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Review

Nerve Injury and Photobiomodulation, a Promising Opportunity: A Scoping Review on Laser Assisted Protocols for Lesions in the Oral Region

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Abstract: The currently available therapeutic options for restoring function and sensitivity in long-term nervous injuries pose challenges. Microsurgery interventions for direct nerve repair often lead to serious complications and limited success. Non-surgical methods, although somewhat effective, have limited benefits. These methods involve drug administration, such as with analgesics or corticosteroids. Photobiomodulation therapy (PBMT) has emerged as a promising approach based on clinical and laboratory studies. PBMT stimulates the migration and proliferation of neuronal fiber cellular aggregates, as reported in the literature. Experimental studies on animal models with peripheral nerve compression injuries have shown that PBMT can enhance the functionality of damaged nerves, preserving their activity and preventing scar tissue formation. The mechanism of action depends on the wavelength, which can positively or negatively affect photo acceptor resonances, influencing their conformation and activities. These findings suggest that photobiomodulation may accelerate and improve nerve regeneration. This review explores various methodologies used in photobiomodulation for regenerating nerve sensitivity after surgical trauma involving nerve structures, in the oral and peri-oral region. Research was conducted to evaluate which laser-assisted therapeutic protocols are used to improve the recovery of nervous sensitivity, using the JBI methodology for scoping reviews and following the PRISMA methodology.

Keywords: dentistry; diode laser; nerve injury; oral pathology; oral surgery; osteonecrosis; photobiomodulation

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1. Introduction

Nerve lesions of iatrogenic origin can affect both sensory and motor trunks; these lesions can lead to potentially painful symptoms and dysfunctions of the oral and maxillofacial region [1–3]. In oral surgery, most of the lesions involve the sensory nerve trunks of the V cranial nerve, the inferior alveolar nerve, the lingual nerve, as well as the greater palatine nerve, albeit less frequently [1–3].

These lesions can be caused by a variety of treatments, such as oral or maxillofacial surgery, implant surgery, injection of local anesthetics, or endodontic treatments [1–3].

The neurological lesions can be divided into three degrees of increasing severity: neurapraxia, if the interruption is only functional and temporary of the nerve conduction; axonotmesis, if there is an anatomical interruption of the axons but with preservation of the sheaths covering the nerve, with functional recovery which happens if the regeneration takes place completely, but it is necessary for up to a few months. Finally, there is

neurotmesis, characterized by the complete interruption of both the axons and the sheaths covering the nerve, where functional recovery of the nerve is rare [1–3].

Thus far, the approaches employed to reinstate the functionality of the impaired nerve have demonstrated challenges in achieving enduring outcomes [3,4]. The currently accessible treatments are categorized as either surgical or non-surgical. Surgical methods encompass nerve transfer, nerve conduits, direct nerve repair, and the application of fibrin glue. Conversely, non-surgical therapies encompass pharmacological agents like analgesics, topical remedies such as corticosteroids, and the utilization of phytochemicals. It is necessary to underline that these therapies have disadvantages, as surgical therapies can have non-negligible adverse effects and require a specialized operator for execution, while non-surgical therapies have shown limited efficacy up to now [4]. Neurorrhaphy, the surgical repair of nerves, offers several alternative techniques to restore nerve function. These options include direct suturing (epineurial repair), which involves stitching the nerve ends together, maintaining nerve alignment. Cable grafting involves using a nerve graft or autograft to bridge a gap between nerve ends. Nerve connectors, such as tubes or stents, aid in nerve regeneration by facilitating the growth of nerve fibers across the gap. The use of nerve conduits, synthetic or biological tubes, guides nerve regrowth and prevents scar tissue formation. Nerve transfer involves rerouting a functional nerve to the injured area, allowing the restoration of lost functions. End-to-side neurorrhaphy involves connecting the injured nerve to a donor nerve's side, promoting axonal growth. Fibrin glue, platelet-rich plasma, and other bioactive substances can enhance nerve repair by promoting cell growth and angiogenesis. Minimally invasive techniques, like robotic-assisted neurorrhaphy, offer precision and reduced scarring. Combining different techniques, tailored to the patient's condition, can optimize nerve repair outcomes [4].

Among these methodologies, light-based therapy, known as photobiomodulation therapy (PBMT), has exhibited promising outcomes in various clinical and in vitro investigations [4]. Existing literature indicates that PBMT induces the migration and proliferation of clusters of neuronal fibers. In animal models of peripheral nerve compression injuries [5], PBMT has been shown to directly enhance the function of the damaged nerve, sustain nerve activity over time, and reduce or prevent scar tissue formation at the injury site [5–7]. Additionally, several researchers have observed that nerve injuries result in escalated oxygen consumption without a corresponding increase in ATP production. This phenomenon may arise from uncoupled respiration and energy production or a reversal of ATP synthetase activity, leading to ATP dissipation [5,6]. The diminished availability of ATP in nerve lesions triggers cell death and neurodegeneration since the low ATP level promotes neuronal depolarization, enhances neurotransmitter release, impairs ATP-dependent reuptake, and heightens the excitability of nociceptors [5,6]. This phenomenon is further linked to the increased production of reactive oxygen species (ROS), which is exacerbated by the inflammation associated with neuronal damage. PBMT enhances the mitochondrial membrane potential (MMP), boosting electron transport. An elevated MMP typically increases ROS production, yet malfunctioning mitochondria also generate ROS via the "ROS-induced ROS release" (RIRR). Excessive oxidative stress triggers channels like the mitochondrial permeability transition pore and inner membrane anion channel, causing MMP to collapse and a heightened ROS via the electron transport chain [7]. This ROS surge may serve as a "second messenger," activating RIRR in nearby mitochondria, compounding cellular harm. In NF-kB luciferase mice, a 810 nm laser PBM activated NF-kB, inducing ROS generation and a rise in ATP. N-acetylcysteine quenched ROS but not ATP, as PBM's MMP elevation increased ATP while provoking a ROS burst that likely activated NF-kB via protein kinase D [7].

PBM is thought to enhance mitochondrial function by increasing the mitochondrial membrane potential (MMP), leading to improved electron transport and adenosine triphosphate (ATP) production. Additionally, PBM can influence cellular signaling pathways, such as NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), which play a central role in immune responses, inflammation, and cell survival. Transforming Growth

Factor Beta (TGF-β) is a multifunctional cytokine that regulates cell growth, differentiation, and immune responses. It is involved in various physiological processes, including tissue repair, wound healing, and immune modulation. TGF-β can stimulate fibroblast activity, leading to tissue remodeling and extracellular matrix production. In the context of PBM, TGF-β may play a role in mediating the effects of light therapy on tissue repair and regeneration, potentially enhancing the healing process and promoting favorable cellular responses [8].

The combination of PBM and TGF-β could have synergistic effects on tissue healing and regeneration. PBM may enhance the cellular responses to TGF-β, leading to improved tissue repair and regeneration outcomes. However, the specific interactions between PBM and TGF-β in various therapeutic contexts would require further research to fully elucidate their combined effects and mechanisms of action [8]. The interaction between red and infrared light and photoacceptors such as cytochromes, water, lipids, S-nitrosylates, nitric oxide, and transient receptor potential channels (TRPC) that regulate that Ca^{2+} passage, leads to a modification of the bioenergetic properties of mitochondria. This alteration includes adjustments in ATP and ROS generation, as well as the discharge of nitric oxide (NO) and calcium ions (Ca^{2+}) at the mitochondrial level [5,6]. The mechanism of action varies depending on the wavelength, which can either positively or negatively interfere with the photoacceptor resonances, influencing their conformation, properties, and activities. These findings strongly suggest that photobiomodulation plays a pivotal role in accelerating and enhancing the regeneration of damaged nerves [5–8]. The article of Amaroli et al. [9] explores the effects of photobiomodulation (PBM) on cellular pathways, including calcium regulation, through various interactions with chromophores. While mitochondrial chromophores and ROS signaling are key targets, alternative photoacceptors like water and TRP ion channels also play roles. The interconnectedness of calcium's roles in cell physiology aligns well with PBM's consistent effects across different lifeforms. PBM-induced effects involve intricate pathways, such as mitochondrial stimulation, leading to ROS generation and calcium uptake. The intricate interactions between ROS, ATP, and calcium signal a complex yet significant impact on cell function and communication. Although PBM's mechanisms are multifaceted and involve various pathways, the article underscores its potential for beneficial effects in medical applications, while cautioning against unintended cellular damage. Further research is needed to fully comprehend these interactions and their implications [9,10].

