REVIEW ARTICLE

Photobiomodulation Therapy for Wound Healing: A Narrative Review

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ABSTRACT

Photobiomodulation is a therapy method that employs light to stimulate cellular function. It has emerged as a promising approach to healing wounds due to its potential to accelerate tissue repair. Wounds can vary in severity from minor cuts to more serious injuries that involve deeper tissue damage. Wound healing is the natural process of the body to repair the injured tissue that causes disruptions to the integrity of the body's tissue. It has been known that photobiomodulation has established its positive effects on wound healing in various factors by modulating the inflammatory response. This review aims to understand the efficacy of photobiomodulation and the clinical application of light transmission as a therapy in enhancing the healing of wounds. Articles on photobiomodulation and its application in wound healing were searched from the available peer-reviewed journals. Published papers were collected from PubMed, Scopus, and Science Direct using photobiomodulation, wound healing, and soft tissue as the keywords. The initial paper search yielded 124 results, and 37 full-text eligible articles were assessed in this review. In conclusion, photobiomodulation has been seen to offer a promising therapeutic approach to enhancing wound healing despite ongoing development. Continued research is essential to comprehend the full potential of photobiomodulation therapy in accelerating wound recovery. It will provide insights into future research areas on photobiomodulation, thus improving the clinical treatment modality and the patient's quality of life.

Keywords
Photobiomodulation, Wound Healing, Light Therapy, Wavelength

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INTRODUCTION

Photobiomodulation (PBM) is a therapy that uses light to stimulate cellular activity and promote tissue healing. Since the discovery of lasers in the 1960s, this advanced therapeutic application has demonstrated enormous potential in assuring efficient and thorough wound healing for decades.[1] The mechanism of this therapy draws on the release of energy packets known as photons, resulting in light emission. The light emission produced by the photon's energy is influenced by the wavelength.

In PBM, the biological action begins upon the absorption of photons, which occurs within the chromophore molecule. The interaction between a chromophore and wavelengths is distinctive due to the chromophore's capacity to absorb light throughout a range of wavelengths.[2] The application is a non-invasive medical treatment that uses low-intensity lasers or LEDs consisting of various light spectra that have been introduced to enhance the biological effects of the healing. Researchers have found that the optimal wavelengths used in clinical practice are between 600 and 1100 nm.[3]

Wound severity can range from minor to severe injuries involving deeper tissue damage. The body's natural process of healing wounds, which disrupts tissue integrity, is called wound healing. This process eventually leads to wound closure by forming scars from connective tissue to replace the damaged area.

When the skin is damaged, the healing process begins with platelet activation, triggered by exposed components like collagen and tissue factors. Platelets then release chemokines and growth factors (GFs), which help form clots and achieve haemostasis. After clotting, neutrophils arrive at the wound site to clear debris and provide microbial defence, preparing the site for further healing stages. Macrophages facilitate phagocytosis by removing foreign agents from the wound area and restoring the tissue's internal integrity after damage. However, wounds can also have devastating consequences and could lead to chronic pain and loss of body parts, which persist long after the initial injury has healed. This can significantly diminish an individual's quality of life, interfering with daily activities and leading to emotional and physiological distress. Various approaches have been established to control and minimise wound progression. However, the probability of wound re-occurrence is still high. Therefore, an innovative application using light emission such as PBM is required to effectively promote reliable and comprehensive wound healing.

Individuals with long-term injuries, such as diabetic foot ulcers, have slower healing times, which raises the possibility of infection. Due to the condition, they are more vulnerable to injuries. Crucially, patients who consistently use conventional wound dressings have a higher risk of infection and experience a slower rate of recovery. This review aims to understand the efficacy of PBM in enhancing wound healing, its mechanism of action, and the clinical application of light transmission as a healing therapy. Further investigation into light therapy can promote its application as a wound healing treatment, thereby improving patients' quality of life by enhancing their cell production and progressively instilling optimism in the healing process of their lesion.

MATERIAL AND METHODS

This comprised of relevant article literature that was extracted, and databases searched for in this review were PubMed, Science Direct, and Scopus. Search terms were "photobiomodulation", "wound healing", and "soft tissue" as in **Table I**. All the retrieved articles were added to the Mendeley citation manager, and duplicates were eliminated.

