotion of wound healing and thus recovery of injured tissues[6]. It may therefore prove to be of great significance in regenerative medicine for the treatment of many injuries, including musculoskeletal injuries such as osteoarthritis (OA), in particular.

OA is still listed as one of the most common degenerative and progressive joint diseases and a major cause of pain and disability in the adult population, affecting 7% of the global population[7]. According to the Global Burden of Disease 2019 study results, the number of individuals affected by this condition increased globally by 48% from 1990 to 2019, classifying OA as the 15th most common cause of years lived with disability, in the same year[8]. This significant increase is likely attributed to extrinsic factors such as aging of the population and the incidence of poor dietary habits, especially in terms of metabolic syndrome[9-11]. This disease appears to be influenced by the complex interplay between local, systemic and external factors, which consequently dictate disease progression and the manner in which patients

respond to treatments[12]. It is typically characterized by a specific set of features encompassing the formation of osteophytes, continuous loss of articular cartilage, thickening of the subchondral bone, unbridled synovial inflammation, degenerative alterations of ligaments and menisci as well as joint hypertrophy[10]. Recent evidence[13] suggests that osteoarthritic progression is not exclusively linked to biomechanical trauma. The pathophysiology of the disease also appears to be closely associated with other biochemical processes, especially the imbalanced overproduction of oxidant molecules, such as ROS, which further aggravate oxidative stress and inflammation[13]. Several management strategies have been proposed albeit with not very optimistic results. Conservative methods, such as the administration of pharmacological agents, only promote temporary alleviation of pain but do not address the etiological source of the disease[13,14]. Non-pharmacological strategies have limited potential since they are usually limited to regular physical therapy, postural education, implementation of physical aids, nerve ablation and low impact exercise and weight loss programs, for example. In more severe cases, however, such as end stage OA, surgical intervention with joint replacement procedures may be inevitable and therefore extremely detrimental to the patient[12,13]. These hurdles motivated researchers to design more convenient non-operative alternatives, such as the application of PBM. Although optimistic results have been revealed, there is still a significant lack of consensus in the literature in regards to dose, power density, wavelengths, exposure duration, area irradiated, manual technique and even a minimum number of sessions for optimal clinical outcomes. The heterogeneity of reported studies makes standardization of PBM for the treatment of musculoskeletal diseases a challenging task. Although various mechanisms of action have been hypothesized and proposed, researchers have barely scratched the tip of the iceberg; the potential of PBM in regenerative medicine remains to be further explored. There may be multiple signaling pathways and mechanisms underpinning this technique, each playing a specific role and contributing to the regenerative processes, collectively. In this review we explore and discuss the biological potential of PBM and how its effects may contribute to the amelioration of osteoarthritic progression.

THE ORIGINS OF PBM

What is known today as ‘photobiomodulation’ first emerged almost 50 years ago in early experiments conducted by Hungarian physician Endre Mester at the Semmelweis Medical University[6,15]. Mester’s goal was to shave the back of mice, implant a tumor *via* an incision and evaluate the effects of applied light from a ruby laser, with a wavelength of 694 nm. This was one of the first attempts to reproduce the studies described by Paul McGruff in Boston, in 1965[6,15]. At that time, ruby lasers were used to treat malignant tumors in rats and were later tested in human patients. Unbeknownst to him, Mester’s equipment was only delivering a small fraction of the power recorded in McGruff’s parameters. Due to this inaccuracy, the Hungarian physician was unable to successfully treat tumors. Interestingly, on the other hand, he noticed that the rate of hair growth in the treated mice was faster compared to the control group[16], naming this effect “laser biostimulation”. Years later, Mester applied HeNe (helium-neon) lasers (632.8 nm) to stimulate wound healing in animals and, subsequently, in clinical studies[17]. It was long thought that coherent laser light was necessary, however, in recent years researchers found that non-coherent light sources such as LED carry as much potential as lasers in PBM therapy[18,19].

PARAMETERS

LLLT typically employs the use of light in the red or near-infrared region, where the wavelengths fall between 600 to 700 nm, and 780 to 1100 nm[6]. Due to the fact that this therapeutic modality can be applied to a wide variety of tissues and anatomical sites and every individual is unique, complications arise. The lack of standardized protocols in the literature generates much variance among reported results, and reproducibility therefore becomes difficult, further confounding an already complex field of study. Practitioners working with LLLT should ideally have a checklist in order to better understand and report all the necessary parameters for a reproducible scientific study (Table 1). Previously, Jenkins & Carroll[20] proposed the eight most important beam parameters to help researchers better report clinical and laboratory studies involving the application of photomedicine. According to the duo, these indispensable parameters encompass: power, wavelength, irradiation time, beam area (at the skin or culture surface), pulse parameters, number of treatments, anatomical location and interval between treatments[20].

