Original article

Molecular biological effects of led-based photobiomodulation therapy on bone regeneration: A systematic review

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Abstract

Background: Bone regeneration is essential for dental procedures such as implant integration and orthodontic movement. Photobiomodulation (PBM), particularly using light-emitting diode (LED), has emerged as a promising non-invasive method to enhance bone healing, though its molecular mechanisms remain unclear and findings across studies are inconsistent. This systematic review aims to synthesize current evidence on the molecular effects of LED-based PBM on bone regeneration, focusing on bone formation and resorption.

Materials and method: A systematic review was conducted following PRISMA 2020 guidelines. Literature searches were performed in PubMed and ScienceDirect up to November 10, 2024. Studies included full-text original research evaluating molecular effects of LED-PBM on bone compared to non-irradiated controls. Risk of bias was assessed using the QUIN tool for in vitro studies and SYRCLE for in vivo studies.

Results: Out of 4646 articles, 16 met the eligibility criteria. Risk of bias was moderate to low overall, with some methodological limitations noted, particularly in blinding and allocation procedures. Wavelengths ranged from 405 to 830 nm, with red light being the most frequently used. Most studies reported increased expression of key osteogenic markers (ALP, *RUNX2*, OCN, OPN), improved calcium deposition, and modulation of inflammatory and signaling molecules (ROS, ATP).

Conclusion: This review confirms that LED-PBM promotes bone regeneration by upregulating key osteogenic markers and signaling pathways, offering a molecular basis for protocol refinement in dental applications.

Keywords*: LED therapy; Bone regeneration; Photobiomodulation; Molecular level.*

1. INTRODUCTION

Bone regeneration is a dynamic and complex physiological process that involves four primary, overlapping phases: inflammation, angiogenesis, mesenchymal proliferation, bone formation, and remodeling [1]. In the field of dentistry, this process is crucial for the success of various clinical procedures, including dental implant osseointegration, alveolar socket healing, and orthodontic tooth movement [2-4]. Over the past few decades, various strategies have been explored to accelerate bone regeneration, with photobiomodulation (PBM) therapy emerging as a promising approach [5].

PBM employs low-intensity Light Amplification by Stimulated Emission of Radiation (LASER) and light-emitting diode (LED). It has gained significant attention as a non-invasive technique in regenerative medicine [6]. PBM has been widely used in clinical practice, and numerous clinical trials have demonstrated its biological efficacy, including pain relief, anti-inflammatory effects, wound healing acceleration, and biological stimulation [7]. However, the clinical effectiveness of PBM is highly dependent on specific parameters, such as wavelength, power output, and energy, necessitating the development of customized protocols for various clinical scenarios [8-10].

Most of the research on PBM in dentistry has focused on LASER, for which well-established guidelines exist. In contrast, the application of LED remains relatively underexplored, despite their advantages over lasers: a broader wavelength spectrum, affordability, ease of use, lower thermal output, and a superior safety profile [8].

Although the clinical potential of PBM is widely recognized, the molecular mechanisms especially those associated with LED-based PBM are still under investigation. While numerous in vitro and in vivo studies have explored the effects of LED on bone tissue, the findings remain inconsistent and

sometimes contradictory. These discrepancies are largely attributed to variations in study design, including differences in irradiation parameters such as wavelength, energy density, and exposure time. These inconsistencies highlight the need for a comprehensive and systematic synthesis of the available literature to elucidate the molecular effects of LED on bone tissue. Such insights could be instrumental in optimizing clinical protocols and improving therapeutic efficacy.

Therefore, the objective of this systematic review is to critically evaluate and synthesize the existing evidence regarding the molecular biological effects of LED-based photobiomodulation on bone regeneration, with a focus on both bone formation and resorption.

2. MATERIALS AND METHODS:

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) guidelines [11].

2.1. Focused question

This systematic review was conducted to answer the following question: What are the molecular-level effects of LED-based photobiomodulation therapy on bone?

2.2. Eligibility criteria

A literature search was conducted using two databases: PubMed and ScienceDirect, limited to studies published up to November 10, 2024. The search strategy was developed based on the PICO framework [12], with the following predefined inclusion and exclusion criteria:

Inclusion Criteria:

+ **P** (Population): Molecules involved in bone formation or resorption.

