Invited Review

Photobiomodulation therapy: Ushering in a new era in personalized supportive cancer care

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Abstract

The human body can utilize light for a broad range of pathophysiological responses, such as circadian rhythm, Vitamin D metabolism, and vision, among others. The therapeutic use of light has spanned many ancient health practices. Recent advances in using low-dose light therapy, termed photobiomodulation (PBM), have made tremendous progress in unravelling precise biological mechanisms and clinical dosimetry, enabling this treatment modality's clinical safety and effectiveness. The evidence for PBM has received its strongest endorsement via recent systematic reviews and meta-analyses recommending its routine use to address various acute and chronic side effects associated with cancer treatment. Carefully done studies have noted unequivocal evidence demonstrating its effectiveness in managing oral mucositis in patients undergoing radiotherapy for head and neck cancer, chemotherapy, or hematopoietic stem cell transplantation. This brief narrative review will explore the therapeutic benefits of PBM therapy, supported by recent research findings, to provide a comprehensive understanding of its potential in clinical settings. Additionally, the review will highlight our current understanding of molecular mechanisms underlying PBM and the importance of novel harmonized dosing that enables its optimal clinical implementation and utilization.

Keywords: Cancer care, light therapy, photobiomodulation, photonic fluence

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INTRODUCTION

In recent years, various forms of phototherapies or light therapy have emerged as promising, non-invasive, and versatile approaches for a vast array of clinical applications in health care.[1] The earliest use of light therapy in health care can be traced back to Dr. Niels Ryberg Finsen, a Danish physician who won the 1903 Nobel Prize for his work on concentrated light (sunlight) radiation as an antimicrobial agent, specifically treating Lupus Vulgaris.[2] The invention of the LASER (Light Amplification by Stimulated Emission of Radiation) occurred 60 years later, reigniting interest in understanding light–tissue interactions and potential benefits when applied in health care. Dr. Endre Mester, a Hungarian scientist, played a crucial role as the pioneer in studying the biological effects of lasers. He conducted experiments involving low-dose laser treatments in mice. He observed significant improvements in wound healing and hair growth, using the term *photobiostimulation*.[3] Later, it was recognized that these low-dose light treatments are not only capable of stimulation but also modifying certain pathophysiological processes such as inflammation or pain, leading to adoption

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of the term photobiomodulation (PBM) therapy. PBM therapy is broadly divided into stimulatory and inhibitory biological effects. It now includes a diverse range of non-ionizing light sources, including lasers, light emitting diodes (LEDs), and visible and near-infrared light, delivered at very low, non-thermal doses. The basic mechanism of PBM includes activation of biological markers, sensitive to a certain wavelength of light. Activation of these biological markers results in complex cytochemical and physiological reaction pathways that ultimately lead to positive clinical therapeutic outcomes.[4]

Since Dr. Finsen's original work on antimicrobial disinfection contrasted with Dr. Mester's work on wound stimulation, the former work on the use of low-dose light treatments to target microbes, and now for tumour cells and tumour-associated endothelial and immune cells termed *Photodynamic Therapy* (PDT).[5] The summary of various types of phototherapies, their biological effects, and clinical applications is presented in Figure 1. Photodynamic therapy focuses on eliminating infections such as bacteria, fungi, viruses, and various types of tumours.[6,7] Multiple laser wavelengths have been used for either direct physical ablation (photothermal) or disinfection (called photoactivated disinfection, PAD, or antimicrobial photodynamic therapy, aPDT) and indirect disinfection by agitative irrigation (photoacoustic). In contrast to these, PBM is a distinctly different treatment that is a non-thermal, non-surgical, and non-invasive technique that utilizes low-level light to stimulate cellular function and promote tissue repair.[8] PBM is used for various clinical applications like pain management for acute and chronic conditions, wound healing, dermatological issues, sports injuries, neurological conditions, cancer pain and management, oral health treatments, and potential applications in ophthalmology and veterinary medicine. PBM's anti-inflammatory properties aid in reducing inflammation, increasing blood flow, and supporting cellular metabolism, making it a promising therapeutic approach.[9] PBM has also been employed to modulate inflammatory or immune-mediated pathologies such as aphthae, lichen planus, oral mucositis (OM), pemphigus, herpes simplex, temporomandibular joint disorders, Sjögren's syndrome, burning mouth syndromes, orofacial pain, and paresthesia post-extraction.[10-13] Both PBM and PDT have gained significant attention from researchers and clinicians as possible adjunct therapies in the management of post-cancer treatment side effects, particularly in patients with head and neck cancers. These non-invasive light therapies have shown promise in alleviating common complications of oncotherapy that include oral mucositis, xerostomia, and dysgeusia, among others, to improve the overall quality of life. This mini-review focuses on the role of PBM applications, safety, clinical dosing, and current clinical evidence in cancer care.

