

Review

# High-Intensity vs. High-Power Laser Therapy: Biophysical Implications of a Semantic Ambiguity and the Distinct Role of Photoacoustic Effects

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## Abstract

Words matter in science, particularly when they define technologies with distinct biological mechanisms. High-Intensity Laser Therapy (HILT) is often conflated with High-Power Laser Therapy or High-Level Laser Therapy (HPLT/HLLT), despite these terms referring to laser systems with fundamentally different physical properties and therapeutic effects. While many therapeutic lasers can elicit photochemical and photothermal effects, only devices delivering high-peak, short-duration pulses at very low duty cycles are able to generate acoustic pressure waves, which are characteristic of true HILT systems. These photoacoustic effects uniquely activate mechanotransduction pathways involved in cellular differentiation, extracellular matrix remodeling, and long-term tissue regeneration. This review highlights the widespread misclassification in the laser therapy literature, where devices lacking genuine photoacoustic capabilities are often incorrectly described as HILT. Such semantic ambiguity not only undermines biological specificity, but also inflates clinical claims, misleading practitioners, and obscures the comparative interpretation of clinical studies. Within the laser science community, it is widely recognized that average power alone is insufficient to characterize a therapeutic mechanism of laser therapies, as it does not provide insight into ability to generate pressure waves. To resolve these issues, we propose a mechanism-based classification that clearly distinguishes photochemical, photothermal, and photoacoustic effects. We further provide a quantitative comparison showing that systems delivering the same total energy produce peak parameters that differ by orders of magnitude depending on duty-cycle architecture, reinforcing the need for mechanism-based classification. We also advocate for greater rigor in reporting technical parameters such as peak power, pulse duration, and duty cycle. By ensuring proper terminology and transparent reporting, this framework will advance scientific rigor, facilitate accurate comparisons across studies, and improve the clinical application of regenerative medicine therapies.

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## 1. Introduction

Therapeutic laser applications have evolved substantially over the past five decades. To provide a coherent framework for this introduction, we first present a brief historical overview of the foundational discoveries by Mester, Karu, and others, which established the biological premises of laser-mediated stimulation. This contextual background is followed by a clarification of the physical quantities that govern laser emission—namely power, intensity, peak values, and duty cycle—which are essential to properly interpret the different operational regimes of therapeutic devices. We then offer a standalone description of the three canonical mechanisms of laser–tissue interaction (photochemical, photothermal, and photoacoustic), which represent the mechanistic basis for understanding their biological effects. Building on these foundations, we examine the semantic ambiguity that has developed around the term “High-Intensity Laser Therapy” (HILT), clarifying its intended meaning and the inconsistencies present in current literature. Finally, we argue for the necessity of a mechanism-based redefinition of HILT, which motivates the present review and sets the stage for the analyses that follow.

The first evidence of biological effects induced by low-level laser irradiation was reported in 1967 by Hungarian physician Dr. Endre Mester [1] at Semmelweis Medical University. His experiment aimed to replicate earlier work by McGuff [2] in Boston, who had used high-power ruby lasers (694 nm) to treat malignant tumors in both animal models and human patients. However, Mester’s ruby laser possessed only a small fraction of McGuff’s power output. While he did not reproduce the antitumor effect, he unexpectedly observed accelerated hair regrowth in the treated group of mice, which had been shaved and surgically implanted with tumor tissue. This observation, later expanded through studies using helium–neon (HeNe) lasers (632.8 nm) on wound healing in both animals and clinical settings, gave rise to the concept of “laser biostimulation”—a phenomenon describing the ability of light to promote tissue repair without inducing thermal damage or ablation.

Initially, coherence was thought essential to these effects, but later research demonstrated that non-coherent light sources such as LEDs could produce similar outcomes. This shifted attention from light delivery properties to the biological pathways activated by wavelength, fluence, and dosing parameters, laying the foundation for what later became known as low-level photobiomodulatory approaches.

In the following decades, research on low-intensity light stimulation expanded, focusing on underlying mechanisms and clinical applications [3]. A key milestone was the work of Tina Karu [4], who identified Cytochrome C oxidase (COX) as a mitochondrial chromophore for red and near-infrared light. Photon absorption by COX enhanced adenosine triphosphate ATP production, modulated cellular redox states, and influenced the release of nitric oxide (NO) and reactive oxygen species (ROS). These findings provided a molecular basis for light-induced photochemical effects and confirmed their ability to influence biological activity without significant temperature increases.

These insights translated into clinical use of low-power lasers and LEDs, typically delivering energy densities of a few J/cm<sup>2</sup>, for conditions such as soft tissue injuries, chronic inflammation, peripheral neuropathies, and delayed wound healing [5,6].

Concurrently, standardization efforts led by Jan Tunér and Lars Hode [7] emphasized key parameters like wavelength, fluence, pulse structure, irradiation time, and tissue type. These contributed to early classifications distinguishing Low-Level Laser Therapy (LLLT) (or Photobiomodulation, PBM), associated with photochemical stimulation, from High-Power Laser Therapy (HPLT) [8], often used for thermal effects and ablation.

In this review, we prefer to use Low-Level Laser Therapy (LLLT) as the primary designation for photobiomodulation-based interventions relying exclusively on photochemical effects. According to recent consensus statements, LLLT and Photobiomodulation

(PBM) are considered interchangeable terms, with PBM preferred in European regulatory contexts and LLLT still widely used in the U.S. and throughout the historical laser-therapy literature. To preserve continuity with the traditional framework contrasting LLLT with High-Power and High-Intensity Laser Therapy, LLLT is used as the main term, with “PBM” specified at first occurrence as an accepted synonym.

However, the growing use of pulsed laser sources capable of generating photoacoustic responses highlighted the limitations of this binary classification, a conceptual evolution later formalized by Fortuna and Masotti [9]. It is worth noting that the terms “photoacoustic” and “optoacoustic” are often used interchangeably in the biomedical optics literature to describe pressure waves generated through thermoelastic expansion following pulsed laser irradiation. In this manuscript, we adopt the term “photoacoustic” consistently to avoid terminological ambiguity.

The following sections first clarify the fundamental physical quantities that govern laser emission, then present a standalone overview of the three canonical laser–tissue interaction mechanisms. Building on these foundations, we examine the semantic ambiguity surrounding the term HILT and finally propose a mechanism-based framework to classify therapeutic laser systems.

### 1.1. Fundamentals of Laser Emission and Dosimetric Quantities

Laser–tissue interaction depends critically on how optical energy is distributed in time and space. Several physical quantities—sometimes used loosely in the clinical literature—must be clearly distinguished to avoid conceptual ambiguity.

Power (P) represents the rate of energy delivery (W). In pulsed lasers, two forms are relevant:

- Average power  $P_{\text{avg}}$ : Time-averaged emission of the device.
- Peak power  $P_{\text{peak}}$ : The instantaneous power during a single pulse, given by

$$P_{\text{peak}} = \frac{E_{\text{pulse}}}{\Delta t},$$

where  $E_{\text{pulse}}$  is the pulse energy and  $\Delta t$  the pulse duration.

Intensity (or irradiance,  $I$ , W/cm<sup>2</sup>) describes how power is spatially distributed:

$$I = \frac{P}{A}$$

Consequently, peak intensity depends on  $P_{\text{peak}}$ , while average intensity depends on  $P_{\text{avg}}$ .

A key parameter linking peak and average power is the duty cycle (DC):

$$DC = \frac{t_{\text{on}}}{T}$$

$$DC = \frac{t_{\text{on}}}{t_{\text{on}} + t_{\text{off}}}$$

where

- $t_{\text{on}}$  is the pulse-on time (the interval during which the laser emits);
- $t_{\text{off}}$  is the pulse-off time (the interval between two consecutive pulses);
- $T = t_{\text{on}} + t_{\text{off}}$  is the duration of one full cycle.

