Acta Scientific Neurology (ISSN: 2582-1121)

Volume 5 Issue 11 November 2022

Review Article

# Clinical Benefits of Photobiomodulation using a 635 nm of Low-Level Laser Therapy (LLLT) from a Mechanism of Action Perspective

**Jennifer Gantzer*, Daniel Strauss and Mark Wieland**

*Department of Clinical Sciences, National University of Health Sciences, USA*

***Corresponding Author:** Jennifer Gantzer, Department of Clinical Sciences, National University of Health Sciences, USA.

**DOI:** 10.31080/ASNE.2022.05.0547

**Received:** September 14, 2022

**Published:** October 05, 2022



## Abstract

Low-level laser (light) therapy, LLLT, is a therapeutic application of light delivered as photons. The ability of absorbed light able to induce physiological effects is known as photobiomodulation. LLLT photobiomodulation is well-documented to provide clinical benefits of improved rates of healing attributed to anti-inflammatory effects, decreased pain, and enhanced tissue regeneration. These clinical outcomes correlate to the mechanism of action of LLLT's photobiomodulation effects of increased generation of ATP and the ability to modulate inflammatory signaling molecules known to influence rapid and optimal tissue healing repair and regeneration. The clinical benefits of 635 nm LLLT is highlighted from a molecular mechanism of action perspective.

**Keywords:** LLLT; Cold Laser; 635 nm; Photobiomodulation

## Introduction

Low-level laser (light) therapy, LLLT, is a therapeutic application of light delivered as photons [1]. The ability of absorbed light able to induce physiological effects is known as photobiomodulation [2,3]. LLLT utilizes red and infrared light therapies typically ranging from 600-1000 nanometer (nm) wavelengths to achieve physiological effects of photobiomodulation. Interestingly, discovered in the 1960s during animal experiments with LLLT conducted on mice with the unexpected observation their injuries healed faster and with more rapid hair regrowth [1]. The photobiomodulation effects are attributed to its ability to deliver photons absorbed by the tissue inducing cellular redox changes currently understood to activate intracellular sensors and molecular responsive changes [2]. LLLT photobiomodulation is well-documented [5-16]. to provide clinical benefits of improved rates of healing attributed to anti-inflammatory effects, decreased pain, and enhanced tissue regeneration [2-5]. These clinical outcomes have been demonstrated to correlate to the mechanism of action of LLLT's photobiomodulation effects at the mitochondrial electron transport chain and generation of ATP [1,2], ability to scavenge damaging excessive free radical reactive species [4,6], and modulating effects on inflammatory signaling molecules and cytokines able to influence rapid and optimal tissue healing repair and regeneration [3,5-7].

### LLLT cold laser mechanism of action and phases of healing

Over the past decade a significant number of studies have successfully elucidated the molecular mechanisms of LLLT correlating to several components of the acute inflammatory response and tissue metabolic switch to regeneration affording injury resolution [4,5]. It's valuable to review the stages of injury and the body's healing response to appreciate the molecular therapeutic effect the LLLT has on these processes.

Robbins., *et al*. describes the acute inflammatory response consisting of 3 primary steps which overlay each other during the first few hours and days after injury, including: increased blood flow to the area with vasodilation of small vessels, increased permeability of the vascular endothelium from chemotactic cellular mediators

