**Fungal perylenequinones**

Afra Khiralla¹ · Aisha Ohag Mohammed² · Sakina Yagi³

Received: 30 September 2021 / Revised: 6 February 2022 / Accepted: 7 February 2022 / Published online: 4 April 2022

© German Mycological Society and Springer-Verlag GmbH Germany, part of Springer Nature 2022

**Abstract**

Perylenequinones (PQs) are aromatic polyketides with an oxidized pentacyclic core that make up a family of natural compounds. Naturally occurring PQs mostly are produced by phytopathogenic fungi, with few aphides, crinoids, and plants. PQs, also known as photosensitizers, absorb light energy which empowers them to produce reactive oxygen species that damage host cells. Therefore, PQs gained a considerable interest in pharmaceutical application notably in photodynamic therapy. This review presents a comprehensive overview of fungal PQs. Their occurrence, categorization, biosynthesis, structures, and bioactivities are all discussed in detail. After that, an analysis outlines their distribution across the kingdom of fungi. A total of 66 fungal PQs have been described from 22 ascomycete genera (*Alternaria*, *Aspergillus*, *Bulgaria*, *Cenococcum*, *Cercospora*, *Cladosporium*, *Curvularia*, *Daldinia*, *Elsinoë*, *Hypocrella*, *Hypomyces*, *Parastagonospora*, *Phaeosphaeria*, *Phylacia*, *Pyrenochaeta*, *Rhopalostroma*, *Rubroshiraia*, *Setophoma*, *Shiraia*, *Stemphylium*, *Stagonospora*, and *Thamnomyces*). Dothideomycetes account for the majority of documented fungal PQs (82%), followed by Sordariomycetes (14%), Leotiomycetes (3%), and Eurotiomycetes (1%). Herein, five families *Pleosporaceae*, *Phaeosphaeriaceae*, *Cladosporiaceae*, *Shiraiaceae*, and *Hypoxylaceae* are highlighted as potential sources of novel PQs due to their diversity. The review intends to pique bioprospectors’ interest in fungal PQs. Indeed, the pharmaceutical and agrochemical industries might gain greatly by exploiting fungal perylenequinones.

**Keywords**  Fungal natural products · Perylenequinones · Photodynamic therapy · Dothideomycetes · Sordariomycetes

**Introduction**

Fungal natural products have received a considerable attention. Several studies unveiled their amazing assortment. Perylenequinones (PQs) are members of natural products’ family characterized by an oxidized pentacyclic core represented by the parent perylenequinone 4,9-dihydroxyperylene -3,10-quinone (25). Fungi are the best source for PQs as 85% of all known PQs are reported from fungi, compared to 12% for *Animalia* and only 3% for *Plantae*. PQ pigments are produced by a wide variety of molds, the most of which are phytopathogens, with few marine sponge-derived, endolichenic, and endophytic fungi (Weiss et al. 1987; Pang et al. 2018; Tantry et al. 2018). Insects are an alternative source of PQs, such as rodoaphin, which is synthetized by aphids. In addition, the stalked crinoid *Gymnocrinus richeri* produced gymnochromes. PQs are also found in few plant species, such as scutiaquinones A and B were discovered in the root of *Scutia myrtina*. Besides, hypericin is one of *Hypericum’s* principal active constituents (Weiss and Altland 1965; Miskovsky 2002; Ayers et al. 2007). Moreover, PQs have been extracted from aquatic sediments and soil matter. 4,9-dihydroxyperylene-3,10-quinone (25) and its derivatives were recovered from Japanese Andosols and Cambisol (Hanke et al. 2019; Kobayashi et al. 2019).

Perylenequinones are anticipated to be some of the most promising photodynamic therapy (PDT) agents (Olivo and Ali-Seyed 2007). PDT is a cancer and non-malignant condition treatment that comprises the delivery of a photosensitizing...
chemical such as PQs, followed by exposure of the tissue to non-thermal visible light (400–760 nm). When the molecule is stimulated by light of the appropriate wavelength, the photosensitizer is activated. This produces a series of molecular energy transfers leading to the release of singlet oxygen, a highly reactive and cytotoxic species, resulting in apoptosis. Drug uptake in malignant tissues combined with selective light treatment has the potential to give an effective cancer therapy with efficient cytotoxicity and minimal impairment to surrounding normal tissue (Ackroyd et al. 2001). PDT also provides several advantages over other standard clinical therapies, including more efficiency, greater safety, and decreased toxicity for surrounding normal tissues due to increasing accumulation of photosensitizers and irradiation on diseased targets (Yano et al. 2011). As compared to other photosensitizers investigated, such as porphyrin and phthalocyanine-like photosensitizers, PQs virtually exhibit all of the characteristics of ideal photosensitizers (Li et al. 2015). Hypocrellins A–B (50–51) have many advantages that might make them fascinating sensitizers for PDT. They are readily obtained, simply purified, very stable, low in toxicity, and do not form aggregates which would decrease their photodynamic activity. Although hypocrellin A (50) is phototoxic, it is rapidly removed from live organisms, usually within 24 h. Its photosensitizing side effects in PDT are considerably reduced as a result of this. In addition, hypocrellin A (50) is non-toxic in the absence of light (Diwu and William 1990).

Several investigations have been conducted on the apoptotic and cytotoxic effects of some fungal PQs, including calphostin C (42), elsinochromes A (45), C (47), hypocrellin (49), and hypocrellin A (50). These studies highlighted their potential as promising anticancer medications and explored their application in cancer therapy (Dubauskas et al. 1998; Fang et al. 2006; Olivo and Ali-Seyed 2007; So et al. 2018; Tantry et al. 2018; Mastrangelopoulou et al. 2019). Furthermore, Sharma et al. (2013) have invented a patent (US 8,506,931 B2), that contains hypocrellin derivatives. These compounds can be particularly useful as photosensitizers or sononsensitizers in photodynamic or sonodynamic therapy. Also useful as therapeutic agents for treating various hyperproliferative disorders. Since two decades, the antiviral activity of various PQs has been studied (Hudson et al. 1997; Krishnamoorthy et al. 2005; Wiehe et al. 2019). Hudson and associates discovered a correlation between singlet oxygen (\( \text{O}_2^+ \)) quantum yield and antiviral activity (Hudson et al. 1997). Other remarkable biological properties of PQs have been noted such as the prevention of skin diseases caused by fungal infections, antileishmanial, antimarial, antimicrobial properties, and mutagenicity (Wang and Bao 1985; Stack and Prival 1986; Diwu 1995; Ma et al. 2004; Fang et al. 2006; Tantry et al. 2018).

PQs were exploited in agriculture field as fungicides. In 2005, a patent (US 6,936,571 B2) was invented by Zhag and Liu. The active constituents of the fungicide are selected perylenequinone derivatives including cercosporin (30), phleichrome (31), cladochromes A–D (33–36), elsinochromes A–C (45–47), hypocrellins A–B (50–51), and hypomycins A–B (53–54) (Zhag and Liu 2005). PQs, on the other hand, have a promising environmental role as pesticides, due to their rapid degradation. Ahonsi et al. (2005) stated that, elsinochrome A (45) degrades rapidly in such conditions. They advocated for the release of elsinochrome A (45) into the environment, particularly in exposed niches such as spraying biocontrol product on plant surfaces, or release from shed diseased leave. This review gathers a comprehensive compilation of published findings on fungal PQs. The taxonomy of PQs and their biosynthesis come first in the introduction. Then, the review is divided into two sections, the first of which highlights a bibliography of fungal PQs and illustrates their structures. The distribution of PQ-producing fungi within the kingdom of fungi is the subject of section two, and the findings are summarized in a brief conclusion.

### Classification of perylenequinones

Natural PQs have been categorized into three broad classes (Fig. 1), according to Weiss et al. (1987).

A. **Class A:** C\(_{20}\) compounds without carbon substituents

Class A consists of the simple PQs including the parent perylenequinone 4,9-dihydroxyperylene-3,10-quinone (25), which is found in *Daldinia* and other fungal taxa. Eleven genera (Table 1) produced partially reduced perylenequinones of class A.

