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REVIEW ARTICLE

The implication of blue light-emitting diode on mesenchymal stem cells: a systematic review

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Abstract

The application of blue light (400–480 nm) in photobiotherapy remains controversial. This systematic review aimed to collect and analyze the biological effects of blue light-emitting diode (LED) on mesenchymal stem cells (MSCs). Inclusion and exclusion criteria were formulated, and relevant English articles from January 1982 to September 2022 were searched in PubMed, Scopus, and Web of Science. Nine articles with a medium ($n=4$) to low ($n=5$) risk of bias were included. Most of the MSCs reported were derived from human tissue; only one article used MSCs derived from mouse. The wavelength of the LED used was in the 400–480 nm range, and the irradiation modes were continuous ($n=8$) and pulse waves ($n=1$). A chiral polarizer was used in one such study in which the irradiance was 14 mW/cm^2 and the irradiation time was 24 h. The energy densities used in other studies were between 0.378 and 72 J/cm^2, and the irradiation times were between 10 and 3600 s. Blue LED light can inhibit proliferation and promote differentiation of MSCs in an appropriate energy density range, which may be related to the activation of transient receptor potential vanilloid 1 (TRPV1). Additionally, polarized light may reduce the toxic effects of blue light on MSCs. However, the heterogeneity of the design schemes and LED parameters, as well as the small number of studies, limited the conclusiveness of the review. Therefore, further studies are needed to determine the optimal irradiation strategy for promoting MSC function.

Keywords Mesenchymal stem cells · Blue light-emitting diode · Photobiomodulation · Phototherapy

Introduction

Mesenchymal stem cells (MSCs) are adult stem cells that have self-replication ability and multi-lineage differentiation potential. MSCs can be obtained from different sources, such as bone marrow, fat, umbilical cord, and dental pulp, and, because of their excellent multi-lineage differentiation ability, are used for the treatment of various diseases [1]. However, due to the influence of the microenvironment in the body, transplanted stem cells are affected by different stressors, including hypoxia, acidosis, ROS, and inflammation, leading to apoptosis and necrosis of stem cells [2]. To overcome these problems, researchers have explored methods to improve cell survival, proliferation, differentiation, and migration, including pretreatment of MSCs, genetic modification, and culture condition optimization [3].

Photobiomodulation (PBM) is based on the impact of low-intensity lasers or LEDs on biological tissues, has anti-inflammatory [4], pain-relieving [5], and wound-healing effects [6], and promotes cell proliferation and differentiation [7]. Compared to lasers, LEDs have a more flexible irradiated area, use less energy, are safer, and do not generate heat [8]. Therefore, pretreatment of MSCs with LED irradiation before transplantation may become a standard practice for improving tissue engineering and cell therapies in the future.

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Currently, the commonly used bands for PBM are red light (600–700 nm) and near-infrared light (780–1100 nm), whereas the blue band (400–480 nm) is less frequently used because it is close to the relatively destructive ultraviolet band of the electromagnetic spectrum [9]. In addition to its use for plant cultivation and disinfection, blue light has been proven in an increasing number of studies to be beneficial for cell proliferation and differentiation. For example, pulsed 475 nm LED can promote vascular differentiation of the stromal vascular fraction (SVF) [10]. Mohamad et al. [11] found that 405 nm LED irradiation significantly inhibited the proliferation of dental pulp stem cells (DPSCs) while enhancing their mineralization. Blue LED regulates human fibroblast metabolism and proliferation [12]. In addition, studies suggest that blue light may be more effective in promoting differentiation than the more commonly used red and near-infrared light [13, 14].

A recent systematic review in 2021 discussed the effect of LEDs on MSC function and concluded that, compared with non-irradiated cells, those exposed to LED showed stronger survival, proliferation, differentiation, cell metabolism, and secretion of angiogenic factors [15]. However, the majority of the studies included used red-band LEDs, and only one used blue-band LED, which is not sufficient to prove that blue LEDs do not have the same biological effects as red-band LED. Therefore, this review aimed to organize and analyze the biological effects of blue LED on MSCs and possible molecular mechanisms, which have been reported on over the past 40 years.

Materials and methods

Search strategy

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. A systematic search was conducted using the Medical Subject Heading (MeSH) terms [photobiomodulation], [mesenchymal stem cells], and related keywords. The PubMed, Web of Science, and Scopus databases were searched for articles published between January 1982 and September 2022. The language of the retrieved articles was limited to English, and the report type was set as "Article." The complete search strategies for each database are presented in detail in Supplementary file 1.

