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REVIEW ARTICLE

Applications of photobiomodulation in hearing research: from bench to clinic

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Abstract
Hearing loss is very common and economically burdensome. No accepted therapeutic modality for sensorineural hearing loss is yet available; most clinicians emphasize rehabilitation, placing hearing aids and cochlear implants. Photobiomodulation (PBM) employs light energy to enhance or modulate the activities of specific organs, and is a popular non-invasive therapy used to treat skin lesions and neurodegenerative disorders. Efforts to use PBM to improve hearing have been ongoing for several decades. Initial in vitro studies using cell lines and ex vivo culture techniques have now been supplanted by in vivo studies in animals; PBM protects the sensory epithelium and triggers neural regeneration. Many reports have used PBM to treat tinnitus. In this brief review, we introduce PBM applications in hearing research, helpful protocols, and relevant background literature.

Keywords Photobiomodulation · Low-level laser therapy · Hearing loss

1 Introduction

Hearing disabilities, hypertension, and arthritis are the three most common human medical conditions [1]. Hearing may degenerate with age, or may be compromised at birth or when young by noise exposure, ototoxic drugs, or genetic problems. Several large cohort studies found that over 45% of all subjects suffered from hearing loss [2–4]; a recent study reported that the prevalence of hearing loss in the young is increasing [5, 6]. Over 75% of those aged 60–69 years may suffer from high-frequency hearing loss [5, 6]. Poor hearing causes communication difficulties and social withdrawal, affecting both the patient and his/her family [6, 7]. Hearing must be preserved to facilitate social engagement as individuals now tend to live longer. Hearing is of great psychosocial importance; however, currently, only hearing aids and cochlear implants are available as treatments.

Photobiomodulation (PBM) and low-level laser therapy (LLLT) use light to reduce pain [8–10] and inflammation [11–15], induce analgesia [16], and promote nerve and tissue repair [17–21]. As the laser power is low, tissue temperature does not rise [22]. After PBM was approved by the United States Food and Drug Administration (FDA), diverse applications were reported. PBM is non-invasive and thus associated with minimal side-effects; however, the lack of a recognized therapeutic mechanism has hindered wider use. Both basic and clinical studies on the use of PBM to protect against hearing loss, tinnitus, and vestibular dysfunction in animals and patients have been published. Here, we review these studies and suggest future PBM applications.

2 Cochlear anatomy and hearing loss

Hearing can be compromised by damage to various auditory organs. The organ of Corti, the peripheral structure associated with signaling transition, is the principal target of external auditory stimulation. The inner hair cells (IHCs) and outer hair cells (OHCs) of the organ of Corti are critical for hearing. One row of IHCs and three rows of OHCs transmit

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sounds. Endolymph ions flow into hair cells via channels that open at the tips of the stereocilia [23], inducing cellular depolarization that in turn releases neurotransmitters within synaptic vesicles in ventral cellular regions [24]. The neurotransmitters bind to post-synaptic receptors and the signals are thus further transduced to the spiral ganglion neurons that connect the hair cells with the cochlear nucleus of the brainstem, via nerve fibers [25, 26]. All of these peripheral inner ear organs (Fig. 1) can be damaged by external insults. Hair cells and stereocilia are the primary targets of noise [27–30] and ototoxic drugs [31–39]. Damage to these components blocks signal transfer from the external ear to the brain, causing hearing loss. A recent study found that the ribbon synapse was the most vulnerable part of the peripheral auditory system [40]. High-level noise or ototoxic drugs can trigger IHC synaptopathy, reducing the peak amplitude of the auditory brainstem response (ABR) without changing the threshold [41–44]. The auditory and spiral ganglion neurons can also be either primary or secondary targets of external insults [45, 46]. Damage to the myelin or satellite cells of nerve fibers delays signal transport, triggering encoding deficits or rendering temporal processing inadequate [47]. All of these systems can be targeted by PBM to prevent or reverse hearing loss.

