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Review

Fungal Pigments: Their Diversity, Chemistry, Food and Non-Food Applications

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Abstract: Colorants have many applications in food, cosmetics, pharmaceutics, textile, paints, plastics, paper, ink and photographic industries. Colorants are classified according to their solubility into dyes and pigments. Those of natural origin have many advantages over synthetic ones, as natural colorants usually do not induce allergies or other health problems. In addition, their consumption in the food and drug industries is fortified with nutritional and health benefits as the majority of them possess antioxidant activity or can be used to produce some vitamins. Plants, animals, insects and microorganisms are rich sources of colorants. However, microbial pigments are favored over other natural pigments due to their higher yield, stability, economical production. Therefore, we focus in this review on fungal pigments, the history of their use, their chemistry and their applications in food and non-food fields. Additionally, the ability of the fungal genus, *Epicoccum*, to produce pigments is discussed. Moreover, the challenges and future prospects concerning fungal pigment production are highlighted in detail.

Keywords: dyes; pigments; fungi; secondary metabolites; biotechnology; applications

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1. Introduction

Colorants are the compounds used to add or change the color of different substrates and are involved in different industries including food, cosmetics, pharmaceutics, textile, paints, plastics paper, ink and photographic industries. The global dye market was valued at USD 31.97 billion in 2019 and is expected to reach USD 50.38 billion by 2023 [1]. According to their solubility, colorants are classified into two classes, dyes and pigments. The main differences are that dyes are soluble in organic solvents and water, while pigments are insoluble in them. The mechanism of coloring differs between dyes and pigments. Dyes color substrates to which they have affinity. In contrast, pigments color any polymeric substrate at the surface level unless the pigment is mixed with the polymer in earlier stages of its formation [2]. Unlike the majority of organic compounds, dyes have color due to many reasons. First, they absorb light in the visible spectrum (400–700 nm) and have at least one color-bearing group (chromophore) or sometimes certain groups known as color helpers (auxochromes) such as hydroxyl groups, sulfo, carboxylic and amino groups. Such groups are not responsible for color appearance, but they affect dye solubility and contribute to shifting the color of a colorant. The structure of dyes carries a conjugated system (the double and single bonds alter their location). Their structure shows electron resonance that is considered as a stabilizing force [3].

Nature is the main source of colorants, but extraction of natural colors and their instability represent problems that are associated with the synthesis of artificial (synthetic) colors, which started with Perkin's mauve pigment in 1856 [4]. The application of such synthetic colors in different industries in general and in food and pharmaceutical industries in particular has raised several concerns and compulsory warnings by the FDA, World Health Organization and European Union regulators, especially for children's food, drugs and cosmetics [5]. Hence, due to various health problems associated with the overuse of synthetic colorants and the increasing customer and consumer awareness and demand for synthetic colorant-free products, scientific research has been oriented toward screening for natural colorants and improving their production and stability [6–10]. The majority of natural colorants also have nutritional and health benefits, especially as antioxidant agents [11,12]. Examples of well-known natural colorants that provide color and are considered safe are carotenoids, betalains, anthocyanins, curcumin and chlorophylls [5,13]. Natural colorants originate from different sources, such as insects, animals, plants and microorganisms. However, pigments originating from microorganisms have many advantages over those produced by animals or plants, such as supply sustainability, higher yield, significant cost efficiency and considerable stability [5]. Among different microbial genera, fungi and algae are ranked first in the production of a variety of water-soluble natural pigments [14,15]. Still, the low pigment yields of algal cultures represents an obstacle to commercial production [16]. Fungi were used centuries ago in dying textiles, especially silk and wool [17]. Hence, the aim of this review is to elucidate the history of fungal pigments and their chemical structure. Well-known fungal producers are discussed, and some of the food and non-food applications of fungal pigments are highlighted.

2. Fungi as a Source of Pigments

The oldest record of using fungal pigments was the use of *Monascus* pigments in producing red mold rice (ang-kak). Fungi are an excellent source of natural pigments with significant advantages over plants. For example, fungi provide season-independent pigment production, and their growth is easier and faster and requires a cheap culture medium [18]. Moreover, fungal pigments are of different color hues and possess higher stability and solubility [19]. The members of specific fungal families are known as promising pigment producers, including Chaetomiaceae, Chlorociboriaceae, Cordycipitaceae, Herpotrichiellaceae, Hypocreaceae, Hyaloscyphaceae, Hymenochaetaceae, Monascaceae, Nectriaceae, Ophiostomataceae, Pleosporaceae, Polyporaceae, Sordariaceae, Tremellaceae, Trichocomaceae, Tuberaceae and Xylariaceae [18,20].

