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REVIEW

Pigments from pathogenic bacteria: a comprehensive update on recent advances

Kusumita Acharya[1] · Swarna Shaw[1] · Sudipta Paul Bhattacharya[2] · Shatarupa Biswas[1] · Suman Bhandary[1] · Arijit Bhattacharya[1]

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Abstract
Bacterial pigments stand out as exceptional natural bioactive compounds with versatile functionalities. The pigments represent molecules from distinct chemical categories including terpenes, terpenoids, carotenoids, pyridine, pyrrole, indole, and phenazines, which are synthesized by diverse groups of bacteria. Their spectrum of physiological activities encompasses bioactive potentials that often confer fitness advantages to facilitate the survival of bacteria amid challenging environmental conditions. A large proportion of such pigments are produced by bacterial pathogens mostly as secondary metabolites. Their multifaceted properties augment potential applications in biomedical, food, pharmaceutical, textile, paint industries, bioremediation, and in biosensor development. Apart from possessing a less detrimental impact on health with environmentally beneficial attributes, tractable and scalable production strategies render bacterial pigments a sustainable option for novel biotechnological exploration for untapped discoveries. The review offers a comprehensive account of physiological role of pigments from bacterial pathogens, production strategies, and potential applications in various biomedical and biotechnological fields. Alongside, the prospect of combining bacterial pigment research with cutting-edge approaches like nanotechnology has been discussed to highlight future endeavours.

Keywords Bacterial pigments · Antibiotic · Biosynthetic gene cluster · Therapeutic application · Industrial application · Nanotechnology

Abbreviations

AXT	Astaxanthin
BGC	Biosynthetic gene cluster
FLR	Flexirubin
IND	Indigoidin
AZP	Azaphenanthrene
MEL	Melanin
MRSA	Methicillin resistant Staphylococcus aureus
PHZ	Phenazine
PCN	Pyocyanin
PVD	Pyoverdin
PDG	Prodigiosin
QS	Quorum Sensing
RFV	Roseoflavin
ROS	Reactive oxygen species
SXT	Staphyloxanthin
TFV	Toxoflavin
VIO	Violacein
ZXT	Zeaxanthin

Kusumita Acharya, Swarna Shaw, and Sudipta Paul Bhattacharya contributed equally to this work.

✉ Suman Bhandary
suman1.bhandary@adamasuniversity.ac.in

✉ Arijit Bhattacharya
arijit.bhattacharya@adamasuniversity.ac.in;
arijbhatta@gmail.com

[1] AMR-Research Laboratory, Department of Biological Sciences, Adamas University, Barasat-Barrackpore Rd, Kolkata 700126, India

[2] Department of Microbiology Lady Brabourne College, Kolkata 700017, India

Introduction

Originally identified as coloring agents, pigments isolated from natural resources including plants and microorganisms, have emerged as molecules of multitudinous

applications with least toxic impact on the environment and human health (Orlandi et al. 2022). Barring their application as chromogens for foods, textiles, cosmetics, and other industries, unravelling the biological action of the pigments rendered those of immense prospect for clinical application (Agarwal et al. 2023). A number of such natural pigments are preferably extracted from microorganisms including chromogenic bacteria owing to greater stability, up-scaling, and easy-tunable down-stream processing (Barreto et al. 2023). Despite such advantages, bacterial pigments are relatively less explored compared to pigments from plant and fungal sources. Except for photosynthetic pigments like bacteriochlorophylls, bacterial pigments are diverse in terms of chemical properties and belong to groups like carotenoids, melanin, phenazines, quinones, indoles, and pyrroles (Barreto et al. 2023). Carotenoids, pyocyanin, violacein, prodigiosin, and melanin and their derivatives are the most profoundly produced bacterial pigments (Acharya et al. 2023). Producers of such pigments are ubiquitous in nature and can be isolated from various niches like marine and terrestrial environments, ambient to extreme environments, and spoilt food to industrial effluent (Chatragadda and Dufosse 2021). Well-characterized pigment producers include actinobacteria, which includes *Streptomyces*, unequivocally the largest genus of pigment formers. *S. shaanxiensis*, *S. griseoviridis*, and *S. coelicolor* are the most well-characterized pigment former species from this group (Ibrahim et al. 2023). Apart from *Streptomyces*, a number of pathogenic bacteria, particularly opportunistic pathogens from the genera *Serratia*, *Pseudomonas*, *Staphylococcus*, *Chryseobacterium*, and *Chromobacterium* have been identified as profound pigment producers (Chatragadda and Dufosse 2021). Similar to alkaloids and antibiotics bacterial pigments are secondary metabolites. Pigment anabolism requires the expression of dedicated biosynthetic gene clusters (BGC), which are regulated by various transcription factors modulated by environmental cues (Wang et al. 2021). The colossal genetic load dedicated to pigment biosynthesis and its regulation underpins the evolutionary relevance of pigment production. The majority of the pigments offer fitness advantages to the producer organism, shaping microbial communities, participating in cell-cell communication processes, and establishing infection in susceptible host (Liu et al. 2024b). For the producers, pigments provide protection against oxidative damage, genotoxicity by ultraviolet radiation and mutagens, and also impart tolerance to elevated temperature and extreme desiccation (Day et al. 2017). Biological action associated with such functions has been linked to antimicrobial, antiviral, antioxidant, antioxidant, and anticancer activities of a number of bacterial pigments. With the identification of such exotic properties, bacterial pigments are attaining mounting interest in clinical and pharmaceutical industries (Barreto et al. 2023). The estimated global market for some of the pigments has been projected in recent years. The predicted global market for natural pigments in the cosmetic industry is USD 54.5 billion in coming years (Kiki 2023). Thriving on the increasing demand for biodegradable and environment-friendly dyes, the market expansion for pigments comprising other groups are also expected to escalate. With accumulating evidence of clinical and pharmaceutical applications like antimicrobial properties, bacterial pigments are expected to offer strategies to combat antimicrobial resistance emergence (Acharya et al. 2023). A number of profound pigment-producing bacteria are opportunistic pathogens, which often hinders scaling up for production. Leveraging synthetic biology for metabolic engineering, development of semisynthetic pigment derivatives, and nanoformulations with bioactive pigments are underway to foster industrial and pharmaceutical applicability of the molecules (Muthukrishnan et al. 2019). Against this backdrop, the present review attempts to offer a comprehensive retrospect of nonphotosynthetic bacterial pigments produced by pathogenic bacteria through a thorough introspection of existing literature (Fig. 1). Some of the pigments of concern are exclusively produced by pathogenic bacteria, and for others, both pathogenic and non-pathogenic origin have been reported. The review begins with outlining the chemical identity and bioactive properties of the pigments. Subsequently, the impact of the pigments on microbial communities and their possible role in pathogenicity is accounted. A detailed discussion on various biotechnical and clinical applications is included. Alongside, an insight into the strategies for the industrial production of bacterial pigments is discussed. Finally, recent approaches for developing novel formulations exploiting the bacterial pigments are highlighted to project possible future endeavours.

Bacterial pigments: producers and chemical properties

Bacterial pigments have been classified into various structural and functional groups. Pigments produced by non-phototrophic pathogenic bacteria have been associated with a higher spectrum of functionalities including adapting to certain environment for survival, protection against radiation and oxidative stress, and exerting antimicrobial effects to offer fitness advantage in their own habitat (Barreto et al. 2023) (Table 1). Majority of the pigments are produced as secondary metabolites, which are diverse in terms of structure (Fig. 2) and physicochemical properties (Fig. 3A and B). In this segment, a brief discussion on ten major groups of bacterial pigments produced by bacterial pathogens are

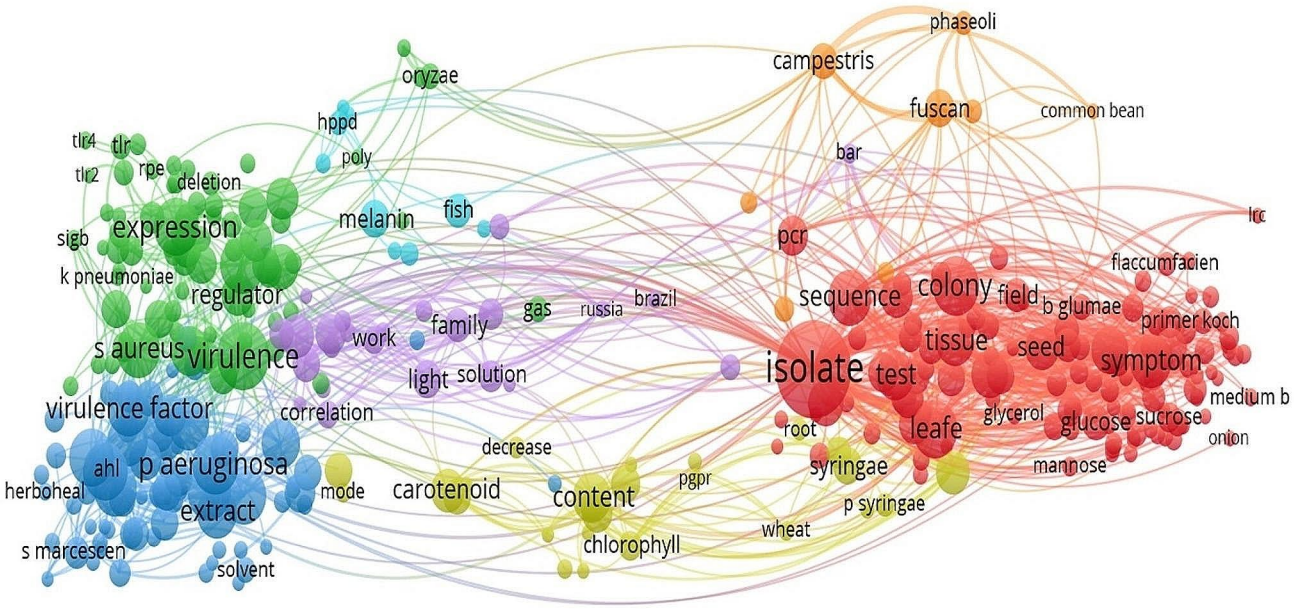

Fig. 1 Bibliographic analysis. VOSviewer generated map-view for relevant terms extracted from titles and abstracts of 632 research articles identified by DimensionsAI (https://www.dimensions.ai/). 60% of the most relevant terms are mapped on the plot with 'occurrence' as the weightage parameter. The map contains 329 items distributed within 7 clusters through 18,871 links

discussed in terms of their chemical features linked to biological function.

Carotenoids

Carotenoids, are one of the most frequently observed pigment in several groups of organisms including bacteria (Devi et al. 2024), archaea, fungi, algae, plants, and even animals (Maoka 2023). More than 850 different types of carotenoids that are found in nature play important roles as photoprotection, color attractant as well as hormonal precursors of plants. In animals, carotenoids act as photo-protector, antioxidants, immunity boosters, and vitamin A precursor (Maoka 2023). The structure of all variants of carotenoids are similar. Although the common precursor for carotenoid biosynthesis is phytoene (C_{40}), some other C_{30} and C_{50} precursors are used by a few bacterial species. All comprise of a general polyene chain with at least nine conjugated double bonds, both sides carrying an end group (Walter and Strack 2011). Phytoene gets converted to lycopene via numerous denaturation and polymerization reactions. A cyclase then converts lycopene, the red-colored pigment, to yield α-, β- and γ-carotenes (Barreto et al. 2023). Zeaxanthin (ZXT) is a yellow-pigmented carotenoid that has a linear structure β,β-carotene-3,3′-diol (Fig. 2A). ZXT can be obtained from plants and even the yolk of egg to different yellow pigmented organism. Among bacteria *Flavobacterium* sp., *Paracoccus zeaxanthifaciens* can be the source of ZXT production (Li et al. 2023a; Raman et al. 2024). Although other higher hierarchical plants, animals, and even algae produce ZXT, it is difficult to isolate the pigment from them as they also produce other carotenoids. In contrast, bacteria such as *F. multivorum* specifically produce 3R,3'R- ZXT (Vila et al. 2020). It also acts as an anticancer and anti-inflammatory agent due to its antioxidant properties (Raman et al. 2024) (Table 1). The pathogenic bacterium *Staphylococcus aureus* has been reported to synthesize a triterpenoid carotenoid, staphyloxanthin (SXT) as a possible virulence factor (Liu et al. 2005). The chemical structure of STX was determined by NMR spectroscopy, which revealed that glucose is esterified with a triterpenoid carotenoid carboxylic acid at the C_1'' position and a C_{15} fatty acid at C_6'' position (Fig. 2B). SXT provides the bacteria protection against antimicrobial attack including the immune system owing to the diaponeurosporenoic group and its ability to lower the membrane fluidity without altering conformation (Table 1), both of which are otherwise coupled events (Munera-Jaramillo et al. 2024). Astaxanthin (AXT), is an extremely important keto-carotenoid produced by nonpathogenic strains of *Paracoccus* and *Pseudoalteromonas* (Patil et al. 2022). Though AXT demonstrates immense bioactive potential, since it is produced primarily by nonpathogens, it is not further discussed here.

Azaphenanthrene

Azaphenanthrene (AZP) is a green-colored pigment that can be isolated from *Bacillus cereus*. Its structure is identified as 9-methyl-1,4,5,8-tetra-AZP, linked with a chromophore

Table 1 Bacterial pigments produced by bacterial pathogens. Various pigments isolated from pathogenic bacteria and their category, producer organisms, mechanism of action, and major biological activities as evidenced by recent reports are enlisted

Bacterial pigment	Group	Producing pathogen	Mode of action	Major biological activity
Zeaxanthin	Carotenoids	*S. aureus*, *Paracoccus app.*	Free radical scavanger - antioxidant	Antioxidant (Raman et al. 2024) Antihelminthic (Bouyahya et al. 2021) Neuroprotection (Stringham et al. 2019) Antidiabetic (Stringham et al. 2019)
Staphyloxanthin	Carotenoids	*S. aureus*	Free radical scavanger - antioxidant, Lowering membrane fluidity	Antibacterial (Barretto and Vootla 2018) Antifungal (Barretto and Vootla 2018) Antioxidative properties (Xue et al. 2019)
Azaphenanthrene	Azaphenanthrene	*Bacillus cereus*	Membrane disruption and loss of membrane potential	Antitumoral, antibacterial, antimalarial, and antifungal (Calabrese et al. 2010)
Roseoflavin	Flavin	*Burkholdaria spp*	Bind to FMN riboswitch aptamers, inhibiting the expression of genes encoding FMN biosynthesis and transport proteins	Antimicrobial (Li et al. 2019)
Toxoflavin	Flavin	*Burkholdaria spp*	By-passing of the cytochrome-system and producing H_2O_2	Antimicrobial (Li et al. 2019)
Phenazin	Phenazin	*P. aeruginosa*, *Burkholderia spp.*	Redox active, impairs redox balance	Antipersister (Garrison et al. 2018) Redox homeostasis (Schiessl et al. 2019)
Pyocyanin	Phenazin	*P. aeruginosa*	Redox active, impairs redox balance	Anticancer-apoptotic and necrotic activities (Abdelaziz et al. 2022) Antibacterial, antibiofilm, and anti-quorum sensing effects (Kamer et al. 2023) Antifungal (Sass et al. 2021; Shouman et al. 2023)
Pyoverdin	Siderophore	*Pseudomonas aeruginosa*	Iron quencher	Antibacterial (Vollenweider et al. 2023), Bioremediation, and phytostimulator (Dell'Anno et al. 2022)
Prodigiosin	Tripyrrole	*Serratia marcescens*,	Loss of membrane integrity, intercalate DNA and acts as inhibitors of topoisomerases I	Antibacterial (Acharya et al. 2023) Anticancer (Tai et al. 2024) UV-screen (Lin et al. 2020)
Violaceine	Bisindole	*Chromobacterium violaceum*, *Janthinobacterium lividum*	membrane damage and depolarization	Antifungal (Duran et al. 2022) UV screen (Zhu et al. 2022) Antibacterial (El-Zawawy et al. 2024) Antioxidants (Kordjazi et al. 2024) Anticancer effects (de Souza Oliveira et al. 2022; El-Zawawy et al. 2024; Kim et al. 2021)
Melanin	Melanin (polymer of phenolic compounds)	*Bordetella parapertussis*, *Pseudomonas otitidis*, *Pseudomonas stutzeri*	UV and Radiation screen	Antibacterial (Kordjazi et al. 2024; Polapally et al. 2022; Singh et al. 2021) Anticancer effects(El-Zawawy et al. 2024) Antifungal (Arun et al. 2015) Antiviral (Abd-El-Aziz et al. 2024)
Indigoidin	bipyridyl	*Dickeya dadantii*	Prevents oxidative stress	Antimicrobial (Xu et al. 2015) Antioxidant (Cude et al. 2012)
Flexirubin	Flexirubin	*Chryseobacterium*, *Flexibacter*	Free radical Scavanging, Immunomodulation	Free radical scavenging and anti-inflammatory activity (Mogadem et al. 2021) Proapoptotic (Venil et al. 2016) Antioxidant (Amorim et al. 2022a) Hepatoprotective (Mogadem et al. 2022)