Study selection

Appropriate inclusion and exclusion criteria were formulated before searching and registration in the Prospective International Registry of Systematic Reviews database to avoid duplication of research (PROSPERO CRD42022371472). After the automatic and manual removal of duplicate literature, two independent reviewers (H. L., Y. R.) evaluated the titles and abstracts of the literature and screened articles that fit the research topic. The abstracts were then reevaluated independently by two additional authors (S. W., Y. H.) according to the inclusion criteria, and disputes were resolved by a third independent reviewer (Y. W.). Finally, four reviewers (H. L., Y. R., S. W., Y. H.) read the full texts of potentially eligible studies and reached a consensus on appropriate inclusions. Articles that matched the inclusion criteria were as follows: (1) English language; (2) describing the effect of LED on MSCs, regardless of where MSCs were derived from (i.e., humans or animals); (3) using LED irradiation for at least one treatment group; and (4) LED-related parameters are mentioned, including wavelength, irradiance, energy density, and irradiation time. The exclusion criteria were as follows: (1) research not related to mesenchymal stem cells; (2) photobiotherapy using lasers or diode lasers; (3) LED parameters that were missing or could not be calculated; (4) LED wavelength not between 400 and 480 nm; and (5) clinical studies, reviews, conferences, and case reports.

Risk of bias

Risk of bias assessment is an important method for assessing the reliability and quality of clinical and experimental research. However, unified risk of bias assessment tools for in vitro experiments are still lacking. Therefore, these studies were analyzed using appropriate in vitro assessment tools with modifications [17]. Three independent reviewers (Y. H., S. W., Y. R.) assessed the studies, and the risk of bias was determined by the number of "yes" or "no" answers for each of the two assessment parameters. The risk level was classified according to the "yes" count, with a score of 0–4 being high risk, a score of 5–8 being medium risk, and a score of 9–11 being low risk.

Data extraction and analysis

To collect and integrate the data obtained from the full text of the included studies, after identifying relevant variables, the data were extracted and recorded using custom-designed data extraction forms, including cell models, irradiation strategies, and the effects of blue LEDs on the biological effects of MSCs.

Results

Study selection

Figure 1 shows the selection process for the included studies. The literature search retrieved 859 potentially relevant

