

Review

Isolation, Synthesis, and Use of Natural Photosensitizers in the Treatment of Central Nervous System Tumors

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Abstract

Cancer is one of the leading causes of illness and death in the world. It is observed that the main reason for the low effectiveness of cancer treatment is limited bioavailability. Another noted cause is the lack of specificity of conventional chemotherapeutics, which contributes to the destruction of not only cancer cells, but also normal cells, and consequently leads to serious adverse effects. In recent years, researchers have paid special attention to the use of photodynamic therapy. Another major step in this progress is turning to photosensitizing natural compounds, which we present in this review. Natural photosensitizers are being investigated for their potential to treat central nervous system (CNS) tumors using photodynamic therapy (PDT). These compounds, derived from natural sources, offer an alternative to synthetic photosensitizers, potentially minimizing toxicity and enhancing therapeutic efficacy. Research focuses on isolating, synthesizing, and evaluating these natural photosensitizers for their ability to selectively accumulate in tumor cells and be activated by light to produce cytotoxic reactive oxygen species, leading to tumor cell death.

Keywords: natural compounds; natural photosensitizers; photodynamic therapy (PDT); chemical structure; cancer; central nervous system (CNS)



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1. Introduction

Cancer continues to be one of the main health problems in most regions of the world [1]. According to the 2020 GLOBOCON report, it is one of the leading causes of death [2,3]. Despite the advanced diagnostic and therapeutic methods currently used, it is estimated that within 15 to 35 years, cancer incidence and mortality rates will double [1]. Moreover, surgical treatment, chemotherapy or radiotherapy are not ideal; they are associated with a large number of side effects, the development of drug resistance, limited therapeutic effects, the occurrence of secondary cancers, or the local recurrence of the disease [2,4]. An alternative to conventional treatment for many cancers is photodynamic therapy (PDT) [5]. Its main features are minimal invasiveness, high effectiveness, the possibility of combining with other forms of treatment, high selectivity, and limited susceptibility to the development of drug resistance [6]. Moreover, its beneficial effects are also used in the fight against non-oncological diseases caused by fungi, viruses [7], and bacteria [8].

1.1. History of Photodynamic Therapy (PDT)

The health effects of light on the human body have been known for thousands of years. The origins of heliotherapy in Egypt, Greece, and India date back to as early as 3000 BCE. The first medical document on the healing effects of sunlight, called the Ebers Papyrus, dates back to around 1550 BCE. Using powders of plant origin, sunlight was supposed to be effective at treating skin lesions. Similar conclusions were also reached by inhabitants of the Indian, Roman, Greek, and Chinese civilizations, using sunlight to treat diseases of other systems. It is believed to have healing effects in diseases such as rickets, pulmonary tuberculosis, acne, vitiligo, or lupus, often in combination with locally or orally applied plant powders and extracts [7]. The fathers of photodynamic therapy are considered to be Herman Von Tappeiner and Oscar Raab, who in 1900 noticed the effect of light on the photoactivation of acridine pigment and, as a consequence, cell death [9]. The next breakthrough discoveries were made by the Danish physician Niels Finzen, whose achievements were recognized with the Nobel Prize in 1903. He noticed that, in addition to sunlight, red and ultraviolet light also had therapeutic properties [7]. In the 1960s, the first photosensitizer (PS) was isolated—a derivative of hematoporphyrin from hemoglobin [10], and in the 1970s, the first photodynamic therapy using it in laboratory conditions was performed in the USA [1]. In 1993, Photofrin was approved in Canada for the treatment of bladder tumors, which finally gave photodynamic therapy the status of a therapeutic method [7,11]. In oncology, PDT is currently in the treatment of brain cancer [12], liver cancer [7], breast cancer [13], gastrointestinal cancer [14], pancreas cancer [15], prostate cancer [16], head and neck cancer [17], lung cancer [18], and used mainly in the treatment of skin cancer [6,19].

1.2. Mechanism of Photodynamic Therapy (PDT)

The essence is the occurrence of a photochemical reaction between photosensitizer molecules, selectively accumulating in pathological tissue, light of a specific wavelength and oxygen [8]. There are two types of photodynamic therapy—I and II. The photosensitizer, under the influence of light of an appropriate wavelength, is excited from the ground state S_0 to the unstable excited singlet states S_1 , S_2 , or other S_n . Then the S_n state relaxes to the S_1 state, and the S_1 state to the ground state S_0'' , according to basic Jablonski. Type I PDT involves the direct interaction of PS in the T_1 state with surrounding substances by generating free radicals as a result of electron transfer. Then the free radical anions react with triplet oxygen and H_2O to form a hydroxyl radical and a superoxide anion. The essence of type II PDT is the transformation of triplet oxygen into singlet oxygen by the photosensitizer into the T_1 state through energy transfer [20]. The newly formed singlet oxygen interacts with electron-rich molecules, causing their oxidation and, as a consequence, damage to some cellular organelles, including mitochondria, the cell membrane, the nucleus, lysosomes, and tissue necrosis [21]. Therefore, type I PDT is more resistant to oxygen deficiency than type II, which is a common phenomenon in cancer tumors [22].

Unlike conventional cancer treatment methods, i.e., chemotherapy and radiotherapy, PDT does not induce immunosuppressive effects, but stimulates the immune system. However, due to tumor hypoxia, incomplete selectivity and PS penetration into the tumor, or poor light penetration into deeper tissues, this method still requires improvement before it can be used on a large scale [3,10].

