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Research Progress of Natural Product Photosensitizers in Photodynamic Therapy

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ABSTRACT

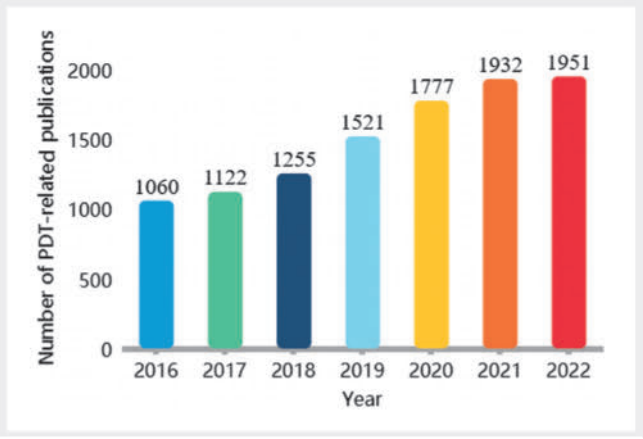
Photodynamic therapy is a noninvasive cancer treatment that utilizes photosensitizers to generate reactive oxygen species upon light exposure, leading to tumor cell apoptosis. Although photosensitizers have shown efficacy in clinical practice, they are associated with certain disadvantages, such as a certain degree of toxicity and limited availability. Recent studies have shown that natural product photosensitizers offer promising options due to their low toxicity and potential therapeutic effects. In this review, we provide a summary and evaluation of the current clinical photosensitizers that are commonly used and delve into the anticancer potential of natural product photosensitizers like psoralens, quinonoids, chlorophyll derivatives, curcumin, chrysophanol, doxorubicin, tetracyclines, Leguminosae extracts, and *Lonicera japonica* extract. The emphasis is on their phototoxicity, pharmacological benefits, and effectiveness against different types of diseases. Novel and more effective natural product photosensitizers for future clinical application are yet to be explored in further research. In conclusion, natural product photosensitizers have potential in photodynamic therapy and represent a promising area of research for cancer treatment.

Introduction

Photodynamic therapy (PDT), as a novel model for treating tumors, was initially applied in the treatment of skin diseases [1]. In 1975, Kelly et al. [2] demonstrated the efficacy of PDT in treating superficial transitional cell carcinoma of the bladder, following which its application has expanded from skin diseases to tumors. At present, PDT has been approved by the FDA as a curative or palliative treatment for a variety of solid tumors [3], such as glioblastoma [4–6], oral cancer [7–9], breast cancer [10, 11], pancreatic cancer [12, 13], and prolonging the survival of inoperable cancer patients and significantly improving their quality of life [14]. In addition, PDT can also effectively treat vascular lesions and microbial infections [15].

To achieve tumor treatment, PDT employs light source of specific wavelengths to activate photosensitizers at the tumor site, where highly toxic reactive oxygen species (ROS) are produced to effectively kill the surrounding tumor cells, resulting in tumor treatment [16]. The mechanisms behind PDT-mediated tumor damage are primarily categorized into three types:

# Xiaoxia Zhou and Xufang Ying contributed equally to this work.



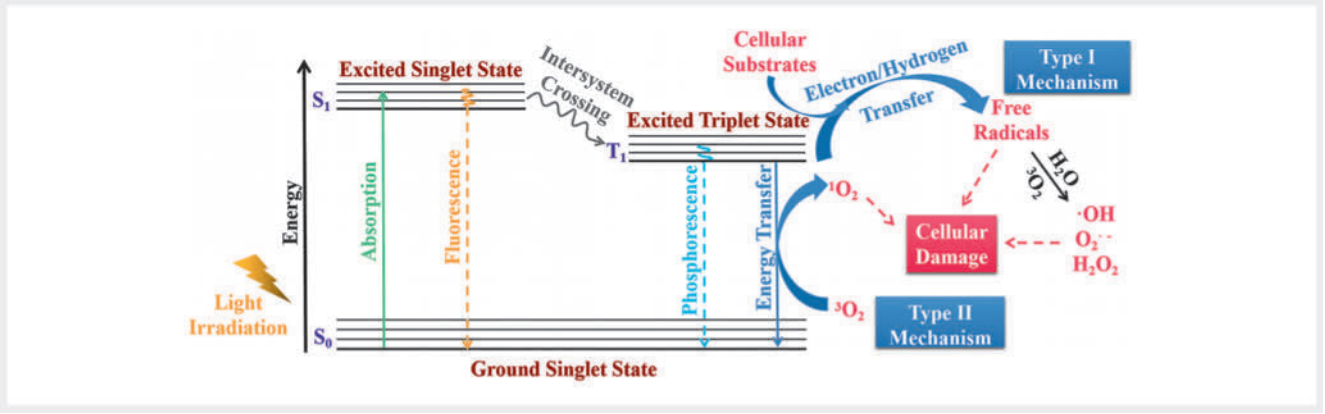
▶ **Fig. 1** PDT-related publications.

