

Natural Photosensitizers in Clinical Trials

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Abstract: Photodynamic therapy (PDT) is a minimally invasive therapeutic method with high selectivity of action. It has gained great popularity in recent years as a new therapy for the treatment of cancer, but is also used in dermatology, ophthalmology, and antimicrobial treatment, among others. The therapeutic regimen involves the administration of a photosensitizer (PS) that selectively accumulates in tumor cells or is present in the blood vessels of the tumor prior to irradiation with light at a wavelength corresponding to the absorbance of the photosensitizer, leading to the generation of reactive oxygen species (ROS). Choosing the right PS is one of the most important steps in PDT and is crucial to the effectiveness of the therapy. Despite the many compounds discovered, the search for new molecules that could fulfill the functions of an optimal photosensitizer and improve the efficiency of PDT is still ongoing. Compounds of natural origin could contribute to achieving this goal. A number of photoactive substances as effective as synthetic photosensitizers have been described in various plant and fungal species. With the increasing identification of photoactive natural products, many new photosensitizers are expected to emerge. Some have already been clinically tested with promising results. In our work, we provide insights into this research and molecules, analyze their advantages and disadvantages, and point out gaps in current knowledge and future directions for their development. We also present natural photosensitizers not yet tested in clinical trials and point out future potential directions for their development.

Keywords: photodynamic therapy; clinical trials; natural photosensitizers



Citation: Aebisher, D.;

Przygórzewska, A.; Bartusik-Aebisher, D. Natural Photosensitizers in Clinical

Trials. *Appl. Sci.* **2024**, *14*, 8436.

<https://doi.org/10.3390/app14188436>

Academic Editor: Roger Narayan

Received: 14 August 2024

Revised: 15 September 2024

Accepted: 16 September 2024

Published: 19 September 2024



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1. Introduction

Ancient civilizations have known for thousands of years that they could combine multiple plants with sunlight to treat various skin diseases [1]. The actual history of photodynamic therapy (PDT), however, began in 1900, when Raab observed that microorganisms immersed in a solution of acridine orange died after exposure to sunlight, while those immersed in pure water and exposed to such light continued to live [2]. However, a landmark article published in 1978 in *Cancer Research* by Dougherty et al. is considered the starting point for clinical PDT [3]. Since then, PDT has found its way into many medical fields, including oncology, dermatology, ophthalmology, and dentistry [4]. The basis of its action is the generation of oxygen-free radicals [5].

The therapeutic regimen consists of specific, consecutive steps. The first is the systemic or topical administration of a photosensitizer (PS) to the patient—a compound that selectively accumulates in target tissues or in the vascular system near the affected tissue [6]. Then, the locally accumulated PS is irradiated with light of the appropriate wavelength, intensity, and exposure time to ensure that the correct fluence is achieved [5]. Absorption of light by the photosensitizer molecule causes its transition from the ground state to a short-lived excited singlet state. This is followed by an intersystem transition to a more

stable excited triplet state. From this triplet state, the photosensitizer molecules can return to the ground state by a type I or type II photodynamic reaction. In a type I reaction, the activated photosensitizer transfers an electron to the substrate to form various reactive oxygen species, while in a type II reaction, energy is directly transferred to the molecular oxygen in the ground state, resulting in the formation of highly reactive singlet oxygen [7]. The type I mechanism, through the possibility of gaining or losing an electron, leads to the formation of a radical ion or anion. The generated radical anion has the ability to interact with oxygen, leading to the formation of a superoxide radical anion ($O_2^{\bullet-}$). This process can lead to dismutation, i.e., one-electron reduction in the oxygen radical, resulting in the formation of hydrogen peroxide (H_2O_2), which in turn can undergo another one-electron reduction, leading to the formation of strong hydroxyl radicals ($HO^\bullet$). The process of producing reactive oxygen species (ROS) through a type II mechanism (which is described under Figure 1) is much simpler than type I. Most photosensitizers used in PDT work mainly through a type II mechanism rather than a type I one. Singlet oxygen and free radicals have specific and short lifetimes (10–320 ns), and their diffusion path in cells is only 10–55 nm [8]. The selection of an appropriate photosensitizer is the basis for the effectiveness of photodynamic therapy. The most commonly used PSs in medicine are porphyrins and their derivatives, phthalocyanines and their derivatives, and chlorines and their derivatives [9]. At the same time, new PSs are constantly being discovered to establish a compound with suitable therapeutic properties [10–12]. The mechanism of photodynamic action is presented in Figure 1.

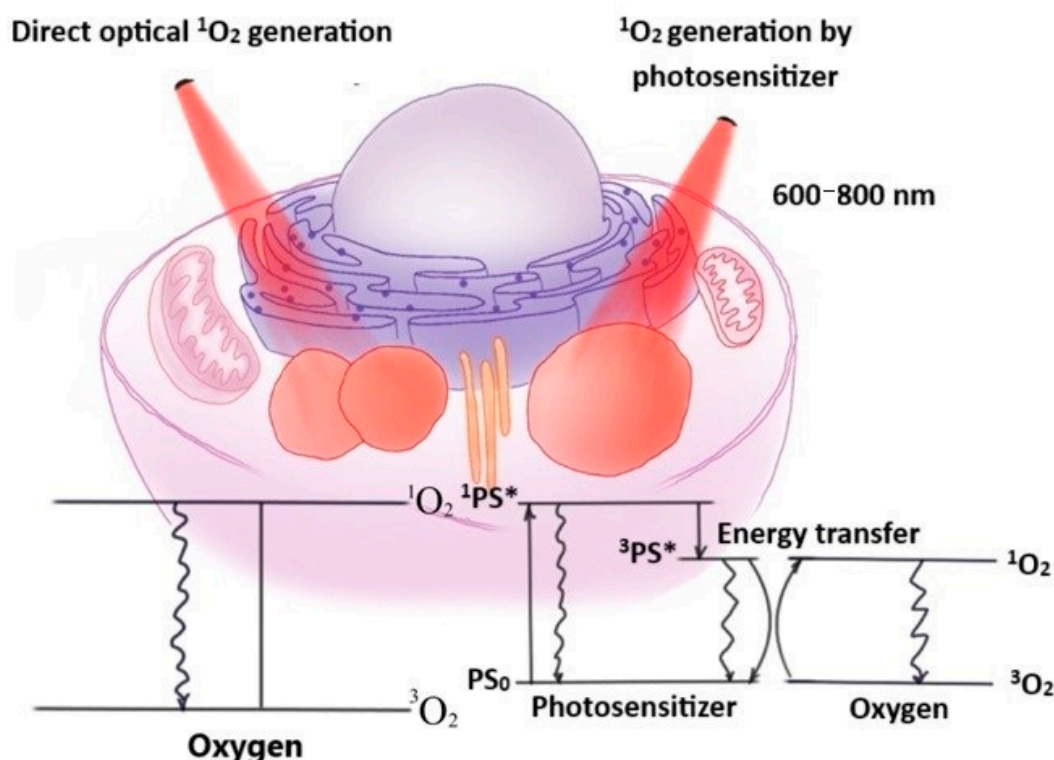


Figure 1. The general mechanisms of photodynamic action and type II reaction. The process occurs in several steps. A photosensitizer (PS) is administered to the patient and accumulates in the target tissue. This tissue is then irradiated with light of a certain wavelength, which is absorbed by the PS. After absorbing the photons, the PS goes from a ground (singlet) state to an excited (triplet) state. In the excited state, it can transfer its energy to the oxygen molecule, which is normally in the triplet state (3O_2). As a result of this interaction, oxygen passes to the singlet state (1O_2), which is a highly reactive form of oxygen and can react with various biomolecules in the cell, leading to their damage. Singlet oxygen (1O_2), which has not reacted with other compounds, returns to its more stable triplet (3O_2) state over time [7].