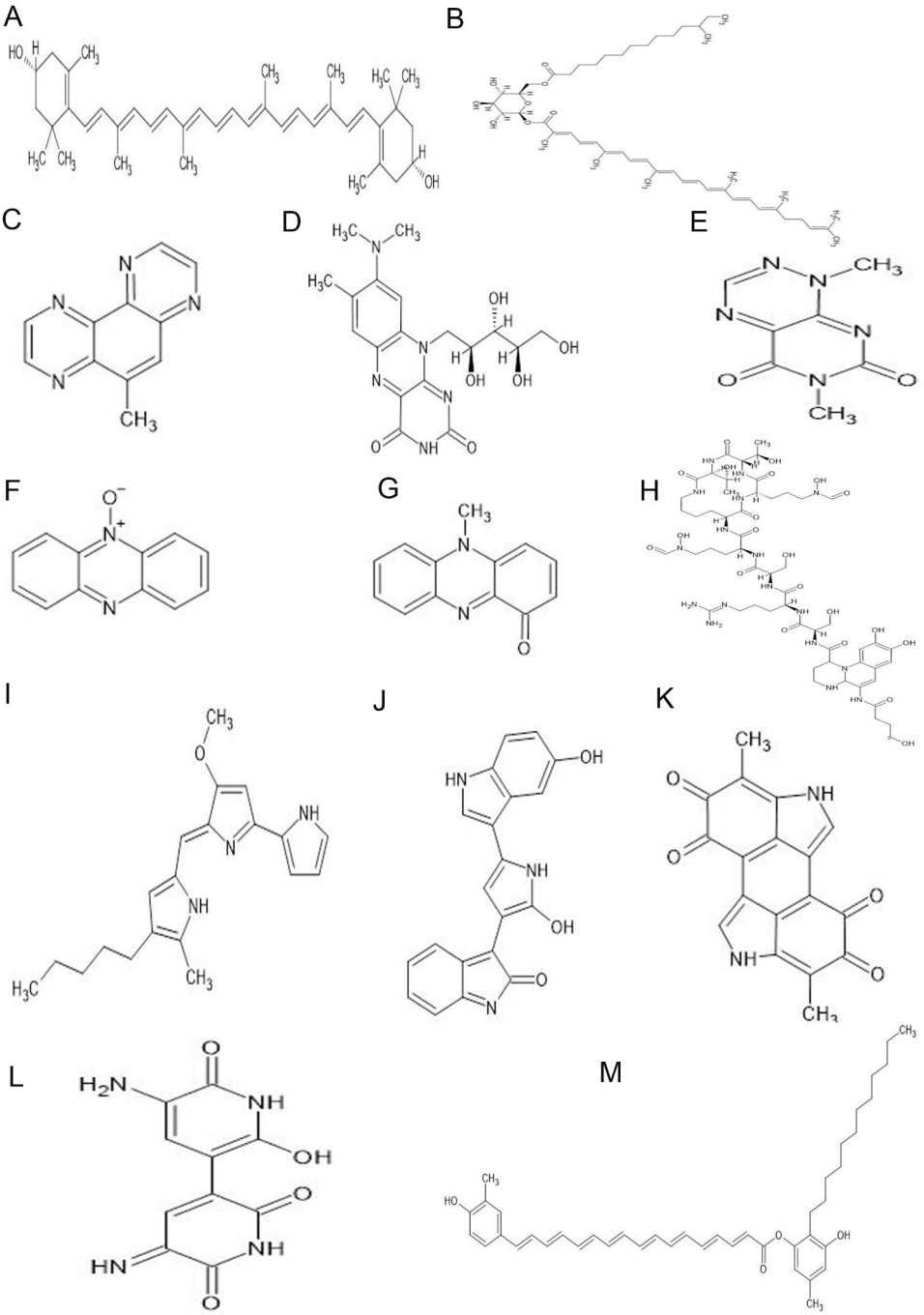

Fig. 2 Pigments produced by pathogenic bacteria. Structures of various bacterial pigments are illustrated using PubChem Sketcher V2.4 and ACD/ ChemSketch based on isomeric SIMLES retrieved from PubChem. (**A**) zeaxanthin (ZXT) (**B**) staphyloxanthin (SXT), (**C**) azaphenanthrene (AZP), (**D**) roseoflavin (RFV), (**E**) toxoflavin (TFV), (**F**) phenazine (PHZ), (**G**) pyocyanin (PCN), (**H**) pyoverdin (PVD), (**I**) prodigiosin (PDG), (**J**) violacein (VIO), (**K**) melanin (MEL), (**L**), indigoidin (IND), and (**M**) flexirubin (FLR)

derivative known as 7-N, N-dibutylamino-2-AZP (Banerjee et al. 2011, 2014) (Fig. 2C). Antibacterial activity of AZP compounds was reported long ago (Gupta et al. 1970); the stability of which was demonstrated to vary depending on the arrangement of different ring structures within the pigment, including the aza, methyl, and benzyl groups (Calabrese et al. 2010). Moreover, the derivatives of AZP, identified from other resources demonstrated a range of pharmacological activities as enlisted in Table 1.

Flavins

The basic structure of the flavins, a group of yellow pigments, is composed of a tricyclic isoalloxazine ring, which is a nitrogen and oxygen-containing heterocycle. Riboflavin also known as vitamin B2 is the major microbial flavin with pigment characteristics and also the origin of all biologically active flavins. Two pentose phosphate pathway intermediates guanosine triphosphate (GTP) and ribulose-5-phosphate (Ru5P) function as the precursor for riboflavin

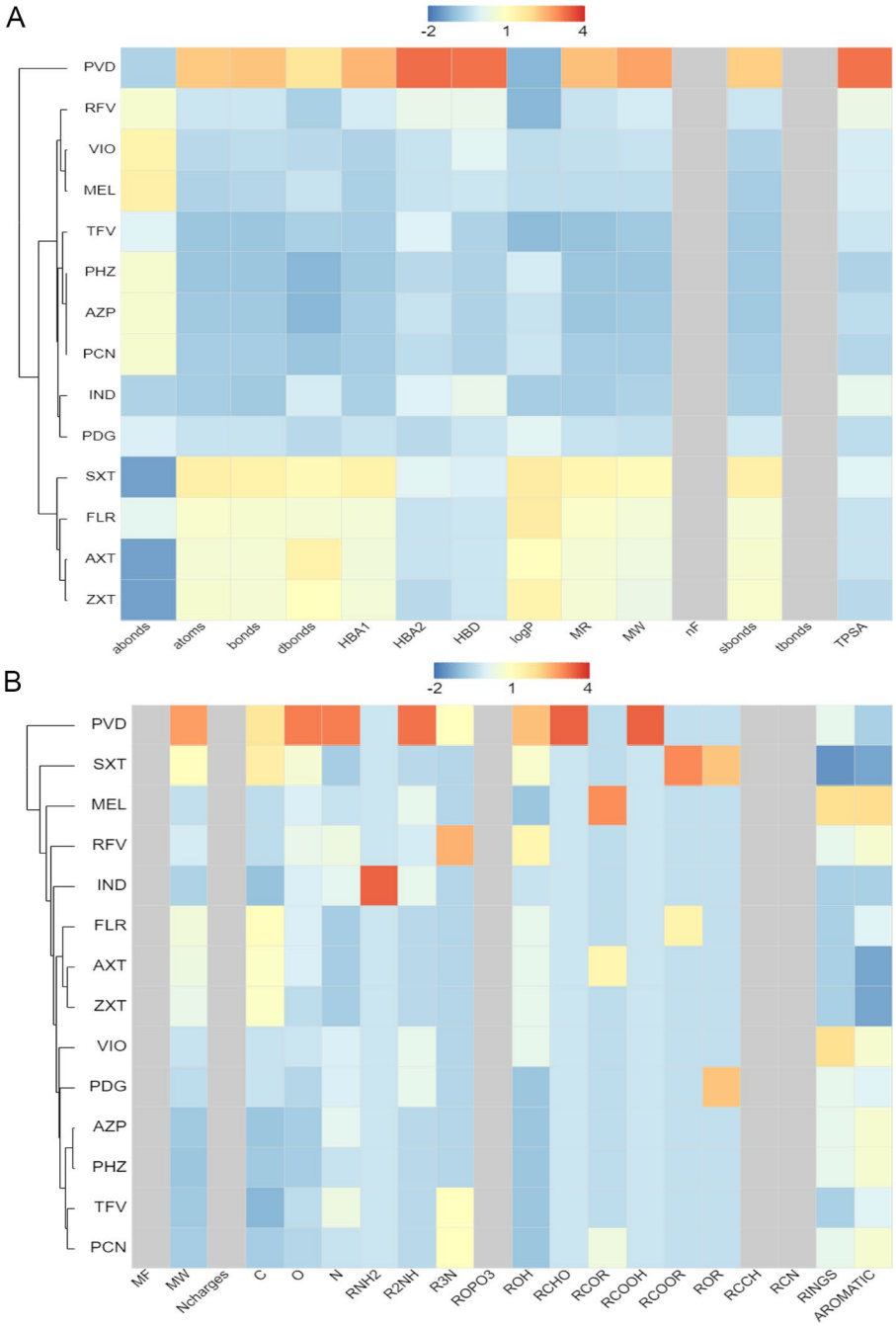

Fig. 3 Diversity of physicochemical property among bacterial pigments. Hierarchical clustering was performed for bacterial pigments on physicochemical analysis by ChemMine tools with average distance with OpenBabel (**A**) ChemimeR (**B**) descriptors. The colour code represent Z-scores

biosynthesis contributing to the pyrimidine part and heterocyclic ring portion of the isoalloxazine ring, respectively. GTP also provides two nitrogen atoms to the ring as well as a ribityl side chain. *Streptomyces* spp. and *Burkholderia* spp. have been reported to synthesize structural analogues, roseoflavin (RFV) (Fig. 2D) and toxoflavin (TFV) (Fig. 2E) respectively, which exert antimicrobial actions (Li et al. 2019; Mora-Lugo et al. 2019) (Table 1).

Pyocyanin

The bacterial genus *Pseudomonas* synthesizes a number of phenazine (PHZ) pigments (Fig. 2F) which are prominent virulence factors for the bacterium. These pigments play a crucial role in biofilm formation by *P. aeruginosa* by regulating gene expression (Fekete-Kertesz et al. 2024). Pyocyanin (PCN) is a nonfluorescent water-soluble blue pigment that changes color according to the oxidation status (Pierson and Pierson 2010). It is a nitrogen-containing PHZ and

the heterocyclic structure is composed of two N-methyl-1-hydroxyPHZ subunits (Goncalves and Vasconcelos 2021) (Fig. 2G). The synthesis begins from the precursor chorismic acid that is converted to an intermediate PHZ-1-carboxylic acid (PCA) involving seven enzymes from two operons (*phz1* and *phz2*). PCA is then converted to PCN either by *phzM-encoded* methyltransferase or *phzS-encoded* monooxygenase (Pierson and Pierson 2010). It stays in a zwitterionic form at neutral pH 7 hence appearing blue and also in the oxidized state under alkaline condition. On the contrary, the color turns red when in an acidic environment (Mudaliar and Bharath Prasad 2024). PCN is capable of showing antimicrobial action by modifying cellular oxidation state. Having both hydrophobic and hydrophilic moieties, PCN easily crosses the cell membrane and being a redox-active molecule kills the target cells by creating oxidative stress via the production of reactive oxygen species such as superoxide and hydrogen peroxide (Goncalves and Vasconcelos 2021). Being a redox-active molecule, PCN specifically exerts its action by oxidizing NADH and NADPH, consequently elevating cytosolic ROS levels and redox potential. This cascade of events results in diminished ATP production and a dysregulation of the reduced-to-oxidized glutathione (GSH/ GSSG) ratio (Hall et al. 2016). Thus PCN can act as an apoptosis inducer along with acting as an antibacterial, antifungal, and QS inhibitor as summarized in Table 1.

Pyoverdine

Pyoverdine (PVD) is a yellow fluorescent pigment secreted by *P. aeruginosa* that acts as a siderophore and helps the organism survive in iron-limiting condition by accumulating, mobilizing, and transporting iron into the cell (Dell'Anno et al. 2022). More than 100 variants of the dye are secreted by *Pseudomonas spp.* depicting considerable structural diversity (Ghssein and Ezzeddine 2022). The structure can be divided into three segments: a 6–12 amino acid long strain-specific peptide linked to a carboxyl *group*, a chromophore responsible for the fluorescence property, and a side chain that is connected to the nitrogen atom present at the C-3 position of the chromophore, which mostly are Krebs cycle intermediates or their derivatives (Schalk and Guillon 2013) (Fig. 2H). It is also a QS-regulator therefore controls its own synthesis apart from contributing to *Pseudomonas* pathogenesis (Dietrich et al. 2006). Non-ribosomal peptide synthetases (NRPSs) containing multiple modules are involved in the biosynthesis of PVD. Four gene products of the *pvd* locus, *pvdL*, *pvdI*, *pvdJ*, and *pvdD* have been identified for coding the NRPSs in PAO1 (Dell'Anno et al. 2022). Each module of the NRPS is responsible for the inclusion of individual amino acids to the peptide and bonding them with peptide linkages. The composition of the peptide varies among PVD secreted by different *Pseudomonas* strains and is attributed to the diverse substrate specificities of the NRPSs (Ghssein and Ezzeddine 2022). Incorporation of the chromophore moiety is also catalyzed by NRPSs which are synthesized in the cytoplasm by three enzymes PvdA, PvdF, and PvdH (Schalk and Guillon 2013). Apart from inducing biofilm formation by regulating QS pathways and exotoxin A production, PVD contributes towards overall nonresponsiveness of *P. aeruginosa* to antimicrobial therapies (Ullah et al. 2017). A recent screen by Vollenweider et al. (2023) with 320 natural *Pseudomonas* isolates against 12 human pathogens identified most potent PVD forms, which, in a concentration and iron-dependent manner, markedly dampened *Acinetobacter baumannii*, *K. pneumonia*, and *S. aureus*. PVD has also been reported as a potential candidate for delivering antimicrobial and/or anticancer agents to the target cells, biosensor for various molecules including pathogens and antibiotics, bioremediation, and phytostimulation (Dell'Anno et al. 2022) as summarized in Table 1.

Prodigiosin

Prodigiosine (PDG) is a member of the prodiginine family which is a red pigment and has a linear pyrrolyl dipyrromethene skeleton produced by a number of microbial groups including *Serratia*, *Phaeocystis*, *Microcystis*, *Vibrio*, *Hahella*, *Janthinobacterium*, and *Streptomyces* (Koksal Karayildirim et al. 2024; Mukhia et al. 2023). The structure of PDG consists of 2-methyl-3-pentyl-6-methoxyprodiginine which is a tri-pyrrole ring with red fluorescence and basic nature (Fig. 2I). Besides PDG, a few other members of the prodiginine family carry a linear chain like undecylPDG and few others are cyclic derivatives like streptorubin B, cyclononylPDG, cycloPDG, and butyl-meta-cycloheptylprodiginine (Darshan and Manonmani 2015; Williamson et al. 2006). The biosynthetic pathway of PDGs includes the condensation of a bipyrrole molecule 4-methoxy-2-2'-bipyrrole-5-carbaldehyde (MBC) with a monopyrrole. Condensation with monopyrrole 2-methyl-3-n-amyl-pyrrole (MAP) yields PDG whereas with 2-undecylpyrrole yields undecylPDG (Williamson et al. 2006). MBC biosynthesis involves successive combination of proline, malonyl- CoA and serine moieties whereas the monopyrrole portion is synthesized from different substrates and enzymes (Barreto et al. 2023). PDG can intercalate DNA and act as an inhibitor of topoisomerases I and II, thereby inducing DNA damage (Lins et al. 2015). It can compromise the integrity of the cytoplasmic membrane and bacterial outer membrane significantly (Danevcic et al. 2016) (Table 1). PDG has been reported to display an array of biological functions as antibacterial, anticancer, antiviral, antifungal, and antiparasitic

agent (Islan et al. 2022). Tai et al. (2024) have reported that it can successfully down-regulate the TGF-β signalling in cancer cell lines and hence could be a potential therapeutic agent. Due to its effectiveness against UV-spectrum, PDG exhibited excellent sun protection factor, hence it is of immense interest for cosmetic industries (Lin et al. 2020).

Violacein

Violacein (VIO) is an excellent example of alkaloid pigment. This violet pigment is a bisindole (Fig. 2J) that is biosynthesized by condensation of two tryptophan molecules by forming indolocarbazole (Choi et al. 2015b). An array of enzymes coded by the *vioABCDE* operon catalyzes the reactions. The bacterium *Chromobacterium violaceum* is recognized as the most prominent producer of this pigment. Multiple Gram-negative organisms that show considerable phylogenetic distances and found in different environmental niches like members of the genera *Janthinobacterium*, *Alteromonas*, *Collimonas*, *Duganella*, *Pseudoalteromonas*, *Massilia*, and *Iodobacter* have been reported to synthesize the pigment (Inan Bektas et al. 2023; Kumar et al. 2022). VIO production by the organisms has been related to biofilm formation and quorum sensing system regulates the production (Batista et al. 2024). VIO is known for its diverse biological effects like antimicrobial (Inan Bektas et al. 2023; Johnson et al. 2023), antitumor (De Leon et al. 2024), and anticancer (Dahlem et al. 2022) action. The major mechanisms underpinned are extensive membrane damage and mitochondrial membrane depolarization (Aruldass et al. 2018; Duran et al. 2022). Aruldass et al. (2018) reported efficient antibacterial action of VIO against *S. aureus* and MRSA strains by affecting the membrane integrity (Aruldass et al. 2018). In osteosarcoma and rhabdomyosarcoma cell lines, VIO has been reported to increase apoptosis in an oxidative stress-independent manner (Milosevic et al. 2023). de Souza Oliveira et al. (2022) reported induction of apoptotic effect on colorectal cancer cells, and in a similar study by Kim et al. (2021) on hepatocellular carcinoma cells. Antioxidant (Xu et al. 2022) and anti-parasitic (Bilsland et al. 2018) properties have also been assigned to VIO (Table 1). DeoxyVIO, a VIO derivative that lacks a hydroxyl group, is extremely cytotoxic as observed against HepG2 cells. Another derivative, oxyVIO, with an additional hydroxyl group, demonstrated potent anti-*Staphylococcal* activity (Marinelli et al. 2015).

