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Effects of Low-Level Light Therapy (LLLT) on Oxidative Stress in the Cutaneous Healing Process: A Literature Review

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Abstract

Introduction: Photobiomodulation (PBM), initially called low-level light therapy (LLLT), is defined as the application of radiation in the form of light for healing since it can modify the cell's behavior to facilitate repair of the tissue. The objective of this review study was to research the known effects of the LLLT on oxidative stress, as well as mitochondrial activity, in the cutaneous healing process.

Methods: We included experimental animal studies that evaluated the effects of the LLLT on the oxidative stress related to the cutaneous healing process. In December 2023, research into the literature was conducted in the following databases: PubMed, Embase, and Web of Science. The methodological quality of the studies was evaluated by the adapted PEDro scale. Additionally, a qualitative and descriptive analysis of the included studies was made.

Results: Nine studies were included, and all the articles presented significant modulation of oxidative stress, with reductions in oxidizing markers (superoxide anion) and apoptosis activators (cytochrome c), and mainly, increases in antioxidant enzymatic defense (catalase, superoxide dismutase, and glutathione peroxidase).

Conclusion: LLLT represents a technique with promising results in the improvement and acceleration of the cutaneous healing process, as well as in the regulation of biochemical reactions related to oxidative stress of the treated areas. Despite that, more studies focusing on the central role of mitochondria in explaining the therapeutic effects of LLLT are necessary.

Keywords: LLLT, Cutaneous healing, Oxidative stress, Mitochondrial activity

Introduction

Photobiomodulation (PBM), initially called Low-Level Light Therapy (LLLT), is defined as the application of radiation in the form of light for healing since it can modify the cell's behavior to facilitate repair of the tissue. It is considered a light type which is non-ionizing, monochromatic, collimated, and coherent.[1,2] Some parameters, such as wavelength, potency, energy density, and time of applied light, must be considered for the application to be effective.[3,4]

Nowadays, this therapy is used to accelerate the healing process, provide a better quality of life to the patients, and optimize the treatment of cutaneous injuries.[3] According to some studies, there is evidence that LLLT can promote the reepithelialization of chronic wounds, accelerate healing, and reduce pain.[2,4,5] This evidence seems to corroborate the conclusions of de Castro et al,[6] which evidenced that the effects of LLLT alter cellular behavior, recruiting epithelial cells on a large scale, thus favoring tissue repair.

It is important to highlight that injury repair also activates inflammatory and oxidative mediators, such as cytokines, reactive oxygen species (ROS), and free radicals (FRs), that cause oxidative effects on the tissue. These radicals can generate mitochondrial membrane damage and activate protein cytochrome c to induce cellular apoptosis.[7-9] ROS have a role in both pathogen defense and cell signaling, but when produced in excess, they may generate oxidative stress, resulting in cell damage.[10]

Thus, some mechanisms involved in the scar response, such as the effects of LLLT on mitochondrial respiratory and oxidative stress markers, are not yet known. Some evidence suggests that the mitochondria of the exposed cells absorb photons emitted by LLLT, stimulating the ATP level and reducing the levels of ROS.[11] Other consistent studies also address that the modulation of the inflammatory processes occurs through mechanisms that

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include the regulation of the biochemical markers' levels, controlling the activity of neutrophils and attenuating the action of oxidative stress.[12]

Cutaneous healing is a physiological process, both complex and necessary. The major problem is the intense inflammatory/oxidative reactions resulting from the excessive production of ROS, which causes the tissue's oxidation that may create irreversible cell damage. There is well-defined evidence that LLLT can accelerate and favor cutaneous healing, conferring anti-inflammatory properties. Lima et al[13] present that some studies estimate that 1.05% of the general Brazilian population has some types of wounds. Furthermore, LLLT is a non-pharmacological therapy, so it does not present the adverse effects of some pharmaceuticals and is a viable, safe therapy with the potential to intervene in this problem effectively.

