Effects and parameters of the photobiomodulation in experimental models of third-degree burn: systematic review analysis

Efeitos e parâmetros da fotobiomodulação em modelos experimentais de queimadura de terceiro grau: revisão sistemática

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This systematic review was performed to identify the role of photobiomodulation therapy in experimental models of third-degree burns used to induce oxidative stress. EMBASE, PubMed, and CINAHL databases were searched for studies published between January 2003 and January 2018 on the topics of photobiomodulation therapy and third-degree burns. Any study that assessed the effects of photobiomodulation therapy in animal models of third-degree burns was included in the analysis. A total of 17 studies were selected from 1182 original articles targeted on photobiomodulation therapy and third-degree burns. Two independent raters with a structured tool for rating the research quality critically assessed the articles. Although the small number of studies limits the conclusions, the current literature research indicates that photobiomodulation therapy can be an effective short-term approach to accelerate the healing process of third-degree burns, to increase and modulate the inflammatory process, to accelerate the proliferation of fibroblasts, and to enhance the quality of the collagen network. However, differences still exist in the terminology used to describe the parameters and the dose of photobiomodulation therapy.

Keywords: Photobiomodulation therapy, Wound healing, Burns.

RESUMO
Esta revisão sistemática foi realizada para identificar o papel da terapia de fotobiomodulação em modelos experimentais de queimaduras de terceiro grau usadas para induzir estresse oxidativo. Os bancos de dados EMBASE, PubMed e CINAHL foram pesquisados para estudos publicados entre janeiro de 2003 e janeiro de 2018 sobre os tópicos da terapia de fotobiomodulação e queimaduras de terceiro grau. Qualquer estudo que avaliasse os efeitos da terapia de fotobiomodulação em modelos animais de queimaduras de terceiro grau foi incluído na análise. Um total de 17 estudos foram selecionados entre 1182 artigos originais direcionados à terapia de fotobiomodulação e queimaduras de terceiro grau. Dois avaliadores independentes, com uma ferramenta estruturada para avaliar a qualidade da pesquisa, avaliaram criticamente os artigos. Embora o pequeno número de estudos limite as conclusões, as pesquisas atuais da literatura indicam que a terapia de fotobiomodulação pode ser uma abordagem eficaz a curto prazo para acelerar o processo de cicatrização de queimaduras de terceiro grau, aumentar e modular o processo inflamatório, acelerar a proliferação de fibroblastos e para melhorar a qualidade da rede de colágeno. No entanto, ainda existem diferenças na terminologia usada para descrever os parâmetros e a dose da terapia de fotobiomodulação.

Palavras-chave: Terapia de fotobiomodulação, Cicatrização de feridas, Queimaduras.
1 INTRODUCTION

Severe burn injuries are the most traumatic and physically debilitating injuries affecting nearly every organ system and leading to significant morbidity and mortality. Early burn wound excision and skin grafting are common clinical practices that have significantly improved the outcomes of patients with severe burn injuries by reducing the mortality rate and the length of hospital stay. However, slow wound healing, infection, pain, and hypertrophic scarring continue to remain major challenges in burn research and management [1].

The first-degree burn is superficial and the lesion is located at the surface of the dermis. A second-degree also known as a partial superficial burn or a superficial dermis burn is when the lesion is located on the surface of the epidermis and the superficial papillary dermis and the upper area of the deep reticular dermis. In this type of burn, the pilosebaceous complexes situated in the lower area of the deep reticular dermis remain intact. A deep burn or a third-degree burn affects the entire thickness comprising the epidermis, dermis, hypodermis and all cutaneous annexes, and, in some cases, even the adipose tissue [2].

Burn depth is related to the temperature and time exposed to the heat source. In animals and humans, a classical inverse relation exists between the temperature and time required to produce a specific degree of burn. It is worth noting that the critical temperature for thermal damage is about 43 °C—below which no damage occurs no matter how long the tissue is exposed to the source. This inverse relation indicates that one can create different degrees of thermal injury by either varying the time of exposure or varying the temperature of the heat source [3].

Burns are the most extensive forms of soft tissue injuries, occasionally resulting in extensive and deep wounds and death. Burns can lead to severe mental and emotional distress, because of excessive scarring and skin contractures [4].