+ **I** (Intervention): LED-based photobiomodulation therapy.

+ **C** (Comparison): A non-irradiated control group.

+ **O** (Outcome): Changes in the expression or concentration of molecules associated with bone formation or resorption.

Exclusion Criteria:

+ Non-English publications.

+ Studies without accessible full text.

+ Conference abstracts, presentations, reports, systematic reviews, and meta-analyses.

2.3. Literature search

Step 1: Identification and Search of Literature

A systematic search was conducted on PubMed and ScienceDirect up to November 10, 2024. Due to the specificity of the two databases employed, for each one a different search string was built. The following search strategies were employed:

PubMed:

('light emitting diode' OR 'LED'[ti] OR 'Photobiomodulation' OR 'low level light therapy' OR 'deep red light' OR 'red light' OR 'blue light' OR 'near infrared light' OR 'green light' OR 'NIR' OR 'orange light' OR 'yellow light') AND ('bone' OR 'osteoblast' OR 'osteoclast') AND english[Filter]

ScienceDirect:

#1=(('LED'[ti] OR 'Photobiomodulation') AND ('bone') AND english[Filter])

#2=(('LED'[ti] OR 'light emitting diode' OR 'Photobiomodulation') NOT ('laser') AND ('bone') AND english[Filter])

#3=("photobiomodulation" AND "bone")

#1 AND #2 AND #3

Results from both databases were exported to an Excel file, and duplicates were removed.

Step 2: Title and Abstract Screening

Two reviewers independently screened the titles and abstracts of the articles based on the inclusion and exclusion criteria outlined above. In case of any discrepancies between the two reviewers, a discussion with the principal investigator was held to reach a consensus.

Step 3: Full-Text Screening

Full-text screening was conducted similarly. To minimize errors, the two reviewers initially screened three studies and discussed them to ensure alignment with the inclusion and exclusion criteria. In case of disagreements, additional discussions were held with the principal investigator.

2.4. Quality Assessment

The quality and reliability of the included studies were assessed using the SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) tool for in vivo studies [13]. For in vitro studies, the QUIN (Quality Assessment Tool for In Vitro Studies) tool was used [14].

2.5. Data Extraction

Two reviewers independently read the full-text articles and extracted data, subsequently cross-checking the information. Any discrepancies were discussed with the principal investigator to achieve consensus. The extracted information from each study included: article title, author(s), publication year, study design, characteristics of LED light therapy (including color, wavelength, energy density, power density, exposure time, evaluation time, distance from the sample, irradiation mode), characteristics

of the molecules monitored in the studies (molecule name, changes in molecule levels compared to the control group without light therapy), and the outcomes of LED photobiomodulation on bone.

