Vol.67: e24220678, 2024
https://doi.org/10.1590/1678-4324-2024220678
ISSN 1678-4324 Online Edition

BABT
Brazilian Archives of Biology and Technology

Review - Human and Animal Health

Efficacy of Acute and Long-Term Photobiomodulation Therapy on Fatigue and Muscle Performance in Different Animal Models: a Systematic Review

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Editor-in-Chief: Paulo Vitor Farago
Associate Editor: Paulo Vitor Farago

Received: 21-Sep-2022; Accepted: 08-Nov-2023

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HIGHLIGHTS

- Experimental studies with animal models confirm decreased from fatigue, through fatigue protocols induced with PBMT.
- PBMT is able to improve muscle recovery and performance in animal models.
- Infrared wavelength is the wavelength most used for fatigue in animal models.
- It needed standardization to PBMT parameters due to the many different energy density, wavelength and number of therapy sessions found, in order to indicate the most efficient protocol of PBMT.

Abstract: Muscular fatigue is associated with repeated muscle contraction exercises and with intense use of muscles with high intensity leading to a decline of performance and inability to continue with the same activity original intensity of activity. One of most promising interventions is the photobiomodulation therapy (PBMT). The objective was to analyze the results of the studies that investigated the effects of acute and long-term photobiomodulation in experimental animal models of muscle fatigue levels. The review was registered with PROSPERO (CRD42021274444). 10 studies were identified (n=366 animals). 77% used histological analysis and blood level of lactate measures to record changes in fatigue and were considered

moderate evidence. Nine chose isotonic contractions and one study opted for isometric contraction to induce fatigue. 77% applied long term PBMT and 33% applied an acute form. Most of the studies used the infrared wavelength; the power output varied from 0.625mW to 300mW and energy per point varied from 0.105J to 12J. This review demonstrates that PBMT has positive effects in acute and long-term treatment decreasing the level of fatigue and accelerating exercise performance in different animal models, even with distinct PBMT parameters and number of therapy sessions

Keywords: muscle fatigue; systematic review; performance; low-level laser therapy; animal models.

INTRODUCTION

Fatigue is characterized by a normal response of the body to physical exhaustion due to an excess of activity such as exercise or a sign of a physical disorder [1]. In healthy individuals, fatigue results from inappropriate perfusion of tissue blood reducing energy provided during and/or after extended muscle contractions and intense activity [2,3] that leads to decreases of muscle performance [3]. Conversely, the fatigue associated to a disease, such as myalgic encephalomyelitis or fibromyalgia for example, is a tiredness and lack of energy, which may be related to exercise or resting, may persist (chronic fatigue) and manifests negative impact on quality of life [1].

In case of heathy individuals' fatigue, it causes a progressive decrease in muscle performance/activity and is not immediately apparent, and eventually manifests an inability to continue the original activity intensity [4, 5]. In older individuals, the fatigue may have a higher impact due to muscle wasting mediated by muscle atrophy with aging (sarcopenia) [6].

In this context, many studies have been investigating the causes and therapeutical interventions able to manage its deleterious effects. Among those, low-level laser therapy (LLLT), or more recently photobiomodulation therapy (PBMT), have appeared as important interventions that are capable of attenuating fatigue levels. PBMT has been shown to interact with biological tissues, promoting a stimulation of tissue metabolism, producing an increase in the muscle energy and improving muscle performance in animal and human research [7, 8, 9].

Some studies have demonstrated that PBMT produces high levels of energy (ATP) in cells due to metabolic and structural changes. PBMT acts on cytochrome c oxidase leading to an increased synthesis of ATP, a release of ions such as calcium, and production of nitric oxide (NO) production, stimulating cell metabolic activity [10]. All of these metabolic modifications can contribute to fatigue recovery process.

Moreover, a recent systematic review highlighted that PBMT applied after or before physical exercise was capable of increasing antioxidant enzymes and of reducing the muscle's inflammatory mediators [11]. Thus, a decrease of fatigue during physical exercise programs and an improvement of muscular performance could be beneficiaries with these physiological effects [2]. These effects provide the justification to study whether PBMT can prevent the increase of skeletal muscle fatigue and improve muscle performance.

