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REVIEW

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Potential Applications of Photobiomodulation in Combinatorial Cancer Therapy: Developments in Diagnosis and Treatment

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ABSTRACT Objective: Over the last two decades, the potential applications of photobiomodulation therapy (PBMT) have garnered increasing attention. The mechanism of PBMT involves the absorption of light energy by cellular components, such as chromophores. This absorption initiates a cascade of biochemical reactions, including cellular signaling pathways, gene expression, and the production of various molecules such as reactive oxygen species, adenosine triphosphate, and growth factors. In this review, we aimed to investigate the potential applications of PBMT when combined with chemotherapy (CT), radiotherapy (RT), and immunotherapy. **Material and Methods:** PubMed (National Library of Medicine, ABD), Scopus (Elsevier, Hollanda), and Google Scholar (Google, ABD) were searched to obtain data. **Results:** Based on the results of in vitro and in vivo studies, PBMT acts as a chemo- and radio-sensitizer. It facilitates dose reduction and, notably, does not decrease but may increase the viability of noncancer cells. This property enables the protection of noncancerous cells against antineoplastic CT-related toxicity. The important factor in effectively employing PBMT for cancer treatment depends on selecting the correct dosage, including wavelength, power density, energy density, and exposure time. The accumulating evidence supporting the benefits of PBMT has led to its recommendation by the World Association for Laser Therapy for managing CT-related adverse effects. **Conclusion:** PBMT is a promising strategy for the combination therapy of cancer. Nevertheless, further studies are warranted to establish the precise protocols for PBMT. These studies are essential to address its limitations and uncover the benefits of light therapy that have not yet been fully explored.

Keywords: Low level laser therapy; chemotherapy; immunotherapy; radiotherapy

BRIEF HISTORY OF LIGHT THERAPY

Electromagnetic energy encompasses a broad spectrum with frequencies ranging from below 1 hertz to above 10^{25} hertz. Within this electromagnetic spectrum, the human eye can only detect a narrow band of 380 nm to 750 nm (Figure 1). The human body can interact with electromagnetic energy in diverse ways, such as by modulating physiological functions or initiating pathological outcomes. Electromagnetic waves are reflected, transmitted through, or absorbed, based on their wavelengths and the composition of the biological system. Ultraviolet (UV), visible, and infrared (IR) bands are either reflected from the body surface or penetrate through the skin and eyes. Based on their wavelengths, the penetrating waves can be absorbed by certain tissue components. UV radiation can be absorbed by organic molecules, such as protein, lipids, and DNA; visible radiation can be absorbed by pigments and blood; and IR radiation can be absorbed by water. While some UV-mediated photochemical reactions are beneficial for the human body, such as light absorbed by the retinal photoreceptors resulting in electrical signals for visual processing or the conversion of 7-dehydrocholesterol to pre-cholecalciferol (pre-vitamin D3) in the skin when exposed to UV, UV exposure is usually harmful to the skin and the eyes.[1,2]

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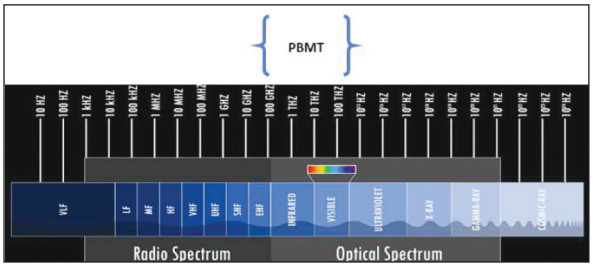


FIGURE 1: Electromagnetic spectrum and the range of PBMT.
PBMT: Photobiomodulation therapy; VLF: Very low frequency; LF: Low frequency; MF: Medium frequency; HF: High frequency; VHF: Very high frequency; UHF: Ultra-high frequency; SHF: Super high frequency; EHF: Extremely high frequency (modified from https://www.nasa.gov/directorates/heo/scan/spectrum/txt_ electromagnetic_spectrum.html).

The history of light therapy dates back to the 14th century BC. In ancient civilizations of Egypt, China, Greece, India, and Rome, plant extracts (such as *Psoralea corylifolia*, *Ammi majus*, parsnip, parsley, and Saint John's wort) followed by exposure to sunlight (heliotherapy) were used to treat disorders, such as vitiligo, psoriasis, rickets, skin cancer, and psychosis.[3,4] The health benefits of light therapy were appreciated gradually during history. The pioneering studies of the 19th and 20th centuries report the use of sunlight- or UV-based artificial light, such as carbon arc lamp and quartz lamp therapies for peritoneal and cutaneous tuberculosis, nonneoplastic and neoplastic skin disorders (such as acne, vitiligo, psoriasis, prurigo, syphilis, leprosy, pellagra, cutaneous T-cell lymphoma, and superficial basal cell carcinoma), venous leg ulcers, wound healing, and neonatal jaundice.[5,6] The novel applications of photobiomodulation therapy (PBMT) are now available or under development. In this review, we have discussed the mechanism of action of photobiomodulation and its potential applications in combination with chemotherapy (CT), immunotherapy, or radiotherapy (RT) for treating cancer.

