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Light-activated green drugs: How we can use them in photodynamic therapy and mass-produce them with biotechnological tools

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ABSTRACT

Photodynamic therapy (PDT) is a promising therapeutic approach to manage the resolution of cancer. Plants in nature are one of the potential sources for obtaining new photosensitizers (PSs) that are less toxic than synthetic compounds. Although several works have been done regarding PDT in the last decades, relatively minor attention has been paid to the study of extracts of medicinal plants called photoactivatable "green drugs". The objective of the review was to identify common photoactive groups of PSs found in nature, mainly obtained from plants, analyzing their photochemical characteristics, and making a detailed botanical description of the plant groups from which they are obtained. In addition, biotechnological strategies in the cultivation of plant-based *in vitro* systems to produce natural PSs on a large scale are discussed. To accomplish it, the retrieval of potentially relevant studies was done by systematically searching scientific databases like Google Scholar and PubMed between the months of June–December of the year 2020. The main keywords used as search terms were related to plant-based photosensitizers, naturally occurring photosensitizers, phototoxins, plant cell cultures, hairy root cultures. Plant-based photoactivable compounds with an adequate botanical description of known and unknown plants used in PDT for the eradication of tumor cells are mandatory in the field of phytomedicine against cancer. On the other hand, potential PSs could be explored based on phototoxic plant species that were associated with photosensitization in animals and humans over time. The underlying principles of biotechnological processes for obtaining the secondary metabolites were addressed due to the need for new technologies to produce these potential pharmaceuticals drugs in an ecofriendly approach. The successes of plant-based PSs in PDT encourage researchers to work together with botanists to identify natural photoactive compounds from different plant species that remain to be identified or studied, and thus, they use them as alternatives for the synthesis of PSs with minimal side effects, low toxicity and greater selectivity in the different cancer treatments using PDT. Furthermore, novel biotechnology-based breeding techniques such as targeted genome editing methods will provide significant opportunities to produce natural products in plants, mainly when associated with the recent developments in scale-up capability and bioreactor design.

Introduction

Natural products have been used since ancient times to treat diseases in traditional medicine. Together with empirical knowledge, the product of the indigenous wisdom, folk knowledge, and the like and the existence and evolution of chemical methodologies to extract active compounds from plants have allowed the discovery of new metabolites to be used as potential drugs and chemotherapeutics. Besides, the active principles obtained from nature have also served as the basis for many

Abbreviations: $^1O_2$, singlet oxygen; A, Annual; AE, aloe-emodin; AQs, anthraquinones; B, Bush; BBR, Berberine; BC, Biological Cycle; CaSki, cervical carcinoma cells; CMK-7, human leukemia cells; Cur NDs, curcumin nanodrugs; Cur, Curcumin; DDS, drug delivery system; ER, endoplasmic reticulum; FDA, Food and Drug Administration; Ha, Habit; H, Herb; HaCaT, immortalized keratinocytes; HL60, human promyelocytic leukemia; Hyp, Hypericin; ICD, immunogenic cell death; NCI, National Cancer Institute; O_2^-, superoxide ions; P, Perennial; PACT, photoactivated chemotherapy; Pba, Pheophorbide A; PDT, Photodynamic therapy; PS, photosensitizers; PTT, photothermal therapy; ROS, reactive oxygen species; S_0, basal state; S_1, singlet; T_1, triplet; WHO, World Health Organization; Φ_Δ, Quantum yield.

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semi-synthetic drugs approved by the FDA, and other national regulatory agencies. It is estimated that 25% of commonly used drugs contain compounds isolated from plants, a figure that increases if drugs modified from natural prototypes are included (Petrakou et al., 2020). Moreover, it is estimated that there are between 300,000 and 500,000 species of plants worldwide and only 15% of these have been studied by the field of phytochemistry and merely a 6% by pharmacology and therefore, it is plausible to believe that many plant-derived drugs have yet to be discovered, including those intended for the treatment of tumor diseases (Cragg and Newman, 2013; Fabricant and Farnsworth, 2001).

The development of therapies for the treatment of infectious, autoimmune, cardiovascular, neurological and inflammatory diseases, as well as cancer have benefited from the abundant diversity of natural products, which allows them to interact with many cell receptors and induces cell death. The advantage of using such compounds for cancer treatment is their relatively non-toxic nature in non-tumoral cells and availability in the nature, in most cases, in an ingestive form (Kumar et al., 2018). A promising light-based therapy called Photodynamic therapy (PDT) employs plant-based drugs called photosensitizers (PSs) which were discovered from phototoxic plants that were subsequently reported as harmful to human beings and animals over the years, however, this knowledge transcended to eradicate tumors with promising results (Cogno et al., 2020; Núñez Montoya et al., 2008; Rumie Vittar et al., 2014).

In an eco-friendly approach and with the development of biotechnology, it is possible to contemplate that it is not necessary to collect plants massively to obtain their photoactivable secondary metabolites, instead, they could be produced in the laboratory. In this review, a summary of plant-based photoactivable compounds is presented with a special focus on the botanical characteristics of known and unknown plants used in PDT for the eradication of tumor cells. Furthermore, the underlying principles of biotechnological processes to obtain the secondary metabolites are addressed due to the need for new technologies to produce these potential pharmaceuticals drugs.

Plants and phytomedicine

Phytomedicine is a practice that brings together the ancestral knowledge of phytotherapy, the uses of medicinal plants, and the scientific knowledge that justifies these uses. Over time, the healing and mitigation of human diseases with the implementation of medicinal plants have been people's main therapeutic ally. Medicinal plants are an important heritage of humanity and, in addition, they are renewable, non-polluting, and of economical or affordable production (Dragos et al., 2017; Naik et al., 2020). A substantial fraction of the world's population continues using natural products, especially extracts of medicinal plants to help control diseases. However, in many cases, knowledge of the proper preparation and use of these materials is disappearing as well as resources themselves which are running out (Tinitana et al., 2016). Additionally, many exotic plants are no longer available; and for that reason, it is imperative to identify the active ingredients and the knowledge of how to use them (Catford et al., 2018). When the active ingredients have been chemically identified, they can be isolated or synthesized inexpensively and turned into pharmaceutical preparations; and they can also be chemically modified to produce more potent analogs (Akbar, 2020). In these man-made approaches, biotechnological tools can help to produce the isolated compounds in a slightly more environmentally friendly process (Alamgir, 2018).

The number of plant species that exist on earth is not fully known. Even though there is an estimated number of 400,000 plant species, the world plant list contains over a million names under 642 plant families and many of them are considered synonyms of the same plant (Ramawat, 2019). The World Health Organization (WHO) has listed approximately 21,000 herbs, bushes, and/or trees that are used for medicinal purposes around the world (Modak et al., 2007). A retrospective study of active plants carried out by the U.S. National Cancer Institute (NCI) program concluded that the yield of plant species with active compounds could have increased by 50–100% by using folk information (Balunas et al., 2006). Therefore, the emphasis, focus, and purpose of scientific research on phytomedicine should be placed objectively in the quality, applied use, and verification of their traditional uses. Approximately 50% of current medications and drugs are derived from different types of plants and it is for this reason that natural products should be investigated more carefully as potentially effective agents in cancer therapy. For instance, several groups of plants containing toxic chemical compounds, which trigger harmful effects under the action of light through a photosensitization phenomenon, are found in nature worldwide (Hudson and Towers, 1991). Plant phototoxins are not biosynthetically related in their vast majority. Apparently, the advantages of photochemical defenses are sufficient for phototoxicity to have evolved several times in plant evolution. These advantages are likely due to the use of light in the environment to produce exceptionally toxic photochemical reactions that are not normally possible in the ground state of these chemicals. Moreover, plant in-depth study in search of therapeutic compounds with a particular interest in those whose therapeutic action depends on its activation with light is detailed in the following section.

Something to consider is that several factors have been identified for the slow progress in the exploitation of medicinal plants (Shakya, 2016). One of the most important impediments is the use of folk knowledge to identify plants and their medicinal uses since different plants are known by the same colloquial name or a single plant is known by several local names that overlap with the local names of other plants. The latter highlights the importance of correctly identifying the species under study with their scientific name and taking into account the diagnostic botanical characters to be able to identify them in their natural environment (Akbar, 2020).

Photo-assisted therapies for cancer treatment

Using light to treat diseases dates back to antiquity and in the last century its application, either alone or in combination with other agents, allowed it to be considered an ally in the fight against cancer. Nowadays, phototherapy has reached new heights with the technological advances of the past decades, such as using lasers as the light sources, which are more powerful and controllable. Some advantages of phototherapy for cancer management are that it provides precise tumor localization for treatment and also it is not usually cross-resistant with other cancer treatments (Shi and Sadler, 2020). Thus, phototherapy can be a component of combination treatments. Therapies that use light include PDT, which is based on the production of reactive oxygen species (ROS) (Ibarra et al., 2018; Rivarola et al., 2013); photothermal therapy (PTT) based on hyperthermia as a trigger for cell damage and death (Ibarra et al., 2016, 2013; Yslas et al., 2015); and photoactivated chemotherapy (PACT) where a biologically active compound is released by light-cleavable of protecting groups (Bonnet, 2018). Among all of these, PDT is the most popular and globally approved by regulatory agents.

Photodynamic therapy

PDT is an alternative therapeutic modality to treat neoplastic diseases that combines the use of a photosensitizer (PS), light, and molecular oxygen (O_2) (Milla Sanabria et al., 2013). A PS is a molecule capable of absorbing electromagnetic radiation producing electronically excited species which can react with O_2 (present in the medium) and eventually generate highly reactive species of this element (ROS). ROS cause an exacerbated imbalance of the redox state of tumor cells and lead to cell death through damage of various cellular components including lipids, DNA, and proteins (Milla Sanabria et al., 2013). More precisely, when a PS is irradiated with visible light of a suitable wavelength, it absorbs the energy and goes from a basal state S_0 to an excited state S_1 (singlet), which through a crossing of intersystem or spin inversion, the S_1 passes to a state of higher energy T_1 (triplet) which

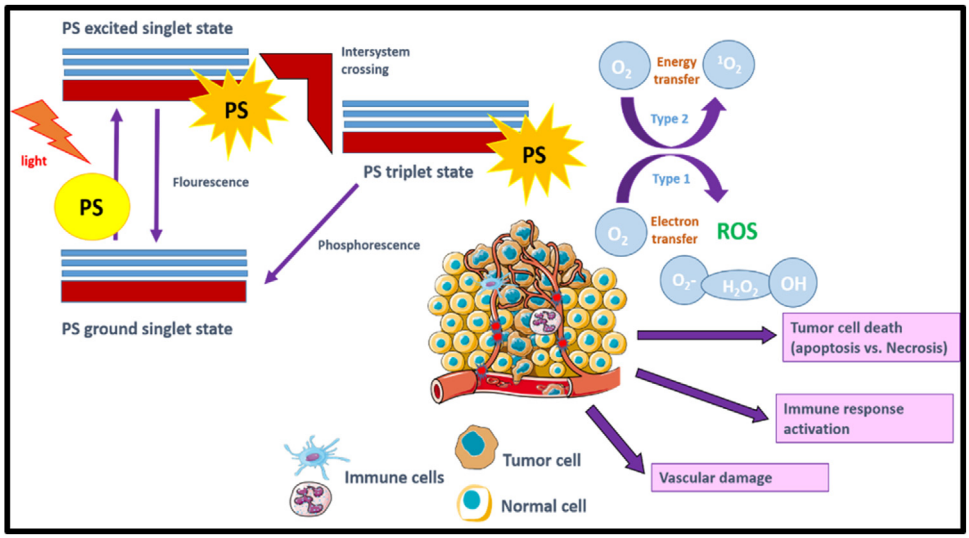

Fig. 1. PDT mechanism of excitation of PSs and generation of ROS after light irradiation. Also, the tumor cell damages associated currently with PDT are illustrated.

has a longer lifetime, allowing it to later transfer energy or electrons to different molecules and at that moment return to its basal state (S_0) (Fig. 1). The process called "Type II Redox Reaction", which involves energy transfer, uses the O_2 in its ground state as the acceptor of energy forming singlet oxygen ($^1O_2$). On the other hand, if transfer reactions of hydrogen atoms or electrons with O_2 or with different substrates (such as proteins, lipids, and carbohydrates present in cells) occur, free radicals and other ROS will form such as superoxide ions (O_2^-). These last reactions correspond to Type I Redox Reactions. Both mechanisms occur simultaneously, and their proportion depends on the PS type and the concentration of substrates and oxygen. The Jablonski diagram illustrates the excited states of a PS molecule and the radiative and non-radiative transitions that can occur between them (Fig. 1). A radiative transition from the $S_1 \rightarrow S_0$ with the emission of photons is known as fluorescence and from the $T_1 \rightarrow S_0$ is known as phosphorescence. These energetic phenomena are used in the photodiagnosis of tumor cells as another procedure using light (Naidoo et al., 2019; Schikora, 2020). A gran variety of PSs are described in the literature with applicability in PDT, many of them are chemically synthesized in the laboratory such as porphyrins (McCormick et al., 2014) or nanoparticle-based PSs (Caverzán et al., 2020; Ibarra et al., 2018), however, as we described before, plants are a source of photoactivatable compounds that are attractive to investigate as PS donors in a more environmentally-friendly fashion.

Over decades, several studies related to the PDT have been performed for various types of cancer, which have converged in the approval of a few synthetic PSs by regulatory agencies such as the FDA (Baskaran et al., 2018). For instance, photofrin, a porfimer sodium, was the first PDT PS approved for bladder cancer treatment in 1993. Nowadays, photofrin has been approved for more types of cancer including esophageal cancer, lung adenocarcinoma, endobronchial cancer, etc. In the clinic, PDT can be used as a sole treatment or in conjunction with surgery, radiotherapy, or chemotherapy and this is because of its mode of action and not competition with the mechanisms of action of the other therapeutics. Meanwhile, PDT also has advantages in terms of safeness, efficiency, repeatability, and minimal invasion which is primacy over chemotherapeutics which are not selective for tumor cells and generate side adverse effects in healthy tissues. PDT presents reduced long-term morbidity when compared with chemotherapy or radiotherapy and this feature was assayed in several types of tumors (Corti et al., 2007; Höblinger et al., 2011; Manyak and Ogan, 2003).

The PDT advantage of only being activated with the suitable delivery of light is also an outstanding feature compared to conventional treatments. In this sense, several efforts have therefore been made to deliver the appropriated light dosimetry to tumor tissues, which provided the impetus for greater acceptance of PDT in the medical community (Mang, 2004; Zou et al., 2020). For example, new light source technologies based on LEDs and diode lasers have been developed that allowed enhancing light output with greater portability and with a precision fiber optic design (Stringasci et al., 2017). All this finally converge in a powerful and uniform illumination, essential to improve the penetration and reproducibility of light doses.

Furthermore, several improvements were made to the development of ideal PSs. From the first-generation PSs, which were effective but also showed some limitations and intrinsic drawbacks, to newly developed third-generation PSs that showed higher tumor specificity with long-wavelength light activation, but they are still in a very early stage of preclinical and clinical research (Baskaran et al., 2018). The vast majority of improvements that have been made to achieve ideal PSs were made mainly in synthetic PSs; however, plant-based PSs also meet the conditions to incorporate them.

