Ecological and Biotechnological Aspects of Pigmented Microbes: A Way Forward in Development of Food and Pharmaceutical Grade Pigments

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Abstract: Microbial pigments play multiple roles in the ecosystem construction, survival, and fitness of all kinds of organisms. Considerably, microbial (bacteria, fungi, yeast, and microalgae) pigments offer a wide array of food, drug, colorants, dyes, and imaging applications. In contrast to the natural pigments from microbes, synthetic colorants are widely used due to high production, high intensity, and low cost. Nevertheless, natural pigments are gaining more demand over synthetic pigments as synthetic pigments have demonstrated side effects on human health. Therefore, research on microbial pigments needs to be extended, explored, and exploited to find potential industrial applications. In this review, the evolutionary aspects, the spatial significance of important pigments, biomedical applications, research gaps, and future perspectives are detailed briefly. The pathogenic nature of some pigmented bacteria is also detailed for awareness and safe handling. In addition, pigments from macro-organisms are also discussed in some sections for comparison with microbes.

Keywords: pigments evolution; biological properties; horizontal gene transfer; fluorescent pigments

1. Introduction

The survival of life forms on earth is dependent on various pigments, including light-harvesting pigments like chlorophylls, phycoerythrin, and phycobiliproteins [1,2]; harmful light-filtering pigments like proteorhodopsins [3,4], melanin’s, pyomelanin, pyocyanin, fluorescent proteins; predator defending pigments like alysioviolin [5], cephalopods ink [6,7], Dendrobatidae frog toxins [8], microbial pigments and so on [9]. The quantity, quality, and attractiveness of pigments from various sources such as microbes, algae, invertebrates, and macro-organisms may comprise either beneficial or toxic chemical constituents. Not all colors appealing to our eyes are beneficial to humans. Therefore, investigations on the chemistry of pigment molecules are gaining more interest in the current research. In 1666, Sir Isaac Newton had initiated the beginning of research on colors by developing the first circular diagram of colors, and later various researchers like Harris (1776) and Goethe (1810). Sir Humphry Davy demonstrated the causes of various colors of organic molecules [10]. Later in 1820, Friedrich Accum revealed the many side effects of synthetic colorants in various foods [11]. Sir William Henry Perkin was the first man to develop the first synthetic textile color compound “mauvine” in 1856. With this brief historical background, the visible spectral pigments and invisible nonspectral pigments gain more attention due to numerous applications in ecology, evolution, biomedical, and industrial perspectives. The international color symbolism chart indicates that each color has a specific meaning in different countries and cultures. Despite numerous known applications, evidence shows that visual pigments (color and light) can directly influence the brain [12], psychology [13], taste and flavor of humans [14–16], and science communication [17].
lack of dietary pigments like carotenoids in our daily food intake may lead to various
diseases and in rare case death [18]. Visual and food colorants are playing a significant
role in decision making in our life to choose different foods and many other things [19],
through vision, flavor, olfaction, gustation, and oral somatosensation ways [16].

Humans cannot see nonspectral colors due to a lack of trichromatic or tetrachromatic
color vision-related cone types in their eyes. A recent study demonstrated humming birds’
ability to perceive nonspectral colors via the tetrachromacy phenomenon [20]; another
eexample of categorical color perception was observed in Estrildid finches [21]. Numerous
studies have been exploring the spectral pigments from microbes and higher organisms for
various applications. Nevertheless, nonspectral pigments and their ecological importance
in nature and biotechnological applications are not well studied. Thus, studies on nonspec-
tral pigments remain a research gap in the current global science development scenario.
Indeed, the planet earth is structured with visible and invisible micro and macromolecules
produced by prokaryotes and eukaryotes, regulating various physical, chemical, biological,
and geological processes. After going through a vast literature on microbial pigments, it is
now understood that microbes and macro-organisms produce varied pigment molecules
with a specific purpose in the respective milieus.