Melanin

Melanin (MEL) is a heterogeneous natural pigment produced by a number of bacterial genera including *Proteus*, *Pseudomonas*, *Streptomyces*, and several fungi (Singh et al. 2021). *Streptomyces* is the most extensively studied for the production of the brown/black pigment as suggested by recent reports on *S. djakartensis* (El-Zawawy et al. 2024) and *S. nashvillensis* (Restaino et al. 2024). Bacterial MEL (Fig. 2K) is a heterogeneous mix of molecules and hence the structure is quite undefined. Fungi and bacteria start the synthesis process using precursors L-tyrosine or malonyl CoA (Carletti et al. 2014). By the action of tyrosinase, L-tyrosine is initially converted to L-3,4-dihydroxyphenylalanine (L-DOPA) and subsequently transformed through intermediates into L-3,4-dihydroxyphenylalanine (L-DOPA) which is the precursor for euMELs. PyoMEL is synthesized by converting L-tyrosine into the precursor homogenistic acid via an intermediate p-hydroxyphenylpyruvate (Pralea et al. 2019). Although the pyoMEL synthesis pathway has been studied in detail in *P. aeruginosa*, enzyme homologs have been reported in *Shewanella spp*, *Vibrio spp and Hypomonas spp.* (Plonka and Grabacka 2006). L-tyrosine and/or L-DOPA are oxidized in the presence of L-cystein, and pheoMEL is generated which is a red-yellow colored pigment. Malonyl CoA is used as precursor to produce the fungal alloMEL (Restaino et al. 2024). Through its polymeric structure, MEL can scavenge free radicals, toxic metal ions, and drugs (El-Naggar and Saber 2022). MEL has been assigned with multiple bioactive characteristics like anti-inflammatory, antioxidant, and antimicrobial properties (Furlani et al. 2024). The pigment functions as an effective UV screen as MEL derivatives have been reported to be present in the spore coat of *Bacillus thuringiensis* to protect against UV-mediated damage (Zhu et al. 2022). El-Zawawy et al. (2024) have recently reported that purified MEL pigment showed antibacterial action against multidrug-resistant strains of *S. aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *P. aeruginosa*. The biological significance of MEL is outlined in Table 1.

Indigoidine

A diverse group of bacteria produces a natural indigoidine (IND). The pigment 3′,3′-bipyridyl pigment (Fig. 2L) is formed through condensation of two molecules of L-glutamine catalyzed by a NRPS (Yu et al. 2013). *Dickeya dadantii* (formerly known as *Erwinia chrysanthemi*), a plant-pathogenic enterobacterium, is one of the prolific IND-producing bacteria (Reverchon et al. 2002). The pigment was also isolated from *Streptomyces*, *Phaeobacter*, *Arthrobacter*, *Corynebacterium insidiosum*, and other bacterial species. The bacteria can mitigate the growth of diverse microorganisms such as *E. coli* and *S. aureus*, and the fungal pathogen *Candida albicans* (Day et al. 2017). This pigment has wide applications in textile, food, and pharmaceutical industries (Zhao et al. 2024). Along with its antibiotic action, IND

displays antioxidant properties (Xu et al. 2015) as a free radical scavenger (Table 1) that allows phytopathogens to tolerate organic peroxides and superoxide generated by plant defence response.

Flexirubin

The yellow-orange pigment is synthesized primarily by *Chryseobacterium* and *Flexibacter* with *C. artocarpi*, *C. shigense*, *F. elegans*, *F. humi*, and *Cytophaga johnsonae* as profound producers (Kim et al. 2019; Mogadem et al. 2022). The pigment has quite a unique chemical build-up. It has an interlocking ring structure, some with four nitrogens (pyrrole) and others with one less nitrogen (pyridine) with alternating single and double bonds (Fig. 2M), which makes flexirubins (FLR) appear yellow or orange. This molecule is composed of aryl polyenes and terminal alkyl substitution with a fatty acid tail of ω-phenyl octanoic acid chromophore with two alkylated resorcinol with ester bonds (Bukowy et al. 2008). Synthesis of FLR, therefore, involves a complex enzyme cascade (Schoner et al. 2014). The biosynthesis of the pigment initiates with the generation of a polyene moiety through a type II fatty acid synthase-like pathway as suggested by the gene composition of the BGC for the pigment, which harbors genes of several putative β-ketoacyl synthases, reductases, dehydratases, and thioesterases. Deamination of L-tyrosine to 4CA and its activation for the polyketide synthase (PKS) machinery by adenylation through the putative acyl-CoA ligase is the next step. An aryl-octane moiety synthesized utilizing 4-coumaroyl-CoA by β-ketoacyl synthases and reductases to form aryl-octane moiety. A ligase joins the aryl octane with 2,5- dialkylresorcinol (DAR). A putative polysaccharide deacetylase, a phospholipid/glycerol acyltransferase, an outer membrane lipoprotein carrier, a glycosyltransferase, and a putative exporter are predicted to be involved in the export of the pigment to outer membrane (Schoner et al. 2014). Biological activities of FLR and FLR-derived molecules include prolific free radical scavenging and anti-inflammatory activity as enlisted in Table 1 (Mogadem et al. 2021).

Role of bacterial pigment in community-level interactions

Pigments produced by bacteria often play a crucial role in determining microbial community structures. Alongside, for pigment-producing bacterial pathogens like *P. aeruginosa* or *S. marcescens*, pigments act as immunomodulators and impact host microbiomes. The impact on the bacterial community is particularly evident for secreted pigments like PHZs, where the producer bacteria gain a fitness advantage against other bacteria in polymicrobial communities. In mixed cultures with *(A) baumannii* or *Enterococcus faecium*, PCN production has been shown to get elevated compared to pure culture condition of *P. aeruginosa* (Laliany et al. 2022). PHZs can promote survival in anoxic condition by acting as an alternate terminal electron acceptor, particularly in biofilm communities (Saunders et al. 2020), as a cross-species signaling molecule (Dietrich et al. 2006), expediting iron acquisition (Wang et al. 2011), and eliminating competitor Gram-positive co-occupants (Wang et al. 2011). A recent report by Jean-Pierre et al. (2023) demonstrated that in an in vivo model of polymicrobial infection, mimicking cystic fibrosis (CF) with *P. aeruginosa*, *S. aureus*, *Streptococcus sanguinis*, and *Prevotella melaninogenica*, enhanced PHZ production that allows *P. aeruginosa* to tolerate tobramycin. PHZs like PCN can interfere with the redox status of bacterial and fungal pathogens and thereby can interfere with the metabolic activity of the pathogen in a community while it precisely controls redox balance in *P. aeruginosa* to reduce intracellular oxidative stress (Jacob et al. 2011; Thalhammer and Newman 2023). Dietrich et al. (2008) demonstrated that redox-active PCN shapes community structure by activating the transcription factor SoxR in *Proteobacteria* and *Actinobacteria*. The complexity of the microbial community in the CF respiratory tract is determined by PHZ content in the community. Extracellular release of PCN can impede neighbouring *E. coli* and induce significant transcriptional reprogramming of *E. coli*, related to respiration and membrane biogenesis (Yuan et al. 2021). PCN has been projected as a major determinant of antimicrobial responsiveness in communities with non-PCN-producing opportunistic pathogens, such as *(B) cepacia* complex, where PCN induces tolerance against fluoroquinolone antibiotics (Meirelles et al. 2021). PCN is involved in QS-mutant cheater suppression by acting as a policing toxin to selectively block the growth of cheaters. In a dual-species community with *S. aureus*, *P. aeruginosa* can determine phage-*S. aureus* interaction by triggering prophage induction through PCN production (Jancheva and Bottcher 2021). Contradictory results considering the impact of PHZ in determining microbial community have been observed by Ibberson et al. (2022), in wound infection model for *P. aeruginosa* and *S. aureus* dual species infection community. In rat and pig gut microbiome PCN exposure has been reported to induce dysbiosis (Peng et al. 2022).

Apart from, toxic metabolites, competition for essential nutrients like iron are key in determining community structure. Pigments like PVD and pyochelin, major siderophores produced by *Pseudomonas*, manifest high iron-binding affinity ($>10^{30}$ M^{-1}) and determine species interaction in aquatic and terrestrial environments (Butaite et al. 2018). The iron-complexed PVD is imported into the cell by specific receptors. PVD shows an extraordinary

structural diversity with three major classes (I, II, and III) and more than 70 described variants that differ in their peptide backbone. pH, iron content, carbon concentration, and community diversity determine PVD production. PVD is secreted extracellularly, and following extracellular iron chelation, the bacterium will uptake the complex PVD-Fe^{3+} to acquire iron. PVD I is stored in the periplasmic space which prevents cellular uptake of other antimicrobial metal ions (Schalk and Guillon 2013). Inhibiting PVD by novel small molecules mitigates the pathogenesis of *P. aeruginosa* (Schalk and Guillon 2013). PVD also plays a crucial role in enriching the soil microbial community and inter-species social dynamics comprising the siderophore-producing *P. fluorescens* (O'Brien et al. 2023).

The antagonistic interaction of VIO with planktonic cells of *S. aureus* and *S. epidermidis* had been documented earlier (Batista et al. 2017; Dodou et al. 2017). Albeit only very few Gram-negative bacteria are susceptible to VIO, Gram-positive bacterial strains including *Staphylococcus*, *Bacillus*, and *Streptococcus* are sensitive to VIO (Choi et al. 2021). At a community level, VIO production is triggered by sub-lethal concentrations of hygromycin B and hygromycin A from *Streptomyces* sp. 2AW in soil (Lozano et al. 2020). Combining VIO with predatory bacteria *Bdellovibrio bacteriovorus* HD100, eventuated the elimination of polymicrobial community comprising Gram-negative bacteria like *Acinetobacter* and *Klebsiella* (Im et al. 2017). VIO has been reported to affect intestinal and skin microbiome. While in the gut microbiome of Wistar rats, at low VIO dose, *Bacillus* and *Clostridia* (Firmicutes) were found as dominant, at high doses, *Bacillus* followed by *Clostridia* and *Actinobacteria* were identified as the abundant members (Pauer et al. 2018).

Direct contact between *S. auerus* and *S. marcescens* has been demonstrated to be a prerequisite for the anti-Staphylococcal action of *S. marcescens* in dual-species culture. The interaction possibly involves the TypeVI secretion system (Lim et al. 2022). PDG can modulate microbial community structure and disease outcomes in amphibian skin infection models (Madison et al. 2019). In mouse models, administration of PDG beneficially altered the structure of cecum microbiota with enrichment of *Lactobacillus reuteri* and depletion of *Desulfovibrio* (Li et al. 2021). PDG derived from chromium-resistant *Serratia* sp was also demonstrated to modulate gut microbiota (Nie et al. 2023) in dextran sulfate sodium-induced colitis mice. In an elaborative study, Kim et al. (2023) explored the impact of PDG on six skin microorganisms available in commercially available skin microbiome mix. The acne vulgaris *Cutibacterium acnes* was evidenced to be highly susceptible to PDG with an alteration of global gene expression pattern. PDG-producing *S. marcescens*, when grown in dual-species biofilms outcompetes *A. baumannii*. Moreover, in co-culture condition, *S. marcescens* enhanced the susceptibility of *A. baumannii* against ciprofloxacin (Acharya et al. 2023). In one of their recent reports, Heu et al. (2021) highlighted the possible impact of PDG on the microbiota of the insect vector *Aedes aegypti*.

The carotenoids in *S. auerus*, have been shown to influence membrane structure and physicochemical properties by increasing the order of the fatty acyl chains. Such altered membrane structure prevents the insertion of a number of antimicrobial peptides including daptomycin and magainin, and thereby prevents pore formation (Manrique-Moreno et al. 2022). STX also fosters fitness by preventing oxidative stress which renders survival in wounds and delays the healing of diabetic wounds as revealed recently by Campbell et al. (2023).

Bacterial pigment in the pathogenicity of the producer

Though a number of pigment-producing bacteria are known as opportunistic pathogens for humans, except PCN and PVD in *P. aeruginosa*, and MEL produced by a *Vibrio cholerae* mutant, no other bacterial pigments have directly been associated with virulence. Strains of *S. marcescens* have been reported as enteric pathogen in human (Murdoch et al. 2011). Several strains of the bacteria can infect other vertebrates in insects and insect larvae (Li et al. 2023b; Shikov et al. 2023). Though PDG elicits immunomodulatory function as observed in in vivo infection models, it does not affect virulence of the bacteria, as demonstrated in insect infection models (Zhou et al. 2016). *C. violaceum* is an opportunistic pathogen that causes ocular infection in humans (Venkatramanan and Nalini 2024). Another VIO-producing bacteria, *J. lividum*, emerged as a pathogen for aquaculture, and caused severe mortality of rainbow trout *Oncorhynchus mykiss* (Oh et al. 2019). Though VIO demonstrates modest cytotoxicity against some mammalian cell lines, it has not been assigned as a virulence factor for the producer (Duran et al. 2021). MEL synthesis has been associated with virulence for a variety of pathogenic fungi by mitigating the efficacy of antimicrobials and by its influence on host immune response (Nosanchuk and Casadevall 2006). For a MEL-producing *V. cholerae* mutant elevated production of toxin-coregulated pilli (TCP), a major virulence factor, was observed. The mutant also demonstrated improved colonization to intestinal tissue of infant mice suggesting possible involvement of MEL production with bacterial pathogenicity (Valeru et al. 2009).

PCN is a QS-regulated virulence factor for *P. aeruginosa*, released through into the infection loci by a type II secretion system and impacts pathophysiology of cystic fibrosis (Caldwell et al. 2009). PCN can disrupt redox homeostasis

in mammalian cells with reduction in cellular ATP generation, NAD/ NADH ratio, and level of reduced glutathione (O'Malley et al. 2004). In contrast to other bacterial pigments that act as antioxidants, PCN induces the generation of ROS and perturbs mitochondrial metabolism (Hall et al. 2016). ROS induction induces MUC2 and MUC5AC expression, both encoding for mucin secretion (Jeffries et al. 2016). PCN activates MAPK signalling, particularly ERK1/2, p38, and JNK signalling (Chai et al. 2014; Hall et al. 2016). PCN can act as an immunomodulator to trigger proinflammatory response through elevated IL-2, IL-6, and prostaglandin E2 production, which eventuates T- and B- lymphocyte proliferation (Jablonska et al. 2023). It can also induce cellular senescence and therefore impair tissue regeneration in *P. aeruginosa*-infected wounds (Muller et al. 2009). PCN can induce dysbiosis of microbiota and damage to the gut mucosal layer (Peng et al. 2022). Moreover, with its potential to permeate the blood-brain barrier, it can influence cognitive function in the murine model (Rashid et al. 2022). Overall, PCN can result in neurotoxicity, hepatotoxicity, and cognitive impairment (Mudaliar and Bharath Prasad 2024).

The siderophore pigments produced by *P. aeruginosa* are also associated with virulence of the pathogen. PVD can directly kill *C. elegans* even in the absence of the bacteria (Kang et al. 2018; Kirienko et al. 2015). It binds with iron in 1:1 stoichiometry and due to its high affinity for Fe^{3+}, it can outcompete host transferrin (Kang et al. 2018). The ferri-PVD complex is recognized by the receptor FpvA which triggers the alternative sigma factor PvdS. PvdS activated expression of the BGC for PVD (Cornelis et al. 2023). Such a positive loop allows PVD generation until Fe^{3+} requirement of the bacteria is satisfied (Cornelis et al. 2009). Accumulation of PVD in extrapharyngeal tissues of *C. elegans* and lung tissues of mice directly correlates with cytotoxicity. Specific PVD inhibitors like gallium, fluoropyrimidines, and LK11 can considerably ameliorate cell survival (Kang et al. 2019).

4,4'-diaponeuresporenoic acid and STX, two major carotenoids produced by *S. aureus*, have been detected to enhance virulence and fitness of the pathogen possibly by providing protection against host innate immune system (Xue et al. 2019). STX biosynthetic pathways have been highlighted as a prospective target for designing anti-virulent drugs (Cueno and Imai 2018). However, an extensive genetic and phenotypic profiling for pigmented and non-pigmented *S. aureus* by Zhang et al. (2018), suggested no significant difference in virulence between the two types of strains.

