Photodiagnosis and Photodynamic Therapy 26 (2019) 395–404

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Review

Photodynamic therapy for cancer: Role of natural products

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ARTICLE INFO

Keywords:
Photodynamic therapy
Photosensitizers
Herbal medicine
Natural products

ABSTRACT

Photodynamic therapy (PDT) is a promising modality for the treatment of cancer. PDT involves administering a photosensitizing dye, *i.e.* photosensitizer, that selectively accumulates in tumors, and shining a light source on the lesion with a wavelength matching the absorption spectrum of the photosensitizer, that exerts a cytotoxic effect after excitation. The reactive oxygen species produced during PDT are responsible for the oxidation of biomolecules, which in turn cause cell death and the necrosis of malignant tissue. PDT is a multi-factorial process that generally involves apoptotic death of the tumor cells, degeneration of the tumor vasculature, stimulation of anti-tumor immune response, and induction of inflammatory reactions in the illuminated lesion. Numerous compounds with photosensitizing activity have been introduced commercially. Although many papers have been published with regard to PDT in the last decade, there has been relatively little focus on natural medicinal plant extracts and compounds derived therefrom. Herbal plants and their extracts are natural substances, and in comparison with synthetic chemicals are considered "green". This review focuses on the different mechanisms of PDT and discusses the role of various plant extracts and natural compounds either alone or in combination for carrying out PDT on different types of cancers.

1. Introduction

Photodynamic therapy (PDT) is a technique for managing malignant tumors, infections, and other lesions, which has drawn increasing attention worldwide [1,2]. The concept goes back thousands of years ago, when herbal medicine combined with sunshine, was used throughout the lands of Egypt, India, and China. However, not much attention was paid to PDT until the 1900s [3–5]. In the early 1900s, PDT was unexpectedly discovered when Oscar Raab successfully triggered the death of some Paramecium species when they had been incubated with acridine dyes and exposed to visible light [6].

PDT is based on a series of photochemical and photobiological reactions leading to destruction of malignant tissue [7]. Nowadays, PDT has been clinically utilized for more than 25 years as a cancer treatment. If PDT can be shown to be equally effective as traditional cancer treatments, but causes fewer undesirable side effects, it may become an accepted approach [8–11]. In 1972, Diamond et al. published the first medical study on PDT for cancer, and introduced hematoporphyrin as a powerful agent for the selective light-mediated killing of glioma cells in vitro and tumors in vivo [12]. PDT destroys malignant tissue through three distinct mechanisms, namely [1] direct damage to cancerous cells [2], vascular damage within the tumor tissue depriving it of oxygen and nutrients, and [3] activation of an anti-cancer host immune response [13].

In recent years there has been a movement towards the use of natural substances and herbal drugs instead of synthetic chemotherapeutic drugs, since they are environmentally sustainable and lack major side effects. Recently, investigations have demonstrated that herbal extracts, including tumor-targeting compounds, can be used in numerous cancer treatments, especially skin cancers [14]. Thereafter,

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https://doi.org/10.1016/j.pdpdt.2019.04.033
Received 15 January 2019; Received in revised form 24 April 2019; Accepted 29 April 2019
Available online 04 May 2019
1572-1000/