Healing is a complex process that involves a series of events, including clotting, inflammation, granulation tissue formation, epithelialization, collagen synthesis, and tissue remodeling. Thus, it has been extensively researched, particularly regarding the factors that could delay or hinder the healing process [5]. Third-degree burns have been a major focus of search and investigation, searching for new treatment methods in order to improve the care of burn patients and also provide greater speed for a satisfactory result without major functional and esthetic sequelae [4].

Low-level laser therapy (LLLT) has been recently used to stimulate the wound healing process [6]. Several effects of LLLT have been claimed to induce this phenomenon, including increased ATP production and increased mitochondrial membrane potential [7]. Several
investigators reported that photobiostimulation of the wound healing process stimulates fibroblast proliferation; significantly increases re-epithelialization, collagen synthesis, and granulation tissue formation; accelerates wound closure; improves tensile strength of the scars; and determines faster healing of burns [8].

However, the cellular mechanisms of photobiomodulation therapy (PBMT) using LLLT are not well understood despite much discussion on these mechanisms in the literature. Controversial results are reflective of the complexity of the appropriate parameter selection before each treatment session. Given the lack of uniform parameters in the literature, the translation of clinical control studies is still incipient. In view of the above considerations, this systematic review aimed to assess and discuss the parameters and results obtained in experimental studies performed on third-degree burn models and to verify based on these results the uniformity of expected effects and ideas for a possible translation of preclinical studies to randomized clinical trials.

2 MATERIALS AND METHODS

2.1 SEARCH STRATEGY

A systematic search of studies published between 2003 and January 2018 was performed in three electronic databases: EMBASE (Excerpta Medica Database), PubMed (Public/Publisher MEDLINE), and CINAHL (Cumulative Index to Nursing and Allied Health Literature). First, keywords were selected from related articles. MeSH and Scopus international data lines were used to find more related keywords with close meanings: (“low-level light therapy” [MeSH Terms] OR (“low-level” [All Fields] AND “light” [All Fields] AND “therapy” [All Fields]) OR “low-level light therapy” [All Fields] OR “lllt” [All Fields]) AND (“wound healing” [MeSH Terms] OR (“wound” [All Fields] OR “repair” [All Fields]) AND (“burns” [MeSH Terms] OR “burns” [All Fields] OR “burn” [All Fields]) AND third [All Fields] AND degree [All Fields] AND (“rats” [MeSH Terms] OR “rats” [All Fields]). The search was repeated after the review of the eligible papers to specifically search for experimental methodologies and outcomes and parameters of photobiomodulation. In addition, we reviewed the retrieved articles to identify possible additional studies (Fig. 1).

2.2 STUDY SELECTION

We examined the title list and abstracts identified by the literature searches for potentially relevant studies. Two independent reviewers (SAS and CO) applied predetermined inclusion criteria to all studies. Conflicts were resolved by a third independent researcher (PTC).
The following inclusion criteria were applied:

1. Live animal subjects
2. Experimental studies performed on third-degree burn models
3. Random allocation of treatment
4. Photobiomodulation provided as an intervention to at least one treatment group
5. A quantitative or semi-quantitative assessment
6. English language

Abstracts were reviewed by at least two raters to determine if they met the eligibility criteria.

The following exclusion criteria were applied:

1. In vitro studies
2. Clinical studies and systematic review articles with or without meta-analysis
3. Papers not published in English language
4. Microbiological studies

**Assessment of study quality**

Potentially eligible articles were printed, reviewed, and critically appraised for quality rating by two independent reviewers. Systematic reviews are commonly performed in human research, but rarely in animal research. To assess the quality of included studies, we used SYRCLE’s RoB [9] tool that contains 10 items to investigate any important sources of bias such as allocation, adjust for confounder, assignment to the different groups adequately concealed during, animals randomized for housed, blinded investigators, animals random selection for outcome assessment, blinded outcome assessor, addressing incomplete outcome, and free of selective outcome reporting and other risk of bias (Fig. 2).
3 RESULTS AND DISCUSSION

