ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

*International Journal of Dental Science and Innovative Research (IJDSIR)*
*IJDSIR : Dental Publication Service*
*Available Online at: www.ijdsir.com*
*Volume – 3, Issue – 4, August - 2020, Page No. : 543 - 554*

# Bio stimulation - The stimulus for the periodontal healing and regeneration

[1]Dr Shivaprasad, Postgraduate, Department of Periodontics, A J Institute of Dental Sciences, Mangalore 575004

[2]Dr Nagarathna DV, Professor , Department of periodontics , A J institute of dental sciences, Mangalore

**Corresponding Author:** Dr Nagarathna DV, Professor, Department of Periodontics, A J Institute of Dental Sciences, Rajiv Gandhi University of Health Sciences, Mangalore 575004.

**Citation of this Article:** Dr Shivaprasad, "Bio stimulation - The stimulus for the periodontal healing and regeneration", IJDSIR- August - 2020, Vol. – 3, Issue - 4, P. No. 543 – 554.



**Type of Publication:** Original Research Article

**Conflicts of Interest:** Nil

## Abstract

The laser dentistry is having a positive effect on the dental treatment in all the fields of dentistry. This has led to the emerging of a new Low level laser therapy (LLLT) treatment that is creating a revolution in the field of dentistry. Photo biomodulation therapy or Low level laser therapy is a light source treatment that produces light of a solo wavelength. The low-level lasers do not result in temperature raise inside the tissue, but fairly produce their effects from photo biostimulation effect within the tissues. Low level lasers do not cut or ablate the tissue. The therapy performed with low-level lasers is called as LLLT. The use of LLLT has become popular in a range of clinical applications in periodontics comprising promotion of wound healing and lessening of pain following nonsurgical and surgical procedures. This article discusses the effect of Laser biostimulation and the potential effects that it can have on the different aspects of the periodontium and how this therapy can be used to enhance the effects of the periodontal surgical procedures.

**Keywords:** Laser, Laser biostimulation, Mechanism of action, Periodontal wound healing, Hard tissues.

## Introduction

Nowadays, the use of laser has a very important role in the field of cosmetic dentistry, providing a source for specialists who perform aesthetic procedures. Lasers have been used for various treatment modalities like, bacterial reduction, calculus removal, decontamination of the roots and implant, soft tissue excision and photo bio modulation of soft and hard tissues in the field of periodontics.

A laser is a device which consists of solid, liquid or gaseous substances which produces a light beam when it is excited by a source of energy. LASER is an acronym for light amplification by stimulated emission of radiation. Laser is monochromatic, coherent and collimated beam which can remain narrow for long distance and can be tightly focused. When directed and focused, it may result in absorption, transmission and scattering of laser,

Lasers can be classified into two categories: high-power lasers (Surgical lasers), featuring thermal effects with cutting, vaporization and hemostasis properties, and low power lasers (Therapeutic lasers), with analgesic, anti-inflammatory and biostimulative properties (Silva et al, 2007; Barros et al., 2008)

Lasers treatment depends on the wavelength and characteristics of the tissue. Degree of absorption of laser energy in tissue will vary as a function of the wavelength and optical characteristics of the target tissue. If the peak emission of the laser matches the absorption spectrum of one or more components of the target tissue, a predictable and specific interactive effect will occur.[1]

Bio stimulation includes irradiation of a cell culture or tissue at a low irradiance with the aim of stimulating or enhancing a variety of interrelated mechanisms, which would eventually result in faster resolution of the inflammatory response, decrease in pain, and better tissue repair osseous stimulation.[2]

The aim of this paper is to present the use of LLLT in periodontal therapy

**Historical background**

The laser is often grouped with the transistor and the computer as landmark inventions of the mid-20th century. The first conceptual building block of the laser was Albert Einstein's 1916 proposal that photons could stimulate emission of identical photons from excited atoms. This led to the burst of the laser concept and physicists started experimenting with higher frequencies and the race began to build a laser device.

