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SYSTEMATIC REVIEW

The effect of photobiomodulation on hearing loss: A systematic review

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Abstract

Objectives: To assess outcomes associated with photobiomodulation therapy (PBMT) for hearing loss in human and animal studies.

Design: Systematic review and narrative synthesis in accordance with PRISMA guidelines.

Setting: Data bases searched: MEDLINE, EMBASE, CENTRAL, ClinicalTrials.gov and Web of Science. No limits were placed on language or year of publication. Review conducted in accordance with the PRISMA 2020 statement.

Participants: All human and animal subjects treated with PBMT for hearing loss.

Main outcome measures: Pre- and post-PBMT audio metric outcomes.

Results: Searches identified 122 abstracts and 49 full text articles. Of these, 17 studies met the inclusion criteria, reporting outcomes in 327 animals (11 studies), 30 humans (1 study), and 40 animal specimens (5 studies). PBMT parameters included 6 different wavelengths: 908 nm (1 study), 810 nm (1 study), 532 & 635 nm (1 study), 830 nm (3 studies), 808 nm (11 studies). The duration ranged from 4 to 60 minutes in a session, and the follow-up ranged from 5–28 days. Outcomes improved significantly when wavelengths within the range of 800–830 nm were used, and with greater duration of PBMT exposure. Included studies predominantly consisted of non-randomized controlled trials (10 studies).

Conclusions: Hearing outcomes following PBMT appear to be superior to no PBMT for subjects with hearing loss, although higher level evidence is required to verify this. PBMT enables concentrated, focused delivery of light therapy to the inner ear through a non-invasive manner with minimal side effects. As a result of heterogeneity in reporting PBMT parameters and outcomes across the included studies, direct comparison is challenging.

KEYWORDS
hearing loss, low level light therapy, near infrared light, otoprotection, photobiomodulation

1 | INTRODUCTION

1.1 | Background and epidemiology

Hearing impairment is one of the most common medical conditions,[1] affecting approximately 466 million people worldwide.[2] Impact can adversely affect employment, communication and social interaction. This can lead to manifold psychosocial burdens,[3] as well as significant detrimental economic impacts to the individual and wider society.[4]

Common rehabilitation options include hearing aids, and surgery such as cochlear implantation, although operative trauma can potentially exacerbate existing hearing loss. Current research suggests there may be scope for photobiomodulation therapy (PBMT) to mitigate ototoxic trauma associated with surgery, traumatic noise exposure or from chemical trauma by ototoxic medications such as platinum-based chemotherapy.

Photobiomodulation therapy (PBMT), also referred to as 'low-level laser light (LLLT)' and 'near-infrared light', is a non-invasive therapy that uses light energy to enhance or modulate the activities of specific cells to improve or change the function of body tissues. It is increasingly used to treat medical conditions, including skin lesions and neurodegenerative disorders, to reduce pain, and to stimulate the regeneration of body tissues.[5–8]

1.2 | PBMT mechanism of action

Cell damage within the inner ear is a complex combination of inflammatory and oxidative stress. The mechanism of PBMT on neural-cell recovery and regeneration is yet to be clarified. The prevailing theory focuses on mitochondrial cytochrome c oxidase, a key protein in cellular metabolism and repair, and one of three major proteins in the human body responding to near infrared wavelength.[9] These proteins absorb near-infrared wavelength energy and then modulate biochemical reactions within cells. Cytochrome c oxidase is a large transmembrane protein complex in the mitochondrial electron transport chain that consists of five protein complexes that together produce adenosine 5-triphosphate (ATP).[10] This theory is supported by research showing that PBMT enhances ATP production.[11] Increased ATP production may lead to enhanced cell metabolism, promoting the damage-repair process.

Several studies have shown that PBMT can reduce inflammation within inner ear cells in vitro.[12,13] Clinical studies on the use of PBMT to protect against hearing loss, tinnitus, and vestibular dysfunction have been published. To the best of the author's knowledge, there are presently no systematic reviews synthesising the effect of PBMT on hearing loss.

1.3 | Objectives

This review is to assess the application of PBMT in the treatment of hearing loss, examining evidence from both animal and human studies.

Key points

- Photobiomodulation therapy (PBMT) is a potential non-invasive treatment option for hearing loss with minimal adverse effects.
- To date, only one human trial has assessed the use of PBMT in the treatment of hearing loss.
- This study showed no statistically significant improvement in hearing outcomes.
- Animal studies utilising *longer* wavelength PBMT for *longer* duration of therapy demonstrated improvements in audiological outcomes.
- Further human trials are required to determine the efficacy and safety of PBMT to treat hearing loss.

Population:	Humans or animals
Intervention:	Photobiomodulation therapy
Comparator:	There is no formal comparator or control. Comparators were expected to vary according to the study type. Comparators may include other methods of hearing preservation, for example, administration of drugs via systemic or local routes.
Outcomes:	Pre- and post-PBMT audiometric outcomes, evidence of inflammation e.g., fibrosis (impedance values, histology), measures of neural responses (evoked compound action potentials, auditory brainstem evoked potentials), spiral ganglion neuron density and/or number, neo-osteogenesis, and hair cell count. Adverse events associated with PBMT.

2 | METHODS

The study protocol was registered in the PROSPERO prospective database of systematic reviews (CRD42020210574 and CRD42020212259) and was created according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) guidelines.[14]

2.1 | Study inclusion criteria

All human experimental study designs were eligible, including case–control, case series, cohort, randomised controlled trials. Animal studies (live, in vitro) were eligible if they included at least one quantitative outcome measure. There were no restrictions placed on the follow-up length or the study duration. Only studies with full texts available were included. Studies with insufficient reporting data on pre-and post-intervention audiometric outcomes and those that did not assess the effect of PBMT on hearing outcomes were excluded.

2.2 | Search strategy

The initial search was conducted in September 2020 and repeated in July 2022 to include relevant papers published since the original search. The following electronic databases were searched: MEDLINE, EMBASE, CENTRAL, ClinicalTrials.gov and Web of Science including Web of Science Core collection. No limit was placed on language or publication year. Search strategy terms used are summarised in the Appendix S2. Hand-searching reference lists of the included relevant systematic reviews and citation searches were conducted to identify additional studies missed from the electronic database searches.

2.3 | Selection of studies

Initial searches were performed by Yasmin Nikookam and verified by Nawal Zia. The two reviewers independently screened titles and abstracts of the studies from the database search inclusion and to identify duplicates. Full texts were reviewed independently against the inclusion and exclusion criteria. Disagreements at the abstract and full-text screening stages were discussed within the author team (Yasmin Nikookam/Nawal Zia) and where applicable, with a third reviewer (Jameel Muzaffar), and consensus was reached in determining eligible studies. The second search was conducted in the same manner by two authors (Jennifer Davis-Manders/Andrew Lotfallah) and corroborated by a third (Jameel Muzaffar).

2.4 | Data extraction

A standardised Microsoft Excel sheet was used for data extraction from the included studies. This was designed and piloted prior to the data extraction phase. The data of interest comprised of study characteristics (study design, location, duration), primary and secondary outcome data and operative adverse events. Missing data were sought, where possible, by email contact with study authors. Any discrepancies were identified and resolved through discussion within the author team.

2.5 | Risk of bias quality assessment

Two reviewers (Yasmin Nikookam/Nawal Zia) independently assessed the methodological quality of the included studies. Animal studies were assessed using the SYRCLE tool.[15] Human studies were assessed using the Oxford Centre for Evidence Based Medicine (OCEBM) grading system, and the Cochrane Risk of Bias 2 (RoB2) tool for randomised control trials.[16,17] Any disagreements were resolved through discussion between the two authors (Yasmin Nikookam/Nawal Zia), and where necessary, consultation with the third review author (Jameel Muzaffar). The above process was followed for the second search conducted by two authors (Andrew Lotfallah/Jameel Muzaffar).

3 | RESULTS

A flowchart detailing study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines is included in Figure 1 (See Supplementary Materials).

3.1 | Description of studies

Seventeen studies met the inclusion criteria with a total of 397 subjects (30 humans in a single study, 327 animals in 11 studies, and 40 animal specimens in 5 laboratory studies).[7,12,13,18–31]

Only one study, a randomised controlled trial, assessed the effect of PBMT on humans. Subjects were selected for inclusion using an unspecified screening questionnaire and randomly allocated to a control, treatment and placebo group.[7] This study used 532/635 nm combination laser, a shorter wavelength than all animal studies. Clinical follow-up period was not stated.

Sixteen studies were conducted on animal models, published between 2012 and 2021. From these, 10 were non-randomised controlled trials, 4 were in vitro studies, one ex vivo study, and one randomised-controlled trial. Three studies used mouse models, ten used rat models, two used a guinea pig model, and one used a gerbil model. The wavelength used was classified in all studies: 11 used 808 nm, 3 used 830 nm, 1 used 908 nm, 1 used 810 nm. The duration of PBMT ranged from 4 to 60 min in a session. The follow-up duration of PBMT in animals ranged from 5 to 28 days. Table 1 summarises study characteristics for both human and animal studies.

3.2 | Quality of studies

The methodological quality of included studies was modest, mainly consisting of non-randomised controlled studies ($n = 10$). All animal studies ($n = 16$) were prospective, and all studies had a minimum of five animals, or two cell lines which underwent PBMT.