In addition, the efficacy of PBMT on muscle fatigue is not clarified yet and the use of different protocols of physical exercise and different parameters make it difficult to compare the results. The purpose of the present investigation was to conduct a systematic review of studies from literature to analyze the effects of PBMT on improving muscle fatigue and muscle performance in animal models.

Thereafter, this review discusses the results of experimental papers of the literature in this area with the objective to promote a better comprehension of the effects of PBMT on fatigue and muscle performance.

MATERIAL AND METHODS

Review protocol

An active search in bibliographic reference was made including articles of present study. The search was conducted in September and October of 2020 using PubMed, Embase and Scopus databases. The search was implemented according to the orientations of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Thus, descriptors of the Medical Subject Headings (MeSH) were defined: "photobiomodulation" OR "low level laser therapy" OR "laser therapy" AND "muscle" AND "exercise" AND "performance". Additionally, the "Other Animals" filter was applied so that the articles searched were restricted to animals. This systematic review was registered on the online international prospective register of systematic reviews (PROSPERO) of the National Institute for Health Research (under the number CRD42021274444).

Study selection

Two reviewers analyzed independently, the title and the abstract of the selected works and identified the potential studies from the inclusion and exclusion criteria. Furthermore, 2 reviewers had access to the selected studies to verify the eligibility. Disaccords were solved by discussion. The selected studies were further reviewed during the full-text screening. Thus, the studies that did not follow the eligibility criteria were excluded.

Inclusion criteria

1. In vivo experiments with animal models;
2. Animals with age ≥ 4 weeks;
3. Use of PBMT as acute and long-term;
4. Articles must be written in English language and published in the last 30 years.

Exclusion criteria

1. Clinical trials, reviews, case reports, white papers, abstracts, dissertations, theses, in vitro studies, and in situ studies;
2. Studies that did not use PBMT as treatment;
3. No fatigue-induced OR no PBMT used;
4. Animal models with other systemic variables (such as osteoporotic, diabetic).

Data extraction

The analyzed variables were muscle oxidative stress, damage and inflammation; activities of citrate synthase (CS), creatine kinase (CK), lactate dehydrogenase (LDH) and the anaerobic threshold (AT); biochemical markers and morphology of skeletal muscle analysis. In addition, the remaining variables were also extracted: such as author, species/strain, animal sex, age, weight, PBMT parameters, physical exercise protocol, way of treatment, analysis performed and outcome measures.

Types of Reported Results

Due to the heterogeneity of the primary studies, it was not possible to perform a meta-analysis. Quality of the body of evidence was determined using the GRADE approach, which analyses the following domains: trial design limitations due to risk of bias (utilizing the PEDro score), inconsistency of results, indirectness, imprecision of results, and publication bias.

RESULTS

The flow diagram demonstrated the search strategy used in the present study (Figure 1). A total of 35 articles were retrieved from the databases (15 from PubMed, 8 from Embase and 12 from Scopus). Then, the duplicated records were excluded (n=20). Thus, 15 records were screened and 5 were excluded. Finally, 10 full-text articles were assessed for eligibility.

