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EXTRACTION, ISOLATION AND CHEMICAL CHARACTERIZATION OF PIGMENTS FROM *PENICILLIUM* SPECIES

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Abstract

Penicillium species produce a wide range of biotechnologically important pigments, the majority of which belong to the aromatic polyketide group of compounds. These pigments are produced extracellularly and intracellularly through suitable culture media conditions and incubation times. The pigments are then extracted according to their mode of synthesis through the fungus via organic solvents accompanied by mechanical techniques such as centrifugation or agitation. The extracted pigments are isolated via chromatographic techniques—Thin Layer Chromatography (TLC) and High-Performance Liquid Chromatography (HPLC). As the pigments are of high biotechnological importance due to their potential to be utilized in industries such as textile, food, cosmetics, and pharmaceuticals, it is, therefore, necessary that they are chemically characterized before declaring their use. Finally, the isolated pigments are characterized through spectroscopic techniques like Ultraviolet-Visible spectroscopy (UV-Vis), Fourier Transform Infrared (FTIR), Nuclear Magnetic Resonance (NMR) and Liquid Chromatography-Mass Spectrometry (LC-MS). The objective here was to review the previous studies on the production of pigments by Penicillium species: their fermentation conditions, extraction—extracellular and intracellular—, isolation or purification, chemical characterization, and biotechnological applications.

Keywords: *Chromatography, FTIR, LC-MS, NMR, Penicillium, UV-Vis Spectroscopy*

INTRODUCTION

Pigments are a type of secondary metabolites produced by microorganisms such as filamentous fungi by different metabolic pathways. Fungi produce a wide range of secondary metabolites of varying importance, besides primary metabolites. The ability of filamentous fungi to produce secondary metabolites has increased the interest in the fungi kingdom due to their many applications in multiple fields, such as commercial or medical (1). Pigments can be of varying chemical natures such as flavins, indigo, violacein, phenazines, monascins, quinones, carotenoids, azaphilones, ankaflavins, and melanins (1-3). Most of the pigments produced by filamentous fungi belong to a chemical group of aromatic polyketides such as azaphilones, quinones, melanins, and flavonoids (4).

Pigments are produced in the fungal cytoplasm as either a result of environmental stress conditions (temperature, dehydration, salinity, or pH) or the stimulus from other pathogenic microorganisms (5). Once produced, these pigments are either secreted or released into their respective culture media or incorporated into the cell wall of the fungi producing them (6). The fungal pigments play vital roles in the survival and protection of the fungi such as providing rigidity to the cell wall, resulting in cross-linkages among the

hyphae, protection against UV-radiations, protection from oxidative free radicals, environmental extremes (due to increased resistance as a result of the accumulation of pigments in the cell wall providing rigidity), and hydrolytic enzymes produced by other microorganisms (5, 6). Besides the wide utilization by fungi, these pigments are also utilized by humans for agricultural (food colorants/taste mediums/fertilizers), medical (antimicrobials/antibiotics), and industrial (textile colorants) purposes (5). Therefore, there is an increased interest in fungal pigments and pigment-producing fungi worldwide owing to their multiple benefits.

Some of the major fungi that produce pigments are the species of genus *Penicillium*, *Paecilomyces*, *Monascus*, *Talaromyces* and *Aspergillus* (7). One of the most crucial fungal genera is the *Penicillium* (filamentous/ascomycetous fungi) genus consisting of over 300 species known to date (1, 8). The species of *Penicillium* genus are widely distributed in various soil types and air, as well as in extreme environmental conditions such as temperature, salinity, pH, or dehydration, and also in different food types or products, and even live as epiphytes (9). *Penicillium* genus is getting wide interest due to its extremophilic characteristics and ability to produce a number of different pigments (1). Another reason that pigments from *Penicillium* species are gaining wide interest is that penicillium species do not produce citrinin—a mycotoxin (10), shifting the interest from *Monascus* genera—which do produce citrinin.