The single human study[7] comprised a randomised, double-blind controlled prospective study that had 30 subjects. This study was OCEBM grade I. Participants were randomly allocated to treatment, placebo and control groups with adjustment to ensure similar baseline characteristics, although the method of randomisation was not described. Double blinding of subjects and researchers administering placebo and treatment laser therapy was also implemented to limit potential bias.

Heterogeneity of audiological, PBMT duration, power, and wavelength outcomes within and between human ($n = 1$) and animal ($n = 16$) studies precluded a meta-analysis. Within the human study, the limitations were the reporting of complications following PBMT and the follow-up duration of patients who had PBMT. Quality assessment of the human studies is summarised in Table 4. Within the animal studies there were limitations in post-treatment observation duration of animals receiving PBMT, audiological data prior to PBMT delivery, age of subjects, housing of animals and PBMT technique. Quality assessment of animal studies is summarised in Table 5.

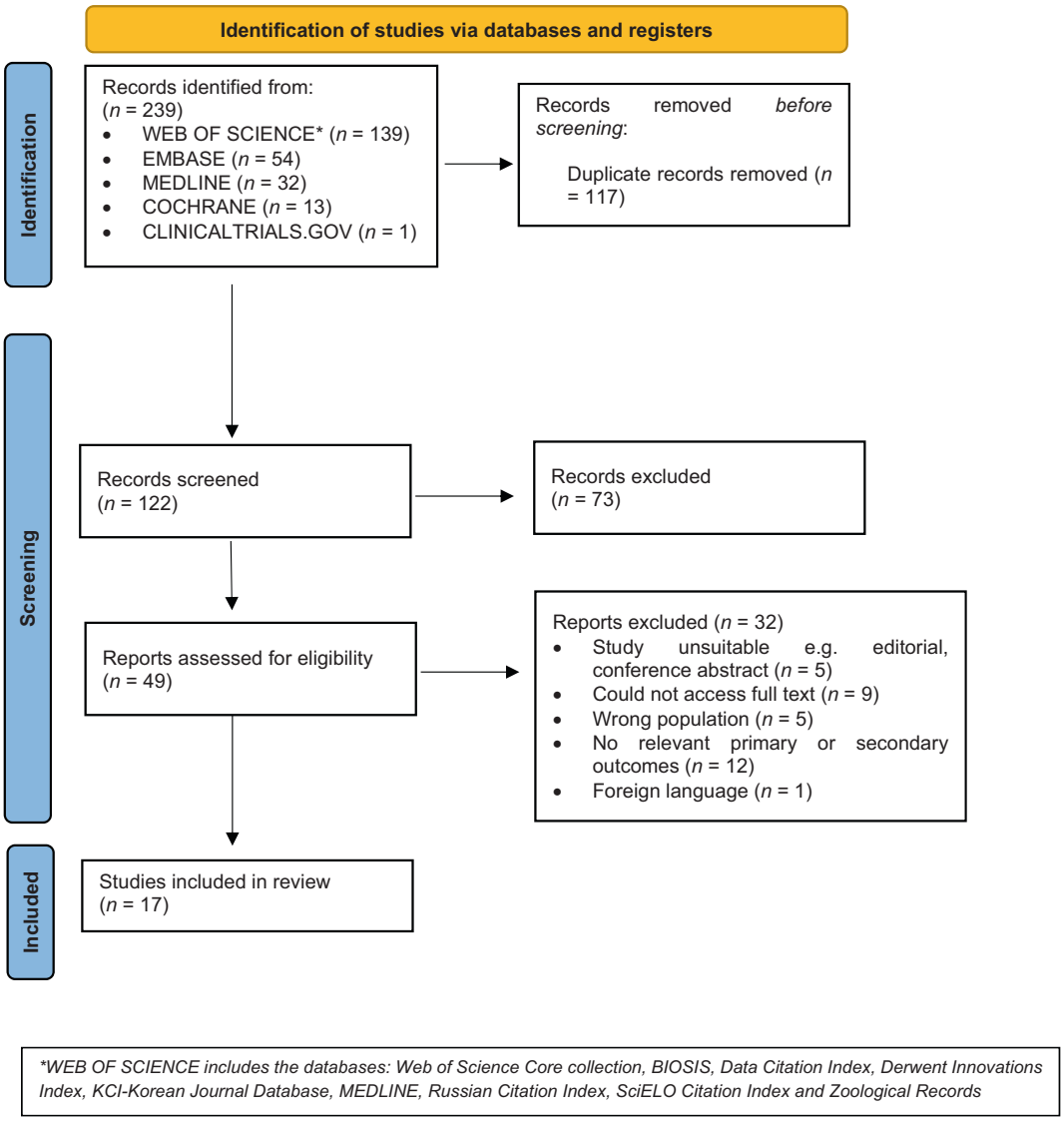

FIGURE 1 PRISMA flow diagram.[16]

3.3 | Audiological outcomes

Audiological outcomes in humans are summarised in Table 2. Audiological outcome measures were assessed using pure-tone audiometry, speech perception, and transient evoked otoacoustic emissions. Pre-PBMT hearing status was reported, and all patients recruited had moderate to severe, non-fluctuating hearing loss, with an average pure-tone audiometric score of 39.6 dB HL (SD 15.3 dB).[7] The causes of hearing loss were not stated. The PBMT treatment protocol was based on a pilot study conducted by HearingMed (unpublished) showing an improvement of word recognition scores following PBMT.[7]

Audiological outcomes in animals are summarised in Table 3. A total of 12 different audiological outcomes measures were used with inconsistency of pre- and post-PBMT reporting across all included studies. Twelve studies reported pre-PBMT audiological assessments. Auditory brainstem responses (ABR) were recorded in 12 studies post-PBMT and 11 pre-PBMT, compound action potential (CAP) scores were measured in 1 study pre- and post-PBMT, distortion product otoacoustic emissions (DPOAE) were recorded in 1 study post-PBMT, and tympanic membrane assessment in 1 study post-PBMT. Histological analysis and immunohistochemistry were also used to assess several outcome parameters post-PBMT including hair cell count (10 studies), inducible nitric oxide synthase (iNOS) (2 studies), cleaved caspase 3 (2 studies), spiral ganglion cell number (SGN) (1 study), cell viability (1 study), reactive oxygen species (ROS) intensity (1 study), morphology of nerve fibres (1 study) and ATP (1 study).

3.4 | PBMT delivery method

All 17 studies outlined the PBMT technique. Twelve studies outlined the distance of the optical fibre tip from the PBMT target site, ranging from 1 mm to 8 cm, with a distance of 1 mm most

TABLE 1 Study characteristics.

	Author, year (ref.)	Country	Participant type	Study type	Prospective/ retrospective	Number of participants	Number of study groups	Number of ears		PBMT characteristics			Max post-PBMT follow-up (d)
								Intervention	Control (s)	Power (mW)	Wavelength (s) used (nm)	Duration of PBMT	
1	S. Goodman et al., 2013[7]	USA	Humans	RCT	Prospective	30	3	18	42	7.5	532 & 635	4 min	-
2	D. Basta et al., 2020[18]	Germany	Animals (mouse)	Non-RCT	Prospective	78	7	55	23	120	808	5–40 min	-
3	S. Chang et al., 2012[19]	Korea	Animals (rats)	Non-RCT	Prospective	6	4	6	6	165	830	60 min/day for 12 days	12
4	S. Chang et al., 2016[20]	Korea	Animals (rats)	Non-RCT	Prospective	17	5	14 NAC & LLLT ($n = 7$) ALCAR & LLLT ($n = 7$)	16	165	808	60 min/day for 12 days	12
5	S. Chang et al., 2019[12]	Korea	Animals (mouse HEI-OC1)	In vitro	Prospective	4[a]	4[a]	2[a]	2[a]	15	808	15 min	-
6	T. Guan et al., 2015[21]	China	Animals (guinea pigs)	In vivo	Prospective	-	-	-	-	0–2200	908	-	-
7	M. Lee et al., 2016[22]	Korea	Animal (gerbils)	Non-RCT	Prospective	30	3	18	29	200	808	60 min/day for 7 days	7
8	J. Lee et al., 2016[23]	Korea	Animals (rats)	Non-RCT	Prospective	18	3	18	6	165	808	60 min/day for 15 days	15
9	J. Lee et al., 2019[24]	Korea	Animals (rats)	Non-RCT	Prospective	15	2	7	8	165	808	60 min/day for 7 days	14
10	C. Rhee et al., 2012[25]	Korea	Animals (rats)	Ex vivo	Prospective	19	4	16	15	8	810	60 min/day for 6 days	6
11	C. Rhee et al., 2012[26]	Korea	Animals (rats)	Non-RCT	Prospective	22	3	16	6	100–165	830	60 min/day for 12 days	
12	C. Rhee et al., 2013[27]	Korea	Animals (rats)	In vivo	Prospective	11	2	8	14	200	830	60 min/day for 10 days	10
13	C. Rhee et al., 2014[13]	Korea	Animals (mouse HEI-OC1)	In vitro	Prospective	6	6[a]	3[a]	3[a]	15	808	15 min	-
14	C. Rhee et al., 2021[28]	Korea	Animals (rats)	Non-RCT	Prospective	30	7	24	6	165	808	60 min/day for 12 days	12
15	I. Strübing et al., 2020[29]	Germany	Animals (guinea pigs)	RCT	Prospective	8	2	8	8	120	808	15 min	28
16	A. Tamura et al., 2015[30]	Japan	Animals (rats)	Non-RCT	Prospective	34	3	5	10	100	808	30 min/day for 5 days	5
17	A. Tamura et al., 2016[31]	Japan	Animals (rats)	Non-RCT	Prospective	69	3	5	10	165	808	30 min/day for 5 days	5

Note: - Correlates to not stated.