Biosynthetic gene clusters for bacterial pigments

The majority of the pigments are synthesized through defined enzymatic reaction cascades. The enzymes are encoded by genes that are part of a BGC, expression of which is precisely modulated by the regulatory circuits. In this segment composition and regulation of BGCs for seven major bacterial pigments are discussed. Alongside, use of the identified BGCs in synthetic biology for improved production of the pigments are mentioned.

BGC for carotenoids

Defined biosynthetic gene clusters (BGC) linked to carotenoid biosynthesis have been identified in a spectrum of bacteria. Overtly, the BGCs are categorized into three different gene clusters the first one is organized in *crtEXYIBZ* order. The second one projects an organization of *crtE-idi-crtXY-IBZ*, and the third one contains *crtE-idi-crtYIBZ* (Fig. 4A). Albeit the genes and organizations are similar in different bacteria, a diverse array of carotenoids can be synthesized by the bacteria (Zhang et al. 2012). Each of the gene products participates in conversion of isopentenyl pyrophosphate (IPP) to a specific carotenoid. For efficient production of carotenoids in *E. coli* Bl21(DE3) metabolic engineering was performed by Yang et al. (2014). A combination of *crt* genes from *Erwinia herbicola* with geranyl diphosphate synthase2 from *Abies grandis* generated a high carotenoid-yielding strain of *E. coli*. A high-yielding ZXT mono or di glycoside synthesizing *E. coli* strain could be developed by expressing seven *crt* genes of *Cronobacter sakazakii* (Zhang et al. 2014). A high amount of accumulation of β-carotene was achieved by expressing *crtE*E, *crtYB* and *crt* I from *Xanthophyllomyces dendrorhous* using marker-less genome editing CRISPR/Cas9 technology (Lopez et al. 2020).

VIO Cluster

A single operon comprising five genes *vioABCDE* constitutes the BGC for VIO production via shikimate pathway from L-tryptophan (Xu et al. 2022) (Fig. 4B). Each of the gene products participates in independent reactions of the pathway. The operon is regulated by the CviI-CviR QS system (Fig. 5A). Expression of the genes and production of VIO, particularly from the Cv206 strain, has long been implemented in screening and identification of inhibitors of the AHL dependent QS system. Cv206, is an AHL-deficient mutant of *C. violaceum*. Upon AHL induction, QS modulation can be estimated quantitatively by determining VIO accumulation (Duran et al. 2016). A visualization reporter system based on Gram-negative bacterial acyl-homoserine lactone quorum-sensing (VRS-bAHL) was constructed

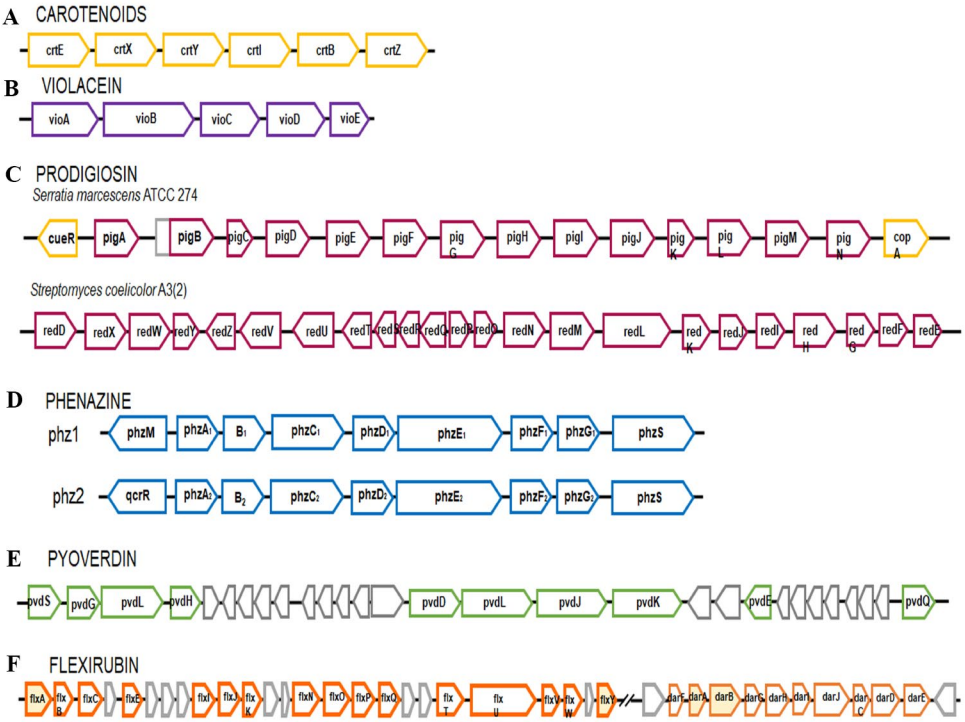

Fig. 4 Organization of bacterial pigment biosynthetic gene cluster. The organization of biosynthetic gene clusters for (**A**) carotenoids, (**B**) violacein, (**C**) prodigiosin, (**D**) phenazine, (**E**) pyoverdin, and (**F**) flexirubin is shown

exploiting the operon. The VRS-bAHL can be implemented in profiling gene expression in *Streptomyces* (Liu et al. 2022). Robust VIO-producing *C. violaceum* strains were developed by altering the ribosome binding site (RBS) of the VIO operon. Such altered cassettes were cloned and expressed in *E. coli* and *Corynebacterium glutamicum* to attain higher yield/ titre for industrial production (Zhang et al. 2021). Other heterologous hosts like the oleaginous yeast *Yarrowia lipolytica*, were used to express the genes of VIO operon through three different promoters and were assembled to a combinatorial pathway library by golden gate cloning (Nemer et al. 2023).

PDG gene cluster

In *Serratia*, the PDG gene cluster is organized in a defined order starting with *pigA* gene and ending with *pigM* gene (Fig. 4C). A certain group of the gene products including *pigD*, *pigE*, and *pigB* are engaged in synthesizing 2-methyl-3-n-amyl-pyrrole (MAP) and another group comprising *pigA*, *pigF*, *pigG*, *pigH*, *pigI*, *pigJ*, pig*L*, *pigM*, and *pigN* yields 4-methoxy-2,2'-bipyrrole-5-carbaldehyde (MBC). PigC condenses the two products at the terminal step of PDG biosynthesis (Williamson et al. 2006). Except for such conserved genes in PDG-producing *Serratia* strains, in some strains, an additional gene *pigO* is harboured in the PDG cluster (Jia et al. 2021). The orthologues of PDG biosynthetic genes in *S. coelicolor* are encoded by distributing 23 genes in four clusters. Two of the 23 genes in the cluster (*redD* and *Z*) are pathway-specific regulators, six are assigned to 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde biosynthesis (*redW, O, M, L, K,* and *I*), eight are assigned to 2-undecylpyrrole biosynthesis (*redX, R, Q, P, N, H, G*, and *F*), and two are assigned as housekeeping genes (*redU* and *J*) (Fig. 4C). Various QS and two-component system genes are attributed to regulation of PDG gene cluster. Among the QS systems, SmaI/SmaR and SpnI/SpnR were reported to control PDG production in *Serratia* spp. strains. Four two-component systems including PigQ/PigW, PhoB/PhoR, RssB/RssA, and EepR/EepS can regulate the synthesis of PDG (Jia et al. 2021). OmpR and PsrA were identified as transcriptional activators for PDG genes in *S. marcescens* JNB5-1 through a Tn5 mutagenesis screen. A robust PDG-producing strain was constructed by cloning the transcriptional activation under a strong constitutive promoter P17 to attain a metabolically engineered strain (PG06) (Pan et al. 2022b). Robust PDG-producing *S. coelicolor* strain was generated by concerted metabolic engineering by (1) inactivation of a gene for repressor (*ohkA*), (2) knocking out the actinorhodin (ACT) and calcium-dependent antibiotic (CDA) BGCs, and (3) multi-copy chromosomal integration of the *red* BGC. Such a strategy resulted in a strain of ~12-fold improvement for PDG production (Liu et al. 2017). Similar to PCN, heterologous expression of PDG BGC from *S. marcescens* ATCC274 has been accomplished in *Pseudomonas putida* (Cook et al. 2021).

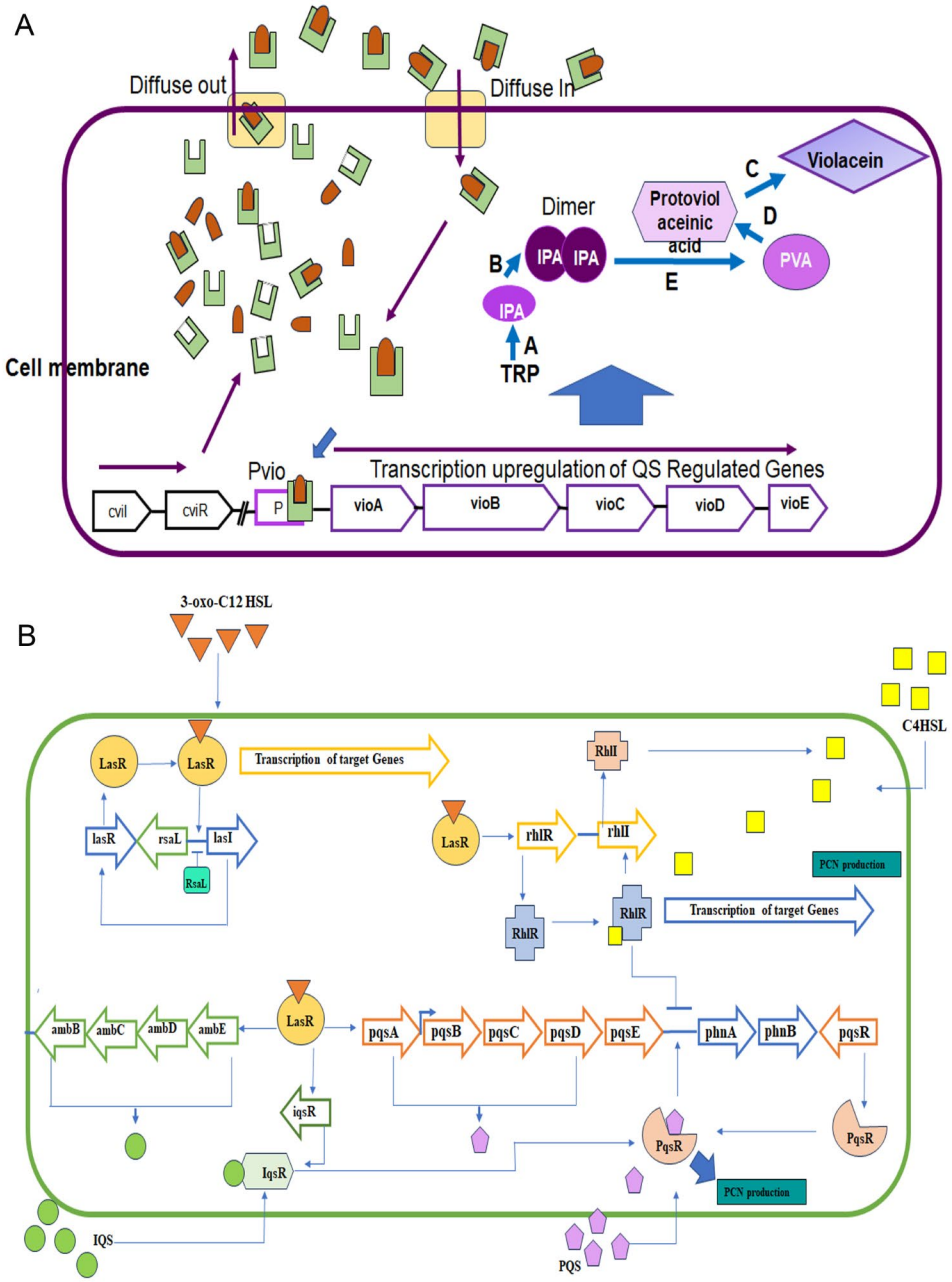

Fig. 5 Quorum sensing mediated regulation of bacterial pigment production. AHL mediated QS system regulating expression of *VIO* gene-cluster in *C. violaceum* depends on CviI-CviR system (**A**). PCN production from *P. aeruginosa* is regulated by a complex network of three QS system, the AHL dependent LasI-LasR, RhlI-RhlR, and the quinone dependent PQS system

PCN gene cluster

The conversion of chorismate to PHZ involves seven enzymes that are conserved among PHZ producers. In *P. aeruginosa*, two independent homologous gene clusters, *phzA1B1C1D1E1F1G1* (*phz1*) and *phzA2B2C2D2E2F2G2* (*phz2*) (Fig. 4D) are associated with PHZ production as revealed by Mavrodi et al. (2001). The gene products mediate the conversion of chorismate to PHZ-1-carboxylic acid (PCA) and PHZ-1,6-dicarboxylic acid (PDC). The product of *phzM* and *phzS* in combination converts PCA to PCN. In the bacteria, there are two QS systems, namely *las* system and *rhl* system. A third signalling system, integrated with the two QS systems, quinolone signalling system (pqs) characteristic also regulates PCN synthesis. While the PHZ operon is directly activated by PqsR and RhlR, the LasR and IqsR indirectly affect the activation by modulating PqsR and RhlR (Abdelaziz et al. 2023) (Fig. 5B). In order to achieve PHZ production in *E. coli*, da Silva et al. (2021) implemented a construct by cloning nine genes of PCN pathway in ePathBrick vectors platform. Optimal PCN production from each strain were further evaluated by altering aeration conditions in bioelectrochemical systems. Heterologous synthesis of PCN has been optimized in non-pathogenic *P. putida*

KT2440 earlier. Here Askitosari et al. (2019) expressed one PHZ operon from PAO1 and two PHZ operon from PA14 and combined each with simultaneous expression of *phzM* and *phzS* to achieve PCN generation.

PVD gene cluster

The gene required for biosynthesis of PVD is localized in the *pvd* locus, which comprises larger genes like *pvdL*, *pvdI*, *pvdJ*, and *pvdD* encoding diverse groups of enzymes linked to NRPSs. Gene *pvdA*, *pvdF*, and *pvdH* produces chromophores and other groups (Fig. 4E). A number of substitutions in different domains of PvdJ and PvdD rendered synthesis of novel modified PVD (Puja et al. 2023).

IND gene cluster

The IND biosynthetic gene cluster was initially characterized from *D. dadantii*. A single module NRPS, catalyses the condensation reaction of L-glutamine to yield IND (Kong et al. 2019). The transcription PecS regulates the synthesis of indigoidine by genes *indA*, *indB*, and *indC* (Zhao et al. 2024). The IND synthase gene was engineered for synthetic biology purposes, for developing chemogenomic reporter system in *E. coli* as well as mammalian cells, including human stem cells (Muller et al. 2012; Xie et al. 2017). Exploiting a dual expression strategy Nanjaraj Urs et al. (2019), recently generated a transgenic blue rose by synthesis of IND. High-level production of IND in *C. glutamicum* was accomplished by heterologous expression of IND synthetase from *Streptomyces lavendulae* (Ghiffary et al. 2021).

FLR BGC

A hypothesized biosynthetic pathway suggests the conversion of resorcinol and aryl polyene into FLR-type pigments. Responsible genes for pigment production are *darA* and *darB* genes (Fig. 4F), which are part of a large group of gene clusters from Fjoh_1080, Fjoh_1084, Fjoh_1095, Fjoh_1097, Fjoh_1098, Fjoh_1100, Fjoh_1108 (McBride et al. 2009). Presence of such gene clusters and identification of typical orthologues were possible from data generated through genomic and metagenomic analysis in other studies including genome analysis of the bacteria *C. pinensis* (Keller-Costa et al. 2021; Schoner et al. 2014; Vacheron et al. 2017).

Biomedical applications of bacterial pigments

The arising problems like multidrug resistance for pathogenic infections, resistance against existing chemotherapeutics in cancer, healthcare expenses, and the irreversible impact post-treatment on the patients are major concerns warranting the quest for novel drugs. Bacterial pigments have recently been explored as a prospective alternatives to tackle some major health concerns of present era. A snapshot of therapeutic potential of the pigments is portrayed in Fig. 6A.

