RESEARCH ARTICLE

Photobiomodulation in Dermatology: Harnessing Light from Visible to Near Infrared for Medical and Aesthetic Purposes

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Abstract

Photobiomodulation (PBM), the therapeutic use of low intensity light, typically in the visible and infrared (IR) wavelengths, has been demonstrated to be efficacious in the treatment and prevention of numerous skin conditions. The PBM biological response begins with chromophores, photon accepting molecules which convert light into signals that can stimulate certain biological processes. Important chromophores initiating the PBM response are Cytochrome C Oxidase (CCO), with absorption peaks in the red and near IR wavelengths, opsins absorbing blue and green wavelengths and intracellular water acting at specific sites in the cell. PBM can activate cell signaling processes. The increase in electron transport, oxygen consumption, mitochondrial membrane potential, and ATP synthesis, particularly in hypoxic or stressed cells, can lead to the up-regulation of cell repair and survival pathways. In PBM, the light delivery parameters which maximize the therapeutic response are defined within specific ranges, with total fluence and irradiance being of particular importance. PBM emerges as a valuable complementary treatment modality in dermatology. In terms of tissue repair, wound healing is accelerated by PBM. Cutaneous wounds, erosive mucositis in oncology, leg ulcers, as well as burns and radiodermatitis all benefit from PBM treatment. Widely used to accelerate healing after aggressive aesthetic treatments, PBM reduces inflammation following treatments like skin resurfacing, vascular and benign pigmented lesions, or chemical peels. It has also been shown to be effective in treating dyspigmentation. In the case of hyperpigmentation, melanin synthesis is inhibited with IR light. Additionally, PBM has shown benefits in the treatment of acne and the prevention / treatment of hypertrophic scars. It has shown promise in skin rejuvenation, the treatment of alopecia, cellulite, as well as other skin diseases. The discovery of new applications for PBM, already an effective form of treatment and prevention for many skin conditions, is continually expanding.

Keywords

Photobiomodulation, low-level laser therapy, LLLT, laser, LED, light emitting diodes, chromophores, cytochrome c oxidase, clinical trials, treatment, complementary, skin, dermatology, cutaneous, phototherapy.

1. Introduction

Human skin is able to absorb the energy of light like a plant and this is not limited to ultraviolet. Indeed, visible and infrared light can also be absorbed, modulating certain cell signaling pathways favorable to the dynamic cutaneous environment. Although the morning and late afternoon sun provide these wavelengths more abundantly, this spectrum can be artificially reproduced using low intensity light. Among the energy-based devices used in dermatology (lasers, etc.), this low-intensity light is classed separately. Initially called LLLT (Low Level Laser Therapy), it has recently been renamed Photobiomodulation (PBM) (1). This term is more appropriate since it is a science that uses visible and infrared light to modulate the metabolism of the cell and thus cause it to self-correct if necessary.

Over the last 20 years, LEDs have overtaken lasers in PBM as a light source since they offer numerous advantages (Table 1). The technological aspects of LEDs have been previously reported by the author (2).

- Multiple wavelengths available (from UV to NIR)
- Covers large area (arrays)
- Broad spectrum (25-30 nm bandwidths)
- Semiconductor chips (reliable)
- Long lasting (50 000 hours)
- Low power (can be battery operated)
- Minimal thermal effects (no pain)
- Portable

Table 1. Most common advantages of LEDs in PBM

Despite nearly 5,000 scientific publications, both *in vitro* and clinical, PBM still faces some skepticism (3). In fact, the total number of PubMed-indexed articles on PBM (using light emitting diodes: LEDs) has more than doubled since 2010. Several studies show its utility to accelerate the healing of wounds and the treatment of inflammatory skin phenomena. Although other fields of PBM are very active (musculoskeletal, neurological, etc.), in this review article, we will limit the discussion to the dermatological effects.

2. PBM's Mechanism of Action

The electromagnetic radiation wavelength range of PBM is essentially between 400 and 1200 nm. Red (600-700 nm) and near-infrared (770-1200 nm) wavelengths have

been shown to be efficacious. However, there is a region of the spectrum (700-770 nm) where the results are rather disappointing. More recently, blue and green were studied despite the weakness of their optical penetration (4). The penetration depth is at its maximum at 810 nm and then decreases because water absorbs photons, thus reducing penetration into the tissues (5). The photobiological response of PBM is determined by the energy absorption by certain photo-accepting molecules or chromophores. The absorption of photons converts light into signals that can stimulate certain biological processes (6).

2.1. The Chromophores

2.1.1. Cytochrome C Oxidase (CCO)

The best known cellular chromophore of PBM is Cytochrome C Oxidase (CCO) located at the end of the respiratory chain in the mitochondrial wall. This enzyme has four redox centers, two hemes, and two copper centers. Each can be reduced or oxidized, defining the spectral absorption with two absorption peaks (red and near IR up to 950 nm) (7). CCO activity is likely to increase as photons are absorbed through the photodissociation of nitric oxide (NO), which usually prevents electron transport in the respiratory chain when linked to CCO.

2.1.2. Ion Channels and Opsins

This is a new class of photoreceptor that responds in the spectrum of blue and green. Three photoreceptors from the light-sensitive G-protein receptor family exist, known as opsins (OPN). The best known is rhodopsin (OPN1) which is responsible for vision through cones and rods located in the mammalian retina. Following the activation of opsin by light, light-gated ion channels open, in particular some members of the TRP (Transient Receptor Potential) family of calcium channels (8). Calcium signaling is a very important pathway in multiple cell types. Other TRPs, particularly TRPV1, are also activated by infrared light (9, 10).

2.1.3. Water as a Chromophore

At higher wavelengths (> 1000 nm) than those absorbed by CCO, water appears to be the most suitable chromophore since it is abundant in biological tissues. A small increase in the vibrational energy of water in or on a sensitive protein such as a heat-gated ion channel would be sufficient to disrupt

the protein's tertiary structure, allowing modulation of the intracellular calcium level (11). Pollack (12) has demonstrated that water at specific sites in the cell is not like water behaving as an inert solvent but as an active molecule. Intracellular water is predominantly dynamic and has a predetermined structure that supports cellular processes.

2.1.4. Other Chromophores

Other molecules that play a minor role can also be photoactivated (crypto-chromes, flavoproteins, porphyrins, hemoglobin, and myoglobin).

The chromophores mentioned above are illustrated in Figure 1.