DEFINITIONS OF PHOTOBIOMODULATION AND PHOTODYNAMIC THERAPIES

Today, light therapy is known as PBMT and photodynamic therapy (PDT). In the Conference of The North American Association for Laser Therapy and the World Association for Laser Therapy (WALT) in 2014, PBMT was included as an official MeSH term under low-level light therapy (LLLT). After resolving the nomenclature conflict, PBMT was defined as "The therapeutic use of light, such as visible, near-IR, IR, absorbed by endogenous chromophores, triggering non-thermal, non-cytotoxic, and biological reactions through photochemical or photophysical events, causing physiological changes".[7] The parameters employed in PBMT are usually within the range of 600-1000 nm with a power density of 5-150 mW/cm^2. However, in PDT, a specific wavelength of light is used to activate a photosensitizer (PS) agent, which can kill cancer cells by inducing oxidative stress, cell necrosis, cell damage, and cell apoptosis. PSs can also be used as carriers to deliver chemotherapeutics to the tumor site to obtain a synergistic therapeutic effect.[8]

MOLECULAR MECHANISMS UNDERLYING PBMT

Light energy is used in PBMT to stimulate cellular processes and promote various biological effects. It typically involves the use of low-level laser devices to target tissues. The mechanism underlying photobiomodulation involves the absorption of light energy by cellular components, including chromophores, which trigger a cascade of biochemical reactions. These reactions can affect cellular signaling pathways, gene expression, and the production of various molecules, such as reactive oxygen species (ROS), adenosine triphosphate (ATP), and growth factors. The precise mechanisms and pathways involved can depend on various factors, such as the specific parameters of the light used, the target tissue, and the desired therapeutic outcomes (Figure 2).

MOLECULAR MECHANISMS OF ACTION OF PBMT ON CELLULAR PROCESSES

Two key characteristics of photobiomodulation are assumed to exhibit significant cellular effects. First, wavelengths ranging from 600 nm-1070 nm exhibit the most remarkable effect on promoting cell proliferation, which is likely due to their light absorption properties.[9] Second, energy density plays an important role as well. Low energy density can stimulate cell proliferation, whereas high-energy density increases apoptotic processes. The data obtained from

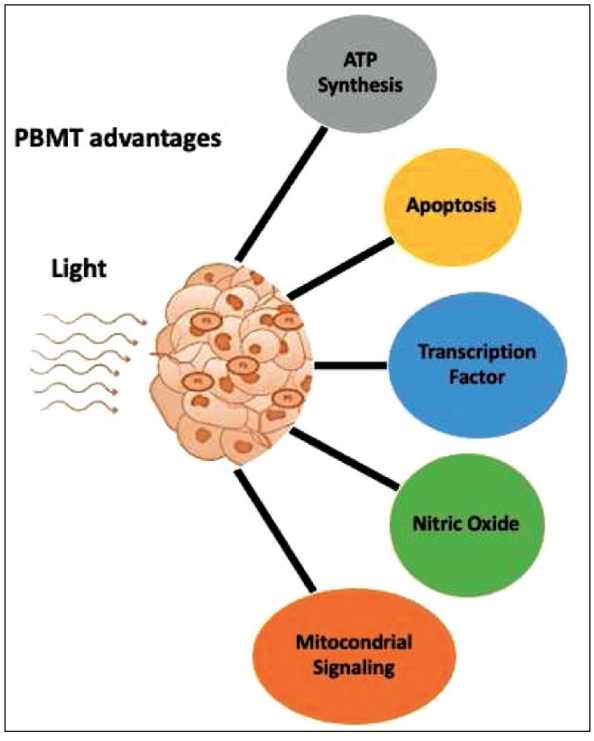


FIGURE 2: Cellular effects of PBMT.
PBMT: Photobiomodulation therapy; ATP: Adenosine triphosphate.

previous studies suggest that PBMT is a safe therapeutic option; however, its applications are limited because its potential proliferative effects on tumor biology remain uncovered. Once these limitations are addressed, PBMT can be safely used for cancer treatment in several clinical studies. While the full investigation of the effects of PBMT on biological processes is challenging, this section will highlight its effect on the molecular mechanisms of cancer cells (Figure 3).