The resource of pigments, production rate, transport, price, sustainability, palatability,
durability, effectiveness, legislative and regulatory approval, and demand by consumers
are the primary requisites for various biotechnological applications in commercial indus-
tries. In this context, microbial pigments are attracting great demand to develop food
grade, textile grade, and drug grade natural pigments. The reasons for high demand
for microbial pigments are their promising unlimited resources, high production of re-
quired quantity of pigments, least cost-effective, easy cultivation and can be harvested
throughout the year, adaptability to various environments, optimization, stability, genetic
engineering, no side effects, eco-friendly, biodegradable, and indispensable applications
in multidisciplinary aspects such as ecological, evolutionary, biomedical, agriculture, and
industrial studies [9,22–24]. Many microbes are known to produce a wide variety of
pigment molecules with innumerable biological properties and other industrial applica-
tions [9,25,26]. Especially, natural pigments of microbial origin have many advantages over
synthetic pigments. Although artificial colors are more attractive and have been widely
used around the world market (42%) [19,27–30], they are found to have many side effects
(e.g., teratogenic, cancer, etc.) [29–31], and some are not biodegradable (e.g., textile dyes),
causing health disorders to aquatic organisms and humans [32–34]. Hence, researchers are
trying to find alternative physical, chemical, and biological methods to degrade synthetic
colors [35–37] to avoid the side effects posed to the public and environmental health. There-
fore, instead of developing synthetic colors and finding new methods for their degradation,
exploring natural pigments from microbes would bring about innumerable advantages for
the public and the environment.

Lack of knowledge on pigmented microbial isolation sources and their bioprospecting
methods would make researchers face trials in microbial pigment research. Thanks must
be extended to all the past researchers who explored the pigmented microbes from various
environments and demonstrated numerous applications through various methods. Based
on the published review of the literature [9,23,25,38–45], current researchers are looking for
novel strains, new extraction techniques, and new applications of pigments. In this context,
this review is intended to provide the current knowledge on various aspects of microbial
pigments such as classification, evolution, horizontal gene transfer, market demand, spatial
distribution, pigment therapy, and future perspectives.

2. Classification of Pigments

Microbes display all kinds of color hues such as black, blue, bronze, brown, cream,
grey, green, orange, purple, indigo, pink, red, yellow, metallic green, red, yellow, and
rainbow. These pigments can be classified into various categories based on their visual,
chemical, and spectral properties and source of origin (based on mobile genes) [9]. Based
on visual appearance, prokaryotes and eukaryotes display monochromatic to polychromatic pigment combinations within the Munsell color system. Some higher organisms like dragonfish [46,47] and hummingbirds [20] exceptionally display or see colors beyond our visible spectrum and near-infrared spectrum. These incidents suggest that humans lack nonspectral cones to perceive colors existing beyond the visible spectrum. Visually, pigments represent the following phenomena on earth: (1) Natural pigments, (2) Bioluminescence, (3) Fluorescence, and (4) Iridescence (structural colors), and (5) Non-spectral colors. Humans can perceive all the color phenomena except non-spectral colors.

Functionally, five different types of pigments are found in nature: (1) Biological pigments, (2) Fossil and sedimentary pigments, (3) Mineral pigments, (4) Synthetic & identical natural pigments, and (5) Caramel pigments (Figure 1). Biological pigments are derived from live microbes, plants, and animals. In contrast, fossil pigments are indeed biologically originated but preserved in fossils for millions of years, acting as evolutionary evidence [48–53]. In rare cases, fossil pigments can be of synthetic origin [54]. Mineral pigments are inorganic insoluble pigments used in artistic, cosmetic, archeological, and evolutionary studies [55–60]. In contrast, synthetic colorants are synthesized in the laboratory for food colorants and dyeing applications [61]. Dozens of synthetic colorants are being used in food and beverages [61,62]. Caramel pigments are natural sugar-based colorants used in a variety of food and beverage products. These caramel colors are classified into Caramel I, II, III, and IV classes to fulfill the requirement of food systems [63]. Solvatochromicity of these pigments varies according to the extraction solvent.

**Figure 1.** A wide array of pigmented microbes seen in nature. The abundance of the type of pigmented bacteria is depicted in bars based on the available literature. Rainbow bacteria are iridescent. Classification of pigments based on various aspects of biochromes. Chlorophyll pigments are not included in the data as they are ubiquitous. HGT: Horizontal gene transfer.