1.3. Photosensitizers (PSs)

Photosensitizers (PSs) are one of the three mandatory components needed to perform PDT [23]. When exposed to light of the appropriate wavelength, they induce photophysical or photochemical processes [9]. In PDT, PSs are crucial for generating reactive oxygen

species (ROS) upon light activation, leading to cell damage and death. However, a critical view of photosensitizers in PDT reveals several limitations and areas for improvement. These include the need for better selectivity, deeper tissue penetration, and enhanced efficacy (Table 1).

Table 1. Limitations of PS and research areas for improvements.

Limited Tissue Penetration:
Many photosensitizers absorb light in the visible spectrum, which has limited tissue penetration, hindering the treatment of deeper-seated tumors.
Lack of Tumor Specificity:
Photosensitizers can accumulate in both tumor and healthy tissues, leading to off-target effects and potential toxicity.
Inadequate Efficacy:
Some photosensitizers exhibit poor efficacy due to factors like low quantum yield, aggregation, or rapid clearance from the body.
Side Effects:
Photosensitizers can cause skin and eye photosensitivity, requiring careful patient management during and after treatment.
Variability in Clinical Protocols:
Early PDT studies faced challenges due to inconsistent light sources, varying photosensitizer formulations, and a lack of standardization in clinical protocols.
Type of Cell Death:
The type of cell death induced by PDT (apoptosis vs. necrosis) can be influenced by the photosensitizer, light intensity, and oxygen levels. Necrosis can trigger inflammation, while apoptosis is generally considered more desirable.
Dosage and Delivery:
Optimal dosage and delivery methods are critical for maximizing therapeutic efficacy and minimizing toxicity. This includes finding the right balance between light fluence, photosensitizer concentration, and targeting strategies.
Development of Next-Generation Photosensitizers:
Ongoing research focuses on developing photosensitizers with improved properties, such as enhanced NIR absorption, better targeting capabilities, and increased biocompatibility.
Areas for Improvement:
NIR-Absorbing Photosensitizers:
Developing photosensitizers that absorb in the near-infrared (NIR) region of the spectrum is crucial for deeper tissue penetration.
Targeted PDT:
Conjugating photosensitizers to antibodies, peptides, or other targeting agents can improve their selectivity for tumor cells.
Nanotechnology-Based Delivery:
Nanoparticles can be used to encapsulate and deliver photosensitizers, enhancing their solubility, stability, and tumor targeting.
Multifunctional Photosensitizers:
Developing photosensitizers with additional functionalities, such as imaging capabilities or drug delivery, can improve PDT's therapeutic potential.
Standardization of Clinical Protocols:
Further research is needed to optimize light sources, photosensitizer dosages, and treatment protocols for various cancer type

PS used in PDT are categorized into generations based on their development and characteristics (Table 2). First-generation photosensitizers, like Photofrin[®], had issues with prolonged photosensitivity and limited tissue penetration due to weak absorption at longer wavelengths. Second-generation photosensitizers, such as benzoporphyrins and phthalocyanines, were developed to address these limitations, offering improved tissue penetration and reduced photosensitivity. Third-generation photosensitizers utilize nanotechnology to enhance tumor targeting and delivery, improving overall PDT efficacy.

Table 2. Characteristics of individual generations of photosensitizers.

	1. Generation	2. Generation	3. Generation
examples of substances	- hematoporphyrin derivative (HpD) - Photofrin	- porphyrinoid compounds—consist of macrocyclic structures such as porphyrin, chlorins, bacteriochlorins, phthalocyanines, pheophorbides, bacteriopheophorbide, porphycene and texaphyrins, - non-porphyrinoid compounds—include anthraquinones, phenothiazines, xanthenes, cyanines and curcuminoids	- modified existing PS with biological conjugates such as peptides, antibodies or antisense molecules, chemical coupling or encapsulation of PS in carriers
feature	- poor light absorption at therapeutic wavelengths—limited penetration depth - low selectivity towards cancer cells—damage to healthy tissue - long-term phototoxicity of the skin—up to several weeks after treatment	- better O₂ quantum efficiency - greater selectivity to cancer cells - better anticancer effects - shorter tissue accumulation time - lower skin photosensitivity	- increased tumor specificity - decreased photosensitivity - activated by longer-wavelength light

2. Natural Photosensitizers

Natural photosensitizers absorb light at specific wavelengths, enabling them to be used in photodynamic therapy (PDT) and other applications. Many natural photosensitizers have peak absorption in the red-to-near-infrared region (650–800 nm), allowing for deeper tissue penetration. Other photosensitizers, like curcumin, absorb in the blue light range (405–435 nm).

2.1. Quinonoids

Quinonoids are a group of substances, almost all of which are photosensitive. Many of them have anticancer properties, which is why they are often used in oncology research. They are divided into three main groups: benzoquinone, anthraquinone, and

perylenequinones [24]. Anthraquinones are a group of compounds with natural phototoxic properties [25]. They have been shown to have antibacterial [26,27], antifungal [28], and anticancer effects, including in the treatment of breast cancer [29].

Hypericin (Figure 1) (HYP; 4,5,7,4',5',7'-hexahydroxy-2,2'-dimethylnaphthodianthrone) is a hydroxylated phenatroperylenequinone [30], a derivative of anthraquinones [4]. It is isolated from the plant *Hypericum perforatum*, also known as St. John's wort [4,24,31].

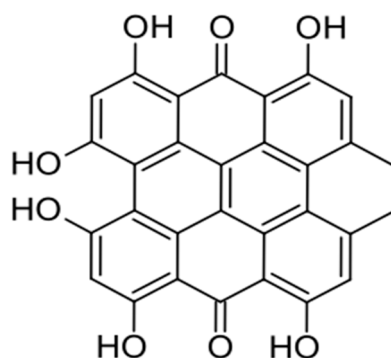


Figure 1. Chemical structure of hypericin.

