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Invited Review

Photoantimicrobials in agriculture

Gilberto Ú.L. Braga [a,*], Geraldo J. Silva-Junior [b], Guilherme T.P. Brancini [a,*], John E. Hallsworth [c,*], Mark Wainwright [d,*]

[a] Departamento de Análises Clínicas, Toxicológicas e Bromatológicas, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto 14040-903, Brazil
[b] Fundecitrus, Fundo de Defesa da Citricultura, Araraquara 14807-000, Brazil
[c] Institute for Global Food Security, School of Biological Sciences, Queen's University Belfast, 19 Chlorine Gardens, Belfast BT9 5DL, Northern Ireland, United Kingdom
[d] School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool L3 3AF, United Kingdom

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ABSTRACT

Classical approaches for controlling plant pathogens may be impaired by the development of pathogen resistance to chemical pesticides and by limited availability of effective antimicrobial agents. Recent increases in consumer awareness of and/or legislation regarding environmental and human health, and the urgent need to improve food security, are driving increased demand for safer antimicrobial strategies. Therefore, there is a need for a step change in the approaches used for controlling pre- and post-harvest diseases and foodborne human pathogens. The use of light-activated antimicrobial substances for the so-called antimicrobial photodynamic treatment is known to be effective not only in a clinical context, but also for use in agriculture to control plant-pathogenic fungi and bacteria, and to eliminate foodborne human pathogens from seeds, sprouted seeds, fruits, and vegetables. Here, we take a holistic approach to review and re-evaluate recent findings on: (i) the ecology of naturally-occurring photoantimicrobials, (ii) photodynamic processes including the light-activated antimicrobial activities of some plant metabolites, and (iii) fungus-induced photosensitization of plants. The inhibitory mechanisms of both natural and synthetic light-activated substances, known as photosensitizers, are discussed in the contexts of microbial stress biology and agricultural biotechnology. Their modes-of-antimicrobial action make them neither stressors nor toxins/toxicants (with specific modes of poisonous activity), but a hybrid/combination of both. We highlight the use of photoantimicrobials for the control of plant-pathogenic fungi and quantify their potential contribution to global food security.

1. Introduction

The progressive increase in the numbers of fungi and bacteria that are tolerant to currently used antimicrobials is a major threat to human health [106,223,231]. Indeed, the intensive antimicrobial use raises concerns regarding both human and environmental health. Furthermore, there is an acute need to improve food security on a global scale [160]. Against this backdrop, it is imperative to develop new and effective strategies for the control of plant-pathogenic microorganisms. Antimicrobial photodynamic treatment (APDT) is a promising alternative to conventional antifungal and antibiotic agents which can be used for the treatment of localized infections in animal and human hosts or to kill plant- or human/animal pathogens in the environment [46,65,78–80,123,130,227,228,243,274,280].

To achieve microbial killing, APDT uses three primary components, namely a photosensitizer, light, and molecular oxygen. The accumulation of a photosensitizer in the cell (either inside or at the surface) of the target microbe is followed by exposure to light that, at an appropriate wavelength, excites the photosensitizer. This causes the production of reactive oxygen species (ROS), such as singlet oxygen ($^1O_2$) and hydroxyl radicals (•OH), which cause biomolecular damage to the cell, effectively killing it with little to no side effects on the host (Fig. 1) [37,46,78,79,121,123,245,280].

Several types of photosensitizers have been used successfully to perform APDT. These include plant-produced, microbe-produced, and synthetic or semi-synthetic photoantimicrobials: chlorins, curcumins, flavins, furocoumarins, hypericins, indocyanines, phenothiazines, phthalocyanines, porphyrins, xanthenes, and others [130,135,259,280].

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* Corresponding authors.
E-mail addresses: gbraga@fcfrp.usp.br (G.Ú.L. Braga), guilherme.brancini@gmail.com (G.T.P. Brancini), johnhallsworth@yahoo.com (J.E. Hallsworth), mark_wainwright@hotmail.com (M. Wainwright).

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When reactive species such as $^1O_2$ are produced at plant surfaces, either via natural plant-produced photosensitizer or via agriculturally applied photosensitizer, they damage fungal spores and mycelia, yeasts, bacteria, as well as the ovipositors of insects that are embedded in the plant tissue [21,107,123].

The chronic and inevitable drawback of conventional (chemical) antifungals, which, like antibiotics, have target-specific modes-of-action, is the development of microbial resistance [280]. By contrast, there is little evidence of the development of resistance to biophysical stressors (e.g. chaotropic, hydrophobic, and oxidative stressors) that act as antimicrobials at multiple target sites and/or via sites-of-action within the cell [17,24,58,59,61,63,129]. Furthermore, most of the photosensitizers used in APDT exhibit low mammalian toxicity and are environmentally-friendly relative to conventional pesticides [8,130,280]. The APDT has the additional advantage of, unlike most conventional fungicides and antibiotics, being able to kill both metabolically-active and -inactive cells, including bacterial and fungal spores [78–80,102,109,118,121,123,177,178,228].

Additionally, APDT is not only able to control plant pathogens pre- and post-harvest [6,78,79,109,123,180,255] but can kill foodborne pathogens and inactivate microbial toxins [145,150]. This said, the identification of effective photosensitizers, and evaluation of potential side-effects on plant- and environmental health, are imperative to the further development of APDT for use in agriculture ([78,79,180,255,276]).

Here, we take a compound-oriented approach, but one based on diverse lines of evidence. We evaluate the natural ecology of photosensitizer-driven antimicrobial processes in plants, including the importance of photosensitizers for phytopathogens and for plant defenses. Additionally, we examine the use of photoantimicrobials in an agricultural context to determine the potential to improve global food security. We discuss inhibitory mechanisms of photosensitizers, in relation to microbial stress biology and agricultural biotechnology, with emphasis on their use for the control of plant-pathogenic fungi, preventing spoilage of foods and feeds, and for controlling mycotoxin-producing fungi and foodborne pathogens, and global food security.

2. Photodynamic Inactivation of Plant-Pathogens

As opposed to topical applications in a clinical setting, the use of APDT to control agricultural plant-pathogens would require bulk application of photosensitizers over considerable areas of land and at reasonable prices, and environmental safety is paramount. Some photosensitizers can be obtained directly from plants, algae, and cyanobacteria or from by-products of processing of fruits such as Tahiti acid lime (*Citrus aurantifolia*) and grapefruit (*Citrus* × *paradisi*) [14,78,109,146,259]. Use of APDT in the field can take advantage of solar radiation, so does not need artificial light for photosensitizer activation. The high irradiances and broad emission spectrum of solar radiation can activate diverse types of photosensitizers, whether they are excited by visible light or by UV radiation [78,146]. Unlike controlled lighting provided by lasers, LEDs, or other artificial sources, incident solar radiation in the field fluctuates. This is due to factors such as climate and weather, time of year, distance from the equator, altitude, atmospheric humidity, dust, and pollution. Furthermore, the periods of illumination in the field are lengthy and the light cycles follow a diurnal pattern [36].

In clinical settings, APDT can be designed to target the pathogen rather than the host by applying the photosensitizer topically on a localized area of infection and by restricting delivery of light to that area of infection [130,280]. On agricultural crops, however, such a protocol would not be feasible as the photosensitizer is applied indiscriminately on pathogen and plant, which are both exposed to solar radiation. Preventing damage to the crop plant, therefore, must be achieved by other means. Nonetheless, fruits and grains can be readily processed post-harvest, using APDT, to reduce the populations of spoilage microbes and foodborne pathogens under controlled conditions and using artificial light sources [39,180].

2.1. Photodynamic Inactivation of Plant-Pathogenic Fungi

Widespread application of synthetic fungicides which have modes-of-action based on site-specific targets within the pathogen cell has been the treatment-of-choice for pre- and post-harvest control of most plant-pathogenic fungi [147,163,208]. However, fungicide resistance has been reported for decades in commercially important pathogens of agricultural crops, including *Alternaria*, *Aspergillus*, *Colletotrichum*, *Erysiphe*, *Fusarium*, *Mycosphaerella*, *Plasmopara,* and *Pythium* [9,19,51,81,147,152,216,224,288,289]. Current concerns about environmental and human health have given rise to recent legislation restricting the use of many of the more dangerous agrochemicals in some regions of the world. Combined with microbial resistance, this has been accompanied by decreasing numbers of commercial fungicides that are approved for agricultural use. For instance, top agricultural producing countries around the world have banned the use of or limited the access to a series of harmful pesticides [88,93,128]. This included restrictions on the concentrations and overall quantity of approved pesticides that can be applied [153]. The need for novel and/or integrated strategies to control fungi both pre- and post-harvest is now, therefore, more urgent than ever.

Taxonomically diverse fungi have been effectively killed by APDT, including human pathogens of the genera *Candida* [65,122,225–227] and *Trichophyton* [228,230,242,266]; entomopathogens used for biological control of insects, such as *Beauveria* [191] and *Metarhizium*

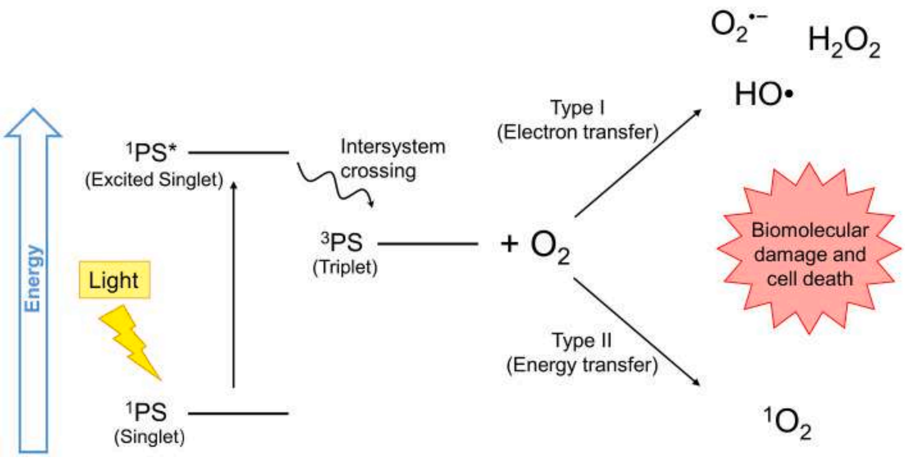

Fig. 1. The principle of antimicrobial photodynamic treatment. A photosensitizer (PS), upon exposure to light, is initially excited to a higher-energy electronic state. Then, via intersystem crossing (transitioning between different electronic states), the excited PS transitions to a triplet state, which reacts with molecular oxygen via either an electron transfer or energy transfer reaction; Type I or Type II reactions, respectively. The former produces reactive oxygen species such as superoxide anion radical ($O2^{•-}$), hydroxyl radical (•OH), and hydrogen peroxide (H_2O_2); the latter generates singlet oxygen ($^1O_2$). These reactive oxygen species cause biomacromolecular damage and pathogen cell death.

[121]; saprophytic fungi that also act as opportunistic pathogens of humans, such as *Acremonium* [183], *Aspergillus* [85,110,116,121,259], *Cryptococcus* [34,229], *Emericella* [266], *Exophiala* [115], *Neurospora* [29,237], *Penicillium* [14,118], and *Rhizopus* [169,181]; endophytes, such as *Papulaspora* [266]; and plant-pathogens, such as *Alternaria*, *Cladosporium* [85,181,183,257], *Botrytis* [6,133,155,176,189,255,257], *Botryosphaeria*, *Mycosphaerella*, *Rhizoctonia*, and *Sclerotium* [255,257], *Colletotrichum* [78,79,85,109,123], *Fusarium* [14,34,80,115,158,166, 174,181,183,189,190,257,277], *Magnaporthe* [276], *Trichothecium* [181], as well as the oomycetes *Pythium* and *Saprolegnia* [85,189,255,257]. The majority of studies for plant-pathogens have been performed in vitro; only a handful of assays have been conducted on a plant host, few experiments have emulated field conditions, and even fewer trials have assessed efficacy in the field. The small number of field trials carried out to test APDT may be explained by the need for wide-scale application of photosensitizers across large areas (where environmental safety is paramount) as opposed to topical applications in a clinical setting.

As explained above, effective APDT of plant-pathogenic fungi relies on the presence of the photosensitizer, simultaneous exposure to solar radiation, and the lifestyle of the fungal species. Some pathogens develop distinct and specialized structures such as asexual spores (e.g., conidia), sexual spores (e.g., ascospores, basidiospores) and other structures (appressoria, fruiting bodies, hyphae/mycelium, sclerotia, biofilms, etc). Invasion and colonization of plant tissue is carried out by hyphae of pathogenic fungi, but spores are usually produced on host-plant surface [3,172,198,216]. Thus, these spores are usually exposed to sunlight, so are a vulnerable structure, among others, that can be targeted by APDT (Fig. 2) [78–80,109].

Therefore, it is fortunate that studies into APDT of fungi have focused on conidia rather than hyphae. The antifungal assays with conidial suspensions can be readily standardized, since conidia are produced by most filamentous fungi, and the inoculum suspension is easy to prepare [13,16,36,56,78,79,85,121,155,181,189,277]. Conidia act as agents of dispersal for the majority of plant-pathogens, and can exhibit robust stress biology upon germination [11,86,87,250,251]. In pathogenic species, conidia are also involved in recognition and infection of the host [18,35,36,201,216]. The biophysical properties (electrostatic charge, hydrophobicity, etc) and chemical composition of the conidia surface differ greatly from those of hyphae (or the vegetative cells of yeast species) [18,121]. Furthermore, conidial properties can vary between developmental stages, nutritional history and physiological status, fungal species and strain, and even within populations of the same strain [221,292,293]. Such factors, particularly surface structure/chemistry, can influence or determine the outcomes of exposure to photosensitizers [79,121,228]. Phototreatment of conidia-producing lesions on plant surfaces can cause a marked reduction in the viability of the fungal propagules present, thereby reducing disease transmission (Fig. 2) [3,263,296].