Regarding dose, the three most commonly used parameters are time, energy and energy density. The authors further propose additional factors to consider, which may include coherence, application technique (projection, contact, scanning and pressure), spectral width and beam profile[20]. It is worth noting that beam power tends to decrease as a consequence of heat generation by the device itself and the inevitable aging of the equipment. This is why such pieces of technology must be routinely checked and calibrated accordingly before any experimentation is carried out. Measurement of beam area and power require precision and special equipment as well as experienced individuals in order to ascertain

Table 1 Technical specifications

Device	Considerations
Manufacturer	Important to consider well known sellers in the market, making wise cost-effective decisions
Device ID	For reference and tracking of malfunctioning equipment
Year produced	It is always best to choose the latest and most recent models to guarantee long-term success
Beam delivery system	Light can be delivered into the tissue <i>via</i> manual probe apparatus, fiberoptic or free air/scanned
Number of emitters	Left to the practitioner's decision
Emitter type	There are different types of laser such as KTP, LEDs, InGaAlP, and GaAlAs
Spatial distribution	Number of emitters and the distance between them as well as the pattern of distribution

KTP: Potassium-titanyl-phosphate; LEDs: Light emitting diodes; InGaAlP: Indium gallium aluminum and phosphorus; GaAlAs: Gallium-aluminum-arsenide.

more accurate data. Power readings must be monitored consistently throughout the applications procedure, which means that this should be done before and after each session, at frequent intervals. Selection of the correct wavelength is rather obvious but also important, because when erroneously configured, poor absorption occurs. According to the Grotthus-Draper law, without absorption there can be no reaction[21]. Additional observations include technical specifications of the device itself. A more complete and clear set of parameters has been created for ease of comprehension, as illustrated by Tables 1, 2 and 3, according to the variables and concepts proposed by Jenkins & Carroll[20].

Considering these variables, it is therefore evident that inappropriate parameters are likely to denigrate the therapeutic value of this modality. The concept of biphasic dose response curve (hormesis) is well-established for PBM. When variables such as radiant exposure, irradiance, delivery time and number of repetitions are either too high or too low, the desired results can often be negligible; sometimes, in the case of excessive photostimulation, the response can generate undesirable inhibitory effects[3]. This concept is based on the Arndt-Schulz law, where weak stimuli slightly accelerate vital activity. Conversely, stronger stimuli raise it further until a peak is reached, and even stronger stimuli suppress it until a negative response is achieved[22].

The relevance of these observations has been previously demonstrated. For instance, an *in vitro* study led by Karu and Kolyakov[23] revealed that stimulation of DNA synthesis rate depends on light intensity at a constant energy density of 0.1 J/cm² with a clear maximum at 0.8 mW/cm². A murine model of myocardial infarction proved that constant energy density and different irradiances after induced heart attack promoted beneficial effects at 5 mW/cm², whereas irradiances as low as 2.5 mW/cm² or as high as 25 mW/cm² had less significant results[24]. A similar study evaluated the reciprocity of exposure time and irradiance on energy density during photoradiation on wound healing in a murine pressure ulcer model. The authors learned that a fixed energy density of 5 J/cm² with only 8 mW/cm² irradiance enabled improvements in pressure ulcers in the treated mice[25]. It is worth noting that the proliferation rate of some cell types, such as fibroblasts, can be suppressed with inadequate energy delivery. Zhang and colleagues observed a significant increase in human fibroblasts after irradiating these cells at 628 nm with an energy density of 0.88 J/cm², an attenuated proliferation rate occurred at a staggering 9 J/cm², a parameter approximately 10 times more intense[26]. Despite these interesting findings, the World Association Laser Therapy guidelines recommend medical experts to use a dosage of at least 1 joule per target point, on 4 to 6 points for knee irradiation, specifically[27].

BIOLOGICAL EFFECTS OF PBM

PBM is rapidly growing and gaining recognition from many experts in the medical field due to its reported stimulatory effects on healing, tissue regeneration, attenuation of oxidative stress and reduction of pain and inflammation without causing severe side-effects[28]. Since osteoarthritic progression is in part correlated with an imbalanced overproduction of ROS and subsequent oxidative stress, application of PBM might prove to be a feasible tool in shifting equilibrium and managing some of the detrimental effects that is generated by this condition.

In addition to these effects, the literature also contains many studies reporting more interesting results arising from the application of this tool at varying wavelengths which may further assist in the fight against OA pathophysiological processes.