Fungal pigments are considered secondary metabolites that are produced by mycelium under certain conditions as the shortage in nutrients or under some unfavorable environmental stresses [21]. Many fungal genera, such as *Aspergillus*, *Trichoderma*, *Fusarium* and *Penicillium,* produce intermediate metabolites (pigments) during their growth [22]. Production of pigments such as melanin has a role in fungi protection, helping the microorganism to survive under severe environmental stresses and protecting from UV light. However, a single fungal species can produce different pigments with different properties.

3. Chemistry of Fungal Pigments

Generally, fungal pigments belong to different chemical classes such as carotenoids, melanins, azaphilones, flavins, phenazines, quinones, monascin, violacein, indigo and polyketides [22,23]. The fungal polyketides are composed of tetraketides and octaketides possess eight C2 units, forming a polyketide chain. Some fungi are capable of producing naphthoquinones, which also have strong antibacterial and antimalarial activities.

Monascus is a well-known producer of different pigments, especially polyketide as it was reported to produce different polyketide pigments, including Monascin and ankaflavin (which are yellow pigments), monascorubrin and rubropunctatin (which are orange pigments) and monascorubramine and rubropuntamine (which are red pigments) [24]. Most *Monascus* pigments are produced mainly by four species, *M. purpureus*, *M. pilosus*, *M. rubber* and *M. froridanus*. Generally, *Monascus* pigments are characterized by sensitivity to both heat and light, instability at low pH and poor dissolution in water, which can be improved by reacting with amino-containing compounds [25]. Nevertheless, pigments produced by *M. ruber* are known as important food colorant sand additives [18]. *M. ruber* produces various pigments, as shown in Table 1, such as rubropunctin, N-glucosylrubropunctamine, N-glucosylmonascorubramine and monarubrin [26]. *M. purpureus* is also known for producing different pigments (Table 2), including monapurone A–C, monasphilone A–B, monapilol A–D and 9-(1-hydroxyhexyl)-3-(2-hydroxypropyl)-6a-methyl-9,9a-dihydrofuro [2,3-h] isoquinoline-6,8 (2H,6aH)-dione [27,28]. Similarly, many species of the genus *Penicillium* are known as potent pigment producers [29–31]. The first commercial fungal pigment, Arpink red™ (also known as Natural red™), is produced by *Penicillium oxalicum*. Other pigments such as talaroconvolutins A–D, sclerotiorin, xanthoepocin, atrovenetin and dihydrotrichodimerol are produced by other *Penicillium* species as *P. convolutum*, *P. mallochii*, *P. simplicissimum*, *P. melinii* and *P. flavigenum* [32–34]. It should be noted that some *Monascus*-like pigments are produced by *Penicillium,* such as PP-V [(10Z)-12-carboxylmonascorubramine] and PP-R [(10Z)-7-(2-hydroxyethyl)-monascorubramine] [18]. Another fungal genus that is reported as a promising source of pigment is *Talaromyces*, especially *T. purpureogenus*, which was formerly known as *Penicillium purpureogenum* [35,36]. Herqueinone-like and *Monascus*-like azaphilone pigments (N-glutarylmonascorubramine and N-glutarylrubropunctamine) are produced by *T. purpureogenus*. Other pigments such as mitorubrin, monascorubrin, PP-R, glauconic acid, purpuride and ZG-1494α are produced by *T. atroroseus*, while trihydroxyanthraquinones such as erythroglaucin, emodin and catenarin are isolated from *T. stipitatus* [37–39]. *Epicoccum* species secrete various secondary metabolites such as polyketides, carotenoids, polyketide hybrids and diketopiperazines. The pigments produced by *E. nigrum* have many industrial applications, especially epicocconone, which is a fluorophore that is used in cell staining cells and proteins in gel electrophoresis for protein detection [40–42].

Additionally, macrofungi (mushrooms) have been reported for the production of different pigments, especially genera of the family Cordycipitaceae such as *Beauveria*, *Cordyceps*, *Hyperdermium*, *Torrubiella* and *Lecanicillium*. For example, the yellow pigments bassianin and tenellin are produced by *Beauveria bassiana* and *B. brongniartii*, while the pale yellow pigments pyridovericin and pyridomacrolidin are secreted by *B. bassiana*. Some species of *Torubiella* produces torrubiellones A–D, *Lecanicillium aphanocladii* produce oosporein, and *Cordyceps farinosa* produces anthraquinone-related compounds, while *Ophiocordyceps unilateralis* produces erythrostominone, 4-O-methyl erythrostominone, deoxyerythrostominone, deoxyerythrostominol, epierythrostominol and 3,5,8-TMON (3,5,8-trihydroxy-6-methoxy-2-(5-oxohexa-1,3-dienyl)-1,4-naphthoquinone) [43–45]. It should be noted that *Aspergillus*, *Trichoderma* and *Fusarium* are well-known producers of the safe pigment, anthraquinone.

Table 1. Well-known chemical classes responsible for different colors.

