*photonics*

MDPI

*Review*

# Can Photobiomodulation Support the Management of Temporomandibular Joint Pain? Molecular Mechanisms and a Systematic Review of Human Clinical Trials

**Jumana Alsarhan [1,†], Rita El Feghali [1,†], Thaer Alkhudari [2], Stefano Benedicenti [1,*] and Claudio Pasquale [1]**

[1] Department of Surgical and Diagnostic Sciences, University of Genoa, 16132 Genoa, Italy; drjumth@hotmail.com (J.A.); rita-feghali@hotmail.com (R.E.F.); clodent@gmail.com (C.P.)
[2] Department of Orthodontics, Istanbul Yeni Yüzyil University, Istanbul 34010, Turkey; thaerkhu@gmail.com
* Correspondence: benedicenti@unige.it
† These authors contributed equally to this work.

**Abstract:** This study aims to point out the correlation between photobiomodulation (PBM) targets and effects and management of temporomandibular disorders (TMDs) pain using diode lasers with infrared wavelengths ranging from 780 up to 980 nanometers (nm). A systematic search of multiple electronic databases was done to identify the clinical trials published between 1st January 2010 and 18th December 2021. The included studies were limited to human subjects who had TMD pain, involving two genders with age > 18 years, and were treated with PBM using a diode laser (780–980 nm) as a non-pharmacological therapy to decrease the intensity of the pain associated to TMDs. The risk of bias for included studies was assessed using the Cochrane RoB tool (for randomized studies). The methodologic quality was rated using the Delphi list. The findings suggest that PBM is an effective tool in alleviating TMDs' pain and increasing the range of movement in patients with Axis 1 of TMDs. However, TMDs' pain related to underlying pathology cannot be solely treated by PBM. The causative factors must be treated first. Studies displaying the highest quality Delphi score may represent a suggested PBM therapy protocol to follow for TMDs pain management.

**Keywords:** Low-Level Laser Therapy; phototherapy; light therapy; chronic pain; analgesic effect



**Citation:** Alsarhan, J.; El Feghali, R.; Alkhudari, T.; Benedicenti, S.; Pasquale, C. Can Photobiomodulation Support the Management of Temporomandibular Joint Pain? Molecular Mechanisms and a Systematic Review of Human Clinical Trials. *Photonics* **2022**, *9*, 420. https://doi.org/10.3390/photonics9060420

Received: 6 May 2022
Accepted: 11 June 2022
Published: 16 June 2022



## 1. Introduction

Temporomandibular joint (TMJ) pain is the third most prevalent chronic pain condition worldwide after tension headache and backbone [1]. The TMJ's position and structure make it an intersection of information and influences that expand throughout the body [2]. Therefore, joint injury generally affects systemic health and leads to serious symptoms and disorders known as temporomandibular disorders (TMDs) [1]. TMD has multifactorial etiologies that affect the TMJ and the muscles of mastication, resulting in various symptoms, among which are pain, trismus, joint dislocation, clicking, and limited mouth opening. This may lead to a disability resulting in serious oral deficiencies, such as the emergence of oral mucositis, and affecting the oral health-related quality of life in 5 to 12% of the population [3,4]. Yet, the exact etiology of TMD is still unknown, and the most strategic conservative management of the condition remains debatable [5,6]. Hence, the treatment should be specific to the respective cause. A wide modality of treatments has been highly investigated, including the use of occlusal splints and/or pharmacotherapies, such as anesthetic, antidepressant, anticonvulsive, and non-steroidal anti-inflammatory drugs. However, long-term treatments lead patients to experience side effects because of adverse drug reactions. Therefore, non-pharmacological therapies, such as ultrasound, massage therapy, physiotherapy, acupuncture, exercise, transcutaneous electrical nerve stimulation, and photobiomodulation therapy (PBM-t) were proposed [7].

Photobiomodulation acts through the manipulation of cellular metabolism and homeostasis following a transfer of photonic energy from visible and (near-)infrared light sources, including light-emitting diodes (LEDs), lasers, and light broadband [8–10]. This therapy is based on non-ablative energies and non-thermal effects and involves endogenous photoacceptors. Indeed, many molecules involved in animal and human physiology retain their primordial photoacceptive properties, and thus, they may react to specific wavelengths of light and parameters [11].

It has been shown that wavelengths from 800 to 980 nm stimulate mitochondrial activity through photoacceptors included in complex IV and complex III of the electron transport chain [12–15]. Therefore, due to the mitochondria's key role in photobiomodulation and cell metabolism, the transformation of photonic (physical) energy into chemical energy (adenosine triphosphate, ATP) occurs.

Furthermore, heme-containing proteins and nitrosyl-iron complexes can form complexes with nitric oxide molecules (NO) (i.e., NO-hemoglobin) and thiol groups (i.e., S-nitrosothiols). The ability of iron and sulfur to interact with light can therefore induce the release of NO from a variety of cellular sources [16]. Plus, near-infrared light appears to excite water, affecting voltage-gated calcium ($Ca^{2+}$) [17] channels and $Ca^{2+}$ stores [18,19] and lipids, which exhibit a mild but significant absorption peak in the range of 900–1000 nm [20] (Figure 1). Moreover, PBM is associated with significant neuropharmacological effects on the synthesis, release, and metabolism of neurochemicals in the cells, including serotonin, acetylcholine, histamine and prostaglandins, and glutamate [21]. From a clinical point of view, it was seen that depending on the wavelength, type of target tissue, and tissue optical properties, the penetration depth of light energy used for PBM-t into human mucous varies considerably. The depth is maximal in the spectral range of near-infrared (~780–1000 nm), where the optical radiation penetrates to depths up to 4–6 mm [22].

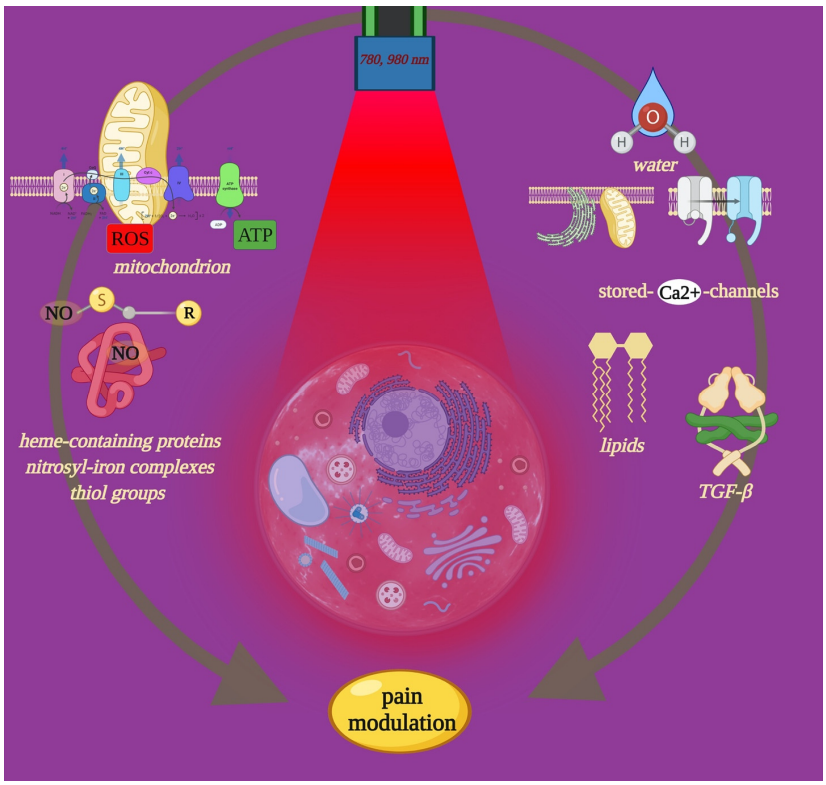



**Figure 1.** Near-infrared light can interact with molecular photoreceptor cellular involved in metabolism and homeostasis. The figure shows such light targets, which also play key roles in nociceptive signals. Through precise PBM-t, it is possible to modulate pain and support its management. Image created with BioRender.com.

Because PBM plays critical role in targeting nociceptive signals (Figure 1), its support for the management of temporomandibular joint pain recovery appears promising. Hence, this paper aims to point out the correlation between PBM's targets and effects and the molecules involved in pain and pain pharmacological management. The current systematic review focuses on evaluating the effectiveness of PBM therapy on the management of TMD and investigates the protocol doses used to this date.

Moreover, the diode laser wavelength range of 780 to 980 nm displays an efficient tissue penetration, and its cellular target interaction has been widely investigated in the literature [14,17,18,23]. As such, this paper considers this spectral range of PBM therapy taking into consideration the deep localization of the TMJ structure.

## 2. Materials and Methods

### *2.1. Search Strategy for the Systematic Review*

A systematic literature search was conducted in databases, and analysis was undertaken.

The review protocol is registered in PROSPERO (CRD42021260541), the International Prospective Register of Systematic Reviews.