Proliferation

In numerous mammalian cells and tissues, light is absorbed by internal photoreceptors of the

Table 2 Photobiomodulation treatment parameters

Parameters	SI units	Additional notes
Exposure duration	Seconds (sec)	Some tissues may require more or less exposure duration, depending on the physical traits of the patient. For instance, obese individuals
Radiant exposure	Joules per centimeter squared (J/cm ²)	Intensity of the equipment must be adequately regulated depending on the different points to be irradiated. If the power density is too low, extending the irradiation time to reach the ideal energy density may not give an adequate final result. This should not be confused with “dose”
Number of irradiated points	-	Left to practitioner's decision depending on the treatment plan
Area irradiated	Centimeter squared (cm ²)	Area of target tissue must be carefully measured with precision for optimal results
Manual technique	-	Physicians must keep consistent pressure against the target point to ensure optimal delivery and penetration into the target tissue
Total number of sessions	-	Number may vary depending on how the patient responds to the treatment
Session intervals		
Irradiance at target point	Milliwatts per centimeter squared (mW/cm ²)	This parameter must be adequately regulated depending on the different points to be irradiated, otherwise, the absorption of photons will not be sufficient to attain the desired result. Additionally, very high intensities may generate excessive heat
Beam spot size at target point	Centimeter squared (cm ²)	This must be carefully measured with precision for optimal results
Radiant energy	Joules (J)	Different tissues may require more or less energy according to the patient's unique physical attributes (e.g. skin pigmentation and mass)
Total radiant energy	Joules (J)	The total accumulated energy delivered per session and over all sessions

SI Units: International System of Units.

respiratory chain in the mitochondria, such as cytochrome c oxidase, subsequently inducing the activation of this organelle within cells[29]. The photons transmitted from a low-power laser, for instance, have been shown to be absorbed by mitochondria (Figure 1), causing an increased production of ATP, especially in mesenchymal stem cells (MSCs)[30]. When adequately stimulated with specific biochemical signals these cells are able to exert many biological roles (Figure 2) which are of great benefit in injured tissues. MSCs can secrete various cytokines and growth factors which, in turn, allow them to modulate neighboring cells *via* paracrine signaling effects. Moreover, they are also highly appreciated for their ability to perform self-renewal and further differentiation into specific mature cell lineages; therefore, enhancing tissue repair mechanisms[31].

A recent study has shown that adipose tissue-derived MSCs, in particular, display a substantial increase in proliferative and secretory activity when irradiated with a power density of 5 J/cm²[30].

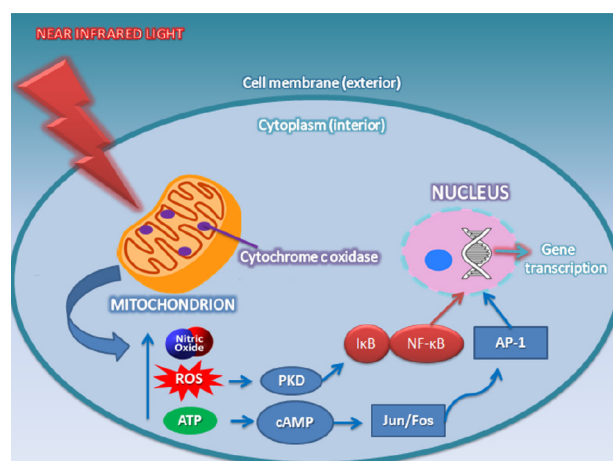
Low-level lasers (LLL) have demonstrated the ability to induce activation of several cell signaling pathways associated with proliferation and migration. Once induced, the tyrosine-protein kinase receptor, for example, can subsequently activate the MAPK/ERK signaling pathway, therefore promoting cell proliferation[32]. LLL can also cause phosphorylation of the PHAS-1 (protein heat and acid-stable) protein, which in turn up-regulates the expression of EIF4E (eukaryotic initiation factor 4E) and Cyclin D, further enhancing proliferative cycles. The EIF4E is a major regulator of cap-dependent mRNA and is known to respond to various biological stimuli including growth factors, hormones and mitogens[32]. Interestingly, LLL can also increase phosphorylation of the PI3K/AKT pathway, subsequently inducing the phosphorylation of mTOR, which ultimately leads to the phosphorylation of PHAS-1 in order to boost proliferative and migratory cell activity[33].

Nitric oxide and its associated signaling pathway also play a pivotal biological role by increasing angiogenesis and vasculogenesis. The expression of endothelial nitric oxide synthase, for instance, can be significantly increased in endothelial cells when irradiated with LLL set at a wavelength of 632.5 nm [34,35]. As a consequence, the enhanced proliferative and migratory capacities of these cells can then contribute to angiogenesis[34,35], which is an essential component that medical experts highly envisage when treating musculoskeletal diseases. In additional studies, LLL at 632.5 nm has also demonstrated the ability to activate the PLC-gamma pathway, which is responsible for catalyzing phospholipids and increasing the concentration of DAG and IP3. IP3 increases calcium levels from the endoplasmic reticulum in order to activate the PKC pathway. This signaling pathway is effective in cell proliferation, differentiation and apoptosis[36].