calling proteins and immune cells to the site, and thirdly thereby allowing for diapedesis and immune cell emigration out of the blood into the damaged site. This cascade is mediated by cytokines (IL-1, TNF), complement (C3a, C5a), eicosanoids (PGI, PGE, LTB, Lipoxins), ROS (O2-, ONNO-), and vasoactive amines (histamine, bradykinin) known to be the causative agents of the cardinal signs of infection and inflammation of swelling, redness, warmth, and pain. Inflammatory resolution consists of antagonistic expression of molecular signaling molecules that induce immune cell apoptosis and halt chemotactic responses promoting regression of the active inflammatory stimulus, which include lipoxins and prostacyclins (PGI2) from arachidonic acid (an anti-inflammatory resolving effect of the omega-6 derivative). As the tissue repair stage takes over there is also a shift in the chemical mediators and vascular changes: cell proliferation begins under the direction of tissue growth factors (TGF-B), angiogenesis occurs for new blood supply to the new tissue (VEGF, FGF-2, NO), and regeneration occurs by cell proliferation of undamaged cells, seen in non-scar full recovery tissue. If the damage exceeds the ability to regenerate, then the process of repair is scar tissue formed from deposits of collagen. The tissue proliferation stage of wound healing is anticipated to begin within 36 hours from the acute inflammatory injury stage. Optimal clinical outcomes are dependent on these appropriately timed events including initiation and resolution. As described by Robbins Basic Pathology, *"Anti-inflammatory mechanisms are activated, serving to control the response and prevent it from causing excessive damage to the host. After inflammation has achieved its goal of eliminating the offending agents, it sets into motion the process of tissue repair. Repair consists of a series of events that heal damaged tissue."* [17].

Advancements in LLLT research has offered insight into how photobiomodulation influences several components of the inflammatory and regenerative response [4,5,7,9]. Huang., *et al*. described the human chromophore tissue proteins able to absorb light, including complex IV of the electron transport chain cytochrome C oxidase, hemoglobin and myoglobin, flavins and flavoproteins, and porphyrins which they compare to plant chromophores of photosynthesis. The ability of the respiratory chain cytochrome C oxidase as a photoacceptor was additionally described as one of the primary effects of increased ATP generation with LLLT [1,7]; observed *in vitro* by Chaudary., *et al*. in hypoxic cell lines [7]. Huang., *et al*. additionally highlighted LLLT effects on nitric oxide availability along with increased reactive oxygen species (ROS) acting as tissue signal mediators, and their subsequent ability to induce downstream effects on transcription of proteins that induced proliferation and decreased cell death [1,2]. ROS are known for causing damage when they occur in excess or out of balance with protective intrinsic levels of antioxidant [4,6]; however, they vitally serve a non-damaging role as potent cell signaling molecules [1,7,17] and have physiological effects of communication [7,17]. Chaudary., *et al*. summarizes, *"ROS are responsible for either causing damage or activating signaling pathways"* and *"while large concentrations of ROS lead to cell death, ROS in a physiological range also act as secondary messengers and trigger the activation of signaling pathway."* [17]. They observed these findings *in vitro* when normal and hypoxic tissue was irradiated and increased ROS was measured with more ROS collectively in the injury cell lines, which were further observed to have optimal oxygenation, not cell death. Furthermore, they confirmed the lack of side effects noting no observable apoptosis or necrosis in the LLLT reperfusion cell-lines [17].

## LLLT clinical applications of therapeutic cold laser as "medicine" and "dose"

LLLT administration must differentiate if the treatment device is from a laser or LED, light-emitting diode, or a combination of each, because the beam of light scatters from LED as noncoherent light, whereas from a laser it follows uniformity as coherent light [1-3]. Chung., *et al*. explains, "*A laser is a device that emits light through a process of optical amplification based on the stimulated emission of photons. The term "laser" originated as an acronym for Light Amplification by Stimulated Emission of Radiation. The emitted laser light is notable for its high degree of spatial and temporal coherence."* [2]. Laser use of LLLT is also called "cold laser" because it's a light therapy of low power that does not induce heat and is significantly below the power of laser-induced ablations [2].

In addition to distinguishing LED vs cold laser as the administrating device, the wavelength has also proven valuable in the purpose and outcome for clinical application. The 635 nm wavelength of the visible red-light spectrum is well-studied for its photobiomodulation effectiveness and is currently accepted to support the injury healing-response reflected through anti-inflammatory effects, decreased pain, and enhanced tissue repair and regeneration pursuant to the above-mentioned effects of absorbed light [7-9]. LLLT of 635 nm has proven clinical value both *in vitro* [4,5,7] and *in vivo* human therapy interventions [7-16], however treatment parameters are an important component for implementing successful effects of 635 nm LLLT photobiomodulation. [1-3,7].

