

Review

Photobiomodulation in Cells' Repair

Yvona Zivic, HP, PgDp^{1,2*}

¹Health Practitioner, Phototherapy, Naturopathic and Hair Clinician, Sorbonne Université, Paris, France

²Cosmetic Medicine, University of South Wales, United Kingdom

*Corresponding author

Yvona Zivic, HP, PgDp

Health Practitioner, Phototherapy, Naturopathic and Hair Clinician, Sorbonne Université, Paris, France; E-mail: pro.yvonazivic@gmail.com

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ABSTRACT

Photobiomodulation is a non-invasive treatment modality acting at different biological levels through the non-thermal transfer of photons to the living matter *via* a photoelectric effect, inducing photochemical reactions in treated cells. The objective of this article is to review the literature on Photobiomodulation, its different fields of application and mechanisms of action, for establishing a comprehensive summary of evidence. The search strategy initially run searches in scientific databases MEDLINE, PubMed, EMBASE and Cochrane registries from 1990 up to March 2020, with entries Photobiomodulation, LLLT-LEDT, PDT, Photobiology, Cytochrome c Oxidase. Selection criteria was based on preferably inclusion of randomized clinical trials (RCTs), systematic reviews (SR) and studies providing qualitative and quantitative data with the best consistency, in a field where heterogeneity of light parameters is often a difficulty to comparison of findings. Published expert opinions were also considered. A total of 80 publications were reviewed out of a thousand obtained from databases, among which were retained 9 RCTs, 6 systematic reviews, 3 meta-analysis and 2 case-reports. Differences were found in treatment parameters as wavelength, dosage, energy output, treatment length, performances of light-sources, quantity of diodes and single power of these, which may explain the paucity of high-level body of evidence in Cochrane databases. However, numerous state-of-the-art researches are also found, led by dedicated research teams paving the way to standardized methods of evaluation and comprehension of light-biological-tissues interaction and optimization of outcomes in a promising field.

Keywords

PhotoBioModulation; Low-Level-Laser-Therapy (LLLT); Light emitting diodes (LED); Biophotons-mitochondria; Adenosine-triphosphate (ATP); Inflammation-pain-skin rejuvenation; Photo dynamic therapy (PDT); Photobiology.

INTRODUCTION

Photobiomodulation (PBM) is defined as the use of low-level-lasers or light-emitting-diodes (LED) of low-intensity and non-ionizing radiation, emitting visible light from 400 nm to 700 nm and near-infrared (NIR) from 700 nm to 1100 nm in the electromagnetic spectrum, aiming at a biostimulation of exposed tissues.^{1,2} PBM has mostly been studied for pain reduction, mitigation of inflammation and stimulation of wound healing. In the settings of a dermatological or aesthetic medicine practice, PBM has also demonstrated to be a useful tool, assisting practitioners to better address adverse events and recovery time in the aftermath of surgical and non-surgical procedures. Potential side-effects of any intervention, even when minor and temporary, remain anxiogenic for both patient and practitioner, when they can be significantly improved with PBM. These therapeutic effects of photonic en-

ergy have been applied since the beginning of humanity with the use of sunlight, as a photomedicine, for the treatment of a variety of diseases and skin disorders.³ With the progress of sciences and technologies, a more comprehensive understanding of the nature of light, its interaction with matter and particularly with biological tissues, improving wound healing, was achieved.⁴ The decoding of the mechanisms of action of PBM, revealed the role of the cytochrome-c-oxidase as photo-acceptor (CCO) but also the importance of interfacial water layers (IWL) interacting with photons and participating in adenosine-triphosphate (ATP) upregulation.^{5,6} National Aeronautics and Space Administration (NASA), US Navy and UK military, with their own therapeutic experiments in the 1990s, demonstrated faster recovery post-injuries, enhanced wound healing, angiogenesis and cytoprotection.^{7,8} Since three decades, research has demonstrated the efficacy, tolerability and high safety profile of low-level-light-therapies—light-emitting-

diodes-therapies (LLLT-LEDT), alone or in combined protocols, in numerous domains which will be reviewed, as dermatology, rheumatology, sports medicine, gynecology, dentistry, oncology and infectiology.⁹ Supporting tissues to self-repair, energizing cells' metabolism for a faster return to homeostasis, this non-invasive, non-ablative, biostimulative therapy has also shown that cohesion was not an absolute requirement for PBM, introducing the labeling of LLLT.¹⁰

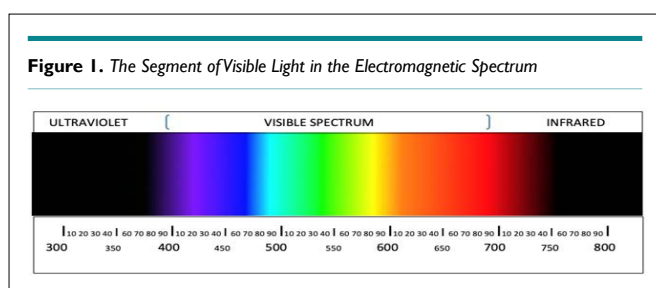
THE NATURE OF LIGHT

Light

Light is a periodic phenomenon, characterized by its frequency (ν) defined into Hertz (Hz), periodicity (T) and wavelength (λ) measured by meter and nanometer (nm) and, the interplay between these parameters participating in the manifestation of light.¹¹ The contact between light and matter generates interaction. Light is absorbed, reflected, deviated or emitted by matter. Absorption occurs when matter retains light without emitting it back, usually transforming light energy into thermal energy; scattering when light is absorbed and re-emitted; reflection when light bounces back on a planar surface with a straightforward, predictable trajectory or multiple trajectories on uneven surface; deviation or refraction when light crosses different propagation mediums and, emission when excited atoms land back from higher orbital levels to their basal level producing radiation in quantifiable emission or luminescence in the visible or non-visible spectrum.^{4,12} Additional properties of the electromagnetic waves are polarization and interference. Hence, light is a wave constituted of a herd of particles or photons behaving wave-like, defined also as light quanta.¹³ Light is carried into waves comprising perpendicular electric and magnetic fields in motion and superposition. Although extremely fast, the speed of light (c) is not infinite, it is considered a universal constant: $c=299,792\,458$ m/s in vacuum, with differences according to the medium it travels.¹⁴

