

Low Level Laser Therapy in Dermatology

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BACKGROUND

Low-level laser therapy (LLLT) refers to the use of a red-beam or near-infrared laser with a wave-length between 600 and 1000 nanometers and power from 5 to 500 milliwatts. Other names for the therapy include low-power laser, soft laser, cold laser, biostimulation laser and therapeutic laser. As high-power lasers ablate tissue, low-power lasers stimulate it, encouraging the cells to function. The laser photons are absorbed by mitochondrial chromophores. (cytochrome-c oxidase) stimulating oxidative phosphorylation to increase ATP production and reduce oxidative stress. This effects lead to improved tissue repair, reduces inflammation and reduces pain. LLLT has beneficial effects on many dermatologic disorders including wound healing, hypertrophic scars and burns, herpes simplex, acne and acne scars; wrinkles, vitiligo and psoriasis. LLLT is safe, simple, non invasive, painless, drugless therapy, easy to apply, with no reported side effect.

Laser is an acronym for Light Amplification by Stimulated Emission of Radiation.

LASER COMPONENTS

All lasers contain 3 primary components to operate:

1-Active medium

2- Excitation mechanism and

3- The optical resonator

1- Active medium:

It is a collection of atoms, molecules, or ions which absorb energy from an outside source and generate laser light through atomic processes. The active medium may be solid, liquid or gas.

2- Excitation Mechanism:

It is the input energy device, which could be an intense light source, an electrical current through an active gas, or in the case of dye lasers, light from another laser.

3- Optical Resonator:

Consists of 2 specially designed mirrors, diagrammatically opposed to each other. The high reflectance mirror reflects 100% of the light which strikes it, while the other mirror (partially transmissive mirror) reflects less than 100% of the light which strikes it. The small fraction of light which passes through the partially transmissive mirror is the beam output.¹

The therapeutic action of laser energy is based on the unique properties of laser light and laser tissue interaction.

LASER PROPERTIES

1. **Monochromatic:** The emitted light is of single, discrete wavelength that can be absorbed by specific targets or chromophores.
2. **Coherence:** Laser light traveling in phase with respect to both time and space.
3. **Collimation:** Emission of a narrow, intense beam of light in parallel fashion to achieve

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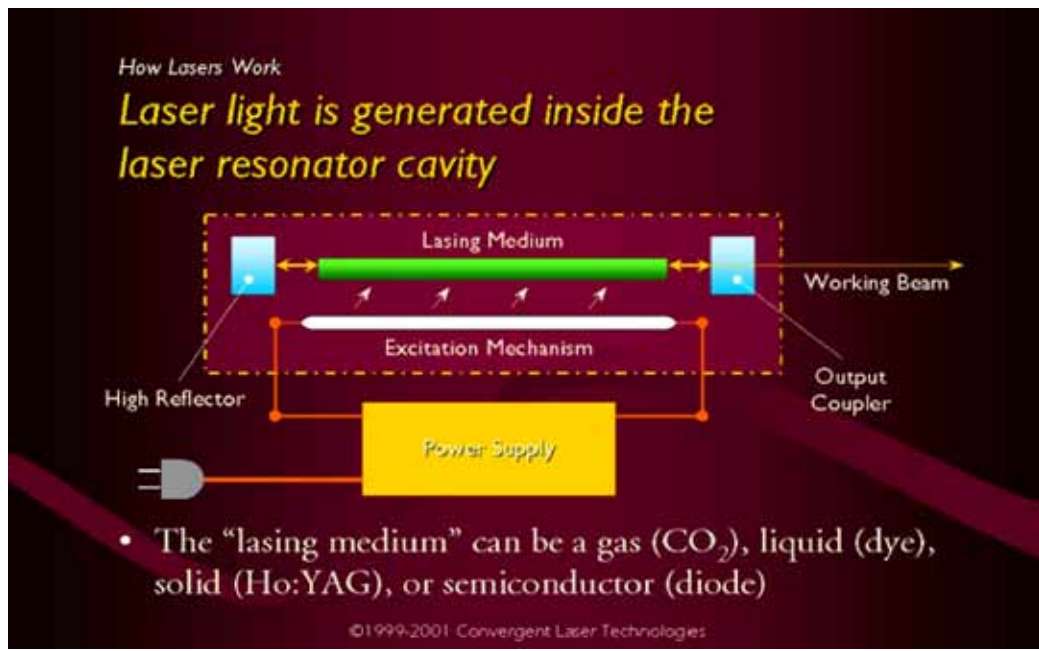


Fig. 1 Primary laser components.

its propagation across long distances without light divergence → so it can be focused into a small spot size.²

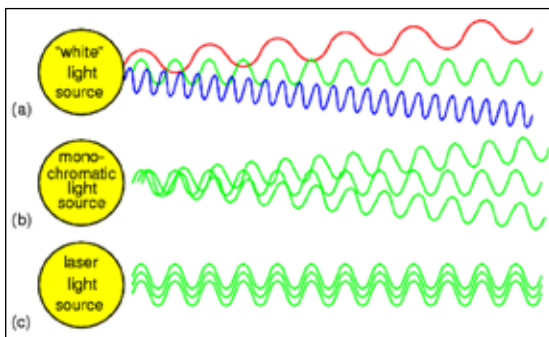


Fig. 2 Characteristics of laser beam.