Types of Light Therapies	Biological Effects	Clinical Uses/Applications
Photobiomodulation Therapy	Inhibitory	• Inhibit / relieve pain • Resolve inflammation • Aberrant immune response
	Stimulatory	• Promote healing • Promote tissue regeneration • Modulate immune responses • Performance and Resilience • Bright Light Therapy • Exogenous UV-B for Vitamin D
Photodynamic Therapy	Endogenous chromophore	• Hair removal • Neonatal jaundice • UV Plasmapheresis • Narrow band UV-B
	Exogenous chromophore	• Anti-Tumor (tPDT) • Anti-microbial PDT (aPDT) • Immune(iPDT)

Figure 1: Comparisons between the non-surgical and non-thermal light-based therapies, photobiomodulation (PBM), and photodynamic therapy, highlighting their similarities and differences

MECHANISM OF PBM

Light-based therapies have been utilized in cancer treatment for various therapeutic outcomes. Among them, PBM treatments in supportive oncology care have been shown to enhance resilience and minimize adverse effects.[14] The impact of PBM on exposed tissues is contingent upon several factors, such as the positioning of cells within the proximity of light exposure, cell type, molecular composition, cellular redox state, tissue microenvironment conditions, and various parameters related to the PBM technique itself including wavelength, power density, delivery method (pulsed or continuous), size and shape of the light beam or spot area being used for irradiation purposes along with duration/frequency of exposure.[15] PBM has been studied extensively to understand its mechanisms of action on biological tissues. Low-intensity light treatments are used in a non-thermal manner, activating various molecular targets such as cytochrome C oxidase, transforming growth factor-beta 1 (TGF-β1), nuclear factor κ-B (NFκB), and Opsins.[16,17] Three specific cellular compartments have been investigated: the mitochondria, cell membrane (photosensitive transporters and receptors), and extracellular milieu (latent TGF-β1 activation). By utilizing PBM, these discrete components have a direct biological effect contributing to the observed therapeutic benefits.[18] The most popular mechanism of PBM involves the intracellular mitochondrial enzyme cytochrome C oxidase (CCO). This enzyme demonstrates distinctive absorption characteristics within the non-ionizing, visible spectrum (blue and red) and near-infrared (NIR) wavelengths.[18] When CCO directly absorbs light, particularly in these specific wavelength ranges, it leads to a noteworthy enhancement of mitochondrial activity. Consequently, there is an increase in ATP production

and the generation of mild, transient reactive oxygen species (ROS). Importantly, the induction of ROS follows a dose-dependent pattern, and its beneficial effects are confined to a specific therapeutic dose window for PBM treatments. Within this optimal dosage range, the redox signalling cascades are activated. These cascades, in turn, can mediate various cellular processes, including cell proliferation, migration, and modulation of cellular functions, such as secretion and maturation.[2,14]

PBM therapies can directly activate the latent growth factor complex, TGF-β1, which holds pivotal roles in bone biology encompassing processes such as development, immune responses, wound healing, and malignancies. Within osteoblasts, PBM treatments have been observed to induce an augmentation in mitochondrial adenosine triphosphate (ATP) levels, coupled with upregulation of essential biomolecules, namely osteocalcin, collagen, RUNX-2, vascular endothelial growth factor, bone morphogenetic proteins (BMPs), and cyclooxygenase-2 (COX-2).[16,17] These intracellular pathways have been identified as playing substantial roles in eliciting the clinical responses associated with PBM, including pain mitigation, modulatory effects on inflammatory and immune responses, and the facilitation of wound healing and tissue regeneration.[2] Additionally, compelling evidence indicates that PBM can effectively regulate key elements within the fibrosis pathway. This regulation includes reducing fibroblast proliferation and migration speed, inhibiting TGF-β1 and its associated pathway production, and downregulating collagen synthesis and deposition. These findings suggest potential clinical benefits in managing conditions such as radiation-induced fibrosis.[15]