The first laser device was created by Theodore Maiman in 1960, based on theories which were derived by Einstein in the early 1900s[3]

He demonstrates ruby laser at Hughes Research Labs on May 16, 1960. Later, Ali Javan, William Bennett, and Donald Herriott of Bell Labs make helium neon laser, the first continuous-wave laser and the first gas laser. Further, H. W. Marcos, and Le Grand van Uitert of Bell demonstrate lasing in Nd-YAG, which would become the dominant solid state laser.[4]

Robert Hall, GE R&D Labs in 1962 come up with the first semiconductor diode laser. Which now are are being extensively used in the field of dentistry[5]

In 1964, Patel at Bell Laboratories developed the CO2 laser.[6]

Sooner dental researchers began investigating lasers' potential and Stern and Sognnaes reported in 1965 that a ruby laser could vaporize enamel.[7] The thermal effects of continuous wave lasers at that time would damage the pulp. Other wavelengths were studied over the ensuing decades for both hard and soft tissue applications. The year 1997 saw the FDA authorization of the first true dental hard tissue Er:YAG laser and the Er,Cr:YSGG a year later.[8]

**Properties of laser**

We need to know some of the properties the laser withholds to understand the behavior of it. They are[9] :

**Velocity:** The speed of light in a vacuum = 2.99×1010cm/sec.

Amplitude: The total height of the wave from peak to peak.

**Wave length:** The distance between any two corresponding points on the wave.

Frequency: A number of wave cycles per second.

**Emission modes**

Laser light is unique in that it is monochromatic (light of one specific wavelength), directional (low divergence), and coherent (all waves are in a certain phase relationship to each other). These highly directional and monochromatic laser lights can be delivered onto target tissue as a continuous wave, gated-pulse mode, or free running pulse mode.[10]

**1. Continuous waves:** The beam is emitted at one power level continuously as long as the foot switch is pressed.

**2. Gated-pulse mode:** The laser is in an on and off mode at periods. The duration of the on and off timer is in microseconds.

**3. Free running pulse mode:** Very large laser energy is emitted for an extremely short span in microseconds, followed by a relatively long time at which the laser is off.

**Uses of lasers in periodontics**

In the field of periodontics, lasers have been used extensively for various treatments of hard and soft tissues. The use of these lasers has made the patients less apprehensive about the treatment and also has helped the clinician in better handling of the soft and hard tissues. Some of the treatment modalities being the treatment of Dentine Hypersensitivity with lasers, which induces occlusion or narrowing of dentinal tubules (Lan & Liu 1995), as well as direct nerve analgesia, via pulpal nerve system. It has been hypothesized that the laser energy interferes with the sodium pump mechanism changes the cell membrane permeability and / or temporarily alters the endings of the sensory axons.[11]

Also, in laser de epithelization for enhanced GTR, CO laser creates a rather unique wound in the gingival tissue. It is not a burn, rather an instantaneous vaporization of the intercellular fluid and a resulted disintegration of the cell structure. The laser wound on skin and gingiva causes a delay in re epithlization because of factors such as reduced inflammatory response and less wound contraction to obtain a new attachment.[12]

Gingival and cutaneous melanin pigmentation is often a source of an aesthetic problem. Several lasers are used for ablation of cutaneous pigmented lesions and oral lesions, among them are ruby, dyed pulsed, Nd:YAG, CO and eximer laser.

Also as LNAP (laser new attachment procedure): the laser is used to remove the epithelial lining of the sulcus as well as junctional epithelium.

Biopsy and excision of soft tissue pathologies.[13]

Osseous surgery: The use of erbium lasers is becoming increasingly popular for bone surgery. Erbium lasers, in general, offer more precision and better access than mechanical instruments. They reduce the risk of collateral damage, particularly when compared with rotary instruments that may become entangled with soft tissue.[14]

Lasers in implant therapy: Use of laser in implant may have several advantages, including improved hemostasis, production of a fine cutting surface with less patient discomfort during the postoperative period, and favorable and rapid healing following abutment placement, thus permitting a faster rehabilitative phase because of the ability of the laser to produce effective bone tissue ablation.[15]

**Laser bio stimulation**

Due to potentially damaging effect of lasers on the tissues depending on their wavelength and thus absorption characteristics, lasers being used at lower intensities showing analgesic, anti-inflammatory and healing properties, that can be widely used in the process of tissue repair as these wavelengths and low densities can penetrate the tissues.[16]

The principle of using low level laser therapy (LLLT) is to supply direct biostimulative light energy to body cells. Absorbed laser energy causes stimulation of molecules and atoms of cells .Using low-intensity laser radiation on the tissues does not cause rapid and significant increase in tissue temperature.[17]

**Mechanism of action**

The biostimulatory and inhibitory effects of LLLT are governed by the Arndt-Schulz law. According to this law, low-dose will increase physiologic processes, and strong stimuli will inhibit physiological activity. The output powers for LLLT range from 50 to 500 mW with wavelengths in the red and near infrared of the electromagnetic spectrum, from 630 to 980 nm with pulsed or continuous-wave emission.