Table 3 Irradiation

Parameters	SI units	Additional observations
Operating mode	-	Physicians may select a continuous or pulsed wave, for example
Pulse on duration	Seconds (sec)	It is important to equally distribute time intervals between pulse on and pulse off cycles
Pulse off duration	Seconds (sec)	
Irradiance at aperture	Milliwatts per centimeter squared (mW/cm ²)	Irradiance can be significantly affected by the angular aperture of the light guide. For instance, irradiance measured with an aperture is greater than that without an aperture. Physicians should always keep this in mind
Aperture diameter	Centimeters (cm)	Values may vary significantly across different manufacturers and specific devices are better suited for different application objectives
Beam divergence	Radians or degrees (rad/deg)	Beam divergence may be an important variable depending on the nature and localization of the target tissue
Beam shape	-	The beams may be circular or elliptical, for instance
Laser beam polarization	-	The electric field vibration can be simple, with only one direction along the beam path (linear polarization) or it can be complex
Beam profile	-	Depending on the scenario (clinical or laboratory study), a specific profile may be indicated, such as Gaussian or Top Hat
Peak radiant power	Milliwatts (mW)	This variable must be carefully adjusted according to the target sample being irradiated
Average radiant power	Milliwatts (mW)	
Center wavelength (CW). And Spectral bandwidth (FWHM - range of wavelengths)	Nanometers (nm)	Practitioners must carefully select a suitable device with the appropriate wavelength and bandwidth specifications for the intended objectives. The FWHM (Full Width at Half Maximum) filter is important because outside the ideal bandwidth range light can be significantly attenuated
Frequency	Hertz (Hz)	The operator should always be aware of the frequency being applied to the area
Energy per pulse	Joules (J)	This parameter must be adequately regulated depending on the different points to be irradiated. Different tissues may require more or less energy per pulse. In clinical scenarios, the corporal density of each patient may vary significantly. In three-dimensional tissue cultures there are fewer layers of materials impeding light penetration and less scattering

SI Units: International System of Units.



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Figure 1 Photobiomodulation at near infrared light stimulates a subset of biochemical reactions in the mitochondrion in order to trigger transcription of genes associated with positive biological effects. ROS: Reactive Oxygen Species; ATP: Adenosine Triphosphate; PKD: Protein Kinase D; cAMP: Cyclic Adenosine Monophosphate; IκB: I kappaB kinase; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; Jun/Fos: Proto-oncogenes; AP-1: Activator protein 1.

Another important signaling pathway stimulated by LLL is the JNK/AP-1, which is also illustrated in Figure 1. The laser can cause elevation in cAMP levels and subsequent JNK phosphorylation, increasing the production of AP-1. This protein, in turn, can augment the expression of target genes involved in proliferation, survival and angiogenesis, especially in MSCs[37].

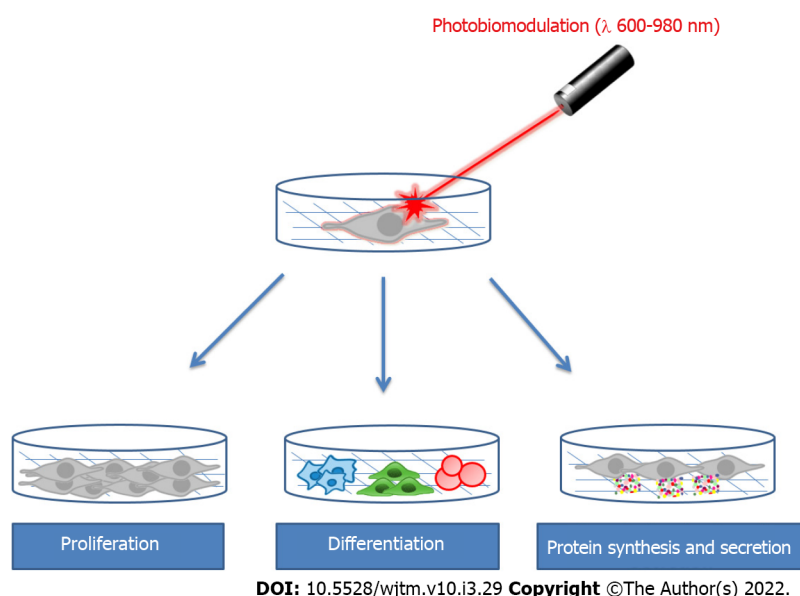


Figure 2 *In vitro* application of wavelengths between 600 – 980 nm stimulates differentiation, proliferation and the secretion of specific cytokines and growth factors for further modulatory roles.