A genus that has been the subject of APDT studies is *Colletotrichum* [78,79,109,123], an ascomycete genus of common plant pathogens of both wild- and crop-plant species [54,113,124,285]. *Colletotrichum* species are potent pathogens, responsible for major economic losses, especially on temperate, subtropical, and tropical fruits [285]. During the asexual stage, *Colletotrichum* species produce acervuli on plant surfaces, which release mucilage containing vast numbers of unicellular conidia [20,94,296]. This mucilage is readily dissolved by water, so conidia spread via rain-splash to other plants, albeit only short distances from the source (Fig. 2) [187,206]. Strategies to minimize *Colletotrichum* epidemics are based on preventive conventional fungicide sprays during the blooming period, particularly on rainy seasons [112,240]. However, fungicide-resistant *Colletotrichum* isolates have been reported [81,94,108,215,288,289].

Chemically diverse photosensitizers have been used in APDT to kill conidia of plant-pathogens in vitro, including: (i) plant metabolites, such as coumarins and furocoumarins [78,109], curcumin [4,259], phenylheptatriyne [34], phenylphenalenone [166], polyacetylenes [52], and thiophenes [85]; (ii) semi-synthetic compounds, such as chlorophyllins

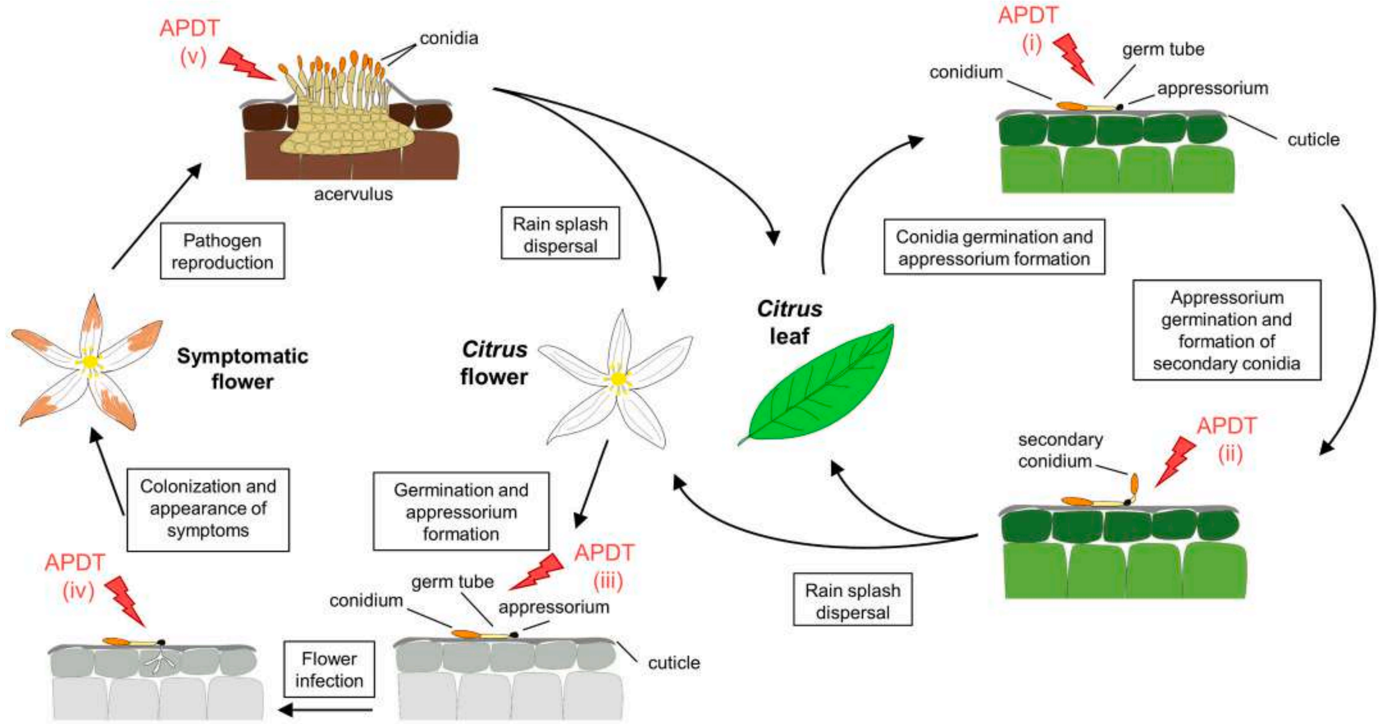

Fig. 2. Stages of the pathogen lifecycle at which antimicrobial photodynamic treatment (APDT; red arrows) can prevent conidial germination and formation of appressorium (i), production of secondary conidia (ii) penetration/infection of the host-plant (iii and iv), and pathogen reproduction/dispersal (v). This schematic is based on Citrus infection by Colletotrichum abscissum. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[133,180] and porphyrins [255,272,277]; phthalocyanine metal complexes [276]; and (iii) synthetic compounds, such as phenothiazinium dyes (e.g., methylene blue, new methylene blue N, and toluidine blue O) [79,80,115,123,169,213,264] and xanthenes [e.g., rose bengal (RB)] [12]. For each of these classes, we closely examine photodynamic inactivation of plant-pathogenic fungi.

2.1.1. *Photodynamic Inactivation of Fungi by Plant Metabolites*

Plants employ various strategies to protect themselves against pathogens, including the constitutive and inductive production of secondary metabolites. Some of these compounds exhibit antimicrobial activities upon photoactivation [78,109,146,165]. Some plants, even those not generally considered to be phototoxic, can rapidly synthesize photosensitizers upon infection by a pathogen [107,162]. Photosensitizers of plant origin include alkaloids with a structure that can be based on tryptamine (e.g., hermane), phenylalanine and tyrosine (e.g., berberine, sanguinarine) or anthranilic acid (e.g., skimmianine and other furanoquinolines); cinnamate derivatives (e.g., coumarins and furocoumarins); polyketides (e.g., polyenes, thiophenes, quinines, and chromenes); and porphyrins that are precursors and degradation products of chlorophylls (Fig. 3) [78,107,109,146].

Coumarins and furocoumarins (e.g., psoralens, angelicins) are found in the oil ducts and cuticles of species within the Apiaceae (e.g., carrots), Fabaceae (e.g., beans and lentils), Moraceae (e.g., figs), Rutaceae (e.g., *Citrus* species), among others [14,78,146,188,204]. They exhibit antimicrobial or insecticidal activities, via either light-independent or light-dependent mechanisms [27,31]. Both coumarins and furocoumarins are typically synthesized continuously (albeit at low levels), so are constitutive. However, their synthesis is upregulated when plants experience bacterial and fungal infection or abiotic stresses [14,82,188]. In general, the highest concentrations of furocoumarins within the leaf occur at the surface, in the epidermal layer [295] and in oil glands within the peel of *Citrus* fruits [105].

Treatment of cells using psoralens and UV-A radiation induces pyrimidine monoadducts and interstrand crosslinks within DNA [33,68,125]. The phototoxicity of psoralens was initially thought to be a consequence of light-activated conjugation with DNA. However, Joshi and Pathak [154] revealed that, whether linear or angular in their molecular configuration, furocoumarins can trigger production of reactive oxygen species upon exposure to light [154]. It is likely that both $^1O_2$ and superoxide radicals contribute to the phototoxicity of these compounds, especially via their adverse effects on the plasma membrane [154,170]. The photoactivation of furocoumarins, and associated damage to membrane systems have been reviewed previously [66]. It is widely recognized that the damage by furocoumarins occurs via multiple mechanisms [170,218,252]. However, in the context of fungal photosensitization, the relative importance of each of these processes has yet to be determined.

Carotenoids and other (blue-green) pigments of *Fusarium oxysporum* and *Fusarium solani* which cause root-rot and wilt in *Citrus* trees, respectively) and *Penicillium digitatum* and *Penicillium italicum* (which cause fruit rot, as agents of green mold and blue mold, respectively) were evaluated as protectants against APDT using the plant-derived photosynthesizers 8-methoxypsoralen (8-MOP) and α-terthienyl (α–T; a thiophene). For each of these fungal species, mutants in conidial pigmentation and wild-type strains were treated with each photosensitizer (at 10 μg mL^{-1}) and exposed to UV radiation (broad-spectrum source; emission from 300 nm to 425 nm; irradiance of 40–43 W m^{-2}). Phototreatment of conidia using α–T was effective, killing most of them, regardless of fungal species. Mutants of *F. oxysporum* and *F. solani* that cannot accumulate carotenoids in their conidia were highly vulnerable to APDT. Likewise, conidial-pigment mutants of *P. digitatum* and *P. italicum* were more sensitive than the wild-type to APDT with α–T. Comparisons of *Fusarium* wild-type conidia and the carotenoid-deficient mutants showed that carotenoids are less effective at protecting against APDT with 8-MOP than APDT with α–T. A different result was observed in the study of *Penicillium*. The heavily pigmented blue-and-green wild-type conidia of *P. digitatum* and *P. italicum*, and a rust-colored mutant of *P. digitatum* were more tolerant to APDT with 8-MOP than their (white) mutant counterparts [15]. The authors hypothesized that carotenoids in wild-type *Fusarium* conidia protect against damage by UV-A-activated α–T by quenching $^1O_2$, while the blue-green pigment(s) of wild-type *P. italicum* conidia (located in the cell wall) prevent DNA damage caused by 8-MOP by filtering out UV wavelengths that would otherwise

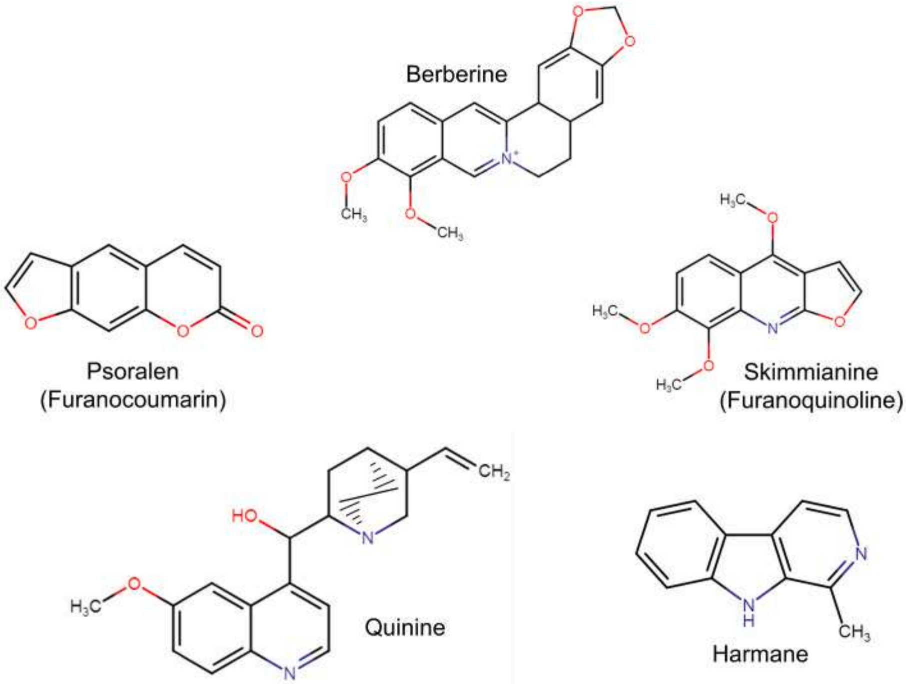

Fig. 3. The chemical structures of common plant-produced photosensitizers. Chemical classes are shown in brackets. Structures were drawn with Marvin JS (ChemAxon).

activate the photosenstitizer.

In a similar study, *Citrus jambhiri* leaf extracts, and the pure furocoumarins bergapten (5-methoxypsoralen; 5-MOP) and psoralen, were evaluated for phototoxicity against wild-type conidia of *F. oxysporum*, *F. solani*, *P. digitatum*, and *P. italicum* and their color-mutant strains [14]. The wild-type strains of both of these *Penicillium* species were less vulnerable than their mutant strains to APDT using furanocoumarins plus UV-A radiation. A 5-$\log_{10}$ reduction in conidia of *F. oxysporum* viability was observed both in the wild-type strain and the pigmentation-mutant strains. However, wild-type conidia of *F. solani* were at least two orders of magnitude less susceptible than the white-mutant conidia. Additionally, Asthana et al. [14] compared ADPT treatment with bergapten of wild-type strains and mutant strains of each *Penicillium* species, and observed different outcomes. In *P. italicum*, conidia of the wild-type and the mutant with altered brown coloration survived with minimal inactivation, whereas white-mutant conidia were extremely susceptible. In *P. digitatum*, killing of wild-type and rust-mutant conidia reached 5 $\log_{10}$. For both *Penicillium* species, the white mutant was highly susceptible to phototreatment (with survival decreasing by as much as six orders of magnitude) [14]. Similar results were observed with psoralen activated by UV-A radiation [14]. Phototreatment using bergapten was one order of magnitude less effective than treatment using psoralen.