Table I: Information on sources and search strategies for the review

Database	Search strategies	Results
PubMed	Photobiomodulation AND wound healing AND soft tissue	34
Science Direct	Photobiomodulation AND wound healing AND soft tissue	69
Scopus	Photobiomodulation AND wound healing AND soft tissue	21
	Total	124

The search was conducted between October 2023 and September 2024. Original research articles from 2018 until 2024 and other additional relevant articles were included in this review. The inclusion criteria applied were English literature, and using PBM/LLLT as an intervention.

DISCUSSION

WOUND HEALING

A wound is defined as any disruption or damage to the normal structure and function of the skin, resulting in a break in the epidermal integrity, characterised by loss of epithelial continuity with or without loss of underlying connective tissue. Usually, wounds can occur due to surgery, trauma, or disease processes.[4]

Phases of wound healing

Wound healing is essential to maintain epidermal integrity after injury-causing cuts and abrasion. The process involved specific sequential events starting from haemostasis, inflammatory, proliferative, and remodelling phases[5] as shown in **Figure 1**. The process of wound formation involves the initial injury, exposing sub-endothelium, followed by haemostasis by releasing tissue factors activating platelet aggregation, which results in degranulation and release of chemotactic factors (chemokines) and growth factors (GFs) forming clots to stop the bleeding. Concurrently, inflammatory mediators are released, initiating the subsequent inflammatory phase.[6] Neutrophils and macrophages are inflammatory cells that migrate to the wound's site, releasing growth

factors and cytokines that promote tissue healing. Pro-inflammatory mediators are also released during this phase, facilitating the release of immune cells and nutrients to the wound site by increasing vascular permeability and vasodilation.[6]

The immune system incorporates inflammation as a dynamic mechanism to eliminate the wound sites from debris, pathogens, and damaged cells. Subsequently, the proliferative phase facilitates tissue repair by forming granulation tissue for tissue regeneration and repair.[7] Fibroblasts, recruited to the wound site, synthesise and deposit extracellular matrix (ECM) components such as collagen, elastin, and proteoglycans, forming a provisional matrix that provides structural support for cell migration and tissue generation.[7] Endothelial cells proliferate to form new blood vessels (angiogenesis), enhancing oxygen and nutrient delivery to the healing tissue. Additionally, epithelial cells at the wound edges proliferate and migrate to cover the wound surface, restoring the epithelial barrier. The final phase of wound healing is the remodelling phase. This phase involves the maturation and reorganization of the newly formed tissue to accelerate its strength and functionality.[5] Excessive collagen synthesis, characteristic of the proliferative phase, is downregulated, and the ECM undergoes remodelling through the action of matrix metalloproteinase (MMPs) and tissue inhibitors of metalloproteinases (TIMPs).[7] This process leads to the alignment of collagen fibres along the lines of mechanical stress, increasing tissue tensile strength. Over time, the scar tissue matures, becomes less vascularised, and gains mechanical stability although it may never fully regain the structural and functional characteristics of the original tissue. In some cases, scar formation occurs.[8]

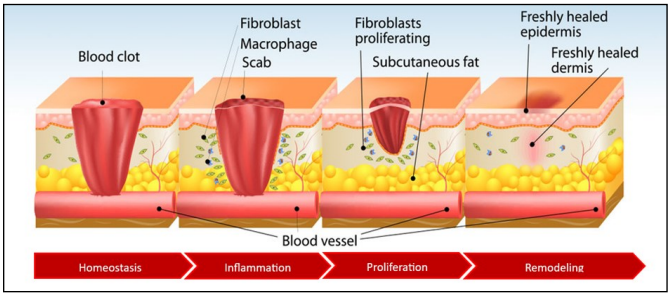

Figure 1: Stages of wound Healing. Adapted from John Maynard, 2015.[9]

PHOTOBIOMODULATION

Photobiomodulation is a therapeutic technique that involves the application of a low-level laser or LED to stimulate cellular function, promote tissue repair, reduce inflammation, and relieve pain.[10] The use of lasers has been discovered in the 1960s. This advanced therapeutic application has demonstrated significant potential for providing efficient and thorough wound healing for years. Although there was initial scepticism within the medical community in the late 20th century, PBM has gained recognition as a safe therapy for patients and has started to be incorporated into clinical practice for various medical conditions.[11] With the laser's development in recent years, this therapy continued to evolve pair with the advancement of technology nowadays, the development of PBM devices become more sophisticated and capable of delivering precise dosage and targeting specific tissues. PBM is now utilised across various medical disciplines, including sports medicine, rehabilitation, dermatology, and dentistry.