Photodynamic therapy has a number of advantages over other forms of treatment. The specificity of its regimen and the activation of photosensitizers depend on light, which allows the therapy to precisely target altered tissues while minimizing damage to healthy cells, which is the case, for example, in radiotherapy or chemotherapy [13]. Unlike other therapies, PDT also preserves fertility and does not affect pregnancy and childbirth [14]. Disadvantages of using PDT relative to other therapies primarily include the suboptimal properties of photosensitizers, such as poor water solubility, limited depth of light penetration, and lack of good tumor-targeting efficiency. Other disadvantages of PDT include a complicated schedule, the need for multiple procedures, post-treatment patient follow-up, and problems with light hypersensitivity during the weeks following therapy [13]. In view of this, the search for new photosensitizers is still ongoing [15].

In recent years, there has been a steady movement toward the use of natural substances and herbal medicines instead of synthetic chemotherapeutic drugs [16]. This direction is also evident in the search for new photosensitizers [17]. Studies show that natural photosensitizers isolated from plants or fungi are an alternative to the use of those of artificial origin [18,19]. There are scientific reports indicating that natural photosensitizers can be used to treat cancer and inflammatory, viral, or bacterial diseases, opening up the possibility of an even more effective form of photodynamic therapy [17]. Natural photosensitizers have a number of advantages: low cytotoxicity, high selectivity, relatively greater safety than their synthetic counterparts, and easy availability [18,20]. The use of natural photosensitizers also faces difficulties, such as identification by the patient's immune system, rapid removal from the bloodstream, and limited accumulation in tumor tissue. To solve these problems, photosensitizers are combined with natural cell membranes to form nanoparticles [21]. Another difficulty is that usually the detailed chemical composition of a given plant is not known, so a time-consuming and labor-intensive extraction process is required to isolate specific compounds precisely. Also important are the place of finding, climatic conditions, substrate composition, and many other conditions that affect the composition of individual plants, so that their properties in the photodynamic process will not be effective [22].

A number of natural compounds derived from plants tested for use as PSs have been established. Some of them have also been studied in the clinical setting. The current review focuses on presenting the results of clinical trials of natural-derived photosensitizers. Since there have been many recent papers extensively summarizing the research on natural photosensitizers [23–25], there is still a lack of papers accurately summarizing their clinical application; our work focuses on clinical trials. We also provide directions for future research for photosensitizers of natural origin that have not yet been clinically tested.

2. Methods

A literature search that focused on clinical trials of natural photosensitizers was conducted using the PubMed/MEDLINE database. The following search terms were used: “natural AND photosensitizer AND clinic”, “PDT AND pheophorbide A”, “PDT AND curcumin”, “PDT AND berberine”, “PDT AND anthraquinone”, “PDT AND furanocoumarin”, “PDT AND chlorophyllin”, “PDT AND riboflavin”, “PDT AND hypericin”, “PDT AND hypocrellin”, “PDT AND cercosporin”, “PDT AND tolyporphin”. A total of 2245 articles were identified (Figure 2). Only original papers describing clinical trials using natural photosensitizers, written in English or Polish, were eligible. Inclusion AND exclusion criteria are shown in Table 1. The final number of identified papers was 15 studies.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria
Papers describing photodynamic therapy
Original research papers
Papers describing clinical trials

Table 1. Cont.

Exclusion criteria
Works in a language other than English and Polish
Works that do not describe PDT using natural photosensitizers

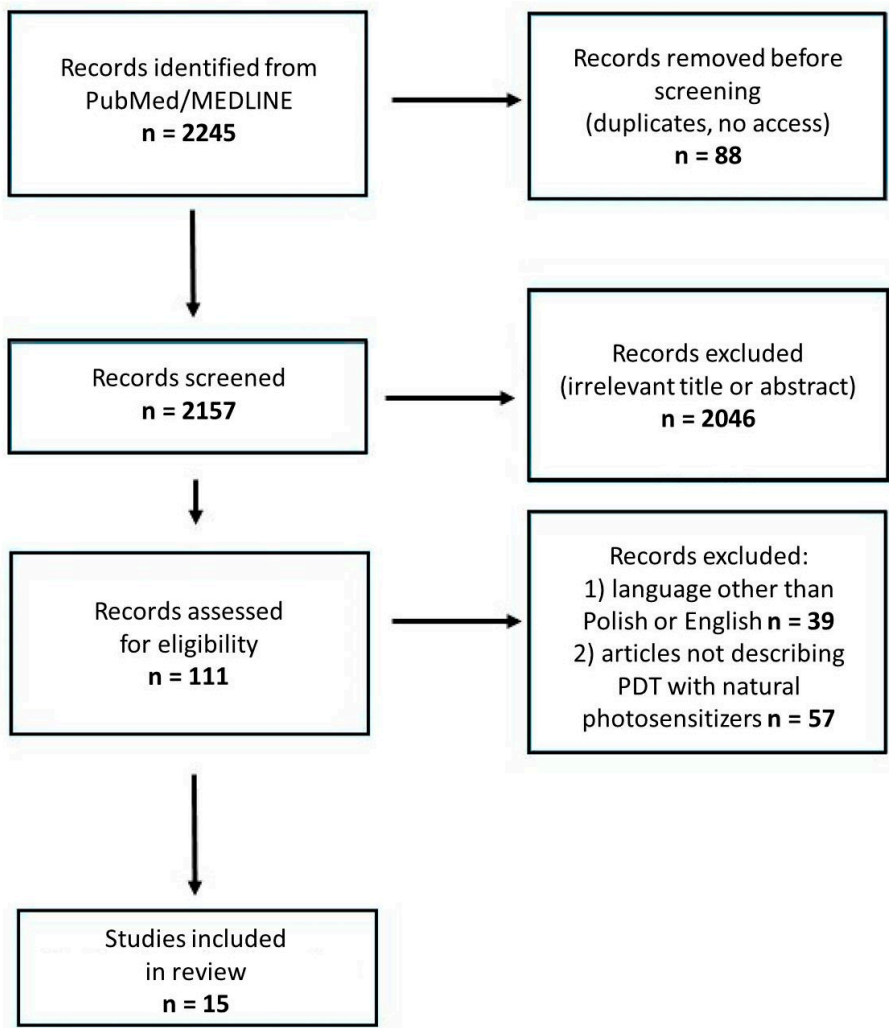


Figure 2. PRISMA flow diagram of the studies included. The diagram shows the steps of searching, analyzing, and qualifying scientific papers describing clinical studies of natural photosensitizers used in our article.

3. Natural Photosensitizers in Clinical Trials

3.1. Curcumine

Curcumin (CUR) is an antioxidant polyphenolic compound isolated from the rhizomes of the long-stemmed oyster (*Curcuma longa*) native to Southeast Asia [26]. Despite promising results from a number of in vitro studies demonstrating many potential medicinal uses for curcumin, no double-blind, placebo-controlled clinical trial of curcumin has been successful [27]. CUR is a photoactive compound, and its utility as a photosensitizer has been demonstrated in numerous in vitro and in vivo PDT studies involving various cancers and demonstrating its antimicrobial and antiviral properties [28,29]. The compound has a broad absorption spectrum of 300–500 nm. The maximum fluorescence excitation wavelength is 425 nm, while the maximum emission wavelength is 530 nm, which can stimulate very strong phototoxicity, even at very low concentrations. CUR-PDT has been shown to induce apoptosis of cancer cells by activating the caspase and p53 protein path-

ways, as well as increasing the expression of pro-apoptotic proteins and inhibiting the NF- κ B pathway. It has also been shown that CUR-PDT can induce autophagy by inhibiting epithelial–mesenchymal transition (EMT) and invasion and migration of tumor cells [30]. A major problem is that CUR has reduced bioavailability because it is insoluble in water [31,32]. To solve this problem, various water-soluble molecules have been invented, such as liposomes or curcumin incorporated into nanometer-scale micelles with enhanced assimilation suitable for cancer research [33]. The nanoparticles not only have the ability to improve the bioavailability of curcumin, but also act as platforms to conjugate subunits aimed at enhancing the efficacy of PDT [34].