1. During PDT, a photodynamic reaction occurs, which directly induces apoptosis and necrosis of tumor cells through the production of ROS, particularly singlet oxygen. Additionally, the mass production of ROS will upregulate autophagy, causing autophagic cell death [17].
2. PDT leads to the destruction of the vascular system associated with the tumor, ultimately resulting in tumor infarction [18, 19].
3. Numerous proinflammatory factors are released after the apoptosis or necrosis of tumor cells, inducing early inflammatory responses and activating the immune system [20].

Although traditional cancer treatments like surgical resection, chemotherapy, and radiotherapy are beneficial, they still have some drawbacks. For example, surgical resection causes big surgical trauma. Cancers treated with chemotherapy can develop resistance. Radiotherapy has significant side effects, lacks specificity, and is prone to produce systemic toxicity. In comparison, PDT has a host of advantages over the aforementioned treatments, including less trauma, lower toxicity, higher tissue targeting, a wider range of applications, reproducible treatment, and lower long-term morbidity [21, 22]. Moreover, PDT can improve therapeutic effects when combined with traditional treatments. The development of PDT has been an active area of research, with many advances being made in the field. Since 2016, the number of academic papers related to PDT in the Web of Science database has been consistently increasing every year (▶ **Fig. 1**). However, the growth of the field has not been without its challenges. In recent years, some companies have failed, and clinical trials have been unsuccessful, leading to stagnation in the field. While the number of research papers and publications in the field has increased, much of this growth is due to the development of nanotechnology with no clinical applications. Despite these challenges, researchers continue to explore new approaches and technologies to advance the field of PDT and improve its effectiveness as a treatment option. One approach that has shown promise is the search for new photosensitizing agents.

The occurrence of photodynamic reactions requires three basic elements: photosensitizers (**PSs**), appropriate illumination, and tissue oxygen [23, 24]. Initially, the photosensitizer is enriched at the tumor site and mainly concentrated in the organelle, then irradiated with a laser.

Upon absorbing energy, the photosensitizer transitions from the ground singlet state (S_0) to the transient excited singlet state (S_1), which then converts into a long-lasting excited triplet state (T_1) [16, 25]. Photodynamic reactions can be classified into two types: the type I mechanism and the type II mechanism (▶ **Fig. 2**). During photodynamic reactions, hydrogen atom (electron) transfer takes place between the photosensitizer in the excited triplet state and the biological macromolecule or substrate, leading to the creation of free radicals (e.g., superoxide anions, hydroxyl radicals, etc.) [26, 27], which damage the target cell. This reaction is known as the type I mechanism. The type II mechanism involves the photosensitizer in its long-lived excited triplet state directly transferring energy to the oxygen molecule in its triplet ground state. This produces singlet oxygen ($^1O_2$), which further interacts with lipids, proteins, and nucleic acids, ultimately resulting in cell necrosis or apoptosis [25, 28]. The two mechanisms occur simultaneously, with the balance between them being deter-



▶ **Fig. 2** Mechanism of photodynamic reactions.

▶ **Table 1** Photosensitizers approved for clinical use worldwide.

Generation	Photosensitizer	Absorption range	Status	Indication	Refs.
First	Photofrin	~ 630 nm	Approved in Canada (1993), Japan (1994), USA (1996), Russia (1997), Germany (1997)	Lung cancer, esophageal cancer, gastric cancer, cervical cancer, etc.	[35–37]
	Photogem				[38]
	Photosan				[39]
	HiPorfin	~ 630 nm	Approved in China (1998)	Detect and treat superficial cancer of oral cavity, bladder, bronchus, lung, digestive system and precancerous lesion of vitiligo, port wine stains	[40–42]
	Hemoporfin	480–580 nm	Approved in China (2003)	Port wine stains	[43]
Second	Levulan	410–635 nm	Approved in USA (1999)	Actinic keratosis, malignant glioma, bladder cancer, Barrett's esophagus, vulvar lichen sclerosus	[44–48]
	Metvix/ Metvixa	~ 635 nm	Approved in EU (2001), New Zealand (2002), Australia (2003), USA (2004)	Actinic keratosis, nodular basal cell carcinoma, squamous cell carcinoma in situ, Bowen's disease	[49–51]
	Hexvix/ Cysview	380–450 nm	Approved in EU (2001), Sweden (2004), USA (2010)	Detection of bladder cancer	[52]
	Visudyne	~ 689 nm	Approved in USA (2000)	Subfoveal choroidal neovascularization caused by age-related macular degeneration, central serous chorioretinopathy, choroidal hemangioma, gastric cancer	[53–56]
	Foscan	652 nm 514 nm	Approved in EU (2001)	Palliative treatment of patients with advanced head and neck cancer, mesothelioma	[57, 58]
	Photolon/ Fotolon	670 nm 663 nm	Approved in Russia (2002)	Cervical intraepithelial neoplasia, diagnosis and treatment for cutaneous malignant tumor	[59]
	Laserphyrin	~ 664 nm	Approved in Japan (2004)	Early-stage endobronchial cancer, prostate cancer, bile duct carcinoma, diagnosis and therapy of malignant glioma, advanced-aged patients suffering from inoperable gastric cancer, oral squamous cell carcinoma, biliary cancer	[60–64]
	Photosense	~ 675 nm	Approved in Russia (2001)	Breast cancer, eye diseases, skin cancer, head and neck tumors	[65–68]
	ICG	795–845 nm	Approved in USA	Occult subfoveal choroidal neovascularization caused by age-related macular degeneration, melanomas, periodontal therapy	[69–71]
	Methylene blue	600–665 nm	Approved in Canada	Basal cell carcinoma, Kaposi's sarcoma, melanoma, virus, fungal infections	[72]

mined by factors such as the type of photosensitizer used, the concentration of substrate and oxygen, and the degree of photosensitizer binding to the substrate. The most important single factor is the redox potential of the photosensitizer.