A study of APDT using either 8-MOP + isopimpinellin (both furocoumarins) or a mixture of citropten +7-methoxy coumarin (both coumarins) compared efficacies against conidia of *Colletotrichum abscissum* (former *C. acutatum* sensu *lato*) and *Aspergillus nidulans* [78]. Isopimpinellin and the mixture of coumarins were obtained from liquid residues after the industrial processing of *C. aurantifolia*. Upon treatment with the photosensitizers, conidia were exposed to solar radiation. Phototreatment with 8-MOP (50 μM) reduced survival by approximately 2 and 4 $\log_{10}$ for *C. acutatum* after 1 and 2 h of exposure, respectively; and by approximately 4 $\log_{10}$ for *A. nidulans*, regardless of the duration of light exposure. Also, APDT using the mixture of coumarins reduced survival by approximately 1 and 3 $\log_{10}$ for *C. acutatum* after 1 and 2 h of light exposure, respectively. As observed for 8-MOP, phototreatment with the coumarin mixture was more effective for *A. nidulans* conidia, for which the reduction in survival was approximately 4 $\log_{10}$, regardless of the duration of light exposure. For *C. acutatum* conidia, isopimpinellin was the least effective treatment, reducing survival by less than 2 $\log_{10}$ after a 2-h light exposure. Nonetheless, isopimpinellin was effective against *A. nidulans* conidia, reducing survival by approximately 4 $\log_{10}$. This study also reported that 8-MOP penetrates conidia and accumulates within cytoplasmic vesicles [78]. Furthermore, APDT using crude extracts from *C. aurantilfolia*, red grapefruit, and white grapefruit at 12.5 mg L^{-1} were performed and killed from 20% to 70% of the conidia. The *C. aurantilfolia* extract was the most effective [109].

Given that APDT with furocoumarins and coumarins was effective against *C. abscissum*, an imporant question is whether the host plant would tolerate such treatment. To address this issue, the effects of phototreatment on the leaves of plant hosts *Citrus sinensis* (sweet orange), *Citrus reticulate* × *C. sinensis* hybrid (Murcott tangerine), and *Fragaria ananassa* (strawberry) were evaluated using furocoumarins and coumarins combined with solar radiation [78,109]. Phototreatment with 8-MOP, isopimpinellin, and coumarins did not damage the leaves of *C. sinensis* or Murcott tangerine. However, successive daily applications of phototreatment (for 2 weeks) using the individual furocoumarins and the coumarin mixture caused considerable damage to the leaves of strawberry, with the death of epidermis- and parenchyma cells and oxidation of leaf pigments [78]. This result is interesting because the photosensitizers used were isolated from *Citrus* spp., so these plants might be expected to have some tolerance to the photosensitizers in order to avoid self-induced damage. Conversely, strawberry plants do not produce these photosensitizers, so self-induced damage is not an issue and mechanisms to avoid it are not necessary. Nonetheless, these results show that host damage can occur, depending on plant species, so that the safety of phototreatment must be assessed on a case-by-case basis.

Polyacetylenes (polyenes) are a highly effective class of photosensitizers that occur in flowers, leaves, stems, and roots of species in the plant families Apiaceae, Asteraceae, and Campanulaceae [26,52,146,189]. Several plant species are known to produce and accumulate acetylenes, polyacetylenes, and thiophenes in response to infection by microbial pathogens [13,34,162]. They are synthesized in plant cells via the desaturation and chain shortening of fatty acids. Derivatives of polyacetylenes include the sulfur-containing thiophenes [146]. Many polyacetylenes exhibit antifungal activity, and these are greatly enhanced by solar radiation or near-UV radiation [13,34,85,189,190]. For diverse biological systems, studies show that the phototoxicity of polyacetylenes depends on oxygen availability [120]. Acetylenes, especially polyacetylenes, are linear, rigid (inflexible), and lipophilic molecules that accumulate in cellular membranes. In vitro experiments suggested that the fungal plasma membrane is the primary site-of-action for photoactivated acetylenes, and that they are not genotoxic [13]. The biological activities of four thiophene photosensitizers on *Saccharomyces cerevisiae* cells (potential genotoxicity and kill rates) were evaluated in the dark or combined with exposure to UV-A radiation (irradiance of 5 W m^{-2} and emission peak at 350 nm) [199]. None of these four tiophenes were found to be genotoxic: α-terthienyl (α-T); 5-(4-hydroxy-1-butenyl)-2,2′-bithienyl (BBT-OH); 5-(3-buten-1-ynyl)-2,2′-bithienyl (BBT); and 5-(4-acetoxy-1-butinyl)-2,2′-bithienyl (BBT-OAc).

Phototreatments were performed in vitro using three naturally-occurring thiophene derivatives as photosensitizers: 5-(3-buten-1-ynyl)-2,2′-bithienyl (Compound I, BBT); 2,2′:5′,2″-terthienyl (Compound II); and 2-chloro-4-[5-(penta-1,3-diyynyl)-2-thienyl]but-3-ynyl acetate (Compound III), combined with exposure to UV-A (320–380 nm) against some plant-pathogenic ascomycetes, oomycetes, and zigomycetes [85]. Compounds I and II were obtained from *Echinops sphaerocephalus* and compound III from *Tagetes erecta* (both members of the Asteraceae). Conidia of *Alternaria alternata*, *Aspergillus niger*, *Cladosporium variable*, and *Colletotrichum* spp., as well as sporangiospores of *Rhizopus nigricans* were placed on media containing 0.01, 0.1, 1, and 10 μg mL^{-1} of the photosensitizers and exposed to UV-A radiation either immediately or after incubations of 17 and 24 h. In all cases, APDT reduced mycelial growth by 50–100% regardless of the photosensitizer or fungal/oomycete species. The oomycetes were the most susceptible, irrespective of the photosensitizer used. Phototreatment using Compound II repressed conidiogenesis in *A. niger* and sporangiogenesis in *R. nigricans*. Germlings were generally more susceptible to APDT than non-germinated propagules. However, the viability of ungerminated conidia of *A. niger* and *R. nigricans* was unaffected by APDT with Compound II. A previous study reported that the UV-mediated cytotoxicity of Compound II occurs in *Escherichia coli* and *S. cerevisiae* only in the presence of available oxygen, which is consistent with the photodynamic basis for its mode-of-action [13].

The APDT was conducted on conidia and mycelia of the cereal pathogen *Fusarium culmorum* using phenylheptatriyne combined with near-UV radiation (300–400 nm, 5 W m^{-2}), which was extracted from the plant *Bidens pilosa* (Asteraceae). The treatment strongly inhibited both germination of macroconidia and growth of mycelia [34]. Phenylheptatriyne disrupts membrane function in *F. culmorum* via both light-dependent and light-independent mechanisms [13]. Phototreatment of mycelia or macroconidia with phenylheptatriyne (10 ppm) led to increasing granulation of the cytoplasm as exposure to near-UV radiation (300–400 nm, 5 W m^{-2}) was increased (indicating cellular damage), inhibited ^{14}C-phenylalanine uptake and respiration, and enhanced K^+ leakage, confirming that the plasma membrane is the primary target site of phenylheptatriyne [13].

Furthermore, the accumulation of phototoxic thiophenes was studied in *T. erecta* that was infected with *F. oxysporum* [162]. The naturally occurring thiophenes BBT-OH, BBT-OAc, α-T, BBT, and 5-(3,4-

diacetoxy-1-butinyl)-2,2′-bithienyl [BBT-(OAc)$_2$]— completely inhibited spore germination at 5 μg mL^{-1} (in vitro) in the presence of near-UV radiation (300–400 nm, 4 W m^{-2}). Also, α-T was strongly phototoxic against mycelia [162].

The plant *Targetes patula* (French marigold; Asteraceae) also accumulates the thiophenes α-T and BBT-OH [230]. The APDT was carried out against the plant-pathogenic fungi *Botrytis cinerea*, *Fusarium moniliforme*, and *Pythium ultimum* using the pure thiophenes α-T and BBT-OH, and a methanol extract of *T. patula* [189,190]. Mycelia were placed on media containing 5, 10, and 50 μg mL^{-1} of each pure thiophene, or *T. patula* extract at a range of dilutions, and then exposed to UV-A radiation (peak at 350 nm, 5 W m^{-2}) or simulated solar radiation. Each of these treatments inhibited growth in a concentration-dependent manner and regardless of pathogen species. In terms of reduction of growth-rate, *P. ultimum* was the most susceptible species, and *F. moniliforme* was the least susceptible [190]. The use of scanning electron microscopy and transmission electron microscopy revealed structural alterations to the plasma membrane of *P. ultimum*, disorganization of the cytoplasm, destruction of the nuclear envelope, and damage to the cell wall [189]. Comparable damage was observed in the dermatophyte fungus *Nannizia cajetani* following APDT using BBT-OH [230].

Phenylphenalenones are phototoxic polycyclic aromatic compounds found mainly in Haemodoraceae and Musaceae families [142]. They protect against pathogens, and their accumulation is upregulated in response to several fungal species [107,173]. Light-induced $^1O_2$ production and antifungal activity was reported for phenylphenalelones extracted and purified from pathogen-infected *Musa acuminate* (dwarf banana) [166]. Conidia of *F. oxysporum* were spread onto potato dextrose agar supplemented with each of the purified phenylphenalenones and then either kept in the dark or exposed to visible light. For each photosensitizer obtained this way, antifungal activity was observed in both light and darkness; but was highest with exposure to light for the majority of the photosensitizers. Furthermore, antifungal activity was proportional to the amount of $^1O_2$ produced by phenalenones. Experiments conducted in D_2O-based culture media confirmed the participation of $^1O_2$ in phenylphenalenone phototoxicity [166]. Interestingly, the synthesis of 4-phenylphenalenone, which exhibited both the highest $^1O_2$ yield and greatest antifungal activity of the phenylphenalenones assayed, occurs only in infected plants. By contrast, the less potent 9-phenylphenalenones occur in both healthy and infected plants from other families. Given the adverse effects of $^1O_2$ on cellular systems, plants could have evolved to minimize $^1O_2$ generation whenever possible [166]. Also, some fungi have evolved partial resistance to photosensitizers produced by plants for self-defense: for instance, *Mycosphaerella fijiensis*, the causative agent of the black sigatoka leaf-spot disease of bananas, can convert phenylphenalenones to sulfate conjugates that are inactive [141].

Decontaminating fungi-infected grain, maize, peanuts, or other seeds (whether used for sowing or consumption) mitigates against dispersal and mycotoxin contamination of the food supply chain. *Aspergillus flavus* is a commonly-occurring seed-borne pathogen that produces mycotoxins, including aflatoxin that is a potent carcinogen [259]. Thus far, chemical antifungals have been used to kill seed-borne fungal pathogens, but with varying levels of success [96]. Furthermore, seed-decontamination treatments must kill fungi and inactivate mycotoxins without reducing seed viability or vigor [184].

Phototreatment of *A. flavus* conidia was evaluated both in vivo and in vitro using curcumin as the photosensitizer [259]. Curcumin, a yellow polyphenol, is obtained from the tubers of the plant *Curcuma longa*. Conidia were treated with different photosensitizer concentrations (from 5 to 100 μM) and exposed to light at 420 nm, both in phosphate buffered saline (PBS) solution and on maize kernels. Fluences used ranged from 12 to 84 J cm^{-2} and were obtained using a xenon arc lamp with adjustable wavelength selection as the light source. Reductions of conidial viability were up to 3 $\log_{10}$ in suspensions and 2 $\log_{10}$ in maize kernels when optimal combinations of photosensitizer concentration and light fluence were used [259]. Also, APDT using curcumin (100 to 1000 μM) combined with white light (24 to 96 J cm^{-2}) were evaluated on conidia of *A. flavus*, *A. niger*, *F. oxysporum, Penicillium crysogenum*, and *Penicillium griseofulvum* [4]. Conidia were killed by curcumin whether in spore suspensions or on the surface of agar plates.

Curcumin was also shown to be effective against *B. cinerea*: phototreatment of spores with a concentration of 800 μM and a light fluence of 120 J cm^{-2} (430 nm wavelength) completely killed the conidia. Furthermore, the toxins botrydial and dihydrobotrydial, which accumulate in spores under normal conditions, could not be detected in treated conidia [145]. These results further emphasize the application of APDT not only for pathogen killing, but also for toxin inactivation or destruction.

2.2. Photodynamic Inactivation of Plant-Pathogenic Fungi Using Synthetic and Semi-Synthetic Photosensitizers

2.2.1. Phenothiazines

Phenothiazines are tricyclic organic compounds derived from a thiazine heterocyclic (Fig. 4). For control of fungi in both agriculture and medicine, phenothiazinium dyes are among the most-commonly used photosensitizers. Generally, they are not toxic to mammals [280] and are environmentally safer than widely-used commercial fungicides [8].

Methylene blue and other phenothiazinium photosensitizers are used for tracing cell malignancy and to treat methemoglobinemia (a blood disorder arising from the oxidation of Fe^{2+} to Fe^{3+} within hemoglobin) at concentrations that are orders of magnitude higher than the minimum concentrations required to kill microbes [236,278]. Novel phenothiaziniums, such as the pentacyclic S137, new methylene blue N, and derivatives with basic side-chains, exhibit higher levels of antifungal activity compared to methylene blue [65,80,228,279,281]. Recent studies have shown that the antimicrobial activity of phenothiaziniums can be enhanced by urea or inorganic salts such as potassium iodide [207,273], which is also observable for other photosensitizers [28,48].

In terms of interaction between photosensitizers and target pathogen, the negatively-charged surfaces of both the fungal plasma membrane and fungal cell wall promote interactions with cationic phenothiaziniums, and several lines of evidence suggest that the plasma membrane is the primary site of damage following light-activation of these molecules [80,149,210,211].

A study of *Saccharomyces fragilis* revealed that the photosensitizer toluidine blue O, which is commonly used for APDT, interacts with polyphosphates localized outside the plasma membrane without entering the cells [267]. Also, it was reported that toluidine blue O does not enter cells of *S. cerevisiae* and that the photodynamic activity a consequence of its action on the extracellular medium and/or on the outer surface of the plasma membrane [148]. A study of APDT on *S. cerevisiae* showed that toluidine blue O causes rapid oxidation of ergosterol and the subsequent accumulation of oxidized ergosterol within the plasma membrane [30]. The damaged plasma membrane facilitates entry of the photosensitizer into the cytosol, which further damages intracellular membranes and biomolecules. This, in turn, leads to impaired mitochondrial function and, ultimately, cell death [30].