Light Spectrum

The various radiations of the electromagnetic spectrum are differentiated according to their wavelength.¹ A smaller segment of this field is observed when white light passes through a prism and refracts separated colored components, known as the light spectrum, constituted of a range from 400 nm to 700 nm of different wavelengths of light visible to the human eye. Infrared (IR) corresponds to wavelengths above the 700 nm nominal edge of red up



to 1 millimeter and frequency beneath 400 THz (Figure 1). The sources, as lasers, emitting light with a sole wavelength and optical frequency are monochromatic, whereas sources emitting with more than one wavelength and frequency are polychromatic, as is the sun.¹⁵

Interaction Light and Matter

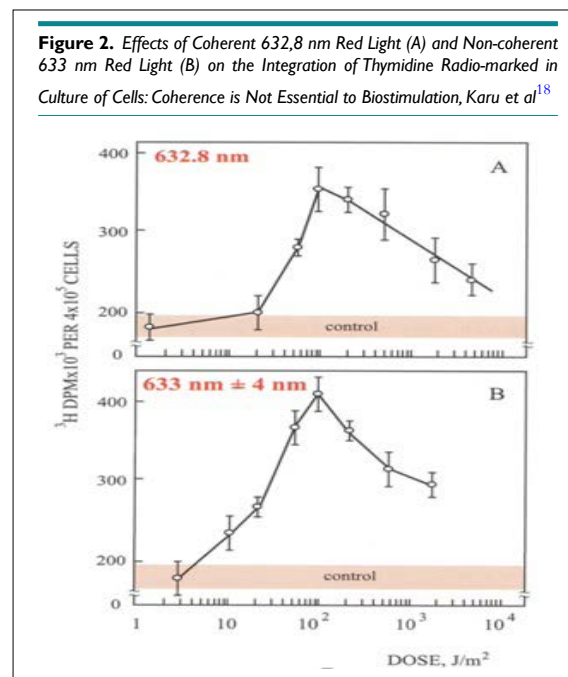
Light interacts with matter by phenomena of absorption, scattering, reflection or refraction. When applied to biological tissues, rays of light constituted of trillions of photons will interact in regard to the optical qualities of the recipient. This communication is the response of biological tissues. The settings and parameters of all light-devices appreciate this response of biological tissues to the light stimuli for optimizing their therapeutic effects. PBM focuses on light absorption by biological tissues, interplay between the photon and its target, also called chromophore or receptor, capturing the energy of light.¹⁶

COHERENCE VS NON-COHERENCE

Distinct Interactions

In 1917, Einstein initiated the concept of monochromatic light in which all photons were to be aligned in a row, leading to the creation of the first laser source in 1960 and later the development of non-coherent light-sources too (Figure 2).^{2,17} Two technologies appeared: the high frequency thermal lasers, applying to targeted chromophores a higher energy than their repairing capacity and, the low frequency non-thermal LLLT or LEDs-sources, applying to chromophores energy levels optimizing cells' repairing capacities.¹⁸ Photobiomodulation was born.

Figure 2. Effects of Coherent 632,8 nm Red Light (A) and Non-coherent 633 nm Red Light (B) on the Integration of Thymidine Radio-marked in Culture of Cells: Coherence is Not Essential to Biostimulation, Karu et al¹⁸



Light interacts with human multi-layered and heterogeneous biological tissues through an array of mechanisms. Depending on the thermal or non-thermal character of light-tissue interaction, the effects induced are either photophysical, photochemical

or photobiomodulative.¹⁸⁻²⁰

Lasers

The thermal effects of coherent lasers characterized by their monochromaticity and single wavelength, produce, depending on the degree and duration of the heating of tissues, either hyperthermia (41-44°), coagulation (50-100°), vaporization (100°) or the melting of tissues (above 300°), thoroughly described by Ansari et al.⁴ These thermal modifications, also influenced by the distribution of temperature in targeted tissues, result into different applications from dermatological surgery, ophthalmology, odontology, gynecology, gastroenterology, arthroscopy with the use of endoscopes, angioplasty and radiological monitoring.⁴

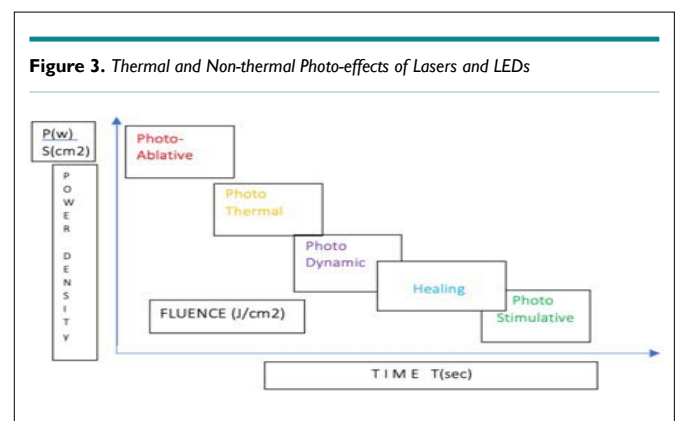
Low-Level-Light and LED

The non-thermal effects of LLLT and LEDs are related to the biophysiological properties of wavelengths, defined as the distance between two consecutive peaks, the chromophore they target and their depth of penetration. Mester et al⁹ demonstrated in 1973 in a study on murines, that He-Neon laser emitting in red 632,8nm had visible effects on cytochromes, accelerating wound healing, evidenced by following studies.¹¹ NASA experimented the influence of light on astronauts' metabolism, weakened in space in the absence of gravity, evidencing improved wound healing post minor injuries⁷ and leading to the equipement of its spaceships with LED panels.⁸