Selecting an appropriate photosensitizer is essential for the success of PDT. The intrinsic properties of the chosen photosensitizer determine its therapeutic efficacy, as it can absorb light of specific wavelengths and trigger photochemical or photophysical reactions [29, 30]. An ideal photosensitizer should be a single well-characterized compound, with a known and constant composition. It ought to effectively generate ROS, selectively accumulate in target tissues, be harmless in the absence of radiation, and be easily eliminated from the body [31–34]. According to literature reports, over ten types of photosensitizers have been approved for clinical use worldwide (▶ **Table 1**).

PDT was initially proposed by the German scholar Raab in 1900. In the 1960 s, the first-generation photosensitizers hematoporphyrin derivative (HpD) [73] emerged, ushering in the advance

▶ **Table 2** Natural products with photosensitive activity.

Component	Absorption range	Clinical application	Cell lines/animals
Psoralen (PSO)	~320–360 nm	Tumor	Siso tumor line, MCE-1 cell line
Hypericin	~600 nm	Tumor, virus	MCF-7 cell line, colon cancer cells, leukemia cells
Hypocrellin	/	Tumor, virus	Human brain tumor cells, A375-S2 cell line
Chlorophyll derivatives	/	Tumor, acne and other diseases related to sebaceous glands	Mouse S180 transplanted sarcoma, human osteosarcoma, golden hamsters
Curcumin	445 nm	Tumor, bacteria, fungi	MCF-7 cell line, H8 cells, gastric adenocarcinoma cells, cervical cancer cells, liver cancer cells
Chrysophanol	> 430 nm	Microvascular diseases	/
Leguminosae extract	504 nm	Tumor	Ehrlich ascites cancer cells (EAC)
Honeysuckle stem extract	468 nm	Tumor	Ehrlich ascites cancer cells (EAC), S180 solid tumors

of PDT. At that time, the component of HpD was not fixed, and the proportion of active ingredients was small. In 1972, Diamond and his team [75] purified HpD and obtained the product Photofrin I. In 1983, Dougherty et al. [75] isolated eight components of HPD using reverse-phase HPLC and gel filtration chromatography and identified their biological activity. Photofrin II was created during this process. In 1993, Photofrin was approved for clinical use, mainly for the treatment of esophageal cancer, lung cancer, minimally invasive bronchial cancer, stomach and bladder cancer, cervical dysplasia, and other conditions. To date, it remains the most widely used photosensitizer in clinical practice. Subsequently, Photogem, Photosan, and HiPorfin, which are similar to Photofrin, were launched in different countries. However, due to the shortcomings of the first-generation photosensitizers such as poor stability, shallow penetration depth, and prolonged residence time *in vivo*, their clinical application was limited [76].

