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INVITED REVIEW

From molecular mechanisms to clinical applications: A comprehensive review of photobiomodulation in cancer treatment

Qi Wang | **Phil-Sun Oh** | **Hwan-Jeong Jeong**

Department of Nuclear Medicine, Molecular Imaging & Therapeutic Medicine Research Center, Research Institute of Clinical Medicine of Jeonbuk National University, Biomedical Research Institute of Jeonbuk National University Hospital, Jeonbuk National University Medical School and Hospital, Jeonju, Republic of Korea

Correspondence
Hwan-Jeong Jeong, Department of Nuclear Medicine, Molecular Imaging & Therapeutic Medicine Research Center, Research Institute of Clinical Medicine of Jeonbuk National University, Biomedical Research Institute of Jeonbuk National University Hospital, Jeonbuk National University Medical School and Hospital, Jeonju, Republic of Korea.
Email: jayjeong@jbnu.ac.kr

Abstract

Photobiomodulation (PBM) is a non-invasive therapeutic technique that regulates biological processes using primarily low-power lasers or light-emitting diodes (LEDs) to achieve therapeutic effects. Its application has expanded significantly, particularly in the field of cancer therapy. This review provides a comprehensive overview of PBM, elucidating its underlying mechanisms of action and its potential applications in cancer therapy. It highlights the benefits of PBM in reducing side effects of cancer treatments such as acute oral mucositis, radiation dermatitis, lymphedema, neuropathic pain, and radiation enteropathy. Furthermore, the ability of PBM to inhibit cancer cell proliferation and induce apoptosis, and discusses safety concerns of PBM in clinical applications, presenting existing research that emphasizes its significant potential in cancer therapy was summarized. PBM therapy may offer promising new clinical options for managing cancer and mitigating the side effects associated with conventional cancer therapies.

KEYWORDS

cancer, clinical treatment, photobiomodulation, phototherapy

INTRODUCTION

Photobiomodulation (PBM), also known as low-level laser/light therapy (LLLT), was first reported by Endre Mester at Semmelweis University in Budapest in 1967.[1] PBM is a non-invasive, safe therapeutic modality that employs low-power lasers or light-emitting diodes (LEDs) to modulate biological processes, eliciting therapeutic effects and garnering increased clinical interest. Unlike photothermal therapy (PTT), which mainly depends on the absorption by endogenous chromophores (e.g., melanin and hemoglobin) or the application of exogenous photothermal agents to produce thermal effects, PBM operates independently of tissue-specific chromophores

Abbreviations: ALL, acute lymphoblastic leukemia; ATP, adenosine triphosphate; BCRL, breast cancer-related lymphedema; BL, blue light; CaMKII, calcium/calmodulin-dependent kinase II; CIPN, chemotherapy-induced peripheral neuropathy; COX, cytochrome c oxidase; CREB, cAMP response element-binding protein; CT, chemotherapy; ETC, electron transport chain; FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; GL, green light; hADSCs, human adipose-derived stem cells; HHT, homoharringtonine; HSCT, hematopoietic stem cell transplantation; IL-1, interleukin-1; LEDs, light-emitting diodes; LLLT, low-level laser/light therapy; MSCs, mesenchymal stem cells; MT-MRS, magnetization transfer magnetic resonance spectroscopy; NIR, near-infrared; NO, nitric oxide; OM, oral mucositis; OPN1, Opsin1; OPN2, Opsin2; OS, osteosarcoma; PBM, photobiomodulation; PTT, photothermal therapy; RD, radiation dermatitis; RL, red light; ROS, reactive oxygen species; RT, radiation therapy; SCAC, squamous cell anal cancer; TNF, tumor necrosis factor; TRP, transient receptor potential.

or external sensitizers, making it broadly applicable across various tissue types.[2] The term PBM is now more commonly used to refer to this technology than the term LLLT.[3] The wavelengths of light used for PBM include red light (RL, 620–700 nm) and near-infrared (NIR, 700–1440 nm).[3] With advancements in optical technology, new light sources such as LEDs and broadband light sources have been developed. These sources are highlighted by their low cost and variable wavelengths that span from ultraviolet to near-infrared, including blue light (BL, 400–500 nm).[4] PBM is employed in managing conditions such as herpes simplex virus, acne, alopecia, diabetes, atherosclerosis, and neural disorders.[5] Additionally, it significantly contributes to promoting wound healing, facilitating tissue repair, alleviating pain and inflammation, and treating various dental conditions.[6–8] The typical irradiance of PBM ranges from 5 mW/cm^2 to 50 mW/cm^2, with each treatment session typically taking about 30 s to several minutes, recurring several times a week over numerous weeks.[9,10] Current research shows that PBM has potential therapeutic applications in managing side effects associated with cancer treatments, such as mucositis, acute radiation dermatitis, and lymphedema after mastectomy.[5] Over the past few years, an increasing number of researchers have concentrated on the inhibitory effects of PBM on cancer cells. PBM can inhibit cancer cell proliferation, promote apoptosis, and exhibit synergistic effects when combined with certain chemotherapy drugs.

This review aims to elucidate the mechanisms and clinical effects of PBM in cancer-related treatments, introduce the direct anticancer effects of PBM in both in vitro and in vivo studies, and discuss the safety issues associated with its clinical use.

MECHANISMS OF PHOTOBIOMODULATION

The commonly used wavelengths in PBM today can be categorized into red light (620–700 nm), near-infrared light (700–1440 nm), blue light (400–500 nm), and green light (495–570 nm).

Red light and near-infrared light

The majority of literature reports that RL and NIR have therapeutic effects in promoting tissue healing and alleviating inflammation.[11,12] According to the first law of photochemistry, a photochemical reaction only occurs if photons are absorbed by molecular light receptors or chromophores.[9] Endogenous photoreceptors, specifically mitochondrial cytochrome c oxidase (COX), primarily absorb RL and NIR photons. COX, the final enzyme (complex IV) in the mitochondrial electron transport chain (ETC), consists of two copper and two heme centers with distinct light absorption spectra.[13] It is widely acknowledged that COX acts as the photoreceptor and photosignal transducer in RL and NIR processes.[14,15] RL and NIR exposure enhance COX activity and mitochondrial respiration, regulating cell metabolism, proliferation, migration, and adenosine triphosphate synthesis.[11,16,17] However, Thomas et al. discovered that NIR (wavelengths of 750 nm and 950 nm, power output of 15 mW and 32 mW) reduced the activity of isolated COX, suggesting that COX-inhibitory NIR could be a potential non-invasive, non-pharmacological treatment for cerebral reperfusion injury.[18]