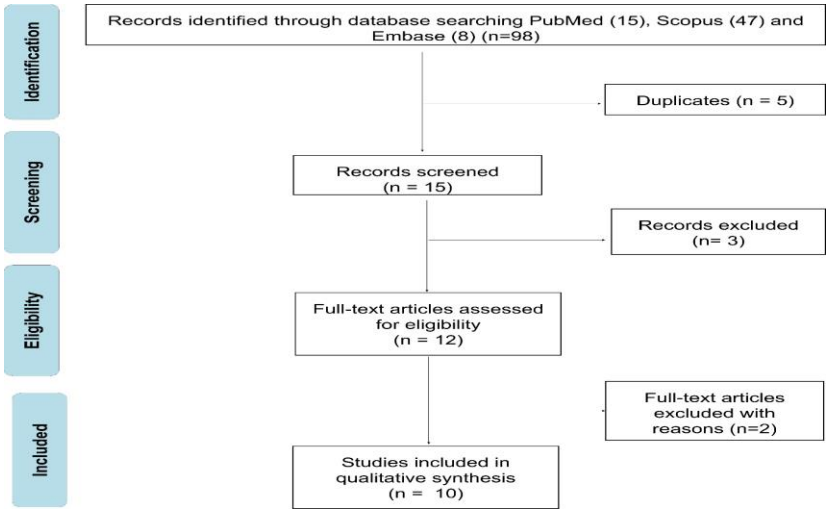

Figure 1. PRISMA flow diagram of search strategy.

Table 1 shows the characteristics of all included studies, such as author, sample size, species, animal sex, age, body mass and outcomes analyzed. Among the articles analyzed, the smallest sample size was composed of 24 [12] and the larger had 69 animals used in 2 experimental protocols [13], with a total of 366 animals. In addition, 8 studies used Wistar rats as experimental models [12, 13, 14, 15, 16, 17, 18, 19] and 2 studies used mdx mice (C57BL/10ScSn-Dmdmdx/J mice and C57BL/10ScSn mice) [20, 21]. In addition, 6 studies used male animals [12, 15, 16, 17, 18, 19], 2 used female animals [13, 14] and 2 studies have not included the information [20, 21]. The experimental animals were a minimum of 4 weeks and a maximum of 4 months old [17, 21] and only 1 study did not include this information [19] (Table 1). According to the selected studies, the variables analyzed were lipid peroxidation makers, synthesis of oxidized proteins, catalase enzyme [14], LDH, skeletal muscle macrophage infiltration, gene expression of tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), interleukin 1 beta (IL1-β), interleukin 10 (IL-10), cytokine-induced neutrophil chemoattractant-1 (CINC-1), and monocyte chemoattractant protein-1 (MCP-1) [13], superoxide dismutase enzymes [14, 21], CK [13, 19, 21], carbonyl protein [21], blood levels of lactate [12, 13, 15, 17, 18], morphometry and histology of muscles [12, 18, 20, 21], protein quantification of dystrophin [20], physical and muscular performance [12, 13, 16, 19, 20], citrate synthase activity [15], myogenin expression [12], oxygen consumption [16], heart rate variability [17], matrix metallopeptidase 2 (MMP-2) gene expression [21], body mass [16, 17, 18], glycogen [18], COX-1 and COX-2 expression [19].

Table 2 shows the animal groups included in each study, the area of PBMT application and the protocols of intervention. Concerning the PBMT region of application, 4 studies applied PBMT to the gastrocnemius muscle [12, 14, 16, 21], 6 studies on the tibialis anterior muscle [12, 15, 17, 18, 19, 20], and 1 study did not specify the application area [13]. All the studies applied PBMT using the contact technique mode, in different sessions of application (acute and long-term PBMT application [12, 15, 16, 17, 18, 20, 21].

Related to intervention protocol, 1 study applied PBMT before the exercise protocol session, composed of 4 climbing bearings with the maximum load and with 2 minutes of interval between each climb [14]. In addition, de Oliveira and coauthors [13] applied PBMT before and after the exercise protocol and De Almeida and coauthors [19] applied PBMT before the fatigue protocol induced by electrical stimulation.

Regarding the studies using a long term PBMT treatment, all of them applied PBMT immediately after the exercise protocol [12,15-18]. Concerning the exercise protocols used by these studies, de Brito Vieira and coauthors [15] applied the aerobic treadmill training protocol daily over 5 weeks. Paolillo and coauthors [17] used High Intensity Training (HIT) protocol performed on a ladder where the animals climbed with an external load attached to their tail (24 training sessions, 3 times per week for 8 weeks). Assis and coauthors [12] used an endurance training performed on a treadmill 1 hour per day, 5 days per week for 8 weeks. Perrini and coauthors [16] submitted the animals to a maximum exercise regime constituted of a metabolic treadmill. Finally, Patrocinio and coauthors [18] used a resistance training protocol (climbing exercises with an external load fixed on the tail, 3 times per week for 5 weeks). Only Albuquerque-Pontes and coauthors [20] and Silva and coauthors [21] did not associate PBMT with an exercise protocol. The protocols of intervention varied from 1 session [13, 14, 19] to 14 weeks [20].