To achieve photobiomodulation clinical benefits there is an appropriate application of "the therapy" described by Huang., *et al*. "*As with other forms of medication, LLLT has its active ingredients or "medicine" (irradiation parameters) and a "dose" (the irradiation time).*" [1]. These are attributed to a biphasic dose-response which follows the Arndt-Schulz Law; to simplify is a window of optimal dose that is not too weak or too short in time for no effect nor so strong or long in time it inhibits the tissue response [1,2]. Huang., *et al*. demonstrated animal studies in support of the biphasic dose-response where optimal healing occurred between 2-5 J/cm2 decreasing in benefit up to 10 J/cm2 and prolonging and even actually reversing effects at 50 J/cm2 [1]. They detail their findings, *"In general, fluences of red or NIR as low as 3 or 5 J/cm2 will be beneficial in vivo, but a large dose like 50 or 100 J/cm2 will lose the beneficial effect and may even become detrimental."* [1]. Chaudary., *et al*. mentioned the same dose-response effect, *"Selecting appropriate photobiomodulation parameters is crucial to trigger positive stimulatory effects, as it has been shown that high energy densities lead to the inhibition of proliferation and viability in fibroblasts as well as myoblasts."* [7]. Of note, other wavelengths have been clinically studied with positive clinical outcomes but with different treatment parameters [1,16]. Additionally, higher wavelengths which were noted as inhibitory and contradictory to the physiological purpose of therapeutic support for injury tissue regeneration have been successfully applied for the purpose of nerve inhibition in pain syndromes [3].

Utilizing a LLLT therapy device and applying this principle can be therapeutically described with the Erchonia XLR8 red light handheld device. The XLR8 is designed as a 7.5 mW/cm2 dual diode monochromatic 635 nm wavelength cold laser emitting a coherent beam of only 635 nm per diode; total of 15 mW/cm2 [18]. Optimal LLLT effects following the Arndt-Schulz biphasic dose-response principles [1,3]. identifies the Erchonia XLR8 device's "medicine" as irradiation parameters (635 nm and 15 mW/cm2) and the "dose" as irradiation parameters x 180 seconds with a treatment dose also called energy density equal to 2.7 J/cm2 delivered LLLT; see figure 1.

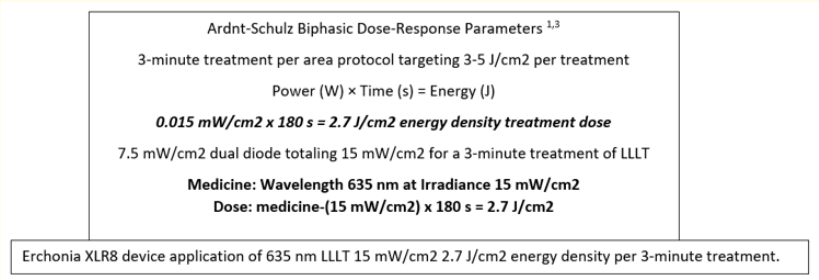


**Figure 1:** Example of LLLT with Erchonia XLR8 handheld device; "medicine" and "dose".

LLLT of 635 nm has proven clinical significance seen as improved rates of healing in excision wounds [5,9-13]. skeletal muscle contusion [4], *in vitro* reperfusion injury from hypoxia [7], ligamentous ankle sprains [10]. tendon injury [14]. oral ulcers [15]. pain relief [8,14]. and hair regrowth [2,16].

## Discussion

LLLT of 635 nm wavelength as an adjunct therapy [8-15] has been shown to have clinical outcomes demonstrated to correlate to the molecular mechanism of action of LLLT's photobiomodulation effects [3-7,17]. Luo., *et al*. used a 635 nm 7 mW/cm2 cold laser for 20 minutes on injured skeletal muscle. They reported antioxidant activity as detectable increased antioxidant enzyme activity of the Superoxide Dismutase during the inflammatory phase congruent as protection against oxidative stress in early injury. They secondarily observed modulation of early inflammatory phase growth factors (IGF-1) which promoted tissue regeneration and of late-phase tissue growth factors (TGF-B) which decreased scarring [4]. Lim., *et al*. used an *in vitro* noncoherent lamp of red light (+15)-635 nm and reported antioxidant and anti-inflammatory activity by LLLT scavenging of ROS and resultant decreased COX activity