Laser tissue interaction

When lasers are used on the skin, the light may be absorbed, reflected, transmitted or scattered. The light must be absorbed by tissue for a clinical effect to take place whereas transmitted or reflected light has no effect.³ The energy absorbed is measured in joules per square centimeter and is known as the energy density or fluence. The amount of absorption is determined by the chromophore present in the skin.

Chromophores are substances in tissue that absorb

a specific wavelength of light, it may be endogenous as hemoglobin, melanin and water or exogenous as tattoo ink.⁴ Once laser energy is absorbed in the skin the possible, effects are:

- **Photothermal effects;** occur when chromophore absorbs the specific wavelength of energy and destruction of the target results from the conversion of absorbed energy into heat.
- **Photochemical effects;** derive from native or photo sensitizer effects, are related reaction that serves as the basis of photo dynamic therapy.
- **Photomechanical effects;** the extremely rapid thermal expansion can lead to acoustic waves and subsequent photomechanical destruction of the absorbing tissue.
- **Photoablative** causes photodissociation or breaking of the molecular bonds in tissue.²

The laser tissue interaction depends on the theory of selective photothermolysis. This theory de-

scribes how controlled destruction of targeted lesion is possible without significant thermal damage to surrounding normal tissue.⁵

To limit the amount of thermal energy deposited within the skin, the exposure duration of the tissue to light (pulse duration) must be shorter than the chromophores' thermal relaxation time (the time required for the targeted site to cool to one half of its peak temperature immediately.⁵

Optical properties of tissue and action spectra

Both the absorption and scattering of the light in the tissue are wavelength dependent (both much higher in the blue region of the spectrum than the red). The principle tissue chromophores (hemoglobin and melanin) have high absorption bands at wave lengths shorter than 600 nm. Water begins to absorb infrared wavelength greater than 1150 nm wavelength. For this reasons there is so called optical window in tissue covering the red and NIR wavelengths where the effective tissue penetration of light is maximized. This optical window runs approximately from 650 nm to 1200 nm.³ (Fig. 3)

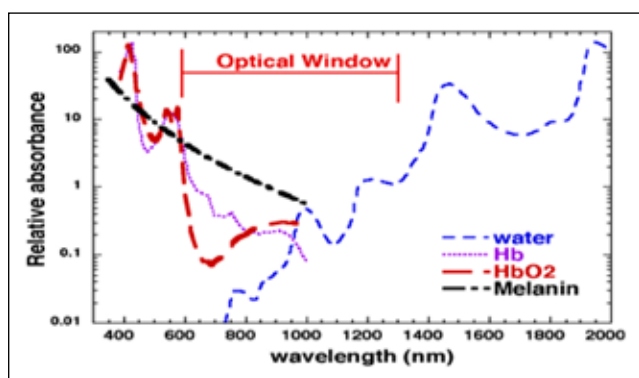


Fig. 3 Optical window in tissue.

LASER CATEGORIES

Lasers are classified either by their active medium, their wavelength or maximum output power.

- Common Laser Solid crystalline materials: e.g. Ruby, Neodymium: YAG

Classification by active medium

Table 1 Common Laser classification by wavelength

Type	Wavelength	
	Nanometer (nm)	Micron (µm)
Ultraviolet (180 to 400nm)		
• Argon fluoride (ArF)	193	0.193
• Krypton Chloride (KrCl)	222	0.222
• Krypton fluoride (KrF)	249	0.249
• Xenon-chloride (XeCl ₂)	308	0.308
• Nitrogen (N ₂)	337	0.337
• Helium- Cadmium (HeCd)	325	0.325
Visible (400 to 700 nm)		
• Helium- Neon (HeNe)	543, 594, 612, 633	0.543, 0.594, 0.612, 0.633
• Krypton (Kr)	647	0.647
• Ruby	694	0.694
• Argon (Ar)	488 to 515	0.488 to 0.515
• Nd: YAG (2 harmony)	532	0.532
Infrared (700nm to 1mm)		
• Gallium Arsenide (diode)	850	0.85
• Carbon Dioxide (Co ₂)	10.600	10.6
• Nd: YAG	1064	1.064
• Ho: YAG	2100	2.1