Adenosine triphosphate (ATP), reactive oxygen species (ROS), and nitric oxide (NO) are all products of cellular aerobic metabolism following COX absorption of photons, primarily released by mitochondria.[19] When activated by RL to NIR light, COX enhances cellular respiration by interacting with the final two complexes of the mitochondrial electron transport chain, which modifies ATP synthesis, alters membrane potential, and increases proliferation rates.[20,21] Elizabeth J. et al. employed ^{31}P magnetization transfer magnetic resonance spectroscopy (MT-MRS) to measure the effects of PBM (wavelength of 670 nm, power output of 18 W, duration of 20 min) on the healthy aging human brain. Their study demonstrated a notable increase in ATP synthase flux following treatment, suggesting that PBM may restore ATP flux by enhancing mitochondrial function, thereby highlighting its potential application in the treatment of neurodegenerative diseases.[22] ROS are signaling molecules regulating a broad range of physiological activities and play a pivotal role in cell proliferation, differentiation, autophagy, transcription factor regulation, metabolic adaptation, immune cell activation, and various other functions.[23–25] Low levels of ROS can enhance cellular metabolism, whereas high levels induce oxidative stress, which damages DNA and proteins, ultimately resulting in cell apoptosis. PBM increases ROS levels, activating redox-sensitive transcription factors such as AP-1, NF-κB, RANKL, p53, HIF-1α, and the AKT/GSK3β/β-catenin pathway.[3,10] AP-1, a redox-sensitive transcription factor, plays a crucial role in regulating the expression of numerous genes involved in cell division, apoptosis, aging, and inflammation. An increase in ROS levels enhances the transcriptional activity of AP-1.[26] NF-κB, a redox-sensitive transcription factor, which is vital in controlling critical cellular processes such as the inflammatory response. It can be

activated directly by ROS or indirectly through interleukin-1 (IL-1), tumor necrosis factor (TNF), and other mediators. Furthermore, PBM stimulation activates NF-κB, which enhances gene transcription, reduces cell death, and improves neurological function.[10] The transcription factor HIF-1α, which is unstable under normal oxygen conditions, stabilizes and activates under hypoxic conditions and can be induced by ROS. It participates in several intracellular metabolic processes including immune response, energy metabolism, and cell proliferation.[26] PBM exerts a pro-survival effect on cells by activating the AKT/GSK3β/β-catenin pathway. It promotes PI3K phosphorylation, which activates AKT and inhibits GSK3β, thus preventing β-catenin degradation. Subsequently, stabilized β-catenin, a central regulator of the Wnt/β-catenin signaling pathway, translocates to the nucleus and initiates transcription of downstream genes that enhance cell survival.[10] Additionally, PBM boosts cell survival by selectively activating the PI3K/AKT signaling pathway while concurrently inhibiting the GSK3β/Bax pathway. Through the regulation of ROS release, PBM activates PI3K, leading to AKT phosphorylation. The phosphorylated AKT then inhibits GSK3β activity, which suppresses Bax translocation and caspase-3 activation, thereby effectively reducing cell apoptosis.[27]

NO is a vasodilator that promotes increased perfusion of oxygenated blood to tissues while also enhancing lymphatic perfusion, causing lymphatic vessels to dilate and reducing their porosity.[28] NO regulates the homeostasis and function of both the skin and vascular systems. However, high levels of NO can have destructive effects on cells, such as causing DNA damage and inducing apoptosis.[3] Research has demonstrated that COX possesses nitrite reductase activity, enabling it to produce NO within mitochondria.[11] Furthermore, PBM stimulates COX within the mitochondria, increasing mitochondrial membrane potential, which subsequently leads to ATP synthesis and changes in the concentrations of ROS, NO, and intracellular calcium (Ca^{2+}).[3] It is now known that a group of ion channels, known as transient receptor potential (TRP) channels, are photosensitive, and their activity can be modulated by light stimulation.[10] Studies have demonstrated that PBM can induce the opening of the TRPV subfamily of TRP channels, allowing Ca^{2+} influx from the extracellular environment, thereby mediating histamine release and promoting wound healing.[29]

Blue light and green light

The majority of existing literature supports the notion that BL can effectively promote wound healing, reduce inflammatory responses, and limit bacterial proliferation.[6] Additionally, green light (GL) has been shown to effectively reduce tissue swelling.[11] Furthermore, recent studies have also demonstrated that GL irradiation enhances the wound healing capabilities of human adipose-derived stem cells (hADSCs) and promotes the proliferation of ADSCs.[30,31] Recently, Yang et al. discovered that high-dose blue light (wavelength of 460 nm) induces apoptosis in osteosarcoma cells by increasing ROS levels and activating caspase-3 and SOCS3, while also enhancing PTEN expression, which subsequently inhibits the PI3K/AKT pathway.[32] This implies that blue light could emerge as a potential therapeutic method for the clinical treatment of osteosarcoma in the future.

Similarly, irradiation with blue and green light stimulates COX activity and enhances mitochondrial function, leading to alterations in cellular metabolic products. In addition, BL or GL can also activate opsin, which functions as a G-protein-coupled receptor.[11] Opsins are categorized into five types: Opsin1 (OPN1), Opsin2 (OPN2), Opsin3 (encephalopsin), Opsin4 (melanopsin), and Opsin5 (neuropsin). Ortiz et al. demonstrated that BL can induce vasodilation in the pulmonary vasculature of rats with chronic pulmonary hypertension, mediated by OPN3 and OPN4.[33] Blue light, directly absorbed by opsins or indirectly activating them by increasing ROS levels, underscores the intricate mechanisms of phototransduction.[34] TRP channels serve as a downstream target of opsins. As mentioned earlier, the opening of TRPV channels facilitates Ca^{2+} influx, which subsequently induces the activation of calcium/calmodulin-dependent kinase II (CaMKII). This activation leads to the phosphorylation of cAMP response element-binding protein (CREB) in the nucleus, ultimately inducing changes in gene transcription.[11] Flavins and flavoproteins function as photoreceptors for BL, as they contain light-sensitive molecules such as flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which play crucial roles in various redox processes.[11] Research indicates that BL irradiation improves the photolysis of FMN/FAD, provides activation energy for FMN, and indirectly raises ROS levels, thus influencing processes like cell proliferation, autophagy, and transcription factor regulation.[35] Porphyrins, regarded as blue light photoreceptors, are heterocyclic aromatic compounds predominantly located in mitochondria, and it is widely accepted that interactions between blue light and porphyrins result in ROS generation and energy transfer.[36]

Given the well-established cellular and molecular mechanisms of PBM, it holds significant promise for clinical applications, particularly in mitigating the side effects of cancer treatment.