PBM DOSAGE AND SAFETY

Over the years, numerous individual patient treatments and successful clinical trials have established PBM as a safe and beneficial therapeutic approach. However, it is essential to understand the proper dosage and safety protocols associated with this treatment to ensure its maximum impact. Although the precise mechanism of laser-induced analgesia requires further research, current clinical practice indicates that dosimetry for pain relief is generally higher than that used for biostimulation.[19] In this context, choosing wavelength and treatment parameters becomes crucial. For example, the dermatology community has devised protocols to avoid excessive heat buildup by employing gated pulses with different shapes, durations, and intervals. Preconditioning with cold or low-dose NIR (near-infrared) might also offer protective benefits to superficial tissues.[19] Additionally, studies have shown that shorter wavelengths lead to higher remittance, suggesting visible to NIR range of 400–1200 nm as the optimum wavelengths for deeper tissue penetration, with approximately 800 nm appearing most effective in terms of least absorption by biological chromophores [Figure 2].[20-23] When employing low-level lasers or LEDs for cancer-supportive care, PBM parameters usually fall within the red and near-infrared wavelength range of 400 to 1200 nm with a power density ranging from 5 to 150 mW/cm^2.[24] The duration of application may vary depending on the treatment site, with a minimal treatment of 30 seconds per spot.

Over more than two decades of using PBM in the management of oral mucositis (OM) in head and neck cancer patients, significant adverse effects have been reported only in one study, where a burning sensation was reported in 50% of paediatric patients.[25] Nevertheless, the overall safety record of PBM remains promising, and its diverse biological impact encourages further exploration of its potential influence on tumour response to therapy and tumour behaviour. However, definitive answers to these questions still await future research. Cancer therapy often leads to a wide range of acute and late complications that negatively impact patients' quality of life. Based on recent evidence, PBM shows promise as a preventive and therapeutic option for managing acute and chronic side effects associated with cancer treatment.[26] Its effectiveness in preventing and managing oral mucositis has already been demonstrated, leading to its inclusion in the treatment guidelines of respected medical organizations such as Multinational Association of Supportive Cancer Care (MASCC)/ISOO, the European Society for Medical Oncology (ESMO), the National Institute for Health and Care Excellence (NICE), and the World Association for Photobiomodulation Therapy (WALT).[27]

Laboratory studies have shown unequivocal responses with PBM treatments on tumour cells, emphasizing critical cell culture conditions as a major determinant.[28] Controlled animal studies have noted a reduced tumour burden in tumour-bearing mice subjected to PBM treatments.[29] Retrospective analysis of PBM treatments in patient populations to prevent oral mucositis has noted reduced recurrences and secondary tumours that can be partly attributed to improved oncotherapy.[30] Furthermore, it is unlikely that the non-ionizing wavelengths used for PBM are capable of any carcinogenic effects on normal cells.[31] Using non-ionizing wavelengths within the red and near-infrared (NIR) spectrum in PBM ensures that these wavelengths are significantly longer than the safety limit

Figure 2: PBM treatment has been noted to be effective for a wide range of wavelengths, including 447 nm (Blue), 589 (Green), and 660 nm (Red) light devices that can be both LEDs or lasers, as shown here. A popular wavelength, 810 nm, is not shown here as it is in the invisible near-infrared wavelength

of 320 nm (ultraviolet), a threshold known to cause DNA damage. Consequently, the risk of DNA harm is minimal.[15]