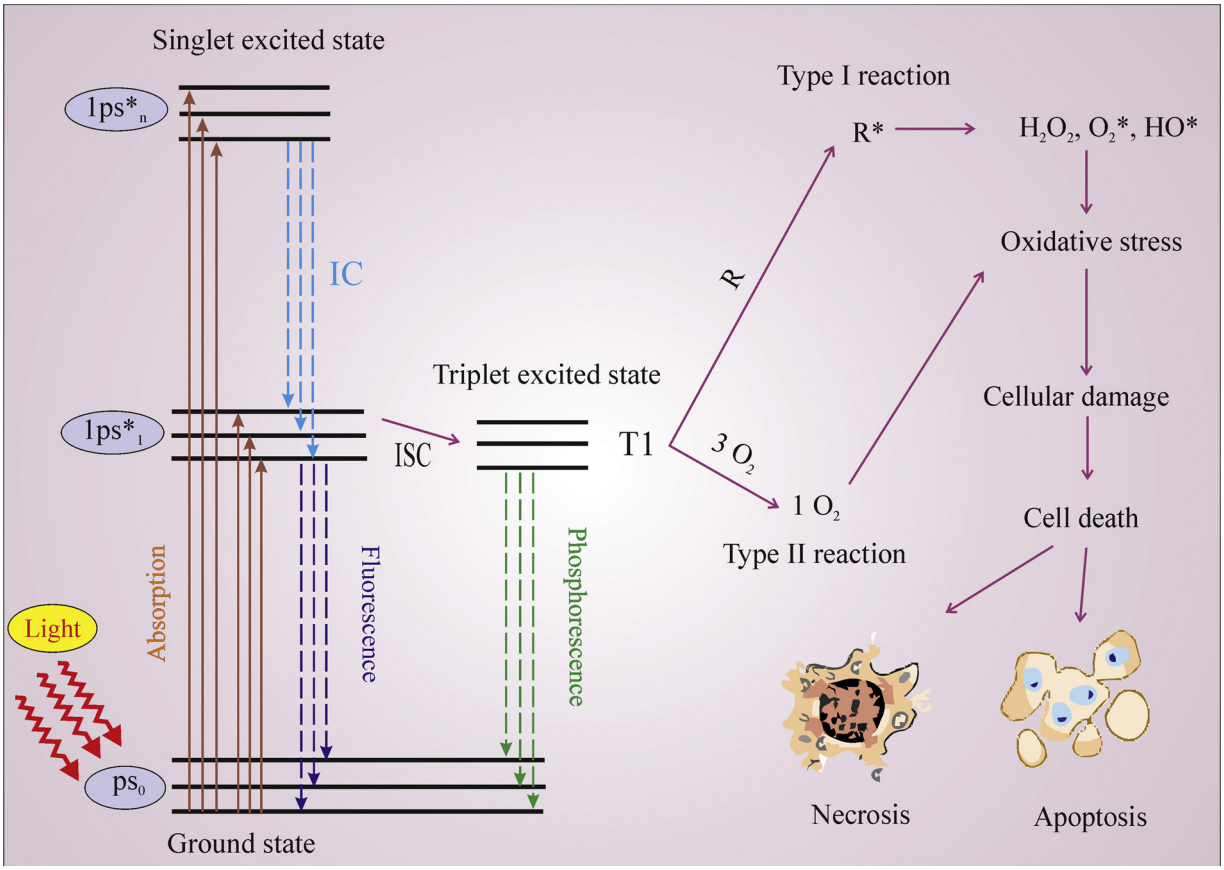


Fig. 1. The mechanism of PDT shown by a Jablonski diagram. When PSs in cells are exposed to a specific wavelength of light, they become excited from the ground singlet state S_0 to the excited singlet states S_1-S_n. By intersystem crossing, they are converted to the excited triplet state T_1. Afterwards, electron transfer from T_1 to biological substrates (type I reaction), or energy transfer to molecular oxygen (type II reaction) that leads to a burst of reactive oxygen species production (HO, O_2, H_2O_2, $[1]O_2$). Finally, this process results in cellular damage followed by apoptosis and/or necrosis [24].

plants containing phototoxic compounds were discovered in various plant families. The main challenges preventing the treatment of patients with phototoxic and photogenotoxic agents extracted from plants and herbal materials, is their safety, need for regulatory approval, and demonstration of equivalent effectiveness to synthetic photosensitizers (PSs) [14].

In this review, we discuss the fundamental principles of PDT, PSs, and a variety of phototoxic plants and their major naturally occurring PSs, in the treatment of cancer.

2. Photodynamic therapy; basics and principles

PDT requires the interaction between three separate factors; the PS, light, and oxygen [15]. After exposing the PS to a specific wavelength of light, the outermost electron in the molecular orbital is excited from the ground state, S_0, to the short-lived first excited state S_1. Then, intersystem crossing or spin inversion occurs, and the molecule transitions to an excited triplet T_1 state with a longer lifetime (Fig. 1) [16]. PSs in both excited states are very unstable and lose their energy by emission of fluorescence or phosphorescence, and by internal conversion to heat [17]. A PS in the T_1 state may react photochemically in either one of the following two pathways [18]. Type I reaction in which the excited PSs react with a molecule in the surrounding environment (including oxygen) by an electron transfer process leading to the generation of free radicals. These free radicals interact rapidly with biomolecules such as lipids, peptides, proteins, and nucleic acids, resulting in their destruction [19,20]. On the other hand, Type II reactions occur by direct energy transfer from the triplet PS to the ground state oxygen molecule, which is also a triplet. This results in generation of ground state S_0 PS, and excited state singlet oxygen $^1O_2$ which by itself is a powerful oxidizing agent [21]. The damage caused by PDT is local since both singlet oxygen and free radicals have a short lifetime (10–320 ns), and its diffusion distance is small (only 10–55 nm within cells) [22,23].

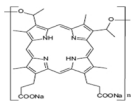
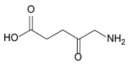
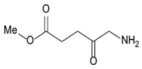
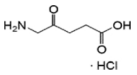
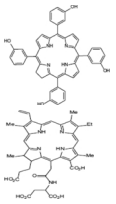
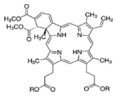
PDT tumor destruction is a multi-factorial process that generally involves neoplastic cell death by apoptosis or necrosis, degeneration or shut-down of the tumor blood supply, stimulation of anti-tumor immune responses, and induction of inflammatory response in the treated location [25].

2.1. Photosensitizers

PSs, whether naturally or artificially obtained, by definition contain a chromophore. A chromophore is a set of conjugated unsaturated bonds, which absorb visible light at a particular visible wavelength with a high molecular absorption coefficient. Choosing the appropriate PS is one of the most critical steps in PDT and is essential for the most effective and efficient therapy [26,27,28,29]. Much effort has been made in defining the characteristics of the ideal PS for cancer [29] and for other conditions

1 The PS should be easily obtained, a pure compound, and its chemical properties must have been previously established in the literature.
2 Lack of toxicity in dark conditions.
3 Soluble and stable in aqueous solvents.
4 High absorption coefficient within the spectral range of 600–800 nm where light penetration of tissue is maximal.
5 Have high quantum yields for triplet state formation and the

Table 1
PSs used for clinical purposes and photodynamic therapy.