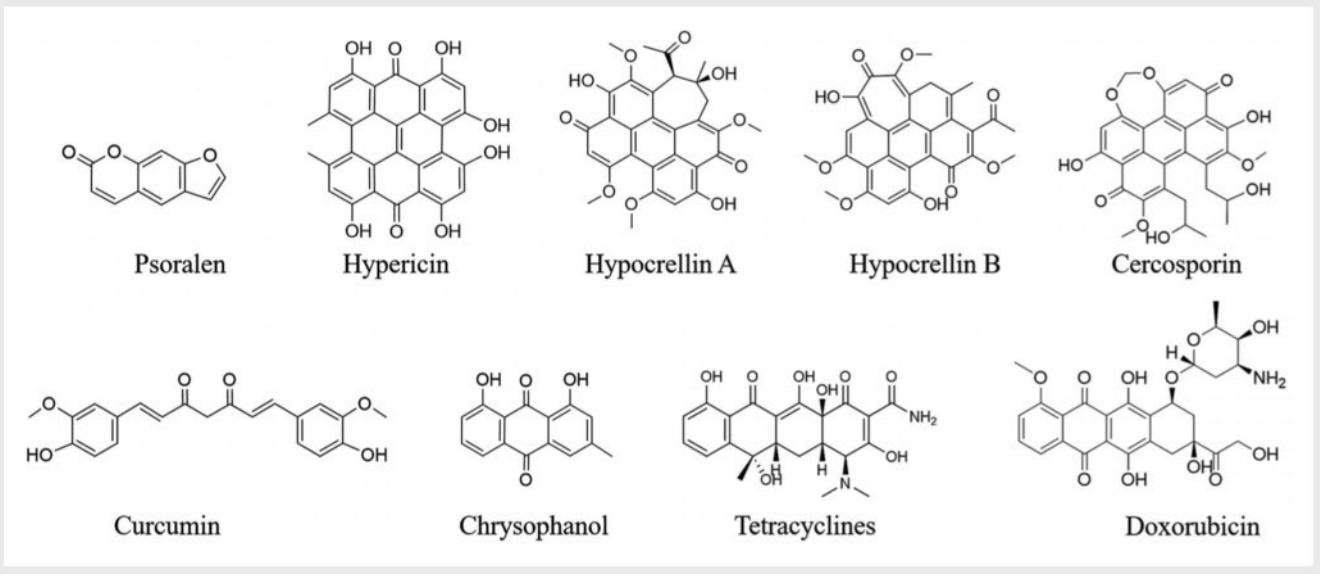
Most of the second-generation photosensitizers are derived from tetrapyrrole structures, mainly including porphyrin derivatives, metallophthalocyanines and polycycloquinones, such as 5-aminolevulinic acid (5-ALA; Levulan), methyl aminolevulinate (MAL; Metvix), hexaminolevulinate (HAL; Hexvix/Cysview), and verteporfin (Visudyne). These are currently available on the market. Notably, 5-ALA and its analogs' therapeutic efficacy is attributed to the metabolic conversion to protoporphyrin, which serves as the active photosensitizer in the treatment process. In addition, chlorin photosensitizers like temoporfin (Foscan) and talaporfin (Laserphyrin) are also available. Chlorin e6 (Fotolon) is a representative second-generation porphyrin photosensitizer approved by the FDA [77]. It has been widely used in PDT [78, 79], with initial applications focused on the treatment of skin and mucous membranes, while researchers are currently exploring its effectiveness in the treatment of breast cancer [80]. Photosense is a phthalocyanine photosensitizer approved in Russia in 2001 for the treatment of breast, eye, and skin cancer. There are also specific photosensitizers available, such as the FDA-approved near-infrared fluorescent dye indocyanine green (ICG), for diagnostic cardiology, hepatology, ophthalmology, and fluorescence-guided cancer surgery, as well as for the treatment of melanoma and periodontal diseases. Derived from phenothiazine, methylene blue functions as a photosensitizer with clinical applications in various fields, including basal cell carcinoma, Kaposi's sarcoma, melanoma, viral infections, fungal infections, and others. The second-generation photosensitizers are considered safer and more stable than their first-generation counterparts. Their absorption in the higher wavelength area (compared with first-generation photosensitizers) allows them to be reached by deeper penetrating light, resulting in deeper penetration and increased singlet oxygen production [81]. However, their poor water solubility poses significant limitations for intravenous administration.

Chemical modification of third-generation photosensitizers through combination with different factors or groups improves their targeting, water solubility, aggregation, and utilization, while reducing accidental injury to normal skin [29, 82]. Although most third-generation photosensitizers are in the clinical research stage, they are not yet available on the market.

In general, photosensitizers used in clinical practice are often complex and susceptible to biological metabolism. Apart from that, the degree of photosensitization damage is difficult to control, limiting their clinical application to varying degrees. However, partial natural product photosensitizers possess higher clinical translational potential [83, 84], specific biological activities, and selectivity [85, 86], making them a viable option for PDT. Owing to the abundance of natural resources in the Nature Kingdom, some of which are light sensitive, there is an increasing interest in developing new and efficient photosensitizers from natural product extracts. Researchers worldwide have explored the light-sensitive substances in natural products for PDT. The research progress of natural product photosensitizers in PDT is summarized in ▶ **Table 2**. The chemical structures of partial natural product sensitizers are illustrated in ▶ **Fig. 3**.

Psoralen

Psoralen (PSO), an early clinical application of photosensitizing natural products, is widely distributed in the plant kingdom. It can be sourced from Fraxini Cortex, Fructus Psoraleae, Radix An-



▶ **Fig. 3** Chemical structures of partial natural product photosensitizers.

gelicae Dahuricae, Radix Angelicae Pubescentis, Radix Peucedani, and Fructus Cnidii. PSO can be excited by light with a wavelength of 320–360 nm. The absorption of the wavelength of PSO is below 600 nm, which is considered a disadvantage as a photosensitizer. Pharmacological studies have shown that it can improve osteogenetic ability, inhibit cancer cell migration and metastasis, reduce inflammation, improve atherosclerosis in rats, and protect the heart. At present, PSO-mediated PDT is primarily used in the field of oncology. To investigate the potential for growth inhibition of Siso tumor strains *in vitro* and *in vivo*, Zhao et al. [87] compared the photosensitization of PSO using different radiation sources. Their findings revealed that while single radiation or in *vitro* treatment alone proved insufficient in killing tumor cells, the combination of PSO and cobalt 60 irradiation resulted in a significant radiosensitizing enhancement effect. Overall, the study highlights the promising potential of PDT for the treatment of cancer, particularly when used in combination with traditional treatments. PSO has been employed by scholars to enhance its antitumor effect through its photosensitivity properties [88–90]. Yan et al. [91] proposed that PSO can markedly reduce the rate of lung metastasis in nude mice with a human mucoepidermoid carcinoma cell line (MCE-1 cell line). This is achieved by damaging DNA under the activation of the light source and affecting the expression of lipids and proteins, leading to antitumor effects.