The pigments produced by *Penicillium* species are useful compounds that are suitable and safe for multiple biotechnological applications; be it in industries such as cosmetics, food, pharmaceuticals, agriculture, or textile. Therefore, it is crucial to identify pigment-producing *Penicillium* species as well as culturing suitable media for the production of pigments, extraction of pigments, isolation or purification, and chemical characterization. As, in order to select a pigment for respective application purposes, it is necessary that the pigments are chemically characterized (11). To that end, this review focuses on the pigments produced by various *Penicillium* species, their fermentation conditions, extraction, isolation, and characterization via various analytical tools followed by biotechnological applications of the pigments.

FERMENTATION CONDITIONS FOR PIGMENT PRODUCTION

Most of the work done on the fermentation conditions for pigment production has used submerged fermentation for pigment production in *Penicillium* species, apart from respective culture refreshment fermentation such as solid-state fermentation. Most research studies have suggested the use of acidic pH in culture medium for pigment production in *Penicillium* species—some acidic, some slightly acidic while others neutral—pH 7. The lower pH media effects might be explained, as acidic pH supports pigment production instead of conidia development while enhancing the transport of respective components of the media and also affecting the activity of enzymes involved in the pigment biosynthesis as explained by the studies (12-14).

The culture media composition and conditions such as temperature and pH affect the product's structure and amount (1, 15-17). Some examples of the effects of media composition and pH include that of *Penicillium sp*. AZ where the addition of ammonium nitrate resulted in the production of red pigment—PP-R and violet pigment—PP-V both of which are homologues of major *Monascas* pigment—monascorubramine, while the absence of ammonium nitrate in the media resulted in the production of yellow pigment—PP-Y and orange pigment—PP-O both of which are homologues of *Monascas* pigment—monascaburamin. The possible explanation for this is that the pH and presence or absence of ammonium nitrate has influenced the biosynthetic pathways of these pigments and, hence, altering the very last step while resulting in different pigments by the same species as the altered media conditions might not support the previous biosynthetic pathways (18-21).

The same behavior is observed in *Penicillium purpurogenum* (22), while in other cases the natural habitats of the fungus determine the type of pigment produced due to the extreme conditions of the habitats as in the case of *Penicillium sp*. (GBI_P155) (1). Hence, media composition, incubation time, temperature, pH, and rotatory status all determine the type of pigment being produced as well as the amounts. Table I below summarizes the type of pigments produced by *Penicillium* species with respective culture media conditions and compositions.

Table I. All *Penicillium* species are cultured in submerged fermentation except for *P. sp*, *P. marneffei*, *P. sp.* HSD07B, *P.verruculosum*

P. species	Pigment	Nitrogen Source	Carbon Source	Salt	Agitation Status	Temp ^{0}C	pH	Incubation Period-days	Buffer	Ref.
Penicillium sp. AZ	Violet	NH_4NO_3, Yeast Extract	Soluble starch	-	185rpm	30	5	2 days	Citric acid/Na_3 citrate	(21)
	Red	″	″	-	″	″	″	″	″	(18)
	Yellow	Yeast extract	″	-	″	″	″	″	″	(19)
	Orange	″	″	-	″	″	″	″	″	(19)
Penicillium purpurogenum	Orange	″	″	-	200rpm	″	″	″	″	(22)
	Violet	NH_4NO_3, Yeast Extract	″	-	″	″	″	″	″	(22)
Penicillium aculeatum ATCC 10409	Yellow	proteins	lactose	-	150rpm	30	6.5	10 days	-	(10)
Penicillium sp. (GBPI_P155)	Orange	Peptone	Glucose, maltose	KH_2PO_4 $MgSO_4$	static	15	3	15 days	-	(1)
Penicillium flavigenum (CML2965)	Yellow	Proteins, amino acids $NaNO_3$	Maltose, sucrose	K_2HPO_4 $MgSO_{4.7}$ H_2O, KCl, $FeSO_{4.}$ $_7H_2O$	150rpm	30	-	7 days	-	(23)
Penicillium aculeatum	Orange	-	-	-	-	-	-	-	-	(3)
Penicillium sp. ZJ-27	Red	-	Potatoes, glucose	Crude sea salt	Static	25	7	28 days	-	(24)
Penicillium marneffei	Red	Proteins, amino acids	Dextrose, maltose	-	Static	26	-	5 days	-	(25)
Penicillium sclerotiorum 2AV2	Yellow-orange	$NaNO_3$	Sucrose	K_2HPO_4 $MgSO_{4.7}$ H_2O, KCl, $FeSO_{4.}$ $_7H_2O$	Static	25	5	14 days	-	(7)
Penicillium verruculosum SG	Red Yellow Brownish red	Yeast extract	Glucose	-	Static	25	5	14 days	-	(26)
Penicillium simplicissimum IFO5762	Yellow	Yeast extract, NZ-amine	Soluble starch, glucose	$CaCO_3$	200rpm	30	7	7 days	-	(27)
Penicillium purpurogenum Li-3	Red	$NaNO_3$	Glucose	K_2HPO_4 $MgSO_{4.7}$ H_2O, KCl, $FeSO_{4.}$ $_7H_2O$	150rpm	-	-	7 days	-	(28)
Penicillium herquei	Blue	Casein enzymatic hydrolys-ate	Molasses	$CaCO_3$	500rpm	25	-	7 days	-	(29)
Penicillium	Red	NH_4NO_3	Carboh	-	280rpm	27-	5.8-	3 days	-	(30)