Plant-based photosensitizers

The first reports of people using natural herbs or their extracts, in combination with exposure to sunlight, for the treatment of different diseases such as psoriasis, eczema, vitiligo, and cancer date back to ancient Egypt, China (Ackroyd et al., 2007). Moreover, Indian medical literature dating to 1500 - 1400 BC described treatments combining herbs with natural sunlight to treat non-pigmented skin areas and vitiligo (Abdelkader, 2016). The PDT term of using dyes as PSs in the photodynamic process was introduced by Oscar Raab from the Tappeiner group, who was the first to examine photosensitized reactions using a synthetic acridine dye in 1898. In a similar approach, von Tappeiner concluded with a prediction of the potential future application of fluorescent substances in medicine (Ackroyd et al., 2007). Later, many dyes have been explored for the antitumor action through PDT; however, it was not until Dr. Dougherty's first studies with the hematoporphyrin derivative (HpD) that there was a great interest in the therapy (Dougherty, 2007). Dr. Dougherty successfully treated cancer with PDT in preclinical models for the first time in 1975.

Plants, as a source of PSs, began to be studied in a similar time. In 1987, Lee et al. reported a new PS consisting of chlorophyll derivates (CpD), which can be obtained from natural sources including plants. Afterward, the photosensitizing efficacy of CpD was compared with that of HpD showing that CpD was as effective as HpD for *in vivo* PDT (Park et al., 1989). Another early PS that has been explored for antitumor PDT and today is one of the most promising is hypericin

(Hyp). Hyp was first isolated from *Hypericum perforatum* L. in 1939 (Brockmann et al., 1939) and then, its PDT action was explored for the following years until today (Jendželovská et al., 2016). Clinical use of Hyp as a PS for PDT was first reported in 1996 by Koren et al. for the local treatment of malignant mesothelioma (Koren et al., 1996) and afterward, different clinical trials with Hyp-PDT applied to various skin tumors have been published to date. Moreover, several compounds were isolated from plants and tested for their potential antitumor action triggered by PDT (Dodge and Knox, 1986). Nowadays, efforts have focused on the identification of new compounds isolated from plants with photodynamic potential (Singh et al., 2020), and many of them are considered secondary metabolites. For instance, the yellow milky sap (latex) from *Chelidonium majus* L., which has been used in traditional folk medicine for centuries to treat skin conditions such as warts, condylomas, and papillae. It is rich in numerous biologically active compounds, like protoberberine alkaloids with growth inhibitory action of a variety of cancer cell lines after light irradiation (Warowicka et al., 2019). Exploring more efficient and safer PSs is a new challenge and traditional plants could be a potential source for such PSs. The number of novel chemicals obtained from plants is generally higher than that obtained synthetically, making natural ingredients a useful resource for the development of new drugs. One way to accomplish this exploration is by evaluating the fluorescence intensities of plant extracts and comparing them to those obtained from commercial PSs (Shi et al., 2019). In the next section, we will describe the major findings of the most important groups of plant-based compounds that have been tested for PDT purposes to date.

Anthraquinones

Among the plant secondary metabolites, anthraquinones (AQs) have been widely studied concerning their photosensitizing properties in PDT anticancer action (Cogno et al., 2020; Comini et al., 2011; Núñez Montoya et al., 2008, 2006; Rumie Vittar et al., 2014). AQs constitute a family of compounds that are extensively distributed in numerous plant species and have a wide spectrum of biological applications (Duval et al., 2016). Different AQs were isolated and purified from *Heterophyllaea pustulata* Hook f. (*Rubiaceae*), a phototoxic plant that grows in the Andean northwest of Argentina (Table 1) (Comini et al., 2011). From leaves and stems, ten AQs were isolated: soranjidiol, soranjidiol 1-methyl ether, rubiadin, rubiadin 1-methyl ether, damnacanthal, damnacanthol, heterophylline, pustuline, 2-hydroxy-3-methyl anthraquinone and (*S*)-5,5'-bisoranjidiol (Comini et al., 2017; Nuñez Montoya et al., 2003; Núñez Montoya et al., 2006). These AQs exhibited photosensitizing properties by the generation of $^1O_2$ and/or O_2^- (Comini et al., 2007; Núñez Montoya et al., 2005). In addition, we reported the efficacy of PDT-treatment on human breast cancer cell lines using four of these AQs: rubiadin, soranjidiol, soranjidiol 1-methyl ether, and rubiadin 1-methyl ether (Comini et al., 2011; Rumie Vittar et al., 2014). Moreover, two of these AQs were also tested in monolayer and spheroids of human colorectal adenocarcinoma (Cogno et al., 2020). Soranjidiol and Rubiadin showed no significant difference in the photosensitizing ability on monoculture of colon cancer cells but they did in spheroid cultures. At the same dose of light and drug concentration, Rubiadin-PDT produced the greatest cytotoxic effect in spheroids cultures (Cogno et al., 2020).

Likewise, three AQs that have not been described before were isolated from aerial parts of *Heterophyllaea lycioides* (Rusby) Sandwith (*Rubiaceae*) (Table 1) (Brako and Zarucchi, 1993; Bringmann et al., 2005). The isolated anthraquinones include a hetero-bianthraquinone identified as (R)-2-hydroxymethyl-20methyl-1,10,6,60-tetrahydroxy-5,50 bianthraquinone (lycionine), and two mono-chlorinated derivatives related to soranjidiol. One of them is a homo-bianthraquinone: (R)-7-chloro-2,20-dimethyl-1,10,6,60-tetrahydroxy-5,50 anthraquinone (7-chlorobisoranjidiol), whereas the second halogenated derivative corresponds to a monomeric structure: 5-chloro-1,6-dihydroxy-2-methyl anthraquinone (chlorinated). Dimmer et al. demonstrated that irradiation of lycionine and chlorinated derivatives enhanced the $^1O_2$ production comparedto the control; 7-chlorobisoranjidiol was raised out by producing an increase of 20%, whereas the other anthraquinones only produced a minor increase of 7% (Dimmer et al., 2017).

Hypericin

Hypericin (Hyp), 4,5,7,4′,5′,7′-hexahydroxy-2,2-dimethylnaphtodi anthrone, is a well-known natural PS found in some plant species of the genus *Hypericum*, especially *Hypericum perforatum* L. (Table 1). Hyp and its derivatives are accumulated in distinct morphological structures, named dark nodules, occurring in the aerial parts of Hyp-producing *Hypericum* species. However, an interspecific variation in localization of Hyps and spatial chemo-profiling of Hyp in some *Hypericum* species was reported previously (Kucharíková et al., 2016; Kusari et al., 2015). Moreover, Revuru et al. recently reported the spatial distribution of a precursor of Hyp, named skyrin, in leaves of five *in vitro* cultivated *Hypericum* species using MALDI-HRMS imaging (Revuru et al., 2020).

Hyp has shown illumination-dependent, anti-proliferative, and cytotoxic effects in various tumor cell lines including pancreas (Liu et al., 2000), cervical (Vantieghem et al., 1998), prostate (Xie et al., 2001), bladder (Zupkó et al., 2001), thyroids (Kim et al., 2018), breast (Abbasi Gamasaee et al., 2018), colorectal (Khot et al., 2018) and skin (Schempp et al., 1999b) cell lines. It is known that Hyp could generate O_2^- radicals and $^1O_2$ with a good quantum yield (Φ_Δ) in the presence of light (at wavelengths around 600 nm) and O_2 (Diwu and William Lown, 1993). The photodynamic action of Hyp targets a variety of subcellular organelles, most importantly the mitochondria and the endoplasmic reticulum (ER)-Golgi complex (Theodossiou et al., 2009). Thus, depending on drug and light administration conditions, the PDT effect leads to cell death, which occurs by the induction of necrosis (Du et al., 2003; Mikeš et al., 2007), apoptosis (Abbasi Gamasaee et al., 2018; Ali and Olivo, 2002), autophagy-associated cell death (Buytaert et al., 2006; Rubio et al., 2012) or even to immunogenic cell death (ICD) (Abhishek D. Garg et al., 2012).

Kessel recently reported the capacity of Hyp to target the ER for photodamage, which provokes a mainly unexplored manner of photokilling that implicates extensive cytoplasmic vacuole formation but does not represent autophagy. This has been called 'paraptosis' and seems to be a response to the appearance of misfolded ER proteins (Kessel, 2020a, 2020b, 2019). This event is important to eradicate the malignant cell population with a reduced apoptotic pathway (Kessel et al., 2020). Overall, Hyp has excellent photosensitizing properties, tumoritropic characteristics, and low cytotoxicity, and it is one of the most effective PS, extracted from plants (Mansoori et al., 2019).

Pheophorbide A

Pheophorbide A (Pba) [(3S,4S)-9-ethenyl-14-ethyl-21(methoxy carbonyl)-4,8,13,18-tetramethyl-20-oxo-3-phorbinepropanoic acid] is a catabolite of the photosynthetic pigment chlorophyll and it is formed in algae and higher plants (Hörtensteiner, 1999). In 2006, Chan et al. isolated Pba for the first time from *Scutellaria barbata* D. Don plant ((Table 1) using bioassay-guided isolation (Chan et al., 2006). *S. barbata* is used as traditional Chinese medicine for clearing heats, releasing toxicity, decreasing swelling, sores, and abscesses (Dharmananda, 2004). Likewise, this plant has long been used for the treatment of liver diseases such as hepatitis and hepatocellular carcinoma (Nie et al., 2016).

Pba potential in PDT has been successfully demonstrated on leukemia, pigmented melanoma, colonic cancer, hepatoma, breast adenocarcinoma, prostate cancer, and uterine carcinosarcoma (Bui-Xuan et al., 2010; Chan et al., 2006; Hajri et al., 2002; Lee et al., 2004; Li et al., 2007; Liu et al., 2017). Pba is a good $^1O_2$ producer and, compared to extensively used Photofrin, is activated at a higher wavelength,

Table 1
Main plant-based PSs and their characteristic associated with antitumoral PDT.

Plant specie	Common name	Plant family	Botanical description	BC	H	Distribution	Photosensitizer	Structural parts of the plant	Antitumoral action*	PS-PDT effective concentrations
Heterophyllaea pustulata Hook. f.	Cegadera	*Rubiaceae*	It is a 2-3 m long shrub, with whole leaves and white with reddish-purple tube flowers. It is identified by its globose glands, dark blue to purple, distributed throughout the body of the plant (lysigenic cavities).	P	B	Argentina (Jujuy, Salta and Tucumán)	Anthraquinone	Leaves and stems	Breast cancer and colorectal cancer	50-100 μM combinated with 3 – 20 J/cm^2 light dose.
Heterophyllaea lycioides (Rusby) Sandwith	Cegadera	*Rubiaceae*	Shrub about 1 m tall, strongly branched, with stiff branches. Small, narrow leaves with black dots on the underside. Tubular flowers violet on the outside and white on the inside. Small, round fruits, when ripe, pale yellow in color.	P	B	Bolivian Andean region and southern Peru	Anthraquinone	Leaves and stems	No reported.	No reported.
Hypericum perforatum L.	St. Johns wort	*Hypericaceae*	60 cm tall, erect; stems with few linear, black glands. Sessile or short petiolate leaves; oblong to linear blades. Inflorescences in terminal dichotomous tops with more than 10 flowers. Flowers of 2-2.5 cm in diameter; sepals 5, isomorphic, imbricate, oblong-lanceolate to linear, 5-7 × 1-2 mm; petals asymmetrical, oblong-elliptical, 1-1.5 × 0.4-0.7 cm, yellow. Ovate-ellipsoid capsules.	P	He	Europe, West Asia, North Africa North, America Australia., Argentina, Brazil, Chile and Uruguay.	Hypericin	Leaves and stems	Hypericin-mediated PDT has been used for the treatment of different type of cancer.	0.1 μM to 1.0 μM combinated with 5–40 J/cm^2 light dose
Scutellaria barbata D. Don	Barbed Skullcap	*Lamiaceae*	Herb of 35 cm high, sometimes taller. The slightly serrated leaves are somewhat lanceolate or triangular in shape and up to approximately 3 cm long. The flowers are born in peduncles that have small and sharp bracts. The slightly hairy purple-blue flower on the corolla is about 1 cm long.	P	He	Southern China	Pheophorbide A	Whole plant	Phototoxic effects in human colorectal adenocarcinoma, hepatocellular carcinoma and uterine sarcoma cell lines.	1 – 5 μM combinated with > 2 J/cm^2 light dose
Chelidonium majus L.	Celandine	*Papaveraceae*	Alternate, petiolate, discolored, pinnate-compound leaves, terminal leaflet generally trilobed Yellow flowers, Silicon capsule.	P	He	Europe, Asia and South America	alkaloidal protoberberine (BBR-F)	Leaves and stems in during the flowering	cytotoxicity against cervical cancer cells after PDT treatment via induction of apoptosis	1–100 μg/mL combinated with 1.8 J/cm^2 light dose.
Curcuma longa L.	Curcuma	*Zingiberaceae*	Oblong-webbed roots or tubers, wrinkled and brown on the outside and deep orange on the inside. It is approximately 2 meters high, with long lanceolate and petiolate leaves of a uniform green color. Inflorescence is pink. It reproduces vegetatively by cuttings from the rhizome.	P	B	Southeast Asia, more specifically in India and Vietnam	Curcumin	Rhizome	inhibitory effects of this natural product followed by visible light irradiation in different tumor cell lines.	2.5–160 μM combinated with 2.5 – 10 J/cm^2 light dose

(*continued on next page*)

Table 1 (*continued*)

Plant specie	Common name	Plant family	Botanical description	BC	H	Distribution	Photosensitizer	Structural parts of the plant	Antitumoral action*	PS-PDT effective concentrations
Echinops latifolius Tausch.	There are no common names associated with this taxon	*Asteraceae*	50–110 cm high. Stems are simple or branching from the base. Leaves are lanceolate or oblong-lanceolate. Flowers in solitary white chapters, roses or violets.	P	He	tropical Africa, the Mediterranean basin, temperate regions of Eurasia, Central Asia, Mongolia and North-eastern China	Thiophenes	Root	Cytotoxic effect on skin and cervix cancer	5–50 μg/mL combinated with UV irradiation
Phyllostachys bambusoides Siebold & Zucc	Japanese timber Bamboo	*Poaceae*	Rhizomes elongated. Leaf-blade base without a false petiole. Culms erect; 40-80 cm long. Leaf-sheaths glabrous on surface. Inflorescence a panicle.	P	He	Africa, Temperate Asia, Tropical Asia, Australasia, North America and South America.	1)-Hydroxypurpurin-7-lactone ethyl methyl diester	Leaves	Inhibited mammary tumor incidence.	0.1–3.5 μM combinated with ≥ 4.8 J/cm^2 light dose
Aglaonema simplex (Blume)	Malayan sword	*Araceae*	Stems dark green, cylindric, 40–80cm tall. Leaves usually 5 or 6, densely crowded at stem apex; petiole green, 6–15 cm, proximally sheathing; leaf blade initially involute, afterward spreading, pale green abaxially, dark green adaxially, ovate-oblong.	P	He	South East Asia	1)-Hydroxypurpurin-7-lactone ethyl methyl diester	Leaves and stems	potent action against the human tumor cell lines HL60, HSC-2, and HSC-3.	0.1–3.5 μM combinated with ≥ 4.8 J/cm^2 light dose
Spinacea Oleracea L.	Spinach	*Amaranthaceae*	Grows up to 30 cm tall. The leaves are alternate, simple, ovate to triangular and very variable in size from about 2-30 cm long and 1-15 cm broad, with larger leaves at the base of the plant and small leaves higher on the flowering stem.	A	He	Central and western Asia.	Chlorophill derivates, Chlorophyllin	Leaves	Bladder cancer, breast cancer, melanoma, etc.	0.5 – 10 μg/ml combinated with 1 – 8 J/cm^2 light dose.
Aloe vera L.	Aloe vera	*Asphodelaceae*	The fleshy leaves arise in a rosette from a short stem; in young plants the leaves appear at ground level, but the stem can grow up to 25 cm long in older plants. There may be 15–30 leaves per plant. Leaves are up to 50 cm long and 8–10 cm across at the base, tapering to a point with saw-like teeth along their margins.	P	He	Natïve to Oman. World while distribution.	Aloe-emodin	Roots and Leaves	Anti-tumor and anti-angiogenic activity against several tumor types such as human oral mucosa carcinoma.	10 – 20 μM combinated with >2.4 J/cm^2 light dose
Annona purpurea Moc. & Sessé ex Dunal	Annona or Black head	*Annonaceae*	Shrubs 1-5 m high. Leaves pubescent; blades generally oval, more rarely elliptical to oval-lanceolate. Yellow flowers, calyx with 3 free sepals, fairings or flattened, deltoids	P	B	Central America	Berberine (isoquinoline alkaloid)	Leaves	Antitumoral activity in neuroblastoma and liver cancer	2,5- 50 μM combinated with 10 _ 100 J/cm^2 light dose
Helleborus niger L.	Black hellebore	*Ranunculaceae*	It is an evergreen plant, 25–30 cm tall, with dark leathery leaves. Roots are black, knotty.	P	He	Europe	Berberine (isoquinoline alkaloid)	Leaves	Antitumoral activity in neuroblastoma and liver cancer	2,5- 50 μM combinated with 10 – 100 J/cm^2 light dose

References: BC: Biological Cycle (P: Perennial; A: Annual) H: Habit (He: Herb; B: Bush). * References are found in the main text, section 5.

