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REVIEW PAPER

The Role of Photobiomodulation to Modulate Ion Channels in the Nervous System: A Systematic Review

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Abstract

Photobiomodulation (PBM) is a safe and effective neurotherapy that modulates cellular pathways by altering cell membrane potentials, leading to beneficial biological effects such as anti-inflammatory and neuroregenerative responses. This review compiles studies from PubMed up to March 2024, investigating the impact of light at wavelengths ranging from 620 to 1270 nm on ion channels. Out of 330 articles screened, 19 met the inclusion criteria. Research indicates that PBM can directly affect various ion channels by influencing neurotransmitter synthesis in neighboring cells, impacting receptors like glutamate and acetylcholine, as well as potassium, sodium channels, and transient receptor potential channels. The diversity of studies hampers a comprehensive meta-analysis for evaluating treatment strategies effectively. This systematic review aims to explore the potential role of optoelectronic signal transduction in PBM, studying the neurobiological mechanisms and therapeutic significance of PBM on ion channels. However, the lack of uniformity in current treatment methods underscores the necessity of establishing standardized and reliable therapeutic approaches.

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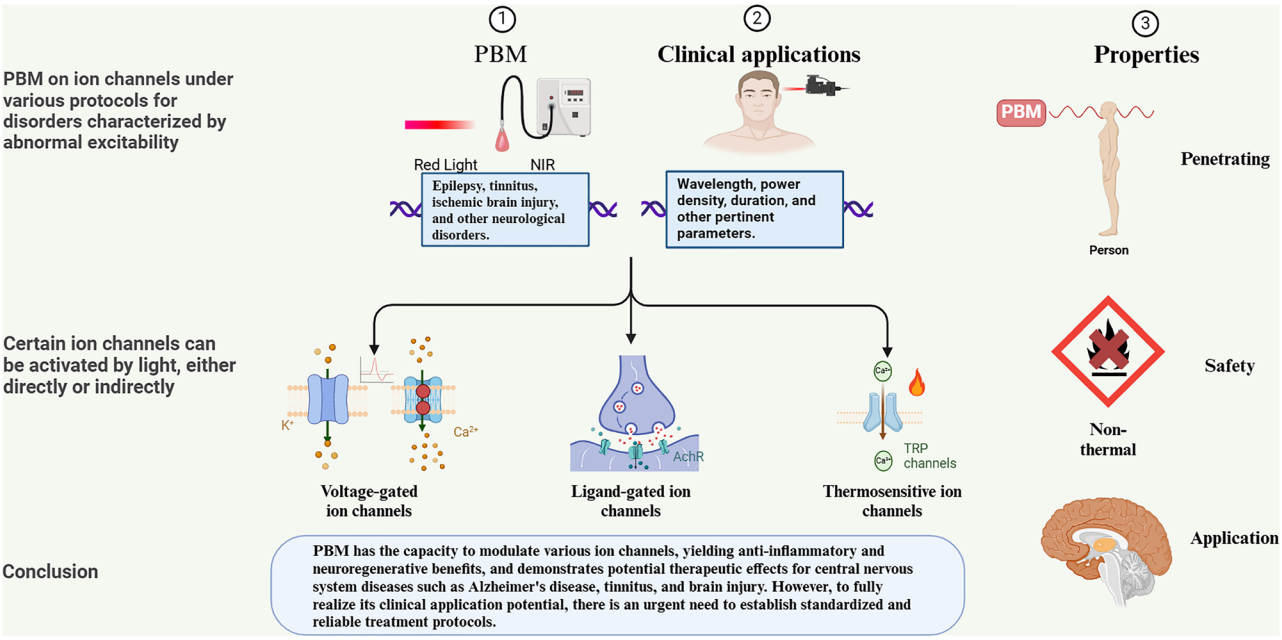
Graphical Abstract

PBM is a promising neurotherapeutic approach with anti-inflammatory and neuroregenerative potential through its effects on cell membrane potential and ion channels. This systematic review analyzes 19 studies, revealing its influence on channel activity and emphasizing the need for standardized treatment protocols.



Keywords Photobiomodulation · Ion channels · Nervous system · Neural plasticity · Non-invasive nerve stimulation

Abbreviations

PBM	Photobiomodulation
CCO	Cytochrome c oxidase
TRPs	Transient receptor potential channels
ROS	Reactive oxygen species
AChR	Acetylcholine receptor
ChR	Channelrhodopsins
KCR	Kalium channelrhodopsin
UVB	Ultraviolet radiation b
FDA	U.S. food and drug administration
ASICs	Acid-sensitive ion channels
CFTRs	Cystic fibrosis transmembrane conductance regulators
CW	Continuous wave
PW	Pulsed wave
DM	Diabetic mellitus
SCI	Spinal cord injury
CCI	Chronic constriction injury
DC	Duty cycle
DRG	Dorsal root ganglia
hASCs	Human adipose-derived stem cells
BMV	Bothrops moojeni venom
MOR	μ-Opioid receptor
GluR1	Glutamate receptor 1
ACC	Anterior cingulate cortex
CNS	Central nervous system
MMP	Mitochondrial membrane potential
NIR	Near-infrared
ATP	Adenosine triphosphate
NMJ	Neuromuscular junction
nAChR	Nicotinic acetylcholine receptor
iGluRs	Ionotropic glutamate receptors
mGluRs	Metabotropic glutamate receptors
NMDARs	N-methyl-D-aspartame receptors
AMPARs	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors
cGMP	Cyclic guanosine monophosphate
PKG	Protein kinase G
cAMP	Cyclic adenosine monophosphate
BBB	Blood–brain barrier
Aβ	Amyloid β protein
COPD	Chronic obstructive pulmonary disease

Introduction

Photobiomodulation (PBM), a non-invasive and precise neuromodulation technique, utilizes light in the red or near-infrared wavelengths to achieve its therapeutic effects with minimal side effects (Hamblin 2024). This method operates by leveraging the interaction of light particles with cellular structures to enhance ATP synthesis, modulate gene expression, control levels of reactive oxygen species (ROS), and modify ion channel activity (Huang et al. 2012; Khuman et al. 2012). In recent years, PBM has emerged as a promising therapy for neurological diseases. Utilizing laser technology, PBM penetrates deep tissues and activates intracellular photosensitive molecules, demonstrating potential for various neurological conditions. Research has also explored PBM's role in modulating the cerebral–gut axis (Blivet et al. 2024) and the use of home portable LED devices (Razzaghi et al. 2024). The U.S. Food and Drug Administration (FDA) has approved several laser devices for medical use, showing positive results in treating Alzheimer's disease (Berman et al. 2019), tinnitus (Choi et al. 2024), ischemic brain injury (Chan et al. 2024), and other disorders. As research advances, PBM may increasingly contribute to the treatment and rehabilitation of these challenging conditions. The efficacy of PBM in influencing organisms can be attributed to three key properties—Penetration, Safety, and Application, which form the basis for our investigation into the mechanism of action of PBM on ion channels.

The Penetration of PBM

Light, with its wave properties manifested through photons at a macroscopic level, exhibits characteristics of penetrability that are essential to clarify the effects of PBM. The relationship between the frequency and wavelength of light is crucial, as longer wavelengths result in better directionality, reduced scattering, energy attenuation, and minimal diffraction (Castaño-Castaño et al. 2024; Escalé et al. 2017; Souto-Neto et al. 2024). This concrete interplay is highlighted in Fig. 1, aiding in comprehending how different wavelengths impact PBM. Selecting the appropriate light wavelength is a complex task for researchers and medical professionals, as it necessitates a delicate balance between penetration and directionality to optimize bioregulation outcomes (Bullock-Saxton et al. 2021; Hamblin 2016). Tissue penetration of light is influenced by various optical parameters like wavelength, power density, and coherence, while tissue structure at the irradiation site can alter light energy absorption (Henderson et al. 2015). Alterations in these parameters significantly affect PBM processes, impacting ion channel activity.