The low-level lasers do not cause temperature elevation within the tissue, but rather produce their effects from photobiostimulation effect within the tissues. Low-level lasers do not cut or ablate the tissue. The therapy performed with low-level lasers is called as LLLT or therapeutic laser therapy, and this therapy has been referred as biostimulation and biomodulation.[18]

The mechanisms of low level laser therapy are complex, but essentially rely upon the absorption of particular visible red and near infrared wave lengths in photoreceptors within sub-cellular components, particularly the electron transport chain within the membranes of mitochondria. Biostimulatory effect of laser irradiation represents a set of structural, biochemical and functional changes in living microorganisms. It acts directly on stimulating components of the so-called antenna pigments of the respiratory chain and manifest as an immediate effect cell vitalization by adenosine triphosphate (ATP) mitochondrial production increase. Laser enhanced biostimulation has been reported to induce intracellular metabolic changes, resulting in faster cell division, proliferation rate, migration of fibroblasts and rapid matrix production.[17]

Biostimulatory effect of laser irradiation is determined by the magnitude of the absorbed light energy. Energy depth of penetration depends on factors such as wavelength, optical and temperature characteristics, power, energy values, exposure time, wave shape, and optical characteristics of tissue-absorption and scattering coefficient.

Photon absorption causes shift in the molecular configuration of the photoacceptor, accompanying with an associated alteration in the molecular signal of the cell. The alterations in photoacceptor function are the primary reactions and subsequent alterations in cellular signaling, and cellular functions are secondary reactions.[18]

**Primary reactions**

The first mechanism, proposed in 1981 for the action of LLLT was the singlet oxygen hypothesis.Certain photo-absorbing molecules like porphyrins after absorption of laser light lead to the generation of singlet oxygen, which are needed for stimulation of RNA and DNA synthesis rate.

The next mechanism proposed in 1988 was redox properties alteration hypothesis. According to this hypothesis, photoexcitation of certain chromatophores in the cytochrome c oxidase molecule influences the redox state and consequently, the rate of electron flow in the molecule.[18]

The latest development proposed NO hypothesis that stated that laser irradiation and activation of electron flow in the molecule of cytochrome oxidase could reverse the partial inhibition of the catalytic center by NO. Transient local heating hypothesis states that local transient rise in temperature of absorbing biomolecules may cause structural changes and trigger biochemical activity.[18]

In 1993, superoxide anion hypothesis suggested that activation of the respiratory chain by irradiation would also increases the production of superoxide anions.[19]

**Secondary reactions**

The secondary reactions that occur after light absorption are cellular signaling pathways and mitochondrial retrograde signaling. The mitochondrial retrograde signaling is the communication in cells from mitochondria to the nucleus that influences many cellular activities, under both normal and pathophysiological conditions. The low-intensity red and near-infrared light act on cells through a primary photoacceptor, cytochrome C oxidase, the terminal enzyme of the mitochondrial electron transport chain. Absorption of light by cytochrome C oxidase can increase the mitochondrial membrane potential, thereby releasing ATP and reactive oxygen species, which leads to increased energy availability and signal transduction.[18]

The overall redox state of a cell represents the net balance between stable and unstable reducing and oxidizing equivalents. Recent studies have revealed that many cellular signalling pathways are regulated by the intercellular redox state. Oxidants stimulate cell signaling systems, and reductants suppress the upstream signaling cascades, resulting in suppression of transcription factors. The redox based gene expression is a fundamental mechanism in cell biology.[18]

In phagocytic cells, irradiation initiates a non-mitochondrial respiratory burst (production of reactive oxygen species, especially superoxide anion) through activation of nicotinamide adenine dinucleotide phosphate-oxidase located in the plasma membrane of these cells. The irradiation effects on phagocyte cells depend on the physiological status of the host organism as well as on radiation parameters.[18]

**Evolution of the Low level Laser**

The first commercialized biostimulative laser was a helium neon (HeNe) laser of <1 mW. The use of HeNe laser for biostimulation is limited by the need for an optic fiber, the size of the machine and the still rather low power option, now typically in the range 5-25 mW. It has generally been replaced by the indium-gallium-aluminum-phosphide laser, a diode producing red laser in the range 600-700 nm and able to deliver as much as 500 mW. The most frequently used laser for LLLT in dentistry is the gallium-aluminumarsenide laser. It often operates in the spectrum between 780 and 830 nm. The output is typically between 10 and 500 mW. An advantage of the diode lasers is the small size and option for battery operation, making them rather handy and portable. These lasers are work in continuous mode, but can be mechanically or electronically pulsed[20]

**Clinical applications of low-level laser therapy**

The application of low-level lasers in medicine was introduced in the 1970s and 1980s. Since then considerable scientific work including the use of cell cultures, animal models and clinical studies has been undertaken to evaluate its potentially beneficial effects. The application of LLLT has become popular in a variety of clinical applications, including promotion of wound healing and reduction of pain. Lowlevel laser applications in dentistry include the promotion of wound healing in a range of sites, like surgical wounds, extraction sites, recurrent aphthous ulcerations, etc.[21]

Applications of LLLT in dental and periodontal treatments show a variety of improved beneficial effects on the hard and soft tissues.