In this context, this study offers an overview of the LLLT applications in the cutaneous healing process, given the current lack of literature that presents this panorama, aiming to analyze scientific studies that demonstrated oxidative changes in cellular metabolism after skin injuries, as well as the potential therapeutic effects of LLLT.

Methods

This systematic review was conducted according to the PRISMA 2020 Statement: an updated guideline for reporting systematic reviews.[14]

The inclusion criteria were as follows: experimental studies conducted on animals; articles published in all periods; articles published in Portuguese, English, French, and Spanish languages; and studies that evaluated the LLLT effect on cutaneous healing and oxidative stress in animals. The following were excluded: systematic or literature review articles; instrument validation articles; case-control and cohort studies; studies that did not utilize LLLT therapy to evaluate cutaneous healing and oxidative stress; abstracts and summaries of scientific articles for events; and scientific articles that used human models in their research.

The search for articles was conducted in the online databases of PubMed, Embase, and Web of Science until December 19th of 2023, without restriction for the year of publication, based on the following combination of descriptors and Boolean: (LLLT OR photobiomodulation) AND ("skin healing") OR ("wound healing") AND ("oxidative stress") OR ("reactive oxygen species"). After searching the databases, we removed duplicate articles and read the titles and abstracts of the studies, along with the exclusion of irrelevant articles. The remaining articles were read in full to check whether they met the inclusion criteria. The screening and selection of studies were made by two independent reviewers (PF and NS), using EndNote x7® software. In case of disagreements, a third reviewer was consulted for consensus.

The methodological quality of the studies was evaluated by the adapted PEDro scale, which presents positive levels of reliability and validity. The scale is composed of 11 items that evaluate the methodological quality of clinical trials. The item responses are scored as yes = 1 or no = 0, and the maximum score obtained by summing is 10. Criterion number 1 is not considered for the final score as it is an item that assesses the external validity of the study. Clinical trials with a score greater than 6 were considered to have a lower risk of bias, and studies with a score of less than or equal to 6 were considered to have an elevated risk of bias [15]. The selected studies were analyzed qualitatively through descriptive analysis.

Results

A total of 559 articles were found, and of these, 107 were found in PubMed, 238 in Embase, and 214 in Web of Science. According to the eligibility criteria, 9 articles were selected to construct this review, as shown in Figure 1.[16-24]

Table 1 presents the scores of the methodological qualities through the adapted PEDro scale. We can verify that the average score on the PEDro scale was 7,0 points, indicating an overall average of low risk of bias among the analyzed studies.

In Table 2, general information about the selected studies [16-24] is presented: Study identification (author/year/location); the Animal sample characterization (species/gender/size); the study design (experimental groups organization); and the type of injury (size/location).

Table 3 presents information concerning the oxidative stress markers analysis performed in the selected studies, as well as the main results found by the authors.

Discussion

This systematic review of published studies was related to the effects of LLLT therapy on oxidative stress resulting from cutaneous healing. It was possible to identify nine original scientific studies approaching the effects of LLLT on oxidative changes resulting from experimental models of scar injury in rats.

It is established that, in order to repair the injured tissue, several cellular and biochemical reactions occur. As a result, increased levels of ROS are expected as a natural and appropriate consequence of inflammation. However, whenever the ROS levels exceed the cell antioxidant defense system capacity to scavenge, then a state of oxidative stress begins. Mitochondria play a key role in aerobic metabolism, and the dysfunction of these organelles is associated with oxidative stress status establishment.[25]

In this review, it was possible to observe that, after skin lesions, an increase in oxidative stress as well as alterations in the skin's mitochondrial functionality occurred. Increased levels of oxidative markers (such as TBARS, DCFH, O_2^-, nitrate, and carbonylated protein) and changes in the cellular antioxidant defense systems (both

Table 1. Score of the Included Studies (n = 9) Presented by the First Author of Each Article and Year of Publication