Moreover, most of the articles used low level laser therapy (LLLT) and only one used light-emitting diode therapy (LEDT) [20] (Table 3). The most common wavelength employed was the near-infrared laser irradiation (used by all studies), in a range from 808nm [12, 18, 21] to 905nm [20]. However, the study of Albuquerque-Pontes and coauthors [20] used the association of infrared (875nm) and red (640nm) wavelengths with a cluster device. The energy density varied from 0.525 [19] to 428.4 J/cm2 [14] with a mean of 96.71J/cm2. Five studies used more than one energy density according to different energies per site [13, 14, 16, 19, 20]. The lowest energy per point was 0.15 J [15, 17] and the highest energy per point was 12 J [14] with a mean of 3.34 J. Total energy delivered was from 0.105 J [19] to 24 J [13]. In addition, the power density per diode observed among the studies was from 0.0375 W/cm² [15] to 1071 W/cm² [21]. The mean value of the power density per diode was almost 2.5 while the power output ranged from a minimum of 0.625mW to a maximum of 300mW.

Spot size varied from 0.028cm2 [13, 14, 18, 21] to 0.2 cm² [19], with a spot size average of 0.06cm². The number of treated points or sites was in a range from 1 [19, 21] to 12 [16] and their irradiation time ranged between 1 [16] to 200 seconds [19]. There was a minimal of 1 session [13, 14, 19] and a maximal of 42 sessions [20] (Table 4).

The quality of evidence for PBMT on fatigue levels in experimental models according to the GRADE approach is presented in Table 5. The methodological variables analyzed by GRADE in the studies contained in this review were: histological analysis and blood lactate level. For both variables, the level of evidence was moderate, suggesting an effectiveness of PBMT in muscle performance.

Table 1. General characteristics of the experimental animals and analyses

Authors	Sample size	Species	Animal sex	Age	Body mass (g)	Analysis
dos Santos et al. [14]	36	Wistar rats	Female	12 weeks	200 - 250	physical performance, Western blot (protein concentration), lipid and protein peroxidation and enzymatic activity (catalase and superoxide dismutase)
de Oliveira et al. [13]	69	Wistar rats	Female	12 weeks	200 - 250	lactate, CK and LDH levels, macrophage infiltration, gene expression of TNF-α, IL-6, IL1-β, IL-10, CINC-1 and MCP-1; and exercise performance (climbing speed).
Albuquerque-Pontes et al. [20]	25	wild type mice mdx mice	–	6 weeks	–	muscle morphology, exercise performance (climbing stairs), Western blot (protein concentration), and RT-PCR (expression of dystrophin)
de Brito Vieira et al. [15]	54	Wistar rats	Male	30 days	112 ± 4.7	exercise performance (running speed), CS and LDH activities
Assis et al. [12]	24	Wistar rats	Male	6 weeks	± 200	exercise performance (running speed), lactate concentration, morphometric analysis, muscle fiber density and myogenin expression
Perini et al. [16]	30	Wistar rats	Male	~90 days	270 - 320	exercise performance (metabolic treadmill with maximal oxygen and carbon dioxide production)
Silva et al. [21]	28	wild type (C57BL/10ScSn) (n=7) and C57BL/10ScSn-Dmdmdx/J (n=21)	–	4 weeks	–	CK, superoxide dismutase, carbonyl protein and skeletal muscle morphology
Paolillo et al. [17]	40	Wistar rats	male	2-4 months	250 - 300	load peak, body mass, lactate, matrix metalloproteinase gelatinase A gene expression and heart rate variability
Patrocinio et al. [18]	30	Wistar rats	male	8 weeks	300 - 350	body mass, maximal load, lactate, glycogen and muscle fiber morphometry
de Almeida et al. [19]	30	Wistar rats	male	–	150 - 200	COX-1 and COX-2, CK and total work performed

CK:creatine kinase; LDH: lactic dehydrogenase; CINC-1: cytokine-induced neutrophil chemoattractant-1; MCP-1: monocyte chemoattractant protein-1; RT-PCR: RNA isolation and real-time polymerase chain reaction; CS: Citrate synthase; COX-1: cyclooxygenase 1; COX-2: cyclooxygenase 2.