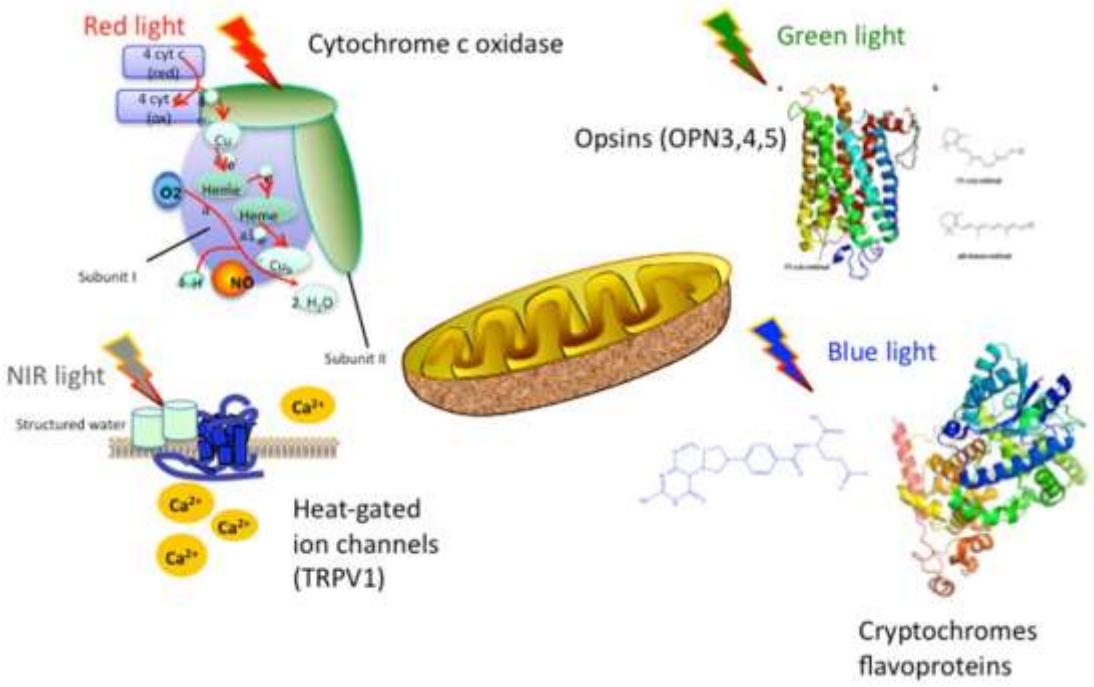

Figure 1. Chromophores in PBM. Cytochrome c oxidase in respiratory chain absorbs mainly red (and NIR) light by heme and copper; Heat-gated TRP ion channels absorb NIR (and blue light) via structured water; opsins absorb mainly blue/green light via cis-retinal; flavoproteins and cryptochromes absorb mainly blue light via pterin. (From Hamblin MR, Mechanisms and applications of the anti-inflammatory effects of photobiomodulation, AIMS Biophysics, 2017, 4(3): 337-361. doi: 10.3934/biophy.2017.3.337.) (13).

3. Cell Signaling

An important finding demonstrates that the NF-kB (nuclear factor-kappa B) cell signaling pathway plays an essential role. It is thought to be activated by mitochondrial cytochrome c oxidase (CCO) serving as a generator of reactive oxygen species (ROS) (14). Changing the redox state of the mitochondrial membrane activates the formation of the transcription factor NF-kB. In the cell cytoplasm, NF-kB is inactive because it is in a complex with its specific inhibitory protein, IkB (I kappa B). ROS stimulate IkB-kinase (IkK), which triggers the phosphorylation of IkB, resulting in IkB complex decay with release of NF-kB. NF-kB is transported into the nucleus, which causes the expression of more than 150 genes many of which are involved in defense mechanisms against cell stress.

At relatively low doses of light, the mitochondria respond by increasing electron transport, oxygen consumption, mitochondrial membrane potential, and ATP synthesis. However, excessive doses may have the opposite effect.

Hypoxic or stressed cells appear to benefit more from PBM through the increases in mitochondrial and ATP activity. In addition, the activation of cell signaling processes is required to achieve a lasting effect on healing and tissue repair after discontinuation of illumination. An interesting phenomenon that arises also in healthy cells (and presumably post illumination as well) is the production of bursts of ROS that can have a beneficial effect by triggering cell signaling processes which lead to the up-regulation of cell repair and survival pathways. Mitochondrial ROS show a triphasic dose-response with two distinct peaks. The Janus nature of ROS is such that it may act as a beneficial signaling molecule at low concentrations and a harmful cytotoxic agent at high concentrations (15). This may partly explain the observed responses *in vivo* (16).

4. The Importance of Parameters

4.1. Optimal Parameter Window (Biphasic Dose Curve)

In PBM, there is an ideal range of parameters within which the therapeutic response is maximized, specifically total fluence (dose) and irradiance (intensity) (16). When these parameters are lower or higher than this range, the beneficial effects

are minimal or absent. An inhibitory effect may even occur in doses that are too high, a phenomenon well represented by the Arndt-Schulz curve (biphasic dose curve) (17). Although the effect of intensity (irradiance) and dose (fluence) from the light source is considerable, several other parameters of PBM are important to consider in order to optimize the biological and clinical effect (Table 2).

Irradiation Parameter	Measurement Unit	Description
Wavelength	nm	Most important parameter: determines chromophore absorption & depth of penetration.
Irradiance	mW/cm²	More important than fluence (law of reciprocity): determines the cellular activation threshold.
Pulsation	Frequency (Hz), Duration (s), Duty cycle (%), Sequence (s)	Sequential pulsing seems superior to regular pulses and CW mode.
Irradiation Time	Seconds	Minimal irradiation time most likely ≥ 2 minutes
Fluence	Joule/cm^2	Classically set at 4 Joules/cm² this parameter may be unreliable considering it assumes a reciprocity relationship with irradiance and time.
Treatment Interval	Hours, days, weeks or months	Different time intervals may result in different outcomes although 48h is the most widely used. It may be modified according to specific clinical applications.
Coherence	Coherence length depends on spectral bandwidth	Once believed to play an important role in PBM. Ultimately, LEDs & lasers have similar effects in skin.
Polarisation	Linear polarized or circular polarized	In highly scattering media like the skin light will lose its polarity. This property is then not frequently considered on the effects of PBM.

Table 2 Description of PBM irradiation parameters

4.2. Pulsed Mode Versus Continuous Wave Mode

Some studies show the pulsed light delivery mode to be superior to the continuous wave delivery mode, in particular with regard to healing and the production of collagen type I (19). In addition, sequential light pulses, repeated sequences of short pulses followed by long intervals, appear to be superior to regular light pulses (*in vitro* (20) and clinically (Figure 2) (21)).