670 versus 630 nm respectively (RÖDER et al., 2000). It was reported that Pba-PDT induces the release of cytochrome c and triggers the activation of the mitochondrial-mediated apoptosis pathway in malignant carcinoma cells (Xodo et al., 2012). However, the increase of expression of Beclin-1, LC3B, and ATG5, which are markers of autophagy, after PDT treatment in human skin cancer (Yoon et al., 2014) and breast adenocarcinoma has been observed (Bui-Xuan et al., 2010). Therefore, Pba is a natural PS in PDT suitable to target deep intraperitoneal tumors due to its photophysical properties.

Curcumin

Curcumin (Cur), 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), is a natural yellow pigment isolated from the rhizome of the perennial herb *Curcuma longa* that has been cultivated for centuries in numerous Asian countries (India, Nepal, China, and Indonesia) (Tan et al., 2011). It was extracted from *C. longa* in 1815 by two scientists, Vogel and Pelletier, from Harvard College Laboratory (Lestari and Indrayanto, 2014). Several studies described Cur as a potential PS. The enhancement of $^1O_2$ production after blue-light irradiation and the induction of strong phototoxic reaction even at lower concentrations of Cur were observed (Haukvik et al., 2010; Koon et al., 2006; Nardo et al., 2011; Rego-Filho et al., 2014). Cur is considered a potential anticancer agent and inhibits cancer cell proliferation in lung, colon, kidney, ovary, and liver tumor cells (Giordano and Tommonaro, 2019). Also, this naturally derived agent induces apoptosis in a variety of different tumor cell lines (Karunagaran et al., 2005; Koon et al., 2006; Mortezaee et al., 2019). Moreover, Cur modulates various signaling pathways in cancer cells, leading to the upregulation of proapoptotic genes such as Bax, PUMA, and caspase cascades, while it downregulates antiapoptotic genes such as Bcl-2 and Survivin (Watson et al., 2010). However, other studies indicate that Cur also induces activation of autophagy in breast cancer and melanoma cells (Guan et al., 2016; Zhao et al., 2016).

Notably, the combination of Cur-based PDT and chemotherapy has exhibited extraordinary efficiency against breast cancer (Lin et al., 2015). Likewise, it was seen that 5-ALA mediated PDT combined with Cur synergistically enhanced antitumor PDT efficacy against colon cancer (Şueki et al., 2019).

In spite of favorable Cur's photobiological activity, curcumin has not yet been approved as a therapeutic agent due to its poor aqueous solubility, relatively low bioavailability, and its intense staining color, which have been highlighted as major problems (Anand et al., 2007). Nevertheless, recent studies have focused more on introducing a drug delivery system (DDS) to increase Cur solubility and raise its cellular internalization and tumor accumulation (Jahagirdar et al., 2019; Jiang et al., 2016; Tsai et al., 2018; Xing et al., 2018). Sun et al. prepared carrier-free curcumin nanodrugs (Cur NDs) and they demonstrated the PDT effect on cancer cells. Cur NDs exhibited different optical properties, light-sensitive, drug release behavior and this resulted in an increased ROS generation and PDT efficacy on cancer cells compared with free Cur. Moreover, cell apoptosis during Cur NDs-based PDT was related to the activation of the ROS-mediated JNK/caspase-3 signaling pathway (Sun et al., 2019). Overall, the use of DDS for Cur may be a favorable system for facilitating the efficacy and safety of PDT against cancer.

Thiophenes

Thiophenes are plant-based therapeutic compounds formed by heterocyclic aromatic rings made up of one sulfur and four carbon atoms. These secondary metabolites derived from plants belonging to the *Asteraceae* family, such as *Tagetes, Echinops, Artemisia, Balsamorhiza, Blumea, Pluchea, Porophyllum, and Eclipta* (Ibrahim et al., 2016). For instance, various thiophenes were isolated from the crude ethanolic extract of *Echinops latifolius* Tausch with phototoxic effects (Table 1) (Wang et al., 2007). The derivatives of these compounds were reported with a variety of potent biological activities, including anti-inflammatory, analgesic, antimicrobial and antitumor activities (Shah and Verma, 2019; Zhang et al., 2008). Thiophenes compounds were characterized by an absorption spectrum of 225–400 nm with a high extinction coefficient for the relevant photobiological effects (Andrisano and Pappalardo, 1958). Notably, these compounds can be activated with ultraviolet (UV) "A" radiation, showing a cytotoxic effect on skin and cervix cancer and this might be due to their unstable nature under UV radiation (Jin et al., 2008). Therefore, UV irradiation of thiophene compounds can form ROS that would induce cell death. As a consequence of the ability to produce ROS after irradiation, these compounds are considered as alternative PSs from natural sources (Muniyandi et al., 2020).

1)-Hydroxypurpurin-7-lactone ethyl methyl diester

In 2005 Chee et al. isolated 15(1)-Hydroxypurpurin-7-lactone ethyl methyl diester (compound 1) for the first time from an ethanol-soluble extract of the leaves and stems of *Aglaonema simplex* (Chee et al., 2005). However, two years earlier, Kim *et al.* reported the extraction of this naturally derived PS from bamboo leaves (*Phyllostachys bambusoides*) (Kim et al., 2003). Compound 1 showed strong phototoxic effectiveness against human promyelocytic leukemia (HL60) and human leukemia cells (CMK-7) upon light activation. This molecule has photophysical characteristics including near-red absorption and it also has photokilling effects inducing apoptosis (Chee et al., 2005; Kim et al., 2003). Furthermore, the phototoxic efficacy of this molecule has been studied in oral and nasopharyngeal cancer cell lines (HSC2 and HK1, respectively). Compound 1 exhibited higher intracellular uptake over 24 h, a major potential as a PS, and more pronounced apoptosis compared with a known PS Pba in both HSC3 and HK1 cells (Lim et al., 2011). Thus, due to the poor knowledge of this molecule, it is necessary to carry out further studies to determine the photodynamic efficacy in cancer.

Aloe-emodin

The anthraquinone derivative aloe-emodin (AE) (1,8- dihydroxy-3-hydroxyl-methylanthraquinone) is the main bioactive component of rhubarb (*Rheum palmatum*), a very popular plant for its use in traditional Chinese medicine (Dong et al., 2020). AE is abundant in the leaves and roots of the well-known plant *Aloe vera* L. (*Asphodelaceae*) (Dutta et al., 2007). Plant characteristics are summarized in Table 1. AE has been widely investigated for its anti-cancer effects (Chen et al., 2014). For instance, Tu et al. demonstrated that AE-PDT induces autophagy and apoptosis in human osteosarcoma cell lines through the activation of the ROS-JNK signaling pathway (Tu et al., 2016). This PDT effect could be attributed to the physicochemical characteristic of AE with an efficient generation of $^1O_2$ when AE was irradiated with UV light ($\Phi_\Delta = 0.56$ in acetonitrile) (Vath et al., 2002). Moreover, the phototoxic effects of AE accompanied by UV radiation or visible light were tested in human foreskin fibroblasts and this photocytotoxicity was accompanied by oxidative damage in both cellular DNA and RNA (Wamer et al., 2003). Recently, AE mediated PDT was assayed in human oral squamous carcinoma cells *in vitro* e *in vivo* (Liu et al., 2018). AE induced cell cycle arrest in G1 phase with an increment of apoptosis by upregulation of Caspase-3 and Bax proapoptotic proteins (Liu et al., 2018).

Berberine

Berberine (BBR) is a significant isoquinoline alkaloid found in at least nine plant families such as *Annonaceae, Papaveraceae, Berberidaceae, Juglandaceae, Magnoliaceae, Menispermaceae, Ranunculaceae, Rubiaceae y Rutaceae* (Philogène et al., 1984). BBR has been used in traditional Chinese medicine due to its multiple pharmacological and biochemical effects, such as antidiabetic, anti-inflammatory, antimalarial, antimicrobial, anticancer, and antioxidant (Luiza Andreazza et al., 2016). The

fluorescent nature of BBR was a conditional piece of evidence that suggested its probable photodynamic activity (Philogène et al., 1984), It was determined that BBR is capable of producing $^1O_2$ and radical species when exposed to UVA irradiation (Cheng et al., 2009; Chignell et al., 2007). Therefore, BBR was used as a potential photosensitizing agent for PDT in various cancers (Ho et al., 2009; Huang et al., 2018; Hur et al., 2009; Kim et al., 2007; Li et al., 2008). BBR-PDT photokilling is mainly by apoptosis after ROS generation (Hur et al., 2009; Wang et al., 2008), however, autophagy cell death was also observed (Lopes et al., 2020; Tillhon et al., 2012).

Recently, Oliveira et al. determined that BBR-associated PDT is a good anticancer treatment strategy for cervical cancer. They observed that BBR-PDT induced a rise in the production of ROS and caspase-3 activity in CaSki (cervical carcinoma cells) and HaCaT (immortalized keratinocytes) cell lines, indicating a preferential cell death mechanism by caspase-dependent apoptosis (Oliveira et al., 2020).

Chlorophyllin

Chlorophyll is an important pigment in the process of photosynthesis, and it is found in plants, blue-green algae (*cyanobacteria*), and eukaryotic algae. Several natural chlorophyll sources can be explored, with spinach, alfalfa meal, and algae as the most studied (Leite et al., 2018). Chlorophyll extracted from spinach leaves was associated with many photobiological induced actions including PDT (Table 1) (Dentuto et al., 2004; Iriyama et al., 1979). Among chlorophyll compounds, chlorophyllin is a semi-synthetic derivative of chlorophyll where the magnesium atom at the center is replaced with copper and the phytol esters replaced with sodium, making the molecule more soluble in water (Sarkar et al., 1995). Chlorophyllin was reported to be activated or excited at a wavelength range of 600–670 nm absorbance for the relevant photobiological effects (Shipman et al., 1976) and it has some interesting attributes such as easy solubility in aqueous solutions or a feasible and low-cost extraction process compared to synthetic PSs (Krasnovsky, 2003). In the last years, many chlorophyllin derivatives were synthesized with improved PDT effects (Gomaa et al., 2012; Uliana et al., 2014). Recently, chlorophyllin e6 has drawn attention due to the ideal PSs characteristics reported, such as low production cost, appropriate optical properties, high stability and purity and minimal toxicity without light irritation (Du et al., 2014). Zhuo et al. demonstrated the PDT antitumoral efficacy of chlorophyllin e6 by using monolayer cells and multicellular tumor spheroid models of human bladder cancer cells (Zhuo et al., 2019). In T24 and 5637 bladder cancer cell lines, this chlorophyll derivate induced apoptosis with PARP cleavage (Zhuo et al., 2019). Du et al. developed another chlorophyllin derivate named chlorophyllin f and found that this PS localizes in mitochondria and lysosomes and induces apoptosis and autophagy in human bladder cancer cells (Lihuan et al., 2014).

Phototoxic plant species with potential applications in PDT

In order to identify plants containing potential PSs, it is inevitable to think about plants which have been identified as harmful to man and animals over time. Many natural plants have photoactive chemicals and were identified as phototoxic plants with the ability to cause a cutaneous reaction in humans or animals when there has been contacting with the skin followed by exposure to the sun. Phototoxicity developed by contact with plants was noticed by Klaber in 1942 who observed sunburn in people exposed to the sunlight and for the first time, the term “phytophotodermatitis” was mentioned (KLABER, 1942). Afterward, many reports showed that humans or animals who ingested phototoxic plants or phototoxic phytochemicals and were subsequently exposed to sunlight were susceptible to phototoxic and photogenotoxic dermal effects, such as skin irritation, sensitization, allergy, mutations, and skin cancers (Collett, 2019; Mantle et al., 2001). Phototoxic phytochemical components are widely present in many different plant families such as *Apiaceae, Rutaceae, Moraceae, Ranunculaceae, Rubiaceae, Brassicaceae, Solanaceae*, and *Fabaceae* (Table 2). It is evident from the above mentioned that phototoxins in the plant kingdom are not related in their great majority. Apparently, the advantages of photochemical defenses of some plants are sufficient to allow this phototoxicity to have arisen independently in plant evolution on several occasions. These advantages are likely due to the use of light in the environment to produce exceptionally toxic photochemical reactions that are not normally possible in the ground state of these chemicals.

Over the years, many plants, including certain valuable forages that are normally considered innocuous, have been associated with photosensitization (Table 2). For most of these plants, the evidence regarding pathogenesis and the nature of the produced phototoxin and phototoxic conditions are vague, anecdotal, or fragmentary. Moreover, outbreaks in animals may be transient and associated with certain times of the year, weather conditions, or growth stage or even disease status of the plants. For this latter, continued surveillance and reporting of observations and objective data from ongoing data collection are necessary. Finally, this information from the fortuitous findings in intoxicated animals or people can be used to identify potential candidates in PDT.

Plant-based *in vitro* systems strategies to produce natural PSs for PDT

Biotechnological demand for natural products has been constantly growing because of their significant value and new applications, mainly as pharmaceuticals (Matsuura et al., 2018). Plant cells and organ cultures represent a source for the easy and accessible production of secondary metabolites of interest, especially when plants are wild, require long periods of cultivation, have low secondary metabolite yields, or do not undergo chemical synthesis processes (Rischer et al., 2013).

Nowadays, several *in vitro* plant culture systems exist (Fig. 2), including callus cultures, cell suspension cultures, and organ cultures (Efferth, 2019; Marisol Ochoa-Villarreal et al., 2016; Rischer et al., 2013). Over these cultivation techniques, it is possible to obtain plants in a nutrient medium free of microbes and under controlled environmental conditions (Frugis, 2019).

Callus cultures are the cultivation of morphologically undifferentiated plant cells (Efferth, 2019), almost any part of the plant can be used to generate it. Explants taken from plant tissues are cultured on a solid gel medium supplemented with growth hormones (i.e., auxin, cytokinin) and they slowly grow *in vitro* into a cell mass amorphous. By passaging the cells regularly, callus cultures can be indefinitely maintained *in vitro*. Following successful callus formation, cell suspension cultures can subsequently be made, basically by adding these cells to a liquid medium (Bhatia, 2015; Efferth, 2019). The resulting cultures usually have a significant scale-up ability for their growth within industrially important bioreactors designed to maximize levels of secondary metabolites of interest (Ramachandra Rao and Ravishankar, 2002).

Plant organ cultures are the cultivation of differentiated cells in organized tissues such as roots or shoots (Fig. 2). Hairy root cultures are obtained following infection of the plant material with the gram-negative, soil bacterium *Agrobacterium rhizogenes* (Otten et al., 2008). During this process, *A. rhizogenes* transfers a section of DNA from its plasmid, the T-DNA, into the genome of host plant cells (Georgiev et al., 2011). The T-DNA carries a set of genes that encode for enzymes responsible for modulating auxin and cytokinin accumulation. The new hormone balance at the infection site mitotically activates surrounding cells encouraging the formation of proliferating roots, so-called hairy roots.