Moreover, it was observed that cell proliferation responds differently to various PBM wavelengths: 660 nm and 810 nm enhance proliferation, while 415 nm and 540 nm inhibit it. Based on protein content measurement, the sulforhodamine B assay gauges cell density. The PBM effects were assessed using four wavelengths (3 J/cm^2) at five-time points: 810 nm and 660 nm increased hASCs proliferation, while 415 nm and 540 nm inhibited it [11]. Intracellular ATP levels varied: 660 nm and 810 nm raised ATP in a biphasic manner, while 415 nm and 540 nm led to dose-dependent decreases [11]. Flow cytometry and microscopy examined the effects on intracellular calcium, MMP, ROS, and pH. TRPV1 expression influenced proliferation, and CAP promoted proliferation through TRPV1. Inhibitory effects of 415 nm and 540 nm on proliferation were counteracted by TRPV1 inhibitors and ROS blockers [11,12].

Considering these studies, it is possible to state that photobiomodulation is a non-invasive treatment with zero side effects; nowadays, it is a treatment still under study for its therapeutic efficacy in some pathologies, although it is a valid alternative for pathologies of other districts especially in the dental and dermatological. Therefore, this scoping review aims to investigate the effects of various wavelengths and the therapeutic strategies implemented to recover sensitivity in patients who have suffered nerve injuries in the oral and peri-oral nerve branches [7–12].

2. Materials and Methods

2.1. Focused Questions

What type of laser and wavelengths are suitable for the photobiomodulation protocol to be applied to patients with nerve injuries in the oral district? What are the results obtained with photobiomodulation in terms of recovery of nervous functions?

2.2. Eligibility Criteria

The following inclusion criteria guided the analysis of the studies:

Type of studies: clinical trials, case-control studies, cross-sectional studies, and cohort studies.

Type of Journal: only articles published in journals indexed on Scopus, Web of Science, or PubMed were considered.

Type of participants: patients with nerve injuries to which a photobiomodulation protocol was applied.

Type of interventions: comparison of the clinical effects of various wavelengths applied and/or different types of lasers used and/or different protocols of application, assessed through clinical trials.

Outcome type: identification of protocols of photobiomodulation that are considered effective in restoring nerve functionality and mid/long term outcomes.

Only research that satisfied all the predefined inclusion criteria was incorporated. Nonetheless, the subsequent exclusion criteria were considered: (I) publications in languages other than English, (II) the existence of concurrent systemic diseases/treatments that could impact the outcomes, (III) animal-based clinical investigations, and (IV) studies lacking approval from an ethics committee.

2.3. Search Strategy

Following the JBI methodology for scoping reviews [13], a three-step search process was conducted: (i) an initial limited search on PubMed (MEDLINE) and Scopus; (ii) identification of key terms from the retrieved articles to devise the search strategy; and (iii) an examination of the reference lists of all included articles for additional research [14].

Moreover, the review applied the Population-Concept-Context (PCC) model, which centers around the following three elements: population (individuals with peripheral nerve lesions), concept (photobiomodulation and its impact on sensory improvement after nerve injury), and context (in this case, the review was not limited to any specific cultural or geographical setting). The abstracts of studies analyzing the effects of photobiomodulation on peripheral nerve injury and sensory recovery, along with their clinical outcomes, were evaluated. Throughout this scoping review of the literature, adherence to the Preferred Reporting Items for Scoping Reviews (PRISMA-ScR) consensus was followed (Table S1 in Supplementary Material) [15].

2.4. Research

The MeSH terms utilized for this study are photobiomodulation, diode laser, laser, oral nerve injury, neurological lesion, and sensibility. An electronic search was performed using PubMed (MEDLINE) and Scopus databases. The targeted publication period was from 2003 to 2023. Data extraction took place between January 2023 and June 2023, with the most recent search conducted on 17 June 2023. During our analysis, 135 articles were selected. Two calibrated reviewers (M.Pe. and F.P.) conducted the search, and any disagreements or discrepancies were resolved through consensus. In case of further issues, three additional reviewers (M.Po., M.B., and F.S.) were consulted. The titles and abstracts of the initially retrieved articles were thoroughly reviewed, and irrelevant studies were excluded. Relevant articles meeting the inclusion criteria were identified and analyzed for any similar studies. Full texts of the included studies were read for the extraction of pertinent results, which were recorded accordingly.

The present protocol has been registered on the Open Science Framework platform (Registration DOI-10.17605/OSF.IO/6X5C7).

The detailed strategies applied for each electronic database can be found in Table S2 (Supplementary Material).

2.5. Quality Assessment of Included Studies

This review was performed by evaluating the risk of bias by conducting a qualitative analysis of the clinical studies via JBI critical appraisal for randomized controlled trials [16].

3. Results

The initial search yielded 135 articles based on MeSH terms, spanning from 2003 to 2023. Subsequently, the focus of the research was narrowed down to clinical trials, meta-analyses, and randomized controlled trials involving human studies, published in the English language, and with full-text availability. As a result, 16 articles were selected and screened for eligibility. Ultimately, these 16 relevant articles were included and thoroughly analyzed in the review. The flowchart depicting the review process is presented in Figure 1.

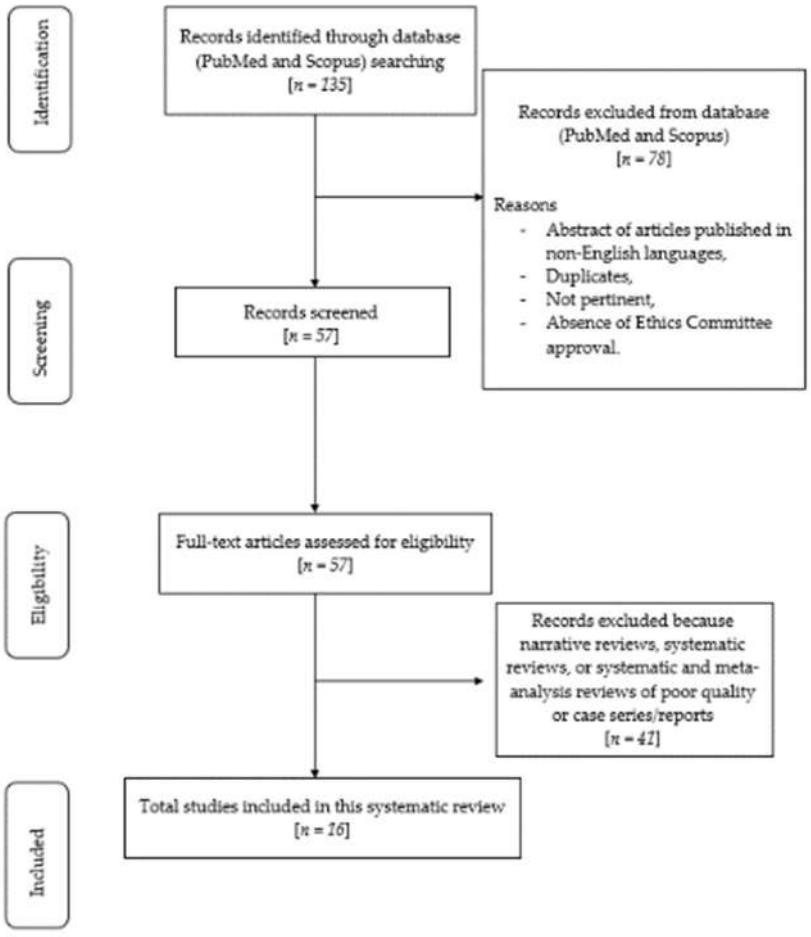

Figure 1. Flow chart of the review process.

Risk of Bias

The JBI critical appraisal tool was applied to assess the risk of bias in the studies included in this review (Table 1), using the judging criteria for the risk of bias shown in Table S3 (Supplementary Materials). Questions and answers to the criteria for judging the risk of bias in the "JBI Critical Appraisal Checklist for Randomized Controlled Trials" [14] are shown in Table 2.

Table 1. The risk of bias in case report studies is represented by symbols (green for low risk of bias, yellow for high risk of bias, and blue for uncertain or unavailable data and medium risk of bias).