Channelrhodopsins (ChR) are light-gated ion channels first discovered in Chlamydomonas reinhardtii (Sineshchekov et al. 2002). These channels respond to light by opening or closing, resulting in various photobiological effects. The primary photosensitive ion channel in humans is Kalium

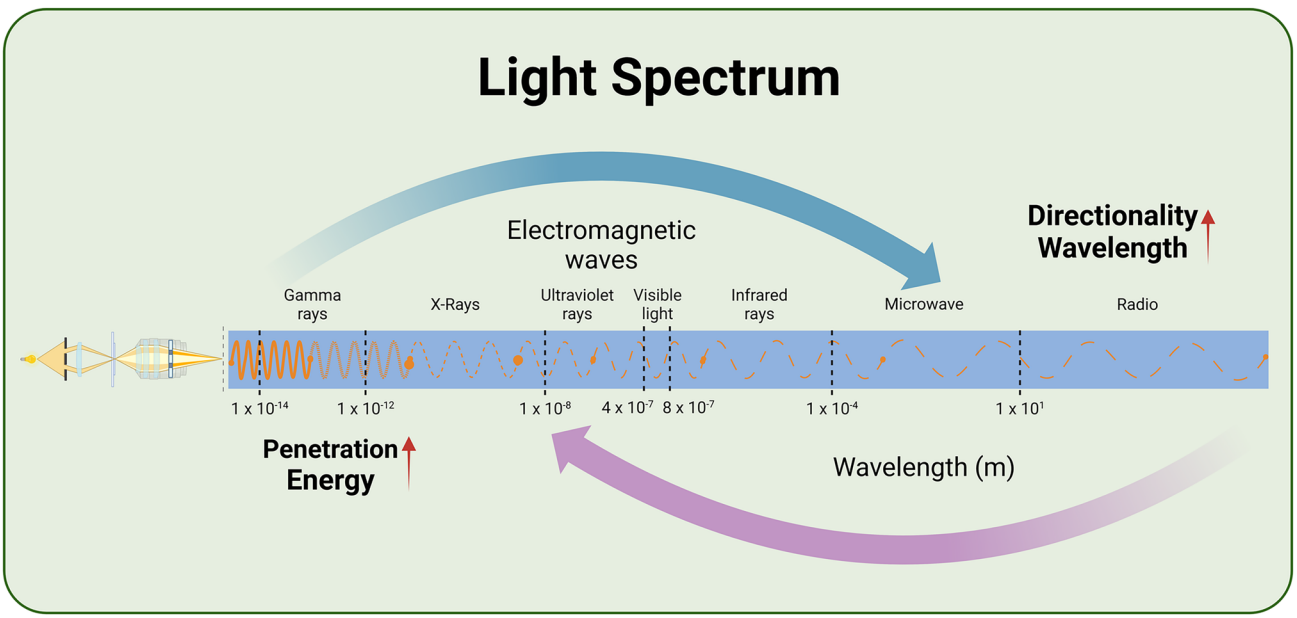


Fig. 1 Impact of varying light wavelengths on PBM. Shorter wavelengths of light reflect mainly the wave properties in the figure with a solid line; longer wavelengths reflect mainly the particle nature in the figure with a dotted line, and the stronger the particles, the wider the distance between the dotted line

channelrhodopsin (KCR) found in the eye (Oppermann et al. 2024). Light-activated retinal undergoes chemical transformations through distinct intermediates, converting light signals into electrical signals that excite optic neurons (Govorunova et al. 2022). Additionally, the TRP channel protein family plays a crucial role in light signal transduction (do Nascimento et al. 2024). Wei Wu et al. (2023) identified TRPA1 as a potential therapeutic target for ultraviolet radiation b-related (UVB-related) skin pigmentation diseases. The TRPA1 antagonist HC-030031, applied topically, reduced UVB-induced pigmentation. Furthermore, the ability of light to penetrate tissues opens the door for bioregulation without relying on optogenetics. Though PBM may not match optogenetics in precision and efficacy, its lack of gene editing requirements and ease of application position it as a promising strategy for treating CNS disorders.

The Safety of PBM

PBM is a safe and effective therapeutic approach that harnesses non-photothermal effects to induce beneficial biological responses (Tang et al. 2023). The wavelength of light plays a crucial role in determining the photothermal effect, with far-infrared light, ranging from 1.4 to 3 μm, being widely utilized in photothermal therapy within fields such as rehabilitation physiotherapy and dermatology (Aggarwal et al. 2023; Mineroff et al. 2024). Uozumi et al. (2010) have shown that at 808 nm and a high intensity of 1.1 W/cm^2, the temperature of laser-irradiated tissues remains stable, with minimal increase in temperature. The safety of PBM is further underscored by the bidirectional dose response (Barolet 2021), as outlined in the Arndt–Schulz law, indicating that both too low and too high doses of light can be counterproductive or even harmful (Huang et al. 2009). Optimal biological effects are achieved within a safe range of light doses, emphasizing the significance of power density over total dose in determining the therapeutic outcomes of PBM (Lanzafame et al. 2007; Oron et al. 2001; Vasilenko et al. 2010).

The Application of PBM

As a technique harnessing the power of photons to activate or inhibit ion channels, PBM is a field with broad applicability and potential. Cells rich in mitochondria and with high metabolic activity, such as neuronal and muscle cells, are particularly responsive to the effects of PBM (Hamblin 2018). Presently, this technology finds application in diverse medical areas, including the treatment of epilepsy (Ma et al. 2024), ischemic encephalopathy (Cardoso et al. 2022), Alzheimer's disease (Gaggi et al. 2024), autism (Ceranoglu et al. 2024), anxiety (Chen et al. 2024a, b), injury recovery (Behroozi et al. 2024; Dehghanpour et al. 2023), arthritis (Du et al. 2024), tumors (da Silva et al. 2023), and various other disorders. The effectiveness of PBM in these diseases needs confirmation through further clinical trials. Individual differences significantly impact PBM. Physiological and psychological traits, such as gender (Gutiérrez-Menéndez et al. 2022), age (Rodríguez-Fernández et al. 2024), and mental state (Chamkouri et al. 2024), can affect how PBM influences biorhythms, mood regulation, and other functions. Candela Zorzo et al. (2024) found that PBM notably increased cerebral metabolic activity in males more than in females, potentially due to higher CCO activity in males. Therefore, understanding these individual differences is crucial for optimizing light interventions and enhancing their effectiveness in clinical and daily applications, allowing for more effective promotion of physical and mental health through tailored light programs.

Ion channels, encompassing ligand-gated, voltage-gated, and stress-activated variants, are pivotal in cell signaling by managing sodium, potassium, and calcium ion concentrations within and outside cells, thus governing cellular function regulation (Liu et al. 2024). Recent studies have made significant advancements in the understanding of various ion channels, including voltage-gated, ligand-gated, TRPs, acid-sensitive ion channels (ASICs), chloride channels (e.g., CFTRs), ATP-gated channels (e.g., P2X7 receptor), and mechanosensitive channels (e.g., Piezo). These ion channels are crucial in regulating cellular signaling, neurotransmission, and a wide range of physiological processes. Their detailed characterization offers valuable molecular targets for elucidating the pathogenesis of associated diseases and for the development of innovative therapeutic strategies. PBM has garnered attention for its applications in the central nervous system due to its penetration, safety, and application. Although the mechanisms of action remain not fully understood, existing research has revealed the influence of PBM on voltage-gated ion channels, ligand-gated ion channels, and TRPs, which play critical roles in PBM. However, the heterogeneity and reproducibility issues of PBM protocols in animal experiments and clinical trials underscore the urgent need for standardized parameters to facilitate further research and clinical application of PBM. Additionally, the biological effects of PBM and its potential in the treatment and prevention of neurological disorders require deeper exploration. Future research should focus on elucidating the cellular mechanisms of PBM, optimizing treatment protocols, and overcoming the limitations of existing studies to advance innovative therapeutic strategies in the field of neuroscience.

Methods

Search of the Literature

We conducted an extensive literature search in the PubMed database to explore the impact of PBM on ion channel

function and its potential applications in the nervous system. Our search, which encompassed studies up to 6 March 2024, utilized MeSH terms such as "photobiomodulation," "low-intensity laser therapy," "ion channel," and "receptor." The detailed search strategy is shown as follows: ((Low-intensity laser therapy) OR (photobiomodulation)) AND ((channel) OR (receptor) OR (ion channel)).

Study Selection

The selection of literature was predicated on the alignment of titles and abstracts with our inclusion criteria. Subsequently, full texts were scrutinized to ascertain adherence to these criteria. This process was conducted manually, with no reliance on software or AI assistance.

Inclusion Criteria

In adhering to the established inclusion criteria, our literature selection process focused on in vitro and in vivo studies investigating the impact of light on ion channels. Wavelengths outside the range of 620–1270 nm were omitted due to their dissimilarity to PBM light and limited effect on the nervous system (Barbora et al. 2021). Exclusions comprised studies from unrelated fields like materials' science, those unrelated to nervous system, non-English publications, and non-original articles such as reviews, case report, and commentary papers.

Extraction of Qualitative Data

Data extraction involved a meticulous cross-review process by two independent reviewers to ensure thoroughness, with discrepancies resolved through consultation with a third reviewer. The final selection encompassed literature pertinent to the role of PBM in ion channel modulation within the nervous system, with extracted information including authors, publication year, study population, PBM parameters, targeted ion channels, and key findings.

Results

In conducting a literature search on PubMed utilizing the specified search strategy, a total of 330 articles were identified, devoid of duplicates or unavailable literature. Upon review of titles and abstracts, 94 papers were selected for eligibility assessment. Following a thorough screening process, 19 articles met the inclusion criteria and pertained to the study population under review. All 19 studies underwent a comprehensive qualitative analysis. The study's inclusion criteria and literature flow are visually represented in Fig. 2.