- Semi-conductor materials (diode): e.g. gallium/arsenide; gallium / aluminum / arsenide
- Liquid dyes: utilize a flowing dye pumped by flash lamp of other lasers

- Gaseous materials: e.g. Helium-Neon, CO₂, Argon, Krypton

Common classification by maximum output power:

I. High power lasers (Thermal lasers)

They are used to cut, coagulate and evaporate tissues. These lasers are often called surgical lasers because they can replace the scalpel of the surgeon as CO₂, KTP (potassium- titanyl-phosphate) and argon pumped tunable dye (APTD).

II. Low level lasers (Therapeutic lasers)

They can be used for the stimulation of cell function. Their biological effect is not thermal.

LLLT is the application of light (usually a low power laser or light emitting diode (LED) in the range of 10 mw- 500 mw) to the tissue to promote tissue regeneration, reduce inflammation and relieve pain. The light is typically of narrow spectral width in the red or near infrared (NIR) spectrum. The reason why the technique is termed low level is that optimum levels of energy density delivered are low when compared to other forms of laser therapy as practiced for ablation, cutting, and thermal coagulation of tissue.⁶ LLLT also known as cold laser, soft laser, biostimulation laser or photobiomodulation laser, and therapeutic laser.⁷ Biomodulations defined as changing the natural biochemical response of cells or tissue within the normal range of its function.

The three main areas of medicine practice where LLLT has a major role to play are as follows: (Fig. 4).

1. Wound healing, tissue repair and prevention of tissue death;
2. Relief of inflammation in chronic diseases and injuries with its associated pain and edema;

3. Relief of neurogenic pain and some neurological problems.

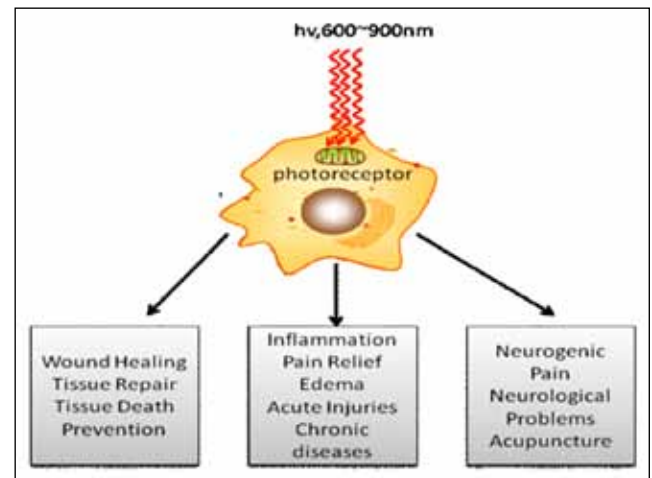


Fig. 4 Schematic representation of the main areas of application of LLLT.

Mechanisms of low level laser therapy:

It was suggested in 1989 that the mechanism of LLLT at the cellular level was based on the absorption of monochromatic visible and NIR radiation by components of the cellular respiratory chain. The inner mitochondrial membrane contains 5 complexes of integral membrane proteins: NADH dehydrogenase (Complex I), succinate dehydrogenase (Complex II), cytochrome c reductase (Complex III), cytochrome c oxidase (Complex IV), ATP synthetase (Complex V) and two freely diffusible molecules ubiquinone and cytochrome c that shuttle electrons from one complex to the next (Fig. 5). The respiratory chain accomplishes the stepwise transfer of electrons from NADH and FADH₂ (produced in the citric acid or Krebs cycle) to oxygen molecules to form (with the aid of protons) water molecules. The energy released by this process of active transport forms a miniature battery.⁸ (Fig. 5).

Cytochrome C oxidase (COX) hypothesis:

Cox is a subunit in the mitochondrial electron transport chain. It is the primary photoacceptor of

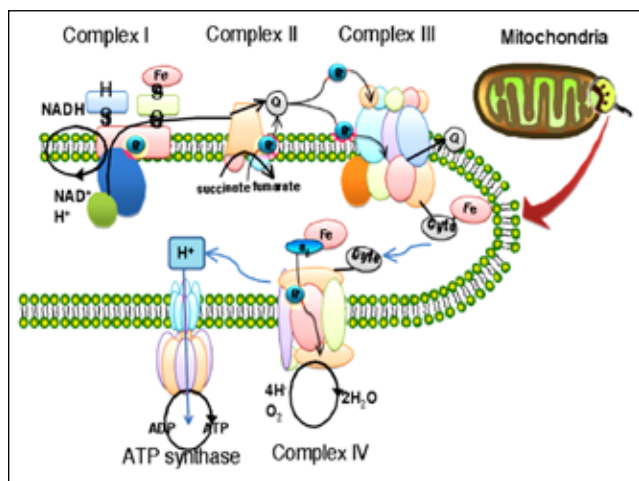


Fig. 5 Structure of the mitochondrial respiratory chain.