We detected 1182 articles in the databases. Of these, 1164 were excluded for not meeting the inclusion criteria of this systematic review: repeated study (n = 5), in vitro study (n = 120), clinical study (n = 62), systematic review (n = 76), abstract only (n = 47), it is not of third-degree burn (n = 854). Finally, 17 studies [4, 10–25] in which diverse treatment parameters of injuries were assessed were included for critical evaluation of the effectiveness of PBMT in third-degree...
burn. The 17 selected studies totaled a sample of 845 animals and showed some common characteristics, namely the use of adult male Wistar rat with a mean weight of 278.5 g as an experimental model and the dorsal region of the animals as the region where burns were performed in all (100%) studies. The burn model was created using a cylinder connected to boiling water (27.7% of cases) [14–18, 20], a heated metal (22.2%) [4, 10–13, 16, 22]. Instrument heated until red and incandescent (11.1%) [24, 25] immersion in water at 95 °C (5.5%) [15], immersion in water at 100 °C (5.5%) [23], or cylindrical brass rod cooled to 77 K (5.5%) [21]. These findings suggested a good standardization between the experimental models of third-degree burns, allowing the reproducibility of the experimental models (Table 1).

![Fig. 2 Representation of the SYRCLE’s risk of bias tool for animal studies. Hooijmans et al. (2014)](9)
A great variation of performed analyses and dependent variables was found in the selected studies; although the majority (50.0%) of them used different methods to assess the effect of PBMT in several phases of the repair process [4, 10–14, 16, 20–25], some studies (5.5%) focused on bacterial infection (Table 2) [15].

Table 3 shows the parameters used in the selected studies. Whereas 72.2% of studies used a laser with a wavelength in the red spectrum, some authors chose a 632.8-nm laser [20, 21]; others used a laser with a wavelength in the range of 660 nm [4, 10–12, 14, 15, 18, 19, 22], 685 nm [17], and 640 nm [13, 23], and 5.5% used a laser with a wavelength of 890 nm [16], 11.1% used a laser with a wavelength of 780 nm [18, 19, 22], 11.1% used a laser with a wavelength of 400 nm [24, 25], 5.5% used a laser with a wavelength of 520 and 550 nm [22], and used a laser with a wavelength of 2000 nm [24, 25]. In relation to the power of the lasers, a very large variation was detected, ranging from 10 mW [20, 21] to 100 mW [10, 11]; the intermediate powers were as follows: 75 mW [16], 40 mW [22], 50 mW [10], 35 mW [12, 18, 19], 30 mW [13, 14], 20 mW [15], 5 mW [4], 0.05 mW [17], 0.11 mW [23], 3.7 mW [24], and 0.95 W [25]. Other important parameters of PBMT were also obtained in this analysis: energy (only 27.4% of studies reported this parameter [10, 12, 13, 22, 23]), beam area (66.6% of reviewed studies assessed this parameter [4, 10, 12–17, 20, 23–25]), exposure time to PBMT (72.2% of studies reported it [4, 10, 12–14, 16, 17, 20–25]), and the density of power (55.5% of papers described it [4, 10, 12, 14–17, 21, 24, 25] (Table 3)). Regarding the effect of PBMT, 22.2% of studies reported statistically significant positive effects, 50.0% of studies reported positive but not statistically significant effects, and 22.2% of studies reported partially positive effects (Table 4).
Table 1 Study the characteristics of selected controlled experimental studies of photobiomodulation therapy effects on third-degree burn