Several theories have been proposed to explain the mechanism of action:

a- Targeted molecules with a smaller thermal relaxation time than selective photothermolysis.
b- The duration of the very short pulses (in μsec or msec) corresponding to the half-life of the mitochondrial ion channels or other membranes in the photoreactive cell.
c- The photodissociation of NO (as in the firefly) could also explain the advantage of the pulsed mode. It would act like a bright Morse code directing a suitable cutaneous response.
d- The concept of a "dark zone" or pulse train interval (PTI). Beneficial ROS bursts would be released during this period of time between pulse trains, when illumination ceases.

Work is currently underway to develop pulse codes tailored to each cutaneous presentation, e.g. inflammation, scarring, hyperpigmentation, prevention, etc., like a Morse Code to optimize PBM treatment.

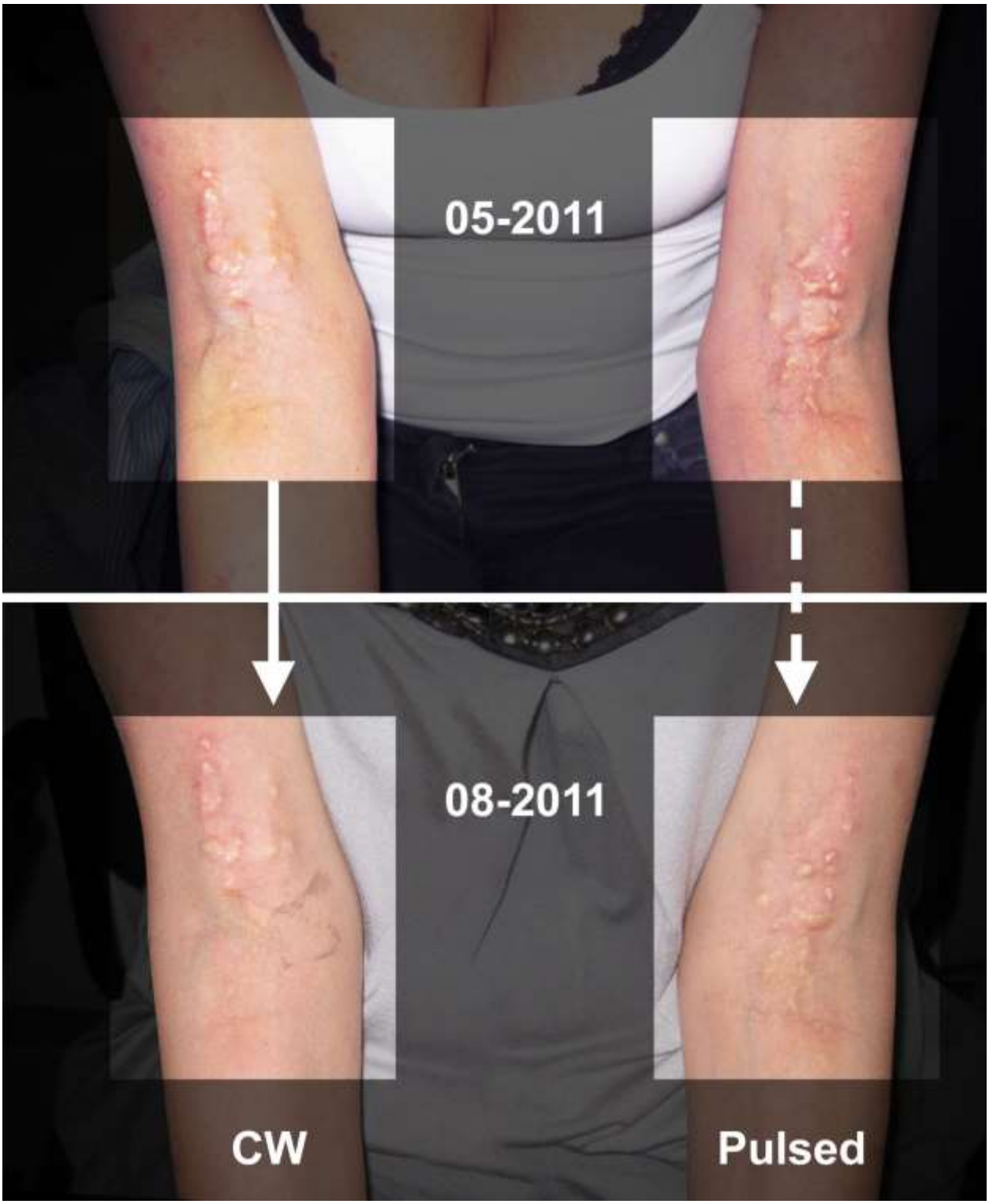

Figure 2. Patient forearms before (upper panel) and after (lower panel) PBM treatments (940nm 2-3 treatments/week X 13 weeks). The left forearm was treated successfully using a sequential pulsing mode and the right forearm did not respond using CW mode (21).

4.3 Tissue Optics

The therapeutic effect of PBM occurs when light is absorbed by the target tissue, by chromophores in particular. This seems simple at first glance, yet the principles of tissue optics in PBM are too often ignored. The dispersion and absorption of photons by the tissues is highly dependent on the wavelength. Thus, in the Near Infrared (NIR) spectrum, 810 nm offers the best penetration and is especially useful for subcutaneous PBM applications, e.g. musculoskeletal inflammation (7). In addition to the depth of penetration of light, it is essential to appreciate the amount of light reaching the depth.

Skin optical properties considering wavelength will predict the scattering and absorption of photons relative to the chromophore content and ultrastructural characteristics of the skin (22). One must also consider the variation from subject to subject, site to site, time to time, and the presence or absence of a skin condition. For example, hypervascularization present in inflammation may reduce photon penetration by half.

5. Dermatological Applications

Although there are several applications of PBM in different areas of medicine, e.g. in neurology, the musculoskeletal system, vision, dental, infection, poisoning, fertility, and stem cells differentiation, this review article will deal exclusively with the dermatological applications known to date.

5.1. Tissue Repair

PBM accelerates the healing of wounds (traumatic, surgical, acute, and chronic) and can even protect against certain types of skin stresses. Some of these applications follow.

5.1.1. Cutaneous Wounds and Accelerating Healing After Aggressive Aesthetic Treatments

Wound therapy is probably one of the most ancient and challenging areas of medicine. Initially, NASA reported significant results using PBM to accelerate the rate of wound healing in singular atmospheric conditions, such as wound healing of astronauts in orbit or in the treatment of submarine crew wounds (23). Immediately after surgery, PBM is ideal for triggering a cascade of inflammatory phases. Successive beneficial

effects will follow including the contraction of the wound, phagocytic chemotaxis and activation, macrophage polarization and differentiation of fibroblasts into myofibroblasts, and collagen deposition. In fact, the three classic phases of wound repair (inflammation, proliferation, and remodeling) can be modulated with early treatments – sometimes only one treatment - during the inflammatory phase leading to faster and optimal wound healing (24). The use of PBM in the red and near infrared spectrum is now established, whether it's post-traumatic, post-surgical, chronic (diabetic, venous, pressure and arterial insufficiency ulcers will be discussed later), or other types of wounds (25) (Figure 3).