#### 2.1.1. Research Question

In order to perform this systematic review, the following questions were put forward:

- Is PBM therapy using diode lasers (780–1000 nm) effective in the management of temporomandibular disorders (TMDs) pain?
- What are the appropriate protocol doses investigated till now?

#### 2.1.2. Systematic Search Strategy

The electronic searches were carried out in the following databases:

- *PubMed/Medline electronic database*;
- *COCHRANE LIBRARY*;
- *ScienceDirect*;
- *Scopus*;
- *Google Scholar*.

The electronic engines were searched to identify interventional studies involving the application of PBM using a diode laser with wavelengths (780–1000 nm) in patients with painful symptoms caused by TMD, including the clinical trial reviews that were published between (1 January 2010–18 December 2021).

Databases were searched using terms in simple or multiple conjunctions as follows: (Diode Laser Therapy OR Photobiomodulation OR Low-Level Laser Therapy AND TMJ Pain OR TMJ Analgesia), (Diode Laser and Temporomandibular Pain). These keywords were chosen according to the PICOS strategy. (Population (adult patients with TMDs), Intervention (photobiomodulation), Comparison (compared or not with placebo group), Outcome (pain), and Study design (in vivo studies)).

The reference lists of included studies in the review and previously published review articles on the subject were checked and screened to identify eligible studies.

The applied inclusion/exclusion eligibility criteria were as follows:

Inclusion criteria:

1. Randomized clinical trials (RCT) and clinical trials (CT) published between 1 January 2010 and 18 December 2021;
2. Articles published in peer-reviewed journals in the English language;
3. Full text;
4. Studies that contain diode laser with wavelengths between 780 and 1000 nm;
5. Studies that have patients with pain that resulted from any axis of RDC/TMD;
6. Studies that contain both genders with age >18.

Exclusion criteria:

1. Duplicate studies or republished articles;

2. Systematic reviews and meta-analysis;
3. Patients with a medical history that involves any other diseases (cancers or syndromes in the head and neck region);
4. Studies that contain one gender only or focus on specific age groups, such as adolescents or elders;
5. Studies that use LEDs or other light sources;
6. Studies that use different laser wavelengths;
7. Comparative studies that compare PBM with a particular aspect of therapy, such as drugs, exercises, acupuncture, injections . . . etc.;
8. Studies that have patients in pain not related to TMD in particular;
9. Patents, degrees, or doctoral theses;
10. In vitro studies.

#### 2.1.3. Study Selection and Data Extraction

The studies were screened by two independent reviewers to determine whether they met the chosen criteria. Titles and abstracts were reviewed to determine the eligibility of the studies. Moreover, the selected studies were subjected to the inclusion and exclusion criteria, resulting in a final group of included studies. Disagreements were resolved following discussions with other authors.

The information and data form included: the first author of the study, publication year, laser wavelength, intervention and comparator group, evaluated variables, measurement scale for pain assessment, laser parameters, laser protocol, follow-up, and outcomes.

### *2.2. Study Quality Assessment*

#### 2.2.1. PRISMA Guidelines

The systematic search was established concerning the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [24].

#### 2.2.2. Delphi Score

Two authors (J.A and R.E.F) independently evaluated the methodologic quality of the included trials using the Delphi list [25]. The Delphi list is one of the most popular formal systems for evaluating trial quality. It consists of nine criteria items. One extra item was added because it was found to be relevant for the included studies, namely withdrawal/dropout rate, which is unlikely to cause bias. The methodologic criteria were scored as yes (1), no (0), or do not know (0). The numerical score from the list is implemented by counting the number of positive responses to the ten questions. Any disagreements were resolved through consensus, when possible, or by arbitration of a third author (C.P).

#### 2.2.3. Risk of Bias

All the included studies were screened to assess the methodological quality of the research. "The Cochrane Collaboration's tool for assessing the risk of bias for systematic reviews" was used [26]. For each included study, the risk of bias was assessed for each scope, and the overall assessment as low risk, high risk, or uncertain risk was given [27].

## 3. Results

### *3.1. Literature Search Outcome*

The initial electronic research resulted in a preliminary database of 827 articles. The titles and abstracts of the records were reviewed to determine the eligibility of the studies. The selected articles were subjected to the inclusion and exclusion criteria, resulting in a final group of eight full texts, including studies [28–35] (Figure 2).

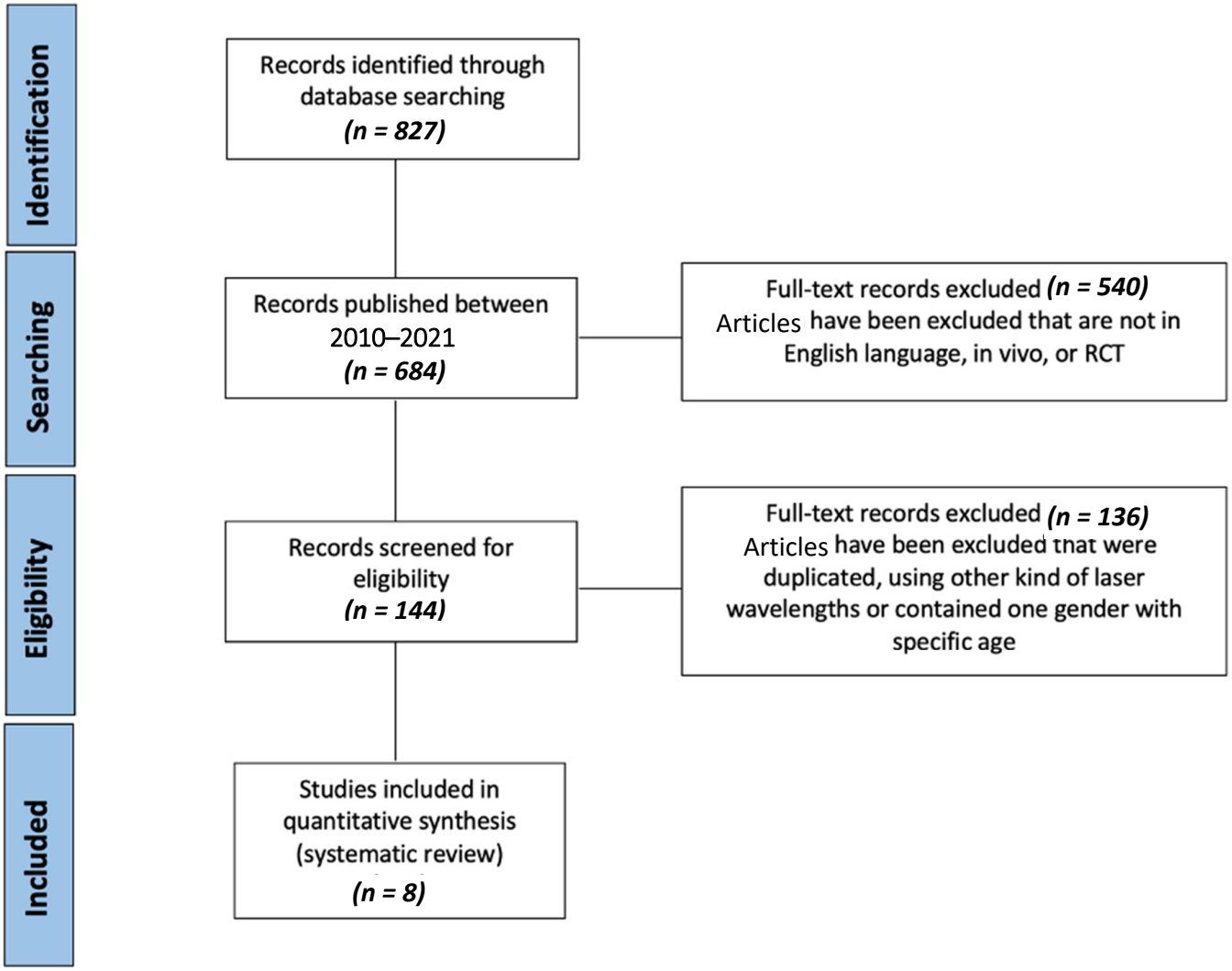



**Figure 2.** Flow diagram of literature search according to PRISMA guidelines.

Because of the relatively low number of the included clinical trials, a meta-analysis was not advisable. Hence, a systematic review was conducted to focus qualitatively and in depth on the results of the studies.