Low Level Lasers are non-thermal lasers, known as soft lasers, emitting a coherent, monochromatic polarized light penetrating deeply into tissues, ranging from 400nm to 800nm and 900nm to 940nm for Near-Infrared (NIR).² As a comparison, the Helium Neon laser (He-Neon), emitting red at 632nm, has a power output between 1 and 25 milliwatts, whereas the Nd:YAG (neodymium-doped yttrium aluminum garnet) laser, used in cataract surgery, delivers up to 10 watts. Low-Level-Lasers have a significant lower power output requiring longer treatment sessions, ranging in minutes rather than seconds yet, energizing tissues they penetrate rather than cutting or burning them.²⁰

Light emitting diodes (LEDs) are electroluminescent diodes producing narrow-band light through the motion of electrons in high-efficiency semi-conducting materials as germanium (Ge) or gallium (Ga) resulting into a specific colored component or wavelength of red (633 nm), yellow (590 nm), blue (415 nm) and their combinations in the visible spectrum. Therapeutic LEDs (247 nm-1300 nm) are non-coherent, monochromatic lights, transferred to tissues for absorption through a photoelectric effect in a non-thermal fashion.^{19,21,22} The infrared wavelengths are absorbed by cell membranes inducing photophysical reactions.^{21,23} Up to date, the therapeutic properties are evidenced for a portion of this scale, although research in lumentherapy is found back to the 19th century when Finsen (1903) demonstrated that red light increases the metabolic level of cells' mitochondria.³ His intensive research on the activity of red light on smallpox and measles, published under the title Phototherapy awarded him a Nobel prize in Physi-

ology and led to the establishment of the first sanatoriums across Europe treating tuberculosis with sunlight.³ Since then, the therapeutic capacities of light have been studied in many fields of medicine. A multi-center research initiated by the Institute of Cellular and Integrative Neurosciences in Strasbourg, France, led by Tsai et al (CNRS)²⁴ studied the role of the photopigments melanopsin, encoded by *OPN4* gene, on sleep control patterns in humans. Light reaching human eye transmits to the brain two types of information, a visual one analyzed by retinal rods and cones photoreceptors and, a non-image-forming one regulated by melanopsin able to detect the intensity and quality of the light emission.²⁴ Haultaufferhyde et al²⁵ demonstrated that photons absorbed through opsins are converted into a cellular response by phototransduction. The authors observed in cell culture that OPN1-SW, OPN2, OPN3 and OPN5 were also expressed at epidermal level in melanocytes and keratinocytes.²⁵ In cultured primary human epidermal melanocytes (HEMs) and primary human keratinocytes (KERs), the authors found opsin receptors, suggesting that they may function as epidermal photoreceptors, which is of interest when considering the application of PBM to the skin (Figure 3).²⁵



MECHANISMS OF ACTION

The Mitochondrial Respiratory Chain

Cellular respiration is achieved *via* the glycolysis and the citric acid cycles, producing the essential energy-carrier adenosine triphosphate (ATP).²⁶ An additional pathway also generates ATP *via* the respiratory electron transport chain and its redox reactions during the aerobic glucose catabolism.²⁶ Karu et al⁵ demonstrated that the mitochondrial protein cytochrome c oxidase (CCO), a terminal enzyme in this mitochondrial respiration in charge of molecular oxygen reduction and ultimately ATP synthesis, was a photo-active acceptor. This major finding enlightened how much communication between the extra-cellular matrix and other cells was fundamental for cells' integrity, growth and differentiation.²⁷ By catching the stimuli of light through the CCO enzyme, cells respond through a signaling pathway, matching together as key and keyhole.^{5,22} In vegetable kingdom, this transformation of light, or photosynthesis, into photochemical energy triggering biochemical modifications is a process well-documented.²⁸ Karu et al¹⁸ demonstrated, while evaluating the effects of wavelengths in the optical band 570 nm-650 nm on deoxyribonucleic acid (DNA) and ribonucleic

acid (RNA,) that light coherence was not an absolute necessity for igniting a biostimulative activity. The authors showed that similar results can be achieved with non-coherent LED-sources.¹⁸ The mitochondria within cells is receptive to visible light, inducing a photochemical response *via* the CCO or a photophysical response when stimulated by NIR (Figure 2).^{23,29} This photoactivation is also related to the redox-sensitive status of the photoreceptor: damaged cells with lower redox potential are more sensitive to light stimuli.²³ In many studies, the repairing and rejuvenating outcomes obtained with LEDT are related to the mitochondria, the CCO and the ATP upregulation,¹⁰ as well as the synthesis in the cytosol of the nicotinamide adenine dinucleotide reduced form (NADH).⁶ The use of appropriate wavelengths, pulsed wave (PW) or continuous wave (CW) modes generated a different impact on the reduction of free radicals, a higher tissues stimulation was observed with pulsed modes in specific contexts. This was also described by Barol et al³⁰ in a case-control study on limited cutaneous systemic sclerosis where significant improvement of osteo-articular symptoms severity was reported in cases treated with (PW) mode at 940nm LLLT, while the augmentation of microcirculation and catabolism may also have participated in the *in situ* calcinosis and overall functional improvement.³⁰ Better and faster wound healing with (PW) was also reported with 810 nm diode laser at 10 Hz, evidencing a significant decrease of inflammation, increase of cellular proliferation, epithelization, neovascularization, enhanced CCO and ATP performance.³¹