The Effect of PBMT on ATP Synthesis

The mitochondrion is a dynamic organelle that plays an important role in intracellular signaling, energy production, and metabolic processes. It is responsible for synthesizing ATP, the primary energy currency of cells. Mitochondria convert nutrients into ATP via oxidative phosphorylation, which fuels different cellular activities. Furthermore, mitochondria are involved in regulating cellular metabolism and can affect important processes, such as apoptosis and calcium signaling.[10] Oxidative phosphorylation is the process of generating high-energy ATP. During metabolic processes, when energy levels are depleted, ATP is converted to adenosine diphosphate or adenosine monophosphate. ATP is primarily synthesized in the mitochondria, where high-energy electrons are transported via the electron transport chain. The electron transport chain depends on cytochrome c, which acts as an electron carrier in the respiratory chain.[11] *In vitro* studies have revealed that PBMT increases mi-

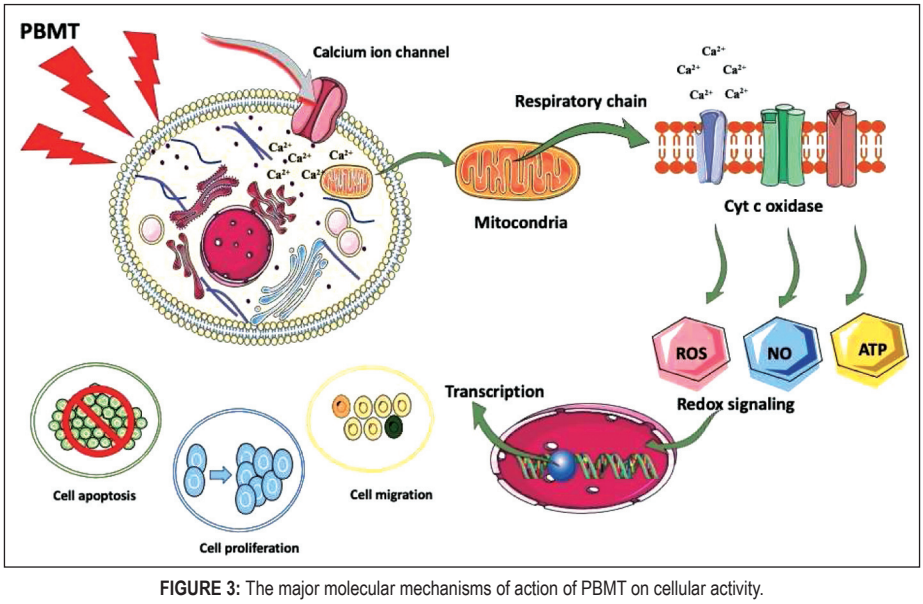


FIGURE 3: The major molecular mechanisms of action of PBMT on cellular activity.
PBMT: Photobiomodulation therapy; ROS: Reactive oxygen species; NO: Nitric oxide; ATP: Adenosine triphosphate.

tochondrial function and ATP production.[12,13] This effect is mediated via the effect of laser irradiation on cytochrome c oxidase (Cox), a transmembrane protein within mitochondria.[14] Consequently, increasing Cox activity can stimulate ATP synthesis.[15] The improvement in ATP synthesis after laser irradiation can exhibit various biological effects, such as healing burn wounds, anti-inflammatory effects, and increased muscle endurance during severe physical exercise.[16-19]

The Effect of PBMT on Mitochondria

The effects of PBMT on mitochondrial membrane potential, ROS, pH, and nitric oxide (NO) are well reported.[10] PBMT stimulates mitogen-activated protein kinase/extracellular signal-regulated kinase signaling by promoting the phosphorylation of tyrosine kinase receptors. This activity has been demonstrated to enhance cell proliferation.[20,21] Furthermore, ROS plays a direct role in amplifying mitochondrial signaling, thus contributing to increased proliferation. PBMT stimulates ROS production and affects the action of various protein kinases.[22] For instance, Src tyrosine kinases activated by ROS regulate essential cellular functions, such as cell proliferation and migration. Importantly, PBMT can exhibit bio-stimulatory effects via the activation of Src kinases by increasing ROS levels.[23] Moreover, PBMT-induced ROS generation activates the transcription factor nuclear factor-kappa B (NF-kB), thereby regulating cell growth and apoptosis.[24]

The Effect of PBMT on NO

NO is acknowledged for its dual role in tumor development, possessing both pro-oncogenic and anti-cancer properties.[25] In both *in vivo* and *in vitro* experimental models, it has been shown that low-energy laser irradiation, such as in PBMT, can enhance the production of NO.[26-28] Additionally, PBMT serves as a potent activator of the mitochondrial respiratory chain, thereby increasing NO production through Cox. PBMT stimulates the release of NO by increasing the activity of the Cox complex.[29]

The Effect of PBMT on Calcium Ions

Calcium ions, playing a vital role in intracellular signal transduction and influencing various biological functions, impact cell viability and activity based on their concentrations. Studies have indicated an increase in calcium permeability following PBMT.[30,31] Moreover, the increase in Ca^{2+} concentrations induced by PBMT appears to be linked to the increased release of Ca^{2+} from intracellular stores.[32] De Lima Santos Hde et al. reported a direct correlation between the increase of calcium and ROS levels after PBMT application. Additionally, PBMT was shown to influence the basal concentrations of sodium and potassium ions and change the ATPase activity of membrane ion pumps in a dose-dependent manner, which results in either an increase or decrease in Na(+), and K(+) ATPase activity.[33]