Conventional photobiomodulation (PBM) utilizes distinct wavelengths with standardized dosing that considers parameters such as fluence, irradiance, and duration of treatment. Adjusting PBM dosing parameters to specific wavelengths can transform the current PBM paradigm.[32] According to the Arndt–Schultz curve, therapeutic responses are confined to a particular therapeutic window. Optimal cell responses are attained at specific stimulus levels, while deviations above or below this range may reduce efficiency.[33] While no harm is anticipated at the low levels of light used for PBM, it is being increasingly appreciated that routine PBM protocols are overtreating and potentially neutralizing their benefits. Current advanced PBM dosing concepts include *Photonic Fluence* and *Einstein* paradigms to improve dosing accuracy. Photon fluence is determined by additionally including individual photons on the tissue surface, termed tissue surface irradiance (TSI) in mW/cm^2, treatment time (seconds). To ensure harmonized universal dosing, independent of the wavelength, we divide the specific photon fluence by a factor of 4.5 to achieve dosing as an *Einstein*. For example, 810 nm laser at 3 J/cm^2 (fluence) and 1.5 eV (individual photon energy) results in a photon fluence of 4.5 pJ/cm^2, which is equal to one Einstein.[32] By employing advanced photonic fluence and Einstein dosing, more precise results can be achieved, accurately aligning within the Arndt–Schultz curve.[32] Furthermore, these concepts allow the rationalized combinatorial use of multiple wavelengths.

PBM IN SUPPORTIVE CANCER CARE

Despite the ongoing improvements in cancer therapy, it is still associated with severe life-impairing side effects. Both treatment- and patient-related risk factors determine the severity of the complications. Moreover, they negatively impact the patient's quality of life (QoL) and daily activities. Therefore, effective supportive care strategies are necessary.[34] There is a considerable body of evidence supporting the efficacy of PBM for the prevention of oral mucositis in patients undergoing radiotherapy (RT) for head and neck cancer (HNC), chemotherapy (CT), or hematopoietic stem cell transplantation (HSCT). PBM has the potential to be a new preventive and therapeutic option for a wide range of acute and chronic side effects associated with cancer therapy [Figure 3]. It effectively prevents and manages oral mucositis (OM) and is included in general treatment guidelines by reputable medical societies. While *in vitro* and *in vivo* studies have indicated its safety, caution is still advised when applying it to cancer patients. Personalized PBM protocols based on precision medicine may optimize its effectiveness for individual patients, considering variations in gene expression and cellular responses. Implementing PBM in clinical oncology practice can improve patient's quality of life, treatment compliance, and success rates in cancer therapy. PBM's immunomodulatory effects show potential for enhancing antitumor immune responses. It is also beneficial for pain management and wound healing in cancer patients. While PBM focuses on supportive care and improving patients' quality of life during cancer treatment, PDT targets cancer cells and is investigated for various cancers. PDT involves using photosensitizing agents activated by light to destroy cancer cells selectively. It can be applied locally and complements other treatments like surgery or chemotherapy. PDT also offers palliative care for relieving symptoms in advanced cancer cases.

Radiation therapy and/or chemotherapy in the head and neck region (HNR) have several side effects that can be debilitating and heavily affect patients' quality of life (QoL) and prognosis. The most common side effects include oral mucositis (OM), xerostomia, dysgeusia, oedema, radiation caries, radiodermatitis, and trismus.[34] These spectra of ailments share a common etiopathology of these