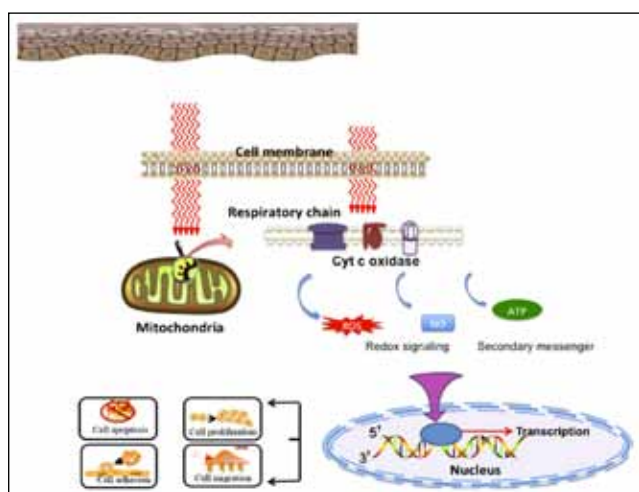


Fig. 6 Mechanism of action of LLLT.

red and NIR range in mammalian cells⁹ (Fig. 6). Cox is multicomponent membrane protein that contains a binuclear copper center (CUA) along with heme binuclear center (α_3 -CUB) both of which facilitate the transfer of electrons from water soluble cox to oxygen to form water and release of energy¹⁰ (Fig. 7).

It is suggested that laser irradiation increases the rate at which Cox transfers electron from cox to dioxygen, also laser irradiation reduces (gain of electron) the catalytic centre of cox making more electrons available for the reduction of dioxygen.¹¹ This acceleration of electron transfer reaction leads to:

1. Increase production of ATP.¹²

2. Reverses the partial inhibition of the catalytic centre by nitric oxide, so increase O₂ binding and respiration.¹³

• **Nitric oxide (NO) hypothesis**

Mitochondria produce an enzyme that synthesizes NO that was identified as neuronal isoforms of NO synthase.¹⁴

Nitric oxide produced in the mitochondria can bind to Cox leading to inhibition of respiration which is explained by direct competition between NO and O₂ for the reduced binuclear centre of Cox, especially in stressed or hypoxic cell.¹⁵ LLLT can reverse the inhibition of Cox caused by NO by photodissociating NO from its binding sites → and so increasing the O₂ binding and respiration rate¹⁶ (Fig. 7).

Nitric oxide can cause vasodilatation that is based on its effect on the enzyme guanylate cyclase (GC) which forms cGMP to phosphorylate myosin and relax smooth muscle cells in the vascular system leading to vasodilatation¹⁷

• **Reactive oxygen species (ROS) hypothesis**

Reactive oxygen species are very small molecules that include oxygen ions such as superoxide, free radicals such as hydroxyl radical and hydrogen peroxide. ROS are formed as a natural by-product of the normal metabolism of oxygen.¹⁸

It is well known that high amount of ROS are lethal to the cell. But, if present at concentrations below what is required for cytotoxicity, ROS have a wide range of positive stimulatory effect on the cell.¹⁹ ROS are involved in the signaling pathways from mitochondria to nuclei, regulation of nucleic acid synthesis, protein synthesis, enzyme activation and cell cycle progression.²⁰