Interestingly, the ROS/Src pathway is also important. LLL can increase ROS, which regulate the activity of different protein kinases, especially Src. These kinases serve as a target for ROS, and this specific interaction triggers proliferation, migration and influences cell survival[37]. Although ROS are often linked to inflammation and degradation, it is worth noting that they are a “necessary evil” since they do play an essential role in natural redox signaling for the maintenance of physiological functions [13]. Under adequate regulation, low levels of ROS trigger the activation of other signaling pathways and initiate the cascade of various biological events. It only becomes a major problem when ROS are overproduced and surpass the amount of antioxidant compounds within the cells, and attack biological components such as proteins, lipids and DNA[13].

In the case of degenerative disorders such as OA, it is important to establish and maintain adequate stimulation of local cells in order to reverse or at the very least prevent aggravation of incessant apoptosis and degenerative effects. Activation of the p53 gene, for example, can inhibit cell growth and induce apoptosis by up-regulating the expression of BAX and P21 genes[37]. BAX is a pro-apoptotic protein of the BCL2 family, and is involved in numerous physiological and pathological processes. In fact, a recent study[38] revealed that chondrocytes from the articular cartilage of OA patients exhibit increased levels of BAX. These proteins are responsible for the delivery of apoptotic signals to the mitochondria, leading to the activation of Caspase-3 and, inevitably, chondrocyte apoptosis. However, LLL has been found to increase the expression of the BCL2 anti-apoptotic orthologues. BCL2 has been implicated in the regulation of apoptotic pathways, especially due to the fact that its increased expression appears to reduce the levels of BAX proteins[36,37,39].

Differentiation

In addition to generating multiple biological effects which favor the proliferation of cells, PBM also stimulates cell differentiation under various circumstances. According to previous research, the application of this tool on stem cells *in vitro* generates promising results in the regenerative medicine context. LLLT irradiation, for instance, is capable of activating intracellular and extracellular chromophores and the subsequent initiation of signaling pathways associated with differentiation events[40, 41]. More specifically, PBM or LLL set at the red or near-infrared wavelengths has been reported to trigger proliferation of stem cells and their differentiation towards the osteogenic lineage[42]. Interestingly, Wang and colleagues[42] in 2016, investigated the effects of PBM (blue and green light) on human adipose-derived stem cells (hASC). The authors examined the effects of four specific wavelengths (420 nm, 540 nm, 660 nm and 810 nm) on hASC cultured in osteogenic medium, at a dose of 3 J/cm² for five times with two-day intervals over a period of three weeks. Following RT-PCR assays, increases in the expression of RUNX2, osterix and osteocalcin proteins were observed. The blue and green (420 nm and 540 nm) wavelengths, in particular, caused significant increases in intracellular calcium, exerting a more significant effect in osteoblast differentiation when compared to 660 nm and 810 nm. These results appear to be mainly attributed to the stimulation and activation of light-gated calcium ion channels by blue and green light, which suggests that these specific wavelengths may be useful in stimulating the differentiation of hASC towards a more specific cell lineage. In the case of certain musculoskeletal disorders, this feature may prove to be more or less attractive to medical experts,

depending on the individual needs of each patient.

Similarly, Fekrazad *et al*[43] investigated the application of single and dual combinations of laser wavelengths on bone marrow-derived MSCs from rabbits. In their set-up, the authors allocated the samples into one control and eight experimental groups as follows: infrared (IR, 810 nm), red (R, 660 nm), green (G, 532 nm), blue (B, 485 nm), IR-R, IR-B, R-G and B-G, respectively. The samples were irradiated every day for 21 days and then examined for cell proliferation and differentiation into osteogenic or chondrogenic lineages *via* analysis of RT-PCR biomarkers such as SOX9, aggrecan, COL2 and COL10 for cartilage; and ALP, COL1, and osteocalcin proteins for bone differentiation.

Proliferative activity was found to be increased in all PBM treatment groups except G. IR and IR-B promoted significant increases in the expression of all cartilage-associated genes but not COL10, which was actually attenuated by IR-B. In terms of osseous differentiation, a significant increase in ALP expression was observed in the R and IR treatment groups, whereas IR-R, IR-B and G diminished ALP expression. Furthermore, whilst COL1 expression was strongly stimulated by R and B-G, it was suppressed in the IR-B, IR-R and G groups. Osteocalcin expression was significantly increased only in the IR group and decreased in the B, B-G and G groups.