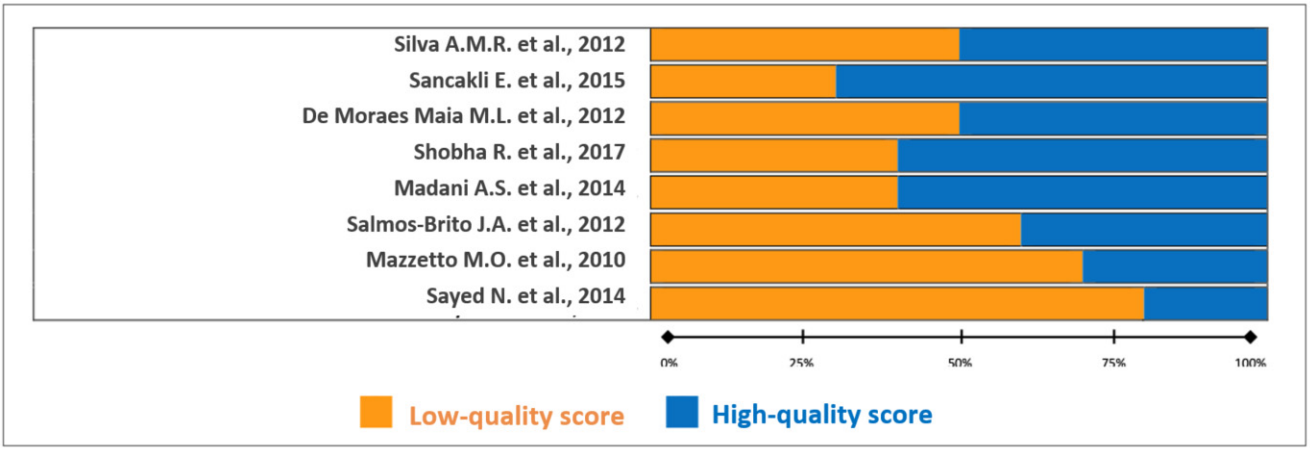
### *3.2. Delphi Score*

A total of eight CTs were assessed for trial quality evaluation using the Delphi list. Accordingly, study [29] showed the highest quality score (70%), while study [35] showed the lowest score (20%) (Figure 3a,b).

**Delphi Score**

| Silva A.M.R. et al, 2012 | Sancakli E. et al, 2015 | De Moraes Maia M.L. et al, 2012 | Shobha R. et al, 2017 | Madani A.S. et al, 2014 | Salmos-Brito J.A.L et al, 2013 | Mazzetto MO. et al, 2010 | Sayed N. et al, 2014 | |
|---|---|---|---|---|---|---|---|---|
| a- 0 | a- 1 | a- 0 | a- 0 | a- 0 | a- 0 | a- 0 | a- 0 | 1. Treatment allocation<br>a) Was a method of randomization performed?<br>b) Was the treatment allocation concealed? |
| b- 1 | b- 1 | b- 1 | b- 1 | b- 1 | b- 1 | b- 1 | b- 0 | |
| 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 2. Were the groups similar at baseline regarding the most important prognostic indicators? |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3. Were the eligibility criteria specified? |
| 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 4. Was the outcome assessor blinded? |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5. Was the care provider blinded? |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 6. Was the patient blinded? |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 7. Were point estimates and measures of variability presented for the primary outcome measures? |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8. Did the analysis include an intention-to-treat analysis? |
| 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 9. Was there a description of withdrawals and dropouts? |

(**a**)

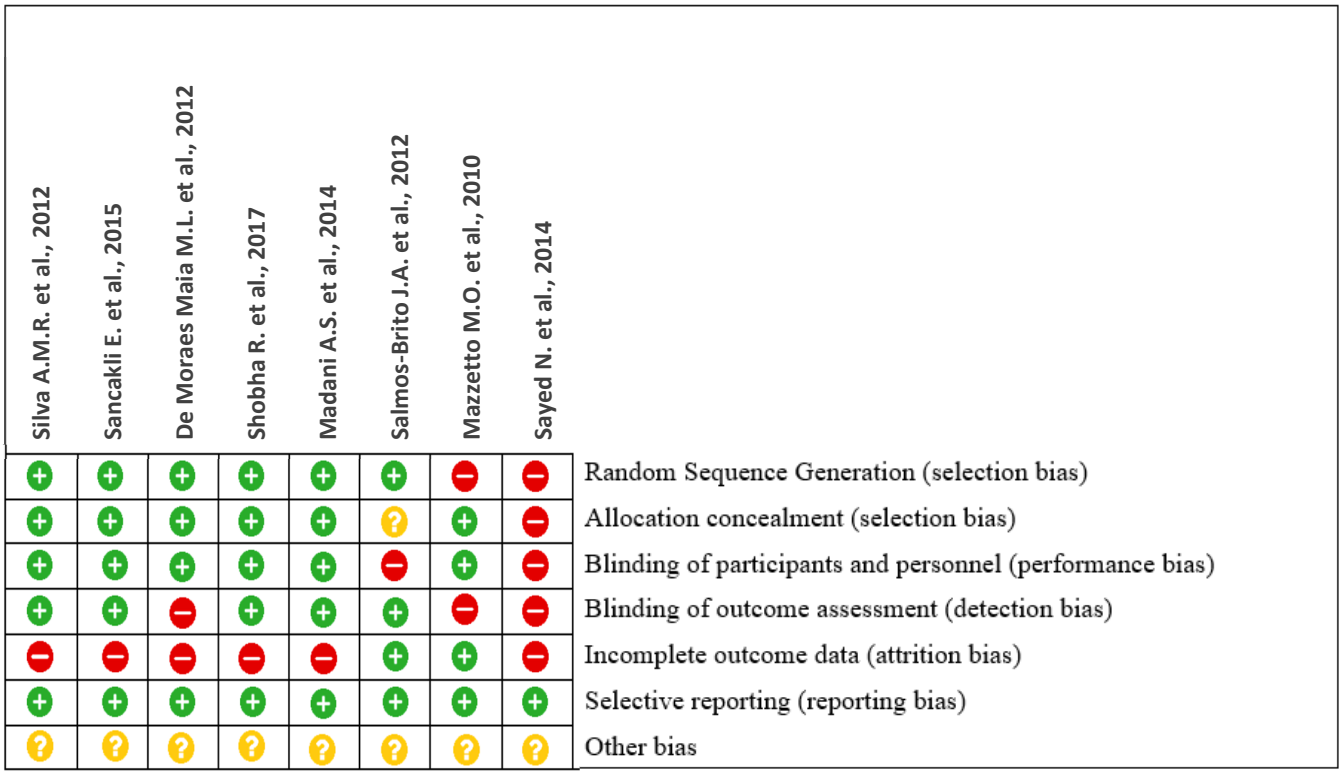



(**b**)

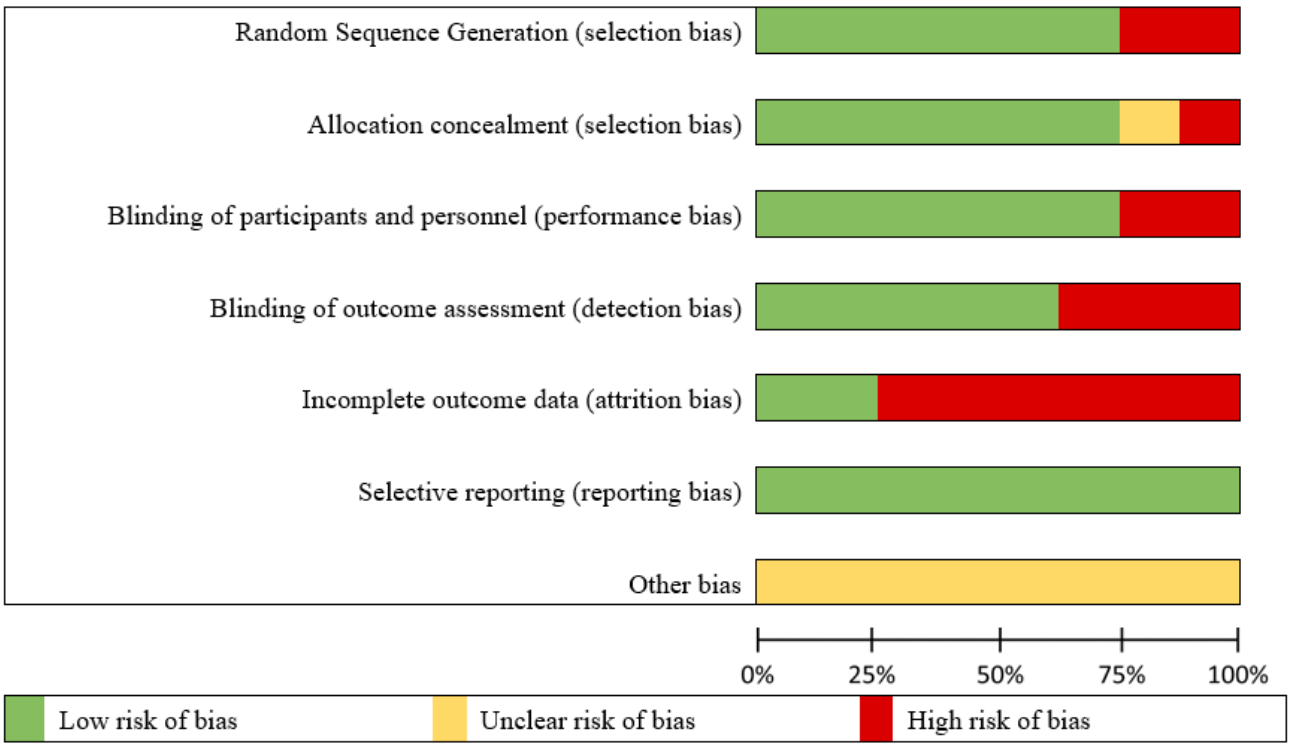
**Figure 3.** (**a**) Delphi list summary: review authors' judgments according to each of its item's Delphi score for each included study. (**b**) Delphi score graph: review authors' judgments according to each of its items Delphi score presented as percentages across all included.