LLLT are reported to produce a shift in over all

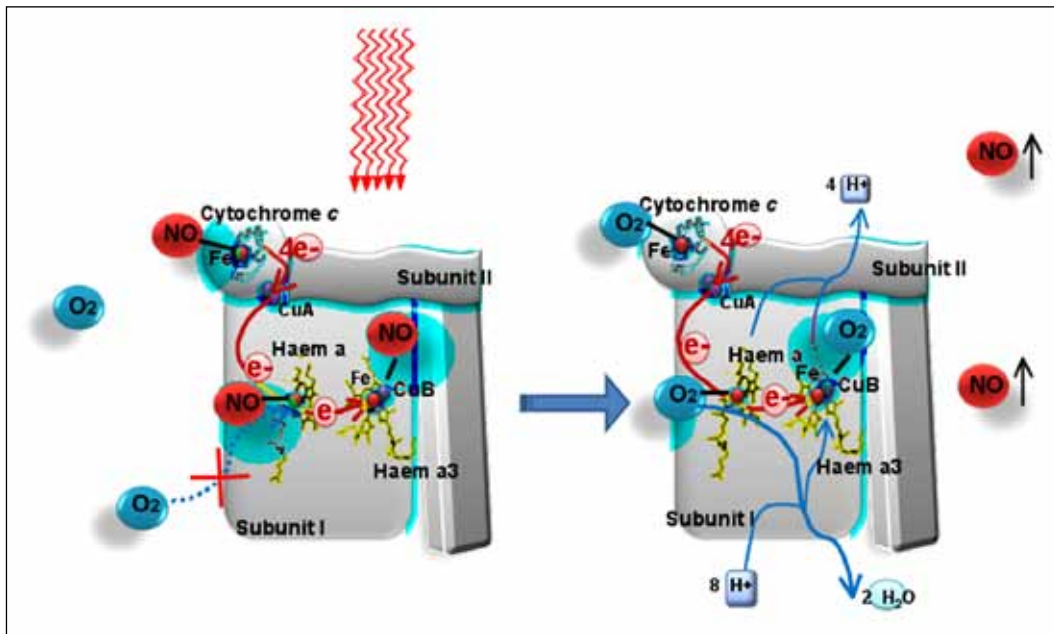


Fig. 7 When NO is released from its binding to heme iron and copper centers in cytochrome c oxidase by the action of light, oxygen is allowed to rebind to these sites and respiration is restored to its former level leading to increased ATP synthesis.⁸

cell redox potential in direction of greater oxidation and increased ROS generation.²¹

Several transcription factors (mainly) nuclear factor kappa B (NF- κ B) and activator protein-1 (AP-1) (Fos and Jun) are regulated by changes in cellular redox state. They become activated following an intracellular redox shift to more oxidized state, with subsequent gene expression and transcription of protective and stimulatory gene product.²² (Fig. 8)

Too much NO and ROS can actually cause damage hence the biphasic dose response of LLLT must be considered.

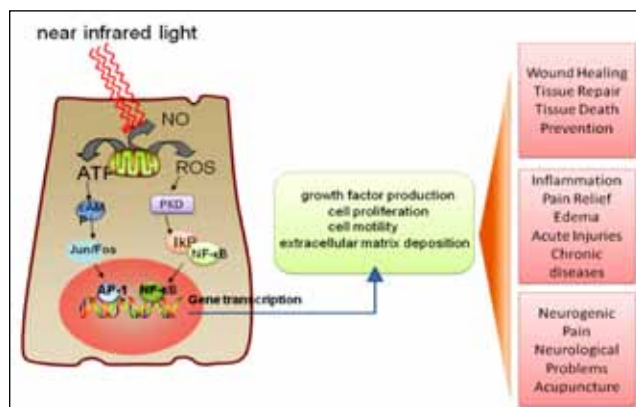


Fig. 8 Proposed mechanism of LLLT

Biphasic dose response

It suggests that if insufficient energy is applied there will be no response (because the minimum threshold has not been met), if more energy is applied the threshold is crossed and biostimulation is achieved but when too much energy is applied the stimulation disappears and is replaced by bio-inhibition instead.⁶ (Fig. 9)

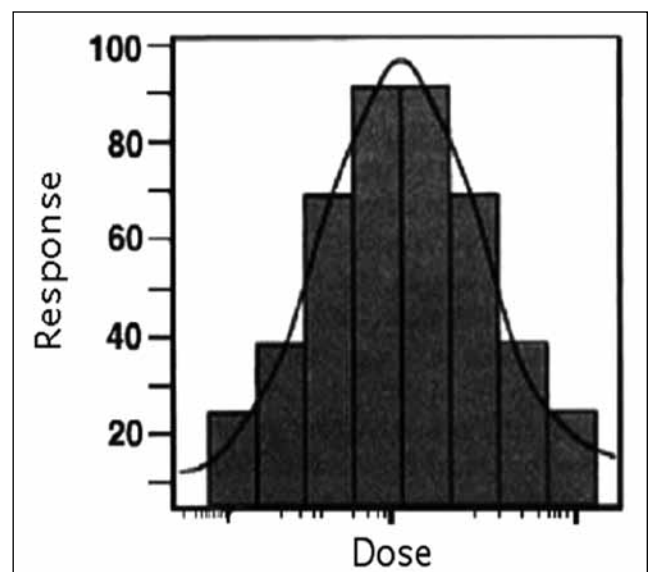


Fig. 9 Idealized biphasic dose response curve (often termed Arndt-Schulz curve) typically reported in LLLT studies.

