



## REVIEW PAPER

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# Naturally occurring photosensitizers and photodynamic therapy: laser or sun?

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## ABSTRACT

**Introduction.** Our understanding of photodynamic therapy (PDT) is crucial for the applications of this treatment. In this physical phenomenon occurs light absorption by the applied photosensitizer, which results in its excitation to higher electron levels. After activation, a series of complex physicochemical processes take place in the tissues,

**Aim.** The aim of this study was to describe the basic naturally occurring photosensitizers used in PDT techniques. This study clarified applications of photosensitizers.

**Material and methods.** This study was used basic information about PDT reaction and the selective destruction of the tumor by photooxidation: a photosensitizer, a light source and oxygen. The papers reviewed here are based on Medline/Pub.

**Analysis of the literature.** Photodynamic therapy is an innovative form of treatment. This method is not a commonly used therapeutic and therapeutic tool, but a supplement to many already tested and analyzed techniques. Thanks to continuous research, this method has a wider and wider range of applications in medicine.

**Conclusion.** The data indicates increased number of papers regarding applications of PDT in medicine.

**Keywords.** diagnosis, oxygen, photodynamic therapy

## Introduction

Photodynamic therapy is a therapeutic tool used in the treatment of diseases (bacterial, viral and fungal) and neoplasms in the field of dermatology, urology, gynecology and dentistry.<sup>1</sup> It can also be used as a supplement to aesthetic medicine treatments. The foreground components are photosensitizers and light – as the central element of this method. The idea of using light (a commonly available and life-giving element) as a healing tool was born in antiquity.<sup>2</sup> The Egyptians, worshiping

the sun god (Ra), believed that all prosperity, prosperity and health come from the sun. phototherapy (aka heliotherapy) to restore health. Most often, this form of treatment was used in chronic skin diseases.<sup>3-5</sup> Phototherapy at that time was characterized by great interest and widespread use. With the abandonment of ancient beliefs and the fall of the Western Roman Empire, this therapy ceased to be practiced. It was returned to it in the 1830s. A significant increase in research and published articles took place only in the 20th century. Pho-

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photodynamic therapy is a synthesis of photochemical and photophysical processes occurring in the tissue after light exposure and after the introduction of a photosensitizer.<sup>6-7</sup> In this therapy, several most important stages can be distinguished.<sup>8</sup> The scheme is presented below (Figure 1).

Photodynamic therapy is a targeted method of destroying cancer cells. Contrary to chemotherapy, it “spares” healthy cells adjacent to diseased cells.<sup>8-10</sup> The selection of an appropriate photosensitizer and light of a specific and appropriate wavelength is extremely important in the general procedure of therapy. There is no single, strictly defined procedure for carrying out the procedure. The entire procedure depends primarily on the type of lesion and the available photosensitizer resources.

**Aim**

The paper presents the classification of photosensitizers, examples and characteristics of natural photosensitizers and a description of photodynamic therapy.

**Material and methods**

The literature review was prepared on the basis of the databases contained in the International Medical Library PubMed, the specialized search engine Google Scholar, and on the basis of the ScienceDirect scientific literature platform. Searches were conducted for “photodynamic therapy”, “natural photosensitizers”, “hypericin”, “hypericin photodynamic”, “curcumin photodynamic therapy” and “hypocrellin photodynamic therapy”. In the PubMed library alone, over 30,000 publications appeared under the slogan “photodynamic therapy”. The articles for the review were used from all three sources and selected on the basis of abstract analysis and the availability of the entire material/publication. The publications concern current research of scientists and research groups in the field of photodynamic ther-