Therapeutic Effects of PBM

PBM exerts therapeutic effects by inducing photophysical and photochemical changes within cells without causing thermal damage. Biological effects from these changes lead to modifications in gene expression, metabolic arrangement, and the production of cellular metabolism.[2] Thus, the parameters which are wavelength (measured in nanometres, nm), fluence (measured in joules per square centimetres, J/cm^2), irradiance (measured in watts per square centimetres, W/cm^2), and timing (measured in seconds, s) require optimum value for treatment.[12]

PBM utilises light sources from the visible spectrum, including blue (405 to 470 nm), red (600 to 700 nm), and near-infrared (NIR). The light within the designated "optimal window" at red and NIR wavelengths (600 to 1070 nm) are commonly utilised for PBM.[13] Due to their limited penetration depth, superficial tissue is treated with the lower wavelengths within the red spectrum (600 to 700 nm). On the contrary, tissues located at greater depths are treated with longer wavelengths (780 to 950 nm), penetrating much deeper. The power of light typically lies in the range of 1 to 1000 mW and depends

on the application. The dose (fluence), which is a function of the combination of irradiance and time, is also important and varies depending on the application.[11,14]

Law of Biphasic Dose Response in PBM

The law of biphasic dose response presented by Arndt-Schultz is followed to prevent excessive light application toward the target cells.[15] This rule in PBM therapy states that low levels of irradiation must be applied upon each experiment and gradually the dosage so that the photons can be absorbed by subcellular chromophores present inside intracellular organelles and facilitate the cytochrome c oxidase (CCO) in the mitochondrial respiratory chain to trigger PBM effects without distressing the cells unexpectedly. It increases both adenosine triphosphate (ATP) production and oxygen consumption while simultaneously causing changes in nitric oxide (NO) and growth factor production.[15] At this very low-level starting point, energy is absorbed by the cell and, at the same time, receives moderate amounts of energy to prevent photochemical damage.[11]

MECHANISM OF PHOTOBIOMODULATION IN WOUND HEALING

Wound healing involves specific phases, and the process also comprises various types of cells to control and regulate cytokines and growth factor expression. The most common therapy for wound healing is the conventional, which treats the ulcers with antibiotics and gauze dressing to prevent infection. While there are alternative methods, some of them have not been able to accelerate the process of wound healing.[6]

PBM as a Potential Therapeutic Treatment for Wound Healing

PBM has emerged as a promising therapeutic modality for wound healing and enhances cellular stimulation by triggering mitochondrial function while promoting ATP production.[11] Furthermore, PBM can produce anti-inflammatory effects by suppressing pro-inflammatory cytokines and having analgesic properties to reduce pain. Collagen synthesis would also be enhanced to support the remodelling phase of tissue repair.[16]

Injured blood vessels constrict in wounds to reduce blood loss, and platelets aggregate to form temporary clots. PBM influences the haemostasis indirectly by improving microcirculation and blood flow to the wound site, facilitating the delivery of platelets and clotting factors.[17] A study has found that PBM modulates various biological effects and regulates disturbance in reparative processes for wound healing by adjusting ROS, cytokines, and platelet aggregation activity.[18] By mitigating excessive inflammation, PBM creates a conducive environment for subsequent stages of wound healing and prevents prolonged inflammation, which can impair tissue repair. PBM also stimulates cellular proliferation by enhancing ATP production, which fuels energy-dependent processes involved in cell migration. This is supported by a study of human gingival fibroblast cells showing high proliferation by utilizing the 980 nm wavelength with 4 J/cm^2 energy density.[19]