B. **Class B:** PQs carrying carbon substituents

Class B is derived from the unit of cercosporin (30) and phleichrome (31), with or without additional alicyclic rings. It appears that PQs of class B are enriched in many phytopathogenic strains and have a role in plant pathogenicity. PQs of class B are produced via 11 genera (Table 1). 4,9-Dihydroxyperylene-3,10-quinone (25) is an achiral planar substance. In most fungal perylenequinones, structural elements such as the two bulky methoxy groups or a strained seven-membered ring in positions 6 and 7, together with two C\(_3\) side chains in positions 1 and 12, are the source of enough steric interruption to force the pentacyclic perylenequinone system into a nonplanar helical shape (Weiss et al. 1987; Mulrooe et al. 2012; Hu et al. 2019). This helicity generates an element of asymmetry, the axial chirality M or P of the perylenequinone molecule (Fig. 2). More information concerning stereochemistry of PQs are available (Weiss et al. 1987). Class B was divided into three subclasses (Fig. 1) based on the core structures: (1) Perylenequinone core...
includes cercosporin, phleichrome, cladochromes, and calphostins (2) Dihydrobenzo (ghi)perylenequinone contains: elsinochromes, hypomycins, and phaeosphaerins (3) Cyclohepta(ghi)perylenequinone involves hypocrellins and shiraiachromes (Hu et al. 2019).

C. Class C

The parent perylenequinone 4,9-dihydroxyperylene-3, 10-quinone (25) with extra alicyclic rings is classified as class C. Other non-fungal species, such as aphids, caddis, and plants formed PQs of class C, e.g., rhodoaphin-be, erythrouphins-fb and –sl, gymnochromes, scutiaquinones A and B (Weiss and Altland 1965; Miskovsky 2002; Ayers et al. 2007). The classification of fungal perylenequinones is shown in Fig. 1.

Biosynthesis of fungal perylenequinones

PQs captivated biologists with their role in fungal virulence, potent biological activities, as well as chemists due to their interesting axial chirality and photochemical characteristics (Diwu and Lown 1993; Mulrooney et al. 2010; Daub et al. 2013; So et al. 2018). Therefore, the biosynthetic gene clusters (BGCs) of some fungal PQs like cercosporin (30), elsinochrome C (47), and hypocrellin A (50) have been identified.

Cercosporin (30) has a typical pentacyclic perylenequinone core; however, it is distinguished by the presence of an asymmetric 1,3-dioxepine moiety. Cercosporin (30) was discovered in Cercospora kikuchii, the pathogenic fungus that causes soy bean purple speck disease (Kuyama and Tamura 1957). CTB cluster for biosynthesis of cercosporin (30) from Cercospora nicotianae was the first BGC to be found (Chen et al. 2007; Newman and Townsend 2016; Hue et al. 2019).

Elsinochromes (45–48) are characterized by the hexacyclic dihydrobenzo(ghi)perylenequinone core, characterized by the hexacyclic dihydrobenzo(ghi)perylenequinone core. In 2017, Chooi and coworkers discovered the ele cluster for biosynthesis of elsinochrome C (47) in Parastagonospora nodorum, that causes septoria nodorum blotch in wheat, which has been proven to be important for its pathogenicity (Chooi et al. 2017). Three bamboo parasitic fungi produced hypocrellins, Hypocrella bambusae, Shiraia bambusicola, and Rubroshiraia bambusae. Hypocrellins (49–52) are considered by the hexacyclic cyclohepta(ghi)perylenequinone core, they are notorious to be present in traditional Chinese medicine (Yu et al. 1993). Based on gene expression correlation, the HYP cluster for hypocrellin A (50) production was discovered in Shiraia sp. Sfl14 (Yang et al. 2014), and subsequently verified by targeted gene deletion, the monoxygenase-

![Fig. 1 Classification of perylenequinones](image-url)
encoding gene (Mono) which is located in the hypocrellin gene cluster of Shiraia sp. (Deng et al. 2018).

Biosynthesis of fungal PQs has been extensively investigated and revised several times to disclose the ambiguity. The CTB, elc, and HYP gene clusters contain multiple shared homologs (Fig. 3) (Chen et al. 2007; Yang et al. 2014; Newman and Townsend 2016; Chooi et al. 2017; Deng et al. 2018; Hu et al. 2019). The phylogenetic analysis of elcA and allied fungal non-reducing PKSs revealed that elcA is more closely related to Shiraia sp. HYP1 than to C. nicotianae CTB1. The elc gene cluster shares more homologues with HYP gene cluster compared with CTB cluster as well. Due to their structures, both hypocrellin A (50) and elsinochrome A (45) have a hexacyclic system while cercosporin (30) is pentacyclic, the additional homologous genes shared between elc and HYP gene clusters but not CTB could be responsible for the formation of the additional ring (Chooi et al. 2017).

**Fig. 2** Axial chirality P and M of perylenequinones

| Perylenequinone classes | Genera                  | References                      |
|-------------------------|-------------------------|---------------------------------|
| Class A                 | Alternaria              | (Idris et al. 2015)             |
|                         | Aspergillus             | (Zhang et al. 2017)             |
|                         | Bulgaria                | (Xian et al. 2006)              |
|                         | Cenococcum              | (Peter et al. 2016)             |
|                         | Curvularia              | (Cruz et al. 2020)              |
|                         | Daldinia                | (Anderson and Murray 1956)      |
|                         | Phylacia                | (Wendt et al. 2018)             |
|                         | Rhopalostroma           | (Stadler et al. 2010)           |
|                         | Setophoma               | (Bazioli et al. 2020)           |
|                         | Stemphylium             | (Podlech et al. 2014)           |
|                         | Thamnomyces             | (Wendt et al. 2018)             |
| Class B                 | Cercospora              | (Mastrangelopoulou et al. 2019) |
|                         | Cladosporium            | (Petiti 2011)                   |
|                         | Elsinoë                 | (Jiao et al. 2019)              |
|                         | Hypocrella              | (Li et al. 2021)                |
|                         | Hypomyces               | (Liu et al. 2001b, a)           |
|                         | Parastagonospora        | (Chooi et al. 2017)             |
|                         | Phaeosphaeria           | (Li et al. 2012)                |
|                         | Pyrenochaeta            | (Kurobane et al. 2006)          |
|                         | Rubroshiraia            | (Dai et al. 2019)               |
|                         | Shiraia                 | (Fang et al. 2006)              |
|                         | Stagonospora            | (Ahonsi et al. 2005)            |
The most recent biosynthesis of perylenequinones was proposed by Hu et al. (2019) (Fig. 4). A common aromatic polyketide precursor serves as the starting point for biosynthesis, nor-toralactone I, which is synthesized by the non-reducing polyketide synthase (PKS) CTB1/elcA/HYP1. The subsequent step was achieved by bifunctional enzyme CTB3/elcB/HYP2 homolog, which possesses fused O-methyltransferase and Favin-dependent monooxygenase domains. This enzyme is responsible for methylation, hydroxylation, ring opening, decarboxylation of nor-toralactone I to afford toralactone II, then naphthol intermediate III. The O-methyltransferase CTB2/elcD/HYP4 is proposed to methylate the nascent OH-6 of intermediate III, blocking further oxidation at this site and yielding compound IV. The oxidative coupling steps to generate the pentacyclic core was elusive. Hu and collaborators have revealed the vagueness by demonstrating a heterologous biosynthesis, that cognate pairing of both Berberine Bridge Enzyme-like Oxidase (BBEO) elcE/CTB5 and Laccase-like Multi Copper Oxidase (LMCO) elcG/CTB12 for the double coupling step of two naphthol intermediates to afford the perylenequinone core V. Elsinochrome A (45) elc is synthesized via a radical process triggered by a single electron transfer from an enolate at the side chain to the FAD in elcH via the putative perylenequinone intermediate V. In the absence of elcH, hypocrellins (49–50) are formed, suggesting that they are most likely derived from the putative intermediate V via a transannular aldol reaction (Newman and Townsend 2016; Deng et al. 2018; Hu et al. 2019). CTB5, 6, 7, 9, and 10 afford cercosporin (30) through different reactions including reduction and homodimerization of the intermediates. The Zinc finger transcription factor CTB8 co-regulates expression of the cluster, while the Major Facilitator Superfamily (MFS) transporter CTB4 exports the final metabolite (Chen et al. 2007; Choquer et al. 2007; Newman and Townsend 2016).