Curcumin in Clinical Trials of Photodynamic Therapy

Curcumin is the most clinically studied natural photosensitizer. We located seven clinical studies involving PDT with this compound. All of the studies focused on the antimicrobial capabilities of PDT. Five of them tested the ability of CUR-PDT to disinfect the oral cavity, one to disinfect root canal dentin, and one to treat acne. None of the studies reported serious side effects of CUR-PDT, underscoring the reported safety of naturally derived photosensitizers. In these papers describing various specific indications, different therapeutic regimens were tested. In a randomized, controlled clinical trial, Labban et al. tested PDT with curcumin for the treatment of stomatitis in patients who are heavy smokers. Their work used a 5 μ g/mL solution of CUR I light with a wavelength range between 440 and 460 nm. Six sessions of PDT of dentures and the oral cavity were carried out, three times a week for half a month on each participant. A statistically significant decrease in mean CUR/mL *Candida* scores from the denture surface and palatal mucosa was observed at 6-week follow-up compared to baseline and at the 12-week follow-up compared to the value at 6-week follow-up, while with nystatin therapy and PDT with synthetic PS rose bengal, a decrease was observed only at the 6-week follow-up [35]. Leite et al. conducted a randomized controlled trial examining the effects of photodynamic therapy with blue light and curcumin as an oral disinfectant rinse. The CUR-PDT group used a mouthwash with 20 mL of a 30 mg/L CUR solution for 5 min, after which it was removed, and blue light at 455 ± 30 nm was introduced to activate curcumin for 5 min. The PDT group showed a significant reduction in CFUs (1 log reduction) after treatment, after 1 h and after 2 h, compared to the pretreatment instance and to the light-only or CUR-only treatment group [36]. Ricci Donato et al. also evaluated CUR-PDT as an oral decontamination agent. Patients rinsed their mouths with 15 mL of curcumin solution at concentrations of 25 mg/L and 100 mg/L for 1 min three times each. The mouth was then irradiated for 6 min with 450 nm light. The results indicate that microflora reduction was more effective at a CUR concentration of 100 mg/L. Moreover, unlike the synthetic PS photogem also studied in this work, CUR-PDT showed a reduction in microbial counts not only immediately after the applied treatment, but also after 24 h [37]. Panhoca et al. investigated oral decontamination of orthodontic patients with CUR-PDT and CUR-PDT combined with sodium dodecyl sulfate (SDS). Patients rinsed their mouths with a 1 mg/L CUR solution or this solution with the addition of a 0.1% SDS solution for 2 min. Then, the buccal and lingual surfaces of the teeth were successively irradiated for 3 min each with light of 450 ± 10 nm. Tested immediately after irradiation, the reduction in *S. mutans* in saliva was from 6.33 ± 0.92 to 5.78 ± 0.96 log 10 CFU/mL for the CUR-PDT group and from 5.44 ± 0.94 to 3.83 ± 0.71 log 10 CFU/mL for CUR-PDT + SDS [38]. Pinheiro et al. also tested the utility of CUR-PDT but in combination with photobiomodulation (PBM-T) in oncology patients with mucositis. Patients rinsed their mouths with 20 mL of 1.5 g/L curcumin solution for 5 min. The oral surface was then irradiated for 5 min with light at a wavelength of 468 nm. This was followed by a PBM-T protocol using a low-intensity laser. Of the 14 patients who received PBM-T + PDT, 12 achieved complete healing of the oral cavity, with healing lasting an average of 12 days. Four patients had no signs of inflammation at the final follow-up; two patients had recurrence of otitis media of (OM) (one after an additional cycle of chemotherapy and the other due to Sjögren's syndrome);

five patients died, and five were not followed up. No treatment-related adverse events occurred in either group [39]. Saini et al. investigated CUR-PDT in combination with a mixture of doxycycline, citric acid, and detergent (MTAD) as a means of disinfecting root canal dentin bonded to a dimethacrylate-based fiberglass post and evaluating the strength of the expulsion bond. The 2.5 mg/mL solution was poured into the canal for 180 s before irradiation. Common irradiation was achieved using a diode laser with a fiber optic tip. The canal was then cleaned with MTAD. The group of canals disinfected with CUR-PDT and MTAD had the highest push-out bond strength (PBS) at two levels: cervical and middle. The authors conclude that this strategy can be recommended in the clinical setting after further studies [40]. The study by Zhang et al. tested CUR-PDT in the treatment of mild to moderate acne. The therapeutic strategy involved applying a mask containing 1% curcumin for 20 min, followed by exposure to light with a wavelength of 445 nm. The treatment consisted of sessions spaced every 3 days, with a total of two treatments per week, administered continuously for 2 weeks. Efficacy evaluation and comparison were performed on both groups of patients before treatment and 2 weeks after the last treatment. Total lesion removal rates for CUR-PDT were $54.7 \pm 21.5\%$, relative to $28.1 \pm 19.9\%$ with light monotherapy. All patients experienced no pain during treatment on either side, only a mild warm sensation. After CUR-PDT treatments, mild erythema occurred on both sides, which resolved by two hours. Two patients experienced mild pigment deposition on both cheeks after two treatments in both the experimental and control groups. This pigmentation resolved spontaneously after a 1-month follow-up. There were no adverse effects such as swelling, scabs, itching, pigment reduction, or scarring [41].

3.2. Hypericin

Hypericin (HYP) is a hydroxylated phenanthroperylenequinone derived from the well-known St. John's wort (*Hypericum perforatum*) herb [42–44]. Due to its hydrophobic nature, hypericin accumulates mainly in the membranes of the endoplasmic reticulum (ER), lysosomes, Golgi apparatus, and mitochondria. When used in PDT, it can induce stress in the ER, leading to the release of calcium ions into the cytoplasm. In turn, increasing their levels can activate various enzymes and lead to mitochondrial damage. Moreover, HYP generates high levels of singlet oxygen and has minimal toxicity in the dark and excellent photosensitivity [45,46]. HYP's photoactivation ability is induced by a delocalized π electron arrangement in its aromatic rings [46–48]. Studies in recent years have demonstrated the anticancer potential of hypericin for use as a photosensitizer in PDT in several types of cancer, including anaplastic thyroid cancer, pancreatic cancer, glioblastoma multiforme, nasopharyngeal carcinoma, and leukemia [49–53].

Hypericin in Clinical Trials of Photodynamic Therapy

We located three clinical trials with this compound, with one using pure hypericin as a photosensitizer and two using *Hypericum perforatum* extract. All focused on the treatment of skin lesions. The side effects of PDT with hypericin have been described, but they were not serious. Kim et al. conducted a multicenter, placebo-controlled, double-blinded, randomized clinical trial testing the efficacy and safety of topical synthetic hypericin 0.25% visible light-activated ointment as non-mutagenic PDT in early-stage mycosis fungoides–cutaneous T-cell lymphoma. The treatment regimen consisted of applying 0.25% hypericin ointment to each index lesion, covering it with an opaque dressing or clothing for 18 to 24 h, and then irradiating it with visible light ranging from 500 to 650 nm. Light treatment began at 5 J/cm^2 and was increased by 1 J/cm^2 with each treatment until a mild skin reaction was observed in the treated lesions or until a maximum light dose of 12 J/cm^2 was reached. The lesions were treated twice a week for each 6-week cycle. Significant clinical responses were observed in both lobular and plaque-type lesions, and the response rate increased with the number of cycles received (up to a maximum of 49%). The most common treatment-related adverse events were mild local skin lesions and injection site reactions. No serious adverse events related to the drug occurred [54]. Kacerovska et al.