Application of PBM Using Different Wavelengths

Comparative studies examine the relative efficacy of PBM at different wavelengths in the range of light from the visible to infrared delivered at constant light intensity and fluence rate.[20] The influences of PBM can also vary based on the various light sources used and the dosimetry employed. The changes in cell proliferation and ATP migration production are among the few significant outcomes assessed in determining the effect of light therapy following irradiation.[21] Dungel and colleagues (2023) have applied three different wavelengths to measure the effects of PBM for wound care in diabetic wounds and found that the most optimal wavelength to accelerate wound closure is between green (540 nm) and red (635 nm) which significantly increased the formation of new blood vessel of the excision wound (Table II).[22]

Etemadi *et al.,* (2021) demonstrated four different wavelengths that delivered the same energy density towards human gingival fibroblast cells following a scratch assay and found that the most desirable setting for cell proliferation is 980 nm (at 1, 1.5, and 4 J/cm^2) and 635 nm (4 J/cm^2).[19] Effects of light therapy have also been found to influence the activation of MÜller cells that are responsible for maintaining retinal haemostasis

Table II: Effects of Photobiomodulation (PBM) on wound healing

Study type	Sample description	Phototherapy dosage			Treatment duration	Treatment outcome
		Wavelength (nm)	Irradiance (mW/cm²)	Fluence (J/cm²)		
In vivo* and *In vitro [23]	39 adult rats exposed to photo-oxidative damage and Scratch model using human Müller cell line (MIO-M1)	670	60	9	The rats are treated with light at 0, 3, and 14 days after 'photo-oxidative damage, and the Müller cells are irradiated following the scratch assay.	*In vivo*, the early treatment of light at 0-3 days showed that it reduces retinal stress, decreases pro-inflammatory cytokines expression decreases the photoreceptor loss thus slowing the retinal degradation progress. *In vitro,* shows that light therapy can activate cells by influencing gene expression and regulating transcription to mitigate damage
In vitro [19]	Human gingival fibroblast cells (HGF-P1)	635 660 808 980	0.33 0.22 0.4 0.25	1, 1.5, 2.5, and 4 each	Cell proliferation was assessed by MTT assay and conducted at 24, 72, and 120-h following the PBM irradiation	The PBM therapy increased the cell proliferation rate of HGF cells and 980 nm wavelength with 1, 1.5, and 4 J/cm² showing the highest proliferation rate of cells followed by 635 nm with 4 J/cm² fluence.
In vitro [35]	Diabetics induce normal and wounded (scratch assay) of Human skin fibroblast (ATCCCRL1502-WS1)	660	12.2	0 and 5 each	Laser irradiation exposure time was 410 sec (6 min 50 sec). Post-irradiation cells were then re-incubated for 24, 48, and 72h.	Cells exposed to the laser irradiation demonstrated quicker and more effective wound closure compared to the non-irradiated controls.
Clinical study [28]	Patients with chronic diabetes (n=60) LED Group: 30 patients Control Group: 30 patients	625[a], 660[b], 850[c] nm	-	5	The wound was treated with light for 5-min exposure time accordingly and the treatment was given three times a week for 8 weeks for both groups.	The phototherapy with LED showed significant improvement in healing for chronic diabetic wounds.
In vitro [36]	Normal and wounded L929 (Mouse Fibroblast), Normal and wounded HGF-1 (Human Gingival Fibroblast)	660	2.5 5.5 8.5	-	Cell proliferations were measured using MTT assay and wound healing assay after exposure for 5, 10, and 20 min. The cell migration was monitored at 12 and 24h after the scratch.	The optimal dose of cell proliferation at 660nm was 8.5 mW/cm² for 5 min (2.55 J/cm²) for HGF-1 and 5.5 mW/cm² for 20 min (6.6J/cm²) for L929. For cell migration rate, irradiation exposure times of 5 min and 10 min are optimum.
Clinical study [30]	Paediatric patients with bilateral primary molar teeth extraction (n=40)	980	0.5 mW	300 J	Pain assessment was performed using the Wong-Baker FACES Pain Rating Scale for seven days and the soft tissue healing was evaluated on the 3rd and 7th days following the extraction session.	The study found that the LLLT provided significant wound healing following the extraction of primary molar teeth and has the potential to effectively reduce post-operative discomfort.
In vivo [22]	Groups of mice (8 in each group) non-irradiated control group •Group 1: Blue Wavelength at 470 nm •Group 2: Green Wavelength at 540 nm •Group 3: Red Wavelength at 635 nm	470 540 635	40	14.4	The light treatment was applied to each group accordingly during day 0 and wound size was assessed every fourth day from day 0 to day 28.	Pulsed red (635 nm) and green (540 nm) LED light was found to be the most effective wavelength in accelerating wound closure and increasing angiogenesis of excision wounds in diabetic mice.
Clinical study [37]	30 patients with type 2 DM having Meggit-Wagner grade 1 foot ulcers.	660	50	3	The foot ulcers were given light exposure daily for 15 days.	Patients treated with LLLT showed significantly increased wound closure.
***In vitro* & Clinical study** [3]	Human fibroblast cells (HS 68)	450 520 633	3	0.9, 2.7, 8.1 respectively	Laser exposure times were 0, 5, and 15 min	There were no significant differences between the red light versus green and blue light for cell viability. A significant decrease in the relative expression of MMP-1, -2, and -9 was observed in the 633 nm group versus the 520 nm and 450 nm group.
	60 patients with chronic wounds	633	3	2-8	Treatment was given twice a week, with a minimal interval of 3 days for 8 weeks. Skin biopsies were performed to investigate the mechanism before LLLT and 4 weeks after the wound healed. Serum samples were collected after irradiation to measure the bFGF and VEGF.	Fibroblast collagen type I production increased which activated collagen production and remodelling. Significantly elevated bFGF and VEGF levels indicated their critical roles in wound healing.
Clinical study [6]	18 patients with chronic diabetic foot ulcers	660	30	6	LLLT sessions were done every 48 hours (16 sessions) for 4 weeks	LLLT enhances the progression of tissue repair in diabetic ulcers.