The primary objective of this paper is to delve into the mechanism of action of PBM in modulating ion channels within the nervous system. The overarching goal is to harness the potential of light for non-invasive neurostimulation. The study also aims to evaluate various PBM protocols, weighing their respective advantages and disadvantages in terms of their impact on ion channels. Furthermore, the research seeks to elucidate the intricate interplay between light and cellular signals and their effects on ion channels. Various discussions on animal models, research goals, and treatment protocols have led to experiments with significant heterogeneity. This diversity presents challenges in accurately assessing the conclusions through Meta-analysis. In Table 1, we have summarized the different treatment protocols used in these experiments as a reference for future research. A detailed synopsis of the included studies is provided in Table 2.

The analysis presented in Fig. 3A underscores the escalating research interest in utilizing PBM for modulating ion channels within the nervous system. Our investigation, guided by specific search parameters, revealed that one of the pioneering studies exploring PBM's impact on ion channel modulation in the nervous system dates back to 2005 (Ignatov et al. 2005). Since 2016, there has been a gradual uptick in the number of related publications, reaching a pinnacle in 2021 with the publication of six original papers. As of 2024, although ongoing research persists, no new papers have been released to date. The graphical representation vividly illustrates the varying degrees of research attention dedicated to distinct ion channels, each denoted by a distinct color. Figure 3B delves into the specific ion channels that have garnered significant interest in recent years within the realm of PBM application in the nervous system. Notably, glutamate receptors emerge as the most extensively studied group, with a total of 8 papers, closely followed by TRPs (6 papers), AChR (2 papers), potassium channels (2 papers), and sodium channels (1 paper).

Discussion

PBM, a technique gaining increasing attention in the realm of neurological disorders, holds promise for modulating ion channels to influence cellular excitability. Various conditions, like epilepsy, tinnitus, and Alzheimer's disease, are known to stem from disruptions in cellular excitability, often linked to ion channel activities (Maiorov et al. 2024; Martin et al. 2023; Negandhi et al. 2014; Ruiz-Clavijo et al. 2023). While existing studies have shed light on the anti-inflammatory and stem cell differentiating effects of PBM through CCO photostimulation, which enhances ATP synthesis and nitric oxide release, investigations into how this modality

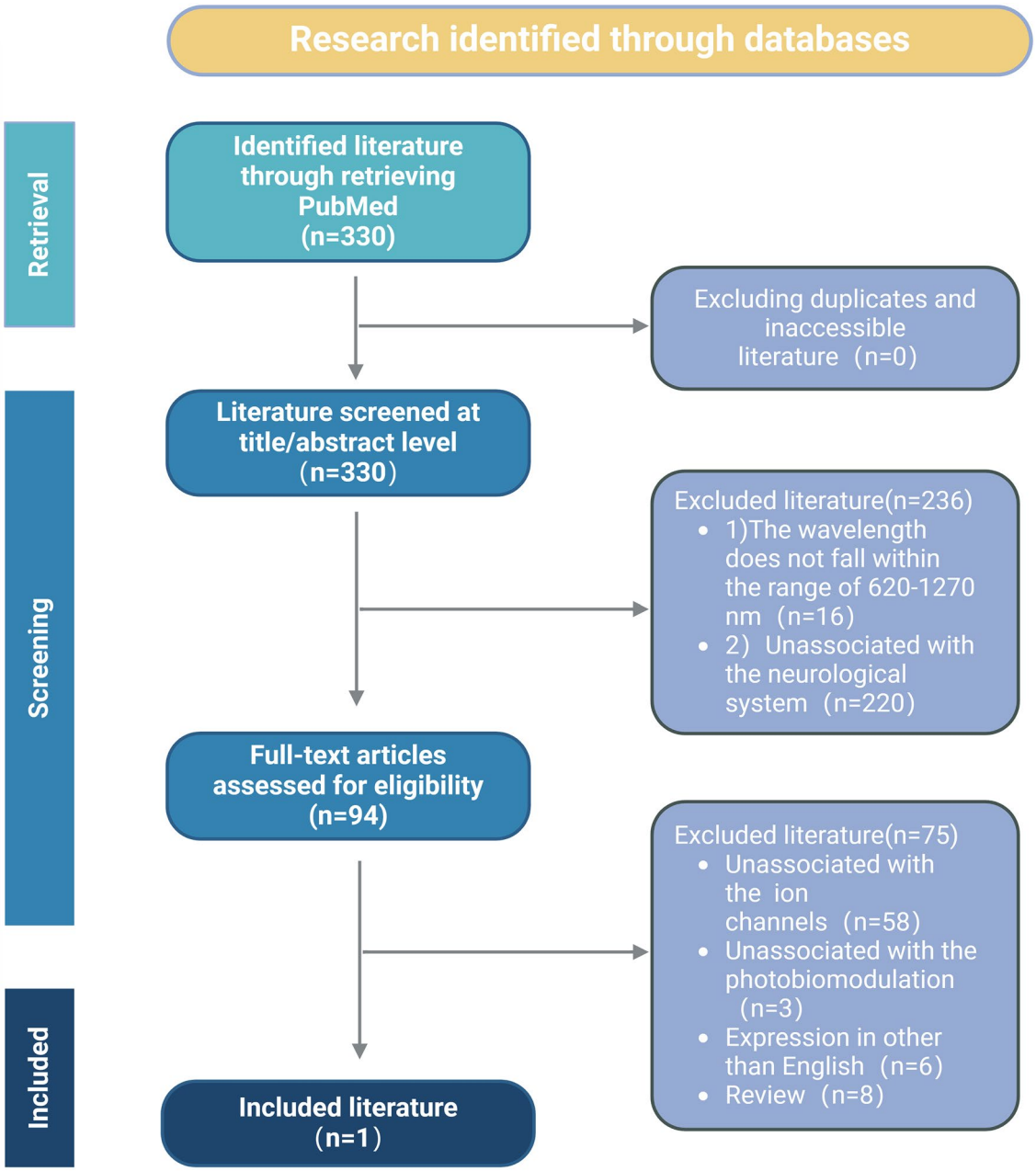


Fig. 2 Flowchart of studies selected for PBM on ion channels

impacts ion channels and cellular excitability are still limited (Moos et al. 2023; Powner et al. 2024).

PBM induces neuromodulatory effects by interacting with various ion channels, altering their activity. (1) PBM harnesses light energy absorbed by photosensitive or thermosensitive ion channels in cell membranes, leading to energy transfer that modifies ion channel function and intracellular signaling. Caiyun Meng et al. (Meng et al. 2020) found that 630 nm LED inhibits the growth of human synovial cell MH7A, likely by regulating the TRPV4/PI3K/AKT/mTOR signaling pathway, resulting in decreased inflammatory factors (IL-6, IL-1β, IL-8, and MMP-3) and increased anti-inflammatory factor IL-10. (2) PBM may also directly impact calcium channels, decreasing Ca2 + influx, which activates downstream transcription factors, alters gene expression, and decreases protein synthesis (Navarro et al. 2024). Iuliia Golovynska et al. (2022) found that PBM significantly reduced pro-inflammatory cytokine expression and increased Ca^{2+} influx in macrophages. These insights not only elucidate the therapeutic potential of PBM in inflammatory conditions but also highlight the intricate interplay between light exposure

Table 1 Protocol and major findings of studies included in the review

Authors	Year	Experimental model	Laser sources	Wavelength (nm)	Mode	Power density (mW/cm^2)	Radiant exposure (J/cm^2)	Duration	Spot area (cm^2)	Location	Distance (cm)
Cervetto et al. (2023)	2023	Mice (males, C57BL/6 J; 8–12 weeks old). Purified nerve terminals (synaptosomes) were made of mouse cerebral cortex	Diode laser (GaAlAs)	810	CW	1000; 100	60; 6	60 s, once daily for 1 day	1	Cell surface	_
Marques et al. (2023)	2023	Rats (males, Wistar, 200–220 g). They had surgical injury of the infraorbital nerve	Diode laser (GaAs)	904	PW, 9500 Hz, pulse time of 65 ns	–	6.23	18 s per point, 10 sessions, performed every other day	0.13*5	Orbital region	1
Correia Rocha et al. (2021)	2021	Rats (males, Wistar, 250-300 g). They were induced with type 1 DM and peripheral nerve injured	Diode laser (GaAs)	904	PW, 9500 Hz, pulse time of 65 ns, duty cycle (DC) 0.0617%	–	6.23	18 s per point, 10 sessions, performed every other day	0.13*9	Right leg (peripheral nerve injured area)	0 or superficial skin contact
Zhang et al. (2021)	2021	Mice (male, C57BL/6 J, 5 weeks old). They were induced with depression	Semiconductor laser	635	CW	Mice: 10.05 Cell: 3.3	Mice:6 Cell: 1/2/4	Mice: 600 s, once daily for 30 days. Cell: 75 s/150 s/300 s	7.06	Mice: above the brain Cell: Cell surface	Mice: 12 Cell: 20