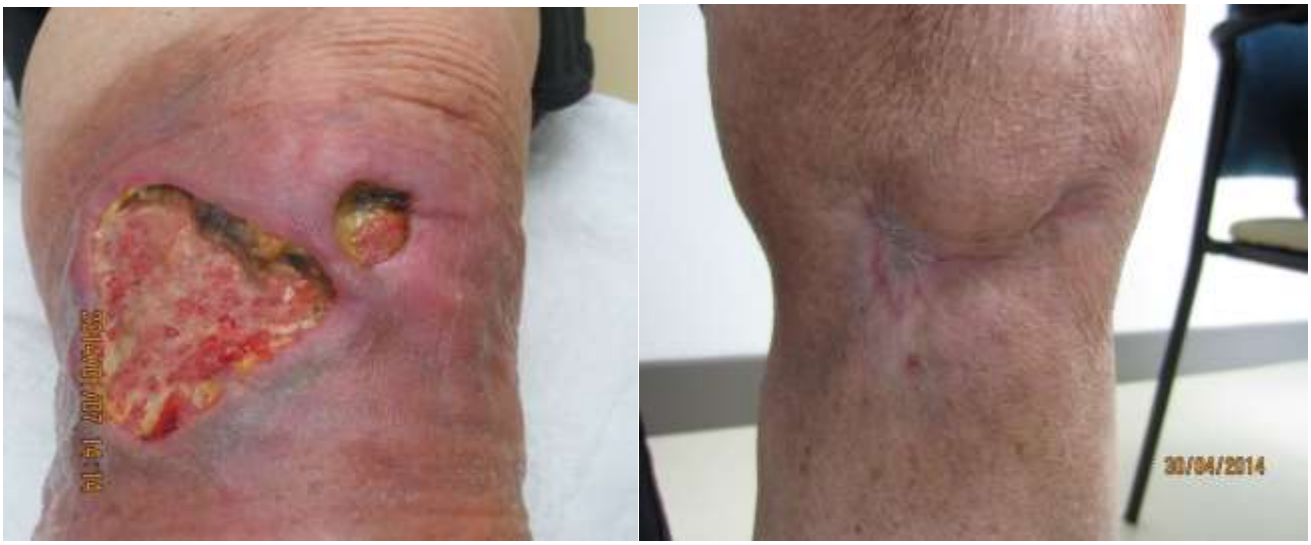

Figure 3. Post-traumatic ulcer with hematoma following PBM using pulsed LEDs at 660nm, 4 J/cm^2, 50mW/cm^2, 3 treatments/week x 4months.

Several randomized controlled trials (RCTs) using LEDs (yellow / red / NIR) report the use of non-FDA cleared LEDs for enhanced wound healing and recovery following acute trauma or light-based skin procedures (26-30). They may reduce healing time and erythema in acute wound healing processes of different etiologies.

LEDs are widely used to reduce the inflammatory consequences of "aggressive" treatments, procedures involving the use of lasers for skin resurfacing or vascular reduction or chemical peels. Alternatively, this may be done prior to the treatment to precondition the skin before the aggressive act and afterwards to aid in healing (31). The optimal effect of reducing redness and edema would occur on day four post-aggression.

5.1.2. Erosive Mucositis in Oncology

Confirmed by numerous (>30) randomized controlled trials, the effectiveness of PBM in treating erosive mucositis (post-chemotherapy) has been confirmed beyond doubt (32).

PBM appears to reduce ROS levels and enhance the immune response, enzyme activity, and protein synthesis (33). Other studies have shown increased fibroblast proliferation, maturation, and locomotion, as well as an increase in the production of collagen, basic fibroblast growth factors (7, 34), and may transform fibroblasts into myofibroblasts (35). It was also associated with a decrease in CXCL8 salivary levels (36).

PBM can reduce the risk of oral mucositis, its duration and/or severity. Most authors recommend red or infrared wavelenghts for prophylaxis (irradiance: 10-100 mW/cm^2, fluence: 2-3 J/cm^2) and a maximum of 4 J/cm^2 for therapeutic effects, applied on a single spot rather than with a scanning motion (37). New guidelines have even been established by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (38). PBM may also benefit other lesions of the oral or genital mucosa, e.g. gingivitis, traumatic wounds, canker sores, HSV, lichen planus, and pemphigus.

5.1.3. Leg Ulcers

A review of the literature shows that PBM is recognized for its positive contribution to the healing process in chronic leg wounds and ulcers of diabetic, venous, arterial insufficiency, or ducubitus origin. The great variability of the protocols and light sources used in the studies published to date makes meta-analyzes very difficult to perform. Note that the best results observed in controlled studies relate to the most difficult cases.

PBM studies on the treatment of diabetic ulcers show positive results and encourage further investigations (39). The Cochrane Wounds Group is conducting an exhaustive literature review on diabetic ulcers treated with PBM (40). Hence, there is a need for high-quality RCTs and a better understanding of the mechanism of PBM effects on venous, arterial, and decubitus ulcers as well.

5.2. Radiodermatitis

PBM is becoming a new treatment modality in supportive care for breast cancer. The yellow light initially proposed for breast radiodermatitis (590 nm) was abandoned. Current studies focus on red (660 nm) or infrared (808 and 905 nm) light which demonstrate a prevention of acute radiodermitis (41). A recent study (n = 79, 20 treatments; 2 times/week; 808 and 905 nm diode lasers, irradiance 0,168W/cm^2; fluence 4 J/cm^2) showed decreases in RISRAS (Radiotherapy-Induced Skin Reaction Assessment Scale) scores in both objective and subjective severity for patients undergoing radiotherapy in the PBM treated versus control group (42).

A recent review by the same group suggests that PBM is becoming a promising option for the management of breast cancer treatment-related side effects (43). Nevertheless, optimization of treatment and irradiation parameters for each condition is key to delivering the best PBM treatment response.

PBM could even be used before radiotherapy treatments to precondition the skin and reduce radiotherapy-related side effects (short term inflammation and perhaps long term hyperpigmentnation, telangiectasia, and textural changes) (44, 45).