**Stimulation of PQs’ production**

Light is an essential factor that regulates several physiological activities of fungi such as growth, reproduction, and biosynthesis of metabolites (Corrochano 2007). Conversely to plants, fungi use light as a source of information rather than energy (Tisch and Schmoll 2010). There is a strong evidence that light influences the synthesis of certain PQs. A significant increase in hypocrellin A (50) yield was observed, when *Shiraia* spp. were cultured under light-dark shift and red light (Sun et al. 2018; Ma et al. 2019a). The role of light in formation of cercosporin and elsinochromes by *Cercospora nicotianae*, *C. kikuchii*, and *Elsinoë fawcettii* was emphasized (Ehrenshaft and Upchurch 1991; Choquer et al. 2007). Light, on the other hand, is not required for biosynthesis of all PQs. Light seemed not to induce the synthesis of elsinochrome C (47) by *Parastagonospora nodorum* (Liao and Chung 2008). Several other factors, such as media, nutrition, growth conditions, and environmental variables, have an impact on PQs production. The synthesis of hypocrellin (49) increased on rice medium compared to Cheerios or oatmeal medium in solid-fermentation cultures (Ma et al. 2019b).
Section one: fungal perylenequinones

Fungal PQs fall into two classes (A and B) of perylenequinones. This section includes the bibliography of known PQs between 1956 and 2021, as well as their structures and biological activities. A total of 66 fungal PQs have been found in 22 fungal genera. Table 2 shows a list of fungal PQs as well as their producers.

Class A perylenequinones

Eleven ascomycete genera (Table 1) have been reported to produce 29 PQs of class A (Figs. 5 and 6). Most of them (24 compounds) are synthetized by *Alternaria* spp. Class A perylenequinones displayed diverse biological properties such as cytotoxicity, antiviral, antimicrobial, antileishmanial, and antimalarial activities.

*Alternaria Nees ex Fr*

The genus *Alternaria* (Pleosporaceae, Pleosporales) contains 366 accepted and recognizable species. Some species cause pre-harvest and post-harvest damage to cereal grains, fruits, and vegetables (Patriarca and Pinto 2018; Wijayawardene et al. 2020). *Alternaria* spp. produced several toxins including PQs. A total of 24 perylenequinones were recovered from *Alternaria* species. Recently, two dark PQ pigments, were isolated from the endophyte *Alternaria* sp. associated with *Pinus ponderosa*, identified as 3,6,6a,9,10-pentahydroxy-7,8-epoxy-4-oxo-4,5,6,6a,6b,7,8,9-octahydroperylene (1), and 3,6,6a,7,10-pentahydroxy-4,9-dioxo-4,5,6,6a,6b,7,8,9-octahydroperylene (2). Compound (1) and (2) displayed antileishmanial activity against *Leishmania donovani* with IC50 values of 2.55 and 4.40 μg/mL, respectively. Also compound (2) revealed antimalarial activity against both chloroquine sensitive (D6) (IC50 4.24 μg/mL) and chloroquine resistant (W2) clones of *Plasmodium falciparum* (3.65 μg/mL), as well as cytotoxicity against mammalian kidney fibroblasts (VERO cells) with IC50 value of 3.59 μg/mL (Tantry et al. 2018). Altertoxins I–III (3–5) were described from *Alternaria alternata*. Mutagenicity of compounds (3–5) was investigated using the Ames test with *Salmonella typhimurium*; these compounds were mutagenic to *Salmonella typhimurium* TA98, TA100, and TA1537 with and without metabolic activation (Stack and Prival 1986). Five perylenequinones (3, 6–9) were recovered from *Alternaria* sp. (DC401) an endophyte associated with *Pinus ponderosa*, altertoxin I (3), 6-methoxy-3,6a,7,10-tetrahydroxy-4,9-dioxo-4,5,6,6a,6b,7,8,9-...
| PQs’ class | Perylenequinone | Producer | Source | Reference |
|------------|-----------------|----------|--------|-----------|
| Class A    | 1) 3,6,9,10-pentahydroxy-7,8-epoxy-4-4-oxo-4,5,6,6a,6b,7,8,9-octahydroperylene | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Tantry et al. 2018) |
|            | 2) 3,6,9,10-pentahydroxy-4,9-dioxo-4,5,6,6a,6b,7,8,9-octahydroperylene | Alternaria alternata | – | (Stack and Prival 1986) |
|            | 3) altertoxin I | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Idris et al. 2015) |
|            | 4) altertoxin II | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Idris et al. 2015) |
|            | 5) altertoxin III | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Idris et al. 2015) |
|            | 6) 6-methoxy-3,6a,7,10-tetrahydroxy-4,9-dioxo-4,5,6,6a,6b,7,8,9-octahydroperylene | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Idris et al. 2015) |
|            | 7) 3,6a,9,10-tetrahydroxy-7,8-epoxy-4-oxo-4,5,6,6a,6b,7,8,9-octahydroperylene | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Idris et al. 2015) |
|            | 8) 6-methoxy-3,6a,9,10-tetrahydroxy-7,8-epoxy-4-oxo-4,5,6,6a,6b,7,8,9-octahydroperylene | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Idris et al. 2015) |
|            | 9) dehydroaltertoxin I | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Idris et al. 2015) |
|            | 10) altertoxin VII | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Idris et al. 2015) |
|            | 11) butyl xanalterate | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Idris et al. 2015) |
|            | 12) alterlosin I | Alternaria sp. | Pathogenic fungus from Centaurea maculosa | (Stierle et al. 1989) |
|            | 13) alterlosin II | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Idris et al. 2015) |
|            | 14) 8β-chloro-3,6aα,7β,9β,10-pentahydroxy-9,8,7,6a-tetrahydroperyl-4-keto-4H-one | Aspergillus fumigatus D | Halotolerant fungus | (Zhang et al. 2012) |
|            | 15) alterperylenol | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Zhang et al. 2017) |
|            | 16) dihydroalterperylenol | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Zhang et al. 2017) |
|            | 17) 7-epi-8-hydroxyaltertoxin I | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Zhang et al. 2017) |
|            | 18) 6-epi-stemphytriol | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Zhang et al. 2017) |
|            | 19) stemphyperylenol | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Zhang et al. 2017) |
|            | 20) alteichin | Alternaria sp. | Endophytic fungus from Pinus ponderosa | (Zhang et al. 2017) |
|            | 21) stemphytoxin III | Alternaria eichhorniae | Phytopathogenic fungus | (Robeson et al. 1984) |
|            | 22) 1,4,6b,7,10-pentahydroxy-1,2,6b,7,8,12b-hexahydroperyl-3,9-dione | Alternaria alternata | – | (Davis and Stack 1991) |
|            | 23) 1,4,9,12a-tetrahydroxy-12-methoxy-1,2,11,12,12a,12b-hexahydroperylene-3,10-dione | Alternaria tenuissima SS77 | Endophytic fungus | (Chagas et al. 2016) |
|            | 24) 1,4,9-trihydroxy-1,2-dihydroperylene-3,10-dione | Alternaria tenuissima SS77 | Endophytic fungus | (Chagas et al. 2016) |
|            | 25) 4,9-dihydroxyperylene-3,10-quinone | Alternaria eichhorniae | Phytopathogenic fungus | (Robeson et al. 1984) |
|            | 26) 4,9-dihydroxy-1,2,11,12-tetrahydroperylene-3,10-quinone | Alternaria sp. | – | (Davis and Stack 1991) |
|            | 27) methylated 12-e-epi-stemphytriol alterperylenol (15) | Alternaria sp. | – | (Davis and Stack 1991) |
|            | 28) stemphytoxin I | Alternaria sp. | – | (Davis and Stack 1991) |
|            | 29) stemphytoxin IV | Alternaria sp. | – | (Davis and Stack 1991) |
| PQs’ class | Perylenequinone | Producer | Source | Reference |
|------------|-----------------|----------|--------|-----------|
| Class B    | 30) cercosporin | *Cercospora kikuchii* | – | (Kuyama and Tamura 1957; Mumma et al. 1973; Mastrangelo and Poulos et al. 2019) |
|            |                 | *C. hayii* | – | |
|            | 31) phleichrome  | *Cladosporium phlei* | Pathogenic fungus of *Phleum pretense* | (Seto et al. 2005) |
|            | 32) en*-isopheichrome* | *Cladosporium cucumerinum* | Pathogen | (Amone et al. 1988) |
|            | 33) cladochrome A | *Cladosporium cladosporioides* | – | (Amone et al., 1990) |
|            | 34) cladochrome B | *Cladosporium cladosporioides* | – | |
|            | 35) cladochrome C | *Cladosporium cladosporioides* | – | |
|            | 36) cladochrome D | *Cladosporium cladosporioides* | – | |
|            | 37) cladochrome E | *Cladosporium cladosporioides* | – | |
|            | 38) cladochrome F | *Cladosporium cladosporioides* | – | |
|            | 39) cladochrome G | *Cladosporium cladosporioides* | – | |
|            | 40) calphostin A | *Cladosporium cladosporioides* | – | (Li et al. 2012) |
|            | 41) calphostin B | *Phaeosphaeria sp.* | – | |
|            | 42) calphostin C | *Phaeosphaeria sp.* | – | |
|            | 43) calphostin D | *Phaeosphaeria sp.* | – | |
|            | 44) calphostin I | *Phaeosphaeria sp.* | – | |
|            | 45) elsinochrome A | *Elsinoë annona* | Pathogen | (Weiss et al. 1987; Meille et al. 1989; Kurobane et al. 2006; Li et al. 2012; Chooi et al. 2017; Al Subeh et al. 2020) |
|            | 46) elsinochrome B | *Stagonospora convolvuli* | Pathogen | |
|            | 47) elsinochrome C | *Parastagonospora nodorum* | Pathogen | |
|            | 48) elsinochrome D | *Pyrenochaeta terrestris* | Pathogen | |
|            |                 | *Shiraia sp.* | Pathogen | |
|            |                 | *Phaeosphaeria sp.* | Pathogen | |
|            | 49) hypocrellin | *Hypocrella bambusae* | Pathogen | (Wu et al. 1989; Ma et al. 2004; Dai et al. 2019; Al Subeh et al. 2020; Li et al. 2021) |
|            | 50) hypocrellin A | *Hypocrella bambusae* | Pathogen | |
|            | 51) hypocrellin B | *Shiraia sp.* | Pathogen | |
|            | 52) hypocrellin D | *Shiraia sp.* | Pathogen | |
|            | 53) hypomycin A | *Hypomyces sp.* | – | |
|            | 54) hypomycin B | *Shiraia sp.* | – | (Li et al. 2001b, a; Shen et al. 2003; Al Subeh et al. 2020) |
|            | 55) hypomycin C | *Shiraia sp.* | – | |
|            | 56) hypomycin E | *Shiraia sp.* | – | |
|            | 57) hypomycin F | *Shiraia sp.* | – | |
|            | 58) hypomycin D | *Shiraia sp.* | – | |
|            | 59) phaeosphaerin A | *Phaeosphaeria sp.* | Endophytic fungus from *Heterodermia obscurata* | (Li et al. 2012) |
|            | 60) phaeosphaerin B | *Phaeosphaeria sp.* | – | |
|            | 61) phaeosphaerin C | *Phaeosphaeria sp.* | – | |
|            | 62) phaeosphaerin D | *Phaeosphaeria sp.* | – | |
|            | 63) phaeosphaerin E | *Phaeosphaeria sp.* | – | |
|            | 64) phaeosphaerin F | *Phaeosphaeria sp.* | – | |
|            | 65) shiraiachrome A | *Shiraia bambusicola* | Pathogenic fungus of bamboo | (Mulrooney et al. 2012) |
|            | 66) en*-shiraiachrome* | *Shiraia bambusicola* | Pathogenic fungus of bamboo | |