3 PBM therapy for hearing loss

3.1 Lasers and light-emitting diodes

A laser (light amplification by stimulated emission of radiation) transmits highly focused amplified light at specific wavelengths [48]. Both continuous-wave (CW) and pulsed lasers are available. Light-emitting diodes (LEDs) emit light of various colors when current flows through semiconductors [49]; LEDs last longer than general light sources, switch more rapidly, and consume less energy [50]. LEDs and lasers exhibit several differences (Fig. 2). LEDs generate light spontaneously; lasers must be stimulated to emit radiation [51]. Lasers generate light of coherent wavelengths but LEDs output light of substantially greater energy [52]. Laser light features a wide emission spectrum, whereas LED light is monochromatic, thus lying within a narrow spectral band [53]. Laser spots are tightly circumscribed; LED beams are wider, thus exhibiting more light-scattering than laser beams, rendering LEDs useful for irradiating larger areas [52]. Thus, lasers and LEDs differ in terms of spectral distribution, absorption, and interaction with photoreceptors, as reflected in their different therapeutic applications.

3.2 Parameters relevant to PBM

Light irradiation and dose parameters are critical for PBM applications. Light is wave-like; wavelength is measured in nanometers and light of wavelength 400–700 nm is visible. PBM uses visible light; chromophores absorbing at different wavelengths exhibit various biological effects. Red and near-infrared (NIR) light of wavelength 600–1,100 nm is commonly used; such light penetrates tissue to depths greater than light of other wavelengths [54–58] and activates cytochrome c oxidase; this is the aim of most PBM therapies. The unit of power is energy; both peak and average energy can be relevant, depending on whether a CW or pulsed laser is used. Beam area is also critical, but is often incorrectly reported. The beams of diode lasers usually exhibit Gaussian distributions, i.e., brighter at the center and dimmer toward the edges; the precise amount of energy that reaches a target can be unclear. The beam combiner of Kim (Fig. 2) smooths energy distribution across the beam; this will greatly aid future research. Irradiance (or power density, mW/cm^2) is the power divided by the beam area, and is also often misreported. Thus, careful calculation of PBM irradiance and power are essential when comparing studies.

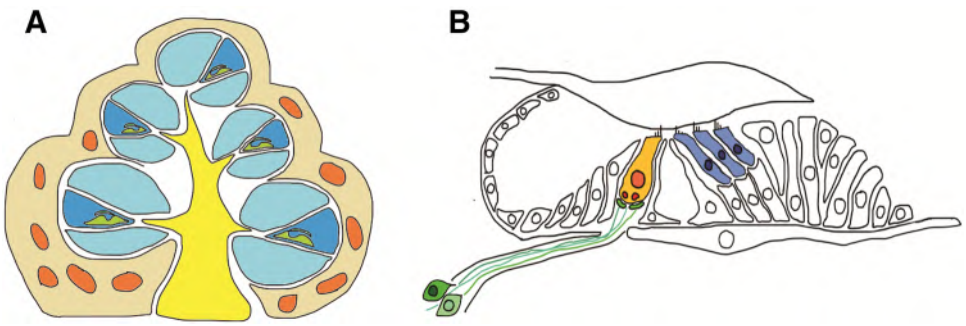

Fig. 1 Schematic anatomy of the cochlea (**a**) and the organ of Corti (**b**). Stereocila at the apex of one line of IHC (yellow cell), and three lines of OHC (blue cells) are attached at tectorial membrane. At the bottom of IHC, synaptic ribbon (red) which is paired with post tynaptic receptor (light green) transmits the auditory signal to spiral ganglion neuron (green cell) through auditory fiber (green lines). (Color figure online)

