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Photodynamic Therapy in Skin Treatment

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Abstract

Photodynamic therapy (PDT) is a treatment that involves light-sensitive medicine and a light source to destroy abnormal cells. It is a modern, non-invasive therapeutic method used for the destruction of various cells and tissues. It requires the simultaneous presence of three components: a photosensitizer (PS), a light source, and oxygen. PDT is a promising treatment method that can be successfully employed in several medical fields including dermatology, urology, ophthalmology, pneumology, cardiology, dentistry, and immunology. Numerous authors, therefore, have studied this technique in order to improve its efficacy. As a result, significant advancement has been achieved with regard to PSs and drug delivery systems. Substantial progress was also obtained with respect to PDT for the treatment of precancerous skin lesions, several authors focusing their efforts on the study of daylight-PDT and on identifying methods of decreasing technique-related pain. This review reports on the most recent findings in PDT, with emphasis on cutaneous precancerous lesions. The ancients used it in treating many medical problems. This report will explain how light is used in solving some skin problems same as Actinic Keratosis, Nonmelanoma skin Cancer, and photorejuvenation. Photodynamic therapy is composed of three main elements: light source, photosensitizer, and Oxygen singlet

Keyword: *Light, laser, skin, oxygen, photosensitizer, cell death*

Introduction

What is the Photodynamic Therapy?

Photodynamic therapy (PDT) is the treatment that combines light energy with a drug (photosensitizer) designed to destroy cancerous and precancerous cells after light activation. The drugs only work after they have been activated through certain kinds of light. PDT also, may be called photo-radiation therapy, phototherapy, or photo chemotherapy. Photosensitizers are activated by a specific wavelength of light energy **[**1,2**]**.

Depending on the part of the body being treated, the photosensitizing agent is either put into, the bloodstream; through a vein or, put on the skin. Over a certain amount of time, the drug is absorbed by the cancer cells. Then the light is applied to the area to be treated. The light causes the drug to react

and form a special kind of oxygen molecule that kills the cells. PDT might also help by destroying the blood vessels that feed the cancer cells and by alerting the immune system to attack cancer**[**3,4**]**.

PDT can be used in people with certain types of cancer to help them live longer and improve their quality of life. It is becoming more widely recognized as valuable treatment option types of localized cancers (cancers that have not spread far from where they started)**[**5**]**.

The light used in PDT comes from certain kinds of lasers or from light-emitting diodes (LEDs). The kind of light used depends on the type of cancer and where it is located in the body. PDT is usually done as an outpatient procedure (meaning you will not have to stay in the hospital) but is sometimes combined with surgery, chemotherapy or other anti-cancer drugs, or radiation therapy.

Light is a form of electromagnetic energy that exists as a particle and that travels in waves at a constant velocity. Photo coming from light and dynamic because it has biological effect inside the tissue and cell. This effect related to the light wavelength and its penetration in living tissue for that we have important parameters to get maximum effect of PDT **[**6,7**]**. This parameters can concluded in equation below,

$$\text{Energy density} = \text{Energy} / \text{Surface Area J/cm}^2$$

Where,

Energy = Power * Time J

Power = Energy / Time W

Power density = Power / Surface Area W/ cm^2

This calculation is very important because we need to calculate to get the maximum effects of this therapy **[**8**]**. The scientist and researcher fund that there is an Optical or Therapeutic Window related to wavelength, power, energy, and time of treatment **[**9**]** as show in Figure.1. This graph shows the absorption of light into different component of the human body. In this graph, we can see a low valley in the center of the range where the light can travel the greatest distance. This is the optical window, it ranges from 650nm to 900nm, and you can see that the high-end extends up to about 940nm **[**10,11**]**. There is a lot of literature emphasizing the optical window and how it is used to predict the best wavelength for therapy lasers. Recent developments show that each wavelength has advantages but 650nm to 900nm is the best wavelength because it has the best combination of depth of penetration

(low absorption), cellular interaction, and energy transfer efficiency [12]. A measurement is important to both how the laser light is delivered to the surgical site and how it reacts with tissue.

Photodynamic Therapy (PDT) uses a photosensitizer (PS) that will accumulate in tumor tissue. Then the PS is activated using light and it becomes cytotoxic and can help destroy the tumor [13]. The majority of this type of therapy is done in the 600nm to 800nm range.