### *3.3. Risk of Bias*

A total of eight CTs were assessed for risk of bias using the Cochrane tool. Accordingly, one study [35] showed a high risk of bias, while the rest of the studies [28–34] showed a moderate risk of bias (Figure 4a,b).




(**a**)




(**b**)

**Figure 4.** (**a**) Risk-of-bias summary: review authors' judgments about each risk of bias item for each included study. (**b**) Risk-of-bias graph: review authors judgments about each risk-of-bias item presented as percentages across all included.

### *3.4. Study Characteristics*

The primary aim of this systematic review was to evaluate the outcome of the included studies and analyze the missing parameters of their protocol. All the included articles are CTs published between January 2010 and December 2021 [28–35]. A summary of the basic characteristics of the eight included clinical trial studies is shown in Tables 1 and 2. The included studies had at least one test group. Silva et al. [28] and Sancakli et al. [29] performed a comparison within two test groups based on laser dose [28] and tender points [29]. Salmos-Brito et al. [33] and Sayed et al. [35] had no control group (placebo group), and they compared the efficiency of the same laser protocol therapy on two different TMDs conditions. In addition, all the included studies had similarities neither in laser parameters used nor in technique/points of application for PBM. Moreover, the post-treatment follow-up time varied and ranged from immediately after treatment to 6 months post-treatment [35], with evaluation at different time points. Furthermore, most of the included studies used the RDC/TMD protocol for screening and examining the symptoms of their patients to determine the diagnosis of TMDs except for studies [34,35], which relied on simple clinical examination. The included studies provided a statistical analysis of their data with different degrees of accuracy and clarity. Hence, regarding the treatment outcomes, 5/8 articles (62.5%) presented a positive therapeutic result, with significant differences observed among the treatment groups, whilst 3/8 articles (37.5%) showed no significant differences among the groups (Figure 5).

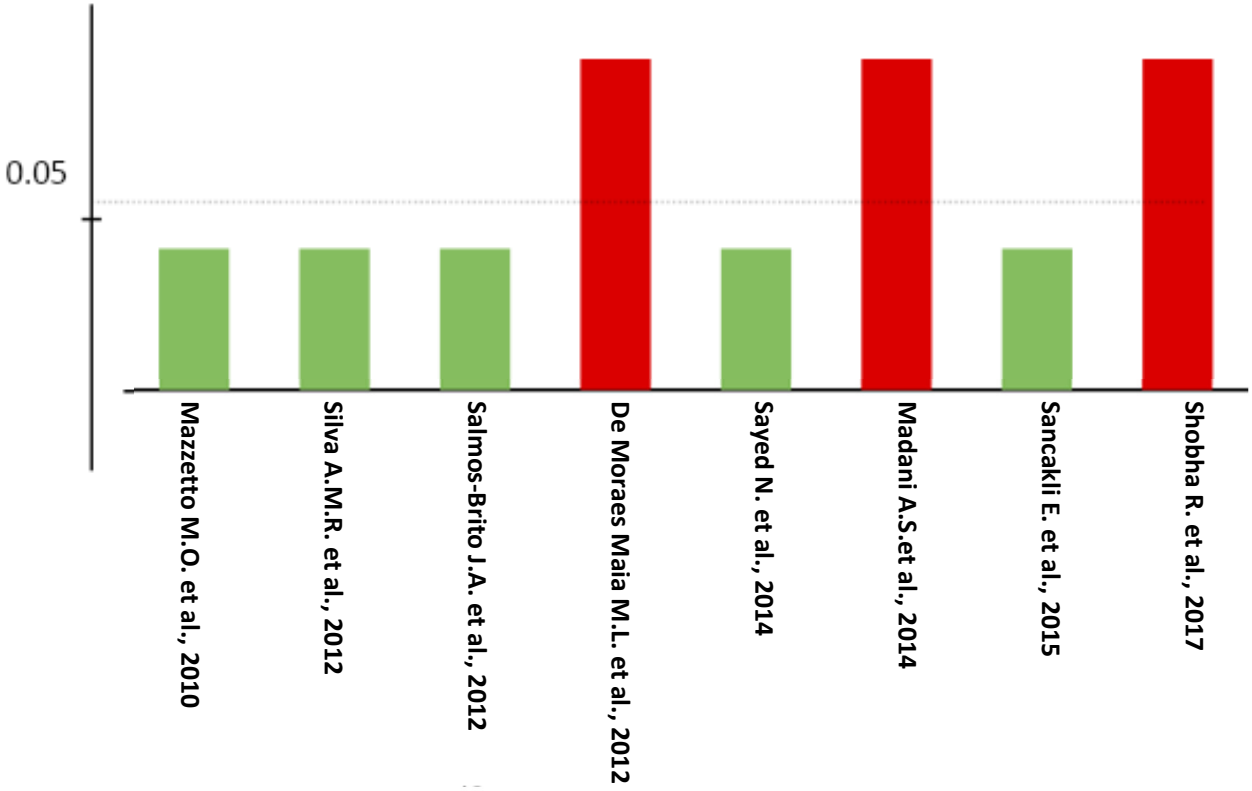



**Figure 5.** Statistical analysis of the final included studies. Red, non-significant; Green, significant.

**Table 1.** Summary of included studies. LLLT, Low-Level Laser Therapy; VA, visual analog scale; MM, maximum mouth opening; M, mouth opening; P, protrusion; LL, left laterality; RL, right laterality; ML, mandibular lateral; MP, muscle performance; PPT, pain pressure threshold; pt, point.

| Author/Year | Groups | Number of Patients Gender Age | Number of Application | Points of Application | Scale | Variables | Follow Up | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Silva et al. (2012) [28] | 1. Diode (LLLT)<br>2. Diode (LLLT)<br>3. Placebo | 30 women<br>15 men<br>25–35 years | 2 times/week<br>5 weeks | Extra-orally:<br>- 1 pt/Anterior Temporalis<br>- 3 pts/Masseter<br>- 5 pts/Condyle<br>- 1 pt/External auditory meatus. | VAS<br>Muscle palpation<br>PPT | Painful symptoms<br>Mandibular movements: (MMO, P, LL, RL) | Baseline<br>After the 1st session<br>After the 5th session<br>After the 10th session<br>After 32 days of completing therapy | The laser Groups showed significant difference compared to placebo group with better outcomes with GL2 that received higher doses. |
| Sancakli et al. (2015) [29] | 1. Diode (LLLT)<br>2. Diode (LLLT)<br>3. Placebo | 21 women<br>9 men<br>18–60 years | 3 times/week<br>4 weeks | Extra-orally:<br>3 pts/Masseter<br>3 pts/Temporal | VAS<br>Muscle palpation<br>PPT | Pain intensity<br>Mandibular mobility<br>PPT | Baseline<br>End of the therapy | Laser groups showed significant reduction for all variables compared to placebo group. |
| De Moraes Maia et al. (2012) [30] | 1. Diode (LLLT)<br>2. Placebo | 19 women<br>2 men<br>Mean of ages<br>27.76 + 10.44 | 2 times/week<br>4 weeks | Extra-orally:<br>5 pts/Masseter<br>5 pts/Anterior Temporal | VAS | Pain intensity<br>PPT<br>MP | Baseline<br>Weekly<br>End of the therapy<br>30 days of final session | Laser group did not show significant differences compared to placebo group. |
| Shobha et al. (2017) [31] | 1. Diode (LLLT)<br>2. Placebo | 31 women<br>9 men<br>18–44 years | 2–3 times/week<br>8 sessions | Extra-orally:<br>Upper joint space<br>Trigger points determined by patients | VAS | Pain<br>MO<br>Joint clicking | Baseline<br>End of treatment 30 days of final session | The laser group did not show significant difference compared to placebo group for all variables. |
| Madani et al. (2014) [32] | 1. Diode (LLLT)<br>2. Placebo | 19 women<br>1 man<br>30–60 years | 3 times/week<br>4 weeks | Extra-orally:<br>4 pts/TMJ area<br>Painful muscles | VAS | Pain intensity<br>Joint sounds<br>MO | Baseline<br>After the 6th session<br>After the 12th session<br>One month of final session | The laser group did not show significant difference for all variables compared to placebo group. |
| Salmos-Brito et al. (2012) [33] | 1. Diode (LLLT)<br>2. Diode (LLLT)<br>No control group | 50 women<br>8 men<br>19–68 years | 2 times/week<br>6 weeks | Extra-orally:<br>5 pts/TMJ area | VAS | Pain intensity<br>MMO | Before the LLLT<br>2 day following final session | The acute TMD group (G1) showed more significant differences for variables compared with chronic TMD group (G2). |