The benefits of LLLT-LEDs could be comprehended as a mitochondrial therapy, care and micronutrition, mitochondrial protection from dysfunction, oxidative stress and molecular degradation and, a photo prophylaxis too.^{26,32,33}

Adenosine Triphosphate Production

Adenosine triphosphate production represents the core energy supply to cellular activity, an inner currency for cells' exchanges synthesized under aerobic conditions in the mitochondria, the organelles containing the respiratory electron transport chain. As seen above, CCO being the end enzyme of the electron transport chain, it combines oxygen and NADH for hydrogen ions synthesis.⁶ The hydrogen ions once increased in number, diffuse out of the matrix space, participating into the phosphorylation of adenosine diphosphate (ADP) into ATP.³⁴ However, this respiration is compromised when mitochondria start generating nitric oxide (NO), binding to the CCO in place of oxygen, resulting into less ATP and more oxidative stress and, potentially more inflammation. He et al³⁴ described that PBM helps recover the binding of CCO with oxygen inducing quantifiable changes in the mitochondrial membrane potential (MMP) and in the ATP content. Therefore, the primary mechanism of action of PBM takes place within the mitochondria, the CCO absorbing the emitted light and water achieving less density, more fluidity.^{5,34} A resonance takes place between cells and light wavelengths, inducing metabolic processes of repair and regeneration. It is now established that at DNA level, cells emit biophotons, which may explain their affinity with light.³⁴ The interest of LLLT and LEDT lies in this capacity to increase MMP and ATP synthesis in various types of cells, protecting them

from oxidative stress, modulating reactive oxygen species (ROS) production, in a dose-dependent way.¹⁰ More recently, Sommer⁶ suggested that the causal relation between CCO, as a primary photo-acceptor, and the extra-ATP synthesis was not necessarily the only hypothesis in red-to-NIR (R-NIR) exposure. The author evaluated that two more aspects have to be considered in the ATP synthesis: the mitochondrial inner membrane and the role of the CCO in reducing molecular oxygen to water. For Sommers, the interaction light-tissues between photons and interfacial water layers (IWL) was causal to ATP upregulation in R-NIR therapies (Figure 4).⁶

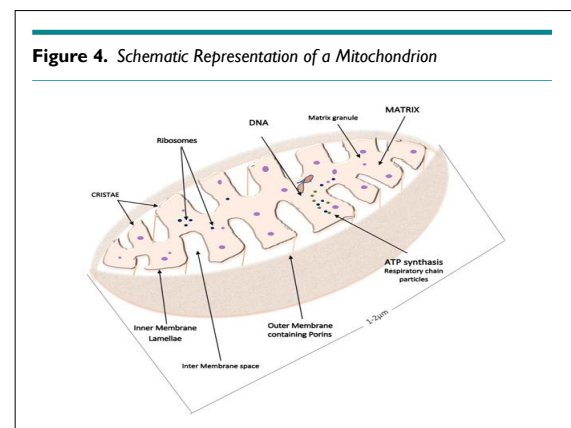


Figure 4. Schematic Representation of a Mitochondrion

Dosing the Stimulation

Dosimetry is to phototherapy what dosage is to medicine; it depends of the ancency, the depth and the surface of the target. It also depends of the physiological or pathological condition of the tissues. Karu et al^{5,35} described that PBM induces a higher stimulation in weaker, stressed or damaged cells, up to the maximum of their biological activity. As is the case for all energy-based therapies, setting the parameters acknowledging this dose-response is primordial for optimizing patient-centered outcomes.³⁵ Biostimulation and cellular effects are modulated by critical parameters: the power density or irradiance or intensity measured in mW/cm², the energy density or fluence, dose or radiant exposure measured in J/cm² and the treatment/irradiation time in seconds.³⁶ Biostimulation is supported by an equation between intensity, surface, total irradiation time and energy density, if not, the result is absence of biostimulation. A similar rule was reported with lasers: under 4 mW, no biological effect was observed, whatever the irradiation time.³⁷ A physiological response can be initiated with a minimal irradiance. On the contrary, a too long exposure with low irradiance will not induce the expected physiological effect, while a too long exposure with too high irradiance may inhibit PBM benefits or lead to cells' exhaustion. The World Association for Laster Therapy (WALT) has provided dosage recommendations in LLLT.³⁸ Treatment frequency, intervals between sessions and correct coverage of the treatment target are also parameters to be considered as light can be reflected, refracted or scattered depending on the treated tissues.^{4,12} The relationship between these parameters is usually adopted with the equation described by Jagdeo et al.²⁹

$$\text{Power density (W/cm}^2\text{)} \times \text{time (seconds)} = \text{fluence (J/cm}^2\text{)}$$

Dosing the stimulation is particularly of prime essence in photo dynamic therapy (PDT) where irradiance source, total light dose and power output in milliwatt, are game changers in treatment protocols and performance.^{38,39}

FIELDS OF APPLICATION

Cells respond to the biostimulation of light during and post PBM, through cellular and molecular mechanisms seen above, particularly with oxygen re-binding with CCO, enhancing cellular respiration and augmentation of ATP synthesis. Restoring the respiratory electron transport chain is essential in the context of inflammatory reactions as an impaired cells' reparation, when NO is also increased and competing with oxygen, endangers the innate immune system and homeostasis.^{29,34}