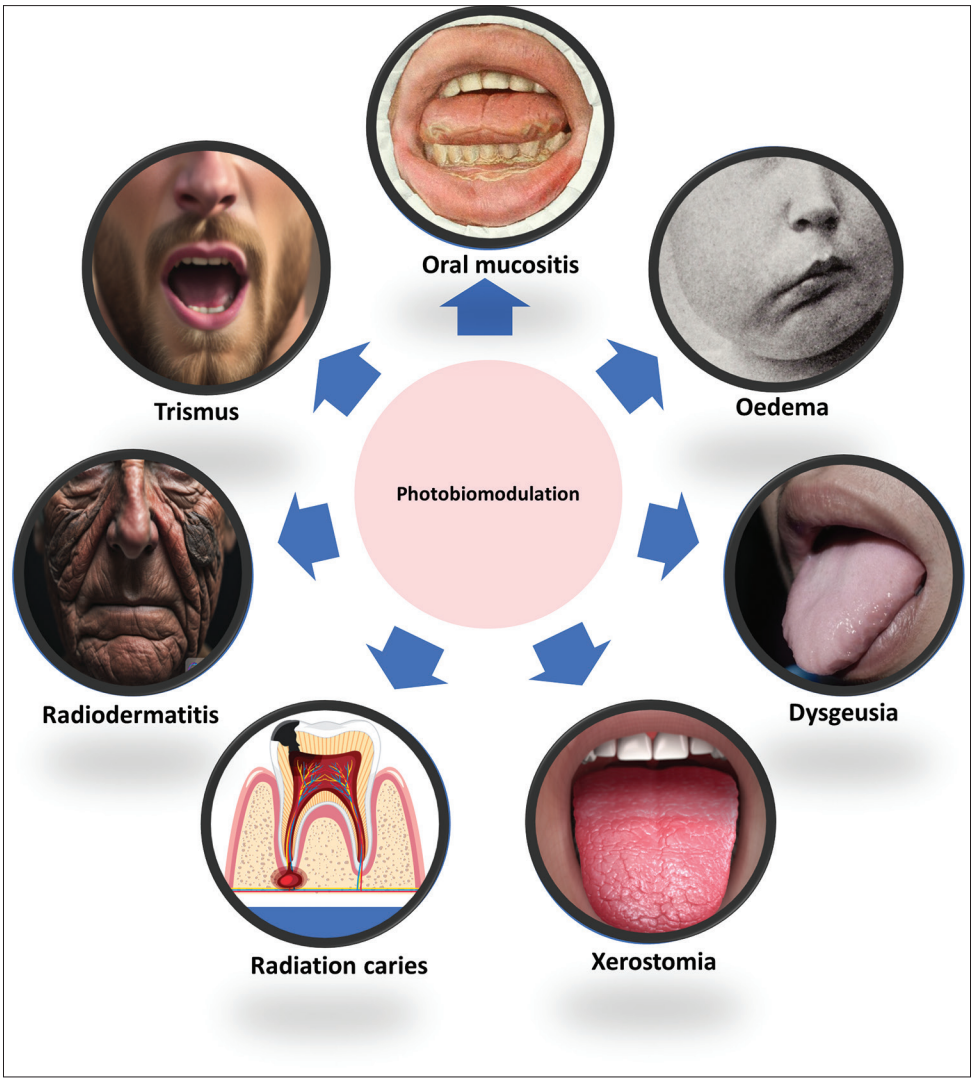

Figure 3: A broad range of clinical applications of photobiomodulation treatments as primary and adjunctive cancer therapy. The reader is encouraged to review the original cited literature for the strength of current evidence and clinical protocol recommendations.[2,15] Attention to the new harmonized PBM dosimetry is suggested[15,32]

complications involving sensitization and tissue damage by the oncotherapy agent. Photobiomodulation (PBM) is a non-invasive light therapy increasingly being applied in supportive care for cancer patients. Its main properties cover the field of wound healing and inflammation.[34] Oral mucositis, hyposalivation, xerostomia, dysphagia, acute radiation dermatitis (ARD), lymphedema, dysgeusia, and trismus are common complications in cancer patients undergoing therapy for head and neck cancer (HNC). These side effects significantly impact patients' quality of life and treatment outcomes. Photobiomodulation therapy (PBM) has shown promise in preventing and managing OM and xerostomia, with some evidence supporting its use in dysphagia and ARD management. However, more research is needed to optimize PBM protocols and validate their effectiveness. The combination of PBM with conventional treatments may improve outcomes for some conditions like lymphedema. Despite the potential benefits, PBM's safety and efficacy in cancer patients require careful consideration, and personalized treatment protocols may be necessary due to variations in cellular responses and tumour microenvironments.

In conclusion, PBM is a safe and effective approach for pain relief, inflammation reduction, and tissue repair. The non-invasive, non-pharmacological, sustainable, and preventive nature of PBM treatments holds great potential in supportive cancer care. The availability of clinical practice guidelines, approved clinical devices, and clear documentation of their tremendous impact on reducing cancer complications and quality of life are poised to improve precision cancer care significantly.

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Conflicts of interest

There are no conflicts of interest.

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