When the pulse train is strictly periodic, this expression is equivalent to

$$DC = t_{\text{on}} \cdot f$$

with  $f$  being the pulse repetition frequency.

Very small duty cycles produce high peak power even at modest average power, whereas large duty cycles produce high average power but comparatively low peak power.

This framework clarifies the physical distinction between High-Intensity Laser Therapy (HILT) and High-Power Laser Therapy (HPLT).

Devices classified as HILT typically operate with very low duty cycles ( $DC \approx 0.01\text{--}1\%$ ), using pulse durations in the tens to hundreds of microseconds delivered at low repetition rates. Such configurations yield high peak power and therefore very high peak intensity, conditions that favor photoacoustic (photomechanical) effects caused by transient thermoelastic expansion.

In contrast, HPLT devices generally operate with duty cycles one to four orders of magnitude higher ( $DC \approx 10\text{--}100\%$ ), often in quasi-continuous or long-pulse regimes. This yields high average power, but peak power—and thus peak intensity—remains far below the threshold required to produce photoacoustic pressure waves. Under these conditions, the dominant mechanism is photothermal, not photomechanical.

Thus, in the context of therapeutic laser applications, “high-intensity” physically corresponds to high peak intensity resulting from high peak power, whereas “high-power” refers to high average power delivered with a large duty cycle. Recognizing this relationship resolves the linguistic ambiguity that has developed historically in the photobiomodulation literature and aligns terminology with the underlying biophysical mechanisms.

## 1.2. Biological Mechanisms of Laser-Tissue Interaction

### 1.2.1. Photochemical Interactions: Mitochondrial Activation and Cellular Biostimulation

Photochemical mechanisms form the foundation of traditional Low-Level Laser Therapy (LLLT) which represents the canonical photochemical mode of action in therapeutic laser applications. In this regime, low-power laser light, typically in the red or near-infrared spectrum (600–1000 nm), is absorbed by intracellular chromophores, most notably Cytochrome C oxidase (COX), a key enzyme in the mitochondrial electron transport chain. This photon absorption enhances mitochondrial membrane potential, accelerates ATP synthesis, and modulates the production of nitric oxide (NO) and reactive oxygen species (ROS), thereby influencing key cellular pathways related to metabolism, inflammation, and proliferation (Karu [4]). In addition to Cytochrome C Oxidase (COX), which is the primary chromophore involved in photobiomodulation, other chromophores, such as porphyrins, flavoproteins, and cytochromes outside of COX, also play significant roles in cellular responses to laser irradiation. These chromophores contribute to various photochemical effects depending on the specific wavelength and parameters of the laser used. However, due to the dominant role of COX in mitochondrial activation and redox modulation, it has been the focus of this review, while other chromophores are acknowledged as secondary contributors in the broader mechanism of action.

A comprehensive review by Ohsugi et al. [10] demonstrated that such photochemical stimulation promotes favorable biological responses across a range of oral-related cell types, including epithelial cells, fibroblasts, osteoblasts, osteoclasts, endothelial cells, and mesenchymal stem cells. In particular, laser settings in the range of 1–10 J/cm<sup>2</sup> were shown to significantly increase proliferation, wound closure, and the expression of genes linked to tissue repair and regeneration, such as ALP, Runx2, BMP-2, and TGF- $\beta$ 1. These effects were dose- and time-dependent, often peaking between 24 and 72 h post-irradiation. However, the authors also noted that higher energy densities (>20 J/cm<sup>2</sup>) could lead to cytotoxic effects or oxidative stress, underscoring the importance of optimized dosimetry.

This dose-dependent response was further confirmed by Sleep et al. [11], who used a multi-wavelength LED array (700, 850, and 980 nm) in osteoblast cultures. Moderate energy densities (5.3 J/cm<sup>2</sup>) effectively stimulated mitochondrial respiration and upregulated osteogenic genes such as RUNX2, COL-1, and BMP-2, while prolonged or repeated exposure to higher doses (10.6 J/cm<sup>2</sup>) led to a suppression of these beneficial effects. This biphasic behavior suggests that without additional biomechanical stimuli, excessive

photonic energy may hinder rather than enhance therapeutic outcomes. Photochemical LLLT (PBM) also modulates inflammatory processes by inducing antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase, and by stimulating the production of growth factors like platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF- $\beta$ ). These mediators play a central role in fibroblast migration, collagen synthesis, wound healing, and inflammatory disease management such as periodontitis.

In the context of gene therapy, a systematic review by Hosseinpour and Walsh [12] identified photochemical internalization as a critical enhancer of nucleic acid transfection. This mechanism involves the light-induced disruption of endosomal membranes, allowing nucleic acids to escape into the cytosol and reach their molecular targets. Although less efficient than photoacoustic methods, photochemical LLLT still offers a favorable safety profile and non-invasive strategy for gene delivery and cellular reprogramming.

The depth of penetration for photochemical effects is limited (due to the optical absorption of the biological tissues), typically between 0.3 and 0.8 cm, making these interactions most suitable for superficial tissues or anatomically thin structures such as the oral mucosa, periodontal ligament, and small joints. Despite these limitations, the therapeutic scope of photochemical LLLT spans soft tissue repair, chronic inflammation management, periodontal therapy, and regenerative medicine.

Taken together, these findings confirm that photochemical mechanisms, although limited in penetration depth, offer a powerful, mitochondria-mediated pathway for metabolic activation, tissue repair, and inflammation control. When carefully dosed, they provide a cornerstone for LLLT applications, particularly in superficial and chronic conditions. However, when used in combination with photothermal and photoacoustic mechanisms, as in true HILT protocols, these effects can be further amplified to support deeper and more complex tissue regeneration.

### 1.2.2. Photothermal Interaction: Heat-Induced Modulation of Tissue Physiology

Photothermal mechanisms involve the conversion of absorbed light into heat. Depending on energy delivery and tissue optical properties, temperature may rise by 2–6 °C, promoting vasodilation, increased circulation, collagen remodeling, muscle relaxation, and transient inhibition of nerve conduction (Orchardson et al. [13]; Zhang et al. [14]; Cronshaw et al. [15]). These effects are especially valuable in pain therapy, analgesia, dentinal hypersensitivity, myorelaxation, and rehabilitation. However, excessive thermal buildup may cause inflammation, protein denaturation, or delayed healing, particularly in the absence of appropriate pulse modulation or cooling.

Photothermal effects are generally produced by continuous-wave or quasi-continuous systems operating in the near-infrared range (800–1064 nm) at power levels above 1 W. Cronshaw et al. [15] demonstrated that among several wavelengths tested on porcine muscle, 980 nm light induced the highest thermal effect, particularly when applied statically or with Gaussian beam profiles. In contrast, scanning modes and flat-top applicators limited temperature rise, highlighting the relevance of beam geometry and movement technique in safe energy delivery.

From a molecular perspective, photothermal stimulation modulates inflammation through TRPV ion channels and heat shock proteins (HSPs), particularly HSP70 and HSP47. These proteins regulate stress responses, collagen folding, and immune signaling. HSP47 facilitates proper collagen assembly, while HSP70 enhances cell survival and tissue recovery. Zhang et al. [14] further reported that photothermal effects stabilize the extracellular matrix and promote regeneration via the PI3K/AKT/mTOR and ERK/MAPK pathways.

Orchardson et al. [13] showed that transient axonal depolarization induced by controlled heat could block peripheral nerve conduction, explaining the localized analgesic effect observed with high-intensity stimulation. This nerve modulation occurs without structural damage, offering a non-invasive modality for acute and chronic pain management.

Alayat et al. [16] observed improved joint mobility and pain reduction in temporomandibular joint dysfunction following HILT due to the combined vasodilatory and muscle-relaxant effects of photothermal mechanisms. Mild hyperthermia ( $\approx 39\text{--}43\text{ }^{\circ}\text{C}$ ) induces HSP-mediated activation of dendritic cells and macrophages, enhancing antigen presentation and downstream T-cell responses [17].