conducted a study in which they evaluated the efficacy of *Hypericum perforatum* extract in the treatment of solar keratosis, basal cell carcinoma, and Bowen's disease (carcinoma in situ). The *H. perforatum* extract used contained 32.5% hypericin and 67.5% pseudohypericin. The therapeutic regimen involved applying hypericin ointment with a concentration of 2 mg/mL to the lesion and 10 mm of surrounding skin in a 1 mm thick layer under an occlusive dressing, removing it after 2 h, and irradiating the area with a PDT lamp emitting incoherent red light with a wavelength of 580 to 680 nm. The total light dose was 75 J/cm² for 15–20 min. The above-mentioned lesions were treated with PDT at weekly intervals; the average treatment period was 6 weeks. The number of PDT treatments depended on the clinical features of the treated areas and persistent fluorescence during photodynamic diagnosis. The percentage of complete clinical response was 50% for cutaneous keratosis, 28% for patients with superficial basal cell carcinoma, and 40% for patients with Bowen's disease. All patients complained of burning and pain during irradiation. No erythema or swelling was observed after treatment, and no other serious side effects were reported [55]. Kim et al. tested PDT with St. John's wort extract for the treatment of acne in a prospective, double-blind, randomized study. The therapeutic regimen consisted of applying 1.5 mL of 0.5% *H. perforatum* extract containing 0.1% hypericin to half of the face for 10 min under occlusion. The face was then illuminated simultaneously with red light with a wavelength of 630 nm and green light with a wavelength of 520 nm from a 35 mW/cm² LED light-emitting device for 10 min (total light dose was 21 J/cm²). Participants received a total of four treatments at 1-week intervals and were followed up 1 and 4 weeks after the last treatment. One week after the last treatment, the number of acne lesions was reduced by 56.5%. A significant reduction in sebum secretion, erythema index, roughness, and wrinkles was also observed. No side effects were observed [56].

3.3. Riboflavin

Riboflavin (RF) is an organic chemical compound that is a combination of ribitol and flavin. Its rich source is leafy vegetables [57]. The RF spectrum has two peaks in the UVA (360 nm) and blue (440 nm) wavelength regions [58]. Riboflavin, after activation and generation of ROS, mainly leads to apoptosis, which is the result of, among other things, damage to mitochondria by ROS. It can also activate MAPK (mitogen-activated protein kinase) pathways, such as p38 and JNK, leading to further activation of apoptotic mechanisms [59]. Previous studies that have been carried out in vitro have demonstrated the usefulness of riboflavin as a photosensitizer in cervical cancer therapy, antibacterial therapy, and dental therapy [60–62].

Riboflavin in Clinical Trials of Photodynamic Therapy

We located three clinical trials with this compound. All of them focused on the use of RF-PDT in dentistry. Al Deeb et al. evaluated the effect of RF-PDT as a surface pretreatment method and also different types of luting cement on the extrusion bond strength of polyetheretherketone (PEEK) inlays bonded to root canal dentin. The therapeutic regimen involved conditioning the surfaces of the posts with RF at a concentration of 25 mol/L, followed by irradiation with a green laser at 540 nm for 60 s. After the irradiation process, the samples were washed with distilled water to remove residual dye and then dried thoroughly to ensure complete drying. This work showed that RF-PDT can be an effective means of conditioning the surface of PEEK inlays [63]. Alkhudhairy et al. demonstrated that RF-PDT provides an alternative for conditioning the surface of PEEK posts. In their work, the therapeutic regimen consisted of pretreating PEEK posts with RF and exposing them to light with a wavelength of 632 nm, a power of 150 mW, and a power density of 23.43 J/cm². The light was exposed continuously for 1 min, after which the post was rinsed with deionized water for 1 min [64]. AlGhamdi et al. investigated the push strength of a fibrous post into the root dentin using RF-PDT as a final root canal irrigator. The therapeutic regimen involved brushing the canals with 150 g/mL of riboflavin solution activated using a 660 nm LED light at 150 mW for about 60 s. The LED light tip was placed

in the canal parallel to its long axis. However, RF-PDT showed significantly lower bond integrity values than all other groups studied in this work [65].

3.4. Phycocyanin

Phycocyanin is an important antenna protein of the light-harvesting pigment in cyanobacteria, rhodophytes, cryptophytes, and glaucophytes, with various biological properties [66]. It localizes primarily in mitochondria, whose disruption of the membrane potential is a key signal to activate the apoptosis cascade. Damaged mitochondria release cytochrome c into the cytoplasm, which is a key step in activating the caspase cascade, particularly caspase-3, ultimately leading to cell death. Although the main mechanism of cell death following PDT with phycocyanin is apoptosis, necrosis has also been observed in some cases, especially at higher doses of phycocyanin and more intense irradiation [67]. Data from various studies suggest therapeutic uses for phycocyanin, such as anticancer, anti-inflammatory, anti-angiogenic activities and the ability to treat certain autoimmune disorders [68]. In earlier work, the compound has shown promise as a photosensitizer in the treatment of several cancers, such as breast and liver cancers, and in dentistry [69–73].

Phycocyanin in Clinical Trials of Photodynamic Therapy

We located one clinical trial with phycocyanin as a photosensitizer. Hashemikamangar et al. studied the effect of PDT with phycocyanin on the bond strength of the resin composite to healthy dentin. The therapeutic regimen they used involved applying a 1000 µg/mL phycocyanin solution to the surface of healthy dentin, leaving it for 5 min, and subsequent irradiation with a 220 mW diode laser at a wavelength of 635 nm and an energy density of 61.2 J/cm² for 3 min in continuous rinse with water and air drying. This study showed that photodynamic therapy with phycocyanin can be recommended as an antimicrobial method and has no negative effect on bonding to healthy dentin using a universal adhesive in a self-etching protocol [74].

3.5. Anthraquinones

Anthraquinones are obtained from plant elements in the *Rubiaceae* group. Several studies have been reported in the literature in which such compounds were used as photosensitizers. ROS generated during PDT with the photosensitizer in question cause severe oxidative damage inside the cell, leading to various forms of cell death, such as apoptosis, necrosis, or autophagy, depending on the intensity of the treatment and the type of anthraquinone. Some anthraquinones can additionally inhibit the defense mechanisms of tumor cells, leading to the accumulation of ROS and increasing the efficacy of PDT [75]. One study involved the treatment of cancer cells of a breast cancer line that was largely cured [76,77]. When exposed to light, these compounds were able to effectively destroy or severely damage cancer cells. The photosensitizing efficacy of anthraquinones was evident at a concentration of 100 µM and a light dose of 1 J/cm². These results suggest that anthraquinones had a strong effect on cancer cells under clearly defined concentration and irradiation conditions. The mechanism of cell elimination by light-activated anthraquinones is related to the production of singlet oxygen, a reactive form of oxygen capable of damaging cells and their components, leading to cell death [77]. The value of these findings suggests the potential use of anthraquinones as a promising phototoxic agent for anticancer therapy, particularly for breast cancer. However, before such a therapy can be used in clinical practice, further thorough research and clinical trials are needed to confirm its efficacy and safety [78]. The anthraquinone being clinically tested as a photosensitizer in PDT is emodin. It is a natural anthraquinone derivative that is found in many commonly used Chinese medicinal herbs, such as *Rheum palmatum*, *Polygonum cuspidatum*, and *Polygonum multiflorum* [79]. It is recognized as a tyrosine kinase inhibitor and anticancer drug, active against various cancer cells, including lung, breast, liver, and ovarian cancer cells [80]. Previous studies have shown its potential as a photosensitizer used in anticancer therapy for skin cancer [81].

Anthraquinones in Clinical Trials of Photodynamic Therapy

We located one clinical trial using emodin as a photosensitizer. Yaghobee et al. studied PDT with nano-emodin in donor site wound healing after free gingival transplantation (Figure 3). The therapeutic regimen consisted of applying n-Emo gel with emodin to the wound surface for five minutes, followed by irradiation with a light-emitting diode with a wavelength of 450 ± 10 nm, an output intensity of 1000 ± 1400 mW/cm², and an energy density of 60–80 J/cm² for one minute. The LED was positioned perpendicular to the wound surface at a distance of 1 mm. Their work showed that this strategy can act as an adjunct to conventional wound care in the treatment of postoperative complications at the donor site after free gingival graft surgery [82].