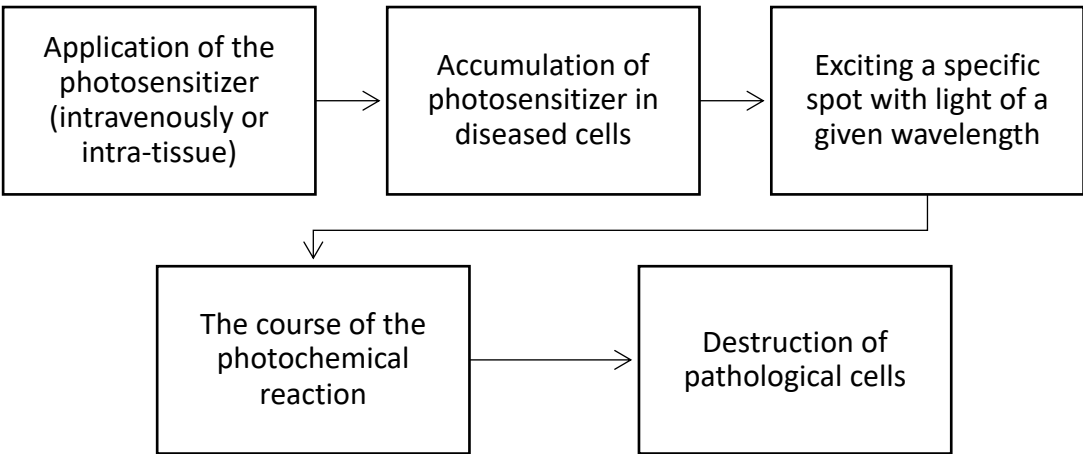
apy. Systematic reviews describing the breakthrough historical discoveries of this form of treatment and the characteristics of natural photosensitizers found in nature were also used.

**Analysis of the literature**

Based on the literature review, it can be concluded that photodynamic therapy is highly effective in lesions and in the initial stages of skin cancer.<sup>11</sup> It is a non-invasive form of treatment, the so-called a non-surgical tool that uses light and photosensitizers.<sup>12</sup> Photosensitizers accumulate in disease cells, in places of the tumor, and are then irradiated with laser light or visible light - followed by absorption.<sup>13,14</sup> singlet (1S0) to the excited singlet state (1S1). Much of the energy is lost through direct photon emission in the excited state. The so-called the phenomenon of fluorescence. A small part of the energy is used in the process of transition to the triplet excited state (3T1). The active form of the photosensitizer in the triplet state, reacting with oxygen, causes the formation of active oxygen species, i.e. singlet oxygen. These molecules cause apoptosis - programmed cell death.<sup>14-20</sup> Interpretations of the entire procedure can be reduced (simplified) to the statement that photodynamic therapy is the conversion of light energy into toxic, reactive oxygen species.<sup>21</sup>

The appropriate selection of the photosensitizer is extremely important, because it affects the effectiveness and efficiency of the treatment therapy.<sup>6</sup> Photosensitizers are characterized by such properties as: minimal harmfulness/toxicity to the patient's body, speed of removal (reconstitution in the tissue) and the number of potential side effects.<sup>22</sup> Currently there are known three generations of photosensitizers (Table 1). These photosensitizers are widely available on the pharmaceutical market and intended for specific clinical applications.

Over the years, research groups around the world have started the process of incorporating natural photo-



**Fig. 1.** The most important stages of photodynamic therapy

Table. 1 Generations of photosensitizers

| First generation photosensitizers   | Second generation photosensitizers   | Third generation photosensitizers                          |
|---|--|--|
| Hematoporphyrin derivatives (HpD, Photofrin)  | 5-aminolevulinic acid and its esters, a benzoporphyrin derivative, lutetium texaphyrin, temoporfin, tin ethiopururine and taloporphin sodium | Combination of photosensitizers with monoclonal antibodies |
| Application: urology (bladder cancer); pulmonology; cancers of the head, neck and esophagus | Application: incl. in surface lesions within the oral cavity   | Purpose: non-neoplastic vascular changes                   |

Table. 2 Characteristics of natural photosensitizers

| Name feature        | Hypericin   | Hypocrelin  | Curcumin  |
|---------------------|---|---|---|
| Source              | St. John’s wort   | Extracted from mushrooms <i>Hypocrella bambusae</i> | <i>Curcuma longa L</i>  |
| Absorbed wavelength | 590   | 600-900   | 405-435   |
| Application         | Tumors of the bladder, ovary, breast, colon, esophagus, psoriasis | Lung cancer, skin diseases                          | Neoplasms of the breast, cervix, stomach, diseases of the surface vessels and respiratory tract |