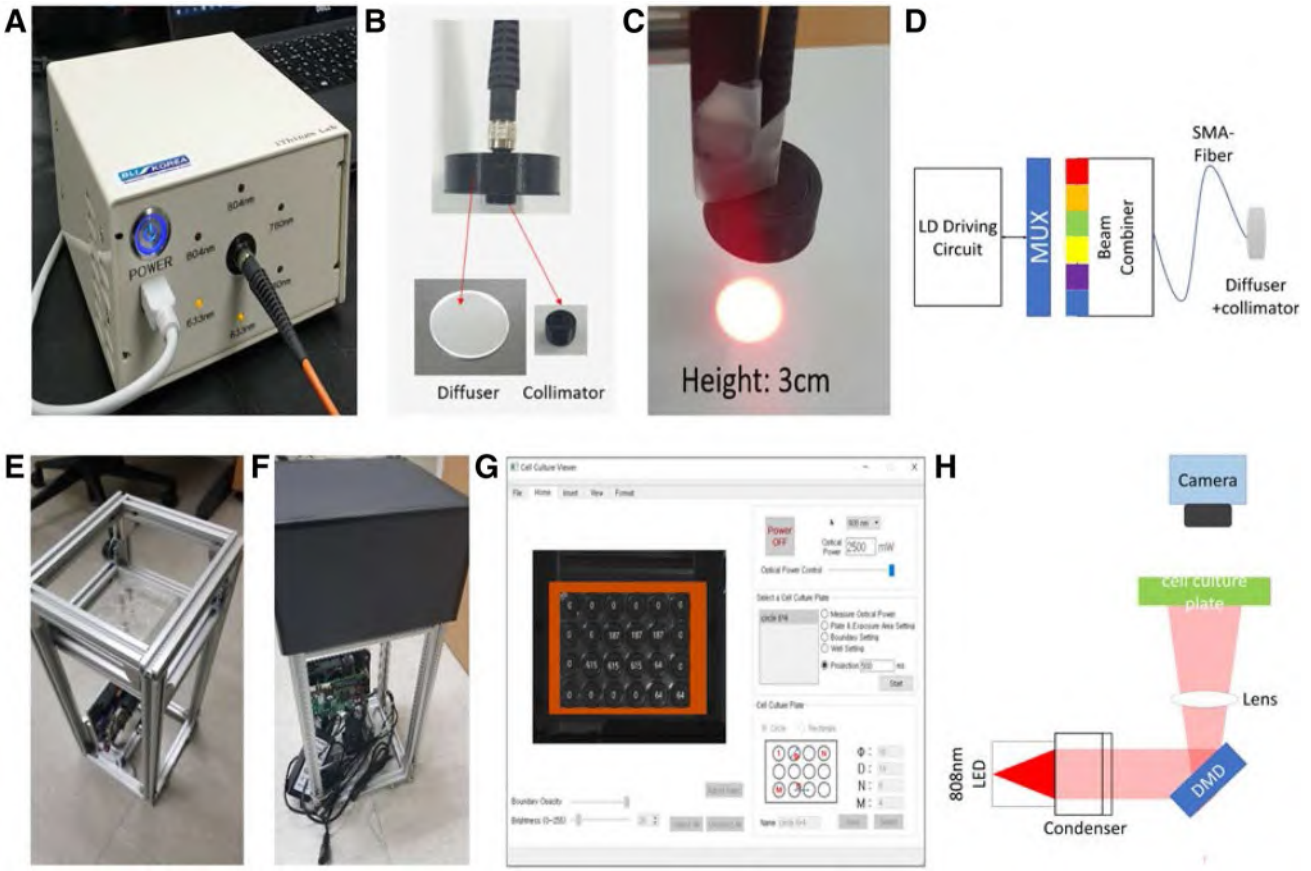

Fig. 2 Multi-LD-based LLLT system for single well culture (**a**–**d**) and LED-based LLLT system for multi-well culture (**e**–**h**). **a** Photo of multi-LD-based LLLT system with three wavelengths (633, 780, 804 nm); **b** light output design composed of diffuser and collimator to guarantee uniform irradiation; **c** light beam pattern of the 633 nm laser diode (LD) at 3 cm height; **d** block diagram of multi-LD-based LLLT system; **e**, **f** photo of LED-based LLLT system with single 808 nm LED; **g** graphic user interface (GUI) for multi-well culture with different powers; **h** block diagram of LED-based LLLT system

3.3 PBM parameters relevant to hearing loss

When PBM is used to address hearing problems, the unique anatomy of the ear must be considered, because it affects the wavelength required for penetration. The light must pass through the tympanic membrane to reach the cochlea of the middle ear. Light of wavelength 680–850 mm is used most commonly [46, 59–65]. PBM must impart maximal benefits with minimal side-effects. Tympanic membrane status is important. Moon et al. [64] assessed PBM safety in an animal model using an 830-nm laser operating at different powers; PBM was delivered through the tympanic membrane for 30 min daily over 14 consecutive days. Histological changes in the tympanic membrane when the laser power was 250 mW included edema, vascular congestion, and inflammation; Only few lymphocytes were observed when the power was 200 mW [64] (Fig. 3).

