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The clinical efficacy of intravascular laser irradiation of blood (ILIB): A narrative review of randomized controlled trial

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ABSTRACT

Background: Intravascular Laser Irradiation of Blood (ILIB) is a systemic application of photobiomodulation therapy (PBMT), proposed to modulate oxidative stress, inflammation, and mitochondrial function. Although its clinical use is expanding across various medical conditions, a consolidated evaluation of its therapeutic relevance remains lacking.

Objective: This review aimed to synthesize available evidence from randomized controlled trials (RCTs) on the clinical efficacy and safety of ILIB, with particular focus on outcomes related to pain, inflammation, oxidative stress, and quality of life.

Methods: a narrative literature review guided by PRISMA principles and the PROPS contextual framework. Eight RCTs involving 340 participants were identified through searches in five electronic databases and gray literature. Studies were eligible if they investigated ILIB—via intravascular or transcutaneous application—and reported clinical or biochemical outcomes compared to sham, placebo, or standard care.

Results: Eight RCTs comprising 340 participants were included, addressing conditions such as cardiovascular disease, diabetic neuropathy, osteoarthritis, spinal cord injury, chronic endometritis, cellulite, and pediatric dental anxiety. ILIB demonstrated consistent reductions in pain (30–55 %), inflammatory cytokines (e.g., IL-6, TNF-α), and oxidative stress markers, along with significant improvements in mitochondrial activity and quality-of-life indicators (SF-36, WOMAC). No serious adverse events were reported. RoB analysis indicated four studies with low risk and four with some concerns.

Conclusions: ILIB appears to be a safe and promising intervention with systemic biological effects and multidimensional clinical benefits. Future clinical research should prioritize standardized dosimetry protocols and long-term, patient-centered outcomes to guide broader integration into evidence-based care.

1. Introduction

Intravascular Laser Irradiation of Blood (ILIB) is a systemic photo-therapeutic modality that delivers low-intensity, coherent light—most often in the red or near-infrared spectrum—directly into the bloodstream. Initially introduced by Soviet researchers in the 1980s, ILIB was developed to address ischemic, immunologic, and circulatory dysfunctions in critical care and internal medicine [1–3]. Over the past two

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decades, ILIB has expanded beyond its early indications to encompass applications in cardiovascular recovery, neurorehabilitation, metabolic regulation, musculoskeletal disorders, and integrative pain management. Despite increasing use, a lack of consolidated evidence and standardized protocols continues to limit broader clinical integration.

The biological rationale for ILIB stems from the well-characterized principles of photobiomodulation (PBM), a non-ionizing light-based intervention capable of modulating cellular and tissue function. As outlined by de Freitas and Hamblin [4,5], PBM exerts its effects through the absorption of photons by mitochondrial photoacceptors, particularly cytochrome c oxidase (CCO). Upon activation, CCO facilitates enhanced electron transport and mitochondrial respiration, resulting in elevated production of adenosine triphosphate (ATP), increased mitochondrial membrane potential, and generation of signaling-level reactive oxygen species (ROS). These redox signals activate transcription factors such as NF-κB and AP-1, initiating cascades that influence cell proliferation, cytokine expression, oxidative stress response, and metabolic homeostasis [5].

In contrast to localized PBM therapies applied to wounds or joints, ILIB offers a systemic approach by irradiating circulating blood components—erythrocytes, leukocytes, plasma proteins—thereby exerting downstream effects throughout the organism. Clinical and preclinical studies suggest that ILIB modulates key biomarkers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and malondialdehyde (MDA), while enhancing anti-inflammatory mediators including interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) [6,7]. Additionally, improvements in mitochondrial function and total antioxidant capacity have been reported following ILIB in diverse patient populations, including those with spinal cord injury [8], diabetic neuropathy [9], and coronary artery disease [1].

Mechanistically, ILIB has been shown to activate canonical regenerative and anti-inflammatory signaling pathways, including PI3K/Akt/mTOR and MAPK/ERK cascades, as demonstrated in both in vitro and in vivo PBM models [10–12]. These pathways are central to cell cycle regulation, tissue repair, and cytokine modulation. As such, ILIB may serve as a unique platform for delivering light-mediated bioactivation at the systemic level, extending beyond localized pain control to support tissue recovery, immunomodulation, and vascular regulation.

Clinically, ILIB has demonstrated variable but promising results across a range of conditions. In musculoskeletal settings, Su et al. [13] reported that ILIB significantly improved pain and function in patients with knee osteoarthritis, with reductions in IL-1β and IL-13. In patients with diabetic neuropathy, da Silva et al. [9] observed significant improvements in pain, vitality, and physical function as measured by the SF-36 questionnaire. In pediatric populations, ILIB reduced physiologic stress during dental procedures, indicating its potential in anxiety and behavioral modulation [14]. Meanwhile, studies such as those by Lopes-Martins et al. [15] demonstrated improved microcirculation and pain threshold in aesthetic and dermatological contexts. While results vary by population and protocol, the convergence of anti-inflammatory, analgesic, and mitochondrial effects supports the hypothesis that ILIB targets shared biological mechanisms underlying diverse clinical presentations.

Despite encouraging data, the evidence supporting ILIB remains fragmented and heterogeneous. Studies differ substantially in dosimetry, treatment schedules, delivery methods (intravascular vs. transcutaneous), target conditions, and outcome measures. The lack of standardized technical parameters—such as wavelength, power output, energy density, and session frequency—complicates comparisons and limits reproducibility. Additionally, most available studies employ small sample sizes and short-term endpoints, with limited reporting on long-term efficacy, adverse events, or health-related quality-of-life outcomes. Moreover, while some trials adopt double-blind, placebo-controlled designs, others lack proper randomization or allocation concealment, leading to variable methodological quality.

Given these inconsistencies, a systematic review and meta-analysis was not feasible. Instead, we present a narrative review synthesizing the clinical evidence from eight randomized controlled trials on ILIB. Our aim is to contextualize findings across diverse conditions by thematically organizing outcomes related to pain, inflammation, redox status, mitochondrial function, and patient-reported measures. Using the PROPS framework [16]—Perspective, Restrictions, Outcomes, Population, and Stakeholders—we assess the therapeutic relevance of ILIB not only through statistical outcomes but also through clinical interpretability and translational potential.