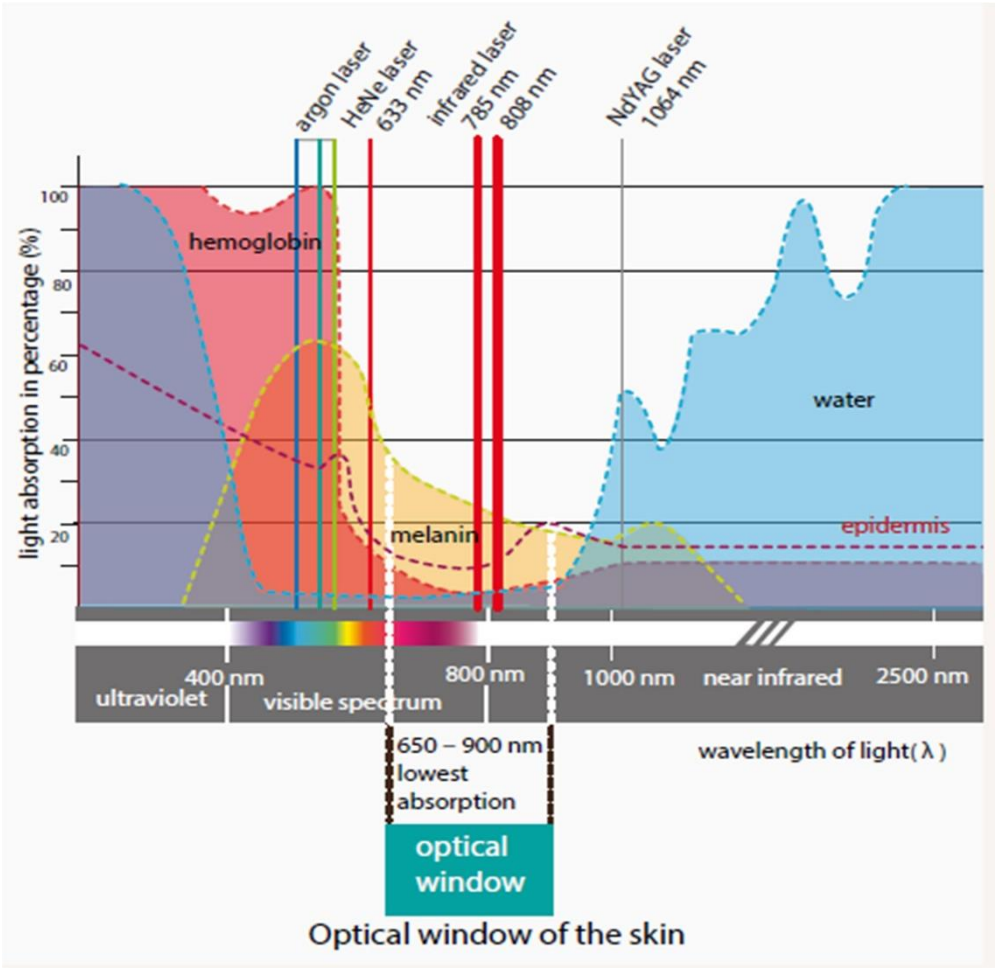

Figure.1: Phototherapeutic window range between 650 nm to 900 nm[14]

Energy density must be range between 0,.01 to 10 j/cm2 following Arndt-Schulz law as well as doses between 0.01 and 10 J/cm2 are stimulating the wound healing but higher doses are inhibitory as show in Figure .2 .