---

Note: The table continues with additional entries not shown in the snippet.
octahydroyperylene (6), 3,6a,9,10-tetrahydroxy-7,8-epoxy-4-oxo-4,5,6,6a,6b,7,8,9-octahydropyrene (7), 6-methoxy-3,6a,9,10-tetrahydroxy-7,8-epoxy-4-oxo-4,5,6a,6b,7,8,9-octahydropyrene (8), and dehydroaltertoxin I (9) (Idris et al. 2015). In 2018, two dark red pigments (PQs’ derivatives) altertoxin VII (10) and butyl xanalterate (11) were purified from a culture of the sponge-derived fungus, Alternaria sp. SCSIO41014. Compound (10) exhibited potent cytotoxicity against human gastric carcinoma cells (SGC-7901) (IC_50 8.75 μM). Also exhibited moderate antiproliferative activity against human lung cancer cell line A549 (IC_50 12.79 ± 0.33 μM) (Zhang et al. 2017).

Bulgaria Fr.

The genus Bulgaria (Phacidiaceae, Phacidiales) consists of 12 species (Wijayawardene et al. 2020). Bulgaria inquinans is a saprophyte that grows on felled oak trunks and fallen branches, and less frequently on ash. 4,9-dihydroxyperylene-3,10-quinone (25), and 4,9-dihydroxy-1,2,11,12-tetrahydroperylene-3,10-quinone (26), were described from the ethanolic extract of B. inquinans fruiting bodies (Weiss et al. 1987; Xian et al. 2006).

Cenococcum Moug. & Fr.

There are five species of the genus Cenococcum (Gloniaceae, Gloniales). The most common and globally abundant ectomycorrhizal fungus is Cenococcum geophilum. This fungus often dominates the root systems of trees in extreme environments (Peter et al. 2016; Wijayawardene et al. 2020). Sclerotia of Cenococcum geophilum were abundant in compound (25) which interpreted the existence of compound (25) in sediment samples from Lake Biwa (Itoh et al. 2012; Hanke et al. 2019).

Curvularia Boedijn

The genus Curvularia (Pleosporaceae, Pleosporales) is commonly found in plants and soil of tropical and subtropical regions. There are 119 recognized species of Curvularia (Khiralla et al. 2019; Wijayawardene et al. 2020). In 2020, three PQs, the methylated 12-epi-stemphytriol (27), (15), and (16) were reported for the first time from malt extract broth of C. lunata (LBQM-04) (Cruz et al. 2020).

Daldinia Ces. & De Not.

The genus Daldinia (Hypoxylaceae, Xylariales) comprises 67 species. Daldinia concentrica is an inedible wood-rotting fungus (Lee et al. 2006; Wijayawardene et al. 2020). 4,9-dihydroxyperylene-3,10-quinone (25) was the first perylenequinone discovered by Anderson and Murray (1956). They isolated compound (25) from the large black fruiting bodies of D. concentrica.

Aspergillus P. Micheli ex Haller

The genus Aspergillus (Aspergillaceae, Eurotiaceae) has a significant economic and social impact. It comprises 428 species. Aspergillus spp. occur worldwide in various habitats such as food producing mycotoxins and are frequently reported as human and animal pathogens (Samson et al. 2014; Wijayawardene et al. 2020). Only one PQ is reported from the genus Aspergillus. Bioassay-guided fractionation of the crude extract of the salty broth of Aspergillus fumigatus D, an endophyte associated with Edgeworthia chrysanthi led to the isolation of a chlorated perylenequinone, 8-chloro-3,6a,7,9,10-pentahydroxy-9,8,7,6a-tetrahydroperylene-4(6aH)-one (14). Compound (14) revealed strong antimicrobial effects against Escherichia coli (MIC 0.78 μM) and Candida albicans (1.56 μM). Also exhibited moderate antiproliferative activity against human lung cancer cell line A549 (IC_50 12.79 ± 0.33 μM) (Zhang et al. 2017).