Dermatology

Non-coherent wavelengths of LLLT-LED-sources applied in PBM target chromophores as the CCO or the endogenous protoporphyrin, as a monotherapy for skin conditions and diseases or associated to systemic or topical therapies. These light-sources have a modulating action on the intrinsic cellular activity, either inhibiting or stimulating it and a biphasic dose-dependent response, demonstrated in wound healing and mitigation of inflammation.⁴⁰ The applications in dermatology are vast and thoroughly studied by authors as Pelletier.⁴¹ Recently, Jagdeo et al³⁹ performed a systematic review of 31 RCTs studying dermatological conditions treated with LED-PBM. According to criteria of the Oxford Centre for Evidence-based Medicine-Levels of Evidence,⁴² the authors attributed a grade B of recommendation for the Food and Drug Administration (FDA)-approved treatment of Acne vulgaris, Herpes complex and zoster and, a grade C of recommendation for skin rejuvenation with LED-PBM. Non-FDA-cleared LED procedures were attributed a grade B of recommendation for the treatment of acute wound healing, grade C for psoriasis and grade D for atopic dermatitis, chronic wound healing, oral mucositis and radiation dermatitis.³⁹

Dermatological conditions are characterized by the suffering of cells depleted from the energy necessary for self-repair. It is particularly the case in the healing of wounds and ischemic tissues lacking trophicity, ulcers or compressed nerves. PBM may be comprehended as an energy supplementation improving DNA and RNA synthesis, as well as cells' adhesion. Wound healing is maybe the most widely spread application of PBM in dermatology, its effects having been demonstrated at all stages of the healing process.^{7-9,43,44} A normal wound healing undergoes three distinct phases. At first inflammatory signs in tissues, secretions from lymph and blood vessels, followed by coagulation by thrombokinas activation and fibrin production start the exudation and detersion phase of wound healing. Increased capillary permeability brings antibodies, leucocytes and macrophages towards the wounded area.⁴⁵ Stimulated fibroblasts generate from approximately Day 4 a muco-polysaccharides matrix for collagen fibers synthesis necessary in the gradual restoration of the wound from the inside out. In this proliferative phase, neo-angiogenesis assures nutrition to growing tissues. Approximately from Day 6, myofibroblasts contract

to progressively close the wound borders; less irrigated, granulation tissues become tighter and ultimately form scar tissues in this differentiation phase which will stop with the re-epithelialization by migration of epidermal cells at wound surface.⁴⁵ Studies have also shown that PBM improves post-operative wound healing at the first stages.⁴⁶ NASA^{7,8} experimental studies monitoring injuries in spaceships reported wound healing improved by 50% in cases receiving LED treatments compared to those not treated. Similarly, the Naval Special Warfare (Norfolk, USA)⁷ evaluated wound healing in the conditions of submarines where there is no light, lower oxygen and higher CO₂ levels, concluding in 50% improvement of muscular-skeletal injuries in cases treated with LLLT-LEDs 670 nm, 720 nm and 880 nm. Accelerated healing of burn injuries and systemic effect of PBM were also observed on mice models.⁴³ In a preliminary study Min et al⁴⁴ evaluated the faster healing of ischemic wounds and recalcitrant diabetic ulcers, reporting increased fibroblasts proliferation, growth factors synthesis, collagen production and angiogenesis. without neoplastic transformation, tissues' growth stops once the wound is healed. The treatment of ophthalmic herpes zoster with PBM was evaluated by Park et al⁴⁷ in a pilot study on 28 individuals all receiving antiviral agents and half receiving 830 nm LED-PBM additionally. The authors concluded in significantly faster healing and lower mean visual analogue scale (VAS) scores in the group who received LED-therapy compared to control groups. Kleinpenning et al⁴⁸ evaluated the treatment of inflammatory skin diseases as psoriasis and atopic dermatitis in a double-blind, randomized comparative study between red and blue wavelengths activity targeting the endogenous photosensitizer protoporphyrin IX. Clinical improvement of psoriasis erythematous plaques was observed in both groups yet, was significantly higher with blue light therapy.⁴⁸ Comprehensive studies have also evaluated the treatment of acne with blue-red therapies, particularly with pulsed wavelengths.^{49,50} Tsoukas et al⁵¹ described the activity of red light in inflammatory processes of acne modulating cytokine release from macrophages while blue light, once absorbed at a peak of 415 nm by the natural porphyrins secreted by Propionibacterium acnes colonizing sebaceous glands, was releasing singlet oxygen and ROS with significant bactericidal action.⁵²⁻⁵⁴ With the emergence of bacterial resistance to antibiotics, blue-red therapy is estimated a safe and efficient tool for treating inflamed lesions in mild to moderate acne.⁴⁹ Many studies have also demonstrated the accelerated healing of edema, erythema and inflammation post-surgical and non-surgical aesthetic procedures as intense pulsed light (IPL) and fractional lasers.^{55,56}

The stimulation of the mitochondria has also substantial effects on the aging process, increasing collagen production and decreasing collagenase activity. Boisnic et al⁵⁷ observed in a hospital-setting study the repairing action of LEDs on connective tissues, directly stimulating the metabolic activity of dermal fibroblasts, inducing new dermal papilla, with synthesis of endogenous collagen and elastin. Fouque-Parachini et al⁵⁸ demonstrated in an *in vivo* study assessed by vivascope confocal microscopy, the benefits of a LED-source (Triwings[®], Biophoton) on skin rejuvenation at epidermal and basal layers, improving lentigos and stimulating neo-collagenesis. The authors findings demonstrated cells' membranes repolarization, modification of the free-water/bound-water ratio,

improvement of microcirculation, emergence and increase of vascularized dermal papillae count and, tissular hydration resulting in an overall rejuvenation of the skin. The authors also observed decrease and homogenization of melanin in treated areas.⁵⁸

