Photobiomodulation in Preventing Radiotherapy-Induced Dermatitis: A Systematic Review

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ABSTRACT

Radiodermatitis (RD) is a major side effect after radiotherapy (RT). It has negative effect on patient's quality of life. Recent studies have explored the use of photobiomodulation therapy (PBMT) in preventing or reducing the incidence of RD. The present study systematically reviews existing literature on PMBT with regards to protection against RD. A systematic search of the electronic databases including PubMed, Scopus, Embase and Google Scholar was conducted to retrieve articles on the protective effect of PBMT against RD. The search timeframe ranged from the inception of each database to date. From an initial search of 647 articles, and after removal of duplicates as well as applying the predetermined inclusion and exclusion criteria, 8 articles were finally included for this systematic review. All included studies were clinical, with their results showing promising protective effect of PBMT against RD. Furthermore, no adverse effect was observed in patients after administering PBMT. PBMT showed potentials to protect against RD while improving patient's quality of life. However, further studies would need to address grey areas such as optimization of PBMT treatment parameters, long time of application and small sample size.

Keywords: Photobiomodulation, Dermatitis, Ionizing radiation, Cancer, Radiotherapy

INTRODUCTION

In today's world, ionizing radiation is of immense benefit in many ways including medical (diagnostic imaging and radiotherapy (RT) for cancer), industrial, agriculture etc. Although in recent times, it has attracted negative aims such as for terrorism. Most radiation exposure to human arises from medical aims. This could give rise to side effects to normal tissues. Exposure to ionizing radiation could lead to detrimental effects, which can be early or late ([1], [2]). The former which occurs within few hours following irradiation could be in the form of vascular permeability, apoptosis, lymphocyte adhesion, endothelial swelling, and edema [3], while the latter which manifests after some years include carcinogenesis, necrosis, organ dysfunction, and death [4].

The DNA is the most critical target when cells are exposed to ionizing radiation, giving rise to chromosomal aberrations or cell death. Most detrimental effects of ionizing radiation are due to the generation of free radicals following the interaction of ionizing radiation with water molecules in living tissues [5]. When free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) interact potently with the DNA, cell death or neoplasm could occur if DNA damage overcomes DNA damage responses [6], [7].

There are several mechanisms through which ionizing radiation cause cell death. They include necroptosis, apoptosis, necrosis, mitotic catastrophe, autophagy and senescence [8]. Inability to repair complex DNA damage could lead to any of these effects. The degree of cell death varies with cell type [9] as well as radiation dose [10]. After DNA damage and cell death following irradiation, some danger alarms are released from damaged cells. Danger alarms can be recognized by macrophages and lymphocytes, leading to several signaling pathways involved in inflammation, DNA repair and redox (reduction/oxidation) metabolism [11]. These mechanisms are responsible for enormous free radical production as well as increase in the level of

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several cytokines and chemokines including TNF-α, TGF-β, IL-1 etc. [12]. They reduce the antioxidant levels in cells, thereby giving rise to further DNA breaks, oxidative stress and cell death [13], [14], [15].

Side effects from exposure to ionizing radiation can also arise in cells or tissues which were not directly irradiated. This is known as systemic effect. Moreover, this has even been observed for radiation doses less than 1 Gy [16].

Radiotherapy is one of the most utilized treatment modalities for cancer. During this process, the skin tissues are inevitably exposed to ionizing radiation. The epithelial layer of the skin can be easily damaged after irradiation [17]. Acute radiodermatitis (ARD) with indications including erosion, ulcer, scaling, edema and erythema may occur 3 months following radiotherapy. Moreover, from 6 months to some years post radiotherapy, chronic radiodermatitis including changes in nature of skin, poikiloderma, and hyperpigmentation may be observed.

Due to negative consequences of exposure to ionizing radiation, it is imperative to have adequate protective measures to counter these effects. Thus, several approaches have been developed to achieve this aim. Recent technological advancements involving modern radiotherapy devices have been developed with the aim of limiting exposure to healthy tissues. The use of natural and chemical agents as radioprotectors have also been employed in several experimental and clinical studies [12], [18].

In recent times, photobiomodulation therapy (PBMT) has been explored. PBMT which is also referred to as low-level laser therapy (LLLT), involves the use of red or near infrared (NIR) light to heal, restore and stimulate multiple physiological processes as well as repair damages from injuries or diseases [19], [20]. The effects of PBMT on various tissues have been confirmed by numerous *in vitro* and *in vivo* studies and are influenced by cell type, laser wavelength and energy dose [21], [22], [23]. It is well known that PBMT increases fibroblast proliferation [24], which also favours collagen synthesis [25] as well as angiogenesis [26]; in which case it reduces cyclooxygenase-2 (COX-2), TNF-α as well as pro-inflammatory cytokines IL-6 and IL-1β [24], [25], [26], [27], [28]. Furthermore, it promotes the differentiation of anti-inflammatory cytokines including IL-2, IL-4, IL-8 and IL-10; and also acts on NF-κB signaling pathway [29].