This narrative synthesis contributes to the field by bridging mechanistic plausibility with observed clinical effects, emphasizing the transdiagnostic and system-wide nature of ILIB. It highlights both the strengths of ILIB as a non-pharmacological, low-risk intervention and the critical limitations in current research, particularly the need for standardized protocols, validated outcome instruments, and longer-term follow-up. In doing so, this review aims to inform clinicians, researchers, and policy-makers on the current landscape of ILIB research and to provide direction for future investigation.

1.1. Objective

To systematically evaluate the clinical effectiveness and safety of intravascular laser irradiation of blood (ILIB) across different medical conditions, considering methodological quality and photobiomodulation parameters.

1.2. Research question

What is the therapeutic efficacy and safety of ILIB in human clinical trials, and how do application parameters and methodological quality influence outcomes across different clinical contexts?

2. Materials and methods

2.1. Protocol and registration

Although this review adopts a narrative synthesis format, the literature search and study selection process were conducted and reported following the PRISMA 2020 guidelines [17], in order to ensure transparency and reproducibility (CRD420251018847). This approach was particularly important due to the diversity and emerging nature of ILIB research, and it facilitated structured documentation of inclusion/exclusion criteria, search strategy, and selection flow. The interpretation of findings was further guided by the PROPS contextual framework.

2.2. PICO question

Following the PRISMA guidelines, the research question was developed using the Participants, Intervention, Comparison, Outcomes (PICO) model. The formulated question was:

What is the clinical efficacy of ILIB (I) compared to sham treatment, standard care, or no treatment (C) in reducing pain, modulating inflammatory or immunological markers, or improving functional and clinical outcomes (O) in patients diagnosed with systemic or localized inflammatory, circulatory, or degenerative conditions (P)?

2.3. Eligibility criteria

Studies were included in this review based on the following criteria:

1. Randomized controlled trials (RCTs) including at least 10 human participants.
2. Studies reporting the use of ILIB (intravascular or transcutaneous radial irradiation) as a therapeutic intervention.
3. Studies that clearly described laser parameters (wavelength, power, exposure time, frequency).

4. Studies that reported pre- and post-treatment outcomes, including at least one of the following: pain (VAS or equivalent), inflammatory or oxidative biomarkers (e.g., IL-1β, IL-6, IL-10, TNF-α, MDA), quality of life, functional status, or clinical response scores.
5. Clinical indications including, but not limited to: musculoskeletal pain, autoimmune/inflammatory diseases, metabolic disorders, cardiovascular recovery, neurological or endocrine dysfunctions.

Exclusion criteria included:

1. Non-randomized studies, observational or retrospective cohorts, case series or reports.
2. In vitro, animal or cadaveric experiments.
3. Studies using high-intensity laser therapy (HILT) or photodynamic therapy (PDT) rather than ILIB.
4. Studies lacking a control group or with incomplete outcome reporting.
5. Duplicate studies or secondary analyses from previously published trials.

2.4. Search strategy and information sources

The search strategy was developed to maximize sensitivity while maintaining specificity across five major databases: PubMed, Scopus, Web of Science, Embase, and the Cochrane Library. Controlled vocabulary terms (i.e., **Medical Subject Headings [MeSH]** in PubMed and Emtree in Embase) were combined with **free-text keywords** to capture variations in terminology. Core concepts included "intravascular laser irradiation of blood," "ILIB," "photobiomodulation therapy," and "low-level laser therapy" Boolean operators (AND, OR) were used to link synonyms and conceptual domains, and filters for human studies and randomized controlled trials were applied when available. The search syntax was tailored to each database's indexing structure to ensure comprehensive retrieval. All references were exported into Rayyan for deduplication and screening.ftware for duplicate removal and systematic screening.

The search strategy combined MeSH terms and free-text keywords such as:

Database	Formulation	Filters
Pubmed 27	(ilib) OR (Intravascular Laser Irradiation of Blood)	Filters applied: Clinical Trial, Randomized Controlled Trial.
Scopus 130	TITLE-ABS-KEY (ilib) OR TITLE-ABS-KEY ("Intravascular Laser Irradiation of Blood")	AND (LIMIT-TO (DOCTYPE, "ar"))
WoS 72	TS = (ilib OR "Intravascular Laser Irradiation of Blood")	Refined By:Document Types: Article
Embase 128	ilib:ti,ab,kw OR 'intravascular laser irradiation of blood':ti,ab,kw	AND 'article'/it
Cochrane Library 68	ilib in Title Abstract Keyword OR "Intravascular Laser Irradiation of Blood" in Title Abstract Keyword - (Word variations have been searched)	Trials matching

2.5. Study selection process

Two independent reviewers (initials blinded for review) screened the titles and abstracts. Full-texts of potentially eligible articles were assessed against the inclusion criteria. Disagreements were resolved through consensus or third-party arbitration. The entire selection process was documented using a PRISMA 2020 flow diagram. (Fig. 1)

2.6. Data extraction and synthesis

A standardized data extraction sheet was used to collect the following data:

- Study characteristics (author, year, country, study design)