Ces. & De Not.
The genus *Phylacia* (*Hypoxylaceae, Xylariales*) was collected from different tropical countries such as Colombia, Brazil, Mexico and French Guiana. Twelve species are documented of the genus *Phylacia* (Fournier and Lechat 2015; Wijayawardene et al. 2020). Several members of *Hypoxylaceae* including *Phylacia* spp. were examined. Compound (25) was frequently encountered in stromata of *Phylacia* spp. (Wendt et al. 2018).

**Rhopalostroma D. Hawksw.**

The genus *Rhopalostroma* (*Hypoxylaceae, Xylariales*) contains currently 11 species. *Rhopalostroma* spp. have been collected exclusively from Africa and Asia (Daranagama et al. 2020).
Stromata extracts of several *Rhopalostroma* spp. were screened using high-performance liquid chromatography with diode array and mass spectrometric detection (HPLC-DAD-MS). The pigment, 4,9-dihydroxyperylene-3,10-quinone (25) was detected (Stadler et al. 2010).
Setophoma Gruyter, Aveskamp & Verkley

Wijayawardene et al. (2020) accepted six species of the genus Setophoma (Phaeosphaeriaceae, Pleosporales). The production of some PQs by Setophoma was reported (Bazioli et al. 2020). Stemphyperylennol (19) and derivatives were recovered from Setophoma sp., compound (19) displayed antifungal effects against Aspergillus fumigatus, Pencillium brasiliannum, and P. digitatum.

Stemphylium Wallr.

Some species of Stemphylium are pathogens of several important crops including onion, alfalfa, sugar beet, and asparagus. The genus Stemphylium (Pleosporaceae, Pleosporales) contains 96 species (Wijayawardene et al. 2020). Four perylenequinones, stemphyloxins I, IV (28–29), besides two further (4), and (21) were recovered from Stemphylium botryosum (Podlech et al. 2014).

Thamnomyces Ehrenb.

Thamnomyces (Hypoxylaceae, Xylariales) is a tropical genus known exclusively from the Neotropics and Africa. Only 11 species are recorded of the genus Thamnomyces (Wijayawardene et al. 2020). Compound (25) was reported in stromata extracts of Thamnomyces spp. (Wendt et al. 2018).

Class B perylenequinones

Thirty-seven fungal PQs of class B have been described to date (Figs. 7, 8, and 9). They are produced by 11 ascomycete genera (Table 1). The majority of them are plant pathogenic strains. Fungal PQs of class B were also investigated for their biological properties, some of them revealed cytotoxicity, antiviral, antimicrobial and antileishmanial activities.

Cladosporium link

The genus Cladosporium (Cladosporiaceae, Capnodiales) is frequently isolated from soil and organic matter; however, some species are pathogens. The genus Cladosporium comprises 237 accepted species (Bensch et al. 2018; Wijayawardene et al. 2020). Cladosporium spp. are distinguished by producing diverse PQs including cladochromes and calphostins. Phlelichrome (31) was reported from the pathogenic fungus Cladosporium pheii associated with the timothy plant (Phleum pratense L.). In the presence of light, compound (31) demonstrated antifungal action against Epichloe typhina (Seto et al. 2005). Ent-isopelichrome (32) besides cladochromes A–G (33–39) were described from different Cladosporium spp. (Arnone et al. 1988, 1990; Williams et al. 2008; Pettit 2011). Calphostins A–D, I (40–44) were purified from the fermented broth of Cladosporium cladosporioides. Calphostin C (42), revealed potent and specific inhibition of protein kinase C, because it was 1000 times more inhibitory to protein kinase C (IC50 0.05 μM) than other protein kinases such as cAMP-dependent protein kinase and tyrosine-specific protein kinase (IC50, >50 μM) (Kobayashi et al. 1989; Iida et al. 2012).

Cercospora Fresen.

The genus Cercospora (Mycosphaerellaceae, Capnodiales) contains 1125 species. Most Cercospora spp. are pathogens (Wijayawardene et al. 2020). In 1957, cercosporin (30) was isolated from mycelial cultures of Cercospora kikuchii, a pathogen that causes soybean purple speck disease (Kuyama and Tamura 1957). Compound (30) demonstrated photocytotoxicity against two glioblastoma multiforme (T98G, U87) and one breast adenocarcinoma (MCF7) human cell lines. However, in the dark compound (30) displayed a synergistic cytotoxicity with copper only in the most respiratory cell lines of MCF7 and T98G. Cercosporin (30) is a powerful photosensitizer, but with a short activation wave-length, mostly appropriate for superficial PDT treatments (Mastrangelopoulou et al. 2019).

Elsinoë Racib.

Species of Elsinoë are phytopathogens, causing scab and spot anthracnose on several economically important crops. The genus Elsinoë (Elsinoaceae, Myriangiales) contains 40 species (Fan et al. 2017; Wijayawardene et al. 2020). Four PQs were reported from Elsinoë. Three bright red pigments, elsinochromes A–C (45–47), and one orange named elsinochrome D (48) were produced in cultures by Elsinoë annanae and its anamorph Spaceloma randii (Weiss et al. 1987; Meille et al. 1989). Elsinochrome phytotoxins are generated also by E. arachidis, the responsible fungus of peanut scab. Elsinochrome A (45) is distinguished by a superior singlet oxygen quantum yield compared to other kinds of photosensitizes. Elsinochrome A (45) could be easily synthesized at present, which makes it an alternative candidate for PDT (Jiao et al. 2019).

Hypocrella Sacc.

Hypocrella spp. (Clavicipitaceae, Hypocreales) are common in tropical regions, particularly in moist old-growth forests. There are more than 170 recognized species in the genus Hypocrella. Some species of Hypocrella are parasites of scale insects and white flies (Mains 1959; Chaverri et al. 2008; Wijayawardene et al. 2020). H. bambusae, a parasite of living inflorescence of bamboo, was studied (Dai et al. 2019). Investigations revealed that H. bambusae produced several types of PQs: hypocrellins.
Hypomycins A (49–51), hypomycins F (57), and shiraiachrome A (65) (Weiss et al. 1987; Diwu and William 1990; Ma et al. 2004; Cheng et al. 2004; Li et al. 2021). Hypocrellins and shiraiachromes have so close structures. Formerly, there has been much confusion in the naming of the same compounds extracted from different sources, hypocrellin A (50) was referred as shiraiachrome B, and hypocrellin B (51) was named as either shiraiachrome C or hypocrellin C (Wu et al. 1989; Kishie et al. 1991; Liu et al. 2001a; Ma et al. 2019b). Herein, we followed the structures and nomenclatures (Fig. 8) proposed by Al Subeh et al. (2020).

**Hypomyces (Fr.) Tul. & C. Tul.**

The genus *Hypomyces* (*Hypocreaceae, Hypocreales*) consists exclusively of fungicolous fungi, parasitizing the fruiting bodies of some members of *Agaricales, Boletales, Helotiales, Pezizales*, and *Polyporales*. *Hypomyces* comprises of 150 species widely distributed in Australia, Asia, and Europe (Wijayawardene et al. 2020; Yu et al. 2020). Four perylenequinones, hypomycins A–C, D1 (53–55, 58) were discovered in the mycelia of *Hypomyces* spp. (Liu et al. 2001b, a; Shen et al. 2003).

Parastagonospora Quaedvl., Verkley & Crous

*Parastagonospora* is an important genus in *Phaeosphaeriaceae* that includes pathogens causing leaf and glume blotch on cereal crops. Nineteen species are recognized of the genus *Parastagonospora* (Goonesekara et al. 2019; Wijayawardene et al. 2020). *Parastagonospora nodorum* is a significant pathogen of wheat. The production of elsinochrome C (47) by *P. nodorum* was reported by Chooi et al. (2017). They stated that elsinochrome C contributes to the virulence of *P. nodorum* against wheat.