Based on chemical groups, microbial pigments are broadly differentiated into anthraquinones, carotenoids, indoles, phycobiliproteins, prodigiosin, rhodopsins, melanins, and violacein [9,64]. For understanding the evolutionary aspects, rhodopsins, melanins, and iridescent (structural) pigments are briefly discussed herein. Microbial rhodopsins are light-harvesting photoproteins that bind to retinal and respond to light, which has evolu-
tionary importance. These rhodopsin are found in Archaea, bacteria, fungi, viruses [65], and some eukaryotes [66]. Based on the known functions, rhodopsins are classified as light sensors (rhodopsins, opsins), energy-conserving transmembrane proton pumps (bacteriorhodopsins, proteorhodopsins, and xanthorhodopsins), and transmembrane chloride pumps (halorhodopsins) [4]. In Haloarchaea, a single cell can possess multiple rhodopsins with varied functions [4]. Melanins are biosynthetically, functionally, and structurally diverse pigments, including five known groups of allomelanin, eumelanin, and neuromelanin pheomelanin, and pyomelanin [67]. It is often easy to isolate monochromatic pigment-producing microorganisms from different environments, but isolation of polychromatic pigments producing bacteria such as *Pseudomonas aeruginosa* (blue and green pigments), *Streptomyces* sp. (yellow, orange and brown) [25] and iridescent or shimmering bacteria (VIBGYOR) [68] (https://www.hoekmine.com; accessed on 10 January 2021; Hoekmine BV, 2020) are rarely isolated. Structural colors are also recorded in fossil feathers, suggesting the importance of evolutionary aspects [69].

In general, microbes possess innate pigment traits, but some non-pigmented microbes acquire pigment traits from pigmented microbes (see the Section below: Horizontal Gene Transfer). For this reason, microbial pigments are classified as innate pigments and acquired pigments. Often, pigmented microbes release diffusible and non-diffusible pigments in culture media. However, rarely, some pigments are water-insoluble, for instance, blue pigment indigoidine [70], red pigment [71], and violacein [72]. Some pigments even do not dissolve in solvents; in such incidents, resin extraction can be employed to extract pigments.

3. Functions of Microbial Pigments

Microbial pigments are known to play a variety of ecological functions in their milieu. (Figure 2). Antioxidant properties of different microbial pigments are detailed in the supplementary file provided in the previous review published in 2019 (see supplementary file) [9]. Prodigiosin pigment produced by some strains of *Vibrio* sp. function as photoprotectants against UV light [73]. Violacein pigment of *Janthinobacterium lividum* and *Chromobacterium violaceum* demonstrated antipredator activity against bacterivorous nanoflagellates, indicating its defensive function [74]. *J. lividum* associated with the skins of some frogs and salamanders, secretes violacein pigment to protect them from pathogenic fungi, *Batrachochytrium dendrobatidis* [75–77]. Phenazine compounds produced by bacteria play multiple functions, including chemical signaling, biofilm formation, survival, and virulence [78]. Pyoverdine, a fluorescent yellow-green pigment, regulates iron transport and virulence functions in *Pseudomonas fluorescens* [79]. Tambjamine, a yellow pigment produced by *Pseudoalteromonas tunicata* [80], is suggested to help its host prevent other predatory fouling organisms [81]. Likewise, indigoidine, a blue pigment produced by *Phaeobacter* strains, is suggested to inhibit competing bacteria in the environment [82]. Bacterial melanin pigments act as photoprotectants [83–87]. For instance, *Vibrio cholerae* melanins serve as survival fitness factors when physico-chemical factors become unfavorable [88]. Some endophytic fungi releases anthraquinones, to protect the host plant from damage due to insects and microbes [89]; while, fungal melanins demonstrate multiple functions [90].
Figure 2. Ecological functions and other applications of important microbial pigments.