Autor, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Overall Appraisal
Sharifi et al., 2020 [17]	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	✓
Miloro et al., 2018 [18]	–	–	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	✓
Gasperini et al., 2013 [19]	✓	✓	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	✓
Bashiri et al., 2021 [20]	✓	–	✓	?	?	?	✓	✓	✓	✓	✓	✓	✓	?
Salari et al., 2022 [21]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Qi et al., 2020 [22]	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	✓	✓
Eshghpour et al., 2017 [23]	✓	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	✓	✓
De Oliveira et al., 2021 [24]	✓	✓	✓	?	?	?	✓	✓	✓	✓	✓	✓	✓	✓
Teixeira Santos et al., 2019 [25]	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	✓	✓
Pinto Faria et al., 2020 [26]	–	–	✓	?	?	?	✓	✓	✓	✓	✓	✓	✓	?
Fuhrer-Valdivia et al., 2014 [27]	✓	✓	✓	?	?	?	✓	✓	✓	✓	✓	✓	✓	✓
Mohajerani et al., 2017 [28]	✓	✓	✓	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	✓
De Assis Santos et al., 2022 [29]	✓	✓	✓	?	?	?	✓	✓	✓	✓	✓	✓	✓	✓
Pol et al., 2016 [30]	–	–	✓	?	?	?	✓	✓	✓	✓	✓	✓	✓	?
Ozen et al., 2006 [31]	?	?	✓	✓	–	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. This review includes criteria for judging the risk of bias in the "JBI Critical Appraisal Checklist for randomized controlled trials", questions, and answers for each case report. The letter Q indicates the question of the dedicated checklist and the corresponding numbering.

Autor, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Overall Appraisal
Sharifi et al., 2020 [17]	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Include
Miloro et al., 2018 [18]	N	N	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Include
Gasperini et al., 2013 [19]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Include
Bashiri et al., 2021 [20]	N	N	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	Include
Salari et al., 2022 [21]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Include
Qi et al., 2020 [22]	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Include

Table 2. *Cont.*

Autor, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Overall Appraisal
Eshghpour et al., 2017 [23]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Include
De Oliveira et al., 2021 [24]	Y	Y	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	Include
Teixeira Santos et al., 2019 [25]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Include
Pinto Faria et al., 2020 [26]	N	N	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	Include
Fuhrer-Valdivia et al., 2014 [27]	Y	Y	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	Include
Mohajerani et al., 2017 [28]	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Include
De Assis Santos et al., 2022 [29]	Y	Y	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	Include
Pol et al., 2016 [30]	N	N	Y	U	U	U	Y	Y	Y	Y	Y	Y	Y	Include
Ozen et al., 2006 [31]	U	U	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Include

4. Discussion

In the realm of medical innovation, the application of photobiomodulation has emerged as a promising approach for treating nerve injuries in the oral district [17–19]. The quest to optimize this therapy hinges upon selecting the appropriate laser type and wavelengths. Researchers delve into the intricate interplay between laser characteristics and their compatibility with the unique anatomical and physiological aspects of the oral nerve network. An exploration of the optimal laser type, such as low-level laser therapy (PBMT), and the most effective wavelengths unfolds as a pivotal pursuit [18,19]. As the medical community strives to unravel the potential of photobiomodulation, questions abound regarding the outcomes that it yields in terms of the recovery of nervous function. Preliminary findings hint at the tantalizing prospect of accelerated nerve regeneration, potentially offering a new ray of hope for patients grappling with nerve injuries in the oral district [20–22]. By examining the documented results, insights emerge into the extent of neural recovery, improvements in sensory and motor functions, and the overall quality of life enhancements experienced by individuals subjected to this innovative treatment paradigm. As research continues to illuminate the intricate mechanisms underlying photobiomodulation, a clearer picture emerges of its transformative potential in revitalizing nerve function and ushering in a new era of oral nerve injury rehabilitation [20–22].

The potential of laser light to impact the peripheral nervous system has been explored in both the neuromuscular and somatosensory systems. This investigation dates to 1978 when it was discovered that laser radiation directed at exposed nerve tissue had a direct and beneficial effect as a preventive measure and a therapeutic intervention [23]. Currently, the preferred treatment for peripheral nerve injuries is advanced microsurgical repair or autologous nerve grafting. However, functional recovery is often unsatisfactory, and there is a need for new therapeutic approaches. Schwann cells in the peripheral nervous system play a crucial role in nerve repair. Various strategies, like pharmacological and cell-based therapies, have been used to enhance recovery, but none provide a universal cure and may have drawbacks and side effects [24]

Various treatment methods, including exercise, electrical stimulation (ES), magnetic stimulation, low-intensity ultrasound (LIU), and phototherapy, have been explored to enhance peripheral nerve regeneration. Exercise, especially aerobic activities like swimming and walking, promotes axonal growth and synaptic improvement, and when combined with ES, it shows better outcomes. Magnetic stimulation increases axon numbers and diameters, likely through stimulating NGF activity. A low-intensity ultrasound induces positive responses by promoting blood circulation and releasing neurotrophic factors. Phototherapy

and photobiomodulation therapy (PBMT) also aid in axonal regeneration and functional recovery. PBMT, utilizing low-level infrared light, stimulates SC proliferation and axonal diameter expansion, yet standardized application parameters remain a challenge [25].

Subsequently, in 1992, Rochkind and Ouaknine [26] demonstrated that photobiomodulation therapy (PBMT) influenced the electrical activity and morphology of injured and intact peripheral nerves in rats. They observed that the action potential of intact nerves increased by up to 33% following a single transcutaneous laser treatment. Similarly, injured nerves subjected to corresponding therapy exhibited a significantly increased action potential amplitude compared to untreated injured nerves [26].

Hakimiha and colleagues [27] conducted an investigation using a rat model to assess the effectiveness of PBMT on nerve regeneration. Their findings revealed that in studies involving highly metabolically active cells like nerve tissue, unfavorable outcomes were more commonly attributed to excessive dosing rather than insufficient dosing. In the current research, a notably expedited nerve recovery was achieved using an energy density of 6 J/cm^2. This discovery lends support to the notion of a "biphase dose-response" phenomenon in PBMT, wherein positive biostimulation responses are triggered at doses below 10 J/cm^2, while inhibitory responses are prominent at doses surpassing 20 J/cm^2 [27]. Nevertheless, this concept of a "window effect" has been extensively examined in existing literature, and the findings from the study under consideration align well with the established data in this field.

The results obtained from the immunoblotting analysis conducted on the second day after the injury indicated elevated concentrations of the nerve growth factor (NGF) in rats that underwent PBMT treatment, in comparison to the control group that did not receive PBMT. This rise in NGF levels corresponded with a swifter restoration of neurosensory functionality [26]. Likewise, a multitude of other investigations, encompassing both controlled and uncontrolled trials, have highlighted favorable subjective enhancements attributed to PBMT across diverse clinical contexts, such as perioral lesions [26], recovery after musculoskeletal surgery [24], and the promotion of osteogenic differentiation [27]. To sum up, PBMT manifests positive influences on distinct nervous, musculoskeletal, and epithelial systems.

In the research carried out by Sharifi et al., the impact of photobiomodulation on the recuperation of the sensory function in the lip and chin following bilateral sagittal split osteotomy (BSSO) was examined [26]. The procedure involved the utilization of a GaAs diode laser emitting continuous waves at a wavelength of 980 nm, generating a power output of 100 mW, and delivering an energy density of 12 J/cm^2. Substantial enhancements were noted in the scores recorded on the visual analogue scales (VAS) for general sensitivity, discrimination of pain, recognition of direction, and discrimination of two points, both after a span of 30 days and once more after 60 days [26].

Miloro et al. [27] considered patients with nerve injury due to odontectomy of the third molars or related practices such as anesthetic injection wounds. They used photobiomodulation with a diode laser 830 nm continuous wave, administrated in 20 applications over 3 months for each patient. Instrumental tests such as VAS or 2-point discriminations did not show any significant improvement in sensibility repairment compared to the control group. However, the limitation of this study is considered by the authors themselves to be the fact that they did not categorize the patients according to the degree of severity of the nerve damage, which could have influenced the significance of the statistics [27].

Gasperini et al. [28], Bashiri et al. [29], Salari et al. [30], Pinto et al. [32], Fuhrer-Valdivia et al. [33], and Ozen et al. [34] used the GaAlAs laser in their trials with wavelengths between 789 and 880 nm; according to their studies, their photobiomodulation protocol could significantly improve healing and sensibility could be regained after nerve injury, based on an improvement on pain scales and mechanical test results. Salari et al. [30], however, show that there is no statistical difference between the control group and the treatment group in regards to thermal sensitivity in all the periods examined, while all three authors agree that during the follow-up, the mechanical tests have better results [28–30,32–37].

The diode laser was used respectively by Miloro et al. [27], Qi et al. [31], Eshghpour et al. [38], De Oliveira et al. [39], Teixera-Santos et al. [36], and Mohajerani et al. [35].

Except for the trial conducted by Miloro et al., the diode laser could be considered as effective as the GaAlAs laser; in fact, in all of the studies, there is a significance in the improvement of pain relief, quality of life, and faster healing. Diode laser wavelengths were used between 632 and 880 nm, in a continuous mode and with the scanning method [27,31,35,36,38,39].