– Data not reported in the study

Table 2. Description of the groups, PBMT application and intervention

Authors	Groups	Application area	PBMT application	Intervention
dos Santos et al. [14]	Control: not submitted to RE or LLLT; RNI: submitted to a RE; RE+LLLT (4J); RE+LLLT (8J); RE+LLLT (12J)	Skin on both legs with a slight overpressure to central, proximal, and distal sites on gastrocnemius muscle	Acute	PBMT applied prior to a high-intensity resistance exercise session
de Oliveira et al. [13]	Prior Exercise LLLT application: Control: n= 12; 2J irradiation: n= 12; 4J irradiation: n= 12; 8J irradiation: n= 13 Post Exercise LLLT application: Control: n= 10; 4J irradiation: n= 10	3 points on the hind legs	Acute	PBMT applied prior or post resistance exercise intervention
Albuquerque-Pontes et al. [20]	Wild type-WT (C57BL/10ScSn) Untreated: n=5; Placebo-control group: DMD^{mdx} mice: n=5; 1 J group-DMD^{mdx} mice: n= 5; 3J group-DMD^{mdx} mice: n= 5; 10J group-DMD^{mdx} mice: n= 5	Tibialis anterior muscle (bilaterally)	Long-term	PBMT was applied 3 times a week on non-consecutive days (Monday, Wednesday, and Friday) for 14 weeks
de Brito Vieira et al. [15]	RCG n= 10; RLG n= 9; ECG n= 16; ELG n= 19	Quadriceps femoris, tibialis anterior, soleus and gluteus maximus muscles of both hind limbs	Long-term	PBMT was applied immediately after aerobic exercise intervention and effort test. The exercise protocol was realized for 5 weeks (from Sunday to Thursday)
Assis et al. [12]	CG n= 8; TG n= 8; TLG n= 8	Middle region of quadriceps, gluteus maximus, tibialis anterior and gastrocnemius muscles in both legs	Long-term	PBMT applied after endurance training for 8 weeks
Perini et al. [16]	P-LLLT n= 10; 8.7 J/cm^2-LLLT n= 10; 61.2 J/cm^2-LLLT n= 10	Biceps femoris, gluteus, gastrocnemius, iliopsoas, adductor longus (bilaterally)	Long-term	The maximal exercise test was realized on a metabolic treadmill (adaptation, before PBMT and after PBMT). PBMT was applied for 10 days
Silva et al. [21]	WT group; mdx control group; mdx fatigue LLLT group; mdx fatigue group	On the foreleg in the posterior region of gastrocnemius muscle	Long-term	PMBT was applied during three consecutive days. A forced exercise test on a treadmill was applied in last day of PMBT protocol.
Paolillo et al. [17]	CG n= 10; HIT n= 10; LLLT n= 10; HIT plus LLLT n= 10	Center of both right and left tibialis anterior muscle	Long-term	PBMT was applied after the high intensity resistance training. It was performed for 24 exercise sessions, three times per week for 8 weeks.
Patrocinio et al. [18]	CG: n= 10; TG: n= 10; TGL: n= 10	Middle region of tibialis anterior belly of both legs	Long-term	PMBT was applied after the resistance training, performed three times per week, for 15 sessions.
de Almeida et al. [19]	CG: n= 6; LLLT 0.1J: n= 6; LLLT 0.3J: n= 6; LLLT 1.0J: n= 6; LLLT 3.0J: n= 6	Central part of dissected tibial muscle belly	Acute	PBMT was applied before the electrical stimulation protocol to induce tetanic contractions

RE: resistance exercise; LLLT: low-level laser therapy; RCG: rest control group; RLG: rest laser group; ECG: exercise control group; ELG: exercise laser group; CG: control group; TG: trained group; TLG: trained and laser irradiated; P-LLLT: placebo photobiomodulation therapy; WT: wild-type mice; HIT: high intensity resistance training; HIT plus LLLT: high intensity resistance training plus photobiomodulation therapy; PBMT: photobiomodulation therapy.