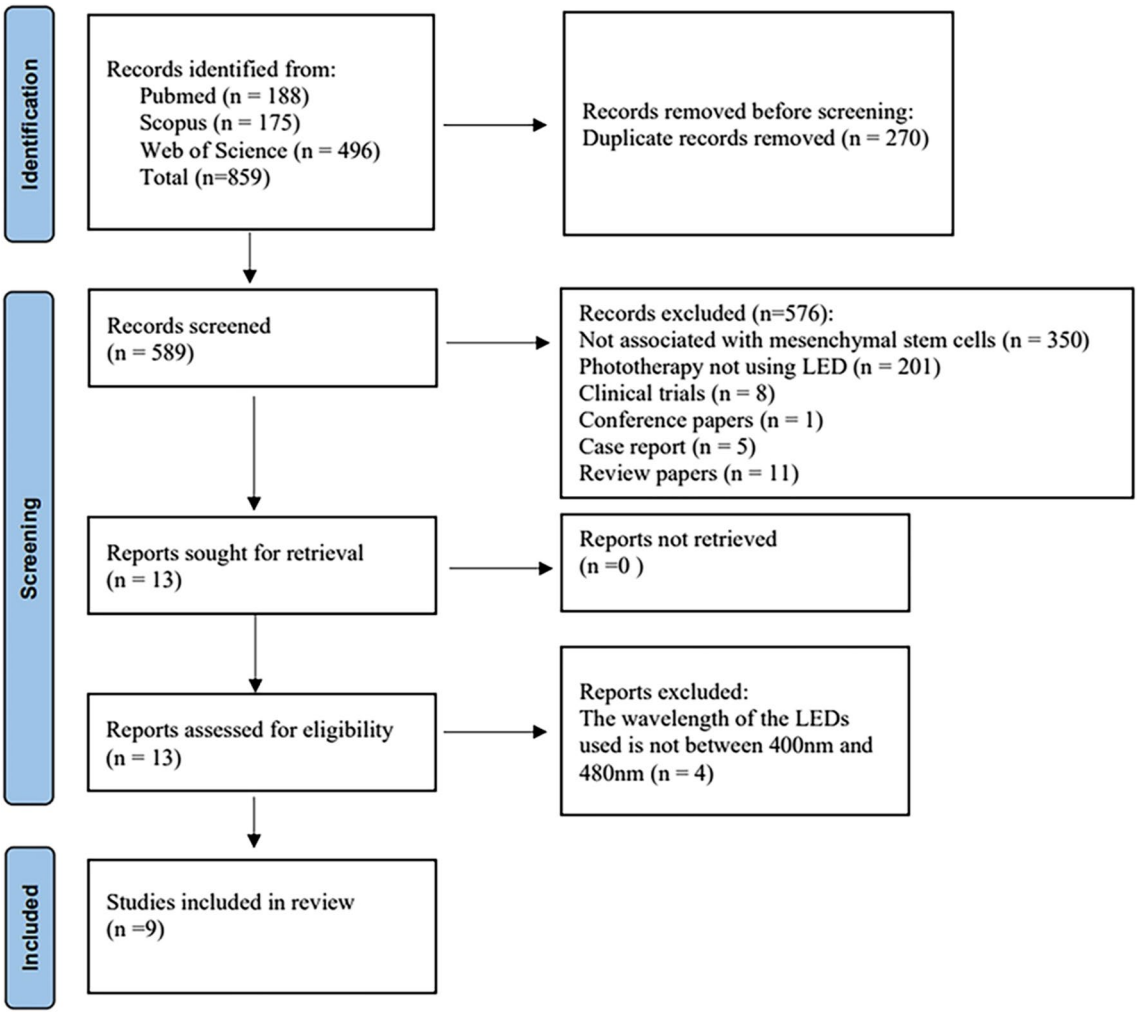

Fig. 1 Flowchart of the article selection process

references, including 188 from PubMed/Medline, 175 from Scopus, and 496 from the Web of Science. After removing 270 duplicate articles, 576 articles were excluded after reading the title and abstract because they did not meet the following inclusion criteria: not associated with mesenchymal stem cells ($n=350$), phototherapy not using LED ($n=201$), clinical trials ($n=8$), conference papers ($n=1$), case reports ($n=5$), and review papers ($n=11$). After reading the full text of the remaining 13 articles, four articles were excluded because the wavelength of the LED used was not between 400 and 480 nm. Only nine articles remained that were included in the review.

Risk of bias

Table 1 presents the risk of bias for each study, for which a score of 0–4 indicates high risk, 5–8 indicates medium risk, and 9–11 indicates low risk. From these criteria, 55.6% were low risk [18–22], 44.4% were medium risk [14, 23–25], and 0% were high risk.

Description of studies and experimental models

Cell models

Most of the cells used in the nine articles were derived from human tissues, including fat [14, 18], tonsils [23], bone marrow [19], gingiva [20], teeth [22, 25], and cartilage [21], and only one study used MSC derived from mouse bone marrow [24]. The MSCs used in all studies conformed to the characteristics of mesenchymal stem cells. Only four studies reported cell passage [18, 21, 23, 24].

Irradiation strategy

Of the nine studies, four investigated the effect of one wavelength of blue light under different parameters [20, 22, 24,

Table 1 Risk of bias assessment of included studies

	Wang et al. [14]	Patel et al. [23]	Yuan et al. [24]	Wang et al. [18]	Tani et al. [19]	Zhu et al. [20]	Yang et al. [25]	Schneider et al. [21]	Chen et al. [22]
Cell source and type	Y	Y	Y	Y	Y	Y	Y	Y	Y
Cell characterization	Y	Y	Y	Y	Y	Y	Y	Y	Y
Cell passage	N	Y	Y	Y	N	N	N	Y	N
Control group characteristics	Y	Y	Y	Y	Y	Y	Y	Y	Y
Are the experimental groups described in the text exposed in the same way?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Dark conditions	Y	N	N	Y	Y	Y	N	Y	Y
Complete LED parameters	N	N	N	N	Y	Y	Y	Y	Y
Is the missing data described in the text?	N	N	N	N	N	N	N	N	N
Full experimental results	Y	Y	Y	Y	Y	Y	Y	Y	Y
Appropriate statistical methods	Y	Y	Y	Y	Y	Y	Y	Y	Y
Conflicts of interest and funding support	Y	Y	Y	Y	Y	Y	Y	Y	Y
Risk of bias rating	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Low	Low