Indeed, APDT with methylene blue, toluidine blue O, new methylene blue N, or S137 increased the plasma membrane permeability of *F. moniliforme*, *F. oxysporum*, and *F. solani* conidia. However, only the most-lipophilic photosensitizers, new methylene blue N and S137, caused peroxidation of membrane lipids [80], which could indicate that photsensitizer localization is heavily dependent on fungal species and/or developmental stage. Furthermore, a recent study compared the mechanism of *C. albicans* photoinactivation with new methylene blue N and S137 [226]. Whereas new methylene blue N targets mitochondria and reduce their membrane potential, S137 partitions into the cell membrane due to its high log *P* (6.26), where it causes destabilization

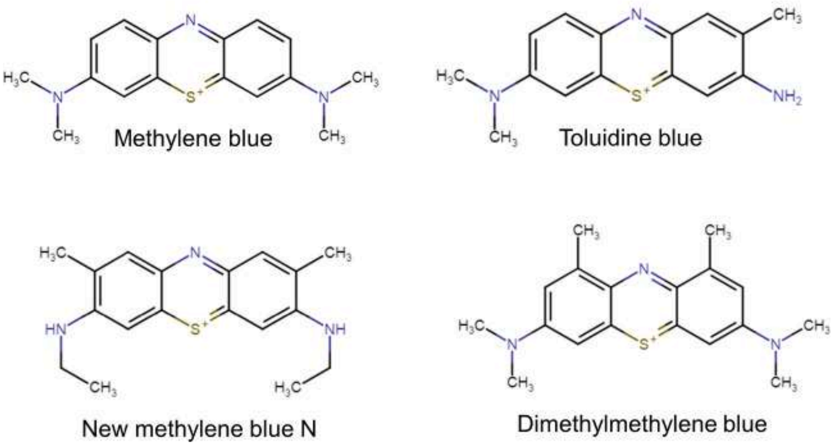

Fig. 4. Chemical structure of phenothiazinium dyes commonly used for photodynamic treatment. Structures were drawn with Marvin JS (ChemAxon).

and increased permeability [226]. Upon light exposure, S137 already present within the cell membrane increases photokilling, especially at lower light fluences [226].

Gonzales and coworkers evaluated the effects of APDT with methylene blue or toluidine blue O on conidia of the saprophyte *A. nidulans* and the entomopathogen *Metarhizium robertsii* (formerly *M. anisopliae lato* sensu) [121]. Conidia of *Metarhizium* species have long been used as inoculum for control of agricultural insect pests, and are still one of the most effective fungal species for this purpose [36,38,104,222]. In the study, concentrations of methylene blue and toluidine blue O ranged from 1 to 400 μM and conidia were exposed to broad-spectrum visible light (irradiance of 50 W m^{-2}) for 30 or 60 min. Mortality rates of up to 99.7% were achieved according to CFU counts, and germination of conidia which remained viable was delayed, suggesting considerable stress or damage to surviving conidia [132]. Washing conidia prior to light exposure slightly reduced the effect of APDT on *M. robertsii* but strongly reduced the effect on *A. nidulans*. These findings suggest that methylene blue and toluidine blue O are taken up by each type of conidia at different rates or interact with conidia via different mechanisms [121].

Additionally, when APDT of *A. nidulans* and *M. robertsii* was attempted for conidia in potato dextrose broth, no loss of viability occurred, indicating that some constituents of the medium may act as antioxidants and scavengers of ROS [121]. Furthermore, conidial pigments conferred some protection against APDT with phenothiazinium photosensitizers. The conidia of the *M. robertsii* dark green wild-type and yellow-colored mutants were more resistant to APDT compared with white (albino)- or violet-colored mutants [121]. Similarly, dark green wild-type conidia of *A. nidulans* were more tolerant to APDT using methylene blue or toluidine blue O than mutants with diverse conidial pigmentation [5].

The efficacy of APDT of *C. abscissum*, *Colletotrichum gloesosporioides*, and *A. nidulans* conidia was determined in vitro using the using phenothiazinium photosensitizers methylene blue, toluidine blue O, new methylene blue N, and S137 [79]. Minimum inhibitory concentration (MIC) was determined for each photosensitizer at different light fluences and S137 was found to be the most effective. At fluences $\geq$20 J cm^{-2}, for example, an S137 concentration of only 10 μM was sufficient to prevent fungal growth, regardless of species. The dark toxicity of S137 was also greater than that of the other photosensitizers assayed, regardless of the species. Superior activity was also reported for S137 and new methylene blue N relative to methylene blue against *Candida* [65,227] and *Trichophyton* spp. [228]. Furthermore, APDT of conidia with new methylene blue N or S137 and solar radiation or red light (emitted by LEDs) was highly effective, regardless of the photosensitizer, light source or species. When conidia were washed prior to light exposure, APDT using new methylene blue N or S137 was about as effective as APDT without washing, indicating that these photosensitizers were taken in by conidia.

Consistent with this, microscopic examination of *C. abscissum* conidia revealed that new methylene blue N and S137 accumulated in cytoplasmic vesicles [79]. Photosensitizer entry and accumulation begins upon contact with conidia, and is independent of light exposure. This study also compared localization of these photosensitizers with the localization of the dyes Sudan III and FM4–64®, which have affinity for lipid bodies and vacuolar membranes, respectively. Both new methylene blue N and S137 accumulated in lipid bodies and small vacuoles. Conidial treatment in the dark with S137 at concentrations $\geq$50 μM modified the structures of the cytoplasmic organelles and caused the formation of large vesicles [79].

One concern about using these photosensitizers on crop plants in the field is their loss of photosensitizing potential after extended light exposure. If new methylene blue N or S137 are exposed to solar radiation prior to application to conidia, their APDT potency is reduced [79], a phenomenon known as photobleaching [202]. For instance, when new methylene blue N and S137 were exposed to solar radiation for 3 h and then used for APDT, conidial survival was reduced only about 3 $\log_{10}$ relative to controls, compared with a reduction of 5 $\log_{10}$ if the photosensitizers were not exposed to solar radiation prior to APDT. After exposure to solar radiation for 12 h, S137 was only weakly active against *C. abscissum* conidia, whereas new methylene blue N retained more of its activity, with an ability to kill 90% (1 $\log_{10}$) of the conidia [79]. However, it is important to note that these experiments were performed under harsh conditions: photosensitizer solutions were exposed continuously to solar radiation at a tropical site (21.2° latitude S) during cloudless, early-autumn days. Thus, the longevity of phenothiazinium photosensitizers is likely to be greater for most agricultural scenarios, especially if geographical location or climatic conditions involve less-intense solar exposure [79].

The effects of photodynamic treatment on the leaves of *C. sinensis* were evaluated using methylene blue, new methylene blue N, toluidine blue O, and S137 (each at 50 μM) and solar radiation [79]. There was no apparent damage to the plant (regardless of the photosensitizer used), presumably because the photosensitizer could not penetrate the 4-μm-thick leaf cuticle [79]. As ROS generated during APDT have relatively short half-life, their diffusion can be very limited, thereby restricting damage to the immediate vicinity of the photosensitizer [241]. Therefore, APDT of plant-pathogenic microbes located on the host-plant surfaces proceeds without compromising the integrity of the latter.

In the last decades, human mycoses caused by species considered to be plant pathogens or fungal saprophytes (rather than human pathogens) increased dramatically [126]. Among the causative agents are species of *Aspergillus*, *Exophila*, *Fusarium*, and *Rhizopus* [115,126,169,290]. Invasive human infections by these fungi are usually refractory to treatment with conventional antifungals

[126,169,212], so APDT of these fungi may have clinical potential. In this sense, a detailed study to evaluate APDT using methylene blue, new methylene blue N, toluidine blue O, and S137 on both ungerminated and germinated microconidia of *F. moliniforme*, *F. oxysporum*, and *F. solani* were evaluated [80]. The intracellular localization of the photosensitizers as well as potential consequences of APDT were determined, including lipid peroxidation, plasma-membrane permeability, and conidial survival. Regardless of the photosensitizer used, APDT killed both ungerminated and germinating microconidia efficiently for all three *Fusarium* species [80].

Another strategy to control and treat fungi-caused human diseases is the combination of APDT and antifungals. In this sense, the effects of APDT with methylene blue at concentrations of 8 to 32 μg mL^{-1} either alone or in combination with standard antifungal compounds were evaluated [115]. The treatment was carried out for both planktonic cells and biofilms of clinical isolates of *Exophiala dermatitidis*, *F. oxysporum*, and *F. solani*. Phototreatment with methylene blue reduced survival by up to 3.8 $\log_{10}$ and 6.4 $\log_{10}$ of planktonic *Exophiala* spp. and *Fusarium spp*., respectively. The reductions for biofilms were 4.2 $\log_{10}$ and 5.6 $\log_{10}$, respectively. However, light fluence used had to be two-fold higher than that used against planktonic cells. Application of APDT prior to the use of standard antifungals resulted in dramatic reduction of MICs when compared to antifungal treatment alone irrespective of fungal species [115].

The mucoromycete *Rhizopus oryzae* causes post-harvest fruit rot and is also a common cause of mucormycosis, an aggressive and frequently fatal opportunistic fungal infection in immunocompromised individuals [271,282]. Phototreatment with methylene blue (32 μg mL^{-1}) and red light (LED, 635 nm, 12 J cm^{-2}) completely inhibited growth and the reduction in CFU counts was up to 4.3 $\log_{10}$. Also, APDT reduced the MIC for the antifungals itraconazole, posaconazole, and amphotericin B [169].

2.2.2. Xanthenes

Xanthene is a tricyclic dibenzopyran organic compound that, while not possessing useful photodynamic properties, has many derivatives that are used in APDT, such as eosin Y and rose bengal (Fig. 5). The in vitro effects of APDT with eosin Y on the endophyte *Papulaspora immersa* and the plant-pathogen *Emericella rugulosa* were evaluated [266]. Ergosterol oxidation and survival were assessed after APDT. Mycelia of these fungi were no longer viable after the treatment and cell death correlated with ergosterol photooxidation, indicating that ergosterol damage may be an effective way of achieving photoinactivation.

In integrated pest management programs, photoactive insecticides, such as xanthene derivatives, may be combined with microbial biocontrol agents [161,197]. However, only a few studies have addressed the potential issue of APDT causing harm to biological control agents. Such biocontrol agents include viruses (e.g. baculoviruses, entomopoxviruses), bacteria (e.g. *Bacillus thuringiensis*), and entomopathogenic fungi (e.g. *Beauveria bassiana*, *Isaria fumosorosea*, and *Metarhizium* spp.).

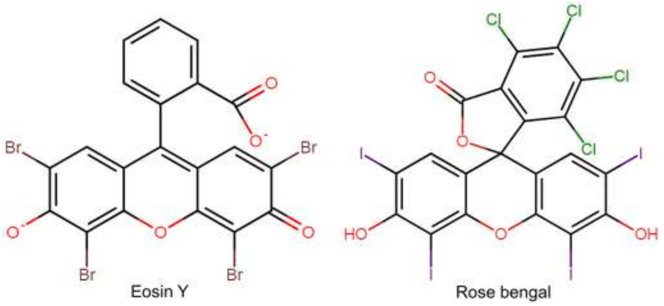

Fig. 5. Chemical structure of the two best known and most used xanthene dyes. Structures were drawn with Marvin JS (ChemAxon).

One study evaluated APDT using the xanthene dyes phloxine B (an insecticidal photoactive compound), rose bengal, fluorescein, or eosin Y combined with white light and observed inhibited growth of the biocontrol agents *B. thurigiensis* and *B. bassiana* [191]. Also, phloxine B was evaluated for compatibility with selected biocontrol fungi to determine its potential for use in integrated pest management programs [197]. These studies found evidence that phloxine B, like other photosensitizers (see below), inhibit some biocontrol fungi. Phloxine B at 0.01% (*w/v*) inhibited the growth of *B. bassiana*, *Coniothyrium minitans*, and *Verticillium lecanii* in the presence of light. Growth of the fungus *Trichoderma virens* was inhibited by phloxine B both with and without light exposure, while growth of *Stilbella erythrocephala* was not affect by phloxine B, irrespective of illumination [197]. Treatment with phloxine B at 0.005, 0.01, and 0.02 g L^{-1} combined with visible light did not affect conidia germination of the entomopathogen *I. fumosorosea* and, interestingly, a complementary effect of phloxine B on the insecticidal efficacy of the fungus against the greenhouse whitefly, *Trialeurodes vaporariorum*, was observed [161]. Collectively, these data suggest that chemically diverse photosensitizers can inhibit phylogenetically diverse biocontrol agents such that each photosensitizer/biocontrol organism combination must be evaluated prior to consideration for use in pest-management programs.

Fungal infections of the human cornea, frequently caused by species of the genera *Aspergillus* and *Fusarium*, are termed fungal keratitis, a disease potentially leading to blindness [261]. Fungal keratitis is more common in agricultural communities, and its management is restricted by the availability of effective antifungal agents, which must be able to penetrate corneal tissue [261]. The effects of APDT on clinical isolates of *A. fumigatus* and *F. solani* using rose bengal and riboflavin as photosensitizers were compared [12]. Rose bengal and other xanthene dyes have been routinely used in ophthalmology clinics to visualize degeneration of, or other defects in, the surface epithelium of the eye [103,214]. Conidia suspensions were treated with rose bengal or riboflavin, both at 0.1% (*w/v*), and were then exposed to green or UV-A light (375 nm, 29.1 W m^{-2}). Phototreatment with rose bengal prevented the growth of both *A. fumigatus* and *F. solani*, but no photoinactivation was observed with riboflavin [12]. The success of APDT with rose bengal at 0.1 or 0.2% and green light (15 min at 5.4 J cm^{-2}) were reported in a pilot clinical study with patients with progressive keratitis caused by *Fusarium* spp. and *Curvularia spp*. [200].