PEDro Scale Items	Hartmann et al[23] 2021	Karkada et al[18] 2021	Keshri et al[20] 2019	Ahmed et al[22] 2018	Denadai et al[21] 2017	Silveira et al[19] 2016	Tatmatsu-Rocha et al 2016	Gonçalves et al[17] 2013	Silveira et al[16] 2011
1. *Specified eligibility criteria	*Y	*Y	*Y	*Y	*Y	*Y	*Y	*Y	*Y
2. The animals were randomly divided into groups by the treatment received	Y	N	Y	Y	Y	N	Y	Y	Y
3. The allocation of the animals was secret	Y	N	Y	Y	Y	N	Y	Y	Y
4. Initially, the groups were similar in the most important prognostic indicators	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. All study evaluators participated blindly	Y	N	N	Y	Y	N	Y	N	N
6. All therapists administered the therapy blindly	N	N	N	N	N	N	N	N	N
7. All evaluators who measured a key result did so blindly	N	N	N	N	N	N	N	N	N
8. Initially, the measurement of at least one key result was obtained in more than 85% of the animals	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. All groups of animals that showed results received the treatment or the control condition according to the allocation	Y	Y	Y	Y	Y	Y	Y	Y	Y
10. The results of the statistical comparisons between groups were described for at least one key result	Y	Y	Y	Y	Y	Y	Y	Y	Y
11. The studies presented both measures of treatment precision (effects) and measures of variability for at least one key result	Y	Y	Y	Y	Y	Y	Y	Y	Y
Total (0-10)	8	5	7	8	8	5	8	7	7

Y (yes), N (no); Y = 1 and N = 0. * Criterion 1 is not considered for the final score as it is an item that assesses the external validity of the study.

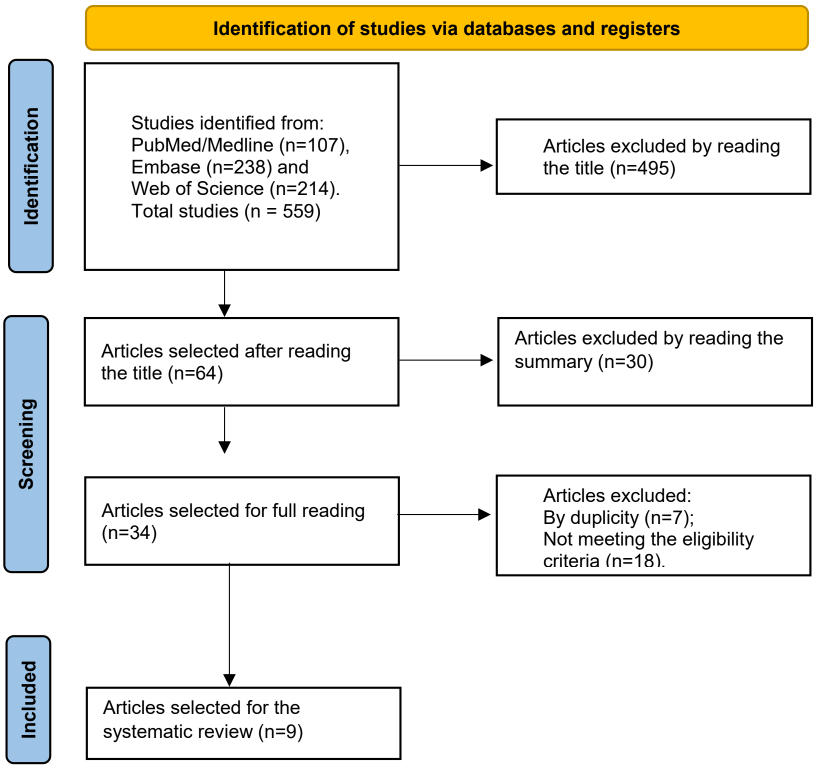

Figure 1. Flowchart of the Number of Articles Found and Selected After Applying the Inclusion and Exclusion Criteria

in the antioxidant enzyme activities - CAT, GPx, and SOD; and non-enzymatic GSH levels) were observed. Moreover, signs of mitochondrial dysfunction were noted by increased levels of cytochrome c leakage, which is also an indicator of cell apoptosis. According to Takeyama et al,[26] it is known that oxidative stress provokes damage in the mitochondrial membrane, which, consequently, releases cytochrome c in the cytosol, initiating a complex cascade

