Review article

Production, characterization, and applications of bacterial pigments- a decade of review

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(Received: January 2022 Reviewed: May 2022 Accepted: June 2022)

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ABSTRACT

Synthetic pigments have been employed universally for decades, resulting in environmental pollution and human health risks. So, it was critical to find out novel natural pigments, such as microbial pigments, that were safe and alternative to synthetic pigments. Bacterial pigments were getting the importance and attention of both researchers and industries for the mass production of various colored pigments. Bacterial pigments were not only used for industrial applications but also have several pharmacological activities like an antibiotic, antioxidant, anti-cancer properties. For the production of natural pigments, bacterial sources are cheap and have large economic potential when compared to plant sources. To make high-end goods, strain improvement, genetic engineering, fermentation conditions, simple extraction and characterization procedures are required. The importance of bacterial pigments is highlighted in this review, which covers their synthesis, characterization, and biological uses.

Keywords: Bacteria; microbial pigments; carotenoids; pigment production; biological applications

INTRODUCTION

Pigments are the colored substances produced by living organisms. Several plants and microorganisms are known to produce natural pigments in response to different environmental factors, while animals obtain them via food. Microorganisms, mostly bacteria and fungi, are explored extensively for pigment production because microbial pigments are more stable than pigments produced by plants.

Microorganisms such as bacteria, fungi, algae, and yeasts are known to produce different coloured substances called microbial pigments, for example, monascins, violaceins, flavones, prodigiosins, pycocyanins, melanins, glaukothalin, quinines, canaxanthins, xanthomonadins, astaxanthins, phenazines and carotenoids. Based on pigment accumulation and secretion, microbial pigments are of two types: extracellular pigments that diffuse into media and intracellular pigments that retain with the cells.

The utilization of microbial pigments as dyes, food colorants, anti-cancerous compounds, and other industrial purposes has increased in recent years due to their biodegradable, environmentally friendly, and generally regarded as a safe in nature. Due to the growing need and extensive biological applications of microbial pigments, there is a need to produce them in large quantities as an eco-friendly alternative to synthetic pigments (1).

Even though several reviews have fully outlined the extensive uses of microbial pigments, knowledge on production, characterization and purification of bacterial pigments appears to be lacking and has not been properly reviewed elsewhere. Hence in the present review, we have summarized what are bacterial pigments and various types of bacterial pigments and their detailed overview of the production, characterization, and biological applications in past ten years, therefore offering helpful knowledge and direction for future research.

Bacterial pigments

Few bacterial groups produce blue, blue-green, green-red, yellow, orange, pink, red, brown, and purple coloured pigments, which are having different chemical properties and functions (2). Production of pigments on selective media is considered one of the phenotypic characteristic features used as a taxonomic tool for categorization and differentiation of bacteria. Pigmented bacterial groups are structurally adapted at the molecular level to withstand extreme environmental conditions. The biochemical pathways that functions under extreme conditions and produce unique pigments in which mesophilic counterparts could not survive because, this unusual property to withstand the harsh conditions has consequently been used in several novel applications in recent years (3).

Pigments from the bacterial origin such as carotenoids offer protection to the microorganism from ionizing radiation. These radiations produce hydride radicals and hydroxyl radicals having the capacity to alter the biopolymers, for example, DNA and proteins. Increased UV radiation causes dense pigmentation of bacteria has been reported in bacteria that are resident in water surfaces (4).

Because of their distinctive features, wide distribution, and different roles, carotenoids are important pigments in a variety of scientific fields. Carotenoids are light-harvesting pigments in photosynthetic organisms. Their primary function in many organisms is to act as an antioxidant, neutralizing free radicals and reducing oxidative damage to cells (5). Carotenoids are extremely vulnerable to oxidant death in a *Staphylococcus aureus* mutant with impaired carotenoids production, suggesting that carotenoids may serve as a virulence factor (6). Carotenoids may limit singlet oxygen entrance by decreasing film fluidity. Ongoing reports demonstrated that polar carotenoids, such as zeaxanthin, can facilitate trans membrane *in vivo* proton transport. From synthetic perspective carotenoids are poly isoprenoid mixes that can be partitioned into two main groups:

β –carotenes

These are carotenoids, which are a type of hydrocarbon with both carbon and hydrogen atoms. Carotene is an essential ingredient in food and feed products because it works as an antioxidant and a precursor to vitamin A (7).