Barolet⁵⁹ and Weiss et al⁶⁰ described a photo prophylaxis role of LLLT-LED therapies in prevention of post-inflammatory hyperpigmentation, solar lentigines and ultraviolet (UV)-induced erythema, concomitant to proper use of broad-spectrum sun care. In a prospective, randomized, placebo-controlled, double-blinded, split-face clinical study Lee et al⁶¹ evaluated with histologic, ultra-structural, profilometric and biochemical analysis the effects of 633 nm and 830 nm LEDT on skin rejuvenation. Their findings demonstrated significant reduction of wrinkles, activation of fibroblasts and increase of collagen and elastin, also observed in a study of Calderhead et al.²³

Another major application of monochromatic lights in dermatology is the treatment with photo dynamic therapy (PDT) of non-melanoma skin cancer (NMSC) and cancerization fields, particularly superficial basal cell carcinoma (sBCC) and *in-situ* squamous cell carcinoma (in-SCC) not exceeding 2 mm thickness according to the international guidelines.⁶² The therapeutic fundamentals of topical PDT for NMSC imply a photosensitizer-precursor of protoporphyrin IX (PpIX), light in the absorption spectrum of the photosensitizer and oxygen.⁶³ More recently, Alam⁶⁴ described the conversion of lipophilic methyl-aminolevulinic acid (MAL) or 5-aminolevulinic acid (5-ALA) into photoactive porphyrins at lesion site once exposed to light at 37 J/cm², as advised by the industry leader.⁶⁵ MAL-PDT is reported for good neoplastic cells selectivity, tissue penetration and intracellular PpIX accumulation in a diffuse uptake fashion. PDT induces a type II photo-oxidation generating ROS affecting cells' membranes, improving dermic echogenicity and reducing lesional vascularization.⁶⁶ PDT is also applied to non-malignant skin diseases and pre-cancerous lesions, experiments are proposed with lower-irradiance red wavelengths for lessening the pain in actinic keratosis⁶⁷ and for treating acne and infections.^{53,54,68} Researchers are also working on the incorporation of light for PDT in a novel fabric.⁶⁹

Since paradoxical hair growth has been observed post-laser and IPL-assisted hair reduction, researchers investigated the use of light to promote hair growth.⁷⁰ Trelles et al⁷¹ first described in 1984 hair re-growth in alopecia areata cases treated with an HeNe laser at 632,8 nm and 4 J/cm² weekly, while daily application resulted in cells' exhaustion and hair thinning, evidencing the bi-phasic dose-dependent response in PBM.⁴⁰ The authors described hair shafts showing increased keratin number in medulla at microscopic analysis.⁷¹ In a systematic review of LLLT at R-NIR 635 nm and 810 nm in adult androgenic alopecia, the authors described that the upregulation of ATP production may reverse bulbs miniaturization and maintain hair follicles longer in their anagen phase.⁷² In a double-blinded randomized controlled trial (RCT), Lanzafame et al⁷³ evaluated the efficacy and safety of 655 nm LLLT-LED *vs* placebo in 47 females with androgenic alopecia. Their findings showed a change in hair count over baseline of 100.3-53.4 (N=24) ($p < 0.0001$) in the treated cases group and a percentage of hair in-

creased by 11.05-48.30 (N=18) in placebo controls while 48.07-17.61 (N=24) ($p < 0.001$) in the treated cases, with an overall hair growth over the study time increased by 37% in the treatment group.⁷³ The stimulative activity of LLLT-LED on epidermal stem cells in hair follicle bulges when applied at 90 mW/cm² R-NIR is estimated to down regulate inflammatory mediators and to shift hair follicles into the anagen phase, enhancing also hair tensile strength and scalp health.⁷⁴ In another recent study, Buscone et al⁷⁵ provided evidence that *OPN2* and *OPN3* are expressed in human hair follicle and interact with blue light at 453 nm resulting in hair growth *ex vivo*. Further research is required in this application, with well-controlled studies. However, LLLT-LED therapies for male and female androgenic alopecia are FDA-approved since 2007 on a safety basis, they may also represent a promising prospective solution for other forms of non-cicatricial alopecia.⁷⁶

Body contouring with the application of LLLT as a non-invasive modality has also been evaluated in a retrospective study entailing 689 individuals, concluding in significant mean circumferential reduction recorded at different measurement points with 3.27 in. ($p < 0,0001$) and overall mean reduction of 5.17 in. ($p < 0,0001$) not related to fluid loss, demonstrating adipocytes' apoptosis and influence of LLLT on systemic lipid metabolism.⁷⁷

Rheumatology, Traumatology and Sports Therapies

PBM for the management of acute and chronic pains has been thoroughly evidenced since decades in scientific literature.⁷⁸ Efficacy, tolerability and safety of treatments require appropriate wavelengths in the optical window between 633 nm and 905 nm in R-NIR and appropriate intensity on elected anatomical site. Beneficial treatment of musculoskeletal pains, orthopedic injuries and post-surgical conditions, in humans and animals, is largely reported in literature.⁷⁸⁻⁸²

Particularly, Konstantinović et al⁸³ in a double-blind, randomized, placebo-controlled study on 60 individuals with acute neck pain with radiculopathy treated with 905 nm LLLT, demonstrated statistically significant pain reduction on VAS measurement in cases against controls ($p = 0.003$, accounting high effect size $d = 0.92$). The mechanism of action of PBM in pain control entails the anti-inflammatory activity of R-NIR wavelengths decreasing also edema, the blockade of the nociceptor transfer along A and C fibers and the mitigation of neurotransmitters.⁷⁸ Overall good reduction of pain induced by masseter muscle fatigue and tinnitus condition have also been reported,⁸⁴ making PBM a cost-effective and evidence-based therapeutic modality in chronic and acute pain.