Hairy root cultures are relatively easy to maintain and are genetically stable. Moreover, this type of culture is used for the industrial-scale production of pharmaceuticals, however, it is necessary to develop appropriate bioreactor production platforms (Pistelli et al., 2010; Srivastava and Srivastava, 2007).

Table 2
Phototoxic plant species and their reported phototoxins.

Plant species	Common name	Plant Family	Phototoxin(s)	Evidence of phototoxicity in animals	Ref.
Fagopyrum tataricum (L.) Gaertn	Tartary buckwheat	*Polygonaceae*	Perylenequinone - fagopyrin	definite phototoxicity with a high evidence	(Eguchi et al., 2009)
Ammi majus L.	Bishop's weed	*Apiaceae*	Xanthotoxin, bergapten, ammirin, imperatorin, alloimperatorin, marmesin, marmesinin, oxypeucedanin	definite phototoxicity with a high evidence	(Schild et al., 2009)
Ammi visnaga (L.) Lam	Viznaga	*Apiaceae*	Xanthotoxin, 8-hydroxybergapten, imperatorin, marmesin	definite phototoxicity with a high evidence	(Le Quesne et al., 1985)
Pastinaca sativa L.	wild parsnip	*Apiaceae*	Xanthotoxin, bergapten, imperatorin, isopimpinellin	definite phototoxicity with a high evidence	(Stegelmeier et al., 2019)
Cymopterus watsonii (J.M.Coult. & Rose) M.E.Jones	spring parsley	*Apiaceae*	Xanthotoxin, bergapten	definite phototoxicity with a high evidence	(Egyed and Williams, 1977)
Bituminaria bituminosa (L.) C.H. Stirt.	Arabian pea or pitch trefoil	*Fabaceae*	Psoralen	definite phototoxicity with a high evidence	(Martínez et al., 2010)
Medicago nigra L.	common trefoil	*Fabaceae*	Unknown	some evidence of primary phototoxicity (field evidence and experimental feeding resulted in photosensitisation)	(Bull and Macindoe, 1926)
Medicago sativa L.	alfalfa	*Fabaceae*	Unknown	some evidence of primary phototoxicity (field evidence only)	(Puschner et al., 2016)
Trifolium repens L.	white clover	*Fabaceae*	Unknown	some evidence of primary phototoxicity (field evidence only	(Johnson, 1982)
Trifolium pratense L.	red clover	*Fabaceae*	Unknown	some evidence of primary phototoxicity (field evidence only	(Johnson, 1982)
Lotus corniculatus L.	birdsfoot trefoi	*Fabaceae*	Unknown	some evidence of primary phototoxicity (field evidence only	(Stafford et al., 1995)
Cullen cinereum (Lindl.) J.W.Grimes	Hoary Scurf-pea	*Fabaceae*	Psoralen	definite phototoxicity with a high evidence	(Del Río et al., 2010)

(*continued on next page*)

Table 2 (*continued*)

Plant species	Common name	Plant Family	Phototoxin(s)	Evidence of phototoxicity in animals	Ref.
Biserrula pelecinus L.	-	*Fabaceae*	Unknown	definite phototoxicity (field evidence and experimental feeding resulted in photosensitisation)	(Kessell et al., 2015)
Ruta graveolens L.	Rua	*Rutaceae*	Psoralen, bergapten, isopimpinellin, isoimperatorin, chalepensin, marmesin, isorutarin	definite phototoxicity with a high evidence	(Schempp et al., 1999a)
Thamnosma texana (Gray) Torr.	Dutchman's breeche	*Rutaceae*	Psoralen, xanthotoxin, bergapten, isopimpinellin	definite phototoxicity with a high evidence	(Oertli et al., 1983)
Brassica napus L.	Biennis group	*Brassicaceae*	Unknown	definite phototoxicity (field evidence and experimental feeding resulted in photosensitisation)	(Allworth et al., 1985)
Brassica rapa L.	leafy or bulb turnip	*Brassicaceae*	Unknown	definite phototoxicity (field evidence and experimental feeding resulted in photosensitisation)	(Allworth et al., 1985)
Froelichia humboldtiana (Roem. Et Schult.) Seub.	-	*Amaranthaceae*	Unknown	definite phototoxicity (field evidence and experimental feeding resulted in photosensitisation)	(Santos et al., 2017)
Alternanthera philoxeroides (Mart.) Griseb	alligator weed	*Amaranthaceae*	Anthraquinones – rubiadin, rubiadin 1-methyl ether and 2- hydroxy-3-methyl anthraquinone	primary phototoxicity (field evidence and phototoxin(s) isolated)	(Fan et al., 2008)
Malachra fasciata Jacq.	roadside leafbract	*Malvaceae*	Unknown	definite phototoxicity (field evidence and experimental feeding resulted in photosensitisation)	(de Araújo et al., 2017)
Erodium moschatum (L.) L'Hér. and E. cicutarium (L.) L'Hér.	storksbill	*Geraniaceae*	Unknown	some evidence of primary phototoxicity (field evidence and experimental feeding resulted in photosensitisation)	(Stroebel, 2002)
Echinochloa frumentacea Link, *E. esculenta* (A. Braun) H. Scholz and *E. crus-galli* (L.) Beauv	barnyard grass or Japanese millet	*Poaceae*	Unknown	some evidence of primary phototoxicity (field evidence only	(Allen et al., 2009)

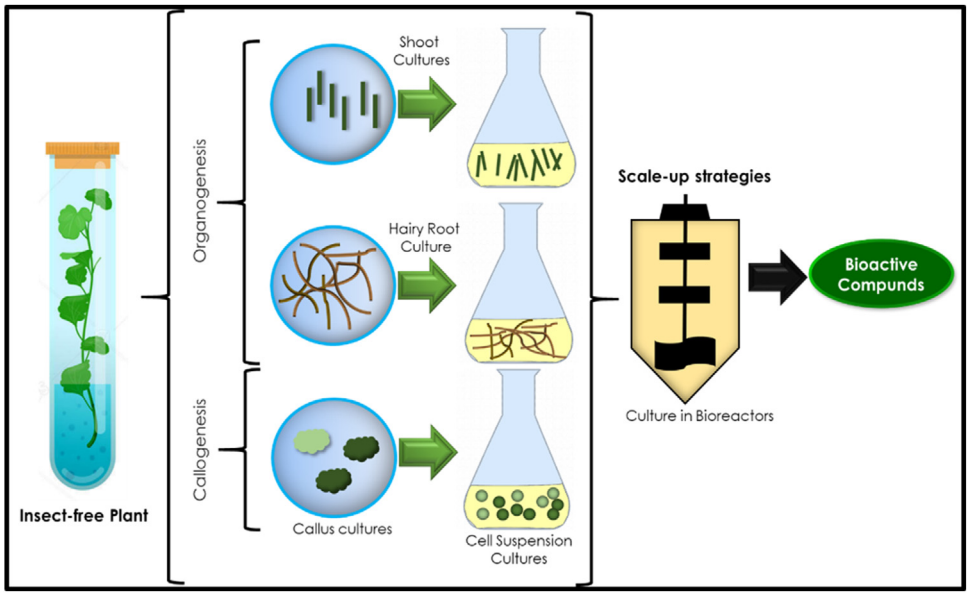

Fig. 2. Two of the most commonly methods used for the large-scale production of bioactive compounds using plant *in vitro* tissue culture.

Besides root cultures, it is possible to cultivate other plant parts (shoots) for the production of secondary metabolites (Fig. 2). Shoot cultures can be transgenic, if they are gained after plant infection with *Agrobacterium tumefaciens*, so-called shooty teratomas (Saito et al., 1989), or non-transgenic through the simple use of correct hormonal balance (Massot et al., 2000). Shoots exhibit some similar properties to hairy roots, specifically genetic stability and good capacities for secondary metabolite production (Massot et al., 2000). However, there are some variances in the metabolic pattern, as some syntheses are precisely located in either roots or shoots (Subroto et al., 1996). Other differences concern a somewhat slower growth rate as the fastest doubling time reported is approximately 3 days (Heble, 1985), and also the requirement to expose shoot cultures to light, which can be a problem with large tank reactors made from steel.

Various *in vitro* plant culture systems have been explored in *Hypericum perforatum L* for production of Hyp, used in PDT (Abrahamse and Hamblin, 2016; Karioti and Bilia, 2010). In general, it was observed that unorganized cell cultures (callus and cell suspension cultures) were lower for the accumulation of Hyps when compared to organized structures such as shoot and hairy roots (Cui et al., 2010; Kirakosyan et al., 2004; Murthy et al., 2014; Pasqua et al., 2003). This is due to the biosynthesis of Hyps with *in vivo* plants and is restricted to several types of secretory structures, including translucent glands, dark glands, or secretory canals (Fornasiero et al., 1998; Kartnig et al., 1996). Concerning this, several successful bioreactor cultures have been established for the production of large-scale adventitious root cultures (Cui et al., 2010; Murthy et al., 2014; Wu et al., 2014).

In the last years, parameters such as light and temperature, which control the biomass and the production of Hyp, have been studied principally in adventitious root cultures. The light and temperature are abiotic elicitors that can trigger the production of plant secondary metabolites (Naik and Al-Khayri, 2016). Sobhani Najafabadi et al. (2019) observed that biomass production was significantly higher in the cultures grown under dark and red light, but in terms of Hyp production, the red light was the best. Recently, Tavakoli et al. (2020) indicated the fact that Hyp biosynthesis is notably affected by UVB exposure time and low-temperature in *H. perforatum* adventitious root culture. The highest content of Hyp was observed upon 60 min UVB followed by the recovery and a temperature of 4 °C for 72 h.

Karakaş et al. (2015) determined Hyp content in callus and cell suspension cultures in another *Hypericum* species, *Hypericum triquetrifolium* Turra. The authors observed that Hyp content levels found in callus were higher than in cell suspension cultures, suggesting that the accumulation of this compound in cell suspension needs further modifications.

Another natural PS agent used in PDT is AE (Tu et al., 2016). The production of AE was compared in callus culture versus fresh leaves collected from the entire Aloe vera plant. AE production was greater in callus culture compared to entire leaves (Matos Acurero, 2008).

Similar results were obtained in our laboratory with two anthraquinones isolated from *Heterophyllaea pustulata*, a phototoxic shrub that inhabits the northwest of Argentina (Comini et al., 2011; Núñez Montoya et al., 2006, 2005). These anthraquinones, called Soranjdiol and Rubiadin, exhibited a significant photocytotoxicity on human cancer cells (Cogno et al., 2020; Comini et al., 2011; Rumie Vittar et al., 2014). The fraction obtained from callus cultures allowed us to get a satisfactory content of these compounds compared to those found in the original plant (Rumie Vittar et al., 2014). There are many reports on the isolation and identification of anthraquinones from plant cultured cells (A et al., 2020; Busto et al., 2013; Krishnan and Siril, 2018; Mizutani et al., 1997), although none related to PDT activity.

The low expression levels of plant active metabolites create a need for tools that allow the change of plant genetic material. Biotechnology offers an opportunity to exploit cells, tissues, organs, or entire organisms by growing them *in vitro* and genetically manipulate them to get desired compounds. Currently, there are several techniques to target genomes capable of managing plant synthetic biology (Niazian, 2019; Techen et al., 2014; Yamazaki et al., 2018). *Agrobacterium*-mediated gene transformation and artificial polyploidy induction are the principal methods used in plant culture systems (Matveeva, 2018).

Limitations and opportunities for further research in the production of natural PSs

In spite of the reduced toxicity and side effects of photoactive substances derived from medicinal plants, natural compounds are often difficult to purify from complex extracts, or are presented in low concentrations and sometimes only found in rare or danger of extinction plant species. Bioprocessing of plant cultures has been considered an alternative system for the production of phytocompounds on a large scale, in an economically viable and environmentally friendly manner (Alamgir, 2018). Remarkably, to date, only limited examples of successful cases including artemisinin, shikonin, berberine, and taxol have been reported for commercial production using this strategy (Matsuura et al., 2018).

The extraction of phytochemicals from natural sources is difficult, costly, and time-consuming. A proper understanding and a rigorous analysis of different parameters are needed to find the way towards the successful commercialization of plant cell bioprocesses. Combining bioprocessing with genetic engineering could benefit in creating the tissue culture processes more productive (Matsuura et al., 2018; Niazian, 2019). Nevertheless, this involves a better understanding of the biosynthetic pathways and their regulation.

In the last years, there has been a growing demand for the production of plant secondary metabolites on an industrial scale by microbial fermentation (Park et al., 2018). Since several natural products of plant origin are not synthesized by microorganisms, synthetic biology has attracted much consideration in terms of the improvement of engineered microorganisms capable of producing these natural compounds (Breitling and Takano, 2016; Niazian, 2019; Palazzotto et al., 2019; Zhao et al., 2019). However, microbial production of various natural compounds of interest even cannot be attempted because biosynthetic pathways of these compounds are long and complex, and the expression of all the enzymes in a single host usually results in poor cell growth and a lower titer of the desired product (Zhao et al., 2019). Therefore, we believe that the use of biotechnological platforms based on plant cell and organ cultures to produce biopharmaceuticals should not be neglected and new technologies must be introduced to advance in improving production.

Conclusions and perspectives

PDT is a promising therapy for cancer due to its ability to fight malignant cells through photochemical reactions, which lead to the production of ROS within malignant cells and, consequently, induce their cell death. This therapy has plenty of beneficial attributes, such as its minimally invasive nature and local treatment that encourage researchers to continue its study to improve conventional cancer treatments. In addition, many studies confirm that natural compounds can be considered promising candidates for PDT. There is a wide range of natural compounds with photoactive and phototoxic properties that would be suitable for their use as plausible natural PSs to be applied in combination with PDT. The successes of plant-based PSs in PDT are through the regulation of cell signaling, apoptotic cell death, disruption of the cell cycle, or autophagic death. This review encourages researchers to work together with botanists to identify natural photoactive compounds from different plant species which remain to be identified and further studied, and thus, use them as alternatives for the synthesis of PSs with minimal side effects, low toxicity, and greater selectivity in the different cancer treatments using PDT. Finally, we believe that bioprocessing of plant cultures holds great potential for the production of phytochemicals. It provides an alternate method for the production of natural compounds on a large scale, in an economically viable and environmentally-friendly manner. Besides, novel biotechnology-based breeding techniques such as targeted genome editing methods will provide significant opportunities to produce natural products in plants, mainly when associated with the recent developments in scale-up capability and bioreactor design.

Finally, we will ask ourselves where are we going to with plant-based PDT? Researchers around the world are currently studying different ways to improve the efficacy of PDT and to extend its use to other forms of cancer. In this sense, pre-clinical and clinical studies are mandatory to the final approval of plant-based PSs since very few of them have completed clinical trials in patients. Natural PSs have all the potential to be used in the clinic as plausible cancer palliative treatments. Other researchers are concentrating their effort on developing more powerful PSs, which can target cancer cells more specifically, and can be activated by light of the appropriate wavelength to penetrate tissue and treat deeper tumors, which is a challenge for many natural PSs. Besides, one of the current challenges will undoubtedly be the identification of plants possessing suitable PSs and the subsequent methodology to obtain them massively. To accomplish this, *in vitro* plant culture systems (callus, cell suspension, and organ cultures), represents a more desirable and far less costly strategy.