The methods of synthesizing hypericin are presented in Table 3. Hypericin synthesis typically involves a multi-step process, often starting from emodin or emodin anthrone. A key step is the dimerization of emodin anthrone to form protohypericin, which is then converted to hypericin through irradiation with visible light. Various methods exist, including chemical synthesis and biosynthesis pathways, with the latter often involving polyketide synthase (PKS) enzymes (Table 4).

Table 3. The characteristics of lasers.

Red to Near-Infrared (650–800 nm):
This range offers better tissue penetration compared to shorter wavelengths, allowing for deeper treatment in PDT.
Examples:
Some natural photosensitizers that absorb in this range include the following:
Chlorophyll derivatives: Found in plants and algae, these molecules can be used in PDT applications, as shown in the study focusing on antibacterial nanoparticles.
Phycobilins: Found in red algae and cyanobacteria, these pigments absorb light in the red and far-red regions.
Blue Light (405–435 nm):
While not as deeply penetrating as red light, blue light can be effective for treating superficial conditions.
Examples:
Curcumin: A compound found in turmeric, curcumin absorbs strongly in the blue region and is being investigated for its potential as a photosensitizer.
Other Wavelengths:
470 nm: Some natural photosensitizers, like hypocrellin and cercosporin, have a maximum absorption peak around 470 nm.
500–600 nm: Anthocyanins, found in flowers like <i>Hibiscus rosa-sinensis</i> , have absorption peaks in this range.
635 nm: Blue light around this wavelength is also used in PDT.
Important Considerations:
Light Source:
The specific wavelength used depends on the photosensitizer and the target tissue.
Tissue Penetration:
Shorter wavelengths are less effective at penetrating tissue than longer wavelengths.
ROS Production:
Photosensitizers must be able to generate reactive oxygen species (ROS) upon light activation to be effective in PDT

Table 4. Synthesis and biosynthesis of Hypericin.

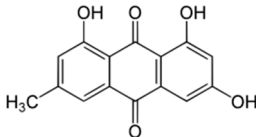
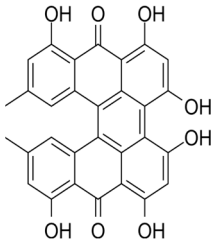
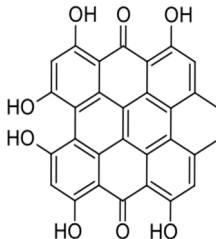
1. Emodin/Emodin Anthrone as a Starting Material [32]

Emodin and its reduced form, emodin anthrone, are common starting materials for hypericin synthesis.
Emodin can be obtained from various plant sources like the <i>Hypericum</i> species.
Emodin anthrone can be synthesized from emodin through reduction, for example, using tin(II) chloride.
2. Dimerization to Protohypericin [33]

A crucial step is the dimerization of emodin anthrone to form protohypericin.
This dimerization can be achieved through various methods, including oxidation with iron(III) chloride or other oxidizing agents.
For instance, in some methods, emodin anthrone is dimerized in the presence of pyridine and pyridine N-oxide, followed by oxidation to form protohypericin.
3. Conversion to Hypericin [34]

Protohypericin, the immediate precursor, is then converted to hypericin through irradiation with visible light.
This light-induced conversion is a key step in the final stage of hypericin synthesis.
4. Biosynthesis [35]
Hypericin biosynthesis in plants is believed to involve polyketide synthase (PKS) enzymes.
The PKS pathway leads to the formation of an octaketide chain, which undergoes cyclization and decarboxylation to form emodin anthrone, a precursor to hypericin.
The hyp-1 gene, identified in <i>Hypericum</i> species, is also involved in hypericin biosynthesis, potentially catalyzing the dimerization of emodin or emodin anthrone and subsequent steps.

Table 4. *Cont.*

5. Recent Advances [36]:
Recent research has focused on improving the efficiency and yield of hypericin synthesis, including exploring green synthesis methods and optimizing reaction conditions.
For example, some studies have investigated the use of ultrasonic-assisted extraction for hypericin from <i>Hypericum perforatum</i> .
Other studies have focused on developing more efficient chemical synthesis routes, such as those involving Diels–Alder reactions.

Since ancient times, hypericin has been used both as an antidepressant and an antiviral agent [31,37]. Its beneficial effects are also noticeable in the treatment of endocrine diseases, e.g., in relieving menopausal symptoms or those related to polycystic ovary syndrome, and skin diseases—including plaque psoriasis, wounds and scars after surgery, or changes caused by HSV-1 and HSV-1 viruses [38].

Its anticancer effects have also long been known and it is used in the treatment of cancers, including those of the urinary bladder, colon, breast, cervix, nasopharynx, liver, melanoma, leukemia, and lymphoma [30].

Its use in PDT of glioma has been confirmed by studies that were among the first to be conducted by Miccoli et al. They showed that by influencing the energy metabolism of SNB-19 cells, HYP-PDT inhibits the binding of hexokinase to mitochondria [39]. In turn, Ritz et al. obtained effective inactivation of three glioma cells—U373 MG, LN229, and T98G—after a short incubation and exposure to low-dose light [40]. While HYP-PDT has shown efficacy in treating various cancers and other conditions, some studies suggest potential “bed” issues, particularly regarding skin reactions and the timing of light application in relation to drug administration (Table 5).

Table 5. Hypericin’s Positive and Negative Aspects in PDT.