sensitizers (common in nature) into the photodynamic therapy procedure (Table 2). Such an example is hypericin. Hypericin is a hydrophobic molecule that requires a special carrier.<sup>23,24</sup> It is obtained from a plant belonging to the St. John’s wort family, called St. John’s wort. This plant belongs to the group of skin medicinal plants.<sup>25</sup> As a photosensitizer, hypericin has excellent properties, relatively low toxicity and antiviral activity.<sup>26,27</sup> It absorbs wavelengths (590nm). It has been confirmed to be important in the treatment of conditions such as cutaneous T-cell lymphoma, psoriasis, bladder and ovarian cancer.<sup>28</sup> Based on literature data, it is known that hypericin inhibits the growth of ATL cells, i.e. adult T-cell leukemia, leading to apoptosis of viral transcription. Moreover, according to the latest research, hypericin can control tumor growth and affect the amount of interleukins in colon cancer cells.<sup>28</sup> It exhibits a cytotoxic effect in esophageal, colorectal, bladder and breast cancer cell lines.<sup>29</sup> It has also been confirmed that this photosensitizer does not exhibit acute toxicity in the absence of light.<sup>30</sup> Thanks to numerous studies, hypericin is gaining more and more importance in photodynamic therapy, improving the procedure and increasing the effectiveness of this method.

Another type of natural photosensitizer is hypocrelin. It is widely used in the treatment of skin diseases. It is characterized by high efficiency, increased metabolism and low toxicity in the absence of light.<sup>31</sup> It exhibits effective antiviral antimicrobial activity, while antifungal activity is analyzed in research centers and discussed.<sup>32</sup> Absorbs light in the wavelength range from 600-900nm, which makes its use limited. Hypocrelin is also being analyzed in terms of its effectiveness in the treatment of keloid fibroblasts by mitochondrial apoptosis and analyzed for antitumor efficacy, e.g. in the lungs.<sup>33,34</sup> In the last 4 years, research centers have emerged to develop

and use other hypokrelin derivatives in photodynamic therapy, aimed at obtaining a photosensitizer with new, unusual properties.

Curcumin, obtained from the Ostryza long root, is also a natural photosensitizer. It exhibits antiviral and antitumor activity.<sup>35</sup> It absorbs light in the wavelength range 405-435nm. In recent years, the use of curcumin in the treatment of oral infections has been analyzed, thus confirming its antifungal and antibacterial activity.<sup>35</sup> Curcumin also has some limitations. It exhibits low solubility, which requires its use in the form of nanometer-sized emulsions.<sup>36</sup> Studies have shown high activity in the treatment of breast, cervical and stomach cancers (including its non-cancerous forms) in surface vessel diseases and in lower respiratory tract infections.<sup>36-40</sup> The table 2 below presents the most important information about the three most popular natural photosensitizers.

The selection of an appropriate photosensitizer alone does not determine the success and effectiveness of treatment. It is also important to choose the right laser. The basic criteria are the maximum and the wavelength range of the photosensitizer used. The depth of radiation penetration depends not only on the wavelength, but also on the type of tissue being treated. The lack of a standard research protocol in therapy opens up opportunities and flexible development paths for research teams working to obtain the best results and the highest treatment effectiveness.<sup>41</sup>

To sum up: the origin of the idea of photodynamic therapy is due to the observations and discoveries of the healing properties of the Sun – the central star of the Solar System. Currently, it is known that ultraviolet (UV) radiation, the source of which is the Sun, in addition to its positive effects, can also cause a number of dangerous skin changes, leading to the development of cancer cells. It is important to mine, the so-called The “golden

mean” and skilful use of the properties of solar radiation. Although the effectiveness of treating any skin lesions with laser photodynamic therapy is very high, you should still be aware of the negative effects and avoid excessive exposure to solar radiation.

## Conclusions

Photodynamic therapy is an innovative form of treatment. Although it was pioneered by the Egyptians in ancient times, a significant development of research took place in the twentieth century. This method is not a commonly used therapeutic and therapeutic tool, but a supplement to many already tested and analyzed techniques. Thanks to continuous research, this method has a wider and wider range of applications in medicine. The wide list of advantages proves that photodynamic therapy can become an increasingly used tool in the field of aesthetic medicine and in the treatment of selected neoplasms.

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