Xanthophylls

These are oxygenated hydrocarbon derivatives with at least one oxygen function, such as epoxy, methoxy, hydroxy, keto, or carboxylic acid groups. One of the most important carotenoids in this category is lutein (8).

Among the bacterial pigments produced in nature which are reported till date, most of the researchers have paid attention to pigments of yellow and red colors, such as monascue produced by *Monascus sp*. (9). However, phenazine, violacein, prodigiosin, etc., are some bacterial pigments that gained attention in various biological applications. More than 50 distinct bacteria from various genera have been discovered to manufacture phenazine pigment, which has a substituted phenazine ring structure and corresponds to each colour of the visible spectrum. Violacein is a violet shade with assumed anti-microbial and antiviral movement, has appeared even influence protozoan brushing (10). The examination and identifying with violacein has basically focused on its therapeutic noteworthiness. Notwithstanding its application in coloring textures, cytotoxic action in human colon malignant growth cells is a key quality of violacein (11), antileishmanial, antiulcerogenic (12), antiviral, anti-toxin, antitumoral and hostile to *Trypanosoma cruzi* exercises. Apart from its use in textile dyeing and medical purposes, prodigiosin has recently been found to be effective as a biological control agent against hazardous algae in natural coastal habitats.

Production of bacterial pigments

Bacteria grown in different geographical regions have different characteristics and to tolerate extreme conditions microorganisms produce pigments. The production of pigments is influenced by a variety of environmental factors including temperature and PH primarily the chemical composition of the organic carbon and the energy source (13). A unique red pigment was isolated from *Bacillus* sp having 34^{o}C as optimum temperature and moderate pigment production was observed at 32^{o}C (14). Using a garden soil isolated *Bacillus safensis*, researchers aimed to optimize the production parameters impacting melanin formation in a cost-effective fruit waste extract. The ideal temperature for producing prodigiosin is 37^{o}C (15). The enhanced pigment production was achieved at 72h of incubation and glucose is the better carbon source to produce red pigment from *Brevibacterium maris,* and dextrose is found to be the suitable carbon source for *Serratia marcescens*. The effect of ethanol, glucose, and glycerol as carbon sources was shown to have a significant influence on prodigiosin synthesis, with fewer productions observed in the case of the lactose-supplemented medium. Dried yeast supported all three selected seclusions for the most intense prodigiosin pigment production. The cysteine containing nutrient broth media supported for maximum prodigiosin pigment production (186.8mg/ml) from Strain *S. marcescens* MBB05.

Pigment extraction

For the analysis of water-insoluble yellow pigment, cells were grown on kings B and nutrient agar for pigment production, and spectral characteristics were conducted by extraction with acetone using a visible–UV Kontron Uvikon 860 spectrophotometer. Acetone was used to isolate intracellular orange pigment from thermostable *Geobacillus*. Ethanol and methanol were used to extract orange pigment from *Staphylococcus kloosi* (16). The orange pigment was extracted using ethanol and ethyl acetate. The blue pigment was extracted using chloroform. The pink pigment was extracted from facultative *Methylobacterium* by using methanol and chloroform. Carotenoid pigments were extracted from *Bacillus subtilis* by using methanol extraction method. Khaneja *et al.*, reported the poor ability of organic solvents to extract the carotenoids from *Bacillus*. Both red and yellow pigments were extracted from *Bacillus megaterium* with chloroform. The most elevated extraction of red color from *Serratia marcescens* KH1R KM035849 was yielded in 2:1= 85% methanol: acetone (17).