Characteristic of clinical work investigating photodynamic therapy with natural photosensitizers are presented in Table 2.

Table 2. Summary of results of clinical work investigating photodynamic therapy with natural photosensitizers.

Photosensitizer	Therapeutic Regimen	Findings	Article
Curcumin	Six sessions of PDT of dentures and oral cavity, three times a week for half a month using a CUR solution of 5 µg/mL and light with a wavelength ranging from 440 to 460 nm	Reduction in mean number of CFU/mL of <i>Candida</i> from denture surface and palatal mucosa after 6- and 12-week follow-up after CUR-PDT for the treatment of stomatitis in patients who are heavy smokers	Labban et al. [35]
	Use of mouthwash with 20 mL of 30 mg/L CUR solution for 5 min, its removal, and exposure to blue light with a wavelength of 455 +/− 30 nm for 5 min	CFU reduction at 1 and 2 h after CUR-PDT	Leite et al. [36]
	Rinsing the mouth three times with 15 mL of 25 mg/L or 100 mg/L curcumin solution for 1 min, followed by irradiation of the mouth for 6 min with 450 nm light	Reduction in microbial count 24 h after CUR-PDT	Ricci Donato et al. [37]
	Rinsing the mouth with a 1 mg/L curcumin solution for 2 min, followed by irradiation of the buccal and lingual surfaces of the teeth sequentially for 3 min with 450 +/− 10 nm light	Reduction in <i>S. mutans</i> in orthodontic patients after CUR-PDT; this effect was enhanced when 0.1% SDS solution was added to curcumin solution	Panhoca et al. [38]
	Rinsing the mouth with 20 mL of 1.5 g/L curcumin solution for 5 min, followed by irradiation of the oral surface for 5 min with 468 nm light and application of the low-intensity laser PBM-T protocol	Cure of 12 of 14 cancer patients from oral mucositis after CUR-PDT	Pinheiro et al. [39]
	Infusion of 2.5 mg/mL curcumin solution into canal 180 s before irradiation, subsequent cleansing with MTAD	Achieving the highest push-back bond strength (PBS) at two levels: cervical and midline after CUR-PDT	Saini et al. [40]
	Application of a mask containing 1% curcumin for 20 min, followed by exposure to 445 nm light; sessions at 3-day intervals, for a total of two treatments per week, administered continuously for 2 weeks	Lesion removal $54.7 \pm 21.5\%$ in the treatment of mild to moderate acne with CUR-PDT	Zhang et al. [41]

Table 2. Cont.

Photosensitizer	Therapeutic Regimen	Findings	Article
Hypericin	Application of 0.25% hypericin ointment to each index lesion, covering it with an opaque dressing or clothing for 18 to 24 h, followed by exposure to visible light in the range of 500 to 650 nm; Light treatment started at 5 J/cm ² and increased by 1 J/cm ² with each treatment, until a mild skin reaction was observed in the treated lesions or until a maximum light dose of 12 J/cm ² was reached. Lesions were treated twice a week for each 6-week cycle	Achieving 49% success rate in treating cutaneous T-cell lymphoma with early-stage mycosis fungoides using HYP-PDT	Kim et al. [54]
	Application of hypericin ointment with a concentration of 2 mg/mL to the lesion and 10 mm of surrounding skin in a layer 1 mm thick under an occlusive dressing, removing it after 2 h, and irradiating the area with a PDT lamp emitting incoherent red light with a wavelength of 580 to 680 nm. The total light dose was 75 J/cm ² for 15–20 min. The aforementioned lesions were treated with PDT at weekly intervals; the average treatment period was 6 weeks. The number of PDT treatments depended on the clinical features of the treated areas and persistent fluorescence during photodynamic diagnosis.	A 50% complete clinical response was achieved in cases of cutaneous keratosis, 28% in patients with superficial basal cell carcinoma, and 40% in patients with Bowen's disease by PDT with <i>H. perforatum</i> extract	Kacerovska et al. [55]
	Application of 1.5 mL of 0.5% <i>H. perforatum</i> extract containing 0.1% hypericin to half of the face for 10 min under occlusion. The face was then illuminated simultaneously with 630 nm red light and 520 nm green light from a 35 mW/cm ² LED light-emitting device for 10 min (total light dose was 21 J/cm ²). Participants received a total of four treatments at 1-week intervals and were observed 1 and 4 weeks after the last treatment.	One week after the last PDT treatment with <i>H. perforatum</i> extract, a 56.5% reduction in acne lesions was observed.	Kim et al. [56]
Riboflavin	Conditioning the surface of the posts with RF at a concentration of 25 mol/L, followed by irradiation with a green laser at 540 nm for 60 s	RF-PDT can be an effective surface conditioner for PEEK inserts	Al Deeb et al. [63]
	RF pretreatment of PEEK posts and exposure to light at 632 nm, 150 mW power, and power density of 23.43 J/cm ² continuously for 1 min	RF-PDT is an alternative to PEEK post surface conditioning	Alkhudhairy et al. [64]
	Brushing the canal with a 150 g/mL riboflavin solution activated with 660 nm LED light at 150 mW for about 60 s	RF-PDT showed significantly lower bond integrity values than the other methods tested in the force test of pressing the fibrous insert into the root dentin	AlGhamdi et al. [65]

Table 2. Cont.

Photosensitizer	Therapeutic Regimen	Findings	Article
Phycocyanin	Applying a phycocyanin solution of 1000 µg/mL to the surface of healthy dentin, leaving it for 5 min, followed by irradiation with a 220 mW diode laser at a wavelength of 635 nm and an energy density of 61.2 J/cm ² for 3 min under continuous water rinsing and air drying	RF-PDT can be recommended as an antimicrobial method and does not adversely affect bonding to healthy dentin using a universal adhesive in a self-etching protocol	Hashemikamangar et al. [74]
Emodin	Application of n-Emo gel with emodin to the wound surface for five minutes, followed by irradiation with a light-emitting diode with a wavelength of 450 ± 10 nm, output intensity of 1000 ± 1400 mW/cm ² , and energy density of 60–80 J/cm ² for one minute	n-Emo-gel-PDT may act as an adjunct to conventional wound care in the treatment of postoperative complications at the donor site after free gingival graft surgery	Yaghobee et al. [82]