**Effects of laser bio stimulation in periodontics**

**Laser bio stimulation on periodontal inflammatory process**

The chronic periodontal inflammatory process leads to the destruction of the periodontal ligament, and subsequently, to loss of alveolar bone.[22] The anti-inflammatory and anti-edema effects exerted by laser occur through acceleration of microcirculation, resulting in changes in capillary hydrostatic pressure with edema reabsorption and disposal of the accumulation of intermediary metabolites.[16] It has been reported that LPT is able to reduce gingival inflammation and metalloproteinase 8 expression when applied after scaling and root planning.[23,24,25]

Ozawa et al.[26] showed that LLLT significantly inhibits the increase in plasminogen activity induced in human periodontal ligament cells in response to mechanical tensile force. Plasminogen activity is capable of activating latent collagenase, the enzyme responsible for cleaving collagen fibres.[27] LLLT also effectively inhibits PGE2 synthesis. LLLT can modulate the periodontal inflammatory process, especially through reducing PGE2release.[28]

Safavi et al. evaluated the effect of LPT on gene expression of IL-1β, interferon-γ (IFN-γ) and growth factors (platelet-derived growth factor [PDGF], transforming growth factor-β [TGF-β] and basic fibroblast growth factor) to provide an overview of laser influence on their interactive role in the inflammatory process.[29]

Nomura et al. reported that LPT significantly inhibited LPS stimulated IL-1β production in human gingival fibroblasts cells, and this inhibitory effect was dependent on radiation time.[29]

**Laser bio stimulation and Analgesia**

The ability of LLLT to exert analgesic effects has historically been a major clinical application of the technique. In vivo studies of the analgesic effect of LLLT on nerves supplying the oral cavity have demonstrated that LLLT decreases the firing frequency of nociceptors, with a threshold effect long-standing post –surgical IDN injury were assessed.[30,31] LLLT involved treatment along the distribution of the nerve for a total of 20 treatments. Control subjects received placebo LLLT. The degree of mechanoreceptor impairment and thermal sensitivity disability was comparable in test and control groups before treatment .Following LLLT, the test group showed a significant improvement in mechanoreceptor sensory testing, as well as a subjective improvement in sensory function, indicating that LLLT can improve mechanoreceptor perception in long-standing sensory aberrations in the IDN. However, there was no significant improvement in thermal responses in either group.[29]

**Laser bio stimulation on periodontal wound healing**

Periodontal wound healing is necessary when periodontitis and gingivitis ,or trauma ,have affected the composition and integrity of the periodontal structures.[29] At the cellular level, low-power laser causes biochemical, bioelectric and bioenergetic changes, leading to increased metabolism, cell proliferation and maturation, increased quantity of granulation tissue and reduction of inflammatory mediators, inducing the healing process. Molecular absorption of laser light allows for an increase in cellular metabolism characterized by stimulation of photoreceptors in the mitochondrial respiratory chain, changes in cellular ATP levels, release of growth factors, and collagen synthesis.[16] LLLT( laser Periodontal therapy) has also been shown to cause vaso-dilation,with increased local blood flow. This vasoactive effect is of relevance to the treatment of joint inflammation .LLLT causes the relaxation of smooth muscle associated with endothelium. This vasodilation brings in oxygen and also allows for greater traffic of immune cells into tissue. These two effects contribute to accelerated healing.[32,33]

Studies show that laser therapy increases the levels of ascorbic acid in fibroblasts, thus increasing the formation of hydroxyproline and, consequently, the production of collagen, since ascorbic acid is a cofactor required for hydroxylation of proline during collagen synthesis.[34] Some main biostimulation effects of low-power laser in the process of tissue repair include induction of mitotic activity of epithelial cells and fibroblasts, stimulation of collagen production by those cells, inhibition of secretion of some chemical mediators, change in capillary density and stimulation of local microcirculation.[35]

Several in vitro studies have shown that LLLT at certain wavelengths may stimulate fibroblast proliferation when certain combinations of exposure parameters and power densities are used.The range of radiation doses at which stimulation of fibroblast proliferation has been observed is wide (0.45-60 J/cm2).Of note high dose LPT suppresses both fibroblast proliferation and autocrine production of basic fibroblast growth factor.[36]