25] and five investigated the effect of different wavelengths of light under fixed parameters [14, 18, 19, 21, 23]. Table 2 lists the optical parameters extracted for wavelengths between 400 and 480 nm. The irradiation mode was continuous wave (CW) in eight studies [14, 18–20, 22–25] and pulsed mode in only one [21]. It is worth mentioning that one of the studies used a chiral polarizer [23], with an irradiance of 14 mW/cm^2 and an irradiation time of 24 h. In other studies, the energy density ranged from 0.378 J/cm^2 to 72 J/cm^2, and the irradiation time ranged from 10 to 3600 s.

Effect of blue LED photobiomodulation on cell response

Cell proliferation, viability, and apoptosis

Yuan et al. [24] found that as irradiation time increased, the proliferation of mouse bone marrow-derived mesenchymal stem cells (mBMSCs) decreased significantly when the light energy density was 12 J/cm^2, and the proliferation rate was the lowest when it reached 72 J/cm^2. The percentage of

Table 2 Cell models and blue LED parameters used in included studies

Reference	Species	Source	Wavelength (nm)	Mode	Irradiation area (cm^2)	Irradiance (mW/cm^2)	Radiant exposure (J/cm^2)	Time of irradiation (s)	Application distance (cm)	Irradiation method
Wang et al. [14]	Human	Adipocyte	410–430	Continuous	4	16	3	188	–	Multiple
Patel et al. [23]	Human	Tonsil	460	Continuous	9.6*	14*	1.2 kJ/cm^{2*}	24 h	7	Once
Yuan et al. [24]	Mouse	Bone marrow	470	Continuous	–	20	1.2	60*	–	Once or multiple
							6	300*		
							12	600*		
							36	1800*		
							72	3600*		
Wang et al. [18]	Human	Adipocyte	400–430	Continuous	4	16	3	188	–	Multiple
Tani et al. [19]	Human	Bone marrow	405 ± 5	Continuous	7.07*	12.59	0.378	30	1.1*	Once
					2.73*					
Zhu et al. [20]	Human	Gingiva	420–480	Continuous	9.6*	100	1, 2, 4, 6	10, 20, 40, 60	1	Multiple
Yang et al. [25]	Human	Tooth papilla	420–480	Continuous	9.6*	100	1, 2, 3, 4	10, 20, 30, 40	1	Multiple
Schneider et al. [21]	Human	Cartilage	475	Pulsed	2D-PBM: 75*	66.67*	40	600*	7	Once or multiple
				Pulse rate: 50%		10*	6		50	
				Repetition frequency: 2.5 Hz	3D-PBM: 0.32*	66.67*	40	600*	7	
				Peak irradiance intensity: 80 mW/cm^2						
Chen et al. [22]	Human	Tooth pulp	456 ± 3	Continuous	9.6*	32	0, 2, 4, 6, 8, 10	0*, 60*, 120*, 180*, 240*, 300*	1	Multiple

*The data is calculated from the known data in the article or the areas of the dishes/flasks/wells

apoptotic cells was opposite to the proliferation rate, which indicates that blue LED has a toxic effect on mBMSCs, which may be related to DNA damage. Wang et al. [18] reported that, under blue LED irradiation with an energy density of 3 J/cm^2, the proliferation of adipose-derived stem cells (ASCs) gradually decreased as the number of irradiations increased. Zhu et al. [20] found that when human gingival mesenchymal stem cells (hGMSCs) were irradiated with blue LED at different energy densities (1, 2, 4, and 6 J/cm^2), their proliferation was inhibited as the number of irradiations increased. Yang et al. [25] reported similar results. Although they are all dental-derived mesenchymal stem cells, Chen et al. [22] showed that there was no significant effect on the proliferation of human dental pulp stem cells (hDPSCs) under irradiation with blue LEDs of different energy densities (2, 4, 6, 8, and 10 J/cm^2). In addition, two other studies have shown that the viability of MSCs is not affected by PBM even after being irradiated with 14 mW/cm^2 polarized blue light for 24 h (Table 3) [19, 23].