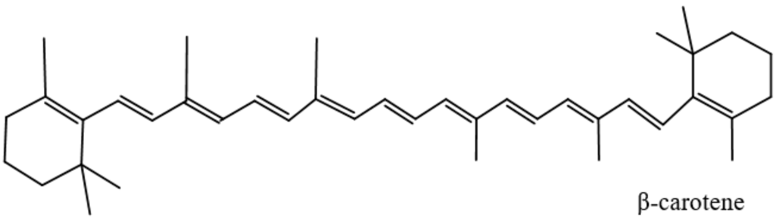
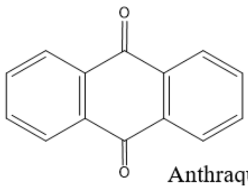
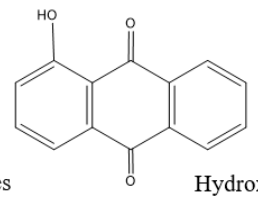
Compound	Color	Chemical Structure
Carotenoids	Yellow Yellowish orange	 β-carotene
Anthraquinones and hydroxyanthraquinones	Orange Bronze Maroon	 Anthraquinones  Hydroxyanthraquinones

Table 1. *Cont.*

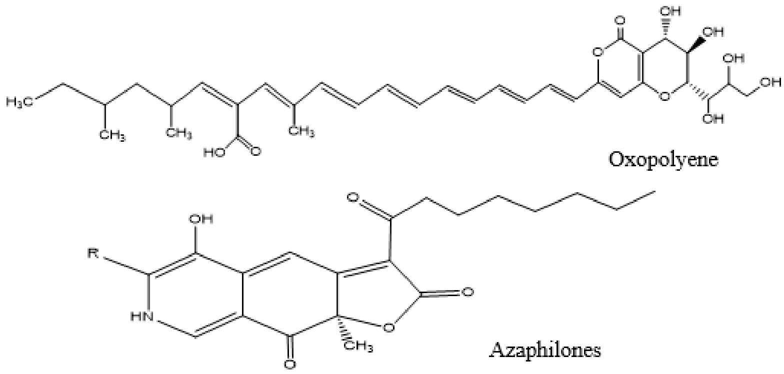
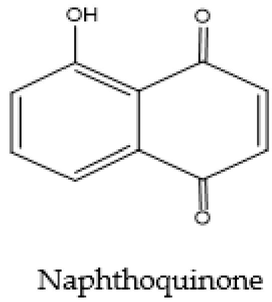
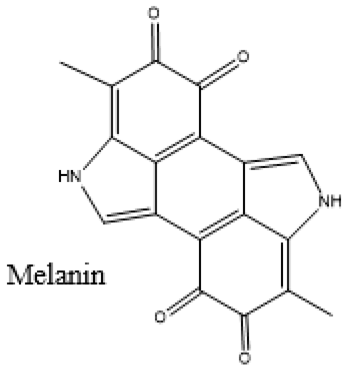
Compound	Color	Chemical Structure
Oxopolyene and azaphilones	Yellow Red Purple red	
Naphthoquinone	Red Purple	
Melanin	Black Greyish black	

Table 2. Examples of well-known fungal pigments and their producers.

Fungal Species	Pigment Name	Color	Reference
Monascus purpureus	Monascin	Yellow	Hsu et al. [28]; Mukherjee et al. [46]; Srianta et al. [47]
	Monapurone A–C	Yellow	
	Ankaflavin	Yellow	
	Monasphilone A and B	Yellow	
	Monopilol A–D	Yellow	
	Citrinin	Yellow	
	Monascorubrin	Orange	
	Rubropunctatin	Orange	
	Monascorubramine	Red	
	Rubropunctamine	Magenta	