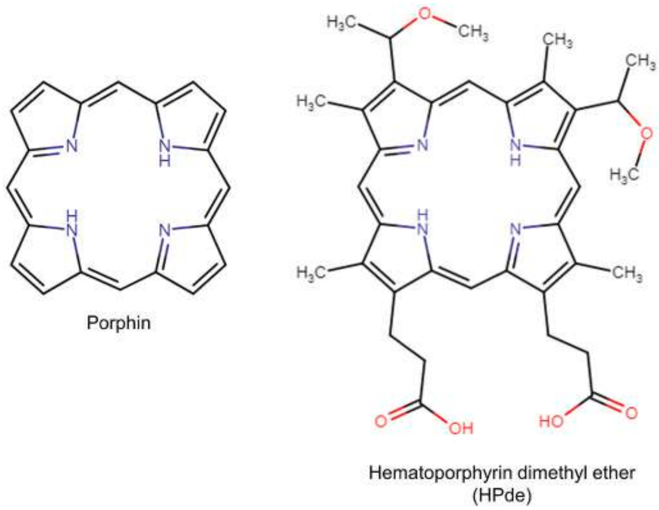

Fig. 6. Chemical structure of porphin, the simplest porphyrin, and the hematoporphyrin dimethyl ether (HPde) derivative. Structures were drawn with Marvin JS (ChemAxon).

2.2.3. Porphyrins

Porphyrins are heterocyclic macrocycles composed by four pyrrole subunits interconnected via methane bridges (Fig. 6) and have been widely evaluated for APDT of phytopathogenic organisms.

Fusarium is a genus of filamentous fungi that contains many agriculturally important plant pathogens, mycotoxin producers, and opportunistic human pathogens [92,185,186,246]. The effects of APDT with hematoporphyrin dimethyl ether (HPde) on spores of plant pathogens (*Fusarium avenaceum* and *Trichothecium roseum*) and saprotrophic opportunistic human pathogens (*A. flavus* and *R. oryzae*) were evaluated [181]. Sporangiospores of *R. oryzae* and conidia of the other fungal species were treated with HPde (0.25 to 71 μM) and exposed to visible light at 300 W m^{-2} for 15 min. HPde accumulated within the spores and exhibited dark toxicity regardless of fungal species, though its potency as an inhibitor of germination varied with fungal species, with *A. flavus* being more susceptible than the other species tested. The APDT using HPde and visible-light exposure inhibited spore germination for all species, but *A. flavus* and *R. oryzae* were more susceptible than the other fungi. In-vitro APDT using HPde and visible-light was also effective at killing conidia of the plant-pathogen *A. alternata* and saprotrophic/human pathogen *Acremonium strictum* [183].

APDT of *F. culmorum* and *Fusarium poae* conia was evaluated in vitro using protoporphyrin IX, which is a hydrophobic dye that localizes to cell membranes [277]. Conidia were treated with protoporphyrin IX (1 to 4 μM) and were then exposed to visible light at 150 W m^{-2}. Phototreatment resulted in protein and lipid oxidation, increased plasma-membrane permeability, and reduced conidial viability. At 4 μM protoporphyrin IX and a fluence of 20 J cm^{-2}, germination decreased by 55 and 96% for *F. culmorum* and *F. poae*, respectively.

Many studies have attempted to improve the efficiency of APDT with porphyrins by modifying their structure and producing a series of cationic derivatives. For instance, APDT of conidia from the saprotrophic fungus *Penicillium chrysogenum* was carried out using five cationic porphyrins (each at 50 μM) and white light (irradiance 2000 W m^{-2}, 20 min) [118]. The most effective porphyrin, 5,10,15,20-Tetrakis (*N*-methylpyridinium-4-yl)porphyrin tetraiodide, caused a 4.1 log$_{10}$ reduction in conidial viability. The size of the *N*-alkyl chain was shown to correlate with photoinactivation efficiency, mainly by affecting the solubility of the photosensitizer and its biding to conidia. In this sense, the best photosensitizer was the molecule with the shortest carbon chain, suggesting that the increase of the *N*-alkyl length of all four alkyl chains does not improve the photodynamic efficiency. The amount of photosensitizer incorporated by conidia was a determinant for photoinactivation efficiency and varied among the different porphyrins. Accordingly, examination using light microscopy revealed that all of the porphyrins penetrated conidia, but some showed a more uniform distribution within cells whereas others localized to the plasma membrane [118].

Colletotrichum graminicola is a destructive pathogen of maize causing both stalk rot and leaf blight [67]. Treatment of *C. graminicola* conidia was carried out using five cationic *meso*-(1-methyl-4-pyridinio)porphyrins which have phenyl or 1-methyl-4-pyridinio group at the macrocycle *meso* position [272]. This was performed using porphyrin concentrations from 1 to 25 μM and fluences ranging from 30 to 120 J cm^{-2} (emitted from a 250-W halogen lamp). Considering the lowest photosensitizer concentration and the lowest light fluence that enabled photoinactivation, the porphyrins efficiencies were ranked as triple-charged (1 μM with a fluence of 30 J cm^{-2}) > double-charged-*trans* (1 μM with a fluence of 60 J cm^{-2}) > tetra-charged (15 μM with a fluence of 90 J cm^{-2}) > mono-charged (25 μM with a fluence of 120 J cm^{-2}). The APDT using the triple-charged porphyrin at 1 μM and 30 J cm^{-2} killed all conidia. Double-charged-*cys*-porphyrin killed conidia in the dark, i.e. without light-activation. The porphyrins that presented high $^1O_2$ quantum yields and accumulated to a high degree in conidia were the best photosensitizer [272].

APDT with a porphyrin (TMPyP) metal-organic framework (PS@MOF) was evaluated against the plant-pathogenic fungi *Sclerotinia sclerotiorum*, *Pythium aphanidermatum* and *B. cinerea* both in vitro and *in planta* [255]. In vitro APDT with PS@MOF strongly inhibited mycelia growth of the three fungal species at photosensitizer concentrations of 6, 12, and 24 mg L^{-1}. Also, APDT was able to control *S. sclerotiorum* on cucumber with efficiency equal to the dicarboximide fungicide dimethachlon without causing damage to the host plant [255]. Also, APDT with the anionic porphyrin tetra-4-sulfonatophenyl porphyrin tetraammonium (TPPS) was tested against *B. cinerea* both in vitro and *in planta* [6]. In vitro APDT with TPPS at 1.5 μM combined with white light caused potent inhibition of mycelium growth. Also, mycelium pretreated with TPPS was unable to infect detached leaves of any of the three grapevine clones from Chadornnay, Merlot, and Sauvignon. Importantly, treatment with the photosensitizer at 12.5 M did not damage the plants [6].

2.2.4. Chlorins, Bacteriochlorins, Chlorophyllins, and Chitosan

A chlorin, the core chromophore of a chlorophyll, is a dihydroporphyrin macrocycle that contains three pyrrole rings and one pyrroline ring (Fig. 7) [256]. Several of the clinically important photosensitizers are chlorins, including *m*-tetrahydroxyphenylchlorin, benzoporphyrin derivative, radachlorin, and chlorin e6 [1]. Structurally, chlorins have a double bond in one pyrrole ring reduced (Fig. 7) whereas bacteriochlorins have two pyrrole rings with reduced double bonds (Fig. 7) (Martinez [193]). The bacteriochlorin group also includes important clinical photosensitizers [1] and both chlorins and bacteriochlorins have been evaluated as photosensitizers for use in APDT against plant pathogens and foodborne human pathogens [171,180,269].

As mentioned earlier, positively-charged photosensitizers tend to be more efficient as antimicrobials because of their affinity for the negatively-charged cell surfaces of bacteria and fungi [130]. Indeed, the attachment of polycationic polymers such as poly-L-lysine and polyethylenimine to chlorins (that otherwise do not possess any intrinsic

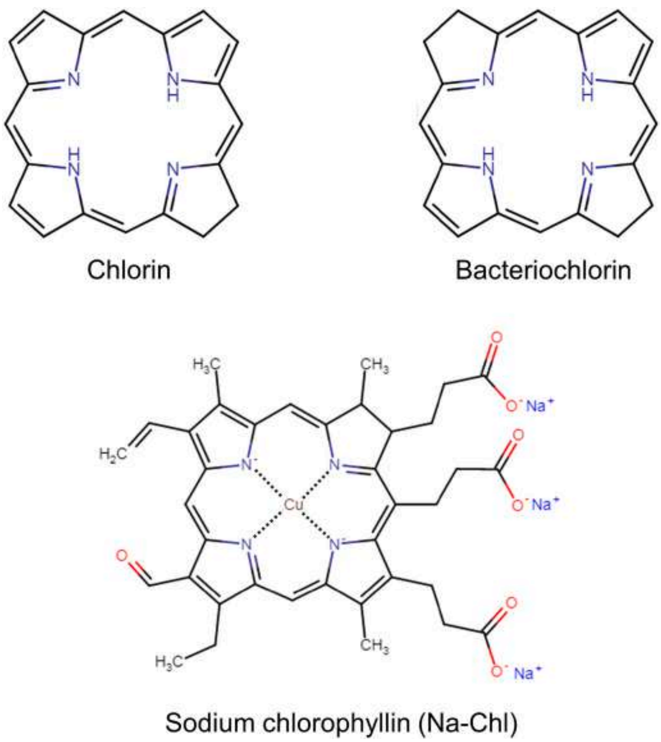

Fig. 7. Chemical structures depicting the differences between chlorin (20 π electrons) and bacteriochlorin (18 π electrons). The structure of a chlorin derivative, sodium chlorophyllin, is also shown. Structures were drawn with Marvin JS (ChemAxon).

positive charge) enhanced their efficiency in APDT [131,258]. Interestingly, it was reported that an asymmetric dicationic bacteriochlorin was significantly more active against Gram-positive bacteria and fungi than a symmetrically-substituted tetracationic bacteriochlorin [144]. Recently, thiopyridinium and methoxypyridinium chlorin derivatives were tested against *F. oxysporum* [238]. Among these, a free-base thiopyridinium chlorin was shown to be the most effective compound, achieving complete conidial killing after 15 min (45 J cm^{-2}) of white-light exposure at a concentration of 15 μM. The other compounds required either higher concentrations and/or longer exposure to light [238]. These results show that chlorin derivatives can be potent photosensitizers against plant-pathogenic fungi.

Chlorophyllins are semi-synthetic, water-soluble salts derived from chlorophyll *a*nd are also approved as food colorants in both the EU and the USA (Fig. 7) [291]. Chlorophyllins have been used as photosensitizers for photodynamic treatment of several types of cancers as well as for APDT [2,174,176,180]. Treatment using sodium salts of chlorophyllin (Na-Chl) and visible light was evaluated for post-harvest control of spoilage microbes on strawberries [180]. Naturally-contaminated strawberry fruits were soaked in Na-Chl at 1 mM for 5 min and illuminated for 20 min with visible light (400 nm and irradiance of 120 W m^{-2}). The growth of fungi and total aerobic mesophiles was reduced by 86 and 97%, respectively. Consequently, shelf life of treated fruits was extended by two days. Also, APDT increased total antioxidant activity of the fruit extracts by almost 20% but did not impact the amounts of either anthocyanins or phenols, nor caused changes to fruit color [180].

Chitosan is a cationic linear polysaccharide produced commercially by deacetylation of chitin. Additionally, chitosan can form films and exhibits antimicrobial activity against a wide range of microorganisms [95,159]. A chlorophyllin-chitosan complex (Chl-CHS) has been used in APDT to kill microorganisms on fruit and grains surfaces. The APDT using Chl-CHS was assessed for the microbiota of strawberries [180]. Naturally-contaminated strawberries were soaked for 30 min in 0.1% (*w/v*) chitosan, 1.5 10^{-5} M chlorophyllin/0.1% chitosan or 1.5 10^{-5} M chlorophyllin and were exposed to 405-nm radiation for 60 min (fluence of 38 J cm^{-2}). Chitosan combined with light exposure reduced colony forming units of fungi by 0.4 $\log_{10}$; chlorophyllin-based APDT reduced colony forming units by as much as 0.9 $\log_{10}$; and APDT using Chl-CHS reduced colony forming units by 1.4 $\log_{10}$ [176], showing the superior performance of the complex. No additional photosensitization-induced free radical was found in the strawberry matrix and no changes were caused to color, texture, and nutritional or visual quality of the fruits [176].

Furthermore, APDT using Chl-CHS was evaluated against fungi present on the surface of wheat grains [41]. Wheat grains were soaked in 0.1% Chl-0.001% chitosan solution and were then exposed to 405-nm radiation for 30 min (at a fluence of 30 J cm^{-2}). This treatment reduced the number of colony forming units of fungi by 0.68 $\log_{10}$ (mortality ~80%). APDT with Chl-CHS was also evaluated to inactivate *Fusarium graminearum* mycelia in vitro and conidia on artificially-contaminated wheat grains. In vitro APDT with 0.005%/Chl-0.5% chitosan combined with exposure to 405-nm radiation inhibited mycelium growth but did not kill the fungus. The results of the study did not make it clear what percentage of conidia was inactivated by APDT on the grain surface, but the treatment did not affect the vigor and viability of the grains [41].