Cell differentiation

Table 3 displays six of the included studies that reported the effect of blue LED on MSC osteogenic differentiation [14, 19, 20, 22, 24, 25] and two studies that reported neural [23] and chondrogenic differentiation [21]. Wang et al. [14] irradiated ASCs with 3 J/cm^2 LED blue light every two days. Compared with the osteogenic induction group, the expressions of the runt-related transcription factor2 (Runx2) gene on day 7 and osteocalcin (OCN) and osterix (OSX) genes on day 21 were significantly increased in the irradiation group, accompanied by an increase in mineralized nodules. Zhu et al. [20] irradiated hGMSCs with blue light at different energy densities (1, 2, 4, and 6 J/cm^2) every two days and found an increase in their mineralization. On day 7, alkaline phosphatase (ALP) activity in the 2 J/cm^2 and 4 J/cm^2 groups was significantly higher than that in the control group, accompanied by an increase in the expression of collagen type I (COL-1), OCN, and Runx2. On day 14, ALP activity continued to increase in each group compared to that in the control group. Yang et al. [25] irradiated stem cells from the apical papilla (SCAPs) with different energy densities (1, 2, 3, and 4 J/cm^2) every two days and found that 4 J/cm^2 contributed to bone differentiation with the most significant effect, accompanied by significant increases in ALP, OCN, dentin sialophosphoprotein (DSPP), and dentin matrix protein-1 (DMP-1). Chen et al. [22] irradiated hDPSCs to the same doses of radiation (2, 4, 6, 8, and 10 J/cm^2) and found that ALP activity in the 6 J/cm^2 and 8 J/cm^2 groups was significantly higher, but only 6 J/cm^2 promoted increased expression of all measured osteogenesis-related genes Runx2, OCN, osteopontin (OPN), and bone morphogenetic protein (BMP), concomitant with the formation of mineralized nodules.

However, two other studies showed that blue LED had no effect on or inhibited MSC osteogenic differentiation. Tani et al. [19] irradiated hBMSCs once with 0.378 J/cm^2 blue light, which did not affect osteogenic differentiation. Yuan et al. [24] irradiated mBMSCs with 12 J/cm^2 blue light every day, and on day 7, ALP activity and calcium nodules decreased, compared with the control group. Furthermore, Patel et al. [23] reported that the expression of neuronal differentiation markers nuclear receptor-related 1 (NURR1), neuron-specific enolase (NSE), and neurofilament M (NFM) in tonsil-derived mesenchymal stem cells (TMSCs) significantly increased after 14 mW/cm^2 chiral polarized blue light irradiation for 24 h, and the effect of the L-polarized light system (PL) was better than that of the R-polarized light system (PR). For ASCs from different donors, Schneider et al. [21] found that 6 J/cm^2 and 40 J/cm^2 had slightly different effects on the 2D and 3D stages of chondrogenic differentiation, but the overall effect was poor and even inhibitory.

Effect of blue LED on cell metabolism and intracellular calcium signaling system

To explore the mechanism by which blue light promotes the neuronal differentiation of TMSCs, Patel et al. [23] irradiated TMSCs with polarized LED light for 2 min and found that, compared with the control group, ATP and Ca^{2+} in the PL system significantly increased. Yuan et al. [24] reported that when mBMSCs were irradiated with 20 mW/cm^2 LED blue light for 10, 30, or 60 min, a significant increase in reactive oxygen species (ROS) was observed. For the purpose of exploring the reason behind the inhibition of ASC proliferation by a 3 J/cm^2 blue LED, Wang et al. [18] irradiated cells with blue light of different energy densities and found that ATP levels decreased in a dose-dependent manner. When the energy density was 3 J/cm^2, the mitochondrial membrane potential (MMP) decreased significantly, whereas Ca^{2+} and ROS increased significantly. After application of capsazepine (CPZ), a specific inhibitor of transient receptor potential vanilloid 1 (TRPV1), Ca^{2+} levels decreased significantly, and the inhibitory effect of blue light disappeared. Similarly, Wang et al. and Chen et al. [14, 22] found that intracellular Ca^{2+} increased after blue light irradiation, and after blocking TRPV1, intracellular Ca^{2+} decreased and the biological effect of blue light disappeared, which may be related to the activation of TRPV1.

