

Safety of Food Fungal Pigments

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Pigments play a major role in many industries. Natural colors are usually much safer when compared to synthetic colors and may even possess some medicinal benefits. Synthetic colors are economical and can easily be produced compared to natural colors. In addition, raw plant materials for natural colors are limited and season dependent. Microorganisms provide an alternative source for natural colors and, among them, fungi provide a wide range of natural colorants that could easily be produced cheaply and with high yield. Along with pigment, some microbial strains are also capable of producing a number of mycotoxins. The commercial use of microbial pigments relies on the safety of colorants.

fungal pigments

mycotoxins

safety evaluation

pigment toxicity

1. Microbial Pigments

Natural pigments obtained from plants, animals and microorganisms are eco-friendly and have usually low or no toxicity ^{[1][2]}. The many disadvantages of using plants and animals prevent them from large-scale exploitation ^[3]. However, advantages of microbial pigments help to utilize their immense potential in various fields ^{[4][5]}. Even though the cost of microbial β -carotene production is several times more expensive, it can still compete with synthetic dyes in terms of it being natural and safe ^{[6][7]}.

Microbial cells that produce color are referred to as microbial pigments producers ^[8]. They produce a wide range of colors (**Figure 1**) and are mostly water-soluble ^{[9][10]}. Natural pigments are mainly used as color additives or intensifiers; moreover, they are used as antioxidants and antibiotics (**Figure 2**). Due to indiscriminate use of synthetic colors and contrary reports on the safety of synthetic dyes, there is an important need to identify safe colorants from natural pigments. Microbial pigments have several advantages, viz., yield, cost efficiency, stability and ease of downstream processing compared to pigments from plant or animal origins ^{[11][12]}.



Figure 1. Pigments produced by different fungi: (a) *Chaetomium* sp. producing red pigment; (b) *Thermomyces* sp. producing yellow pigment; (c) *Penicillium purpurogenum* producing red pigment; (d) *Fusarium* sp. producing red pigment; (e) *Penicillium purpurescens* producing brown pigment (f) *Trichoderma* sp. producing yellow pigment.