oxalicum var. armeniaca			ydrates			29	6.2			
Penicillium mallochii	Orange-yellow	-	Glucose potatoes	-	Static	24	3.6	10 days	-	(31)
Penicillium rubrum	Orange-Yellow, Yellow	Wheat	Wheat sucrose	-	Static	30	-	14 days	-	(32)
Penicillium	Crimson	-	-	-	-	-	-	-	-	(33)
Purpurogenum stoll	Red	-	-	-	-	-	-	-	-	(34)
Penicillium sp. HSD07B	Red	-	Glucose Potatoe-s	-	Static	30	-	3 days	-	(35)
Penicillium sp.	Yellow	Rice and wheat	Rice and wheat	-	Static	28	-	10-12 Days	-	(36)

" indicates 'same', - indicates 'either not mentioned clearly in the respective paper or is not known'

EXTRATION OF PIGMENTS

Typically, *Penicillium* species produce pigments in submerged fermentation which are secreted extracellularly but in other cases, pigments are not able to diffuse into the culture media. Therefore, the procedures for the extraction of pigments vary according to their mode of secretion.

INTRACELLULAR EXTRACTION

For intracellular extraction of pigments, the cell is disturbed via solvents such as ethanol or methanol after separating the mycelium from the rest of the media through filtration (18, 19). Although, in other studies, hexane is used for extracting pigment from mycelium (31). Whereas, studies like (37) evaluate various methods for intracellular pigment extraction which involve a combination of other techniques such as dehydration, oven drying, homogenization, and microwave along with different organic solvents.

EXTRACELLULAR EXTRACTION

For extracellular pigment extraction in submerged media, the mycelium is removed from the media through filtration, and the pigment is recovered from the filtrate in solvent extraction via solvents like ethyl acetate (19, 22, 23, 28, 32, 38), n-butanol (28), and chloroform (1). While for solid-state media, the media containing the pigment is cut from the rest of the media containing the fungal colonies before the pieces are placed in warm sterile water of respective volume and temperature with the water containing the pigment then centrifuged for a certain period and filtered, which is then further treated for analysis (25).

PURIFICATION OF PIGMENTS

After extraction, the pigments are purified via chromatographic techniques. The most common chromatographic techniques used in literature are Column Chromatography, Thin-Layer Chromatography—separates based on retention factor, and High Performance Liquid Chromatography—separates based on retention time. Different solvents are used as mobile phases with different ratios. HPLC is also used to characterize pigments apart from purification, such as, in the case of the red pigment from *Penicillium sp*. HSD07B, which is characterized to be a mixture of six components (35). Table II summarizes the chromatographic techniques—the solvents used and a number of fractions separated along with their retention time and retention factors.