Photosensitizer	Structure	Absorption	Localization	Incubation time	Approved Application	Ref
Porfimer sodium (Photofrin)		λ_{max} = 630 nm	Golgi apparatus, plasma membrane	24-48 h	Used in the treatment of early and late-stage lung cancers, esophageal cancer, bladder cancer, early stage cervical cancer, and malignant and nonmalignant skin diseases. It is also being considered as a potential therapy for Kaposi's sarcoma, Barrett's esophagus with high-grade dysplasia, psoriasis, and cancers of the head, neck, brain, and breast.	(33, 34)
5-Aminolevulinic acid or ALA (Levulan)		λ_{max} = 635 nm	Mitochondria, cytosol, cytosolic membranes	4-6 h	US FDA approved for non-oncological PDT treatment of actinic keratosis in 1999. Its potential PDT applications extend to Bowen's disease, basal cell carcinoma, and other diseases. ALA can also be used to detect tumors in bladder, skin, lung, and gastrointestinal tract.	(35-38)
Methyl aminolevulinate (Metvixia)		λ_{max} = 635 nm	Mitochondria, cytosol, cytosolic membranes	3 h	Approved by the US FDA in 2004 for the treatment of actinic keratosis.	(39, 40)
Aminolevulinic acid hydrochloride (Ameluz)		λ_{max} = 635 nm	Mitochondria, cytosol, cytosolic membranes	3 h	Approved by the US FDA in 2016 for the treatment of actinic keratosis.	−41
Meta-tetra(hydroxyphenyl) chlorin (Foscan)		λ_{max} = 652 nm	Endoplasmic reticulum (ER), mitochondria	96 h	Treatment of neck and scalp cancer with m-THPC was approved in Europe, and the drug was used successfully for the treatment of breast, prostate, and pancreatic cancers.	(25, 42, 43)
N-aspartyl chlorin e6 (NPe6, Laserphyrin)		λ_{max} = 664 nm	Lysosome, endosome	2-4 h	Approved for the treatment of fibrosarcoma, liver cancer, brain cancer, and oral cancer. Approved in Japan in 2003 to treat lung cancer.	(34, 44)
Benzoporphyrin derivative monoacid ring A (Verteporfin)		λ_{max} = 690 nm		30-150 min	In 1999, US FDA approved Verteporfin for age-related macular degeneration in Ophthalmology.	−28

production of singlet oxygen and other reactive oxygen species [27,28].
6 Binds to intracellular locations that are highly sensitive to oxidative damage
7 Selectively absorbed into the target tissue.
8 Excreted from the body rapidly, in order to avoid post-treatment phototoxicity
9 Optimum pharmacokinetic properties [29].
10 Short drug light interval to facilitate out-patient treatment
11 No toxic effects on healthy tissues and organs.

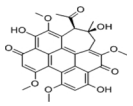
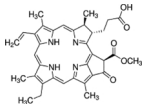
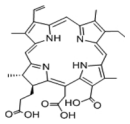
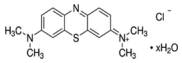
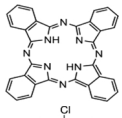
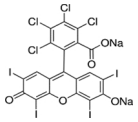
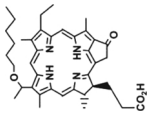
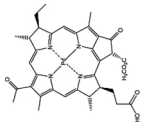
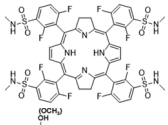
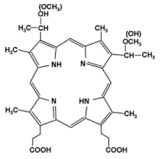
Up to the present time, more than 400 individual compounds have been recognized as possible candidates for use as PSs [6]. However, among these, only a handful have been approved for clinical application in PDT, while others have been clinically tested and eventually discontinued, while yet more are still under investigation. PSs, which are clinically applicable for cancer therapy and other compounds, which are under investigation, are shown in Tables 1 and 2 respectively [28,30–32].

As shown in Table 1, only a limited number of PSs have been clinically approved for use in PDT [62]. It is fair to say that no PS has yet been proposed that embodies all of the ideal features discussed above [11,63]. Therefore, efforts continue to be made to develop newer and more efficient PSs for optimal PDT [64]. In many fields of biomedical research the focus and tendency has been steadily moving towards more natural compounds due to the considerable side effects produced by synthetic chemotherapeutic drugs, and a trend towards environmentally sustainable green approaches. Modern techniques have allowed separation, purification, structural determination and characterization of active principles extracted from natural materials. Nature is a useful and economical resource for development of medications and discovery of new PSs [65]. From 2005–2010, 19 drugs received approval throughout the world, that were derived from a natural source [66]. Despite the vast resource of pharmaceutically active compounds occurring within nature, and a sizable body of literature, no truly comprehensive systematic study of natural products has yet been described. Furthermore, only less than 15% of laboratory identified plants have been biologically studied [67]. Potential drugs derived from natural sources usually need to be fully purified, which entails expending a significant amount of time, effort and money. In addition, high-throughput drug discovery trials using plant extracts may result in the isolation of already-known compounds. However, there have been some efforts made to discover new chemical compounds from active natural extracts that may act as efficient PSs [68–70]. In 2013, Jong et al. assayed the phototoxicity of 2400 extracts from 888 Sarawak jungle plants, in order to discover new PSs. According to the results of this study, several Sarawak jungle plants may be considered as a possible resource for novel PSs for PDT [62]. One year later in another study they surveyed 278 phototoxic extracts and managed to detect two new PSs that may be active for PDT. Both of these contained a cyclic tetrapyrrolic structure [64]. In 2015, Rodrigues et al. introduced the hydrophobic extract of the *Arrabidaeachica* (Crajiru) plant as a rich resource of PSs for PDT [65]. Extracts of various plants therefore have some potential as novel PS to be used in PDT.