Table 2. *Cont.*

Fungal Species	Pigment Name	Color	Reference
Monascus ruber	Monascin	Yellow	Mapari et al. [29]; Loret and Morel [48]
	Citrinin	Yellow	
	Ankaflavin	Yellow	
	Monarubrin	Yellow	
	Rubropunctin	Yellow	
	Rubropunctatin	Orange	
	Monascorubrin	Orange	
	Monascorubramine	Red	
	N–glucosylrubropunctamine	Red	
	N–glucosylmonascorubramine	Red	
	Rubropunctamine	Purple-red	
Trichoderma harzianum	Pachybasin	Yellow	Caro et al. [30]
	Emodin	Yellow	
	Chrysophanol	Orange-red	
Aspergillus ruber	Asperflavin	Yellow	Caro et al. [30]
	Guestin	Yellowish orange	
	Emodin	Orange	
	3–O–(α–D–ribofuranosyl)–questin	Orange	
	Catenarin	Red	
	Rubrocristin	Red	
	Eurorubrin	Brown	
Talaromyces purpureogenus	Mitorubrin	Yellow	Mapari et al. [29]; Ogbonna et al. [36]
	Purpurogenone	Yellowish orange	
	Mitorubrinol	Orange-red	
	Rubropunctatin	Red	
	Azaphilones	Red	
Penicillium viridicatum	Viomellein	reddish-brown	Mapari et al. [29]; Ogbonna et al. [36]
	Xanthomegnin	Orange	
Penicillium oxalicum	Secalonic acid D	Yellow	Mapari et al. [29]; Caro et al. [30]
	Arpink red™	Red	
	Anthraquinone derivative	Red	
	Anthraquinones	Red	
Ophiocordyceps unilateralis	Erythrostominone	Red	Caro et al. [30]
	Deoxyerythrostominone	Red	
	deoxyerythrostominol	Red	
	4–O–methyl erythrostominone	Red	
	Epierythrostominol	Red	
	Naphthoquinones	Bloody red	
Cerioporus squamosus	Melanin	Black	Tudor [49]
Fomes fomentarius	Melanin	Black	Tudor [49]; Tudor et al. [50]

Table 2. *Cont.*

Fungal Species	Pigment Name	Color	Reference
Chaetomium globosum	Chaetoviridins A–D	Yellow	Caro et al. [30]
	Chaetoglobin A–B	Purple	
	Chaetomugilins A–F	Purple	
	Cochliodinol	Purple	
Epicoccum nigrum	Carotenoids	Yellow	Mapari et al. [29]; da Costa Souza et al. [44]
	Chromanone	Yellow	
	Orevactaene	Yellow	
	Epicoccarines A–B	Fluorescent yellow	
	Epicocconone	Fluorescent yellow	
	Epipyridone	Red	
	Flavipin	Brown	
	Isobenzofuran	Brownish yellow	
Fusarium fujikuroi	Bikaverin	Red	Mapari et al. [29]; Frandsen et al. [51]; Avalos et al. [52]
	Norbikaverin	Red	
	O–demethylanhydrofusarubin	Red	
	8–O–methybostrycoidin, 2–(4–((3E,5E)–14–aminotetradeca–3,5–dienyloxy) butyl)–1,2,3,4–tetrahydroisoquinolin–4–ol (ATDBTHIQN)	Pink	
	Neurosporaxanthin	Orange	
	β–carotene	Orange-red	
	Fusarubin	Red	
	O–methylsolaniol	Orange-red	
Fusarium oxysporum	2,7–dimethoxy–6–(acetoxyethyl)juglone	Yellow	Medentsev et al. [53]; Avalos et al. [52]; Lebeau et al. [54]
	Nectriafurone	Yellow	
	O–methyl–6– hydroxynorjavanicin	Yellow	
	Bikaverin	Red	
	Bostrycoidin	Red	
	Norjavanicin	Red	
	O–methylfusarubin	Red	
	O–methylanhydrofusarubin	Orange-red	
	Neurosporaxanthin	Orange	
	β–carotene	Orange-red	
	Naphthaquinones	Purple	

Table 2. *Cont.*

Fungal Species	Pigment Name	Color	Reference
Beauveria basiana	Tenellin	Yellow	Wat et al. [55]; Caro et al. [30]
	Bassianin	Yellow	
	Pyridovericin	Yellow	
	Pyridomacrolidin	Yellow	
	Oosporein	Red	
Curvularia lunata	Chrysophanol	Red	Mapari et al. [29]; Caro et al. [30]
	Erythroglaucin	Red	
	Catenarin	Red	
	Cynodontin	Bronze	
	Helminthosporin	Maroon	
Pyrenophora species	Catenarin	Red	Mapari et al. [29]; Caro et al. [30]
	Erythroglaucin	Red	
	Cynodontin	Bronze	
	Helminthosporin	Maroon	
	Tritisporin	Reddish brown	
Alternaria alternate	Alternariol	Red	Devi et al. [56]
	Alternarienoic acid	Red	
	Alterperylenol	Red	
	Altenuene	Violet-red	
	Alternariol-5-methyl ether	Brownish red	
	Tenuazoic acid	Orange-red	
	Stemphyperylenol	Yellow–orange-red	
Neurospora crassa	Neurosporaxanthin	Yellow-orange	Avalos et al. [57]; Caro et al. [30]
	Phytoene	Yellow-orange	
	Neurosporen	Yellow-orange	
	β–carotene	Red-orange-yellow	
	Lycopene	Red	
	Spirilloxanthin	Violet	
	γ–carotene	Yellow-orange	

4. Application of Fungal Pigments in Different Industries

Natural pigments have different applications (Figure 1) in food- and non-food-related fields. This came as a result of scientific research, which has warned of the health hazards accompanying the use of artificial synthetic pigments. Hence, we highlight here some of the applications of fungal pigments.