Hypericin’s Positive Aspects in PDT:
Effective Photosensitizer:
Hypericin is a strong photosensitizer, meaning it becomes activated by light and can then destroy targeted cells.
Tumor-Tropic:
It tends to accumulate in tumor tissue, enhancing its effectiveness in cancer treatment.
Antiviral Activity:
Light-activated hypericin has shown effectiveness against various viruses, including HIV.
Low Cytotoxicity:
In the absence of light, hypericin exhibits low toxicity, making it a safer option compared to some other photosensitizers.
Induces Cell Death:
Hypericin-PDT can induce both apoptosis (programmed cell death) and necrosis (uncontrolled cell death) in cancer cells.
Immunomodulatory Effects:
Sublethal doses of hypericin-PDT can have immunomodulatory effects, potentially helping in the treatment of persistent skin inflammation.

Table 5. Cont.

Promising in Onychomycosis:
Studies suggest hypericin-PDT is a promising treatment for onychomycosis (nail fungal infection).
Potential “Bed” Issues with Hypericin-PDT:
Phototoxic Skin Reactions:
High doses of hypericin can cause phototoxic skin reactions, even without detectable antiviral activity.
Timing of Light Application:
The efficacy of hypericin-PDT can be highly dependent on the timing between drug administration and light exposure. Studies suggest maximal effect is achieved when light is applied shortly after drug administration (e.g., 0.5 h), with efficacy decreasing as the interval increases.
Skin Distribution:
Hypericin distribution in the skin may not be homogenous, with accumulation in the stratum corneum and less in deeper layers.
Limited Topical Efficacy:
When applied topically, hypericin-PDT can be less efficient than other photosensitizers like methyl aminolevulinate (Me-ALA).
Vascular Damage:
Studies suggest vascular damage is a primary effect of hypericin-PDT, and its distribution within the tumor vasculature is crucial for PDT response.
Potential for Reduced Efficacy:
In some cases, hypericin’s efficacy in PDT may decrease when used in combination with other treatments, such as with 17-DMAG.
In conclusion, while hypericin offers several advantages as a photosensitizer in PDT, clinicians and researchers need to be mindful of its potential limitations, particularly regarding skin reactions and the timing of light application. Further research is needed to optimize hypericin-PDT protocols and minimize potential adverse effects.

Perylenequinolones are dark pigments containing an oxidized pentacyclic core, represented by the parent perylenequinolone 1 [41]. In 1956, the first, simplest perylenequinolone—Diol 1—was isolated from the fungus *Daldinia* [42].

Hypocrelin (Figure 2) belongs to the perylenequinone derivatives [4,24], and hypocrelin A (HA), B (HB), C (HBC), and D (HBD) are distinguished [43]. They are characterized by the same perylene–quinone structure and similar properties, but contain different side rings [43,44]. Both hypocrelin A and B are characterized by photodynamic activity. Hypocrelin is isolated from parasitic bamboo fungi—*Hypocrella bambusea* and *Shiraia bambusicola* [43].

The installation of axial chirality of perylenequinone enables the synthesis of more complex perylenequinone natural products. The stereochemical transfer is complicated due to the dynamic state of the perylenequinone helical axis. The stereochemical helix of perylenequinone is stable at room temperature, but after the formation of the seven-membered ring it loses its integrity, leading to rapid atropisomerization. The synthetic process includes several steps, such as enantioselective biaryl coupling, deacylation, and protection of free naphthols. Then, after hydroxylation, the allyl groups are transformed to form a diketone. The key step is the aldol cyclization of the diketone, which allows the formation of a seven-membered ring. After the synthesis is developed, the aldol reaction is

carried out, leading to the formation of hypocrellin A as the main product. This product has the desired stereochemical properties, and a small amount of the E enolate gives the anti-aldol product, leading to diastereomers, including shiraiachrome A [41,45–48]. Hypocrellin has long been used as a traditional medicinal compound in Asia. It is primarily known for its antiviral, antidepressant [43], and antifungal [49] effects. Both hypocrellin A and B are characterized by photodynamic activity [50].

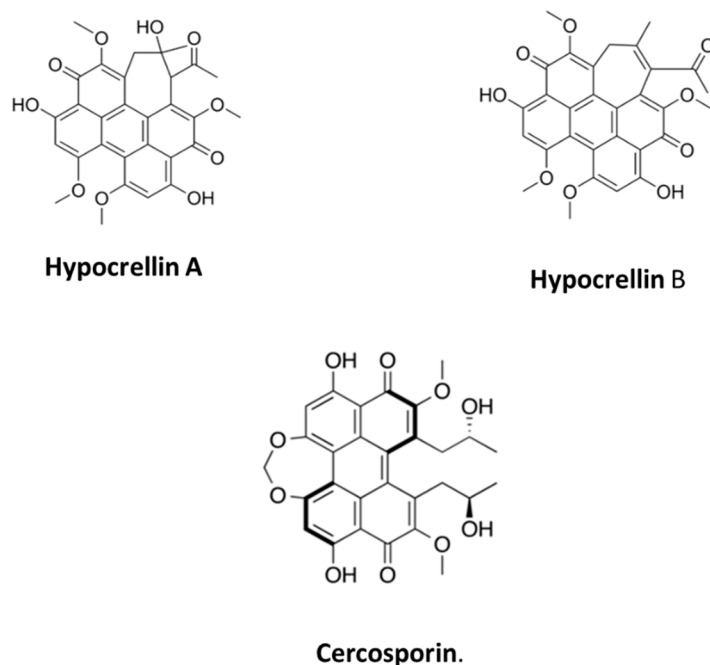


Figure 2. Chemical structure of hypocrellin A, B, and Cercosporin.