Table 1 (continued)

Authors	Year	Experimental model	Laser sources	Wavelength (nm)	Mode	Power density (mW/cm^2)	Radiant exposure (J/cm^2)	Duration	Spot area (cm^2)	Location	Distance (cm)
Shen et al. (2021)	2021	Transgenic mice (APP/PS1)	Semiconductor laser	635	CW	117.2	6	Mice: 600 s, once daily for 30 days. Cell: 75 s/150 s/300 s	0.875	The upper part of the exposed brain to the interior of the hippocampus	0 or superficial skin contact
Golovynska et al. (2021)	2021	Primary rat hippocampus neurons, human neuroblastoma (SH-SY5Y), and human cervical cancer cells (HeLa)	Diode laser	650/808/1064	–	100	–	300 s/600 s/1500 s, once daily for 1 day	–	Cell surface	–
de Oliveira et al. (2021)	2021	Rats (males, Wistar, 200–220 g, 2 months old). They had surgical injury of the sciatic nerve	Diode laser (GaAs)	904	PW, 9500 Hz, pulse time of 60 ns	700	6	18 s per point, 10 sessions, performed every other day	0.1*9	The skin over the chronic constriction injury (CCI) area	0 or superficial skin contact
Zupin et al. (2021)	2021	50B11 cell line	Diode laser	800/970	PW, 5 Hz, DC 50%	300	–	20 s/40 s/80 s/120 s, once daily for 1 day	1	Cell surface	–

Table 1 (continued)

Authors	Year	Experimental model	Laser sources	Wavelength (nm)	Mode	Power density (mW/cm^2)	Radiant exposure (J/cm^2)	Duration	Spot area (cm^2)	Location	Distance (cm)
Zupin et al. (2019)	2019	Dorsal root ganglia (DRG) were dissected from cluster of differentiation 1 (CD1) male mice at 6–8 weeks of age	Diode laser	800/970	PW, 5 Hz, DC 50%	100	6	120 s, once daily for 1 day	–	Cell surface	–
Han et al. (2019)	2019	Mice (C57/BL6 8–12 weeks old), knockout mice (*Tac1*$^{-/-}$). *A* mouse model of acid-induced chronic muscle pain, or the Sluka model was in the hind paws	–	685	–	–	4/8	–	–	The surface of the left legs of mice	0 or superficial skin contact
Golovynska et al. (2019)	2019	HeLa cells	Semiconductor laser	650/808	CW	1/10/100/300	6/12/30	720 s/720 s/60 s, 120 s, 300 s/–, once daily for 1 day	–	Cell surface	–
de Sousa et al. (2018)	2018	Mice (male, BALB/c, adult, weight 20–24 g)	Semiconductor laser	810	CW	300/50/50	36/0, 1.2, 6, 30/6	120 s/0 s, 24 s, 120 s, 600 s/120 s, once daily for 7 day	1/6/6	Head, neck, DRG, tail, abdomen, ipsilateral right hind-paw, contralateral left hind-paw	–

Table 1 (continued)

Authors	Year	Experimental model	Laser sources	Wavelength (nm)	Mode	Power density (mW/cm^2)	Radiant exposure (J/cm^2)	Duration	Spot area (cm^2)	Location	Distance (cm)
Neves et al. (2018)	2018	Mice (male, Swiss-albino, 25-40 g). They were induced as hind paw edema	Semiconductor laser	660	CW	–	1/10/50/100/150/200	2 s/20 s/100 s/200 s /300 s/400 s, once daily for 1 day	0.06	Hind paws	0 or superficial skin contact
Wang et al. (2017b)	2017	Human adipose-derived stem cells (hASCs)	Diode laser (GaAlAs)	660/810	CW	16	3	188 s, once daily for 1 day	4	Cell surface	–
Pissulin et al. (2017)	2017	Rats (males, Wistar, about 300 g). They had induction of degeneration–regeneration of muscle fibers by local anesthetics	Diode laser (GaAs)	904	CW	1428.6	68.6	48 s, once daily for 5 days	0.035	The ventral surface of the neck	0 or superficial skin contact
Pires de Sousa et al. (2016)	2016	Mice (male, BALB/c, adult, weight 20–24 g). The nociceptive tests were conducted, in the following order: cold plate, radiant heat, and formalin injection	Diode laser	810	CW	300	7.2/36	24 s/120 s, once daily for 1 day	1	The head	0 or superficial skin contact

Table 1 (continued)

Authors	Year	Experimental model	Laser sources	Wavelength (nm)	Mode	Power density (mW/cm^2)	Radiant exposure (J/cm^2)	Duration	Spot area (cm^2)	Location	Distance (cm)
Huang et al. (2014)	2014	Mice (female, CD1, 8–10 weeks old). They were used to prepare primary mouse cortical neurons	Diode laser	810	CW	25	3	120 s, once daily for 1 day	78.5	Cell surface	–
Rochkind et al. (2013)	2013	Rats (males, Wistar, about 250 g, 12 weeks old). They had removed of the sciatic nerve segment resulted in complete denervation of the muscles	Diode laser	632.8	CW	–	–	1800s, once daily for 14 days	–	Right leg (peripheral nerve injured area)	–
Ignatov et al. (2005)	2005	Neurons of the periglottal ring of neural ganglia of the pond snail	Diode laser	632.8	–	15	–	60 s/600 s, once daily for 1 day	0.0144	Cell surface	0.1

The parameters outlined above have been sourced from the literature provided. In cases where information is not explicitly stated or could not be determined from the data calculations, the symbol "–" has been used to indicate this

Table 2 Major findings of studies included in the review

Authors	Title	Ion channels	Major findings
Cervetto et al.	Photons Induce Vesicular Exocytotic Release of Glutamate in a Power-Dependent Way	Voltage-dependent Na^+ channels	PBM facilitates the vesicular glutamate release in a power-dependent way. This process can be facilitated by the activation of voltage-dependent Na^+ and voltage-dependent Ca^{2+} channels
Marques et al.	Photobiomodulation and vitamin B treatment alleviate both thermal and mechanical orofacial pain in rats	TRPV1	CCI-IoN leads to the upregulation of TRPV1, Substance P, and CGRP in the trigeminal ganglion of rats, which plays a vital role in the neuronal hyperexcitability in response to inflammation or nerve injury. PBM can modulated the expression of nociceptive mediators after CCI-IoN, such as TRPV1
Correia Rocha et al.	Modulatory effects of photobiomodulation in the anterior cingulate cortex of diabetic rats	Glutamate Receptor 1 (GluR1)	PBM decreased even further GluR1 and μ-Opioid Receptor (MOR) protein levels in the ACC of diabetic rats that were treated with PBM
Zhang et al.	Photobiomodulation Therapy Ameliorates Glutamatergic Dysfunction in Mice with Chronic Unpredictable Mild Stress-Induced Depression	GluA1	PBM was likely to reduce glutamate levels by upregulating GLT-1 expression to exert neuroprotective effects. PBM promotes AMPA receptor insertion through activation of PKA in corticosterone-treated primary neurons
Shen et al.	Photobiomodulation suppresses JNK3 by activation of ERK/MKP7 to attenuate AMPA receptor endocytosis in Alzheimer's disease	AMPA receptor	The inhibition of JNK3 phosphorylation by PBM treatment can effectively rescue AMPA receptor endocytosis and dramatically reduce amyloid load, neuroinflammation, and synaptic loss in APP/PS1 transgenic mice
Golovynska et al.	Red and near-infrared light evokes Ca^{2+} influx, endoplasmic reticulum release and membrane depolarization in neurons and cancer cells	NMDA receptor	650 and 808 nm light promotes elevation of intracellular Ca^{2+} level. The Ca^{2+} influx occurs primarily via NMDARs, which become open due to the plasma membrane depolarization
de Oliveira et al.	Effects of photobiomodulation therapy on neuropathic pain in rats: evaluation of nociceptive mediators and infrared thermography	TRPV1	PBM reduces the expression of TRPV1. PBM is an effective technique for neuropathic pain relief and may modulate important nociceptive mediators involved in thermoregulation and thermal sensitivity
Zupin et al.	In vitro effects of photobiomodulation therapy on 50B11 sensory neurons: evaluation of cell metabolism, oxidative stress, mitochondrial membrane potential (MMP), and capsaicin-induced calcium flow	TRPV1	Although the mechanism by which PBM could modulate TRPV1 and calcium flow remains elusive, laser light could directly and specifically act on TRPV1 functionality
Zupin et al.	Analgesic effect of Photobiomodulation Therapy: An in vitro and in vivo study	TRPV1	970 nm markedly reduces Ca^{2+} peaks induced by capsaicin stimulation. 970 nm is effective in reducing calcium flow and pain sensation in vivo
Han et al.	Involvement of substance P in the analgesic effect of low-level laser therapy in a mouse model of chronic widespread muscle pain	TRPV1	Low-level laser at a wavelength of 685 nm showed potent analgesic effect, while applied to muscles with a dose of 8 J/cm^2. Although the analgesic effect was transient and only lasted < 24 h, the LLLT analgesia was reproducible after repeated treatment. The LLLT analgesia was impaired when substance/NK1R or TRPV1 signaling was blocked