Nevertheless, exceeding thermal thresholds (typically  $>45\text{ }^{\circ}\text{C}$ ) can impair mitochondrial function, denature proteins, and cause tissue injury. Therefore, precise control over pulse duration, duty cycle, and total exposure is crucial to optimize therapeutic effects while avoiding adverse outcomes. HILT systems help achieve this balance through low duty cycles (0.05–1%) and long thermal relaxation intervals, allowing high peak powers without cumulative overheating.

Photothermal effects typically penetrate to depths of 1–1.5 cm depending on tissue composition and vascularization. Their utility spans from localized pain relief to enhancement of microcirculation, angiogenesis, and fascial release. While not sufficient alone for deep regenerative activation, their synergy with photochemical and photoacoustic stimuli in HILT contributes significantly to therapeutic success.

In summary, photothermal mechanism offers a powerful but nuanced approach to tissue modulation. Its biological efficacy depends on fine-tuned parameters and appropriate delivery, reinforcing the need for accurate laser classification and personalized treatment planning.

### 1.2.3. Photoacoustic Interactions: Mechanical Stimulation and Regenerative Signaling

A key distinction of HILT lies in its photoacoustic effects, where high-energy pulses generate acoustic pressure waves that propagate deep into tissues, activating mechanotransduction pathways critical for cellular function. Tarantino et al. [18] demonstrated that these effects trigger the tyrosine kinase (TK) pathway, regulating cellular proliferation, extracellular matrix (ECM) remodeling, and inflammation control. Remarkably, even when the TK pathway was pharmacologically inhibited, HILT restored cellular proliferation and reactivated anabolic processes, underscoring its capability to counteract degenerative conditions such as fibrosis and chronic inflammation.

Monici et al. [19] and Cialdai and Monici [20] provided further insights into HILT-induced cytoskeletal remodeling, showing that pulsed Nd:YAG lasers reorganize microtubules and intermediate filaments while enhancing integrin-mediated ECM interactions. These changes optimize cellular adhesion, improve tissue resilience, and stimulate ECM synthesis. Research also confirms that photoacoustic stimulation significantly boosts collagen and glycosaminoglycan production, reinforcing tissue structural integrity.

Studies by Monici [19], Cialdai and Monici [20], Bosco [21], Cheng et al. [22], De Cesari et al. [23], and Genchi et al. [24] have demonstrated that biological responses to mechanical stimulation can be triggered by increases in gravitational acceleration as low as 1 g in centrifuge-based hypergravity models, and become significantly more pronounced at 10–80 g, which represent the range of mechanical loads typically used to induce cytoskeletal and ECM remodeling. Notably, De Cesari et al. [23] found that exposure to accelerations  $\geq 4\text{ g}$  significantly enhances angiogenesis, cellular motility, and ECM organization. Similarly, Genchi et al. [24] showed that extreme hypergravity levels (up to 150 g) accelerate neurogenesis and neurite outgrowth, highlighting the importance of mechanical loading in neuronal differentiation.

Although centrifugal hypergravity and laser-induced photoacoustic transients are fundamentally different physical phenomena—one based on sustained acceleration fields ( $g$ ) and the other on microsecond thermoelastic pressure waves (kPa)—both stimulate cells through mechanical loading. In both models, the imposed mechanical forces activate similar mechanosensitive pathways, including cytoskeletal remodeling, integrin clustering, and downstream signaling cascades involved in tissue adaptation.

Preclinical and clinical studies further validate these findings. Fortuna et al. [25,26] demonstrated significant cartilage regeneration and ECM organization improvements in models of osteoarthritis and in severe tendonitis of horses [27], while Zati et al. [28] confirmed these effects in human clinical trials, underscoring HILT potential as a non-invasive alternative for cartilage repair.

HILT photoacoustic effects also promote fibrocyte-to-fibroblast differentiation [29,30], a critical process in tissue repair. By activating mechanotransductive pathways, HILT enhances cellular metabolism and ECM deposition, supporting functional tissue regeneration. HILT-generated photoacoustic waves induce transient mechanical stresses in the kilopascal range, which are known to activate mechanosensitive signaling cascades. Although these stresses differ physically from the continuous acceleration fields used in centrifuge-based hypergravity studies, both models impose mechanical stimuli capable of modulating cytoskeletal organization, enhancing cell motility, and influencing differentiation pathways, as reported in hypergravity research [19–24].

The ability of HILT to generate such mechanical waves depends on key parameters such as pulse energy, tissue absorption coefficients, and duty cycle. The most precise method for quantifying pressure wave generation is the Margheri [31] equation, which offers a detailed analytical model for estimating pressure amplitude. However, due to its complexity, its use in clinical settings is limited. Earlier calculations by Fortuna and Masotti [9] used the PIF model in aqueous media at 27 °C to simulate *in vitro* conditions. In contrast, as noted by Salomatina et al. [32], biological tissues possess significantly higher absorption coefficients, suggesting that actual *in vivo* pressure amplitudes are likely an order of magnitude greater—thus amplifying the mechanical stimuli delivered during clinical HILT treatments.

Because photoacoustic mechanisms operate independently of thermal accumulation, their effects can penetrate 3–5 cm into tissue, making them particularly advantageous for non-invasive interventions in orthopedics, dentistry, sports medicine, and soft tissue regeneration. This unique depth of action and mechano-transductive profile clearly distinguish photoacoustic stimulation from photochemical and photothermal effects, positioning it as a safe and potent mechanism within modern regenerative therapy.

#### 1.2.4. Mechanistic Overlap and Therapeutic Implications

Although photochemical, photothermal, and photoacoustic interactions are often described as distinct categories, they are not mutually exclusive. In practice, a given laser device may elicit more than one mechanism simultaneously, depending on its architecture and on how energy is delivered to the tissue. The relative contribution of each mechanism is governed by parameters such as pulse duration, peak power, energy per pulse, repetition rate, mean power, and duty cycle.

Each mechanism affects tissue through different physical pathways and reaches different depths, but their biological actions may combine in a complementary or synergistic manner. Photochemical effects primarily modulate mitochondrial and redox pathways; photothermal effects influence perfusion, collagen remodeling, and nociceptive modulation; photoacoustic effects activate mechanotransduction signaling and extracellular matrix reorganization through transient pressure waves.

From a functional standpoint, this mechanistic continuum allows therapeutic laser systems to be categorized according to the dominant or combined interactions they are capable of producing:

- Single-effect systems (LLLT): Predominantly photochemical;
- Dual-effect systems (HPLT): Photochemical + photothermal;
- Triple-effect systems (HILT): Photochemical + photothermal + photoacoustic.

This framework highlights that output power alone does not predict the biological outcome of laser irradiation. Instead, pulse architecture—particularly peak power, pulse duration, and duty cycle—is the key determinant of whether photochemical, photothermal, and photoacoustic mechanisms can coexist.

The following table summarizes the characteristic triggers, primary effects, depth of action, and typical power ranges associated with each mechanism (Table 1).

**Table 1.** Photoacoustic stimulation, unique to true HILT, requires high-peak-power pulses despite low average power. ↑ Indicates increased activity or upregulation.