**Phaeosphaeria I. Miyake**

*Phaeosphaeria* is a member of *Phaeosphaeriaceae*. There are around 96 species of the genus *Phaeosphaeria*. Most of the *Phaeosphaeria* species are parasites of *Poaceae* and grass-like monocot plants (Stchigel et al. 2004; Wijayawardene et al. 2020). Twelve different PQs are produced by *Phaeosphaeria*: phaeosphaerins A–F (59–64), five are yellow (phaeosphaerins A–C, E, and F), while one is orange (phaeosphaerin D), as well as calphostin D (43) elsinochromes A–C (45–47), and hypocrellins A–B (50–51). These PQs were purified from an endolichenic fungus *Phaeosphaeria* sp. found.
in the lichen *Heterodermia obscurata*. The unusual $\alpha,\beta$-unsaturated ketone moieties present in phaeosphaerins A – F resulted in their yellow coloration. Phaeosphaerins' cytotoxicity against human prostate cancers intensified in the presence of light (Li et al. 2012).

**Pyrenochaeta De Not.**

*Pyrenochaeta* spp. (*Pleosporales*) inhabit soil and plant debris and are well-known as pathogens of plants and occasionally humans. The genus *Pyrenochaeta* contains five accepted species (Levic et al. 2013; Yadav et al. 2015; Wijayawardene et al. 2020). *Pyrenochaeta terrestris*, a pathogen that causes onion pink root disease, produced both elsinochrome C (47) and D (48) (Kurobane et al. 2006).

**Rubroshiraia D.Q. Dai & K.D. Hyde**

*Rubroshiraia* (Shiraiaceae, *Pleosporales*) contains one species named *Rubroshiraia bambusae* D.Q. Dai & K.D. Hyde, a common pathogen of bamboos. *R. bambusae* is a well-known taxon used in Chinese traditional medicine which is called “Zhuhongjun” (Dai et al. 2019; Wijayawardene et al. 2020). The HPLC profiles of methanol stromata extracts of *R. bambusae* contained high quantities of hypocrellin A and B (50–51). Stromata extracts of
R. bambusae contains almost double the content of hypocrellin A and B compared to Shiraia bambusicola (Dai et al. 2019). Hypocrellins have gained much attention due to their light-induced antitumor, antimicrobial, antileishmanial, and antiviral activities (Diwu and William 1990; Hudson et al. 1994; Ma et al. 2004). Some clinical trials showed that hypocrellins have promising treatment for various skin diseases, such as skin cancer and white lesions of the vulva (Wan and Chen 1981; Li et al. 2000).

The genus Shiraia (Shiraiaceae, Pleosporales) comprises one species. Shiraia bambusicola is a pathogen of several genera of bamboos. Large stromata of S. bambusicola have been used in folk Chinese medicine (Wu et al. 1989; Wijayawardene et al. 2020). Nine PQs were reported from S. bambusicola: elsinochromes A–C (45–47), hypocrellins A–B, D (50–52), hypomycin E (56), shiraiachrome A (65), and ent-shiraiachrome A (66) (Wu et al. 1989; Fang et al. 2006; Ma et al. 2019b; Al...
Subeh et al. 2020; Li et al. 2021). Endophytes, identified as *Shiraia* spp., were also shown to produce hypocrellins on media (Morakotkarn et al. 2008; She et al. 2014). Compound (50) demonstrated promising antifungal activity against *Candida albicans* (0.65 ± 0.14 μg/mL), and exhibited potent antileishmanial activity (IC50 of 0.27 ± 0.03 μg/mL), while compound (51) revealed moderate antileishmanial activity (IC50 12.7 ± 2.1 μg/mL). Interestingly, the antileishmanial activity of hypocrellin A was three- and six fold more potent than that of amphotericin B and pentamidine, respectively. Compound (52) reduced tumor cell proliferation in Bel-7721 (IC50 1.8 mg/mL), A-549 (8.8 mg/mL), and Anip-973 (38.4 mg/mL) (Fang et al. 2006). Compound (56) inhibited pseudotyped SARS-CoV-2 infection in 293T-ACE2 cells (IC50 0.17 μM), as well as compound (66) (0.038 μM), and both even suppressed live SARS-CoV-2 infection (EC50 0.22 and 0.21 μM, respectively) (Li et al. 2021).

**Stagonospora (Sacc.) Sacc.**

The genus *Stagonospora* (*Massarinaceae, Pleosporales*) comprises 220 species. Some species of *Stagonospora* are commonly known as aggressive pathogens of wheat. While other *Stagonospora* spp. have been implicated in bioremediation of aromatic compounds and lignin derivatives (Bergbauer et al. 1992; Zeiner et al. 2016; Wijayawardene et al. 2020). *Stagonospora convolvuli* LA39 is a pathogen of field and hedge bindweeds, and was reported to produce elsinochrome A (45). Hence, *S. convolvuli* has been studied as a bindweed biocontrol agent (Ahonsi et al. 2005; Boss et al. 2007).

### Table 3 List of families and number of PQ-producing genera

| Family             | Number of genera* | Reference                                      |
|--------------------|-------------------|------------------------------------------------|
| Aspergillaceae     | 1                 | (Zhang et al. 2017)                            |
| Cladosporiaceae    | 1                 | (Arnone et al., 1990; Williams et al. 2008; Iida et al. 2012) |
| Clavicipitaceae    | 1                 | (Wu et al. 1989; Li et al. 2021)                |
| Elsinoaceae        | 1                 | (Jiao et al. 2019)                             |
| Gloniaceae         | 1                 | (Itoh et al. 2012)                             |
| Hypocreaceae       | 1                 | (Liu et al. 2001b, a; Shen et al. 2003)         |
| Hypoxylaceae       | 4                 | (Anderson and Murray 1956; Stadler et al. 2010) |
| Massarinaceae      | 1                 | (Boss et al. 2007)                             |
| Mycosphaerellaceae | 1                 | (Mastrangelopoulou et al. 2019)                |
| Phacidiaceae       | 1                 | (Weiss et al. 1987; Xian et al. 2006)           |
| Phaeosphaeriaceae  | 3                 | (Li et al. 2012; Chooi et al. 2017; Bazioli et al. 2020) |
| Pleosporaceae      | 3                 | (Kurobane et al. 2006; Tantry et al. 2018; Cruz et al. 2020) |
| Shiraiaceae        | 2                 | (Wu et al. 1989; Al Subeh et al. 2020)          |

*Pyrenochaeta (Pleosporales genus incertae sedis) is excluded from the table

### Section two: distribution of PQ-producing fungi among the kingdom of fungi

This section covers the main information gleaned from the aforementioned fungal PQ reports. In addition, classification of PQ-producing fungi as well as a conclusion.

In this review, 66 fungal PQs were reported from 22 fungal genera between 1956 and 2021. The review revealed that, despite appearances, the synthesis of fungal PQs is not exclusive to phytopathogens. PQ-producing fungi include endophytic, endolichenic, soil, and marine strains. Interestingly, color diversity of fungal PQ pigments was observed to be quite considerable, various colors including red, orange, yellow, and even dark blue are available (Weiss et al. 1987; Meille et al. 1989; Mulrooey et al. 2012; Li et al. 2012; Al Subeh et al. 2020).

Obviously, 29 compounds belonging to class A have been reported from 11 ascomycete genera (Fig. 10). Twenty-four PQs were isolated from *Alternaria* (12 unique), seven from *Setophoma*, four from *Stemphylium* (two unique), three from *Curvularia* (one unique), two from *Bulgaria* (one unique) and one each from *Aspergillus*, *Cenococcum*, *Daldinia*, *Rhopalostroma*, *Thamnomyces*, and *Phylacia*, whereas 37 of
the described fungal PQs belong to class B and were recovered from 11 ascomycete genera (Fig. 10). Cladosporium has 14 unique PQs, Phaeosphaeria has 12 (six unique), Shiraia has nine (three unique), Hypocrella has six (two unique), Elsinoë has four (one unique), Hypomyces has four (two unique), Pyrenochea and Rubroshiraia each has two, Cercospora has one unique, Stagonospora and Parastagonospora each has one PQ.