Purification of pigment

The colors removed from the culture broth on silica gel GF254 utilizing ethyl acetic acid derivation and hexane (1:1) as dissolvable demonstrated three portions on thin layer chromatogram, the green pigment was extricated from *Bacillus cereus* M116 (MTCC 5521). The extricated rough pigment was exposed to a thin layer and column chromatography for decontamination, and the significant division C_3 was isolated out. The black pigment melanoidins was purified from the crude pellet after centrifugation at 4600 rpm for 15 min from bacterium *Bacillus safensis.* The fractions obtained from the column chromatography depicted the purity of fractions of red pigment, which was again fractionated to get a purified one. Immaculateness of the color was controlled by thin-layer chromatography, utilizing silica gel G (Merck and Co., Inc., Rahway, N.J.) uni plates (Analtech, Newark, Del.) created with a 70:30 (v/v) ethanol-water dissolvable framework. A homogeneous mixture of pyoverdine was noted by the nearness of just a single reddish-brown colored detect no fluorescent spots were seen when plates were lit up with UV light (366 nm). The orange pigments carotenoids were purged by stage partition utilizing natural layer (lower stage) was gathered and the watery (upper) layer and re-extricated twice with chloroform. Unrefined pyocyanin portions were eluted as yellow-green, light blue, and dull blue groups were gathered with 15% methanol in chloroform on the silica gel segment (18). When pyocyanin was eluted with 1% methanol in chloroform eluted as yellow, red, light blue, and dim blue groups were gathered utilizing silica gel section, and yellow-green groups were gathered with elution of 15% methanol in chloroform, while blue band effectively eluted as unadulterated pyocyanin.

The solitary blue color fraction was observed by using chloroform, further it was extracted using chloroform by adding 0.2N HCl. The presence of pyocyanin pigment was shown by a change in colour to red. Silica gel column chromatography was used to separate orange pigment that was eluted with ethyl acetate with the column (2 cm 30 cm) was packed with silica gel suspended in 70% ethanol and thin layer chromatography was used to identify dark orange (Rf 0.96), purple (Rf 0.80), blue (Rf 0.64), and greenish-yellow bands with Rf values 0.58-0.47 using silica gel G-60 F25 (Merck, Mumbai, India (19).

Characterization of pigments

UV-Visible spectrophotometry

The absorption spectra of prodigiosin pigment were measured at 535 nm and the highest absorption spectrum of prodigiosin was found to be at 534.6 nm. The UV-Vis measurement of the crude violet pigment revealed the maximal absorption peak at 623.67 nm for pH 0.54, 576.61 nm for pH 0.61, 589.81 nm for pH 0.64, and 573.17 nm for pH 3, 7, 9, and 13 using a scanning range of 200-800 nm and methanol as a blank.

The fluorescent orange pigment yields three major peaks, at 519, 368, and 290 nm under UV-Visible light absorption spectrum, and the emission spectrum had the yields the peaks at 290, 368, or 519 nm by fixing the wavelength at 560 nm (20).

Mahadevan *et al.*, reported similar results of yellow-orange colored pigment from 200-700 nm yields six major peaks at 260, 361, 392, 421, 485, and 521 nm of absorption spectra and fluorescence emission results in two excitation peaks at 421 nm and 476 nm, shows that the organism was fluorescent. The yellow pigment had absorption maxima at 410, 435, 463, and 495 nm. The blue and green pigments have absorbance maxima at 690nm and 682nm when dissolved in chloroform. Carotenoids appearing outrageous at 455nm predominates in species classified as being yellow, while orange strains contain the carotenoids with the best at 467nm and the pink strains have a carotenoid with a 492nm most prominent. Thus, the light essentialness devoured by these pigments arranges the visual shade of the strains (21).

High performance liquid chromatography (HPLC)

HPLC was used to separate and characterize yellow, orange, and red pigments from *R. glutinis*, found that there were two -carotenes, with peak times at 2.99 min^{-1} and 3.24 min^{-1}, which indicates all trans-β-carotenes and cis-isomer of β-carotene by its ingestion range because the backup crest in the close bright (349 nm) is a trademark for a cis-isomer and identified that, all trans-β-carotenes appeared comparative peak time and R_f value (22).

Liquid chromatography and mass spectra (LCMS)

The green pigment (9-methyl-1, 4, 5, 8-tetra-azaphenanthrene) from *Bacillus cereus* was identified by recording a major peak at 16.99min and corresponding mass fragmentation peaks at m/z 196 (97%), 169 (100%), 142 (32%), 115 (18%), and the same was matched with mass fragmentation data from an existing library (NIST/Wiley) (23). Carotenoid was identified using an LC system with a diode array detector (DAD) that recorded UV-VIS spectra ranging from 200 to 650 nm with methanol-water as the mobile phase (80:20). Carotenoids were eluted at intervals of 0-0.5 minutes, with a linear gradient reaching 70% B after 4 minutes. To confirm that retention times were consistent throughout the runs, external standards such as ß-carotene (Sigma) and astaxanthin (Sigma) were used. Pandey *et al.*, discovered carotenoid tangeraxanthin with a mass of 507.32g/mol ([M + Na] +), flavonoid specific sophoraiso flavoanone C with a mass of 499.25g/mol ([M + Na] +), and anthracene subordinates such as anthracene, 2, 3,9,10-tetramethyl and 4-methyl-3,4-dihydro-2H-benz (24).