Hypocrellin has long been used as a traditional medicinal compound in Asia. It is primarily known for its antiviral, antidepressant [43], and antifungal [49] effects. Both hypocrellin A and B are characterized by photodynamic activity [50]. Hypocrellin A is an excellent photosensitizer and is characterized by selective accumulation in cancer cells, which leads to their death [43].

The main anticancer application of hypocrellin is related to the treatment of breast cancer [51] and skin cancer [52]. There is also evidence of the effectiveness of PDT using hypocrellin as a PS in the treatment of lung cancer [53], ovarian cancer [54], bladder tumor [55], and gastric adenocarcinoma [56]. However, some studies show that both hypocrellin A and B can also lead to the death of human brain cancer cells by inhibiting angiogenesis via photodynamic action [57].

Cercosporin (Figure 3), a deep red pigment, was first isolated by Kuyama et al. in 1957 from *Cercospora kikuchii* Gardner, a pathogenic fungus on the purple spot of Japanese soybeans [58–60]. Chemically, it is a dihydroxy-perilenequinone [56]. The structure of this phytotoxin was originally proposed by Kuyama in 1962, but it was modified by Lousber et al. [60,61] and confirmed by Yamazaki et al. Based on mass spectrometry and elemental analysis, the chemical formula was $C_{29}H_{20}O_{10}$ and the molecular weight was 534 [62]. Some naturally occurring red pigments, such as elsinochromes, fagopyrin, and erythroaffin, exhibit photodynamic activity. In connection with the above, studies have been conducted which have shown that in an oxygen environment it exerts a photosensitizing effect on mice or microbiomes, which makes it a photodynamic pigment [60]. Its photosensitizing function has also been demonstrated in the photooxygenation reaction, including 2,5-dimethylfuran and amino acid residues [59].

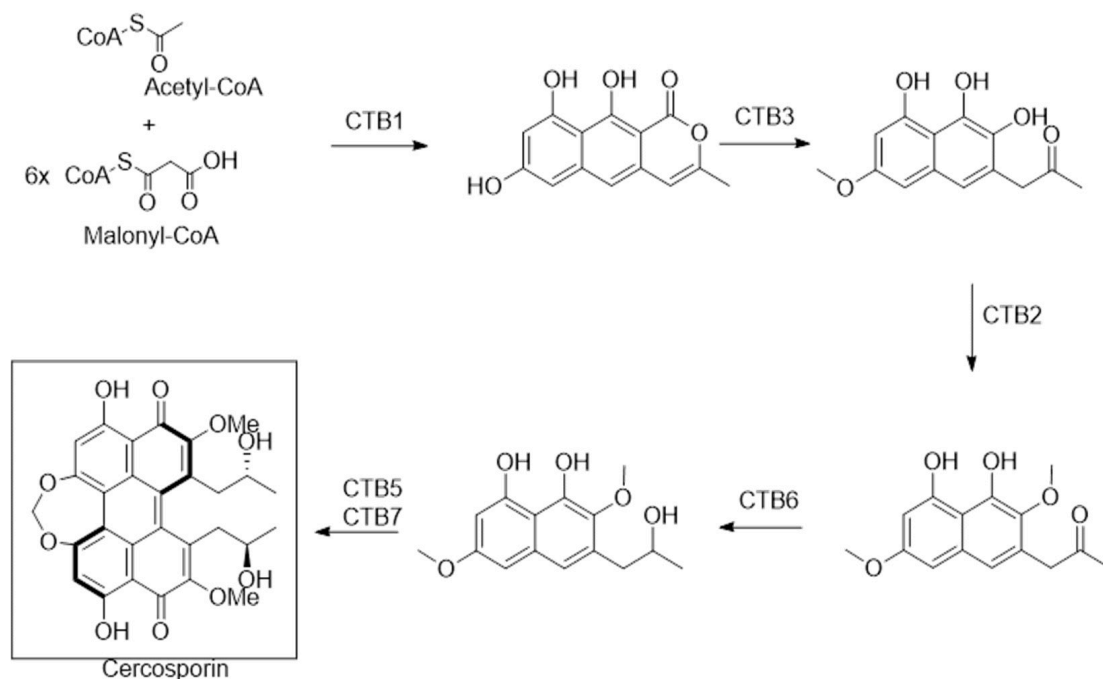


Figure 3. Cercosporin synthesis.

The synthesis of cercosporin is shown in the scheme (Figure 3) below.

Cercosporin is known primarily for its harmful effect on the leaves of cultivated plants [63]. It plays a key role in the development of white leaf spot disease [64,65]. It may be useful in the fight against harmful blooms of cyanobacteria, taking care of water resources [66,67]. Scientific studies conducted by Cadelis et al. have shown that isolates of *Cercospora beticola* exhibit strong antibacterial activity against methicillin-resistant *Staphylococcus aureus* strains [68]. In the study conducted by Mastrangelopoulou, Grigalavicius et al., two human glioma cell lines (T98G and U87) were used in 2D cultures, obtaining clear bioenergetic breakdowns, which confirmed its anticancer activity [69]. These results were confirmed in their subsequent work in 3D cell culture [70].

2.2. Curcumin

Turmeric, a plant related to the ginger family, has active polyphenolic compounds in its structure, which include curcumin, bisdemethoxycurcumin, and demethoxycurcumin, called curcuminoids [71]. They constitute up to 6% of the dry weight of turmeric [72]. Traditionally, the powdered rhizome of *Curcuma longa* is used in Asian and Indian cuisine as a curry spice, and also as an antimicrobial, insect repellent or dye [71,72]. In the traditional medicines of some cultures, turmeric is also used as a preparation for treating fresh wounds and bruises, scabs in smallpox and chickenpox, insect bites, anthelmintics or in the treatment of urological, liver, and biliary tract diseases [72].