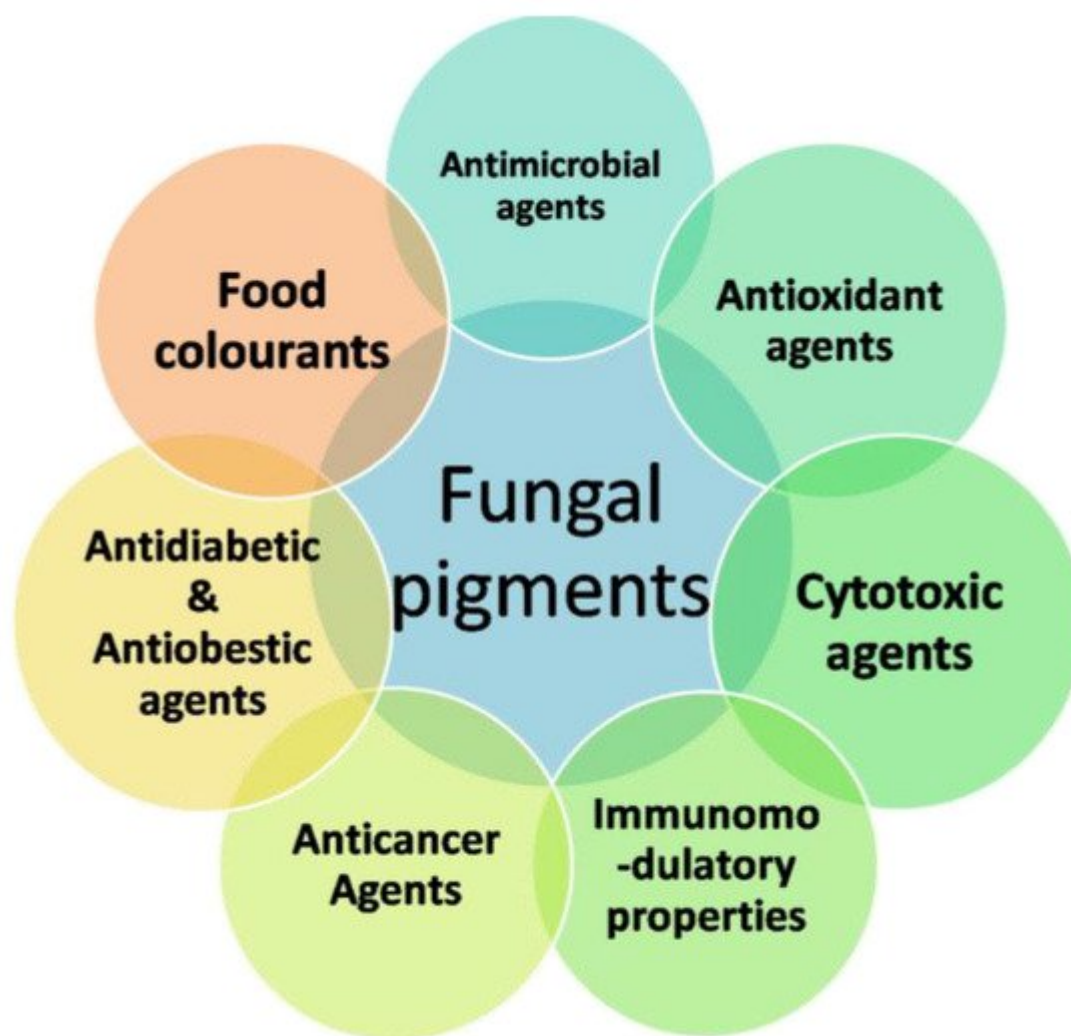


Figure 2. Applications of fungal pigments in the food industry.

Among pigment-producing microbes, fungi produce a wide range of water-soluble bio-pigments that have a variety of functions. Pigments extracted from fungi that are isolated from soil have various industrial applications. Filamentous fungi, viz., *Monascus*, *Aspergillus*, *Penicillium*, *Neurospora*, *Eurotium*, *Drechslera* and *Trichoderma* [13][14][15] are potential producers of bio-pigments. The pigments include carotenoids, melanins, flavins, phenazines, quinones, monacins and indigo [16]. Hence, they are the subject of many studies.

Recently, fungal pigments have been used for textile dyes, food colorants, antimicrobial and anticancer applications. They are also natural without having undesirable effects on the environment. Many scientific researchers have proved that pigments from soil fungi are a safer alternative to synthetic colorants, and there is good scope for industrial application [17][18].

2. Fungal Pigments and Toxicity Evaluation

Most fungi produce pigments along with mycotoxins. The presence of mycotoxins in pigments restricts the application of pigments as an additive in the food industry [1][19]. The European Union and the United States

prohibit the consumption of *Monascus* pigments that are produced along with citrinin toxin, which poses a challenge over its safe use [20]. In short, natural pigments are a potential source of colorants that are eco-friendly, biodegradable, antimicrobial and have antioxidant properties. Apart from food additives, they are also used in cosmetics, pharmaceuticals and drug applications [21] (Table 1).

Table 1. Important fungal pigments and their safety evaluation.

Fungus	Pigment(s)	Color	Mycotoxin(s)	Safety Evaluation	Biological Activity	Reference(s)
<i>Aspergillus carbonarius</i>	Melanins	Yellow	Not described/not found up to now	Subacute toxicity study	Antioxidant	[22]
<i>Blakeslea trispora</i>	β -carotene	Red-orange	Aflatoxin Mycotoxin	Genotoxicity and subacute toxicity study	Antioxidant, anticancer, suppression of cholesterol synthesis	[23][24]
<i>Fusarium graminearum</i>	Rubrofusarin	Red	Fumonisin, Zearalenone, Fusaric Acid, Fusarins and Beauvericins	Cytotoxic in colon cells	Antimicrobial, antiallergic, phytotoxic	[25][26][27]
<i>Fusarium fujikuroi</i>	Fusarubin	Orange	Fumonisin, Zearalenone, Fusaric Acid, Fusarins and Beauvericins	Cytotoxic against leukemia cells	Anticancer, antimicrobial	[27][28]
<i>Fusarium oxysporum</i>	Bikaverin	Red	Fumonisin, Zearalenone, Fusaric Acid, Fusarins and Beauvericins	Cytotoxic against tumour cells, apoptosis suppressor	Antimicrobial, antitumour	[29]
<i>Monascus purpureus</i>	Monascorubramine rubropunctamine	Red	Citrinin	Acute oral toxicity	Antihypertensive metabolite	[30]
<i>Monascus anka</i>	Ankaflavin and Monascin	Yellow	No coproduction of toxin	Acute oral toxicity	Antibacterial, antitumor and immunosuppressive	[31]
<i>Monascus ruber</i>	Monascorubrin and rubropunctatin	Orange-red	No coproduction of toxin	Oral toxicity	Anti-inflammatory, anticancer and antihyperlipidemic activities	[32]