[a]Correlates to number of cell wells used.

TABLE 2 Primary outcomes in human studies.

Study reference	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
S. Goodman et al., 2013, USA	**Groups:** 3 Group 1: laser treatment ($n = 9$) Group 2: placebo ($n = 10$) Group 3: control ($n = 11$) **Investigational device:** ErchoniaEHLlaser Two laser diodes: 532 nm wavelength, and 635 nm wavelength **PBMT power:** 7.5 mW **PBMT duration:** 4 min **Mean age of subjects:** 52.8 **Hearing loss:** Not stated? Severe?	**PBMT administration details:** Followed a protocol that included 7 steps. The laser was placed in 4 different positions: 1). Temporomandibular joint, anterior to the external auditory meatus of the ear, 2 inches from the surface of the skin. 2). Midline of the cervical spine, 3 inches from the skin surface. 3) Top of the head, 2 inches from the skin surface. 4) External auditory meatus. **Audiological data:** Pure-tone audiometry, TEOAE and HINT conducted pretest. Before enrolment a list of screening questions determined eligibility. This was used to exclude subjects whose hearing may fluctuate	**Pure-Tone Audiometry:*** *Calculated as change in PTA (posttest minus pretest), negative values indicate improvement in thresholds. Following expressed as a range*: Group 1: −1.8 to +1.8 Group 2: −1.8 to +1.8 Group 3: 0 to −1.8 *Change in the audiometric HFA. Change calculated as posttest minus pretest; negative values indicate improvement in thresholds. Following expressed as a range*: Group 1: −1.8 to +1.8 Group 2: −1.8 to +2.5 Group 3: −1.8 to +3.2 **Speech understanding:*** *Change in CST scores expressed as rationalised arcsine units (rau). Following reported as a range*: Group 1: −13.0 to +8.0 Group 2: −9.0 to +8.0 Group 3: +2.0 to +10.0 **Transient Evoked Otoacoustic Emissions:*** *Change in TEOAE PTA amplitudes (1–2 kHz). Following reported as amplitude difference (dB SPL) range*: Group 1: −2.0 to +1.5 Group 2: −3.0 to +1.5 Group 3: −2.2 to +1.5 *Change in TEOAE HFA (2–8 kHz) amplitudes. Following reported as amplitude difference (dB SPL) range*: Group 1: −1.6 to +1.8 Group 2: −1.8 to +0.8 Group 3: −1.6 to +0.2 *5 subjects not included in the analysis.*	No statistically significant effect of LLLT on auditory function was found, as assessed by pure-tone audiometry, speech understanding, and TEOAEs. Additionally, no individual subjects showed any clinically significant change.	**OCEBM grade:** 1 **Brazzelli risk of bias checklist:** low = 12, high = 0, unclear = 6

TABLE 3 Primary outcomes in animal studies.

Study reference	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
D. Basta et al., 2020, Germany	**Groups:** Group 1: control, no noise exposure or NIR pre-treatment ($n = 7$) Group 2: noise only, noise-exposure but without NIR-treatment ($n = 16$) Group 3: 5 min NIR-treatment ($n = 16$) Group 4: 10 min NIR-treatment ($n = 16$) Group 5: 20 min NIR-treatment ($n = 7$) Group 6: 30 min NIR-treatment ($n = 8$) Group 7: 40 min NIR-treatment ($n = 8$). **Investigational device:** 808 nm (DB808-120-3(22 × 65), Picotronic, Germany) **Power density:** 312 mW/cm^2. **PBMT power:** 120 mW **PBMT duration:** 5–40 min **Mean age of subjects:** 10–11 weeks **Hearing loss:** Noise-induced hearing loss.	**PBMT administration details:** The laser module was placed at the outer ear canal at exactly the angle that allowed a total coverage of the cochlea with the laser beam of approximately 7 mm diameter. NOTE: PBM was administered before NIHL was induced. **Audiological data:** ABR recordings 2 days before and 2 weeks after noise exposure.	**ABR-threshold shift** Groups 3–7 showed a lower group mean hearing loss following the noise exposure compared to group 2. **Cochlear hair cells** No loss of inner hair cells could be detected bilaterally for any of the groups. Group 2: a significant decrease in outer hair cell counts was found for both ears compared to group 1.	Good outcomes. A single NIR pre-treatment induces a very effective protection of cochlear structures from noise exposure. Pre-exposure of 10 min seems to emerge as the optimal dosage for our experimental setup. A saturated effect occurred with higher dosage-treatments. These results are relevant for protection of residual hearing in otoneurosurgery such as cochlear implantation.	**SYRCLE's risk of bias tool:** Low = 7; high = 0; unclear = 3
S. Chang et al., 2012, Korea	**Groups:** 2 Group 1: LLLT 3 days post noise exposure Group 2: LLLT 7 days post noise exposure Group 3: control ears (right ears from group 1) Group 4: control ears (right ears from group 2) **Investigational device:** 830 nm diode laser **PBMT power:** 165 mW/cm^2 (594 J/cm^2) **PBMT duration:** 60 min for 12 days **Mean age of subjects:** not stated **Hearing loss:** Noise-induced—subjects exposed to narrow band noise, 120 dB, 16 kHz, 6 h	**PBMT administration details:** Left ears were irradiated from groups 1 and 2. Laser fibre was delivered through a hollow tube into the external auditory canal so that the distance from the tip of the fibre to the surface of the tympanic membrane was approximately I mm. **Audiological data:** Not stated.	**ABR Threshold Shifts** kHz are in order of 4, 8, 12, 16, 32. *After the 12th irradiation*: Group 1: 22 ± 4.2, 30 ± 3.5, 65 ± 11.9, 30 ± 12.9 and 25 ± 2.2 dB SPL Group 2: 32.5, 41.3, 60.0, 57.5, and 45.0 dB SPL Group 3: 70 ± 22.9, 85 ± 15.8, 90.3 ± 22.9, 80 ± 16.8 and 75.8 ± 21.4 dB SPL Group 4: 25.0, 37.5, 52.5, 38.8, and 26.3 dB SPL.	Good outcomes. Treating ears with LLLT sooner (group 1) versus later (group 2) leads to better outcomes and better hearing recovery.	**SYRCLE's risk of bias tool:** Low = 2; high = 0; unclear = 10
S. Chang et al., 2016, Korea	**Number of participants:** 17 **Groups:** 5 Group 1: Control (noise only) ($n = 6$ ears). Group 2: NAC ($N = 6$ ears). Group 3: ALCAR ($N = 4$ ears). Group 4: NAC plus Laser ($N = 7$ ears). Group 5: ALCAR plus Laser ($N = 7$ ears). **Investigational device:** 808-nm diode laser (WON-TECH, Korea). [insert the details of the PBMT device e.g. the wavelength used]	**PBMT administration details:** PBMT delivered 1 day after noise insult. Delivered via optic fibre (core fibre 62.5 μm/ cladding 125 μm) inserted into the external acoustic canal through a hollow tube. Tip of fibre positioned	**Auditory brainstem response (ABR)** *Threshold of 6th laser irradiation*: Group 1: 8 kHz = 69.2 ± 8.9; 16 kHz = 60.8 ± 7.1; 32 kHz = 53.3 ± 8.0 Group 2: 8 kHz = 61.7 ± 11.9; 16 kHz = 50.8 ± 5.0; 32 kHz = 47.5 ± 3.8. Group 3: 8 kHz = 59.0 ± 15.1; 16 kHz = 43.0 ± 8.7; 32 kHz = 41.0 ± 7.1 Group 4: 8 kHz = 59.2 ± 14.6; 16 kHz = 50.0 ± 8.0; 32 kHz = 45.0 ± 7.8	Good outcomes. NAC in combination with LLLT was more effective at improving NIHL earlier than LLLT alone. However, this additive or synergistic effect wasn't as effective at improving NIHL when compared to LLLT alone after 12 daily therapy.	**SYRCLE's risk of bias tool:** Low = 7; high = 0; unclear = 3

(Continues)

TABLE 3 (Continued)

