INTRODUCTION

Lighting-emitting diode (LED) photobiomodulation is the newest category of non thermal light therapies. LEDs are complex semiconductors that convert electrical current into incoherent narrow spectrum light ***(Khoury and Goldman, 2008).***

Light emitting diodes can trigger intracellular photobiochemical reactions. To have any effect on a living system, LED-emitted photons must be absorbed by a molecular chromophore or photoacceptor. Light, at appropriate doses and wavelengths, is absorbed by chromophores such as porphyrins, and other light-absorbing molecules within the mitochondria and cell membranes ***(Alexiades-Armenakas, 2007).***

Light emitting diode exposed cells show increased adenosine triphosphate (ATP) production, modulation of reactive oxygen species, reduction and prevention of apoptosis, stimulation of angiogenesis, increase of blood flow, and induction of transcription factors. These signal transduction pathways lead to increased cell proliferation and migration, modulation in the levels of cytokines, growth factors and inflammatory mediators, and increased anti-apoptotic proteins. Emitted light are now available at wave-lengths ranging from ultraviolet (UV) to visible to near infra-red (NIR) bandwidth (247 -1300 nm) ***(Barolet and Boucher, 2007).***

Light emitting diodes are known for their healing and anti-inflammatory properties and are mostly used in clinical practice as a supplement to other treatments such as nonablative thermal technologies ***(Hawkins and Abrahamse, 2007).*** Furthermore, they have a role in esthetic dermatology as in photorejuvenation, sunburn prevention ***(Weiss et al., 2005a)*** and the treatment of cellulite ***(Alexiades-Armenakas, 2007).***

Moreover, LEDs have a role in the prevention of post surgical hypertrophic scars and keloids ***(Barolet and Boucher, 2010).***

Furthermore, LEDs have been long used in other non dermatologic problems such as in the treatment of neonatal hyperbilirubinemia ***(Tridente and De Luca, 2012)*** and in the treatment of denture stomatitis ***(Pavarina et al., 2011)*** and oral squamous cell carcinoma ***(Lim and Oh, 2011).***

Therefore, LED therapy is considered an innovative technology that has a great importance in medicine and especially in the dermatologic field. It has been shown to be safe, non thermal, non toxic and non invasive modality with nearly no side effects ***(Roelandts, 2005).***

Aim of the Essay

The aim of this essay is to elucidate the field of LED photobiomodulation, and to shed light on its evolution within esthetic and medical Dermatology, as a stand-alone and/or a complementary treatment modality.

Chapter One

Light Emitting Diode Photobiology

I. Historical Aspects of Light Emitting Diodes

The modern accepted definition of phototherapy is “the use of low incident levels of light energy to achieve an athermal and atraumatic, but clinically useful, effect in tissue”. Over many centuries, treatment with sunlight or "heliotherapy" was used in the treatment of skin diseases. More than 3500 years ago, ancient Egyptian and Indian healers used the ingestion of plant extracts or seeds in addition to sunlight for treating "leucoderma" ***(Calderhead, 2011).***

Modern phototherapy began with Nobel Prize winner Niels Finsen who developed a "chemical rays" lamp with which he treated patients with skin tuberculosis. However, it took several decades until phototherapy was introduced into the dermatological armamentarium. It was the development of photochemotherapy in 1974 that marked the beginning of a huge upsurge in photodermatology. The subsequent development of high intensity UV sources with defined spectra facilitated an optimized therapy for psoriasis and led to an expansion of indications for photo (chemo) therapy also in combination with topical and systemic agents ***(Hönigsmann, 2013).***

The development of the first laser systems, a race which was narrowly won by Theodore Maiman in 1960 with his flashlamp-pumped ruby-based laser gave clinicians and researchers a completely different and unique light source to play with. Between 1960 and 1964, the ruby laser was followed by the argon, helium-neon (HeNe), neodymium: yttrium-aluminum-garnet (Nd:YAG) and carbon dioxide (CO2) lasers all of which have remained as workhorses in the medical field, and the HeNe laser (632.8 nm) has in fact provided a large bulk of the phototherapy literature over the last three decades.