Chemically, curcumin (Figure 4) is 1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione, with the chemical formula $C_{21}H_{20}O_6$. It is insoluble in water at neutral and acidic pH, but soluble in acetone, methanol, dimethyl sulfoxide, and ethanol [73].

Curcumin was first isolated in 1815 by Vogel and Pelletier, and its pure structure was isolated by Vogel in 1842. Its chemical structure was first described by Milobedzka et al. in 1910, and its synthesis by Lampe and Milobedzka in 1913 [73].

Anderson et al. in 2000 proposed a method for isolating the compound curcumin from ground turmeric plants [73]. The first step was to stir magnetically ground turmeric in dichloromethane, then heat it for about 1 h at boiling temperature. Then the obtained mixture was filtered under suction. The remaining filtrate was concentrated in a water

bath at 50 degrees Celsius. The last steps were to combine the oily substance with hexane, collect the obtained precipitate under suction, and analyze the sample [73].

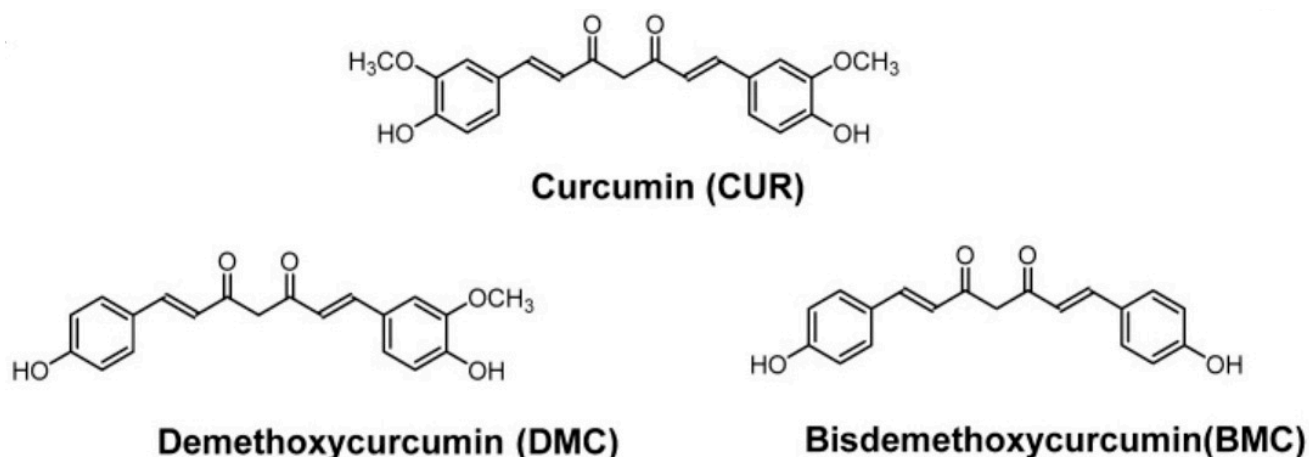


Figure 4. Curcumin and derivatives.

Chemically, curcumin is diferuloylmethane or 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E, 6E) [73]. Curcumin is characterized by low bioavailability, which results from its rapid metabolism, poor water solubility, low chemical stability, and a negatively charged state [74,75]. Therefore, various techniques are being tested to modify these features. One of them is the modification of curcumin compounds from the basic form to the nanometric form [76,77]. Nanocomplexation consists of dissolving the substance in a suitable solvent and then mixing it with a protein solution [76]. Another potential modification is gelation, the essence of which is to combine the compound with a protein or protein/polysaccharide and then with a gelling agent. Gelling agents include aerogels and emulsion-filled gels, emulsion gels, organogels, and hydrogels [74,78]. Encapsulation of curcumin is achieved by electrospraying, which involves the generation of monodisperse particles ranging in size from submicrometers to hundreds of micrometers. It involves exposing a liquid droplet in a capillary nozzle to a high electric field, under the influence of which it deforms and then disintegrates into small droplets due to varicose instability [79]. Changing the pH is also considered to increase the bioavailability of curcumin [74]. Studies conducted using curcumin in PDT show that it is particularly useful in the treatment of cancers such as breast [79], uterine [80], ovarian [81], skin [82], colon [83], liver [84], lung [85], and leukemia [86]. However, studies have also been conducted to demonstrate the effect of PDT using curcumin nanoparticles on glioma cells [86–89]. The studies conducted by Kielbik et al. focused on the effect of PDT using curcumin nanoparticles on human glioblastoma multiforme cells. They showed that over 90% of the cancer cells underwent apoptosis. Within approx. 2 h, curcumin was distributed in the cytoplasm, suggesting that curcumin is a promising substance for use as a photosensitizer in the therapy of glioblastoma multiforme [89].

As for the other properties of curcumin, numerous studies indicate that it can also exhibit anti-aging, [90] anti-inflammatory [91], and healing effects on skin diseases [91], diabetes [92], circulatory system diseases [93], eye diseases [94], osteoarthritis [95], or neurological diseases [96].

2.3. Chlorophyll Derivatives and Pheophorbide A

Chlorophyll derivatives instead of magnesium as the core atom contain palladium, zinc, copper, nickel, cobalt, and iron [24]. Pheophorbide A (PBA, (3S,4S)-9-ethenyl-14-ethyl-21(methoxycarbonyl)-4,8,13,18-tetramethyl-20-oxo-3-phorbinepropanoic acid) [97]

is a chlorophyll derivative [4]. Pheophorbide A (Figure 5) is isolated from the Chinese medicinal herb *Scutellaria barbata* and silkworm excrement [4].