Table 3 Effect of blue LED photobiomodulation on MSCs

Reference	Viability	Proliferation	Apoptosis/DNA damage	Differentiation	Metabolism/intracellular calcium system
Wang et al. [14]	NA	NA	NA	Osteogenic differentiation *Gene expression:* Runx2: ↑7d*-14d*-21d*; OCN: ↑21d*; OSX: ↑21d* *AR staining and mineralization assays:* ↑↑↑21d*	↑Intracellular calcium*
Patel et al. [23]	Viability -24 h* (PL/PR)	NA	NA	Neuronal differentiation *Gene expression:* NURR1: ↑↑24 h (PL: 14+; PR: 4+)*; NSE: ↑↑24 h (PL/PR: 20+)*; NFM: ↑↑24 h (PL/PR: 2+)* *Immunofluorescence:* NURR1: (PL: ↑↑24 h*; PR: ↑24 h*); NSE: ↑24 h (PL/PR)*; NFM: ↑24 h* (PL/PR)	↑ATP/intracellular calcium* (PL)
Yuan et al. [24]	NA	Proliferation ↓10/30/60 min*	Apoptosis ↑10/30/60 min* DNA damage ↑5/10/30/60 min*	Osteogenic differentiation *ALP and AR staining*: ↓7d* (BMSCs were irradiated by blue LED light at a power density of 20 mW/cm^2 for 10 min every day during osteogenic induction)	ROS ↑↑10/30/60 min (20 mW/cm^2)*
Wang et al. [18]	NA	Proliferation ↓1/3/6/24/48 h*	NA	NA	↓ATP/MMP/intracellular PH* ↑Intracellular calcium* ↑↑ROS*
Tani et al. [19]	Viability -24 h*	Proliferation -24 h*	NA	Osteogenic differentiation *Gene expression:* Runx2: ↓7d*; ALP: -7d* *Fluorescent mineralized nodule assay:* -18d*	NA
Zhu et al. [20]	NA	Proliferation ↓1/3/5/7/9d (1, 2, 4, 6 J/cm^2)*	NA	Osteogenic differentiation *Gene expression:* COL-1, Runx2, OCN: ↑↑7d (2, 4 J/cm^2)* *ALP staining:* ↑7d (2 J/cm^2≈4 J/cm^2 > 1, 6 J/cm^2)* ↑↑14d (1, 2, 4, 6 J/cm^2)* *ALP activity:* ↑↑7d (2 J/cm^2 > 4 J/cm^2)* ↑↑14d (2, 4 J/cm^2 > 1, 6 J/cm^2)* *AR staining and mineralization assays:* ↑↑28d (6 J/cm^2 > 1, 2, 4 J/cm^2)*	NA
Yang et al. [25]	NA	Proliferation ↓1/3/5/7/9d (1, 2, 3, 4 J/cm^2)*	NA	Osteogenic differentiation *Gene expression:* ALP, DSPP: ↑7d (4 J/cm^2)*; OCN,DMP-1: -7d (4 J/cm^2)* ALP, DMP-1: ↑14d (4 J/cm^2)*; OCN, DSPP: ↑↑14d (4 J/cm^2)* *ALP staining:* ↑7d (4 J/cm^2 > 1, 2, 3 J/cm^2)* ↑↑14d (4 J/cm^2 > 1, 2, 3 J/cm^2)* *ALP activity:* ↑7d (4 J/cm^2 > 3 J/cm^2)* ↑↑14d (4 J/cm^2 > 3 J/cm^2)* *Mineralization assays:* ↑↑28d (3 J/cm^2 > 2, 4 J/cm^2)*	NA

Table 3 (continued)

