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# Photobiomodulation in Cancer Therapy

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## ABSTRACT

**Background and Aim:** Photobiomodulation (PBM), also known as low-level light therapy (LLLT), is a new adjuvant therapy in oncology that holds promise for improving treatment outcomes by reducing side effects related to conventional therapies like chemotherapy, radiotherapy, and immunotherapy. PBM uses selected wavelengths of light to modulate the biological processes, which induce therapeutic effects by interacting with mechanisms such as cytochrome c oxidase, increased adenosine triphosphate (ATP) production, control of reactive oxygen species (ROS), modulation of gene expression, and anti- inflammatory responses. The current review aims to discuss the applications, benefits, challenges, and future directions of PBM in oncology.

**Methods and Materials:** A wide literature review was carried out in order to assess the clinical and experimental data for PBM applications in oncology. In particular, this paper will aim to understanding the mechanism, the safety concern, and its potentiality as a personalized therapeutic approach. Variability in the responses obtained in different patients due to non- standardization of the parameters of PBM treatment, like wavelength, dosage, and treatment time, is analyzed.

**Results:** PBM has shown significant promise in the promotion of tissue repair and reduction of inflammation, thus being effective in the management of complications such as mucositis, dermatitis, and neuropathy. However, concerns about potential tumor stimulation effects under certain conditions raise a call for caution in its application. Variability in patient and tumor- specific responses remains a critical barrier to standardization and broader adoption.

**Conclusion:** PBM could revolutionize cancer care by acting complementary to the standard treatments, improving therapeutic outcomes, and enhancing quality of life. Further research will be required to optimize protocols, address safety concerns, and establish PBM as a personalized and standard component of oncology treatment plans.

## INTRODUCTION

The low- level laser therapy (LLLT) based on photobiomodulation (PBM) is a non-invasive therapeutic approach that uses the energy from light all through the biological tissues. Light irradiation in biological tissues, resulting from the absorption of red or near-infrared wavelengths, penetrates the tissue and modulates various biological responses. PBM is non- thermal because it acts in cells and tissues through photochemical and photophysical mechanisms in order to produce certain biological effects (1-3). The physiologic effects of PBM are assumed to be through typical absorption by mitochondrial chromophores, more so by cytochrome c oxidase, an important enzyme in the mitochondrial respiratory chain (4). This uptake evokes enhanced mitochondria activity, resulting in the generation of adenosine triphosphate (ATP), modulation in reactive oxygen species (ROS), and the release of nitric oxide (NO). These bioenergetics may trigger most cellular processes such as cell proliferation, migration, and anti-inflammatory responses (5). Importantly, PBM has also been shown to modulate gene

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expression, protein synthesis, and cellular signaling pathways that underlie its therapeutic activity. Practically, PBM is also widely used in the clinical settings for practicing wound healing and pain therapies. In the wound healing scheme of action, PBM helps in tissue repair that occurs through the synthesis of collagen, angiogenesis, and restoration of damaged tissues (6, 7). Here it is very successful, especially in the case of chronic wounds such as diabetic ulcers and pressure sores, in which many conventional treatments have failed. PBM has been used in the management of pain through anti- inflammatory, circulatory- enhancing, and neuro- modulatory mechanisms for the treatment of both acute and chronic types of pains (8). Due to the fact that it is a non-invasive modality with negligible side effects, the therapy attracts patients looking for alternative or complementary treatments for pain and wound healing (2, 9). PBM is an emerging adjunct technique in cancer treatment, mainly because of its non- invasive nature and the possibility of improving treatment outcome. PBM has been used for a long time for wound healing and pain; therefore, it generated interest in using it within oncology for its cell- modulating effects without inducing thermal damage. The potential of PBM in supporting cancer treatment was investigated for the reduction of mucositis, dermatitis, and neuropathy- some major side effects resulting from chemotherapy and radiation therapy (10). By the effect of anti-inflammatory and the promotion of tissue repair, the quality of life of the patient can be enhanced and they may be more tolerant of conventional therapy for cancer. The potential uses of PBM for cancer therapy do not necessarily form only on symptom management. In fact, emerging evidence is beginning to suggest that PBM may also sensitize tumors to radiotherapy or chemotherapy, thereby possibly increasing the efficacy of these treatments. Modulation of the tumor microenvironment by PBM, in turn, could support more potent cancer treatment strategies related to the improvement of blood flow, reduction in tumor hypoxia, and regulation of immune responses (11, 12). The use of PBM in oncology is still in its nascent phase, and current evidence is far from sufficient to fully understand the mechanisms, optimal protocols, and long-term effects of using PBM as an adjuvant to conventional cancer treatment (11).