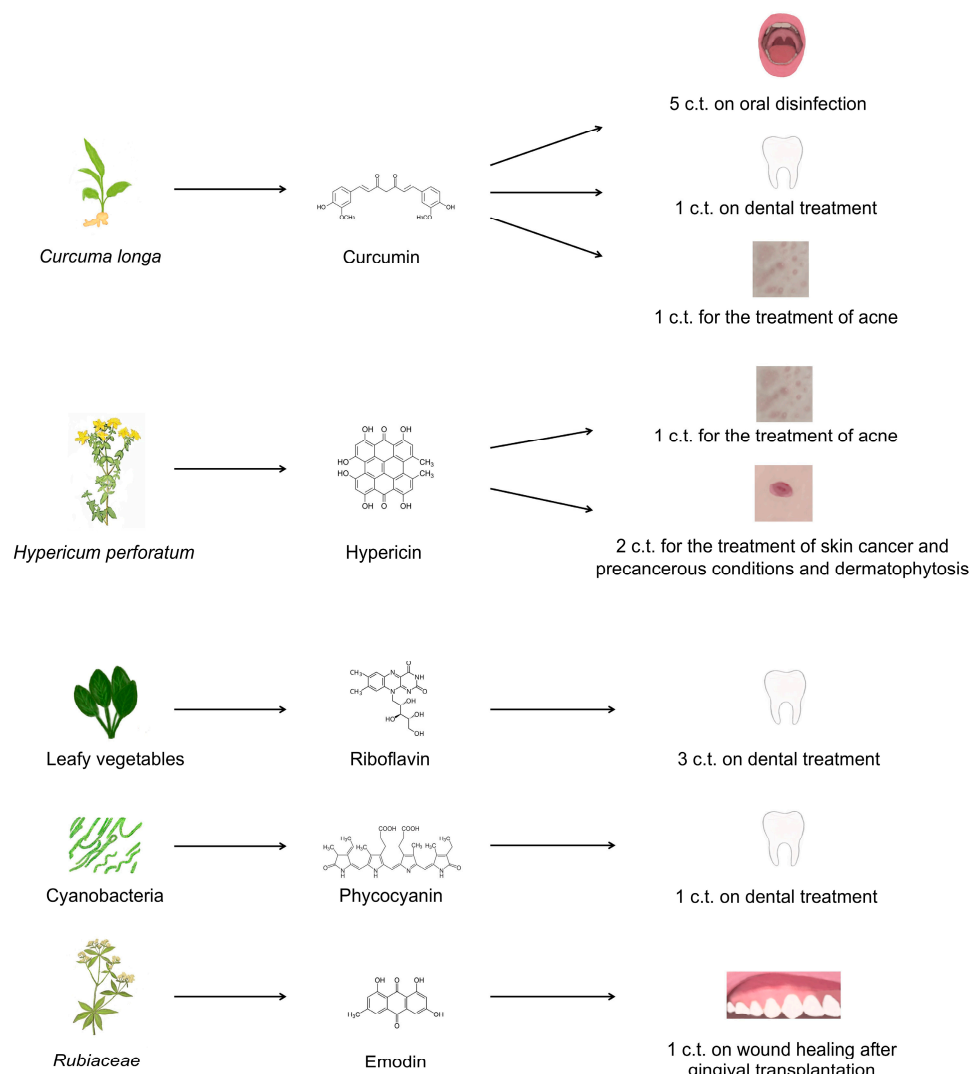


Figure 3. Figure showing natural photosensitisers in clinical trials—their example source, structural formula, and the subjects of the clinical trials in which they were used. Explanation: c.t. stands for clinical trial/trials. (1) curcumin, the source of which is, e.g., *Curcuma longa* that was tested in seven clinical papers in oral disinfection [35–39] and in dental [40] and acne treatments [41]; (2) hypericin, the source of which is, e.g., *Hypericum perforatum* that was tested in three clinical papers in the

treatment of skin cancers, precancerous conditions and dermatophytosis [54,55], and acne [56]; (3) riboflavin, the source of which is, e.g., green vegetables that were tested in three clinical papers in dentistry [63–65]; (4) phycocyanin, the source of which is, e.g., cyanobacteria that were tested in one clinical paper in dentistry [74]; (5) emodin anthraquinone, the source of which is, e.g., plants of the family *Rubiaceae* that were tested in one clinical paper in wound healing after gingival transplantation [82].

4. Natural Photosensitizers Pending Clinical Trials

4.1. Furanocoumarins

Furanocoumarins are a class of natural compounds produced by several plants. They have been used in the medicine of Eastern countries for centuries [83]. Psoralen is the primary compound in the group of linear furanocoumarins, characterized by photosensitive properties. It initially forms a non-linear bond with DNA. Upon exposure to UV radiation, cycloaddition occurs and a covalent bond is formed between psoralen and the pyrimidine base. Additional interactions between the psoralen monoadduct and the pyrimidine base can occur during subsequent phases of UV exposure, resulting in the formation of cross-links between DNA strands. In addition, psoralens react with other cellular components, such as proteins or lipids [84]. To date, it has not been clearly established whether oxygen-dependent mechanisms are important for the induction of apoptosis in therapy. The involvement of oxygen-dependent reactions in induced apoptosis appears to be mainly related to psoralen photo-oxidation and opening of the mitochondrial permeability transition pore (PTP), rather than direct damage caused by reactive oxygen species. Previous work has shown the potential of using psoralen as a photosensitizer in PDT of melanoma and cutaneous T-cell lymphoma [85–87].

4.2. Pheophorbide a

Pheophorbide a is a catabolite of chlorophyll obtained mainly from algae [88–90]. This compound is characterized by photoactive properties, so it has been tested as a photosensitizer [91]. ROS generated by the combination of PDT and the photosensitizer in question induce damage to various cellular structures, leading to apoptosis of cancer cells. Pa-PDT also significantly increases the levels of pro-apoptotic proteins, while decreasing the levels of anti-apoptotic proteins. Pa-PDT not only promotes apoptosis, but also inhibits the proliferation, migration, and invasion of cancer cells. It works by inhibiting EMT and reducing the expression of matrix metalloproteinases, which are crucial in the process of tumor invasion [92,93].

Previous work has demonstrated its potential for use in photodynamic therapy for uterine sarcoma, prostate cancer, hepatocellular carcinoma, and glioma [92,94,95]. Pa-PDT was tested in vivo for the treatment of Hep3B hepatocellular carcinoma xenografts in nude mice. The therapeutic regimen consisted of intravenous administration of Pa at a dose of 300 µg/kg and subsequent light irradiation at 126 J/cm² and 610 nm wavelength for 30 min after 24 h. It was shown that after 14 days, Pa-PDT significantly reduced tumor size by 57% compared to the control group [96]. Another study tested Pa-PDT in the treatment of MCF-7 breast cancer cell xenografts in mice. The therapeutic regimen consisted of intravenous administration of Pa at a dose of 2.5 mg/kg and subsequent 6 h irradiation of the tumors with a diode laser at 675 nm ± 3 nm at a dose of 90 J/cm². On day 15, the size of tumors in the Pa-PDT group was on average 50% smaller compared to the control groups. In two mice (15.4%) in the Pa-PDT group, the tumor had completely regressed [97]. The study by Ahn et al. compared intravenous administration of this PS with intraperitoneal administration. One week after inoculation of oral squamous cell carcinoma cells with AT-84, one test group of mice was administered Pa at a dose of 10 mg/kg intravenously into the tail, while the other was administered Pa at a dose of 30 mg/kg intraperitoneally. After 24 h, irradiation was carried out at a wavelength of 664 nm. The light dose was 100 J/cm². After 15 days of treatment, the tumor volume in the group that received Pa intraperitoneally decreased by about 70% compared to the control group at the end of the study period. In the group with

intraperitoneal administration of Pa, tumor growth inhibition was 43.4% compared to the control group [98].

4.3. Alkaloids

Alkaloids are a naturally occurring group of organic compounds [99–101]. One of them is berberine (BRB). It is a compound belonging to the group of isoquinoline alkaloids of plant origin, found naturally in such plant species as *Berberis vulgaris*, *Berberis aristata*, *Mahonia quifolium*, *Hydrastis canadensis*, *Coptis chinensis*, and *Arcangelisa flava*. Due to its potent biological activity, BRB has been used in traditional Chinese medicine for many years. Berberine also has photosensitizing properties, so it has been tested as a potential photosensitizer in PDT [24,101–104]. Berberine's mechanisms of action may include inhibition of cell proliferation, DNA damage, and changes in protein and gene expressions. It readily binds to DNA, increasing the efficiency of singlet oxygen generation. Upon photoexcitation, BBR causes guanine-specific oxidation in DNA, leading to DNA damage that can induce apoptosis or cell death by necrosis [105]. Berberine has been shown to be an effective photosensitizer in PDT of various cancers, including cervical cancer, melanoma, and glioblastoma kidney cancer [102–104,106–109].

4.4. Chlorophyllin

Chlorophyllin is a derivative of chlorophyll, and its source is cyanobacteria. This compound is readily soluble in water, has low toxicity, and is rapidly removed from the body [110–114]. It has favorable optical properties, with an absorption maximum in the 600–670 nm range [24]. ROS generated with PDT in target cells damage mitochondria, which activates a cascade of apoptotic proteins such as caspase-8 and caspase-9. This induces the release of cytochrome C from mitochondria, leading to the activation of apoptosis. Chlorophyllin has been shown to decrease the expression of the anti-apoptotic protein BCL-2 and increase the level of the pro-apoptotic protein Bax, which alters the BCL-2/Bax ratio, promoting apoptosis of cancer cells [115]. Previous work has demonstrated the potential of chlorophyllin as a photosensitizer in PDT of cervical cancer and bladder cancer [111–114].