The present study aimed to systematically assess current literatures on the use of PBMT in preventing radiation-induced dermatitis following RT.

MATERIALS AND METHODS

Search strategy

This study was conducted in accordance with the statement of preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher et al, 2009). The following online databases including Scopus, PubMed, Google Scholar and Embase were searched for articles investigating the protective effect of PBMT against ionizing radiation-induced dermatitis, without restriction on year of publication. The search keywords were as follows: “photobiomodulation” and “dermatitis”, “ionizing radiation”, “photobiomodulation therapy” “radiotherapy”, “cancer and radiotherapy”. To ensure that no relevant study was missed, manual screening of the references from studies from initial search was conducted.

Inclusion criteria

Articles were included based on the following criteria:

- Studies which made use of PBMT techniques such as LLLT, LED, laser therapy (LT) and phototherapy, whose language of publication is English.
- Studies about the protective effective effect of PBMT against ionizing radiation-induced dermatitis.
- Studies which involved cancer treatment with ionizing radiation.

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- Preclinical/experimental as well as clinical studies with full texts.

Exclusion criteria

Exclusion of studies was as follows:

- Studies which did not utilize PBMT.
- Studies which did not investigate the effect of PBMT with ionizing radiation.
- Review studies, abstracts, editorials, studies without full texts as well as studies whose language of publication is not English.

Study selection

Relevant studies from online and manual literature searches were exported into EndNote software X6 (Thomson Reuters, New York, USA) for removal of duplicates. Subsequently, the titles and abstracts of remaining studies were carefully screened by two authors for eligibility according to the predetermined inclusion and exclusion criteria. Factual evidences were used in cases of disagreements involving inclusion.

Data extraction

The following data were carefully extracted from each included article: first author name, number of patients, cancer type, radiation dose, PBMT parameters, time for outcome assessment and main outcomes. Afterwards, these data were presented in a tabular form.

RESULTS

Summary of our search result is presented in figure 1. Initial search produced 647 articles. After removing duplicates, 580 articles were left, from which 529 articles were excluded after reviewing their titles and abstracts. A further 43 articles were excluded based on our predetermined inclusion and exclusion criteria as well as careful examination of their full texts. Finally, 8 studies ([30], [31], [32], [33], [34], [35], [36], [37]) were selected for this systematic review.

The included studies were all clinical studies involving a total of 276 cancer patients (breast cancer = 246 and head and neck cancer (HNC) = 30) treated with PBMT (LED, LT and RLPT). Furthermore, the RT treatment doses ranged from 50.4-66 Gy. Table 1 gives a summary of the included studies.

In a study by [30]; 19 breast cancer (BC) patients were treated with LED PBM after IMRT (with total doses up to 50.4 Gy). Their result showed that 94.7% of patients treated with LED had grade 0 or 1 reaction while 5.3% of patients had grade 2 reactions. Furthermore, treatment of BC patients with LED PBM immediately after IMRT reduced the incidence of grades 1, 2 and 3 skin reactions (based on National Cancer Institute (NCI) grades) as well as reduced inflammation. They attributed this protective effect to the stimulation of fibroblast function with reduced inflammation, thereby preventing radiotherapy-induced skin damages. No side effect from treatment with LED PBM was observed in all patients.

[31] demonstrated the efficacy of PBMT in ameliorating radiation-induced dermatitis. In this study, 18 BC patients received LED PBM in addition with 3D conformal RT (of total dose up to 61.2 Gy). From their results, it was observed that in the LED PBM treated group, no patient had grade 0 reactions, 33.3% had grade 1 reactions, 66.7% had grade 2 reactions and none had grade 3 reactions. However, in contrary to the study by DeLand *et al.*, (2007) there was no significant reduction in radiation induced-dermatitis when RT was administered with LED. They attributed these discrepancies to small sample size and also because subjects were treated before and after each RT session, instead of only after each session. Nevertheless, no adverse effect from this method was observed.

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[32] investigated the effect of low-power laser treatment in preventing RD. Twenty-six BC patients were treated with PBMT for 5 days a week before each RT session (with total dose up to 57.5 Gy). Their results showed that this approach prevented RD via reducing inflammation and inducing collagen synthesis. Similar to previous studies, no adverse effect was observed.

The effectiveness of PMBT + RT in comparison with RT only was assessed by [33]. In this study, 38 BC patients received PMBT + RT (up to 66 Gy) while 41 BC patients received RT only. Their results showed significant reduction of skin toxicity in the PMBT + RT group compared to the RT only group. A limitation of their study was that allocation of patients into treatment groups was done without randomization. In terms of patient's quality of life, no significant difference between both groups was observed. Nevertheless, this treatment approach was found to be more effective compared to RT only regimen.