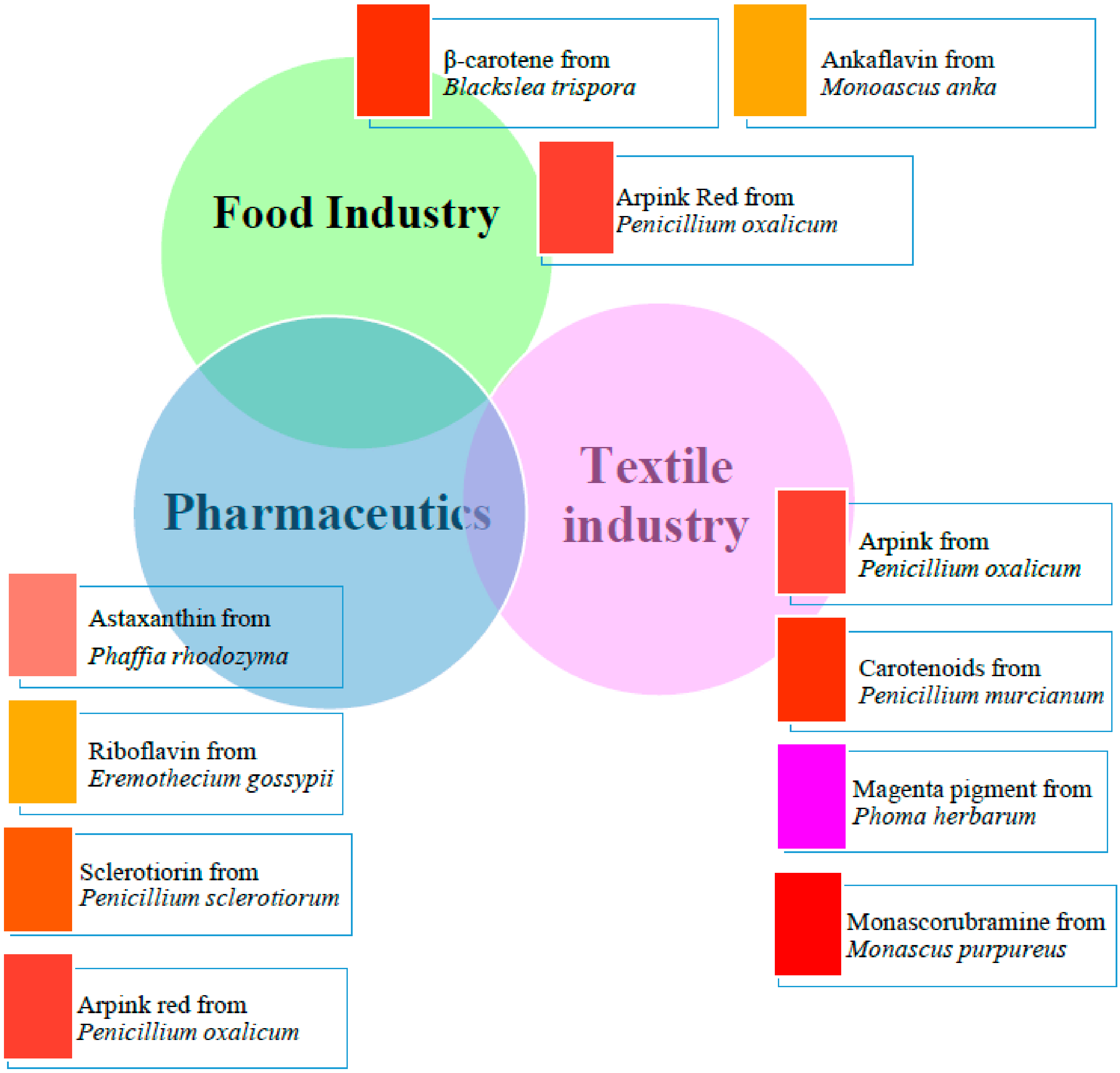


Figure 1. Examples of fungal pigments that are involved in some food and non-food applications.