LLLT effects on macrophages include increased ability to act as phagocytes, and greater secretion of basic fibroblast growth factor. Macrophages resorb fibrin as part of the demolition phase of wound healing more quickly with LLLT, because of their enhanced phagocytic activity during the initial phases of the repair response (for example,6 hours after trauma).More rapid demolition of the wound establishes conditions necessary for the proliferative phase of the healing response to begin.[29]

Wound healing consists of several distinct phases, all of which can be affected at the cellular level by LLLT. The initial, pro-inflammatory and vaso-active phases of inflammation include clotting of any cut blood vessels and deposition of a platelet plug, after which the site is infiltrated by neutrophils and macrophages.[37]

The second phase of wound healing involves proliferation, with the formation of granulation tissue as a result of new blood vessel growth. Direct evidence for enhanced collagen gene expression both in skin fibroblast cultures in vitro, as well as in animal models of wound healing in vivo, has been presented.[38] A final aspect of the effect of LLLT on cells relates to the effects of laser light on the cytoskeleton. Several studies have suggested that LLLT can modulate cell behaviour by causing re-arrangements of the cytoskeleton.[39,40]

Faster wound closure is of great importance in compromised patients, such as diabetics, and patients undergoing treatment for malignancies. Because LLLT can enhance the release of growth factors from fibroblasts, and can stimulate cell proliferation, it is able to improve wound healing in such compromised patients. Histological studies have demonstrated that laser irradiation improves wound epithelialization, cellular content, granulation tissue formation, and collagen deposition in laser-treated wounds, compared to untreated sites.[35,41] These findings have been confirmed in oral mucosal wound healing in clinical studies in humans.[42]

In order to analyze the effect of low-power laser on the proliferation of gingival fibroblasts in vitro, Almeida-Lopes, Rigau, Zangaro, Guidugli-Neto, and Jaeger 23 applied a laser diode on cultured human gingival fibroblasts with a fluence of 2 J/cm2 and the following wavelengths: L1= 670nm, L2 = 780nm, L3 = 692nm and L4 = 786nm. For the analysis of growth, non-irradiated cultures (control group) and those treated with the laser (experimental group) were placed on a 60mm-diameter Petri dish 12 hours before irradiation. In this experiment, the researchers concluded that low-level laser enhances proliferation of gingival fibroblasts regardless of the wavelength used and that the shorter the time of exposure to the laser, the higher the proliferation.[43]

A systematic review by Bjordal et al. concluded that LPT can modulate the inflammatory process in a dose-dependent manner and that it can be titrated to significantly reduce acute inflammatory pain in the clinical setting. The author confirmed that, in acute pain, the optimal effects of LPT can be achieved when it is administered in higher energy densities during the first 72 h in order to reduce inflammation, followed by lower dosages to the target tissue during the following days with the aim of promoting tissue repair.[44]

**Laser bio stimulation on Antimicrobial Photodynamic Therapy**

Differently from high-power lasers, low-power lasers do not increase tissue temperature.[45] Thus, when used alone the same antimicrobial effect as that of high-power lasers in periodontitis active sites cannot be expected.[46] The antimicrobial effect low-power lasers is achieved by association with extrinsic photosensitizers ,which results in the production of highly reactive oxygen species[47] that cause damage to membranes, mitochondria and DNA, culminating in the death of the microorganisms.[48,49,50] This is the process of a PDT, and its use is being increasingly studied with the aim of complementing the microbial reduction achieved by conventional mechanical periodontal therapy.

**Laser biostimulative effects on hard tissues**

Low power laser exerts pronounced effects on cultures of osteoblasts, influencing the processes of proliferation, differentiation and calcification.

In some studies on new bone formation, it is suggested that the biostimulation effect of laser is not only due to its specific properties, but also to the creation of a series of local conditions that accelerate bone formation and resolution of edema.[16]

There are several mechanisms through which low-power laser can induce mitotic activity of fibroblasts. This type of laser stimulates the production of basic fibroblast growth factor (bFGF), which is a multifunctional polypeptide secreted by fibroblasts. It is not only able to induce fibroblast proliferation but also differentiation and it affects the immune cells that secrete cytokines and other regulatory growth factors of fibroblasts. In vitro studies using macrophage lineage cells show that these cells release soluble factors that promote fibroblast proliferation when stimulated by low-power laser radiation. Maturation of fibroblasts and their movement through the matrix are also influenced by this laser.[51]