Reference	Viability	Proliferation	Apoptosis/DNA damage	Differentiation	Metabolism/intracellular calcium system
Schneider et al. [21]	NA	NA	NA	Cartilage differentiation *Pellet size and GAG/DNA content (2D-PBM):* donors 1, 3, 4: -35d*; donor 2: ↑35d*; donors 5,6: ↓35d* *Collagen type II immunostaining (2D-PBM):* donor 1: -35d (6 J/cm^2)* ↑35d (40 J/cm^2)*; donor 2: ↑35d (6, 40 J/cm^2)*; donors 3, 4: -35d (6, 40 J/cm^2)*; donors 5, 6: ↓35d (6, 40 J/cm^2)* *Pellet size and GAG/DNA content (3D-PBM):* donors 1, 2, 3, 4: -35d*; donor 5: ↓35d*; donor 6: ↑35d* *Collagen type II immunostaining (3D-PBM):* donors1, 2, 3, 4, 6: -35d (6, 40 J/cm^2)*; donor 5: ↓35d (6, 40 J/cm^2)*	NA
Chen et al. [22]	NA	Proliferation -1/3/5/7/9d (2, 4, 6, 8, 10 J/cm^2)*	NA	Osteogenic differentiation *Gene expression:* Runx2: ↑↑↑7d (4, 6, 8 J/cm^2)*; OCN: ↑↑7d (4, 6 J/cm^2)*; OPN: ↑↑7d (2, 4, 6, 8 J/cm^2)*; BMP2: ↑↑7d (6, 8, 10 J/cm^2)* *ALP staining and activity:* ↑↑↑7d (4, 6, 8 J/cm^2)* ↑↑14d (6, 8 J/cm^2) *AR staining assay:* ↑↑21d (4, 6 J/cm^2)*	↑Intracellular calcium (6 J/cm^2)*

↑: significant increase; -: no significant change; ↓: significant decrease; *: post-irradiation time; +: multiple

NA not applicable, *PL* L-polarized blue LED, *PR* R-polarized blue LED, *NURR1* nuclear receptor-related 1, *NFM* neurofilament M, *NSE* neuron-specific enolase, *DMP-1* dentin matrix acidic phosphoprotein-1, *DSPP* dentin sialophosphoprotein

Discussion

The quality of the evidence and possible bias

According to the risk of bias assessment, 55.6% (five studies) of the included publications were at low risk, and 44.4% (four studies) were at medium risk. In general, the included studies met the minimum standards for in vitro studies, but the following reasons increased their risk of bias: (1) whether to report the passage number of the cells used, (2) to avoid light exposure during the irradiation process, (3) to report the complete optical parameters, and (4) whether to report missing data. The fewer cell passages, the closer the cell characteristics are to those of primary cells, and the better the cell activity, proliferation, and differentiation ability [26]. Avoiding light during the irradiation process can avoid the influence of photons in other bands on PBM, and at the same time, a complete report of light parameters can maximize the repeatability of the experiment and enhance the authenticity of the experimental data.

Although the mechanism of PBM regulation of MSC proliferation and differentiation has not been elucidated, it is widely accepted that photons of red/near-infrared light are absorbed by cytochrome C oxidase (CCO). This causes the transfer of electrons in the respiratory chain and the alteration of cAMP, ATP, ROS, and other signaling molecules, resulting in relevant biological effects [27, 28]. The PBM effect of blue light is believed to occur because flavin absorbs blue light photons and transmits signals through redox molecular chains. Another hypothesis is that blue light may produce biological effects by activating the photosensitive ion channel TRPV to increase intracellular calcium ions [29, 30].

Effects of blue LEDs on the proliferation of MSCs

Yuan et al. [24] irradiated mBMSCs with blue light of different energy densities (1.2, 6, 12, 36, and 72 J/cm^2) and found that the number of EdU + cells decreased significantly from 12 J/cm^2 onward and the percentage of apoptotic cells increased significantly, suggesting that light inhibition of cell proliferation was accompanied by a significant increase in ROS. Wang et al. [18] irradiated hASC five times with blue light at an energy density of 3 J/cm^2 to inhibit cell proliferation, which resulted in a decrease in ATP/MMP and a significant increase in Ca^{2+} and ROS. Tani et al. [19] reported that the irradiation of hBMSCs with blue light at an energy density of 0.378 J/cm^2 does not affect cell proliferation. The above three studies showed that the effect of blue light on MSC proliferation may be different from the biphasic effect of red/NIR light, but is dose-dependent; i.e., low-dose light does not affect cell proliferation and gradually inhibits cell proliferation as the dose increases. This inhibitory effect may be related to a significant increase in ROS after irradiation, which can destroy MMPs and induce the release of mitochondrial proapoptotic factors that participate in the autophagic death of cells [31, 32].