Study reference	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
	PBMT power: 165 mW (59.4 J). **PBMT duration:** 60 min a day over 12 days. **Mean age of subjects:** not stated. **Hearing loss:** Noise-induced hearing loss. Rats exposed to one-time exposure to a narrow band noise of 116 dB SPL centered at a frequency of 16 kHz (bandwidth 1 kHz) for 5 h.	1–2 mm away from the tympanic membrane. **Audiological data:** ABRs were measured before noise exposure for group 1 only. Prior to PBMT all participants were deemed to have NIHL. ABR readings from groups 2–5 following PBMT were compared to group 1.	Group 5: 8 kHz = 57.0 ± 12.1; 16 kHz = 49.0 ± 8.2; 32 kHz = 43.8 ± 6.6 *Threshold of 12th laser irradiation*: Group 1: 8 kHz = 75.0 ± 3.8; 16 kHz = 60.0 ± 10.0; 32 kHz = 55.0 ± 7.7 Group 2: 8 kHz = 75.0 ± 11.9; 16 kHz = 50.0 ± 11.5; 32 kHz = 42.5 ± 8.7 Group 3: 8 kHz = 52.5 ± 2.9; 16 kHz = 35.0 ± 4.5; 32 kHz = 30.0 ± 5.3 Group 4: 8 kHz = 65.0 ± 8.8; 16 kHz = 50.0 ± 7.7; 32 kHz = 46.7 ± 6.8 Group 5: 8 kHz = 61.7 ± 2.6; 16 kHz = 45.0 ± 4.5; 32 kHz = 40.0 ± 3.8 **Hair cell count** *Apical*: Group 1: 82.4 ± 5.8 Group 2: 81.8 ± 4.1 Group 3: 88.9 ± 2.3 Group 4: 84.8 ± 1.4 Group 5: 84.3 ± 2.9 *Middle*: Group 1: 72.0 ± 6.9 Group 2: 80.6 ± 2.2 Group 3: 85.1 ± 1.5 Group 4: 80.8 ± 2.5 Group 5: 80.6 ± 3.2 *Basal*: Group 1: 61.2 ± 9.7 Group 2: 81.0 ± 1.2 Group 3: 82.4 ± 3.6 Group 4: 71.6 ± 8.6 Group 5: 75.8 ± 2.5		
S. Chang et al., 2019, Korea	**Groups:** 4 Group 1: control (no GM and no PBM) Group 2: PBM only Group 3: GM only Group 4: GM and PBM **Investigational device:** 808 nm near-infrared diode laser (WonTech, Daejeon, Republic of Korea) **PBMT power:** 15 mW for 15 min (total energy density: 13.5 J/cm^2) **PBMT duration:** 15 min	**PBMT administration details:** Started 0.5–9 h after GM treatment. **Audiological data:** Not stated.	**ATP levels:*** *Relative ATP level in 10^6 cells following PBM*: Group 1: immediately = 1.00; +1 h = 0.98; +2 h = 1.00 Group 2: immediately = 1.19; +1 h = 1.12; +2 h = 1.00 Group 3: immediately = 0.55; +1 h = 0.68; +2 h = 0.82 Group 4: immediately = 0.92; +1 h = 0.82; +2 h = 0.84 **Cell viability:** Increased cell viability of auditory cells by PBM after GM-induced ototoxicity, which can cause permanent hair cell damage and sensorineural hearing loss, by increasing ATP levels and MMP	Good outcomes. LLLT improved cell viability of auditory cells and increases ATP immediately after exposure. However, it reaches control (group 1 levels) after 2 h of exposure to PBM.	**SYRCLE's risk of bias tool:** Low = 6; high = 0; unclear = 4

TABLE 3 (Continued)

Study reference	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
	Mean age of subjects: not stated **Hearing loss:** Gentamicin-induced ototoxicty				
T. Guan et al., 2015, China	**Groups:** unclear **Investigational device:** 980-nm diode laser **PBMT power:** 0 to 2.2 W **PBMT duration:** unclear **Other:** calculated radiant exposures ranged from 0 to 53.2 mJ/cm^2 at a pulse duration of 50 μs **Mean age of subjects:** not stated **Hearing loss:** Surgery to deafen the animal.	**PBMT administration details:** The end of the optical fibre was placed in prox- imity to the round window membrane and was visually oriented toward the spiral ganglion cells in Rosenthal's canal in the basal turn. The distance between the end of the fibre and the spiral ganglion cells in the Rosenthal's canal is approxi- mately 1.03 mm and the spot size is about 0.21 mm^2 inside the cochlear. **Audiological data** **aCAP:** The amplitude of the aCAP between N1–P1 is more than 400 μV before deafening, while after surgery no obvious aCAPs were evoked by acoustic stimuli.	**oCAPs:** *With different radiant exposures*: Power at the end of the optical fibre was gradually increased from 1.52 to 2190 mW, with the corresponding radiation exposure ranging from 0.037 to 53.2 mJ/cm^2 at a pulse duration of 50 μs. The amplitude of oCAPs did not obvi-2 hourly increase when the radiant exposure was above 30 mJ/cm *With different stimulus rate*: Stimulation rates from 182 to 1000 Hz with a constant pulse width of 50 μs. N2 in the oCAPs was evident at stimulation rates of less than 400 Hz, however, at stimulation rates above 667 Hz, only N1 and P1 can be seen. **aCAPs:**	Good outcomes. Stimulation with a laser of 980 nm wavelength can successfully induce CAPs outside the cochlea. This showed that shorter-wavelength near-infrared pulsed laser (980 nm) can elicit CAP from a deafened guinea pig cochlea, suggesting the use of a short-wavelength near-infrared laser as an alternative stimulus for cochlea implants.	**SYRCLE's risk of bias tool:** Low = 0; high = 3; unclear = 7
M. Lee et al., 2016, Korea	**Groups:** 3 Group 1: control (n = 11) Group 2: ouabain only group (n = 18) Group 3: ouabain plus laser group (n = 18) **Investigational device:** 808-nm diode laser (WONTECH Co., Ltd, Korea) **PBMT power:** 200 mW **PBMT duration:** 1 h/day for 7 days **Mean age of subjects:** 4–6 months **Hearing loss:** Auditory neuropathy induced by oubain administration	**PBMT administration details:** Optic fibre (core size: 62.5 mm) was delivered through a hollow tube into the external acoustic canal. Laser was irradiated to the tympanic membrane. Laser energy was expected to be delivered to the cochlea, specifically spiral ganglion (Rosenthal	**ABR** *Baseline*: Group 1: 4 kHz = 23.0 ± 12.3; 8 kHz = 22.3 ± 12.3; 12 kHz = 25.7 ± 14.0; 16 kHz = 23.0 ± 14.1; 32 kHz = 25.9 ± 12.7 dB SPL Group 2: 4 kHz = 30.6 ± 17.4; 8 kHz = 22.2 ± 11.3; 12 kHz = 25.3 ± 13.2; 16 kHz = 23.1 ± 11.9; 32 kHz = 25.0 ± 13.2 dB SPL Group 3: 4 kHz = 32.6 ± 12.3; 8 kHz = 27.1 ± 10.0; 12 kHz = 26.5 ± 10.7; 16 kHz = 26.2 ± 10.5; 32 kHz = 29.4 ± 9.8 dB SPL *1 day after oubain application*: Group 2: 4 kHz = 80.0 ± 0.0; 8 kHz = 78.9 ± 2.2; 12 kHz = 78.9 ± 2.2; 16 kHz = 77.2 ± 3.6; 32 kHz = 77.2 ± 3.6 dB SPL	Good outcomes. Photobiomodulation alleviated the hearing loss caused by ouabain induced auditory neuropathy. Photobiomodulation effect on hear- ing rescue was related with preserved numbers of spiral ganglion cells throughout the cochlear turn, synaptic puncta, and nerve fibres.	**SYRCLE's risk of bias tool:** Low = 6; high = 0; unclear = 4

(Continues)

TABLE 3 (Continued)

Study reference	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
		canal) which is located within the cochlea. **Audiological data:** ABRs measured before, on day 1 and day 7 after ouabain administration.	Group 3: 4 kHz = 78.8 ± 3.5; 8 kHz = 76.9 ± 4.6; 12 kHz = 80.0 ± 0.0; 16 kHz = 78.8 ± 2.3; 32 kHz = 77.5 ± 3.8 dB SPL *7 days after oubain application*: Group 2: 4 kHz = 78.1 ± 4.2; 8 kHz = 77.5 ± 4.6; 12 kHz = 76.4 ± 4.8; 16 kHz = 75.0 ± 6.2; 32 kHz = 70.0 ± 8.4 dB SPL Group 3: 4 kHz = 69.7 ± 7.2; 8 kHz = 64.4 ± 6.8; 12 kHz = 65.3 ± 8.6; 16 kHz = 61.5 ± 7.5; 32 kHz = 57.9 ± 8.1 dB SPL **DPOAE** *Baseline*: Group 1: 4 kHz = 65.9 ± 4.8; 8 kHz = 37.7 ± 5.5; 12 kHz = 39.1 ± 5.0; 16 kHz = 35.7 ± 5.0 dB SPL Group 2: 4 kHz = 64.2 ± 9.3; 8 kHz = 38.9 ± 7.0; 12 kHz = 36.7 ± 5.7; 16 kHz = 39.4 ± 8.2 dB SPL Group 3: 4 kHz = 65.0 ± 7.7; 8 kHz = 39.7 ± 4.8; 12 kHz = 37.1 ± 5.0; 16 kHz = 35.0 ± 4.7 dB SPL *At 7 days*: Group 1: 4 kHz = 68.9 ± 6.9; 8 kHz = 37.3 ± 4.0; 12 kHz = 37.5 ± 4.6; 16 kHz = 37.3 ± 5.5 dB SPL Group 2: 4 kHz = 67.5 ± 5.8; 8 kHz = 39.2 ± 6.0; 12 kHz = 39.4 ± 4.5; 16 kHz = 39.7 ± 5.0 dB SPL Group 3: 4 kHz = 67.6 ± 5.0; 8 kHz = 41.5 ± 4.6; 12 kHz = 41.5 ± 5.5; 16 kHz = 39.7 ± 6.5 dB SPL *No significant difference* **Morphologies of nerve fibres and synaptic puncta** Group 1: peripheral nerve fibres were visible as a dense meshwork of neuronal processes medial to IHC (IHCs were contacted by roughly 10 afferent nerve fibres). GluR2 puncta count = 172 ± 12.7. Group 2: thin and loose mesh- work of neuronal process was evident (IHCs were contacted by about three afferent nerve fibres) and markedly fewer post synaptic puncta were observed compared to the control group. GluR2 puncta count = 40 ± 6.1. Group 3: puncta were reduced in number compared to the control group but were more numerous than in the ouabain only group. GluR2 puncta count = 104 ± 13.1. **Morphology and density of SGNs** Group 2: significant decline of SGN density, but there was no change in IHCs and OHCs in the low basal, high basal, low mid- dle, and high middle region. Group 3: SGN counts significantly higher in low basal, high basal, low middle, and high middle regions compared to the ouabain group, but less than group 1 (without statistical significance).		