with decreased generation of COX-generated PGE2 during the inflammatory phase systematically confirming anti-inflammatory effects [5]. Chaudary., *et al*. administered 635 nm 45 mW/cm2 pulsed red light LED to *in vitro* myoblasts and fibroblasts under hypoxia-induced conditions, a nutrient-deficient cellular state, to determine effects of LLLT on ischemia-reperfusion regeneration of wounds. In their study they observed increased oxygen flow to the reperfusion tissue as well as increased activity of the electron transport chain for oxygen consumption and generation of ATP in the injured cell lines [7].

Adjunct cold laser at 635 nm and optimal power density following the dose-response described and Huang., *et al*. [1] and Chung., *et al*. [3] has proven successful for modulated inflammation, injury recovery, and pain management [8-15]. Kilik., *et al*. used a 635 nm 5 mW/cm2 and 15 mW/cm2 cold laser comparison performed daily at a total energy density of 5 J/cm2 applied to excisional wounds and compared outcomes to non-irradiated wounds. They compared the rate of healing and secondarily performed tissue histological analysis. In addition to accelerated rates of healing in the irradiated group, they histologically confirmed acceleration of the regenerative phase observed as proliferation and migration of fibroblasts, epithelization, angiogenesis, and collagen synthesis identifying tissue repair and regenerative effects [9]. Vasilenko., *et al*. used a 635 nm 15 mW/cm2 cold laser applied to full thickness wounds and achieved enhanced tensile strength of the healing wounds compared to the non-irradiated group [11]. Calin and Botea used an application of LLLT 635 nm laser 15 mW/cm2 double-fractionated laser irradiation of 300 seconds (4.5 J/cm2 per treatment) performed twice daily for 3 consecutive days to acute ankle sprains along with standard of care consisting of rest, ice, compress, and elevate. The irradiation plus standard of care treatment group demonstrated superior clinical outcomes at the onset of therapy and at 10 days including pain relief and improvements in ankle function scores when compared to the control group who received standard of care only [13]. Rocca., *et al*. treated painful recurrent aphthous stomatitis comparing the pain-relieving effects of 450 nm, 635 nm, and 808 nm concluding, "it is possible to observe that during and immediately after treatment, 635 nm diode had the best effect" confirming a pain-relieving effect [15].

To successfully implement LLLT treatment, each application must define the wavelength and power densities. LLLT clinical adjunct therapy prescriptive parameters must include laser treatment "medicine" with the necessary "dose" to ensure capturing the treatment window under the Arndt-Shulz Law and laser biphasic dose response where the higher the treatment energy density (J/cm2 per treatment) the loss of tissue regenerative effects [1]. The "medicine" component includes the LLLT treatment device wavelength (nm) and intensity of irradiance (mW/cm2 or W/cm2). The "dose" component describes the time (s; seconds) and total energy (J; Joules) delivered to the treatment area with a calculation of (W x s = J), so that the "dose" is described as J/cm2, also termed the energy density of the treatment. The latter (energy density) determines the tissue response as stimulatory or inhibitory molecular physiological events under the biphasic dose-response of tissue photobiomodulation [1-3]. In line with biphasic dose-response, the maximal regenerative and anti-inflammatory effects have been well-documented at energy density treatments of 3-5 J/cm2, up to a maximum of 10 J/cm2 per treatment, before the LLLT had inhibitory (no effect) and at higher J/cm2 became detrimental to the healing response reported by Huong., *et al*. at 50 cm/2 and 100 cm/2 [1] and further referenced by Chaudary., *et al*. [7].