Quinonoids

Quinonoids include benzoquinone, anthraquinone, and perylenequinones. Almost all quinonoids are photosensitive, and many of them have antitumor effects. Therefore, current research on quinonoids are chiefly focused on their potential in the field of oncology. Quinonoids that undergo photodynamic reactions are widely distributed in various plants, including hypecorine, fagomine, and cercosporin.

Hypericin

Hypericin (Hyp), a natural photosensitizer isolated from *hypericum* species, is a polycyclic anthraquinone compound that is easily taken up by tumor cells. It possesses strong photosensitivity properties, low dark toxicity, and high singlet oxygen quantum yields. As a result, it is an effective agent for PDT and can be used to treat a variety of solid tumors [92–96]. Chen et al. [97] showed that human breast cancer cells (MCF-7) induced by Hyp-PDT (PDT mediated by Hyp) were more sensitive to killer cells (CIK), indicating a positive correlation between Hyp concentration and the effectiveness of CIK. Hu et al. [98] observed that Hyp was capable of inducing S-phase cell cycle arrest and apoptosis, thereby inhibiting the proliferation of colon cancer cells. Zhang et al. [99] proved the effectiveness of Hpy-mediated PDT in inhibiting the proliferation of various leukemia cells and achieving anticancer effects. Chen et al. [100] found that Hpy can inhibit apoptosis caused by infectious bronchial virus (IBV) in chickens. Current research indicates that Hyp can perform photochemical reactions under specific light conditions, and that the ability to kill viruses and tumor cells is more pronounced under these conditions than in the absence of light. These findings suggest that Hpy possesses photochemical reaction characteristics and demonstrates potential for PDT [101, 102].

Hypocrellin

Hypocrellin, a secondary metabolite found in a few bamboo parasitic fungi, such as *Hypocrella bambusea* and *Shiraia bambusicola* of Hypocreaceae, belongs to the perylenequinones derivative. Its main source is through the intramycelial secondary metabolic synthesis pathway. As a perylenequinones compound, the structure of hypocrellin endows it with certain photodynamic activity and exhibits a promising phototherapeutic effect. It was first isolated from the fleshy fruiting body of the medicinal fungus *H. bambusae* in 1980 by Wan et al. [103] and was named after its place of origin. In 1991, Kishi et al. [104] isolated hypocrellin from

S. bambusicola, another medicinal fungus. Further research has revealed that hypocrellin also has effects such as good photosensitivity to kill tumor cells and inhibition of HIV-1 [105], making it a promising therapeutic option. Compared with the antitumor drug hematoporphyrin derivative, hypocrellin offers certain advantages. It is easily purified, has a high quantum yield of photochemical reactions, and can be eliminated from normal tissues quickly [106]. Hypocrellin A (HA) and hypocrellin B (HB) can promote human brain tumor cell death by producing factors that can inhibit angiogenesis through photodynamic action [107]. The chemical structure of HA may play a key role in inducing apoptosis. HA has been found to produce hydroxyl radicals, which can damage the DNA of tumor cells and induce apoptosis under light conditions. Additionally, HA has been shown to induce apoptosis in human melanoma cells (A375-S2) under light-free conditions and increase expression of Cylin B1 mRNA and stall the cell cycle in the S-phase [108, 109]. However, as a fat-soluble substance, hypocrellin has low water solubility and no specific tissue distribution, which limits its application in PDT. To address this, physical embedding or chemical modification techniques such as embedding with liposomes or cyclodextrin can be used to enhance its water solubility [110]. The photodamage mechanism of hypocrellin involves not only free radicals and singlet oxygen, but also semiquinone radical anion and semiquinone radical cations, which are produced by self-exchange electron transfer of HA and HB under light conditions. In short, hypocrellin causes cell death or apoptosis through a comprehensive multisite, and multi-mechanism photosensitive damage.

Cercosporin

Cercosporin is a well-known fungal metabolite recognized for its role in inducing light-activated plant damage through singlet oxygen generation. Mastrangelopoulou et al. [111] examined the photocytotoxicity of cercosporin in human cell lines, including two glioblastoma multiforme lines (T98G and U87) and one breast adenocarcinoma line (MCF7). Upon excitation at 532 nm, cercosporin exhibited remarkable efficiency in producing singlet oxygen. Although cell loading of cercosporin was comparable between MCF7 and U87 cell lines, it was notably elevated by approximately threefold in T98G cells. Cercosporin consistently exhibited subcellular localization within both mitochondria and the endoplasmic reticulum across all cases. Upon irradiation with light around 450 nm, T98G cells displayed heightened susceptibility to cercosporin-mediated PDT, primarily attributed to their elevated uptake of cercosporin. Metabolic analyses conducted prior to and 1 hour after cercosporin-mediated PDT revealed that such treatment led to a pronounced bioenergetic collapse affecting both respiratory and glycolytic activities across all tested cell lines. Cercosporin acts as a potent photosensitizer, ideally suited for superficial PDT due to its short activation wavelength. This makes it especially effective when avoiding perforations is a priority.