TABLE 3 (Continued)

Study reference	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
J. Lee et al., 2016, Korea	**Groups:** 3 Group 1: control, noise only ($n = 6$) Group 2: unilateral laser ($n = 6$) Group 3: bilateral laser ($n = 6$) **Investigational device:** 808 nm diode laser (Wontec, Seoul, South Korea) **PBMT power:** 165 mW/cm^2 (594 J) **PBMT duration:** 60 mins for 15 days **Mean age of subjects:** not stated **Hearing loss:** Noise-induced (acute acoustic trauma).	**PBMT administration details:** Optical fibre was attached to a hollow tube and placed into the external ear canal while leaving a distance of 1 mm between the fibre tip and tympanic membrane. **Audiological data:** ABR performed.	**ABR** Are in order of 4, 8, 12,16, 32 kHz. *Baseline*: Group 1: 18.33, 15.83, 15, 14.17, 15.83 Group 2: 20, 15, 20, 15.83, 17.5 Group 3: 17.5, 17.5, 15.83, 18.33, 15.83 *After noise exposure*: Group 1: 48.33, 56.67, 57.5, 63.33, 61.67 Group 2: 53.33, 63.33, 60, 62.5, 60 Group 3: 51.67, 53.33, 63.33, 63.33, 60 *After 6th laser irradiation*: Group 1: 43.33, 52.5, 60.83, 63.33, 61.67 Group 2: 42.5, 49.17, 55.83, 62.5, 56.67 Group 3: 36.67, 40, 51.57, 51.67, 46.67 *After 15th laser irradiation*: Group 1: 38.33, 42.5, 50, 48.33, 47.5 Group 2: 25.83, 35, 31.67, 30, 32.5 Group 3: 22.5, 25, 24.17, 25.83, 21.67 **Hair cell count** *Average OHCs at the*: *Apex*: Group 1: 70.33 Group 2: 72 Group 3: 73.67 *Middle*: Group 1: 73 Group 2: 72.67 Group 3: 71 *Basal turn*: Group 1: 59 Group 2: 67.5 Group 3: 72.67	Good outcomes. Greater positive effects of bilateral laser therapy after noise-induced hearing loss. Bilateral laser therapy resulted in faster hearing threshold recovery than did unilateral laser therapy.	**SYRCLE's risk of bias tool:** Low = 4; high = 0; unclear = 6
J. Lee et al., 2019, Korea	**Groups:** 2 Group 1: noise only ($n = 8$) Group 2: PBM ($n = 7$) **Investigational device:** 808 nm diode laser (Wontec, Daejeon, South Korea) **PBMT power:** 165 mW/cm^2 (594 J) **PBMT duration:** 60 min for 7 days **Mean age of subjects:** 5–6 weeks **Hearing loss:** Noise-induced	**PBMT administration details:** The optical fibre was attached to a hollow tube and placed into the external ear canal 1 mm from the tympanic membrane. **Audiological data:** The ABRs were measured with each tone stimuli at the left ear to identify changes in the hearing	**ABR*** *Changes in threshold (dB) after noise exposure (day [dB])**: *12 kHz*: Group 1: 1 [20], 3 [10], 7 [12], 14 [7] Group 2: 1 [20], 3 [4], 7 [5], 14 [2] *16 kHz*: Group 1: 1 [38], 3 [25], 7 [22], 14 [8] Group 2: 1 [35], 3 [13], 7 [11], 14 [4] *32 kHz*: Group 1: 1 [33], 3 [23]. 7 [16], 14 [10] Group 2: 1 [38], 3 [17], 7 [16], 14 [7] *ABR recovery threshold (ms)** Group 1: 5.5	Good outcomes. PBM had a protective effect on synaptic ribbons and the ABR recovery threshold, suggesting that the PBM can target not only the HC level but also the subcellular level, such as synaptic ribbons.	**SYRCLE's risk of bias tool:** Low = 5; high = 0; unclear = 5

(Continues)

TABLE 3 (Continued)

Study reference	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
		threshold before and after noise exposure.	Group 2: 2.75 Control: 3.5 **Immunofluorescence analysis** **Number of ribbons/IHCs*** *Apex*: Group 1: 12.5 Group 2: 14 *Middle*: Group 1: 11 Group 2:16 *Base*: Group 1: 7 Group 2: 17		
C. Rhee et al., 2012, Korea	**Groups:** Group 1: Control ears (C, $n = 6$) Group 2: Noise only ears (N, $n = 16$) Group 3: Noise and laser ears (NL, $n = 16$) **Investigational device:** An 830-nm diode laser (Hi-Tech Optoelectronics, Beijing, China) **Power density:** 100–165 mW/cm^2 **PBMT duration:** 60 min for 12 consecutive days **Mean age of subjects:** not stated **Hearing loss:** The rats were placed in small, separate cages to prevent defensive behaviours such as blockage of the ears and were set inside the noise box. The rats were given a one-time exposure to a narrow band noise of 116 dB SPL centred at a frequency of 16 kHz (bandwidth 1 kHz) for 6 h	**PBMT administration details:** The following day after the noise exposure, the rats were irradiated at their left ears for 60 min at an energy density of 100 to 165 mW/cm^2 for 12 days in a row. The optic fibre (core fibre 62.5 μm/cladding 125 μm) was delivered through a hollow tube into the external acoustic canal so that the distance from the tip of the fibre to the surface of the tympanic membrane was around 1 mm. Laser irradiation was done only in the left ear (NL ear) and the right ear (N ear) served as the control. **Audiological data:** ABRs were recorded using tone-burst auditory stimuli, delivered through a tube into the rat's ear canal with measurements taken at 4, 8, 12, 16 and 32 kHz.	**ABR threshold shift:** *At 24 h Post Noise* Group 2 (N ears)—58.3 ± 8.7, 55.0 ± 14.9, 71.3 ± 16.3, 60.6 ± 6.8 and 55.3 ± 11.2 dB at 4, 8, 12, 16 and 32 kHz respectively Group 3 (NL ears)—54.4 ± 8.8, 52.2 ± 11.5, 70.9 ± 6.4, 60.6 ± 6.3 and 52.5 ± 8.0 dB at 4, 8, 12, 16 and 32 kHz respectively *After 12th irradiation* Group 2 (N ears)—46.7 ± 16.2, 45.3 ± 17.3, 59.1 ± 18.5, 50.6 ± 12.6 and 45.6 ± 12.0 dB at 4, 8, 12, 16 and 32 kHz respectively Group 3 (NL ears)—27.2 ± 4.4, 26.9 ± 7.3, 38.1 ± 14.6, 30.0 ± 9.3 and 29.7 ± 6.2 dB at 4, 8, 12, 16 and 32 kHz respectively **Cochlear hair cells:** Group 1 (C ears)—176.5 ± 16.3, 146.0 ± 5.6 and 154.8 ± 6.7 at apical, mid, and basal turns respectively Group 2 (N ears)—110.3 ± 21.1, 95.2 ± 21.7 and 101.1 ± 32.4 at apical, mid, and basal turns respectively Group 3 (NL ears)—147.2 ± 41.1, 136.2 ± 33.5 and 114.7 ± 38.7 at apical, mid, and basal turns respectively	Good outcome: LLLT may have a positive effect on hair-cell recovery after acute acoustic trauma. The hearing threshold became lower after repeated laser irradiation, and the final hearing result was significantly better than that of the untreated ears	**SYRCLE's risk of bias tool:** High = 1, Low = 4, Unclear = 5

TABLE 3 (Continued)