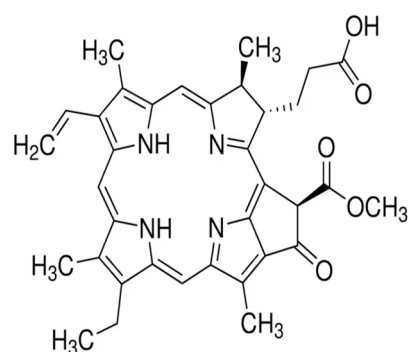


Figure 5. Chemical structure of pheophorbide A.

Treatment of ethanolic solution of chlorophyll a under acidic conditions led to obtaining crude pheophytin, thanks to the possibility of easy removal of Mg^{2+} ion. Hydrolysis of pheophytin with 80% TFA in water made it possible to obtain pheophorbide-a in the form of a fine powder. The synthesis of pheophorbide is shown in the scheme below (Figure 6) [98–100].

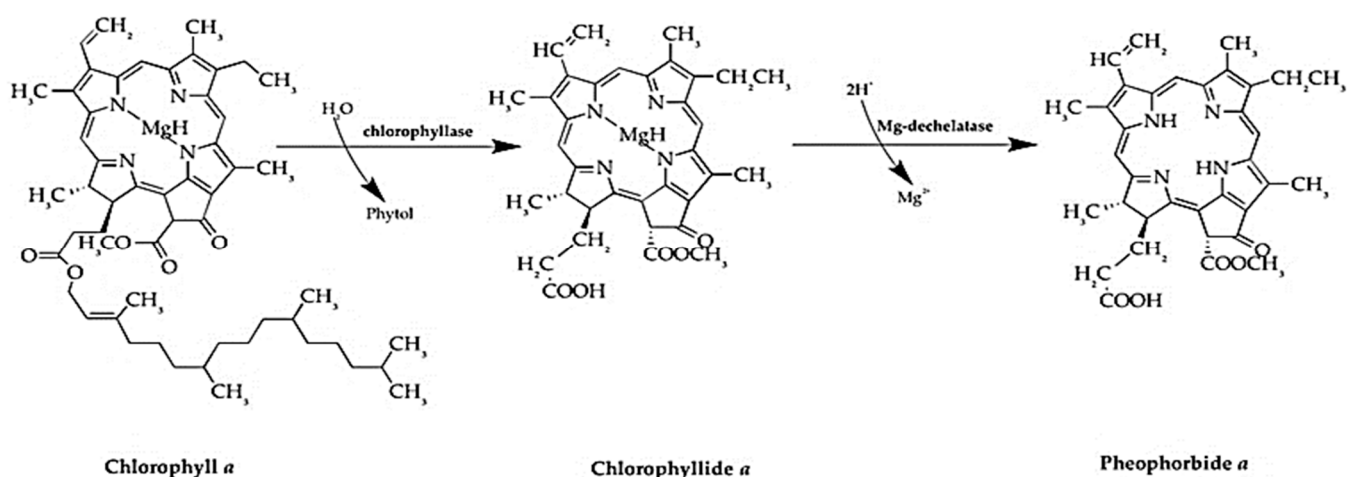


Figure 6. Pheophorbide A synthesis.

Pheophorbide A is classified as a compound with various properties—antiviral [101,102], anti-inflammatory [103], antioxidant [104], immunostimulating [105], and antiparasitic [106]. Additionally, one of the latest applications of pheophorbide A is the treatment of lymphatic vessel failure, which prevents the development of its complications, such as lymphedema, chronic inflammation, or impaired wound healing [107].

Pheophorbide A is also used in the treatment of neoplastic diseases, such as hepatocellular carcinoma [108], squamous-cell carcinoma of the oral cavity [109], uterine sarcoma [110], prostate cancer [111], cancer [112], and breast tumors [113]. Cho et al. demonstrated its inhibitory effect on glioblastoma multiforme cells using U87MG in dark conditions. In addition, they observed a lack of cytotoxic effects on normal cells [114].

2.4. Alkaloids and Berberine

Alkaloids are organic chemical compounds that have one or more basic nitrogen atoms in their structure. They are characterized by a cyclic ring structure. Natural photoactive alkaloids can be divided into five groups (Figure 7) [115].