Chlorophyll Derivatives

Chlorophyll derivatives (CPDs) are a new type of photosensitizer recently extracted from natural product silkworm excrement. Apart from those containing magnesium, many derivatives have been artificially synthesized. The term “derivatives” primarily refers to the replacement of the core magnesium atom of chlorophyll with metal ions, including palladium, zinc, copper, nickel, cobalt, iron, and others. This process generates derivatives that are resistant to both light and heat, but which also lose their fluorescence. This synthetic approach significantly broadens the applicability of CPD. Liu et al. [112] conducted a prospective study on the prevention of recurrence of invasive bladder cancer in 32 patients with chlorophyll derivative-PDT (CPD4-PDT) after surgery, and the results demonstrated that compared with the traditionally used HpDs, CPD4 exhibits similar clinical efficacy but with reduced phototoxic side effects. Notably, the time patients need to spend in darkness after CPD4-PDT is shorter, contributing to a more favorable post-treatment experience. Moreover, the photoinactivation effect of human cancer cells *in vitro* and the photodynamic efficacy of animal transplanted tumors were significantly higher than HPpDs. Cao et al. [113] proposed that CPD4-induced PDT has a direct killing effect on endothelial cells (ECs) and has the characteristics of irreversibility and dose dependence. According to Zhang et al. [114], PDT was found to have an inhibitory effect on mouse S_{180} transplanted sarcoma. This research provided experimental evidence for the development of new drugs for the treatment of malignant tumors. CPD, represented by methyl pyropheophorbide-*α* (Mppα), is a chlorin compound with high photosensitivity. It is made of chlorophyll extracted from natural product silkworm excrement and undergoes reprocessing for use in PDT. MPPα-PDT is a common treatment for tumors in clinical practice, including ovarian cancer, nasopharyngeal cancer, and breast cancer, which can induce apoptosis, autophagy, inhibit the growth and reproduction of tumor cells, and is usually associated with endoplasmic reticulum stress pathways. At the same time, studies have indicated that the sensitivity of human osteosarcoma (HOS) cells to MPPα- PDT can be enhanced, and the clinical treatment effect can be improved greatly by silencing the expression of X-box binding protein 1 (XBP1) or blocking the protein kinase RNA-like endoplasmic reticulum kinase (PERK) signaling pathway [115, 116]. In addition to tumors, as evidenced by Wang [117], MPPα-PDT was found to significantly reduce the number, volume, and thickness of sebaceous glands in golden hamsters, providing a basis for the potential use of MPPα-PDT in the treatment of acne and other diseases related to sebaceous glands.

Curcumin

Curcuma longa L. is the rhizome of a perennial herb of Zingiberaceae, a natural product that activates blood circulation and resolves stasis, removes masses and alleviates pain, and clears and reduces stagnant heat. Curcumin is a diketone component extracted from the rhizomes of certain plants, such as those in the Zingiberaceae and Araceae families. *C. longa* L. contains about 3 ~ 6% curcumin, which is a rare pigment with a diketone structure in the plant world and is often used as a seasoning and food dye in daily life. Zeng [118] proved that curcumin has a significant inhibitory effect on human breast cancer MCF-7 cells when exposed to light. This effect increases with higher concentration of curcumin.

In a cell experiment conducted by Mou et al. [119], curcumin was found to have a cytotoxic effect on H8 cells when activated by an excitation wavelength of 445 nm. The study also found that the killing effect of PDT on tumor cells was proportional to the concentration of the drug. Curcumin-mediated PDT has been shown to effectively inhibit and kill gastric adenocarcinoma, cervical cancer, liver cancer, and other tumor cells. In addition, this therapy has a strong antibacterial effect and can inactivate a variety of bacteria and fungi, including *Pseudomonas fluorescens* and *Candida albicans*. Curcumin can be used not only as a photosensitizer but also as a sonosensitizer for sonodynamic therapy. Studies have shown that curcumin is more effective in inducing apoptosis under light conditions (photosensitized curcumin) than under no light conditions (non-photosensitized curcumin) [120]. This suggests that curcumin possesses photochemical reaction properties, making it an efficient and low-toxic photosensitizer for inducing apoptosis.

However, there are studies that suggest certain drawbacks associated with curcumin. These include its poor pharmacokinetic/pharmacodynamic (PK/PD) properties, limited efficacy in various disease models, and potential toxic effects observed under specific testing conditions [121]. Consequently, when evaluating the therapeutic effectiveness of curcumin, a comprehensive analysis of its limitations becomes essential.

Chrysophanol

Chrysophanol, a natural anthraquinone with a wide range of biological therapeutic potential, is the main active ingredient of the natural products *Rheum palmatum* L., *Polygonum multiflorum* Thunb. and *Polygonum cuspidatum* Sieb. et Zucc. Rao et al. [122]. investigated the photosensitization activity of chrysophanol, which was isolated and purified from *R. palmatum* L. by electron spin resonance. As discovered in the study, when chrysophanol was irradiated with visible light with a wavelength greater than 430 nm, a semiquinone radical anion could be produced. Furthermore, the addition of dihydrocoenzyme to enhance light can assist chrysophanol in producing singlet oxygen and hydroxyl radicals, suggesting that the photosensitization mechanism of chrysophanol involves both the type I mechanism of electron transfer and type II mechanism of energy transfer. Based on its observed effects, chrysophanol has the potential to be developed as a promising photodynamic agent for the treatment of microvascular diseases.