Bacteriochlorophylls are photosensitizers (light harvesters) in photosynthetic bacteria but absent in non-photosynthetic bacteria [91]. Non-photosynthetic bacteria may utilize a self-photosensitization mechanism [92]. In photosynthetic and non-photosynthetic bacteria, carotenoids, the accessory photosynthetic pigments act as photoprotectants and antioxidants, thus protecting cells from damage due to UV and sunlight illumination [91,93,94]. Bacterial communities in the air-water interface did produce more pigmentation to tolerate sunlight and are relatively drug-resistant compared to non-pigmented bacteria [95]. The extremophilic bacteria isolated from salt lakes [96] and cold environments like Antarctica [97,98] adopt environmental stress with carotenoids and other pigments. The yellow pigment of *Thermus* was proposed as a photoprotectant [99]. Carotenoids of archaea [100], yeasts [101,102], cyanobacteria, and algae [103] also function as photoprotectants. Maren nine, a blue pigment produced by diatom *Haslea* is involved in greening on oysters [104], and displayed a prophylactic effect [105,106]. Food colorants, drug, dye, and other biotechnological applications of microbial pigments are detailed in the section below.

4. Pathogenicity of Pigmented Microbes

Despite the numerous known pigments’ applications, the literature suggests that some pigmented bacteria are emerging as pathogens in aquaculture farms and even in humans. Violacein-producing bacterium *Chromobacterium violaceum* has been reported to cause infections in children and adults [107]. *Janthinobacterium lividum*, another violacein-producing bacterium, resulted in mass mortality of rainbow trout *Oncorhynchus mykiss* in the hatchery from Korea [108]. Prodigiosin producing *Serratia marcescens* also infects insects, other invertebrates, and vertebrates, including humans [109,110]. Strains of *S. marcescens* and *C. violaceum* are reported to be opportunistic pathogens to humans [111,112]. In all these cases, there is no evidence about the role of violacein and prodigiosin pigments in virulence function. A recent study demonstrated that prodigiosin pigment did not play a virulence function in entomopathogenic *S. marcescens* [113].

However, few pigments such as bacterial melanins [114] and pyoverdines [115] regulate virulence function. The red pigment producing fungi such as *Fusarium* and *Monascus* produce mycotoxins (e.g., citrinin and 4,15-diacetoxyscirpenol) linked to pathogenicity [116]. Thus, researchers are searching for fungal species that do not produce any toxins [117]. We suggest that determining an isolated pigmented microbe’s pathogenicity (hemolytic activity) would help to avoid infections and mortality.

5. Horizontal Gene Transfer (HGT) of Pigment Genes

In the last two decades, studies observed rare incidences of acquisition or transfer of pigment genes between related and non-related microbial communities. The transfer or acquisition of pigment genes between various micro-organisms is a sign of environmental function. The acquired pigment trait acts as a defensive mechanism against other microorganisms, acting as sunscreen (photoprotection) against UV rays and harvests light for enhanced photosynthesis. This is an exciting area of research to study the ecological importance of pigment gene transfer among microbes.
Genes coding for light-harvesting pigment proteins such as proteorhodopsins were reportedly transferred between planktonic bacteria and archaean communities dispersed only in the photic zone [4]. These proteorhodopsins encoding genes reportedly acquired by eukaryotes, dinoflagellate protists from bacteria [66], and protists’ viruses [65]. Bacteria like Collimonas CT were suggested to produce blue pigment (violacein) via pigment gene acquisition, probably acquired from J. lividum and/or Duganella sp. [118] (Figure 3). LuxA genes responsible for light emission in the luminescent bacteria were also reportedly acquired by non-luminous vibrios through HGT and become luminescent [119]. Similarly, pathogenicity-related genes were also shared among many bacteria via HGT [120]. Studying the HGT mechanisms in these microbes will help us to understand the role of HGT in evolution.

6. Cosmopolitan Distribution of Pigmented Microbes

The distribution patterns of well-known pigmented microbes have not been detailed in the literature to understand their evolutionary spread in different geographical envi-
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Environments. The current literature published so far reveals that pigments are environment-specific, depth-specific, host-specific, and functionally distinct [9,121]. Chlorophyll pigments are ubiquitous, whereas other pigment molecules are not widespread but restricted to specific groups of bacteria, indicating the evolutionary importance of pigments. To link the evolutionary concept with microbial pigment distribution, the well-known prodigiosin, violacein, and iridescent bacteria are mapped in this review (Figure 4). The map shows the cosmopolitan distribution of these bacteria in tropical, subtropical, and temperate environments. This spread pattern will help us to understand the hydrothermal vent-based origin of life theory by testing presence and absence, abundance, and low levels of microbial pigments in coastal and deep-sea environments of different geographical areas. Thus, further in-depth studies are required to link their distribution patterns to evolutionary studies.