Study reference	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
C. Rhee et al., 2012, Korea	**Groups:** Group 1: control ($n = 8$) Group 2: laser-only ($n = 8$) Group 3: gentamicin only ($n = 8$) Group 4: gentamicin + laser ($n = 7$) **Investigational device:** 810-nm diode laser (LAS-30A, TNL, Incheon, Korea) **PBMT power:** 8 mW/cm^2 (0.48 J/cm^2) **PBMT duration:** 6 days **Mean age of subjects:** not stated. **Hearing loss:** Gentamicin-induced hearing loss / ototoxicity-induced.	**PBMT administration details:** Started on day 5. **Audiological data:** Not completed.	**Hair cell count:** Group 1: Day 5 = 67.5 ± 18.6; day 8 = 59.9 ± 31.6; day 11 = 54.0 ± 25.9 (per 200 μm) Group 2: day 5 = 70.9 ± 28.4; day 8 = 77.1 ± 32.0; day 11 = 80.0 ± 29.2 (per 200 μm) Group 3: day 5 = 27.3 ± 13.2; day 8 = 23.8 ± 5.6; day 11 = 25.0 ± 9.1 (per 200 μm) Group 4: day 5 = 37.3 ± 12.9; day 8 = 36.0 ± 23.7; day 11 = 58.6 ± 27.8 (per 200 μm)	Good outcomes. Significant effect of LLLT in group 4 compared to group 3. LLLT was effective for gentamicin-induced ototoxicity.	**SYRCLE's risk of bias tool:** Low = 7; high = 0; unclear = 3
C. Rhee et al., 2013, Korea	**Groups:** Group 1: untreated Group 2: GM Group 3: GM + laser **Investigational device:** 830-nm diode laser (Hi-tech Optoelectronics, Beijing, China) **PBMT power:** 200 mW **Total radiant energy:** 356–428 J **Poswer density:** 900 mW/cm^2 (162–194 J) **PBMT duration:** **Mean age of subjects:** 8 weeks **Hearing loss:** Ototoxic hearing loss—gentamicin/furosemide induced hearing loss.	**PBMT administration details:** Laser was only performed in the right ear. Distance from the tip of the fibre to the surface of tympanic membrane = 1 mm. Laser was performed after day 2. **Audiological data:** Animals were treated daily by gentamicin 100 mg/kg intravenously (i.v.) followed 10 min later by furosemide 90 mg/kg i.v. for 2 days. 48 h after gentaamicin + furosemide treatment, hearing loss was confirmed with clicked ABR. Hearing threshold was normal in all animals before: <30 dB SPL	**Endoscopic findings of the tympanic membrane:** Group 1–3: all intact without any clinically significant adverse tissue reaction. Group 3: vessels on the tympanic membrane and external auditory canal started to become hyperemic. Vascular congestion was noted from the 1st–3rd days of LLLT and kept on pro- gressing until the end of the experiment **Histologic evaluation of the tympanic membrane and external auditory canal skin (after 10 days):** Group 3: no significant adverse tissue reaction; tympanic membrane seemed slightly thicker Group 2: tympanic membrane slightly thinner when compared to group 3 Overall, seemed there was no difference between group 2 and 3. **Hair cell count** Group 1: normal. Total = 197.0 12.5 cells/300 μm Group 2: basal turn = 10.0 4.8 cells/100 μm [mostly damaged]; middle turn = 26.7 21.2 cells/100 μm [partially conserved]; apical = 60.4 23.5 cells/ 100 μm [relatively intact]. Total = 97.1 40.9 cells/300 μm Group 3: basal turn = 13.67.0cells/100 μm; middle turn = 49.7 24.0 cells/100 μm; apical turn = 66.1 5.9 cells/100 μm. Total = 129.4 34.3 cells/300 μm **ABR** Group 2: day 2 = 54.3 11.0 dB SPL; day 12 = 57.1 18.0 dB SPL. Group 3: day 2 = 52.9 12.5 dB SPL; day 12 = 44.3 12.7 dB SPL.	Good outcomes. Hearing threshold and hair cell count improved following LLLT. Hearing threshold improvement was significant.	**SYRCLE's risk of bias tool:** Low = 6; high = 0; unclear = 4

(Continues)

TABLE 3 (Continued)

Study reference	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
C. Rhee et al., 2014, Korea	**Groups:** 6 Group 1: control (no treatment) Group 2: LLLT only Group 3: GM 6.6 mM Group 4: GM 6.6 mM + LLLT Group 5: GM 13.1 mM Group 6: GM 13.1 mM + LLLT **Investigational device:** 808-nm diode laser (LAS-30A, TNL, Incheon, Korea) **PBMT power:** 13.5 J (15 mW) **PBMT duration:** 15 min **Mean age of subjects:** not stated/not applicable **Hearing loss:** Gentamicin-induced ototoxicity	**PBMT administration details:** HEI-OC1 cells were cultured and PBMT was delivered to the samples evenly. The distance of the fibre from the bottom was 8 cm. **Audiological data:** Not stated and not applicable.	**ATP:** Group 1: 0.26 ± 0.07 Group 2: 0.32 ± 0.14 Group 3: 0.25 ± 0.07 Group 4: 0.28 ± 0.09 Group 5: 0.22 ± 0.03 Group 6: 0.29 ± 0.09 **ROS intensity:** Group 1: 1.00 ± 0.00 Group 2: 1.04 ± 0.06 Group 3: 1.45 ± 0.02 Group 4: 0.82 ± 0.03 Group 5: 1.58 ± 0.05 Group 6: 1.08 ± 0.16	Good outcomes. LLLT shown to be effect at reducing ROS intensity and increasing ATP levels.	**SYRCLE's risk of bias tool:** Low = 3; high = 0; unclear = 7
C. Rhee et al., 2021, Korea	**Groups:** Group 1: noise only ($n = 6$) Group 2: N-acetyl-cysteine (NAC) only ($n = 6$) Group 3: NAC plus photobiomodulation (PBM) ($n = 7$) Group 4: acetyl-L-carnitine (ALCAR) only ($n = 4$) Group 5: ALCAR plus PBM ($n = 7$) **Investigational device:** 808-nm diode laser (Won-tech, Daejeon, South Korea) **Power density:** **165 mW/cm^2** **PBMT duration:** 60 min once a day for 12 days **Mean age of subjects:** not stated **Hearing loss:** Rats were placed in 'noise boxes' to restrict movement and exposed to 5 h of narrowband noise with a 1/3 octave bandwidth, centred at 16 kHz, at a sound pressure level (SPL) of 116 dB.	**PBMT administration details:** 1 day after noise exposure the left ear of rats in the PBM groups (Groups 3 & 5) were irradiated for 1 h at an energy density of 165 mW cm^2 daily for 12 days. An optic fibre was placed through a hollow tube into the external ear canal with the tip approximately 1 mm from the tympanic membrane. **Audiological data:** ABRs were measured using tone-burst frequency-specific stimuli. Tone burst stimuli of 8, 16 and 32 kHz were delivered via a tube inserted into the left ear canal. ABR measurements taken before and after noise exposure but precise timing not stated.	**ABR threshold shift:** *Pre-noise* Group 1: 8 kHz–10.0 ± 0.0, 16 kHz–10.6 ± 1.7, 32 kHz–11.3 ± 2.2 Group 2: 8 kHz–10.8 ± 2.0, 16 kHz–12.5 ± 4.0, 32 kHz–11.7 ± 2.5 Group 3: 8 kHz–12.5 ± 4.0, 16 kHz–12.5 ± 4.0, 32 kHz–10.0.3 ± 0.0 Group 4: 8 kHz–10.8 ± 2.0, 16 kHz–12.0 ± 2.5, 32 kHz–10.8 ± 2.0 Group 5: 8 kHz–10.8 ± 2.0, 16 kHz–10.8 ± 2.0, 32 kHz–12.0 ± 2.5 *Post noise* Group 1: 8 kHz–73.1 ± 9.6, 16 kHz–69.4 ± 4.8, 32 kHz-61.2 ± 4.3 Group 2: 8 kHz–71.7 ± 12.7, 16 kHz–65.0 ± 8.0, 32 kHz–57.5 ± 4.0 Group 3: 8 kHz – 65.8 ± 17.4, 16 kHz – 61.7 ± 5.8, 32 kHz-57.5.3 ± 4.0 Group 4: 8 kHz–73.1 ± 9.6, 16 kHz–65.6 ± 5.4, 32 kHz-60.0 ± 5.2 Group 5: 8 kHz–70.0 ± 15.1, 16 kHz–64.2 ± 6.3, 32 kHz-59.2 ± 4.7 **Cochlear hair cells:** The morphology in the PBM/NAC group showed less hair cell loss than the other groups.	Good outcome: PBM/NAC combination therapy may prevent hearing loss more effectively than PBM alone.	**SYRCLE's risk of bias tool:** High = 1, Low = 1, Unclear = 8

TABLE 3 (Continued)