The articles examined in our review are all clinical trials. Peripheral nerve lesions are mainly caused by osteotomies involving the maxillofacial area and, to a lesser extent, nerve lesions following the extraction of the third molars. In the clinical trials examined, the evaluation of nerve sensitivity and the sensation of paraesthesia were evaluated through different tests: mechanosensory tests for routine assessment of surgical trigeminal nerve injuries, such as the brush stroke test, the 2-points discrimination test, and Semmes–Weinsten monofilament test and thermal sensitivity test to evaluate the neurological response to temperature change. Regarding the disturbance the patient perceived, a VAS scale is administered in almost all studies [26–40].

As far as photobiomodulation is concerned, the authors mostly used diode lasers or GaAs or GaAlAs lasers, and only in one case, a LED laser is used. The wavelengths used vary from a range from 632 to 910 nm for an application time of at least 10 sessions. Most of the treatments were administrated with a continuous wave. All of the authors report, because of the experimentation, an objective and subjective improvement of the symptoms without side effects, although in some cases, it was a matter of very long therapeutic plans in terms of time. In the cited studies, none of the authors report medium and long-term follow-ups of the effects of photobiomodulation on the patients examined. Table 3 summarizes the studies analyzed, highlighting the type of study, the sample, the type of laser used, and the application protocol. The outcomes and tests conducted to verify the recovery of sensitivity are also reported [26–40]. Table 4 indicates the laser parameters used in the clinical trial protocols being reviewed.

Table 3. Systematic literature review results.

Author, Year	Patient Sample	Type of Study	Type of Lesion	Neurological Tests Applied	Type of Laser	Wavelength	Number of Sessions	Outcome
Sharifi et al., 2020 [26]	18	A triple-blinded randomized controlled trial	Neurosensory disturbances after sagittal split ramus osteotomy	visual analogue scales (VAS), directional discrimination, 2-point discrimination, pain discrimination, and thermal discrimination	GaAs diode laser	980 nm for a 60-s continuous wave	7 sessions once a week	Pain discrimination, directional discrimination, and two-point discrimination improved after 30 days. The thermal discrimination rate was significantly higher in the laser group than in the control group 30 days after surgery.
Miloro et al., 2018 [27]	33	Multicentric randomized trial	Neurosensory hypoesthesia	VAS assessment, CNT (3-level dropout algorithm) including directional discrimination, 2-point discrimination, contact detection, and thermal discrimination and pinprick	Diode laser	830 nm continuous wave	20 applications in 3 months	No difference between the PBMT group and placebo.

Table 3. *Cont.*

Author, Year	Patient Sample	Type of Study	Type of Lesion	Neurological Tests Applied	Type of Laser	Wavelength	Number of Sessions	Outcome
Gasperini et al., 2013 [28]	10	Randomized Cross-over trial double-blinded	Neurosensory disorders resulting from bilateral mandibular sagittal split osteotomy	2-point discrimination, sensory test with a needle	GaAlAs Diode Laser	660 nm after surgery for intraoral spots, 789 nm after surgery for mandibular ramus, continuous wave	5 daily applications after surgery	Neurosensorial recovery of the treated side was faster than that of the non-treated side.
Bashiri et al., 2021 [29]	71	Parallel controlled trial	Neurosensory disturbance after zygomatic trauma	(VAS) for general sensitivity, two-point discrimination, and pain discrimination	GaAlAs Diode Laser	810 nm continuous wave	12 sessions in 6 weeks	Baseline results showed non-significant differences between the two groups based on VAS, pain, and two-point discrimination. Moreover, for the VAS scale, some significant differences were observed between the groups by passing "one month and three months from therapy". Pain and two-point discriminations showed a significant difference between the intervention and control groups in "one month after therapy" and "at the end of the therapy, one month after therapy, and three months after therapy", respectively.
Salari et al., 2022 [30]	19	Randomized triple-blinded clinical trial	Neurosensory disturbance in patients with mandibular nerve neurotmesis following traumatic mandibular fracture	Light touch sensations (with a cotton swab and wooden cotton swab), 2-point discrimination test, thermal discrimination (cold and warm stimulus), and electric pulp test	GaAlAs Diode Laser	810 nm continuous wave	12 sessions 2 times per week for 6 weeks	The results showed significantly improved light (cotton swab), light (wooden cotton swab), and sharp (dental needle) touch sensations, and two-point discrimination test in the PBMT group after the 10th, 11th, 10th, and 10th sessions, respectively. Two-way repeated measure ANOVA revealed that the trend of light touch sensation with cotton swabs and two-point discrimination test was statistically significant (p-value = 0.002 and 0.001, respectively). The results of OHIP-14 tests showed a significantly higher mean in the PBMTT group 3 months after PBMTT. There was no statistically significant difference in EPT and thermal discrimination tests regarding the patients' group.
Qi et al., 2020 [31]	20	Randomized controlled trial	neurosensory disorders resulting from bilateral mandibular sagittal split osteotomy	CNT test and VAS	Diode laser	808 nm continuous wave	Daily for 2 weeks	An effective approach to manage paresthesia post-IAN injury following impacted third molar surgery.

Table 3. *Cont.*

Author, Year	Patient Sample	Type of Study	Type of Lesion	Neurological Tests Applied	Type of Laser	Wavelength	Number of Sessions	Outcome
Eshghpour et al., 2017 [38]	16	Randomized double-blinded trial	neurosensory disorders resulting from bilateral mandibular sagittal split osteotomy	2-point discrimination test	Diode Laser	660 nm intraoral, 810 nm extraoral continuous wave	2 times a week for 3 weeks	Effective in the treatment of neurosensory disturbances.
De Oliveira et al., 2021 [39]	60	Randomized clinical trial	Paraesthesia after extraction of the third molar	The general perception, thermal perception, vibratory perception, pain perception, and 2-point discrimination test	Diode Laser	808 nm continuous wave	Not clear	PBMT showed effective.
Teixeira Santos et al., 2019 [40]	20	Randomized double blinded trial	neurosensory disorders resulting from bilateral mandibular sagittal split osteotomy	Semmes-Weinstein monofilament test	Diode Laser	780 nm continuous wave	5 sessions with $\frac{3}{4}$ weeks of distance	PBMT showed effective.
Pinto Faria et al., 2020 [32]	20	Parallel controlled trial	neurosensory disorders resulting from sagittal ramus osteotomy	Mechanical evaluations	GaAlasDiode Laser	808 nm continuous wave	2 sessions per week for 10 weeks	PBMT showed effective.
Fuhrer-Valdivia et al., 2014 [33]	31	Randomized double-blinded trial	neurosensory disorders resulting from bilateral mandibular sagittal split osteotomy	VAS and 2-point discrimination	GaAlas Diode laser	810 nm continuous wave	8 applications	PBMT showed effective.
Mohajerani et al., 2017 [35]	20	Randomized double-blinded trial	neurosensory disorders resulting from bilateral mandibular sagittal split osteotomy	Tactile and thermal sensitivity test	Diode Laser	combination of 810 nm laser and 632 nm LED beams	6 applications	Low-level laser therapy and light-emitting diode may improve VAS scores, 2-point discrimination, and brush stroke test results without any effect on the pinprick or contact detection test results.
De Assis Santos et al., 2022 [36]	42	Randomized controlled trial	Sensorial disorders after mandibular fractures	Tactile and thermal sensitivity test	LED	660 nm and 850 nm	6 months or until regression of symptoms	LED photobiomodulation accelerated the process of sensory change remission.
Pol et al., 2016 [37]	57	Randomized controlled trial	Neurosensory recovery of alveolar inferior nerve	Quantitative and qualitative tests	GaAs Diode Laser	904–910 nm continuous wave	10 sessions once a week	Potential in neurosensorial recovery.
Ozen et al., 2006 [34]	4	Randomized controlled trial	Neurosensory recovery of alveolar inferior nerve	Brushstroke test, 2- points discrimination, VAS	GaAlAs Diode Laser	820–830 nm continuous wave	20 sessions 3 times a week	Neurosensory recovery of alveolar inferior nerve.

Table 4. Summary table of the laser parameters used in the clinical trials analyzed.