As for LEDs, the first light from a semiconductor was produced in 1907 by the British experimenter Round. Independently, in the mid 1920s, noncoherent infrared light was produced from a semiconductor (diode) by Losev in Russia. It was not till 1962 that the first practical and commercially-available visible-spectrum (633 nm, red) LED was developed in the USA by Holonyak, regarded as the 'Father of the LED'. In the next few years, LEDs delivering other visible wavelengths were produced, with powers ten times or more that of Holonyak's original LED ***(Zheludev, 2007).***

These LEDs were really inappropriate as therapeutic sources, although they were extremely bright and very cheap compared with laser diodes, and it was not till the late 1990s that a new generation of extremely powerful, quasimonochromatic LEDs was developed by Whelan and colleagues as a spin-off from the National Aeronautic and Space Administration (NASA)

Space Medicine Program. Unlike their cheap and cheerful predecessors, the so-called "NASA LEDs" finally offered clinicians and researchers a new and truly practical therapeutic tool ***(Whelan et al., 2000).***

II. Technology of Light Emitting Diodes:

Light-emitting diodes belong to the solid state device family known as semiconductors. These are devices which fall somewhere between an electrical conductor and an insulator, although when no electrical current is applied to a semiconductor, it has almost the same properties as an insulator. LEDs are complex semiconductors that convert electrical current into incoherent narrow spectrum light ***(Khoury and Goldman, 2008)***.

Simply explained, LEDs consist of negative (N-type) and positive (P-type) materials, which are 'doped' with specific impurities to produce the desired wavelength. The N-area contains negatively charged electrons which move in one direction and the P-material contains positively charged holes, which move in the opposite direction. When the materials are apart and not connected to any power source, movement continues, so both materials are conductors **(Figure 1a).** When the materials are sandwiched together, however, without any power applied to the electrodes attached to opposite ends, the negatively charged electrons in the center of the chip are attracted to the holes, and form an area called the depletion layer as seen in **(Figure 1b-c)** and all movement ceases in both the N- and P-

materials: the chip is now an insulator. **Figure 1d** demonstrates the situation when an electric current is applied to the electrodes, with the positive electrode or anode at the origin of movement of the holes and the negative electrode or cathode at the origin of movement of the electrons. Power flows through the junction between the materials, called the N/P junction, and movement of both electrons and holes starts again, but with power applied the electrons move to a higher energy level from their ground or resting state. **Figure 1e** shows that the N-electrons are attracted to the P-holes, but in moving down through the N/P junction they must return to their ground energy level, and lose their extra stored energy in the form of a photon, the smallest packet of light energy. When power is applied this action continues endlessly and no depletion layer is formed. The N- and P-materials are 'doped' with other materials which determine the distance of the 'fall' between electrons and holes: the greater the distance the electrons have to fall, the higher is the energy level of the photons emitted. Photons with high energy levels have shorter wavelengths than those with lower energy levels, thus the wavelengths of the emitted light are determined by the materials and their doping. High quality N- and P-materials and pure doping substances will give photons of very nearly the same wavelength, i.e., quasimonochromatic light. The wavelength emitted is noncoherent, ideally very narrow-band, and depends on both the materials from which the LED is constructed, the substrates, and the N/P junction gap. **Table 1** shows a list of the main substrates and associated colors ***(Calderhead, 2011).***

Table (1): Most common substrate combinations and colors they are capable of producing ***(Calderhead, 2011).***

Substrates	Formula	Color produced
Aluminum gallium arsenide	(AlGaAs)	Red, infrared
Aluminumgallium phosphide	(AlGaP)	Green
Aluminum gallium indium phosphide	(AlGaInP)	Green, yellow, orange, orange-red(all high-intensity)
Gallium arsenide phosphide	(GaAsP)	Yellow, orange, orange-red, red
Gallium phosphide	(GaP)	Green, yellow, red
Gallium nitride	(GaN)	Blue, green, pure green (emerald green): also white (if it has an AlGaN Quantum Barrier, so-called 'white light' LED)
Indium gallium nitride	(InGaN)	Near ultraviolet, blue, bluish-green