*bFGF, basic fibroblast growth factor; VEGF, vascular endothelial growth factor; LLLT, low-level light therapy; ATP, adenosine triphosphate; MMP, matrix metalloproteinase; a,b,c ,Contributing ratio of irradiance of corresponding wavelength.

following photo-oxidative damage by irradiating both *in vivo* and *in vitro* stress models using 670 nm wavelength at 60 mW/cm^2 delivering 9 J/cm^2 irradiation to the retina.[23] Furthermore, by incorporating two different methods in search of the most optimal wavelengths for wound healing, Yang *et al.,* (2020) began with an *in vitro* assay, testing three different wavelengths; 633 nm, 520 nm, and 450 nm on human fibroblast cells. They found that wavelength at 633 nm has the most significant results on cell proliferation. Following the result, in a clinical trial, they applied the same wavelength to patients with complicated wounds. The implied light exposure showed an increase in fibroblast collagen I which helps in tissue remodelling. These results served as proof that LLLT assists in the cell growth of damaged tissue and could become a foundation for further application of light as a tool in enhancing healing for chronic patients.[3]

CLINICAL APPLICATION OF PHOTOBIOMODULATION IN WOUND HEALING

Wavelengths in the 500-700 nm range are suitable for treating superficial tissue traumas, while wavelengths between 800-1000 nm are effective for more profound tissue injuries such as diabetic wounds or trauma after surgery.[24] There are various findings on PBM parameters for enhancing wound healing, however, effectiveness is determined by several parameters such as the wavelength (nm), power dosage (mW/cm^2), irradiation dose (J/cm^2), and treatment duration.[12]

Diabetic Wounds

PBM application has been utilised and found to be beneficial, especially for diabetic wounds. Visible light devices in the 400-800 nm range have demonstrated efficacy in treating venous foot ulcer patients where 90% of them showed a high wound closure rate.[25] This showed that the mechanism of light therapy reinforces the modulation of cellular processes, including increased cellular metabolism, ATP production, and collagen synthesis, leading to the enhancement of overall tissue repair.[22] In another clinical study, PBM illumination 660 nm with 30 mW/cm^2 light intensity and fluence of 6 J/cm^2 using LED irradiation exposure on the wound surface in a single application for 14 days resulted in the promotion of the natural healing process of the diabetic wound.