APPLICATION OF PBM IN THE TREATMENT OF CANCER SIDE EFFECTS

Cancer is a major public health issue worldwide. Its incurable nature and rapid spread continue to rank among the top causes of mortality in communities. Advanced-stage illness and increased death rates can result from delayed diagnosis and treatment.[37] Common types of cancer include breast, liver, lung, prostate, colorectal, and stomach cancers.[38] Various clinical treatment options for cancer exist, primarily comprising surgical resection, radiation, chemotherapy, targeted therapy, immunotherapy, and interventional therapy. While these treatments have significantly curbed cancer progression and improved survival, they still produce numerous side effects. PBM has attracted interest for its potential applications in cancer, particularly for mitigating the adverse effects associated with cancer treatments and its potential influence on cancer progression.

Acute oral mucositis

One of the most frequent and dangerous adverse effects of conventional-dose chemotherapy (CT), radiation therapy (RT), and pretreatment for hematopoietic stem cell transplantation (HSCT) is oral mucositis (OM), which is defined as inflammatory and/or ulcerative lesions of the oral mucosal epithelium.[39] The prevalence of OM in patients undergoing head and neck radiation therapy for oral or oropharyngeal cancer ranges from 59% to 100%, while approximately 80% of those receiving myeloablative HSCT with high-dose conditioning regimens experience OM.[40] The overproduction of ROS induced by chemotherapy and the activation of NF-κB, which prompts apoptosis and damage to the epithelium while amplifying signals associated with the activation of oxidative stress and inflammatory pathways are pivotal in the development of OM.[39–41] OM can impact a patient's nutritional intake and quality of life, potentially disrupting their treatment regimen. Numerous studies have demonstrated the beneficial effects of PBM therapy on OM. Additionally, PBM not only enhances ATP synthesis and reduces ROS but also modulates inflammatory cytokine production, stimulates fibroblast proliferation and migration, promotes collagen synthesis, and induces angiogenesis, which collectively facilitates tissue repair.[42,43]

Rocco et al. conducted a literature review and meta-analysis on the efficacy of phototherapy for mucositis following HSCT, demonstrating that it effectively reduces the symptoms and severity of transplant-related mucositis.[44] As noted in the systematic review, PBM (wavelength range of 630 to 830 nm and the energy density range of approximately 1.2 J/cm^2 to 72.0 J/cm^2) is an effective method for the treatment and prevention of oral mucositis in head and neck cancers.[45] Furthermore, another systematic review of phototherapy for the treatment of OM in cancer patients provides evidence that specific parameters of PBM (wavelength range of 630 to 660 nm, energy density range of 1.0 J/cm^2 to 70.0 J/cm^2) are effective in mitigating OM in certain patient populations.[46] Laiz et al. indicate that the use of PBM (wavelength of 660 nm with an energy density of 2 J/cm^2 and a power density of 3.33 W/cm^2) has a protective regulatory effect on OM in pediatric patients undergoing chemotherapy. PBM markedly decreased the severity of OM in patients with osteosarcoma (OS) and acute lymphoblastic leukemia (ALL).[47] The WALT Recommendation 2022: Clinical Practice Guidelines suggest the use of an intra-oral device with a 630–680 nm LED and a power density of 10–50 mW/cm^2 to prevent OM within 30–120 min prior to tumor treatment. For the treatment of OM, guidelines recommend using a 650 nm LED, with treatments being administered 3–4 times per week until tumor therapy concludes.[40] These studies have confirmed the beneficial effects of PBM in managing cancer-related oral mucositis, demonstrating its efficacy across various patient demographics. However, these studies encompass a range of cancer types, including HSCT, head and neck cancers, and pediatric chemotherapy. The retrospective study by Laiz et al. specifically highlights the prophylactic use of 660 nm PBM for OM in pediatric chemotherapy patients, whereas other studies concentrate more on managing OM in affected individuals. The authors recommend that future research should focus on refining treatment parameters and pursuing large-scale clinical trials for validation.

Radiation dermatitis

Radiation dermatitis (RD), a type of skin inflammatory reaction, is among the most frequent adverse effects of radiation therapy, with an incidence rate as high as 95%.[48] Acute radiation dermatitis typically manifests within the first 4 weeks of treatment, characterized by symptoms such as erythema, dry skin, desquamation, and potential ulceration.[49] Late-stage toxicity is characterized by marked erythema, moist desquamation, edema, and severe discomfort, along with itching and burning sensations.[48] While most cases of acute RD are self-limiting and resolve within 2 to 3 weeks, late toxicities tend to persist, compromise patient quality of life, and necessitate dosage adjustments.[49] Treatment and prevention typically involve topical steroid administration and maintaining good hygiene practices.[29] In the past few years, the application

of PBM in clinical settings for the treatment of RD has seen a significant increase. PBM alleviates the inflammatory response triggered by RD, reduces the expression of pro-inflammatory cytokines, and decreases inflammatory cell infiltration.[50] Additionally, PBM promotes fibroblast proliferation and migration, enhances collagen synthesis, fosters angiogenesis, and accelerates the repair and regeneration of damaged skin tissue.[50]

The following prospective controlled trials have evaluated the efficacy of PBM in mitigating RD during adjuvant radiotherapy for breast cancer. A controlled experiment with breast cancer patients undergoing breast-conserving surgery demonstrated that administering PBM (wavelengths of 660 nm and 850 nm, energy density of 0.15 J/cm^2, average power density of 44.6 mW/cm^2, for 4 to 5 min per session, twice a week) prior to radiation therapy can significantly reduce the incidence of radiation-induced skin toxicity and its sequelae, as well as alleviate treatment-related discomfort in breast cancer patients.[51] A comparative study on the effectiveness and acceptability of PBM (wavelengths of 905 nm and 808 nm, power density of 0.168 W/cm^2, energy density of 4 J/cm^2, 6 sessions, at a frequency of twice a week) for treating acute RD in patients undergoing post-operative radiation therapy for breast cancer demonstrated the effectiveness of PBM in treating acute RD.[52] Jolien's results from a randomized, placebo-controlled trial suggest that PBM (wavelengths of 905 nm and 808 nm, power density of 0.168 W/cm^2, energy density of 4 J/cm^2, 14 sessions in 7 weeks) during RT effectively prevents grade 2 or higher acute RD in breast cancer patients and reduces symptoms associated with RD.[53] All three studies implemented PBM during adjuvant radiotherapy in breast cancer patients, utilizing both RL (635–660 nm) and NIR (808–905 nm); although specific wavelengths and energy densities varied across the studies. While all three research studies confirmed the effectiveness of PBM in mitigating RD, Jolien emphasized a prophylactic approach—initiating PBM before radiotherapy—to highlight its dual role in both prevention and treatment, in contrast to the other studies that applied PBM only after the onset of skin damage.