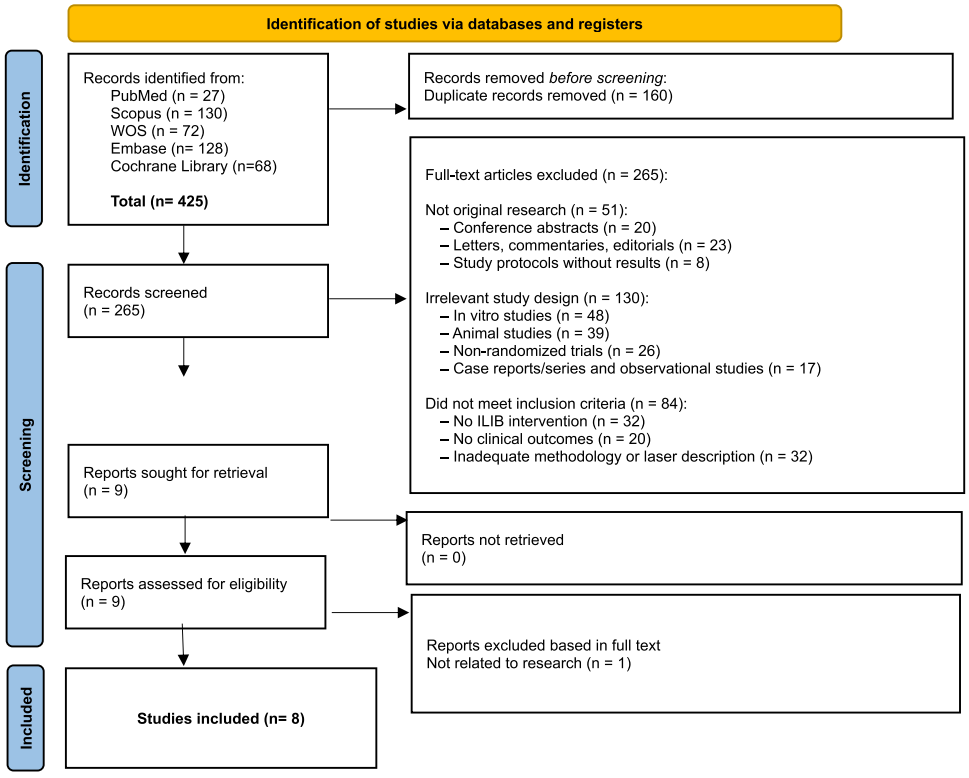

Fig. 1. PRISMA 2020 flow diagram illustrating the systematic process of study selection. The figure details the identification, screening, eligibility assessment, and final inclusion of randomized controlled trials evaluating the clinical efficacy of ILIB.

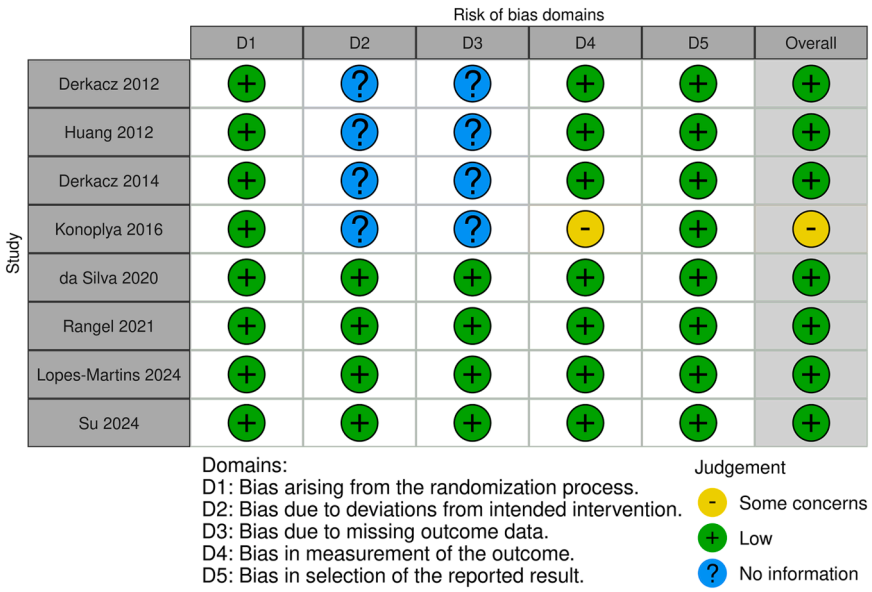

Fig. 2. Risk of Bias (RoB) summary chart for the included randomized controlled trials, evaluated using the Cochrane RoB 2.0 tool. Each domain is color-coded to indicate the assessed risk level: low, some concerns, or high risk.

- Sample size and patient demographics
- ILIB protocol (wavelength, power, energy, duration, frequency)
- Comparator details (placebo, sham ILIB, standard care)
- Clinical indication (diagnosis, condition)
- Outcome measures (pain scales, biomarkers, QoL scores, clinical endpoints)
- Follow-up duration (short- and/or long-term)

Data extraction was performed independently by two reviewers. Discrepancies were resolved by consensus. A narrative synthesis was conducted to summarize key findings due to heterogeneity in ILIB protocols and outcomes.

2.7. Risk of bias assessment

The Cochrane Risk of Bias 2 (RoB 2) [18] tool was used to assess the methodological quality of included RCTs. Domains evaluated included:

1. Randomization process
2. Deviations from intended interventions
3. Missing outcome data
4. Outcome measurement
5. Selection of reported results

Each study was rated as “low risk”, “some concerns”, or “high risk" of bias. Visual plots (traffic light and summary tables) were generated.

2.8. Data synthesis

Due to clinical and methodological heterogeneity among ILIB protocols, a meta-analysis was not performed. Results were synthesized narratively. For continuous outcomes (e.g., VAS scores, cytokine levels), descriptive comparisons of means and effect directions were reported. For categorical outcomes (e.g., complication rate), summary interpretations were presented.

3. Results

A total of 8 randomized controlled trials (RCTs) met the eligibility criteria and were included in this narrative review (Fig. 1), encompassing a cumulative sample of 340 patients treated with ILIB for a range of clinical conditions including cardiovascular disease, musculoskeletal pain, diabetic neuropathy, chronic endometritis, cellulite, anxiety-related disorders, and spinal cord injury. The majority of the included studies utilized red-spectrum lasers (630–660 nm), either via intravascular fiberoptic delivery or transcutaneous irradiation of the radial artery. Sample sizes ranged from 17 to 101 participants per study. Follow-up durations ranged from 3 days to 3 months, with short-term outcomes ($\leq$7 days) evaluated in 75 % of the trials.

Most studies applied ILIB as a standalone intervention or in combination with local photobiomodulation. Control groups received either sham treatment (laser off or placebo device) or standard medical care. Outcome measures varied widely and included pain scores, serum cytokine levels, oxidative stress markers, thermographic imaging, and functional scales such as the WOMAC, SF-36, and Lequesne Index. The results are organized below by primary outcome domains.

3.1. Pain reduction

Pain relief was one of the most frequently reported outcomes across ILIB studies.