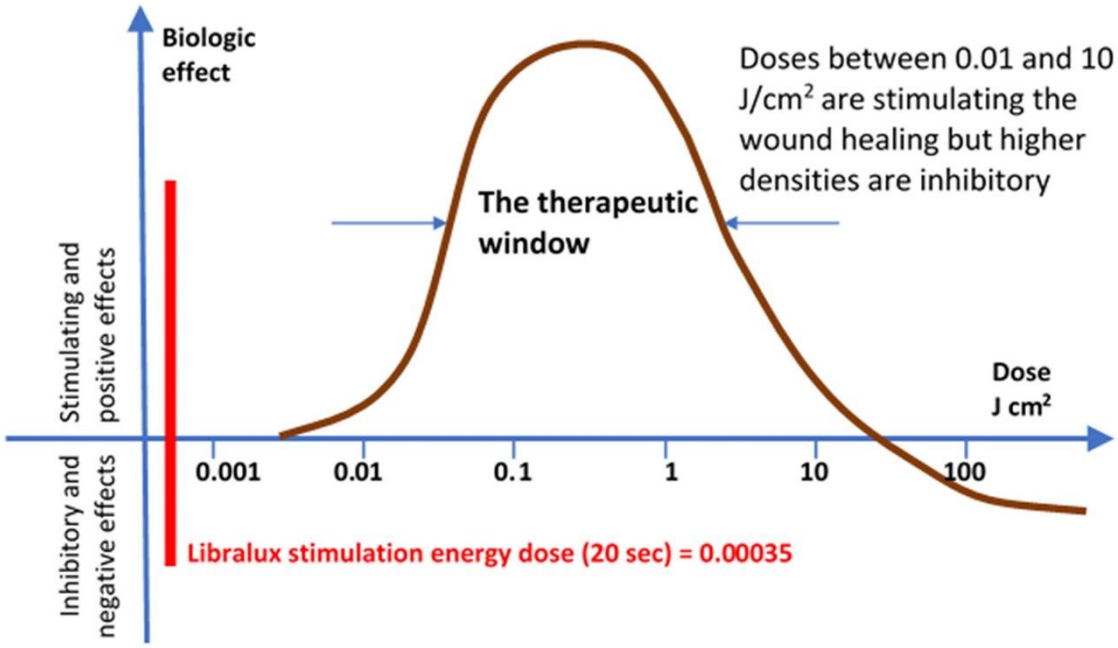

Figure .2: The Arndt and Schulz law for Laser therapy**[**15**]**

Devices Uses in PDT

Laser in the wavelength range between (650 -800 nm)

LED (Light Emitted Diode)

IPL (Intensive Pulse Light)

Most Common Photosensitizer

1. 20 % 5 – Aminolevulinic Acide (ALA)
2. A Methyl Ester
3. Hematoprophyrin Purified Derivative (HPD)

Human Skin

The skin is the largest organ in the body with total 20 square feet. The functions of the skin are the protection, sensation and save body temperature **[**16**]**. The skin is primarily made up of three layers. The upper layer is the epidermis, the layer below the epidermis is the dermis, and the third and deepest

layer is the subcutaneous tissue [17]. The epidermis, the outermost layer of skin, provides a waterproof barrier and contributes to skin tone [18] as given in Figure.3.