Author, Year	Type of Laser	Wavelength	Power	Power Density (Total)	Irradiated Area (Each Spot)	Time of Application (Each Spot)
Sharifi et al., 2020 [26]	GaAs diode laser	980 nm for a 60-s continuous wave	100 mW	12 J/cm^2	0.5 cm^2	60 s

Table 4. *Cont.*

Author, Year	Type of Laser	Wavelength	Power	Power Density (Total)	Irradiated Area (Each Spot)	Time of Application (Each Spot)
Miloro et al., 2018 [27]	Diode laser	830 nm continuous wave	400 mW	-	0.15 cm^2	-
Gasperini et al., 2013 [28]	GaAlAs Diode Laser	660 nm after surgery for intraoral spots, 789 nm after surgery for mandibular ramus, continuous wave	20 mW–60 mW	5 J/cm^2–30 J/cm^2	-	10 s
Bashiri et al., 2021 [29]	GaAlAs Diode Laser	810 nm continuous wave	200 mW	5.5 W/cm^2	0.0364 cm^2	5 s
Salari et al., 2022 [30]	GaAlAs Diode Laser	810 nm continuous wave	200 mW	12–14 J/cm^2	0.0364 cm^2	30 s
Qi et al., 2020 [31]	Diode laser	808 nm continuous wave	50 mW	3 J/cm^2	3.14 cm^2	188 s
Eshghpour et al., 2017 [38]	Diode Laser	660 nm intraoral, 810 nm extraoral continuous wave	200 mW	1.5 J/cm^2–7 J/cm^2	-	10 s
De Oliveira et al., 2021 [39]	Diode Laser	808 nm continuous wave	100 mW	4 J/cm^2	-	40 s
Teixeira Santos et al., 2019 [40]	Diode Laser	780 nm continuous wave	-	-	0.04 cm^2	90 s
Pinto Faria et al., 2020 [32]	GaAlas Diode Laser	808 nm continuous wave	100 mW	2.8 J/cm^2	1 cm^2	28 s
Fuhrer-Valdivia et al., 2014 [33]	GaAlas Diode laser	810 nm continuous wave	100 mW	3 J/cm^2	0.283 cm^2	90 s
Mohajerani et al., 2017 [35]	Diode Laser	combination of 810 nm laser and 632 nm LED beams	-	5 J/cm^2 diode laser–2 J/cm^2 LED	-	90 s
De Assis Santos et al., 2022 [36]	LED	660 nm and 850 nm	6.4 mW/cm^2	7.64 J/cm^2	-	-
Pol et al., 2016 [37]	GaAs Diode Laser	904–910 nm continuous wave	0.27 W/cm^2	244.8 J/cm^2	0.5 cm^2	900 s
Ozen et al., 2006 [34]	GaAlAs Diode Laser	820–830 nm continuous wave	70 mW	7 J/cm^2	0.5 cm^2	90 s

Photobiomodulation is a non-invasive therapeutic approach, as the literature confirms, that involves the use of light to stimulate cellular activity and promote tissue regeneration. It has shown promising results in the regeneration of peripheral nerves. Studies conducted on animal models, such as rats [41–52], have demonstrated that PBM can enhance nerve regeneration by promoting axonal growth, reducing inflammation, and increasing cellular metabolism. These experiments typically involve applying specific wavelengths of light to the injured nerve area, leading to improved nerve function and accelerated healing [53–56]. While more research is needed to fully understand the underlying mechanisms and optimize treatment protocols, the potential of photobiomodulation as a tool for peripheral nerve regeneration is an exciting avenue for future medical applications [57–59]. The studies analyzed in our scoping review confirm encouraging results detectable instrumentally,

regarding the recovery of nervous sensitivity of the areas affected by a lesion, confirming the results of the literature regarding the applications of laser-assisted protocols and for the wavelengths tested. Indeed, for a targeted photobiomodulation treatment aimed at recovering sensitivity following peripheral nerve injury, specific wavelengths of light are typically used [57–64]. Wavelengths within the near-infrared range (600–1100 nm) are commonly employed for this purpose. These wavelengths have a greater ability to penetrate tissues and reach the nerve fibers, allowing for deeper stimulation and interaction with cellular components. Wavelengths around 800–850 nm are often favored due to their optimal tissue penetration and interaction with the mitochondrial enzyme cytochrome c oxidase [57–64]. This interaction triggers a cascade of cellular responses, including enhanced ATP production, reduced oxidative stress, and the modulation of signaling pathways involved in nerve repair and regeneration. Furthermore, wavelengths in the red-light range (around 630–670 nm) can also contribute to the stimulation of cellular activity and blood flow, aiding in tissue oxygenation and nutrient supply to support nerve healing. By utilizing these specific wavelengths, photobiomodulation can effectively promote nerve tissue repair, axonal growth, and sensory function recovery after peripheral nerve injury. However, it is important to note that treatment parameters, such as power density, duration, and frequency of exposure, need to be carefully optimized based on the severity of the injury and individual patient characteristics for optimal therapeutic outcomes [64–71].

4.1. Treatment Alternatives

A wide array of therapeutic approaches are employed to mitigate pain, showcasing the versatility of medical interventions in addressing this complex issue. These methods encompass the utilization of painkillers, which encompass both non-opioid analgesics and anti-inflammatory medications, offering rapid relief by targeting pain pathways and reducing inflammation [72–77]. Additionally, corticosteroids find application due to their potent anti-inflammatory properties, effectively alleviating pain associated with inflammatory conditions. Painkillers play a pivotal role in managing neuropathic pain, a complex condition characterized by aberrant nerve signaling. Drugs such as tricyclic antidepressants, anticonvulsants, and serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly prescribed. These medications target specific pathways involved in nerve transmission and modulation, helping to alleviate the distinctive burning, shooting, or tingling sensations associated with neuropathic pain [72–77]. While painkillers offer relief, their effectiveness varies among individuals, and a multidisciplinary approach may be needed for comprehensive neuropathic pain management. In cases where nerve-related pain is a concern, nerve denervation, or ablation, emerges as a potential solution. By interrupting the transmission of pain signals along the affected nerves, this technique can provide substantial relief. Similarly, muscle relaxants are employed to ease pain stemming from muscle tension or spasms, allowing for enhanced comfort and improved mobility. Nerve denervation or ablation is considered in cases of severe neuropathic pain that is unresponsive to conservative treatments [72–77]. This procedure involves deliberately disrupting the nerve pathways responsible for transmitting pain signals, often providing relief when other methods have failed. The decision to opt for nerve denervation is based on several criteria. Firstly, a thorough evaluation of the patient's medical history, pain duration, and response to prior treatments is conducted [76]. Candidates for denervation typically exhibit localized neuropathic pain that is well-defined and refractory to conventional interventions. Moreover, imaging studies, such as MRI or nerve blocks, may be utilized to precisely identify the pain source and the nerves involved. A successful nerve denervation outcome hinges on accurate identification and targeting of the specific nerve responsible for the pain. Patient selection is critical, with consideration given to factors such as overall health status, potential risks of the procedure, and the patient's willingness to undergo a more invasive treatment approach [72–74]. The outcomes of nerve denervation can vary, with some patients experiencing significant and sustained pain relief, while others may see only partial improvement. The procedure's success often depends on the nerve's regrowth capacity and

the underlying cause of neuropathy. Post-denervation rehabilitation, including physical therapy, is crucial to optimize outcomes. The close collaboration between the patient, pain specialist, and interdisciplinary team is vital to making informed decisions regarding nerve denervation as a therapeutic option for refractory neuropathic pain [72–77]. Physical therapy is a cornerstone in pain management, focusing on rehabilitation, strengthening, and restoring functional capacity. This approach not only addresses the root causes of pain but also empowers patients with long-term coping mechanisms and an improved overall well-being. An intriguing avenue lies in the administration of parietal hyaluronic acid preparations or biological substances, such as stem cells [72–77]. These innovative therapies target tissue regeneration and repair, holding the potential for more sustainable pain relief by addressing underlying structural issues. Stem cells hold considerable promise as a potential therapeutic avenue for neuropathic pain management. These versatile cells have the capacity to differentiate into various cell types and secrete bioactive molecules that can modulate inflammation, tissue repair, and nerve regeneration. In the context of neuropathic pain, stem cell therapy aims to address underlying pathophysiological mechanisms by promoting nerve tissue regeneration and reducing neuroinflammation [72–77]. Preclinical studies involving animal models have demonstrated encouraging results, showing improved pain-related behaviors and enhanced nerve function after stem cell transplantation. However, translating these findings into clinical practice requires careful consideration of factors such as the stem cell source, delivery methods, and long-term safety and efficacy. While stem cell-based therapies offer a promising avenue for neuropathic pain treatment, further research and clinical trials are necessary to establish their definitive role and optimize their potential benefits. It is noteworthy, however, that while each of these interventions demonstrates efficacy to varying extents, their impact tends to be temporally constrained, usually offering relief for a limited duration, spanning from several weeks to a few months [72–77]. To further the discourse, I propose an expansion of the discussion section, guided by the following essential questions, thereby delving deeper into the long-term effectiveness, potential synergies, and avenues for enhancing the durability of pain management interventions [72–77].

4.2. Limits of the Study and Future Perspectives

Nowadays, there is no validated protocol for the use of photobiomodulation in patients who have suffered damage to the nerve fibers and for the recovery of sensitivity, a consensus from the scientific authorities would be needed to establish a single treatment protocol considering the available scientific evidence.