Furthermore, PBM has also been applied to dermatitis caused by RT in other cancers. Fabiana et al. published a case report on the application of PBM therapy (RL, power density of 100 mW, dose of 2 J, 48 h between sessions for 4 weeks) for treating RD in patients with squamous cell anal cancer (SCAC), which illustrated the therapy's effectiveness in managing RD and its potential to enhance patient's quality of life.[54] Moreover, Breno et al. reported two cases of using PBM to treat acute RD of the neck, detailing the laser equipment and dosage parameters (wavelength of 660 nm, energy density of 35.71 J/cm^2 at 10 sec/point with a power density of 3.57 mW/cm^2; energy density of 27.77 J/cm^2 at 25 sec/point with a power density of 1.11 mW/cm^2, 6 and 9 sessions, at a frequency of once a day). They demonstrated the positive effects of PBM on the healing process of RD and its efficacy in alleviating patient discomfort.[55] A network meta-analysis summarized 14 treatments for RD and indicated PBM as more effective in reducing the prevalence of grade 2 RD.[48] The findings have important implications for clinicians in the prevention and management of RD. Two case reports support the potential benefits of PBM in the treatment of RD; however, they lack control groups and large-scale validation. The network meta-analysis evaluated various interventions, including PBM, without providing novel clinical trial data. Future studies should concentrate on multi-center, randomized controlled trials with standardized PBM devices and parameters to enhance comparability and further substantiate its efficacy in the prevention and treatment of RD.

Lymphedema

Approximately 20% of breast cancer patients undergoing treatment develop upper limb lymphedema, caused by alterations in the lymphatic structure due to surgery, radiotherapy, or both, significantly compromising their quality of life.[28] Several risk factors for lymphedema development have been found by prior research, including axillary surgery, the quantity of lymph nodes resected, chemotherapy, photon radiation therapy, and an elevated body mass index.[56] Treatment approaches for breast cancer-related lymphedema typically involve compression garments and lymphatic drainage, although these methods are not consistently effective. A systematic review of 11 clinical trials, including seven randomized controlled trials, suggests that PBM might be a promising treatment for managing breast cancer-related lymphedema (BCRL).[57] The potential mechanism may involve PBM reducing the production of TNF-α, increasing the levels of IL-10, decreasing lymphoid tissue fibrosis, stimulating lymphangiogenesis, and enhancing lymphatic drainage.[58,59]

Nonetheless, existing studies are limited, and further research is necessary. Smoot's meta-analysis and systematic review present moderate evidence that supports the use of PBM in managing BCRL, demonstrating significant reductions in upper limb lymphedema volume and improving pain management compared to no PBM treatment, with statistical analysis indicating a limb volume reduction of 75.7 mL post-PBM therapy.[60] In a double-blind, randomized, placebo-controlled trial spanning 12 months, Kilmartin reported that adjuvant PBM substantially alleviated lymphedema symptoms and improved mental distress among breast cancer patients.[61]

The systematic reviews of these studies support the potential efficacy of PBM in patients with BCRL. Although they outline a general trend, additional high-quality randomized controlled trials are required. Kilmartin's study validated the efficacy and safety of PBM; however, its small sample size necessitates further large-scale validation.

Neuropathic Pain

A documented side effect of neurotoxic chemotherapeutic drugs such as taxanes, vinca alkaloids, platinum compounds, thalidomide, and bortezomib is known as chemotherapy-induced peripheral neuropathy (CIPN).[62] The primary sensory effects of CIPN include pain, tingling, loss of sensation, and numbness in the hands and feet.[63] Additionally, dysfunction of the motor and/or autonomic nervous systems may also manifest.[64] A meta-analysis and systematic review revealed that out of 4179 patients, 1960 developed CIPN, with an overall prevalence of 48%. The prevalence of CIPN post-chemotherapy was 68.1%, 60%, and 30% at 1, 3, and more than 6 months, respectively.[64] However, therapeutic options remain limited for managing established CIPN. As PBM treatment technology gains acceptance, researchers are exploring its use for treating CIPN. PBM may alleviate CIPN symptoms by enhancing neuronal survival and repair through improved mitochondrial function and by reducing neuroinflammation via inhibition of the NF-κB signaling pathway, thereby decreasing the release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6.[65]

Joy et al. investigated PBM's effectiveness in preventing CIPN among 32 breast cancer patients receiving chemotherapy in a prospective, randomized, placebo-controlled pilot study. The trial's results indicated positive outcomes for PBM (wavelengths of 905 nm and 808 nm, power density of 0.168 W/cm^2, energy density of 4 J/cm^2) in preventing CIPN in breast cancer patients. Additionally, patients treated with PBM reported an improved quality of life.[66] The randomized, sham-controlled clinical trial by Argenta et al.,[67] the randomized phase II trial by Teng et al.,[68] and the review by Lodewijckx et al.[69] all indicate that PBM may serve as an effective treatment for CIPN. All of the aforementioned studies suggest that PBM can alleviate pain, enhance neurological function, and improve quality of life. The study by Joy primarily focuses on the use of PBM for the prevention of CIPN in cancer patients, whereas the other studies provide evidence supporting the therapeutic efficacy of PBM in treating CIPN.

Radiation-Induced Enteropathy

The usual treatment for abdominal and pelvic malignancies is radiotherapy, however, these organs are particularly susceptible to radiation, which can damage the small intestine and colon regions.[70] Radiation damage to the intestines diminishes the effectiveness of therapy, leading to functional loss and prolonged declines in patients' quality of life.[71] Kim et al.'s research demonstrates that PBM-treated (wavelength of 633 nm, power density of 1.65 W/cm^2 and 7.12 W/cm^2, energy density of 0.3–6 J/cm^2) mesenchymal stem cells (MSCs) can alleviate radiation-induced endothelial damage in vivo and in vitro, highlighting the vital role vascular components play in radiation-induced intestinal toxicity. PBM pretreatment significantly enhances the pro-angiogenic properties of MSCs, leading to improved mitigation of radiation-induced intestinal injuries compared to treatment with MSCs alone.[72]

The mechanisms by which PBM mitigates cancer treatment side effects may include activation of COX, increased ATP production, enhanced cellular metabolism, promoted cell regeneration, reduced apoptosis, and regulated collagen synthesis, which collectively facilitate tissue healing.[41] PBM inhibits the production of pro-inflammatory factors such as TNF-α, IL-1, and IL-6, while enhancing the release of anti-inflammatory factors, thus diminishing inflammatory responses and yielding analgesic effects.[73] Furthermore, it stimulates NO production, leading to vasodilation of blood and lymphatic vessels, which improves local circulation, lymphatic drainage, and supports tissue repair and regeneration. Concurrently, PBM activates antioxidant enzyme systems, reduces cellular oxidative stress, and provides cellular protection.[58] Additionally, it regulates immune cell activities, prevents excessive immune response, enhances macrophage clearance of necrotic tissue, accelerates tissue healing, and reduces infection risks.[43]

In addition to its role in managing side effects related to cancer treatment, PBM has been investigated for its direct influence on cancer progression. Understanding these dual roles of PBM is essential for optimizing its therapeutic potential in oncology.