Table 3. PBMT parameters

Authors	Light	Treatment time per point or site (s)	Wavelength (nm)	Power Output (mW)	Energy density per diode (J/cm2)	Energy per site (J)	Power density Per diode (W/cm²)	Spot size (cm2)	Number of treated points or sites	Total sessions
Dos Santos et al., [14]	LLLT	40 80 120	830	100	142.8, 285.6 or 428.4	4 8 12	3.57	0.028	6	1
De Oliveira et al., [13]	LLLT	20 40 80	830	100	71.4, 142.8 or 285,6	2 4 8	3.57	0.028	6	1
Albuquerque -Pontes el al., [20]	LLLT LEDT (4 red LEDT and 4 infrared LEDT)	8 23 77	LLLT: 905 Red LEDT: 640 Infrared LEDT: 875	LLLT: 0.625 Red LEDT: 15 Infrared LEDT: 17.5	5.07, 15.23, or 50.76	1.0, 3.0, or 10.0	0.66307	0.197	2	42
De Brito Vieira et al., [15]	LLLT	10	780	15	3.8	0.15	0.0375	0,04	8	26
Assis et al., [12]	LLLT	47	808	30	180	1.4	3.8	0.00785	8	40
Perrini et al. (2015) [16]	LLLT	1 or 7.3	850	300	8.7 or 61.2	0.315 or 2.205	8.33	0.012	12	10
Silva et al., [21]	LLLT	100	808	30	107	3	1071	0.028	1	3
Paollilo et al., [17]	LLLT	10	780	15	3.8	0.15	0.0375	0.04	2	24
Patrocinio et al., [18]	LLLT	33	808	100	120	3.3	3.57	0.028	2	15
De Almeida et al., [19]	LLLT	7, 20, 67 or 200	904	15	0.525, 1.5, 5.025 or 15	0.105, 0.300, 1 or 3	0.075	0.2	1	1

LLLT: low-level laser therapy; LEDT: light-emitting diode therapy. ─ Data not available in the study.

Table 4. Minimum, maximum, mean and median of numerical variables

	Treatment time per point or site (s)	Wavelength (nm)	Power output (mW)	Energy density per diode (J/cm²)	Energy per site (J)	Energy delivered per treatment/session (J)	Total energy delivered per experiment / whole protocol	Power density per diode (W/cm²)	Spot size (cm²)	Number of treated points or sites	Total Sessions
Minimum	1	640	0.625	0.525	0.105	0.105	0.105	0.0375	0.00785	1	1
Maximum	200	905	300	428.4	12	72	840	8.33	0.2	12	42
Mean	49.5	818.16	61.51	96.71	3.34	14.63	105.18	2.4724	0.060885	4.41	10
Median	36.5	819	23.75	55.98	2.60	6.3	27.6	2.3205	0.028	6	1

s: seconds; nm: nanometers; mW: milliWatts; J/cm: joules per square centimeter; J: joules; W/cm^2: Watts per square centimeter; cm^2: square centimeters.

Table 5. Summary of findings: PBMT versus control/sham

PBMT on fatigue levels- in experimental model										
Outcome	Limitations	Inconsistency	Indirectness	Imprecision	Publications Bias	Trials	Intervention (n)	Comparison (n)	Significant difference or statistics	GRADE level of evidence
Intervention: PBMT x control/sham										
Variable: histological analysis										
						Albuquerque-Pontes et al., [20]	5	5	Yes	
						Assis et al., [12]	8	8	Yes	
						Silva et al., [21]	5	5	Yes	
						Patrocinio et al., [18]	10	10	Yes	
	Serious	No	No	No	Undetected					Moderate **
Variable: Blood level of lactate										
						de Oliveira et al., [13]	12	12	Yes	
						de Brito Vieira et al., [15]	19	10	Yes	
						Assis et al., [12]	8	8	Yes	
						Paolillo et al., [17]	10	10	Yes	
						Patrocinio et al., [18]	10	10	Yes	
	No	No	No	Serious	Undetected					Moderate **