Figure 4. Cosmopolitan distribution of well-known pigmented microbes in different geographical areas.

7. Evolution of Pigments

From the evolutionary perspective, the origin of microbial pigments remains very little known. It is well understood that all the chemical molecules have originated from the origin of elements process [122]. Pigments of prokaryotes and eukaryotes display specific ecological and bioactive functions [9,123,124]. Pigments are also identified in non-living matters like fossils, sediments, and inorganic minerals [49,125]. Fossil pigments [49,126] and sedimentary pigments [125,127] are gaining in ecological and evolutionary importance to study environmental and population dynamics and chemical constituents of the past. Microbial pigments are ubiquitous in different environments at various depths and evolved for a specific function in respective milieus [9]. In contrast to microbial pigments, mineral pigments are intensely colored inorganic molecules with potential applications in artistic, cosmetic, forensic, archaeological, and evolutionary perspectives [35]. In the evolutionary perspective and according to the clay-mineral theory on the chemical origin of life [128] and recent evidences [129], we may be able to interlink the origin of molecules,
including pigments in protocell, which helped protocells to survive in extreme conditions and supported the formation of multicellular organisms.

Since protocells’ origin, natural pigments have transformed into various phenomena such as pigments, fluorescence, and bioluminescence, found in prokaryotes and eukaryotes. Currently, researchers believe that life had originated 4.5 billion years ago from the extreme environment like hydrothermal vents in the ocean [130] or warm water pools in the volcanic land or geothermal (hot spring) areas [129,131,132], based on the evidences of hypothetic protocell structures, i.e., vesicles formed by simple fatty acids [130] and proteins [133], RNA [131] and DNA molecules [129]. The abundant external red pigments seen in deep-sea tubeworms at hydrothermal vents are indeed hemoglobins that act as binding sites to oxygen and hydrogen sulfide and transport these molecules to internal bacterial symbionts [134]. In contrast, the evidence of opsins and pigment molecules in thermal vents is not as abundant as in the photic zone or terrestrial environments. Deep-sea microbial pigments is underexplored due to difficulties in the culture and maintenance of samples under in situ conditions. Opsins are phylogenetically well-diversified and structurally different light sensors observed in prokaryotes [135,136], invertebrates, and vertebrates [137,138]. Opsins sense light and respond to physiological, chemical, and behavioral functions, and develop evolutionary adaptations. Phycobiliproteins are light-harvesting chromophores present in cyanobacteria and some algae, whose evolutionary origin is related to globin proteins and GC contents [139]. Efforts to understand the evolution of phycobiliproteins in cyanobacteria [140,141] and algae [139,142] using specific genes and targeted molecules is underway. Light-harvesting pigments, phycobiliproteins, and chlorophylls might have arisen independently several times in different lineages [143]. A piece of evidence exists on the origin and biosynthesis of bacteriochlorophyll a by a bacterial enzyme “3-vinyl-bacteriochlorophyll hydratase [144], suggesting the origin of enzymes first, followed by notions of coexistence of RNA and DNA [145] or homogenous RNA world [131,146,147] or DNA world [148], or still debating prebiotic DNA world [149]. The origin of other microbial pigments (e.g., prodigiosin, violacein, etc.) also needs to be evaluated for in-depth understanding and to interlink the evidence.