PBM therapy is critically dependent on the power of the laser that reaches the cochlea; a detailed understanding of ear anatomy from the external ear to the cochlea is indispensable. Coronal computed tomography was used to define the laser irradiation angle in an animal study [66]. Customized devices featuring protractors facilitate precise laser irradiation (Fig. 4).

4 Studies using PBM to prevent hearing loss

4.1 Previous in vitro and in vivo studies

Previous in vitro PBM studies are listed in Table 1. Organ of Corti tissue cultures and the HEI-OC1 cell line have been used to explore the effects of PBM after stress was imparted in vitro [62, 65, 67]. Diode lasers of similar wavelengths (808 and 810 nm) and powers (8–15 mW/cm^2) were used to deliver light either once or repeatedly. PBM enhanced gene transfection [67], reduced inflammatory cytokine levels [65], and protected against cell loss after aminoglycoside treatment [62]. PBM using an 808-nm diode laser increased mitochondrial membrane potential (MMP) and adenosine

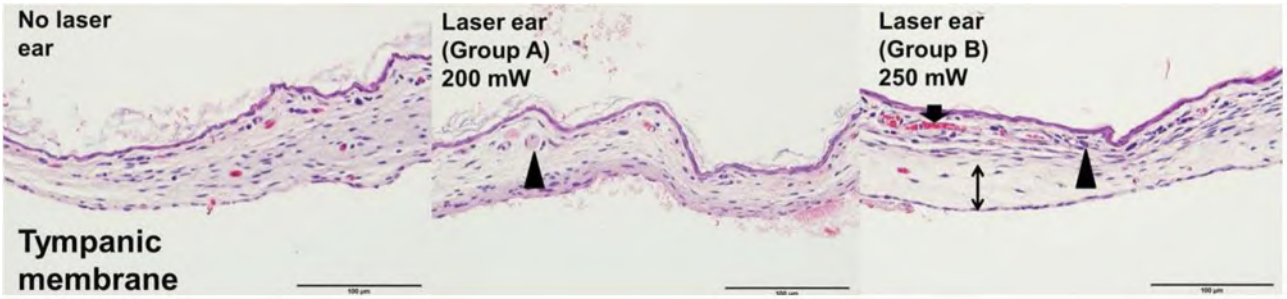

Fig. 3 Histological changes in tympanic membrane after low-level laser therapy. Lymphocytes (*arrowhead*), edema (*arrowed line*), and vacular congestion (*arrow*) were found in the group with 250 mW laser while, only few lymphocytes were observed in the group with 200 mW [64]