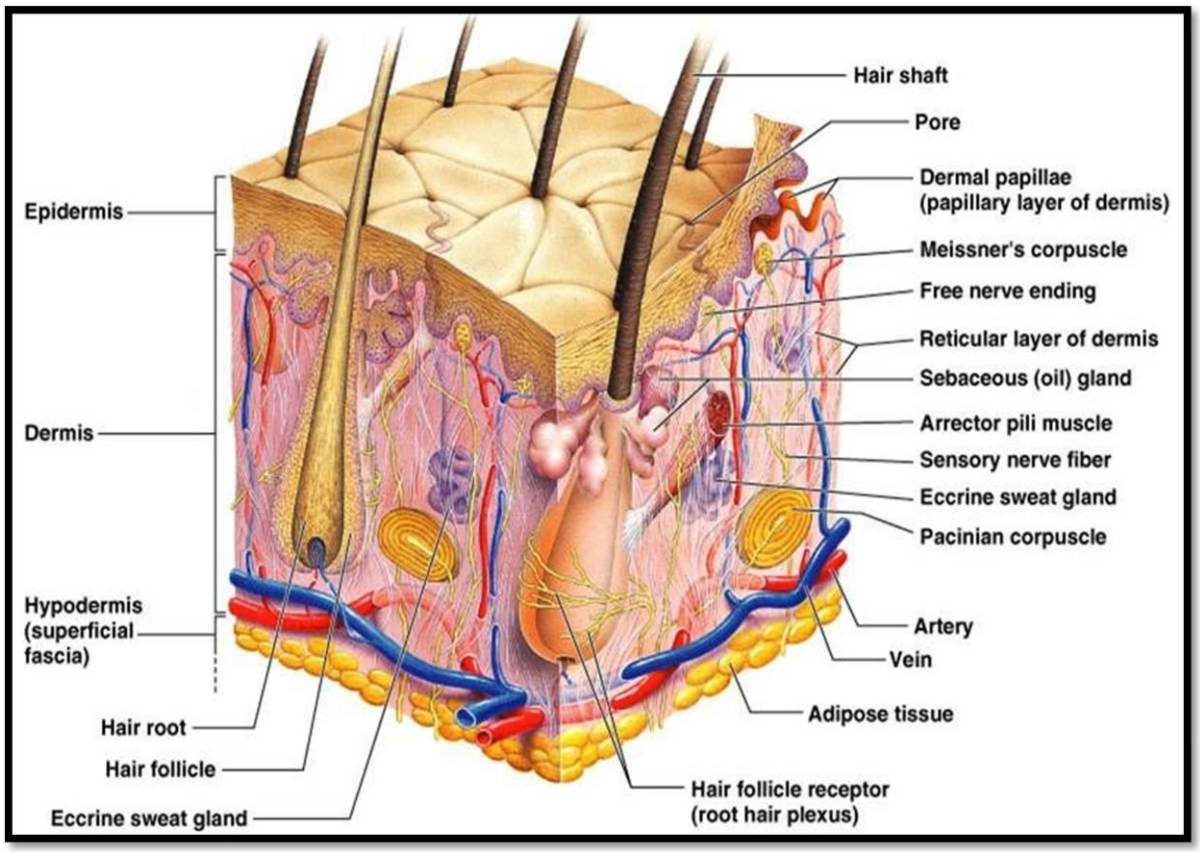

Figure.3: Anatomy of the Skin[19]

Epidermis: The epidermis is the outer layer of the skin, defined as a stratified squamous epithelium, primarily comprising keratinocytes in progressive stages of differentiation Keratinocytes produce the protein keratin and are the major building blocks (cells) of the epidermis[20]. As the epidermis is avascular (contains no blood vessels). It is entirely dependent on the underlying dermis for nutrient delivery and waste disposal through the basement membrane. The physical and biological barrier to the external environment, preventing, penetration by irritants and allergens [21]. It prevents the loss of water and maintains internal homeostasis The epidermis is composed of layers; Stratum conium (horny layer); Stratum lucidum (only found in thick skin – that is, the palms of the hands, the soles of the feet and the digits);Stratum granulosum (granular layer);Stratum spinosum (prickle cell layer);Stratum basale (germinative layer) [22].

Dermis: The dermis forms the inner layer of the skin and is much thicker than the epidermis (1-5mm). Situated between the basement membrane zone and the subcutaneous layer. The functions are Protection; cushioning the deeper structures from mechanical injury; providing nourishment to the epidermis; playing an important role in wound healing. Layers of dermis are superficial papillary dermis; the deeper reticular dermis **[**23,24**]**.

Hypodermis: The subcutaneous layer lying below the dermis; it consists largely of fat. It provides the main structural support for the skin, as well as insulating the body from cold and aiding shock absorption. It is interlaced with blood vessels and nerves **[**24**]**.

Laser Skin Interaction

Laser tissue interactions can be classified into four types on contact: reflection, absorption, scattering, and transmission **[**25**]** as shown in Figure.4.

- Reflection wastes laser energy and makes it unsuitable for medical applications.
- Absorption at the surface is influenced by various chromophores.
- Transmission helps the beam to penetrate the surface tissue to reach layers underneath.
- Scattering opposes precise delivery of the laser energy to a spot.

Each Wavelength has deferent penetration depth according to water absorbsion Increase water absorption =decrease penetration depth **[**26**]**.