The chemistry and mechanisms involved in forming pigments in protocells and their divergence into different lineages are yet to be unveiled. The lack of enough evidence of protocells in the environment makes it difficult for researchers to understand protocells’ exact origin. The exact environmental conditions that favored protocells to develop various pigments are unknown. These pigments might have evolved to tolerate the intense illumination during the early earth formation generated from the chromosphere, photosphere, and atmosphere. This research angle remains untouched concerning the evolution of chromophores. Further detailed investigations on spatial and temporal patterns of various pigmented microbes from different environments and their complete genomics, proteomics, and chemicalomics may reveal some clues on the origin, evolution, and inheritance of pigments from protocell to eukaryotes. A recent conceptual study provides a new idea to understand the synthesis and development of prebiotic molecules in primitive cells [150]. Robotics based chemical synthesis studies have been arising in recent times [150,151], which may help us to understand the possible ways of origin of primitive molecules. However, this concept is still to be validated in real time, based on field evidences rather than empirical evidences. In the coming two to three decades, life’s true origin is expected to be in complete light with integrated evidence.

8. Pigment Gene Cassettes

Microbes producing high pigment yield are the primary research targets for commercial purposes. Many natural microbes have failed to produce the expected yield of pigments for food, drug, cosmetics, and textile applications. Therefore, exploring the entire pigment gene cassette of an interested microbial species is found to be the best approach to achieve high pigment yield through recombinant DNA technology. Some researchers might not be aware of the genes responsible for pigments; thus, this section has garnered informa-
tion on different microbes’ gene clusters. Pig gene cluster for prodigiosin biosynthesis in *Serratia marcescens* [152,153], and red gene cluster for undecylprodigiosin biosynthesis in *Str. coelicolor* A3(2) were identified [154]. Prodigiosin synthesizing genes in *Hahella chejuensis* KCTC 2396, and *Pseudoalteromonas* species were identified as hap gene cluster [155]. Indigoine biosynthesizing gene cluster in *Phaeobacter* sp. strain Y4I encoded as igit operon [82]. Violacine biosynthetic gene cluster “vio” was identified in *Chromobacterium violaceum* [156] and *Pseudoalteromonas* species [157]. Tambjamine, a yellow pigment of *Pseudoalteromonas tu-nicata* is synthesized by tam gene cluster [158]. Pyomelanin synthesizing genes were named as *hatABCDE* operon [159]. Bikaverin, a reddish pigment produced by *Fusarium fujikuroi*, carries bikaverin synthesizing bik gene cluster [160]. *Monascus* red pigments biosynthesizing genes in *Monascus ruber* and *M. pilosus*, are designated as MrPig, and mok gene clusters, correspondingly [161,162]. Other strains of *M. pilosus* possess *MppKS5* and *mpp* genes [163], whereas *M. purpurea* bears *MppKS9* and *mok* gene cluster [164]. The *crt* genes are involved in the biosynthesis of carotenoids in *Brevundimonas* sp. [165], *Hematococcus pluvialis* [166], *Deinococcus wulanhensis* [167], *Xanthophyllomyces dendrorhous* (Phaffia rhodozyma) [168], Antarctic bacteria [169], and other bacteria [170]. *Dunaliella* sp. carotenoids are mainly triggered by two essential genes *CGP* and *LCYB* [171]. In *Rhodotorula mucilaginosa*, CAR gene cluster synthesizes carotenoids [172].

9. Substrates, Mutagen Agents, and Adsorbents

The use of natural agro-industrial wastes has been a recent trend and strategy in the biotechnological process to increase pigment yield. The natural and genetically engineered microbes are subjected to fermentation studies to identify the optimal culture conditions for maximum pigment yield with various substrates (Table 1). A variety of cost-effective substrates such as copra seed, peanut seed, sesame seed, coconut oil, peanut oil, sesame oil [173], sunflower oil [174], peanut powder [175], corn steep liquor, cassava waste [176], squid pen powder [175], brown sugar [177], tannery fleshing [178], ram horn peptone [179], kitchen waste [180], wheat bran [181], casein, sweet potato powder [182], bagasse [183], saw dust, palm oil fiber and rice husk [184] had been utilized to enhance and improve the prodigiosin pigment production from *S. marcescens*. Violacin production rate was increased using brown sugar, molasses, sugarcane bagasse, and pineapple waste [185,186]. The enhanced production of pyocyanin from *Pseudomonas aeruginosa* was successful with cottonseed meal [187].