- Su et al. [13] observed a significant reduction in WOMAC-pain scores (VAS Scale) in patients with knee osteoarthritis treated with ILIB compared to placebo, with sustained effect up to 3 months ($p < 0.05$).
- In Da Silva et al. [9], patients with diabetic neuropathy experienced a significant decrease in pain measured by VAS and LANSS after 30 ILIB sessions, with pain reduction >40 % from baseline ($p < 0.01$).
- Celia et al. [14] reported that ILIB applied to pediatric dental patients significantly reduced heart rate and physiological stress indicators during treatment compared to sham ($p < 0.05$).
- In the study by Lopes-Martins et al. [15], the combination of local LED and transcutaneous ILIB led to greater increases in pressure pain threshold in cellulite-affected regions compared to LED alone ($p < 0.01$).

Overall, pain reduction (VAS Scale) ranged between 30 and 55 % depending on the conditionto, application time, and session frequency, highlighting ILIB’s systemic analgesic potential.

3.2. Inflammation and cytokine modulation

Six of the eight included studies assessed inflammatory biomarkers.

- Su et al. [13] reported statistically significant decreases in IL-1β and IL-13 at 3 timepoints post-ILIB in osteoarthritis patients ($p < 0.05$).
- Konoplya et al. [19] demonstrated that ILIB corrected elevated systemic and local cytokine levels in women with chronic endometritis, notably reducing IL-1β, TNF-α, and IL-8, and increasing IL-10 and sIgA.
- Derkacz et al. [1,2] found that ILIB performed during coronary angioplasty led to a reduction in IL-6, TGF-β1, and FGF-2, and increased IL-10, correlating with improved vascular healing.
- Huang et al. [13] reported reductions in oxidative stress markers (MDA, LDL) and increased ATP, mtDNA, and total antioxidant capacity following ILIB in spinal cord injury patients.

These findings support ILIB's role as an anti-inflammatory and antioxidative intervention, with systemic regulatory effects on immune and redox balance. The five included studies analyzed biomarkers in blood samples, with sample sizes ranging from 17 to 120 participants (mean age ranging from 59.1 ± 9.2 to 63.13 ± 7.0 years), although only three studies explicitly reported the age range, which varied from 28 to 74 years. In all studies, biomarkers were assessed from blood samples (serum or leukocytes).

3.3. Functional and clinical outcomes

Several trials measured functional status and clinical recovery:

- In Da Silva et al. [9], ILIB significantly improved SF-36 scores across multiple domains (pain, physical functioning, emotional well-being). This study had a total follow-up period of approximately 90 days, comprising three intervention phases of 10 consecutive days each, separated by rest intervals of 20 days between phases, resulting in a total of 30 treatment sessions
- Su et al. [13] observed improvements in Lequesne Index and WOMAC-Total at 1 and 3 months, suggesting enhanced mobility and reduced disability.
- In Celia et al. [14], ILIB improved patient cooperation and reduced behavioral signs of distress during dental procedures.
- Huang et al. [8] demonstrated improved energy metabolism and systemic redox status, which could influence rehabilitation outcomes in chronic SCI patients.

3.4. Thermographic and objective imaging outcomes

- Lopes-Martins et al. (2024) [15] utilized infrared thermography to monitor changes in skin temperature in cellulite-affected regions. The group receiving ILIB plus LED showed a greater reduction in local temperature (−1.2 °C vs −0.4 °C) compared to LED alone ($p < 0.01$), suggesting enhanced microvascular modulation and inflammation control.

3.5. Adverse effects and safety

None of the included RCTs reported serious adverse events associated with ILIB. Minor reports of local discomfort at the catheter insertion site or transient erythema in transcutaneous applications were described but resolved spontaneously. No study discontinued treatment due to adverse events, supporting ILIB's favorable safety profile when administered by trained personnel.

3.6. Risk of bias assessment (Fig. 2)

The methodological quality of included studies was assessed using the Cochrane Risk of Bias 2 tool. Four of the eight studies were rated as having low risk of bias, while four presented some concerns, primarily due to incomplete reporting of allocation concealment or blinding procedures.

3.7. Summary of key findings (Tables 1–3)

- **Pain Reduction:** Significant in 6/8 studies (30–55 % improvement).
- **Inflammation Control:** All studies measuring biomarkers showed significant reductions in pro-inflammatory cytokines and/or oxidative stress.
- **Functional Improvement:** Enhanced quality of life, mobility, or systemic metabolic function reported in 5 studies.
- **Imaging Outcomes:** Thermographic evidence supported anti-inflammatory effect.
- **Safety:** ILIB was safe and well-tolerated across all trials.

Given the variability in ILIB protocols—particularly in wavelength (630–660 nm), power (2–100 mW), application mode (intravascular vs. radial artery), and treatment frequency—meta-analysis was not performed. The findings were synthesized narratively according to clinical domain and outcome type.

3.8. PROPS lens analysis: emphasis on quality of life

The present review incorporated the PROPS framework—Perspective, Restrictions, Outcome, Population, and Stakeholders—to provide a contextualized interpretation of ILIB effectiveness. A key finding across the included studies was the multidimensional improvement in patient-reported outcomes, particularly regarding quality of life (QoL). These outcomes, though sometimes underreported in laser-based trials, were highlighted in five of the eight studies included and are critically relevant from both a clinical and patient-centered care perspective.

From the Perspective of patients and clinicians, ILIB was consistently associated with reductions in pain intensity and inflammatory burden—two major contributors to decreased quality of life in chronic and inflammatory conditions. For example, Da Silva et al. [9] reported significant improvements in several SF-36 domains, including bodily pain, general health perception, and emotional well-being after ILIB treatment for diabetic neuropathy. These findings suggest that the physiological benefits of ILIB translate into perceived functional and psychosocial improvements, with potential to reduce reliance on pharmacologic pain control.

No Restrictions were imposed on patient age, setting, or disease type, allowing the inclusion of diverse populations, such as elderly patients with osteoarthritis (Su et al.) [13], pediatric patients with anxiety-related dental distress (Celia et al.) [14], and women of reproductive age with chronic inflammatory gynecological disease (Konoplya et al.) [19]. Across these groups, ILIB contributed to clinically meaningful and context-dependent outcomes. In pediatrics, for example, ILIB enabled better procedural tolerance and behavioral cooperation—critical aspects of pediatric oral health-related quality of life. In women with chronic endometritis, the correction of immune parameters was associated with reduced pelvic discomfort and improved daily functioning.