The Effect of PBMT on Growth Factors

Transforming growth factor-β (TGF-β) is a cytokine that influences the transcription of many target genes involved in the differentiation, proliferation, and activation of different cells.[34] TGF-β plays a significant role in collagen production by inducing the expression of extracellular matrix components and inhibiting their degradation by interfering with matrix metalloproteinases.[35] PBMT has been linked with increased collagen synthesis via the TGF-β molecular pathway, thereby promoting increased regeneration of connective tissue.[36] Notably, PBMT is assumed to suppress the immune response via the TGF-β signaling.

In angiogenesis, vascular endothelial growth factor (VEGF) plays a crucial role. PBMT increases the expression of VEGF, playing a pivotal role in the etiopathogenesis of several tumors.[37,38]

The Effect of PBMT on Transcription Factors

PBMT modulates various transcription factors. One of these factors is NF-kB, which controls various cellular processes, such as migration, proliferation, and inflammation.[39] NF-kB activation can be induced by different factors, such as tumor necrosis factor-α (TNF-α), ROS, interleukins, and PMDT.[24,40] An appropriate dose of radiation activates this enzyme, promoting cell proliferation and anti-inflammatory potential.[41,42] However, exceeding the optimal radiation dosage can result in increased oxidative stress and excessive NF-kB activation.[43] Another transcription factor that undergoes modification in response

to PBMT is the hypoxia-inducible factor (HIF), a small protein involved in the response of cells to hypoxia. Activation of HIF results in the upregulation of genes associated with glycolysis, allowing for ATP synthesis in an oxygen-independent manner, particularly under hypoxic conditions.

The Effect of PBMT on Apoptosis

The mechanism of action of PBMT enhances cellular metabolism and proliferation; however, it causes apoptosis at high doses. The precise mechanism is not yet fully elucidated, but it has been indirectly linked to the production of ROS. Laser irradiation initiates the activation of glycogen synthase kinase 3 (GSK3), which can trigger apoptosis.[44] Another ROS-related mechanism that promotes apoptosis is the Akt/GSK3 pathway.[45] PBMT irradiation affects proliferation and apoptosis by modulating the activity of specific kinases, such as C-kinase.[46] Furthermore, PBMT inhibits apoptosis via the activation of the ROS/Src/Stat3 signaling pathway.[44] Although the mechanism of apoptosis induced by LLLT is not entirely known, existing knowledge indicates that the energy delivered by the laser plays a differentiating role in determining whether proliferation or apoptosis can occur.[47] After PBMT, the upregulation of proapoptotic genes, such as BCL-2-associated X, has been observed at the mitochondrial membrane, along with the release of cytochrome c.[48-55]

PBMT: MOLECULAR MECHANISMS OF ACTION IN CANCER

PBMT has the potential to influence the immune system by activating the anti-tumor immune response (Figure 4). The stress and damage induced in cells by ROS may augment the recognition of tumor antigens by the immune system. This, in turn, can facilitate an immune attack against cancer cells, thereby strengthening the systemic anti-tumor immune response. These effects underscore the crucial impact of photobiomodulation on the molecular targets within tumor cells.[56] PBMT stimulates the generation of ROS, inducing oxidative stress and cellular damage in cancer cells. The heightened production of ROS amplifies oxidative stress, causing damage to cellular components such as lipids, proteins, and DNA. This disruption impairs the functions of cancer cells, either inhibiting tumor proliferation or leading to cell death. Additionally, PBMT can induce vascular damage in tumor blood vessels. The oxidative stress created by ROS affects blood flow within the tumor, diminishing the supply of nutrients and oxygen uptake. Consequently, hypoxia occurs in the cells, negatively impacting tumor growth and metastasis.[56]

PBMT holds the potential to either destroy cancer cells or control their growth. However, in utilizing PBMT for cancer treatment, it is crucial to establish an appropriate treatment protocol that takes