In the laboratory setting, LLLT using a HeNe laser exerts pronounced effects on proliferation, differentiation and calcification of cultured osteoblastic cells, although there is a specific therapeutic window for these effects. Cell proliferation and DNA synthesis are increased by LLLT only when the cells are in a phase of active growth. LLLT causes increased accumulation of calcium and accelerates calcification in vitro. If the in vivo parallel holds true, LLLT of healing sites within bone would be expected to increase bone deposition and promote bone regeneration.[17] In a study of wound healing after tooth extraction in a rat model, LLLT delivered on a daily basis for one week using a gallium-aluminium-arsenide (Ga Al As) laser, both increased fibroblast proliferation and accelerated formation of bone matrix were found.[52]

However, studies of the influence of LLLT on bone and connective tissue regeneration in the palate in a canine animal model failed to find an effect. While at first glance this would suggest major species variations in the response of bone cells to to LLLT, in the case in point irradiation levels were low and LLLT treatments were administered every second day rather than daily. Whether LLLT exerts positive results on bone regeneration following tooth extractions in humans remains controversial, although there are reports that the formation of granulation tissue during post-extraction healing is accelerated.[53]

For the treatment of intrabony defects, the use of barrier membranes and different types of grafting materials are usually indicated. In the study of effect of LLLT on the healing of bone defects associated with autologous bone grafts, bone remodeling was both quantitatively and qualitatively more evident in irradiated animals than in non-irradiated animals.[54] LLLT bio stimulation of bone tissue attachment to implant surfaces has also been reported.[55] It has been shown that LLLT influences the expression of osteoprotegerin, receptor activator of nuclear factor Kb ligand and receptor activator of nuclear factor k B, and results in the expansion of bone cells metabolic activity.[56,57]

**Conclusion**

The encouraging effect of LLLT is owing to unclear stimulatory action of laser beam by increasing the collagen production, enzyme activity, micro- and lymph-circulation, and fibroblast proliferation, reduction of local hypoxia, anti-inflammatory effect, and pain reduction. There is respectable proof that the heightened cell metabolic functions seen after LLLT are the outcome of initiation of photo-receptors inside the electron transport chain of mitochondria. Upcoming trials of new LLLT applications in dentistry have to make usage of consistent, authenticated outcomes, and should discover how the success of the LLLT protocol used may be influenced by wavelength, treatment duration, dosage, and the site of application.

**References**


1. Barzè, F., Palmieri, B., Scalise, L., & Rottigni, V. (2012). Laser in dentistry: Biostimulation and surgery. *AIP Conference Proceedings*, *1486*(2012), 77–88. https://doi.org/10.1063/1.4757826
2. Deana, A. M., de Souza, A. M., Teixeira, V. P., Mesquita-Ferrari, R. A., Bussadori, S. K., & Fernandes, K. P. S. (2018). The impact of photobiomodulation on osteoblast-like cell: a review. *Lasers in Medical Science*, *33*(5), 1147–1158. https://doi.org/10.1007/s10103-018-2486-9
3. Maiman TH. Stimulated optical radiation in ruby. Nature 1960;187:493-4.
4. Hecht J. Lasers and the glory days of industrial research. Optics and Photonics News. 2010 May 1;21(5):20-7.
5. Gref LG. The rise and fall of American technology. Algora Publishing; 2010.
6. Patel C. Lasers-Their development and applications at AT&T Bell Laboratories. IEEE journal of quantum electronics. 1984 Jun;20(6):561-76.
7. Wilder-Smith P, Nguyen A, Lin S, Berns MW. Effects of cavity preparation using a nanosecond-pulsed Nd-YAG laser on tooth-restoration interface. Lasers in Medical Science. 1997 Mar 1;12(1):11-9.
8. Rowan RC. The effect of two energy density and dose applications of low level laser therapy on orthodontic tooth movement (Doctoral dissertation, Saint Louis University).
9. Sharma BK. Instrumental methods of chemical analysis. Krishna Prakashan Media; 1981.
10. Elavarasu S, Naveen D, Thangavelu A. Lasers in periodontics. Journal of pharmacy & bioallied sciences. 2012 Aug;4(Suppl 2):S260.
11. David CM, Gupta P. Lasers in dentistry: a review. International Journal of Advanced Health Sciences. 2015 Dec;2(8):7-13.
12. Rossmann JA, Israel M. Laser de-epithelialization for enhanced guided tissue regeneration. A paradigm shift?. Dental Clinics of North America. 2000 Oct;44(4):793-809.
13. Ramesh A, Bhandary R, Thomas B, Dsouza SR. Laser-A ray of hope in periodontics-A review article. Nitte University Journal of Health Science. 2014 Sep 1;4(3):138.
14. Padmanabhan P. Lasers and its Application in Periodontology: A Review. Indian Journal of Public Health Research & Development. 2019 Nov 1;10(11).
15. Prabha C, Shreshtha SM. An insight into Lasers in Periodontics: A Review.
16. Lins RD, Dantas EM, Lucena KC, Catão MH, Granville-Garcia AF, Carvalho Neto LG. Efeitos bioestimulantes do laser de baixa potência no processo de reparo. Anais Brasileiros de Dermatologia. 2010 Dec;85(6):849-55.
17. Surendranath P, Arjunkumar R. Low level laser therapy–a review. IOSR J Dent Med Sci. 2013;12:56-9.
18. Suresh S, Merugu S, Mithradas N. Low-level laser therapy: A biostimulation therapy in periodontics.