Fourier Transform Infrared Spectrophotometry (FTIR)

Bands at 2955 cm and 2920 cm are due to asymmetrical stretching vibration of aliphatic -CH and -CH groups and bands at 2869 cm and 2851 cm are due to symmetrical stretching vibration of same gatherings as well as hilter kilter and symmetrical disfigurement vibrations, according to the FT-IR spectrum of yellow fraction (22). At 1463 cm and 1377 cm, CH_3 clusters can be discovered. Low-intensity bands at 1713 cm may be owing to the C = O group, and the FT-IR spectrum of the red portion displays bands at 2954 cm and 2921 cm respectively, due to the asymmetrical stretching vibration of aliphatic -CH and -CH groups. Mass data of molecular-ion peak was observed at m/z 568 (M^+, $C_40H_56O_2$) and lutein is being considered for its impacts on human eyes. Lutein and lycopene are both found in various nourishments (25). Lutein and lycopene are normally happening substances found in numerous plants. Carotenoids, when all is said and done, have experienced various research thinks about as to their conceivable advantages against maladies, among other medical problems. Lycopene is considered as a cell reinforcement and anticancer operator while lutein indicated checked impacts on visual conditions exceptionally cataract. Lutein is especially being concentrated for its consequences for the human eyes. Lutein and lycopene are both found in various dietary supplements. Diverse hierarchical types of lutein and zeaxanthin in the model framework investigated are discussed in terms of potential physiological functions of these pigments in the retinal membranes: zeaxanthin in the protection of the lipid stage against oxidative damage and lutein in the retention of short wavelength radiation infiltrating the retina layers (26).

Chemical processes within the retina produce mevo-zeaxanthin (27). It was suggested that meso zeaxanthin is a transformation product formed from retinal lutein since lutein outperforms zeaxanthin in plasma while the mixed zeaxanthin stereoisomers outperform lutein in the retina. Under non-physiologic conditions, the creators demonstrate a base-catalyzed conversion of lutein to zeaxanthin. The explicitness of the lutein-binding protein, was similarly appropriated all through the length of the midgut every single larval instar have the lutein-binding protein in equivalent sums proposing that this protein is engaged with lutein take-up all through the larval advancement stages.

NMR Spectrophotometry

The fluorescent compound (Chloroxanthomycin) is a pentacyclic, chlorinated atom with the sub-atomic recipe C22H15O6Cl and a sub-atomic load of 409.786 g/mol (28). Explanation of the 1H NMR information demonstrated the proximity of a disengaged methyl assembling, a diamond dimethyl gathering, and two bound detached protons, each occurrence as a singlet.

Biological applications

Bacterial pigments offer a tremendous assortment of naturally dynamic properties and keep on giving confident roads for connected biomedical research. Most specialists examining microorganisms demonstrate the value and the potential clinical utilization of pigmented auxiliary metabolites in treating a few ailments and likewise have certain properties like anti-infection, anticancer, and immunosuppressive mixes. Significant advance has been accomplished in this field, and examinations of bioactive mixes delivered by these microorganisms are quickly expanding. In that capacity, the quantity of mixes disengaged from microorganisms is expanding quicker when contrasted and different sources**.**

Few bacterial animal varieties, including the gram-negative species *Chromobacterium violaceum, Janthinobacterium lividum, Pseudoalteromonas luteoviolacea*, Ps.sp.520P1, and Ps. sp. 710P1 are makers of violacein (29). It was accounted for to have hostile to protozoan, anticancer, against bacterial and cell reinforcement exercises depicted *Janthino bacterium* sp.Ant5-2(J-PVP), produces two colors, violacein, a purple-violet shade showing hostility to mycobacterial action, and flexirubin, a yellow-orange shade from *Flavobacterium* sp. Ant 342 (F-YOP) would be the important combination for the chemotherapy of tuberculosis. This unique property provides the potential utilization of violacein for remedial purpose.