5.3. Photoprevention

The preventive effect of PBM (photoprevention) with respect to UVB has been demonstrated *in vitro* and *in vivo* with red (660 nm) or near IR wavelengths (figure 4) (45). The proposed mechanism of action of this preconditioning method is related to p53 signalling pathway anti-apoptotic effects. It has been formerly reported that IR inhibited UVB-induced apoptosis *in vitro* by modulating the Bcl2/Bax balance, pointing to the role of p53 without heat shock protein (Hsp72-70) induction (46, 47). Another study reported *in vivo/in vitro* results on pig skin and quantitative PCR (RT-PCR) data in which LEDs at 940 nm (10 mW/cm^2, 4 J/cm^2) 24h pre-UVB exposure abrogated the expected gene expression in primary human fibroblasts 24h post-UVB. Collagen type I and p53 were upregulated and MMP-1 downregulated as if it had not been exposed to UVB 24 h earlier (48).

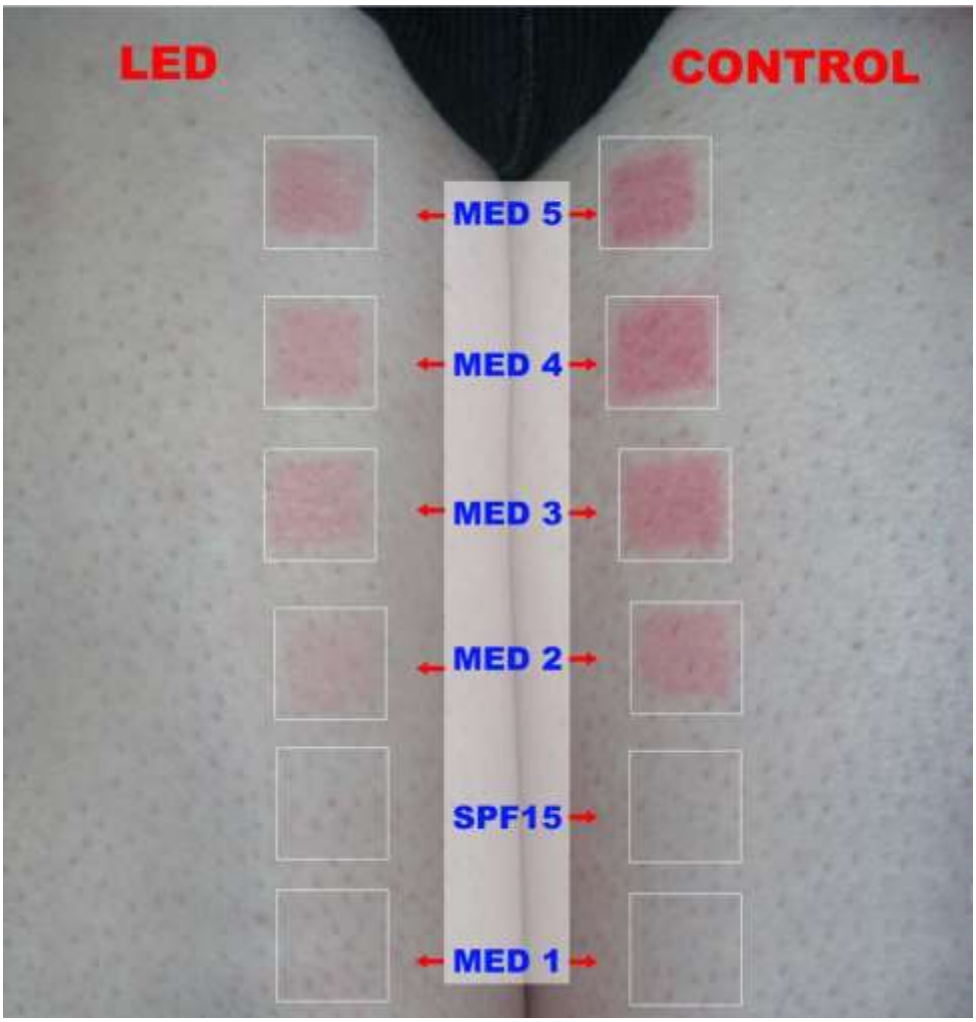

Figure 4. Photoprevention at 24h following different MEDs (MED 1 to 5) showing reduced UV-induced erythema on 660nm LED pre-treated side (45).

By analogy with nature, the sun's most abundant IR wavelengths in the morning are likely preparing the skin for the detrimental UV rays at noon, at the zenith (9). As a precursor to the day's coming UV insults to the skin, the ratio of UV to IR-A, as measured in the tropics, is lower in the morning and at the end of the day (figure 5). Consequently, IR-A prevents and repairs the likely mid-day UVR damage to the skin (due to higher UV/IR-A ratio at noon). It is thus possible to picture the use of this UV-protective method combined with its anti-inflammatory effects for the remediation of photo-induced inflammatory pathologies, like polymorphous light eruption or lupus.

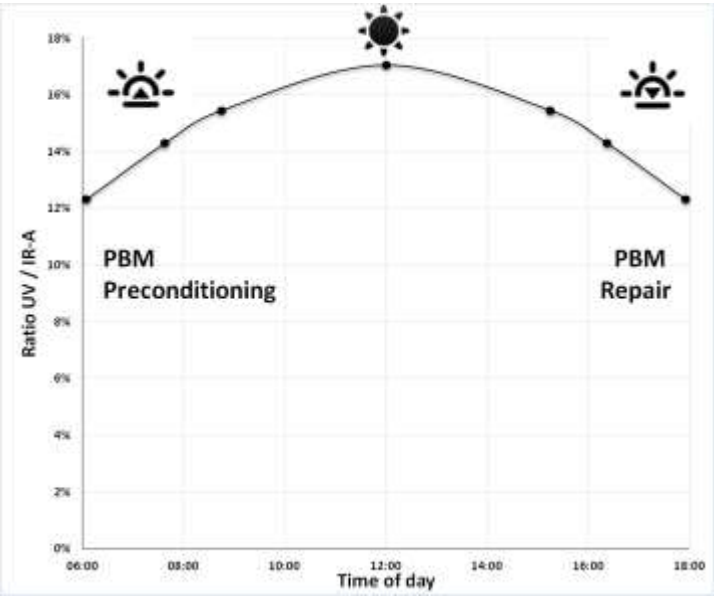

Figure 5. Ratio of UVR / IR-A solar irradiances, at sea level, with no clouds overhead, as available in the inter-tropics zone (where zenithal sun happens). Calculations were made using the Simple Model of the Atmospheric Radiative Transfer of Sunshine (SMARTS), 2.9.5 model, available from NREL and obtained in July 2015 at http://www.nrel.gov/rredc/smarts/about.html (9).

Furthermore, post-inflammatory hyper-pigmentation and scars can be prevented using specific parameters in the NIR spectrum that will be discussed in the next sections.