Mechanism	Trigger	Primary Effect	Depth [cm]	Mean Power [W]	Typical Device Parameters	Clinical Use
Photochemical	Photon absorption (COX)	ATP ↑, ROS/NO modulation	0.3–0.8	0.5	High-duty-cycle (DC: 10–100%), low avg. power (0.5 W), very low peak power (1 W),	LLLT, chronic wounds, neuropathies
Photothermal	Heat conversion	Perfusion ↑, collagen remodeling	<1.5	<10	High-duty-cycle (DC: 10–100%), high avg. power (<10 W), low peak power (<50 W),	Pain relief, muscle relaxation
Photoacoustic	Acoustic wave (kW pulse)	Mechano-transduction, ECM remodeling	<3	<10	Low-duty-cycle (DC: 0.01–1%), high avg. power (<10 W), very high peak power (1–2 kW),	HILT, TMJ, bone/cartilage regeneration

### 1.3. Semantic Ambiguity of the Term HILT

This binary model proved inadequate. Professor Leonardo Masotti, founder of El.En. Group and professor at the University of Florence, in 1996 introduced the term High-Intensity Laser Therapy (HILT) to define a distinct modality based on photoacoustic effects. The key parameter was not average power, while intensity, specifically, high-peak-power pulses (kilowatt range) delivered in short durations (tens to hundreds of microseconds), at low frequencies (5–30 Hz) and extremely low duty cycles (0.05–1%). This configuration enables high-energy delivery per pulse and the generation of acoustic pressure waves in tissue, thereby activating mechanosensitive pathways.

To further formalize this concept, Fortuna and Masotti [9] proposed the PIF (Peak Intensity Fluence), a mathematical model integrating pulse energy, duration, and frequency to distinguish true HILT devices from systems that produce only photochemical or photothermal effects. This distinction is essential: continuous-wave or quasi-continuous high-power lasers may exceed power thresholds but lack the capacity to induce photoacoustic waves. Misclassification of such devices as HILT risks conflating mechanisms and producing inconsistent clinical or scientific outcomes.

### 1.4. Toward a Mechanism-Based Redefinition of HILT

Recent *in vitro* investigations further refined our understanding of how different laser parameters modulate cellular responses. A review by Ohsugi et al. [10] summarized how oral-related cells—epithelial, fibroblasts, osteocytes, osteoclasts, endothelial, and mesenchymal stem cells—respond differently depending on laser settings. For instance, diode lasers (810–910 nm) enhanced epithelial proliferation via MAPK/ERK and reduced pro-inflammatory cytokines in carcinoma cells. Gingival fibroblasts showed increased

viability and decreased COX-2/PGE2 expression via Akt and JNK. Osteocytes and osteoclasts exhibited reduced sclerostin and increased osteogenic markers.

Parallel research by Hosseinpour and Walsh [12] reviewed 49 studies on laser-assisted gene transfection. They identified three contributing mechanisms: photochemical internalization, photothermal modulation, and photoacoustic stimulation. While photochemical and photothermal processes improved uptake, only photoacoustic stimulation (achievable via high-peak, short-pulse lasers) was effective *in vivo*. This “triple effect” underscores the importance of delivering all three mechanisms simultaneously for optimal regenerative outcomes.

This evidence aligns with biomechanical studies. Research on hypergravity and shear stress (Tarantino et al. [18], Monici et al. [19], Cialdai and Monici [20], Genchi et al. [24], De Cesari et al. [23]) demonstrated that mechanical loading promotes cytoskeletal reorganization and gene expression. HILT systems, through photoacoustic waves, replicate these effects non-invasively and may serve as surrogates for mechanical therapies.

Collectively, these findings highlight the importance of parameter-specific effects, suggesting that the biological outcomes of PBM cannot be predicted by output power alone. Rather, wavelength, pulse structure, and energy density must be carefully tailored to the biological target and clinical objective.

Additional experimental studies have confirmed that laser irradiation outcomes depend not only on the total delivered energy, but also on the temporal structure of light delivery. In a study on osteoblast cultures, Sleep et al. [11] demonstrated that even continuous-wave LED exposure with carefully selected energy density could transiently enhance mitochondrial respiration and osteogenic gene expression. However, this effect declined with repeated treatments, illustrating a biphasic response typical of photochemical-only stimulation. These findings emphasize that photochemical mechanisms alone, although biologically active, may be insufficient for sustained regenerative stimulation. This supports the notion that only laser systems capable of inducing all three mechanisms (photochemical, photothermal, and photoacoustic)—can elicit the so-called “triple effect”, with true HILT representing the clearest expression of this capability.

Building on this understanding, laser technology has progressively evolved toward systems more complex pulse architectures and higher peak powers, enabling biological effects that go beyond traditional photochemical and photothermal modulation.

Among these, High-Intensity Laser Therapy (HILT) emerged as a promising modality [25,33] that combines the penetration depth of HPLT with the metabolic benefits of LLLT. However, the term “HILT” is nowadays inconsistently applied. In many cases, devices classified as HILT lack the pulse characteristics needed to induce photoacoustic effects and behave instead as purely photothermal systems.

This inconsistency carries important implications: a device with high average power but lacking the ability to generate high-peak, short pulses will act primarily through superficial photothermal effects, while a lower-power device capable of kilowatt-scale peaks may trigger genuine regenerative pathways. Current classifications often fail to reflect these nuances, leading to potential misinterpretation of clinical outcomes and confusion in scientific reporting.

This review does not question the efficacy of laser devices when used appropriately. Instead, it highlights taxonomic inconsistencies, particularly regarding HILT, that risk obscuring biological specificity. A mechanism-based classification will better align terminology with therapeutic action, benefiting research, device development, and clinical decision-making. The goal is not to rank the effectiveness of different laser devices or protocols, but rather to propose a biologically coherent framework that distinguishes

laser systems based on their dominant mechanism of interaction with biological tissues. This review is based on an analysis of contemporary clinical trials published between 2010 and 2015, where the term “High-Intensity Laser Therapy” (HILT) appeared in the title. We classified devices as “true HILT” if they utilized 1064 nm pulsed lasers with a duty cycle of 0.01–1%, and “false HILT” if they did not meet these criteria.

It is important to emphasize that all laser systems—LLLT, HPLT, and HILT—can produce beneficial biological effects when properly applied, each within the scope of its dominant interaction mechanism. Some devices primarily induce photochemical effects and others combine photochemical and photothermal mechanisms, while only a subset can also trigger photoacoustic effects. Each modality has therapeutic value within its intended application context.

## 2. Materials and Methods

This article is structured as a narrative, focused on clarifying the semantic ambiguity surrounding the use of the term High-Intensity Laser Therapy (HILT). We aimed to determine whether the studies included true HILT devices, emitting high-intensity laser light (with the parameters described below), or if they simply used devices with higher average power ( $>0.5$  W), typically classified as HPLT or HLLT, which are the majority of lasers currently on the market but do not deliver the high peak intensity that defines HILT.

Based on this rationale, we performed a targeted literature search on PubMed for the years 2010–2025 including only clinical trials with controlled design that explicitly mention “High Intensity Laser Therapy” or “HILT” in the title or abstract. Reviews and meta-analyses were excluded.

A total of 60 studies were selected for analysis. The decision to include 60 studies was based on a practical and statistical rationale. This sample size is sufficient for estimating a proportion and provides a clear and reliable indication of the use of the term HILT in literature. While 30 studies are commonly considered the minimum number for reliable estimates in simple descriptive statistics, 60 studies offer a more robust sample to observe the frequency of correct versus incorrect use of the term HILT, without requiring a complex statistical analysis. For each study, we extracted available technical details on the laser system used: wavelength, source type, peak power, average power, emission mode, pulse duration, pulse energy, repetition rate, and duty cycle. When full specifications were not provided in the article, we referred to device manuals and manufacturer datasheets.

The studies were then analyzed based on whether the used laser system met the biophysical requirements to induce photoacoustic effects, defined as: (1) Peak intensity  $\geq 5$  kW/cm<sup>2</sup>, (2) Pulse energy in the hundreds of mJ, (3) Pulse duration  $\leq 200$   $\mu$ s, (4) Duty cycle preferably in the 0.05–0.5% range and always below 1%. These thresholds are based on the original criteria proposed by Fortuna and Masotti [9] and are intended as indicative values that reflect the order of magnitude required for thermoelastic stress confinement. Exact thresholds may vary depending on tissue geometry, optical absorption, and acoustic relaxation time.