SRM Journal of Research in Dental Sciences. 2015 Jan 1;6(1):53.

19. Freitas PM, Simoes A, editors. Lasers in dentistry: guide for clinical practice. John Wiley & Sons; 2015 Feb 17.
20. Chung H, Dai T, Sharma SK, Huang YY, Carroll JD, Hamblin MR. The nuts and bolts of low-level laser (light) therapy. Annals of biomedical engineering. 2012 Feb 1;40(2):516-33.
21. Neiburger EJ. The effect of low-power lasers on intraoral wound healing. N Y State Dent J 1995;61:40-3.
22. Kreisler M, Al Haj H, d'Hoedt B. Clinical efficacy of semiconductor laser application as an adjunct to conventional scaling and root planning. Lasers Surg Med 2005; 37:350-5.
23. Qadri T, Miranda L, Tuner J, Gustafsson A (2005) The short term effects of low-level lasers as adjunct therapy in the treatment of periodontal inflammation. J Clin Periodontol 32 (7):714–719.
24. Qadri T, Bohdanecka P, Tuner J, Miranda L, Altamash M, Gustafsson A (2007) The importance of coherence length in laser phototherapy of gingival inflammation: a pilot study. Lasers Med Sci 22(4):245–251.
25. Ribeiro IW, Sbrana MC, Esper LA, Almeida AL (2008) Evaluation of the effect of the GaAlAs laser on subgingival scaling and root planing. Photomed Laser Surg 26(4):387–391.
26. Ozawa Y, Shimizu N, Abiko Y (1997) Low-energy diode laser irradiation reduced plasminogen activator activity in human periodontal ligament cells. Lasers Surg Med 21(5):456–463
27. Pejcic A, Zivkvic V (2007) Histological examination of gingival treated with low-level laser in periodontal therapy. J Oral Laser Appl 71(1):37–43
28. Shimizu N, Yamaguchi M, Goseki T, Shibata Y, Takiguchi H, Iwasawa T, Abiko Y (1995) Inhibition of prostaglandin e2 and interleukin 1-beta production by low-power laser irradiation in stretched human periodontal ligament cells. J Dent Res 74(7):1382–1388
29. Sudhakar U, Thilagar S, Suresh S. Clinical efficacy of low-level laser therapy as an adjunct to nonsurgical treatment of chronic periodontitis. Journal of Dental Lasers. 2015 Jan 1;9(1):31.
30. Kitsmaniuk ZD, DemochkoVB, Popovich VI. The use of low energy lasers for preventing and treating postoperative and radiation induced complications in patients with head and neck tumors. Vopr Onkol 1992:8:980-986
31. Mezawa S, Iwata K, Naito K, Kamogawa H. The possible analgesic effect of soft laser irradiation on heat nociceptors in the cat tongue. Arch Oral Biol 1988:3:693-694
32. Grzesik WJ, Narayanan AS (2002) Cementum and periodontal wound healing and regeneration. Crit Rev Oral Biol Med 13 (6):474–484
33. Pitaru S, McCulloch CA, Narayanan SA (1994) Cellular origins and differentiation control mechanisms during periodontal development and wound healing. J Periodontal Res 29(2):81–94
34. Colven RM, Pinnell SR. Topical vitamin C in aging. Clinics in dermatology. 1996 Mar 1;14(2):227-34.
35. Yu W, Naim JO, Lanzafame RJ. Effects of photostimulation on wound healing in diabetic mice. Lasers in Surgery and Medicine: The Official Journal of the American Society for Laser Medicine and Surgery. 1997;20(1):56-63.
36. Yu W, Naim JO, Lanzafame RJ. The effect of laser irradiation on the release of bFGF from 3T3 fibroblasts. Photochem Photobiol. 1994:59:167-170