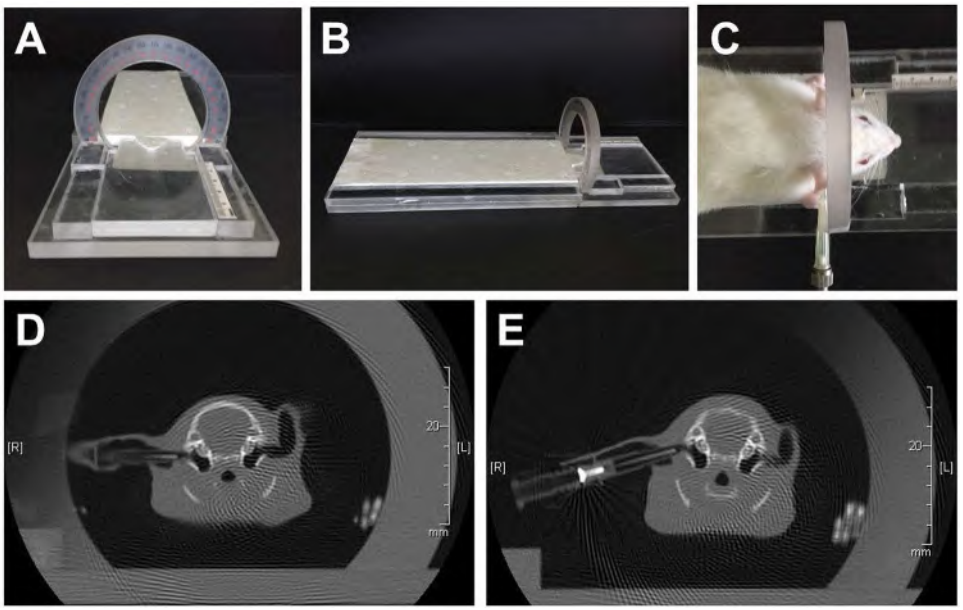

Fig. 4 PBM system for in vivo study was customized for accurate laser irradiation. Frontal (**a**) and lateral (**b**) view of PBM therapy tool for animal. **c** SD rat with laser tip attached at right ear. Frontal (**d**) and lateral (**e**) view of computed tomography scans of laser irradiation

Table 1 PBM parameters of previous in vivo studies

Laser type	Wavelength (nm)	Animal	Power (mW/cm^2)	Irradiation time (min)	# of treatment (# per day)	Year	Reference number
Diode laser	830	SD rat	200	60	10 (1)	2013	[66]
Diode laser	808	SD rat	110, 165	30	5 (1)	2015	[72]
Diode laser	830	SD rat	200, 250, 300	30	14 (1)	2016	[64]
Diose laser	808	SD rat	165	30	5 (1)	2016	[63]
Diode laser	808	Gerbil	200	60	7 (1)	2016	[46]
Diode laser	808	SD rat	165	60	15 (1)	2016	[59]

triphosphate (ATP) levels, and decreased the generation of reactive oxygen species (ROS) by stimulating the Bcl-2, JNK, and c-Jun pathways (unpublished data), consistent with the findings of previous studies showing that PBM increased intracellular ATP levels and the MMP, and reduced ROS levels [68–71]. We were the first to evaluate PBM (using a low-level 808-nm laser that penetrated the tympanic membrane) in a rat model (Male, 6 weeks) (Table 2). As noise exposure is the most common cause of hearing loss, we explored the protective effect of PBM after noise exposure [61]. After 14 days of once-daily irradiation, treated rats exhibited better hearing thresholds and less hair cell loss than controls [61]. Tamura et al. [72] delivered LLLT to the noise-exposed cochlea using our protocol, at two different powers (110 and

Table 2 PBM parameters in previous in vitro and ex vivo studies

Laser type	Wavelength (nm)	Cell line	Power (mW)	Irradiation time	# of treatment (# per day)	Year	Reference number
Diode	810	OC culture	8	60 min	6 (1)	2012	[62]
Diode	810	HEI-OC1	9.5	100 s	1 (1)	2016	[65]
Diode	808	HEI-OC1	15	15 min	2 (2)	2018	[67]

165 mW); the higher power was same to what we delivered previously (165 mW) and was associated with an improved hearing threshold and less hair cell loss. Histologically, PBM inhibited apoptosis and iNOS expression [72]. In a later study using the same laser conditions, PBM reduced apoptosis and oxidative stress by activating the NF-KB signaling pathway [63]. We administered unilateral/bilateral laser irradiation over 14 consecutive days after noise exposure, as above [59]. The bilateral group evidenced faster hearing threshold recovery than the unilateral group [59]. We did not explore cochlear effects, but PBM protected hair cells from the effects of noise exposure. We then explored the effect of PBM on spiral ganglion neurons [46]. Ouabain, a neurotoxin, was directly applied to the round window membranes of gerbils, greatly elevating the hearing threshold and triggering complete loss of spiral ganglion neurons but with retention of intact organs of Corti. PBM (an 808-nm laser) was applied for 7 consecutive days commencing 24 h after ouabain treatment. Test animals evidenced less spiral ganglion neuron and post-synaptic receptor loss than controls [46]. Histology revealed major effects of PBM on auditory nerve fibers; PBM protected the cochlea.

PBM (low-level 830-nm laser irradiation) was protective in an animal model of salicylate-induced tinnitus; the gap pre-pulse inhibition of acoustic startle (GPIAS) served as a measure of tinnitus. After PBM, the GPIAS normalized, indicating that PBM was effective, but the mechanism remained unclear. We investigated the effect of PBM on vestibular function after an aminoglycoside insult [60]. Gentamicin was injected intraperitoneally into rats (Male, 12 weeks) to induce vestibulopathy. PBM (808-nm diode laser irradiation) was performed on 7 consecutive days. PBM treatment normalized the vestibule, while control vestibules remained compromised [60]. Thus, PBM of the cochlea aided recovery of both hearing and balance after application of external stress.