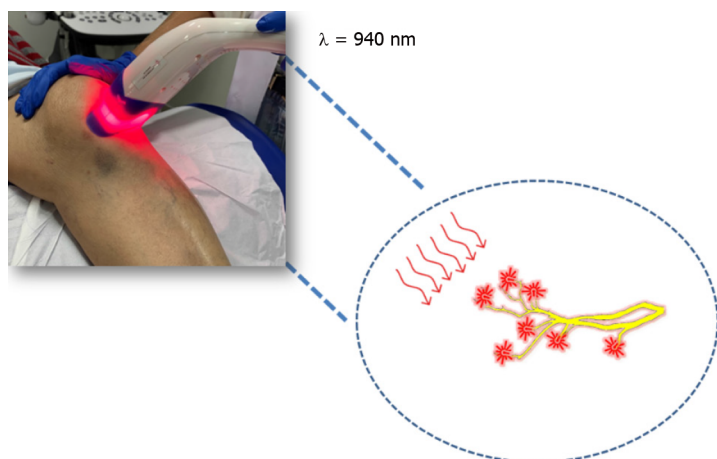
Overall, these recent findings show that cartilage differentiation appears to be significantly stimulated by the IR and IR-B wavelengths. Although in this study the effects of single or combined PBM irradiation procedures were not fully clear on osseous differentiation, osteogenesis appeared to be stimulated by the R and IR spectrum. Conversely, green light exhibited inhibitory effects. Therefore, at least in an *in vitro* experimental model of OA, PBM may convey beneficial effects. It must be considered that MSCs do not always display high proliferative capacities in culture, especially due to the fact that these cells may undergo replicative senescence during repeated passages *in vitro*, which would hinder potential clinical applications[44]. In addition, their ability to differentiate into more specific and mature cell types is quite restricted to a wide variety of biochemical signals, be it in the form of growth factors, proteins, physiological stress or even a combination of external sources of stimuli which can be induced with the application of PBM therapy (Figure 2).

In more recent developments, George and colleagues further elucidated other effects of PBM on the differentiation capacity of immortalized adipose tissue-derived stem cells (iASCs) into a specific cell line [44]. To elaborate, the authors determined the biological effects of low-intensity lasers on neurospheres generated from iASCs *in vitro*. NIR diode laser (825 nm) set at 5, 10 and 15 J/cm² with an average power output of 104 mW was applied in continuous waves to the respective culture plates *via* an optical fiber and adjusted to cover the entire area of the 35 mm diameter plate, achieving a spot size of 9.1 cm². The researchers learned that the irradiation procedure was capable of enhancing the differentiation of neurospheres into neurons. In particular, the power density of 5 J/cm² generated statistically significant increases in the early neuronal marker but not the expression of late neuronal markers. George *et al*[44] proposed that PBM is responsible for enhanced stem cell differentiation and, in this scenario, an increased yield of neurons by specifically modulating cellular metabolism and redox status. This is in parallel with similar results previously reported by other authors. These findings hold particular significance as PBM itself is more of a stimulatory tool (Figure 2) rather than an invasive technique. It has the capacity to guide the desired clinical outcomes towards differentiation of stem and progenitor cells into more specialized cell types without causing major alterations to the original tissue properties [44]. This allows medical experts and researchers to explore the clinical potential of these cells towards musculoskeletal health without raising major drawbacks linked to regulatory compliance[45].

NOICEPTIVE MODULATION

Photoneuromodulation

PBM is also renowned for its analgesic effects and may therefore be indicated for mitigation of pain associated with different pathologies. For this very reason, application protocols may then vary in terms of appropriate wavelength, irradiance and fluence depending on the physiological properties and anatomical location of the specific target tissues[46]. Although not entirely clear, the mechanisms of action underpinning this technique have been previously hypothesized; it appears that PBM is capable of directly modulating the nociceptive response, thereby reducing pain transmission[46]. Zupin *et al*[46] recently conducted an animal study aiming to investigate the probable analgesic effects of 800 (WL1) and 970 (WL2) nm wavelengths on processed dorsal root ganglia of male mice at 6-8 weeks of age. Before induction of nociception, the mice were allocated into 4 groups as follows: Vehicle injection (saline) without PBM treatment; capsaicin injection without PBM; and capsaicin injections with PBM treatment protocols at WL1 and WL2, respectively. It was found that both wavelengths were effective in decreasing the production of ATP in neurons of murine dorsal root ganglia whilst increasing the intracellular levels of ROS and anion superoxide. ATP molecules are essential for proper functioning of the Na⁺/K⁺-ATPase system and subsequently the generation of action potentials[46]. Elaborating these concepts further, the PBM-mediated inhibition of this system may block the transmission of pain through sensory neuron fibers, promoting an analgesic effect, especially in painful conditions such as OA (Figure 3). Zupin and colleagues observed that the rodents pre-treated with PBM at 970 nm



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Figure 3 Photobiomodulation at a wavelength of 940 nm blocks the transmission of pain through sensory neuron fibers, thus promoting analgesic effects.