4.1. Fungal Pigment Applications in Food Industry

As mentioned previously, there are continuous demands of consumers for less synthetic and artificial colors in their food and dairy products due to the health hazards and adverse effects caused by these artificial colors. In the middle of the 1980s, tartrazine was nominated as potential cause of sleep disturbance, hyperactivity and irritability in children [58]. Furthermore, azo-dyes, which are commonly used as additives in the food industry, were regarded as potential carcinogens after being transformed by the gut microbiota [59]. Artificial colors such as tartrazine, sunset yellow and ponceau are also capable of inducing allergic reactions in many individuals even when consumed at low concentrations [60]. In addition, glossitis was linked to ponceau 4R consumption at high concentrations [61]. Hence, natural colors are favored; however, the safety of colors from microbial origins must be firstly checked. It is known that the majority of fungi produce mycotoxins, which can restrict their application in food and pharmaceutics. Some fungal species, such as *Aspergillus carbonarius*, produce a yellow pigment without producing any mycotoxins [62]. *A. carbonarius* produces polygalacturonase, which tolerates UV irradiation, and during its growth phase, a safe yellow pigment is accumulated in its biomass which can be used in food industry [63]. *Thermomyces* sp. produces a thermophilic yellow pigment that has antioxidant activity [60]. Pigmentation varies from yellow to red, according to many growth conditions such as temperature, age of the fungus and the used substrate. Food and beverages fortified by the yellow pigment recorded high antioxidant properties, antimicrobial properties and color stability [64]. *Blackslea trispora* is a promising source of safe β-carotene as this fungus does not produce mycotoxins [65]. The β-carotene from this fungus was the first approved microbial food colorant in the European Union. Different *Fusarium* species are capable of producing a wide range of diverse pigments, especially *F. graminearum*, which produces rubrofusarin, a red naphthoquinone pigment [66]; *F. fujikuroi*, which produces fusarubin, an orange carotenoid pigment [67]; and *F. oxysporum*, which secretes bikaverin, a red naphthoquinone [68]. However, there are safety concerns about such pigments because the metabolites produced by *Fusarium* species contain different mycotoxins such as fumonisins, fusaric acid, fusarins, zearalenone and beauvericins [57]. On the contrary, *Monascus* species are generous producers of safe pigments with strong contributions in food industry, such as *M. purpureus*, which produces monascorubramine and rubropunctamine; *M. anka*, which secretes ankaflavin and monascin; and *M. ruber*, which produces monascorubrin and rubropunctatin [69–71]. *Monascus* pigments are produced on rice using solid-state microbial fermentation, and red mold rice was used centuries ago as a food colorant in traditional oriental medicine [72]. Many *Penicillium* species produce antibiotics and pigments and are used in manufacturing cheese [73]. *P. purpurogenum* secretes an azaphilone-like, brick-red pigment. Additionally, violet and orange pigments were obtained by modifying conditions of culturing [74]. Pigment production using *Penicillium* as a source is more efficient and highly preferred because it secretes water-soluble and stable pigments extracellularly, so it can be easily purified [75]. *Talaromyces purpureogenus* (previously known as *Penicillium purpureogenum*), secretes safe yellow and red pigments under submerged fermentation conditions, while other strains of *Talaromyces* as *T. aculeatus*, *T. funiculosum*, *T. purpurogenum* and *T. pinophilus* produce *Monascus*-like polyketide azaphilone pigments [76]. *Trichoderma viride* secretes a brown pigment and can synthesize the yellow pigment emodin [60]. *Neurospora crassa* produces safe yellow to orange-red polyketide and carotenoid fungal pigments that are used as food colorants. Mushrooms are known for producing pigments, especially members of family Cordycipitaceae such as *Cordyceps*, *Torrubiella*, *Hyperdermium*, *Beauveria* and *Lecanicillium*. *Beauveria bassiana* produces tenellin, pyridomacrolidin and pyridovericin, which is blood-red dibenzoquinone, while *B. brongniartii* secretes bassianin, and *Torubiella* produces torrubiellones [60].

4.2. Non-Food Applications of Fungal Pigments

Safe fungal pigments can be used for various industrial applications such as dyes for textiles, paper, paints, leather and cosmetics. Many fungal pigments originating from genera such as *Monascus*, *Talaromyces*, *Penicillium*, *Trichoderma* and *Aspergillus* showed antibacterial activity against many pathogenic bacteria [77–80]. Such antimicrobial potential leads to application of these pigments in different fabrics, with promising results that suggest their potential use in suture threads, bandages, face masks and other related medical applications [81,82]. Some fungal pigments such as naphthoquinones, melanin, violacein and carotenoids showed antioxidant activity [83,84]. Interestingly, some *Monascus* fungal pigments such as monascin, monapurone A–C, ankaflavin, monasphilone A–B, monaphilone A–B and monapilol A–D show anticancer or antitumor activity against different cancer cells such as mouse skin carcinoma, human colon adenocarcinoma, pulmonary adenocarcinoma, human laryngeal carcinoma and human hepatocellular carcinoma [85,86]. Fungal pigments are utilized in the cosmetics industry due to their reported biological activities. Carotenoids, melanin and lycopene are already applied in cosmetics, sunscreens, sunblocks, sun lotions, anti-ageing creams, face creams, skin conditioning and lipsticks. [18,87]. Fungal pigments, as natural pigments with different advantages (eco-friendly, easy degradation, safe and high staining capability) over synthetic pigments, represent a good alternative to the synthetic dyes in the textiles industry. Pigments of the fungal genera *Monascus*, *Curvularia*, *Aspergillus*, *Penicillium*, *Talaromyces*, *Trichoderma*, *Alternaria*, *Cordyceps*, *Bisporomyces* and *Cunninghamella* were applied to different fabrics such as cotton yarn, wool, silk, nylon and polyester [21,88].