## Conclusion

The clinical benefits of 635 nm LLLT has demonstrated value *in vitro* and *in vivo* as current research better elucidates its molecular mechanism of action. LLLT photobiomodulation clinical benefits include improved rates of healing attributed to anti-inflammatory effects, decreased pain, and enhanced tissue regeneration. These clinical outcomes correlate to the molecular mechanism of action of LLLT's photobiomodulation effects at the mitochondrial electron transport chain and generation of ATP and its ability to modulate effects on inflammatory signaling molecules able to influence rapid and optimal tissue healing repair and regeneration. The advancements in research *in vitro* and *in vivo* have proven the clinical significance of incorporating adjunct cold laser as an adjunct therapy from an injury recovery as well as from the supportive mechanism of action perspective.

## Bibliography

1. Huang YY., *et al*. "Biphasic dose response in low level light therapy". *Dose Response* 7.4 (2009): 358-383.

2. Chung H., *et al*. "The nuts and bolts of low-level laser (light) therapy". *Annual Review of Biomedical Engineering* 40.2 (2012): 516-533.

3. Huang YY., *et al*. "Biphasic dose response in low level light therapy - an update". *Dose Response* 9.4 (2011): 602-618.

4. Luo L., *et al*. "Effects of low-level laser therapy on ROS homeostasis and expression of IGF-1 and TGF-β1 in skeletal muscle during the repair process". *Lasers in Medical Science* 28.3 (2013): 725-734.

5. Lim W., *et al*. "Anti-inflammatory effect of 635 nm irradiations on *in vitro* direct/indirect irradiation model". *Journal of Oral Pathology and Medicine* 44.2 (2015): 94-102.

6. Liguori I., *et al*. "Oxidative stress, aging, and diseases". *Clinical Interventions in Aging* 13 (2018): 757-772.

7. Chaudary S., *et al*. "*In vitro* effects of 635 nm photobiomodulation under hypoxia/reoxygenation culture conditions". *Journal of Photochemistry and Photobiology B* 209 (2020): 111935.

8. Nammour S., *et al*. "Photobiomodulation Therapy vs. Corticosteroid for the Management of Erosive/Ulcerative and Painful Oral Lichen Planus. Assessment of Success Rate during One-Year Follow-Up: A Retrospective Study". *Healthcare (Basel)* 9.9 (2021): 1137.

9. Kilík R., *et al*. "Effect of equal daily doses achieved by different power densities of low-level laser therapy at 635 nm on open skin wound healing in normal and diabetic rats". *BioMed Research International* 2014 (2014): 269253.

10. Calin MA., *et al*. "Fractionated Irradiation in Photobiomodulation Therapy of Ankle Sprain". *American Journal of Physical Medicine and Rehabilitation* 98.8 (2019): 692-698.

11. Vasilenko T., *et al*. "The effect of equal daily dose achieved by different power densities of low-level laser therapy at 635 and 670 nm on wound tensile strength in rats: a short report". *Photomedicine and Laser Surgery* 28.2 (2010): 281-283.

12. Gupta A., *et al*. "Effect of red and near-infrared wavelengths on low-level laser (light) therapy-induced healing of partial-thickness dermal abrasion in mice". *Lasers in Medical Science* 29.1 (2014): 257-265.

13. Calin MA and Botea S. "*In vivo* comparison of simple and double-fractionated low- level laser irradiation schemes on the healing of rat skin lesions". *Photomedicine and Laser Surgery* 28.2 (2010): 245-2250.

14. Poorpezeshk N., *et al*. "Early Low-Level Laser Therapy Improves the Passive Range of Motion and Decreases Pain in Patients with Flexor Tendon Injury". *Photomedicine and Laser Surgery* 36.10 (2018): 530-535.

15. Rocca JP., *et al*. "Effect of laser irradiation on aphthae pain management: A four different wavelengths comparison". *Journal of Photochemistry and Photobiology B* 189 (2018): 1-4.

16. Amer M., *et al*. "Results of low-level laser therapy in the treatment of hair growth: An Egyptian experience". *Dermatologic Therapy* 34.3 (2021): e14940.

17. Kumar V., *et al*. "Robbins basic pathology". Tenth edition. Kumar V, Abbas AK, Aster JC, editors. Philadelphia, Pennsylvania: Elsevier (2018).

18. Erchonia. "XLR8 Handheld Cold Laser".