Anti-bacterial

AZP shows antibacterial activity against *Pseudomonas fragi*, *P. putida*, *P. pyocyanae*, *V. cholerae*, *E. coli*, *S. aureus*, *Salmonella paratyphi*, *Bacillus cereus*, *Mycobacterium smegmetis*, *M. phlei* (Gupta et al. 1970). A number of studies consistently showed antibacterial activity of MEL against pathogenic species of *Bacillus* including *B. cereus* and *Pseudomonas* including *P. aeruginosa* and even on *E. coli*, *K. pneumoniae* and *S. aureus* (Ghattavi et al. 2022; Polapally et al. 2022; Singh et al. 2021). PDG is observed to be effective even against members of the ESKCAPE group of pathogens (Acharya et al. 2023; Lapenda et al. 2015). PDG inhibits staphylococcal infection by disrupting cell membranes, leading to cell lysis and death (Koksal Karayildirim et al. 2024). Recently profound anti-adherence activity of PDG was reported (Diken-Gur 2024). An extensive transcriptomic analysis of PDG treatment (Liu et al. 2024a) indicated cell wall synthesis, cell membrane, and biofilm formation impairment as possible mechanisms. VIO is efficient in inhibiting Gram-positive bacteria like *E. faecalis*, *S. aureus* at extremely low concentrations but are ineffective even in higher concentrations against some Gram negatives like *Morganella morganii*, *K. pneumoniae*, and *Proteus mirabilis* (Mudaliar and Bharath Prasad 2024). VIO exerts antimycobacterial effects against *M. tuberculosis* (Duran et al. 2016, 2021; Inan Bektas et al. 2023). With its iron (Fe) scavenging siderophore action, PVD demonstrated concentration-dependent and iron-limited suppression of the growth of the bacteria. PVD also possesses antimicrobial activity against bacteria like *Vibrio sp.*, and *Xanthomonas oryzae* (Chen et al. 2016; Zhang et al. 2016). A recent screen identified 12 effective PVD derivatives; exerting inhibitory effects on *A. baumannii*, *K. pneumoniae*, and *S. aureus* in a concentration- and iron-dependent manner (Vollenweider et al. 2023). PCN exhibits a robust antibacterial effect by disrupting the microbial cell membrane and thereby compromising the function of the respiratory chain (Jayaseelan et al. 2014). PCN facilitates cell lysis by increased ROS production (Abdelaziz et al. 2023). Collectively, these multifaceted antimicrobial properties position PCN as a critical factor in the persistence and proliferation of *P. aeruginosa* within various environments. PHZs have been shown to accept metabolic electrons and facilitate redox balancing, ATP production, and survival in *P. aeruginosa* (Glasser et

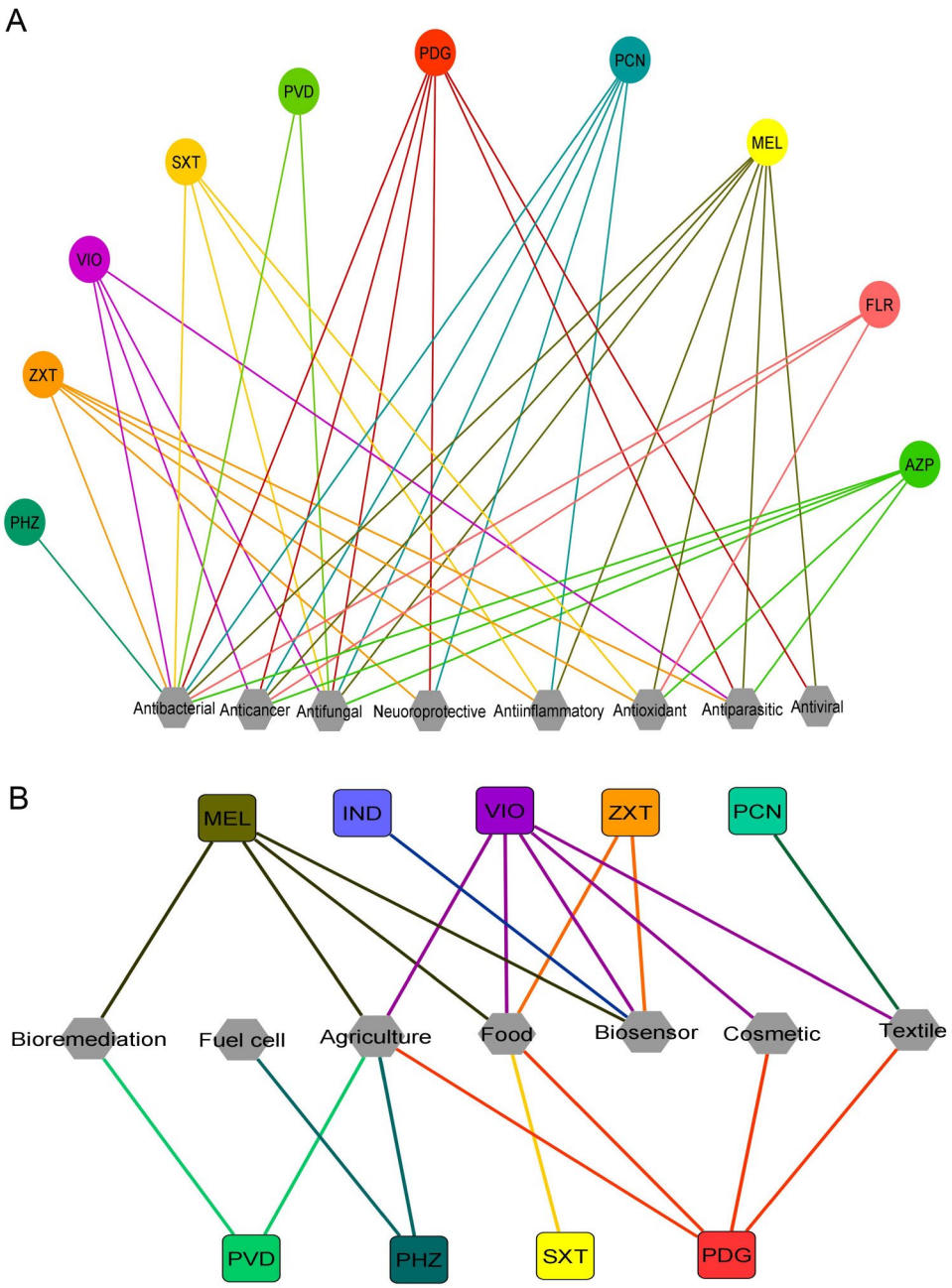

Fig. 6 Networks highlighting application for bacterial pigment. (**A**) Nondirectional network demonstrating various therapeutic applications of bacterial pigments are demonstrated with therapeutic application as source node and the pigments as the target node. (**B**) Similarly a nondirectional network depicting various industrial applications of the pigments are projected. The networks were generated using Cytoscape with a network file generated from the data available in the literature

al. 2014; Schiessl et al. 2019). Eventuating restoration of electron transport chain (ETC), like fumarate, it can potentially revert metabolic dormancy in persisters. In fact, back in 2018, halogenated derivatives of PHZ were shown to act as antipersister against *M. tuberculosis* and MRSA (Garrison et al. 2018). SXT pigment has been evidenced to possess antibacterial activity against pathogenic strains of *E. coli* (Barretto and Vootla 2018). FLR, a yellow-orange pigment from *Flavobacterium* sp. Ant342 (F-YOP,) was projected as a prospective compound for chemotherapy of tuberculosis (Agarwal et al. 2023).

Anti-protozoan

AZP exhibits significant anti-protozoan activity against various protozoan parasites, including *Plasmodium*, *Trypanosoma*, and *Leishmania* species. The mechanisms underlying their anti-protozoan effects involve disruption of essential metabolic pathways, inhibition of key enzymes vital for parasite survival, and interference with protozoan membrane integrity. Additionally, AZPs have been shown to possess low cytotoxicity towards mammalian cells, highlighting their potential as safe and effective anti-protozoan agents

(Tahghighi et al. 2018). Activity of PDG against *Plasmodium falciparum* indicated that PDG exhibits antiparasitic activity which inhibits the growth and proliferation of malaria parasites (Castro 1967) and *Leishmania sp.* (Moraes et al. 2008). VIO displays anti-protozoan, anti-helminthic, and anti-parasitic activity against various pathogens such as *Plasmodium* spp., *Leishmania* spp., and *Trypanosoma* spp. (Duran et al. 2016). ZXT has potential activity against helminthiasis caused by nematodes, platyhelminths, and anti-malarial activity of the carotenoid was also reported (Bouyahya et al. 2021).

Anti-fungal

Limited data suggest potential antifungal activity of AZPs against clinically relevant fungi such as *C. albicans* and *Cryptococcus neoformans* (Gupta et al. 1970; Zhao et al. 2018). MEL plays a critical role in the virulence of fungal pathogens like *C. neoformans*. Fungi produce MEL, a dark pigment, which significantly contributes to their ability to resist the body's immune defenses and antifungal medications. However MEL demonstrates antifungal properties against *Trichophyton simii*, and *T. rubrum* (Arun et al. 2015). VIO exhibits effectiveness as an antifungal compound, particularly against the fungi *Rosellinia necatrix*, *Rhizopus arrhizus*, and *C. aurius* (Duran et al. 2022). PDG demonstrated antifungal activity against plant pathogenic fungi (Islan et al. 2022). Some antifungal activity can be observed by PVD on fungi like *Piricularia oryzae*, *Botrytis cinerea*, and *A. fumigatus* (Liu et al. 2021). Antagonistic activity is observed against some fungi and phytopathogens. Additionally, PCN demonstrates potent antifungal activity by interfering with the electron transport chain within fungal cells. The pigment also showed antifungal actions against *Aspergillus spp*, *Candida spp.*, and *C. neoformans* (Kaur et al. 2015; Sass et al. 2021; Shouman et al. 2023) and was also found to be effective in treating *T. rubrum* infection in human (El-Zawawy and Ali 2016). Antifungal activity of SXT against *C. albicans* has also been reported (Barretto and Vootla 2018).

Anti-viral

The mechanisms underlying MEL's antiviral activity are multifaceted and may involve direct interaction with viral particles (El-Naggar and Saber 2022). MEL exhibits broad-spectrum antiviral activity, hindering various stages of the viral lifecycle. Studies suggest that it disrupts viral entry, replication, and maturation. Additionally, MEL possesses immunomodulatory properties, bolstering the host's immune response against viral infections. The mechanisms underlying this antiviral activity are multifaceted and may involve interference with viral binding to host cells, and the induction of antiviral cytokines. Antiviral properties can be observed against human immunodeficiency virus (HIV), SARSCoV2, and herpes simplex virus (Abd-El-Aziz et al. 2024; Montefiori and Zhou 1991). VIO also exhibits antiviral activity against herpes simplex virus and poliovirus (Duran et al. 2016). Suryawanshi et al. (2020) reported anti-HSV activity of PDG through inhibition of prosurvival NF-κB and Akt signalling pathways and eventual death of infected cells.

Anti-cancer

AZPs exhibit activity against multiple signaling cascades implicated in cancer progression and can target the leukemic cells K562 (Lucio et al. 2011). MEL pigment shows anticancer properties against skin cancer cell lines and anti-tumor properties by controlling tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6) (El-Obeid et al. 2006), and vascular endothelial growth factor (VEGF) synthesis by monocytes (El-Naggar and El-Ewasy 2017). MEL is a potential singlet oxygen scavenger and hence shows antioxidant properties (Ju et al. 2011). MEL has a unique skin wound healing and regeneration capacity, and coated nano-hydroxyapatite formulation is used for healing (Furlani et al. 2024). It also poses an anti-hemolytic effect by neutralizing free radicals from erythrocytes membrane and cell lysis. Across species, MEL acts as a protector against radiation-induced and free radical stress (Kordjazi et al. 2024) and has also been reported to have anticancer effects (El-Zawawy et al. 2024). PDG has low cytotoxicity and can show anticancer and antitumor activity by programmed cell death system for cancer cell line and inhibition of cell cycle (Anwar et al. 2022). VIO possesses antitumoral and anti-cancer properties, and can function as an immunomodulator. VIO prompts myeloid leukemia cells and TF1 leukemia cells to program cell death. In breast cancer cells VIO showed a non-canonical mechanism of cell death. VIO also acts on glioblastoma and lung cancer cell lines and reduces metastasis and glioblastoma migration (Duran et al. 2016; Mehta et al. 2015; Queiroz et al. 2012). PCN demonstrated significant cytotoxic effects on human pancreatic cancer cell line PANC-1 cells, triggering both apoptotic and necrotic pathways. Subsequent in vivo studies employing animal models are imperative to assess its efficacy as a potential anti-tumor therapy (Moayedi et al. 2018). PCN suppresses the cell proliferation of human melanoma cells SK-MEL-30 and human colon cancer cells HT-29. PCN shows anti-cancer properties against human breast cancer cell line MCF-7, human hepatoma cell HepG2, and colorectal carcinoma HCT-116 (Zhao et al. 2014). FLR produced by *C. artocarpi* CECT8497 demonstrated a proapoptotic effect against

human breast cancer cell line MCF7. The pigment also demonstrated anti-cancer activity for 7,12-dimethylbenz(a) anthracene (DMBA) induced breast cancer in the Sprague Dawley rat model (Venil et al. 2016, 2021). STX isolated from *S. gallinarum* against Dalton's lymphoma ascites, Ehrlich ascites carcinoma, adenocarcinomic human alveolar basal epithelial cells, and *Mus musculus* skin melanoma (B16F10) (Barretto and Vootla 2018).

Antioxidant

The antioxidant potential of AZPs has been evaluated using established assays, such as DPPH radical scavenging and ferric-reducing antioxidant power (FRAP) assays. These compounds also inhibit lipid peroxidation. This dual mechanism mitigates cellular damage caused by oxidative stress. Furthermore, AZPs appear to up-regulate the activity of endogenous antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT), resulting in enhanced overall antioxidant capacity (Girgis et al. 2018). MEL showed oxygen-scavenging properties and metal-chelating activity, hence having high antioxidant properties (Manivasagan et al. 2013). IND has high antibiotic activity with antioxidant properties (Cude et al. 2012; Xu et al. 2015). The structure of the pigment suggests hydroxyl-radical-scavenging properties (Ali et al. 2013). ZXT protects from reactive oxygen intoxication and hence is an effective antioxidant and plays a major role in condensing central fovea of retina to protect it from light-initiated oxidative damage and macular degeneration (Landrum and Bone 2001; Widomska et al. 2020). Antioxidant property is evaluated to be high in an FLR-type pigment from *C. artocarpi* CECT 8497 by a number of standard antioxidant assay. The pigment demonstrated scavenging of superoxide, hydroxyl free radicals, and H_2O_2, along with mitigation of lipid peroxidation. FLR can bind directly with SOD and modulate its activity (Amorim et al. 2022a; Mogadem et al. 2021).

Anti-inflammatory

MEL has some biological applications such as anti-tumoral, reduced ROS production oxidative liver damage, and DNA damage (Tong et al. 2023). Other utilities of MEL are that it can be used in implantable devices like biosensors, and fluorescent probes and as hydrogel in photothermal therapy (Kim et al. 2020; Vahidzadeh et al. 2018). MEL has been suggested to act as a free radical scavenger, thereby mitigating oxidative stress often associated with inflammatory processes. Different proinflammatory cytokine levels decrease with VIO administration and different growth factors like endothelial, hepatocyte, epidermal, and hepatocyte increase, leading to major activity in mucin secretion and ulcer healing (Antonisamy et al. 2014). PCN exerts its cytotoxic effects through the generation of ROS. While ROS are endogenously produced during cellular respiration, their excessive accumulation triggers oxidative stress. This disrupts cellular homeostasis, compromising metabolic processes and ultimately leading to cell death. PCN specifically mediates its toxicity by oxidizing NADH and NADPH, consequently elevating cytosolic ROS levels and redox potential. This cascade of events results in diminished ATP production and a dysregulation of the reduced-to-oxidized glutathione ratio. Notably, PCN has been implicated in the pathogenesis of various physiological systems, including the urological, nervous, hepatic, and vascular systems (Hall et al. 2016). The impact of PCN is demonstrated to be dose-dependent. At lower concentrations, PCN exhibits immunomodulatory properties, stimulating the proliferation of T and B lymphocytes, enhancing IL-2 production, and promoting B cell differentiation (Ulmer et al. 1990). Conversely, in vivo studies demonstrated that PCN accelerates neutrophil apoptosis, thereby mitigating local inflammation and potentially favouring *P. aeruginosa* persistence during infection (Allen et al. 2005). ZXT acts as an anticancer and anti-inflammatory due to its antioxidant properties (Raman et al. 2024). SXT is a carotenoid pigment that reduces the activity of ROS, and thereby increases neutrophil resistance and virulence in the host for the bacteria (Xue et al. 2019). FLR demonstrated hepatoprotective effects to ameliorate oxidative stress, steatosis, ballooning degeneration, leukocytic infiltration, and necrosis (Mogadem et al. 2022).

Neuroprotection

The role of MEL in the central nervous system (CNS) has gained interest, especially in the context of neurodegenerative diseases. The potential neuroprotective effects stem from its proposed functions. One key function is its ability to act as a free radical scavenger. By neutralizing free radicals, MEL helps reduce oxidative stress, a cellular condition implicated in neuronal damage and neurodegeneration. Furthermore, MEL might play a role in regulating neurotransmitter levels and synaptic function, both crucial for maintaining healthy and functional neurons (Petrosyan 2015; Petrosyan et al. 2012; Tang et al. 2022). The tripyrrole, PDG shows promise as a neuroprotectant. Studies suggest it improves chronic unpredictable mild stress (CUMS)-induced depression-like behaviour in rats (Albrakati et al. 2021). Beyond its antioxidant effects, PDG also combats inflammation in the brain, potentially aiding neurodegenerative diseases. PDG further protects neurons by interfering with cell death pathways, making it a strong candidate for the treatment of neurodegenerative diseases. Its multifaceted approach includes boosting natural antioxidants and

lowering harmful molecules (ROS) in neurons, further protecting them from damage (Salem et al. 2022). Furthermore, PDG modulates neuroinflammatory responses by inhibiting the NF-κB signalling pathway and down-regulating the expression of pro-inflammatory cytokines, thereby creating a neuroprotective milieu. Because of its well-known bioactive qualities, PDG from *S. marcescens* has been proposed as a potential medication for the treatment of neurodegenerative along with cancerous disorders as summarized by Tunca Koyun et al. (2022). Acetylcholine esterase (AChE) enzyme activity responsible for neurodegenerative diseases can be inhibited using PCN (Mudaliar and Bharath Prasad 2024). Even neural injury caused by AChE induced by H_2O_2 can be protected by PCN (Ibberson et al. 2022). ZXT reduces Alzheimer's disease and neural disorders related to visualization and auditory signals (Wong et al. 2017). Even regular ZXT in a diet reduces pro-inflammatory hormones, anxiety, depression, and diabetics (Stringham et al. 2019).