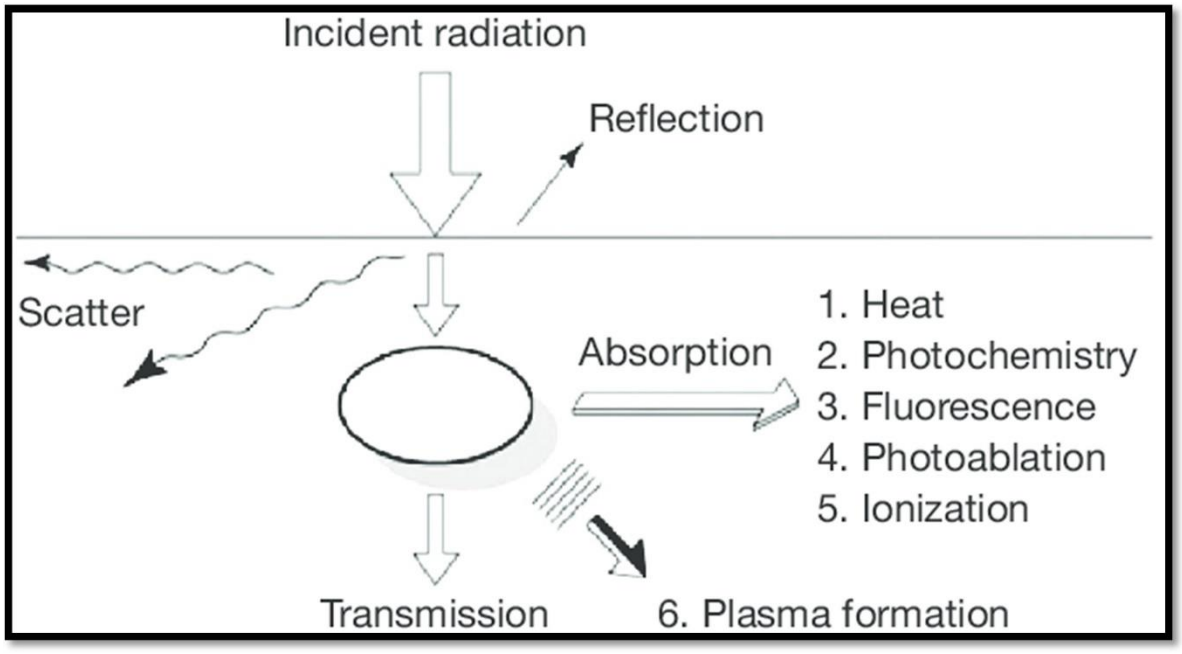

Figure.4: Laser Skin Interaction **[**27**]**

Biological Effect of Laser in the Skin:

Photothermal effects occur when the chromophores absorb the laser energy and heat is generated. Such as incising tissue or coagulating blood**[**28**]**.

Photoacoustic hard tissues are removed through a process known as photo disruptive ablation. Short-pulsed of laser light with extremely high power interact with water in the tissue causing rapid thermal expansion of the water molecules. This causes a thermo- mechanical acoustic shock wave**[**29**]**.

Photochemical reactions occur when photon energy causes a chemical reaction **[**30**]**.

Photo biomodulation such as increased collagen synthesis, fibroblast proliferation, increased osteogenesis, enhanced leukocyte phagocytosis. it is theorized they occur mostly through photochemical and photobiological interactions within the cellular matrix and mitochondria**[**31**]**.

When a laser heats Skin certain reversible or irreversible changes can occur **[**32**]**:

- Hyperthermia – below 50 ºC
- Coagulation and Protein Denaturation – 60 ºC
- Vaporization – 100 ºC
- Carbonization – 200 ºC

The Mechanism Action of Photodynamic Therapy

The reaction process is required: Photosensitizer, Source of light and Oxygen singlet **[**33,34**]** as explain below:

1) **Photosensitizer:** The physical-chemical properties of the photosensitizer are:

- Chemical Purity
- Capability to localize tissue
- Short Time Interval between the administration of the drug and hyper proliferating tissue
- Rapid Clearance from normal tissues
- Activation Wavelength with optimal tissue penetration
- High Generation of Singlet Oxygen
- Lack of Toxicity

The Most Common Type Uses:

a. Porphyrins Hematoporphyrin Derivative

b. Porphyrin precursors

- D-Aminolevulinic Acid (ALA)
- D-Aminolevulinic Acid (ALA)-Methyl-, Propyl-, Hexyl-Esters

c. Phthaallocyanines

- Chloroaluminum Tetra-Sulfonated Phthalocyanine
- Zinc (II) Phthalocyanine

d. Porphycenes

- 9-Acetoxy-2,7,12,17-Tetra-N-Propylporphycene
- 2-Hydroxyethyl-7,12,17-Tris (Methoxyethyl)Porphycene.

e. Pheophorbides

- Pheophorbide A, Bacteriopheophorbide

2) Light Sources:

a. Lasers: The types of lasers available for clinical PDT as given in the Figure.5