3. RESULTS:

3.1. Study Selection

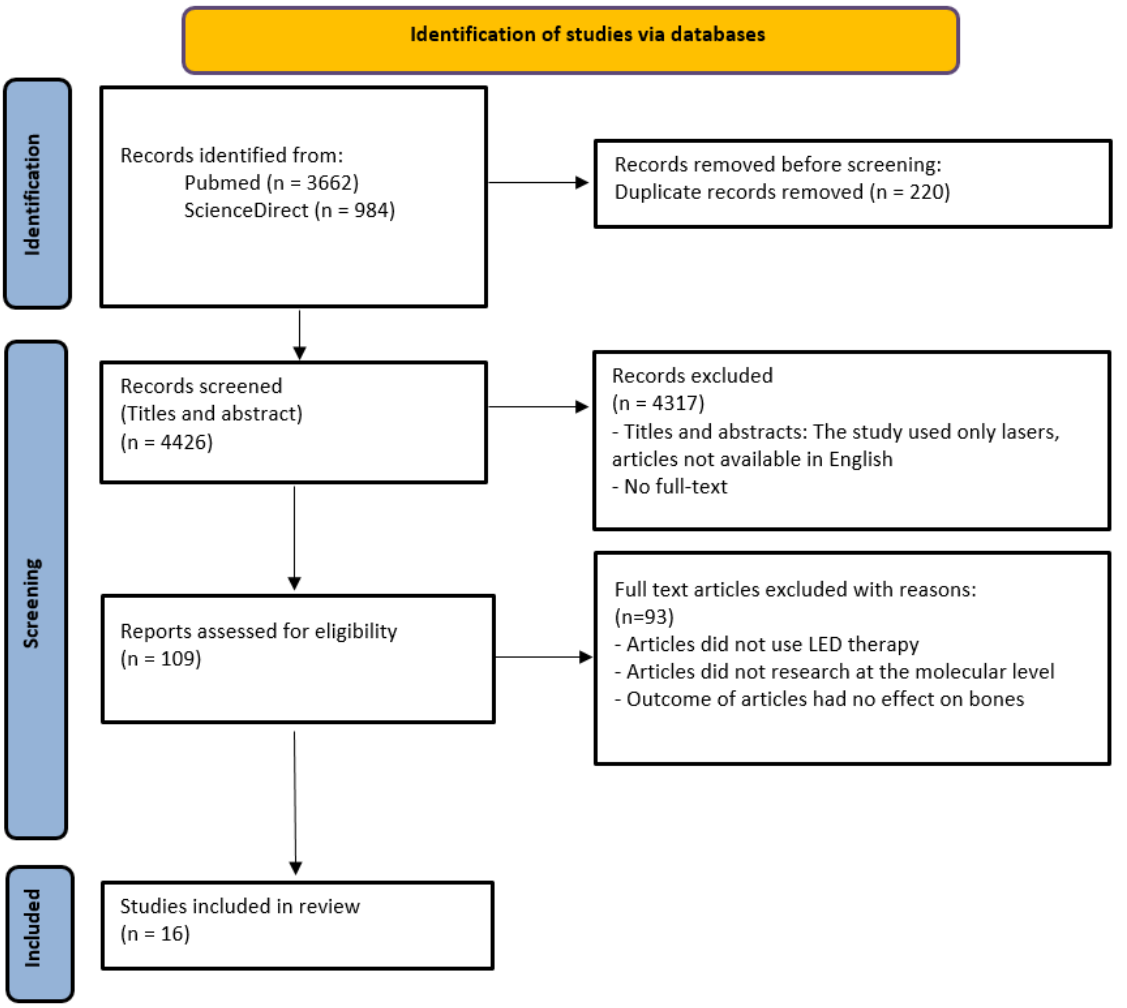

Figure 1: Flowchart depicting the study selection process (PRISMA)

As shown in figure 1, the search process yielded a total of 4646 results across all databases, including 3662 from PubMed and 984 from ScienceDirect. After removing duplicates, 4426 articles were screened based on their titles and abstracts. Of these, 4317 articles did not meet the inclusion criteria and were excluded, leaving 109 full-text articles for detailed assessment. Following the full-text review, 93 articles were excluded due to reasons such as the absence of LED light usage, lack of focus on molecular effects, or failure to analyze the impact on bone tissue. Ultimately, 16 articles were included in the systematic review.

3.2. Quality Assessment of the Included Studies

Table 1: Risk of Bias Assessment of in vitro studies with QUIN tool

Publication	Clearly stated aims/objectives	Detailed explanation of sample size calculation	Details explanation of sampling technique	Detailed explanation of methodology	Operator details	Randomization	Method of measurement of outcome	Outcome assessor details	Blinding	Statistical analysis	Presentation of results	Risk of bias
Rahmati et al., 2022 [15]	2	0	2	2	1	NA	2	0	NA	2	2	75% Low risk
Chaweewanakorn et al., 2021 [16]	2	0	2	2	0	NA	2	0	NA	2	2	70% Medium risk
Wu et al., 2021 [17]	2	0	2	2	1	NA	2	0	NA	2	2	75% Low risk
Ruan et al., 2021 [18]	2	0	2	2	0	NA	2	0	NA	2	2	70% Medium risk
Chang et al., 2019 [19]	2	0	2	2	0	NA	2	0	NA	2	2	70% Medium risk
Zhu et al., 2019 [20]	2	0	2	2	1	NA	2	0	NA	2	2	75% Low risk
Tani et al., 2018 [21]	2	0	2	2	0	NA	2	0	NA	2	1	60% Medium risk
Wang et al., 2017 [22]	2	0	2	2	0	NA	1	0	NA	2	2	65% Medium risk
Yuan et al., 2017 [23]	2	0	1	2	0	NA	1	0	NA	1	2	50% Medium risk
Wang et al., 2016 [24]	2	0	2	2	0	NA	1	0	NA	2	2	65% Medium risk
Sohn et al., 2015 [9]	2	0	2	2	0	NA	2	0	NA	2	2	65% Medium risk
Kwon et al., 2012 [25]	2	0	2	2	0	1	2	0	NA	1	2	59.1% Medium risk
Higuchi et al., 2011 [10]	2	0	2	1	0	NA	1	0	NA	2	2	60% Medium risk
Li et al., 2010 [26]	2	0	2	2	0	NA	2	0	NA	2	2	70% Medium risk
Kim et al., 2009 [27]	2	0	2	2	0	NA	2	0	NA	1	2	65% Medium risk