APPLICATION OF PBM IN DIRECT ANTICANCER EFFECTS

PBM is increasingly utilized in oncology applications, potentially impacting prognosis. Research indicates that PBM can induce apoptosis, inhibit cancer cell proliferation, and synergize with chemotherapy drugs.

Inhibiting cell proliferation by inducing apoptosis

Based on current literature, Matsumoto et al. were among the pioneers in investigating the effects of PBM on cancer cells. They examined the impact of three different LEDs (red, blue, and green) on colon cancer cells, revealing that blue LEDs (465 nm) irradiation suppressed the proliferation of HCT116 and HT29 cells. This irradiation not only induced apoptosis in colon cancer cells through the extrinsic apoptotic pathway and the MAPK pathway but also inhibited the cell cycle.[74] Subsequent research in the author's laboratory demonstrated that blue LEDs (450 nm) induce apoptosis in B16-F10 cells via a mitochondria-mediated pathway and showed that blue LEDs inhibit the early cell growth rate of melanoma in vivo. This marks the first confirmation of the effect of blue LEDs on solid tumors in animal models.[75] Similarly, Kim et al. demonstrate that BL irradiation at 460 nm suppresses pancreatic cancer cell growth and promotes apoptosis.[76] They showed that in human pancreatic cancer cells, BL irradiation stimulates the AKT/mTOR pathway, crucial for cell death. Additionally, by suppressing AKT2 protein expression, BL irradiation prevents the formation and growth of tumors in experimental xenograft tumor models, offering a novel strategy for anticancer therapy in pancreatic cancer.[76]

Thus, BL irradiation may influence the redox state of mitochondria, elevate ROS levels, and induce oxidative stress in cells, damaging DNA and proteins, thereby triggering apoptotic pathways to inhibit cancer cell proliferation. Apoptosis is a process stringently regulated by genes, involving the expression and regulation of various proteins and genes. The extrinsic pathway is primarily initiated through the binding of death receptors to ligands, while the intrinsic pathway is predominantly activated by changes in mitochondria. Moreover, the mechanisms through which BL irradiation induces apoptosis vary according to the type of cancer cells involved. Yan et al. demonstrated that BL irradiation (470 nm) induces apoptosis in colon cancer cells by encouraging ROS generation and DNA damage.[77] Zhuang et al. found that apoptosis induced by BL (456 nm) in HL60 cells is linked with the mitochondria-mediated signaling pathway.[78] Jiang et al. demonstrated that BL irradiation (420 nm) induces apoptosis in oral squamous cell carcinoma cells by promoting endoplasmic reticulum stress and mitochondrial dysfunction.[79] Enhanced understanding of these specific mechanisms will establish a robust foundation for the future clinical application of PBM.

Inducing autophagy inhibits cancer cell growth

Research from the author's laboratory indicates that BL irradiation can inhibit the growth of B-cell lymphoma and induce apoptosis by triggering autophagy. Exposure to blue LED radiation (450 nm) leads to increased levels of intracellular superoxide anion and DNA damage, resulting in mitochondrial dysfunction and the formation of autophagosomes. Furthermore, the growth of mouse B-cell lymphoma can be significantly inhibited by BL in animal studies. Exposure to BL increases the survival rate of leukemic mice.[80] In another study, Yoshimoto et al. assessed the effect of blue LED irradiation (465 nm) in vitro on colorectal cancer cells and the role of photoreceptor opsin 3. Their findings suggest that BL irradiation triggers autophagy and inhibits the growth of colon cancer cells by modulating the Gi/o α-subunit of the G-protein via the OPN3 photoreceptor pathway. OPN3 is posited to become a significant target in colon cancer treatment.[81]

Autophagy is a metabolic process within cells whereby cytoplasmic proteins or organelles are degraded and recycled via lysosomes. The interplay between apoptosis and autophagy is complex, with autophagy having the potential to either delay or expedite apoptosis. PBM may promote autophagy by inhibiting the mTOR signaling pathway and raising ROS levels, which will trigger cell apoptosis. Recent research suggests that autophagy in cancer cells can trigger caspase-independent apoptosis and inhibit tumor growth.[81] These findings imply that autophagy is essential for LED irradiation to induce apoptosis in certain cancer cells.

Suppressing the migration and invasion of cancer cells

The author's laboratory discovered that suppressing the expression of matrix metalloproteinases MMP-2 and MMP-9 correlates with the anti-metastatic effects of BL irradiation (450 nm).[82] Experiments utilizing HT-1080 human fibrosarcoma cells and CT-26 mouse colon cancer cells demonstrated that BL irradiation inhibits cancer cell migration by suppressing MMP-9 expression via p38 MAPK phosphorylation. Nonetheless, further research is required to elucidate the specific mechanism underlying this process. Moreover, mice injected with luciferase-expressing CT-26 cells and subjected to BL irradiation exhibited a reduced risk of early lung metastasis compared to the untreated control group. These findings indicate that BL irradiation prevents the migration and invasion of cancer cells both

in vivo and in vitro.[82] While the precise mechanisms by which blue light LEDs suppress tumor metastasis in vivo remain unclear, it is likely due to the suppression of cancer cell proliferation and induction of apoptosis in the bloodstream during blue light LED irradiation. Additionally, Yan et al. subjected SW620 and HT29 cells to blue LED irradiation (470 nm), followed by conducting cell migration assays and Western blot analysis. These studies showed that blue light effectively inhibited CRC cell migration and suppressed the EMT process.[77]

Suppressing cancer cell proliferation in combination with chemotherapy drugs or radiotherapy