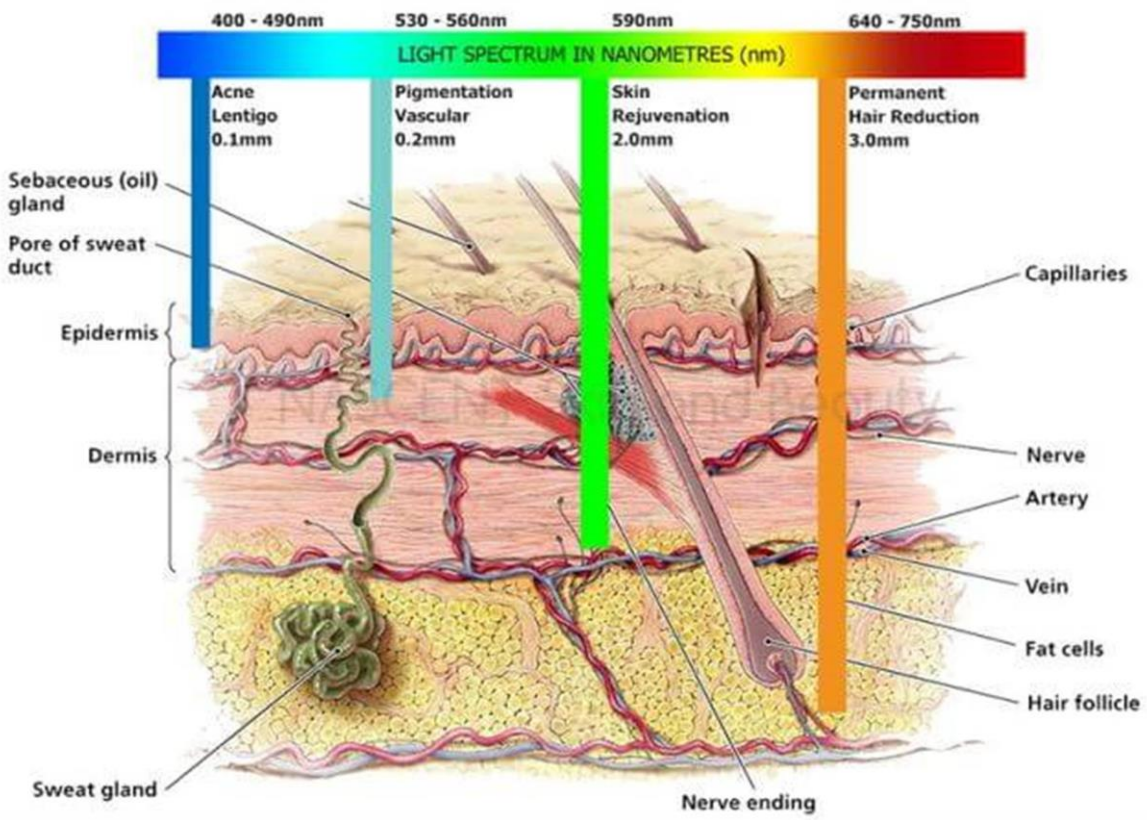

Figure.5: Medical lasers available for clinical PDT **[**35**]**

b. Lamps: The types of light sources available for clinical PDT are given in the Table.1 below

	Wavelength(s)	Bandwidth	Irradiance	Light delivery
Tungsten filament	400–1100 nm	10–100 nm (depending on filters used)	Up to 250 mW/cm^2 or typically up to 1.8 mW/cm^2/nm	Direct or via liquid light guide
Xenon arc	300–1200 nm	10–100 nm (depending on filters used)	Up to 300 mW/cm^2 or typically up to 3 mW/cm^2/nm	Normally liquid light guide
Metal halide	Depending on the metal, lines between 250–730 nm (can be phosphor coated)	10–100 nm (depending on filters used)	Up to 250 mW/cm^2 or typically 1.2 mW/cm^2/nm	Direct or liquid light guide
Sodium (phosphor coated)	590–670 nm	10–80 nm (depending on filters)	Up to 100 mW/cm^2	Direct illumination
Fluorescent	400–450 nm	Approximately 30 nm	Up to 10 mW/cm^2	Direct illumination

Table.1: Types of lamps available for clinical PDT **[**36**]**

c. Light Emitting Diodes (LED): LED can be arranged in arrays to irradiate large areas. They can be powered by batteries, making them totally and easily portable. Prototypes for the use of LED in phototherapy and PDT are currently under development[37].

3) Oxygen: A light excited molecule of an appropriate photosensitizer transfers energy to molecular oxygen giving rise to singlet oxygen. Photosensitizer (PS) is excited with light of a specific wavelength to generate reactive molecular species or free radicals that can react with the local microenvironment. Selectivity in PDT can be achieved by: Specifically targeting the PS to the tumor compartment by utilizing various methodologies such as immunoconjugates or nanoconstructs ; and by Locally delivering light to the region of interest to cause damage to malignant tissue while sparing surrounding healthy tissues [7,38] as show in Figure .6