| Authors | Animal type | Gender (M/F) | Animal race | Age (months) | Weight (g) | Induction modal | temperature / exposure time | Site Injury Ethics committee |
|---------|-------------|--------------|-------------|--------------|------------|-----------------|-----------------------------|-----------------------------|
| Gomes 2017[4] | Rat | Female | Wistar | - | 300 g | hot water at 60 °C | 45 s | Dorssm | Not |
| Brascollati 2016[10] | Rat | Male | Wistar | 12 weeks | 280 g | Aluminum plate 150 °C | 10 s | Dorssm | Yes 022/2013 |
| Tejano 2014[11] | Rat | Male | Wistar | - | 250-350 g | Metal rod. 80 °C | 15 s | Dorssm | Yes |
| Fierro 2014[12] | Rat | Male | Wistar | - | 260 ± 20 g | Aluminum plate 120 °C | 5 s | Dorssm | Yes A107/CEP/2007 |
| Fierro 2011[13] | Rat | Male | Wistar | - | 260 ± 20 g | Aluminum plate 120 °C | 5 s | Dorssm | Yes A107/CEP/2007 |
| Nuñez 2013[14] | Rat | Male | Wistar | Adult | 300 g | Rubber tube connected boiling water | 5 s | Dorssm | Yes |
| Moraes 2013[15] | Rat | Male | Wistar | - | 300-350 g | Immersion in water at 95 °C | 14 s | Dorssm | Yes 098/2009 |
| Khoshavaghi 2011[16] | Rat | Male | Wistar | 4 months | 300 g | Cylinder connected boiling water | 2 s | Dorssm | Yes |
| Garcia 2010[17] | Rat | Male | Wistar | Adult | 180-220 g | Heated punch 80 °C | 30 s | Dorssm | Yes |
| Maireses 2008[18] | Rat | Male | Wistar | Young adult | 200-230 g | Instrument heated | 20 s | Dorssm | Yes |
| Maireses 2008[19] | Rat | Male | Wistar | Young adult | 200-230 g | Instrument heated | 20 s | Dorssm | Yes |
| Bavai 2008[20] | Rat | Male | Wistar | Adult | 250 ± 30 g | Cylinder connected boiling Water | 7 s | Dorssm | Yes |
| De Silva D de F 2006[21] | Rat | Male | Wistar | Adult | 300 g | Cylindrical brass rod cooled to 77 K | 2 sequences of 5 s Repeated 3 days | Dorssm | Not |
| Cacho 2015[22] | Rat | Male | Wistar | - | 200-230 g | Iron heated | 20 s | Dorssm | Yes 0019/240712 |
| Neves 2014[23] | Rat | Male | Wistar | - | 250 ± 25 | Tube with water heated to 100 °C | 20 s | Dorssm | Yes 4962008 |
| Oliveira 2010[24] | Rat | Male | Wistar | Adult | 200-230 g | Instrument heated until red and incandescent | 20 s | Dorssm | Yes |
| Oliveira 2011[25] | Rat | Male | Wistar | Adult | 200-230 g | Instrument heated until red and incandescent | 20 s | Dorssm | Yes 013/05 |
Table 2  Study the characteristics (sample sizes, number of groups, number of animals/group, dependent variables) of selected experimental studies of controlled animals on effects of photobiomodulation therapy on third-degree burn

| Authors          | Sample sizes | Number of groups | Number of animals/group | Dependent variables                                                                 |
|------------------|--------------|------------------|-------------------------|-------------------------------------------------------------------------------------|
| Gomes 2017 [4]   | 12           | 3                | 4                       | Morphological analysis (inflammatory response; granulation tissue; presence or absence of hair follicles; presence or absence of ulcers; analysis of the collagen organization) |
| Brassolati 2016 [10] | 30           | 3                | 10                      | Histopathological Analysis; Blood Vessel Morphometry; Morphometry of Collagen Fibers; Immunohistochemistry. |
| Trajano 2014 [11] | 18           | 3                | 6                       | Total RNA extraction; complementary DNA synthesis.                                  |
| Fiorio 2014 [12] | 48           | 4                | 12                      | Morphological analysis (histologic analysis, morphometric analysis) count the inflammatory cells, type of collagen fibers. |
| Fiorio 2011 [13] | 24           | 4                | 6                       | Histological analysis (measured at the skin surface); count the inflammatory cells.   |
| Nuñez 2013 [14]  | 36           | 2                | 18                      | Histomorphometrical analysis; quantitative assessment of new vessels; leukocyte differential counting; Laser doppler flowmetry. |
| Morais 2013 [15] | 36           | 3                | 12                      | Macroscopic evaluation; morphometric evaluation; microscopic evaluation; massoscopic analysis. |
| Khosravaghi 2011 [16] | 48           | 2                | 24                      | Morphometric estimation (histologic estimation) members of types 1, 2, and 3 mast cells, and the total number of mast cells in 100 zones of burned skin. |
| Garcia 2010 [17] | 96           | 4                | 24                      | Histological analysis by light microscopy.                                           |
| Meireles 2008 [18] | 55           | 3                | 15/20                   | Microscopy analysis.                                                                |
| Meireles 2008 [19] | 55           | 3                | 15/20                   | Microscopy analysis.                                                                |
| Bayat 2008 [20]  | 60           | 4                | 15                      | Morphometric estimation (histologic estimation) members of types 1, 2, and 3 mast cells, and the total number of mast cells in 100 zones of burned skin. |
| Da Silva D de F 2005 [21] | 20           | 5                | 4                       | Collagen birefringence.                                                            |
| Catto 2015 [22]  | 100          | 5                | 20                      | Histological processing morphological aspects of inflammatory cells and collagen fibers; Quantitative analysis of the collagenization area. |
| Navas 2014 [23]  | 72           | 6                | 12/6                    | Digital photomicrography—massoscopic analysis; Histomorphometric analysis.          |
| Oliveira 2010 [24] | 45           | 3                | 15                      | Histological analysis.                                                             |
| Oliveira 2011 [25] | 90           | 18               | 5                       | Histological analysis.                                                             |
Risk of bias and quality of included studies