The pigment anthocyanin has a wide range of natural qualities that have favourable effects on wellbeing and the reduction of malignant growth hazards, inflammatory insult, and immune response modulation. Prodigiosin, metacyclo prodigiosin, and desmethoxy prodigiosin, which are generated by the bacteria *Serratia* or *Streptomyces* sp., have been shown to exhibit antimalarial and antimicrobial properties. Prodigiosin25-C has an immuno-suppressive effect. Nakamura and associates initially depicted prodigiosin's immune-suppressive movement in 1989. Long periods of research revealed the presence of prodigiosin and meta cyclo prodigiosin in Serratia culture broth, as well as a distinct restraint of polyclonal growth of immune system bacteria when compared to b-cells. Aside from that, prodigiosin's cytotoxic potential has been investigated in human tumour cells derived from lung, colon, renal, ovarian, and brain tumours, as well as melanoma and leukemia. In these cell lines, there has been a restriction on cell proliferation as well as the enlistment of cell death. Distinctive prodigiosin analogs and synthetic indole subsidiary of prodigiosin have likewise been accounted for in vitro anticancer action (30). Prodigiosin has been studied for its antiproliferative and cytotoxic effects in refined tumour cell lines as well as human essential malignancy cell lines from patients with b-cell chronic lymphocytic leukemia. According to reports, the use of prodigiosin for treating diabetes mellitus is an important aspect of preventing and treating diabetes mellitus (31).

Antibacterial activity

The genus *Bacillus* actively produces several antibiotics with high specificity against several microorganisms like *Salmonella typhi, Streptococcus mutans, Bacillus subtilis,* and *Shigella sonnei*. The *Bacillus endophyticus* strain seems to be highly potent in controlling bacterial pathogens of health significance and result in the development of a potential biocide. A *Proteobacterium* isolated from the seaside district produced an obvious secondary metabolite, and fractional cleansing of the obtained secondary metabolites were proven to have efficient antibacterial activity against the both Gram positive and Gram negative bacteria, such as *Bacillus subtilis, S. aureus, Pseudomonas aeruginosa, K. pneumonia, Shigella flexneri* and also MRSA (methicillin-resistant *Staphylococcus aureus*).

The carotenoids of 6 rough ethyl acetic acid derivation extricate were set up from the color delivering strains developed on marine agar 2216 and screened for their antibacterial activity against test bacterial strains. Out of 6 extracts, 3 separate demonstrated movement against clinical disengages. Antibacterial activity of carotenoids extricated from *Rhodotorula glutinis* was expanded by expanding focus and shown greater antibacterial activity than antifungal activity against the tested microbial cultures. A comparative finding was observed for the extracted carotenoid pigments from the *Micrococcus luteus* and *Sporobolomyces* sp. obtained from the normal source. Specifically, the results were proved that gram negative bacteria highly protection from the carotenoid pigments (32). The bluish green pigment extracted from *Pseudomonas* sp. JJTBVK have shown antibacterial activity against human pathogens *S. aureus, B.subtilis, P. aeruginosa,* and *Salmonella typhi*.

Antioxidant activity

The antioxidant activity of the microbial pigments using DPPH assay is a most frequently used method to evaluate antioxidant property and it is of 54.7%. The red pigment prodigiosin produced by halophilic strain *Serratia marcescens* KH1R (KM035849) which color which has numerous valuable properties like antibacterial, cancer prevention agent, and siderophore generation (17). A light filter of pigments prevents oxidative stress by diminishing the light exposure and plays a prominent role of pigments as pro-oxidants and implication of their pro-oxidants activity in adverse reactions.