exhibited a far less reactive response to nociceptive stimuli after having their paws inoculated with capsaicin. This was mainly expressed by minimal licking, biting or shaking of the treated limbs in comparison to the other treatment groups. These observations are also in alignment with the findings of the systematic review conducted by Chow *et al*[47] where ROS were shown to cause axonal varicosities, subsequently leading to the blockade of fast axonal flow in the small diameter A γ and C fibers, which are involved in nociceptive mechanisms. Also, in a similar study conducted by Wang *et al*[48], a wavelength of 980 nm was able to promote a thermal response and activation of the TRPV1 in adipose tissue-derived stem cells. The TRPV1 is a specific type of receptor mainly found in nociceptive neurons of the peripheral and central nervous system, thus is involved in the transmission of pain and integration of diverse painful stimuli[49]. Temperature increase at the cell membrane is a possible mechanism whereby TRPV1 is activated, suffers reduced activity upon the given stimuli and then subsequent desensitization toward capsaicin stimulation[46]. In simple terms, PBM at wavelengths close to or within the NIR range can reduce TRPV1 activity and calcium flow, thus is more effective in diminishing nociceptive responses (Figure 3), at least *in vivo*. Interestingly, other authors have shown that 830 nm continuous wave lasers are also capable of reducing the velocity of action potential conduction, increasing latencies in the median and sural nerves, and producing analgesic effects[50]. In additional rodent studies, PBM also suppressed nerve conduction in myelinated A δ and unmyelinated C fibers[51,52].

Inflammatory photoregulation

PBM can also exert 'inflammomodulatory' roles by influencing secretory activity in cells (Figure 4). This is also essential in the attenuation of nociception in many disorders where inflammatory stress is escalated due to exacerbated pro-inflammatory cytokine secretion, especially in OA patients. Yamada *et al*[27] recently investigated the effects of PBM on the knees of rats after inducing OA with intra-articular injections of MIA (monosodium iodoacetate). In comparison to the control group (saline), MIA mice had significantly higher levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α and interleukins (IL)-1 β and IL-6. The authors then designed a PBM treatment with a wavelength of 904 nm at doses of either 6 J/cm² or 18 J/cm² and applied them to the rat knees 3 d per week, for eight sessions. Capsule, menisci and cruciate and collateral ligaments samples were collected from knees and the corresponding biochemical assays were performed. The researchers then observed that the dose of 18 J/cm², in particular, proved to be far more effective in reducing the levels of the aforementioned pro-inflammatory cytokines. The effects of this specific parameter appeared to be more expressive from the fourth day of treatment and continued until the eighth day, when the researchers noted that the protective behavior in MIA mice was significantly diminished, indicating reduced pain. This observation is most likely attributed to a decrease in the levels of inflammatory mediators as well.

Furthermore, PBM can also increase antioxidant capacity and dampen oxidative stress damage at distant sites, which also contributes to attenuation of pain by peripheral and central sensitization reduction[53]. This tool has been shown to be responsible for increasing the levels of the enzyme superoxide dismutase (SOD), which provides an essential antioxidant defense system against oxidative stress. SOD acts as a good therapeutic agent against ROS-mediated diseases[27]. In the case of OA, in particular, SOD is often found to be scarce and in association with increased levels of nitric oxide, leading to mitochondrial dysfunction and subsequent chondrocyte apoptosis[54]. Cartilage degeneration alone is not the principal culprit in OA-associated pain as this structure has no sensory innervation. However, activation of the primary afferent nerve fibers of the knee joint might be. The

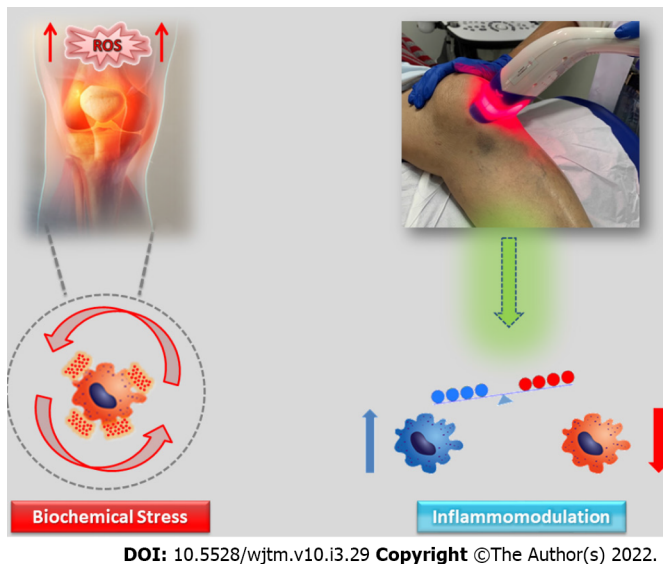


Figure 4 The application of photobiomodulation between 600 – 980 nm can attenuate inflammation by decreasing the production of pro-inflammatory agents and regulating the activation of immune cells.

predominant pro-inflammatory microenvironment in osteoarthritic knees is outlined by extensive cellular damage, mast cell degranulation, and unbridled secretion of inflammatory mediators and enzymes which sensitize nociceptors[55]. Nociceptors usually respond to noxious stimuli with more intensity, however, they may also ‘perceive’ and interpret non-harmful stimuli as painful due to peripheral sensitization. Overexposure of the periphery to nociceptive signals in turn increases excitability and activity in the spinal cord, giving rise to central sensitization[27,56].