Declaration of Competing Interest

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References

A, M., Satdive, R., Fulzele, D.P., Ramamoorthy, S., C, G.P.D., Zayed, H., Younes, S., C, R., 2020. Enhanced production of anthraquinones by gamma-irradiated cell cultures of Rubia cordifolia in a bioreactor. Ind. Crops Prod. 145, 111987. doi:10.1016/j.indcrop.2019.111987.

Abbasi Gamasaee, N., Student, M., Radmansouri, M., Ghiasvand, S., Shahriari, F., Zare Marzouni, H., Aryan, H., Jangholi, E., Amin Javidi, M., 2018. Hypericin induces apoptosis in MDA-MB-175-VII cells in lower dose compared to MDA-MB-231. Arch. Iran. Med..

Abdel-kader, M.H., 2016. CHAPTER 1. The journey of PDT throughout history: PDT from pharos to present. R. Soc. Chem. 1–21. doi:10.1039/9781782626824-00001.

Abrahamse, H., Hamblin, M.R., 2016. New photosensitizers for photodynamic therapy. Biochem. J. 473, 347–364. doi:10.1042/BJ20150942.

Ackroyd, R., Kelty, C., Brown, N., Reed, M., 2007. The history of photodetection and photodynamic therapy. Photochem. Photobiol. 74, 656–669. doi:10.1562/0031-8655(2001)0740656thopap2.0.co2.

Akbar, S., 2020. Handbook of 200 Medicinal Plants, Handbook of 200 Medicinal Plants. Springer International Publishing doi:10.1007/978-3-030-16807-0.

Alamgir, A.N.M., 2018. Biotechnology, in vitro production of natural bioactive compounds, herbal preparation, and disease management (treatment and prevention). In: Progress in Drug Research. Birkhauser Verlag AG, pp. 585–664. doi:10.1007/978-3-319-92387-1_7.

Ali, S.M., Olivo, M., 2002. Bio-distribution and subcellular localization of Hypericin and its role in PDT induced apoptosis in cancer cells. Int. J. Oncol. 21, 531–540. doi:10.3892/ijo.21.3.531.

Allen, J.G., Creeper, J.H., Forshaw, D., Kabay, M.J., Main, D.C., Richards, R.B., 2009. Plant-associated diseases, either new or new to the state, encountered over the last decade (1991-2001) in Western Australia., in: Poisonous Plants and Related Toxins. CABI, pp. 540–547. 10.1079/9780851996141.0540

Allworth, M.B., West, D.M., Bruere, A.N., 1985. Ovine dermatophilosis in young sheep associated with the grazing of Brassica SPP crops. N. Z. Vet. J. 33, 210–212. doi:10.1080/00480169.1985.35238.

Anand, P., Kunnumakkara, A.B., Newman, R.A., Aggarwal, B.B., 2007. Bioavailability of curcumin: problems and promises. Mol. Pharm. doi:10.1021/mp700113r.

Andrisano, R., Pappalardo, G., 1958. Absorption spectra in the near ultraviolet of some α- and β-monosubstituted derivatives of thiophene. Spectrochim. Acta 12, 350–354. doi:10.1016/0371-1951(58)80061-2.

Balunas, M.J., Jones, W.P., Chin, Y.W., Mi, Q., Farnsworth, N.R., Soejarto, D.D., Cordell, G.A., Swanson, S.M., Pezzuto, J.M., Chai, H.B., Kinghorn, A.D., 2006. Relationships between inhibitory activity against a cancer cell line panel, profiles of plants collected, and compound classes isolated in an anticancer drug discovery project. Chem. Biodivers. 3, 897–915. doi:10.1002/cbdv.200690092.

Baskaran, R., Lee, J., Yang, S.G., 2018. Clinical development of photodynamic agents and therapeutic applications. Biomater. Res. 22, 1–8. doi:10.1186/s40824-018-0140-z.

Bhatia, S., 2015. Plant tissue culture. In: Modern Applications of Plant Biotechnology in Pharmaceutical Sciences. Elsevier Inc., pp. 31–107. doi:10.1016/B978-0-12-802221-4.00002-9.

Bonnet, S., 2018. Why develop photoactivated chemotherapy? Dalt. Trans. 47, 10330–10343. doi:10.1039/c8dt01585f.

Brako, L., Zarucchi, J.L., 1993. Catalogue of the flowering plants and gymnosperms of Peru. Monogr. Syst. Bot. Missouri Bot. Gard..

Breitling, R., Takano, E., 2016. Synthetic biology of natural products. Cold Spring Harb. Perspect. Biol. 8, 23994–23995. doi:10.1101/cshperspect.a023994.

Bringmann, G., Mortimer, A.J.P., Keller, P.A., Gresser, M.J., Garner, J., Breuning, M., 2005. Atroposelective synthesis of axially chiral biaryl compounds. Angew. Chem. - Int. Ed. doi:10.1002/anie.200462661.

Brockmann, H., Haschad, M.N., Maier, K., Pohl, F., 1939. Über das hypericin, den photodynamisch wirksamen Farbstoff aus Hypericum perforatum. Naturwissenschaften 27, 550. doi:10.1007/BF01495453.

Bui-Xuan, N.-H., Tang, P.M.-K., Wong, C.-K., Fung, K.-P., 2010. Photo-activated pheophorbide-a, an active component of Scutellaria barbata, enhances apoptosis via the suppression of ERK-mediated autophagy in the estrogen receptor-negative human breast adenocarcinoma cells MDA-MB-231. J. Ethnopharmacol. 131, 95–103. doi:10.1016/j.jep.2010.06.007.

Bull, L.B., Macindoe, R.H.F., 1926. Photosensitization in sheep: trefoil dermatitis. Aust. Vet. J. 2, 85–91. doi:10.1111/j.1751-0813.1926.tb05332.x.

Busto, V.D., Calabró-López, A., Rodríguez-Talou, J., Giulietti, A.M., Merchuk, J.C., 2013. Anthraquinones production in Rubia tinctorum cell suspension cultures: down scale of shear effects. Biochem. Eng. J. 77, 119–128. doi:10.1016/j.bej.2013.05.013.

Buytaert, E., Callewaert, G., Vandenheede, J.R., Agostinis, P., 2006. Deficiency in apoptotic effectors Bax and Bak reveals an autophagic cell death pathway initiated by photodamage to the endoplasmic reticulum. Autophagy doi:10.4161/auto.2730.

Catford, J.A., Bode, M., Tilman, D., 2018. Introduced species that overcome life history tradeoffs can cause native extinctions. Nat. Commun. 9, 1–7. doi:10.1038/s41467-018-04491-3.

Caverzán, M.D., Beaugé, L., Chesta, C.A., Palacios, R.E., Ibarra, L.E., 2020. Photodynamic therapy of glioblastoma cells using doped conjugated polymer nanoparticles: an in vitro comparative study based on redox status. J. Photochem. Photobiol. B Biol. 212, 112045. doi:10.1016/j.jphotobiol.2020.112045.

Chan, J.Y.W., Tang, P.M.K., Hon, P.M., Au, S.W.N., Tsui, S.K.W., Waye, M.M.Y., Kong, S.K., Mak, T.C.W., Fung, K.P., 2006. Pheophorbide a, a major antitumor component purified from Scutellaria barbata, induces apoptosis in human hepatocellular carcinoma cells. Planta Med. 72, 28–33. doi:10.1055/s-2005-873149.

Chee, C.F., Lee, H.B., Ong, H.C., Ho, A.S.H., 2005. Photocytotoxic pheophorbide-related compounds from Aglaonema simplex. Chem. Biodivers. 2, 1648–1655. doi:10.1002/cbdv.200590134.

Chen, R., Zhang, J., Hu, Y., Wang, S., Chen, M., Wang, Y., 2014. Potential antineoplastic effects of aloe-emodin: a comprehensive review. Am. J. Chin. Med. doi:10.1142/S0192415X14500189.

Cheng, L.L., Wang, M., Zhu, H., Li, K., Zhu, R.R., Sun, X.Y., Yao, S.De, Wu, Q.S., Wang, S.L., 2009. Characterization of the transient species generated by the photoionization of Berberine: a laser flash photolysis study. Spectrochim. Acta - Part A Mol. Biomol. Spectrosc. 73, 955–959. doi:10.1016/j.saa.2009.05.001.

Chignell, C.F., Sik, R.H., Watson, M.A., Wielgus, A.R., 2007. Photochemistry and photocytotoxicity of alkaloids from goldenseal (Hydrastis canadensis L.) 3: effect on human lens and retinal pigment epithelial cells. Photochem. Photobiol. 83, 938–943. doi:10.1111/j.1751-1097.2007.00086.x.

Cogno, I.S., Gilardi, P., Comini, L., Núñez-Montoya, S.C., Cabrera, J.L., Rivarola, V.A., 2020. Natural photosensitizers in photodynamic therapy: in vitro activity against monolayers and spheroids of human colorectal adenocarcinoma SW480 cells. Photodiagnosis Photodyn. Ther. 31, 101852. doi:10.1016/j.pdpdt.2020.101852.

Collett, M.G., 2019. Photosensitisation diseases of animals: classification and a weight of evidence approach to primary causes. Toxicon X 3, 100012. doi:10.1016/j.toxcx.2019.100012.

Comini, L.R., Fernandez, I.M., Vittar, N.B.R., Núñez Montoya, S.C., Cabrera, J.L., Rivarola, V.a., 2011. Photodynamic activity of anthraquinones isolated from Heterophyllaea pustulata Hook f. (Rubiaceae) on MCF-7c3 breast cancer cells. Phytomedicine 18, 1093–1095. doi:10.1016/j.phymed.2011.05.008.

Comini, L.R., Morán Vieyra, F.E., Mignone, R.A., Páez, P.L., Laura Mugas, M., Konigheim, B.S., Cabrera, J.L., Núñez Montoya, S.C., Borsarelli, C.D., 2017. Parietin: an efficient photo-screening pigment in vivo with good photosensitizing and photodynamic antibacterial effects in vitro. Photochem. Photobiol. Sci. 16, 201–210. doi:10.1039/C6PP00334F.

Comini, L.R., Núñez Montoya, S.C., Sarmiento, M., Cabrera, J.L., Argüello, G.A., 2007. Characterizing some photophysical, photochemical and photobiological properties of photosensitizing anthraquinones. J. Photochem. Photobiol. A Chem. 188, 185–191. doi:10.1016/J.JPHOTOCHEM.2006.12.011.

Corti, L., Toniolo, L., Boso, C., Colaut, F., Fiore, D., Muzzio, P.-C., Koukourakis, M.I., Mazzarotto, R., Pignataro, M., Loreggian, L., Sotti, G., 2007. Long-Term survival of patients treated with photodynamic therapy for carcinoma in situ and early non-small-cell lung carcinoma. Lasers Surg. Med. 39, 394–402. doi:10.1002/lsm.20513.

Cragg, G.M., Newman, D.J., 2013. Natural products: a continuing source of novel drug leads. Biochim. Biophys. Acta - Gen. Subj. 1830, 3670–3695. doi:10.1016/j.bbagen.2013.02.008.

Cui, X.H., Chakrabarty, D., Lee, E.J., Paek, K.Y., 2010. Production of adventitious roots and secondary metabolites by Hypericum perforatum L. in a bioreactor. Bioresour. Technol. 101, 4708–4716. doi:10.1016/j.biortech.2010.01.115.

de Araújo, V.O., Oliveira Neto, T.S., Simões, S.V.D., da Silva, T.K.F., Riet-Correa, F., Lucena, R.B., 2017. Primary photosensitization and contact dermatitis caused by Malachra fasciata Jacq. N.V. (Malvaceae) in sheep. Toxicon 138, 184–187. doi:10.1016/j.toxicon.2017.09.009.

Del Río, J.A., Ortuño, A., Pérez, I., Bennett, R.G., Real, D., Correal, E., 2010. Furanocoumarin content in Bituminaria bituminosa varieties and Cullen species. Options Méditerranéennes. Sér. A. Mediterr. Semin. 67–70.

Dentuto, P.L., Catucci, L., Cosma, P., Fini, P., Agostiano, A., 2004. Photophysical and electrochemical properties of chlorophyll a-cyclodextrins complexes. Bioelectrochemistry 117–120. doi:10.1016/j.bioelechem.2003.09.019.

Dharmananda, S., 2004. Oldenlandia and Scutellaria: Antitoxin and Anticancer Herbs.

Dimmer, J.A., Núñez Montoya, S.C., Mendoza, C.S., Cabrera, J.L., 2017. Photosensitizing anthraquinones from Heterophyllaea lycioides (Rubiaceae). Phytochemistry 137, 94–100. doi:10.1016/j.phytochem.2017.02.003.

Diwu, Z., William Lown, J., 1993. Photosensitization with anticancer agents 17. EPR studies of photodynamic action of hypericin: Formation of semiquinone radical and activated oxygen species on illumination. Free Radic. Biol. Med. 14, 209–215. doi:10.1016/0891-5849(93)90012-J.

Dodge, A.D., Knox, J.P., 1986. Photosensitisers from plants. Pestic. Sci. 17, 579–586. doi:10.1002/ps.2780170515.

Dong, X., Zeng, Y., Liu, Y., You, L., Yin, X., Fu, J., Ni, J., 2020. Aloe-emodin: a review of its pharmacology, toxicity, and pharmacokinetics. Phyther. Res. 34, 270–281. doi:10.1002/ptr.6532.

Dougherty, T.J., 2007. A Personal History of Photodynamic Therapy, in: Regional Cancer Therapy. Humana Press, pp. 117–132. doi:10.1007/978-1-59745-225-0_9.

Dragos, D., Gilca, M., Gaman, L., Vlad, A., Iosif, L., Stoian, I., Lupescu, O., 2017. Phytomedicine in joint disorders. Nutrients 9, 70. doi:10.3390/nu9010070.

Du, H.Y., Olivo, M., Tan, B.K.H., Bay, B.H., 2003. Hypericin-mediated photodynamic therapy induces lipid peroxidation and necrosis in nasopharyngeal cancer. Int. J. Oncol. 23, 1401–1405. doi:10.3892/ijo.23.5.1401.

Du, L., Jiang, N., Wang, G., Chu, Y., Lin, W., Qian, J., Zhang, Y., Zheng, J., Chen, G., 2014. Autophagy inhibition sensitizes bladder cancer cells to the photodynamic effects of the novel photosensitizer chlorophyllin e4. J. Photochem. Photobiol. B Biol. 133, 1–10. doi:10.1016/j.jphotobiol.2014.02.010.

Dutta, A., Bandyopadhyay, S., Mandal, C., Chatterjee, M., 2007. Aloe vera leaf exudate induces a caspase-independent cell death in Leishmania donovani promastigotes. J. Med. Microbiol. 56, 629–636. doi:10.1099/jmm.0.47039-0.

Duval, J., Pecher, V., Poujol, M., Lesellier, E., 2016. Research advances for the extraction, analysis and uses of anthraquinones: a review. Ind. Crops Prod. 94, 812–833. doi:10.1016/j.indcrop.2016.09.056.

Efferth, T., 2019. Biotechnology applications of plant callus cultures. Engineering 5, 50–59. doi:10.1016/j.eng.2018.11.006.

Eguchi, K., Anase, T., Osuga, H., 2009. Development of a high-performance liquid chromatography method to determine the fagopyrin content of Tartary buckwheat (Fagopyrum tartaricum Gaertn.) and common buckwheat (F. esculentum Moench). Plant Prod. Sci. 12, 475–480. doi:10.1626/pps.12.475.

Egyed, M.N., Williams, M.C., 1977. Photosensitizing effects of cymopterus watsonii and cymopterus longipes in chickens and turkey poults. Avian Dis. 21, 566–575. doi:10.2307/1589415.

Fabricant, D.S., Farnsworth, N.R., 2001. The value of plants used in traditional medicine for drug discovery. Environ. Health Perspect. 109, 69–75. doi:10.1289/ehp.01109s169.