Table 1: Natural pigments produced by bacteria

Bacteria	Pigment/ molecule	Colour	Applications
Agrobacterium aurantiacum, Paracoccus carotinifaciens, Xanthophyllomyces dendrohous.	Astaxanthin	Pink-red	Feed supplement
Rhodococcus maris	Beta carotene	Bluish red	Used to treat various diseases such as erythropoietin protoporphyria reduces the risk of breast cancer.
Bradyrhizobium haloferaxalexandrines	Canthaxanthin	Dark red	Colorant on food, beverages, and pharmaceutical preparations.
Corynebacterium Insidiosum	Indigoidine	Blue	Protection from oxidative stress
Rugamonas rubra, Streptovercillium rubrireticuli,Vibrio gaogens, Alteromonas rubra, Serratia marcescens, Serratia rubidaea.	Prodigiosin	Red	Anticancer, immunosuppressant, antifungal, algicidal, Dyeing (textiles, candles, paper, and ink.
Pseudomonas aeruginosa	Pyocanin	Blue-green	Oxidative metabolism, reducing local inflammation
Chromobacterium violaceum, Janthinnobacterium lividum,	Violacein	Purple	Pharmaceutical (antioxidant, immunomodulatory, antitumoral, antiparasitic activities); dyeing (textiles); Cosmetics (lotion).
Flavobacterium sp, *Paracoccus zeaxanthinifaciens, Staphylococcus aureus*	Zeaxanthin	Yellow	Used to different disorders, mainly with affecting the eyes.
Xanthomonas oryzae	Xanthomonadin	Yellow	Chemotaxonomic and diagnostic markers.

The radical searching action and against oxidant action of the β-cryptoxanthin was essentially higher than β-carotene yet had inconsequential contrast with ascorbic corrosive were as β-cryptoxanthin removed from *K.marina* DAGII may have potential nutraceutical significance. The scavenging of the free radical property of pigments separated from the bacterium *Streptomyces* sp. D 25 was extended with the expanding focus.

The antioxidant activity of the yellow pigment obtained from the *Streptomyces* sp. Eri 12 isolated from *Rhizomecuma longae* of rhizosphere soil was observed to 28.89 % free radical scavenging activity at the concentration 500 µg/ml by DPPH method. Marine bacteria are probably going to deliver carotenoids to shield themselves from activated oxygen created by daylight. The microbial pigments are eco-accommodating and utilized in the textile business, as sustenance colorants, cancer prevention agents, bio-pointers, and antimicrobial and anticancer specialists (33).

Anticancer activity

The unrefined carotenoid concentrates of orange, pineapple, banana, and lemon indicated expanded cytotoxicity when contrasted with the other two solvents. The fucoxanthin impacts a large number of molecular and cellular processes and applies solid consequences for malignant growth cells and shows synergistic action in a mix with setting up cytotoxic medications (34).

The carotenoids created by *Kocuria marina* QWT 12 have been appeared to smother the malignancy cell in vitro, by inciting separation and apoptosis and cell cycle capture and showed the practicality decline of numerous diseased cell lines such as Melanoma, colon, prostate, lung, oral and bosom malignancy cells. HepG2 cells were treated with an expanded concentration of carotenoids demonstrated a noteworthy ($P < 0.05$) decline in cell practicality in a period and portion subordinate route and in low CE concentration (0.2 - 0.5 μM), no critical abatements in cell viability were recorded, when contrasted with the control. This observation is as per the critical change observed for the cell morphology of HepG2 after treating with 0.5 – 1 mg/l (0.9-1.8 μM) for 24h of the haloferax Mediterranean separate.

The actinomycetes *Streptomyces gresioaurianticus* JUACT 01 secretes yellow-colored pigments from soil known to have cytotoxic potential and it is proved to be nontoxic to human which restrains the development and multiplication of the HEPG2 and HeLa cells *in vitro* through the apoptosis process (35). The halo Archaea was obtained from the sunlight based Sfax, Tunisia has showed the hopeful bio-potential that may open new doors for the advancement of powerful bioactive compounds for example, antitumor and cell reinforcement metabolites, is activating apoptosis in disease cell presented to CE. The after effects of MTT examination on the breast cancer cell lines of humans, MCF 7 demonstrated portion subordinate increment in cytotoxicity of the carotenoid extricates on the disease cells and the convergence of the concentrates expanded, the cytotoxicity to the cells likewise expanded proposing the anticancer action of the concentrates (36).

CONCLUSION

Synthetic pigments have been widely employed in a variety of applications, even though they are carcinogenic and non-biodegradable. As a result, there is a vital need for development of alternative natural, less cost and biodegradable pigments. Bacterial pigments are alternative sources of pigments used in dyes, food coloring, anti-cancer compounds, biological imaging, and other commercial applications. In this regard, genetic engineering, and fermentation techniques play an important role in the production of large quantity of low-cost, high-stability pigments to fulfill the growing demand for bacterial pigments on the worldwide market.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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