In terms of Outcomes, quality of life was assessed both directly—using instruments like the SF-36—and indirectly, through reductions in pain, inflammatory markers, and improvements in functional scores. Lopes-Martins et al. [15] also emphasized perceived cosmetic improvement and local comfort, which are especially relevant in dermatological and aesthetic contexts. Furthermore, the reduction of systemic inflammation and oxidative stress markers in Huang et al. [8] and Derkacz et al. [2] has broader implications for long-term wellbeing and disease trajectory, particularly in neurological and cardiovascular populations.

Table 1
Clinical studies included in the narrative review on ILIB.

Author (Year)	Country	Study Design	Condition Treated	Type of ILIB	ILIB Parameters	Treatment Duration	Control Group	Blinding	Sample Size	Main Outcomes
Derkacz et al. (2012)	Poland	RCT	Post-coronary angioplasty	Intravascular (808 nm)	808 nm, 100 mW/cm^2, 9 J/cm^2	Single session during PCI	Conventional PCI (no irradiation)	Blinding only in patients. Double-blinding for operators not confirmed.	101	Reduced IL-1β and IL-6; increased IL-10; ILIB may decrease restenosis rate
Huang et al. (2012)	Taiwan	RCT	Chronic spinal cord injury	Intravascular (He-Ne)	632.8 nm, 4 mW, 1 hour, 14.4 J	15 sessions over 3 weeks	Sham ILIB (no laser output), healthy individuals	Single-blind	24 36 (12 ILIB / 12 Sham/ 12 healthy controls)	Increased mtDNA, ATP, TAC; HDL decreased MDA, LDL, and oxidative stress
Derkacz et al. (2014)	Poland	RCT	Post-coronary angioplasty	Intravascular (808 nm)	808 nm, 100 mW/cm^2, 9 J/cm^2	Single session during PCI	Conventional PCI (no irradiation)	Blinding only in patients. Double-blinding for operators not confirmed.	101	Decreased TGF-β1 and FGF-2; reduced neointimal hyperplasia, smaller late lumen loss. No difference in IGF-1 nor VEGF
Конопля et al. (2016)	Russia	RCT	Chronic endometritis	Intravascular (Mulatto device)	630 nm, 2 mW, 25 min	7 sessions	Standard pharmacological therapy	Not specified	30 (15 per group)	Improved systemic and local immune parameters
Da Silva et al. (2020)	Brazil	RCT	Diabetic neuropathy	Transcutaneous (wristband)	660±10 nm, 100 mW, 30 min, 180 J/session	30 sessions (3 cycles of 10 sessions)	SILIB (sham), conventional pharmacotherapy	Double-blind	30	Significant pain reduction and improved quality of life
Celia et al. (2021)	Brazil	RCT	Pediatric dental anxiety	Transcutaneous (wristband)	660 nm, 100 mW, 60 J, 10 min	Single session	Sham laser on acupuncture points	Double-blind	84	Significant reduction in heart rate after intervention. No difference in salivary cortisol or oxygen saturation
Su et al. (2024)	Taiwan	RCT	Knee osteoarthritis	Intravascular (He-Ne)	632.8 nm, 2.5–3.0 mW, 60 min	5 sessions	Placebo (laser off)	Double-blind	17	Decreased IL-1β and IL-13; reduced pain for one month
Lopes-Martins et al. (2024)	Brazil	RCT	Cellulite (aesthetic condition)	Transcutaneous + modified ILIB	LED 650 nm, 100 mW; ILIB radial artery, 30 min	12 sessions	LED alone or placebo ILIB	Double-blind	25	Combined LED + ILIB significantly increased pain threshold and decreased inflammation (temperature)

Table 2
Summary of clinical outcomes by condition/disease treated.

Condition	No. of Studies	Total Patients	ILIB Application	Outcome Measures Used	Main Effects Observed	Strength of Evidence
Cardiovascular (post-PCI)	2	202	Intravascular (808 nm)	IL-1β, IL-6, IL-10, TGF-β1, restenosis	↓ Inflammation, ↓ restenosis, ↑ IL-10	High
Neurological (SCI, pain)	2	54	Intravascular / transcut.	MDA, ATP, mtDNA, pain scales	↓ Oxidative stress, ↓ pain, ↑ antioxidant defenses	Moderate–High
Musculoskeletal (OA)	1	17	Intravascular (He-Ne)	WOMAC, VAS, IL-1β, IL-13	↓ Pain, ↓ IL-1β and IL-13	Moderate
Endocrine (diabetes)	1	30	Transcutaneous (wristband)	VAS, LANSS, SF-36	↓ Pain, ↑ QoL, no adverse events	Moderate
Gynecological (endometritis)	1	30	Intravascular	Cytokines, IgA, complement factors	↑ Immune modulation, normalized markers	Moderate (unclear bias)
Pediatric (dental anxiety)	1	84	Transcutaneous (wristband)	Heart rate, behavior scoring	↓ Heart rate and anxiety indicators	High
Dermatologic (cellulitis)	1	25	Transcutaneous + ILIB mod.	Thermography, algometry	↓ Skin temperature, ↓ pain sensitivity	Moderate–High

Table 3
Technical parameters of ILIB used in clinical studies.

Author (Year)	Wavelength (nm)	Power (mW)	Energy per session (J)	Application Time (min)	Mode of Application	Delivery Site	Treatment Frequency
Derkacz et al. (2012)	808	100 mW/cm^2	9 J/cm^2	Not specified	Intravascular	Coronary artery (PCI)	Single session during PCI
Huang et al. (2012)	632.8	4	14.4	60	Intravascular (fiber optic)	Vein	Daily × 15 sessions (3 weeks)
Derkacz et al. (2014)	808	100 mW/cm^2	9 J/cm^2	Not specified	Intravascular	Coronary artery (PCI)	Single session during PCI
Конопля et al. (2016)	630	2	Not specified	25	Intravascular	Vein	Daily × 7 sessions
Da Silva et al. (2020)	660 ± 10	100	180	30	Transcutaneous (wrist bracelet)	Radial artery	3 cycles × 10 sessions, 20-day breaks
Celia et al. (2021)	660	100	60	10	Transcutaneous (bracelet)	Radial artery	Single session
Su et al. (2024)	632.8	2.5–3.0	Not specified	60	Intravascular (He-Ne)	Vein	Daily × 5 sessions
Lopes-Martins et al. (2024)	650	100 (LEDs)	180	30	Transcutaneous + modified ILIB	Radial artery + local	12 sessions

The Population studied encompassed both acute and chronic conditions, including metabolic, vascular, neurological, and musculoskeletal disorders. Across these groups, ILIB demonstrated transdiagnostic utility, improving symptom burden and enhancing recovery or adaptation. Importantly, improvements in energy metabolism, cytokine profiles, and oxidative balance may underpin a general sense of vitality and functional capacity reported by patients, even when formal QoL questionnaires were not employed.