**Table 1.** *Cont.*

| Author/Year | Groups | Number of Patients Gender Age | Number of Application | Points of Application | Scale | Variables | Follow Up | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Mazzetto et al. (2010) [34] | 1. Diode (LLLT)<br>2. Placebo | 40 patients | 2 times/week<br>4 weeks | Extra-orally:<br>5 pts/TMJ area | VAS | Pain intensity<br>Mandibular movements (ML, MO). | Before<br>After each session<br>7 days of final session<br>30 days of last session | The laser showed significant improvement compared to placebo group for all variables. |
| Sayed et al. (2014) [35] | 1. Diode (LLLT)<br>2. Diode (LLLT)<br>No control group | 9 women<br>11 men<br>19–47 years | 3 times/week<br>2 weeks | Extra-orally:<br>TMJ area<br>Intra-orally:<br>Masseter, Anterior Ramus, Temporalis, Buccal molar area, Pterygoid muscle | VAS<br>Muscle palpation (PPT) | Pain intensity<br>Joint movements<br>Joint sounds<br>Number of tender points | After 1 week<br>After 2 weeks<br>After 1 month of first session<br>After 3 months of first session<br>After 6 months of first session | The laser groups showed improvement for all variables. |

**Table 2.** Details of laser parameters in the included studies. NM, not mentioned; GaAlAs, gallium-aluminum-arsenide; nm, nanometer; W, watt; mW, milli-watt; Sec, second; μm, micro-meter; J/cm$^2$, Joules per centimeter square; PP, peak power; Hz, Hertz; μs, micro-second.

| Study | Wavelength | Power | Tip Diameter | Irradiation Time | Speed of Movement | Tip–Tissue Distance | Delivery Mode | Contact Non-Contact | Energy Density | Power Meter |
|---|---|---|---|---|---|---|---|---|---|---|
| Silva et al. (2012) [28] | 780 nm (GaAlAs) | 70 mW | 5 mm | 30 s<br>60 s | NM | 0 mm | CW | Contact | 52.5 J/cm$^2$<br>100 J/cm$^2$ | Yes |
| Sancakli et al. (2015) [29] | 820 nm | 300 mW | 6 mm | 10 s | NM | 2 mm | CW | Non-contact | 3 J/cm$^2$ | Yes |
| De Moraes Maia et al. (2012) [30] | 808 nm (GaAlAs) | 100 mW | NM | 19 s/point | NM | 0 mm | CW | Contact | 70 J/cm$^2$ | Yes |

**Table 2.** *Cont.*

| Study | Wavelength | Power | Tip Diameter | Irradiation Time | Speed of Movement | Tip–Tissue Distance | Delivery Mode | Contact Non-Contact | Energy Density | Power Meter |
|---|---|---|---|---|---|---|---|---|---|---|
| Shobha et al. (2017) [31] | 810 nm (GaAlAs) | 100 mW | 300 µm | 60 s | NM | NM | CW | Non-contact | 6 J/cm$^2$ | NM |
| Madani et al. (2014) [32] | 810 nm | 50 mW PP: 80 W | NM | 120 s | NM | 0 mm | SP 1500 Hz 1 µs (Pulse width) | Contact | 3.4 J/cm$^2$ | Yes |
| Salmos-Brito et al. (2012) [33] | 830 nm (GaAlAs) | 40 mW | 6 mm | 60 s | NM | 0 mm | CW | Contact | 8 J/cm$^2$ | Yes |
| Mazzetto et al. (2010) [34] | 830 nm (GaAlAs) | 40 mW | NM | 10 s | NM | 0 mm | CW | Contact | 5 J/cm$^2$ | NM |
| Sayed N et al. (2014) [35] | 904 nm (GaAs) | 0.6 W | NM | 60 s | NM | 0 mm | CW | contact | 4 J/cm2 | NM |

## 4. Discussion

### *4.1. Effect of PBM-t on Cell Pathways of Pain*

The ability of PBM to modulate mitochondria and the mitochondrial dysfunction correlated to the etiology of pain were highly investigated. Mitochondria play an important role in a myriad of cell processes, including ATP production, biosynthetic pathways, oxygen sensing signaling, cellular redox homeostasis, ion homeostasis, and regulation of programmed cell death. As such, mitochondria modulation was suggested as an encouraging therapeutic strategy to prevent or mitigate chronic pain states [36]. More precisely, the mitochondria's vital role in cellular energy metabolism is long-known; mitochondria may generate more than 90% of the cell's energy through ATP.

Literature evidence supports the role of ATP in pain mechanisms [37]. Higher ATP levels are found in the articular fluid of arthritic knee joints, and endogenous ATP levels increase during inflammation [38]. Thus, administration of ATP by iontophoresis in pain models increases the average pain evaluation in a dose-dependent way. Basically, the expression and the disruption of ATP receptors in sensory neurons are both involved in the increment and decrement of pain, respectively, in mice [37].

In addition to ATP, reactive oxygen species (ROS) are by-products of mitochondria activities. In the physiological condition, they are usually removed by specialized cellular enzymes, such as superoxide dismutase, glutathione reductase, or catalase. Recent studies indicate that ROS play an important role in persistent pain [39,40]. ROS increment was observed in many pathophysiological conditions, including inflammation, where they may act as sensitizing on nociceptors [41]. Removal of the high level of ROS by drugs produces analgesic effects in both neuropathic and inflammatory pain [36,41].

Therefore, PBM could support pain management thanks to the interaction of cytochrome with light as photoacceptors. For instance, isolated rat liver mitochondria in vitro irradiated by a low-power He-Ne laser experienced an increase in membrane potential, proton gradient, and ATP synthesis [42]. Electron transfer and proton pumping activity are increased by laser stimulation as well [43]. Recently, the effects of photobiomodulation on the redox state of healthy and cancer cells were described and the role of ROS elucidated [44]. In addition, it was demonstrated that the 808 nm diode laser positively photobiomodulated the mitochondria oxygen consumption, the activity of the complexes III and IV, and ATP production [12,45,46]. The 980 nm irradiation showed similar effects as well [14]. However, the latter wavelength worked through window effects, and as a consequence, the mitochondria was stimulated, uncoupled, or not affected according to the therapy parameters used.

Abnormal neuronal $Ca^{2+}$ homeostasis, $Ca^{2+}$ channel expression, and function have been implicated in numerous diseases and common disorders such as pain [47]. Voltage-gated calcium channels belonging to transient receptor potential (TRP) channels cellular sensors are mediators of pain signals in primary afferent neurons [48]. Additionally, changes in $Ca^{2+}$ concentration may contribute to cell's acidosis, which may be responsible for the enduring pain changes in nociceptor sensitivity. Hence, the calcium issue and the implication of voltage-gated calcium channels continue to be major areas of focus in the development of novel therapeutic approaches for pain treatment. Moreover, mitochondria play a key role in $Ca^{2+}$ intracellular homeostasis and affects membrane excitotoxicity. Wang et al. [40] concluded that 980 nm affected temperature-gated calcium ion channels through intracellular water's role as a photoacceptor. Amaroli and collaborators also showed the ability of 808 and 980 nm diode laser light to release intracellular stored calcium [19,49]. Notably, the $Ca^{2+}$ release induced the NO production through a like-neuronal NO synthase. The networking among $Ca^{2+}$, mitochondrion, ROS, ATP, and nitric oxide in PBM was highly investigated to point out the ability of light to modulate cellular fate [18]. In addition, Colombo et al. reviewed the ability of PBM to affect NO homeostasis, leading to endothelial dysfunction recovery [16]. Indeed, neuronal NO synthase activity is primordial in nociception, and the modulation of its expression is rapidly correlated to pain [50]. Inflammatory cytokines and NO are involved in the pathogenesis of persistent

and exaggerated pain states [51]. In particular, evidence suggests that TGF-β is a relevant mediator of nociception with protective effects against pain [52].

PBM-t increases the release of the anti-inflammatory cytokines IL-1RA and IL-10 and concurrent reduction of the pro-inflammatory IL-1α, IL-1β, IL-6, and IL-17 in irradiated murine mesenchymal cells [53]. The 808 nm PBM-t mechanism might involve TGF-β-mediated control of pro-inflammatory interleukins [53]. Additionally, photoactivation of the latent TGF-ß1 isoform but not TGF-ß2 or TGF-ß3 has been investigated after irradiation with an 810 nm laser diode system; it occurred via a specific methionine (position 253 on TGF-ß1) [23].

### *4.2. Influencing Pain Recovery through PBM-t*

Although the studies carried all the inclusion criteria, the comparison between them was difficult because of laser protocol variability and differences in the outcomes.