NA: Not Applicable

Adequately specified = 2; Inadequately specified = 1; Not specified = 0

Final score > 70% = Low risk of bias; 50 to 70% = Medium risk of bias; < 50% = High risk of bias based on the formula of QUIN tool: Final score = Total score*100/(2*number of criteria applicable)

Table 2: Risk of Bias Assessment of in vivo studies with SYRCLE's tool

Publication	Selection bias			Performance bias		Detection bias		Attrition bias	Reporting bias	Others
	Randomization	Baseline characteristics	Concealment of groups	Random housing of animals	Blinded to intervention	Random selection for assessment	Assessor blinded	Missing animal data	Selective reporting based on methods/results	Others source of bias
Park et al., 2016 [28]	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No

As shown in Table 1, the risk of bias assessment using the QUIN tool indicated that three in vitro studies [15, 17, 20] were classified as low risk of bias, with a completion rate of 75%. The remaining studies had completion rates ranging from 50% to 70% and were categorized as having a medium risk of bias. Commonly well-reported domains included clearly stated objectives, detailed comparison groups, comprehensive methodology descriptions, statistical analysis, and the presentation of results. In contrast, domains such as blinding, randomization, and outcome assessor concealment were frequently underreported or not addressed.

As shown in Table 2, the SYRCLE tool assessment for in vivo studies revealed a generally low risk of bias, particularly in domains related to attrition and reporting bias. However, domains related to blinding (performance bias, detection bias), randomization, and allocation concealment were frequently rated as "unclear" due to insufficient methodological details in the study reports.

3.3. General Characteristics of the Included Studies

According to Table 3, the compiled data indicate that the studies utilized LED light therapy within a wavelength range of 405 nm to 830 nm, predominantly employing continuous wave irradiation. Among the 16 studies analyzed, red light (630 - 700 nm) was the most frequently used, featured in 11 studies. Blue light was applied in 5 studies, near-infrared light in 2 studies, while violet-blue, green, and yellow lights were each utilized in one study.

There was considerable variability in the irradiation parameters across the studies. Energy density ranged from 0.378 J/cm² to 8 J/cm², while power density varied from 1 mW/cm² to 100 mW/cm², reaching up to 1,100 mW/cm² in one case. Irradiation durations varied between 30 seconds and 48 hours. The distance from the light source to the sample ranged from 1 mm to 100 mm, with several studies not reporting this parameter. Effectiveness assessments were conducted between 24 hours and 28 days post-irradiation.

3.4. Main Study Outcomes

Outcomes from the included studies are summarized in Table 4. Among the 16 primary studies, alkaline phosphatase (ALP) was the most frequently assessed biomarker, followed by calcium ions (Ca^{2+}), osteopontin (OPN), and osteocalcin (OCN).

In the studies utilizing blue light, the majority reported positive effects on osteogenesis, as evidenced by increased levels of ALP, Ca^{2+}, and other related molecules. However, Yuan et al. observed that blue light could inhibit osteoblast differentiation, as indicated by a decrease in ALP expression [23]. In contrast, Tani et al. found that violet-blue light did not significantly affect bone regeneration [21].

Red light was the most commonly used wavelength, featured in 11 studies. Most of these studies demonstrated a marked enhancement in osteoblast differentiation, accompanied by elevated expression of ALP, *RUNX2*, OCN, and Ca^{2+}. Several studies also noted a reduction in osteoclastic activity, possibly through inhibition of ROS, NF-κB, or osteoclast function. However, Higuchi et al., using red light at 630 nm, reported no significant changes following the intervention [10].