5. *Epicoccum* as an Example of Pigment-Producing Fungi

Many studies have discussed the promising potential of different fungal genera to secrete pigments. However, few reports have described pigments secreted by the genus *Epicoccum*. *Epicoccum* is an endophytic dematiaceous ascomycetous fungus that is known for its application as biocontrol agent against many phytopathogens [89]. Colonies of *Epicoccum* are fast-growing, suede-like to downy, showing a deep yellow to brownish orange diffusible pigment. During sporulation, many black conidiophore aggregates can be observed. Conidia of *Epicoccum* appear singularly on densely compacted, determinant and faintly pigmented conidiophores. Conidia are characterized by being globose to pyriform, with a characteristic funnel-like base and broad attachment scar, frequently seceding with a protuberant basal cell. Conidia are multicellular, deeply pigmented and have a surface that appears verrucose externally. *Epicoccum* sp. secretes different metabolites from different chemical classes such as polyketides, diketopiperazines, polyketide hybrids, carotenoids and siderophores. Some of these metabolites showed promising biological activities, such as antimicrobial, antioxidant and anticancer properties, and there are many promising and important metabolites with potent biological activities such as the anticancer drug taxol, D8646-2-6 orsellinic acid and curvularin. Additionally, many *Epicoccum* species produce pigments that have potential industrial applications, such as *E. nigrum* (Tables 2 and 3), for example epicocconone, which is commercially known as fluorophore and is used in cell staining and in gel electrophoresis for protein detection [40,41]. Other reported *Epicoccum*-derived pigments are listed in Table 3.

Table 3. Some of the pigments produced by *Epicoccum* species.

Compound	Type	Pigment Color	References
Flavipin	Polyketide	Yellow pigment	Brown et al. [90]; Madrigal et al. [91]
Epicoccones A and B	Polyketide	Brown pigment	Abdel-lateff et al. [92]; Kemami et al. [93]; El Amrani et al. [94]
3-methoxy epicoccone	Polyketide	Yellow pigment	El Amrani et al. [94]
3-methoxy epicoccone B	Polyketide	Yellow pigment	El Amrani et al. [94]
2,3,4-trihydroxy-6-(methoxymethyl)-5-methylbenzaldehyde	Polyketide	Brown pigment	El Amrani et al. [94]
7-methoxy-4-oxo-chroman-5-carboxy acid methyl ester	Polyketide	Pale yellow pigment	Lee et al. [95]
1,3-dihydro-5-methoxy-7-methyl isobenzofuran	Polyketide	Light brown pigment	Lee et al. [95]
Epicoccalone	Polyketide	Yellow pigment	Kemami Wangun et al. [93]
Epicocconone	Polyketide	Pigment of high orange-red fluorescent in the presence of proteins	Bell and Karuso [40]
Acetosellin	Polyketide	Yellow pigment	Talontsi et al. [96]
Quinizarin	Polyketide	Red pigment	Dzoyem et al. [97]

Table 3. *Cont.*

Compound	Type	Pigment Color	References
Orevactaene	Polyketide	Orange pigment	Shu et al. [98]
Epipyridone	Polyketide–nonribosomal peptide hybrid	Red pigment	Kemami Wangun and Hertweck [99]
Epicoccarines A and B	Polyketide–nonribosomal peptide hybrid	Antibacterial and red pigment	Kemami Wangun and Hertweck [99]
β-Carotene	Carotenoid	Antioxidant and yellow pigment	Foppen and Gribanovski-Sassu [100]
γ-Carotene	Carotenoid	Orange pigment	Foppen and Gribanovski-Sassu [100]
Rhodoxanthin	Carotenoid	Red pigment	Foppen and Gribanovski-Sassu [100]
Torularhodin	Carotenoid	Violet pigment	Foppen and Gribanovski-Sassu [100]

As shown in Table 3, the pigments secreted by *Epicoccum* species are of polyketide and/or carotenoid origin [101,102] with pigment color shades ranging in yellow, orange and red spectra.