Zhuang et al. discovered that BL irradiation not only specifically inhibits the proliferation of U937 cells but also promotes their apoptosis. Furthermore, the combination of BL irradiation (456 nm) with the chemotherapeutic drug homoharringtonine (HHT) results in a greater inhibitory effect on cell proliferation than either BL irradiation or HHT treatment alone.[83] Similarly, Tartaglione et al. found that combining BL (465 nm) with cisplatinum treatment significantly reduced A431 cell viability and triggered the apoptotic death of cells more effectively than single treatments.[84] Additionally, research by Li et al. indicates that the combination of the anticancer drugs Rocaglamide and AT406 with 465 nm BL irradiation induces apoptosis in colorectal cancer cells by triggering apoptotic pathways, suppressing autophagy and proliferation, and generating ROS, suggesting that this combination is a promising therapeutic strategy for clinical application.[85] Furthermore, studies in the author's laboratory demonstrate that BL irradiation (450 nm) significantly reduces A20 cell proliferation without causing cytotoxicity at doses less than 20 J/cm^2. When mice injected with A20 cells were exposed to BL irradiation daily for 10 days, the metastatic capability of the cancer cells was reduced, and the survival rate of the mice increased. Furthermore, the anti-proliferative effects of BL on lung cancer A549, colorectal cancer HCT116 cells, and pancreatic cancer cells (Mia PaCa-2, PANC-1) have been confirmed. BL irradiation also enhanced the anti-proliferative effects in conjunction with chemotherapeutic agents such as gemcitabine and 5-FU, which affected mRNA translation.[86] Lastly, Silva et al. were the first to validate the therapeutic effects of PBM combined with RT in mice bearing triple-negative breast cancer. PBM effectively inhibited tumor growth, alleviated the adverse effects of radiation therapy, and reduced the number of lung metastatic nodules. Furthermore, when combined with high-dose RT, PBM significantly extended the survival time of the mice.[87] These findings suggest that an optimal dose of PBM, when used in conjunction with chemotherapy or radiotherapy, has a synergistic effect on inhibiting tumor proliferation, as demonstrated in animal models. This highlights the potential for future clinical applications.

Different irradiance levels and doses vary in their effects on inhibiting cancer cell proliferation

The study by Chen et al. reveals that B16F10 melanoma cells exhibit varying responses to PBM under different irradiances and doses. With a constant total dose, high-irradiance blue light demonstrates a more potent inhibitory effect on the cells compared to low irradiance, presumably because high irradiance produces more ROS, which subsequently impairs mitochondrial function.[88] Additionally, Jiang et al. found that A549 cells show differential responses to variations in irradiance and dose densities of blue light (457 nm). Cell viability reduction stabilizes once the irradiance reaches 3 mW/cm^2 and the dose density achieves 3.6 J/cm^2. Furthermore, BL inhibits A549 cells by increasing the expression of p53 and JNK while suppressing the PI3K/AKT pathway.[89] These findings suggest that future studies should focus on more detailed and precise experiments to establish optimal irradiances and dosages for inhibiting cancer cell proliferation.

The details regarding PBM's impact on inhibiting cancer cell proliferation are presented in Table 1. The mechanisms of BL action on tumor cells are illustrated in Figure 1.

Summary

As evidenced earlier, BL influences the proliferation, apoptosis, and metabolic activity of cancer cells. The effects of BL on cells are termed 'photobiogoverning effects'. Extensive research in the author's laboratory on the inhibitory effects of BL on various tumor types, including melanoma, lymphoma, colorectal, pancreatic, and lung cancers, has uncovered significant findings by examining its impacts from multiple perspectives.[75,80,82,86] These studies elucidate that photobiogoverning effects manifest when cancer cells are exposed to BL, whereby intracellular photosensitizers like COX absorb the light energy, leading to alterations in vital molecular structures within the cells. This results in the generation of substantial amounts of ROS and other oxidative metabolic products, causing damage to cellular macromolecules such as DNA, proteins, and lipids, thereby inducing cell death. BL not only promotes cell death through ROS production but

TABLE 1 Parameters of PBM for inhibiting cancer cell proliferation.

Year	Cancer Cell Type	Light Source	Wavelength (nm)	Irradiance	Irradiation Time	Dose	Result
2023	A549 Lung cancer cells	Blue LED	457	1; 2; 3; 4; 5; 10; 20; 50 (mW/cm^2)	600; 1200; 2400; 4800 (sec)	1.2; 1.8; 2.4; 3.6; 4.8; 6.0; 7.2; 10.8; 12; 24; 60 (J/cm^2)	The effects of blue light irradiation on A549 cells vary depending on the light intensity and dose density. Blue light suppresses A549 cell proliferation.[89]
2023	Human hepatoma HepG2 and HepG2.2.15 cells	Red LED	650	0.035 (W/cm)	7.2; 14.4; 18.8; 36 (sec)	2; 4; 8; 10 (J/cm^2)	Following PBM irradiation, there was a significant reduction in viability, proliferation, and HBVsvp production in the liver cancer cell lines HepG2.2.15 and HepG2.[100]
2023	A20; A549; HCT116; HepG2; Mia PaCa-2; PANC-1; RAMOS cells	Blue LED	450	7.0 (mW/cm^2)	24 h/day for 10 days in vivo; 24–48 h in vitro	5–20 (J/cm^2)	Blue light inhibits the proliferation of metastatic cancer cells and enhances the efficacy of chemotherapy drugs.[86]
2021	A431 cutaneous squamous cell carcinoma	Blue and red LED	465; 685	0.84; 1.10 (W/m^2)	12 h/day for 3 days	1.23 (J/mm^2)	Compared to single treatments, the combined use of blue light and cisplatin is more effective in reducing cell viability; furthermore, blue light promotes apoptosis.[84]
2021	4T1 murine breast cancer cells	Red laser	660	500 (mW/cm^2)	300 sec/exposure; 75 sec per set of 4 exposures	150; 37.5 (J/cm^2)	PBM can inhibit TNBC tumor growth and prevent hemolytic anemia.[87]
2021	B16F10 melanoma cells	Blue LED	457	Continuous wave: 0.19 (mW/cm^2) Pulse wave: 0.95 (mW/cm^2)	100 (min)	1.14 (J/cm^2)	Pulsed mode exhibits a more potent inhibitory effect on the viability of B16F10 melanoma cells compared to the CW mode. Furthermore, Pulse-PBM significantly augments the efficacy of PBM on cellular activities.[101]
2020	B16F10 melanoma cells	Blue and red LED	418; 457; 630	0; 0.31; 0.62; 0.93; 1.24; 1.55; 1.86; 2.17; 2.48; 4.96; 9.92; 19.84 (mW/cm^2)	0; 40; 60; 80; 120; 160; 240; 320; 360; 400; 480; 600; 720; 900; 960; 1200; 1440; 1800; 3600 (sec)	0; 0.04; 0.07; 0.15; 0.22; 0.30; 0.37; 0.45; 0.56; 1.12 (J/cm^2)	Blue light inhibited the growth of B16F10 melanoma cells, and the suppression was more effective under high irradiance compared to low irradiance conditions.[88]
2020	MIA PaCa-2 cells; PANC-1 cells; BxPC-3 cells	Blue and orange led	460; 610	5; 10 (mW/cm^2)	3 or 5 h/day for 5 days	12 (J/cm^2)	Blue LED inhibits pancreatic cancer cells and tumor growth by regulating AKT/mTOR signaling.[76]