Risk of bias was assessed using the SYRCLE Risk of Bias Tool for all 17 studies that met inclusion criteria for our review. None of the experiments were judged to be low risk of bias across all domains. All studies reported similar experimental and control groups at baseline, which reduces the risk of selection bias based on animal characteristics. Despite stating that allocation of subjects to experimental and control groups was random, only one [17] of the studies explicitly described the method of random sequence generation.

Table 3 Study the parameters of photobiomodulation therapy in third-degree burn

For this reason, risk of bias in the sequence generation domain was judged as “High risk of bias” in 94.1% of studies. One result that should be emphasized is that 100% of studies do not adequately described the method used to conceal allocation. Only two [10, 17] of the studies stated that animals were randomly housed. One hundred percent of studies do not reliably report blinding.
of caregivers and investigators from knowing which intervention each animal received. Only 5.8% [4] of studies reported random outcome assessment, but 100% of studies were not documented with the blinding of the outcome assessor. Also it was not clear in 100% of the studies if the incomplete outcome data adequately addressed, i.e., if they were reported that all animals were included in the analysis or even what were the reasons for missing outcome data unlikely to be related to true outcome? (e.g., technical failure). Using the signaling questions provided, all studies were rated as low risk of attrition and reporting bias.

Furthermore, we did not identify any additional sources of bias not already covered by the SYRCLE Risk of Bias Tool, such as industry funding, conflict of interest, or failure to publish in a peer-reviewed journal. With regard to journals where articles were published, 100% are indexed and found in journals with impact factor ranging from 0.931 to 2.7. Of note, none of these studies documented a calculation for sample size (Table 5 Figs. 3 and 4).

Table 4 Classification according to the type of results found in the studies of selected experimental on effects of photobiomodulation therapy on third-degree burn

| Authors               | Positive effect: statistically significant | Positive effect: not significant | Partial effect: statistically significant | No effect |
|-----------------------|--------------------------------------------|---------------------------------|------------------------------------------|-----------|
| Gomes 2017[4]         | X                                          |                                 |                                          |           |
| Brassolati 2016[10]   | X                                          |                                 |                                          |           |
| Trajano 2014[11]      | X                                          |                                 |                                          |           |
| Fiorio 2014[12]       | X                                          |                                 |                                          |           |
| Fiorio 2011[13]       | X                                          |                                 |                                          |           |
| Núñez 2013[14]        | X                                          |                                 |                                          |           |
| Morales 2013[15]      | X                                          |                                 |                                          |           |
| Khoshanrah 2011[16]   | X                                          |                                 |                                          |           |
| Garcia 2010[17]       | X                                          |                                 |                                          |           |
| Mateles 2008[18]      | X                                          |                                 |                                          |           |
| Macielles 2008[19]    | X                                          |                                 |                                          |           |
| Bayat 2008[20]        | X                                          |                                 |                                          |           |
| Da Silva 2006[21]     | X                                          |                                 |                                          |           |
| Caipo 2015[22]        | X                                          |                                 |                                          |           |
| Neves 2014[23]        | X                                          |                                 |                                          |           |
| Oliveira 2010[24]     | X                                          |                                 |                                          |           |
| Oliveira 2011[25]     | X                                          |                                 |                                          |           |
Table 5: Assessment of study quality (Quatr) and Journal and impact factor where selected experimental studies of photobiomodulation therapy on third-degree burn were published