In sports medicine, PBM for the treatment of injury-related pain has demonstrated significant reduction of all-pain, enhanced tissues' repair and faster recovery, by improvement of inflammation, micro-circulation and tissues' oxygenation.^{85,86} PBM in tendinopathy, golfer or tennis elbow and injuries influencing knee or wrist mobility and ankle stability, impacting the return-to-play of athletes has demonstrated significant results.⁸⁷ Additionally, by increasing mitochondrial respiration and ATP production mediated by MMP at muscle levels, PBM is considered a preventive

measure for muscle conditioning prior to physical performance, in men and women.^{88,89} In a systematic review with meta-analysis, Leal-Junior et al,⁸⁷ evaluated 12 RCTs in which LLL-LED therapies were applied in the course of exercise with 50 to 200 mW, 5J per spot. Findings demonstrated significant improvement of athletes' performance up by 5.47 (95 % CI 2.35-8.59, $p < 0.0006$) and increase of time until exhaustion up by 4.12 (95 % CI 1.21-7.02, $p < 0.005$) against placebo. The authors reported that the improvement of muscle metabolism was dose-dependent and they evaluated a time-response of 3-6 h,⁸⁷ confirmed in other studies.^{10,40} PBM is an evidence-based therapeutic option for optimizing the return-to-play of athletes.⁸⁷

Neurology

Hamblin⁹⁰ first reviewed the interest of transcranial-photobiomodulation (t-PBM) in brain disorders, including trauma, degenerative diseases and psychiatric disorders and, the existing evidence on light applied to the prefrontal cortex. The global aging of the population and the augmentation of lifespan may involve higher occurrence rates of neurodegenerative diseases as dementia, Alzheimer or Parkinson, burdening public health policies. Hamblin⁹⁰ also initiated a current of thoughts for future hypothesis of research on t-PBM, focusing on neurodevelopmental disorders as autism and depression and, how attention bias and ischemia risk can be improved. The question of light penetration to the cerebral cortex has been addressed by many researchers, the debate being still on in regard of optimal light-source, laser or non-coherent LED, wavelength range and power density for achieving the best biological effects.^{91,92} The outcomes observed in these studies have enlightened significant improvement of cognitive function in individuals with long-standing traumatic brain injury, which unfortunately, faded away once treatment was stopped. Furthermore, Gordon et al⁹³ have discussed that the effects of PBM were not restricted to the sole area illuminated and that a remote, indirect benefit is to be explored in the future. The interest of t-PBM on healthy individuals as a cognitive capacity improvement light-therapy, enhancing capacity to stay focused, is also in the pipeline of research.^{90,94}

A few authors have described a mood-enhancement and regulation of sleep patterns effect following PBM, it is known that pro-inflammatory cytokines participate to mood disorders. In a recent review, Askalsky et al⁹⁵ consider that t-PBM in range of 808-835 nm NIR at higher powers outputs could be a novel neuromodulating strategy for major depressive disorders (MDD). In previous research, the mechanism of action of t-PBM was estimated to stimulate the respiratory chain and ATP production at the mitochondrion as well as the regional blood circulation.⁹⁶ Current knowledge stimulates further research, evidencing if coherent lights are mandatory or if non-coherent lights can be a more practical and cost-effective alternative. Also, demonstrating if (PW) mode would be superior to (CW) mode as anti-depressor application of t-PBM.^{90,95}

Oncology

Photo dynamic therapy has a strongly evidenced background in

the treatment of superficial skin cancers but has also limitations in the capacity of light to penetrate tissues deeply, depending on the elected photosensitizers and *in-situ* dosimetry.⁹⁷ Expanding this therapeutic modality from superficial to deep-seated diseases and malignant tumors has raised interest in research in the past years. Scientific reflections have focused on different light-sources for exciting a mono-photosensitizer, two-photon photosensitizers or conjugated with nanosystems for achieving synergetic action.^{98,99} Research evolves towards a NIR-activated PDT allowing deeper tissues penetration with longer wavelengths and less off-targeting or normal tissues damaging.⁹⁸ This interstitial PDT challenges scientists with barriers to overcome as the non-homogeneity and three dimensions (3D) shape particular to solid tumors.¹⁰⁰ Clinical translation requires this new modality to be approved and light and photosensitizers parameters to be consolidated in well-designed trials before expanding treatment options.¹⁰¹

Bensadoun et al¹⁰² have also thoroughly described the relieving effects of PBM in mucositis reduction. A research followed in 2017 by a clinical trial for establishing a treatment protocol reducing chemo and radio-induced oral mucositis in children applied LLLT-LED 635 nm (Oncolase) every other day at doses of 4 J/cm² in a sweeping fashion in cheeks, tongue dorsum, lateral and belly, palate, superior and inferior gums.¹⁰³ The findings demonstrated significant reduction in recovery time, in pain and inflammation associated to the condition and no aggravation towards a higher grade of mucositis.¹⁰³ Improvement of quality of life was also assessed with the recovery of chew and swallow capacity.

Gynecology

The gynecological internal applications of lasers originated from applications in cancerology as described above and from applications in odontology as will be reviewed below.