5.4. Pigmentation Problems

Vitiligo management represents a challenge for dermatologists. Segmental vitiligo responded to PBM (He-Ne laser, 632.8 nm, 3.0 J/cm^2 with point stimulation once or twice weekly) by normalizing dysfunctions of cutaneous blood flow and adrenoceptor responses of this sympathetic nerve dysfunction (49).

Although the results are quite variable and many treatments are necessary to repigment vitiligo, the association between blue and red wavelengths should be mentioned. Blue has pigment-forming power, being less deleterious than UV light, while red is beneficial for its immunomodulatory effects. An *in vitro* study showed the effects of the PBM visible wavelengths of 457 nm and 635 nm (at 2J/cm^2) on the ultra-structure and number of melanosomes in normal cultured human melanocytes. The study reported that the number of melanosomes observed in developmental stage I was significantly higher in PBM-treated cells compared to

control, an indication of significant stimulation of melanogenesis (50).

Regarding dermal hyperpigmentation like melasma and post-inflammatory hyperpigmentation (PIH), the use of IR light is a logical choice. IR wavelengths can penetrate deep in the dermis and, *in vitro* (51), can inhibit the synthesis of melanin and the expression of tyrosinase. Using cultured human melanocytes, Kim et al. showed that NIR LED wavelengths (PBM) effectively inhibit melanin biosynthesis and its molecular mechanisms underlying its effects on tyrosinase, TRP-1, TRP-2, and MITF protein expression with an intracellular signaling pathway. They showed that LED irradiation at wavelengths of 830, 850 and 940 nm effectively decrease melanin synthesis without cytotoxic effects in a normal human melanocyte monoculture and 3D multiple cell type co-culture model (51). Furthermore, it was shown that VEGF2 is downregulated and PTG (prostaglandins PTGIS nad PTGS1) is upregulated in melasma lesions (52). It has been shown that PBM NIR wavelengths can abrogate this reaction by increasing VEGF (53) while downregulating PEG2 gene expression (54).

A pilot study conducted by the author shows a significant improvement in dermal melasma and a significant tolerance to future solar exposures (photoprevention) by the use of PBM (55). This split-face pilot study included female patients (mean: 38.5 yrs) with bilateral dermal melasma. The procedure involved a mild bilateral microdermabrasion (to decrease photon scattering & increase epidermal turnover) immediately followed by unilateral light-based treatment (near infrared 940nm LED sequentially pulsed at D50, 60 mW/cm2). Weekly treatments were performed for 8 consecutive weeks. MASI score went from 21 at baseline to 13 at 8 weeks and 5 at 12 weeks on the LED-treated side. No significant improvement was found on the control side. These objective data were positively correlated with subjective analysis of plain and UV photos assessed by 3 independent observers. The melanin index average reduction was 25% compared to the control side even if clinical pictures showed much more improvement (55).

In terms of photoprevention, PBM can also prevent post-inflammatory hyperpigmentation (PIH) if applied in the week (x7d) preceding an aggressive treatment like CO_2 laser resurfacing, in patients predisposed to this phenomenon (56) (Figure 6).

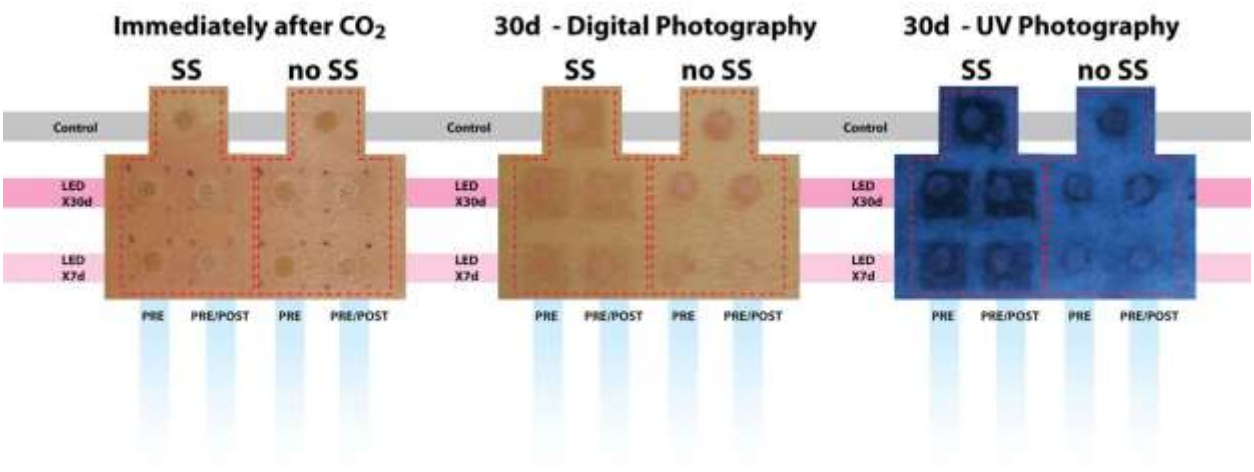

Figure 6. Post-inflammatory hyperpigmentation (PIH). CO_2 laser-induced PIH with or without exposure to Oriel sun simulator (SS). PIH reduction is possible following 660nm LED exposure pre and post SS particularly if applied 7 days before CO_2 laser (56).

Since most depigmentation creams (such as hydroquinone) cannot reach resistant dermal pigmentation such as melasma and PIH, PBM becomes a great alternative to modulate these deeply located dynamic pigmentary disorders.

5.5. Prevention of Keloids and Hypertrophic Scars

PBM can be used to prevent the re-emergence of keloids (Figure 7) (57).