Study reference	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
I. Strübing et al., 2020, Germany	**Groups:** 2 Group 1: PBMT ($n = 8$ ears) Group 2: Control ($n = 8$ ears) **Investigational device:** 808-nm diode laser **PBMT power:** 120 mW **PBMT duration:** 15 min **Mean age of subjects:** 28–32 weeks **Hearing loss:** Not applicable/not stated	**PBMT administration details:** Before cochlea implantation, via the open bulla a randomly selected cochlea was pretreated with PBMT. **Audiological data:** 2 weeks before surgery ABR performed.	**ABR—average hearing loss** Group 1: 18.4 ± 5.8 dB Group 2: 33.5 ± 5.1 dB **Protective effect of PBMT:** 10.7–21.4 dB **Hair Cell Count** **IHC:** no loss bilaterally **OHC:** statistically significant difference between group 1 and 2. Average loss: Group 1: 88.7 ± 7.3 cells Group 2: 129.3 ± 7.8 cells	Good outcomes. Single PBMT pretreatment before CI surgery appears to be neuroprotective.	**SYRCLE's risk of bias tool:** Low = 3; high = 0; unclear = 7
A. Tamura et al., 2015, Japan	**Groups:** 3 Group 1: non-treatment (noise exposure only) ($n = 5$) Group 2: LLLT 110 mW/cm^2 ($n = 6$) Group 3: LLLT 165 mW/cm^2 ($n = 5$). **Note:** Animals were also divided into three groups for immunohistochemistry of iNOS: naive ($n = 3$), non-treatment (noise exposure only) ($n = 3$) and LLLT (165 mW/cm^2, $n = 3$) and for immunohistochemistry of cleaved caspase-3: naïve (no noise exposure) ($n = 3$), non-treatment (noise exposure only) ($n = 3$) and LLLT (165 mW/cm^2, $n = 3$). **Investigational device:** 808 nm CW diode laser beam (B&W Tek-Inc., Newark, DE, USA) **PBMT power:** 110 mW/cm^2 ($n = 60$ or 165 mW/cm^2 ($n = 5$) **PBMT duration:** 30 min **Mean age of subjects:** not stated **Hearing loss:** Noise-induced hearing loss. Induced hearing loss—exposed to 1 octave band noise centered at 4 kHz for 5 h (121 dB sound pressure level) in a ventilated sound exposure chamber.	**PBMT administration details:** Transmitted through an optical fibre was applied to the right tympanic membrane through the external auditory canal. Optical fibre tip was positioned 6 mm away from the right tympanic membrane. **Audiological data:** ABR taken before, immediately after, and at 2, 4, 7, 14 and 28 days after noise exposure. Thresholds obtained immediately before noise exposure were used as the baseline for estimating noise-induced threshold shifts.	**ABR** Lower in groups 2–3. **Immunohistochemistry** *iNOS* 1 h after noise exposure, strong immunoreactivity for iNOS was observed in group 1 in the organ of Corti and in the fibrocytes of the lateral wall. Less immunoreactivity was observed in groups 2–3. *Cleaved caspase-3* 8 h after noise exposure, strong immunoreactivities for cleaved caspase-3 were observed in the organ of Corti and in the fibrocytes of the lateral wall. Less immunoreactivity was observed in groups 2–3. *OHCs* IHCs in groups 1–3 were well preserved after sound exposure. 28 days after noise exposure, average OHC losses in: *Basal turn* Group 1 = 20.0% Group 2 = 2.0% Group 3 = 2.2% *Middle turn* Group 1 = 30.2% Group 2 = 2.8% Group 3 = 2.2% *Apical* Group 1 = 32.7% Group 2 = 4.6% Group 3 = 8.3%	This study has shown that LLLT prevents cochlea damage if started within 1 h of noise exposure	**SYRCLE's risk of bias tool:** Low = 7; high = 0; unclear = 3
A. Tamura et al., 2016, Japan	**Groups:** 3 *Assessement of auditory function*: Group 1: control, no noise exposure ($n = 5$) Group 2: non-treatment, noise exposure only ($n = 5$)	**PBMT administration details:** Initiated within 1 h after noise exposure. Applied to the right tympanic membrane through the	**ABR*** Days after noise exposure and threshold shift (dB) 8 kHz: Group 1: 0 (7), 4 (12), 7 (12), 14 (18), 28 (20) Group 2: 0 (75), 4 (45), 7 (40), 14 (35), 28 (35) Group 3: 0 (75), 4 (30), 7 (22), 14 (20), 28 (20)	Good outcomes. PBM activates NF-κB signalling for cytoprotection, and that PBM can protect against iNOS-triggered ROS/RNS production and caspase-	**SYRCLE's risk of bias tool:** Low = 7; high = 0; unclear = 3

(Continues)

TABLE 3 (Continued)

Study reference	Study data	Pre-PBMT data	Post-PBMT data	Overall benefit (subjective assessment)	Quality assessment
	Group 3: PBM, noise exposure and PBM ($n = 5$) We also divided the animals into three groups for *immunohistochemistry* of iNOS: naïve ($n = 5$), non-treatment ($n = 5$), and PBM ($n = 5$); cleaved caspase-3: naïve ($n = 5$), non-treatment ($n = 5$), and PBM ($n = 5$); and NF-κB: naïve ($n = 5$), non-treatment ($n = 5$), and PBM ($n = 5$); and for NF-κB and p-Akt western blotting: naïve ($n = 3$), non-treatment ($n = 3$), and PBM ($n = 3$). **Investigational device:** 808-nm continuous wave diode laser beam (B&W Tek, Newark, DE, USA) **PBMT power:** 2.9 mW (26 J total energy) **PBMT power density:** 165 mW/cm^2 **PBMT duration:** 30 min/day for 5 days **Mean age of subjects:** not stated **Hearing loss:** Noise-induced	external auditory canal. Optical fibre tip was positioned 6 mm from the right tympanic membrane. **Audiological data:** ABRs performed before and immediately after noise exposure.	12 kHz: Group 1: 0 (20), 4 (10), 7 (20), 14 (20), 28 (20) Group 2: 0 (75), 4 (55), 7 (50), 14 (45), 28 (40) Group 3: 0 (82), 4 (24), 7 (18), 14 (20), 28 (16) 16 kHz: Group 1: 0 (10), 4 (10), 7 (10), 14 (18), 28 (18) Group 2: 0 (75), 4 (50), 7 (52), 14 (40), 28 (30) Group 3: 0 (82), 4 (22), 7 (18), 14 (18), 28 (18) 20 kHz: Group 1: 0 (15), 4 (10), 7 (20), 14 (22), 28 (20) Group 2: 0 (75), 4 (60), 7 (58), 14 (50), 28 (45) Group 3: 0 (95), 4 (18), 7 (16), 14 (22), 28 (22) **Immunofluorescence** **iNOS:** At 1 h after noise exposure, there was strong immunoreactivity for iNOS in the basal, middle and apical turns of OHCs in the surface preparations (group 2), whereas less immunoreactivity was observed in group 3 **Cleaved caspase-3:** 8 h after noise exposure there was strong immunoreactivity for cleaved caspase-3 in the basal, middle and apical parts of OHCs in the surface preparations (group 2), whereas less immunoreactivity was observed in group 3	3-mediated apoptosis that occur following NIHL. Thus, PBM may be a new candidate treatment strategy for NIHL.	

TABLE 4 Cochrane risk of bias 2 tool.

Author(s), year, country	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
S. Goodman et al., 2013, USA																			

Note: Green = low risk of bias; red = high risk of bias; yellow = unclear risk of bias. 1. Was the allocation sequence random? Yes. 2. Was the allocation sequence concealed until participants were enrolled and assigned to interventions? Yes. 3. Did baseline differences between intervention groups suggest a problem with the randomisation processs? No. 4. Were participants aware of their assigned intervention during the trial? No. 5. Were carers and trial personnel aware of participants' assigned intervention during the trial? Yes and No. 6. Deviations that arose because of the trial context? No. 7. Was an appropriate analysis used to estimate the effect of assignment to intervention? Yes. 8. Participants aware of intervention? No. 9. Personnel Aware of intervention? Yes and No. 10. Balanced non-protocol interventions? Yes. 11. Failures in implementation affecting outcome? No. 12. Non-adherence affecting outcome? No. 13. Outcome data for all participants? Yes. 14. Method of measuring the outcome inappropriate? No. 15. Measurement or ascertainment of outcome differ between groups? No. 16. Outcome assessors aware of intervention received? Unsure. 17. Could assessment have been influenced by knowledge of intervention? No. 18. Results selected from multiple outcome measurements and multiple analyses of the data? No. 19. Trial analysed in accordance with a pre-specified plan? Yes.

common.[13,19–25,27,28,30,31] All studies, except two, outlined where PBMT was anatomically focussed.[12,25]

3.5 | Photobiomodulation therapy outcomes

Twelve studies summarised all three of wavelength used, duration of PBMT, and follow-up period. Wavelength size of 808 nm was used most frequently ($n = 11$). PBMT was effective in hearing enhancing recovery, reducing loss of hair cells and reducing the immune inflammatory response in the included animal studies. One study found pre-emptive PBMT therapy before noise-induced hearing loss (NIHL) was effective at hearing preservation.[18] One study found that pre-treatment using PBMT prior to cochlear implantation resulted in better hearing outcomes.[29] Another study found a PBMT power of 165 versus 110 mW/cm^2 resulted in a greater preservation of hearing.[30]

A range of otological insults were used to induce hearing losses in each animal study: noise induced hearing loss (NIHL) ($n = 9$), gentamicin-induced ototoxicity ($n = 4$), surgical trauma ($n = 1$), oubain-induced auditory neuropathy ($n = 1$) and pre-treatment for CI surgery induced hearing loss ($n = 1$).[12,13,18–31] Direct comparison of differing ototoxic agents was not conducted in any of the studies included.