Table 2. Study Identification (Authors/Year/Location of the Study), Animal Sample (Specie, Gender and Size), Study Design; and Type of Cutaneous Injury

Study Identification (Authors/Year/Location)	Animal Sample (Specie/Gender/Size)	Study Design (Experimental Groups)	Type of Injury (Size/Location)
Hartmann et al[23]/ 2021/ Brazil	Wistar rats/male/120 animals (n = 6 per experimental group)	Control: no Injury and no Treatment; Sham: no Injury and AlGaInP (660 nm) 20 J/cm² LLLT; Injury: no LLLT treatment; Injury + AlGaInP (660 nm) 20 J/cm² LLLT	15 mm diameter and 5 mm deep skin wound/animal's back (between the shoulder blades)
Karkada et al[18]/ 2021/ India	Wistar rats/male/18 animals (n = 9 per experimental group)	Injury: no LLLT treatment; Injury + Combined Red (655 nm) 4 J/cm² + Infrared (808 nm) 4 J/cm² LLLTs	2 mm diameter skin wound/animal's back (between the shoulder blades)
Keshri et al[20]/ 2019/ India	Sprague Dawley rats/male/48 animals (n = 12 per experimental group)	Control: no Injury and no Treatment; Injury: no LLLT treatment; Injury + AlGaAs (810 nm) 22,6 J/cm² (continuous) LLLT; Injury + AlGaAs (810 nm) 22,6 J/cm² (10 Hz) LLLT; Injury + AlGaAs (810 nm) 22,6 J/cm² (100 Hz) LLLT	15 mm diameter skin wound/ animal's back (between the shoulder blades)
Ahmed et al[22]/ 2018/ Egypt	Albino rats/male/30 animals (n = 10 per experimental group);	Control: no Injury and no Treatment; Injury: no Treatment and Injury; Injury + HeNe (660 nm) 6.4 J/cm² LLLT	2 mm² skin wound/animal's back (between the shoulder blades)
Denadai et al[21]/ 2017/ Brazil	Wistar rats/male/18 animals (n = 9 per experimental group)	Injury: no Treatment and Injury; Injury + AlGaInP (660 nm) 6 J/cm² LLLT	2 mm² skin wound/animal's back (between the shoulder blades)
Silveira et al[19]/ 2016/ Brazil	Wistar rats/male/60 animals (n = 10 per experimental group)	SHAM: no Injury and no Treatment; Injury: no LLLT treatment; Injury + AlGaInP (660 nm) 3 J/cm² LLLT; Injury + AlGaInP (660 nm) 10 J/cm² LLLT; Injury + LED (632 nm) 160 J/cm²; Injury + LED Infrared (850 nm) 160 J/cm²	Burn skin injury (metal plate 100 ºC, 10s contact)/animal's back (between the shoulder blades)
Tatmatsu-Rocha et al[24]/ 2016/ Brazil	Swiss albino mice/male/10 animals (n = 5) per experimental group)	Injury: No treatment and injury; Injury + GaAs (904 nm) 18.3 J/cm² LLLT	2 mm² skin wound/animal's posterior iliac crest
Gonçalves et al[17] / 2013/ Brazil	Wistar rats/male/24 animals (n = 8 per experimental group)	Injury: no LLLT treatment; Injury + GaAsAl (830 nm) 30 J/cm² LLLT; Injury + GaAsAl (830 nm) 90 J/cm² LLLT	12,5 mm diameter skin wound/ animal's back (between the shoulder blades)
Silveira et al[16] / 2011/ Brazil	Wistar rats/male/30 animals (n = 6 per experimental group)	Injury: no LLLT treatment; Injury + HeNe (660 nm) 1 J/cm² LLLT; Injury + HeNe (660 nm) 3 J/cm²LLLT; Injury + GaAs (904 nm)1 J/cm² LLLT; Injury + GaAs (904 nm) 3 J/cm² LLLT	8 mm diameter skin wound/animal's back (between the shoulder blades)

LLLT: Low level laser therapy; LED: Light emitting diode; HeNe: Helium-neon; GaAs: Gallium-arsenide; GaAsAl: Gallium-aluminium-arsenide; AlGaInP: Aluminium-gallium-indium-phosphorus; AlGaAs: Aluminium-gallium-arsenide.

of molecular reactions that culminate in cell apoptosis.