Chitosan has also been chemically combined with other photosensitizers, such as protoporphyrin XI and riboflavin, yielding the conjugates PPIX-CHS and RF-CHS, respectively [83,84]. Both conjugates were used for the APDT of *P. digitatum*. The PPIX-CHS compound inhibited fungal growth by 100% at 0.005% (*w/v*) after one hour of white-light exposure. Interestingly, using a mixture of unconjugated protoporphyrin IX and chitosan did not result in fungal killing, showing the improved properties of the conjugate [84]. The RF-CHS conjugate was also effective against the fungus, albeit only at higher concentrations (0.5–0.9%) compared to PPIX-CHS [83]. Nonetheless, the conjugation of riboflavin and chitosan greatly improved the photodynamic properties of the former: the RF-CHS conjugate had higher $^1O_2$ yield and improved interaction with fungal cells compared to riboflavin alone [83].

2.2.5. Phthalocyanines

Phthalocyanines are two-dimensional, 18 π-electron aromatic porphyrin analogues consisting of four isoindole subunits linked together via nitrogen atoms (Fig. 8) [55]. Phototreatment using different types of phthalocyanines can kill various fungi, including plant-pathogenic species [219,225,229,276].

The filamentous ascomycete *Magnaporthe oryzae* (formely *Magnaporthe grisea*) causes rice blast, the most economically devastating disease of cultivated rice [287]. Rice blast occurs throughout crop areas and is typically responsible for a 10 to 30% reduction of rice yield [192,294]. Use of conventional antifungals to control *M. oryzae* has proven expensive and of limited efficacy [294]. Therefore, the effects of 20 phthalocyanine-metal complexes on conidia germination of *M. grisea* (= *M. oryzae*) both with and without light exposure were evaluated [276]. Photosensitizer concentrations tested ranged from 0.5 to 100 μg mL^{-1} and light was provided by a xenon lamp with water filter. Inhibition of conidia germination varied between zero and 78% depending on the type of phthalocyanine-metal complex. The authors also evaluated the phytotoxicity of these complexes using rice-plant leaves. Most of the phthalocyanine-metal complexes did not damage the leaves, but some did cause chlorotic or necrotic lesions that were however local and negligible at the low photosensitizer concentrations required to control the pathogen. Interestingly, some of these complexes also protected rice plants from blast disease. The authors hypothesize that, *in planta*, the phthalocyanine redox activity in the dark along with its photosensitizing ability promote the generation of ROS, which damage the fungus and, consequently, favor disease resistance [276].

The chemical derivatization of phthalocyanine-metal complexes is an important process to obtain better photosensitizers. For instance, a thiopyridinium derivative of Zn(II) phthalocyanine was shown to be very effective against *C. abscissum*, achieving complete conidial killing at only 5 μM and a fluence of 37.5 J cm^{-2} (640-nm red light) [219]. Furthermore, ammonium derivatives of Si(IV) phthalocyanines were shown to be effective against *E. coli* and *S. aureus*, also at low concentrations (3 and 6 μM) and a white-light fluence of 540 J cm^{-2} [114].

2.2.6. 5-Aminolevulinic Acid

Microbial contamination of seed- and bean sprouts that are produced for human consumption is a chronic problem in the food supply chain

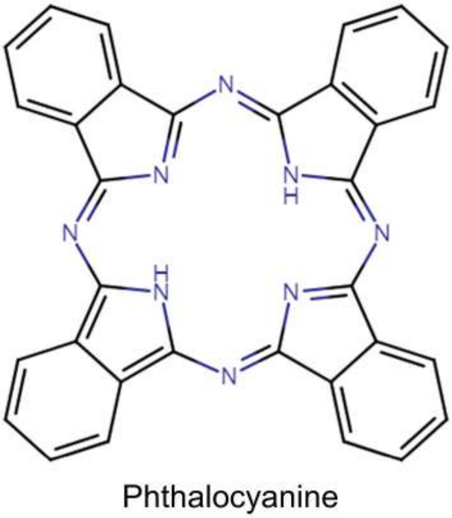

Fig. 8. Basic chemical structure of a phthalocyanine. The structures were drawn with Marvin JS (ChemAxon).

[196,254]. Sprouts are produced from plants such as legumes (e.g. beans, chickpeas, lentils, peas, and soybean), cereals (e.g. rye, wheat, barley, and oats), and vegetables (including alfalfa, radish, mustard, and other *Brassica* species). The methods currently employed to decontaminate seeds and beans prior to sprouting (e.g. washing with chlorine, chlorine dioxide, sodium and calcium hypochlorite, and hydrogen peroxide) have a number of drawbacks [184,196].

Studies have been carried out to evaluate APDT of seeds (prior to sprouting) using 5-aminolevulinic acid (5-ALA) [182,184]. 5-ALA is a naturally-occurring precursor to heme synthesis in eukaryotic and prokaryotic cells, which induces the production of the endogenous photosensitizers protoporphyrin IX, uroporphyrin, and coproporphyrin [157]. When present in the extracellular milieu, 5-ALA is taken up by cells of bacteria, yeast, and filamentous fungi. This can in turn stimulate synthesis of porphyrin-type photosensitizers which can be light-activated to enable control of the microbes [134,157,182,217].

The APDT using 5-ALA has proved effective to control fungal contaminants of wheat grains [184]. Wheat grains naturally contaminated with fungi were soaked for 4 h in a solution of NaCl (5%) with 5-ALA (6 mM) at 26 °C and were then exposed to light (522 nm, emitted by an incandescent lamp equipped with optical filters). Twelve hours after exposure, grains were examined for the presence of viable fungi, which revealed that *Apergillus* spp., *Fusarium* spp., *Mucor* spp., and *Rhizomucor* spp. were susceptible to APDT with 5-ALA while *Acremonium* was not. Treatment with 5-ALA not only reduced fungal contamination but also stimulated the growth of wheat seedlings and roots during the subsequent sprouting procedure, all without impairing grain germination and viability [184]. A similar molecule, methyl aminolevulinate, is the methyl ester of 5-ALA and has also been used as photosensitizer in APDT. Methyl aminolevulinate-based APDT was used against finger nail infections of *F. oxysporum* and *Aspergillus terreus* [116]. This treatment cured refractory onychomycosis caused by these fungi.

2.2.7. Riboflavin and Riboflavin Derivatives

Riboflavin, widely known as vitamin B_2, is a water-soluble compound which can be synthesized by plants and microorganisms, but is essential for animals as they lack an endogenous biosynthetic pathway [235]. Riboflavin acts as cofactors for oxidoreductases as well as prosthetic groups for enzymes in the β-oxidation pathway [195]. The vitamin is synthesized biotechnologically using microorganisms, and is mainly used as feed and food addictive as well as for pharmaceutical applications [235].

When exposed to visible light, riboflavin acts as a potent photosensitizer by producing $^1O_2$ [44,47,111]. However, due to the lack of positive charge, riboflavin is not a very effective photosensitizer for use in APDT [203]. For instance, riboflavin combined with UV-A could not inhibit the growth of either hyphae or conidia of *A. fumigatus*, *F. solani*, and other *Fusarium* spp. [12,158,233]. However, the addition of riboflavin at 250 μM significantly enhanced the efficacy of simulated solar disinfection at 150 W m^{-2} against a variety of microorganisms, including *F. solani*, with mortality rates of 100% being achieved after a 6-h exposure [137]. Pretreatment of fungi with amphotericin B can increase the effectiveness of APDT using riboflavin and UV-A (365 nm, 30 W m^{-2}), according to an in vitro study of *A. fumigatus*, *C. albicans*, and *Fusarium* spp. [233]. Also, synthetic riboflavin derivatives that are positively charged have been successfully used in APDT against *Bacillus* endospores [102]. In this sense, and as mentioned earlier, the conjugation of riboflavin with chitosan improved the interaction of the former with *P. digitatum* cells [83].

3. Post-Harvest Photoinactivation of Foodborne Pathogens and Microbial Contaminants

Plant surfaces are typically subject to extreme fluctuations in water activity [248], solar radiation, temperature, and other parameters. As such, they tend to be nutrient-poor [168] and can be inhospitable for human pathogens such as enteric bacteria. Damage to plant tissues, such as that caused by plant pathogens or food processing, can create a habitable substrate for, and so promote the growth of, enteric pathogens of humans [138,284].

Among the main foodborne bacterial pathogens are *Bacillus cereus*, *E. coli*, *Listeria monocytogenes*, and *Salmonella enterica*, none of which is capable of growth on low water-activity surfaces of <0.850–800 [90,232,247]. Microbial contamination of fruits and vegetables and other types of food/feeds can also greatly shorten their shelf life, especially by fungal psychrophiles and xerophiles, some of which are capable of growth even at subzero temperatures and at ≤0.585 water activity [50,57,249–251]. Several studies, carried out in vitro using different photosensitizers, have established that APDT can efficiently kill diverse foodborne pathogens and spoilage microbes, including cells and spores of bacteria [10,40,89,90,102,127,175,176,239,244].

Natural and semi-synthetic photosensitizers such as 5-ALA [43,177], sodium magnesium and sodium copper chlorophyllin (approved as food addictives E-140 and E-141, respectively) [39,40,135,176,178–180], curcumin (approved as the food additive E-100) [117,119,143,259,265], furocoumarins [78,109,268], hypericin [10,156], and riboflavin derivatives [102] are among the most studied in relation the food microbiology.

APDT of the Gram-negative *S. enterica* using 5-ALA efficiently kills the bacterium, according to in vitro studies [43]. Bacterial cells were taken from an exponential-phase culture and incubated with 7.5 mM 5-ALA for up to 1 h in the dark, and then exposed to visible light (LED, with emission at 400 nm and irradiance of 200 W m^{-2}). Bacterial photodynamic inactivation was dependent on the incubation time with 5-ALA and fluence. Viable cell number was reduced by up to 6 $\log_{10}$. In vitro APDT with 5-ALA was also able to kill the Gram-positive *B. cereus*, regardless of whether vegetative cells or spores were tested [177]. Photoinactivation of *B. cereus* on the surfaces of grains and packaging materials was also observed [177]. Cells and spores of *B. cereus* suspended in PBS or on the surface of food-packaging material and wheat grains were treated with 5-ALA (3 to 7.5 mM) and then exposed to visible light. Survival of vegetative cells in suspension was reduced by 6.3 $\log_{10}$ and on the surface of food packing by 4 $\log_{10}$. *B. cereus* spores both in suspension and on packaging material were also susceptible to APDT and survival was reduced by 3.7 and 2.7 $\log_{10}$, respectively. Similar results were observed for the highly pathogenic L. *monocytogenes* which was killed by 5-ALA-based APDT both in suspension (survival reduction up to 4 $\log_{10}$) and as biofilm on the surface of packaging material (survival reduction up to 3.1 $\log_{10}$) [42]. *B. cereus* spores were also efficiently inactivated by APDT (> 3 $\log_{10}$ reduction in survival) when a tricationic porphyrin was used as the photosensitizer. However, the susceptibility of spores to porphyrin-based APDT was highly variable among different species of *Bacillus* [64].

Sodium magnesium chlorophyllin (E-140) and sodium copper chlorophyllin (E-141) were incorporated into gelatin films, and their potential to inhibit *Staphylococcus aureus* and L. *monocytogenes* was evaluated [171]. Bacterial cell suspensions were spread on the surface of tryptone soy agar. Control gelatin films (no photosensitizer) and gelatin films supplemented with E-140 or E-141 were placed on the surface of the inoculated agar, and then irradiated for 5 or 15 min. Following these treatments, plates were incubated for 24 h and bacterial colonies were then counted. Results showed that the E-140- and E-141-based APDT reduced the number of colony forming units of *S. aureus* and L. *monocytogenes* by 5 and 4 $\log_{10}$, respectively. In vitro APDT with sodium magnesium chlorophyllin at 5 μM combined with blue light (433 nm, 6.6 J cm^{-2}) reduced the survival of *S. aureus* by more than 7 $\log_{10}$ [135]. However, APDT with the two chlorophyllins had no effect on the viability of the Gram-negative bacteria *E. coli* and *Salmonella* spp. [171].

APDT using Na-Chl on survival of cells and spores of *B. cereus* [178] and *L. monocytogenes* [179] was evaluated in vitro, both in suspension and on the surface of yellow packaging trays (polyolefin-mixture of polyethylene and polypropylene). Cells and spores of *B. cereus* suspended in PBS or on packing material were incubated with Na-Chl (7.5×10^{-8} to 7.5×10^{-5} M) and then exposed to visible light (peak emission at 400 nm and irradiance of 200 W m^{-2}). Treatment with 7.5×10^{-7} M of Na-Chl reduced the survival up to 7 $\log_{10}$ of the cells of *B. cereus* suspended in PBS and those on the surface of packaging trays. *B. cereus* spores were more tolerant to APDT than cells, but were also killed depending on photosensitizer concentration and light-exposure time. Treatment with 7.5×10^{-5} M of Na-Chl reduced the survival of the spores suspended in PBS up to 4 $\log_{10}$. Reduction of the survival of the spores on packaging tray was 5 $\log_{10}$ at 7.5×10^{-5} M of Na-Chl.

Also, APDT using Na-Chl was tested on the survival of thermosensitive and thermotolerant strains of L. *monocytogenes* both in suspension and on the surface of yellow packaging trays [179]. Phototreatment reduced the survival of both strains up to 7 $\log_{10}$ when cells were suspended in PBS and killed all the cells when they were on packaging trays. The APDT of *B. cereus* and L. *monocytogenes* using Na-Chl was considerably more effective than washing with 200 ppm sodium hypochlorite [178,179]. Mechanistic studies conducted with Gram-negative bacteria has shown that during Na-Chl-based APDT, chlorin binds to the surface of the bacterial cell causing $^1O_2$-mediated membrane damage and cell wall disruptions, increased release of intracellular components, and cell death [298].