4.2 Previous human studies

Clinically, PBM has been used principally to treat tinnitus (Table 3). In the 1990s, He–Ne and Ga-Al-As lasers operating at 632 and 904 nm were used to this end [73–78]. Most studies reported positive effects [73, 74, 76, 77] but two using a similar [75] and a different [78] laser

Table 3 PBM parameters of previous clinical studies

Laser type	Wavelength	Treatment target	Power (mW)	Irradiation time (min)	# of treatmen (#/# day)	Year	Reference number
He–Ne, Ga–AL–As	632, 904	Tinnitus	12, 2–20	10	12 (1/1 day)	1993	[73]
He–Ne, Ga–AL–As	632, 904	Tinnitus	12, 30	8	8 (1/1 day)	1993	[74]
He–Ne, Ga–AL–As	632, 904	Tinnitus	12, 9–20	10	12 (1/1 day)	1995	[75]
He–Ne, Ga–AL–As	632, 904	Tinnitus	12, 30	8	8 (1/1 day)	1995	[76]
He–Ne, Diode	632, 830	Tinnitus	20, 100	9	10 (1/1 day)	1996	[77]
Diode	830	Tinnitus	40	9	10 (1/1 day)	1997	[79]
Ga–Al–As	830	Tinnitus	50	10	15 (1/1 day)	1999	[78]
Diode	635, 690, 780, 830	Tinnitus	50	Not provided	10 (1/1 day)	2003	[80]
Diode	650	Tinnitus	5	20	90 (1/1 day)	2008	[83]
Diode	650	Tinnitus	5	15	7 (1/1 day)	2008	[84]
Diode	650	Tinnitus	5	20	90 (1/1 day)	2008	[81]
Diode	650, 808, 904	Hyperacusis, SSNH	35, 490, 120	16–28, 4–16, 7	10–20 (2/7 days)	2010	[85]
Diode	650	Tinnitus	5	20	20 (1/1 day)	2011	[87]
Diode	650	Tinnitus	5	20	90 (1/1 day)	2012	[82]
Diode	531, 635	Tinnitus	7.5	5	3 (1/2–4 days)	2013	[86]

did not. PBM therapy, at least weekly, at a wavelength of 630–900 nm and an average power of 20 mW, improved tinnitus. Studies continued up to 2013. Shiomi et al. [79] were the first to use a PBM diode laser to treat tinnitus; 58% of patients reported loudness reductions and 55% less annoyance. Later studies used PBM diode lasers to treat tinnitus [80–84], hyperacusis [85], and poor hearing [86]. Any effect of PBM remains controversial. Zazzio [85] reported that PBM improved hyperacusis. Okhovat et al. reported that PBM improved tinnitus but the effects varied by patient age and profession/job. Thus, patient characteristics may affect PBM outcomes [87].

5 Possible mechanism of PBM on hearing research

There are several possible mechanisms of PBM on hearing research. Cytochrome c oxidase (Cox), one of chromophore and the terminal enzyme of the electron transport chain, has considered a major target of PBM. Modulation of Cox can increases the adenosine triphosphaste (ATP), cyclic adenosine monophosphate (cAMP), and the mitochondrial membrane potential (MMP) [68]. Photodissociation of NO in the cox by PBM converts mitochondrial inhibition of cellular respiration resulted from NO binding [88]. Transient receptor potential (TRP) families, light sensitive ion channels, can also be inhibited by infrared light, resulting in activation of neuronal voltage variation [89–91]. Known molecular mechanism of PBM protection through ROS modulation [58, 92, 93] and/or NF-kB activation [58, 63, 94] would occurred in the cochlea.

6 Conclusion and future applications

We summarize previous work on PBM in the context of hearing research. PBM is non-invasive and reduces hearing problems; the future is bright for this technology. However, despite positive laboratory and clinical reports, the absence of any explanation as to how PBM aids hearing is a major stumbling block. Mechanistic studies (transcriptome or genetic analyses) are essential.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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