** Large_Effect: Large (+1); PBMT: Photobiomodulation Therapy

DISCUSSION

This systematic review aimed to compile scientific evidence about the effects of PBMT on fatigue and muscle performance in experimental animal models. To the best of our knowledge, this is the first work demonstrating the interaction of PBMT and muscle tissue considering the following aspects: muscle oxidative stress, damage and inflammation, activities of citrate synthase (CS), LDH, anaerobic threshold (AT), biochemical markers and muscle morphology.

Fatigue is a complex process that can affect both healthy and diseased individuals (1). In this context, researchers have pointed out the importance of investigating resources capable of preventing the deleterious effects of fatigue [7, 22]. Although, clinical studies have demonstrated the positive effects of PBMT on the fatigue levels, the mechanisms upon which this resource acts are not fully understood. In this review, many different animal models (rats and mice, healthy or with associated diseases) were used to investigate the effects of PBMT on fatigue levels. Also, it is important to emphasize the use of different PBMT protocols, application modes, sites of irradiation and parameters. Most of the studies irradiated lower limb muscles in different sessions of application and associated to physical exercises.

It is well known that the choice of therapeutic dose has a great influence on clinical outcomes, since tissue can be under stimulated or overstimulated by this parameter [11]. Another important point to be considered is the PBMT wavelength. The studies of this review used an interval ranging from 640nm to 905nm but most of the authors used the infrared wavelength. It is a consensus that infrared wavelengths are capable of reaching deeper tissues and are more effective in interacting with muscles, being capable of decreasing fatigue levels [23]. Interestingly, some authors also observed positive effects in the fatigue levels using red wavelengths [11, 24, 25]. A previous systematic review and meta-analyses determines that the wavelengths from 655nm to 950nm are capable of reducing muscle fatigue and improving muscle performance in humans [26]. Moreover, recent studies have used cluster devices that could present a combination of laser and LEDs [24, 25]. Also, the power output varied from 0.625mW to 300mW, energy per point varied from 0.105J to 12J, energy delivered ranged from 0.105J to 840J and power density per diode varied between 0.0375 W/cm^2 and 8.33 W/cm^2. Vanin and coauthors [26] observed that the most effective results of PBMT on the reduction of fatigue were reached with a power output of 200mW per diode, similar to those we found in our systematic review.

Another important issue to be considered is the type of muscular contraction involved in the experimental protocols. The type of contraction has an important role in it, as certain variables such as concentric peak torque, total work, 1-RM test, peak torque, mean peak torque, maximal force and mean force may be related to the muscular “performance fatigability” or muscular contractile capabilities [26, 27]. Then, the choice of this variable must be in accordance with the type of training, exercise and muscular test to obtain the most appropriate result. All studies included in this review showed improvement in the muscle performance. This may be justified because isotonic contractions were presented in 9 studies [12, 13, 14, 15, 16, 17, 18, 20, 21]. Only 1 study opted for isometric contraction [19].

Besides the type of muscular contraction, the time of exercise training protocol may also interfere in the results of exercise training plus PBMT [26, 28]. Results of the present review showed that the duration of protocols that associated the PBMT with physical exercises varied among five weeks to eight weeks [12, 15, 17, 18, 20]. Even though there is a considerable difference between the training times, all studies have shown that the PBMT associated with the training protocol had positive effects on muscle performance.