CHARACTERIZATION OF PIGMENTS

Pigments are characterized via various techniques, including NMR, LC-MS, FT-IR, UV-VIS, with NMR being most common for chemical characterization and structural determination.

CHARACTERIZATION VIA UV-VIS, FTIR AND LC-MS

UV-Vis spectroscopy can be used to characterize pigments based on transmission, absorption, and reflectance of the electromagnetic radiation (39) supplied to the pigment. Many works of literature have

adopted this analytical tool to characterize pigments from *Penicillium* species. The UV-Vis analysis of the red pigment from *Penicillium* Li-3 revealed that the red pigment was likely either that of *Monascus* pigments or had identical coloring molecules as in pigments of *Monascus* (28). Whereas UV-Vis scanning of the orange pigment from *Penicillium sp*. (GBPI_P155) revealed two major peaks at 495nm with a shoulder peak at 530nm (1). UV-Vis analysis along with fluorescence spectra also suggested that the red pigment from *Penicillium marneffei* consists of a conjugated ring-like system with delocalized electrons that are susceptible to low energy and high wavelength photons (25).

Table II. Chromatographic results of pigments from various *Penicillium* species

***Penicillium* sp.**	**TLC**		**Column Chromatography**		**HPLC**		**Ref.**
	Solvents	**Rf**	**Solvent**	**Fractions**	**Solvent**	**RT**	
Penicillium aculeatum	-	0.821	-	-	-	-	(3)
Penicillium sp. AZ	n-BuOH: AcOH: H_2O 12:3:5 ratios	0.75	Me_2CO	Final-single fraction	-	-	(21)
	n-BuOH: AcOH: H_2O (12:3:5), $CHCl_3$: MeOH (10:1)	0.87	$CHCl_3$:Me2CO (3:2), $CHCl_3$: MeOH (5:1), n-Hexane: Me_2CO (1:1), Me_2CO	Single fraction	-	-	(18)
	n-BuOH: AcOH: H_2O (12:3:5), n-Hexane: Me_2CO (2:1)	0.72	n-Hexane: Me_2CO (4:1), $CHCl_3$: MeOH (100:1), $CHCl_3$: MeOH (200:1)	Single fraction	-	-	(19)
	n-BuOH: AcOH: H_2O (12:3:5), n-Hexane: Me_2CO (2:1)	0.91	n-Hexane: Me_2CO (10:1), $CHCl_3$: MeOH (200:1)	Single fraction	-	-	(19)
Penicillium purpurogenum	n-BuOH: AcOH: H_2O (12:3:5)	0.75	-	-	-	-	(22)
Penicillium marneffei	-	-	-	-	Acetonitrile-water	3.43	(25)
Penicillium sp. (GBPI_P155)	Hexane: acetone: toluene: ethanol (10:7:7:6)	0.911, 0.852, 0.808	-	-	-	-	(1)
Penicillium sclerotiorum 2AV2	Hexane: ethyl acetate	11 fractions	Methanol	22 fractions	-	-	(7)
Penicillium purpurogenum Li-3	-	0.40	Ethyl acetate: methanol (1:0, 50:1, 30:1)	Red fraction collected	-	-	(28)
Penicillium simplicissimum IFO5762	$CHCl_3$: MeOH (20:1)	0.34	-	-	CH_3CN-	9.5 min	(27)
Penicillium sp.	Chloroform: ethanol: water (65:25:4)	0.87, 0.83	Chloroform: Ethanol (9:1)	-	-	-	(36)

- indicates 'either not mentioned clearly in the respective paper or is not known'.

FTIR is used to characterize pigments; as by this technique, vibrational frequencies of every bond type are measured (40), which are then used to determine the structure of pigments. This makes FTIR a useful tool in many pieces of literature for structural elucidation. Such as, the FTIR analysis of the yellow pigment from *Penicillium aculeatum* ATCC 10409 indicates the presence of NH groups, many CH_2 groups, benzol structure, CH_3 groups and revealed the pigment as from the ankaflavin class of fungal pigments (10).