Antibiotics

Tetracyclines

Tetracyclines are widely recognized as established antibiotics but can exhibit phototoxicity as a side effect. Antimicrobial photodynamic inactivation employs harmless light in combination with nontoxic dyes to eliminate microbial cells by generating ROS. Tetracyclines have the capability to function as light-activated antibiotics by binding to bacterial cells and inducing cell death exclusively upon illumination. Bacteria are killed by photoactivation of tetracyclines in the absence of oxygen [123].

Doxorubicin

Doxorubicin is in the anthracycline and antitumor antibiotic family of medications. It works in part by interfering with the function of DNA. Researchers exploited the intrinsic photosensitizing properties of doxorubicin to enhance its anticancer activity in leukemia, breast, and epidermoid carcinoma cells, upon irradiation. Light can selectively induce the localized formation of ROS, following photophysical pathways. Upon irradiation, doxorubicin exhibited a concentration-dependent capability to produce peroxides and singlet oxygen. The underlying mechanisms leading to the increase in its cytotoxic activity were intracellular ROS generation and the induction of necrotic cell death. The nuclear localization of doxorubicin represents an added value for its use as a photosensitizer. Employing doxorubicin in photodynamic cancer therapy (PCT), where it functions concurrently as both a chemotherapeutic agent and a photosensitizer, may allow (i) an augmentation of the drug's anticancer effects, and (ii) a reduction in its dosage, consequently mitigating dose-related adverse effects [124].

Other Natural Product Extracts

Leguminosae extract

In a study conducted by Chen et al. [125], the photosensitization properties of an extract from the natural product Leguminosae were analyzed. The results demonstrated that the extract exhibited a significant excitation peak at 504 nm, which is a crucial factor for the occurrence of photosensitization. Experiments have proved that this extract has a significant photodynamic inactivation effect on Ehrlich ascites cancer (EAC) cells. It is capable of mediating light energy to effectively kill tumor cells, indicating its potent photosensitizing activity. Therefore, natural product Leguminosae can be considered an effective natural photosensitizer. There is a dose-effect relationship between Leguminosae extract and the photodynamic inactivation of EAC cells. As the concentration of Leguminosae extract increases, more molecules are excited by photons and undergo photochemical reactions. This leads to increased production of singlet oxygen or free radicals, resulting in a stronger killing effect on EAC cells. While Leguminosae extract itself does exhibit a direct killing effect on EAC cells, this effect is significantly less potent compared to the cell death induced by photodynamic effects.

Lonicera japonica extract

To observe the photosensitization of two extracts of *Lonicera japonica*, 85 221A60 and 85 221A95, Yao and Wu [126] conducted experiments on EAC cells *in vitro* and photodynamic studies on S_{180} solid tumors *in vivo* using a xenon high-pressure lamp as the excitation light source and mouse transplanted tumors as an animal model. Extract 85 221A95 has a significant photodynamic therapeutic effect on Kunming mice with S_{180} solid tumors and shows a significant photosensitization effect on EAC cells, particularly at a concentration of 500 mg/mL. At this concentration, the mortality rate of EAC cells was over 97 %. Extract 85 221A60 has a unique excitation peak at 468 nm and has been shown to have photosensitizing activity *in vitro*. While it also exhibits a direct killing effect on EAC cells, this effect is significantly lower compared

to the mortality rate caused by the photodynamic effects of 85 221A60 on EAC cells. In conclusion, it can be stated that *L. japonica* contains photosensitizers with promising applications.

Other natural products

Liao et al. [127] conducted a study to analyze the fluorescence properties of thirteen natural product extracts, including Cortex Phellodendri Chinensis, Radix Sophorae Flavescentis, Radix Scutellariae, Rhizoma Coptidis, Cortex Fraxini, Fructus Psoraleae, Radix Arnebiae, Radix Peucedani, Radix Angelicae Dahuricae, Herba Lycopi, Rhizoma et Radix Notopterygii, Radix Angelicae Pubescentis, and Radix Sophorae Tonkinensis. The fluorescence excitation and emission wavelengths were measured as well as the cellular fluorescence intensity after being taken up by 823 human gastric cancer cells. Additionally, the distribution and affinity sites of the fluorescent substances were studied using fixed and live-cell staining techniques. The effect of pH on the fluorescence intensity of the cells stained by extracts was also measured. Based on this, further experiments were selectively carried out to test the photosensitive anticancer of 13 natural products. The results showed that the chromosomes of 13 natural products exhibited strong fluorescence due to the presence of fluorescent substances that were partially absorbed by living cells, to a certain extent. However, it should be noted that the fluorescence intensity of approximately half of the extracted sample was affected by pH during uptake and distribution in living cells. This information provided valuable insights into the optimal storage conditions and administration routes for the corresponding natural product. Among the 13 natural products previously mentioned, only Radix Scutellariae, Cortex Fraxini, and Herba Lycopi did not exhibit detectable excitation and emission wavelengths of fluorescence. Several fluorescence detection indicators consistently showed that Cortex Phellodendri Chinensis and Rhizoma Coptidis had strong fluorescence, good cell uptake, and a wide distribution of fluorescent substances. The indicators also revealed that these substances were minimally affected by changes in the pH value and had obvious retention sites within cells. As such, these findings suggested that these substances may have the most significant photosensitivity effect, followed by Radix Arnebiae and Radix Sophorae Flavescentis. The authors concluded that there is potential for further research and attention on natural products such as Rhizoma Coptidis, Cortex Phellodendri Chinensis, Radix Sophorae Flavescentis, Fructus Psoraleae, Radix Arnebiae, and Rhizoma et Radix Notopterygii. These natural products may serve as sources for new photosensitizers with low toxicity and high efficacy.