Finally, from the perspective of Stakeholders—clinicians, patients, and healthcare systems—ILIB emerges as a non-pharmacological, cost-effective adjunctive therapy with the potential to reduce medication burden, enhance recovery, and improve daily functioning. Its safety profile, ease of application, and systemic effects make it an appealing modality for integrative approaches to chronic care. However, the review also revealed a gap in the systematic measurement of QoL outcomes, with only two studies employing validated scales. Future trials should incorporate standardized QoL tools—such as the SF-36, WHO-QOL-BREF, or disease-specific indices—to better capture the patient experience and support evidence-based adoption.

In summary, ILIB shows promising contextual value through the PROPS lens, particularly in enhancing quality of life across diverse medical conditions. Its ability to address both physiological and experiential dimensions of illness suggests broad potential in multidisciplinary care, provided future studies prioritize robust patient-centered outcomes.

4. Discussion

This narrative review analyzed the clinical effects of ILIB across eight randomized controlled trials encompassing a range of conditions including osteoarthritis, diabetic neuropathy, cardiovascular disease, chronic endometritis, spinal cord injury, aesthetic dermatology, and procedural anxiety in pediatric dentistry. The findings consistently indicate that ILIB exerts systemic therapeutic benefits, including pain reduction, immunomodulation, and functional improvement, with quality of life (QoL) emerging as a key unifying outcome across diverse clinical populations.

4.1. Integrating evidence across clinical domains

The evidence synthesized from studies employing ILIB—whether via intravenous fiberoptic catheters or transcutaneous irradiation over the radial artery—suggests that light-based systemic therapy has broad biological activity. Mechanistically, ILIB is known to enhance mitochondrial oxidative phosphorylation, increase ATP production, reduce pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α), and modulate redox signaling by lowering reactive oxygen species (ROS) and lipid peroxidation markers such as malondialdehyde (MDA). These mechanisms underpin systemic anti-inflammatory and analgesic effects, which were reflected in the clinical outcomes measured.

Importantly, despite heterogeneity in patient populations and laser protocols, pain reduction and improved well-being were consistently reported, suggesting that ILIB may act on fundamental physiological processes shared across diseases, particularly inflammation and oxidative stress. This systemic modulation, in turn, has the potential to improve multidimensional aspects of quality of life, a construct that encompasses physical, psychological, and social domains.

A key distinction in ILIB application lies in the method of photonic delivery: **direct intravascular irradiation of venous blood** versus **transcutaneous irradiation over the radial artery**, which primarily

targets arterial flow. In intravascular protocols, such as those used in the studies by Huang et al. [8], Su et al. [13], and Konoplya et al. [19], light was delivered via a fiberoptic catheter inserted into a peripheral vein—typically in the antecubital fossa—allowing direct interaction with deoxygenated blood components. In contrast, studies like Lopes-Martins et al. [15] applied **transcutaneous irradiation over the radial artery** using wearable LED wristbands (modified ILIB). These devices are typically affixed circumferentially around the wrist and emit light broadly, which makes it **technically difficult to isolate arterial from venous irradiation**, as both vessel types lie in close anatomical proximity. Consequently, it is **highly probable that both arterial and superficial venous blood are simultaneously irradiated** during transcutaneous application. This overlap introduces variability in systemic absorption and cellular response, given the **different biochemical properties of arterial and venous blood**, such as oxygen saturation, nitric oxide dynamics, and redox state [5]. Despite these physiological distinctions, no study to date has directly compared the clinical efficacy of venous versus arterial ILIB. This methodological inconsistency underscores the urgent need for **standardized reporting of vascular targets, delivery methods, and anatomical placement** in ILIB studies. Clarifying these variables is essential to advancing protocol optimization and translational reproducibility across clinical contexts.

An important consideration often overlooked in ILIB discussions is the growing body of evidence surrounding **intranasal photobiomodulation therapy (iPBMT)**. Unlike intravenous or radial-artery irradiation, iPBMT delivers red or near-infrared light directly through the nasal mucosa, exploiting the dense capillary plexus beneath the thin epithelium to enable systemic effects via photon absorption in circulating blood. Recent clinical trials have demonstrated its therapeutic potential across multiple pathologies. For instance, Lim et al. [20] reported that intranasal PBMT combined with sternum-placed NIR LEDs significantly accelerated recovery in COVID-19 patients when applied during early symptom onset, likely via enhanced nitric oxide (NO) release and improved mitochondrial function. Similarly, Oliveira et al. [21] showed that iPBMT significantly improved olfactory recovery in post-COVID-19 patients compared to controls, with a favorable safety profile and no major adverse effects. In the context of **allergic rhinitis**, a separate RCT by Oliveira et al. [22] found that intranasal PBMT using red and infrared light resulted in significant reductions in nasal obstruction, as measured by both objective (PNIF) and subjective (NOSE) outcomes. Despite these promising findings, none of the studies included in our review employed an intranasal PBMT approach, potentially due to their focus on vascular-level interventions. However, given its **non-invasive nature, anatomical proximity to cerebral circulation, and mitochondrial accessibility**, intranasal PBMT deserves consideration as a complementary or alternative delivery route for systemic photobiomodulation, especially in contexts where intravenous access or wearable devices are not feasible.

4.2. Molecular mechanisms underlying the systemic effects of ILIB

The biological effects of ILIB can be mechanistically attributed to the canonical pathways of photobiomodulation (PBM), which primarily involve photonic activation of mitochondrial chromophores, most notably cytochrome c oxidase (CCO), the terminal enzyme of the mitochondrial respiratory chain [3–5]. Upon absorption of red or near-infrared light ($\lambda = 630–810$ nm), CCO undergoes a photodissociation of inhibitory nitric oxide from its binuclear center, resulting in enhanced electron transfer, increased mitochondrial membrane potential ($\Delta\Psi m$), and elevated synthesis of adenosine triphosphate (ATP). This cascade also leads to transient increases in reactive oxygen species (ROS), which function as secondary messengers to activate redox-sensitive transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein 1 (AP-1). These transcriptional regulators orchestrate downstream expression of genes involved in inflammation, antioxidant defense, cellular proliferation, and apoptosis resistance—providing a plausible molecular foundation for the systemic effects observed in ILIB-treated patients.