(Continues)

TABLE 1 (Continued)

Year	Cancer Cell Type	Light Source	Wavelength (nm)	Irradiance	Irradiation Time	Dose	Result
2020	HCT116 and HT29 human colon cancer cell	Blue; green; yellow; red LED	465; 520; 580; 630	No information	1; 2; 3; 4; 5; 6 (h)	No information	Combination of 465 nm blue LED irradiation with the anticancer agents AT406 and Rocaglamide has a strong inhibitory effect on colorectal cancer cells, suppressing the proliferation of HCT116 and HT29 cells.[85]
2018	U937 cell	Blue; green; red; near-infrared LED	456; 515; 630; 840	0.25 (mW/cm^2)	2; 4; 8 (h)	No information	BL irradiation inhibits the proliferation of U937 cells and promotes their apoptosis. When BL is used in combination with HHT, the inhibition of proliferation is greater than with either treatment alone.[83]
2017	Human colon cancer HT29 and HCT116 cell	Blue LED	465	30 (mW/cm^2)	30 (min)	No information	Blue LED irradiation suppressed the growth of colon cancer cells and Opn3 may play an important role as a photoreceptor.[81]
2017	Human cervix adenocarcinoma HeLa cell	Laser	685	16.6 (mW/cm^2)	0; 5; 10; 20 (min)	0; 5; 10; 20 (J/cm^2)	The higher energy density of PBM could be a promising radiosensitizer in cervical cancer, potentially reducing the required radiation dose and thereby preventing side effects associated with cancer RT.[102]
2016	Mouse B-cell lymphoma A20 cell and human B-cell lymphoma RAMOS cell	Blue LED	450	6.3 (mW/cm^2) in vitro; 4.1 (mW/cm^2) in vivo	3 h/day 3 times in vitro; 0–4 h in vivo	No information	Blue LED irradiation induces apoptosis through mitochondrial-mediated pathways and autophagy.[80]
2014	HT29 and HCT116 human colon cancer cell	Blue; green; red LED	465; 525; 635	15;30 (mW/cm^2)	10 min/day for 5 days	No information	The 465 nm blue LED light inhibits the proliferation of HT29 and HCT116 cells and promotes apoptosis through an extrinsic apoptotic pathway.[74]

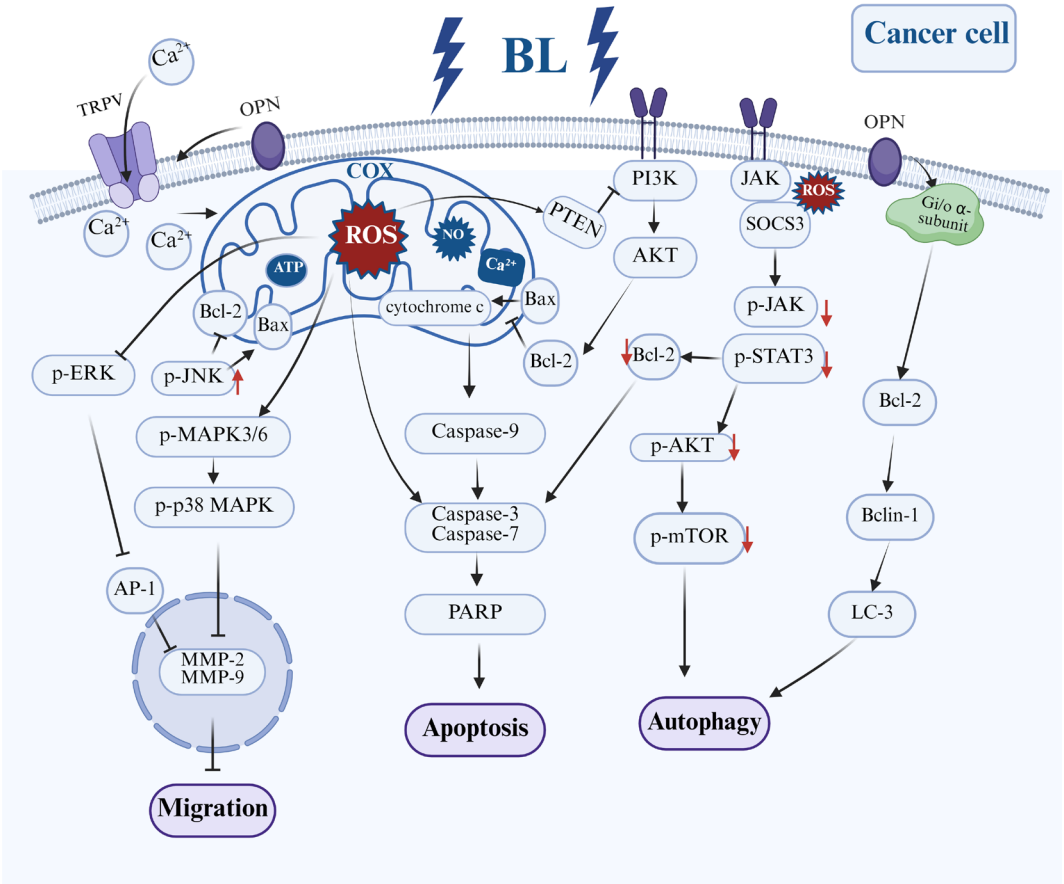

FIGURE 1 The possible mechanisms of BL action on tumor cells. BL is absorbed by photoreceptors (such as COX and OPN), leading to ATP synthesis and changes in the concentrations of ROS, NO, and Ca^{2+}. BL directly targets mitochondria, reducing mitochondrial membrane potential, which facilitates cytochrome c release and activates the caspase cascade, ultimately inducing apoptosis. Additionally, BL promotes ROS generation, leading to oxidative stress, mitochondrial dysfunction, and DNA damage, further triggering apoptotic pathways. BL-mediated apoptosis is associated with increased ROS levels, activation of caspase-3 and SOCS3, and upregulation of phosphatase and PTEN, which inhibits the PI3K/AKT signaling pathway. BL also activates TRP channels, such as TRPV, resulting in intracellular Ca^{2+} accumulation. Excessive Ca^{2+} influx disrupts mitochondrial function, enhances caspase activation, and promotes apoptosis. Moreover, elevated ROS levels induced by BL can inhibit mTOR phosphorylation, thereby promoting autophagy. BL has also been shown to induce autophagy in cancer cells by modulating the Gi/o α-subunit of the G-protein via the OPN photoreceptor pathway.

also modulates specific signaling pathways by inhibiting mTOR phosphorylation, which activates the autophagy mechanism and induces apoptosis. These complex interactions further inhibit cancer cell proliferation by disrupting the cell cycle. Additionally, BL exposure influences cancer cell gene expression and even curbs the translation process, ultimately suppressing cancer cell proliferation. Therefore, 'photobiogoverning effects' broadly describe the impact of BL on cancer cells.