## MECHANISMS of PBM at the CELLULAR and MOLECULAR LEVEL

PBM mainly works by activating the interaction of the absorbed light with cellular components. Chromophores in the mitochondria are known as the powerhouses of the cell and, within the mitochondria, one of the most important enzyme complexes is cytochrome c oxidase of the mitochondrial respiratory chain. Application of PBM would allow penetration of the light through the tissue, and the light would be absorbed by cytochrome c oxidase with a chemical preference for the red and the near- infrared wavelengths (13, 14). This absorbed light energy in the enzyme activates it and leads to improvement in electron transport across the mitochondrial membrane. It is through this stimulation that the activity of the mitochondrial respiratory chain increases, amplifying proton gradient and, hence, adenosine triphosphate production (15). ATP is a major energy currency of the cell, whereby increased production fuels various cellular functions, including repair, proliferation, and mechanisms of defense. Improved ATP production, under PBM conditions, serves not only cellular metabolism but also contributes to improved cell viability and function (7, 16). This mechanism forms the basis for the therapeutic effect of PBM in such a way that this energy enhancement supports the recovery of cells against damage and thus acts as a useful modality for established and emerging medical therapies. The downstream effects of PBM are cardinal in the furtherance of its therapeutic role, especially in cancer therapy (12). This is thoughtfully debated upon as one of the most important consequences: the moderation of ROS, which are metabolic byproducts and at the same time serve a dual role in cell physiology. Additionally, high ROS levels can be responsible for cellular damage and the progression of cancer (17). On the other hand, moderate levels of ROS are essential in the signaling mechanisms that regulate cell growth or apoptosis. It could finely adjust the production of ROS, through an interaction with cytochrome c oxidase to maintain a proper balance. The moderate levels of ROS induced by PBM could further enhance cellular signaling and defense mechanisms without crossing the line into stressful oxidation, probably particularly beneficial in the changeable environment of a cancer cell during carcinogenesis (14, 18). Besides the modulation of ROS, PBM is involved in modulating gene expression and triggering an anti- inflammatory response, important beyond even its pivotal role in cancer therapy. PBM can upregulate the gene expression involved in cell survival, repair, and anti-apoptotic pathways that help to support healthy tissue while putting the cancer cells on hold. Effects from anti- inflammatory actions, mediated by PBM through a reduction in pro- inflammatory cytokines and pathways for anti- inflammatory activation, would help in the mitigation of inflammations related to cancer (19, 20). The decrease in inflammation not only alleviates symptoms, but also creates a more conducive environment that may make conventional cancer therapies more effective. These downstream effects of PBM provide the emerging scenario for supportive modalities in the management of cancer (21).