Table 2 (continued)

Authors	Title	Ion channels	Major findings
Golovynska et al.	Red and near-infrared light induces intracellular Ca^{2+} flux via the activation of glutamate N-methyl-D-aspartate receptors	NMDA receptor	The irradiation of 650 and 808 nm lasers elevated intracellular Ca^{2+} influx in HeLa cells without altering NMDAR function. Light partially relieved NMDAR pharmacological blockade, thereby enhancing Ca^{2+} influx. Specifically, 650 nm light stimulated cell proliferation, leading to apoptosis and necrosis with increasing dosage, while 808 nm light solely promoted cell proliferation
de Sousa et al.	Pain management using photobiomodulation: Mechanisms, location, and repeatability quantified by pain threshold and neural biomarkers in mice	GluR1	810 nm laser irradiation to the lower back of mice reversibly increased the pain threshold in the hind paw up to threefold, with a peak at 2–3 h post-PBM. Irradiation of the head, neck and ipsilateral paw was also effective, but not irradiation of the abdomen, tail, or contralateral paw. The treatment was equally effective when repeated daily for one week. mGluR1 was reduced and PAP and tubulin-positive varicosities were increased at 3 h post-PBM
Neves et al.	Photobiomodulation Therapy Improves Acute Inflammatory Response in Mice: the Role of Cannabinoid Receptors/ATP-Sensitive K^+ Channel/p38-MAPK Signalling Pathway	ATP-Sensitive K^+ Channel	PBM anti-inflammatory property seems likely related with its ability to activate CB1 and CB2 cannabinoid receptors, as well as signaling pathway downstream of CB receptors activation, such as ATP-dependent K^+ channels and p38-MAPK
Wang et al.	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	TRPV1	The effects of red and near-infrared (NIR) light are consistent with a mitochondrial chromophore (giving more ATP, increasing MMP, and producing only a low level of ROS). Red and NIR (810 nm) light stimulate proliferation of hASCs
Pissulin et al.	GaAs laser therapy reestablishes the morphology of the NMJ and nAChRs after injury due to bupivacaine	AChRs	LLLT effectively mitigates bupivacaine-induced structural modifications in the neuromuscular junction (NMJ) and molecular alterations in the nicotinic acetylcholine receptor (nAChR), thereby serving as a potential therapeutic approach for the treatment of the degeneration–regeneration of muscle fibers by local anesthetics
Pires de Sousa et al.	Transcranial low-level laser therapy (810 nm) temporarily inhibits peripheral nociception: photoneuromodulation of glutamate receptors, prostatic acid phophatase, and adenosine triphosphate	GluR1	PBM decreases glutamate receptor expression, and increases ATP and prostatic acid phosphatase
Huang et al.	Low-level laser therapy (810 nm) protects primary cortical neurons against excitotoxicity in vitro	GluR	PBM enhances intracellular ATP and MMP biosynthesis, while suppressing glutamate receptor-mediated calcium influx in excitotoxic cells, yet promoting it in healthy cells
Rochkind et al.	Protective effect of laser phototherapy on acetylcholine receptors and creatine kinase activity in denervated muscle	AChRs	During the initial stages of muscle degeneration, PBM temporarily maintained AChR and CK levels in denervated muscle near pre-injury thresholds, and subsequently sustained CK activity and AChR quantity throughout subsequent stages of muscle degeneration

Table 2 (continued)

Authors	Title	Ion channels	Major findings
Ignatov et al.	Effects of helium–neon laser irradiation and local anesthetics on potassium channels in pond snail neurons	Voltage-dependent slow potassium channels	Laser irradiation modulates the magnitude of transmembrane potassium ion current, reflecting alterations in the total number of functionally active channels, with the specific effect of radiation varying according to its dose

and cellular ion homeostasis, offering avenues for further research and clinical applications in the management of inflammatory diseases.

PBM modulates crucial intracellular signaling pathways like MAPK/ERK and AKT/PI3K, which are vital for neuronal growth, differentiation, and synaptic plasticity (Bathini et al. 2022). Its mechanism for promoting neural regeneration involves altering ion channel activity and enhancing the synthesis of neurotrophic factors. Yun-Hee Rhee et al. (2019) demonstrated that PBM reversed cellular morphology disruption and improved cell viability in neurons inhibited by ouabain, indicating that PBM treatment alleviates Na/K imbalance and aids neural repair. Xiaodong Yan et al. (2017) highlighted the Ca^{2+}-ERK-CREB cascade as a key pathway in PBM-induced BDNF synthesis, underscoring the role of calcium ions in enhancing neurotrophic factor production. Collectively, these effects contribute significantly to the repair and regeneration of neuronal cells. By promoting cellular resilience and enhancing the intrinsic regenerative mechanisms, these interventions facilitate the restoration of neural function. Such positive outcomes are crucial for advancing treatments for neurodegenerative diseases and injuries, ultimately improving patient recovery and quality of life.

Ion Channels

Ion channels are particularly vital for the nervous system due to their involvement in transmembrane ion flow, affecting cellular electrophysiology (Kariev et al. 2024). Neuronal communication, essential for transmitting sensory, cognitive, and motor signals in the brain, relies on electrical signaling through synapses (González-Cota et al. 2024). When we receive external stimuli, neurons generate electrical signals and transmit these signals to other neurons through synapses. This process is fundamental to the normal functioning of the nervous system and is an important mechanism that enables us to perceive and respond. PBM influences the action potentials of neurons through various pathways, including enhancing mitochondrial function, regulating the activity of ion channels, providing neuroprotection, and increasing synaptic plasticity (Ishibashi et al. 2024; Yoo et al. 2013). The ability of PBM to modulate ion channels offers a non-invasive means of neurostimulation, crucial not only for disease treatment but also for applications in optical communication and brain–computer interfaces (Ghaderi et al. 2021; Savić et al. 2023). Our research has identified several key ion channels influenced by PBM, such as glutamate receptors, AChR, potassium channels, sodium channels, and TRPs. Further exploration into the modulation of these channels by PBM is anticipated to deepen our understanding of its therapeutic mechanisms and potential applications in the future.