It is important to note that some devices nominally labeled as HILT may not meet these physical criteria for photoacoustic effects, even though they are often classified as HILT in literature.

Due to the lack of consistent reporting in many of the studies, only partial data could be retrieved in several cases. Furthermore, it is important to note that technical specifications were not always fully disclosed in the reviewed studies. As a result, the classification presented in Table 2 includes only those laser parameters (such as wavelength and duty cycle) that could be explicitly extracted from the publications or reasonably inferred from the manufacturer’s documentation. The summary table in the following section reports only those parameters that could be verified from either the

article or official technical documentation. This methodological limitation highlights a broader issue in Laser Therapy research: the urgent need for standardized and transparent reporting of laser characteristics, especially when classifying systems under specific therapeutic labels such as HILT.

**Table 2.** Summary of selected clinical studies labeled as HILT, detailing laser source, wavelength, duty cycle, and the primary interaction mechanism. C = photochemical, T = photothermal, A = photoacoustic.

Ref.	Author	Source	Wavelength [nm]	Duty Cycle (%)		Primary Mechanism (C/T/A)
				Min	Max	
[34]	Ezzati et al., 2020	GaAs	808	ND	ND	C/T
[35]	Ezzati et al., 2024	GaAs	808	ND	ND	C/T
[36]	Siriratna P. et al., 2022	GaAs	808/905	50	50	C/T
[37]	Zielińska P. et al., 2022	InGaAs/AlGaAs	808/980	ND	ND	C/T
[38]	Gocewska et al., 2019	GaAs	940	ND	ND	C/T
[39]	Kim GJ et al., 2016	GaAs	980	CW	ND	C/T
[40]	Zare Bidoki M. et al., 2024	GaAs	980	ND	ND	C/T
[41]	Xie, Y. et al., 2025	GaAs	980/810	ND	ND	C/T
[42]	Abdelbasset et al., 2021	Nd:YAG	1064	0.05	0.6	C/T/A
[43]	Abo Elyazed et al., 2023	Nd:YAG	1064	0.05	0.6	C/T/A
[44]	Alayat et al. 2016	Nd:YAG	1064	0.05	0.6	C/T/A
[45]	Dundar et al., 2015	Nd:YAG	1064	0.05	0.6	C/T/A
[46]	Dundar et al., 2015	Nd:YAG	1064	0.05	0.6	C/T/A
[47]	Ebid et al., 2015	Nd:YAG	1064	0.05	0.6	C/T/A
[48]	Ebid et al., 2017	Nd:YAG	1064	0.05	0.6	C/T/A
[49]	Ekici et al., 2022	Nd:YAG	1064	0.05	0.6	C/T/A
[50]	Ekici et al., 2023	Nd:YAG	1064	0.05	0.6	C/T/A
[51]	El-Shamy et al., 2018	Nd:YAG	1064	0.05	0.6	C/T/A
[52]	Fiore et al., 2011	Nd:YAG	1064	0.05	0.6	C/T/A
[53]	Hamed et al., 2023	Nd:YAG	1064	0.05	0.6	C/T/A
[54]	Ince S. et al., 2024	Nd:YAG	1064	0.05	0.6	C/T/A
[55]	Kheshie et al., 2014	Nd:YAG	1064	0.05	0.6	C/T/A
[56]	Pekyavas et al., 2016	Nd:YAG	1064	0.05	0.6	C/T/A
[57]	Saleh et al., 2024	Nd:YAG	1064	0.05	0.6	C/T/A
[58]	Salli et al. 2016	GaAs	1064	0.05	0.6	C/T/A
[59]	Santamoto et al., 2009	Nd:YAG	1064	0.05	0.6	C/T/A
[60]	Thabet et al., 2017	Nd:YAG	1064	0.05	0.6	C/T/A
[61]	Thabet et al., 2018	Nd:YAG	1064	0.05	0.6	C/T/A
[62]	Venosa et al., 2019	Nd:YAG	1064	0.05	0.6	C/T/A
[63]	Viliani T et al., 2012	Nd:YAG	1064	0.05	0.6	C/T/A
[64]	Yesil et al., 2020	Nd:YAG	1064	0.05	0.6	C/T/A
[65]	Yilmaz at al., 2022	Nd:YAG	1064	0.05	0.6	C/T/A
[66]	Alayat et al., 2017	Nd:YAG	1064	0.05	0.6	C/T/A
[67]	Ozge Ozlu et al., 2024	Nd:YAG	1064	0.05	0.6	C/T/A
[68]	Abdelbasset et al., 2020	GaAs	1064	CW	25 ±20	C/T
[69]	Abdelhakiem NM et al., 2024	GaAs	1064	CW	25 ±20	C/T
[70]	Akaltun et al., 2021	GaAs	1064	CW	25 ±20	C/T
[71]	Akkurt et al., 2016	GaAs	1064	CW	25 ±20	C/T
[72]	Angelova et al., 2016	GaAs	1064	CW	25 ±20	C/T
[73]	Atan et al., 2021	GaAs	1064	CW	25 ±20	C/T
[74]	Bayburt et al., 2025	GaAs	1064	CW	25 ±20	C/T

[75]	Chen et al., 2018	GaAs	1064	CW	25 ±20	C/T
[76]	Haładaj et al., 2017	GaAs	1064	CW	25 ±20	C/T
[77]	Karakuzu Güngör Z, 2025	GaAs	1064	CW	25 ±20	C/T
[78]	Kaydok et al., 2019	GaAs	1064	CW	25 ±20	C/T
[79]	Kolu et al., 2018	GaAs	1064	CW	25 ±20	C/T
[80]	Kulchitskaya et al., 2017	GaAs	1064	CW	25 ±20	C/T
[81]	Lu Q et al., 2021	GaAs	1064	CW	25 ±20	C/T
[82]	Naruseviciute et al., 2020	GaAs	1064	CW	25 ±20	C/T
[83]	Ordahan et al., 2018	GaAs	1064	CW	25 ±20	C/T
[84]	Ordahan et al., 2023	GaAs	1064	CW	25 ±20	C/T
[85]	Rahimi et al., 2024	GaAs	1064	CW	25 ±20	C/T
[86]	Sudiyono & Handoyo, 2020	GaAs	1064	CW	25 ±20	C/T
[87]	Tache-Codreanu et al., 2024	GaAs	1064	CW	25 ±20	C/T
[88]	Yilmaz at al., 2020	GaAs	1064	CW	25 ±20	C/T
[89]	Nazari et al., 2019	GaAs	1064	Pulsed	70	C/T
[90]	Boyraz I. et al., 2015	GaAs	1064	ND	ND	C/T
[91]	Taheri P. et al., 2023	GaAs	1064	ND	ND	C/T
[92]	Tkocz P et al., 2021	GaAs	1064	ND	90	C/T
[93]	Casale R. et al., 2013	Nd:YAG/Diode	1064/830	ND	ND	C/T

To complement the qualitative classification of HILT vs. HPLT devices, we also performed a quantitative comparison of temporal emission structures delivering the same total energy. Since total energy equals the product of average power and exposure time ( $E = P_{avg} \times t$ ), and assuming identical exposure times across configurations, average power was used as a proxy for total energy. Three clinically realistic configurations were evaluated. In scenario (A), peak power was calculated for HPLT-like duty cycles (25–75%) and HILT-like duty cycles (0.1–0.5%) while keeping a constant emitting spot diameter (0.5 cm). In scenario (B), peak intensity ( $W/cm^2$ ) was computed from peak power using the same emitting area.

Scenario (C) reflects practical operating conditions in which high-duty-cycle diode sources typically use larger spot diameters (1.5–2.5 cm) to limit radiant exposure and avoid cumulative thermal effects due to reduced thermal relaxation intervals. Therefore, peak intensity was compared between HPLT-like operation at 1.5 cm and pulsed HILT-like operation at 0.5 cm. Numerical data for these three scenarios are reported in Table 3.