2.2. Herbal extracts as natural PSs in PDT

Herbal medicine plants, herbal extracts and natural products have been used for treating a wide range of human ailments since ancient times [71]. Since about half of current medicines and drugs are derived

Table 2
PSs used in research applications of PDT.

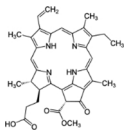
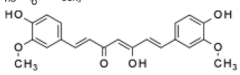
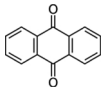
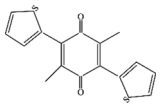
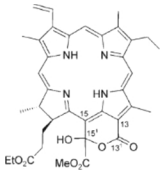
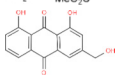
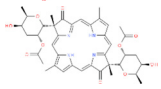
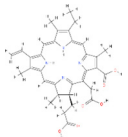
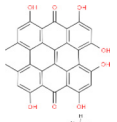
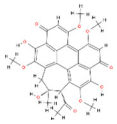
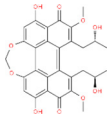
Photosensitizers	Structure	Potential indication	Ref
Hypocrellin A		White lesions of vulva and keloid cases, antiviral activity against human immunodeficiency virus type 1 and age-related macular degeneration	(45, 46)
Pheophorbide-a		Early stage lung cancer, superficial head and neck cancer and human uterine cancer	(47, 48)
Chlorin e6		Superficial squamous cell carcinoma of the lung, human nasopharyngeal and bladder carcinomas	(49-51)
Methylene blue		Basal cell carcinoma, Kaposi's sarcoma and melanoma	(52, 53)
Phthalocyanine		Cutaneous/subcutaneous lesions from diverse solid tumor origins	−54
Rose Bengal		Metastatic melanoma	−55
HPPH: 2-(1-Hexyl-oxyethyl)-2-devinylpyropheophorbide-alpha		Equine periocular squamous cell carcinoma, rodent colon carcinoma,and xenografts of human glioma	(56, 57).
TOOKAD		Prostate small cell carcinoma	−58
Redaporfin		Melanoma	−59
Hematoporphyrin monomethyl ether		Cervical cancer, ovarian cancer	(60, 61)

from different types of plants, it is clear that natural products should be further investigated as potentially effective agents in cancer therapy [72–78].

Combinations of PDT with other treatment methods, such as chemotherapy, radiotherapy, immunotherapy, or even herbal medicine therapy, could be a promising approach against various types of cancer, where the results obtained with monotherapy have been less than stellar [79]. It is worth mentioning that, in comparison to single-agent therapies, combination therapy tends to have diminished side effects, and can more effectively reduce cancer cell proliferation. In some cases combination therapy can increase the uptake of anticancer chemotherapy drugs into the cancer cells and tumors resulting in an improved response. Thus, PDT combination therapy may be a useful technique to overcome drug-resistant tumors [80]. Although there have been several PSs developed during the last 30 years, only a handful of them have been used in human clinical applications.

As mentioned above, herbal medicine has been used since ancient times. In India, the seeds of *Psoralea corylifolia* were used for vitiligo treatment, and in Egypt, the active compounds of *Ammimajus* were applied onto skin regions that were affected by vitiligo, before its exposure to sunlight [81]. One of the most well-known plants used in PDT is *Hypericum perforatum* (HP) [82]. Hypericin is a compound isolated from HP having the potential to be utilized as a first choice PS. Studies have demonstrated that the phototoxic effect of hypericin can be multiplied by combination with other PSs such as chlorin(e6) and both can be excited by white light, and other physical approaches such as hyperthermia can be used. It has been shown that apoptosis is mainly induced by the mitochondrial pathway involving caspase-3 and caspase-9, and cell growth is inhibited by suppression of activation of the vascular endothelial growth factor-A (VEGF-A)-mediated PI3K/Akt pathway [82]. In another study, researchers reported that hypericin acted as a novel PS, which could destroy cancer cells *in vitro* and tumors *in vivo* when activated with suitable wavelength light (610 nm). One *in vitro* study demonstrated that the polar methanolic fraction of HP had antiproliferative and proapoptotic effects in human bladder cancer cell lines [83]. In a study conducted by Liao Jing et al. new PS compounds extracted from Chinese medicinal herbs, *Cortex phellodendri*, and *Rhizoma coptidis* were introduced as PSs with good fluorescence properties [84]. They also showed that the combination of those herbal extracts with illumination could remarkably reduce the metabolic cell viability,

Table 3
Physicochemical feature of herbal extracts.