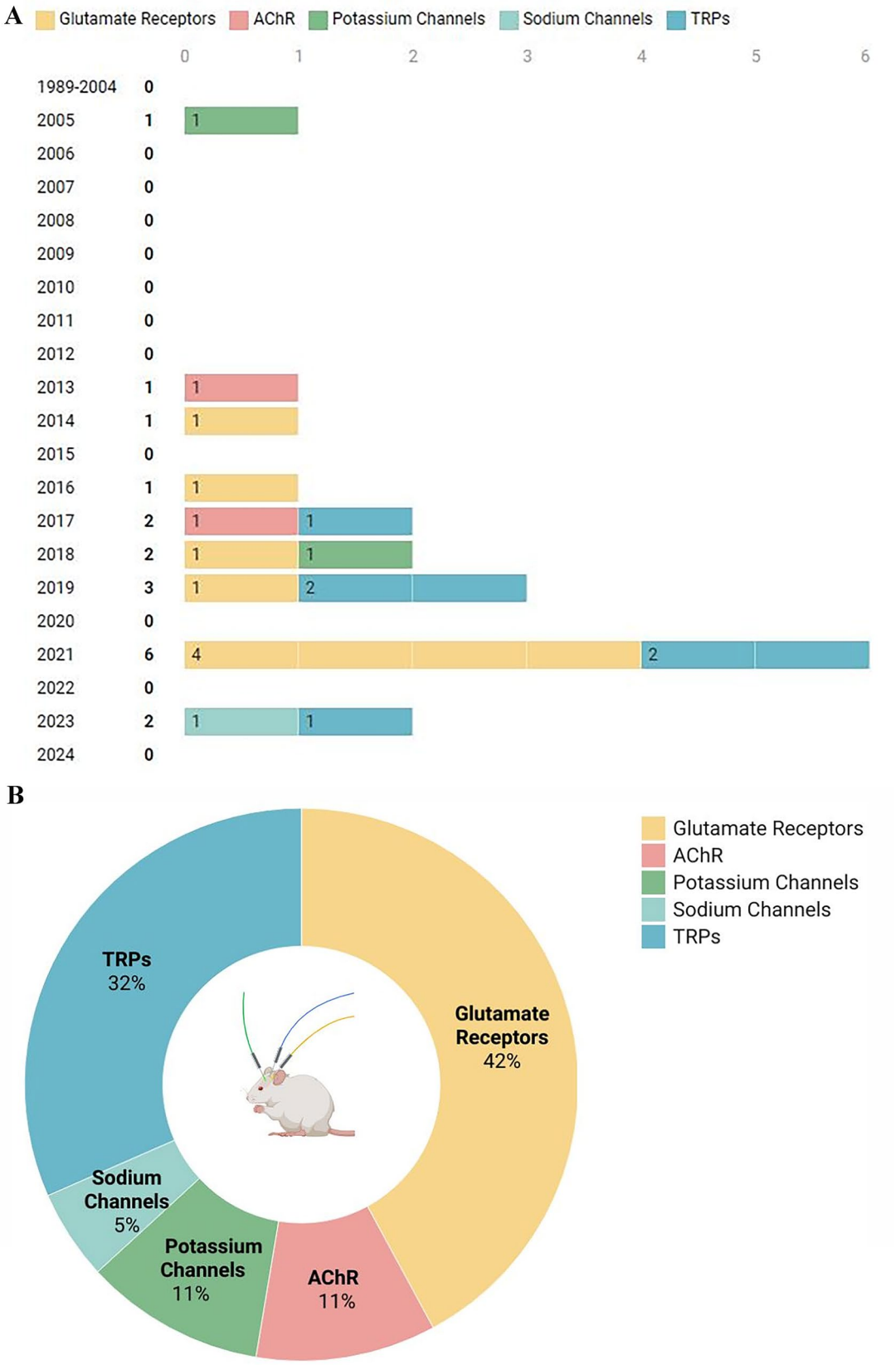


Fig. 3 Visualization of the included literature. Selected article statistics on the mechanism of PBM in ion channel regulation in the nervous system. **A** Publication schedule of papers on PBM in ion channel regulation in the nervous system. **B** Relative number of papers on PBM effects on various ion channels

Glutamate Receptors

Glutamate receptors are ubiquitous in the nervous system, serving as key regulators of neuronal excitability, synaptic transmission, learning, memory, and various physiological processes (Gurung et al. 2016; Ladagu et al. 2023). These receptors are involved in excitatory neurotransmission, being the primary excitatory neurotransmitter in the central nervous system (CNS) (Chakraborty et al. 2023). Glutamate receptors can be broadly classified into two major categories: ionotropic and metabotropic (McElroy et al. 2024; Parent et al. 2024). Ionotropic glutamate receptors (iGluRs) are ligand-gated ion channels that directly gate the flow of ions across the cell membrane, while metabotropic glutamate receptors (mGluRs) are G-protein-coupled receptors that regulate ion channel activities indirectly through second-messenger systems (Paoletti et al. 2013).

Within the ionotropic glutamate receptors, there are three major subclasses: N-methyl-D-aspartame receptors (NMDARs), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), and erythrocyanine receptors, of which the first two types have been studied the most (Goldsmith 2019). NMDARs play a crucial role in synaptic plasticity and learning and memory processes (Kim et al. 2024). When the cell membrane remains unpolarized, voltage-gated Mg^{2+} channels prevent NMDAR activation (Dingledine et al. 1999). NMDAR can evoke cellular depolarization upon binding to glutamate or NMDA, altering the membrane voltage and relieving Mg^{2+} blockade of voltage-dependent channels.

This leads to a significant influx of Ca^{2+} and subsequent modulation of cellular functions (Golovynska et al. 2019; Paoletti et al. 2007). Golovynska et al. (2019, 2021) demonstrated that 808 nm laser irradiation of neuronal and HeLa cells in vitro induced a substantial Ca^{2+} influx. Application of dizocilpine, a specific NMDAR blocker, reduced this influx, indicating that the laser's effect on Ca^{2+} influx primarily occurs via NMDAR activation. NMDAR's rapid response and low depolarization potential highlight its importance in the initial stages of Ca^{2+} influx. Subsequently, the influx of Ca^{2+} activates AMPAR, enhancing its synthesis and promoting Na^{+} and K^{+} influx, thereby maintaining membrane depolarization (Nanou et al. 2007). Zhang et al. (Zhang et al. 2021) demonstrated that PBM can alleviate glutamatergic dysfunction in mice with depression induced by chronic unpredictable mild stress. This effect is achieved by stimulating ATP synthesis through activation of CCO, leading to elevated cAMP levels. This subsequently enhances AMPA receptor phosphorylation and surface expression through the cAMP/PKA signaling pathway. Separately, Shen et al. (2021) investigated the impact of PBM using a 635 nm semiconductor laser on an Alzheimer's disease mouse model. Their findings revealed that PBM effectively inhibited JNK3 phosphorylation, which reduced AMPA receptor endocytosis and restored surface levels. This treatment also significantly decreased amyloid accumulation, neuroinflammation, and synaptic loss in APP/PS1 transgenic mice.

Neuroplasticity refers to the brain's remarkable capacity to reorganize and adapt its neural connections in response to environmental changes, including injuries and various experiences that affect the nervous system (Chou et al. 2024). This inherent plasticity plays a crucial role in how organisms react to both internal and external stimuli. Recent studies have provided valuable insights into the mechanisms underlying neuroplasticity. For instance, research by Pascal Jorratt et al. (2023) highlights that prolonged stimulation of NMDAR can intensify activity in glutamatergic neurons, leading to dendritic field expansion that may worsen psychiatric conditions such as anxiety. Conversely, findings from Hongli Chen et al. (2024a, b) demonstrate that PBM can alleviate behavioral deficits, reduce neuroinflammation, and restore synaptic function in the hippocampus of depressed mice, likely through the enhancement of brain-derived neurotrophic factor signaling. Moreover, Katayoon Montazeri et al. (2024) showed that the expression of doublecortin, a neuroplasticity marker, was significantly reduced in the dentate gyrus of rats experiencing tinnitus, suggesting that PBM may promote neuroplasticity that is compromised by sodium salicylate-induced auditory disorders. In summary, these studies emphasize the complex interplay between neural plasticity and PBM in the treatment of neurological and psychiatric disorders, with glutamate receptors potentially playing a significant role. Further research is necessary to explore how PBM influences neural plasticity through its effects on glutamate receptors.

Excitotoxicity, a series of pathologic changes in the CNS triggered by neuroinflammation or ischemic trauma, can result from the over-synthesis of glutamate by microglia or abnormally active glutamate function in neuronal cells (Neves et al. 2023). This abnormal activation of glutamate receptors can lead to elevated intracellular Ca^{2+} levels, ultimately causing cell death and contributing to the pathogenesis of conditions such as epilepsy (Sarlo et al. 2021). Furthermore, chronic noise damage affecting the cochlear nucleus can elevate glutamate concentrations and increase glutamate receptor expression, potentially leading to conditions like tinnitus (Muly et al. 2004). Research on PBM as a treatment for CNS disorders has shown promising results by improving mitochondrial function, boosting ATP synthesis, and countering neuroinflammation (Lim 2024). However, the impact of this therapy on ion channels and the specific mechanisms involved in the therapeutic process require further investigation. Studies have indicated that PBM can both promote and inhibit glutamate

receptor activity, with its biological effects likely dependent on the light regimen employed (Amaroli et al. 2019).

AChR

AChR plays a crucial role in various bodily functions, particularly in synapses, where they are pivotal in parasympathetic action and motor function (Sine 2012). These receptors are categorized into M and N receptors (Ved et al. 2020). M receptors, upon binding with acetylcholine, elicit parasympathetic excitatory effects such as inhibiting cardiac contraction and promoting smooth muscle contraction in the digestive tract (Eglen et al. 2001). On the other hand, N receptors trigger skeletal muscle contraction or excitation of postganglionic neurons following acetylcholine binding (Changeux et al. 1992). Pissulin et al. (2017) have shown promising outcomes in using GaAs laser therapy to restore the morphology of the neuromuscular junction and AChR post-injury caused by bupivacaine. Their studies on PBM for nerve injury due to local anesthetics demonstrated that irradiation with 904 nm laser light reduced myonecrosis and significantly increased the expression of the ε-subunit of the AChR. The ε-subunit of the nAChR ion channel plays a crucial role in regulating calcium ion influx, thereby ensuring stable initial interactions between nerves and muscles, leading to synaptic maturation (Castro et al. 2022). These findings shed light on potential therapeutic interventions for nerve injuries and underscore the intricate mechanisms underlying nerve–muscle interactions.