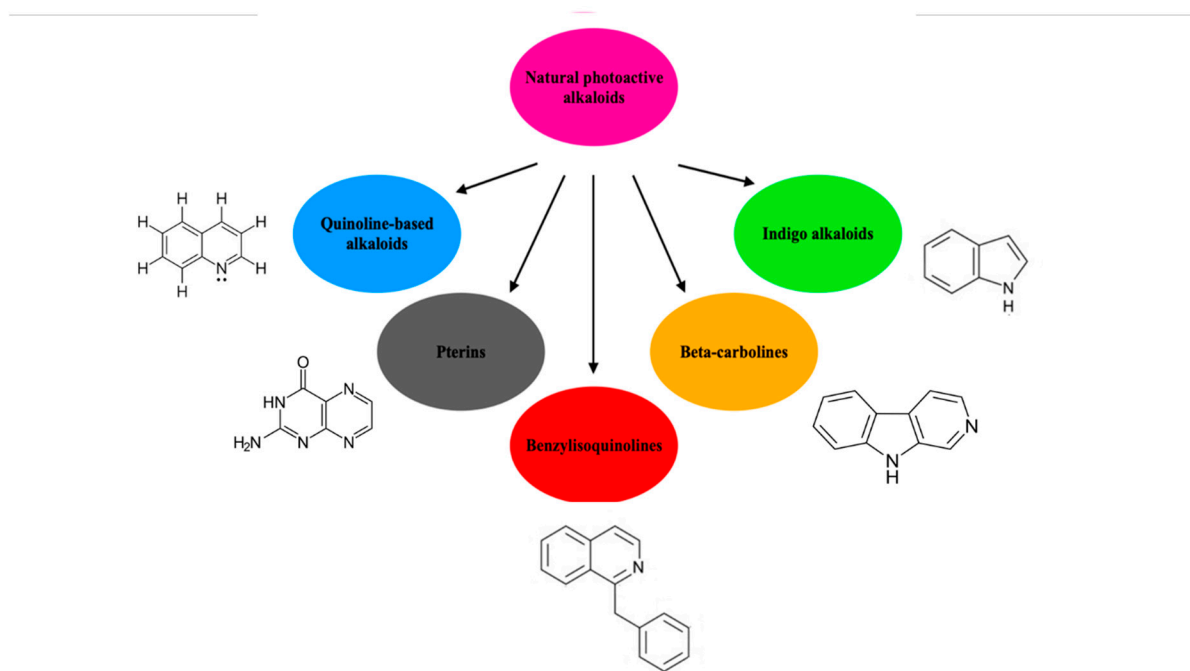


Figure 7. Classification of natural photoactive alkaloids.

Alkaloids are secondary metabolites of plants and animals. They can also be found in leaves, stems, roots, and seeds of plants of families such as Papaveraceae, Amaryllidaceae, Menispermaceae, Loganiaceae, Ranunculaceae, or Solanaceae. In the plant, they probably perform defensive functions against pathogens that threaten the host [115].

Berberine (Figure 8) is an isoquinoline alkaloid, based on quinoline, isolated from the Chinese herb *Coptis chinensis*, as well as other *Berberis* plants [116,117].

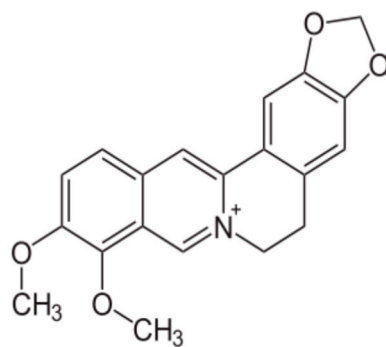


Figure 8. Chemical structure of berberine.

Berberine is credited with a number of health benefits [118]. Many studies confirm that it has a cholesterol-lowering effect [119], prevents obesity, and helps in the treatment of obesity [120], atherosclerosis [121], liver diseases [122], neurodegenerative diseases [123], ischemic stroke [124], inflammation and cancer of the pancreas [125], inflammatory diseases and cancers of the digestive tract [126,127], lung cancer [128], and ovarian cancer [129].

Cancer cells are characterized by a high cholesterol metabolism and the expression of a large amount of receptors for low-density lipoproteins (LDLs) [130]. Since berberine has an affinity for low-density lipoproteins, Andreazza et al. experimentally demonstrated that it accumulates in larger amounts in cancer cells than in normal cells. The above findings resulted in berberine being used as a photosensitizer, including in the therapy of central nervous system tumors [131]. In this regard, studies conducted by Carriero et al. showed that the use of PDT with berberine as PS on human astrocytoma cell lines

resulted in increased activation of apoptosis pathways, increased ROS production, increased mitochondrial depolarization, and increased activation of caspases [130]. Glial tumor cells are also characterized by having N-acetyltransferase activity. Wang et al. showed that this activity was inhibited in a dose-dependent manner after the use of PDT with berberine on these cells, confirming the efficacy of this substance as a PS [132].

A future research direction includes Photon Upconverting Nanoparticles (PUNPs); these nanoparticles convert infrared light into higher energy visible light, allowing for deeper tissue penetration and the activation of photosensitizers. The next future research direction is to synthesize inorganic photosensitizers and use them like quantum dots and plasmonic nanoparticles. Also, researchers can attach photosensitizers to targeting molecules or use stimuli-responsive systems to control their release at the target site. And finally, combining PDT with other therapies like chemotherapy or immunotherapy to enhance treatment efficacy can be used. The literature reports the synthesis of curcumin and symmetric curcuminoids of the aromatic (bisdemethoxycurcumin) and heterocyclic types, with yields ranging from good to excellent using the cyclic difluoro-boronate derivative of acetylacetone prepared by a reaction of 2,4-pentanedione with boron trifluoride in THF (ca. 95%) [133]. Also, the total syntheses of berberine hydrochloride and its analogs was achieved by a convergent strategy from available meconine derivatives, which were based on base mediated isoquinoline annulation followed by a trifluoroacetic anhydride-promoted decarbonylative elimination protocol [134].

3. Conclusions

The search for new photosensitizers and the modification of existing ones shows therapeutic potential. The search for effective drugs makes natural compounds the future and a challenge for modern oncology. The development of photodynamic therapy is one of the main and promising directions of research. To meet these requirements, current cancer therapy and diagnostics focus on the use of nanotechnology achievements. Ongoing research focuses on developing more effective and selective photosensitizers, as well as improving their delivery and activation. The development of new photosensitizers with improved properties and targeted delivery systems is an active area of research. Further studies are needed to optimize PDT protocols and understand the mechanisms of action in different disease settings. The exploration of new PDT applications beyond cancer treatment, such as antimicrobial therapy and wound healing, is also promising.

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