• **Singlet- oxygen hypothesis**

Certain molecules like porphyrins and flavoproteins can be converted into a long-lived triplet state after photon absorption. This triplet state can interact with ground state oxygen with energy transfer leading to production of singlet oxygen. This is the same molecule utilized in photodynamic therapy (PDT) to kill cancer cells, destroy blood vessels and kill microbes. Researchers in PDT have known for a long time that very low doses of PDT can cause cell proliferation and tissue stimulation instead of the killing observed at high doses.²³

Cellular response to LLLT

LLLT can prevent cell apoptosis and enhance cell proliferation in several types of cells including fibroblasts,²⁴ Endothelial cells,²⁵ and lymphocyte.²⁶ LLLT can also improve cell proliferation,²⁵ migration²⁷ and adhesion.²⁸ These cellular effects support clinical application. (Fig. 10)

Type of Lasers used in LLLT: The vast majority of therapeutic lasers are Semiconductor (Diode) type.

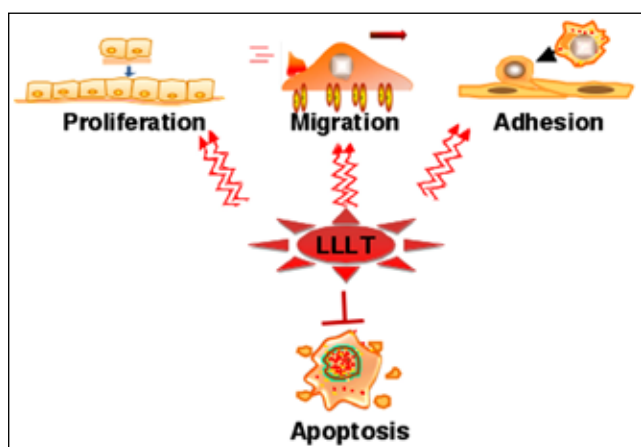


Fig. 10 The downstream cellular effects of LLLT signaling.

(1) Indium, Gallium - Aluminum - Phosphide (In GaAlP):

This is a visible red light diode laser that operates

in the 630-700 nm range. The laser output light is in a continuous manner or pulsed by an electro-mechanical method; it has the least amount of penetration 6-10mm; it affects skin and superficial tissue.

(2) Gallium-Aluminum Arsenide (GaALAS):

This is a near infrared laser (invisible). This laser operates in the 780-980 nm range. It has a continuous and pulsed output. This laser penetrates to 2-3 cm depth. It is utilized for medium to deep tissue structure such as muscles tendons and joints.

(3) Gallium-Arsenide (GaAs):

This laser is a near infrared laser that operates in 904 nm. It is unique in that it is always operates in super pulsed mode (produce very short pulses of high peak power, which allows for deep penetration to the tissue in a short time penetration is 3-5 cm or more.

It is used for medium and deep tissues such as tendons, ligaments and joint.²⁹

(4) Helium-neon (HeNe) laser:

HeNe laser is the oldest and best documented of all the bio-stimulatory lasers. It emits red visible light in continuous wave or pulsed manner. It operates in the 632.8 nm range

The main disadvantages of this laser are its big size and the sensitive laser tube made of glass.³⁰

Light Emitting Diode (LED): It is light source that produce low power, neither mono chromatic nor coherent wave length.

Types of LED:

- Blue LED (400 – 450 nm).
- Red LED (630 – 660 nm).

The difference between a LED and laser diode are negligible at extremely superficial surface. But when targeting deep tissue; it is essential that a coherent laser source is administered.³¹ The coherent light when interact with chromophore, plays a role in biostimulation interaction. The biostimulation effects with LED would be less than with a laser when used at same parameter³² because refraction, reflection, scattering and absorption of non coherent light emitted from LED sources can occur at tissue boundaries leading to greater destructive effect.³³

Indications of LLLT: LLLT was indicated mainly for wound healing and pain relief.

Dermatological indication:

- Wound healing
- Leg ulcers
- Herpes simplex and herpes zoster
- Aphthous stomatitis
- Burns
- Scar and keloid
- Skin rejuvenation
- Hair loss
- Acne vulgaris
- Vitiligo
- Psoriasis

Role of LLLT in wound healing:

The beneficial effect of LLLT on wound healing can be explained by:

- Stimulation of leukocyte chemotaxis and increase macrophage activity (phagocytosis, growth factor secretion).³⁴
- Inhibition of mast cell degranulation (histamine and biological amines secretion).³⁵
- Increase neovascularization due to vascular endothelial growth factor (VEGF) secretion.³⁶