Future research prospects could include further randomized controlled clinical trials that should be conducted to evaluate the effects of different types of lasers and wavelengths on patients. Laboratory studies on cell lines and animal models could be useful to establish what is the cellular and metabolic effect of laser light on tissues, to contribute to the choice of the right wavelength and application according to the pathology and the tissues to be treated.

Another possible research line could be the evaluation of a possible amplification of the photobiomodulation effect through pharmacological treatment.

5. Conclusions

The results of this thorough and extensive review provides substantial evidence that the application of photobiomodulation across various wavelengths has a remarkable and expedited impact on the improvement of Visual Analog Scale (VAS) scores concerning general sensory perception and thermal discrimination. Notably, the utilization of photobiomodulation demonstrates its capacity to accelerate the recovery of these sensory functions. This is particularly significant considering the non-invasive nature of photobiomodulation and its high level of patient tolerance. Therefore, photobiomodulation emerges as a robust and efficacious therapeutic strategy for effectively addressing and managing neurosensory disruptions that may arise postoperatively. The promising outcomes observed in this

review highlight its potential as a valuable addition to the array of treatments available for mitigating and treating postoperative neurosensory complications.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app13169258/s1, Table S1: PRISMA-ScR Checklist; Table S2: Search strategies for electronic databases; Table S3. JBI critical appraisal checklist for randomized controlled trials, a tool used for risk of bias assessment.

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References

1. Søren, H. Iatrogenic injury to oral branches of the trigeminal nerve: Records of 449 cases. *Clin. Oral. Investig.* **2007**, *11*, 133–142.
2. Coulthard, P.; Kushnerev, E.; Yates, J.M.; Walsh, T.; Patel, N.; Bailey, E.; Renton, T.F. Interventions for iatrogenic inferior alveolar and lingual nerve injury. *Cochrane Database Syst. Rev.* **2014**, *4*, CD005293. [CrossRef] [PubMed]
3. Weyh, A.; Pucci, R.; Valentini, V.; Fernandes, R.; Salman, S. Injuries of the Peripheral Mandibular Nerve, Evaluation of Interventions and Outcomes: A Systematic Review. *Craniomaxillofac Trauma. Reconstr.* **2021**, *14*, 337–348. [CrossRef] [PubMed]
4. Wang, M.L.; Rivlin, M.; Graham, J.G.; Beredjiklian, P.K. Peripheral nerve injury, scarring, and recovery. *Connect. Tissue Res.* **2019**, *60*, 3–9. [CrossRef] [PubMed]
5. Andreo, L.; Ribeiro, B.G.; Alves, A.N.; Martinelli, A.S.A.; Soldera, C.B.; Horliana, A.C.R.T.; Bussadori, S.K.; Fernandes, K.P.S.; Mesquita-Ferrari, R.A. Effects of Photobiomodulation with Low-level Laser Therapy on Muscle Repair Following a Peripheral Nerve Injury in Wistar Rats. *Photochem. Photobiol.* **2020**, *96*, 1124–1132. [CrossRef]
6. Diker, N.; Aytac, D.; Helvacioglu, F.; Oguz, Y. Comparative effects of photobiomodulation therapy at wavelengths of 660 and 808 nm on regeneration of inferior alveolar nerve in rats following crush injury. *Lasers Med. Sci.* **2020**, *35*, 413–420. [CrossRef]
7. Hamblin, M.R. Mechanisms and Mitochondrial Redox Signaling in Photobiomodulation. *Photochem. Photobiol.* **2018**, *94*, 199–212. [CrossRef]
8. Arany, P.R. Photobiomodulation-Activated Latent Transforming Growth Factor-β1: A Critical Clinical Therapeutic Pathway and an Endogenous Optogenetic Tool for Discovery. *Photobiomodul Photomed. Laser Surg.* **2022**, *40*, 136–147. [CrossRef]
9. 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]
10. 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] [PubMed]
11. Wang, Y.; Huang, Y.Y.; Wang, Y.; Lyu, P.; Hamblin, M.R. Red (660 nm) or near-infrared (810 nm) photobiomodulation stimulates, while blue (415 nm), green (540 nm) light inhibits proliferation in human adipose-derived stem cells. *Sci. Rep.* **2017**, *7*, 7781. [CrossRef]
12. Sommer, A.P. Mitochondrial cytochrome c oxidase is not the primary acceptor for near infrared light-it is mitochondrial bound water: The principles of low-level light therapy. *Ann. Transl. Med.* **2019**, *7* (Suppl. 1), S13. [CrossRef] [PubMed]
13. Peters, M.D.J.; Marnie, C.; Tricco, A.C.; Pollock, D.; Munn, Z.; Alexander, L.; McInerney, P.; Godfrey, C.M.; Khalil, H. Updated methodological guidance for the conduct of scoping reviews. *JBI Evid. Implement.* **2021**, *19*, 3–10. [CrossRef] [PubMed]
14. Aromataris, E.; Munn, Z. JBI Manual for Evidence Synthesis. 2020. Available online: https://synthesismanual.jbi.global (accessed on 24 April 2023).