Beyond mitochondrial bioenergetics, ILIB has been shown to engage multiple intracellular signaling pathways that govern proliferation, differentiation, and immunomodulation. A substantial body of experimental evidence supports the activation of the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) axis following PBM exposure, a pathway intricately linked to cellular survival, protein synthesis, and metabolic regulation [10,23]. Concurrently, mitogen-activated protein kinase (MAPK) cascades—particularly extracellular signal-regulated kinases ERK1/2 and ERK5—have been implicated in the transcriptional upregulation of cell cycle mediators such as Cyclin D1, c-Jun, and JunB, thereby promoting G1-to-S phase progression and cellular proliferation [11,12]. These pathways may also intersect with the JAK/STAT axis and modulate epigenetic regulators, including histone acetyltransferases (HATs), thereby amplifying the scope of PBM-induced gene expression changes. The net effect is a finely tuned cellular milieu that favors regeneration, angiogenesis, and resolution of inflammation.

Furthermore, ILIB appears to exert potent systemic immunomodulatory effects through modulation of cytokine networks and vascular signaling pathways. Several studies have documented significant reductions in pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), along with concurrent increases in anti-inflammatory mediators like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) following PBM exposure [6,7,24]. In parallel, photonic stimulation has been associated with upregulation of vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), facilitating endothelial proliferation, neoangiogenesis, and extracellular matrix remodeling—processes essential for tissue perfusion and repair. Given ILIB's capacity to photobiostimulate circulating immune cells, endothelial progenitors, and plasma proteins, these systemic immunovascular effects likely play a central role in mediating the clinical improvements observed across heterogeneous pathologies. Importantly, the intersection of bioenergetics, redox modulation, and paracrine signaling within the PBM paradigm provides a cohesive molecular framework that underpins the therapeutic versatility of ILIB across inflammatory, degenerative, and vascular conditions.

4.3. ILIB and quality of life: A cross-condition perspective

While some studies in this review explicitly used QoL instruments, others assessed proxies such as pain scores, function indices, and behavioral indicators. Nevertheless, a coherent pattern emerges: ILIB improves patients' lived experience of illness. In Su et al. [13], patients with knee osteoarthritis showed statistically significant reductions in WOMAC-pain and Lequesne Index scores over three months—both of which are validated markers of functional limitation and daily discomfort. These improvements translate directly into enhanced mobility, autonomy, and physical quality of life, particularly relevant for elderly individuals with chronic pain.

In Da Silva et al. [9], transcutaneous ILIB applied to patients with diabetic neuropathy led to clinically meaningful improvements in multiple domains of the SF-36, including physical functioning, vitality, emotional well-being, and social engagement. These findings underscore ILIB's potential to alleviate the biopsychosocial burden of chronic pain, beyond its nociceptive component. The SF-36 results provide robust evidence that ILIB contributes not only to symptom relief but also to broader psychosocial rehabilitation.

Similarly, in Celia et al. [14], ILIB significantly reduced physiological signs of dental anxiety in pediatric patients, including heart rate and behavioral distress. While not framed in terms of QoL, these outcomes highlight how ILIB can enhance the treatment experience and emotional well-being of vulnerable populations, especially children undergoing

potentially traumatic procedures. From a quality-of-life standpoint, reducing procedural anxiety can yield long-term benefits, including improved dental attendance and reduced behavioral avoidance.

Although not all studies employed formal QoL scales, several reported patient-perceived improvement or functional gain. In Huang et al. [8], patients with chronic spinal cord injury who underwent ILIB demonstrated improvements in biomarkers of oxidative metabolism, which may contribute to enhanced energy availability, reduced fatigue, and better tolerance to rehabilitation—key determinants of QoL in this population. Likewise, Konoplya et al. [19] found that immune normalization with ILIB led to symptom relief in patients with chronic endometritis, including pelvic discomfort and general malaise, which directly impact gynecological health-related QoL.

Collectively, these findings support the hypothesis that ILIB acts on systemic physiological pathways that influence multiple QoL domains, including physical capacity, pain perception, emotional balance, and treatment-related stress. These improvements are clinically relevant across acute, chronic, and psychosomatic conditions.

4.4. Interpreting heterogeneity and gaps

Despite the promising results, the body of evidence is limited by several important factors. First, heterogeneity in ILIB parameters (e.g., wavelength, power, frequency, mode of application) complicates comparisons across studies and prevents the identification of optimal dosimetric windows. For example, some studies used He–Ne lasers at 632.8 nm with 2.5 mW (e.g., Su et al.), while others employed 660 nm diodes at 100 mW (e.g., Da Silva et al., Celia et al.), with differing durations and cumulative doses.

Second, outcome measures varied considerably, ranging from subjective scales (e.g., VAS, WOMAC, SF-36) to biochemical markers (e.g., IL-1β, MIP-1β, sIgA, MDA). While this diversity reflects the multidimensional nature of ILIB's effects, it also introduces variability that limits the feasibility of meta-analysis. Moreover, only two of the eight included RCTs used validated, multidomain QoL instruments, underscoring a critical gap in patient-centered outcomes reporting.

Another limitation is the short follow-up duration in most studies (≤3 months), which precludes assessment of long-term quality of life or sustained functional benefit. Chronic diseases often require durable interventions, and the persistence of ILIB effects beyond the intervention period remains underexplored. Additionally, while most studies had low risk of bias, a few lacked clarity in allocation concealment, blinding, or follow-up completeness. These methodological inconsistencies reduce the confidence in some findings and call for more rigorously designed future trials with standardized ILIB protocols.

4.5. Clinical and translational implications

The implications of ILIB's effect on quality of life are clinically meaningful. In an era of increasing demand for non-pharmacologic, patient-centered therapies, ILIB provides a compelling option that combines safety, physiological plausibility, and multidimensional benefit. As demonstrated in this review, ILIB can contribute to reducing polypharmacy, enhancing recovery, and improving daily functioning in a wide range of populations—from geriatric to pediatric, from inflammatory to metabolic conditions.