**Table 3.** Peak power and peak intensity for HPLT and HILT configurations delivering equal average power (3, 5 and 10 W) across three clinically representative scenarios (A–C).

<b>A: HPLT vs. HILT: Peak Power [W]</b>						
Avg. Power [W]	Duty Cycle [%]					
	HPLT			HILT		
	25%	50%	75%	0.1%	0.3%	0.50%
3	12	6	4	3000	1000	600
5	20	10	7	5000	1667	1000
10	40	20	13	10,000	3333	2000
<b>B: HPLT vs. HILT: Peak Intensity [W/cm<sup>2</sup>] @ same spot size</b>						
Avg. Power [W]	Duty Cycle [%]					
	HPLT			HILT		
	25%	50%	75%	0.1%	0.3%	0.50%
3	61	31	20	15,279	5093	3056
5	102	51	34	25,465	8488	5093
10	204	102	68	50,930	16,977	10,186

<b>Spot Size f [cm]</b>	0.5	0.5	0.5	0.5	0.5	0.5
<b>Spot Area [cm<sup>2</sup>]</b>	0.1963	0.1963	0.1963	0.1963	0.1963	0.1963
<b>C: HPLT vs. HILT Peak Intensity [W/cm<sup>2</sup>] @ different spot size</b>						
<b>Avg. Power [W]</b>	<b>Duty Cycle [%]</b>					
	<b>HPLT</b>			<b>HILT</b>		
	<b>25%</b>	<b>50%</b>	<b>75%</b>	<b>0.1%</b>	<b>0.3%</b>	<b>0.50%</b>
<b>3</b>	7	3	2	15,279	5093	3056
<b>5</b>	11	6	4	25,465	8488	5093
<b>10</b>	23	11	8	50,930	16,977	10,186
<b>Spot Size f [cm]</b>	1.5	1.5	1.5	0.5	0.5	0.5
<b>Spot Area [cm<sup>2</sup>]</b>	1.7671	1.7671	1.7671	0.1963	0.1963	0.1963

Peak power (A) and Peak Intensity (B–C) for HPLT and HILT emission architectures delivering equal total energy (represented by equal average output power at 3, 5, and 10 W). (A) Peak power for HPLT (25–75% duty cycle) and HILT (0.1–0.5% duty cycle), calculated using the same emitting spot diameter (0.5 cm). (B) Corresponding peak irradiance (W/cm<sup>2</sup>) derived from peak power using the same emitting area (0.5 cm). (C) Peak Intensity under clinically realistic conditions in which HPLT typically employs larger spot sizes (1.5 cm) to limit radiant exposure, while HILT commonly uses a 0.5 cm spot.

To quantify the magnitude of separation between paired configurations, we computed Cohen’s *r* from the standardized effect size (*d*), using the expression:

$$r = \frac{d}{\sqrt{d^2 + 4}}$$

where *d* represents the difference between paired values normalized to their pooled variance. This approach expresses the strength of separation independently of inferential assumptions or sample size and is therefore appropriate when differences arise from deterministic physical relationships rather than stochastic measurement variability.

The conventional interpretative thresholds (negligible <0.1; small 0.1–0.3; moderate 0.3–0.5; large 0.5–0.8; very large >0.8) were adopted. Statistical values are reported in Table 4.

**Table 4.** (A, B, C) Cohen’s *r* values expressing the magnitude of separation between HPLT and HILT emission architectures at equal total energy.

<b>A: HPLT vs. HILT: Peak Power [W]</b>			
<b>Avg. Power [W]</b>	<b>Cohen-<i>r</i> Test</b>		
	25% vs. 0.1%	50% vs. 0.3%	75% vs. 0.50%
<b>3</b>	0.70	0.70	0.70
<b>5</b>	0.70	0.70	0.70
<b>10</b>	0.70	0.70	0.70
<b>B: HPLT vs. HILT: Peak Intensity [W/cm<sup>2</sup>] @same spot size</b>			
<b>Avg. Power [W]</b>	<b>Cohen-<i>r</i> Test</b>		
	25% vs. 0.1%	50% vs. 0.3%	75% vs. 0.50%
<b>3</b>	0.70	0.70	0.70
<b>5</b>	0.70	0.70	0.70
<b>10</b>	0.70	0.70	0.70
<b>C: HPLT vs. HILT Peak Intensity [W/cm<sup>2</sup>] @ different spot size</b>			
<b>Avg. Power [W]</b>	<b>Cohen-<i>r</i> Test</b>		
	25% vs. 0.1%	50% vs. 0.3%	75% vs. 0.50%
<b>3</b>	0.71	0.71	0.71

5	0.71	0.71	0.71
10	0.71	0.71	0.71

Cohen's  $r$  values quantifying the magnitude of separation between HPLT and HILT emission architectures delivering the same total energy (equal average output power at 3, 5 and 10 W). (A) Separation based on peak power values (corresponding to Table 3A). (B) Separation based on peak intensity using the same emitting area (corresponding to Table 3B). (C) Separation based on peak intensity under clinically realistic spot-size conditions, where HPLT commonly employs a 1.5 cm spot and HILT a 0.5 cm spot (corresponding to Table 3C).  $R$  values around 0.70–0.71 across all comparisons indicate a large effect size and a strong separation between HPLT and HILT configurations.

### 3. Results

A total of 60 clinical studies published between 2010 and 2025 and referring explicitly to High-Intensity Laser Therapy (HILT) were identified and included in this analysis. All studies were focused on therapeutic applications of HILT and excluded reviews or meta-analyses. Among them, 38 were designed as double-blind and/or randomized trials, while 22 adopted alternative designs.

From a technological perspective, only 26 studies (43.3%) employed solid-state Nd:YAG laser systems, which, according to the parameters defined in our Materials and Methods section, are capable of delivering high-peak power density ( $\geq 5$  kW/cm<sup>2</sup>), short-duration ( $< 200$   $\mu$ s) pulses with duty cycles below 1%, often in the 0.05–0.6% range. These parameters are typically associated with thermoelastic stress confinement and with the generation of photoacoustic transients, the key mechanism distinguishing true HILT from other photo-induced biomodulation modalities.

Conversely, the remaining 34 studies (56.7%) utilized gallium-arsenide (GaAs) diode lasers, most commonly emitting at 1064 nm, the same wavelength used in Nd:YAG systems. Despite their capability to produce high average powers, these diode devices typically operate in continuous wave (CW) mode or at very high duty cycles (e.g., ~25%) and lack the pulsing architecture required to induce photoacoustic stimulation. These systems are well suited to inducing photochemical and photothermal effects, but their capacity to generate significant photoacoustic responses remains questionable or unverified.

A quantitative comparison of emission configurations delivering equal total energy was performed as described in the Materials and Methods. Table 3 reports peak power and peak intensity values under three clinically representative conditions:

- Table 3A: Peak power of HPLT (duty cycle 25–75%) vs. HILT (duty cycle 0.1–0.5%), with the same spot diameter (0.5 cm).
- Table 3B: Corresponding peak intensity (W/cm<sup>2</sup>) values calculated from peak power using the same emitting area as in 3A.
- Table 3C: Peak intensity comparison reflecting typical operating conditions, in which HPLT systems use larger spot sizes (1.5 cm) to limit radiant exposure, whereas HILT systems commonly use 0.5 cm.

The relative magnitude of separation between HPLT and HILT configurations under equal total energy was quantified using Cohen's  $r$ , as described in the Materials and Methods.

### 4. Discussion

The results of this review reveal a profound inconsistency in how the term "High-Intensity Laser Therapy" (HILT) is used across clinical studies. Out of 60 analyzed trials, only 43% utilized laser systems whose parameters are associated with the generation of

photoacoustic stimulation, namely, high-peak-power, short-duration pulses delivered at low duty cycles. The remaining 57% of studies employed devices that, while potentially effective for photochemical and photothermal stimulation, lacked the structural prerequisites for generating photoacoustic pressure waves. These findings indicate that the label HILT is often applied based solely on nominal output power or manufacturer designation, rather than on measurable interaction mechanisms.