The main differences were related to the laser parameters according to the dose-dependency for the treatment and the irradiation time. All of the included studies used continuous wave mode with no thermal relaxation except Madani [32], which adopted the gated mode characterized by a thermal relaxation time (TRT). However, TRT is not an important factor in PBM therapy, as this treatment has no appreciable thermal effects in the irradiated area due to the low-power parameter values used [54]. The power values in the included studies ranged from 0.04 W [33,34], 0.07 W [28], 0.1 W [30,31], and 0.3 W [29] up to 0.6 W [35].

Moreover, the irradiation time was not consistent among the studies. Refs. [28,31–33] stated the total time irradiation for each session, while refs. [30,34,35] provided the irradiation time for each trigger point. Sancakli [29] talked about the irradiation time without clarifying whether the corresponding values were the total processing time or the time per trigger point. In studies [28,30,32–35], the laser light beam was applied in contact mode. Studies [29,31] followed a non-contact protocol with a tip-to-tissue distance of 2 mm [29], while ref. [31] lacked to give any measurement. Consequently, the dose of energy density varied among studies and ranged between the least applied dose of 3 J/cm$^2$ [29] and the highest applied dose of 100 J/cm$^2$ [28]. In addition, the included studies did not specify in detail whether the fluences stated in their studies represented the total amount of energy density that was delivered to all the treated areas or the dose amount applied for each trigger point. Therefore, all this may present a distorted picture of the effectiveness of the applied dose. It is well-established that PBM is dependent on the dose delivered to the treated area [54]. The dose itself is dependent on the amount of energy delivered to the treated area at a certain time and through various delivery systems. Different dosages lead to different cellular responses and subsequently different clinical outcomes [12]. In addition, "if the power doubled and the time is halved, then the same energy is delivered but a different biological response is often observed" [13]. For deeper components such as TMJ, both the parameters and the procedure therapy description become mandatory. Thus, it is crucial to understand how much energy density should be applied to the skin to obtain this range of 4–10 J/cm$^2$ at the cellular level, where the main problem exists, and taking into consideration the dramatical attenuation of light photonic energy as it crosses tissue multiple divergent layers. The Beer–Lambert law usually defines such a relationship. Additionally, none of the included studies mentioned any details about the beam profile characteristics, vitiating the therapy reproducibility of the selected studies. Indeed, the amount of energy density delivered into the treated area is closely related to the beam profile. With a conventional laser handpiece, the spatial beam profile is inherently Gaussian, and generally, as the tip-to-tissue distance increases, the energy density decreases [8]. These variables appear to be the main challenge for the PBM researchers and are key factors to take into consideration in PBM studies in the precision medicine field [55]. Different outcome variables were evaluated before and after PBM therapy in the eight included clinical trials. Yet, pain was the main feature assessed. In fact, pain remains the chief complaint of TMD patients that usually present for the treatment [1]. The way to evaluate

the efficiency of treatment comprises subjective methods, through self-report of pain by the patient, and objective methods, such as evaluation of pressure pain threshold (PPT). Moreover, PPT is an objective and quantitative pain evaluation tool, which enhances the quality of data and enables outcome standardization and comparison [56]. Furthermore, pain intensity levels in all included studies were evaluated subjectively by using the visual analog scale (VAS) at least twice during the PBM therapy. Although the VAS is one of the most common ways used in research to measure the intensity of pain and the effect of therapy, there is still a risk of over- or underestimating the pain reported by the patients [57]. Nevertheless, five of eight studies (5/8) showed a decrease in pain intensity during the evaluation times that lasted along the assessment periods, which varied from one month to six months after laser application, compared to the placebo group or other control groups [28,29,33–35]. On the other hand, three of eight studies (3/8) did not show statistically significant differences in reduction of pain intensity compared to the placebo groups [30–32]. In addition, three studies [28,29,35] only incorporated PPT to assess pain. Those studies stated that the subjective improvement in pain intensity, measured by VAS, was not influenced by "LLLT", as it occurred for both the laser and placebo groups, while the measurements of PPT and masticatory efficiency were higher in the laser group. On the other hand, Salmos-Brito and Sayed [33,35] did not involve any placebo group even though the placebo-controlled trial is widely regarded as the golden standard for testing the efficacy of new treatments [58].

The differences among the included studies were not only limited to the operational laser parameters but also included:

- The number of sessions that ranged from six sessions [35] to eight [30,31,34], ten for study [28], and up to twelve sessions in [29,32,33];
- The duration of assessments extended from one month [29] up to six months [35];
- The number and the position of the tender points: some studies applied the laser treatment directly to the painful trigger points determined by the patient himself during the clinical examination [31,35]. Other studies applied the laser treatment to the painful trigger points determined by the patient himself in addition to other points predetermined by the clinician himself [29,30,32]. Meanwhile, the rest [28,33,34] selected the trigger points following previously published papers to obtain the desired analgesic effect in the TMJ area. In addition, the exact number of tender points was not cited in the clinical trials [29,31,32,35], which leads to confusion on how accurate equal doses were applied between the laser groups in each session.

Moreover, laser therapy was applied extra-orally in all of the included studies. Besides, Sayed et al. [35] irradiated intra-orally the pre-determined area while specifying the exact benefit of the procedure. However, it is relevant to point out that the distance to reach the desired target point is deeper when working from inside the oral cavity [59].

Furthermore, TMDs can be classified as unilateral or bilateral syndrome [3]. In their relative inclusion and exclusion criteria, none of the authors mentioned this issue. Only studies [29,33,34] stated that the PBM therapy affected both sides. Besides, studies [31,35] contradicted the exclusion criteria cited in their trials, such as the diversity in the chosen samples [35], in which the author declared that three patients were treated two years earlier by arthrocentesis and reported relapse symptoms. Additionally, in the study of Shobha [31], all samples were advised self-care including a soft diet, moist heat application, and TMJ exercises, which are considered a part of physical therapy. This directly contradicts their research's exclusion criteria.

The risk of bias assessment showed that study [35] demonstrated a high risk of bias in the majority of domains of internal validity, while the rest of the studies [28–34] showed a moderate risk of bias. However, the incomplete outcome data domain was at high risk for all the studies, which may distort the effect estimates. Additionally, it has been well-documented that ideal PBM therapy should lead to the desired clinical effect without causing any local thermal increase or ablative effect. None of the included studies reported no adverse outcomes/thermal collateral damage. Therefore, PBM using NIR laser

wavelengths (780–980 nm) is regarded as safe and effective since it met most of the criteria of an ideal PBM therapy.

Another crucial consideration is the use of an optical power meter, which is an instrument for the measurement of the optical power (the delivered energy per unit time) in a light beam as a laser beam. It is well-established that light loses it is energy over time, and this applies to laser light as well. Many problems can cause a loss in power, including dirty optics, electrical problems, and limited lifespan [60]. Most of the included studies (~50%) did not mention the use of a power meter, and in those studies, the average power values investigated can be less accurate.

The diversity and some missing operational laser parameters, as shown in Table 1, reflect the inconsistency in delivering valid reliable accurate PBM protocol and doses. In addition, all these discrepancies in laser operational parameters, method of laser application, and other conditions would surely influence the reliability and the uniformity of the outcomes. This in turn would limit the widespread acceptance of the PBM therapy as an effective treatment in the management of painful conditions such as TMD pain. Note that TMJ problems fluctuate, with spontaneous remission of some acute symptoms. They are also self-limiting sometimes, and thus, they may improve naturally without any intervention in some cases [5].

## 5. Conclusions

The PBM-t acts on cellular target photoreceptors involved in a wide range of responses in normal and diseased cells. Particularly, its effect on mitochondria paves the way to the possible scenarios in tissue dysfunction and pain-related recovery.

Indeed, the effect of PBM on pain stimuli makes the therapy suitable for developing therapeutic strategies to alleviate the experience of chronic inflammatory or neuropathic pain. However, window effects (positive; no effect; negative), targets involved in the cell growing and death fate, and undesirable effects on malignant or bacteria cells suggest a clinical cautious approach supported by in-depth studies.

Unfortunately, the current systematic review showed only a very limited number of studies following reliable experimental setups. The selected studies prevalently had a moderate risk of bias and supported the use of PBM therapy as a noninvasive treatment in the management of TMDs pain and other symptoms. While three out of the eight included studies could not show statistically significant outcomes, they did not demonstrate any adverse effects. Therefore, scrupulously monitored PBM laser-assisted therapy can be suggested as a useful physical modality in the management of TMJ pain associated with TMDs although causative pain factors must first be cured.

Due to the variation of laser irradiation protocol that was reported in the included studies in terms of dosage, number of tender points, number of sessions, and time evaluation, we cannot suggest an optimal treatment protocol. Further double-blind, placebo-controlled RCTs are needed to refine and standardize the PBM therapy in the management of TMDs in an attempt to establish a highly reliable sample population for replication. However, as study [29] showed the highest quality Delphi score, it may represent a suggested PBM-t protocol to follow for TMDs pain management using diode laser wavelengths in the range of 780–980 nm.