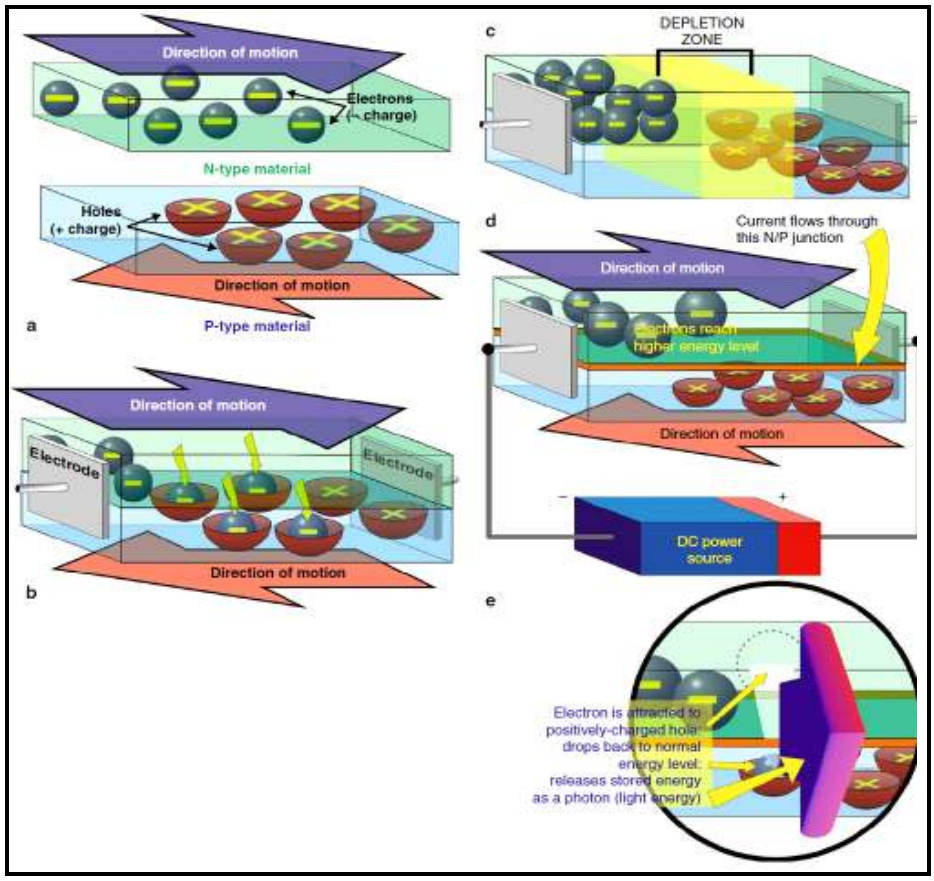

Figure (1): Light emitting diode technology ***(Calderhead, 2011).***

The anatomy of a typical dome-type LED also known as t-pack LED is shown in **(Figure 2).** Assemblies built from t-pack LEDs are often unsatisfactory in that they do not always provide sufficiently uniform lighting, are not well heat-sinked, and they are bulky due to the size (several millimeters) of each t-pack device **(Figure 3).** The latest generation of LEDs actually forms part of the board (so-called 'on-board' chips) which are much more compact than the dome-type LED and more efficient. The LED chips are attached to conductive tracks on a printed circuit board as shown in **(Figure 4)** ***(Roelandts, 2005).***

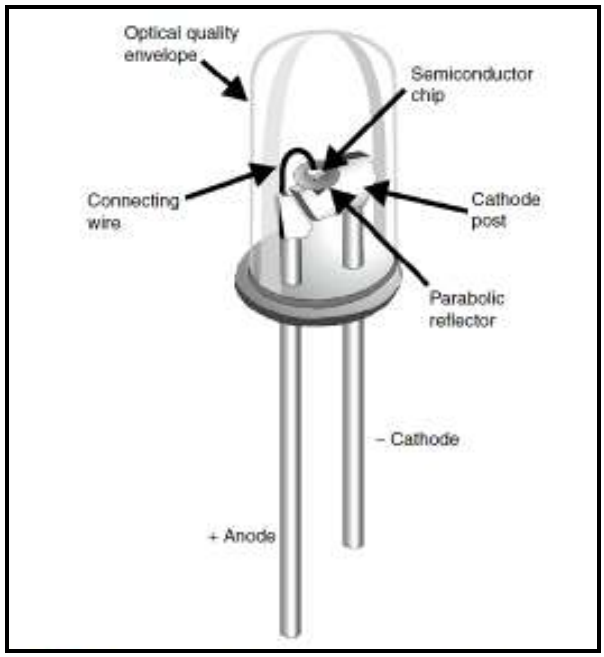

Figure (2): Anatomy of a typical high-quality dome-type LED.