Herbal extract	structure	absorption wavelength	indications	cellular target
Pheophorbide A		410-668 nm	Phototoxic effects in human colorectal adenocarcinoma, human hepatocellular carcinoma and human uterine sarcoma cell lines	Localized in mitochondria
Curcumin		350 to 450 nm	antioxidant, anti-inflammatory and anticancer effects, cytotoxicity against neural progenitor cells	lysosomal membrane
Anthraquinones		220–400 nm	Breast cancer treatment in combination with caspase 3 induction	Localized in mitochondria
Thiophenes		225 and 400 nm	Cytotoxic effect on human cancer such as skin and cervix cancer	Lysosome
15(1)-Hydroxypurpurin-7-lactone ethyl methyl diester		~ 700 nm	Inducing apoptosis in human leukemic cells (CMK-7), phototoxic effect on oral and nasopharyngeal cancer	NI
Aloe-emodin		370-500 nm	Anti-angiogenic	Lysosome
Tolyporphin		676 nm	Metastasis	Perinuclear region and specific vesicles.
Chlorophyllin		600-670 nm	Bladder cancer, breast cancer, melanoma,	lysosomes and mitochondria
Hypericin		514–593 nm	Bladder cancer, nasopharyngeal carcinoma cells	membranes of nuclear, endoplasmic reticulum (ER), Golgi complex and mitochondria
Hypocrellin		Less than 600 nm around 470nm	Skin disease, cervical cancer	lysosomal compartment, mitochondria
Cercosporin		532nm	glioblastoma multiforme, breast adenocarcinoma	mitochondria and endoplasmic reticulum

NI, not identified.

proliferative ability, and increase cell death. Recently, active components or fractions extracted from traditional Chinese medicinal herbs, such as *Radix bupleuri*, *Rhizoma polygoni cuspidati*, *Rabdosia rubesens*, *Cortex magnolia officinalis*, and *Rhizoma chuanxiong*, in combination with light activation were reported to exert an anti-cancer effect via initiation of autophagy [85]. Results of these studies suggest that photosensitizing compounds isolated from natural plants could be an alternative for utilization in PDT. These compounds include pheophorbide A, tolyporphin, chlorophyllin, curcumin, anthraquinones, hypericin, hypocrellin, cercosporin, thiophenes, 15(1)-hydroxypurpurin-7-lactone ethyl methyl diester, and aloe-emodin. Some non-PS natural product compounds that may potentiate PDT including indole-3-acetic acid, carvacrol, β-glucans, and ascorbic acid are discussed briefly.

2.3. Pheophorbide A

Pheophorbide is a degradation product of chlorophyll, which occurs in green plant cells (Table 3). This compound can be isolated from many natural resources, such as the traditional Chinese medicine, *Scutellaria barbata*, silkworm excreta, *etc*. Hajri et al. measured pheophorbide A phototoxicity in human colorectal adenocarcinoma cells (HT29) and showed its effectiveness after irradiation at 670 nm [86]. Tang et al. studied pheophorbide-A-based PDT showing that the high levels of ROS produced could induce the death of human hepatocellular carcinoma cells (Hep3B). They also reported that pheophorbide A triggered apoptosis by localization within mitochondria [87]. In another study designed to investigate the effect of this compound on human uterine sarcoma cell line (MESSA), a growth-inhibitory effect in a dose-dependent manner after irradiation was demonstrated; however,

no cytotoxic effects were observed without light illumination [86].

2.4. Curcumin

Curcumin is isolated from the rhizome of *Curcuma longa* (Table 3). Studies have demonstrated antioxidant, anti-inflammatory and anticancer effects of this natural compound [88]. Koon et al. have shown the dark cytotoxicity of curcumin in a neural progenitor cell line (NPC/CNE2); however, biological activity was enhanced by illumination with white and blue light [89]. Dujiic et al. investigated the tumor growth inhibitory effects of this natural product by intraperitoneal injection of curcumin, followed by visible light irradiation in a xenograft tumor model of human epithelial carcinoma (A431) [88].

2.5. Anthraquinones

Rubiaceae are a family of flowering plants that have been reported to have a naturally phototoxic effect if they make their way into animal feedstuffs (Table 3). Anthraquinones are a class of compounds that have been isolated from these plant species The isolated anthraquinones include rubiadin 1-methyl ether, damnacanthal, soranjidiol, postuline, damnacanthol, and heterophylline [90]. These compounds have photosensitizing properties and can generate superoxide (O_2^-) under illumination. In a study by Comini et al., it was demonstrated that anthraquinones, such as soranjidiol, soranjidiol 1-methyl ether, rubiadin, and rubiadin 1-methyl ether, have PDT activity against caspase-3-transfected human breast carcinoma cells (MCF-7). In the following study, the percentage of cell internalization was positively correlated with the phototoxic activity of anthraquinones (Table 3) [91].

2.6. Thiophenes

Tricyclic linear terthiophenes have been isolated from *Echinops latifolius Tausch* and have shown cytotoxic and phototoxic properties against neoplastic cells (Table 3) [92]. Some of the novel compounds derived from *Echinops latifolius* can be activated with ultraviolet A (UVA) radiation, and exert a cytotoxic effect on human cancer cell lines, including A375-S2 and HeLa [93]. Interestingly, these compounds do not show any cytotoxic effects in the dark (Table 3).