[34] demonstrated the beneficial effects of PBMT in reducing or preventing radiation-induced dermatitis. In one group, 25 BC patients were treated with LED PBM twice a week before 3D conformal RT (up to 50.4 Gy) while in the other group, 45 BC patients received only RT. Their results showed that PBMT was effective in reducing RD (with 12% developing grade 2 RD in the PBMT group and 40% in the RT only group). Furthermore, in terms of the intensity of pain, 60% of patients reported no pain in the PMBT group while 28.9% reported no pain in the RT only group.

[35] studied the effect of red-light phototherapy (RLPT) in the treatment of RD. Thirty HNC patients were enrolled to receive RLPT twice daily till the end of RT. Compared to the control group which received only RT, patients who received RLPT+ RT showed grades 0-2 RD while the former showed grades 2-3 RD. Thus, these results showed the effect of PBMT in reducing RD. Furthermore, PBMT accelerated wound healing as well as reduced pain within a short time. They concluded that PBMT could ensure the smooth progress of RT and also improve patient's quality of life.

[36] evaluated the effectiveness of PBMT in preventing ARD. Sixty BC patients received LT twice a week immediately after each RT session (up to 66 Gy). By contrast to control group (RT only), PBMT was effective in preventing the development of grade 2 ARD or higher in BC patients. Moreover, in comparison to control, patients' quality of lives in the LT group were significantly improved. In a further study by this group, using similar parameters, they also showed this method to be effective in ameliorating moist desquamation in BC RT patients [37].

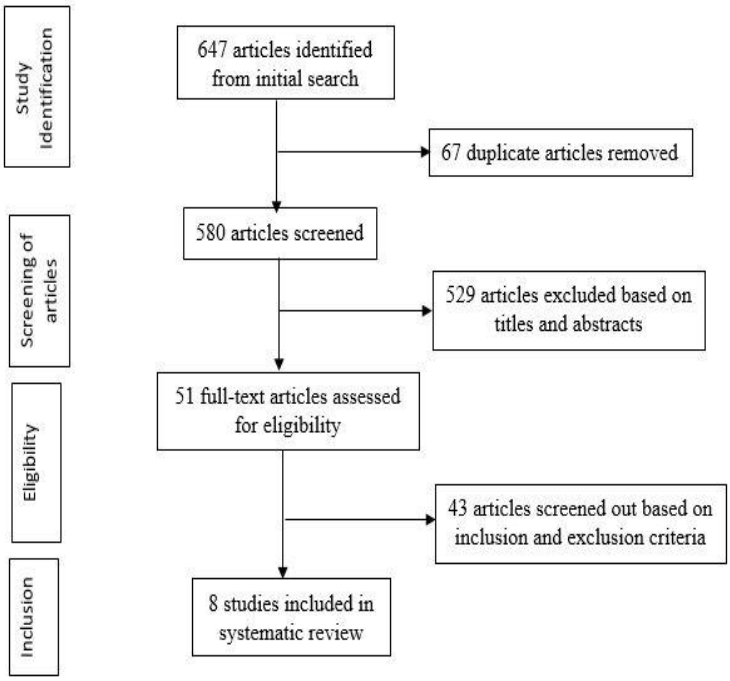

Fig. 1 PRISMA flow diagram of the systematic literature search.

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Table 1. Summary Of Included Studies In The Systematic Review.

First author	Number of patients	Cancer type	Radiation dose (Gy)	Photobiomodulation parameters				Time for outcome assessment	Main outcome
				Wavelength (nm)	Power (mW)	Time (s)	Energy (J/cm^2)		
DeLand *et al.*, 2007 [30]	19	BC	50.4	590	-	-	0.15	90/180	LED PBMT treatments immediately after IMRT reduced the incidence of NCI grades 1, 2, and 3 skin reactions in BC patients treated with RT after lumpectomy.
Fife *et al.*, 2010 [31]	18	BC	61.2	590	-	-	1.5	35	LED PBMT is of no harm to patients undergoing RT for BC, but the efficacy of LED PBMT in preventing RD requires further studies.
Costa *et al.*, 2014 [32]	26	BC	57.5	660	80	1320	108	90	Application of PBMT enhanced tissue repair via reduction of inflammation and inducing collagen synthesis.
Censabella *et al.*, 2016 [33]	38	BC	66	808/905			4	-	PBMT could be effective in preventing ARD.
Strouthos *et al.*, 2017 [34]	25	BC	50.4	660/850	44.6	300	0.15		LED PBMT applied prior to RT might be effective in decreasing the incidence and sequelae of radiation-induced skin toxicity in BC patients.
Zhang *et al.*, 2018 [35]	30	HNC	-	620/760	-	-	-	-	RLPT can accelerate the healing ability of wound and significantly shorten the healing time. It relieves pain, promotes healing and ulcer, but also guarantees the smooth progress of RT and improves patient's quality of life.
Robijns *et al.*, 2018 [36]	60	BC	66	808/905	3.3	46,727	4	42-49 days	PBMT is able to prevent the development of severe acute skin reactions and it seems to provide symptomatic relief during RT.
Robijns *et al.*, 2019 [37]	60	BC	66	808/905	0.168	-	4	42-49 days	PBMT is an effective tool to prevent the development of severe ARD in BC patients. Further, screening patients on breast volume before the start of RT can allow the radiotherapist to optimize the skin management during the course of RT.