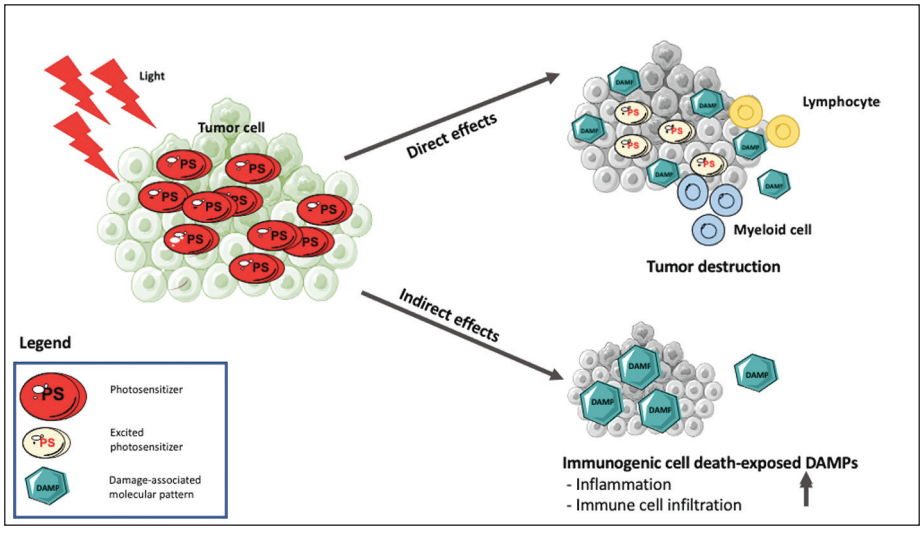


FIGURE 4: PBMT in cancer.
PBMT: Photobiomodulation therapy; DAMPs: Damage-associated molecular patterns; PS: Photosensitizer.

into account factors such as tumor type, location, and patient characteristics. The direct anti-tumor effects of PBMT-mediated damage lead to the reduction of tumor size through the activation of various cell death pathways, including apoptosis, autophagy, and necrosis. The localization of PS to mitochondria has been shown to induce apoptosis, whereas the localization at the plasma membrane is more likely to trigger necrosis.[57-61] Necrosis typically occurs due to excessive low-level radiation damage to the cell, disrupting the structural integrity of the plasma membrane.[62]

PBMT facilitates mitochondrial membrane permeability by opening the inner membrane pore of the mitochondria, causing photosensitization and the inhibition of cytochrome c release after photodynamic injury, and finally inducing apoptosis.[63-67] PBMT can also induce autophagy, which is another cell death pathway.[52,68-70] PBMT-induced autophagy contributes to photodynamic damage to cellular structures, such as organelles, causing irreversible oxidation damage.[52,71] Furthermore, autophagy markers LC3-I and LC3-II proteins are increased after PBMT.[72]

The Effect of PBMT on Immunogenic Cell Death

Immunostimulatory molecules released from dying cells are called damage-associated molecular patterns (DAMPs). Cell death pathways, such as apoptosis, can initiate the release of DAMPs, causing immunogenic cell death (ICD) and inflammation.[73-77] PBMT using various PSs can release DAMPs.[78-86] During ICD, certain heat shock proteins, which are among the critical DAMPs, translocate to the cell surface, affecting phagocytosis by immune cells such as dendritic or recognition of CD94-mediated natural killer (NK).[77] Triggering ICD can also lead to the extracellular release of ATP, which signals dendritic cells (DCs) and promotes the release of proinflammatory cytokines.[87,88] Nevertheless, the signaling mechanism underlying ATP release during ICD is complex and depends on the specific type of ICD initiation and the apoptotic stage of the cell.[80]

The Effect of PBMT on Anti-Tumor Immune Responses

The effectiveness of PBMT in inducing ICD and exposing DAMPs can cause critical inflammation in the tumor microenvironment, triggering an anti-tumor immune response. During the earlier stage of the immune reaction, tumor-infiltrating lymphocytes of myeloid lineage play an important role in neutralizing injured cells generated by PBMT.[89,90]

Photodamage to the tumor vasculature can cause contraction of endothelial cells, facilitating neutrophil adhesion via integrin receptors.[90,91] PBMT-induced damage can activate macrophages and induce the production of TNF-α through the stimulation of toll-like receptor 2/4.[86] NK cells, along with CD8+ cytotoxic T cells, are involved in the immune reaction following PBMT.[92] Nevertheless, dying cancer cells following PBMT can promote the maturation of DCs, a process inhibited by the neutralization of DAMPs.[84,93-95] Despite the crucial role of DCs in the PBMT-induced anti-tumor immune activation via cross-presentation of tumor antigens and phagocytosis, all functions of DCs have not been completely elucidated.