- Increase fibroblast number through up regulation of cytokines responsible for fibroblast proliferation such as BFGF,³⁷ also upregulate TGF-B, a growth factor responsible for inducing collagen synthesis from fibroblast³⁸ (Fig. 11).
- LLLT can induce fibroblasts to undergo transformation to myofibroblast, a cell type that expresses smooth muscle, actin and desmin. It has the phenotype of contractile cells that hasten wound contraction.³⁶
- LLLT have oedema reducing effects through increased vascularization, acceleration of lymphatic flow and enhanced tissue oxygen uptake.³⁹
- Pain relief by LLLT results from suppression of nociceptors (pain receptors) response mediated by increase endorphin release.⁴⁰
- LLLT can induce keratinocyte proliferation and stimulate early epithelialization.⁴¹
- Greater healed wound tensile strength through enhancement of collagen gene expression, increased amount of collagen production/synthesis, reorientation of collagen fibres and increased complex mucopolysaccharides

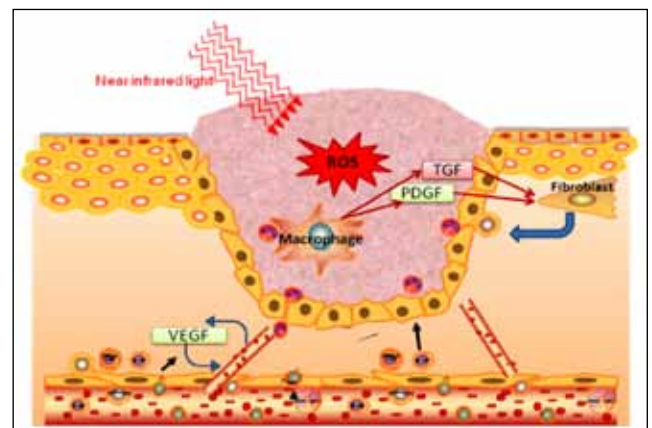


Fig. 11 Mechanism of LLLT wound healing

content.³⁹

Types of wounds can be treated with LLLT: Leg ulcers, bed sores, surgical wounds, oral ul-

cers, neuronal tissue disease.

Herpes simplex and herpes zoster:

Although potent agents against herpes virus infections have become available, there is increase in drug-resistant herpes virus strains to acyclovir and famciclovir.⁴² Moreover, the intermittent administration of acyclovir does not alter the frequency of recurrence.⁴³ LLLT has been suggested as an alternative to current medications for accelerated healing, reducing symptoms, and influencing the length of the recurrence period.⁴⁴ LLLT stimulates healing of ulcer, relief of pain and have immune modulatory effect.⁴⁵

LLLT have an indirect effect of on cellular and humoral components of the immune system involved in antiviral responses rather than a direct virus-inactivating effect.⁴⁶ Laser rays penetrate directly into the nerve tissue - ganglion where the virus is usually localized in latent state, that makes it possible for eliminating the virus and for curing the patients.⁴⁷ LLLT is contraindicated in case of corneal affection. Recommended dosages are 1–2 J/cm², daily sessions, 5–15 times in total.⁴⁸

Aphthous stomatitis:

LLLT brings a quick and visible effect. Quick healing and significant relief of soreness and sensitivity, similar to herpetic eruptions, can be noticed. Aphthae usually heal up within several hours, the worst cases in less than two days. Dosage 0.4–0.6 J/cm², 1–2 applications per day recommended.⁴⁸

LLLT of burns:

Biostimulation effect speeds up regeneration and epithelization of I–III grade burns. We proceed along the same lines as in wounds and ulcers management. LLLT also provides analgesia, prevents

infection and improves the quality of the scar by inducing normal collagen production (prevent keloid).⁴⁸ Decreased symptoms of burning, redness, swelling, and peeling were reported by patients receiving LED treatment (590 nm) for acute sunburn using a once-or twice daily treatment regimen for 3 days, treating only half of the affected anatomic area.⁴⁹ Applied dosages range between 3–8 J/cm², according to burns grade. In contrast to other types of wounds, burns should be treated daily to fulfill the high energy demand of the healing tissue; also direct skin contact with the laser probe should be avoided.⁴⁸

LLLT for hair growth:

There is little scientific data supporting laser/light sources in hair loss treatment, the mechanism of action by which photobiomodulation stops or reverse male or female pattern hair loss is unknown.⁵⁰ One theory suggests that the infrared light increases the cellular metabolism accompanied by an augmentation of the capillary vascular bed of the radiant zone with increased blood flow and oxygen supply.⁵¹

Clinical examples of photo-induced hair growth include the paradoxical growth of hair that occurs in a small percentage of patients undergoing laser hair removal and PUVA to treat alopecia totalis.⁵² It has been suggested that LLLT transfers light energy to the hair cells. Causes increased ATP and growth activity.⁵³ Acceleration of hair cycle is another hypothesis by Satino and Markou.⁵⁴