The results of LLLT therapy, observed in the studies, vary since the parameters differ, ranging from wavelengths of 655 nm to 904 nm and energy densities of 1 J/cm² to 90 J/cm². They can be organized in two ways: (1) reducing oxidative/apoptotic levels, and (2) improving the cell antioxidant systems. In the present review, LLLT therapy was clearly related to oxidative stress modulation. Studies in the literature suggest that inflammatory reactions after injuries are accelerated by LLLT, modulating the levels of oxidative damage markers and also resulting in an increase in the production of mitochondrial ATP.[24,27-31] The significant reduction of the protein cytochrome c leakage, shown in this review,[32] suggests that LLLT presents an anti-apoptotic action. This result is also corroborated by Salehpour et al's study,[33] where LLLT (810 nm) reduced the caspase enzyme activation, which is a well-known route of cellular apoptosis. Despite that, the effects of LLLT on the specific functioning of the mitochondrial electron transport chain are still unknown. The potential effects of LLLT on mitochondrial functionality can reveal its therapeutic mechanism of action.

The effects of LLLT on cellular enzymatic antioxidant defense systems, presented in this review, have been the most extensively studied topic to date. SOD, GPx, and CAT activities are clearly modulated by LLLT, pointing towards a direction of reduction in oxidative stress present in tissue healing.[26,31,33-38] It is important to mention the light emitting diode (LED) as another technique used for PBM purposes. The LED, as well as LLLT therapy, was also effective in reducing ROS levels during the acute phase of muscle injury and epithelial injury, thus acting as a modulator of oxidative stress.[28,37,38] Despite some biophysical similarities between LLLT and LED, few studies have explored the potential therapeutic effects of an LED on the state of oxidative stress resulting from tissue injuries.

It is possible to highlight, as a limitation of this review, the small number of studies suitable for inclusion. Furthermore, the experimental trials did not standardize

Table 3. Type of LLLT used in the studies, intervention conducted, which antioxidant and oxidative stress markers were evaluated, and the results