This is why resolution and control of inflammatory stress is of utmost importance in the treatment of these degenerative disorders. Synovitis, for instance, is a relevant source of both pro-inflammatory and anti-inflammatory agents. Synoviocytes are known to secrete $\text{TNF-}\alpha$, $\text{IL-1}\beta$, and IL-6 , facilitating cartilage degeneration and joint hyperalgesia, which contribute to OA progression[57,58]. $\text{TNF-}\alpha$ does not only activate sensory neurons but also stimulates the production of interleukins, giving continuity to an inflammatory cascade. IL-6 , in particular, is highly detrimental as it stimulates the synthesis of matrix metalloproteinase-1, an enzyme involved in the breakdown of extracellular matrix and cartilage degradation[59]. Unresolved inflammation progresses towards chronic biochemical stress, where cytokines may trigger ROS overproduction, aggravating pain and oxidative stress, generating a complicated negative feedback loop (Figure 4) which is difficult to break[9,13,60,61]. PBM has demonstrated the potential to contribute to the alleviation of exacerbated biochemical stress and chronic inflammation through its capacity to downregulate the expression of various pro-inflammatory mediators in different scenarios[27,62,63].

Regulation of immune cell activity is also another robust attribute of PBM (Figure 4). Neutrophils, in particular, are well-known for their immunological properties as well as their inflammatory and hyperalgesic reactions that arise from their increased activity[64]. Migration of these cells from circulation to the peripheral tissues, for instance, is significantly intensified in patients with knee OA; their infiltration into synovial tissues can be quite harmful to the knee joint due to the release of proteolytic enzymes[27]. This means that, upon receiving nociceptive stimuli, neutrophils react and further amplify inflammation by subsequently producing more biochemical signals to recruit more neutrophils and additional immune cells into the site of tissue injury, which is especially true for osteoarthritic patients[27,65]. In comparison to their inactivated states in circulation, neutrophils are more reactive with increased activity in peripheral tissues, where they release more cytokines and inflammatory mediators that contribute to the aggravation of pain and inflammation[66,67]. More specifically, the leukocyte-derived enzyme myeloperoxidase is released by these immune cells, catalyzing the formation of ROS and therefore contributing to extensive tissue damage during inflammation[68,69]. These detrimental effects can and have been reversed *via* the application of PBM in the study by Yamada *et al*[27], where the dose of 18 J/cm^2 successfully reduced the increased MPO activity associated MIA-induced OA in the knees of mice. This study provides sufficient evidence to indicate that PBM may effectively reduce neutrophil migration and MPO release, consistent with reported changes in pain, which then again, may reflect attenuated oxidative stress. Lastly, this may also suggest a secondary systemic effect associated with PBM.

CONCLUDING REMARKS

The application of PBM could prove to be a feasible tool in managing some of the detrimental effects generated by mild to moderate degrees of OA. PBM has recently shown interesting results in the literature, especially in regards to the proliferation and differentiation of MSCs towards osteogenic and chondrogenic lineages, for example. This could be particularly beneficial in the treatment of some musculoskeletal disorders, such as OA, under specific circumstances. This technique has multiple comparable benefits, at least in terms of ease of application, non-invasiveness, no serious adverse effects, financial viability and efficacy particularly for pain alleviation. These are perhaps the most prominent features which a debilitated patient primarily seeks when he or she walks into the clinic, as OA pain alone is often the most expressive symptom and driver in clinical decision making. Although photomedicine is slowly expanding and showing some optimism in the medical community, additional studies are highly warranted in order to further elucidate and support its regenerative medicine potential in musculoskeletal disorders.

FOOTNOTES

Author contributions: Santos GS and Giolo FP wrote the manuscript; Pacheco VF and Huber SC proposed the research subtopics; Rodrigues BL, Malange KF and Bassora F were responsible for navigating the literature and sharing the relevant studies included in this review. Mosaner T formatted the citations and compiled the references; Parada CA revised and formatted the body of the manuscript, correcting spelling, punctuation and grammatical errors. Azzini G and Ribeiro LL created the figures and tables. As the leader, Lana JFSD was responsible for reviewing and approving all the modifications made to the manuscript, from draft to final version.

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