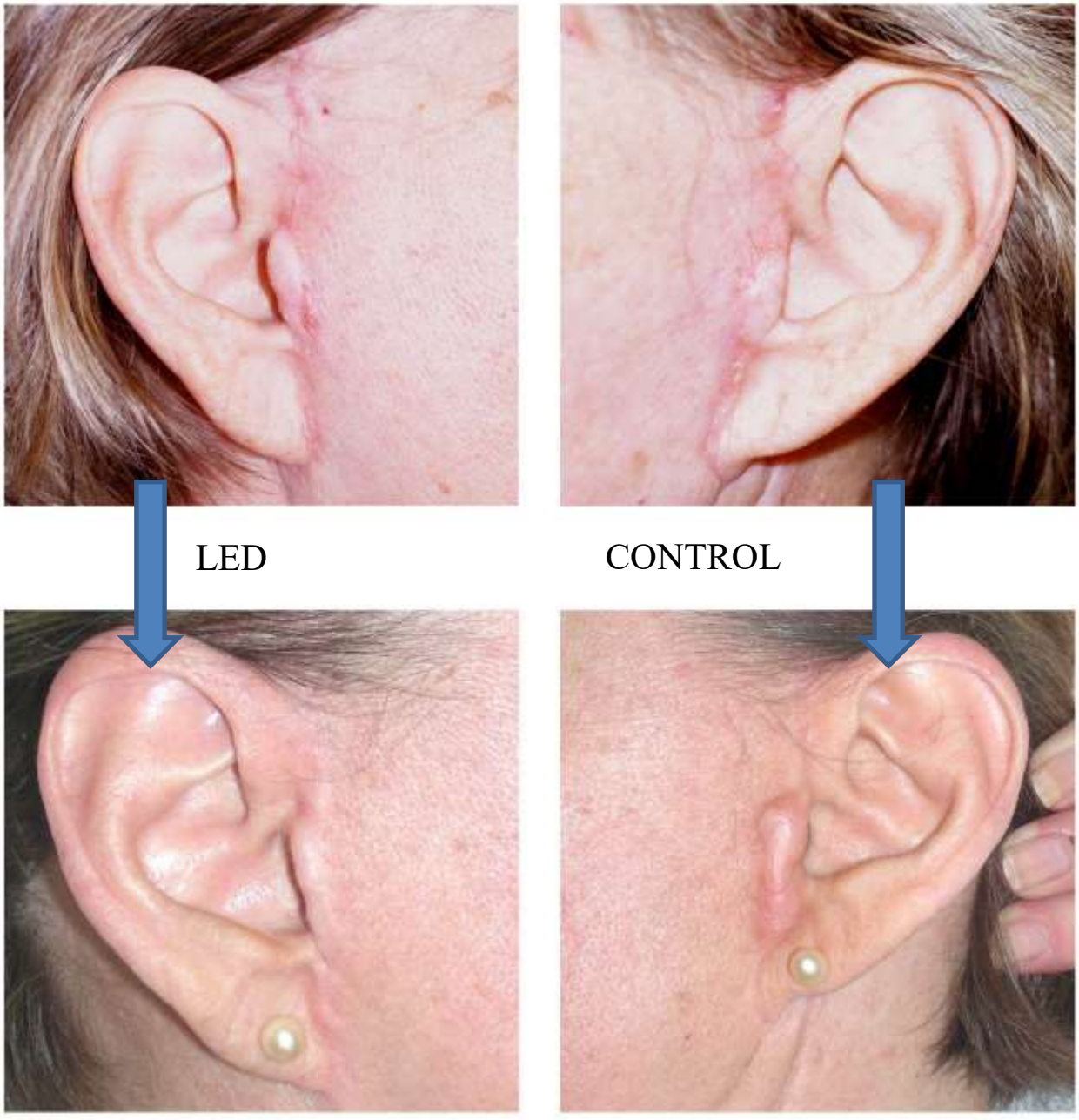

Figure 7. Post facelift keloid prevention 12 months post scar revision on R side using 905 nm LED daily x 30days post revision. L side = untreated control (no LED) showing preauricular keloid formation at the site of scar revision (57).

However, already present keloids or hypertrophic scars, could benefit from the use of high fluence PBM devices. Mamalis et al. showed that high-fluence light-emitting diode-generated red light (HF-LED-RL is defined as equal to or greater than 160 J/cm^2) can modulate the key cellular features of skin fibrosis. It increases

ROS generation, inhibits fibroblast proliferation without increasing apoptosis, inhibits collagen production, and inhibits migration speed through modulation of the phosphoinositide 3-kinase (PI3K)/Akt pathway (58).

Very high-fluence low-power laser irradiation (HF-LPLI) (at 1200J/cm^2; irradiance 500mW/cm^2 X 40min), can also selectively photoinactivate respiratory chain oxidase to trigger fatal mitochondrial superoxide anion bursts, producing oxidative damage in tumor cells (59). Such high fluence PBM may represent a new approach to treat excessive scarring.

5.6. Skin Rejuvenation

The anti-aging effects of LED monotherapy are controversial. Many studies report good results but often come from the same teams who are not without conflicts of interest. The results published with yellow 590 nm LEDs are to be taken with a grain of salt because of the absence of a control group even though supported by remarkable histoimmunochemical investigations (60).

There are a number of noteworthy investigations. Red (660 nm) associated or not with IR has been the subject of more successful studies. The author, using reconstructed human skin and live subjects, conducted an interesting study using 660 nm LED light. In the latter part of this investigation, 40 subjects were treated (hemiface only) with significant reduction of the wrinkles on the treated side. An overall improvement in skin appearance after LED treatment was observed in most participants, with improvements of up to 56% recorded (19). Another study compared the effectiveness of 633 nm red, 830 nm IR, and their association (61). Of these three groups, wrinkles were improved with LED treatment, most markedly when the two wavelengths were associated. Behind the scenes, collagen and elastic fibers are being reorganized with changes in cytokines and adhesion molecules known to play a role in skin repair. There are increases in procollagen type-1 and decreases in metalloproteinases.

There have been studies attempting to refute PBM. For example, Boulos et al. (62) showed multiple biases which could not have allowed for the conclusions drawn. Their choice of the 590 nm wavelength was not an appropriate choice for photo rejuvenation outcomes. As well, the absence of control subjects and an objective evaluation technique combined with

recruitment biases diminished the credibility of the results of this study.

However, there is much work to be done in this area. Red shows great promise with effects demonstrated in pulsed mode and in continuous mode as well. Broad spectrum polychromatic lamps have also been tested with interesting results. Home use devices (HUD) have appeared and allow for long term frequent use leading to more consistent anti-aging results. Several HUD studies have been done with quite interesting results (63). Used regularly to optimize the results of aggressive techniques like CO_2 laser resurfacing, PBM alone has shown positive results but, as for any anti-aging technique, the responses are variable from one subject to another.

5.7. Acne

Acne is the most common skin condition in the world. PBM is effective in treating mild to moderate inflammatory acne and Photodynamic Therapy (PDT) is used for moderate to severe forms. The anti-inflammatory action of 630 nm and 660 nm light modulates the sebaceous glands. Blue (405 nm) targets the porphyrins of *P. acnes* to destroy the bacteria via free radicals. The porphyrins in *p. acnes* are 5-10 times more sensitive to the violet-blue light emitted by PBM as compared to green or red light (64-66).

Hamilton et al conducted a systematic review of 25 randomized controlled trials and found that multiple treatments with blue, blue-red, or infrared light had the greatest likelihood of resulting in successful outcomes as compared to green, yellow, or red light (67).

The use of complementary anti-acne topicals, especially anti-comedonal, combined with PBM (especially blue for *P. acnes* and red for inflammatory acne lesions) has a high therapeutic potential.