LLLT does not appear to be effective in treating areas which are already bald and is more effective at treating areas which are thinning. The treatment protocols involve 15 to 30 minute treatment on alternating days for 2–4 weeks, tapering to one to two treatments per week for 6–12 months fol-

lowed by bi weekly and once per month maintenance treatment. Recommended dosage is 0.05–0.1 J/cm².⁵⁰

Acne vulgaris:

Acne is one of the most common skin conditions. Different treatment modalities have been used including topical and systemic antibiotic, retinoids and chemical peel with variable success rates.⁵⁵ However, an increase in antibiotic resistance of propionibacterium acne (*P. acne*)⁶⁵ and adverse effects of systemic retinoids are becoming obstacles for acne treatment.⁵⁷

Mechanism of acne treatment by LED source:

(1) Blue light Diode therapy 405–420 nm (Optimum 415 nm):

Kills bacteria: *P. acnes* produce coproporphyrin III as a part of its normal metabolism. When this porphyrin is exposed to blue light (415nm), it is excited and photodynamic reaction can occur with release of ROS and singlet oxygen that results in bacterial destruction. This reaction occurs inside the bacteria with sparing of surrounding tissue.⁵⁸

(2) Red light Diode therapy 655–665 nm (Optimum 660nm):

Anti-inflammatory action reduces the redness and inflammation associated with LED sources.

Mechanism of acne treatment by NIR laser light:

Increased cell activity during wound healing, stimulate new collagen production and improve skin firmness and elasticity.⁵⁹ Combined treatment of blue LED and red LED can be used alternatively to improve severe inflammatory and cystic acne.

Lee et al.⁵⁸ treated facial acne patients by both blue and red LED. The treatment includes two sessions/week for 4 weeks with 415 nm blue light being used for the 1st treatment followed by 633 nm red treatment for the second session. They reported that the clearance rates were significantly higher than antibacterial and anti-inflammatory effect of blue and red light respectively.

LLLT and vitiligo:

Vitiligo is skin disorder characterized by loss of functional melanocyte. Keratinocytes contribute to melanocyte homeostasis and keratinocytes alternation may play a role in melanocyte dysfunction. Both nerve growth factor (NGF) and basic fibroblast growth factor (bFGF) stimulate melanocyte migration, and deficiencies of these mediators may participate in the development of vitiligo.⁶⁰

In 2003, Yu et al.⁶¹ reported that helium-neon laser irradiation stimulates migration and proliferation in melanocytes and induces repigmentation in segmental type vitiligo. They found a significant increase in bFGF release from both keratinocytes and fibroblast and a significant increase in NGF release from keratinocytes. Another study by Lan et al.⁶² demonstrated that the HeNe laser (632.8 nm, 1 J/cm², and 10mW) stimulates melanocyte proliferation through enhanced $\alpha 2\beta 1$ integrin expression and induces melanocyte growth through upregulation of the expression of phosphorylated cyclic-adenosine monophosphate response element-binding protein, which is an important regulator of melanocyte growth.

LLLT and skin rejuvenation:

Intrinsic aging and photoging of the face result in the typical “aged” face, it usually presents with

wrinkles, dyspigmentation, telangiectasia, and loss of elasticity.⁶³ Ablative and nonablative resurfacing have been used.⁶⁴ In ablative resurfacing the epidermis is removed and replaced with a new epidermis which has long patient down time. LLLT as non ablative modality the epidermis is spared, so there is no prolonged post operative recovery period in which the skin is scalded and the patient has to rest at home. Furthermore, there is no prolonged redness or skin hyperirritability.⁶⁵ LLLT of aged skin depends on its ability for new collagen synthesis, collagen remodeling with removal of abnormal and damaged collagen. LLLT increases cell vitality by increasing ATP production.⁴ LLLT is already known to increase microcirculation and vascular perfusion in the skin, alter platelet-derived growth factor (PDGF) and transforming growth factor (TGF- β 1) expressions, and inhibit apoptosis.⁶⁶

Psoriasis:

In 2010 Ablon.⁶⁷ investigated the efficacy of a combination of 830nm (NIR) and 630 nm (visible red light) to treat recalcitrant psoriasis using LED irradiation. All patients with psoriasis resistant to conventional therapy were enrolled and treated sequentially with 830 nm and 630 nm wavelengths in two 20-minute sessions, with 48 Hours between sessions, for 4 or 5 weeks. The results showed no adverse side effects and a resolution of psoriasis.

CONCLUSION

LLLT is safe, simple, non invasive, painless, drugless therapy, easy to apply, with no reported side effect. Treatment time are less, may last from 1 minute up to 2 minute. Unlike high powered surgical lasers, LLLT can be used on all skin types

and cause no discomfort at all.

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