Fungus	Pigment(s)	Color	Mycotoxin(s)	Safety Evaluation	Biological Activity	Reference(s)
<i>Penicillium purpurogenum</i>	Azaphilone	Brick red pigment	No coproduction of toxin	Brine shrimp <i>Artemia salina</i> study	Pharmaceutical and food industry	[33][34][35]
	Purpurogenone	Yellow-orange				
	Mitorubrin	Orange-red				
	Mitorubrin	Yellow				
<i>Penicillium europium</i>	Benzoquinone	Pinkish red	Nontoxic	Subacute toxicity study	Antimicrobial	[36]
<i>Penicillium resticulosum</i>	Not described/not found up to now	Red	Nontoxic	Subacute toxicity study	Antimicrobial	[37]
<i>Penicillium aculeatum</i>	Ankaflavin	Yellow	Nontoxic, selective toxicity in cancer cells	Cytotoxicity study	Antimicrobial	[38]
<i>Talaromycespurpureogenus</i>	Purpuride, monascorubrin, purpurquinone-A, ankaflavin,	Yellow and red	Nontoxic	Subacute toxicity study	Antioxidant	[39]
<i>Thermomyces</i> sp.	Napthoquinone	Yellow	Nontoxic	Subacute toxicity study	Antioxidant, antimicrobial and food industry	[40]
<i>Trichoderma viride</i>	Emodin Viridol	Brown Yellow	Nonphytotoxic	Phytotoxicity assay	Antimicrobial	[13]
<i>Scytalidium cuboideum</i>	Xylindein	Red	Nontoxic	Zebrafish toxicity study	UV resistant	[41]
<i>Rhodotorula glutinis</i>	β-carotene, torulene and torularhodin	Red and orange	Nontoxic	Standard subchronic toxicity study	Antioxidant, Antimicrobial Food and feed additive	[42]
<i>Rhodotorula gracilis</i>	β-carotene, torulene and torularhodin	Red and orange	Nontoxic	Standard subchronic toxicity study	Antimicrobial	[43][44]
<i>Yarrowia lipolytica</i>	β-carotene	Brown	Nontoxic	Genotoxicity models and a standard	Antimicrobial	[45]
		[47]				

Toxicity studies in both sexes of albino rats at acute and subacute doses of the pigment revealed that feeding of fungal biomass did not show any mortality in rats and there are no significant differences in food intake or organ and body weight. When comparing treated and untreated rats, hematological parameters, serum enzymes lactate dehydrogenase (LDH), alkaline phosphatase (ALP), alanine aminotransferase (ALT or ALAT) and cholesterol assay also remain normal [48].

2.2. Blackslea trispora

Fungus	Pigment(s)	Color	Mycotoxin(s)	Safety Evaluation	Biological Activity	Reference(s)
				subchronic toxicity study		

fungus does not produce any toxic compounds, hence, it is of industrial interest as a source of β -carotene for commercial exploitation [49][50]. β -carotene from *B. trispora* was the first authorized microbial food colorant in the European Union. It is efficient and can achieve the highest yield of all trans β -carotene at the expense of other structurally related carotenoids [18]. The process production was improved over a number of years, producing carotenoid contents of up to 20% dry weight [51][52].

The safety assessment of β -carotene, derived from *B. trispora*, has revealed no genotoxicity or subacute toxicity for 4weeks [23][53]. A subchronic toxicity study of 90 days was performed with oral administration of F344.Rats of both sexes showed no adverse effects on their biological systems [24]. β -carotene derived from the *B. trispora* at a 5.0% dietary level, equivalent to 3127 mg/kg/day and 3362 mg/kg/day for male and female rats, caused no adverse effects. The findings revealed that the daily intake of synthetic β -carotene from *B. trispora* by human beings is a negligible toxicological hazard [54].

2.3. Fusarium sp.

Fusarium are Ascomycota fungi that belong to the order Hypocreales, family Nectriaceae. They produce a wide range of fungal pigments that are structurally and functionally diverse. However, among the *Fusarium* sp., *Fusarium graminearum* (red naphthoquinone pigment, *rubrofusarin*) [25], *Fusarium fujikuroi* (orange carotenoids pigment, *fusarubin*) [28][55] and *Fusarium oxysporum* (red naphthoquinone pigment, *bikaverin*) [29] are the major pigment-producing fungi. Secondary metabolites from these fungi contain numerous toxic compounds, viz., fumonisins, zearalenone, fusaric acid, fusarins and beauvericins [56].

Toxicity analysis revealed that the red dimeric naphthoquinone pigment from *F. oxysporum*-contaminated products affects human health. Recently, red naphthoquinone pigment has often been reported as a mycotoxin. However, naphthoquinone pigment was not genotoxic according to a DNA synthesis assay. Biotechnological approaches and intelligent screening of the toxic metabolite pathway of the pigment from *Fusarium* sp. will be helpful in producing the pigment for food coloring [26][27].