The role of AChR in cognitive processes has been widely acknowledged in the scientific community. By either increasing acetylcholine synthesis or directly activating AChR, researchers have found that these approaches can be effective in treating neurodegenerative diseases such as Alzheimer's disease (Castro et al. 2022), schizophrenia (Dean 2023) and Parkinson's disease (Castro et al. 2022; Vallés et al. 2023). In the case of Parkinson's disease, the lack of dopamine synthesis in the brain leads to an imbalance with acetylcholine neurotransmitters, resulting in symptoms like tremors (Morris et al. 2024). Chiao-Hsin Lan et al. (2022) reported a myasthenia gravis patient treated with PBM, who regained muscle strength. SPECT brain imaging revealed a significant increase in perfusion in the prefrontal lobe and anterior cingulate gyrus. We speculate that this may be linked to PBM's activation of AChR, but further investigation is needed to clarify the underlying mechanism. While the exact mechanism of this treatment method is still being explored, it offers a potential alternative for diseases related to AChR dysfunction. Further research into the use of PBM for neurodegenerative diseases holds great promise and may lead to new therapeutic approaches for patients in the future.

Potassium Channels

Potassium channels play a crucial role in the regulation of cellular excitability within all cells (Abbott 2021). These channels can be categorized into four main types based on their structure and function: calcium-activated potassium channels, inwardly rectifying potassium channels, tandem pore domain potassium channels, and voltage-gated potassium channels (Griffith 2001). Among these, calcium-activated and inwardly rectifying potassium channels are particularly influenced by photobiological regulation. (1) Calcium-activated potassium channels are activated through an indirect pathway involving the absorption of specific wavelengths by CCO within the mitochondrial oxidative respiratory chain (Liebert et al. 2023; Salehpour et al. 2018). This activation leads to the release of NO, a key intracellular signaling molecule that triggers a cascade resulting in the opening of potassium channels and the regulation of vasodilation (Hennessy et al. 2017). NO plays a crucial role as a significant intracellular signaling molecule by triggering soluble guanylate cyclase to produce cyclic guanosine monophosphate (cGMP). This cGMP then initiates the activation of protein kinase G (PKG), which subsequently facilitates the influx of calcium ions, opens calcium-activated potassium channels, and governs the process of vasorelaxation (Bardou et al. 2001). (2) ATP-sensitive potassium channels, a subtype of inwardly rectifying potassium channels, are also activated indirectly. Laís et al. (2018) have demonstrated that CB1 receptors play a role in modulating calcium and potassium channels in response to light exposure, with the ATP-sensitive potassium channel inhibitor glibenclamide reversing certain effects.

Potassium channels are pivotal in the modulation of neuronal electroactivity, with aberrant potassium channels being intricately linked to the pathogenesis of numerous CNS disorders. Notably, acquired mutations in the α1 subunit of calcium-activated potassium channels have been associated with 50% of individuals afflicted by petit mal seizure (Du et al. 2005), while mutations in the β4 subunit have been shown to induce epileptiform behavior in mice (Wang et al. 2009). Various potassium channels are implicated in conditions such as epilepsy (Gribkoff et al. 2023), tinnitus (Lai et al. 2024), and Alzheimer's disease (Taylor et al. 2022), although a comprehensive exploration of the interplay between these ion channels and diseases is beyond the scope of this discourse. For further insights, the commentary paper authored by Yian Huang et al. (2018) provides a valuable resource. While a plethora of potassium channel activators have been developed for treating CNS disorders, their utility is hampered by non-specific drug targets, severe side effects, and the emergence of drug resistance. Consequently, pharmacotherapy may not always represent the optimal treatment modality (Sills et al. 2020). PBM emerges as a promising

alternative, enabling precise modulation of neuronal activity without affecting non-target sites, thereby reducing adverse reactions. Moreover, PBM circumvents the issue of drug resistance, offering novel avenues for managing CNS ailments. Future investigations in neuromodulation are poised to unravel the intricate mechanisms governing the regulation of distinct potassium channel subtypes, paving the way for tailored interventions in various diseases.

Sodium Channels

Sodium channels play a crucial role in cellular function by facilitating the entry of sodium ions into the cell through an electrochemical gradient. These membrane proteins are essential for various physiological processes and can be classified into different types based on their mode of activation, such as ionic and ligand-type sodium channels (McDougall et al. 2024). Cervetto et al. (2023) have demonstrated how the irradiation of nerve endings with an 810 nm laser in adult mice cultured in vitro can activate ligand-type sodium channels and Ca^{2+} channels in the postsynaptic membrane. This activation process may involve photon-induced stimulation of the CCO in the presynaptic membrane, leading to ATP synthesis and the release of glutamate into the cytosol. Additionally, Li et al. (2013, 2014) have revealed the association between the opening of sodium channels and the photothermal effect. Neuronal cells depolarized by electrical pulses from − 70 to − 30 mV exhibit peak Na^+ currents, with the 980 nm near-infrared laser appearing to decrease ion channel resistance. Furthermore, there is a positive correlation between the accelerated inward flow of Na^+ in the extracellular fluid induced by irradiation and the transient temperature rise.

Maintaining the normal function of sodium channels is crucial for the proper functioning of the CNS. Numerous research studies have highlighted the significance of mutations or irregular activities in sodium channels in the onset and progression of various CNS disorders. Conditions such as epilepsy, Parkinson's disease, and Alzheimer's disease have been linked to abnormalities in sodium channels, as evidenced by several studies (Barbieri et al. 2023; Thompson et al. 2023; Vaidya et al. 2024). In response to these findings, pharmaceutical interventions in the form of sodium channel blockers like lidocaine, quinidine, and phenytoin sodium have been developed for the management of epilepsy, tinnitus, and other associated disorders. Sodium channels, akin to potassium channels, have emerged as pivotal therapeutic targets in the treatment of CNS disorders (Zierath et al. 2023).

Sodium channels are crucial for neuronal excitability, and studying their structure and function has revealed important insights into this process. These complex protein molecules, which consist of about 3000 amino acids, typically comprise four subunits, each featuring intra- and extra-membrane transmembrane regions (Schott et al. 2024). This arrangement forms a channel that allows sodium ions to flow across the cell membrane during potential changes, triggering electrical activity in neurons and modulating their excitability. Overactivation of sodium channels can lower the threshold for action potentials, enhancing neuronal firing and leading to abnormal excitation (Miralles et al. 2024). Conversely, reduced sodium channel function can impede normal action potential firing, resulting in diminished excitability. Thus, studying sodium channel's role in regulating neuronal excitability is vital for understanding related diseases and developing new therapies.

Despite the acknowledged importance of sodium channels in CNS disorder pathogenesis, the exploration of the effects of PBM on their modulation remains relatively uncharted territory, as indicated by our comprehensive review of the existing literature. We posit that further fundamental research in this area will pave the way for a more seamless transition of PBM technology from theoretical understanding to practical clinical applications.

TRPs

TRPs, initially discovered in Drosophila mutants and predominantly associated with vision development in insects, have now been recognized as pivotal light- and heat-gated ion channels crucial for modulating cellular functions (Feng 2014). The PBM process works with chromophore CCOs and heat/light-gated ion channels to raise secondary messengers like calcium ions, cAMP, and ROS. These secondary messengers play a vital role in initiating the activation of transcription factors and signaling molecules, which subsequently trigger downstream signaling cascades leading to profound photobiological effects within the cell (Ma et al. 2024). Notably, TRPs exhibit responsiveness to both green and near-infrared light, although the limited penetration capability of green light through the cranium necessitates the predominant utilization of near-infrared light in PBM practices to activate TRPs effectively (Gholami et al. 2022). Wang et al. (2017a) have demonstrated that when subjecting adipose-derived stem cells to laser irradiation in vitro using wavelengths exceeding 900 nm, the primary chromophore absorbing the light is the TRPs located on the cell membrane. Della Pietra A et al. (2024) have highlighted a significant correlation between TRPs and migraine. Their findings suggest that individuals suffering from migraines exhibit elevated levels of TRPs compared to those without the condition. Moreover, these TRPs appear to be more responsive to external stimuli such as light, heat, and mechanical pressure in migraine patients. Our research also highlights the critical role of TRPs in mediating the analgesic properties associated with PBM.

However, it is puzzling that the activation of TRPs appears to be triggered not only by light stimulation but also by capsaicin, other vanilloids, acid, and heat (Caterina et al. 1997; Gunthorpe et al. 2007; Julius et al. 2001). This contradicts the concept of PBM, which focuses on the non-thermal effects of light. The debate continues on whether the regulation of TRPs through photobiological means truly falls under PBM. Despite this, our study includes relevant TRPs studies for the reference of other researchers. Delving into the regulation of TRPs through photobiological methods presents significant challenges, particularly in completely eliminating non-light stimuli. Even with the most rigorous experimental setups, controlling cell temperature may have limitations, and subtle temperature changes undetectable by instruments could activate TRPs, leading to the erroneous attribution of biological effects to light exposure. Therefore, further precise and meticulous experimental designs are essential for studying the regulation of TRPs through photobiological means.