Two studies involving near-infrared (NIR) light also showed positive effects on bone formation, including increased ALP and Ca^{2+} expression. Green light (525 nm), investigated in a single study, was found to upregulate OPN expression, thereby promoting osteoblast differentiation. Meanwhile, yellow light (600 nm) had no significant effect on bone-related biomarkers, as indicated by the absence of observable changes in the study by Higuchi et al. [10].

Table 3: Details of intervention (photobiomodulation).

Publication	Type of study	Human/Animal/Cell	Method treatment and dosage						
			LED light		Method				
			Color	Wavelength	Energy density (J/cm2) Power density (mW/cm2)	Distance	Exposure time	Evaluation time	Mode
Sohn et al., 2015 [9]	In vitro	Mouse bone marrow-derived macro phages (BMMs).	Red	635 nm	4 J/cm^2 (5 mW/cm^2)	NR	1 hours	3 days	CW
Chang et al., 2019 [19]	In vitro	The mouse MC3T3-E1	Red	630±5 nm	1J/ cm^2 (5 mW/cm^2)	5cm	200 seconds	7, 14 and 21 days	CW
			NIR	810±10 nm					
Tani et al., 2018 [21]	In vitro	Human osteoblast and mesenchymal stromal cell (hMSC)	Violet blue	405 ±10 nm	0.378 J/cm2 (12.59 mW/ cm2)	11mm	30s	24 hours	CW
Higuchi et al., 2011 [10]	In vitro	Amniotic Fluid-Derived Stem Cells (AFSCs)	Blue	470nm	1 mW/cm^2	NR	1, 6, 12, 24, 36, and 48 hours	14, 21 and 28 days	NR
			Green	525nm					
			Yellow	600nm					
			Red	630nm					
Chaweewanakorn et al., 2021 [16]	In vitro	Periodontal ligament stem cells (PDLSCs)	Red	630nm	3, 5 J/cm^2	52mm	20 minutes	8, 10, 28 days	CW
			Deep Red	680nm					
			NIR	830nm					
Ruan et al., 2021 [18]	In vitro	Human bone marrow mesenchymal stem cells (BMSCs)	Deep Red	600-700nm (peak at 650nm)	2, 4, 6, 8 J/cm^2 (1100 mW/ cm^2)	40 mm	10, 20, 30, 40 seconds	1, 2 weeks	CW
Wang et al., 2017 [22]	In vitro	Human adipose-derived stem cells (hASCs)	Blue	415 nm	3 J/cm^2 (16 mW/cm^2)	NR	188 seconds	1, 24 hours	CW
Kim et al., 2009 [27]	In vitro	Mouse mesenchymal stem cells (D1 cells)	Red	647 nm	0.093, 0.279, 0.836 J (9.29 mW/ cm^2)	3cm	10, 30, 90 seconds	48 hours	NR
Kwon et al., 2012 [25]	In vitro	The osteoblastic, clonal cell line MC3T3-E1	Red	635nm	1 mW/cm^2	100mm	1 hour	2, 4, 8, 12, 24 hours	CW
Yuan et al., 2017 [23]	In vitro	Bone marrow derived mesenchymal stem cells (BMSCs)	Blue	470nm	20 mW/cm^2	NR	1, 5, 10, 30, 60 minutes	6 hours and 1 week	NR
Park et al., 2016 [28]	In vivo	Athymic nude mouse implanted with mesenchymal stem cells embedded in PLGA microspheres	Red	647nm	NR	NR	60, 90 seconds	1, 2, 3 weeks	NR
Li et al., 2010 [26]	In vitro	Rat Bone Marrow Mesenchymal Stem Cells (Rat BMSCs)	Red	630 ± 5 nm,	4 J/cm^2 (15 mW/cm^2)	1.2cm	266 seconds	1 hour 1, 7, 14, 21, 28 days	NR
Rahmati et al., 2022 [15]	In vitro	Stem cells from the apical papilla (SCAPs)	Red	640nm	100 mW/cm^2	1cm	30s	24, 48 hours	CW

Zhu et al., 2019 [20]	In vitro	Human gingival mesenchymal stem cells (hGMSCs)	Blue	420–480 nm	1, 2, 4, 6 J/cm^2 (100 mW/cm^2)	1cm	10, 20, 40, 60 seconds	7, 14, 28 days	CW
Wu et al., 2021 [17]	In vitro	Periodontal ligament stem cells (PDLSCs)	Red	600-700nm	1, 3, 5 J/cm^2 (66.7 mW/cm^2)	2cm	15, 45, 75 seconds	7, 14 days	CW
Wang et al., 2016 [24]	in vitro	Human adipose-derived stem cells (hASCs)	Blue	420nm	3 J/cm^2 (16 mW/cm^2)	NR	188s	21 days	CW

Table 4: Characteristics of the study outcomes.