The genera Alternaria, Cladosporium, Phaeosphaeria, and Shiraia have the most distinct PQs (Fig. 10). In comparison to class A, the uniqueness of PQs per genus was higher in class B. Remarkably, all PQ-producing fungi described in this review affiliate with one phylum Ascomycota, and only four classes. Dothideomycetes (14 genera) accounts for the bulk of the documented PQs 82%, followed by Sordariomycetes (six genera) 14%, Leotiomycetes (one genus) 3%, and Eurotiomycetes (one genus) 1%. The distribution of PQs among fungal genera is summarized in Fig. 11.

Fungal PQs were extracted from cultures, mycelia, stromata, and fruiting bodies, using various solvents including acetone, ethyl acetate, ethanol, and methanol. The tendency of fungal PQs appears to be extracted from cultures over stromata/fruiting bodies. Only 4,9-dihydroxyperylene-3,10-quinone (25) was isolated from stromata/fruiting bodies of Bulgaria and Daldinia (Weiss et al. 1987; Anderson and Murray, 1956). There is a strong inconsistency in the chemotaxonomy of the PQ-producing fungi. They are described from a total of 13 separate families (Table 3). Fig. 12 shows the classification of PQ-producing fungi based on the recent outline of fungi (Wijayawardene et al. 2020). A chemotaxonomic approach is required to substantiate the hypothesis that members of a specific family could produce PQs. A number of fascinating Hypoxylaceae chemotaxonomic studies have been achieved (Helaly et al. 2018; Becker and Studler 2021; Kuhnert et al. 2021). They documented the occurrence of several secondary metabolites in Daldinia, Phylacia, Rhopalostroma, and Thamnomyces stromata, including (25). In this review, five families, Pleosporaceae, Phaeosphaeriaceae, Cladosporiaceae, Shiraiaecae, and Hypoxylaceae are distinguished by their considerable number of PQs and genera. As a consequence, members of these families should be taken into account as potential sources of novel PQs.
Conclusion

Bioprospectors have been captivated by the diversity, novelty, and biological activity of fungal natural products. Perylenequinones (PQs) are naturally occurring aromatic polyketides. They are unique and fascinating compounds because of their chemical and biological properties. Fungi, aphids, crinoids, and plants are the sources of PQs. Fungal PQs have been first discovered in some phytopathogenic species, and it was subsequently recognized that PQs have a role in pathogenicity. Because of their capacity to absorb light and generate reactive oxygen species, fungal PQs possessed different bioactivities including antitumor, antiviral, antileishmanial, antimalarial, and antimicrobial properties, most notably their protein kinase C inhibitory activity. Fungal PQs are divided into two categories: class A simple PQs consists of the parent perylenequinone (4,9-dihydroxyperylene-3, 10-quinone) without carbon substituents. PQs with carbon substituents are compiled in class B. To date, 66 fungal PQs have been described from 22 genera. According to the analysis, fungi are the best source of PQs, accounting for 85% of all known PQs, whereas only 15% were obtained from both the kingdoms Animalia and Plantae. One phylum, Ascomycota, and four classes (Dothideomycetes, Sordariomycetes, Leotiomycetes, and Eurotiomycetes) are responsible for the documented fungal PQs. Dothideomycetes is distinguished by having the greatest diversity of PQ-producing fungi as well as the greatest amount of PQs. The families Pleosporaceae, Phaeosphaeriaceae, Cladosporiaceae, Shiraiaceae, and Hypoxylaceae could be significant sources of novel PQs. Fungal PQs merit more consideration as PDT agents, due to their advantages over other photosensitizers. Hypocrellins are an excellent example of the application of PQs. Certainly, more investigations are necessary to reveal novel fungal PQs using modern techniques.

Acknowledgements The authors express their sincere gratitude to Prof. Marc Stadler and two anonymous reviewers for their contributions to the manuscript’s improvement.

Code availability Not applicable.

Author contribution Conceptualization: Afra Khiralla. Literature search and analysis: Afra Khiralla and Aisha O. Mohammed. Writing and review: Afra Khiralla. Editing and revision: Sakina Yagi.

Data availability Not applicable.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

References

Ackroyd R, Kelty C, Brown N, Reed M (2001) The history of photodetection and photodynamic therapy. Photochem Photobiol 74:656–669
Ahoni MO, Maurhofer M, Boss D, Défago G (2005) Relationship between aggressiveness of Stagonospora sp. isolates on field and hedge bindweeds, and in vitro production of fungal metabolites cercosporin, elsniochrome A and leptosphaeriadione. Eur J Plant Pathol 111:203–215. https://doi.org/10.1007/s10658-004-2578-5
Al Subeh ZY, Raja HA, Monro S et al (2020) Enhanced production and anticancer properties of photoactivated perylenequinones. J Nat Prod 83:2490–2500. https://doi.org/10.1021/acs.jnatprod.0c00492
Anderson JM, Murray J (1956) Isolation of 4,9-dihydroxy-perylene-3, 10-quinone from a fungus. Chem Ind 376–376
Amone A, Assante G, Di Modugno V et al (1988) Perylenequinones from cucumber seedlings infected with Cladosporium cucumerinum. Phytochemistry 27:1675–1678. https://doi.org/10.1016/0031-9422(88)80424-2
Amone A, Assante G, Merlini L, Nasini G (1990) Structure and stereochemistry of cladochrome D and E, novel perylenequinone pigments from Cladosporium cladosporioides. Chem Inform 21. https://doi.org/10.1002/chin.199001284
Ayers S, Zink DL, Mohn K et al (2007) Scutiaquinones A and B, perylenequinones from the roots of Scutia myrtina with antihelminthic activity. J Nat Prod 70:425–427. https://doi.org/10.1021/np0604937
Bazioli JM, Fill TP, Rocha MC et al (2020) Perylenequinones production induced by co-culturing Setophoma sp. and Penicillium brasilianum. Phytochem Lett 40:76–83
Becker K, Stadler M (2021) Recent progress in biodiversity research on the Xylariales and their secondary metabolism. J Antibiot (Tokyo) 74:1–23. https://doi.org/10.1038/s41429-020-00376-0
Bensch K, Groeneveldt IZ, Meijer M et al (2018) Cladosporium species in indoor environments. Stud Mycol 89:177. https://doi.org/10.1016/j.simyco.2018.03.002
Berghauer M, Eggert C, Kalnowski G (1992) Biotreatment of pulp mill bleaching effluents with the coelomycetous fungus Alternaria tenuissima. FEMS Microbiol Ecol 59:194–208. https://doi.org/10.1016/j.femsec.2020.06.021
Bosch D, Maurhofer M, Schläpfer E, Défago G (2007) Elsinochrome A production by the bindweed biocontrol fungus Stagonospora convolvuli LA39 does not pose a risk to the environment or the consumer of treated crops. FEMS Microbiol Ecol 59:194–205. https://doi.org/10.1111/j.1574-6941.2006.00207.x
Chagas FO, Dias LG, Pupo MT (2016) New perylenequinone derivatives from the endophytic fungus Alternaria tenuissima SS77. Tetrahedron Lett 57:3185–3189. https://doi.org/10.1016/J.TETLET.2016.06.035
Chaverri P, Liu M, Hodge KT (2008) A monograph of the entomopathogenic genera Hypocrella, Molleriella, and Samuelsia gen. nov. (Ascomycota, Hypocreales, Clavicipitaceae), and their aschersonia-like anamorphs. Stud Mycol 60. https://doi.org/10.1016/j.simyco.2018.03.002
Chen H-Q, Lee M-H, Chang K-R (2007) Functional characterization of three genes encoding putative oxidoreductases required for cercosporin toxin biosynthesis in the fungus Cercospora nicotianae. Microbiology 153:2781–2790. https://doi.org/10.1099/mic.0.2007/007294-0
Cheng TF, Jia XM, Ma XH et al (2004) Phylogenetic study on Shiraia bambusicola by rDNA sequence analyses. J Basic Microbiol 44:339–350. https://doi.org/10.1002/jb.200410434
Levíc JT, Petrovic TM, Stankovic SC, Ivanovic DM (2013) The incidence of *Pyrenochoa terrestris* in root of different plant species in Serbia. Zb Matice Srp za Prir Nauk 125:21–30. https://doi.org/10.2298/ZMSPNI325021L