As presented earlier, APDT using Na-Chl and visible light was tested in strawberries that had been inoculated with L. *monocytogenes* [180]. Strawberries were inoculated with L. *monocytogenes*, soaked in 1 mM Na-Chl solution for 5 min, and then exposed to visible light (400 nm, irradiance of 120 W m^{-2}) for 30 min. The treatment reduced the viability of the cells by 1.8 $\log_{10}$ compared to control samples.

The effect APDT with the Chl-CHS chlorophyllin-chitosan complex on survival of L. *monocytogenes* on the surface of wheat grains was evaluated [41]. Also, coating of strawberries with Chl-CHS and illumination with visible light at 76 J cm^{-2} inactivated yeast/microfungi on the fruits by 1.4 log and prolonged the shelf life by 3 days without any negative effect on the fruits [176]. Details for these two studies were discussed above and can be found on section 2.2.4. Furthermore, the effects of APDT using Na-Chl alone and combined with chitosan or high-power pulsed UV (200–1000 nm, peak at 260 nm) on the survival of *S. enterica* were determined in vitro [40]. The APDT alone reduced the survival of the bacteria by 2.05 $\log_{10}$ while APDT combined with chitosan or pulsed UV reduced the viability by 7.28 and 7.5 $\log_{10}$, respectively. Interestingly, Na-Chl-based APDT induced the transcription of genes responsible for ROS inactivation in *S. enterica* [40].

Hypericin-based APDT and hypericin-based APDT combined with high power pulsed light (HPPL) were evaluated for L. *monocytogenes* and *S. enterica* [156]. Cells were incubated with hypericin (10^{-5} or 10^{-7} M) in PBS and exposed to visible light (peak emission at 585 nm and irradiance of 38.4 W m^{-2}). For the combined treatment, after APDT, bacteria were exposed to 350 pulses of HPPL (UV fluence of 0.023 J cm^{-2}). Hypericin interacted with the cells of both species and APDT reduced the survival of *Listeria* and *Salmonella* by 7 and 1 $\log_{10}$, respectively. Electron microscopy studies showed that APDT induced total collapse of the *Listeria* cell wall, but not that of *Salmonella*. Combined treatment of APDT and pulsed light reduced the survival of *Listeria* and *Salmonella* by 6.7 to 7 $\log_{10}$, respectively. The effect of APDT with hypericin (1.5×10^{-5} to 1×10^{-8} M) and visible light (585 nm, irradiance of 38.4 W m^{-2}, and fluences up to 9.2 J cm^{-2}) on the survival of *B. cereus* both in vitro and inoculated on the surface of fruits (apricots and plumes) and vegetables (cauliflowers) were also investigated [10]. Hypericin-based APDT reduced the survival of the bacteria up to 4.4 $\log_{10}$ in vitro. Inactivation of mesophilic bacteria on the surface of fruits and vegetables reached up to 1.3 $\log_{10}$.

The use of APDT employing curcumin bound to polyvinylpyrrolidone (PVP-C) and NovaSol®-curcumin for the decontamination of *S. aureus* from cucumber, peper, and chicken meat was evaluated [265]. Both curcumin and PVP-C have been approved as food additives. Vegetables and meat were contaminated with the bacteria, sprinkled with PVP-C and NovaSol®-curcumin at concentrations of 50 and 100 μM, respectively, and illuminated immediately using visible light (emission peak at 435 nm, irradiance 94 W m^{-2} and fluence 33.8 J cm^{-2}). Photodynamic inactivation of *S. aureus* caused a mean reduction of 2.6 $\log_{10}$ on cucumbers, 2.5 $\log_{10}$ on pepper, and 1.7 $\log_{10}$ on chicken meat relative to controls. Also, no visible changes of the exterior appearance of the foodstuff after APDT were observed [265].

APDT using phenotiazinium photosensitisers, porphyrins, and xanthenes have also been tested against foodborne pathogens and microbial contaminants post-harvest. The spore-forming bacterium *Alicyclobacillus acidoterrestris* can cause great losses to fruit juice industries due to its thermal and chemical resistance and spoilage potential. Phototreatment with new methylene blue or tetracationic porphyrin combined with white light inactivated the spores both in suspension (PBS and orange juice) and on orange peels. Reductions in viability reached up to 7.3 $\log_{10}$ in suspensions and 2.8 $\log_{10}$ on peels. The presence of potassium iodide increased the effect of APDT [91].

APDT with cationic porphyrins were also used to photoinactivate the Gram-negative phytopathogenic bacterium *Pseudomonas syringae* pv. *actinidiae* both in vitro and in kiwifruit plants under solar radiation. Photoinactivation reached up to 7.4 $\log_{10}$ in vitro and 6.2 $\log_{10}$ on leaves [194]. Also, APDT with eosin Y combined with green light was evaluated against the pathogenic bacteria *S. enterica*, *E. coli*, *P. aeruginosa*, *S. aureus*, and *B. cereus*. *P. aeruginosa* was completely inactivated at 10 μmol L^{-1}, and reductions in viability reached 2.7 and 1.7 for *B. cereus* and *S. enterica*, respectively. *E. coli* viability was slightly reduced while *S. aureus* was the most susceptible, being completely inactivated by eosin at 5 μmol L^{-1} and 5 min of light exposure [32].

4. Fungal Tolerance to Photoantimicrobials

Plants that produce furocoumarins and other potent photosensitizers can still experience severe microbial infections, and this is due to the development of tolerance or resistance to photosensitization in some specialized pathogens. *Fusarium sambucinum*, as well as some other plant pathogens, can metabolize, and thereby detoxify, xenobiotics such as furocoumarins. *F. sambucinum* is cosmopolitan in terms of habitat and lifestyle (both soil saprophyte and plant-pathogen), but is not generally regarded as any more stress tolerant than comparable species of fungi [60]. Circumstantial evidence from ecophysiological/toxin-resistance studies suggests that individual strains may preferentially inhabit either soils or the plant host [82]. *F. sambucinum* tolerance to the furocoumarin xanthotoxin has been tested in vitro for 62 strains obtained from soils and diseased plants. As all the experiments were conducted in the dark, only direct inhibition by compounds was evaluated. Twenty-one out of 24 *F. sambucinum* strains isolated from plants and only two out of 38 strains isolated from soil were found to be highly tolerant to xanthotoxin. Of 16 *F. sambucinum* strains tested against 16 furocoumarin precursors and furocoumarins, all those that had been isolated from plants were highly tolerant and, in most cases, completely able to metabolize all of the compounds assayed. Conversely, most of the soil-derived strains tested were tolerant to furanocoumarin precursors but sensitive to certain furocoumarins [82].

Metabolic inactivation of phototoxic plant metabolites is not the only mechanism that plant pathogens use to protect themselves against host-induced photosensitization. For instance, conidia of some fungi contain high concentration of pigments, such as carotenoids, that scavenge reactive species and can mitigate stresses such as those induced by solar UV radiation and photodynamic processes [29,36,237,262]. Pigments such as carotenoids are usually located within the plasma membrane and are able to quench both singlet oxygen and other types of reactive species produced by photosensitizers [237,262,286]. Other pigments, which are structural components of the conidial cell wall (including melanins and melanin-like compounds), can selectively absorb solar radiation at the wavelengths required to activate the plant's photosensitizers [15]. The wild-type conidia of several *Colletotrichum*, *Fusarium*, and *Neurospora* species that are yellowish accumulate carotenoids, while *Alternaria*, *Aspergillus*, *Metarhizium, and Penicillium* conidia that are dark colored (brown-, gray- green- or bluish) are characterized by high levels of melanins or melanin-like pigments within the cell wall [15,121].

The above discussion contains examples of plants which produce photosensitizers that act as photoantimicrobials, protecting them against infections by pathogenic microbes. However, in plant-microbe interactions, there are also cases in which the opposite occurs. Plant-pathogenic fungi of the genera *Alternaria*, *Cladosporium*, *Elsinoë* and *Mycosphaerella* produce perylenequinone pigments during host infection, such as cercosporin, elsinochromes, hypocrellins, calphostin, and rubellin which are potent photosensitizers and damage the plant [53,75,76,139,260,297]. Most of the characterized perylenequinones produced by fungi share a common 4,9-dihydroxy-3,10-perylenequinone core and differ in side chain composition [76]. These pigments are very potent $^1O_2$-generating photosensitizers that have a crucial role in the establishment of pathogenic association between fungi and their plant host [53,76]. The production of these photosensitizers during infection causes lipid peroxidation and damage to the plasma membrane of the host cells, leading to leakage of nutrients into the intercellular spaces colonized by the pathogen (Fig. 9) [70,72,76].

Interestingly, the producing fungi are resistant to these photoactivated toxins [76]. Among these fungi, those of the genus *Cercospora* are the best studied [76,297]. *Cercospora* species cause devastating leaf-blighting disease on a wide range of important plant host species worldwide [22]. Several species of the genus *Cercospora* produce large quantities of the phototoxin cercosporin, a lipid-soluble 4,9-hydroxyperylene-3,10-quinone derivative, which absorbs light and reacts with oxygen, generating reactive oxygen species, mostly $^1O_2$ [74]. Unlike free-radical forms of ROS against which resistance mechanism are well characterized, the cellular bases of $^1O_2$ resistance are still being elucidated [23,76,260]. Light is required, not only for cercosporin activation, but also for cercosporin production [101]. *Cercospora* species can, under light, produce and thrive in concentrations of cercosporin up to 1000-fold higher than that which is lethal to other organisms [100]. These fungi are highly tolerant not only to cercosporin but also to a broad range of structurally unrelated $^1O_2$-generating photosensitizers, including porphyrins, xanthenes, and phenothiazinium dyes [99]. Some fungi other than *Cercospora* species, such as *Alternaria solani*, *Cladosporium cucumerinum*, *Cladosporium fulvum*, *Colletotrichum lagenarium*, *Verticillium* sp., *S. cerevisiae* and *Sporobolomyces* sp. are also highly resistant to cercosporin and other $^1O_2$-generating photosensitizers [71]. Due to their high intrinsic tolerance, these fungi are excellent models for the elucidation of molecular and genetic bases of resistance to $^1O_2$-generating photosensitizers.

Much of what is known about the tolerance of *Cercospora* to cercosporin and to other $^1O_2$-generating photosensitizers came from Daub's group and some of their reviews are recommended for an in-depth approach on this subject [73,75,76,297]. *Cercospora* auto-resistance to light-activated cercosporin is a complex and yet not completely understood characteristic mediated by multiple mechanisms including the reversible reduction and detoxification of the cercosporin inside the fungal cells, the production of $^1O_2$ quenchers, and the transport of the toxin out of the cells (Fig. 10) [22,76,77].

Carotenoids are the most efficient quenchers of $^1O_2$ identified in biological systems, and are able to quench not only $^1O_2$, but also the activated triplet state of $^1O_2$-generanting photosensitizers [69,75,164]. Carotenoids were also the first endogenous compounds identified that can protect fungi against cercosporin-based APDT [69]. Carotenoid-deficient mutants of *Neurospora crassa* are significantly more sensitive to cercosporin than the carotenoid-producing wild-type isolates [29]. Carotenoids also protect fungi against other $^1O_2$-generanting photosensitizers that damage the plasma membrane. Conidia of *N. crassa* and mycelia of *Ustilago violaceae* mutants lacking carotenoids are less tolerant to methylene blue- and toluidine blue O-based APDT than the wild-type strains [262,286]. However, experiments performed with *Cercospora nicotianae* showed a different and unexpected result [99]. Target gene disruption was used to create carotenoid-minus mutants of a wild-type and two cercosporin-sensitive *C. nicotianae* mutants. These carotenoids-deficient mutants had similar sensitivity to either photoactivated cercosporin or five others $^1O_2$-generanting photosensitizers (rose bengal, hematoporphyrin, methylene blue, toluidine blue O, eosin Y) compared to the parent strains. Together, these data suggested that carotenoids are important to fungal tolerance to photoactivated cercosporin but they are not involved or have only a minor effect on *Cercospora* resistance to $^1O_2$-generating photosensitizers [69].

The term vitamin B_6 is used to describe all biologically interconvertible forms of pyridoxine [25]. Vitamin B_6 and its derivatives are good $^1O_2$ quenchers; also, the pyridoxine moiety can function as a redox quencher for excited cercosporin by forming the cercosporin radical

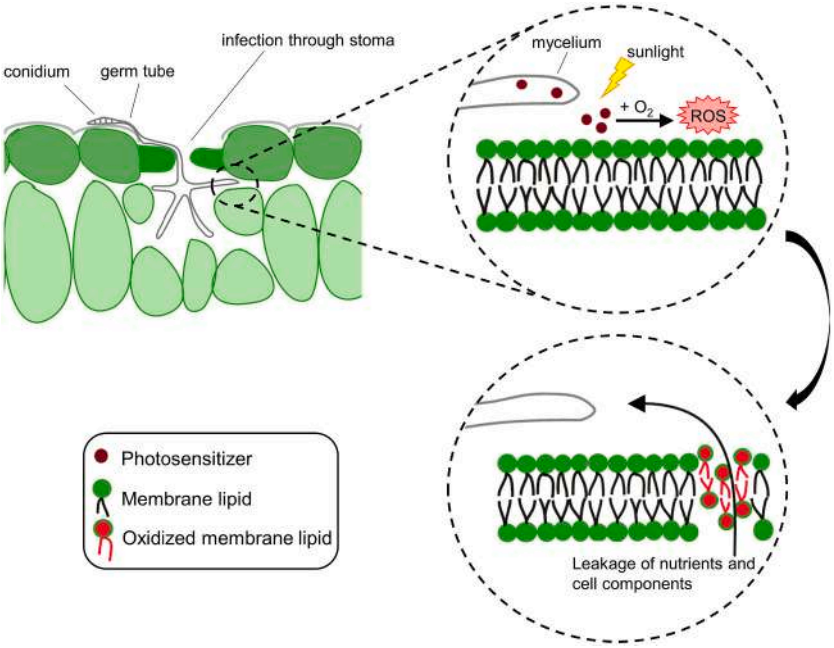

Fig. 9. Schematic mechanism depicting the mode-of-action of phytopathogenic fungi that use photosensitizers for pathogenesis. After penetration through stomata, the fungus releases a photosensitizing molecule in the intercellular space. Activation of this molecule by light results in the production of reactive oxygen species that damage lipids at the cell membrane, releasing plant nutrients into the medium and allowing sustained fungal growth. The depicted mechanism is based on that of Cercospora fungi.