PBMT initiates a tumor-specific adaptive immune defense while decreasing tumor size and/or disrupting tumor vascularity. Previous studies have reported an increase in the number of CD8+ T cells within the tumor and the inhibition of treatment-induced tumor growth compared with those in control groups.[96-99] Furthermore, the intra-tumoral injection of naive DCs after PBMT can arrest tumor antigens, migrate to draining lymph nodes, and amplify tumor-specific T cells.[100] Furthermore, CD8+ T cell deficiency can significantly decrease tumor growth and increase PBMT-induced progression-free survival.[84,92,93,101-103]

IN VITRO COMBINATION STUDIES IN CANCER

PBMT may display a biphasic effect, either stimulating proliferation or triggering cell death, based on the parameters used, such as wavelength, power, and energy density, and dosing style and duration. In *in vitro* studies, PBMT was usually used as a continuous wave in the range of 660-810 nm and 0-150 J/cm^2 for wavelength and energy density, respectively. As shown in Table 1, PBMT acts as a chemo- and radio-sensitizer, allowing for dose reduction and thus alleviating chemotherapeutic-related adverse effects.[104-107] PBMT

increases autophagy to kill cancer cells, decreases osteoclastogenic potential, and does not promote cancer stem cell self-renewal.[108-110] Furthermore, PBMT does not decrease but may increase the viability of non-cancer cells, protecting against antineoplastic-induced toxicity (Table 1).[111-115]

IN VIVO COMBINATION STUDIES IN CANCER

In vivo studies have used PBMT as a continuous wave in the range of 600-850 nm and up to 1050 J/cm^2 for wavelength and energy density, respectively with exposure time usually between 10 and 420 s. A recent review analyzing 15 *in vivo* studies concluded that PBMT is safe and effective; however, the applied PBMT parameters result in variable responses in diverse tumor models, and the cellular microenvironment is a crucial factor affecting the outcome.[121] PBMT can also decrease antineoplastic drug-induced adverse effects. Following PBMT, hair regrowth occurred 5 days early compared with the control groups (cyclophosphamide, etoposide, or a combination of cyclophosphamide and doxorubicin or sham laser-treated).[122] *In vivo,* combination studies reported some beneficial effects of PBMT. When combined with antineoplastic agents, immunotherapeutics, and RT, PBMT can decrease tumor size, increase efficacy, and protect healthy cells (Table 2).

PHOTOBIOMODULATION IN TODAY'S CLINICAL PRACTICE

Over the past two decades, the significance of PBMT has been increasingly recognized. In 2022, the WALT published a position paper that underscored the potential of PBMT in managing adverse effects associated with CT, RT, and hematopoietic stem cell transplantation (HSCT). Adverse effects induced by cancer therapy, such as dysphagia, xerostomia, dysgeusia, trismus, radiodermatitis, alopecia, oral and dermatologic chronic graft versus host disease, voice/speech alterations, peripheral neuropathy, and late fibrosis, may find potential prophylaxis and treatment through PBMT.[126]

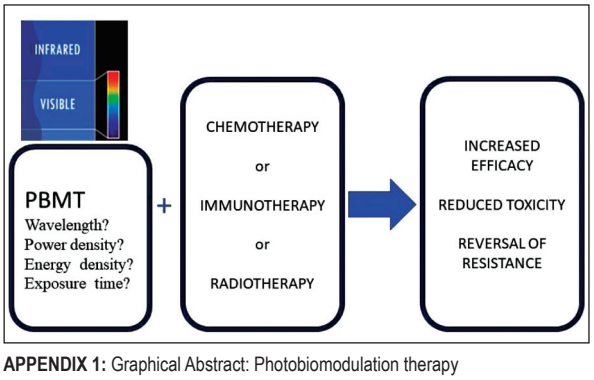
PBMT has been incorporated into a clinical practice guideline. The latest guideline from the Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology guideline recommends intraoral PBMT (LLLT) to prevent of oral mucositis in adults undergoing HSCT with high-dose CT, RT, and combined RT plus CT for head and neck (H&N) carcinoma.[127] Extraoral PBMT, which reaches distal mucosa, seems to be more advantageous.[128] In pediatric practice, the use of intraoral PBMT in the red-light spectrum (620-750 nm) is also recommended in pediatric practice in patients undergoing HSCT and RT for H&N conditions. The pediatric guideline also emphasizes strong evidence against the routine use of palifermin due to its associated short- and long-term adverse effects.[129]

CONCLUSION AND FUTURE PROSPECTS

The effectiveness of PBMT in various cancer types is influenced by specific parameters, such as wavelength, power density (irradiance), energy density (fluence), and exposure time. For instance, low-energy density exhibits a stimulatory effect on proliferation, whereas high-energy density inhibits proliferation (Appendix 1).

Selecting the appropriate dosage for PBMT in cancer treatment exhibits the following advantages: It can trigger the apoptotic process in the cancerous tissue while protecting and even increasing the number of healthy cells.

- It improves the efficacy of antineoplastic agents, immunomodulators, and RT.
- It can reverse antineoplastic drug resistance.



APPENDIX 1: Graphical Abstract: Photobiomodulation therapy
PBMT: Photobiomodulation therapy.

TABLE 1: *In vitro* efficacy studies on the combination of PBMT with CT or RT in cancer.