Fan, W.Q., Xiong, M.X., Ma, Z., Li, Q.Y., Liu, Y.W., 2008. Chemical constituents of Alternanthera philoxeroides. Chin. J. Nat. Med. 6, 112–115. doi:10.3724/SP.J.1009.2008.00112.

Fornasiero, R.B., Bianchi, A., Pinetti, A., 1998. Anatomical and ultrastuctural observations in hypericum perforatum L. Leaves. J. Herbs, Spices Med. Plants 5, 21–33. doi:10.1300/J044v05n04_04.

Frugis, G., 2019. Plant development and organogenesis: from basic principles to applied research. Plants 8. doi:10.3390/plants8090299.

Garg, Abhishek D., Krysko, D.V., Verfaillie, T., Kaczmarek, A., Ferreira, G.B., Marysael, T., Rubio, N., Firczuk, M., Mathieu, C., Roebroek, A.J.M., Annaert, W., Golab, J., De Witte, P., Vandenabeele, P., Agostinis, P., 2012. A novel pathway combining calreticulin exposure and ATP secretion in immunogenic cancer cell death. EMBO J. 31, 1062–1079. doi:10.1038/emboj.2011.497.

Georgiev, M.I., Ludwig-Müller, J., Alipieva, K., Lippert, A., 2011. Sonication-assisted Agrobacterium rhizogenes-mediated transformation of Verbascum xanthophoeniceum Griseb. for bioactive metabolite accumulation. Plant Cell Rep. 30, 859–866. doi:10.1007/s00299-010-0981-y.

Giordano, A., Tommonaro, G., 2019. Curcumin and cancer. Nutrients 11. doi:10.3390/nu11102376.

Gomaa, I., Ali, S.E., El-Tayeb, T.A., Abdel-kader, M.H., 2012. Chlorophyll derivative mediated PDT versus methotrexate: an in vitro study using MCF-7 cells. Photodiagnosis Photodyn. Ther. 9, 362–368. doi:10.1016/j.pdpdt.2012.04.001.

Guan, F., Ding, Y., Zhang, Y., Zhou, Y., Li, M., Wang, C., 2016. Curcumin suppresses proliferation and migration of MDA-MB-231 breast cancer cells through autophagy-dependent Akt degradation. PLoS One 11. doi:10.1371/journal.pone.0146553.

Hajri, A., Wack, S., Meyer, C., Smith, M.K., Leberquier, C., Kedinger, M., Aprahamian, M., 2002. In vitro and in vivo efficacy of photofrin® and pheophorbide a, a bacteriochlorin, in photodynamic therapy of colonic cancer cells. Photochem. Photobiol. 75, 140. doi:10.1562/0031-8655(2002)075<0140:ivaive>2.0.co;2.

Haukvik, T., Bruzell, E., Kristensen, S., Tønnesen, H.H., 2010. Photokilling of bacteria by curcumin in selected polyethylene glycol 400 (PEG 400) preparations: Studies on curcumin and curcuminoids. XLI. Pharm. 65, 600–606. doi:10.1691/ph.2010.0048.

Heble, M.R., 1985. Multiple Shoot Cultures: A Viable Alternative in Vitro System for the Production of Known and New Biologically Active Plant Constituents. Springer, Berlin, Heidelberg, pp. 281–289. doi:10.1007/978-3-642-70717-9_27.

Ho, Y.T., Yang, J.S., Lu, C.C., Chiang, J.H., Li, T.C., Lin, J.J., Lai, K.C., Liao, C.L., Lin, J.G., Chung, J.G., 2009. Berberine inhibits human tongue squamous carcinoma cancer tumor growth in a murine xenograft model. Phytomedicine 16, 887–890. doi:10.1016/j.phymed.2009.02.015.

Höblinger, A., Gerhardt, T., Gonzalez Carmona, M., Hüneburg, R., Sauerbruch, T., Schmitz, V., 2011. Feasibility and safety of long-term photodynamic therapy (PDT) in the palliative treatment of patients with extrahepatic cholangiocarcinoma. Z. Gastroenterol. 49. doi:10.1055/s-0030-1269715, P5_09.

Hörtensteiner, S., 1999. Chlorophyll breakdown in higher plants and algae. Cell. Mol. Life Sci. doi:10.1007/s000180050434.

Huang, Y., Wang, K., Gu, C., Yu, G., Zhao, D., Mai, W., Zhong, Y., Liu, S., Nie, Y., Yang, H., 2018. Berberine, a natural plant alkaloid, synergistically sensitizes human liver cancer cells to sorafenib. Oncol. Rep. 40, 1525–1532. doi:10.3892/or.2018.6552.

Hudson, J.B., Towers, G.H.N., 1991. Therapeutic potential of plant photosensitizers. Pharmacol. Ther. 49, 181–222. doi:10.1016/0163-7258(91)90055-Q.
Hur, J.-M., Hyun, M.-S., Lim, S.-Y., Lee, W.-Y., Kim, D., 2009. The combination of berberine and irradiation enhances anti-cancer effects via activation of p38 MAPK pathway and ROS generation in human hepatoma cells. J. Cell. Biochem. 107, 955–964. doi:10.1002/jcb.22198.
Ibarra, L.E., Bongiovanni, S., Barbero, C.A., Rivarola, V.A., Mabel, B.L., Yslas, E.I., 2016. The chronic toxicity of pani-NPS to the larvae stage of Rhinella arenarum. J. Nanosci. Nanotechnol. 16, 7983–7988. doi:10.1166/jnn.2016.12761.
Ibarra, L.E., Porcal, G.V., Macor, L.P., Ponzio, R.A., Spada, R.M., Lorente, C., Chesta, C.A., Rivarola, V.A., Palacios, R.E., 2018. Metallated porphyrin-doped conjugated polymer nanoparticles for efficient photodynamic therapy of brain and colorectal tumor cells. Nanomedicine 13, 605–624. doi:10.2217/nnm-2017-0292.
Ibarra, L.E., Yslas, E.I., Molina, M.A., Rivarola, C.R., Romanini, S., Barbero, C.A., Rivarola, V.A., Bertuzzi, M.L., 2013. Near-infrared mediated tumor destruction by photothermal effect of PANI-Np in vivo. Laser Phys 23. doi:10.1088/1054-660X/23/6/066004.
Ibrahim, S.R.M., Abdallah, H.M., El-Halawany, A.M., Mohamed, G.A., 2016. Naturally occurring thiophenes: isolation, purification, structural elucidation, and evaluation of bioactivities. Phytochem. Rev. doi:10.1007/s11101-015-9403-7.
Iriyama, K., Shiraki, M., Yoshiura, M., 1979. An improved method for extraction, partial purification, separation and isolation of chlorophyll from spinach leaves. J. Liq. Chromatogr. 2, 255–276. doi:10.1080/01483917908060061.
Jahagirdar, P.S., Gupta, P.K., Kulkarni, S.P., Devarajan, P.V., 2019. Polymeric curcumin nanoparticles by a facile in situ method for macrophage targeted delivery. Bioeng. Transl. Med. 4, 141–151. doi:10.1002/btm2.10112.
Jendželovská, Z., Jendželovský, R., Kuchárová, B., Fedoročko, P., 2016. Hypericin in the light and in the dark: two sides of the same coin. Front. Plant Sci. 7, 1–20. doi:10.3389/fpls.2016.00560.
Jiang, S., Zhu, R., He, X., Wang, J., Wang, M., Qian, Y., Wang, S., 2016. Enhanced photocytotoxicity of curcumin delivered by solid lipid nanoparticles. Int. J. Nanomedicine Volume 12, 167–178. doi:10.2147/IJN.S123107.
Jin, W., Shi, Q., Hong, C., Cheng, Y., Ma, Z., Qu, H., 2008. Cytotoxic properties of thiophenes from Echinops grijissi Hance. Phytomedicine 15, 768–774. doi:10.1016/j.phymed.2007.10.007.
Johnson, A.E., 1982. Toxicologic aspects of photosensitization in livestock. J. Natl. Cancer Inst. 69, 253–258. doi:10.1093/jnci/69.1.253.
Karakaş, Ö., Özen, H.Ç., Onay, A., 2015. Determination of hypericin content in callus and cell suspension cultures of hypericum triquetrifolium turra. Adv. Zool. Bot. 3, 184–189. doi:10.13189/AZB.2015.030404.
Karioti, A., Bilia, A.R., 2010. Hypericins as potential leads for new therapeutics. Int. J. Mol. Sci. 11, 562–594. doi:10.3390/ijms11020562.
Kartnig, T., Göbel, I., Heydel, B., 1996. Production of hypericin, pseudohypericin and flavonoids in cell cultures of various Hypericum species and their chemotypes. Planta Med. 62, 51–53. doi:10.1055/s-2006-957796.
Karunagaran, D., Rashmi, R., Kumar, T., 2005. Induction of apoptosis by curcumin and its implications for cancer therapy. Curr. Cancer Drug Targets 5, 117–129. doi:10.2174/1568009053202081.
Kessel, D., 2020a. Exploring modes of photokilling by hypericin. Photochem. Photobiol. 96, 1101–1104. doi:10.1111/php.13275.
Kessel, D., 2020b. Hypericin accumulation as a determinant of PDT efficacy. Photochem. Photobiol. 96, 1144–1147. doi:10.1111/php.13302.
Kessel, D., 2019. Apoptosis, paraptosis and autophagy: death and survival pathways associated with photodynamic therapy. Photochem. Photobiol. 95, 119–125. doi:10.1111/php.12952.
Kessel, D., Cho, W.J., Rakowski, J., Kim, H.E., Kim, H.C., 2020. Effects of HPV status on responsiveness to ionizing radiation photodynamic therapy in head and neck cancer cell lines. Photochem. Photobiol. 96, 652–657. doi:10.1111/php.13150.
Kessell, A., Ladmore, G., Quinn, J., 2015. An outbreak of primary photosensitisation in lambs secondary to consumption of *Biserrula pelecinus* (biserrula). Aust. Vet. J. 93, 174–178. doi:10.1111/avj.12318.
Khot, M.I., Perry, S.L., Maisey, T., Armstrong, G., Andrew, H., Hughes, T.A., Kapur, N., Jayne, D.G., 2018. Inhibiting ABCG2 could potentially enhance the efficacy of hypericin-mediated photodynamic therapy in spheroidal cell models of colorectal cancer. Photodiagnosis Photodyn. Ther. 23, 221–229. doi:10.1016/j.pdpdt.2018.06.027.
Kim, D.W., Ahan, S.H., Kim, T.Y., 2007. Enhancement of arsenic trioxide (As 2 O 3)-mediated apoptosis using berberine in human neuroblastoma SH-SY5Y cells. J. Korean Neurosurg. Soc. 42, 392. doi:10.3340/jkns.2007.42.5.392.
Kim, H., Kim, S.W., Seok, K.H., Hwang, C.W., Ahn, J.C., Jin, J.O., Kang, H.W., 2018. Hypericin-assisted photodynamic therapy against anaplastic thyroid cancer. Photodiagnosis Photodyn. Ther. 24, 15–21. doi:10.1016/j.pdpdt.2018.08.008.
Kim, K.K., Kawano, Y., Yamazaki, Y., 2003. A novel porphyrin photosensitizer from bamboo leaves that induces apoptosis in cancer cell lines. Anticancer Res. 23, 2355–2361.
Kirakosyan, A., Sirvent, T.M., Gibson, D.M., Kaufman, P.B., 2004. The production of hypericins and hyperforin by in vitro cultures of St. John's wort (Hypericum perforatum). Biotechnol. Appl. Biochem. 39, 71. doi:10.1042/ba20030144.
KLABER, R., 1942. Phyto-photo-dermatitis. Br. J. Dermatol. 54, 193–211. doi:10.1111/j.1365-2133.1942.tb10682.x.
Koon, H.K., Leung, A.W.N., Yue, K.K.M., Mak, N.K., 2006. Photodynamic effect of curcumin on NPC/CNE2 cells. J. Environ. Pathol. Toxicol. Oncol. 25, 205–215. doi:10.1615/jenvironpatholtoxicoloncol.v25.i1-2.120.
Koren, H., Schenk, G.M., Jindra, R.H., Alth, G., Ebermann, R., Kubin, A., Koderhold, G., Kreitner, M., 1996. Hypericin in phototherapy. J. Photochem. Photobiol. B: Biol. 113–119. doi:10.1016/S1011-1344(96)07357-5.
Krasnovsky, A.A., 2003. Chlorophyll isolation, structure and function: major landmarks of the early history of research in the Russian Empire and the Soviet Union. Photosynth. Res. doi:10.1023/A:1024934317155.
Krishnan, S.R.S., Siril, E.A., 2018. Elicitor mediated adventitious root culture for the large-scale production of anthraquinones from Oldenlandia umbellata L. Ind. Crops Prod. 114, 173–179. doi:10.1016/j.indcrop.2018.01.069.
Kucharíková, A., Kusari, S., Sezgin, S., Spiteller, M., Čellárová, E., 2016. Occurrence and distribution of phytochemicals in the leaves of 17 in vitro cultured Hypericum spp. adapted to outdoor conditions. Front. Plant Sci. 7. doi:10.3389/fpls.2016.01616.
Kumar, V.V., Swamy, M.K., Akhtar, M.S., 2018. Anticancer plants and their conservation strategies: an update. In: Anticancer Plants: Properties and Application. Springer, Singapore, pp. 455–483. doi:10.1007/978-981-10-8548-2_20.
Kusari, S., Sezgin, S., Nigutova, K., Cellarova, E., Spiteller, M., 2015. Spatial chemoprofiling of hypericin and related phytochemicals in Hypericum species using MALDI-HRMS imaging mass spectrometry imaging. Anal. Bioanal. Chem. 407, 4779–4791. doi:10.1007/s00216-015-8682-6.
Le Quesne, P.W., Do, M.N., Ikram, M., Israrkhan, M., Mir, I., 1985. Furocoumarins from the fruit of ammi visnaga. J. Nat. Prod. 48, 496. doi:10.1021/np50039a030.
Lee, W.Y., Lim, D.S., Ko, S.H., Park, Y.J., Ryu, K.S., Ahn, M.Y., Kim, Y.R., Lee, D.W., Cho, C.W., 2004. Photoactivation of pheophorbide a induces a mitochondrial-mediated apoptosis in Jurkat leukaemia cells. J. Photochem. Photobiol. B Biol. 75, 119–126. doi:10.1016/j.jphotobiol.2004.05.005.
Leite, A.C., Ferreira, A.M., Morais, E.S., Khan, I., Freire, M.G., Coutinho, J.A.P., 2018. Cloud point extraction of chlorophylls from spinach leaves using aqueous solutions of nonionic surfactants. ACS Sustain. Chem. Eng. 6, 590–599. doi:10.1021/acssuschemeng.7b02931.
Lestari, M.L.A.D., Indrayanto, G., 2014. Curcumin, in: Profiles of Drug Substances, Excipients and Related Methodology. Academic Press Inc., pp. 113–204. doi:10.1016/B978-0-12-800173-8.00003-9.
Li, H., Guo, L., Jie, S., Liu, W., Zhu, J., Du, W., Fan, L., Wang, X., Fu, B., Huang, S., 2008. Berberine inhibits SDF-1-induced AML cells and leukemic stem cells migration via regulation of SDF-1 level in bone marrow stromal cells. Biomed. Pharmacother. 62, 573–578. doi:10.1016/j.biopha.2008.08.003.
Li, W.T., Tsao, H.W., Chen, Y.Y., Cheng, S.W., Hsu, Y.C., 2007. A study on the photodynamic properties of chlorophyll derivatives using human hepatocellular carcinoma cells. Photochem. Photobiol. Sci. 1341–1348. doi:10.1039/b704539e.
Lihuan, D., Jingcun, Z., Ning, J., Guozeng, W., Yiwei, C., Wei, L., Jing, Q., Yuanfang, Z., Gang, C., 2014. Photodynamic therapy with the novel photosensitizer chlorophyllin f induces apoptosis and autophagy in human bladder cancer cells. Lasers Surg. Med. 46, 319–334. doi:10.1002/lsm.22225.
Lim, S.H., Lee, H.B., Ho, A.S.H., 2011. A new naturally derived photosensitizer and its phototoxicity on head and neck cancer cells. Photochem. Photobiol. 87, 1152–1158. doi:10.1111/j.1751-1097.2011.00939.x.
Lin, H.Y., Lin, J.N., Ma, J.W., Yang, N.S., Ho, C.T., Kuo, S.C., Way, T.Der, 2015. Demethoxycurcumin induces autophagic and apoptotic responses on breast cancer cells in photodynamic therapy. J. Funct. Foods 12, 439–449. doi:10.1016/j.jff.2014.12.014.
Liu, C.D., Kwan, D., Saxton, R.E., McFadden, D.W., 2000. Hypericin and photodynamic therapy decreases human pancreatic cancer in vitro and in vivo. J. Surg. Res. 93, 137–143. doi:10.1006/jsre.2000.5949.
Liu, L.Y., Man, X.X., Yao, H.X., Tan, Y.Y., 2017. Effects of pheophorbide a-mediated photodynamic therapy on proliferation and metastasis of human prostate cancer cells. Eur. Rev. Med. Pharmacol. Sci. 21, 5571–5579. doi:10.26355/eurrev_201712_13994.
Liu, Y.qing, Meng, P.song, Zhang, H.chao, Liu, X., Wang, M.xi, Cao, W.wu, Hu, Z., Zhang, Z.guo, 2018. Inhibitory effect of aloe emodin mediated photodynamic therapy on human oral mucosa carcinoma in vitro and in vivo. Biomed. Pharmacother. 97, 697–707. doi:10.1016/j.biopha.2017.10.080.
Lopes, T.Z., de Moraes, F.R., Arni, R.K., Rahal, P., Calmon, M.F., 2020. Berberine associated photodynamic therapy promotes autophagy and apoptosis via ROS generation in renal carcinoma cells. Biomed. Pharmacother. 123, 109794. doi:10.1016/j.biopha.2019.109794.
Luiza Andreazza, N., Vevert-Bizet, C., Bourg-Heckly, G., Sureau, F., José Salvador, M., Bonneau, S., 2016. Berberine as a photosensitizing agent for antitumoral photodynamic therapy: insights into its association to low density lipoproteins. Int. J. Pharm. 510, 240–249. doi:10.1016/j.ijpharm.2016.06.009.
Mang, T.S., 2004. Lasers and light sources for PDT: past, present and future. Photodiagnosis Photodyn. Ther. 1, 43–48. doi:10.1016/S1572-1000(04)00012-2.
Mansoori, B., Mohammadi, A., Amin Doustvandi, M., Mohammadnejad, F., Kamari, F., Gjerstorff, M.F., Baradaran, B., Hamblin, M.R., 2019. Photodynamic therapy for cancer: role of natural products. Photodiagnosis Photodyn. Ther. 26, 395–404. doi:10.1016/j.pdpdt.2019.04.033.
Mantle, D., Gok, M.A., Lennard, T.W.J., 2001. Adverse and beneficial effects of plant extracts on skin and skin disorders. Adverse Drug React. Toxicol. Rev. 20, 89–103.
Manyak, M.J., Ogan, K., 2003. Photodynamic therapy for refractory superficial bladder cancer: long-term clinical outcomes of single treatment using intravesical diffusion medium. J. Endourol. 17, 633–639. doi:10.1089/089277903322518644.
Marisol Ochoa-Villarreal, Howat, S., Hong, S.M., Jang, M.O., Jin, Y.W., Lee, E.K., Loake, G.J., 2016. Plant cell culture strategies for the production of natural products. BMB Rep. 49, 149–158. doi:10.5483/BMBRep.2016.49.3.264.
Martínez, S., Correal, E., Real, D., Ortuño, A., Río, J.A.del, 2010. Bituminaria bituminosa: a source of furanocoumarins of pharmaceutical interest. Drug plants I 307–322.
Massot, B., Milesi, S., Gontier, E., Bourgaud, F., Guckert, A., 2000. Optimized culture conditions for the production of furanocoumarins by micropropagated shoots of Ruta graveolens. Plant Cell. Tissue Organ Cult. 62, 11–19. doi:10.1023/A:1006430508169.
Matos Acurero, Á., Aloesin, aloin and aloe-emodin production in *Aloe vera* L. calli CIENCIA 16(4), 2008, 389–395.
Matsuura, H.N., Malik, S., de Costa, F., Yousefzadi, M., Mirjalili, M.H., Arroo, R., Bhambra, A.S., Strnad, M., Bonfill, M., Fett-Neto, A.G., 2018. Specialized plant metabolism characteristics and impact on target molecule biotechnological production. Mol. Biotechnol. 60, 169–183. doi:10.1007/s12033-017-0056-1.