In addition, Yoo et al. [33] found that blue LED increases Ca^{2+} influx by activating TRPV1, leading to ROS and tumor necrosis factor-α (TNF-α) production, while TRPV1 upregulation can reduce epidermal growth factor receptor (EGFR) protein levels and inhibit the AKT/GSK3-β/FoxO3a signaling pathway, resulting in decreased cell proliferation. Of note, Zhu et al. [20] and Yang et al. [25] found that GMSCs and SCAPs irradiated with blue light (1–6 J/cm^2) inhibited the proliferation of dental stem cells. However, Chen et al. [22] irradiated DPSCs with 0–10 J/cm^2 blue light, which had no significant effect on their proliferation. This can be attributed to two points. (1) The difference in the irradiation methods, and according to the equation energy density (J/cm^2) = irradiance (W/cm^2) × time (s), even if the energy density is similar, the difference in irradiance and time may have different effects on the cells [30, 34]. (2) Although they are both stem cells, there are differences in their proliferation and differentiation abilities [35, 36].

Effects of blue LEDs on the differentiation of MSCs

The osteogenic differentiation of MSCs is often regulated by a variety of transcription factors (Runx2, BMP, and OSX) that are important for the regulation of bone extracellular matrix protein genes (such as ALP, COL-1, bone sialoprotein BSP, OSC, and OPN) and the induction of bone mineralization [37, 38]. This also confirms the findings of Zhu et al. [20] and Yang et al. [25] that blue-light-induced osteogenic differentiation of odontogenic stem cells is related to an increase in osteogenic markers. Chen et al. [22] irradiated DPSCs with 6 J/cm^2 blue light every two days to promote osteogenic differentiation. In addition to the increased expression of osteogenesis-related genes (Runx2, OCN, OPN, and BMP2), this process was accompanied by a significant intracellular Ca^{2+} increase. After treatment with the TRPV1-specific inhibitor CPZ, intracellular Ca^{2+} decreased significantly and the osteogenic effect disappeared, suggesting that this was related to the activation of TRPV1. Similarly, Wang et al. [14] found that 3 J/cm^2 blue light promotes hASC osteogenic differentiation related to the activation of TRPV and compared the effects of red light (660 nm) and near-infrared light (810 nm) on ASC osteogenic differentiation. The results showed that red and near-infrared light had weaker osteogenic effects than blue light and did not

activate TRPV1 channels. Other studies have shown that the effect of blue light on promoting osteogenesis in amniotic fluid-derived stem cells is stronger than that of red and near-infrared light [13]. This suggests that the effect of blue light on promoting MSC osteogenic differentiation may be better than that of red and near-infrared light, which may be due to the activation of the TRPV1 channel, resulting in a significant increase in intracellular Ca^{2+}. As a result of ion channel activation or secondary messengers, calcium ions can participate in various signal transduction processes in cells and affect various cellular activities [39].

The other two included studies showed contrasting results. Yuan et al. [24] irradiated mBMSCs with blue light with an energy density of 12 J/cm^2 to inhibit their osteogenic differentiation, while Tani et al. [19] irradiated hBMSCs with 0.378 J/cm^2 blue light, which had no significant effect on their osteogenic differentiation. This suggests that the effect of blue light on osteogenic differentiation may manifest as a biphasic response; i.e., low energy density does not affect cell differentiation, and with a gradual increase in energy density, cell differentiation is first promoted and then inhibited. In addition to its effect on osteogenic differentiation, Patel et al. [23] irradiated TMSC with an irradiation dose of 14 mW/cm^2 for 24 h and found that blue light promoted the differentiation of cells into neural cells by upregulating the expression of NURR1, NFM, and NSF. Although the total energy density of blue light was very high, it had no effect on cell viability and promoted cell differentiation. We speculate that this may be because chirally polarized light is similar to chiral materials and has better biocompatibility, which can effectively reduce the toxic effects on cells and make them safer [40].

After analyzing the studies included in this review, it is necessary to highlight some of their limitations. In addition to the light parameters, which are the most important in the PBM, the passage of cells and dark conditions should also be described in detail. The lack of these data leads to the irreproducibility of the experiments. Secondly, considering the complexity of the environment for transplanting stem cells in vivo, there is still a lack of both in vivo and in vitro experimental data after simulation of harmful environments. Finally, considering the difference in the location of cell implantation, the depth of irradiation and energy attenuation must also be considered.

Conclusion

Although there are certain limitations to this systematic review, it was found, through the relatively few included studies, that blue LED light inhibits proliferation and promotes the differentiation of MSCs in an appropriate energy density range, and its promotion of differentiation may be related to the activation of TRPV1. Additionally, polarized light may reduce the toxic effects of blue light on MSCs.

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Declarations

Competing interests The authors declare no competing interests.

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