| Authors          | Journal                                      | Impact factor |
|------------------|----------------------------------------------|---------------|
| Gomes 2017 [4]   | Revista da Associação Médica Brasileira       | 0.931         |
| Brasolati 2016 [10] | Microscopy Research and Technique           | 1.147         |
| Trajano 2014 [11] | Lasers in Medical Science                    | 2.229         |
| Fiorio 2013 [12]  | Lasers in Medical Science                    | 2.229         |
| Fiorio 2011 [13]  | Journal of Cosmetic and Laser Therapy        | 1.113         |
| Nuñez 2012 [14]   | Lasers in Medical Science                    | 2.229         |
| Moraes 2012 [15]  | Lasers in Medical Science                    | 2.229         |
| Khoshavaght 2011 [16] | Photomedicine and Laser Surgery            | 1.680         |
| Garcia 2009 [17]  | Lasers in Medical Science                    | 2.229         |
| Meireles 2008 [18] | Photomedicine and Laser Surgery             | 1.680         |
| Meireles 2008 [19] | Photomedicine and Laser Surgery             | 1.680         |
| Bayat 2008 [20]   | Journal Rehabilitation Research & Development | 1.277         |
| Da Silva 2006 [21] | Journal of Biomedical Optics               | 2.700         |
| Catão 2015 [22]   | Lasers in Medical Science                    | 2.229         |
| Neves 2014 [23]   | Lasers in Medical Science                    | 2.229         |
| Oliveira 2010 [24] | Photomedicine and Laser Surgery             | 1.680         |
| Oliveira 2011 [25] | Photomedicine and Laser Surgery             | 1.680         |

Fig. 3 Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies

In this review, studies that mainly focused on the effects of PBMT on experimental lesions caused by third-degree burns were analyzed. No unanimity was detected regarding the used experimental technique or regarding the methods used to measure obtained results. Frequently, different classifications and evaluations were used to designate similar variables. This fact may be related to different analyzed processes, such as healing, inflammation, or even isolated stages of the healing process. Enwemeka et al. [26] stated that such failures are the cause of inconsistencies in
the literature, especially regarding the application of PBMT. Regarding the used models, it should be noted that the burn itself can vary according to used animal for experimentation, as well as according to the time and the method the animal is exposed to heat or even chemical. The most common etiologies requiring care in a burn center are fire/flame (43%), followed by scalds (34%), contact with hot objects (9%), electricity (4%), and chemical agents [27].

A search for an ideal experimental animal model is important for burn research. In our review, we observed that 100% of the evaluated studies used the Wistar rats as the animal model, which is in agreement with what seems to be the most practical and widely used model in other studies. Animal models can replace direct testing in human beings, especially when the toxicity of the test material is unknown. New Zealand rabbits, Sprague-Dawley rats, Wistar albino rats, BALB/c mice, and pigs have been used as animal models in burn research; rats are the most commonly used of all these animals [28].

The form that was used to trigger the burn has an important role in the type of injury and complications triggered after the burn. Of 17 analyzed articles, 23.5% [14, 15, 17, 18] used cylindrical metal systems connected to hot water and 41.1% [4, 10–13, 16, 20] used a heated metal to produce burns; only a small percentage used immersion in hot water [15]. According to Guo et al. [28] and Venter et al. [29], temperature, duration, and contact pressure are the three primary variables needed to achieve a uniform burn. However, these three factors varied greatly or even have not been described in some evaluated studies, indicating a lack of standardization and uniformity in burns induction.

In evaluated studies, a series of analyzed variables were focused on tissue repair (100%) [4, 10–25] and different methodologies were used to evaluate the action of PBMT in various phases of tissue repair. These results demonstrate that most studies still consider that PBMT affect tissue repair (collagen deposition and proliferation of fibroblasts and neoformation of blood vessels) and modulate the inflammatory process. Moreover, some of these studies were focused on the interference of the infection process in the healing of burns. However, we believe that there is a lack of investigations regarding the role of PBMT on inflammatory mediators and oxidative stress following this type of burn, given the evidence in the literature on the action of PBMT and modulation of inflammatory bio-markers [30] and the increase of antioxidant substances [31, 32] during the use of PBMT.

Burn injuries result in various local and systemic responses. In response to injury, a local and systemic release of inflammatory mediators, reactive oxygen species, and reactive nitrogen species occurs, which is often confounded with local infection. Among the circulating vasoactive
and inflammatory mediators are the histamines, prostaglandins, kinins, platelet aggregation factors, angiotensin II, vasopres- sin, and corticotropin-releasing factors, and cell signaling pro- teins, such as cytokines and chemokines [27].