15. Tricco, A.C.; Lillie, E.; Zarin, W.; O'Brien, K.K.; Colquhoun, H.; Levac, D.; Moher, D.; Peters, M.D.; Horsley, T.; Weeks, L.; et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. *Ann. Intern. Med.* **2018**, *169*, 467–473. [CrossRef]
16. Tufanaru, C.; Munn, Z.; Aromataris, E.; Campbell, J.; Hopp, L. Chapter 3: Systematic reviews of effectiveness. In *JBI Manual for Evidence Synthesis*; Aromataris, E., Munn, Z., Eds.; JBI: San Diego, CA, USA, 2020.
17. Hakimiha, N.; Dehghan, M.M.; Manaheji, H.; Zaringhalam, J.; Farzad-Mohajeri, S.; Fekrazad, R.; Moslemi, N. Recovery of inferior alveolar nerve by photobiomodulation therapy using two laser wavelengths: A behavioral and immunological study in rat. *J. Photochem. Photobiol. B* **2020**, *204*, 111785. [CrossRef]
18. El Mobadder, M.; Nammour, S.; Ortega, M.; Grzech-Le´sniak, K. Photobiomodulation Therapy Applied after 6 Months for the Management of a Severe Inferior Alveolar Nerve Injury. *Life* **2021**, *11*, 1420. [CrossRef]
19. Muniz, X.C.; de Assis, A.C.C.; de Oliveira, B.S.A.; Ferreira, L.F.R.; Bilal, M.; Iqbal, H.M.N.; Soriano, R.N. Efficacy of low-level laser therapy in nerve injury repair-a new era in therapeutic agents and regenerative treatments. *Neurol. Sci.* **2021**, *42*, 4029–4043. [CrossRef]
20. Ravera, S.; Colombo, E.; Pasquale, C.; Benedicenti, S.; Solimei, L.; Signore, A.; Amaroli, A. Mitochondrial Bioenergetic, Photobiomodulation and Trigeminal Branches Nerve Damage, What's the Connection? A Review. *Int. J. Mol. Sci.* **2021**, *22*, 4347. [CrossRef]
21. Kobiela Ketz, A.; Byrnes, K.R.; Grunberg, N.E.; Kasper, C.E.; Osborne, L.; Pryor, B.; Tosini, N.L.; Wu, X.; Anders, J.J. Characterization of Macrophage/Microglial Activation and Effect of Photobiomodulation in the Spared Nerve Injury Model of Neuropathic Pain. *Pain. Med.* **2017**, *18*, 932–946. [CrossRef]
22. Abdelkarim Elafifi, H.; Acevedo Carrero, M.; Parada Avendaño, I.; España-Tost, A.; Arnabat-Domínguez, J. Effect of Photobiomodulation (Diode 810 nm) on Long-Standing Neurosensory Alterations of the Inferior Alveolar Nerve: A Case Series Study. *Photobiomodul Photomed. Laser Surg.* **2021**, *39*, 4–9. [CrossRef]
23. Li, B.; Wang, X. Photobiomodulation enhances facial nerve regeneration via activation of PI3K/Akt signaling pathway-mediated antioxidant response. *Lasers Med. Sci.* **2022**, *37*, 993–1006. [CrossRef] [PubMed]
24. Rochkind, S.; Ouaknine, G.E. New trend in neuroscience: Lowpower laser effect on peripheral and central nervous system. *Neurol. Res.* **1992**, *14*, 2. [CrossRef] [PubMed]
25. Hakimiha, N.; Bassir, S.H.; Romanos, G.E.; Shamshiri, A.R.; Moslemi, N. Efficacy of photobiomodulation therapy on neurosensory recovery in patients with inferior alveolar nerve injury following oral surgical procedures: A systematic review. *Quintessence Int.* **2021**, *52*, 140–153. [PubMed]
26. Sharifi, R.; Fekrazad, R.; Taheri, M.M.; Kasaeian, A.; Babaei, A. Effect of photobiomodulation on recovery from neurosensory disturbances after sagittal split ramus osteotomy: A triple-blind randomised controlled trial. *Br. J. Oral. Maxillofac. Surg.* **2020**, *58*, 535–541. [CrossRef] [PubMed]
27. Miloro, M.; Criddle, T.R. Does Low-Level Laser Therapy Affect Recovery of Lingual and Inferior Alveolar Nerve Injuries? *J. Oral. Maxillofac. Surg.* **2018**, *76*, 2669–2675. [CrossRef]
28. Gasperini, G.; de Siqueira, I.C.; Costa, L.R. Lower-level laser therapy improves neurosensory disorders resulting from bilateral mandibular sagittal split osteotomy: A randomized crossover clinical trial. *J. Craniomaxillofac Surg.* **2014**, *42*, e130–e133. [CrossRef]
29. Bashiri, S.; Malekzadeh, H.; Fekrazad, R. The effect of delayed photobiomodulation on neurosensory disturbance recovery after zygomatic trauma: A parallel controlled clinical trial. *J. Photochem. Photobiol. B* **2021**, *217*, 112153. [CrossRef]
30. Salari, B.; Nikparto, N.; Babaei, A.; Fekrazad, R. Effect of delayed photobiomodulation therapy on neurosensory recovery in patients with mandibular nerve neurotmesis following traumatic mandibular fracture: A randomized triple-blinded clinical trial. *J. Photochem. Photobiol. B* **2022**, *232*, 112460. [CrossRef]
31. Qi, W.; Wang, Y.; Huang, Y.-Y.; Jiang, Y.; Yuan, L.; Lyu, P.; Arany, P.R.; Hamblin, M.R. Photobiomodulation therapy for management of inferior alveolar nerve injury post-extraction of impacted lower third molars. *Lasers Dent. Sci.* **2020**, *4*, 25–32. [CrossRef]
32. Esteves Pinto Faria, P.; Temprano, A.; Piva, F.; Sant'ana, E.; Pimenta, D. Low-level laser therapy for neurosensory recovery after sagittal ramus osteotomy. *Minerva Stomatol.* **2020**, *69*, 141–147. [CrossRef]
33. Führer-Valdivia, A.; Noguera-Pantoja, A.; Ramírez-Lobos, V.; Solé-Ventura, P. Low-level laser effect in patients with neurosensory impairment of mandibular nerve after sagittal split ramus osteotomy. Randomized clinical trial, controlled by placebo. *Med. Oral. Patol. Oral. Cir. Bucal.* **2014**, *19*, e327–e334. [CrossRef] [PubMed]
34. Ozen, T.; Orhan, K.; Gorur, I.; Ozturk, A. Efficacy of low level laser therapy on neurosensory recovery after injury to the inferior alveolar nerve. *Head. Face Med.* **2006**, *2*, 3. [CrossRef] [PubMed]
35. Mohajerani, S.H.; Tabeie, F.; Bemanali, M.; Tabrizi, R. Effect of Low-Level Laser and Light-Emitting Diode on Inferior Alveolar Nerve Recovery After Sagittal Split Osteotomy of the Mandible: A Randomized Clinical Trial Study. *J. Craniofac Surg.* **2017**, *28*, e408–e411. [CrossRef] [PubMed]
36. Santos, V.P.d.A.; Rocha-Junior, W.G.P.; Luz, J.G.C. Effects of light-emitting diode (LED) therapy on sensory changes in the inferior alveolar nerve after surgical treatment of mandibular fractures: A randomized controlled trial. *Oral. Maxillofac. Surg*, 2022; *online ahead of print*.
37. Pol, R.D.; Gallesio, G.D.; Riso, M.D.; Ruggiero, T.D.; Scarano, A.D.; Mortellaro, C.M.; Mozzati, M.M. Effects of Superpulsed, Low-Level Laser Therapy on Neurosensory Recovery of the Inferior Alveolar Nerve. *J. Craniofac Surg.* **2016**, *27*, 1215–1219. [CrossRef] [PubMed]

38. Eshghpour, M.; Shaban, B.; Ahrari, F.; Erfanian, M.; Shadkam, E. Is Low-Level Laser Therapy Effective for Treatment of Neurosensory Deficits Arising From Sagittal Split Ramus Osteotomy? *J. Oral. Maxillofac. Surg.* **2017**, *75*, 2085–2090. [CrossRef] [PubMed]
39. De Oliveira, R.F.; da Silva, C.V.; de Paula, J.T.; de Oliveira, K.D.C.M.; de Siqueira, S.R.D.T.; de Freitas, P.M. Effectiveness of Laser Therapy and Laser Acupuncture on Treating Paraesthesia After Extraction of Lower Third Molars. *Photobiomodul Photomed. Laser Surg.* **2021**, *39*, 774–781. [CrossRef]
40. Santos, F.T.; Sciescia, R.; Santos, P.L.; Weckwerth, V.; Dela Coleta Pizzol, K.E.; Queiroz, T.P. Is Low-Level Laser Therapy Effective on Sensorineural Recovery After Bilateral Sagittal Split Osteotomy? Randomized Trial. *J. Oral. Maxillofac. Surg.* **2019**, *77*, 164–173. [CrossRef]
41. da Silva, T.G.; Ribeiro, R.S.; Mencalha, A.L.; Fonseca, A.d.S. Photobiomodulation at molecular, cellular, and systemic levels. *Lasers Med. Sci.* **2023**, *38*, 136. [CrossRef]
42. Hosseinpour, S.; Tunér, J.; Fekrazad, R. Photobiomodulation in Oral Surgery: A Review. *Photobiomodul Photomed. Laser Surg.* **2019**, *37*, 814–825. [CrossRef]
43. Dompe, C.; Moncrieff, L.; Matys, J.; Grzech-Leśniak, K.; Kocherova, I.; Bryja, A.; Bruska, M.; Dominiak, M.; Mozdziak, P.; Skiba, T.H.I.; et al. Photobiomodulation-Underlying Mechanism and Clinical Applications. *J. Clin. Med.* **2020**, *9*, 1724. [CrossRef]
44. Shoman, A.; Hassan, A.; Kassab, A. A Study on the Effect of 850 nm Low-Level Diode Laser versus Electrical Stimulation in Facial Nerve Regeneration for Patients with Bell's Palsy. *ORL J. Otorhinolaryngol. Relat. Spec.* **2022**, *84*, 370–377. [CrossRef]
45. De Oliveira, R.F.; de Andrade Salgado, D.M.; Trevelin, L.T.; Lopes, R.M.; da Cunha, S.R.; Aranha, A.C.; de Paula Eduardo, C.; de Freitas, P.M. Benefits of laser phototherapy on nerve repair. *Lasers Med. Sci.* **2015**, *30*, 1395–1406. [CrossRef] [PubMed]
46. Rochkind, S. Phototherapy in peripheral nerve regeneration: From basic science to clinical study. *Neurosurg. Focus.* **2009**, *26*, E8. [CrossRef] [PubMed]
47. Anders, J.J.; Moges, H.; Wu, X.; Erbele, I.D.; Alberico, S.L.; Saidu, E.K.; Smith, J.T.; Pryor, B.A. In vitro and in vivo optimization of infrared laser treatment for injured peripheral nerves. *Lasers Surg. Med.* **2014**, *46*, 34–45. [CrossRef]
48. Mohammed, I.F.; Al-Mustawfi, N.; Kaka, L.N. Promotion of regenerative processes in injured peripheral nerve induced by low-level laser therapy. *Photomed. Laser Surg.* **2007**, *25*, 107–111. [CrossRef]
49. von Leden, R.E.; Cooney, S.J.; Ferrara, T.M.; Zhao, Y.; Dalgard, C.L.; Anders, J.J.; Byrnes, K.R. 808 nm wavelength light induces a dose-dependent alteration in microglial polarization and resultant microglial induced neurite growth. *Lasers Surg. Med.* **2013**, *45*, 253–263. [CrossRef] [PubMed]
50. Alayat, M.S.M.; Basalamah, M.A.; Elbarrany, W.G.E.A.; El Sawy, N.A.M.; Abdel-Kafy, E.M. Efficacy of multi-wave locked system laser therapy on nerve regeneration after crushing in Wister rats. *J. Phys. Ther. Sci.* **2021**, *33*, 549–553. [CrossRef] [PubMed]
51. Alayat, M.S.M.; Basalamah, M.A.; Elbarrany, W.G.E.A.; El-Sawy, N.A.M.; Abdel-Kafy, E.M.; El-Fiky, A.A. Dose-dependent effect of the pulsed Nd:YAG laser in the treatment of crushed sciatic nerve in Wister rats: An experimental model. *Lasers Med. Sci.* **2020**, *35*, 1989–1998. [CrossRef]
52. Fernandes-Neto, J.A.; Simões, T.M.; Batista, A.L.; Lacerda-Santos, J.T.; Palmeira, P.S.; Catão, M.V. Laser therapy as treatment for oral paresthesia arising from mandibular third molar extraction. *J. Clin. Exp. Dent.* **2020**, *12*, e603–e606. [CrossRef]
53. Buchaim, D.V.; Andreo, J.C.; Ferreira Junior, R.S.; Barraviera, B.; Rodrigues, A.C.; Macedo, M.C.; Rosa Junior, G.M.; Shinohara, A.L.; Santos German, I.J.; Pomini, K.T.; et al. Efficacy of Laser Photobiomodulation on Morphological and Functional Repair of the Facial Nerve. *Photomed. Laser Surg.* **2017**, *35*, 442–449. [CrossRef]
54. Rosso, M.P.O.; Rosa Júnior, G.M.; Buchaim, D.V.; German, I.J.S.; Pomini, K.T.; de Souza, R.G.; Pereira, M.; Favaretto Júnior, I.A.; Bueno, C.R.S.; Gonçalves, J.B.O.; et al. Stimulation of morphofunctional repair of the facial nerve with photobiomodulation, using the end-to-side technique or a new heterologous fibrin sealant. *J Photochem Photobiol B.* **2017**, *175*, 20–28. [CrossRef] [PubMed]
55. Andreo, L.; Soldera, C.B.; Ribeiro, B.G.; de Matos, P.R.V.; Bussadori, S.K.; Fernandes, K.P.S.; Mesquita-Ferrari, R.A. Effects of photobiomodulation on experimental models of peripheral nerve injury. *Lasers Med. Sci.* **2017**, *32*, 2155–2165. [CrossRef] [PubMed]
56. Bittencourt, M.A.; Paranhos, L.R.; Martins-Filho, P.R. Low-level laser therapy for treatment of neurosensory disorders after orthognathic surgery: A systematic review of randomized clinical trials. *Med. Oral. Patol. Oral. Cir. Bucal.* **2017**, *22*, 780–787.
57. Brignardello-Petersen, R. Low-level laser therapy may reduce the time of recovery from paresthesia after orthognathic surgery. *J. Am. Dent. Assoc.* **2018**, *149*, e44. [CrossRef]
58. Barbosa, L.M.; de Luna Gomes, J.M.; Laureano Filho, J.R.; do Egito Vasconcelos, B.C.; Dantas Moraes, S.L.; Pellizzer, E.P. Does the use of low-level light therapy postoperatively reduce pain, oedema, and neurosensory disorders following orthognathic surgery? A systematic review. *Int. J. Oral. Maxillofac. Surg.* **2022**, *51*, 355–365. [CrossRef] [PubMed]
59. Prazeres, L.D.; Muniz, Y.V.; Barros, K.M.; Gerbi, M.E.; Laureano Filho, J.R. Effect of infrared laser in the prevention and treatment of paresthesia in orthognathic surgery. *J. Craniofac Surg.* **2013**, *24*, 708–711.
60. da Fonseca, E.V.; Bussadori, S.K.; da Silva Martinho, L.F.C.; de Sousa Melo, M.C.; de Andrade, F.L.; Gonçalves, M.L.L.; Mesquita-Ferrari, R.A.; Horliana, A.C.R.T.; Fernandes, K.P.S. Evaluation of photobiomodulation effects on pain, edema, paresthesia, and bone regeneration after surgically assisted rapid maxillary expansion: Study protocol for a randomized, controlled, and double blind clinical trial. *Medicine* **2019**, *98*, e17756.
61. Leyane, T.S.; Jere, S.W.; Houreld, N.N. Cellular Signalling and Photobiomodulation in Chronic Wound Repair. *Int. J. Mol. Sci.* **2021**, *22*, 11223. [CrossRef]