Bacterial pigment and antibiotic interaction

MEL can bind to certain antibiotics, potentially affecting their distribution and bioavailability within the body. This interaction may consequently influence the pharmacokinetics and pharmacodynamics of the antibiotics. MEL can bind to fluoroquinolones like ciprofloxacin and moxifloxacin, potentially affecting their distribution and bioavailability (Alyami et al. 2022; Beberok et al. 2011). The pigment also interacts with β-lactam antibiotics, including penicillins and cephalosporins, influencing the pharmacokinetics of β-lactams and impacting their effectiveness against bacteria (Barza et al. 1976). MEL binding to tetracyclines such as doxycycline and minocycline has been observed. This may affect their distribution and efficacy within the body (Rok et al. 2021). Some potential interactions between MEL and macrolide antibiotics like erythromycin and azithromycin, potentially influence their pharmacokinetics and bioavailability (Barza et al. 1976). VIO can be used to treat bovine mastitis either in single or in combinatorial treatment with antibiotics. It is observed that combinatorial usage of VIO along with antibiotics like azithromycin, cefadroxil, gentamycin, and kanamycin accentuates antibacterial activity against multidrug-resistant pathogenic bacteria (Duran et al. 2016). During combinatorial treatment along with antibiotics, VIO-gentamicin and VIO-cefadroxil treatments, effective results can be observed in *S. epidermidis*, *Salmonella typhi*, *V. cholerae*, *P. aeruginosa*, *K. pneumoniae*, and *S. aureus* (Dodou et al. 2017; Subramaniam et al. 2014). PDG exhibits synergistic or additive effects against many bacteria like *E. coli*, *S. aureus*, *Bacillus cereus*, *C. violaceum*, *M. smegmatis*, and *P. aeruginosa* when used in a combinatorial antimicrobial system (Gohil et al. 2020). When PCN is used to treat along with novobiocin and nalidixic acid then it shows potentiation of antibacterial activity against *S. aureus*. In combination with ciprofloxacin and nalidixic acid it shows such activity against *E. coli*. With meropenem synergy was observed against *S. marcescens* and *Proteus mirabilis* (Abdelaziz et al. 2023). Subinhibitory concentrations of ciprofloxacin, tobramycin, and meropenem can modulate PCN production by various strains of *P. aeruginosa* (Mojsoska et al. 2021).

Industrial application of bacterial pigment

Though a number of bioactive pigments are profoundly produced by opportunistic pathogenic bacteria, considering their potential of as natural dye, the molecules have immense prospect in food, agriculture, textile, and cosmetic industries. Alongside, the pigments are gaining novel implication in bioremediation, biofuel cell designing, and biosensor development. An association network map for the diverse industrial use of the pigments is provided in Fig. 6B to offer a snippet of their industrial application.

Food

In order to make their food appealing, the food industries began to use synthetic colorants. Since the synthetic colorants were made out of petroleum by-products they pose health risks to the consumers, which insist industries to switch to natural colorants. In the food industry, among the bacterial pigments, riboflavin, β-carotene, PDG, PCN, MEL, VIO, and lycopene have been identified as safe and edible colorants (Sen et al. 2019). In contrast, yellow-colored water-soluble pigment riboflavin has been reported to have applications as a dietary supplement and additive in dairy products, baby foods, and energy drinks for their ability to break down polymeric components like carbohydrates, proteins, and fat to release energy. It is also extensively used as a component of the vitamin B complex to treat specific deficiency (Peechakara et al. 2024). Red-orange colored bacterial pigment β-carotene is an excellent source (provitamin) of vitamin A that helps boosting the immune system and is necessary to prevent night blindness in human (Eroglu et al. 2012). Some other members of the carotenoid family have also been reported to have applications as food additives for animal and fish feed for aquaculture, and pharmaceutical fields (Stafsnes et al. 2010). PDG, the red pigment produced by a number of bacteria has been recognized as a multipurpose pigment that can be used extensively in commercial preparations of milk, yoghurt, and carbonated drinks (Namazkar 2013). Another blue-colored pigment, PCN, can be used in sweets, ice creams, and in proteinaceous dietary supplements. It can also purposed as a protective

supplement due to its anti-bacterial, anti-fungal, and neuroprotective properties (Jayaseelan et al. 2014). MEL has also been reported to have application as food additive (Sen et al. 2019). VIO is in demand for use in cosmetics, medicine, textile as well as food industries (Sutherland et al. 2011) owing to its diverse bioactivities including antiulcerogenic, anticancer, antimicrobial, enzyme modulation, and anti-parasitic activities (Soliev et al. 2011). Furthermore, a number of pigments are undergoing laboratory analysis and may soon be used in the food industry as non-toxic, therapeutic food colorants. Examples of these pigments include undecylprodigiosin (isolated from *S. marcescenes*), and STX (derived from *S. aureus*) (Agarwal et al. 2023). A new class of immune-fortified foods may soon become widespread as a result of increased studies into the quest for new bacterial pigments. These foods would not only be aesthetically pleasing to eat, but they would also provide therapeutic immunity to the consumer—a valuable benefit in the current period where infectious diseases and lifestyle problems are more prevalent than ever.

Textile

The application of microbial pigments as industrial fabric dyes is not yet common and further exploration is warranted. In recent times, textile industries are venturing into bacterial pigments rather than synthetic ones because they are non-carcinogenic, eco-friendly, and also have antimicrobial activity. A number of bacterial pigments have found application in the field of textile dyeing owing to their ability to bind to the textile fiber and the most commonly used ones are PDG, MEL, and VIO. PDG from *S. marcescens* SB08 is used frequently for dyeing fibers like nylon, acrylics, cotton, and silk, and is quite stable when tested at variable conditions of washing, perspiration, and rubbing. PDG from *Vibrio sp.* is used for dying nylon, acrylics, silk, and wool (Barreto et al. 2023). Similarly, VIO extracted from *C. violaceum* has been used for dyeing pure silk, cotton, rayon, and polyester. The coloring could be obtained by either dipping the fabric into the dye solution or by boiling the fabric along with the bacteria and the intensity varies with the time and the temperature of exposure of the fabric to the dye. The process is divided into three stages – preparation of dyeing solution with pigment fixing additives, hot dyeing at 60 °C – 80 °C, washing and drying of dyed fabric. Dissolution of pigment depends on the nature of the pigment requiring solvents like ethanol, acetone, and methanol (Kramar et al. 2021). Dye baths produced using acetone, water, or ethanol are also considered eco-friendly. Appropriate pH optimization is also necessary while preparing dye baths depending on the type of textile material. Protein-based fibres like wool and silk require an acidic dye-bath whereas plant-based materials like cellulose require higher pH as acidic conditions may cause the cellulose to degrade. Again pigments are also sensitive towards pH change. Pigments from *Serratia sakuensis* change color at different pH: pH 4 (pink), pH 5 (red), pH 7 (orange), and pH 9 (yellow) (Ren et al. 2018). PDG from the strains *Streptomyces* sp. NP2 and NP4 showed brownish-to-red colour at low pH 3.5 and 4.5 and grey-to-blue at a pH of 8, thus dying at different pH induce different colour in multifibre fabric (Kramar et al. 2014). Pigment isolated from *P. aeruginosa* under alkaline conditions is blue but when dying polyester at 130 °C, the polyester dyed yellow. This is because of the pyrolysis of the PCN pigment; hence it is important to determine the sensitivity of both the pigment and the fabric towards pH and temperature. Frequently salts are used as additives in dyebaths for improving the fixation of natural dyes to fibres. These salts are called mordents, which form a complex with the pigment and are also able to attach to the fibre. Some conventional mordents are iron, copper, aluminium. Mordants have an effect on the resulting color of the fabric. Mordents like Al and Ti have significant positive impact on washing fastness, perspiration, and dry-cleaning of the dyed silk using PDG extracted from *Zooshikella rubidus* (Kim and Choi 2015). The synergistic antimicrobial activity of the pigment and silver nanoparticle (AgNP) exhibited remarkable effect against bacteria and *C. albicans* (Kim and Choi 2015). Synergy between the antimicrobial property of the pigment VIO extracted from *J. lividum*, and silver and titanium dioxide nanoparticles was observed when a viscose fabric was coated with the nanoparticle. After dying with the pigment, it showed greater antimicrobial activity against *E. coli* than the regular-dyed fabric (Khaksar et al. 2021). The works highlighted obstacles that must be surmounted in order to make microbial pigments widely used for commercial dyeing, including the high costs, yield, and color stability, as well as advancements in the extraction methods. But in spite of all of this, the market is growing, full of creative and innovative opportunities, and offering more environment-friendly products, opening up new avenues for biotechnological solutions.

Cosmetics

Cosmetic industries are also switching to the safer alternative i.e. the microbial pigments especially the carotenoids as they also have excellent capacity to reduce ROS production and are the major active ingredients in anti-aging creams. External environmental factors such as the UV exposure, smoke pollution, and intrinsic factors like genetics and lifestyle resulting in damage and degradation of the dermis and epidermis are the major factors in skin aging (Guillerme et al. 2017). A number of bacterial pigments have found their

application in the cosmetics industry owing to their antioxidant properties. Carotenoids like lycopene, β-carotene, and canthaxanthin belong to this category (Wan et al. 2014). The red pigment PDG has also been found to be incorporated in a number of dermatological formulations to enhance their UV protection ability as measured by sunscreen protection factor by 25–65%. The combination of PDG with aloe Vera and *Cucumis sativus* fruit extract was also found to enhance the order of protection (Suryawanshi et al. 2015). VIO, isolated from the genus *Pseudoalteromonas* has been extensively tested in various cosmetic preparations due to the nonpathogenic character of the bacterium (Duran et al. 2016). It has been examined as an ingredient of products that come in direct and prolonged contact with the airways, mucous membrane, and skin, like antiperspirants, lipsticks, and eye makeup.

Biosensor

Gu and Cheung (2001) projected IND production from *Vogesella indigofera* up on exposure to Cr^{6+} as a biosensor for hexavalent Cr. Subsequently, IND production has been used in various metal ion detection with sensitivity between 200 and 300 µg/ml (Bereza-Malcolm et al. 2015). In an intensive effort, Gustavsson et al. (2016), engineered *E. coli*, for outer membrane expression of tyrosinase for complete oxidation and polymerization of tyrosine to melanin. Thus an efficient system in removal of pharmaceutical contaminants from polluted waters was generated with a rapid regeneration of the melanin matrix by simple pH cycling. A number of whole-cell biosensors based on pigment biosynthesis have been engineered in the recent past. For detecting low concentrations of QS signal, a *N*-butyryl homoserine lactone sensing biosensor was developed by genetically modifying *P. aeruginosa* CGMCC 1.860 RhlR (Yong and Zhong 2009). A strategy for developing copper biosensors was configured by Chen et al. (2017), using the production of the plant pigment β-xanthene. Using a similar strategy, bacterial pigment biosynthetic genes have been implemented in developing biosensors, particularly for metal and metalloid ions. Hui et al. (2020) described development of a whole-cell biosensor for lead with *E. coli* cells by integrating a circuit for expression of *vio*-genes under the control of PbrR, a Pb(II) dependent transcriptional regulator. Direct visualization for Pb contamination was achieved with a linear detection for VIO accumulation ($OD_{490\ nm}$) within a range of 0.19–1.5 µM. Further improvement of the sensor was accomplished with the incorporation of triggers for *vio* ABE-catalysed production of green prodeoxyVIO, *vio* ABDE-catalysed production of blue proVIO, *vio* ABCE-catalysed production of purple deoxyVIO, and *vio-ABCDE*-catalysed production of navyVIO to detect varied concentrations of Pb(II) (Hui et al. 2022b). A whole-cell biosensor for detecting cadmium was subsequently developed using the cd (II) sensory element fused with IND BGC and expression of CadR. Naked-eye detection for induction of blue coloration was achieved along with a colorimetric detection system with a limit of detection as low as 0.024 µM. The system also demonstrated modest nonspecificity as it could weakly detect other metal ions like Zn(II), Pb(II), and Hg(II) (Hui et al. 2022a). Through incorporation of *vio*-genes under mercury resistance (mer) promoter and mercury resistance regulator (MerR), a Hg(II) detection biosensor was developed with a colorimetric detection range of 0.78–12.5 µM (Guo et al. 2021).

Implementing two Zn-responsive transcription factors and regulatory element system, a tricolor sensor system for Zn present in serum was developed by Watstein and Styczynski (2018). The gene for conversion of lycopene to β-carotene (*crtY*) was placed in the promoter P_{zntA}. Under P_{znuC}, with additional "decoy" binding sites to sequester zinc-bound zinc uptake regulator (Zur), VIO-producing genes were placed. Thus two systems responding to two different concentrations of Zn, rendered development of a three-colored biosensor for Zn. Recently, in an effort to develop a bacterial pigment-based biosensor for detecting bacterial pathogens in water samples constructed on the basis of the QscR quorum sensing signal generated by the pathogenic bacteria. The system was primarily optimized with eGFP as reporter and subsequently the red pigment lycopene synthesizing module *ctrE*, *ctrB*, and *ctrI* genes were introduced in the system with *ctrI* under the regulation of QscR. The configured strain enabled point-of-care detection of water contamination by *P. aeruginosa* and *Burkholderia pseudomallei* (Wu et al. 2021). In the recent most effort to develop bacterial pigment-based biosensor, Hui et al. (2023) designed a high throughput system through profiling nine stress-responsive promoters. A set of such promoters was fused with purple deoxyVIO synthetic enzyme cluster and another set was fused with the blue IND gene cluster. Through this system, sensitive and efficient detection of genotoxic compounds like mitomycin C and nalidixic acid was accomplished.

Agriculture

Safe agricultural practices have included the use of biological agents mostly due to safety and specificity in their actions. Bacterial pigments have also been explored with the same goal. VIO was found to be effective as a component of an insecticide in preventing fungal infection in plants like grass sclerotinia stem rot, bean sprout seedling blight, pythium blight, as well as parasitic infections like *Meloidogyne* spp. diseases in watermelon (Orlandi et al. 2022). Similarly,

PDG was found to be effective in inhibiting *Drosophila* larvae, *Aedes aegypti*, and *Anopheles stephensi* (Suryawanshi et al. 2015). PDG has also been found to be effective in restricting viral infections involved in sericulture. This dye has also been effective in restricting the environmental pollution caused by bloom of the cyanobacteria *Microcystis aeruginosa* (Wei et al. 2020). Scientists have reported a melanin-synthesizing mutant strain of *B. thuringiensis* to be resistant against UV-mediated damage (Zhu et al. 2022). This finding has opened the pathway for industrial production of light-stable eco-friendly insecticide. PHZ has been reported to have beneficial effect on plant roots as it helps to overcome ROS-mediated stress. Some PHZ-derivatives display inhibitory effects on the plant pathogen *Rhizoctonia solanii* (Xiang et al. 2018). Antifungal activity has also been reported for PVD against *Aspergillus* (Sass et al. 2021).

Bioremediation

A major cause of low crop yield is iron deficiency, even though Fe being the fourth most abundant metal on Earth. Fe in soil reacts with the insoluble bicarbonates causing the micronutrient deficiency in plants. This is mostly noted in soils with pH of 7.4–8.5 as in calcareous and alkaline soil. To counter this reduced availability, chelators such as ethylendiamine-N-N'bis(o-hydroxyphenylacetic) acid (o, o-EDDHA) are employed to efficiently chelate Fe but are harmful to the environment and are expensive. Siderophores produced and released by bacteria have high affinity for Fe due to groups like catecholate, hydroxamate, carboxylate, and can act as chelators (Cordero et al. 2017). PVD-type siderophores are produced by *P. fluorescens*, in uranium mines. These are able to enhance mobility and reduce heavy metal toxicity (Edberg et al. 2010). The binding capability of siderophores to Fe is stronger than to toxic heavy metals (Baysse et al. 2000; Braud et al. 2009), still, siderophores bind to toxic heavy metals, like Cr^{3+}, Cu^{3+}, Pb^{2+}, Cu^{2+}, V^{4+}, and Al^{3+} (Braud et al. 2009), thus the detoxifying and binding capability of siderophore plays a remarkable role in plant growth on heavy metal-polluted lands.

E. coli can be genetically engineered to melanize its surface and remove pharmaceutical pollutants from wastewater with high efficiency (Cordero et al. 2017). Melanotic microorganisms are particularly attractive given their remarkable ability to grow in highly radioactive sites. The capacity of melanin pigments to readily adsorb radionuclides such as uranium and cobalt is advantageous. For instance, MEL has a significantly greater capacity to adsorb uranium (~10-fold) than activated carbon (Saini and Melo 2013).