4.5. Hypocrellin

It was isolated from the parasitic fungus *Hypocrella bambusea* [116]. As a particular type of natural photosensitizer, hypocrellin has high singlet oxygen quantum yield, low biological toxicity, and the ability to be rapidly removed from normal tissues [117]. It shows absorption maximum at 470 nm [10]. Excited hypocrellin generates ROS that damage cellular structures, including but not limited to mitochondria, leading to a decrease in their membrane potential, release of cytochrome c into the cytoplasm, and an activation of caspases (in particular, caspase-3, -7, and -9). The activation of caspases leads to apoptosis of cancer cells. It also showed that hypocrellin can affect mitochondrial oxidative stress-related signaling pathways regulated by proteins such as JunB and BAG-4, further confirming the key role of mitochondria in the mechanism of cell death induced by this photosensitizer [118]. Hypocrellin used as a photosensitizer achieved encouraging results in A431 squamous cell carcinoma cells [119,120], A549 lung adenocarcinoma [118], MDA-MB-231 breast cancer [121], HepG2 hepatocellular carcinoma [122], and keloid fibroblasts [123,124] or by evaluating its bactericidal activity against *Staphylococcus aureus* [125]. Its effects on LN229 glioblastoma multiforme cells were also investigated, where the focus was on factors regulating angiogenesis. The combination of PDT with hypocrellin has been shown to induce a complex angiogenic response, which can have both beneficial and detrimental effects on tumor growth [126]. However, its poor solubility, short absorption wavelength, and low bioavailability limit its use [127,128].

4.6. Cercosporin

Cercosporin is an important perylenequinone that plays a role in fungal pathogenicity of the genus *Cercospora* [129,130]. Cercosporin is a light-activated toxin and also acts as a

photosensitizer [131]. The subcellular localization of cercosporin includes mitochondria and the endoplasmic reticulum. The ROS generated during PDT, together with the photosensitizer in question, cause damage to cell membranes, including mainly the organelles described earlier. Damage to mitochondria leads to disruption of the respiratory chain, resulting in a decrease in ATP production and subsequent bioenergetic breakdown of the cell. The maximum absorption peak of cercosporin is at about 470 nm. Due to this short wavelength, this photosensitizer can be used mainly for the treatment of superficial cancerous lesions. Previous work has shown that PDT with cercosporin induces cell death in glioblastoma multiforme (T98G and U87) and breast adenocarcinoma (MCF7 and T47D) cells [132,133].

4.7. Toliporphins

Toliporphins (TPs) are green tetrapyrrole pigments that are isolated from cyanobacteria [134]. Toliporphins localize mainly to the perinuclear region and primarily to the endoplasmic reticulum. The nuclear membrane damage observed after PDT with TPs can be attributed to either direct photosensitization by reactive oxygen species bound to the nuclear membrane or to the transfer of photo-oxidative damage from photoactivated TPs bound to the rough ER to the nuclear membrane, via inactivation of acyl-CoA:cholesterol-0-acyltransferase, a sensitive marker of ER membrane integrity [135–137]. The absorption maximum occurs at a wavelength of 660–680 nm. Its photosensitizing potential was tested with EMT-6 cancer cells in vitro and in vivo [135,136]. TPs were tested in vivo in the treatment of subcutaneously injected EMT-6 tumor cells into mice with severe combined immunodeficiency. This PS was administered via the tail vein. One hour after administration of the photosensitizer, the tumors were irradiated with 681 nm laser light. TPs showed the highest efficacy in PDT in vivo. At doses of 0.5, 1.0, or 2.0 µg/g and irradiation with 30 J of 681 nm light, tumor growth delays comparable to those obtained at much higher doses (2.0 µg/g) and light energy (300 J) were obtained for the other PS tested in this work: Ph4-OH (N-Butanol-6-pheophorbamide) and MPPH (Hexyl ether of 6-methylpyropheophorbide). TPs were found to be 10–20 times more potent photosensitizer compared to Ph4-OH and MPPH [137].

Table 3 below shows information described in the article about the PDT mechanisms.

Table 3. Characteristic information described in the article about the mechanisms of action of each photosensitizer.

Photosensitizer	Characteristic Information Described in the Article about the Mechanisms of Action of Each Photosensitizer	Article
Curcumine	Inhibits the NF-κB pathway. Can induce autophagy, inhibit EMT, and invasion and migration of tumor cells.	[30]
Hypericin	It can induce stress in the ER, leading to the release of calcium ions into the cytoplasm. Increasing their levels can activate various enzymes and lead to mitochondrial damage.	[46]
Riboflavin	It can activate MAPK (mitogen-activated protein kinase) pathways such as p38 and JNK, leading to further activation of apoptotic mechanisms.	[59]
Phycocyanin	Depending on the dose of PS and light, it can activate either apoptosis or necrosis.	[67]
Anthraquinones	Some anthraquinones may additionally inhibit the defense mechanisms of cancer cells, leading to the accumulation of ROS and increasing the effectiveness of PDT.	[75]
Furanocoumarins	Cycloaddition occurs, and a covalent bond is formed between the psoralen and the pyrimidine bases. During the subsequent phases of UV irradiation, additional interactions can occur between the psoralen monoadduct and the pyrimidine base, resulting in the formation of cross-links between DNA strands.	[84]

Table 3. Cont.

Photosensitizer	Characteristic Information Described in the Article about the Mechanisms of Action of Each Photosensitizer	Article
Pheophorbide <i>a</i>	Significantly increases the levels of pro-apoptotic proteins while decreasing the levels of anti-apoptotic proteins. Inhibits proliferation, migration, and invasion of cancer cells. It works by inhibiting the EMT process and reducing the expression of matrix metalloproteinases, which are key in the process of tumor invasion.	[93]
Alkaloids	It readily binds to DNA, increasing the efficiency of singlet oxygen generation. Upon photoexcitation, berberine causes guanine-specific oxidation in DNA, leading to DNA damage that can induce apoptosis or cell death by necrosis.	[105]
Chlorophyllin	Decreases the expression of the anti-apoptotic protein BCL-2 and increases the level of the pro-apoptotic protein Bax, which alters the BCL-2/Bax ratio, further promoting apoptosis of cancer cells.	[115]
Hypocrellin	It can affect mitochondrial oxidative stress-related signaling pathways regulated by proteins such as JunB and BAG-4.	[118]
Cercosporin	Causes cell death mainly by necrosis mechanism through damage to mitochondria and ER cell membranes.	[133]
Toliporphins	Nuclear membrane damage by transferring photo-oxidative damage from photoactivated TPs bound to the rough ER through inactivation of acyl-CoA:cholesterol-0-acyltransferase, a sensitive marker of ER membrane integrity.	[137]