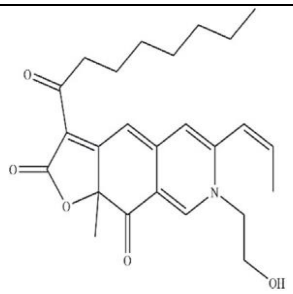
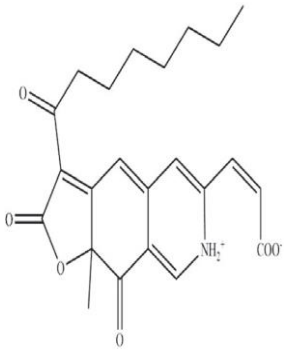
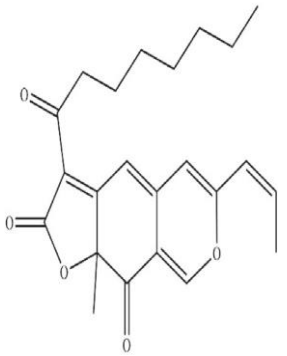
Furthermore, ankaflavin analysis revealed the presence of OH groups, carbonyl, and C=C (3). While the analysis of the red pigment from *Penicillium purpurogenum* Li-3 revealed the presence of C=C, N—H, C=O, a long chain of CH_2 and C—O in the structure (28). The analysis of the red pigment from *Penicillium marneffei* revealed the presence of aromatic CH, NH/OH, aliphatic CH groups, ether groups and indicated the pigment to be ◎, β unsaturated carbonyl compound (25). The orange pigment analysis indicated the presence of CH_3, C—O, C=C, and C—H (1). Finally, FTIR spectral analysis of the yellow pigment from *Penicillium simplicissimum* IFO5762 indicated the presence of carbonyl groups, OH groups, and conjugated olefin groups (27).

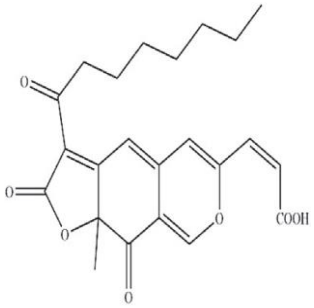
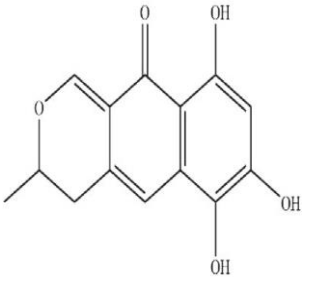
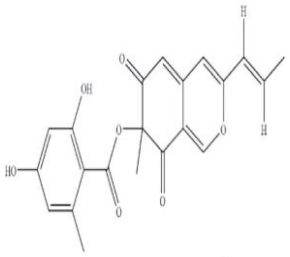
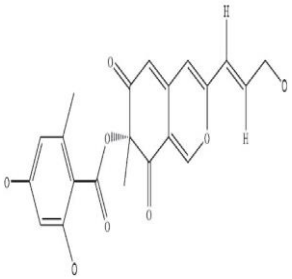
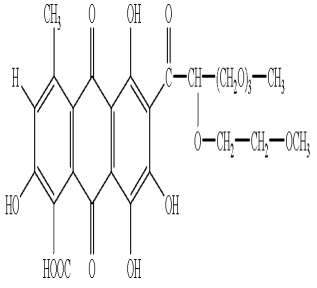
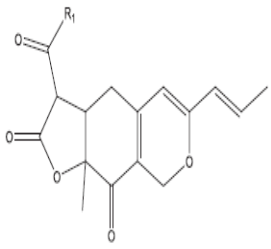
LC-MS is mass spectroscopy coupled with chromatography, which is used to determine composition and structure—molecular analysis (40). LC-MS analysis determined the red pigments from *Penicillium verruculosum* SG as polyketides (26). Whereas the orange pigment was characterized via LC-MS spectroscopy as various derivatives of carotenoids (1).