2.7. (1)-Hydroxypurpurin-7-lactone ethyl methyl diester

15(1)-Hydroxypurpurin-7-lactone ethyl methyl diester was first isolated from the *Araceae* family. However later on, it was more commonly isolated from leaves of bamboo plants (Table 3) [94,95]. This molecule has photophysical properties including near-red absorption. It also has phototoxic effects inducing apoptosis in human leukemic cells (CMK-7). Additionally, the phototoxic effects of this molecule have been examined in oral and nasopharyngeal cancer cell lines (HSC2 and HK1, respectively) (Table 3) [96].

2.8. Aloe-emodin

Aloe-emodin is isolated from *Aloe vera* roots, and the leaves of other plants (Table 3) [97]. Studies have established the anti-cancer effects of this natural agent. The phototoxic effects of Aloe-emodin accompanied by UV or visible light irradiation have been tested on human foreskin fibroblasts. It was revealed that the phototoxic effect caused oxidative damage to DNA and RNA in the malignant cells [98]. Càrdenas et al. have shown anti-angiogenic effects of Aloe-emodin when combined with white light in human osteosarcoma and fibrosarcoma cells (U2OS and HT-1080, respectively) [97]. Also, they showed that excited Aloe-emodin was more cytotoxic than its unexcited state (Table 3) [99].

2.9. Tolyporphin

Tolyporphin (TP) belongs to the porphyrin family, and is extracted from cyanobacteria. A study showed that compared to second-generation PDT PSs such as the pheophorbides (Ph4 − OH and MPPH), TP was much more effective using in vitro systems (Table 3). The investigation on TP-PDT in cells showed singlet oxygen, produced upon illumination of TP-stained ER membranes, could not diffuse far from the site of production. Therefore, after PDT with TP, nuclear membrane damage was observed. The strong phototoxicity of TP in cells is probably is related to its specific localization in the endoplasmic reticulum (ER) (Table 3). However, the results showed a different mechanism in the PDT response in vitro, and the in vivo tumor response, probably caused by factors related in the PDT response in vivo. Therefore beside the direct effect (on the tumor cells) an indirect effect (vascular damage) combine to produce the PDT response induced by TP [100].

2.10. Chlorophyllin

Chlorophyllin belongs to the family of chlorophyll derivatives and is extracted from cyanobacteria and the chloroplasts of algae and plants (Table 3). Studies have demonstrated that chlorophyllin could localize in lysosomes and mitochondria, suggesting the major mechanisms of chlorophyllin PDT in cancer cells is autophagy and apoptosis. Recently chlorophyllin has drawn the attention of researchers because of its favorable optical properties (600–670 nm), easily solubility in aqueous solutions, easy and low cost extraction process compared to synthetic PSs. It displays only slight toxicity and is quickly cleared from the body (Table 3) [101–103].

2.11. Hypericin

Hypericin is an anthraquinone derivative that is naturally extracted from *Hypericum perforatum* a yellow flowering herb generally known as St. John's Wort. Hypericin-mediated PDT has been used for the treatment of different type of cancer including skin (Table 3) [104], cervical [105,106], glioma [107], and bladder [108] tumors. It is known that photo-activation of hypericin could generate superoxide anion radicals and singlet oxygen with a good quantum yield. Reactive oxygen species (ROS) produced after PDT could induce oxidative damage and destroy tumors. Another mechanism of cell death is related to formation of lipid hydroperoxides by an oxidative process [109]. It has been reported that light activation of hypericin could inhibit protein kinase C (PKC) and other growth factors, and increase membrane lipid peroxidation. This can induce superoxide dismutase activity and reduce cellular glutathione levels in mitochondria. Moreover, it can cross-link acetylcholinesterase and cause photo-oxidation of lens alpha-crystallin [110].

Cellular localization studies in cancer cell lines have shown that hypericin accumulates in membranes of the nuclear envelope, endoplasmic reticulum (ER), Golgi complex and mitochondria. Evidence has shown the main mechanism of cancer cell death following hypericin–PDT is apoptosis, autophagy and necrosis [111,112]. The study showed accumulation of hypericin in the ER membrane leading to a rapid loss of the Ca2+ stores and cell death from caspase-dependent apoptosis or an autophagy-dependent pathway. Mitochondrial damage has been recognized as another event to have a critical role in the initiation of the intrinsic apoptotic pathway after hypericin–PDT by releasing cytochrome c from the mitochondria causing a rapid increase in procaspase-9/procaspase-3 activation and poly ADP-ribose polymerase (PARP) cleavage. Overall, the studies have suggested hypericin as one of the most potent PSs, extracted from natural sources [113].

2.12. Hypocrellin

Hypocrellins are extracted from *Hypocrella bambusae* which is a

parasitic fungus belonging to *Sinarundinaria* species, which grows in Yunnan and Tibet provinces in China and in some regions of Sri Lanka (Table 3) [114]. Previous studies have shown that a limitation of the use of hypocrellin in clinical PDT, is that it needs to be activated by UV or blue light. Hypocrellin has a lipophilic molecular structure with low water solubility, causing aggregation in blood plasma. This may cause serious blockage of the vascular system after intravenous injection. In order to use hypocrellin for deep tissue PDT, the excitation wavelength should be modified to the red or near-infrared (NIR) region, and chemical modification can make it soluble in the aqueous solvents. Derivatives of hypocrellin include hypocrellin A (HA), hypocrellin B (HB), and deacetylated hypocrellin A (DAHA) [115,116].