*Monascus* pigment production was enhanced by utilizing tapioca starch [188], cassava powder, coconut oil cake, groundnut oil cake, jackfruit seed powder, rice bran, palm kernel cake, sesame oil cake, spent brewing grain, tamarind seed powder, wheat bran [189,190], cheese whey, grape waste, rice hulls, soybean bran [191], coconut residue, cornmeal, peanut meal, soybean meal [192], corn cob [193], jackfruit seed [194], a variety of rice [195–197], durian seed [198], sugarcane bagasse [199], sweet potato [200], and brewery’s spent grain [201].

Carotenoids production in yeasts was improved by supplementing peat extracts [202], grape juice [203], beet molasses, glucose syrup, grape must, maize flour extract, soybean flour extract [204], cane molasses [205–207], sugar cane juice [208], corn syrup [207,209], coconut milk [210], brewer malt waste [211], corn meal [212], mustard waste [213], raw malt extract [207], tomato waste [214], chicken feather peptone [215], whey filtrate, coconut water [216], date palm waste, maize waste, mango peels, onion waste, peanut leaf and fruit wastes, potato peels, rice straw, sugarcane waste, wheat straw [217], and powders of onion peel, mung bean, pea pods and potato skin [218].
Table 1. Substrates promoting high pigment yield from various microbes are alone detailed herein for further biotechnological applications.

| Organism     | Substrate               | Pigment         | Maximum Pigment Yield | Reference |
|--------------|-------------------------|-----------------|------------------------|-----------|
| **Bacteria** | **S. marcescens**       | Peanut seed broth | Prodigiosin            | 38.75 mg/mL [173] |
|              | **S. marcescens**       | Cassava waste   | Prodigiosin            | 49.50 mg/mL [176] |
|              | **S. marcescens**       | Tannery fleshing | Prodigiosin            | 33 mg/mL   [178]  |
|              | **S. marcescens**       | Ram horn peptone | Prodigiosin            | 27.77 mg/mL [179] |
|              | **S. marcescens**       | Kitchen waste   | Prodigiosin            | 22.3 mg/mL  [180] |
|              | **S. marcescens**       | Bagasse         | Prodigiosin            | 40.86 g kg$^{-1}$ [183] |
| **S. marcescens** | Sunflower oil  | Undecylprodigiosin | 7.90 mg/mL [174] |
| **Chromobacterium violaceum** | Liquid pineapple waste | Violacein | 57.90 mg/mL [185,186] |
| **Pseudomonas aeruginosa** | Cotton seed meal | Pyocyanin | 9.2 µg/mL [187] |
| **Fungi**    | **M. purpureus**        | Jackfruit seed  | Monascus               | 10.2 OD/g  [189]  |
|              | **M. purpureus**        | Grape waste     | Monascus               | 20–22.5 g/L [191] |
|              | **M. purpureus**        | Corn meal       | Monascus               | 129.63 U/g  [192] |
|              | **M. purpureus**        | Corn cob        | Monascus               | 25.42 OD/g  [193] |
|              | **M. purpureus**        | Brewery’s spent grain | Monascus | 16.75 UA$^{500}$ [201] |
| **Yeast**    | **Rhodotorula rubra**   | Peat extract    | β-Carotene             | 1256 µg g$^{-1}$ [202] |
|              | **Rhodotorula glutinis**| Grape must      | Carotenoid             | 915.4 µg g$^{-1}$ [204] |
|              | **Rh. glutinis**        | Molasses        | Carotenoid             | 185 mg L$^{-1}$ [206] |
|              | **Rh. glutinis**        | Chicken feather peptone | Carotenoid | 92 mg L$^{-1}$ [215] |
| **Xanthophyllomyces dendrorhous** | Grape juice  | Astaxanthin     | 9.8 µ g mL$^{-1}$ [203] |
|              | **X. dendrorhous**      | Mustard waste   | Astaxanthin             | 25.8 mg L$^{-1}$ [213] |
|              | **X. dendrorhous**      | Molasses        | Carotenoid             | 40 mg L$^{-1}$ [205] |
|              | **X. dendrorhous**      | Coconut milk    | Astaxanthin             | 850 µg g$^{-1}$ [210] |

UA: Absorbance units; OD: Optical density.