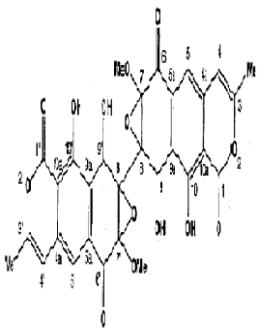
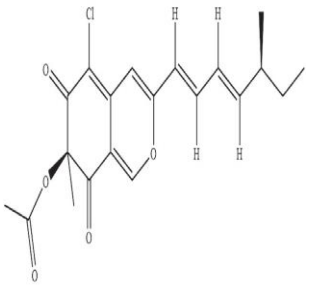
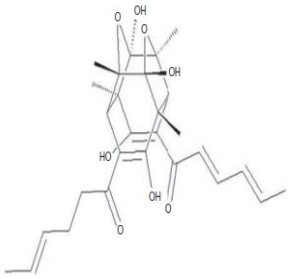
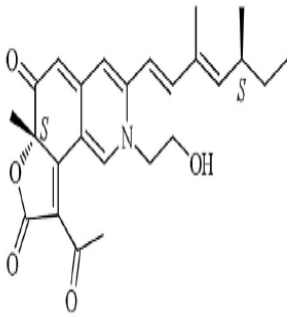
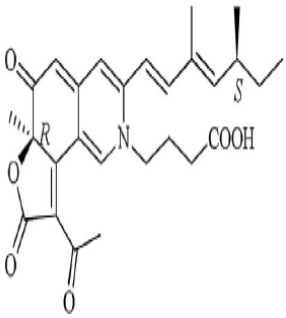
CHARACTERIZATION VIA NMR

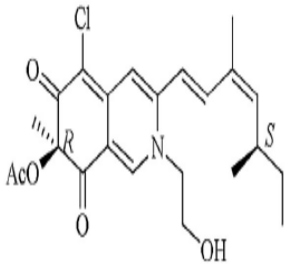
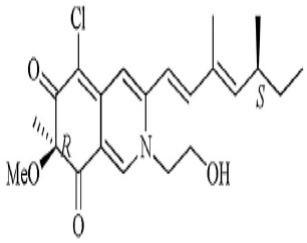
NMR spectroscopy is the most common analytical tool utilized for the structural or molecular determination of pigments. NMR spectroscopy provides information on how each atom or element in a molecule is connected—structural elucidation, whereas 2D-NMR is very useful for the structural determination of complex molecules (40). NMR and 2D-NMR are used in many pieces of literature for the determination of molecular structures of the pigments from *Penicillium* species. Table III summarizes the *Penicillium* and the structures of the respective pigments determined via NMR spectroscopy.

Table III. Characterization vis 1D and 2D NMR

***Penicillium* sp.**	**Pigment**	**Pigment Class**	**Chemical Name/Structure**	**Structure**	**Ref.**
Penicillium sp. AZ	Red (PP-R)	Azaphilone	7-(2-hydroxyethyl)-monascorubramine		(18, 41)
Penicillium sp. AZ, *Penicillium purpurogenum*	Violet (PP-V)	Azaphilone	3-(9a-methyl-3-octanoyl-2, 9-dioxo-2,7,9,9a-tetrahydro-furo [3,2-g] isoquinolin-6-yl) acrylic acid.		(21, 22, 41)
Penicillium sp. AZ	Yellow (PP-Y)	Azaphilone	(10Z)-monascorubrin		(19, 41)