Matveeva, T.V., 2018. Agrobacterium-mediated transformation in the evolution of plants. In: Current Topics in Microbiology and Immunology. Springer Verlag, pp. 421–441. doi:10.1007/82_2018_80.

McCormick, B.P.P., Pansa, M.F., Sanabria, L.N.M., Carvalho, C.M.B., Faustino, M.A.F., Neves, M.G.P.M.S., Cavaleiro, J.A.S., Vittar, N.B.R., Rivarola, V.A., 2014. Cationic porphyrin derivatives for application in photodynamic therapy of cancer. Laser Phys. 24, 045603. doi:10.1088/1054-660X/24/4/045603.

Mikeš, J., Kleban, J., Sačková, V., Horváth, V., Jamborová, E., Vaculová, A., Kozubík, A., Hofmanová, J., Fedoročko, P., 2007. Necrosis predominates in the cell death of human colon adenocarcinoma HT-29 cells treated under variable conditions of photodynamic therapy with hypericin. Photochem. Photobiol. Sci. 6, 758–766. doi:10.1039/b700350a.

Milla Sanabria, L., Rodríguez, M.E., Cogno, I.S., Rumie Vittar, N.B., Pansa, M.F., Lamberti, M.J., Rivarola, V.A., 2013. Direct and indirect photodynamic therapy effects on the cellular and molecular components of the tumor microenvironment. Biochim. Biophys. Acta - Rev. Cancer 1835, 36–45. doi:10.1016/j.bbcan.2012.10.001.

Mizutani, H., Hashimoto, O., Nakashima, R., Nagai, L., 1997. Anthraquinone production by cell suspension cultures of rubia akane nakai. Biosci. Biotechnol. Biochem. 61, 1743–1744. doi:10.1271/bbb.61.1743.

Modak, M., Dixit, P., Londhe, J., Ghaskadbi, S., Devasagayam, T.P.A., 2007. Indian herbs and herbal drugs used for the treatment of diabetes. J. Clin. Biochem. Nutr. doi:10.3164/jcbn.40.163.

Mortezaee, K., Salehi, E., Mirtavoos-mahyari, H., Motevaseli, E., Najafi, M., Farhood, B., Rosengren, R.J., Sahebkar, A., 2019. Mechanisms of apoptosis modulation by curcumin: implications for cancer therapy. J. Cell. Physiol. 234, 12537–12550. doi:10.1002/jcp.28122.

Muniyandi, K., George, B., Parimelazhagan, T., Abrahamse, H., 2020. Role of photoactive phytocompounds in photodynamic therapy of cancer. Molecules 25. doi:10.3390/molecules25184102.

Murthy, H.N., Kim, Y.S., Park, S.Y., Paek, K.Y., 2014. Hypericins: biotechnological production from cell and organ cultures. Appl. Microbiol. Biotechnol. 98, 9187–9198. doi:10.1007/s00253-014-6119-3.

Naidoo, C., Kruger, C.A., Abrahamse, H., 2019. Simultaneous photodiagnosis and photodynamic treatment of metastatic melanoma. Molecules 24, 3153. doi:10.3390/molecules24173153.

Naik, G.G., Alam, M.B., Pandey, V., Dubey, P.K., Parmar, A.S., Sahu, A.N., 2020. Pink fluorescent carbon dots derived from the phytomedicine for breast cancer cell imaging. ChemistrySelect 5, 6954–6960. doi:10.1002/slct.202001613.

Naik, P.M., Al-Khayri, J.M., 2016. Abiotic and biotic elicitors–role in secondary metabolites production through in vitro culture of medicinal plants. Abiotic and Biotic Stress in Plants - Recent Advances and Future Perspectives. InTech doi:10.5772/61442.

Nardo, L., Andreoni, A., Masson, M., Haukvik, T., Tønnesen, H.H., 2011. Studies on curcumin and curcuminoids. XXXIX. Photophysical properties of bisdemethoxycurcumin. J. Fluoresc. 21, 627–635. doi:10.1007/s10895-010-0750-x.

Niazian, M., 2019. Application of genetics and biotechnology for improving medicinal plants. Planta 249, 953–973. doi:10.1007/s00425-019-03099-1.

Nie, J., Zhao, C., Deng, L., Chen, J., Yu, B., Wu, X., Pang, P., Chen, X., 2016. Efficacy of traditional Chinese medicine in treating cancer. Biomed. Rep. 4, 3–14. doi:10.3892/br.2015.537.

Nuñez Montoya, S., Agnese, A., Pérez, C., Tiraboschi, I., Cabrera, J., 2003. Pharmacological and toxicological activity of Heterophyllaea pustulata anthraquinone extracts. Phytomedicine 10, 569–574.

Núñez Montoya, S.C., Agnese, A.M., Cabrera, J.L., 2006. Anthraquinone derivatives from Heterophyllaea pustulata. J. Nat. Prod. 69, 801–803. doi:10.1021/np050181o.

Núñez Montoya, S.C., Comini, L.R., Rumie Vittar, B., Fernández, I.M., Rivarola, V.A., Cabrera, J.L., 2008. Phototoxic effects of Heterophyllaea pustulata (Rubiaceae). Toxicon 51, 1409–1415. doi:10.1016/j.toxicon.2008.03.011.

Núñez Montoya, S.C., Comini, L.R., Sarmiento, M., Becerra, C., Albesa, I., Argüello, G.a., Cabrera, J.L., 2005. Natural anthraquinones probed as Type I and Type II photosensitizers: singlet oxygen and superoxide anion production. J. Photochem. Photobiol. B Biol. 78, 77–83. doi:10.1016/j.jphotobiol.2004.09.009.

Oertli, E.H., Rowe, L.D., Lovering, S.L., Ivie, G.W., Bailey, E.M., 1983. Phototoxic effect of Thamnosma texana (Dutchman's breeches) in sheep. Am. J. Vet. Res. 44, 1126–1129.

Oliveira, P.M., Lopes, T.Z., Tedesco, A.C., Rahal, P., Calmon, M.F., 2020. Effect of berberine associated with photodynamic therapy in cell lines. Photodiagnosis Photodyn. Ther. 32, 102045. doi:10.1016/j.pdpdt.2020.102045.

Otten, L., Burr, T., Szegedi, E., 2008. Agrobacterium: a disease-causing bacterium. In: Agrobacterium: From Biology to Biotechnology. Springer, New York, pp. 1–46. doi:10.1007/978-0-387-72290-0_1.

Palazzotto, E., Tong, Y., Lee, S.Y., Weber, T., 2019. Synthetic biology and metabolic engineering of actinomycetes for natural product discovery. Biotechnol. Adv. doi:10.1016/j.biotechadv.2019.03.005.

Park, S.Y., Yang, D., Ha, S.H., Lee, S.Y., 2018. Metabolic engineering of microorganisms for the production of natural compounds. Adv. Biosyst. 2, 1700190. doi:10.1002/adbi.201700190.

Park, Y.J., Lee, W.Y., Hahn, B.S., Han, M.J., Yang, W.I., Soo Kim, B., 1989. Chlorophyll derivatives - a new photosensitizer for photodynamic therapy of cancer in mice. Yonsei Med. J. 30, 212–218. doi:10.3349/ymj.1989.30.3.212.

Pasqua, G., Avato, P., Monacelli, B., Santamaria, A.R., Argentieri, M.P., 2003. Metabolites in cell suspension cultures, calli, and in vitro regenerated organs of Hypericum perforatum cv. Topas. Plant Sci. 165, 977–982. doi:10.1016/S0168-9452(03)00275-9.

Petrakou, K., Iatrou, G., Lamari, F.N., 2020. Ethnopharmacological survey of medicinal plants traded in herbal markets in the Peloponnisos. Greece. J. Herb. Med. 19, 100305. doi:10.1016/j.hermed.2019.100305.

Philogène, B.J.R., Arnason, J.T., Towers, G.H.N., Abramowski, Z., Campos, F., Champagne, D., McLachlan, D., 1984. Berberine: a naturally occurring phototoxic alkaloid. J. Chem. Ecol. 10, 115–123. doi:10.1007/BF00987648.

Pistelli, Laura, Giovannini, A., Ruffoni, B., Bertoli, A., Pistelli, Luisa, 2010. Hairy root cultures for secondary metabolites production. Adv. Exp. Med. Biol. 698, 167–184. doi:10.1007/978-1-4419-7347-4_13.

Puschner, B., Chen, X., Read, D., Affolter, V.K., 2016. Alfalfa hay induced primary photosensitization in horses. Vet. J. 211, 32–38. doi:10.1016/j.tvjl.2016.03.004.

Ramachandra Rao, S., Ravishankar, G.A., 2002. Plant cell cultures: chemical factories of secondary metabolites. Biotechnol. Adv. 20, 101–153. doi:10.1016/S0734-9750(02)00007-1.

Ramawat, K.G., 2019. An Introduction to Biodiversity and Chemotaxonomy. Springer, Cham, pp. 1–14. doi:10.1007/978-3-030-30746-2_1.

Rego-Filho, F.G., De Araujo, M.T., De Oliveira, K.T., Bagnato, V.S., 2014. Validation of photodynamic action via photobleaching of a new curcumin-based composite with enhanced water solubility. J. Fluoresc. 24, 1407–1413. doi:10.1007/s10895-014-1422-z.

Revuru, B., Bálintová, M., Henzelyová, J., Čellárová, E., Kusari, S., 2020. MALDI-HRMS imaging maps the localization of Skyrin, the precursor of hypericin, and pathway intermediates in leaves of hypericum species. Molecules 25. doi:10.3390/molecules25173964.

Rischer, H., Hakkinen, S., Ritala, A., Seppanen-Laakso, T., Miralpeix, B., Capell, T., Christou, P., Oksman-Caldentey, K.-M., 2013. Plant cells as pharmaceutical factories. Curr. Pharm. Des. 19, 5640–5660. doi:10.2174/1381612811319310017.

Rivarola, V.A., Rumie Vittar, N.B., Lamberti, M.J., Sanabria, L.M., Pansa, M.F., Fernández, I.M., Cogno, I.S., Rodríguez, M.E., 2013. Cell death and resistance mechanisms triggered by photodynamic therapy, pp. 187–230.

RÖDER, B., HANKE, T., OELCKERS, S., HACKBARTH, S., SYMIETZ, C., 2000. Photophysical properties of pheophorbide a in solution and in model membrane systems. J. Porphyr. Phthalocyanines 04, 37–44. doi:10.1002/(sici)1099-1409(200001/02)4, 1<37::aid-jpp183>3.0.co;2-o.

Rubio, N., Coupienne, I., Di Valentin, E., Heirman, I., Grooten, J., Piette, J., Agostinis, P., 2012. Spatiotemporal autophagic degradation of oxidatively damaged organelles after photodynamic stress is amplified by mitochondrial reactive oxygen species. Autophagy 8, 1312–1324. doi:10.4161/auto.20763.