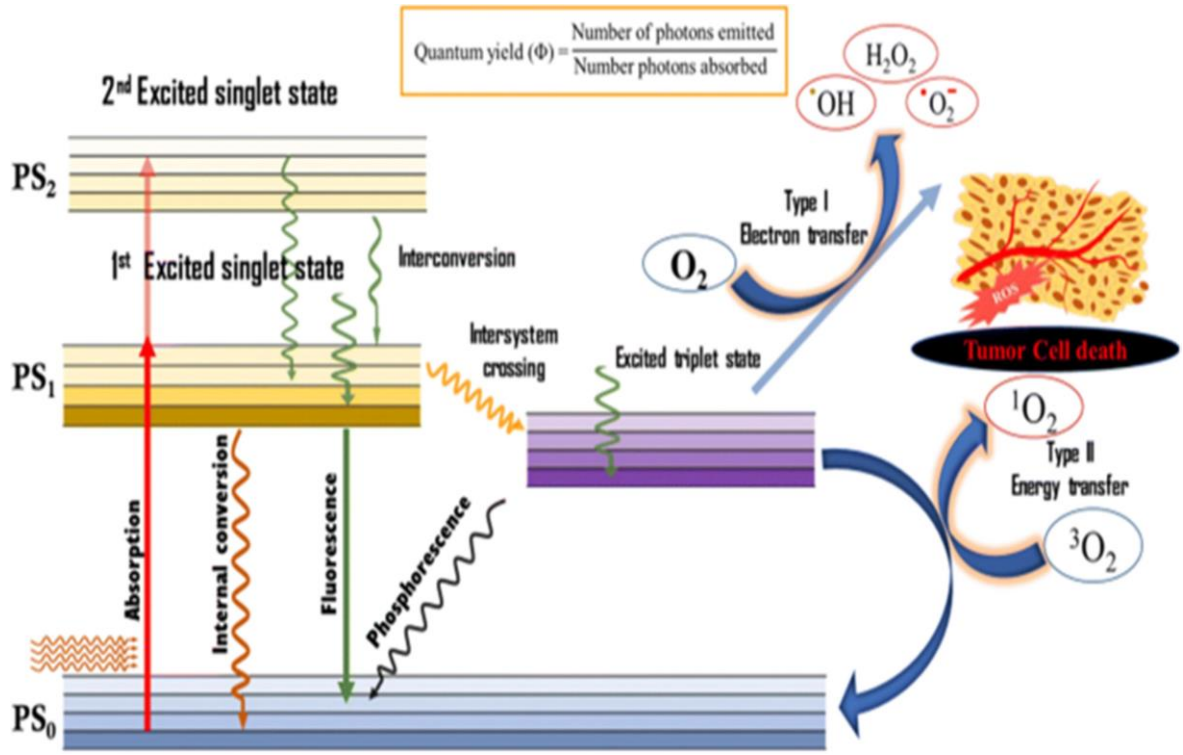

Figure .6: Diagram depicting the process of photodynamic therapy [39]

Methods and results:

1) Patient Selection

- The proper indication for PDT has been chosen.
- The patient understands that the majority of all PDT treatments we are performing at this time are considered off - label in the eyes of the FDA, although most have become the stander of care.
- Patient must understand fully the risks and benefits of this treatment.

2) Expected benefits and results:

It's according to the disease that would be treated for example in case of actino keratosis and photorejuvination would expect clearance and improvement and respond in 5-6 visits. For inflammatory acne vulgaris we will expect relief and improvement and respond in 1-3 visits.

3) Treatment Technique:

- Discus with patient all benefit and risks of this technique.
- Assigned written consent.
- Medical history
- Clean the face with mild cleanser.
- Mix the 20% 5-aminocluvunic acid with 48 % alcohol.
- This solution apply to the skin area for 1 hour in case of photorejuvination and sebaceous gland hyperplasia 45 min for inflammatory acne vulgaris
- Skin must be clean before use of light.
- Apply the laser or LED therapy.
- Cold application by Ice to relief any pain
- Use any sun protection in cream in the home to avoid any reverse effect.

Complication

Pain: we can manage it by cold application

Erythema: use of Neocutis cream to reduce erythematic skin

Phototoxicity: patient may suffer off desquamation of the skin after several days, use of good skin miniaturization.

Discussion

As mentioned before, PDT requires the presence of three components: light, PS and oxygen. A wide range of light sources can be used for PDT, including light emitting diodes, lasers and fluorescent lamps [15]. Blue light is preferred for the maximum absorbance while red and infrared radiations best penetrate the tissues. However, only light up to 800 nm can generate singlet oxygen. The light source should be chosen based on PS absorption, disease characteristics and costs [40].