The cathode is always shorter than the anode and there is a flat surface in the base of the LED by the cathode so polarity is clearly determined when connecting to a DC power source. On top of the cathode post and forming part of the negative electrode of the LED chip is a parabolic reflector in which the chip itself is mounted thus ensuring as much light as possible is directed forwards, with a consistent angle of divergence, typically 60° steradian or less depending on the specifications of the LED. A fine wire connects the positive electrode of the chip to the anode post, thus completing the circuit. The entire assembly is encapsulated in an optical quality clear plastic envelope, giving the final assembly its robust nature ***(Calderhead, 2011).***

Figure (3): Various colored t-pack LEDs ***(Roelandts, 2005).***

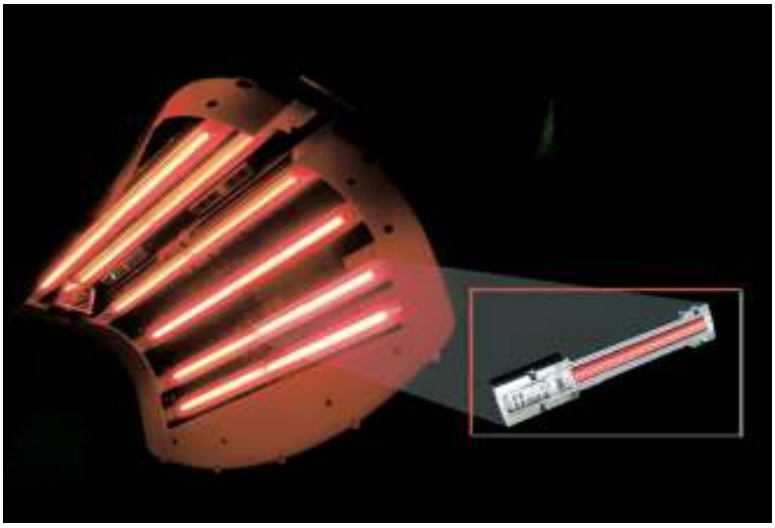

Figure (4): Linear chip-on-board LEDs ***(Roelandts, 2005).***

III. Mechanism of Action of LED Phototherapy

In LED phototherapy, there are two main mechanisms of action: photodynamic therapy (PDT) and photobiomodulation which are totally different mechanisms of action.

1. Photodynamic Therapy

The goal of PDT is the selective destruction of targeted abnormal cells while preserving normal structures. The initial step to PDT is the photosensitization of the abnormal cells. PDT can be exogenous or endogenous, the better known form of which is exogenous ***(Kormeili et al., 2004).***

a) Exogenous Photodynamic Therapy

Exogenous PDT is typically defined as: "The use of a substance (or photosensitizer) given orally, intravenously or topically, that can be activated or energized by light to destroy a target tissue in which the substance has preferentially located". This activation causes the formation of new molecules and free radicals such as reactive oxygen species (ROS) which may also form other chemicals that, in turn, may destroy the targeted material to a varying extent, such as through ROS-mediated apoptosis of the photosensitized cells or closure of blood vessels feeding the target tissue." PDT is another arm of phototherapy, and whilst exogenous PDT is thus still an athermal reaction, it is not atraumatic as deliberate induction of apoptotic cell death is the main goal ***(Ceburkov and Gollnick, 2000).***

The first main application for PDT was in the treatment of certain cancers, with such photosensitizers as hematoporphyrin derivatives activated with low incident levels of laser light, particularly with visible red light such as from the HeNe laser due to this wavelength's better penetration than the

shorter visible wavelengths in living human tissue. This activated an oxygen-dependent phototoxic cytocidal action within the cells containing the agent, and the free radical singlet oxygen ($^{-}O2$), a short-lived product from the reaction between an excited sensitizer molecule and oxygen, played a very important part in the induction of cell death (apoptosis) and destruction of the microvasculature feeding the tumor ***(Dougherty, 1984).***