Light Source (wavelength, nm; power density, W/cm^2; energy density, J/cm^2)	Combined treatment	Cell line	Results	Therapeutic potential	Reference
CW; 670 nm; for 2 min at power outputs of 100 mW/cm^2	Cis Zoledronic acid (PS)	PHF; HNSCC	LLLT increases cytotoxicity of Cis and zoledronic acid in PHF and HNSCC cells	PBMT plus Cis may also be a novel therapeutic option for keratocystic odontogenic tumors in the cranio-maxillofacial region and other appropriate indications	116
CW; 660 nm; 30, 90 and 150 J/cm^2	IR, 2.5 and 10 Gy	Human gingival fibroblasts (FMM1); human breast cancer cells (MDA-MB-231)	PBMT increased cell viability and proliferation in a fluence-dependent manner but reduced senescence in FMM1. PBMT decreased proliferation but increased senescence in MDA-MB-231.	LLLT (90 J cm^{-2} and 150 J cm^{-2}) stimulates proliferation in fibroblasts, while its influence in cancer cells could not be observed	114
CW, once 685 nm; 16.6 mW/cm^2; 0-20 J/cm^2; 0-20 minutes	X-ray IR	Human cervix adenocarcinoma cell line HeLa	PBMT induced no toxicity at 5-20 J/cm^2. 685 nm PBMT at 20 J/cm2 enhanced inhibition of colony formation following IR (4 and 6 Gy). Mechanisms include oxidative stress, DNA damage, apoptosis, and autophagy.	685 nm PBMT at 5-20 J/cm^2 may be used as a radiosensitizer in cervical cancer to enable reduction of the radiation dose, hence adverse effects	117
660 nm; 1.07 mW/cm^2; 0.2, 0.4, and 0.7 J	DOX	Rat adipose tissue-derived MSC	PBMT (0.2 J) inhibited DOX-induced apoptosis, and oxidative stress in the MSCs.	PBMT is protective against DOX-induced toxicity	118
CW, once Red, 660 nm; 60 mW; 11.7 J/cm^2	Cis	Keratinocytes (HaCat); tongue squamous cell carcinoma cells (SCC25); upper aerodigestive tract carcinoma cells (HN12)	Cis-PBMT treatment increased proliferation index Ki-67 in all cell lines, when compared to Cis alone. Cis or Cis-PBMT significantly decreased VEGF expression in cancer cells The expression of TGF-β 1 or EGF were not changed as compared to control	PBMT may potentiate Cis-induced cytotoxicity and death	104
Diode laser, CW (808 nm, 350 mW, 3 min, 190.91 J/cm^2)	Cis	Laryngeal cancer (HEp-2) cells	Photobiomodulation increases Cis-induced apoptotic effect	PBMT by enabling dose reduction for Cis, may reduce Cis-associated morbidity and mortality	119
660 nm, 3 J/cm^2 for 90 seconds	Sinensetin	Cervical cancer cells (Hella) and CHO cell lines	LLLT and sinensetin combination decreases cancer cell survival and increases ROS production in both cell lines	Only combined therapy (LLLT plus sinensetin) but neither LLT or sinensetin alone, can decrease viability of CHO and Hela cells	105
610, 630 and 810 nm; 0.45 J/cm^2	Cis	Prostate cancer cell line (LnCap)	LLLT + Cis combination reduced cell viability more than Cis, alone. LLLT alone did not change cell viability	PBMT alone is not effective but may enhance Cis cytotoxicity in LnCap cells	106
780 nm, 30 mW/cm2 at a total energy density of 5 J/cm^2, delivered in 2 min and 46 s.	Radiotherapy, 1.7 Gy	Human epidermoid carcinoma cell line A431	PBMT did not increase proliferation PBMT "enhanced radiation-induced foci/cell"	PBMT acts as a radiosensitizer	107
660 nm; 21.6 mW/cm^2, 0-6 J/cm^2	IR; 4Gy	HaCaT, head and neck squamous cell carcinoma cell line (SCC61)	PBMT w/o increased HaCaT proliferation and migration PBMT at 3-6 J/cm^2 did not increase pro- liferation of irradiated SCC61 cells	PBMT supports wound healing without promoting cancer development	112
681 nm; CW 14 min.; 20, 50, 100 J/cm^2	ZnPcS4/ps; PDT	Resistant MCF-7 breast cancer cells	Additive effect on the viability and Annexin-V/PI-staining cell death	PBMT might improve the anti-tumor effect of PDT by inducing autophagy in resistant MCF-7 breast cancer cells that evade apoptosis	120

CW: Continuous wave; Cis: Cisplatin; PS: Photosensitizer; IR: Ionizing radiation; DOX: Doxorubicin; RT: Radiotherapy; ZnPcS4: Zinc tetrasulfonic acid phthalocyanine; PDT: Photodynamic therapy; PHF: Primary human fibroblasts; HNSCC: Head and neck squamous cell carcinoma cells; MSC: Mesenchymal stem cells; CHO: Chinese hamster ovary; LLLT: Low-level laser irradiation; PBMT: Photobiomodulation therapy; VEGF: Vascular endothelial growth factor; TGF-β: Transforming growth factor-β; EGF: Endothelial growth factor; ROS: Reactive oxygen species; CT: Chemotherapy.