2.4. Monascus sp.

Monascus sp. are fungi placed under order Eurotiales, family Monascaceae. There are many species in this genus, among which *M. purpureus* (monascorubramine and rubropunctamine) [30], *M. anka* (ankaflavin and monascin) [31] and *M. ruber* (monascorubrin and rubropunctatin) [32] are of greatest significance to the food industry. Traditionally, *Monascus* pigments were produced on rice using solid-state microbial fermentation. Synonyms for this food product include, Hon-Chi, Hong Qu, Dan Qu, Anka, Ankak rice, Beni-Koji, red koji, red Chinese rice, red yeast rice and red mold rice (RMR). RMR was utilized as a food colorant in traditional Chinese medicine for more than 1000 years [57].

Chinese, as well as other East Asian people, have confirmed the safety of red yeast rice. The European Food Safety Authority (EFSA) and the United States excluded red yeast rice on the list of permissible food additives, due to complex secondary metabolites [58][59]. The toxigenic strain of *Monascus purpureus* is capable of producing nephrotoxic and hepatotoxic mycotoxin citrinin, which limits the wide application of the pigment [60].

For more than a thousand years, pigments produced by *Monascus* sp. were legally used as food colorants in South East Asia, even though they were demonstrated to have physiological effects. There are numerous toxicological data available on this *Monascus* red pigment.

A genetically modified industrial strain, *M. purpureus* SM001 isolated in China, is capable of producing pigment without citrinin, which is the best *Monascus* pigment producer. This results in the prolonged safety of *Monascus*-related products and their application [61].

2.5. *Penicillium* sp.

Penicillium are Ascomycota fungi belonging to the order Eurotiales, family Trichocomaceae. They are capable of producing many pigments. *Penicillium* are ubiquitous saprophytic soil fungi, present wherever organic material is available. Several species are capable of producing highly toxic mycotoxins. Some species of the genus *Penicillium* are capable of producing antibiotics, while some other species are used in cheese making; however, pigment production by these fungi is less well known [34][62]. Patents contain information about acute oral toxicity in mice. A 90-day subchronic toxicological study found acute dermal irritation, acute eye irritation, antitumor activity, micronucleus test in mice, AMES test (*Salmonella typhimurium* reverse mutation assay) and an estimation of antibiotic activity, including results of estimation of five mycotoxins [63].

Penicillium purpurogenum is capable of producing an azaphilone-like pigment. It secretes a brick red pigment during growth, which generally diffuses into commonly used media. However, violet pigment (PP-V) and orange pigment (PP-O) were also reported by altering culture conditions [64]. The production of pigment from *Penicillium* is more efficient and profitable than any other microorganism. It secretes enzymes and pigments out of the cell and the secreted pigment is water-soluble and relatively stable; thus, it is easily purified [65].

Toxicity studies of *P. purpurogenum* DPUA 1275 on brine shrimp, *Artemia salina*, showed antimicrobial effects and absence of toxicity to go along with pigment production. It also does not produce any known mycotoxins and is nonpathogenic to humans. It is a potential strain for the production of food pigments [66]. Although many species of *Penicillium* are found to produce pigments, only a few toxicological studies have been conducted.

Penicillium europium, isolated from forest soil, is capable of producing a pinkish pigment by using longifolene as a sole carbon source. A toxicity study on albino rats revealed that the pigment had no toxic effect on rats. Synthesized pigments from *P. europium* could be used in food, feed and pharmaceutical industries. Apart from the food industry, it could be used for various industrial applications, viz., dyes for textile and non-textile substrates such as paper, leather, paints and cosmetics. Moreover, as it is non cytotoxic, the pigment could be a potential replacement for hazardous synthetic dyes [36][67].

Penicillium resticulosum is capable of producing red pigments. An evaluation of the subacute toxicity of oral exposure on the synthesized pigment on adult male and female mice for 28 days, using a pigment dose of up to 500 mg kg⁻¹ body weight daily, had no effect on body weight, organ weight, or the activity of lactate dehydrogenase (LDH), alkaline phosphatase (ALP), alanine aminotransferase (ALT or ALAT) enzymes or blood urea nitrogen (BUN) levels. However, mice taking the pigment over 500 mg·kg⁻¹ body weight daily showed fatty degeneration and mild necrosis of liver cells, indicating that doses under 500 mg·kg⁻¹ body weight were safe for daily consumption [37][68].

Penicillium aculeatum produces a yellow (ankaflavin) pigment under submerged fermentation. Cytotoxicity studies of the pigment interacting with human colon carcinoma cell lines (HCT116) and human prostatic carcinoma cell lines (PC3) exhibited apoptosis and cell cycle inhibition at lower concentrations. An assay of human erythrocytes and human embryonic kidney (HEK-293) cell lines showed the least cytotoxicity at the highest concentrations tested. Displaying selective cytotoxicity is an important property for an ideal anticancer drug [38].

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