The implications of this finding are twofold: (1) a significant proportion of studies labeled as “HILT” in the literature have likely evaluated therapies based only on dual effects (photochemical + photothermal), rather than the triple effect which defines true High-Intensity Laser Therapy; (2) the current terminological inconsistency in classifying therapeutic lasers may introduce interpretative bias in clinical trials, especially when devices with fundamentally different mechanisms of action are grouped under the same label.

This misalignment has significant implications. Clinically, it may lead practitioners to overestimate the regenerative capabilities of certain devices, especially when deeper tissue effects are expected. Scientifically, it compromises the comparability of studies and reduces the interpretability of meta-analyses, particularly when devices with distinct mechanisms of action are grouped under the same terms.

The core of the issue lies in a power-based classification model that prioritizes average output power, neglecting pulse structure, particularly peak power, pulse energy, repetition frequency, and duty cycle. These parameters are crucial because they determine not only the quantity of energy delivered but also how it interacts with biological tissues. Specifically, only laser systems capable of delivering brief, high-intensity energy bursts can generate photoacoustic pressure waves, a phenomenon governed by thermoelastic expansion and following the laws of acoustics.

This conceptual discrepancy was quantitatively verified in the present work. As shown in Table 3, when HPLT and HILT deliver the same total energy (equal average output power), their peak parameters differ substantially across clinically realistic conditions. Peak power values (Table 3A) differ orders of magnitude solely due to duty-cycle structure, and these differences translate directly into peak intensity (Table 3B). Furthermore, when typical operating spot sizes are considered (Table 3C), the achievable peak intensities diverge even further. The strength of this separation was quantified using Cohen's  $d$  (Table 4), which consistently yielded values around 0.70–0.71, corresponding to a large effect size. This indicates a strong separation between HPLT and HILT configurations even when total delivered energy is held constant. This confirms that the architectural differences in temporal emission do not represent incremental variations within a common modality, but rather distinct operational regimes. These safety considerations are fully consistent with the classical laser–tissue interaction map originally described by Boulnois (1986) [94] and reproduced in Niemz [95]. When the typical HILT pulse parameters (microsecond-scale pulse duration, peak intensities in the  $10^3$ – $10^6$  W/cm<sup>2</sup> range, and fluence around 1–2 J/cm<sup>2</sup>) are plotted on this diagram, they fall entirely within the thermal-interaction domain—well below the thresholds for plasma formation or photodisruption. Under these temporal conditions, heat dissipates between pulses well within the local thermal relaxation time, preventing thermal accumulation while still generating the thermoelastic expansion necessary for photoacoustic stimulation. This placement on the Boulnois–Niemz map demonstrates conclusively that true HILT remains fully within established safety boundaries while still generating the thermoelastic conditions required for photoacoustic stimulation.

The use of relatively small spot diameters ( $\approx 5$  mm) in true HILT systems does not imply excessive radiant exposure to the tissue surface. Due to their extremely low duty cycles (typically 0.05–0.5%), even pulse energies in the 50–300 mJ range remain within the

established safety limits for radiant exposure, as reported by Boulnois [94] and Niemz [95]—when delivered through microsecond pulses. These temporal conditions allow HILT systems to maintain thermal safety while achieving the high peak intensities required for photoacoustic stimulation. By contrast, lasers operating at high duty cycles or in quasi-continuous modes must employ much larger spot sizes (some centimeters in diameter) to remain below thermal-safety thresholds, which inherently lowers peak intensity and prevents the generation of meaningful photoacoustic effects. This distinction underscores that, in HILT, safety is governed primarily by energy density and temporal delivery rather than by pulse energy alone.

Unlike light or heat, acoustic pressure waves propagate rapidly and deeply through tissues, some centimeters beyond the absorption limit of photons or the dissipation range of thermal gradients. This property is well-known in clinical practice, particularly in ultrasound therapies. In HILT, the ability to mimic this dynamic through light-induced acoustic waves represents a biophysical breakthrough with direct implications for mechano-transduction, cellular differentiation, and extracellular matrix remodeling.

Despite the importance of these mechanisms, many published studies fail to report basic technical details. Parameters such as fluence are frequently reported without explicit definition, leaving ambiguity as to whether they refer to average power over time and area, or to pulse energy normalized to spot size. Similarly, device descriptions are frequently imprecise or even contradictory, for example, referencing “Nd:YAG diode lasers” or “semiconductive neodymium sources,” when the same manufacturers identify these systems as near-infrared diode emitters. Such terminological ambiguities make it impossible to assess the true mode of action and invalidate comparisons across studies.

Other publications refer vaguely to “intensity level 2” or “frequency 11 Hz” without specifying peak power, pulse duration, or pulse energy. Even worse, some devices classified as HILT are reported as using diode sources emitting in cw mode, with duty cycles exceeding 20–50%, far outside the range necessary to produce photoacoustic effects. In these cases, HILT is used more as a nominal or commercial label than as a mechanism-based scientific category a practice that misleads clinicians, confuses readers, and undermines the validity of systematic reviews. While all the cited devices may induce beneficial biological responses, this review aims to clarify semantic confusion and promote a more mechanism-based classification, rather than judging one laser as superior to another one in its clinical effects. Every system can be effective when used correctly and appropriately, but different mechanisms require different terminology. This section avoids citing specific studies and instead focuses on general trends observed in literature. The aim is not to discredit the clinical results achieved, but to emphasize that inadequate or inconsistent reporting of technical parameters hampers scientific clarity and leads to semantic inflation. Much of this confusion appears to stem not from negligence, but from commercial influence and an underestimation of the biophysical complexity involved.

While this review does not question the clinical efficacy of High-Intensity Laser Therapy (HILT) devices, it aims to provide a clearer and more biologically grounded classification model. The focus of our work is on the physical characteristics of laser devices—such as peak power, pulse duration, and duty cycle—and how these parameters influence the mechanisms of action. Our review does not address the specific clinical outcomes of HILT in fields such as dentistry, orthopedics, or sports medicine, but rather emphasizes the need for a more precise classification of laser therapies based on their inherent physical properties.

It is also noteworthy that some devices classified as HILT by authors or manufacturers are, upon closer inspection, diode lasers operating in continuous wave or quasi-continuous modes with high duty cycles, structures that inherently prevent the generation of true photoacoustic effects. Without pulsed emission in the kilowatt range

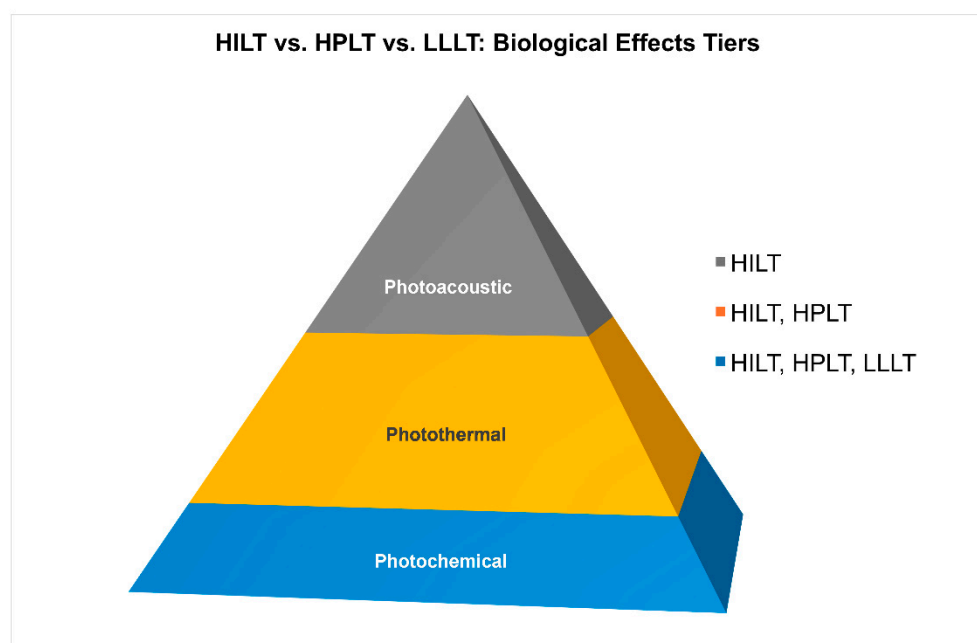
and sub-millisecond durations, the capacity to induce mechano-transduction remains unsupported.