Results showed that PBMT was effective for almost all studied variables, with exception to catalase activity [14] and IL-10 [13]. It is well known that catalase, one of the crucial antioxidant enzymes, is of fundamental importance to limit damages caused by muscle fatigue, due to its capacity of attenuating oxidative stress. Also, IL-10 has an important anti-inflammatory effect. Moreover, when PBMT was delivered before an exercise protocol, there was a decrease in the excessive muscle oxidative stress [14, 21], muscle damage [13, 19, 21] and inflammation [19, 21]. Moreover, when PBMT was delivered before an exercise protocol, there was a reduction of excessive muscle oxidative stress [14, 21], muscle damage [13, 19, 21] and inflammation [19, 21], and improved cellular redox state [21] and muscle performance [19]. Furthermore, the application of PBMT after the exercise program produced an increase in the oxidative capacity in tissues with predominant aerobic metabolism [15], a decrease of lactate concentration at rest [12, 18], improved muscle fiber morphology and a decrease in the myogenic expression [12], an increased oxygen uptake and muscle exercise performance [16, 18] and an improvement in muscle fiber morphology [18]. All these positive effects are possibly related to the interaction of PBMT with cell metabolism, probably by the decrease the production of reactive oxygen species (ROS) and tissular oxidation or the reduction of oxidative stress [29]. ROS are produced, at a low level, in response to the absorption of the laser light by the cytochromes c oxidase. As a result, an increase in mitochondrial membrane potential can be seen, leading to an upregulation

of proteins affected by the increased redox reactions. All of these metabolic modifications can contribute to fatigue recovery process. Also, PBMT presents extra effects on the modulation of inflammatory response and oxidative stress, which contribute to reducing muscle injury and fatigue-induced oxidative stress [26]. Identically, Ferraresi and coauthors [24] conclude that an increase of muscle performance after PBMT during strength training can be linked to the oxidation and removal of lactic acid produced by anaerobic mechanism by exercise, which consequently leads to lower lactate accumulation and increased energy availability during exercise.

Another factor that may have influence on muscle performance is whether PBMT is applied before or after the exercise training. Two studies included in the present review applied PBMT prior to exercise training [13, 14] and 5 studies applied PBMT after exercise [12, 13, 15, 17, 18]. All studies showed that PBMT favors the reduction of fatigue and improves muscle performance. Randomized clinical trials that included healthy individuals and delivered PBMT before exercise [9, 33-36] and after exercise [30,37-39] showed that this resource has effectiveness in some variables related to muscle performance.

However, 3 meta-analysis including research clinical trials (RCTs) showed low to moderate quality of evidence that PBMT improves muscle performance, since no difference was found in the analysis between active and placebo groups for muscle power [29], number of repetitions [27, 40], isometric peak torque [27], time to exhaustion [27, 29], lactate levels [29, 40], workload, time to perform the exercises, CK, maximum voluntary contraction, mean peak forces, and visual analog scale [40]. Additionally, two RTCs published posteriorly also showed that PBMT did not reduce muscle fatigue [38, 39]. However, Vieira and coauthors [38] showed that PBMT improves number of repetitions and Tucci and coauthors [39] observed that PBMT altered the levels of TNF--α, IL-6 and LDH. Authors justified results based on the difference between studies' design, primary outcomes and sample sizes. In this context, it is possible to observe that not all variables included in these trials are possible or were evaluated in animal models. Thus, translational studies could help to identify parameters that are effective to use PBMT to improve muscle performance.

To the best of our knowledge, this is the first systematic review analyzing the effects PBMT on fatigue levels and muscle performance in experimental animal models. The present results have significant implications since this study presents a comprehensive overview of available evidence on a specific topic. However, the heterogeneity in the experimental procedures of included studies did not allow us to perform a meta-analysis.

CONCLUSION

In conclusion, this review demonstrates that PBMT regime of application used in all studies decreased the fatigue and improved muscle recovery and performance in animals' models. However, it is necessary to point out that many different PBMT parameters, such as energy density, wavelength and number of therapy sessions, were used by the different authors, making it difficult to compare the findings in order to indicate the more efficient protocol of PBMT for improving these variables.

Funding This research was funded by São Paulo Research Foundation, grant number 2020/01513-5.
Acknowledgments: Not applicable.
Conflicts of Interest: The authors declare no conflict of interest.

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