Healing of recalcitrant diabetic ulcers can be induced by PBM at 660 nm wavelengths in a pulsed manner at constant irradiance, peak power (30 mW), treatment duration in 4 weeks, and radiant exposure (6 J/cm^2) promotes more extensive healing. This treatment can also reduce inflammatory processes and increase tissue proliferation and granulation, thus significantly reducing lesions in the wound area.[26] Additionally it can also be seen in both diabetic and healthy human skin fibroblast cells irradiated at the same wavelength (660 nm) which respond with greater extents of cell migration, viability, and proliferation, leading to faster wound closure compared to the non-irradiated cells.

Some studies suggest that combining different wavelengths such as red and near-infrared light in a single application, may produce synergistic effects on tissue proliferation by targeting multiple aspects of cellular function and metabolism.[27] These different wavelengths work together amplifying the penetration and enabling simultaneous treatment of a broader range of tissue, thus promoting healing in both superficial and deeper wounds. A combination of 625, 660, and 890 nm wavelengths are found to improve blood flow and neovascularisation of patients with chronic diabetic wounds, which also induces better healing of recalcitrant diabetic ulcers giving the chance for the patients to have a better chance of full recovery.[28] Enhanced collagen accumulation and total wound re-epithelialisation are defining characteristics of the healing process as opposed to other wavelengths and non-illuminated controls.[29]

Oral Disease

In dental phototherapy, PBM has a wide range of applications in the treatment and management of various oral diseases. It has been seen to stimulate cellular processes that accelerate healing, reduce inflammation, alleviate pain, and promote tissue regeneration, especially during the post-operative dental treatment period.[30] PBM is also an adjunctive therapy for the initial healing process and can decrease pain reception following gingivectomy

oral surgery.[31] Previous research also found that applying 830 nm and 30 mW light therapy effectively reduces swelling and alleviates postoperative discomfort from mandibular third molar surgery.[32] Furthermore, in a study incorporating LED irradiation as part of periodontal therapy, light therapy contributed to restoring the periodontium and reducing inflammation.

In different conditions, patients usually encounter discomfort after treatment or dental surgery. The pain is usually unpleasant and is the most common complication faced during dental treatment. Managing pain tolerance will help a lot in reducing dental fear and anxiety when undergoing these treatments. It also encourages much faster healing.[33] PBM has an advantage in reducing pain perception following tooth extraction and provides significant wound healing in the extraction socket, especially among paediatric patients. Low-level light therapy was also proven to improve tissue healing after dental surgery [30]. A study found that exposure of 810 nm with an irradiation dose at 3.87 J/cm^2 showed favourable effects on pain and enhanced soft and hard tissue healing in the early phase of the healing period after endodontic surgery.[34]

CHALLENGES AND LIMITATION

A key challenge is the absence of standardised treatment protocols, with variations in device parameters, for example, the specific usage of wavelength, irradiance, fluence dosage, treatment duration, and treatment techniques.[38]

Despite insignificant evidence of side effects from PBM suboptimal parameter choices can lead to unsatisfactory findings or adverse therapeutic outcomes, and the lack of standardised protocols makes it difficult to compare study outcomes.[14] Healing trajectories also depend on wound aetiology since PBM effectiveness varies by wound type, location, and etiology.[11] Strategies to reduce cost and improve accessibility for developing countries in integrating PBM into the wound care protocol are needed to make this modality more attainable to patients and healthcare providers.

CONCLUSION

In summary, these data suggest that the most effective wavelengths for wound healing are in the red spectrum, between 635 and 670 nm, and the near-infrared wavelengths are between 810 and 960 nm. Therefore, the optimal wavelength range is 600-960 nm, though it also includes wavelengths that are inhibitory to wound healing. The optimum fluence or dose for the light therapy which induces photochemical damage, ranges from 1-16 J/cm^2. Additionally, the treatment duration must be considered, as it varies depending on the wound type and severity.

These findings indicate that PBM shows promise as a therapeutic approach for wound healing, and this review has evaluated its effectiveness. While the wavelength, radiant exposure, and light intensity were generally identified, several challenges and limitations need to be addressed. Continued research, innovation, and collaboration among clinicians and researchers are essential to overcoming these obstacles and realising the full potential of PBM therapy to accelerate wound healing and improve the patient's quality of life.

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