Publication	LED light	Biological effect on Molecule	Outcome
Tani et al., 2018 [21]	Violet blue (405 ±10 nm)	ALP***, Ca2+***, *RUNX2****, OPN***	No significant changes induced.
Wang et al., 2017 [22]	Blue (415 nm)	Ca2+*, ROS*, ATP*, MMP*	Most studies suggest that blue light has a positive effect on osteogenesis. However, Yuan et al. (2017) observed that blue light inhibits osteoblast differentiation, while Tani et al. (2018) found that violet-blue LED light does not impact the bone regeneration rate.
Wang et al., 2016 [24]	Blue (420 nm)	Ca2+*, *RUNX2**, OSX*, OCN*	
Yuan et al., 2017 [23]	Blue (470nm)	ALP**, ROS*, COX*	
Higuchi et al., 2011 [10]	Blue (470nm)	ALP*, Ca2+*, OPN*	
Zhu et al., 2019 [20]	Blue (420–480 nm)	ALP*	
Higuchi et al., 2011 [10]	Green (525nm)	OPN*	Enhances osteoblast differentiation.
Higuchi et al., 2011 [10]	Yellow (600nm)	OPN***	No significant changes induced.
Higuchi et al., 2011 [10]	Red (630nm)	OPN***	Most studies suggest that red light promotes osteoblast differentiation and boosts bone formation, as well as reducing bone resorption and inflammation. However, Higuchi et al. (2011) reported no significant changes.
Li et al., 2010 [26]	Red (630 ± 5 nm)	ALP*, OCN*, ATP*	
Chang et al., 2019 [19]	Red (630±5 nm)	ALP*, OPN*, OPG*	
Chaweewanakorn et al., 2021 [16]	Red (630nm)	ALP*, Ca2+*	
Sohn et al., 2015 [9]	Red (635nm)	ROS**, MAPK**, NF-kB**	
Kwon et al., 2012 [25]	Red (635nm)	ROS**, MAPK**, COX-1**, COX-2**	
Kim et al., 2009 [27]	Red (647 nm)	ALP*, *RUNX2**, OCN*, COL1A1*, OPN*	
Park et al., 2016 [28]	Red (647nm)	ALP*, Ca2+*, COL1A1*, BSP*	
Rahmati et al., 2022 [15]	Red (640nm)	ALP*, BSP*, DSPP*, DMP1*	
Wu et al., 2021 [17]	Red (650nm)	ALP*, Ca2+*, *RUNX2**, OCN*, OPN*, BSP*	
Ruan et al., 2021 [18]	Red (650nm)	ALP*, Ca2+*, *RUNX2**, OCN*, COL1A1*	
Chaweewanakorn et al., 2021 [16]	Deep Red (680nm)	ALP*, Ca2+*	Enhances osteoblast differentiation.
Chang et al., 2019 [19]	NIR (810±10 nm)	ALP*, OPN*, OPG*	Enhances osteoblast differentiation.
Chaweewanakorn et al., 2021 [16]	NIR (830nm)	ALP*, Ca2+*	

** (Increase), ** (Decrease), *** (Constant)*

4. DISCUSSION

In the field of dentistry, bone healing plays a critical role in various clinical interventions, such as dental implant placement, bone grafting, orthodontic tooth movement, and the management of periodontal diseases. Accelerating bone regeneration not only shortens treatment duration but also significantly improves clinical outcomes [29].