Fuel cell

PHZ, is a class of pigments that has electron transfer abilities and thus is used as an electron shuttle by a number of bacteria including the producer. This particular characteristic of the dye has made it a potent candidate for the production of biofuel cells (Simoska et al. 2023). Respiratory electrons generated by a group of microorganisms are diverted toward an electrode for the production of electrical energy. Constant oxidation of the dye additionally ensures overproduction aided by increasing cell density.

The use of bacterial pigments is currently supported and regulated by laws, and this trend is expected to persist in the coming years (Sen et al. 2019). Commercial processes for this are either already operational or in the developmental stages. According to Dufossé (2018), the industrial production of bacterial pigments such as PDG has already commenced for use as anticancer drugs and immunosuppressants. On the other hand, bacterial pigments such as rubrolone, heptylPDG, and ZXT are still in their developmental stages (Dufossé 2018). The present colorant production figure consists 75% of petroleum derivatives and 25% of plant extraction, both of which are challenged in terms of sustainability and environmental impact. Keeping aside the technical aspects in translating bacterial pigment to market ready product, the business perspective, in terms of embracing newer sustainable technologies within a reasonable financial limit, remains a major challenge in expanding market for natural pigments. With Europe widening the avenue for natural colorants including pigments originating from bacteria with raising their use in various industries including food and textile, an escalation of market entry for bacterial pigment-based product across the globe is anticipated (Venil et al. 2020b). The market share for carotenoids, particularly in food and nutraceutical industry, is till date overwhelmingly dominated by synthetic carotenoids with 68.24% market share for synthetic AXT, beta-carotene, and canthaxanthin (Market Research Report, 2022). Though ZXT can be produced from *Chryseobacterium proteolyticum* and *Flavobacterium granuli* with a yield of > 90%, and more than 99% yield could be achieved for canxanthin when produced by *Dietzia schimae* (Lopez et al. 2023), high production cost remains a prime factor. Deinove, a cleantech company, earlier pointed out that high cost of natural carotenoids against synthetic carotenoids ($350–7,500/ kg vs. $250–2,000/ kg) is restricting its market. Deinove recently identified deinoxanthin from *Deinococcus sp.* along with the identification of terminal enzymes for synthesizing various carotenoids and optimizing the yield and market finish (https://www.labiotech.eu/trends-news/synbio-carotenoids-market-deinove-greentech-industry-milestones/). In a major leap towards application of bacterial pigment in textile industry,

Colorifix, a UK-based biotech company have engaged in implementing synthetic biology in genetically modifying bacteria to produce a range of natural pigments. Colorfix implements an on-site live whole dying process for fabrics in fermenter, which significantly reduces use of water and other chemicals. The industry trial for Colorfix in Portugal demonstrated 30-80% lesser impact on 10 critical environmental impact assessment parameters (https://colorifix.com/app/uploads/2022/12/colorifix-environmental-impact.pdf and https://colorifix.com/colorifix-proves-lower-environmental-impact-at-every-stage-of-its-biological-dyeing-process/). Pili Bio, a France based biotech farm, has developed bacterial biofactories integrated with pigment-producing enzyme cascades to produce pigments emphatically with least pollution (https://www.pili.bio/9/technology).

Industrial production of bacterial pigments

The pigments discussed here are produced profoundly by pathogenic bacteria, and are often associated with infection establishment. However pathogenic strains of bacteria are not considered as an ideal cell factories considering the risk as public and occupational health hazard. To our advantage, most of the pigments are not exclusively produced by pathogenic strains and a number of non-pathogenic producer strains, generally considered as safe (GRAS), have been identified. For pigments like VIO, PDG, and IND a number of such non-pathogenic producers have been isolated from soil or other environmental sources (Paillié-Jiménez et al. 2020). Apart from native pigment producers, pigment production by expression of the BCGs in amicable hosts by implementing synthetic biology strategy have been achieved (Banerjee et al. 2020). Even cell-free multienzyme systems have been optimized for pigment production at industrial scale (Hooe et al. 2024).

In the context of industrial production of pigments, traditional methods are limited by their dependence on natural sources and the typically low yield of target molecules. To address these challenges and scale up industrial production, significant efforts have been made to enhance pigment yields from natural producers (Lyu et al. 2022). The quality and yield of bacterial pigments synthesized in different species depend on specific growth conditions and growth medium-supplementation for optimal synthesis of specific pigment at a desired growth phase (Galasso et al. 2017). Hence intense observation of production kinetics and yield at laboratory scale is required prior to scaling up the production (Agarwal et al. 2023). Physical stress associated with the scaling up includes the hydrostatic pressure gradient, which affects the membrane integrity, cell viability, and metabolic flux (Wehrs et al. 2019b). Major chemical stresses linked to scaling up pigment production are the raw material, microbial contaminants, and toxic by-products (Dasgupta Mandal and Majumdar 2023). Agro-industrial wastes like sugarcane juice, sugar beet, and molasses are utilized for pigment production at minimal production cost. Optimization of fermentation media through advanced statistical methods like response surface methodology (RSM), artificial neural networks (ANNs), and genetic algorithms (GAs) has enhanced production efficiency, although challenges remain in optimizing complex factor-response interactions (Padhan et al. 2021; Singh et al. 2015). Scale-up optimization with intense monitoring hence becomes a prerequisite to minimize the physical and chemical stress for industrial pigment production. Like other metabolites, strain improvement is exigent for the industrial production of pigments. Certain strategies have been adopted to develop high-yield strains that enhance pigment production along with cost rationalization for stringent fermentation conditions aiming an increase in pigment production per unit mass. Innovative bioreactor designs, such as bubble columns, contribute to higher pigment production rates by maintaining optimal oxygen transfer and reducing energy consumption, thereby improving overall process economics (Lyu et al. 2022). Following production, the downstream method used in the purification of pigment from the fermentation media defines the pigment quality, making a systematic purification scheme essential for pigment purification. Bacterial pigments can either be extracellular where they permeate from the biosynthesizing cell, or they can be intracellular where it is contained and stored within the producing cell (Agarwal et al. 2023). The extracellular pigment can be isolated from the culture matrix through chromatography. For intracellular or insoluble pigments, isolation first requires the cells to be disrupted to release the pigment into the surrounding medium (Agarwal et al. 2023). Most of the bacterial pigments are hydrophobic and are soluble selectively in organic solvents. After obtaining the pigment in desired organic solvent the solvent is allowed to evaporate and the powdered residue is analysed further (Agarwal et al. 2023). An enormous amount of effort has been put into optimizing the production of all the industrially relevant bacterial pigments. Industrial production of MEL, and PHZs including PCN has recently been elegantly elaborated by Orlandi et al. (2022) and Jabłońska et al. (2023). Here we discuss recent progress made in industrial production of the industrially relevant bacterial pigments- VIO, IND, PDG, and FLR with emphasis on strain isolation and improvement by genetic engineering, combinatorial strategy integrating synthetic biology, metabolic engineering. Alongside, development of production media and scale up, and extraction and downstream processing are delineated.

Rettori et al. (1998) reported successful isolation of VIO from *C. violaceum* cultivated on cotton and extracted by

ethanol. Subsequently, various agricultural waste materials (sugarcane bagasse, solid pineapple waste, molasses, and brown sugar) were examined for optimal VIO production with tryptophan supplementation (Ahmad et al. 2012). Kanelli et al. (2018) reported an optimal fedbatch culture condition for VIO with production as high as 1.8 g/ L from *J. lividum*. Addition of a sub-inhibitory concentration of ampicillin and 1%V/V glycerol for fed-batch fermentation substantially improved VIO-producing biomass. Recently Cheng et al. (2022) reported that augmenting QS with formic acid enhanced the production of VIO from *C. violaceum*. The group successfully scaled up the formulation up to bioreactor level to achieve an elevated VIO level. Optimization of VIO production from a number of native-producing species has been attempted for quite a long time. Gohil et al. (2022) recently formulated a soybean meal-based cost-effective growth medium for achieving a crude VIO yield of 1.5 g/L from *C. violaceum*. Using *C. violaceum* MTCC2626 strain Gharat and Singhal (2024), formulated a medium and fed-batch condition with pulse feeding of glucose and tryptophan to attain markedly enhanced yield of VIO. Apart from *C. violaceum*, a number of VIO-producing strains have been identified through a consistent effort by several groups. From the Pacific coast of Japan, VIO-producing *Pseudoalteromonas* strains were identified by Yada et al. (2008). For VIO production, an extremely high yielding strain of *Duganella violaceinigra* str. NI28 was identified (Choi et al. 2015a). Sequencing and functional characterization of *VIO* BGC was performed by August et al. (2000), which widened the avenue for metabolic engineering-based strain improvement. Wu et al. (2017) published the draft genome sequence of *J. lividum* which further unveiled the regulation of *VIO* BGC expression. A VIO-producing recombinant *Citrobacter freundii* strain was developed by cloning and expression of *VIO* gene cluster in a plasmid. The fed-batch fermentation condition was optimized with controlled dissolved oxygen and pH with continuous feeding of glycerol, ammonium chloride, and tryptophan to attain a final production for crude VIO of 4.13 g/ L (Yang et al. 2011). *E. coli* was engineered for VIO production utilizing glucose through combinatorial knockout of three genes linked to regulation of tryptophan metabolism (*trpR*, *tnaA*, and *pheA*) and overexpression of two rate-limiting genes of tryptophan metabolism (*trpE* and *trpD*). Subsequently, VIO BCG was introduced for downstream expression. At a bioreactor level scale-up, the strain could produce a VIO titre of 1.75 g/ L (Fang et al. 2015). Strong heterologous expression of *vioB*, *vioC*, and *vioD* in the yeast *Y. lipolytica* enabled increased yield of VIO production. With optimization of the medium and culture condition, a production of 70.04 mg/L could be achieved in shake-flask scale. In the same study, strong correlation of weak expression of *vioD* and deoxy-VIO production was established (Tong et al. 2021). Nemer et al. (2023), recently optimized a protocol of VIO extraction from engineered *Y. lipolytica* through extraction by ethyl acetate/cyclohexane mixture and subsequent column chromatography. Kholany et al. (2020) earlier described a two-step downstream process based on solid-liquid extraction and a second step addressing the separation of VIO from contaminant proteins using aqueous bi-phasic separation with Tween 20 and cholinium-based ionic liquids. A synthetic *VIO* BGC expressing construct was generated for expression in *C. glutamicum* ATCC 21,850 with a host-specific RBS positioned upstream of *VIO* BGC. When optimized for fermentation condition and medium for bio-reactor scale a VIO titre of 5436 mg/ L was attained (Sun et al. 2016). Aiming for further optimization of the bioprocess of VIO production a number of synthetic biology-based designing of its synthesis in heterologous system has been attempted. In one of the earliest of such efforts, Lee et al. (2013) screened a library generated and analysed by TaqMan Rapid Analysis of Combinatorial assemblies (TRAC) of a set of constitutive promoters with the genes for the five-enzyme VIO biosynthetic cascade. Satisfactory production of VIO, deoxyVIO, proVIO, and prodeoxyVIO was observed in downstream analysis. Using a cell-free multi-enzyme system, Hooe et al. (2024), explored substrate analogues for enzymes of VIO biosynthetic cascade. A number of homo-substituted compounds like 6,6′-difluoroVIO could be synthesized without interrupting tryptophan metabolism. A CRISPRi-mediated metabolic flux engineering method was optimized recently by designing a single-guide RNA (sgRNA) library to function with dCas9. An extensive metabolic rewiring was possible to tune metabolic flux through VIO biosynthetic cascade employing the approach (Byun et al. 2023). With further optimization of such processes implementing robust prediction models, striking advancement for industrial production of VIO in the near future is anticipated.

The natural blue pigment, IND, is produced by several bacteria formed through the condensation of two molecules of L-glutamine to 3′,3′-bipyridyl pigment by a single NRPS (Takahashi et al. 2007). Being a monoenzymatically synthesized pigment, in recent years production of the pigment has been immensely improved by employing various genetic engineering strategies. Brachmann et al. (2012), successfully activated the silent *IND* BGC in *Photorhabdus luminescens* by promoter exchange. In the same work, the group reported heterologous expression of IND genes in *E. coli*. Cloning and expression of IND-synthase and its activator in *E. coli* resulted in IND synthesis. The fermentation was further optimized by supplementation with L-glutamine or by in situ L-glutamine synthesis by over-expression of glutamine synthetase. The media optimization with various nitrogen sources enabled the production of 7 g/ L IND (Xu

et al. 2015). *S. lavendulae* NRPS (blue-pigment indigoidine synthetase, BpsA) was heterologously expressed in *S. cerevisiae*. With media optimization for carbon sources and process optimization at the bioreactor-scale 980 mg/l production was attainable for IND (Wehrs et al. 2018). *BpsA* and *sfp* were expressed in the basidiomycete *Rhodosporidium toruloides* to produce IND in a low-cost renewable carbon and nitrogen sources enriched medium. With sorghum lignocellulosic hydrolysate in a batch process ~ 3 g/ L IND could be produced with the strain while in a glucose fed-batch process, ~ 86 g/ L production could be attained (Wehrs et al. 2019a). Heterologous expression of *bpsA* from *S. lavendulae* in *C. glutamicum* was performed for IND production. IND production from this strain was further improved by tuning the influx of precursors L-glutamate and L-glutamine, bolstering glucose uptake, and minimizing by product formation. An optimized fed-batch fermentation protocol yielded 49.30 g/L IND from the engineered strain (Kim et al. 2020). Recently *Aspergillus oryzae* has been utilized as a platform cell factory for expression of IND synthetase gene from *Streptomyces chromofuscu* s. Media optimization and addition of Tween 20 for fostering pigment release resulted in a production of ~ 1.4 g/ L (Panchanawaporn et al. 2022). Cell-free systems have been adopted for synthesizing secondary metabolites, particularly to avoid the complexity of cellular metabolic cross-talks that impair product yield. For IND, the minimal complex PURE system was exploited to express the NRPS *bpsA* from *S. lavendulae*. The enzyme produced from cell-free system can be evaluated for efficacy of IND production (Siebels et al. 2020). In an intense effort to optimize genome-scale rewiring for metabolite production Banerjee et al. (2020), aimed IND production by *P. putida*. A minimum cut set model was implemented to set up strong growth-coupled IND production leveraging the genome-scale metabolic model (GSMM) for *P. putida* KT2440. A multiplex CRISPRi-based knockdown approach was exploited to edit *P. putida* and rewire the host metabolically through detailed introspection of the multi-gene engineered production strain. At a bioreactor-scale production of 12.5–25 g/ L was achieved through the approach. Recently, the same group rewired *P. putida* KT2440 for the production of IND from *para*-coumarate. Following optimization of *para*-coumarate minimal medium, 7.3 g/L IND production could be obtained from the final *growth-coupled* strain (Eng et al. 2023). Thus rationalizing genome engineering combined with omics data is expediting higher production of the pigment for industrial use.

Though increasing reports on diverse bioactivity of PDG is warranting extensive therapeutic and industrial application of the pigment, industrial production of the pigments remains a major hindrance to the broader applicability of the pigment. Though PDG was initially identified from *S. marcescens*, in subsequent years a number of species of *Serratia* and *Pseudoalteromonas rubra*, *Janthinobacterium*, *Hahella chejuensis*, and *S. coelicolor* were reported to produce and accumulate PDG. These isolated strains demonstrated variation in terms of PDG generation. *S. marcescens* is considered as the most prolific PDG producer with the highest recorded production of 49.5 g/L from UCP 1549 strain, which was isolated from a semiarid soil by de Araújo et al. (2010). A number of indigenous PDG-producing strains have been isolated from diverse ecological niches including soil, sea, freshwater lakes, polar region, and glaciers. A comprehensive profile of such isolated strains and their PDG-producing potential has been aptly summarized by Han et al. (2021). Though *S. marcescens* isolates from soil have been projected as profound PDG producers for high-level industrial production of PDG, strain improvement is exigent. Following the identification of the biosynthetic pathway for PDG (Williamson et al. 2005), the understanding of the regulation of PDG biosynthetic cassette has gradually accumulated. PigP, a positive regulator of *pig* operon, is negatively regulated by LysR-type regulator MetR (Pan et al. 2020). OmpR family transcriptional regulator, CpxR was identified as a temperature-sensitive regulator of *pig* operon (Sun et al. 2020). A transcriptional regulator RcsB represses *pig* operon by regulating FhlDC, which is an activator of *pig* operon (Pan et al. 2021). The MarR-family transcriptional repressor OhrR was identified as a negative regulator of PDG synthesis (Sun et al. 2022). Disruption of *barA* or/and *uvrY* results in elevated level PDG production in *S. marcescens* (Liu et al. 2023). A recent genome-wide Tn5 random loss of function mutagenesis screen by Jia et al. (2021) identified essential genetic elements for PDG biosynthesis. Exploiting such knowledge recombinant PDG producers have been designed by engineering on *Serratia* or by heterologous expression of PDG-biosynthetic network in *P. putida*. CpxR-deleted *S. marcescens* strains demonstrated considerable improvement in PDG production with a production of ~ 6 g/ L (Sun et al. 2020). *P. putida* has been exploited as a heterologous host to express *pig* genes by chromosomal integration. With promoter shuffling and media optimization, a production of 1.1 g/ L was attained in non-baffled shake-flask level (Cook et al. 2021). Pan et al. (2022a), recently reported a constitutive promoter screening linked to the application of expression of *pig* genes in *S. marcescens* to enhance PDG production. However, such directed engineered strain development involves huge effort and also there are finite chances of genetic compensation against secondary metabolite production. In this regard, random mutagenesis might provide culture condition-specific selective advantage to the hyperproducers. However, barring some intermittent trials with ethyl methane sulfonate (EMS) or γ-ray (Elkenawy et al. 2017), intensive effort to

exploit random mutagenesis for PDG production is still awaited.