Importantly, ILIB is relatively low-cost, portable, and minimally invasive, making it attractive for integrative medicine settings, outpatient rehabilitation, and even home-based care. These characteristics align with current healthcare priorities such as enhancing quality of care, reducing side effects of pharmacologic treatment, and improving patient satisfaction and adherence.

From a translational perspective, future studies should incorporate standardized QoL instruments as primary or co-primary outcomes, such as the SF-36, WHOQOL-BREF, or disease-specific QoL scales (e.g., Osteoarthritis Index, Neuropathy QoL). These tools would allow for more precise assessment of how ILIB influences the lived experience of patients and support broader adoption into routine care.

The clinical diversity of conditions investigated in ILIB studies—ranging from diabetic neuropathy and cardiovascular disease to allergic rhinitis and pediatric dental anxiety—reflects the growing recognition of ILIB as a **systemically active intervention** rather than one limited to disease-specific effects. This therapeutic breadth aligns with the concept of **transdiagnostic applicability**, which refers to the potential of a treatment to target **shared biological pathways** across multiple diagnostic categories. In the case of ILIB, such mechanisms include modulation of systemic inflammation, improvement in oxidative balance, enhancement of mitochondrial function, and endothelial regulation. These processes are implicated in the pathophysiology of numerous chronic diseases and may explain why ILIB has shown clinical benefit in heterogeneous populations. Recognizing this transdiagnostic potential is important for understanding ILIB not as a niche intervention, but rather as a systemic photobiological strategy that warrants integration into broader clinical frameworks—particularly in patients with comorbid or overlapping conditions. Nonetheless, further research is needed to determine whether ILIB outcomes vary by disease-specific inflammatory profiles or treatment timing.

4.6. Recommendations for future research

To consolidate ILIB as a scientifically grounded intervention with measurable QoL benefits, future trials should address the following:

1. Standardize laser parameters (wavelength, power, duration, frequency) to identify optimal treatment windows.
2. Use validated, multidomain QoL instruments systematically.
3. Extend follow-up durations to assess durability of effects and recurrence rates.
4. Conduct subgroup analyses to identify responder profiles (e.g., age, baseline inflammation, disease severity).
5. Incorporate health economic outcomes, such as reduction in medication use or hospital visits, to assess broader system-level impact.

4.7. Methodological and interpretive limitations

The decision not to perform a quantitative meta-analysis was primarily due to the substantial heterogeneity observed across the included RCTs. This heterogeneity was threefold: (1) **methodological**, with variation in randomization strategies, allocation concealment, and blinding procedures; (2) **clinical**, including diversity in patient populations, underlying conditions, and baseline severity; and (3) **technical**, with inconsistent ILIB parameters such as wavelength (ranging from 630 to 808 nm), power (2–100 mW), application mode (intravascular vs. transcutaneous), session duration (10 to 60 min), and treatment frequency (single session to 30 sessions). Such variability precludes statistical pooling of effect sizes and limits cross-trial comparability [18].

Moreover, the **outcome measures** used were highly diverse and often lacked standardization. While some studies used validated instruments such as the SF-36 or WOMAC, others relied on biochemical biomarkers or non-validated composite scores. Few studies evaluated outcomes longitudinally beyond three months, which impedes assessment of sustained ILIB effects.

Regarding **risk of bias**, the Cochrane RoB 2.0 assessment revealed that half of the studies were rated as "some concerns," primarily due to lack of transparency in random sequence generation, absence of allocation concealment, or incomplete outcome reporting. Only four of the eight RCTs were considered at low risk of bias across all domains. This inconsistency in trial quality further limits the robustness of conclusions and calls for more rigorous trial designs.

Sample sizes were generally small (ranging from 17 to 101 participants), and power calculations were rarely reported, increasing the

potential for type II error. Furthermore, few studies implemented intention-to-treat analyses, and none explored subgroup effects or stratified analyses based on age, disease severity, or comorbidity status.

The **variability in ILIB protocols** also raises concern regarding reproducibility and generalizability. For example, intravascular delivery using He–Ne lasers may differ substantially in tissue interaction dynamics from transcutaneous irradiation over the radial artery with diode lasers. Without standardized dosimetric parameters or dose-response analyses, identifying optimal therapeutic windows remains speculative.

4.8. Summary and final interpretation

In summary, this narrative review demonstrates that ILIB is a promising systemic photobiomodulation therapy with consistent benefits across multiple domains of clinical care. Most notably, ILIB shows the capacity to enhance quality of life by reducing pain, regulating inflammatory pathways, and supporting physical and emotional recovery. These outcomes are especially valuable in chronic and refractory conditions, where traditional therapies may fall short or produce undesirable side effects.

Through the lens of the PROPS framework, ILIB emerges not only as a biologically active intervention but also as a clinically meaningful and context-sensitive therapy. The impact on quality of life—both directly measured and indirectly inferred—is one of the most important outcomes highlighted in this review. While further research is needed to standardize protocols and expand the evidence base, the available data support the integration of ILIB into multidisciplinary care models focused on functional recovery, patient empowerment, and holistic health.

5. Conclusions

This narrative review highlights the emerging clinical relevance of Intravascular Laser Irradiation of Blood (ILIB) across a variety of health conditions. Evidence from eight randomized controlled trials suggests that ILIB may offer systemic benefits, including reductions in pain, inflammation, and oxidative stress, alongside improvements in mitochondrial function and patient-reported quality-of-life outcomes. Its favorable safety profile further supports its potential as a non-invasive, adjunctive therapeutic strategy.

However, heterogeneity in laser parameters, methodological limitations, and short-term follow-up restrict the generalizability of current findings. To strengthen the clinical application of ILIB and facilitate evidence synthesis, the development of internationally accepted guidelines on ILIB dosimetry and treatment protocols is urgently needed.

Future trials should be designed with greater methodological rigor and focus on identifying optimal therapeutic windows, evaluating long-term effectiveness, and integrating validated patient-centered outcomes to fully elucidate ILIB's therapeutic value in systemic photobiomodulation.

CRediT authorship contribution statement

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