The present review synthesizes current evidence on the molecular effects of photobiomodulation

using light-emitting diode (LED-PBM) on bone tissue, with particular emphasis on the upregulation of key osteogenic markers such as ALP, *RUNX2*, OCN, and OPN, as well as the modulation of signaling pathways including ROS, ATP, and NF-κB. While previous studies have reported inconsistent outcomes, this systematic analysis helps clarify molecular patterns by comparing variations across wavelengths, cell types, and dosimetric parameters.

Overall, the majority of studies reported increased expression of osteogenic biomarkers such as ALP, *RUNX2*, OCN, and OPN, along with improved cellular microenvironments conducive to differentiation and mineralization. In particular, red and near-infrared wavelengths were frequently associated with osteogenic responses. However, these effects were not universal, as one study reported no significant change in osteogenic activity under constant red LED exposure [10]. Similarly, other wavelengths such as violet LED at 405 nm, yellow LED at 600 nm, and red LED at 630 nm did not show significant enhancement in bone formation [10, 21]. Differences in outcomes may be attributed to variations in cell types, LED source's structure and output power, wavelength, exposure duration, and the frequency. For example, although both studies employed 470 nm blue LED irradiation, significant differences in intensity and exposure duration may account for the divergent outcomes. Higuchi et al. utilized a low intensity of 1 mW/cm² over prolonged exposure periods (1–48 hours), which significantly enhanced osteoblast proliferation [10]. In contrast, Yuan et al. applied a higher intensity of 20 mW/cm² but for shorter durations (1–60 minutes), which was associated with suppressed osteoblast differentiation [23]. Differences in cell types also play a crucial role in biological responses. Specifically, Higuchi used AFSCs, while most other studies used osteoblasts or BMSCs [10]. The 405 nm violet LED, used only in Tani's study, was applied to a unique cell type, which may have contributed to the inconsistent findings [21].

These findings highlight the strong biological potential of LED-PBM in modulating bone healing at the molecular level. The healing process involves several sequential stages: inflammation, differentiation, bone formation, and remodeling [1]. During the inflammatory phase, LED irradiation can activate molecules such as reactive oxygen species (ROS) and ATP, which initiate signaling pathways and provide metabolic energy for bone repair [30]. Furthermore, LED modulates intracellular calcium levels and inflammatory mediators such as COX and NF-κB, creating a favorable environment for cell differentiation [9, 30]. In the bone formation phase, molecules such as ALP, *RUNX2*, OCN, OPN, COL1A1 and BSP were upregulated, supporting matrix mineralization and new bone formation. [18, 19, 28]. Some studies also noted regulation of signaling pathways such as MAPK and extracellular matrix enzymes like MMPs [9, 22, 25]. Notably, the upregulation of OPG suggests that LED-PBM may help inhibit bone resorption, contributing to a balanced bone remodeling process. [19]

Risk of bias assessments indicated that most in vitro studies achieved moderate to high methodological quality based on the QUIN tool, with most studies clearly stating their objectives, including appropriate control groups, describing detailed methodologies, employing systematic outcome assessments, and comprehensively reporting statistical analyses. This contributes to the overall reliability and credibility of the present systematic review. However, limitations such as the lack of blinding and insufficient control of confounding factors were noted. Similarly, in vivo studies evaluated using the SYRCLE tool showed low risk of bias in attrition and reporting domains but often had unclear risks in performance and detection bias due to inadequate reporting. These findings underscore the need for greater methodological transparency and standardization in future experimental studies.

By contextualizing molecular responses across different experimental designs, this review helps clarify previously inconsistent findings and identifies wavelength- and dose-specific biological patterns. These insights offer a molecular framework for optimizing LED-PBM protocols and transitioning toward patient-specific strategies in clinical dentistry.

Restricting the search to the PubMed and ScienceDirect databases may pose a potential risk of omitting information from other sources; however, these are the most prestigious biomedical platforms, covering the majority of leading molecular biology journals, thereby ensuring high representativeness and scientific reliability for this review. Nevertheless, to minimize publication bias, future studies are recommended to expand the search scope to a broader range of databases (such as Scopus and Cochrane).

5. CONCLUSION

This review demonstrates that LED-based photobiomodulation supports bone regeneration by modulating key molecular pathways, including the upregulation of ALP, RUNX2, OCN, OPN, and signaling

molecules like ROS, ATP, and MAPK. These findings provide a molecular basis for refining LED-PBM protocols and enhancing their clinical application in dentistry.

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