One of the first applications for LED phototherapy was in fact PDT for non-melanoma skin cancers (NMSCs), such as basal cell carcinoma (BCC), superficial squamous cell carcinoma (SCC), or and actinic keratosis (AK) with the use of another exogenously-applied compound, 5-aminolevulinic acid (5-ALA) in any of its forms. This application continues to the present with good success and robust longlasting results ***(Garcia-Zuazaga et al., 2005).*** The topically applied 5-ALA penetrates into the dermis under an occlusive wrap, and is converted as part of the mitochondrial-based heme cycle into coproporphyrin III (Cp III), a member of the powerful porphyrin photosensitizing family. When the maximum amount of Cp III has been converted, the remainder of the 5-ALA is converted into another porphyrin, protoporphyrin IX (Pp IX). These two porphyrins become the specific targets of the LED energy at specific wavelengths and following photoactivation, nonselectively damage all of the superficial dermal tissue in which they exist ***(Gold and Goldman, 2004).***

When a photoreaction is desired such as in 5-ALA PDT for any purpose, an action spectrum has to be run to investigate the action potential of a range of wavelengths in the target compound. **Figure 5** shows the absorption spectra of Pp IX and Cp III. There is a very large peak at 415 nm in the visible blue Soret band, but as will be remembered from the previous section on wavelength, blue light has very poor penetrative capability into the dermis, and so it would not cause deep enough damage to treat NMSCs successfully. Another much smaller peak is however seen at around 633 nm, which was used in the early days of hematoporphyrin derivative PDT for other cancer types as a much better penetrating wavelength, thus giving a much deeper zone of porphyrin activation and hence a deeper zone and greater volume of controlled photodamage ***(Calderhead, 2011).***

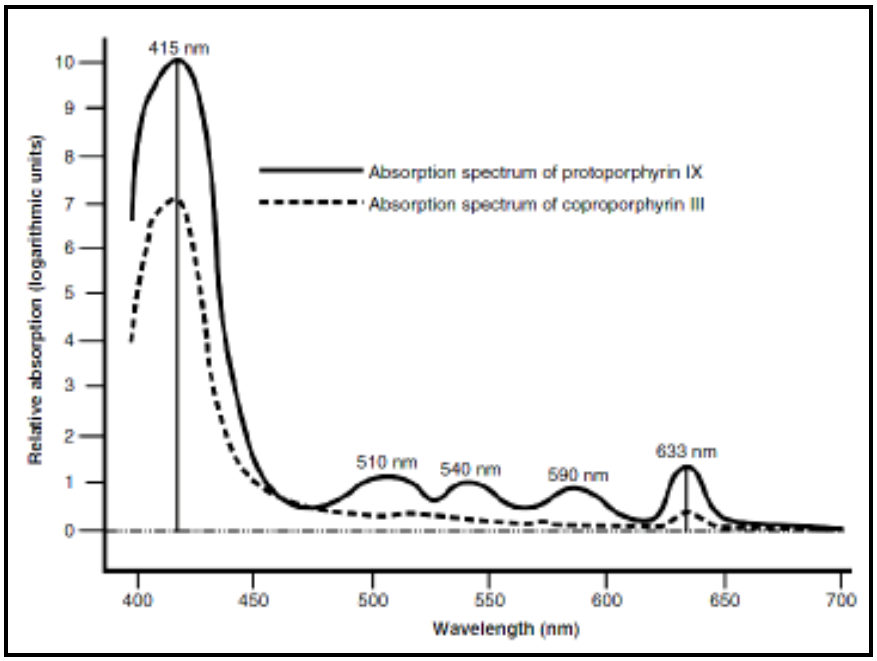

Figure (5): Action spectra for coproporphyrin III and protoporphyrin IX. Note the extremely high peak at 415 nm, and the minor peak at 633 nm, visible red, particularly in Pp IX ***(Calderhead, 2011).***

b) Endogenous Photodynamic Therapy

In endogenous PDT, the photosensitizer can be found occurring naturally within the target cells or tissue. The exogenous application of 5-ALA induces the synthesis of the porphyrins PpIX and CP III nonselectively in the epidermis and dermis under the area of application as already explained above. However, in the case of acne vulgaris the inflammatory acne lesions are associated with the presence of their causative bacterium, *Propionibacterium acnes* (*P. acnes*). It has been well demonstrated that both Pp IX and Cp III are endogenous to active *P. acnes*, and the more active is the bacterium, the higher the porphyrin concentration ***(Charakida et al., 2004).***