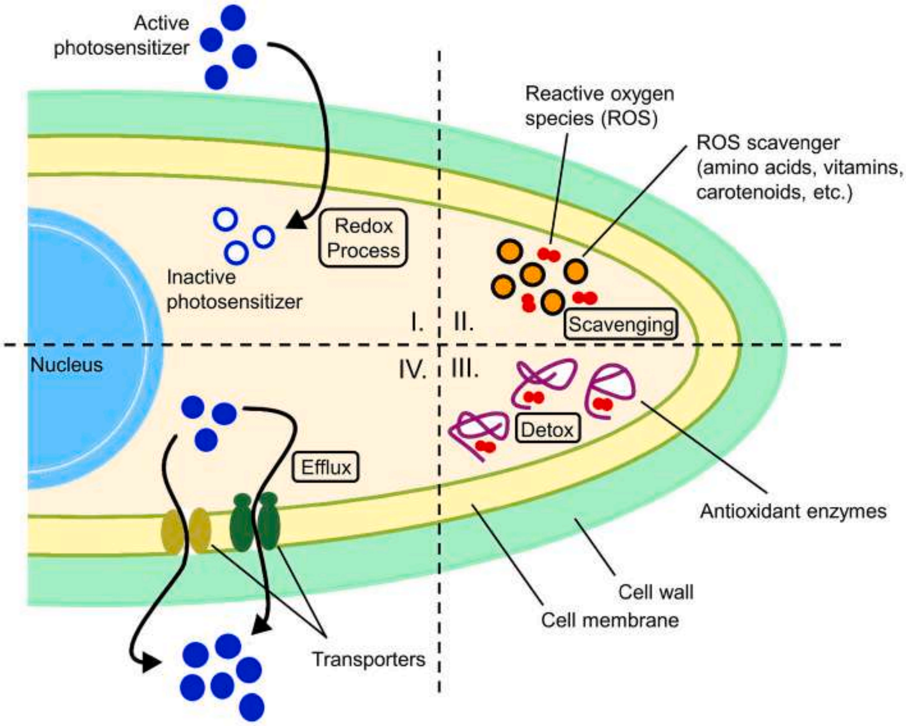

Fig. 10. Examples of mechanisms via which cells may be either tolerant or resistant to photodynamic inactivation. These mechanisms include: (I) inactivation of photosensitizers via redox reactions; (II) scavenging of reactive oxygen species by specialized molecules (e.g., carotenoids, vitamin B6); (III) detoxification of reactive oxygen species by antioxidant enzymes (e.g., superoxide dismutase); and (IV) efflux of photosensitizers from the intracellular medium by transporters. These mechanisms are based on current knowledge on tolerance/resistance to APDT on Cercospora fungi, but they are potentially present in all microorganisms.

anion [25]. Mutants of *C. nicotianae* deficient in biosynthesis of vitamin B_6 are highly sensitive to cercosporin and other $^1O_2$-generanting photosensitizers, such as hematoporphyrin, rose bengal, eosin Y, methylene blue, and toluidine blue O [97,98,100]. Analysis of cellular levels of vitamin B_6 also showed that *C. nicotianae* has 2- to 3-fold higher levels of B_6 vitamers than the cercosporin-sensitive fungi *A. flavus* and *N. crassa* [140].

In contrast to $^1O_2$ quenchers, there is little evidence for a role of antioxidant enzymes in cercosporin resistance in *Cercospora*. *C. nicotianae* does not have higher levels of superoxide dismutase (SOD), catalase, or peroxidase activities as compared to cercosporin-based APDT sensitive fungi and there is also no difference in overall antioxidant activity [71].

The ability to transport cercosporin and other photosensitizers out of the cell also contributes to fungal resistance to these compounds [22,76]. Both the Major Facilitator Superfamily (MFS) and ATP-binding cassette (ABC) family of transporters are able to transport cercosporin out of *Cercospora* cells and provide partial resistance against cercosporin-based APDT [22]. Targeted disruption of the gene for CFP (*C*ercosporin *F*acilitator *P*rotein), an MFS transporter, in the soybean pathogen *Cercospora kikuchii* drastically reduced the production of cercosporin, greatly impaired virulence of the fungus, and increased sensitivity to exogenous cercosporin in comparison to the wild-type strain [45]. Also, the transgenic expression of *CFP* gene in the cercosporin-sensitive fungus *Cochiobolus heterostrophus* resulted in increased tolerance to cercosporin due to its export out of the fungus [270].

The importance of MFS transporters to the resistance to $^1O_2$-generating photosensitizers was also observed in other fungal pathogens. *Bcmfs1*, an MFS transporter from *B. cinerea*, provides tolerance to cercosporin-based APDT [136]. Deletion mutants showed increased sensitivity to photoactivated cercosporin, while overexpression mutants displayed decreased sensitivity [136]. Mutants of the citrus pathogen *A. alternata* lacking the *AaMFS19* gene, which encodes an MFS transporter, display profound sensitivity to the $^1O_2$-generating photosensitizers eosin Y, rose bengal, hematoporphyrin, methylene blue, and cercosporin [49].

The importance of ABC transporters to cercosporin resistance was demonstrated in *C. nicotianae*. Mutants with disruption of *ATR1*, which is an ABC transporter gene, had dramatic reductions in cercosporin production and also showed moderately higher sensitivity to cercosporin indicating that ATR1 acts as a cercosporin efflux pump and has a partial role in cercosporin-based APDT resistance [7]. CnATR2, another ABC transporter involved in partial resistance to cercosporin, was recently characterized. Transformation and expression of *CnATR2* in the cercosporin-sensitive fungus *N. crassa* significantly increased cercoporin resistance. However, target gene disruption of *CnATR2* in the wild type *C. nicotianae* did not decrease resistance. The overexpression of the gene that codes for Snq2p, a well-characterized multidrug, ABC-type, efflux protein conferred resistance to cercosporin and to other $^1O_2$-generating photosensitizers such as methylene blue and toluidine blue O to an otherwise sensitive *S. cerevisiae* strain [275]. In contrast, the *snq2* null mutant was not more sensitive to methylene blue and toluidine blue O than a wild-type control strain [275].

Studies with redox-sensitive dyes, reducing agents, and with detection of reduced and oxidized forms of cercosporin indicated that the most relevant mechanism responsible for *Cercospora*'s resistance to cercosporin is the ability of these fungi to maintain cercosporin within the hyphae in a reduced form (Fig. 10) [73,75–77,151,297]. Reduced cercosporin is a poor generator of $^1O_2$, particularly in aqueous solution [167]. As the reduced form is labile, and readily reoxidizes on aeration or removal from the reducing agents, cercosporin that diffuses away from the fungal cell spontaneously reoxidizes to the photoactive form needed for the infection of the host plant [77,167].

Other fungal species were also tested for cercosporin-reducing ability [77]. *A. alternata*, which is cercosporin-resistant, was able to reduce cercosporin but *A. flavus* and *N. crassa*, which are cercosporin-sensitive, had only limited ability. Evidence suggested that the reduction of the photosensitizer may be a generalized mechanism of resistance for *Cercospora* to other $^1O_2$-generating photosensitizers [77]. *Cercospora* species were also resistant to eosin Y- but not to rose bengal-based APDT. Microscopic observation showed that *Cercospora* species were not capable of reducing rose bengal but were capable of reducing eosin Y. The reduction of the photosensitizer as a protective mechanism was also observed in other fungal species. The over-expression of the gene *CPD1* (*C*ercosporin *P*hotosensitizer *D*etoxification) that codes for a putative plasma membrane-associated reductase conferred resistance to cercosporin, methylene blue and toluidine blue O in *S. cerevisiae* [275].

It is often stated that, due to its multiple-target mode of action, the selection of fungi displaying resistance to APDT is unlikely. However, the existence of several fungal species that are intrinsically resistant to APDT with $^1O_2$-generating photosensitizer, indicates that the possibility of the emergence of tolerance to APDT in fungal species of medical or agricultural importance deserves more attention. A recent study performed by da Cruz and coworkers has showed that *C. abscissum* submitted to successive cycles of APDT can become more tolerant to the treatment, although the decrease in susceptibility was small. Also, the study revealed that the more-tolerant strain also accumulated higher amounts of carotenoids (da Cruz et al., in preparation). Unfortunately, other studies performing long-term experimentation with filamentous fungi to determine whether or not it is possible to select resistant strains during successive cycles of APDT are still lacking. There is no doubt that the understanding of the mechanisms responsible for the intrinsic resistance to APDT of some fungal species, such as of the genus *Cercospora*, will be important to understand and eventually anticipate a possible emergence of resistance to APDT in species of medical and agricultural importance, which may occur with the expansion of its use.

The discussion above may seem heavily based on Type II reactions, i.e., those producing $^1O_2$. However, some of the mechanisms presented (Fig. 10) can also operate to avoid cell damage arising from Type I reactions. For instance, the redox processes that render photosensitizers not reactive to light would also prevent Type I reactions from occurring. Similarly, efflux pumps that prevent photosensitizers from being light activated inside cells do not discriminate between Type I and Type II photosensitizers.

The same cannot be said about the other two mechanisms, i.e., detoxification and scavenging. Cells have known lines of defense against Type I ROS –such as superoxide anion radical and hydrogen peroxide– in the form of the enzymes superoxide dismutase, catalase, and glutathione reductase, as well as specific scavengers for these reactive species. Both the expression of the enzymes and the production/accumulation of scavengers can be modulated to achieve increased tolerance to photosensitizers operating via Type I reactions. On the other hand, there is no known first line of defense against $^1O_2$, so an effective antioxidant system may prevent exclusively against Type I photosensitizers. Evidence of this can be found on extremophilic microorganisms. The bacterium *Deinococcus radiodurans* has a remarkable antioxidant system that effectively protects the proteome from ionizing radiation, desiccation, and oxidative stresses at high levels [220], making the microbe very tolerant to Type I ROS. Nonetheless, *D. radiodurans* cannot sustain the damages imposed by $^1O_2$-producing photosensitizers, with at least one report showing that its tolerance falls bellow that of *E. coli* [205,234].

At present, it is not possible to say whether the tolerance mechanisms to Type I and to Type II photosensitizers would emerge and occur concomitantly (if at all). However, if tolerance to APDT is a multifactorial process operating at many levels, then alternating chemically-diverse photosensitizers that operate via different reactions will provide some protection against the emergence of tolerance.

5. Conclusions and Unresolved Questions

Plants, as do microbes, produce a mechanistically (and chemically) diverse array of antimicrobials which can vary with species, habitat, and environmental conditions [62,168,209,253,283]. Of these, photosensitizers can have elegant mechanisms and are some of the most potent antimicrobials; yet, they are relatively undervalued in relation to their biotechnological potential.

The above discussion covers the ecologies of naturally-occurring, photodynamic processes including the light-activated antimicrobial activities of some plant metabolites, and the intriguing use of the photodynamic process by some plant-pathogenic fungi as an important virulence factor. The use of natural and synthetic photosensitizers to kill plant-pathogenic fungi and foodborne pathogens were also reviewed and discussed. The inhibitory mechanisms of both natural and synthetic light-activated substances were covered in the contexts of microbial stress biology and agricultural biotechnology. Implications were also made in relation to treatment of clinical infections caused by opportunistic fungi pathogens, once considered only plant pathogens and/or saprotrophic.

The development of conventional pesticides is a complex, costly, and time-consuming process that can be divided into three main steps: (i) research on the synthesis and screening of molecules, (ii) product development; and (iii) registration. The research evaluates the biological, chemical, toxicological, environmental, and commercial characteristics of candidate molecules to be registered. The development includes several processes, such as optimization of formulation, assessment of products in field trials against different biological targets in a variety of crops, and evaluation of toxicological and environmental impacts. Finally, product data are submitted to different regulatory agencies, which may agree or disagree with the registration and commercialization (McDougall, 2016). Therefore, as in the development of conventional pesticides, photosensitizers may be submitted to similar processes before large-scale use in agriculture. In addition, the average time spent by a company to develop a conventional pesticide is approximately 11 years and the cost is about US$ 286 million (McDougall, 2016). Currently, the cost for obtaining a photosensitizer-based product is unknown, and future research on economic feasibility is needed. Furthermore, there is still a considerable knowledge gap due to numerous unresolved questions. For example, although it is well established that APDT with most of the photosensitizers tested is able to kill, to a greater or lesser extent, most of the different species of fungi in vitro, little is known about the efficacy of the treatment in the field on different crops. An important issue that needs attention is the negative effect of shadowing, which may be caused by the plant canopy and/or by an extensive cloud cover lasting many days. Similarly, little is known about the side effects of the different photosensitizers on the host plants and in the environment. Also, formulations containing photosensitizers will have to be developed and approved for use in the field.

Despite its great potential, it seems that the development and use of APDT in agriculture has been delayed by the fact that this antimicrobial approach is unknown to the majority of agricultural professionals and by the apparent lack of interest by the chemical and pharmaceutical industries in the development of photosensitizer-based products for agricultural use. This parallels a similar lack of interest from these industries in the development of clinical anti-infectives based on this approach for both human and veterinary application. Here we showed that the use of photoantimicrobials is a viable and needed alternative to control plant- and foodborne pathogens, and has the potential to contribute to improving global food security.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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