Several agents have been developed and studied in the attempt to identify ideal PS. Hematoporphyrin derivative and photofrin are first generation PSs. They have several limitations, including a complex composition and low light absorption rate [41]. Hence, there was a real need to identify new PS. The second-generation PS was therefore developed. Most have a cyclic tetrapyrrolic structure and are represented by porphyrins and porphyrin analogs, chlorins, bacteriochlorins, phthalocyanines and metallo-phthalocyanines [40,42].

5-Aminolevulinic acid (ALA), a biological precursor of protoporphyrin IX (PpIX) and its methylated ester, methyl aminolaevulinate (MAL), have been widely used in dermatology [43]. Mono-L-aspartyl chlorin e6 (NPe6), temoporfin and hexylpyropheophorbide (HPPH) have a chlorin structure and have been used in head and neck cancer, bile duct cancer, brain cancer, lung cancer and sarcoma [44,45].

Second-generation PS are pure compounds, are well absorbed in the range of 650–800 nm and are less toxic than first generation PS. However, the degree of selectivity for the target tissue and the insufficient depth of treatment are the main limitations of these agents[42].

Third generation PS are currently being developed to improve PDT outcomes. Nanotechnology in PDT and gene engineering mediated PDT are therefore intensely researched[46]. Nan medicine is the medical application of nanotechnology and it uses nanomaterials which can improve drug delivery to target area, can improve drug solubility, can minimize degradation and increase drug bioavailability, among others [47].

Nanoparticles can be used as PS, they can help deliver PS by conjugation with antibodies, folate, transferrin or antibodies against the transferrin receptor or can be used as energy transducers [48].

PS can be encapsulated in liposomes to improve tumor-selective accumulation[44], in micelles to resist elimination by the reticuloendothelial system, but also in gold nanoparticles, biodegradable polymer-based nanoparticles, quantum dots carbon nanoparticles and silica nanoparticles[49].

Although PDT is based on the preferential accumulation in the tumor tissue, this selectivity is not absolute and some damage can occur to the surrounding tissue. Thus, a deeper understanding of the molecular mechanisms involved in drug delivery and specific targeting of tumors should contribute to the development of more specific technologies to deliver light and/or drugs to the tumor site and also to minimize resistance to PDT[29,50].

Accordingly, the developments of new PS targeting specific tumor sites have led to the modality of targeted-PDT. Another approach consists of the photochemical delivery of drugs through photochemical internalization (PCI), a modified form of PDT. PCI is actually a light- controlled drug-delivery alternative in which light activation enables spatiotemporal specificity and control of the intracellular drug release [51]. Moreover, the potential of PCI to circumvent the resistance and increase the efficacy of a variety of anticancer agents, have been demonstrated in several tumor models including approaches to overcome PDT-resistance in breast cancer cells [31,47].

focusing on the molecular differences of cell death mechanisms induced by PDT, starting with an optimized PS choice and conditions of its delivery and activation, will certainly provide valuable clues for the development of new therapeutic strategies aiming at improving the efficacy of PDT against cancer cells [44,52].

Conclusion

The challenges in fighting the disease rely on intrinsic tumour resistance properties, molecular heterogeneity, and metastasis. Considering all the information provided one can conclude that there are almost no doubts that one relevant advantage of PDT over other cancer treatments is the possibility of generating less side effects to the patients.

In summary, in this report we have explored and presented a broad up-date on the use of PDT as a therapeutic approach in the treatment of primary cancer as well as metastasis. We have covered several topics ranging from the photochemical mechanisms involved, the different cell death mechanisms being triggered by several photosensitizers up to the more recent-on-going clinical trials. Additionally, we have presented a significant amount of information underscoring the relevance of PDT as an alternative therapeutic approach capable of inducing several mechanisms of cell death, some of them simultaneously. This capacity could be an interesting way of overcoming the problem of death resistance displayed by many tumours since one of the characteristics that is important for an alternative therapy for cancer treatment is to broaden the spectrum of cell death mechanisms being gathered in order to by-pass the different resistance mechanisms displayed by malignant cells.

Dedication

I dedicate this research to my friend Aziza Saad, who supported me throughout the process of publishing it. Without their help, I would not have been able to complete this project. I am also thankful for my father and mother who have always been there for me and believed in me. Their love and support has enabled me to pursue my dreams and achieve success. This research is a testament to their hard work and dedication that has made it possible for me to become the person I am today.

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