5. Reported Toxicity and Adverse Side Effects of Natural Photosensitizers

No serious side effects have been described in clinical studies of CUR-PDT. No negative effects of curcumin on healthy tissues have been reported in them [35–41]. While treating acne, Zhang et al. described a mild warm sensation accompanying CUR-PDT. They saw mild erythema on both sides, which resolved by 2 h. Two patients experienced mild pigment deposition on both cheeks after the two treatments in both the experimental and control groups. This pigmentation resolved spontaneously after a 1-month follow-up [41]. In two of the three clinical studies describing hypericin as a photosensitizer, side effects were reported, indicating the relevance of the therapeutic regimen used in causing them. In the study by Kim et al., the side effects observed were mild local skin lesions and injection site reactions. No serious adverse events related to the drug occurred [54]. In the study by Kacerovska et al., all patients complained of burning and pain during irradiation. No erythema or swelling was observed after treatment, and no other serious side effects were reported [55]. In the papers in which riboflavin was studied, no adverse effects were described [63–65]. Hashemikamangar et al. reported no adverse effects of PDT with phycocyanin. This PS did not cause discoloration of healthy tissue or have toxic effects on healthy dentin [74]. In a clinical trial, nano-emodin showed no negative side effects. Moreover, PDT with this PS can reduce inflammation and promote tissue healing and reduce postoperative pain [82]. We did not locate any study describing the safety and toxicity of using psoralen in photodynamic therapy, but PUVA therapy using this compound and UVA light can cause side effects such as discomfort, skin disease, and even melanoma [138,139]. In vivo studies determining the toxicity of PDT with pheophorbide *a* indicate the overall safety of this photosensitizer. Tang et al. observed no significant side effects of PDT with this PS on mice: PDT was well tolerated, and there was no increase in liver enzymes or cardiac LDH levels [96]. Ahn et al. also found no systemic toxicity in a mouse study during treatment of oral squamous cell carcinoma [98]. Hoi et al. reported no serious side effects in mice during Pa-PDT treatment of breast cancer [97]. However, studies precisely verifying toxicity to healthy cells are conflicting. Normal human liver cells (WRL-68) showed low sensitivity to Pa-PDT, with cell viability remaining at 85% [96]. On the other hand, in four primary cultures of normal mammary epithelial cells, Pa-PDT showed a similar cytotoxic effect to cancer cells [97]. Pa-PDT was also found to be toxic to neutrophils [140]. We have not located any in vivo study evaluating the toxicity and

side effects of PDT with berberine. The only available in vitro study found less than 10% mortality of healthy HaCaT keratinocytes after administration of berberine without irradiation and about 53% mortality of these cells after irradiation [103]. In an in vitro study, chlorophyllin did not induce cytotoxicity against RAW 264.7 macrophages both in the dark and after illumination [115]. The in vivo safety of PDT with hypocrellin alone has also not been evaluated. Liposomal hypocrellin B used as a photosensitizer on a rat model of choroidal neovascularization led to little damage to the retina and retinal pigment epithelium. In addition, treated mice showed low skin phototoxicity under simulated sunlight 24 h after administration [141]. The lack of safety data is also apparent with cercosporin. In the case of toliporphins, the only in vivo study conducted did not describe the side effects of PDT with this PS in the mice tested. However, TPs were found to have relatively low blood levels and more uniform distribution in muscle, liver, and tumor tissues, which may lead to an increased risk of damage to healthy tissues [137]. The toxicity and side effects of photodynamic therapy with natural photosensitizers are summarized in Table 4.

Table 4. Summary of toxicity and side effects induced by photodynamic therapy with natural photosensitizers.

Photosensitizer	Toxicity	Side Effects	Article
Curcumine	No serious adverse effects in clinical trials No adverse effects on healthy tissues in clinical trials	Mild sensation of warmth, mild erythema on both sides (resolving up to 2 h), mild pigment deposition on both cheeks after two treatments in both experimental and control groups in two patients (this pigmentation resolved spontaneously after 1-month follow-up)	[35–41]
Hypericin	No serious side effects in clinical trials	Mild local skin lesions and injection site reactions, burning and pain during irradiation	[54,55]
Riboflavin	No described side effects in clinical trials	No described side effects in clinical trials	[63–65]
Phycocyanin	No described side effects in clinical trials	No described side effects in clinical trials	[74]
Antrachinones	No described side effects in clinical trials	No described side effects in clinical trials	[82]
Furanocoumarins	No data available	No data available	[138,139]
Pheophorbide <i>a</i>	Conflicting data in in vitro studies: (1) low sensitivity to Pa-PDT of WRL-68 liver cells; (2) cytotoxic effects of Pa-PDT in four primary cultures of normal mammary epithelial cells; (3) cytotoxic effect of Pa-PDT of neutrophils	No serious side effects in in vivo mouse studies	[96–98,140]
Alkaloids	Less than 10% mortality of healthy HaCaT keratinocytes after berberine administration without irradiation and about 53% mortality of these cells after in vitro irradiation	No data available	[103]
Chlorophyllin	No in vitro cytotoxicity against RAW 264.7 macrophages both in the dark and after illumination	No data available	[115]

Table 4. Cont.

Photosensitizer	Toxicity	Side Effects	Article
Hypocrellin	Minor retinal and retinal pigments, epithelial damage, and low dermal phototoxicity under simulated sunlight 24 h after in vivo administration of liposomal form of hypocrellin B in a rat model of choroidal neovascularization	No data available	[141]
Cercosporin	No data available	No data available	
Toliporphins	Increased risk of damage to healthy tissues due to even distribution in muscle, liver, and tumor tissues	No in vivo side effects described in mice	[137]

6. Conclusions

The selection of an appropriate photosensitizer is one of the most important steps in photodynamic therapy and is crucial to the efficacy of PDT. The ideal photosensitizer must meet a number of criteria, including lack of toxicity in the dark, solubility in suitable solvents, high absorption coefficient in the wavelength range for tissue penetration, and selective binding to the target tissue. Findings to date indicate that naturally occurring compounds can act as photosensitizers. Some of them have already been tested in clinical trials. The clinical work conducted so far has confirmed the overall safety of natural PSs. No serious, dangerous side effects have been observed in any of them. In some indications, natural PSs have proven more effective than synthetic ones. These are valuable papers providing information on the first effective therapeutic regimens for photodynamic therapy using PSs of natural origin. At the same time, these are only initial observations, in which a small number of indications have been tested and few therapeutic regimens have been tested. As presented in our work, natural PSs have been the most clinically tested in dental treatment. In dentistry, bacterial infections that lead to caries, gingivitis, or periodontal disease are a common problem. Photodynamic antibacterial therapy is effective and minimally invasive, making it particularly attractive for treating and preventing oral infections. Compounds of natural origin are often more readily available and less expensive to produce, allowing them to be more widely studied and facilitating potential large-scale introduction into the clinical setting, so the work described above provides an attractive basis for further research. As demonstrated in this review, the number of natural photosensitizers untested clinically is impressive, which creates the potential for extensive testing in various clinical indications. The production of natural photosensitizers presents many challenges. They often have a complex chemical structure, making them difficult to isolate on an industrial scale. It is also critical to obtain a high-purity product that retains the correct biological activity. An additional challenge, especially for natural compounds, is the chemical and biological stabilities of photosensitizers, which can degrade when exposed to light, oxygen, or temperature. For some natural PSs, appropriate pharmaceutical formulations may need to be developed to ensure effective delivery of the photosensitizer to its target site in the body. All of these challenges come at a potential cost for the widespread implementation of natural photosensitizers in the future. Moreover, photosensitizers of natural origin with optimal properties also provide an attractive basis for the synthesis of artificial compounds, which could also contribute to increasing the number of photosensitizers used in the clinical setting. However, further work is needed. These should be based on standardizing the extraction and production of natural photosensitizers to ensure consistency and reproducibility of established therapeutic properties. Further research is needed on efficacy, safety, and determination of the optimal therapeutic regimen for specific indications. Choosing the right photosensitizer is the basis of PDT's effectiveness, so the discovery of compounds with ideal properties is the cornerstone of this therapy's development.

Author Contributions: Conceptualization, D.A., A.P. and D.B.-A.; methodology, D.A., A.P. and D.B.-A.; validation, D.A., A.P. and D.B.-A.; formal analysis, D.A., A.P. and D.B.-A.; investigation, D.A., A.P. and D.B.-A.; resources, D.A., A.P. and D.B.-A.; data curation, D.A., A.P. and D.B.-A.; writing—original draft preparation, D.A., A.P. and D.B.-A.; writing—review and editing D.A., A.P. and D.B.-A.; visualization, D.A., A.P. and D.B.-A.; supervision, D.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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