**Author Contributions:** Conceptualization, R.E.F. and J.A.; methodology, R.E.F., J.A. and C.P.; software, R.E.F. and J.A.; validation, C.P.; formal analysis, R.E.F., J.A. and C.P.; investigation, J.A., R.E.F. and T.A.; resources, S.B.; data curation, R.E.F., J.A. and C.P.; writing—original draft preparation, R.E.F., J.A. and C.P.; writing—review and editing, R.E.F., J.A., T.A., S.B. and C.P.; supervision, C.P.; project administration, R.E.F.; funding acquisition, S.B. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References


1. Prasad, S.R.; Kumar, N.R.; Shruthi, H.R.; Kalavathi, S.D. Temporomandibular pain. *J. Oral. Maxillofac. Pathol.* **2016**, *20*, 272–275. [CrossRef]
2. Bordoni, B.; Varacallo, M. *Anatomy, Head and Neck, Temporomandibular Joint*; StatPearls Publishing: Tampa, FL, USA, 2021.
3. Butts, R.; Dunning, J.; Perreault, T.; Mettille, J.; Escaloni, J. Pathoanatomical characteristics of temporomandibular dysfunction: Where do we stand? Narrative review. *J. Bodyw. Mov. Ther.* **2017**, *21*, 534–540. [CrossRef] [PubMed]
4. Liu, F.; Steinkeler, A. Epidemiology, diagnosis, and treatment of temporomandibular disorders. *Dent. Clin. N. Am.* **2013**, *57*, 465–479. [CrossRef] [PubMed]
5. Mercuri, L.G. Management of temporomandibular joint disorders. *J. Oral. Biol. Craniofac. Res.* **2012**, *2*, 141–142. [CrossRef] [PubMed]
6. Abdel Hamid, M.A.; Hassan, E.A.; Zaied, A.A.; Amaroli, A.; Sorour, N.H. Dose-Dependent Clinical, Radiographic, and Histopathologic Changes of 17β-Estradiol Levels within the Temporomandibular Joint: An Experimental Study in Ovariectomized Dogs. *J. Oral. Maxillofac. Surg.* **2020**, *78*, 1304–1313. [CrossRef]
7. Maia, M.L.; Bonjardim, L.R.; de Quintans, J.S.; Ribeiro, M.A.; Maia, L.G.; Conti, P.C. Effect of Low-Level Laser Therapy on pain levels in patients with temporomandibular disorders: A systematic review. *J. Appl. Oral. Sci.* **2012**, *20*, 594–602. [CrossRef]
8. Amaroli, A.; Colombo, E.; Zekiy, A.; Aicardi, S.; Benedicenti, S.; De Angelis, N. Interaction between Laser Light and Osteoblasts: Photobiomodulation as a Trend in the Management of Socket Bone Preservation—A Review. *Biology* **2020**, *9*, 409. [CrossRef]
9. De Freitas, L.F.; Hamblin, M.R. Proposed Mechanism of Photobiomodulation or Low-Level Light Therapy. *Sel. Top. Quantum Electron.* **2016**, *22*, 7000417. [CrossRef]
10. Hamblin, M.R. Photobiomodulation or Low-Level Laser Therapy. *J. Biophotonics* **2016**, *9*, 1122–1124. [CrossRef]
11. Amaroli, A.; Ravera, S.; Zekiy, A.; Benedicenti, S.; Pasquale, C. A Narrative Review on Oral and Periodontal Bacteria Microbiota Photobiomodulation, through Visible and Near-Infrared Light: From the Origins to Modern Therapies. *Int. J. Mol. Sci.* **2022**, *25*, 1372. [CrossRef]
12. Amaroli, A.; Ravera, S.; Parker, S.; Panfoli, I.; Benedicenti, A.; Benedicenti, S. An 808-nm Diode Laser with a Flat-Top Handpiece Positively Photobiomodulates Mitochondria Activities. *Photomed. Laser Surg.* **2016**, *34*, 564–571. [CrossRef] [PubMed]
13. Amaroli, A.; Ravera, S.; Parker, S.; Panfoli, I.; Benedicenti, A.; Benedicenti, S. 808-nm laser therapy with a flat-top handpiece photobiomodulates mitochondria activities of *Paramecium primaurelia* (Protozoa). *Lasers Med. Sci.* **2016**, *31*, 741–747. [CrossRef] [PubMed]
14. Amaroli, A.; Pasquale, C.; Zekiy, A.; Utyuzh, A.; Benedicenti, S.; Signore, A.; Ravera, S. Photobiomodulation and Oxidative Stress: 980 nm Diode Laser Light Regulates Mitochondrial Activity and Reactive Oxygen Species Production. *Oxidative Med. Cell Longev.* **2021**, *3*, 6626286. [CrossRef]
15. Pastore, D.; Greco, M.; Passarella, S. Specific helium-neon laser sensitivity of the purified cytochrome c oxidase. *Int. J. Radiat. Biol.* **2000**, *76*, 863–870. [CrossRef]
16. Colombo, E.; Signore, A.; Aicardi, S.; Zekiy, A.; Utyuzh, A.; Benedicenti, S.; Amaroli, A. Experimental and Clinical Applications of Red and Near-Infrared Photobiomodulation on Endothelial Dysfunction: A Review. *Biomedicines* **2021**, *9*, 274. [CrossRef]
17. Wang, Y.; Huang, Y.Y.; Wang, Y.; Lyu, P.; Hamblin, M.R. Photobiomodulation of human adipose-derived stem cells using 810 nm and 980 nm lasers operates via different mechanisms of action. *Biochim. Biophys. Acta Gen. Subj.* **2017**, *1861*, 441–449. [CrossRef]
18. Amaroli, A.; Ferrando, S.; Benedicenti, S. Photobiomodulation Affects Key Cellular Pathways of all Life-Forms: Considerations on Old and New Laser Light Targets and the Calcium Issue. *Photochem. Photobiol.* **2019**, *95*, 455–459. [CrossRef]
19. Ferrando, S.; Agas, D.; Mirata, S.; Signore, A.; De Angelis, N.; Ravera, S.; Utyuzh, A.S.; Parker, S.; Sabbieti, M.G.; Benedicenti, S.; et al. The 808 nm and 980 nm infrared laser irradiation affects spore germination and stored calcium homeostasis: A comparative study using delivery hand-pieces with standard (Gaussian) or flat-top profile. *J. Photochem. Photobiol.* **2019**, *199*, 111627. [CrossRef]
20. Jansen, K.; Wu, M.; van der Steen, A.F.; van Soest, G. Photoacoustic imaging of human coronary atherosclerosis in two spectral bands. *Photoacoustics* **2013**, *2*, 12–20. [CrossRef]
21. Amaroli, A.; Marcoli, M.; Venturini, A.; Passalacqua, M.; Agnati, L.F.; Signore, A.; Raffetto, M.; Maura, G.; Benedicenti, S.; Cervetto, C. Near-infrared laser photons induce glutamate release from cerebrocortical nerve terminals. *J. Biophotonics* **2018**, *11*, 201800102. [CrossRef]
22. Bashkatov, A.; Genina, E.; Kochubey, V.; Tuchin, V. Optical properties of human skin, subcutaneous and mucous tissues in the wavelength range from 400 to 2000 nm. *J. Phys. D Appl. Phys.* **2005**, *38*, 2543–2555. [CrossRef]
23. Khan, I.; Rahman, S.U.; Tang, E. Accelerated burn wound healing with photobiomodulation therapy involves activation of endogenous latent TGF-β1. *Sci. Rep.* **2021**, *11*, 13371. [CrossRef] [PubMed]
24. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: The PRISMA Statement. *PLoS Med.* **2009**, *6*, 1000097. [CrossRef] [PubMed]
25. Berger, V.W.; Alperson, S.Y. A general framework for the evaluation of clinical trial quality. *Rev. Recent Clin. Trials.* **2009**, *4*, 79–88. [CrossRef] [PubMed]
26. Higgins, J.; Savovic, J.; Page, M.; Elbers, R.; Sterne, J. Assessing Risk of Bias in Randomized Trial. In *Cochrane Handbook for Systematic Reviews of Interventions*, 2nd ed.; John Wiley & Sons: Chichester, UK, 2019; pp. 205–228.
27. Bellal, S.; El Feghali, R.; Mehta, A.; Namachivayam, A.; Benedicenti, S. Efficacy of near infrared dental lasers on dentinal hypersensitivity: A meta-analysis of randomized controlled clinical trials. *Lasers Med. Sci.* **2021**, *3*, 733–744. [CrossRef] [PubMed]