Penicillium sp. AZ, *Penicillium purpurogenum*	Orange (PP-O)	Azaphilone	(10Z)-3-(9a-methyl-3-octanoyl-2, 9-dioxo-9,9a-dihydro- 2H-furo [3,2-g] isochromen-6-yl) acrylic acid.		(19, 22, 41)
Penicillium purpurogenum stoll	Red (Deoxypurpurogeno-ne)	Quinone	Deoxypurpurogenone (1; $R^1 = R^2 = H$)	-	(34, 41)
	Crimson (Purpurogenone)	Quinone	Purpurogenone (1; $R^1 = OH$, $R^2 = H$)		(33, 41)
Penicillium rubrum	Orange-Yellow (Mitorubrin)	Azaphilone	-		(32, 41)
	Yellow (Mitorrubinol)	Azaphilone	-		(32, 41)
Penicillium oxalicum var. armeniaca	Red	Anthraquino-ne derivative	Anthraquinonyl carboxylic acid derivative		(30)
Penicillium aculeatum	Yellow	Ankaflavin	-		(3, 41)

Penicillium simplicissimum IFO5762	Yellow (Xanthoepocin)	Xanthomegnin	14-(2,15-dihydroxy-12-methoxy-6-methyl-4,11-dioxo-5,13-dioxatetracyclo [8.5.0.03,8.012,14] pentadeca-1(10),2,6,8-tetraen-14-yl)-2,15-dihydroxy-12-methoxy-6-methyl-5,13-dioxatetracyclo [8.5.0.03,8.012,14] pentadeca-1(10),2,6,8-tetraene-4,11-dione		(27),
Penicillium sclerotiorum 2AV2, *Penicillium mallochii*	Yellow-orange (sclerotiorin)	Azaphilone	(7R)-5-chloro-3-[(1E,3E, 5E)-3, 5-dimethylhepta-1,3-dien-1-yl]-6-8 dioxy-7,8 dihydro-6H-2-benzopyran-7-yl acetate.		(7, 31, 41)
Penicillium flavigenum (CML2965)	Yellow (dihydrotrichodimerol)	Bisorbicillinoid polyketide	-		(23)
Penicillium sp. ZJ-27	Red (Peniazaphilone -A)	Azaphilone	-		(24)
	Red (Peniazaphilone-B)	Azaphilone	-		(24)

Red (Peniazaphilone-C)	Azaphilone	-	(24) 
Red (Peniazaphilone-D)	Azaphilone	-	(24) 

- indicates 'either not mentioned clearly in the respective paper or is not known'.

BIOTECHNOLOGICAL APPLICATION OF THE PIGMENTS

Pigments from *Penicillium* species are of potential use in various fields for various purposes such as in food, textile, pharmaceuticals, and cosmetics. For instance, xanthoepocin, a yellow pigment produced by *Penicillium simplicissimum* IFO5762 showed activity against yeasts and gram-positive bacteria—and, thus, can be used as an antibiotic (27). Whereas the red pigment from *Penicillium oxalicum var. armeniaca* and *Penicillium sp.* HSD07B, and the yellow-orange pigment, sclerotiorin from *Penicillium sclerotiorum* 2AV2 can be used as natural coloring agents in cosmetic and food industries (7, 30, 35). *Penicillium mallochii* produces a yellow-orange pigment, sclerotiorin that can be used as a chemotaxonomic marker for *Penicillium* species identification, as well as an antibacterial and antioxidant agent (31). Additionally, the yellow pigment, dihydrotrichodimerol from *Penicillium terrestre* can be used for the treatment of certain cancers, inflammatory diseases, and type II diabetes (42, 43). Finally, monascorubrine, the reddish-orange pigment from *Penicillium verruculsom* SG, due to its high stability, can be used in dyeing and printing industries (26), as well as an anti-inflammatory agent (44, 45) and an antibiotic (46).

CONCLUSION

Pigments from *Penicillium* species are suitable agents/colorants for use in multiple industries, such as textile, food, cosmetics, and pharmaceuticals. A major reason that makes pigments produced by *Penicillium* species more suitable for biotechnological applications is that there is no production of citrinin—a mycotoxin, along with the pigment produced. However, the production, extraction, and isolation through chromatographic techniques as well as the chemical characterization through spectroscopic tools of the pigments from *Penicillium* species are of prime importance before their consideration for any form of utilization. Finally, more research and biological tests are required for the stability and biotoxicity of the pigments to be used for different biotechnological purposes.

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