## PBM in REDUCING CANCER TREATMENT SIDE EFFECTS

Clinical evidence from randomized controlled trials (RCTs) support PBM administration and the relief it provides for common cancer treatment side effects, including but not limited to, mucositis, dermatitis, and neuropathy. Mucositis is an inflammation of the mucous membranes and is a common side effect for many chemotherapy and radiation therapy patients (22). It often occurs in patients who suffer from head and neck cancer. It is abundantly clear that PBM can lower the grades of mucositis, as well as shift its timeline. PBM promotes tissue repair, reduces inflammation, and potentiates cellular activities, all contributing to maintaining mucosal lining integrity, reducing pain, and improving the quality of life of patients (23, 24). The promising results shown by these studies have thus warranted PBM in the recommendation of several clinical guidelines as supportive treatments for oral mucositis. Similarly, the application of PBM has been encouraging in the management of radiation-induced dermatitis, a frequent side effect of radiotherapy that causes pronounced discomfort and impacts the continuity of treatments (25, 26). Clinical trials proved that it reduced the incidence and severity of dermatitis by fostering skin regeneration, reducing inflammation, and increasing local circulation. On top of that, PBM has been found to be effective in the treatment of chemotherapy- induced peripheral neuropathy-a condition where nerves are damaged, leading to pain and numbness, especially in the extremities. By modulating neural activity and reducing oxidative stress, PBM could ease the restoration of nerve function and thus reduce neuropathy symptoms (27, 28). These clinical findings thus open a window of opportunity for PBM as a non- invasive adjunctive therapy in enhancing patient outcomes in cancer treatments. Photobiomodulation (PBM) helps reduce cancer treatment side effects mainly through its tissue repair and anti-inflammatory effects. By stimulating cellular activity, PBM promotes tissue healing and regeneration. Light absorbed by cellular chromophores—especially cytochrome c oxidase in mitochondria—boosts ATP production, providing energy for the healing process. PBM also regulates the production of ROS and activates multiple cell-signaling pathways that lead to the down-regulation of pro-inflammatory cytokines and up-regulation of anti-inflammatory mediators (19, 29). It is this dual effect that not only enhances the repair of tissues from treatments such as chemotherapy and radiation but also has an anti-inflammatory effect, which therefore alleviates pain. These combined effects come to mean the mitigation of mucositis, dermatitis, and neuropathy side effects by PBM, all of which combine to significantly improve patient comfort and quality of life during cancer therapies (10).

## DIRECT ANTI- CANCER EFFECTS of PBM

Emerging studies indicate that PBM might have some direct influence on tumor growth, apoptosis, and metastasis, although complex and sometimes context- dependent. Some research has indicated the possibility of PBM modulating cellular signaling pathways influential in tumor biology and thus may have an impact on cancer cell proliferation and survival (12). For example, while PBM is a potent modulator of mitochondrial function and ATP synthesis, its use in active cancer could promote tumor growth under some circumstances. Yet another hypothesis is that PBM might facilitate programmed cell death of cancer cells, apoptosis, particularly when applied within certain wavelength and dosage parameters. Additionally, the PBM was shown to affect the tumor microenvironment and may affect processes such as neovascular formation and immune responses, both very important in the progression and metastasis of a tumor (11). These findings again lead to careful consideration and further research into optimizing PBM protocols in oncology, ensuring that its application supports therapeutic outcomes and does not inadvertently promote growth or metastasis of tumors (30). The application of PBM within oncology is embroiled in much controversy, especially regarding its effects directly on malignant cells. While PBM is widely recognized for its therapeutic benefits in reducing treatment side effects, there's been concern raised about the possibility of PBM inadvertently promoting tumor growth under certain conditions. These represent the basis for concerns because PBM has been shown to promote cellular metabolism, increase ATP production, and influence multiple signaling pathways, effects that are beneficial for normal tissue repair but conceivably could stimulate the proliferation of neoplastic cells (31, 32).

Some studies have examined double action of PBM according to dose and wavelength. Low- level laser treatment in the red (approximately 630-660 nm) and near infrared (780-830 nm) has been shown by in vitro studies to induce or inhibit tumor cell proliferation with modulation of fluence and exposure time. For example, low fluences ($\leq$ 3 J/cm$^2$) have been found to increase cell viability and proliferation in certain tumor cell lines, whereas elevated fluences (> 10 J/cm$^2$) induce oxidative stress and trigger apoptosis. Further, in vivo experiments indicated that 808 nm and 830 nm light with moderate energy densities (5-15 J/cm$^2$) enhanced immune responses and apoptosis in cancer models, while doses too low could inadvertently promote tumor development through increased local vascularization and metabolism. These findings all indicate that both wavelength and dose need to be well optimized in order to achieve

therapeutic benefit without promoting tumor growth. Therefore, PBM parameters must be optimized for oncologic diseases to ensure safe and therapeutic outcomes.(33, 34).