TABLE 2: *In vivo* safety and efficacy studies on the combination of PBMT with CT or RT in cancer.

Light source (wavelength, nm; power density, W/cm²; energy density, J/cm²)	Combined treatment	In vivo model	Results	Therapeutic potential	Reference
CW 830 nm, 60 mW	ACNU, Mu-β-IFN	Glioma cell line 203 GL Anti-cancer drug (ACNU) group (n=10), Mu-β-IFN group (n=10) Direct LLLT plus Mu-β-IFN group (n=11) Mu-β-IFN plus ACNU group (n=10) Indirect LLLT plus Mu-β-IFN plus ACNU group (n=7)	The direct PBMT plus Mu-β-IFN group was the most successful in reducing tumor growth and incidence	Both direct (site of implantation) and indirect PBMT (abdominal skin) reduces tumor growth. Combination of PBMT with cancer- and immune-therapeutic agents increases efficacy.	123
λ660nm, 50 mW, CW, Ø = 3 mm, 0.07 cm², 714.2 mW/cm², 133 s, 95 J/cm², 6.65 J at every other day for 4 weeks	Imiquimod cream (applied topically)	DMBA-induced SCC in Syrian hamster cheek pouch model n=5 in each group G1, G2 (control) G3: PBMT G4: imiquimod G5: PBMT +imiquimod	Malignant tumors Mild dysplasia: G1, G2 and G3 (0%); G4 (60%) G5 (40%) Well differentiation: G1 (80%), G2 (100%), G3, G4 and G5 (40%) S100+ dendritic cells: G1, G2 and G3 (-); G4 (+); G5 (±); normal mucosa (+++)	PBMT and imiquimod, alone and in combination reduce tumor development. Imiquimod treatment supports immune surveillance which decreases when PBMT is added	124
5 J using a GaAlAs diode laser system at 780 nm, 20 mW/cm² and a spot area of 4.0 mm²	RT (1.7 Gy)	Human epidermoid carcinoma cell line A431 xenografts n=56, 7 per group	PMB and radiation increased median animal life by +4 days PBMT increases tumor necrosis due to radiation PMB increased mean differentiation grade and mean vascular density and decreased mitotic count Consistent tumor regression after treatment	PBMT is a radiosensitizer. PBMT protects normal tissue PBMT use is convenient (low cost and low staff training requirements)	107
NIR-II (100-1700 nm) laser, cw Dual treatment: 1064 nm, 300-6000 mW/cm² + 1270 nm, 50-1000 mW/cm²	Immune checkpoint inhibitor (anti- mouse PD-1-specific monoclonal antibody)	Syngeneic mouse model of breast cancer	Dual laser illumination induced T cell proliferation and decreased ROS generation in T cells in vitro. PBMT (1064 nm, 3 W/cm² plus 1270 nm, 1 W/cm²) decreased PD-1 expression in CD8+ T cells, enhanced tumor growth delay by the adoptive transfer of laser treated CD8+ T cells ex vivo against a model tumor antigen and augmented the effect of the immune checkpoint inhibitor on tumor growth	PBMT increases the efficacy of immunotherapy via CD8+ T cells. PBMT is safe and low-cost. PBMT has the potential to be combined with other treatment modalities.	125

CW: Continuous wave; Mu-β-IFN: Mouse-β-interferon; RT: Radiotherapy; PD-1: Programmed cell death protein 1; LLLT: Low-level laser irradiation; SCC: Squamous cell carcinoma; PBMT: Photobiomodulation therapy; ROS: Reactive oxygen species. PBM: Photobiomodulation

Furthermore, PBMT does not promote cancer stem cell renewal and phenotypes in certain cancer types.

To conclude, further studies are warranted to establish the precise protocols for PBMT dosage. These studies are essential to address the aforementioned limitations and uncover the potential advantages of light therapy that have not yet been fully explored.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ferda Kaleağasıoğlu;* ***Design:*** *Ebru Nur Ay, Ferda Kaleağasıoğlu;* ***Control/Supervision:*** *Ferda Kaleağasıoğlu;* ***Data Collection and/or Processing:*** *Ebru Nur Ay, Ferda Kaleağasıoğlu, Duygu Hüsna Acar;* ***Analysis and/or Interpretation:*** *Ebru Nur Ay, Ferda Kaleağasıoğlu;* ***Literature Review:*** *Ebru Nur Ay, Ferda Kaleağasıoğlu, Duygu Hüsna Acar;* ***Writing the Article:*** *Ebru Nur Ay, Ferda Kaleağasıoğlu,* ***Critical Review:*** *Ferda Kaleağasıoğlu.*

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