62. Nascimento, J.J.A.C.; Machado, A.S.D.; Della-Santa, G.M.L.; Fernandes, D.C.; Ferreira, M.C.; Machado, G.A.P.; Chaves, B.C.G.; Costa, K.B.; Rocha-Vieira, E.; Oliveira, M.X.; et al. Effects of photobiomodulation therapy on functional recovery, angiogenesis and redox status in denervated muscle of rats. *Einstein* **2021**, *19*, eAO6001. [CrossRef]
63. Gambarotta, G.; Raimondo, S.; Udina, E.; Phillips, J.B.; Haastert-Talini, K. Editorial: Peripheral nerve regeneration. *Front. Cell Neurosci.* **2019**, *13*, 464. [CrossRef]
64. Araujo, T.; Andreo, L.; Tobelem, D.D.C.; Silva, T.; Malavazzi, T.C.D.S.; Martinelli, A.; Lemes, B.; Fernandes, K.P.S.; Bussadori, S.K.; Mesquita-Ferrari, R.A. Effects of systemic vascular photobiomodulation using LED or laser on sensory-motor recovery following a peripheral nerve injury in Wistar rats. *Photochem. Photobiol. Sci.* **2023**, *22*, 567–577. [CrossRef] [PubMed]
65. Modrak, M.; Talukder, M.A.H.; Gurgenashvili, K.; Noble, M.; Elfar, J.C. Peripheral nerve injury and myelination: Potential therapeutic strategies. *J. Neurosci. Res.* **2020**, *98*, 780–795. [CrossRef] [PubMed]
66. Lopes, B.; Sousa, P.; Alvites, R.; Branquinho, M.; Sousa, A.C.; Mendonça, C.; Atayde, L.M.; Luís, A.L.; Varejão, A.S.P.; Maurício, A.C. Peripheral Nerve Injury Treatments and Advances: One Health Perspective. *Int. J. Mol. Sci.* **2022**, *23*, 918. [CrossRef]
67. Zwick, H.; Beatrice, E.S. Long-term changes in spectral sensitivity after low-level laser (514 nm) exposure. *Mod. Probl. Ophthalmol.* **1978**, *19*, 319. [PubMed]
68. De Rezende, R.A.; Silva, D.N.; Frigo, L. Effect of GaAIAs low-level laser therapy on mouth opening after orthognathic surgery. *Lasers Med. Sci.* **2018**, *12*, 1.
69. 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**, *9*, 123. [CrossRef]
70. Boras, V.V.; Juras, D.V.; Rogul, A.A.; Pandurić, D.G.; Verzak, Z.; Brailo, V.L. Applications of low level laser therapy. In *A Textbook of Advanced Oral and Maxillofacial Surgery*; Motamedi, M.H.K., Ed.; Intech: London, UK, 2013; pp. 327–339.
71. Della Santa, G.M.L.; Ferreira, M.C.; Machado, T.P.G.; Oliveira, M.X.; Santos, A.P. Effects of Photobiomodulation Therapy (LED 630 nm) on Muscle and Nerve Histomorphometry after Axonotmesis. *Photochem. Photobiol.* **2021**, *97*, 1116–1122. [CrossRef]
72. Finnerup, N.B.; Kuner, R.; Jensen, T.S. Neuropathic Pain: From Mechanisms to Treatment. *Physiol. Rev.* **2021**, *101*, 259–301. [CrossRef]
73. Baron, R.; Binder, A.; Wasner, G. Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol.* **2010**, *9*, 807–819. [CrossRef]
74. Cavalli, E.; Mammana, S.; Nicoletti, F.; Bramanti, P.; Mazzon, E. The neuropathic pain: An overview of the current treatment and future therapeutic approaches. *Int. J. Immunopathol. Pharmacol.* **2019**, *33*, 2058738419838383. [CrossRef]
75. Attal, N.; Bouhassira, D. Advances in the treatment of neuropathic pain. *Curr. Opin. Neurol.* **2021**, *34*, 631–637. [CrossRef] [PubMed]
76. Gossrau, G.; Sabatowski, R. Diagnostik und Therapie neuropathischer Schmerzen [Diagnostics and therapy of neuropathic pain]. *Anaesthesist* **2021**, *70*, 993–1002. [CrossRef] [PubMed]
77. Alcántara Montero, A.; Ibor Vidal, P.J.; Alonso Verdugo, A.; Trillo Calvo, E. Actualización en el tratamiento farmacológico del dolor neuropático [Update in the pharmacological treatment of neuropathic pain]. *Semergen* **2019**, *45*, 535–545. [CrossRef] [PubMed]