## PBM and the TUMOR MICROENVIRONMENT

This does have notable effects on the tumor microenvironment, especially with respect to its influence on immune cells such as macrophages and T cells. PBM modulates the activity and polarization of macrophages from a pro-tumorigenic M2 phenotype toward an anti-tumorigenic M1 phenotype, which increases the capacity of the immune system to attack the cancerous cells (35). Other than that, PBM can trigger T-cell activity by stimulating their proliferations, further increasing cytotoxicity against the tumor cells. It can develop the antitumor immune response in the tumor microenvironment and thus can be an adjuvant to current cancer therapies; however, optimal dosing and timing must be highly considered in order to avoid off-target effects. PBM can influence the extracellular matrix (ECM), which plays an important role in the process of invasion and metastasis (19, 36). The ECM is considered to provide structural support for tissues and takes part in the regulation of cell activities such as migration and proliferation. PBM modulates expression and activity of Matrix metalloproteinases (MMPs), enzymes responsible for the degradation of the ECM, thus potentially modifying the tumor capability for invading surrounding tissues. Influencing the balance of ECM remodeling might turn PBM either inhibiting metastasis or, in case it is not kept within narrow frames, even inadvertently facilitating tumor metastasis (37). The dual potential mentioned above points to optimization of the protocols of application as the condition sine qua non for guaranteeing that the therapeutic benefit will not be balanced by increased tumor aggressiveness (38).

## PBM IN COMBINATION with CONVENTIONAL CANCER THERAPIES

There is cumulative evidence to support the combined use of PBM with conventional cancer therapies, chemotherapy, radiotherapy, and immunotherapy, pointing at increased efficacy with decreased toxicity. Indeed, a series of clinical trials have evidenced that PBM reduces mucositis, dermatitis, and neuropathy- some of the noxious side effects of these treatments-so that patients can better tolerate and adhere to their therapeutic regimens (2, 10, 21). Also, PBM may enhance the efficacy of conventional therapies through enhanced tissue oxygenation, reduced inflammation, and modulation of immune responses, thereby creating conditions more favorable to tumor eradication. While these findings are heartwarming, incorporating PBM into standard oncology care will need clear- cut protocols so maximum benefits can be ensured with the lowest risk of any side effects (39).

## CURRENT CHALLENGES and FUTURE DIRECTIONS

Standardization of PBM parameters of wavelength, dosage, and treatment time presents a bigger challenge in sustaining similar therapeutic outcomes in the treatment of cancer. The biological effects of PBM are very sensitive to these parameters; different wavelengths and dosages have produced different effects on the cellular processes involved in the progressions of cancer (40). Furthermore, patient-related criteria and tumor type and location in each patient, added to biological variability, could further complicate the issue. The lack of unified guidelines on these researches leads to the inconsistency of the success of different studies and the application of PBM in clinics. In view of this, intensive studies and further clinical trials need to be carried out on finding the appropriate PBM parameters which ensure safety and effectiveness in treating cancer so that more reliable and reproducible therapeutic success is ensured (33, 34).

Future studies in PBM should be focused on wavelength, dosage, and duration of treatment for the optimization of treatment protocols that will elicit maximum therapeutic benefits with minimal risks in cancer therapy. For safe integration into oncology, the long-term tumor progression and recurrence due to PBM need to be clarified. Moreover, personalized PBM treatments- considering tumor type, patient genetics, and individual responses- will lead to higher effectiveness and will ensure that therapeutic approach is personalized to meet the needs of a particular patient. These areas of research will be crucial in ensuring full potential for PBM in cancer treatment.

## CONCLUSION

To date, significant progress has been made in the application of PBM as a complementary modality in cancer therapy. Its primary clinical value lies in the management of side effects from conventional treatments like chemotherapy, radiotherapy, and immunotherapy. Non- invasive, the potential of modulating cellular effects by increasing ATP, the level of ROS, and regulating gene expression, marks PBM as a useful tool to enhance tissue repair and reduce inflammation. However, direct impacts of PBM on tumor growth, apoptosis, and metastasis are still complex and context- dependent, and PBM should be applied cautiously with further investigation. The influence of PBM on the tumor microenvironment underlines its potential in curbing or worsening cancer progression by showing crosstalk between immune cells and the ECM. Standardization of parameters for PBM, taking into consideration its long- term

effects and devising personalized treatment protocols according to tumor and patient genetics, are the main points of future research. Addressing such challenges will allow PBM to be effectively integrated into oncology, hence boosting therapeutic outcome and increasing the quality of life among patients.

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## CONFLICT OF INTEREST

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