6. Extraction and Optimization of Pigment Production

Extraction process of metabolites such as pigments from microbial sources is conducted using different solvents depending on various variables, for example the type of used solvent, temperature used during the extraction process, the time of extraction process and the solid/liquid ratio [103]. Nevertheless, application of this extracted pigment in the industrial field will be economical only if high yield (efficient extraction) is achieved. Many approaches were applied in order to optimize fungal pigment production, such as optimization of production medium components, culturing conditions and using statistical optimization methods [104]. Some statistical optimization methods are based on applying one factor at a time, which is less efficient, consumes time, is relatively expensive and fails to determine the relationship between different variables [105]. Meanwhile, other statistical optimization methods such as the response surface model can investigate variable independent parameters and their interactive relationship and subsequently can be utilized to develop relevant mathematical models that can predict the whole process. In other words, applying such statistical optimization models produces substantial results from a small number of experiments [106]. Hence, it is critically important to use such efficient methods for optimization of pigment production for industrial application. The main obstacle in the fungal pigment production process is the difficulty in optimizing both biomass yield and pigment yield, since both are indirectly proportional. Therefore, such a relationship (between pigment yield and biomass) must be studied. The use of genetic engineering approaches can solve such a problem and control pigment production through employing recombinant DNA, for example, to change the activity of enzymes responsible for carotenoid biosynthesis [22].

7. Conclusions and Future Directions

Fungal pigments are promising metabolites with a wide range of applications when compared to artificial pigments. Additionally, the elevated consumer awareness of the advantages of using natural pigments in general and fungal ones in particular has oriented researchers toward screening for other novel and safe pigments from fungi. Ascomycetous fungal genera are favorable in this field as they are characterized by the ease of their growth any time of the year under relatively simple laboratory conditions and therefore can be applied in large industrial production (in contrast to plant-derived pigments where their availability is affected by the producer plant's growing season). Many scientific studies have described the large-scale production of fungal pigment production in a bioreactor under controlled conditions. Industrial use of fungal-derived pigments has gradually progressed throughout history. In the beginning, natural food colorant from fungal sources was restricted to the semi-fermentative production of the yellow natural food colorant, riboflavin, which is secreted by the filamentous fungus *Eremothecium gossypii* (previously known as *Ashbya gossypi*) [107]. However, the use of riboflavin as food colorant has some limitations because it is sensitive to light. After that, the fungus *Blakeslea trispora* was used to produce β-carotene as a food colorant. Previously, tomato was the sole source of lycopene, but nowadays *Blakeslea trispora* is approved as a promising source of lycopene [108,109]. *Cordyceps unilateralis* (also known as *Ophiocordyceps unilateralis*) is capable of producing pigments that have similar structure to shikonin and alkanin (red pigments derived from plants) [110].

There are various color hues of polyketide pigments with anthraquinone, naphthoquinone, azaphilone and hydroxyanthraquinone structure. However, for centuries, polyketide pigments secreted by the fungus genus *Monascus* have been the most widely used in Asian countries such as Southern China, Southeast Asia and Japan for making anka, red soybean cheese and red rice wine [111]. As described previously, *Monascus* sp. secretes many pigments such as monascin and ankaflavin (yellow in color), rubropunctatin and monascorubrin (orange in color) and rubropunctamine and monascorubramine (purple-red in color). Hence, different companies have filed many patents for *Monascus*-like pigments, and their products are now available in the market. It should be noted that *Monascus* secretes a hepato-nephrotoxic mycotoxin (citrinin); however, the literature does not describe any death due to consumption of red rice wine, red soybean cheese or anka made using *Monoascus* pigments. Hence, evaluation of toxicity of different fungal pigments is of critical importance before testing their potential and allowing them to enter the market as food colorants or as drugs, which explains why application of fungal pigments in food and medical fields is relatively difficult. Nowadays, researchers are focusing on screening of fungal diversity for pigment production with an emphasis on two major points, which are finding a non-mycotoxin producing strain and a pigment that is water-soluble [110]. Challenges facing the industrial application of some *Monascus* pigments include their weak water solubility, poor pH stability and sensitivity to heat and light. One of the proposed solutions for such challenges is changing the pigment's chemical structure through substituting oxygen with nitrogen from the amino group in its structure [112]. Moreover, another serious problem is the co-production of toxic metabolites with the pigment, which prevents its application, or production of a mixture of pigments, which represents a challenge when trying to produce a pigment with one color tone. This problem can be solved by optimizing culturing conditions such as changing the used substrates, temperature, pH and dissolved oxygen either in submerged or solid-state fermentation. However, it was reported that solid-state fermentation results in higher secondary metabolites yield because it resembles the natural habitat of fungi besides providing a solid support that fungal strain can attach to [113]. Another critical point that affects the application of a pigment in industry is the stability of this pigment over time, but some approaches such as nanoencapsulation can address both the stability and solubility problems [5]. A recent study has described the effect of ozone processing, which is used during the pasteurization process of some juices and foods on some fungal pigments, and fungal pigments showed higher stability compared with other tested natural pigments [114]. Interestingly, biological activities of fungal pigments may open new opportunities for their use in the production of functional textiles with medical properties or functional colored food with nutritional and health-improving benefits. Finally, construction of an online database that carries all information about fungal producers of different pigments and their chemical characteristics will facilitate the work of scientists and save their time.

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