BC: Breast cancer; HNC: Head and neck cancer; LED: light emitting diode; PBMT: Photobiomodulation therapy; ARD: Acute radiodermatitis;

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NCI: National Cancer Institute; RT: Radiotherapy; RLPT: Red light phototherapy;

DISCUSSION

This study systematically reviewed the available literature on the use of PBMT in protecting against RD. Radiotherapy, though effective for cancer treatment, often leads to collateral damage in normal tissues due to oxidative stress, inflammation, and impaired tissue repair [55]. Photobiomodulation therapy (PBMT) has emerged as a supportive treatment to mitigate these effects, especially in conditions like oral mucositis, dermatitis, fibrosis, and neuropathy.

PBMT uses non-ionizing light in the red to near-infrared (NIR) spectrum (600–1100 nm) to stimulate beneficial cellular responses [19]. Recent advances have further clarified how PBMT influences cellular metabolism, gene expression, inflammation, and tissue regeneration ([56], [57]).

Findings from these studies have shown promising results for this aim. Furthermore, its safety was not in question as no study showed no side effect following treatment with PBMT. While this approach has been shown to induce apoptosis and cell death in malignant neoplastic cells in a dose-dependent manner; [25], [38], [39]; however, some studies have shown that PBMT could influence cellular metabolic activities via stimulation of malignant cells' proliferation as well as altering tumor microenvironment, thereby increasing tumor volume [40], [41]. These conflicting evidences should be given due consideration in future studies.

PBMT has been shown to stimulate and enhance wound healing, regeneration, and immune responses as well as preventing aberrant immune responses, inflammation and pain [42]. These properties of PBMT have been utilized in protecting against oral mucositis (OM) from chemotherapy or RT [43], [44], [45], [46], [47], [48]. It has also been shown to protect against lymphedema [49], [50], [51], [52] and peripheral neuropathy [53].

In terms of PBMT treatment parameters, the reviewed studies showed variations in their parameters used. Thus, for maximum protection against RD, the parameters would need to be optimized so as to achieve common therapeutic ground for clinical purposes. A systematic review for PBMT in protecting against radiation-induced OM recommended the following PMBT parameters: wavelength centered at 650 nm, power density of 40 mW and tissue energy dose of 2 J/cm^2, in adult patients receiving hematopoietic stem cell transplantation conditioned with high-dose chemotherapy, with or without total body irradiation [54]. Furthermore, they suggested a wavelength of 632.8 nm for the prevention of OM in patients undergoing RT with PBMT, without concomitant chemotherapy for HNC.

From the reviewed studies, a major advantage of PBMT is its convenience for patients and ease of use by medical personnel [34]. Furthermore, its cost effectiveness was also reported [32]. However, its long duration during application could lead to patient's discomfort.

Limitations were observed in the included studies. One of such is the small sample size of patients enrolled. As a result, some insignificant effects between study groups were observed [31]. We suggest larger sample sizes in order to detect small differences in skin reactions between groups. Another limitation is the very few clinical studies evaluating the use of PBMT in protecting against RD. This is in contrast to the many studies which have utilized this technique in protecting against OM. Therefore, we suggest more clinical investigations for PBMT against RD, for more insights.

RD has a negative effect on the quality of life of RT patients. Going by the findings from the reviewed studies, PMBT has shown potentials to prevent or even reduce the incidence of RD. However, it remains to be seen how this method would fare in future clinical trials.

PBMT is a highly cost-effective adjunct in the management of radiation-induced tissue damage [59]. While the initial capital and training investment are modest, the clinical and economic returns are significant, particularly in reducing side effect burden, enhancing patient comfort, and improving compliance with oncologic treatment.

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Future directions include integration into clinical pathways, adoption of standardized treatment protocols, and inclusion in reimbursement frameworks, which will enhance PBMT's viability and scalability in routine cancer care.

CONCLUSION

In conclusion, findings from this systematic review gives further credence to existing evidences on the potentials of PBMT in reducing or preventing RD. Grey areas such as optimization of PBMT treatment parameters, small sample size and longer treatment time should be further addressed in future studies. This would go a long way in ensuring optimal protection as well as improving RT patients' quality of lives.

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