37. Walsh LJ, Murphy GF. The role of adhesion molecules in cutaneous inflammation and neoplasia. J Cutan Pathol 1992:19:161-171
38. Abergel RP, Lyons RF, Castel JC, Dwyer RM, Uitto J. Biostimulation of wound healing by lasers: experimental approaches in animal models and in fibroblast cultures. J Dermatol Surg Oncol. 1987:13:127-133
39. Noble PB, Shields ED, Blecher PDM, Bentley KC. Locomotory characteristics of fibroblasts within a three-dimensional collagen lattice: Modulation by a Helium/Neon soft laser. Lasers Surg Med 1992:12:669–674.
40. Pourreau-Schneider N, Ahmed A, Soudry M, Jacquemier J, Kopp F, Franquin JC, Martin PM. Helium-Neon laser treatment transforms fibroblasts into myofibroblasts. Am J Pathol 1990:137:171–178
41. Lyons RF, Abergel RP, White RA, Dwyer RM, Castel JC, Uitto J. Biostimulation of wound healing in vivo by a helium-neon laser. Ann Plast Surg. 1987:18(1):47-50.
42. Marei MK, Abdel-Meguid SH, Mokhtar SA, Rizk SA. Effect of low-energy laser application in the treatment of denture-induced mucosal lesions. J Prosthet Dent. 1997:77(3):256-264
43. Almeida-Lopes L, Rigau J, Amaro Zângaro R, Guidugli-Neto J, Marques Jaeger MM. Comparison of the low level laser therapy effects on cultured human gingival fibroblasts proliferation using different irradiance and same fluence. Lasers in Surgery and Medicine: The Official Journal of the American Society for Laser Medicine and Surgery. 2001 Aug;29(2):179-84.
44. Bjordal JM, Couppé C, Chow RT, Tunér J, Ljunggren EA. A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders. Australian journal of physiotherapy. 2003 Jan 1;49(2):107-16.
45. Dickers B, Lamard L, Peremans A, Geerts S, Lamy M, Limme M, Rompen E, de Moor RJ, Mahler P, Rocca JP, Nammour S (2009) Temperature rise during photo-activated disinfection of root canals. Lasers Med Sci 24(1):81–85
46. Ishikawa I, Aoki A, Takasaki AA (2004) Potential applications of Erbium:YAG laser in periodontics. J Periodontal Res 39 (4):275– 285.
47. Wainwright M (1998) Photodynamic antimicrobial chemotherapy (PACT). J Antimicrob Chemother 42(1):13–28
48. Bhatti M, MacRobert A, Meghji S, Henderson B, Wilson M (1998) A study of the uptake of toluidine blue O by Porphyromonas gingivalis and the mechanism of lethal photosensitization. Photochem Photobiol 68(3):370–376
49. Bhatti M, Nair SP, Macrobert AJ, Henderson B, Shepherd P, Cridland J, Wilson M (2001) Identification of photolabile outer membrane proteins of Porphyromonas gingivalis. Curr Microbiol 43(2):96–99
50. Harris F, Chatfield LK, Phoenix DA (2005) Phenothiazinium based photosensitisers – photodynamic agents with a multiplicity of cellular targets and clinical applications. Curr Drug Targets 6(5):615–627
51. de Freitas LF, Hamblin MR. Proposed mechanisms of photobiomodulation or low-level light therapy. IEEE Journal of selected topics in quantum electronics. 2016 Jun 9;22(3):348-64.
52. Takeda Y. Irradiation effect of low-energy laser on alveolar bone after tooth extraction. Experimental study in rats. Int J Oral Maxillofac Surg 1988:17:388-391.

53. Wahl G, Bastanier S. Soft laser in postoperative care in dentoalveolar treatment. ZWR 1991:100:512-515
54. Weber JB, Pinheiro AL, de Oliveira MG, Oliveira FA, Ramalho LM (2006) Laser therapy improves healing of bone defects submitted to autologous bone graft. Photomed Laser Surg 24 (1):38–44.
55. Ozcelik O, Cenk Haytac M, Seydaoglu G (2008) Enamel matrixderivative and low-level laser therapy in the treatment of intrabony defects: a randomized placebo-controlled clinical trial. J Clin Periodontol 35(2):147–156
56. Kim YD, Kim SS, Hwang DS, Kim SG, Kwon YH, Shin SH, Kim UK, Kim JR, Chung IK (2007) Effect of low-level laser treatment after installation of dental titanium implant – immunohistochemical study of RANKL, RANK, OPG: an experimental study in rats. Lasers Surg Med 39(5):441–450.
57. Lopes CB, Pinheiro AL, Sathaiah S, da Silva NS, Salgado MA (2007) Infrared laser photobiomodulation (lambda 830 nm) on bone tissue around dental implants: a Raman spectroscopy and scanning electronic microscopy study in rabbits. Photomed Laser Surg 25(2):96–101.