Study identification (authors/year/location)	Oxidative stress markers analysis	Main Results
Hartmann et al[23]/ 2021/ Brazil	SOD and CAT antioxidant enzymes activities; and GSH levels (skin); TBARS and DCFH levels (skin); Mitochondrial dehydrogenase enzymes activity (MTT reduction assay) (skin)	- Skin injury determined significant increase in TBARS and DCFH levels; also increased SOD and CAT activities; - AlGaInP (660nm) LLLT reduced oxidative stress markers (TBARS and DCFH levels) and modulated (avoiding the increase) SOD and CAT enzyme activities; and also increased MTT reduction levels;
Karkada et al[18]/ 2021/ India	CAT antioxidant enzyme activity (skin); TBARS levels (skin)	- The combined treatment with Red (655nm) and Infrared (808nm) LLLT increased CAT activity and reduced TBARS levels after injury
Keshri et al[20]/ 2019/ India	Cytochrome c leakage (serum)	- Significant increase in Cytochrome c leakage after lesion (without LLLT); - AlGaAs (810nm) LLLT (at continuous, 10Hz or 100Hz conditions) reduced significantly Cytochrome c leakage after lesion
Ahmed et al[22]/ 2018/ Egypt	GSH levels (serum); TBARS levels (serum)	- Skin injury determined significant increase in TBARS and decrease in GSH levels; - HeNe (660nm) LLLT did not change TBARS and GSH levels
Denadai et al[21]/ 2017/ Brazil	TBARS levels (skin)	- AlGaInP (660nm) LLLT reduced TBARS levels
Silveira et al[19]/ 2016/ Brazil	GPx and CAT antioxidant enzymes activities; and GSH levels (skin); O_2^{-}; Nitrite; Carbonyl protein; and DCFH levels (skin)	- $O_2^{-\cdot}$ Nitrate, Carbonyl protein, and DCFH levels, and also GPx and CAT activities, were increased; while GSH was reduced after lesion (without treatment); - Infrared LED (850nm) and AlGaInP (660nm) LLLT reduced O_2^{-}, Nitrite, Carbonilated protein, and DCFH levels, and also GPx and CAT activities; and also increased the GSH levels
Tatmatsu-Rocha et al[24]/ 2016/ Brazil	CAT antioxidant enzyme activity (skin); TBARS and Nitrite levels (skin)	- GaAs (904nm) LLLT increased TBARS levels and CAT activity; and decreased nitrite levels
Gonçalves et al[17] / 2013/ Brazil	CAT antioxidant enzyme activity (skin); TBARS levels (skin)	- TBARS levels were significantly increased after injury in control conditions (without LLLT); - The treatment with GaAs (90 J/cm²) LLLT increased the CAT activity and reduced TBARS levels in the 7th and in the 14th days after injury
Silveira et al[16] / 2011/ Brazil	SOD and CAT antioxidant enzymes activities (skin); TBARS and Carbonyl protein levels (skin).	- SOD and CAT activities, and also TBARS and Carbonyl protein levels were significantly increased in the 5th day after injury in control conditions (without LLLT); - The treatment both with HeNe (1 J/cm²) and GaAs (1 J/cm²) LLLT reduced significantly the SOD and CAT activities, and also the TBARS and Carbonyl protein levels in the 5th day after injury.

LLLT: Low level laser therapy; LED: Light emitting diode; HeNe: Helium-neon; GaAs: Gallium-arsenide; GaAsAl: Gallium-aluminium-arsenide; AlGaInP: Aluminium-gallium-indium-phosphorus; SOD: Superoxide dismutase; CAT: Catalase; GPx: Glutathione Peroxidase; TBARS: Thiobarbituric acid reactive substances; DCFH: Oxidized dichlorofluorescein; GSH: Reduced glutathione; O_2^{-} Superoxide anion.

the parameters for LLLT, making it difficult to summarize the results in a review.

Conclusion

LLLT has proven to be a technique with promising results for improving and accelerating the cutaneous healing process, as well as regulating the biochemical reactions related to oxidative stress in the treated areas. Despite this, the explanation for the mechanisms of these effects is still unclear, showing us the necessity of more studies focusing mainly on mitochondrial analysis. Therefore, it is necessary to conduct in-depth experimental studies that analyze the LLLT effects on mitochondrial cell activity, both in normal situations and in healing conditions.

Authors' Contribution

Conceptualization: Jaíne Dalmolin, Gustavo O. Puntel.
Data curation: Jaíne Dalmolin, Danielli S. da Silva, Cecília C. Pimentel, Eduarda R. Kozoroski, Gustavo O. Puntel.
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Investigation: Paola F. Irber, Jaíne Dalmolin.
Methodology: Paola F. Irber, Jaíne Dalmolin, Felipe B. Schuch, Gustavo O. Puntel.
Project administration: Gustavo O. Puntel.
Resources: Gustavo O. Puntel, Felipe B. Schuch.
Software: Paola F. Irber, Felipe B. Schuch.
Supervision: Gustavo O. Puntel, Felipe B. Schuch.
Validation: Gustavo O. Puntel, Felipe B. Schuch.
Visualization: Paola F. Irber, Jaíne Dalmolin, Danielli S. da Silva, Cecília C. Pimentel, Eduarda R. Kozoroski, Felipe B. Schuch, Gustavo O. Puntel.
Writing–original draft: Paola F. Irber.
Writing–review & editing: Jaíne Dalmolin, Danielli S. da Silva, Cecília C. Pimentel, Eduarda R. Kozoroski, Gustavo O. Puntel.

Competing Interests

None to declare.

Ethical Approval

Not applicable.

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