The interesting features of hypocrellins as PSs is their light-activated antiviral and antitumor activity and rapid clearance in vivo. Hypocrellins could be an efficient agent for cancer phototherapy including treatment of skin cancer [117].

Hypocrellins efficiently generate singlet oxygen after light activation. Not only do hypocrellins produce reactive oxygen species but hypocrellin radicals can contribute to the phototoxicity of cells. In particular semiquinone radical anions formed from HA and HB can damage mitochondria and microsomal enzymes. Lipid peroxidation of the membranes triggers apoptosis or necrosis. Hypocrellin-mediated PDT can re-establish the chemosensitivity and radiosensitivity of human tumor cells during hypoxia [118]. One of the serious disadvantage of hypocrellins for phototherapy is the wavelength absorption, which is shorter than 600 nm [119]. Hypocrellins have affinity for binding to lipids, and some experiments have demonstrated hypocrellin and its derivatives might be localized in lysosomal compartments, mitochondria and cell membranes [120].

2.13. Cercosporin

Cercosporin is extracted from *Cercospora kikuchii,* and the structurally related elsinochromes come from the Elsinoe family of fungi (Table 3) [121]. It was found that cercosporin could generate singlet oxygen when activated with light shorter than 532 nm wavelength. It was shown that when cercosporin PDT was carried out in the presence of reducing agents (such as urate and ergothionine) the singlet oxygen production was reduced and at the same time the formation of superoxide anion strongly increased [122,123].

Similar to hypocrellins, the toxic effects of cercosporin-based PDT are induced by lipid peroxidation caused by singlet oxygen, followed by formation of free radicals causing cytoplasmic membrane damage and finally cell lysis [25]. The disadvantage of cercosporin in clinical application is its short activation wavelength and poor water solubility. Although hypocrellins and cercosporin are not particular suitable for excitation by an external light source, they could be very useful for PDT triggered by intracellular chemiluminescence [124,125]. Studies have confirmed that cercosporin is localized in both endoplasmic reticulum and mitochondrial membranes, and causes cell death based on apoptosis and necrosis [126].

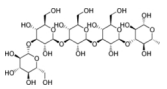
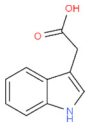
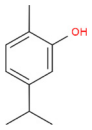
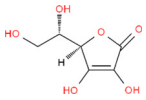
2.14. Natural compounds which are not PS but can be used in PDT

2.14.1. β-glucan

β-glucans are polysaccharides produced by a variety of natural plants such as oat and barley as well as by various fungal species (Table 4). β-glucans can activate the immune system against the early and late stages of tumors. Akramene et al. have shown that intravenous and oral co-administration of β-glucan may enhance PDT efficiency compared with the single administration route (Table 3) [127].

β-glucans belong to a class of immunostimulants and which exist in OK432, CpG and various bacterial preparations which stimulate the immune system. response these make limitation of using this PS in PDT [128].

Table 4
Non PS natural compounds.

Herbal extract	structure	indications
β-glucan		Activation of the immune system against the early and late stages of tumors
indole-3-acetic acid		Liver cancer, Melanoma, prostate cancer
Carvacrol		Breast cancer
Ascorbic acid		Acute myeloid leukemia

2.14.2. Indole-3-acetic acid

Indole-3-acetic acid (IAA) is derived from the amino acid tryptophan, which act as a plant growth hormone and has also been identified as an auxin (Table 4) [129]. IAA itself does not have any toxicity, but might cause cell death in human cancer cells after oxidative decarboxylation via horseradish peroxidase (HRP) [130,131]. It has been demonstrated that IAA induces apoptosis cell death in melanoma cells after visible and ultraviolet irradiation which introduces it as a potential PS by producing reactive oxygen species and a variety of free radicals such as superoxide anion (O2 −), hydrogen peroxide (H2O2), and hydroxyl radical (HO.) [132]. The mechanism of light activation of IAA is uncertain, as it does not appear to be a PS in the traditional sense, *i.e.* possess a high absorption coefficient in the visible spectrum. The beneficial effects of IAA compared to well-known PSs such as ALA, are that is painless, safe, possesses anti-inflammatory effects, and does not need time for metabolism [133]. Green light (520 nm) could activate IAA more efficiently than other visible wavelengths. The pilot study showed IAA-PDT using green light was painless and did not need a lengthy incubation compared to ALA-PDT [134]. IAA based PDT has shown anti-cancer activity in melanoma and liver cancer [132,135].

2.14.3. Carvacrol

Carvacrol is a monoterpenic phenol (Table 4), which is found in essential oils of aromatic plants including genera Origanum and Thymus [136]. It has been demonstrated that carvacrol has anti-inflammatory, antioxidant, and antiangiogenic properties so it could be good candidate for cancer therapy [137,138]. Although published evidence that carvacrol potentiates PDT is presently lacking, preliminary studies have shown that carvacrol can potentiate blue-light mediated killing of bacteria, which is accepted to work via photodynamic activation of endogenous porphyrins [139].

2.14.4. Ascorbic acid

Ascorbic acid also known as vitamin c found in fruits and vegetables including strawberries, kiwifruit, broccoli, Brussels sprouts, tomato, and raw bell peppers [140]. Ascorbic acid is one of the most popular antioxidants, and the studies suggest it would be quench singlet oxygen, hydrogen peroxide other ROS essential for PDT (Table 4).