Protocols for PBM of Effects on Ion Channels

PBM is a sophisticated therapeutic technique that requires careful consideration of multiple parameters to effectively harness its potential in non-invasive neuromodulation. In Table 3, we outline the key parameters influencing PBM. It is concerning that, despite previous research on PBM parameters, a consensus has yet to be reached on a reasonable and standardized set of parameters. This lack of agreement not only introduces systematic bias, diminishing result

Table 3 Description of the parameters in PBM

Parameters	Descriptions
Laser sources	Light sources can be classified into two categories: diode lasers and semiconductor lasers. Each type has distinct biological effects. Diode lasers emit coherent light with an uneven energy distribution from the center to the edge of the spot, while semiconductor lasers emit light energy that is evenly distributed throughout the spot. Diode lasers have greater penetration capabilities compared to semiconductor lasers; however, semiconductor lasers are more cost-effective and are advantageous for creating array laser sources. Depending on the specific research requirements, both diode and semiconductor lasers can be utilized effectively in experiments
Wavelength (nm)	Defined as the distance between two consecutive wave peaks, wavelength plays a significant role in determining the depth of penetration and biological effects of these waves. In the field of PBM, a wavelength range of 620–1270 nm is commonly chosen for its therapeutic benefits
Mode	Lighting modes are commonly classified into two categories: continuous and pulsed wave. In the continuous wave mode, the light source emits light continuously during the illumination process, whereas in the pulse wave mode, light emission occurs periodically according to a specific time wave. In this context, the frequency at which these pulses occur is referred to as the pulse frequency, measured in Hertz (Hz), while the duration of each pulse is known as the pulse width, measured in seconds (s). The duty cycle, which is the ratio of the total time of illumination to the total time, reflects the actual degree of illumination achieved. Typically, the pulse frequency ranges from 1 to 3000 Hz (Sommer et al. 2012). Research suggests that pulsed light may influence the electronic oscillations within nerve cells, potentially enhancing the opening or closing of ion channels(Kampa et al. 2004)
Power density (mW/cm^2)	Power density is a crucial parameter that must be carefully considered in any application involving electromagnetic fields. It plays a significant role in determining the potential effects on living organisms, including modulation effects and the risk of tissue damage. Typically, power density levels are maintained within the range of 0.1–100 mW/cm^2 to minimize the risk of thermal damage
Radiant exposure (J/cm^2)	Radiant exposure serves as a crucial parameter in quantifying the accumulation of light energy on the surface of action. It is defined as the product of power density, which represents the amount of power per unit area, and the actual illumination time
Duration	The determination of illumination time stands as a pivotal parameter in experimental design, directly shaping the course of research endeavors. This factor, which encompasses both the number and duration of illuminations, exhibits remarkable flexibility, adapting to the unique demands of each study subject
Spot area (cm^2)	The spot area is a crucial parameter that is often underestimated in its importance. Even with identical power levels, variations in spot area can lead to substantial differences in power density. Moreover, the size of the spot area directly influences the precision of PBM manipulation. In research involving rodents as experimental subjects, maintaining the spot diameter at the millimeter level is imperative. If the spot size is too large, multiple areas may inadvertently receive irradiation simultaneously, introducing a notable system bias due to the anatomical curvature of the irradiation point. This factor cannot be disregarded, as it may contribute to the diminished credibility of numerous experiments
Location	The location of illumination in a study can vary depending on the specific research objectives. Common areas for illumination include the head, limbs, chest, and abdomen. Researchers should carefully consider the purpose of their study when selecting the appropriate location for illumination to ensure accurate and reliable results
Distance (cm)	Distance refers to the space separating the light source from the subject, impacting the spot size and the thermal influence of the rising ambient temperature from the light source

reliability, but also hampers experimental reproducibility and impedes in-depth investigation into the mechanism of action. Among the reviewed studies, only five papers included all parameters, with spot area and distance being the most commonly omitted (de Oliveira et al. 2021; Pires de Sousa et al. 2016; Pissulin et al. 2017; Shen et al. 2021; Zhang et al. 2021). This paper aims to establish a detailed and standardized experimental design framework for PBM to assist researchers in conducting more effective experiments.

Promising Applications of PBM

Recently, PBM applications have expanded beyond traditional CNS irradiation, demonstrating potential in various areas, particularly brain–gut axis intervention and enhancing blood–brain barrier (BBB) permeability. (1) PBM modulates interactions between the nervous system and gut microbiota, improving mood and cognitive function (Huang et al. 2024). Qianqian Chen et al. (2021) found that PBM on the abdomen of amyloid β protein (Aβ)-induced Alzheimer's disease mice led to significant changes in intestinal microflora after 8 weeks, affecting pathways related to hormone synthesis, phagocytosis, and metabolism. This suggests that PBM can diversify the intestinal flora and mitigate Alzheimer's-related damage. (2) Additionally, PBM enhances blood–brain barrier permeability, enabling more efficient drug delivery to the CNS. Ting Zhou et al. (2021) showed that an 808 nm laser significantly increased permeability in a cellular model of the BBB, likely due to inhibited metalloproteinase activity and altered tight junction protein expression in endothelial cells. These findings position PBM as a promising method for improving drug delivery through the blood–brain barrier, providing innovative treatment avenues for neurological diseases, and paving the way for further exploration of PBM mechanisms in clinical settings. Despite these preliminary results, the specific mechanisms behind these applications require further investigation, particularly concerning the potential role of ion channels.

Limitations and Potential for Future Research

- Despite the promising therapeutic effects that PBM has demonstrated in various central nervous system disorders, there remains a notable lack of convincing evidence from randomized controlled trials to support its efficacy (Figueiro Longo et al. 2020). Consequently, the effectiveness of PBM requires more rigorous scientific investigation and well-structured experimental designs, aspects that are currently insufficiently addressed in the existing research. The variability in parameters across different experimental protocols, coupled with the frequent omission of critical factors such as spot size and the distance between the light source and the treatment area, significantly hampers the comparability of PBM treatments and does not accurately reflect their therapeutic potential. Moving forward, it is imperative to standardize the selection of treatment parameters for PBM and conduct more scientifically robust randomized controlled trials to compare PBM with widely accepted treatment modalities, ultimately elucidating its therapeutic efficacy.
- Research on the relationship between PBM and ion channels remains limited, primarily addressing voltage-gated, ligand-gated, and TRP channels. Further investigation into the roles of different channels in PBM is necessary. The P2X7 receptor has garnered significant attention due to its link with inflammation, particularly in the context of chronic obstructive pulmonary disease (COPD) and temporomandibular arthritis (da Cunha Moraes et al. 2018; Mazuqueli Pereira et al. 2021). However, GABAR, acid-sensitive ion channels, chloride channels, and mechanosensitive ion channels have yet to be explored, presenting opportunities for future research.
- The opening of many ion channels relies on ATP, so PBM not only modifies ion channel protein structure through photon interactions but also enhances ATP synthesis, influencing ion channel function. Different cell types exhibit significant variations in mitochondrial number and activity, and it remains unclear how PBM affects mitochondria in these diverse cell types—a topic that requires further investigation in future research.

Conclusions

PBM demonstrates the ability to effectively regulate the excitatory and inhibitory states of neurons by directly influencing the activity of ion channels, thereby fine-tuning the transmission and processing of neural signals. A plethora of studies have underscored the capacity of PBM to influence an array of ion channels, encompassing glutamate receptors, AChR, potassium and sodium channels, and TRPs, among others. This modulation intricately adjusts the dynamics of neuronal membrane potentials, impacting the initiation and propagation of action potentials. Such a regulatory mechanism assumes a pivotal role in the pathological progression of neurological disorders. This article endeavors to present the available data in a comprehensible manner, serving as a springboard for future investigations and offering insights into potential therapeutic avenues for combating neurological conditions arising from aberrant excitability. Of the 19 studies we reviewed, all involved rodent and cellular models, indicating a lack of clinical studies on the mechanisms of ion channels following PBM treatment for various CNS

disorders. This is why we have not focused extensively on clinical research when discussing the mechanisms of action of different PBMs on ion channels. The limited exploration may stem from PBM's experimental status in the CNS, focusing more on treatment efficacy than on mechanistic understanding. Therefore, this paper summarizes all PBM studies on ion channels conducted to date, aiming to inspire researchers and broaden applications and clinical inquiries into other ion channels yet to be studied. While numerous aspects remain to be elucidated or refined, the evolving comprehension of PBM mechanisms and the exploration of diverse ion channels represent a quest to unveil novel and promising therapeutic domains. Therefore, a thorough exploration of the interplay between PBM and ion channels is of paramount significance in unveiling the principles governing nervous system activity and in devising innovative strategies for the treatment and prevention of neurological ailments.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request. This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non-Commercial-Share Alike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, if appropriate credit is given and the new creations are licensed under the identical terms.

Declarations

Conflict of interest The authors do not have any financial support or relationships that may pose conflict of interest to disclose.

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