The focus of the current review was to assess the parame- ters of LLLT used during PBMT to improve the healing and inflammatory process in third-degree burns. In this respect, we realized that there is agreement regarding the type of wave- length used in studies, with wavelength ranging from red (632.8 nm; [20, 21] 640 nm; [13, 23] 660 nm; [4, 10–12, 14, 15, 18, 19, 22] and 685 nm [17] nm) to the infrared (780 nm; [18, 19, 22], 890 nm; [16]) and 2000 nm [24, 25] spectrum (82.3% of the studies opted for PBMT operating in the red band). Such an option is because of the depth of the structures to be stimulated, as, according to Oliveira Silva et al. [32], the effective penetration of the tissue by the light and the specific light wavelength absorbed by the photoacceptors are two of the main parameters to be considered in light therapy. In the fabric, there is an optical window running from approximately 650 to 1200 nm, where effective tissue penetration into light is maximized.
In relation to the power of the lasers, a very large variation was detected, ranging from 10 to 100 mW. Few studies reported the energy, beam area, exposure time, and power density of used lasers. We consider the lack of these parameters a great failure, hindering or preventing the reproducibility of the studies. The absence of these parameters weakens the studies once the literature has shown that the results of PBMT depend on the irradiation time and used dose. If we take into account the fact that different areas of beam and powers need different irradiation times and energy densities, the reproducibility of these studies is threatened [33].

PBMT has demonstrated positive effects in stimulating cellular activities involved in the wound healing process. The action of PBMT is based on the absorption of light by the tissues, which generates modifications in cellular metabolism and alter the exchange of calcium through the cell membrane. These PBMT-promoted alterations may enhance the synthesis of DNA, RNA, and cell cycle regulatory proteins, stimulating cell proliferation and connective tissue reestablishment during tissue repair and wound healing [34].

The small number of studies for third-degree burns does not allow us to affirm that there is clear scientific evidence of the benefits of PBMT in this type of burn. Bjordal et al. [35] reports that evidence for most interventions lack sufficient statistical power to make valid conclusions. However, on the other hand, if we follow the results presented by the studies included in this review, we may suggest that photobiomodulation is an effective short-term approach to accelerate the healing of wounds caused by third-degree burns, modulate the inflammatory process, increase deposition of type I and III collagen, and downregulate matrix metalloproteinases.

Moreover, the parameters used for PBMT in the examined studies, such as laser output power, irradiation distance, irradiation frequency per day, number of treatment sessions, irradiated energy per day, and total irradiated energy, did not meet the current recommendations for reproducible studies. (Inflammatory phase, proliferation and remodeling) and modulation of the inflammatory process (chemokines, growth factor cytokines), in third-degree burns. In conclusion, it is important to note that PBMT is an effective short-term approach for third-degree burns. However, the lack of uniformity in the terminology used to describe parameters and the dose used for PBMT limits the ability to reach firm conclusions.

According to Khatib et al. (2015) [36], in general, animal studies in comparison to human RCTs have low internal validity as well as standard practice to randomize allocation of the animal to the intervention and control arms and to blind the investigators and outcome assessors. However, some systematic reviews of animal studies show that a similar effect of an intervention can be found over a number of species/strains which suggests that there is a high probability that it can be
extrapolated to humans. The quality of the included studies varied widely; none of the included studies exhibited an overall low risk of bias in all criteria analyzed by the SYRCLE Tool, while the bulk of the remaining experiments ranged in the unclear risk of bias. This fact is rather sobering, when placed in the context of potential translational applications of the evaluated interventions. De Vries et al. [37], describes the importance of systematic reviews of animal experimental studies as a precursor for the implementation of subsequent preclinical and clinical studies. However, there is a problem in systematic review of animal studies. Negative results are often not published, leading to publication bias.

In conclusion, it is important to note that PBMT is an effective short-term approach for third-degree burns. However, the lack of uniformity in the terminology used to describe parameters and the dose used for PBMT and the risk of vies in the methodological conduction of some studies limits the ability to reach firm conclusions.

COMPLIANCE WITH ETHICAL STANDARDS
Conflict of interest The authors declare that they have no conflict of interest.
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