Besides, the integration of small HUD will likely change the way we approach this frequent dermatological problem.

5.8. Alopecia

There are already many FDA cleared PBM devices on the market that emit red for the treatment of Androgenetic Alopecia (AGA). These can be found in combs, caps, helmets, and panels. Although the use of red dominates, the optimization of parameters and the introduction of near IR are

promising. The proposed mechanism of action is related to the mobilization of stem cells and the induction of their proliferation and differentiation (68). Using PBM at 660 nm and 830 nm, Kim et al. reported the induction of hORSC proliferation and migration and inhibited apoptosis *in vitro* associated with direct stimulation of the Wnt5a/β-catenin and ERK signaling pathway in human outer root sheath cells (69). Another study by Carrasco et al. showed that *in situ* ROS production in mouse skin activated cell proliferation in the bulge region of the hair follicle promoting hair growth (70).

PBM is now part of the three proven non-surgical anti-AGA methods including finasteride and minoxidil (71).

5.9. Cellulite and Body Remodeling

Here red and IR are used to reach the deeply localized adipocytes. It is claimed that PBM drains adipocytes by transiently increasing their permeability (72), although this mechanism of action is highly controversial (73). Scientific studies on PBM as a stand-alone procedure for fat reduction are often weak and still inadequate (74). Moreover, it is difficult to draw conclusions on the actual efficacy of PBM for this indication since the results will also depend on simultaneous dietary changes and increased physical activity.

5.10. Other Skin Diseases

The anti-inflammatory effects of PBM and their impact on the modulation of autoimmune processes make it possible to promote their use in many pathologies: psoriasis, eczema, lichen, scleroderma (most probably via modulation of TGF-β: Figure 8). Few studies exist so far, often limited to a small number of clinical cases. Note the recent introduction of a HUD for psoriasis (75).

More recently, PBM has been used successfully for the treatment of vulvar lichen sclerosus atrophicus (LSA). In comparison to PDT and corticosteroid therapy, PBM was the only treatment method showing a significant reduction in reflection spectroscopy (76).

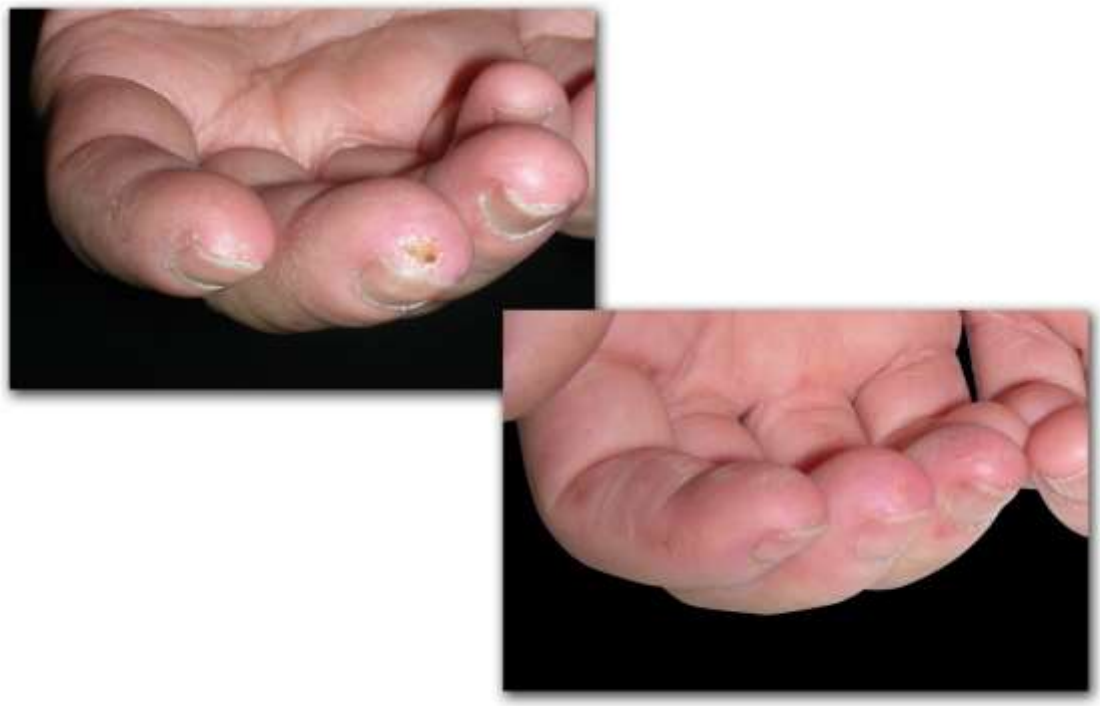

Figure 8. Pre and post PBM using LEDs at 810nm, 80mW/cm^2, 1-3 treatment(s) / week x 10 weeks. Not only calcinosis cutis disappeared but nocturnal pain was eradicated (77).

5.11 PBM systemic effects

The skin as a neuroendocrine organ forms a bidirectional platform for a signal exchange with other peripheral organs, endocrine, and immune systems or brain (78). What if one could mobilize specific molecules like nitric oxide (NO) from the body's largest organ (the skin) by using PBM with potential beneficial systemic cardiovascular effects. Hence, some work has been done using blue light capable of releasing photolabile NO non-enzymatically (79), the same way ultraviolet does (80). Lately, red and near infrared wavelengths have been shown to release NO non-enzymatically from ex-vivo skin (81).

The systemic effects of PBM on mood via neurorehabilitation have been reported (82). This application could be of great help in dermatology especially in neurodermatitis and prurigo nodularis where the two components of these psycho-cutaneous diseases (behavior and skin) are targeted. However, the systemic effects on mood are often subjective and therefore not easy to measure (83). Further studies are needed to

optimize PBM parameters (wavelength, fluence, irradiance, pulsing mode, treatment intervals, etc.) in order to improve such systemic response.

6. Conclusion

PBM is an emerging branch of phototherapy which uses visible light and near IR. Several cutaneous pathologies can now benefit from PBM whether it is used alone (monotherapy) or to complement other treatment modalities. A better understanding of the mechanisms of action will help us to optimize the known indications and to discover new ones.

The use of small PBM devices for home use (HUD) will extend the management of aesthetic and medical dermatology. Large surface PBM devices will trigger potential systemic effects via the delivery of photolabile molecules from the vast skin reservoir that, in turn, will interact with remote areas of the body with distinct mechanisms of action. This development will be accelerated by the technological improvement of LEDs and other light sources, powerful enough in masks, hats, clothes, and beds.

After skepticism, we are currently witnessing a growth in the use of PBM which continues to surprise us. It is a safe, fast, and effective method that will undoubtedly become a must for the practitioner. The future is bright.

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