Additionally, it is important to note that most studies suggest that RL and NIR are primarily used to alleviate the side effects of cancer treatment, whereas BL is more commonly investigated for its direct antitumor effects. This distinction may be attributed to differences in tissue penetration and biological mechanisms. RL (620–700 nm) and NIR (700–1440 nm) penetrate deeper into skin, muscle, and neural tissues, making them more suitable for tissue repair and regeneration.[90] In contrast, BL (400–500 nm) has a shallower penetration depth and is often associated with potential antitumor mechanisms, leading to its predominant exploration in direct cancer cell inhibition rather than in the management of chemotherapy-induced adverse effects.

In short, the potential advantages of phototherapy—non-invasiveness, high precision, and strong controllability—cannot be overlooked. These qualities make it a promising strategy that could be crucial for treating cancer. However, to advance its clinical application, a comprehensive evaluation of its safety profile is necessary.

SAFETY OF PBM TREATMENT

PBM has been widely applied in the medical field due to its roles in tissue repair, anti-inflammatory effects, and

neuroprotection. However, its safety in cancer treatment remains a concern. PBM may influence cellular metabolism, inflammation regulation, and the tumor microenvironment in anticancer therapies, with dual effects on tumor cells.[91] It may enhance antitumor immunity but could, under certain conditions, promote tumor cell survival.[92,93] Therefore, optimizing dosage, wavelength, exposure time, and treatment protocols is crucial for ensuring safety.

In recent years, several studies have investigated the safety of PBM and its specific wavelengths, such as BL, in various biological systems. Existing studies indicate that BL exhibits good tissue tolerance in human skin, respiratory, and oral tissues while providing treatment.[94,95] Experimental evidence indicates that controlled application of 425 nm blue light at doses below 120 J/cm^2 demonstrates a favorable safety profile regarding cytotoxic effects in oral mucosal tissues.[94] Irradiation with an intensity not exceeding 200 mW/cm^2 and a light dose not exceeding 60 J/cm^2 does not cause photoinduced histopathological damage. In preclinical evaluations, light doses not exceeding around 50 J/cm^2 and irradiation intensities not exceeding around 200 mW/cm^2 are unlikely to cause thermal injury to the tissues of the oral cavity.[94] Studies in the author's laboratory demonstrate that BL irradiation of no more than 20 J/cm^2 has no genotoxicity on CCD-1131Sk human skin cells or Vero monkey kidney cells. Furthermore, no cytotoxicity was observed in CCD-1131Sk cells within 48 h of treatment with BL (5–15 J/cm^2).[96] These findings support the safety of PBM in biological systems and provide evidence for its potential safety in cancer treatment. In addition, multiple research teams have conducted comprehensive evaluations of PBM's clinical safety in cancer treatment.[97–99] Their findings suggest that PBM is both safe and beneficial for the prevention and management of cancer-related symptoms at the current stage.

Clinicians still have an obligation to inform patients about the potential risks and benefits of PBM therapy, despite the broad consensus in the research community that PBM is safe for cancer treatment and related issues. Furthermore, long-term follow-up and comprehensive clinical research are required to verify the safety of PBM treatment.

CONCLUSION

In summary, PBM therapy can alleviate side effects of cancer treatments such as acute oral mucositis, radiation dermatitis, lymphedema, neuropathic pain, and radiation enteropathy, significantly enhancing the quality of life for cancer patients. In addition, a growing body of preclinical and clinical evidence indicates that PBM not only mitigates adverse effects but may also inhibit cancer cell proliferation and induce apoptosis, suggesting its potential as a complementary tool in tumor management.

However, the current variability in treatment parameters and dosages remains a critical challenge, as inconsistent outcomes have been observed across different studies. This variability highlights the need for a more comprehensive understanding of the mechanisms underlying PBM's effects. Future research should focus on several key areas. First, expanding clinical trials with larger cohorts and longer follow-up periods is essential to confirm the efficacy and safety of PBM therapy across diverse patient populations. Second, rigorous preclinical studies are necessary to elucidate the cellular and molecular pathways affected by PBM, which could aid in identifying the most effective treatment protocols. Third, efforts to standardize PBM parameters—including wavelength, dosage, and treatment duration—are crucial for minimizing outcome variability and ensuring reproducibility across clinical settings.

Overall, while PBM therapy presents a promising adjunctive approach to cancer care, its successful integration into mainstream treatment regimens will depend on protocol standardization and a deeper mechanistic understanding of its effects.

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CONFLICT OF INTEREST STATEMENT

The authors have no financial conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Hwan-Jeong Jeong https://orcid.org/0000-0002-9539-342X

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AUTHOR BIOGRAPHIES

Dr. **Qi Wang** is currently a Ph.D. student in Professor Jeong's laboratory. She received her Master's degree in Clinical Medicine from Shandong University, China in 2023. Her current research focuses on the feasibility of blue light therapy for cancer treatment.

Dr. **Phil-Sun Oh** received her PhD in Animal Science and Biotechnology from Chonnam National University, Korea in 2010. After completing a postdoctoral fellowship at the Department of Internal Medicine, Wayne State University, USA, on the role of cancer stem or stem-like cells in the development and progression of colorectal cancer, she joined Prof. Jeong's laboratory at Jeonbuk National University, Korea in 2013. Her research interests include the effect of photo-energy and the relevant signaling mechanism in cancer and virus-infected cells.

Dr. **Hwan-Jeong Jeong** earned his MD (1993), Master's in Medical Engineering (2000), and Ph.D. in Medicine (2003) from Chonnam National University. He completed his residency in Nuclear Medicine at Chonnam National University Hospital and a fellowship at Seoul National University Hospital. Following post-doctoral research at MD Anderson Cancer Center, University of Texas at Houston (2008–2010), Prof. Jeong has served as Professor and Director of Nuclear Medicine at Chonbuk National University Medical School & Hospital since 2005. His research focuses on nuclear medicine molecular imaging and photobiogoverning.

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