However, it has also been demonstrated that ascorbate can induce novel oxidation cascades and cause an increase in the cytotoxicity of light-activated PS by producing hydrogen peroxide upon its reaction with singlet oxygen. Singlet oxygen has an extremely short-lifetime within lipid bilayer membranes (nearly 100 ns), especially when if diffuses into the aqueous space, thus it has a shorter diffusion distance compared to hydrogen peroxide. Most of the singlet oxygen, which is

generated in lipid membranes, reacts with components in the aqueous phase. Thus, it is possible to react with aqueous solutes such as ascorbate. The reaction of ascorbate with singlet oxygen in the aqueous phase leads to two contrary effects. Firstly a "pro-oxidant" effect, whereby ascorbate increases the cytotoxicity and damage of PDT action by producing hydrogen peroxide and hydroxyl radicals via initiation of oxidative cascades via heme-peroxidase enzymes in different cellular locations.

Secondly there is an antioxidant effect whereby ascorbate chemically quenches singlet oxygen in the aqueous phase. This results in protection of aqueous components from oxidation. Moreover ascorbate could inactivate the longer-lived hydroperoxides.

The balance between these opposite processes will depend on the activity of peroxide removing enzyme systems and endogenous antioxidants including ascorbate and glutathione. It is known that glutathione is key to remove hydrogen peroxide. It was hypothesized that ascorbate could enhanced the flux of hydrogen peroxide during PDT. It was shown that ascorbate could increase the production of hydrogen peroxide during PDT [141,142]. A study using a phototoxicity assay showed that ascorbate could suppress cell death in breast cancer cells (MCF-7) in aqueous media. The same study showed that pre-treatment of cells with ascorbic acid reduced cell death by PDT, while other antioxidants used in this experiments did not show similar effects [143].

2.15. Conclusions and future perspectives

As discussed in this paper, natural PSs isolated from plants and other biological sources may be considered to be a green approach to PDT in cancer therapy. Low systemic cytotoxicity to normal cells and selective action against malignant cells are one of the main advantages of natural PSs for PDT. PDT, in combination with other natural compounds, fights malignant cells by means of three main components; PSs (derived from plants), light, and oxygen. All of these components promote photochemical reactions, which lead to ROS production within the malignant cells, and consequently, cell death via the induction of apoptosis and/or necrosis. Nowadays, PDT is widely used to treat skin cancer, and recent studies have shown the advantage of related therapeutic strategies, which could help eliminate various types of cancers. The results of recent studies confirm that natural compounds may be considered promising candidates for PDT. Also, since natural compounds are usually ubiquitous, they may be more readily-accessible compared with synthetic chemotherapeutic agents. In addition, the use of natural PSs in PDT usually triggers fewer and negligible side effects (such as erythema and/or edema) than other routinely-used drugs. Many studies suggested that PDT also could be used for solid tumors via delivery strategies including passive and active targeting. These strategies increase the accumulation of PSs into the tumor microenvironment and even inside the targeted tumor cells.

We believe there may be many unknown natural agents with different phototoxicity properties. The criticism is sometimes raised that it is unlikely that evolution would have selected for the expression of very powerful PS within plants, for then they would have undergone self-destruction in the sunlight upon which all plants depend for their growth and survival. The answer to this criticism is that along with the development of the photosensitive compound itself, the plants could also evolve a self-defense mechanism to ensure that the plant cells themselves are protected against PDT destruction, while predators (such as undesirable grazing livestock *etc* would still suffer phototoxicity reactions). Henceforth, researchers may discover these photoactive plants in nature and compare the effects with more conventional PSs. Furthermore, loading of conventional PSs or natural phototoxic agents into nanostructures may help to achieve better cancer treatment via PDT.

Funding information

Michael R Hamblin was supported by USNIH grant R01AI050875.

Conflicts of interest

Dr Hamblin is on the following Scientific Advisory Boards
Transdermal Cap Inc, Cleveland, OH
Photothera Inc, Carlsbad, CA
BeWell Global Inc, Wan Chai, Hong Kong
Hologenix Inc. Santa Monica, CA
LumiThera Inc, Poulsbo, WA
Vielight, Toronto, Canada
Bright Photomedicine, Sao Paulo, Brazil
Quantum Dynamics LLC, Cambridge, MA
Global Photon Inc, Bee Cave, TX
Medical Coherence, Boston MA
NeuroThera, Newark DE
JOOVV Inc, Minneapolis-St. Paul MN
AIRx Medical, Pleasanton CA
FIR Industries, Inc. Ramsey, NJ
UVLRx Therapeutics, Oldsmar, FL
Ultralux UV Inc, Lansing MI
Illumiheal & Petthera, Shoreline, WA
MB Lasertherapy, Houston, TX
Dr Hamblin has been a consultant for
Lexington Int, Boca Raton, FL
USHIO Corp, Japan
Merck KGaA, Darmstadt, Germany
Philips Electronics Nederland B.V.
Johnson & Johnson Inc, Philadelphia, PA
Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany
Dr Hamblin is a stockholder in
Global Photon Inc, Bee Cave, TX
Mitonix, Newark, DE.

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