Li C, Wang HQ, Xie JL et al (2000) Analysis and comparisons of compounds among three medical fungi of *Hypocreaceae*. Chinese Tradit Herb Drugs 31:250–251

Li G, Wang H, Zhu R et al (2012) Pheasaphoerisins A-F, cytotoxic perylenequinone from an endophlic fungus, *Pheasaphoeira* sp. J Nat Prod 75:142–147. https://doi.org/10.1021/np200614h

Li T, Deng H, Zhao J, Gu Y (2015) Elsinochrome A photosensitizers: alternative drugs for photodynamic therapy. J Innov Opt Health Sci 08:1530001. https://doi.org/10.1142/s1793545815300013

Li YT, Yang C, Wu Y et al (2021) Axial chiral binaphthoquinone and perylenequinones from the stromata of *Hypocrella bambusae* are SARS-CoV-2 entry inhibitors. J Nat Prod 84:436–443. https://doi.org/10.1021/acs.jnatprod.0c01136

Liao HL, Chung KR (2008) Genetic dissection defines the roles of elsinochrome phytotoxin for fungal pathogenesis and conidiation of the citrus pathogen *Elsinoe fawcettii*. Mol Plant-Microbe Interact 21:469–479

Liu WZ, Ma LY, Li C et al (2001a) Structural elucidation of a new perylenequinone. Acta Pharm Sin 36:313–314

Liu WZ, Shen YX, Liu XF et al (2001b) A new perylenequinone from *Hypomyces* sp. Chin Chem Lett 12:431–432

Ma G, Khan SJ, Jacob MR et al (2004) Antimicrobial and antileishmanial activities of hypocrellins A and B. Antimicrob Agents Chemother 48:4450–4452. https://doi.org/10.1128/AAC.48.11.4450-4452.2004

Ma YJ, Sun CX, Wang JW (2019a) Enhanced production of hypocrellin A in submerged cultures of *Shiraia bambusica* by red light. Photochem Photobiol Photocatal 95:812–822

Ma YJ, Zheng LP, Wang JW (2019b) Inducing perylenequinone production from a bacteriocinsulcous fungus *Shiraia* sp. S9 through co-culture with a fruiting body - associated bacterium *Pseudomonas fulva*. Microb Cell Factories 18:1–14. https://doi.org/10.1186/s12934-019-1170-5

Mains EB (1959) Species of *Hypocrella*. Mycopathol Mycol Appl 11:311–326

Mastrangeloouli M, Grigalavičius M, Berg K et al (2019) Cytotoxic and photocytotoxic effects of cercosporin on human tumor cell lines. Photochem Photobiol Photocatal 95:387–396. https://doi.org/10.1111/php.12997

Meille SV, Malpezi L, Allegra G et al (1989) Structure of elsinochrome phytotoxin for fungal pathogenesis and conidiation. *Hypocrella bambusae*. Chin Chem Lett 12:431–432

Miskovsky P (2002) Hypericin, a new antiviral and antitumor photosensitizer: mechanism of action and interaction with biological macromolecules. Curr Drug Targets. https://doi.org/10.2174/138945002348091

Morakotkam D, Kawasaki H, Tanaka K et al (2008) Taxonomic characterization of *Shiraia*-like fungi isolated from bamboos in Japan. Mycoscience 49:258–265. https://doi.org/10.1007/S10267-008-0419-3

Mulrooney CA, Morgan BJ, Li X, Kozlowski MC (2010) Perylenequinone natural products: enantioselective synthesis of the oxidized pentacyclic core. J Orgomet Chem 75:16–29. https://doi.org/10.1128/AAC.48.11.4450-4452.2004

Mulrooney CA, Morgan BJ, Kozlowski MC (2012) Perylenequinones: isolation, synthesis, and biological activity. Eur J Org Chem 21:3887. https://doi.org/10.1038/jjgcd.2014.371

Mumma RO, Lukezic FL, Kelly MG (1973) Cercosporin from *Cercospora hajii*. Phytochemistry 12:917–922. https://doi.org/10.1016/0031-9422(73)80703-4

Newman AG, Townsend CA (2016) Molecular characterization of the cercosporin biosynthetic pathway in the fungal plant pathogen *Cercospora nicotianae*. J Am Chem Soc 138:4219–4228. https://doi.org/10.1021/jacs.6b00633.Molecular

Olivo M, Ali-Seyed M (2007) Apoptosis signalling mechanisms in human cancer cells induced by calphostin PDT. Int J Oncol 30:537–548

Pang X, Lin X, Wang P et al (2018) Perylenequinone derivatives with anticancer activities isolated from the marine sponge-derived fungus, *Alternaria* sp. SC81041014. Mar Drugs 16:1–13. https://doi.org/10.3390/md16080280

Patriarca A, Pinto VF (2018) Alternaria. In: Reference Module in Food Science. Elsevier, pp 1–8. https://doi.org/10.1016/B978-0-08-100596-5.22527-9

Peter M, Kohler A, Ohm RA et al (2016) Ectomycorrhizal cultivation is imprunted in the dominant symbiotic fungus *Cenococcum geophilum*. Nat Commun 7. https://doi.org/10.1038/ncomms12662

Petit RK (2011) Small-molecule elicitation of microbial secondary metabolites. Microb Biotechnol 4:471–478. https://doi.org/10.1111/j.1751-7915.2010.01096.x

Podlech J, Fleck SC, Metzler M et al (2014) Determination of the absolute configuration of perylene quinone-derived mycotoxins by measurement and calculation of electronic circular dichroism spectra and specific rotations. Chem - A Eur J 20:11463–11470. https://doi.org/10.1002/chem.201402567

Robeson D, Strobel G, Matusmoto GK et al (1984) Alteichin: an unusual phytotoxin from *Alternaria eichhorniae*, a fungal pathogen of water hyacinth. Europhycologia 40:1248–1250

Samson RA, Visage CM, Houbraken J et al (2014) Phylogeny, identification and nomenclature of the genus *Aspergillus*. Stud Mycol 78:141–173. https://doi.org/10.1016/j.simyco.2014.07.004

Seto Y, Kogami Y, Shimamaki T et al (2005) Production of phleichrome by *Cladosporium phlei* as stimulated by diketopiperazines of *Epichloehypila*. Biosci Biotechnol Biochem 69:1515–1519

Sharma SK, Woo T, Naicker S (2013) Perylenequinone dravatives and uses thereof. United States Patent No. US 8,506,931 B2. Quest Pharmatech Inc. https://patents.google.com/patent/US8506931B2/en. Accessed 20 June 2021

Shen XY, Cheng YL, Cai CJ et al (2014) Diversity and antimicrobial activity of culturable endophytic fungi isolated from moso bamboo seeds. PLoS One 9:1–7. https://doi.org/10.1371/journal.pone.0095838

Shen Y, Liu W, Rong X, Sun Y (2003) Studies on the chemical constituents of a fungus producing perylenequinones. Acta Pharm Sin 38:834–837

So KK, Chun J, Kim DH (2018) Antimicrobial and antitumor photodynamic effects of phleichrome from the phytopathogenic fungus *Cladosporium phlei*. Mycobiology 46:448–451

Stack ME, Prival MJ (1986) Mutagenicity of the *Alternaria* metabolites altertoxins I, II, and III. Appl Environ Microbiol 52:718–722

Stadler M, Ju Y, Rogers JD et al (2004) Chemotaxonomy of *Rhopalostroma* sp. Mycol Res 108:239–247

Stierle AC, Caddlina JH, Strobel GA (1989) Phytotoxicins from *Alternaria alternata*, a pathogen of spotted knapweed. J Nat Prod 52:42–47. https://doi.org/10.1021/np50061af003

Sun CX, Ma YJ, Wang JW (2018) Improved hypocrellin A production in *Shiraia bambusica* by light-dark shift. J Photochem Photobiol B Biol 182:100–107

Sun CX, Ma YJ, Wang JW (2017) Enhanced production of hypocrellin A by ultrasound stimulation in submerged cultures of *Shiraia bambusicala*. Ultrason Sonochem 38:214–224