One study assessed the effect of PBMT in combination with antioxidants N acetyl-L-cysteine (NAC) or acetyl-L-carnitine (ALCAR).[20] This study showed conflicting results on the effectiveness of PBMT, in that the laser in combination with an antioxidant was not superior to the antioxidant alone when comparing ABRs. However, the hair cell count illustrated that PBMT in addition to an antioxidant was superior to the antioxidant alone.

Overall, there was a trend toward benefit from PBMT in animal studies, irrespective of delivery method, wavelength and power used or the animal species treated. Audiological outcomes improved in all 16 animal studies following PBMT compared to no PBMT, with statistically significant improvement stated in 11 studies.[12,13,19,20,22–27,29] In the single human study included, no statistically significant effect of PBMT on hearing was detected.[7] Notably, the PBMT wavelength *was shorter, and the power used lower* compared to all animal studies. No study reported any intra- or post-PBMT adverse events or deaths.

4 | DISCUSSION

This systematic review is the first to report outcomes of PBMT on hearing loss. Generally, animal subjects showed improvements in hearing preservation outcomes whereas no statistically significant improvement was detected in the single human study.

4.1 | PBMT versus placebo

The only human results from Goodman et al.'s study found none of the three measures of hearing (audiometric thresholds, speech recognition test, or otoacoustic emissions) showed statistically significant difference between the treatment, placebo, or control groups.[7] Therefore, this study concluded that PBMT was not effective in recovering hearing loss. However, the sample size was small ($n = 30$) and comparison with animal studies is difficult as the delivery characteristics differed. In the human study, PBMT was delivered in seven cycles across different anatomical locations, including the temporomandibular joint, spine, ear and top of the head. The duration of therapy ranged from 15 to 60 s. Overall duration of therapy was relatively very short, lasting approximately 4 min in total with low power (7.5 mW). In contrast, animal studies that produced positive results from PBMT, typically irradiated through the tympanic membrane for 60 min. Moreover, the wavelength used by Goodman et al. was 532 nm constantly, with 635 nm in a pulsed manner.[7] Prior evidence suggests that the wavelength with the highest potency of biomodulation is 800–830 nm.[27] This is likely due to the absorption spectrum of cytochrome *c* oxidase which has a peak of 830 nm, and the penetration of light through tissue is superior at 830 nm than 532 nm.[32] Hence, there were duration, power, anatomical site and wavelength differences between the human and animal studies.

Goodman et al.'s findings contrast with the 16 animal studies that assessed the effect of PBMT for a range of ototoxic insults. Ten studies assessed ABRs and showed an improvement in hearing, and inner ear elements on histology when compared to the placebo or non-treatment group.[18,20,22–25,27,29,30,31] Hearing was better preserved or maintained in the PBMT group versus non-PBMT group in most studies.[12,13,18,20,22,23,25,26,28–31] The effect of PBMT in reducing

TABLE 5 SYRCLE risk of bias assessment.

Author(s), year, country	1 Sequence generation	2 Baseline characteristics	3 Allocation concealment	4 Random housing	5 Blinding	6 Random outcome assessment	7 Blinding	8 Incomplete outcome data	9 Selective outcome reporting	10 Other sources of bias
D. Basta et al., 2020, Germany										
S. Chang et al., 2012, Korea										
S. Chang et al., 2016, Korea										
S. Chang et al., 2019, Korea										
T. Guan et al., 2015										
J. Lee et al., 2016, Korea										
M. Lee et al., 2016, Korea										
J. Lee et al., 2019, Korea										
C. Rhee et al., 2012, Korea										
C. Rhee et al., 2012, Korea										
C. Rhee et al., 2013, Korea										
C. Rhee et al., 2014, Korea										
C. Rhee et al., 2021, Korea										
I. Strübing et al., 2020, Germany										
A. Tamura et al., 2015, Japan										
A. Tamura et al., 2016, Japan										

Note: 1. Was the allocation sequence adequately generated and applied? (*). 2. Were the groups similar at baseline or were they adjusted for confounders in the analysis? 3. Was the allocation adequately concealed? (*). 4. Were the animals randomly housed during the experiment? 5. Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment? 6. Were animals selected at random for outcome assessment? 7. Was the outcome assessor blinded? 8. Were incomplete outcome data adequately addressed? (*). 9. Are reports of the study free of selective outcome reporting? (*). 10. Was the study apparently free of other problems that could result in high risk of bias? (*). *Items in agreement with the items in the Cochrane risk of bias tool.

inflammation was also supported through histology and immunohistochemistry findings, such as increased SGNs, hair cells, and ATP.[18,23,25,28]

4.2 | PBMT versus systemic therapy

One animal study evaluated the added effect of PBMT in addition to systemic antioxidant therapy (NAC and ALCAR).[20] This study found combination therapy of NAC and PBMT to significantly improve NIHL when compared to a previous study that assessed the effect of PBMT alone. It appears that NAC may have a role in accelerating hearing improvement with PBMT (improved on the 6th day of irradiation), when compared to PBMT alone (improved on the 10th day of irradiation).[20,26] Additionally, authors found the antioxidant NAC to be superior to ALCAR, but NAC and ALCAR alone was not superior to combination therapy with PBMT.[20]

4.3 | PBMT positioning and characteristics

In contrast to most animal studies which irradiated in close proximity to the tympanic membrane, Goodman et al.'s human study utilised external irradiation (temporomandibular joint, cervical spine, top of head and external auditory meatus). They state that a transmeatal approach would have resulted in greater penetration but suggest that it would be less practical.[7]

The positioning of PBMT for optimal delivery varied across studies. Beyer et al. found that irradiation of the mastoid leads to therapeutically insufficient light doses when compared to irradiation through the tympanic membrane.[33] Beyer et al. used a PBMT power and dose similar to Goodman et al. (1 mW, 593 and 633 nm vs. 7.5 mW, 532 and 635 nm in Goodman et al).[7] Therefore, for optimum dosimetry, evaluation of light transmission factors for chosen irradiation modalities is necessary. The externally applied light dose needs to be calculated according to the tonotopy of the cochlea, as different anatomical landmarks and mediums will transduce different frequencies; this is relevant when considering the anatomical location of the PBMT probe.

An excess amount of laser irradiation may lead to destruction rather than promotion.[34] Subsequently, determining optimal PBMT parameters is vital and must be balanced against safe PBMT delivery. There are peaks in the typical responsive wavelengths for cytochrome *c* oxidase (670 and 830 nm).[9] Cytochrome *c* oxidase mediates photobiomodulation in the far-red and near-infrared range. Although cytochrome *c* oxidase also absorbs strongly at wavelengths less than 630 nm, this is within the visible light range and has a lower rate of tissue penetrance than wavelengths in the near-infrared range.[9] Penetrance of lasers through the tympanic membrane and other tissue structures of the inner otic capsule is superior in the near infrared range (780–1100 nm).[25] Therefore, wavelengths must be carefully selected according to PBMT delivery method and structures the light must pass through to reach the cochlea. Additionally, it is important to ascertain whether shorter, concentrated delivery of PBMT induces a more significant effect on hearing loss when compared to a more prolonged delivery at lower concentration.

4.4 | PBMT as a pre-treatment therapy

Basta et al. assessed the effect of PBMT prior to noise exposure. They found a single pre-treatment dose of PBMT induced statistically significant protection of cochlear structures based on ABR recording and histological analysis.[18] Pre-exposure of 10 min was the optimal dosing.[18] These findings suggest the scope for the implementation of PBMT as a pre-treatment therapy prior to procedures known to cause inner ear damage and hearing loss, such as cochlear implantation. More research is required to ascertain the true benefits of PBMT as a pre-treatment in hearing preservation.

4.5 | Future of PBMT

Overall, results suggest that PBMT could be an effective method for hearing preservation. However, almost all studies to date have been conducted on animal models *with only one conducted on human subjects*. Most studies assessed outcomes over a short duration of time, with the longest period of follow up being 28 days. This precludes comment on the long-term effects PBMT may have on hearing loss, or whether further courses are needed to maintain benefit. Including a longer follow-up period would enable researchers to assess the longer-term effects and complications of PBMT. Thus, enabling researchers to determine the suitability of using PBMT in further human trials.

5 | CONCLUSION

Though the evidence base is far from comprehensive, hearing outcomes following PBMT appear to be superior to non-PBMT in animal studies. PBMT theoretically enables a non-invasive mode of delivering therapy which may enable audiological function to be preserved and maintained following injury to inner ear structures. The low-risk profile and promising data from animal models suggest PBMT warrants further investigation as an intervention to prevent or treat hearing loss. Further research should focus on optimising PBMT light delivery and dosing for the inner ear to inform future human trials.

AUTHOR CONTRIBUTIONS

Manohar Bance, Jameel Muzaffar and Peter Kullar conceived the paper and supervised the work undertaken. Searches and data extraction were performed by Yasmin Nikookam, Nawal Zia, Andrew Lotfallah and Jennifer Davis-Manders. All authors reviewed the study protocol and were involved in drafting and providing critical edits to the manuscript. All authors agree to be accountable for all aspects of the work presented.

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The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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