To address this confusion, we propose a mechanism-based taxonomy that classifies laser therapies by their predominant biological effects:

- Photochemical LLLT → Mitochondrial activation and redox modulation via low-power continuous or long-pulse emission.
- Photothermal HPLT → Heat-induced vasodilation, collagen remodeling, and analgesia via high average power.
- Photoacoustic HILT → Mechano-transductive stimulation via short, high-peak-power pulses generating acoustic pressure waves.

In addition to these, a complete and transparent description of the protocol should also include the diameter of the laser spot on tissue (in centimeters), the pulse repetition frequency (in hertz), and the total treatment duration (in seconds or minutes). These additional values are not only helpful for replication purposes but also provide essential context for dosimetry analysis. The photochemical phase of LLLT modulates mitochondrial redox chains and raises ATP, priming cell metabolism for repair. Within micro- to milliseconds, thermoelastic expansion of the illuminated volume launches an acoustic pressure wave. This photoacoustic component travels several centimeters through tissue, mechanically exciting the cytoskeleton and focal adhesions and thereby driving mechanotransduction that promotes protein and extracellular-matrix synthesis—even when kinase signaling is blunted by chronic inflammation [18]. The same physics explains rapid nerve-function modulation and analgesia through transient conduction block [13]. Finally, across pulse trains, residual heat accumulates locally and more shallowly than the acoustic wave, producing photothermal effects—vasodilation, lymphatic drainage, and muscle relaxation—that improve perfusion and pain control; among near-infrared wavelengths, static 980-nm delivery produces the greatest local temperature rise, whereas scanning/flat-top beams limit it [15].

This tripartite classification offers a biologically coherent and clinically meaningful framework (Figure 1). While all laser modalities can induce beneficial effects when properly applied, only systems capable of producing all three mechanisms—the “triple effect”—can fully support regenerative processes that depend on mechanical signaling.



**Figure 1.** Biological effects of therapeutic lasers illustrated as a pyramid. The basal photochemical layer is shared by LLLT, HPLT, and HILT; the intermediate photothermal layer characterizes HPLT and HILT; the apical photoacoustic layer is unique to HILT. LLLT mainly produces the photochemical step; HPLT adds photothermal heating; only true HILT—with high-peak-power, short pulses at low duty cycle—co-delivers all three mechanisms concurrently and synergistically in each treatment sequence: photochemical (first & superficial) → photoacoustic (fast & deep) → photothermal (later & local). This tri-modal, co-temporal action is what distinguishes HILT biologically and clinically.

## 5. Conclusions

Laser Therapy is a field with well-documented effects on cellular metabolism, inflammation, and tissue repair. However, as the field matures, it becomes increasingly evident that the current classification of therapeutic lasers, still largely based on nominal power output, fails to reflect the complexity of their biological effects. In particular, the term High-Intensity Laser Therapy (HILT) is frequently misapplied to systems lacking the temporal architecture required to induce photoacoustic stimulation, the hallmark mechanism that distinguishes true HILT from other modalities.

Biophysically, the defining factor of a laser's therapeutic mechanism is not average power, but rather pulse structure, including peak power, pulse energy, duty cycle, and repetition frequency. Only devices capable of delivering short, high-peak-power pulses at low duty cycles can generate the acoustic pressure waves necessary to activate mechanosensitive pathways involved in long-term tissue regeneration. Without these features, a device may still be effective through photochemical or photothermal effects, but it should not be classified as HILT.

To restore clarity, we propose a revised classification based on the dominant biological mechanism of action:

1. Photochemical effects → mitochondrial and metabolic stimulation (LLLT);
2. Photothermal effects → temperature-mediated modulation (HPLT and HILT);
3. Photoacoustic effects → regeneration via acoustic pressure wave-induced mechano-transduction (HILT).

This mechanism-based taxonomy provides a biologically coherent foundation for both clinical and research applications. It enables more accurate interpretation of results, supports better clinical decision-making, and avoids conflating technologies with divergent modes of action.

To ensure accurate classification, reproducibility, and meaningful comparison across clinical studies, a standardized set of laser parameters should always be reported. These include laser source (e.g., Nd:YAG, GaAs), wavelength, emission mode (CW or pulsed), average and peak power, duty cycle, pulse duration, and frequency. Reported values must reflect the actual settings used during treatment, not the maximum specifications listed by the manufacturer. Only through such rigorous and transparent reporting can we advance toward a mechanism-based classification of therapeutic lasers and avoid interpretative bias in clinical research. Journals, reviewers, and regulatory bodies should consider mandating this minimal data set as a prerequisite for publication.

Our findings do not question the efficacy of existing laser therapies but highlight the urgent need for a more precise and biologically grounded classification model. The term HILT should be reserved for systems capable of photoacoustic stimulation, not simply those exceeding arbitrary power thresholds.

This clarification is supported by the quantitative comparison presented in Tables 3 and 4, where configurations delivering the same total energy resulted in peak power and peak intensity values differing by orders of magnitude. The corresponding Cohen's  $r$

values around 0.70–0.71 (large effect size) confirm that these differences are structural, not incremental, and arise from the temporal emission architecture rather than absolute energy delivery. Such evidence reinforces the need to classify therapeutic lasers based on mechanism rather than nominal output specifications. Clarifying this distinction is essential to distinguishing true photobiomodulation—defined as light-induced photochemical modulation of cellular activity—and for differentiating it from laser-based therapies that rely predominantly on photothermal or photoacoustic mechanisms. This distinction ensures that clinical terminology reflects underlying biological mechanisms rather than commercial conventions.

While this review does not assess the clinical efficacy of laser therapies, it emphasizes the need for a classification system based on measurable physical properties. The review focuses on categorizing devices according to laser parameters such as peak power, pulse duration, and duty cycle, rather than evaluating their effectiveness in specific clinical contexts such as dentistry, orthopedics, or sports medicine.

Future research should aim to define physiologically relevant parameter ranges for photoacoustic stimulation and develop validated metrics to characterize treatment protocols. By establishing a common language rooted in biology and physics, this work aims to support a more rigorous, effective, and transparent use of laser therapy in regenerative medicine.

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**Conflicts of Interest:** Fabrizio Margheri is employed in the R&D department of El.En. Group (Florence, Italy), a manufacturer of HILT lasers. Other manufacturers of HILT devices are also active worldwide. Scott Parker is employed as VP of Clinical Affairs at DEKA Dental Lasers (Nashville, TN, USA), a company that markets HILT devices in dentistry. Damiano Fortuna acts as an external consultant for DEKA Dental Lasers (Nashville, TN, USA). The authors declare that these affiliations did not influence the design, analysis, or interpretation of the review.

## List of Abbreviations

(Only acronyms not explicitly defined at first occurrence in the text)

MAPK	Mitogen-Activated Protein Kinase
ERK	Extracellular Signal-Regulated Kinase
PI3K	Phosphoinositide 3-Kinase
mTOR	mechanistic Target of Rapamycin
JNK	c-Jun N-terminal Kinase
TRPV	Transient Receptor Potential Vanilloid
HSP	Heat Shock Protein
TMJ	Temporomandibular Joint
RCT	Randomized Controlled Trial

## References

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