Rumie Vittar, N.B., Comini, L., Fernadez, I.M., Agostini, E., Nuñez-Montoya, S., Cabrera, J.L., Rivarola, V.A., 2014. Photochemotherapy using natural anthraquinones: rubiadin and Soranjidiol sensitize human cancer cell to die by apoptosis. Photodiagnosis Photodyn. Ther. 11, 182–192. doi:10.1016/j.pdpdt.2014.02.002.

Saito, K., Murakoshi, I., Inzé, D., Van Montagu, M., 1989. Biotransformation of nicotine alkaloids by tobacco shooty teratomas induced by a Ti plasmid mutant. Plant Cell Rep. 7, 607–610. doi:10.1007/BF00272040.

Santos, D.S., Silva, C.C.B., Araújo, V.O., de Fátima Souza, M., Lacerda-Lucena, P.B., Simões, S.V.D., Riet-Correa, F., Lucena, R.B., 2017. Primary photosensitization caused by ingestion of Froelichia humboldtiana by dairy goats. Toxicon 125, 65–69. doi:10.1016/j.toxicon.2016.11.258.

Sarkar, D., Sharma, A., Talukder, G., 1995. Comparison of the effects of crude extract of spinach-beet leaves and equivalent amounts of chlorophyll and chlorophyllin in modifying the clastogenic activity of chromium (VI) oxide in micein vivo. Phyther. Res. 9, 199–202. doi:10.1002/ptr.2650090309.

Schempp, C.M., Schöpf, E., Simon, J.C., 1999a. Dermatitis bullosa striata pratensis durch Ruta graveolens L. (Gartenraute). Der Hautarzt 50, 432–434. doi:10.1007/s001050050937.

Schempp, C.M., Winghofer, B., Langheinrich, M., Schöpf, E., Simon, J.C., 1999b. Hypericin levels in human serum and interstitial skin blister fluid after oral single-dose and steady-state administration of Hypericum perforatum extract (St. John's wort). Skin Pharmacol. Appl. Skin Physiol. 12, 299–304. doi:10.1159/000066256.

Schikora, D., 2020. In vivo detection of circulating tumour cell clusters by photodiagnostic spectroscopy. Photodiagnosis Photodyn. Ther. 30, 101755. doi:10.1016/j.pdpdt.2020.101755.

Schild, A.L., Motta, A.C., Riet-Correa, F., Karam, F.C., Grecco, F.B., 2009. Photosensitization in cattle in Southern Brazil. In: Poisonous Plants and Related Toxins. CABI, pp. 162–166. doi:10.1079/9780851996141.0162.

Shah, R., Verma, P.K., 2019. Synthesis of thiophene derivatives and their antimicrobial, antioxidant, anticorrosion and anticancer activity. BMC Chem. 13, 54. doi:10.1186/s13065-019-0569-8.

Shakya, A.K., 2016. Medicinal plants: future source of new drugs. Int. J. Herb. Med. 4, 59–64. doi:10.13140/RG.2.1.1395.6085.

Shi, H., Sadler, P.J., 2020. How promising is phototherapy for cancer? Br. J. Cancer 1–3. doi:10.1038/s41416-020-0926-3.

Shi, S., Cho, H., Sun, Q., He, Y., Ma, G., Kim, Y., Kim, B., Kim, O., 2019. Acanthopanacis Cortex extract: a novel photosensitizer for head and neck squamous cell carcinoma therapy. Photodiagnosis Photodyn. Ther. 26, 142–149. doi:10.1016/j.pdpdt.2019.02.020.

Shipman, L.L., Cotton, T.M., Norris, J.R., Katz, J.J., 1976. An analysis of the visible absorption spectrum of chlorophyll a monomer, dimer, and oligomers in solution. J. Am. Chem. Soc. 98, 8222–8230. doi:10.1021/ja00441a056.

Singh, J., Hussain, Y., Luqman, S., Meena, A., 2020. Purpurin: a natural anthraquinone with multifaceted pharmacological activities. Phyther. Res. ptr. 6965. doi:10.1002/ptr.6965.

Sobhani Najafabadi, A., Khanahmadi, M., Ebrahimi, M., Moradi, K., Behroozi, P., Noormohammadi, N., 2019. Effect of different quality of light on growth and production of secondary metabolites in adventitious root cultivation of Hypericum perforatum. Plant Signal. Behav. 14. doi:10.1080/15592324.2019.1640561.

Srivastava, S., Srivastava, A.K., 2007. Hairy root culture for mass-production of high-value secondary metabolites. Crit. Rev. Biotechnol. 27, 29–43. doi:10.1080/07388550601173918.

Stafford, K.J., West, D.M., Alley, M.R., Waghorn, G.C., 1995. Suspected photosensitisation in lambs grazing birdsfoot trefoil (Lotus corniculatus). N. Z. Vet. J. 43, 114–117. doi:10.1080/00480169.1995.35866.

Stegelmeier, B.L., Colegate, S.M., Knoppel, E.L., Rood, K.A., Collett, M.G., 2019. Wild parsnip (Pastinaca sativa)-induced photosensitization. Toxicon 167, 60–66. doi:10.1016/j.toxicon.2019.06.007.

Stringasci, M.D., Fortunato, T.C., Moriyama, L.T., Filho, J.D.V., Bagnato, V.S., Kurachi, C., 2017. Interstitial PDT using diffuser fiber—investigation in phantom and in vivo models. Lasers Med. Sci. 32, 1009–1016. doi:10.1007/s10103-017-2225-7.

Stroebel, J.C., 2002. Induction of photosensitivity in sheep with Erodium moschatum (L.) L'Hérit. J. S. Afr. Vet. Assoc. 73, 57–61. doi:10.4102/jsava.v73i2.556.

Subroto, M.A., Kwok, K.H., Hamill, J.D., Doran, P.M., 1996. Coculture of genetically transformed roots and shoots for synthesis, translocation, and biotransformation of secondary metabolites. Biotechnol. Bioeng. 49, 481–494. doi:10.1002/(SICI)1097-0290(19960305)49, 5<481::AID-BIT1>3.0.CO;2-F.

Şueki, F., Ruhi, M.K., Gülsoy, M., 2019. The effect of curcumin in antitumor photodynamic therapy: In vitro experiments with Caco-2 and PC-3 cancer lines. Photodiagnosis Photodyn. Ther. 27, 95–99. doi:10.1016/j.pdpdt.2019.05.012.

Sun, M., Zhang, Y., He, Y., Xiong, M., Huang, H., Pei, S., Liao, J., Wang, Y., Shao, D., 2019. Green synthesis of carrier-free curcumin nanodrugs for light-activated breast cancer photodynamic therapy. Colloids Surf. B Biointerfaces 180, 313–318. doi:10.1016/j.colsurfb.2019.04.061.

Tan, W., Tan, W, Lu, J, Huang, M, Li, Y, Chen, M, Wu, G, Gong, J, Zhong, Z, Xu, Z, Dang, Y, Guo, J, Chen, X, W.Y., Lu, J., Huang, M., Li, Y., Chen, M., Wu, G., Gong, J., Zhong, Z., Xu, Z., Dang, Y., Guo, J., Chen, X., Wang, Y., 2011. Anti-cancer natural products isolated from Chinese medicinal herbs. Chin. Med. 6, 27. doi:10.1186/1749-8546-6-27.

Tavakoli, F., Rafieiolhossaini, M., Ravash, R., Ebrahimi, M., 2020. Subject: UV-B radiation and low temperature promoted hypericin biosynthesis in adventitious root culture of Hypericum perforatum. Plant Signal. Behav. 15. doi:10.1080/15592324.2020.1764184.

Techen, N., Parveen, I., Pan, Z., Khan, I.A., 2014. DNA barcoding of medicinal plant material for identification. Curr. Opin. Biotechnol. 25, 103–110. doi:10.1016/j.copbio.2013.09.010.

Theodossiou, T.A., Hothersall, J.S., De Witte, P.A., Pantos, A., Agostinis, P., 2009. The multifaceted photocytotoxic profile of hypericin. Mol. Pharm. doi:10.1021/mp900166q.

Tillhon, M., Guamán Ortiz, L.M., Lombardi, P., Scovassi, A.I., 2012. Berberine: new perspectives for old remedies. Biochem. Pharmacol. 84, 1260–1267. doi:10.1016/j.bcp.2012.07.018.

Tinitana, F., Rios, M., Romero-Benavides, J.C., de la Cruz Rot, M., Pardo-de-Santayana, M., 2016. Medicinal plants sold at traditional markets in southern Ecuador. J. Ethnobiol. Ethnomed. 12, 29. doi:10.1186/s13002-016-0100-4.

Tsai, W.-H., Yu, K.-H., Huang, Y.-C., Lee, C.-I., 2018. EGFR-targeted photodynamic therapy by curcumin-encapsulated chitosan/TPP nanoparticles. Int. J. Nanomed. Volume 13, 903–916. doi:10.2147/IJN.S148305.

Tu, P., Huang, Q., Ou, Y., Du, X., Li, K., Tao, Y., Yin, H., 2016. Aloe-emodin-mediated photodynamic therapy induces autophagy and apoptosis in human osteosarcoma cell line MG-63 through the ROS/JNK signaling pathway. Oncol. Rep. 35, 3209–3215. doi:10.3892/or.2016.4703.

Uliana, M.P., Pires, L., Pratavieira, S., Brocksom, T.J., De Oliveira, K.T., Bagnato, V.S., Kurachi, C., 2014. Photobiological characteristics of chlorophyll a derivatives as microbial PDT agents. Photochem. Photobiol. Sci. 13, 1137–1145. doi:10.1039/c3pp50376c.

Vantieghem, A., Assefa, Z., Vandenabeele, P., Declercq, W., Courtois, S., Vandenheede, J.R., Merlevede, W., De Witte, P., Agostinis, P., 1998. Hypericin-induced photosensitization of HeLa cells leads to apoptosis or necrosis: involvement of cytochrome c and procaspase-3 activation in the mechanism of apoptosis. FEBS Lett. 440, 19–24. doi:10.1016/S0014-5793(98)01416-1.

Vath, P., Wamer, W.G., Falvey, D.E., 2002. Photochemistry and phototoxicity of aloe emodin. Photochem. Photobiol. 75, 346–352. doi:10.1562/0031-8655(2002)0750346papoae2.0.co2.

Wamer, W.G., Vath, P., Falvey, D.E., 2003. In vitro studies on the photobiological properties of aloe emodin and aloin A. Free Radic. Biol. Med. 34, 233–242. doi:10.1016/S0891-5849(02)01242-X.

Wang, X.N., Han, X., Xu, L.N., Yin, L.H., Xu, Y.W., Qi, Y., Peng, J.Y., 2008. Enhancement of apoptosis of human hepatocellular carcinoma SMMC-7721 cells through synergy of berberine and evodiamine. Phytomedicine 15, 1062–1068. doi:10.1016/j.phymed.2008.05.002.

Wang, Y., Li, X., Li, L.H., Meng, D.L., Li, Z.L., Li, N., 2007. Two new thiophenes from Echinops latifolius and their phototoxic activities. Planta Med. 73, 696–698. doi:10.1055/s-2007-981541.

Warowicka, A., Łukasz, P., Grażyna, B., Oskar, M., Litowczenko, J., Dorota, K., Robert, N., Stefan, J., Anna, G.J., 2019. Protoberberine compounds extracted from Chelidonium majus L. as novel natural photosensitizers for cancer therapy. Phytomedicine 64, 152919. doi:10.1016/j.phymed.2019.152919.

Watson, J.L., Greenshields, A., Hill, R., Hilchie, A., Lee, P.W., Giacomantonio, C.A., Hoskin, D.W., 2010. Curcumin-induced apoptosis in ovarian carcinoma cells is p53-independent and involves p38 mitogen-activated protein kinase activation and down-regulation of Bcl-2 and survivin expression and akt signaling. Mol. Carcinog. 49, 13–24. doi:10.1002/mc.20571.

Wu, S.Q., Yu, X.K., Lian, M.L., Park, S.Y., Piao, X.C., 2014. Several factors affecting hypericin production of Hypericum perforatum during adventitious root culture in airlift bioreactors. Acta Physiol. Plant. 36, 975–981. doi:10.1007/s11738-013-1476-6.

Xie, X., Hudson, J.B., Guns, E.S., 2001. Tumor-specific and photodependent cytotoxicity of hypericin in the human LNCaP prostate tumor model. Photochem. Photobiol. 74, 221. doi:10.1562/0031-8655(2001)074<0221:tsapco>2.0.co;2.

Xing, H., Wang, Z., Shao, D., Chang, Z., Ge, M., Li, L., Wu, M., Yan, Z., Dong, W., 2018. Janus nanocarriers for magnetically targeted and hyperthermia-enhanced curcumin therapy of liver cancer. RSC Adv. 8, 30448–30454. doi:10.1039/c8ra05694c.

Xodo, L.E., Rapozzi, V., Zacchigna, M., Drioli, S., Zorzet, S., 2012. The chlorophyll catabolite pheophorbide a as a photosensitizer for the photodynamic therapy. Curr. Med. Chem. 19, 799–807. doi:10.2174/092986712799034879.

Yamazaki, M., Rai, A., Yoshimoto, N., Saito, K., 2018. Perspective: functional genomics towards new biotechnology in medicinal plants. Plant Biotechnol. Rep. 12, 69–75. doi:10.1007/s11816-018-0476-9.

Yoon, H.E., Oh, S.H., Kim, S.A., Yoon, J.H., Ahn, S.G., 2014. Pheophorbide a-mediated photodynamic therapy induces autophagy and apoptosis via the activation of MAPKs in human skin cancer cells. Oncol. Rep. 31, 137–144. doi:10.3892/or.2013.2856.

Yslas, E.I., Ibarra, L.E., Molina, M.A., Rivarola, C., Barbero, C.A., Bertuzzi, M.L., Rivarola, V.A., 2015. Polyaniline nanoparticles for near-infrared photothermal destruction of cancer cells. J. Nanoparticle Res. 17. doi:10.1007/s11051-015-3187-y.

Zhang, P., Jin, W.R., Shi, Q., He, H., Ma, Z.J., Qu, H.Bin, 2008. Two novel thiophenes from Echinops grijissi Hance. J. Asian Nat. Prod. Res. 10, 977–981. doi:10.1080/10286020802240467.

Zhao, G., Han, X., Zheng, S., Li, Z., Sha, Y., Ni, J., Sun, Z., Qiao, S., Song, Z., 2016. Curcumin induces autophagy, inhibits proliferation and invasion by downregulating AKT/mTOR signaling pathway in human melanoma cells. Oncol. Rep. 35, 1065–1074. doi:10.3892/or.2015.4413.

Zhao, X., Park, S.Y., Yang, D., Lee, S.Y., 2019. Synthetic biology for natural compounds. Biochemistry doi:10.1021/acs.biochem.8b00569.

Zhuo, Z., Song, Z., Ma, Z., Zhang, Y., Xu, G., Chen, G., 2019. Chlorophyllin e6-mediated photodynamic therapy inhibits proliferation and induces apoptosis in human bladder cancer cells. Oncol. Rep. 41, 2181–2193. doi:10.3892/or.2019.7013.

Zou, J., Li, W., Meng, N., Jiang, J., Wu, C., Lei, T.C., Sroka, R., Huang, Z., 2020. Evaluation of lensed fibers used in photodynamic therapy (PDT). Photodiagnosis Photodyn. Ther. 31, 101924. doi:10.1016/j.pdpdt.2020.101924.

Zupkó, I., Kamuhabwa, A.R., D'Hallewin, M.A., Baert, L., De Witte, P.A., 2001. In vivo photodynamic activity of hypericin in transitional cell carcinoma bladder tumors. Int. J. Oncol. 18, 1099–1105. doi:10.3892/ijo.18.5.1099.