28. Da Silva, M.A.; Botelho, A.L.; Turim, C.V.; da Silva, A.M. Low level laser therapy as an adjunctive technique in the management of temporomandibular disorders. *Cranio* **2012**, *30*, 264–271. [PubMed]
29. Sancakli, E.; Gökçen-Röhlıg, B.; Balık, A.; Öngül, D.; Kıpırdı, S.; Keskın, H. Early results of low-level laser application for masticatory muscle pain: A double-blind randomized clinical study. *BMC Oral. Health* **2015**, *15*, 131. [CrossRef]
30. De Moraes Maia, M.L.; Ribeiro, M.A.; Maia, L.G.; Stuginski-Barbosa, J.; Costa, Y.M.; Porporatti, A.L.; Conti, P.C.; Bonjardim, L.R. Evaluation of Low-Level Laser Therapy effectiveness on the pain and masticatory performance of patients with myofascial pain. *Lasers Med. Sci.* **2014**, *29*, 29–35. [CrossRef]
31. Shobha, R.; Narayanan, V.S.; Jagadish Pai, B.S.; Jaishankar, H.P.; Jijin, M.J. Low-level laser therapy: A novel therapeutic approach to temporomandibular disorder—A randomized, double-blinded, placebo-controlled trial. *Indian J. Dent. Res.* **2017**, *28*, 380–387. [CrossRef]
32. Madani, A.S.; Ahrari, F.; Nasiri, F.; Abtahi, M.; Tunér, J. Low-level laser therapy for management of TMJ osteoarthritis. *Cranio* **2014**, *32*, 38–44. [CrossRef]
33. Salmos-Brito, J.A.; de Menezes, R.F.; Teixeira, C.E.; Gonzaga, R.K.; Rodrigues, B.H.; Braz, R.; Bessa-Nogueira, R.V.; Gerbi, M.E. Evaluation of Low-Level Laser Therapy in patients with acute and chronic temporomandibular disorders. *Lasers Med. Sci.* **2013**, *28*, 57–64. [CrossRef] [PubMed]
34. Mazzetto, M.O.; Hotta, T.H.; Pizzo, R.C. Measurements of jaw movements and TMJ pain intensity in patients treated with GaAlAs laser. *Braz. Dent. J.* **2010**, *21*, 356–360. [CrossRef] [PubMed]
35. Sayed, N.; Murugavel, C.; Gnanam, A. Management of Temporomandibular Disorders with Low Level Laser Therapy. *J. Maxillofac. Oral. Surg.* **2014**, *13*, 444–450. [CrossRef] [PubMed]
36. Sui, B.D.; Xu, T.Q.; Liu, J.W.; Wei, W.; Zheng, C.X.; Guo, B.L.; Wang, Y.Y.; Yang, Y.L. Understanding the role of mitochondria in the pathogenesis of chronic pain. *Postgrad. Med. J.* **2013**, *89*, 709–714. [CrossRef]
37. Hamilton, S.G. ATP and pain. *Pain Pract.* **2002**, *2*, 289–294. [CrossRef]
38. Ryan, L.M.; Rachow, J.W.; McCarty, D.J. Synovial fluid ATP: A potential substrate for the production of inorganic pyrophosphate. *J. Rheumatol.* **1991**, *18*, 716–720.
39. Wang, Z.Q.; Porreca, F.; Cuzzocrea, S. A newly identified role for superoxide in inflammatory pain. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 869–878. [CrossRef]
40. Zheng, J.; Zhang, J.; Zhang, X.; Guo, Z.; Wu, W.; Chen, Z.; Li, J. Reactive Oxygen Species Mediate Low Back Pain by Upregulating Substance P in Intervertebral Disc Degeneration. *Oxid. Med. Cell. Longev.* **2021**, *2021*, 6681815. [CrossRef]
41. Chung, J.M. The role of reactive oxygen species (ROS) in persistent pain. *Mol. Interv.* **2004**, *4*, 248–250. [CrossRef]
42. Passarella, S.; Casamassima, E.; Molinari, S.; Pastore, D.; Quagliariello, E.; Catalano, I.M.; Cingolani, A. Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. *FEBS Lett.* **1984**, *175*, 95–99. [CrossRef]
43. Pastore, D.; Greco, M.; Petragallo, V.A.; Passarella, S. Increase in <–H+/e− ratio of the cytochrome c oxidase reaction in mitochondria irradiated with helium-neon laser. *Biochem. Mol. Biol. Int.* **1994**, *34*, 817–826. [PubMed]
44. Gonçalves de Faria, C.M.; Ciol, H.; Salvador Bagnato, V.; Pratavieira, S. Effects of photobiomodulation on the redox state of healthy and cancer cells. *Biomed. Opt. Express.* **2021**, *12*, 3902–3916. [CrossRef] [PubMed]
45. Ravera, S.; Bertola, N.; Pasquale, C.; Bruno, S.; Benedicenti, S.; Ferrando, S.; Zekiy, A.; Arany, P.; Amaroli, A. 808-nm Photobiomodulation Affects the Viability of a Head and Neck Squamous Carcinoma Cellular Model, Acting on Energy Metabolism and Oxidative Stress Production. *Biomedicines* **2021**, *9*, 1717. [CrossRef] [PubMed]
46. Amaroli, A.; Ravera, S.; Baldini, F.; Benedicenti, S.; Panfoli, I.; Vergani, L. Photobiomodulation with 808-nm diode laser light promotes wound healing of human endothelial cells through increased reactive oxygen species production stimulating mitochondrial oxidative phosphorylation. *Lasers Med. Sci.* **2019**, *34*, 495–504. [CrossRef]
47. Fernyhough, P.; Nigel Calcutt, A. Abnormal calcium homeostasis in peripheral neuropathies. *Cell Calcium* **2010**, *47*, 130–139. [CrossRef]
48. Zheng, J. Molecular mechanism of TRP channels. *Compr. Physiol.* **2013**, *3*, 221–242.
49. Amaroli, A.; Benedicenti, A.; Ferrando, S.; Parker, S.; Selting, W.; Gallus, L.; Benedicenti, S. Photobiomodulation by Infrared Diode Laser: Effects on Intracellular Calcium Concentration and Nitric Oxide Production of Paramecium. *Photochem. Photobiol.* **2016**, *92*, 854–862. [CrossRef]
50. Miclescu, A.; Torsten, G. Nitric oxide and pain: 'Something old, something new'. *Acta Anaesthesiol. Scand.* **2009**, *53*, 1107–1120. [CrossRef]
51. Koch, A.; Zacharowski, K.; Boehm, O. Nitric oxide and pro-inflammatory cytokines correlate with pain intensity in chronic pain patients. *Inflamm. Res.* **2007**, *56*, 32–37. [CrossRef]
52. Lantero, A.; Tramullas, M.; Díaz, A. Transforming Growth Factor-β in Normal Nociceptive Processing and Pathological Pain Models. *Mol. Neurobiol.* **2012**, *45*, 76–86. [CrossRef]
53. Amaroli, A.; Agas, D.; Laus, F.; Cuteri, V.; Hanna, R.; Sabbieti, M.G.; Benedicenti, S. The Effects of Photobiomodulation of 808 nm Diode Laser Therapy at Higher Fluence on the in Vitro Osteogenic Differentiation of Bone Marrow Stromal Cells. *Front. Physiol.* **2018**, *23*, 123. [CrossRef] [PubMed]
54. Kim, H.B.; Baik, K.Y.; Choung, P.H.; Chung, J.H. Pulse frequency dependency of photobiomodulation on the bioenergetic functions of human dental pulp stem cells. *Sci. Rep.* **2017**, *7*, 15927. [CrossRef] [PubMed]

55. Sommer, A.P.; Pinheiro, A.L.; Mester, A.R.; Franke, R.P.; Whelan, H.T. Biostimulatory windows in low-intensity laser activation: Lasers, scanners, and NASA's light-emitting diode array system. *J. Clin. Laser Med. Surg.* **2001**, *19*, 29–33. [CrossRef] [PubMed]
56. Hakgüder, A.; Birtane, M.; Gürcan, S.; Kokino, S.; Turan, F.N. Efficacy of Low-Level Laser Therapy in myofascial pain syndrome: An algometric and thermographic evaluation. *Lasers Surg. Med.* **2003**, *33*, 339–343. [CrossRef]
57. Sung, Y.T.; Wu, J.S. The Visual Analogue Scale for Rating, Ranking and Paired-Comparison (VAS-RRP): A new technique for psychological measurement. *Behav. Res.* **2018**, *50*, 1694–1715. [CrossRef]
58. Gupta, U.; Verma, M. Placebo in clinical trials. *Perspect. Clin. Res.* **2013**, *4*, 49–52. [CrossRef]
59. Stocum, D.L.; Roberts, W.E. Part I: Development and Physiology of the Temporomandibular Joint. *Curr. Osteoporos Rep.* **2018**, *16*, 360–368. [CrossRef]
60. Parker, S.; Cronshaw, M.; Anagnostaki, E.; Bordin-Aykroyd, S.R.; Lynch, E. Systematic Review of Delivery Parameters Used in Dental Photobiomodulation Therapy. *Photobiomodul. Photomed. Laser Surg.* **2019**, *37*, 784–797. [CrossRef]