Scotti et al. [128] screened ten medicinal plants from the Chinese Pharmacopoeia for compounds with known or potential photosensitizing activity, and conducted a detailed evaluation of their chemical composition, pharmacological activity, toxicity, and safety. These ten medicinal plants are Bistortae Rhizoma, Conyzae Herba, Echinopsis Radix, Knoxiae Radix, Polygalae Japonicae Herba, Polygoni Perfoliati Herba, Saururi Herba, Semiaquilegiae Radix, and Trachelospermi Caulis et Folium. These plants contain compounds with antibacterial, anti-inflammatory, wound healing, and photosensitizing activities, such as flavonoids, anthraquinones, and indole alkaloids. Further research and assessment are needed to explore the photosensitizing activity and PDT potential of these compounds.

Research reveals the crucial role of octyl gallate (OG) in PDT. It collaborates with blue light, swiftly eliminating *Vibrio parahaemolyticus* in both planktonic and biofilm states. Combining with ascorbic acid (AA) significantly enhances its effectiveness, while potassium iodide (KI) boosts efficient sterilization in water. This provides novel strategies for microbial safety and environmental-friendly approaches in the food industry and drinking water treatment [129–131].

It is worth noting that highly active singlet oxygen is produced within photosynthetic organisms when they absorb more light energy than is required for photosynthesis. This can result in photo-oxidative stress. The singlet oxygen can be quenched by β-carotene and α-tocopherol or react with the D1 protein of photosystem II as a target. If not completely quenched, it can specifically trigger the upregulation of gene expression involved in the molecular defense response of plants to photo-oxidative stress [132]. This implies that evolution has ensured that plants reliant on sunlight for growth do not possess highly active photosensitizers, as they would destroy themselves. Chlorophyll is a good example because there are complex systems designed to protect plants against any singlet oxygen generated as a by-product of photosynthesis.

Conclusion

To sum up, natural product photosensitizers have shown great potential in the field of PDT. Natural product photosensitizers that are currently available can be classified into several categories, including PSO, quinonoids, CPDs, curcumin, chrysophanol, Leguminosae extracts, and *L. japonica* extract. The depth of action of photosensitizers is directly related to their absorption wavelength, with longer wavelengths allowing for deeper penetration. In this paper, the depth of action of natural photosensitizers is listed in the following order: PSO, curcumin, Hpy, and hypocrellin. Depending on the nature of the lesion, various photosensitizers may be selected for PDT. Although using natural products as photosensitizers has not yet demonstrated significant advantages in terms of absorption wavelength and safety, some photosensitizers derived from natural sources show higher clinical translational potential due to the diversity and complexity of their molecular structures [83, 84]. Moreover, the specific biological activities and selectivity exhibited by natural products give them more prominent photosensitive characteristics compared to traditional photosensitizers [85, 86]. This is likely to offer valuable insights and serve as a reference for the future development of novel photosensitizers. The main disadvantage of natural product photosensitizers is their short absorption wavelengths. To address those issues, chemical modification can be employed to increase their absorption wavelengths and enhance PDT efficacy. The inherent targeting capability of photosensitizers is limited. Therefore, various strategies have been explored to achieve targeting in PDT. One approach involves conjugating the photosensitizer with targeting molecules such as antibodies, peptides, or ligands that can recognize and bind to specific receptors or biomarkers overexpressed on the surface of target cells. Furthermore, nanotech-

nology has played a significant role in enhancing the targeting effect of photosensitizers. Nano-sized carriers, such as liposomes, nanoparticles, and micelles, can encapsulate photosensitizers and provide controlled release and improved cellular uptake. These carriers can also be functionalized with targeting ligands to achieve active targeting to specific cells or tissues [133, 134]. Beyond the natural product photosensitizers discussed in this article, there are numerous others that remain unexplored. The discovery of novel and more effective natural product photosensitizers is an essential objective for future research. Further investigation and development of natural product photosensitizers may lead to significant progress and breakthroughs in the field of PDT.

Contributors' Statement

Conception and design of the work: X. Zhou, M. Han; Data collection and analysis and interpretation of the data: X. Zhou, X. Ying, L. Wu, L. Liu, Y. Wang, Y. He; Drafting the manuscript: X. Zhou, X. Ying; Critical revision of the manuscript: X. Zhou, X. Ying, L. Wu, M. Han.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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