PBM in gynecology can be applied with LED or laser sources, internally and externally according to the indication, for alleviating inflammation, sanitizing the tissues, enhancing the healing of gynecological and obstetrical wounds,¹⁰⁴ improving functional disorders of the vulvar-vaginal and uro-genital regions¹⁰⁵ and, decreasing low-grade inflammation and endometriosis-related pelvic pain.¹⁰⁶ PBM alone or combined to other therapies is reported in the treatment of genital cutaneous diseases as lichen, herpes or eczema.¹⁰⁷ Lanzafame et al¹⁰⁸ recently discussed the application of PBM for relieving genitourinary syndrome in menopausal women, concluding in high efficacy and tolerability of this option. Morphological and physiological changes occurring in menopausal women, particularly with the decrease of intra-mucous microcirculation leading to vaginal dryness, lack of trophicity, atrophy and irritation are syndromes well-treated with PBM with intravaginal probes and external light-exposure. Red and NIR have showed interesting effect by stimulating collagen production¹⁰⁹ and angiogenesis.¹¹⁰

Dentistry

The LLLT-LEDT have been reported since three decades in Rus-

sian¹¹¹ and Japanese¹¹² scientific literature in fields of dentistry and oral diseases, for hard and soft tissues, triggering biochemical exchanges for the healing of wounds in the oral cavity, the reduction of pain with endorphins' release, the enhancement of bone and nerves repair after oral surgery.¹¹³ In a systematic review Shukla et al¹¹⁴ analyzed findings of 13 studies in which LLLT-LED was applied in temporomandibular (TMD) or craniomandibular disorders. The reduction of pain in individuals suffering from TMD was effective in the majority of these studies, with the hypothesis proposed of modulation of inflammation at the TMD joint capsule.¹¹⁵ However, the discrepancies in trials standards call further research for consensus on light dosage. PDT with toluidine blue patch has also been described as a useful tool for disrupting the adherence of bacterial biofilms at root canal.^{116,117} As seen in previous chapter Dermatology, the stimulative action of PBM on fibroblasts was mainly evidenced with cultured dermal fibroblasts yet, it is estimated that similar analgesic, anti-inflammatory and regenerative effects on buccal and gingival fibroblasts is possible in reason of their close response profile. PBM is a relevant option for optimizing wound healing, alleviating pain, as trigeminal neuralgia or in TMD and repairing tissues by biostimulation.¹¹⁸

Infectiology

We have seen in the treatment of acne and cutaneous superficial or deep-seated malignant lesions, the antibacterial and anticarcinoma activity triggered by PDT with ROS and singlet oxygen generation.⁵²⁻⁵⁴

Another field of application of the antimicrobial effect of visible violet-blue light at 405-470 nm has been researched for the decontamination of hospitals and healthcare premises.^{68,119} Disinfection policies for risk control of hospital-acquired infections are a major public health concern, aggravating with antimicrobial resistance.¹²⁰ Therefore, PDT has been explored as an alternative solution with demonstrated efficacy on bacteria and fungi but also on viruses.^{121,122} Gram-positive, sensible to major photosensitizers, respond to anionic types, while Gram-negative bacteria to cationic photosensitizer.¹²³ Viruses also have shown sensitivity to PDT, according to their nucleic acid and capsid type, whereas fungi require higher doses of light and photosensitizer.^{124,125} The photodisinfection of environmental surfaces with blue light is also of interest in clinical practice for sanitizing and reducing the risk of pathogens proliferation, in adjunction of asepsis rules, by application of LEDs on facial and body areas immediately after aesthetic procedures, when not contraindicated.¹²⁶

Addressing the field of photobiomodulation, the blue light hazards shall be mentioned. Blue wavelengths are shorter yet, intense, while retinal tissues are rich in chromophores. The retinal mitochondria are susceptible to potential photochemical damage in case of prolonged and unprotected exposure,¹²⁷ which implies proper knowledge and training of healthcare professionals for adopting preventive measures against this public concern.

Interest of Photobiomodulation in Acute Pulmonary Disorder

As discussed in the previous section, visible light in the blue spec-

trum demonstrated substantial antimicrobial activity and capacity to inactivate certain viruses. This could possibly be of interest in the fight for jugulating pandemics, a fortiori in viruses having host pathways replicating in humans.¹²⁸

Photobiomodulation has also a potential role in the prevention of respiratory complications in coronavirus disease-2019 (COVID-19) pandemic through its capacity to modulate the inflammatory response in individuals. A recent review of Enwemeka et al¹²⁹ evaluated the evidence-based data on the effects of PBM concluding that light-therapies at 660 nm may alleviate pulmonary inflammation, down regulate pro-inflammatory and pro-fibrotic cytokines, reduce collagen deposits in murine lungs and improve airways edema.^{130,131} Furthermore, a protective role on cardiomyocytes from hypoxia with R-NIR wavelengths has also been demonstrated supporting that PBM, when individuals are in need for extra mitochondrial ATP, may play an important role, improving also cutaneous manifestations.¹³²

Finally, in the prevention of infectious diseases, the respect of individual's microbiome is a principle now largely integrated and, the interaction light-microbiome recently researched by Libert et al¹³³ may have a natural role for maintaining individual's integrity towards a better health.

CONCLUSION

The efficacy of PBM is not always easy to understand, particularly when the outcomes of this therapy have sometimes a certain latency. However, PBM and more specifically LEDT may be considered as an homeopathic counterpart, assisting aesthetic interventions, inducing a regeneration, rejuvenation and foremost, a repair at organelles, cells and organs levels with a dynamic flux of biophotons.¹³⁴ A better understanding of the life of underlying tissues, their interplay with light and the mechanisms of action of PBM at cellular level will enable clinicians to define parameters optimizing benefits of light therapies. There is also the necessity for rigorous methodology, randomized controlled clinical trials enabling further research to achieve higher statistical power and overpass any further controversy in a very promising therapeutic modality with arrays of indications, deeply revolutionizing healing concepts and healthcare professions.

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