Scaling up of PDG production using diverse strategies and conditions has been attempted by different groups (Abdul Manas et al. 2020; de Araujo et al. 2010; Dos Santos et al. 2021; Elkenawy et al. 2017; Nguyen et al. 2020), albeit satisfactory yield and purity remain unattained through any kind of economical production strategy. Hence, mass-scale production of PDG by *S. marcescens* remains highly expensive as the culture medium should contain glucose, sucrose, and fructose as pure carbon sources, at least 1.5% casein hydrolysate as nitrogen source, and plant seed oils for satisfactory growth. So, the development of an economical culture medium is exclusively needed to make the process economically favorable. Consistent efforts through the last decade to optimize media composition for PDG production underscored the nutritional prerequisites for its production. All such efforts engaged robust statistical methodology. PDG production of 2.6 g/ L was attained from *H. chejuensis* M3349 by Kim et al. (2008), with a media containing sucrose 10.0 g/L, peptone 8.0 g/L, and yeast extract 2.0 g/L. Chen et al. (2013), identified starch 6/peptone as C and N-source for SmC3 strain. The composition elevated PDG production up to ~7 g/ L. Su et al. (2011) subsequently attained PDG production of ~2.5 g/ L with 0.454% peptone, 0.5% sucrose as C and N-source respectively. Miglani et al. (2023) optimised a medium with xylose derived from rice straw and peanut de-oiled cake as an economical carbon source. An extremely high production of PDG (~6 g/ L) was attained through the fermentation condition. A number of media supplementation improved PDG production. Elkenawy et al. (2017) demonstrated that crude glycerol induced PDG production by several folds in *S. marcescens* strains. A number of oil supplements including olive oil and plum oil have been tested for PDG production by *S. marcescens* by Abdul Manas et al. (2020). A number of amino acid supplementations have been profiled with diverse impacts on PDG production by *S. marcescens* (Han et al. 2021). A medium was developed for PDG production by *Serratia* from Cassava waste water with 2% mannitol supplementation to attain 45 g/ L PDG production (de Araujo et al. 2010). A low-cost scaling-up approach was adopted using demineralized crab shell powder by Nguyen et al. (2020), for pilot scaling up of PDG production to ~5.1 g/ L of PDG. Dos Santos et al. (2021) optimized a solid substrate fermentation on agro-waste to attain PDG production of 119.8 g/ kg dry substrate with a medium containing wheat bran and soybean oil. Using bagasse as an inert matrix excelled PDG yield up to 40.86 g/kg dry solid was attained by Xia et al. (2016). A detailed list of such media optimization and supplementation is reviewed by Han et al. (2021). Downstream processing and isolation of PDG after fermentation is also challenging as PDG is intracellular and insoluble in water. Following culture, PDG-containing cells are harvested by centrifugation. Acidified ethanol (95%, pH3.0) is added following harvest and lysis of cells. The PDG is trapped in the organic phase and can be separated from ethanol by evaporation. Subsequently, the dried mass is resuspended in ethanol and PDG is purified by liquid chromatography or column chromatography. PDG is purified from the columns using organic elution by hexane-acetone (Paul et al. 2022). The extracted PDG fraction can be further purified by TLC. Since the use of organic solvent for extraction is expensive and toxicogenic to a certain extent, optimization of environment-friendly low-cost methods like the use of chitin or resin for separation of PDG is underway. Often incorporation of additives in culture broth facilitates isolation or secretion of pigment from the cells. Addition of SDS at suboptimal concentration was observed to promote release of PDG possibly by forming an effective negative macromolecular charge cloud around cells. Hydrophobic polyurethane foam cubes allow absorption of PDG from the lysates, which can be subsequently washed off from the foam cubes by organic solvents (Han et al. 2021).

FLRs are unique type of bacterial pigments produced by the bacteria from the genera *Flavobacterium* and *Chryseobacterium*. For industrial production of the pigment, *C. artocarpi* CECT 8497, has been exploited for optimizing maximum yield by Venil et al. (2015). Optimizing a medium with lactose and tryptophan, and culture condition variables a maximum production of 521.64 mg/L could be achieved in a 50 L bioreactor scale. The pigment is soluble in acetone, alkaline aqueous, and DMSO while insoluble in water and most organic solvents (Venil et al. 2014) which makes the extraction arduous.

Bacterial pigments implication in nanotechnology

Bacteria-derived pigments are looked in to as a possible beneficial replacement for synthetic pigments in the field of natural dyes because of their many benefits, which include color stability, improved environmental friendliness, economics, and ease of production. However, in the presence of extreme heat, radiation, pH, or oxygen, bacterial pigments frequently show noticeable instability, finding it difficult to retain their properties under certain natural conditions (Chiba et al. 2006; Devi et al. 2024; Narsing Rao et al. 2017; Pagano et al. 2018). To address this challenge, microencapsulation emerges as a promising technique, which is capable of enhancing the solubility, stability, and photo-oxidation of materials by encapsulating active ingredients within micro/ nanoparticles (Martinez-Alvarez et al. 2020). Encapsulated pigments within polymers enhance their stability and solubility under ambient conditions, consequently extending

the shelf life of the final product (Soukoulis and Bohn 2018; Zabot et al. 2022). Microencapsulation significantly improved the stability of FLR isolated from *C. artocarpi* CECT8497 compared to their unencapsulated counterparts, offering increased protection. Additionally, the improved characteristics and potent antioxidant activity of the microcapsules, the pigment derived from *C. artocarpi* CECT8497 may find application as a natural colorant in the food sector (Mogadem et al. 2021). Using the human breast cancer cell line MCF-7, Venil et al. (2016) examined the anticancer effects of FLR-mediated AgNP and discovered that they suppressed 99% of the cells. Their method is unique because it produces stable AgNPs that have strong anticancer effects in an environmentally friendly manner. The findings indicate that AgNP mediated by FLR have potential as sophisticated chemotherapeutic interventions.

A recent study shows light, pH changes, and variations in temperature cause poor stability for PDG. Encapsulated PDG, on the other hand, improves stability and solubility, and presents a viable alternative to the synthetic colorants that are presently marketed (Desai 2012). In a study, the water-in-oil emulsion approach was implemented to create 40 to 60 µm chitosan microspheres loaded with PDG, and glutaraldehyde as the cross-linker. Breast cancer cells (MDA-MB-231 cells), when utilized to assess drug release, exhibited significantly reduced viability following 24 h of PDG therapy (Dozie-Nwachukwu et al. 2017). An alternative approach for administering cancer chemotherapy entails crafting microparticles composed of biodegradable poly (lactide-co-glycolide) (PLGA) encapsulating PDG by the evaporation of a single emulsion solvent, wherein polyvinyl alcohol served as the emulsifying agent. In addition, as a control, paclitaxel (PTX)-loaded particles were created. Compared to the PLGA microspheres loaded with PTX, these PDG-loaded microspheres showed comparatively high and comparable drug loading and encapsulation efficiency, with particle diameters ranging from 5 to 50 µm. This renders them appropriate for controlled and targeted drug delivery system in cancer therapy. Upon testing their cytotoxicity on MDA-MB-231 cells, the results were comparable to those of PTX, causing apoptosis by inhibiting the growth of the cells during a mitotic phase of the cell cycle (Obayemi et al. 2016). A rapid single-step method was employed to produce PDG-conjugated AgNPs, harnessing the amphoteric properties of silver oxide in an alkaline solution. With an average diameter of 10 nm, these very stable and spherical nanoparticles showed an IC_{50} value of 29.85 µg/ mL against the human liver cancer cell line HepG2, while free PDG showed an IC_{50} of 44.83 µg/ mL (El-Batal et al. 2017). In a similar targeted delivery approach, dendrigraft poly-L-lysines (DGL) underwent modification with a synthetic peptide capable of binding to placental chondroitin sulfate (CSA), known as plCSA-BP, derived from the malarial protein VAR2CSA. This produced PDG-loaded nanoparticles, which had a negatively charged surface and an average diameter of 396 nm. These nanoparticles demonstrated an encapsulating efficacy of 90% and a loading capacity of around 41%. Studies conducted on the in vitro release revealed a rapid initial release within 12 h at pH 5.3 and 7.4, indicating its prospect as a delivery system. Assessment of their cytotoxic impact on choriocarcinoma cells (JEG3 cells) demonstrated significantly enhanced anticancer efficacy both in vitro and in the JEG3 tumor model in vivo, as compared to free PDG (Zhao et al. 2019). Utilizing PDG nano-micelles, a cotton dyeing technique was developed to exploit the antimicrobial properties of PDG. The hydrophobic pigment was encapsulated into micelles by means of microbial fermentation with constant agitation in presence of a nonionic surfactant, Tween 80. The dyed cotton demonstrated strong bacteriostatic effects against *E. coli* and *S. aureus*, with efficacy rates of 85% and 99%, respectively (Gong et al. 2017).

The restricted water solubility, low bioavailability, oxidation propensity, photo- and heat instability, and poor solubility all contribute to their limited use. In order to preserve ZEA from degradation and enhance their intestinal stability and permeability, the work reported by Radic et al. (2023) aimed to create nano-structured lipid carriers (NLCs) loaded with these substances. For the first time, they have demonstrated a considerable increase in intestinal absorption of ZEA-NLCs, which may help their applications in the food and pharmaceutical industries.

Due to their capability to function as either electron donors or acceptors in enzyme reactions, PHZs exhibit significant promise as support materials for enzyme immobilization and biosensing purposes. This feature improves the efficiency of the catalyst as well as long-term stability (da Silva et al. 2020). Moreover, when combined with Fe_2O_3 nanoparticles to form a nanocomposite, the complementary electrochemical catalytic characteristics of polyPHZ films and Fe_2O_3 nanoparticles suggest improved performance in both conductivity and sensing applications. Additionally, these novel nanostructured materials create an ideal environment for biomolecule immobilization, thereby further enhancing biosensing capabilities (da Silva et al. 2020).

MEL nanoparticles (MNPs) have been shown in several studies to have potential applications in a variety of fields; their semiconductor qualities have prompted the development of electronic films (Vahidzadeh et al. 2018). They have been used as adjuvants in cancer radiation therapy (Cuzzubbo and Carpentier 2021; Yue and Zhao 2021; Zhou et al. 2019) and sun protection against UV

radiation (Mavridi-Printezi et al. 2020) because of their strong radiation-absorption and antioxidant abilities.

The main hindrance to the delivery and bioavailability of VIO is its hydrophobic character (Arif et al. 2017). Compared to starch-capped silver NPs (cAgNPs), VIO-capped silver NPs (vAgNPs) are more stable and have therapeutic efficacy against multidrug-resistant bacteria and fungi that are three to ten times higher. The attributes of VIO-capped nanoparticles (VNPs) include antibacterial, anticancer, and anticancer effects (Konzen et al. 2006). There have been prior investigations on the antibacterial and anticancer properties of VNPs (Arif et al. 2017). Comparing low doses of VNPs to high doses of free VIO, the former demonstrated stronger antioxidant properties. The scavenging ability of peroxides and superoxides by VIO was the plausible reason for such observation. The characteristics and advantages of various nano combinations with bacterial pigments are summarized Table 2. Also, the benefits offered by the nanoformulations to enhance sustainability and bioavailability of the pigments are highlighted.

Concluding remarks

Despite their striking bioactive potential, bacterial pigments have been overlooked to a certain extent with limited effort to systemically explore, evaluate, and invent strategies for application. A plethora of reports emerging throughout the last decade or so in their impact on pathogenicity, function in community and host interface, have precisely illuminated the significance of various groups of bacterial pigments. Attempts for optimization of industrial production of bacterial pigments and developing formulations to maximally exploit properties like antioxidant, antimicrobial, anti-inflammatory, and anticancer are underway for pharmacological application along with the obvious application as dye by replacing chemical dyes in various industries.

Bacterial pigments represent a part of the vast spectrum of organic pigments which are biodegradable and sustainable. The global organic pigment market is set to reach around 4.89 billion USD by the present year (https://menafn.com/1097992026/Global-Organic-Pigments-Market-Worth-Reach-USD-489-Billion-By-2024). Though till now pigments extracted from microalgae and fungi are predominating over the bacterial pigments in terms of use in industry, diverse groups of bacterial pigments are gaining attention, particularly for their diverse bioactive potential and advent of effective encapsulation strategies to increase sustainability. In contrast to the industrially important pigment-producing bacterial strains, a number of the pigment-producing fungi synthesize mycotoxins along with the pigments as enlisted by Poorniammal et al. (2021). Coproduction of such toxic metabolites impairs safety of the pigments and thereby restricts application in food, pharmaceutical, and cosmetic industry (Lin and Xu 2022). A second impediment for fungal pigment production is the product yield. As a cell factory fungal cells are less tuneable compared to bacteria and the array of chemical entities present in the pigment-containing biomass limits its yield through purification (Chadni et al. 2017). Apart from purification,

Table 2 Nano formulation with bacterial pigments. Various nanoformulations developed with bacterial pigments are enlisted. The improvements in terms of application are also mentioned

Pigment	Nanoparticles (average particle size, nm)	Advantages
Flexirubin	(a) Flexirubin-mediated silver nanoparticles (49)	Potentially toxic for human breast cancer cell line (Venil et al. 2016)
	(b) Polyvinyl alcohol/kefiran/ polycaprolactone nanofibers loaded with flexirubin (211)	Higher antioxidant activity (Amorim et al. 2022b)
Melanin	Melanin nanoparticles (40)	Used as adjuvants in cancer radiation therapy (Yue and Zhao 2021; Zhou et al. 2019)
Phenazine	Nanostructured Poly(Phenazine)/ Fe_2O_3 nanofilm	Enhanced biosensing for the detection of H_2O_2 (da Silva et al. 2020)
Prodigiosin	(a) chitosan –PDG microspheres (60)	Significantly reduced triple negative breast cancer cell viability (Dozie-Nwachukwu et al. 2017)
	(b) PLGA-PDG microparticles (400)	Potentially toxic for triple negative breast cancer cells (Obayemi et al. 2016)
	(c) PDG-AgNPs (10)	Potentially toxic against liver cancer cells (El-Batal et al. 2017)
	(d) DGL/CSA-PNPs (396)	Shown cytotoxicity against choriocarcinoma cells and JEG3 tumor model (Zhao et al. 2019)
	(e) PDG Nanomicelles with Tween 80 (224)	Strong bacteriostatic agent against *Escherichia coli* and *Staphylococcus aureus* (Gong et al. 2017)
Violacein	VIO-capped silver NPs (70)	Therapeutic potential against multidrug-resistant bacteria (Nielsen and Nielsen 1989)
Zeaxanthin	ZEA-loaded nano-structured lipid carriers (ZEA-NLC) (280)	Considerable increase in intestinal absorption (Radic et al. 2023)

media and process optimization for maximizing pigment production involves substantial cost, which limits scalability for fungal pigments (Kalra et al. 2020). Owing to such pluses in comparion to fungal pigments, and immense prospect as natural pigment for biotechnological and other industrial application considering the detrimental impact of synthetic pigments, the market for bacterial pigment is anticipated to surge gradually. With large industrial markets are inclining toward natural pigment, the 2021 market value for natural pigments attained a value of USD 1.21 billion. As summarized by Barreto et al. (2023), for natural pigments, the market carotenoid segment alone is projected to reach USD 2.7 billion. Among the bacterial pigments, AXT have already been approved by FDA for direct human consumption. Though plants have been a traditional source of natural colorant, their production and scalability are dependent of seasonal cultivation and weather conditions (Di Salvo et al. 2023). Compared to plant carotenoids, bacterial carotenoids are conveniently isolated and their production has escalated in recent years (Venil et al. 2020b).

A major group of bioactive pigment producers are opportunistic pathogens which remains a possible bottleneck in terms of industrial production of pigment like PDG or PCN. However the advancement of strategies for strain development, genetic engineering, and synthetic biology integrated to AI-ML, allowing to maneuver over the strong foundation of the colossal omics data available for tractable systems such hindrances are expected to get resolved in near future. For industrial production, the other bottleneck of cost optimization is being addressed by formulating medium with agro and dairy industrial wastes (Grewal et al. 2022). Process optimization with cutting-edge simulations and tuning the downstream processing for maximal yield are expected to overcome existing impediments in near future. A major area of research delving into the sustainability of bacterial pigments in various applications is nanotechnological exploration for developing novel formulations with bacterial pigments (Venil et al. 2020a). Along with discovering novel pigments and pigment producers, intensive effort is still warranted to exploit the complete potential of bacterial pigments.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval The study does not involve any human and/or animal subjects or clinical isolates. No personally identifiable patient/ human subject information was disclosed to the researchers.

Consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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