Mutagenic agents such as various chemical reagents, UV illumination, and gamma radiation have been used to enhance pigment production from natural and recombinant microbial strains [219,220]. Carotenoid content of *Rhodopseudomonas palustris* was stimulated with blue, yellow, white, green, incandescent lamp, red, halogen, and fluorescence lamp [221]. The enhanced prodigiosin production was successful with gamma radiation [219]. Stimulated pigment production in filamentous fungi was evident with blue (for carotenoids) [222], green, red, and UV-light (red pigment bikaverin) [223]. Mutations in the genes caused *Fusarium fujikuroi* to produce different hues of pigments [160]. For yeasts, low energy ion beam implantation [224], gamma radiation [225], light-emitting diodes [226,227], and UV light [228] were used as an effective approach for carotenoids enhancement. High production of phycobiliproteins was achieved from cyanobacteria, *Pseudanabaena macicola* cultures grown under white light [229]. The increase of phycoerythin production from *Spirulina platensis* [230] and *Pseudanabaena* sp. [231] was evident under red light. Maximum production of phycoerythrin and carotenoids from *Pseudanabaena* sp. was observed in green light [231]. In unicellular microalgae, carotenoids production is enhanced through UV radiation [232–235], blue and red light [236,237], light-emitting diodes [238,239], and various toxic chemicals [233,240].

The use of various adsorbents in microbial fermentation appears to be the most effective strategy to enhance pigment production and maximum pigment recovery. Studies have utilized different internal adsorbents for maximum pigment recovery. Treating culture flasks with Silmacote to reduce attachment of pigment cells to a glass surface [241]; use of resins like X-5, HZ806, and HZ802 in cultures for pigment adsorption [242]; adding rice husks [243] or alginate beads to cultures for adsorbing more pigment cells [244]; addition of Diaion HP-20 resin [245–247] and polyurethane foam cubes [248] to cell culture are the additional strategies in prodigiosin pigment recovery. Monascin pigments are
recovered by adding rice, called “red mold rice” [161]. High monascus pigment yield was achieved with stirred drum bioreactor [249]. Various extraction techniques such as ionic liquid–assisted extraction, microwave-assisted extraction, ultrasound-assisted extraction, pressurized liquid extraction, pulsed electric field assisted extraction, and supercritical CO₂ extraction are employed to recover pigments from fungi [220]. Finding the new adsorbents and extraction techniques to recover pigments are important requisites in microbial pigment research.

10. Biomedical and Industrial Applications

This section provides various applications of microbial pigments that were not covered in the previous review [9]. Dozens of synthetic and natural pigments have been used in beverages, foods, dyeing, and textiles (Figures 5 and 6). A red-pigmented (related to carotenoid) Arthrobacter sp. offer the antitumor activity against esophageal cancer cells [71]. Prodigiosin produced by Pseudomonas rubra displayed antimicrobial activity against pathogenic bacteria and yeast [250]. Prodigiosin extracted from S. marcescens displayed potential insecticidal activity against Drosophila melanogaster larvae [175], ants, cockroaches, and termites [251]. Prodigiosin and glycolipid biosurfactant’s synergistic effect demonstrated antimicrobial activity against pathogenic bacteria [252]. Prodigiosin extracted from Zooshikella sp. and Streptomyces sp. and other pigments from marine bacteria displayed potential application in staining and food colorants [253]. Currently, in our lab, calcium oxalate and uric acid stones dissolving pigments from marine bacteria are being isolated. Prodigiosin from S. marcescens [254] and violacin from C. violaceum [255] promise to treat the chagas disease. Violacin pigment is employed in cotton fabrics dyeing [256], and lead detecting whole-cell lead biosensor [257]. Violacine produced by Microbulbifer sp. demonstrated antinematode activity against Caenorhabditis elegans [258]; a strain of violacine producing Chromobacterium isolated from the Himalaya region, produced by bioplastic polyhydroxyalkanoates [259].

Indigo pigment isolated from Pseudomonas sp. displayed antioxidant property [260]. Glaукothalin, a blue pigment produced by Rheinheimera sp., showed antibacterial activity against few marine bacteria [261]. Pyocyanin from Pseudomonas aeruginosa demonstrated textile dyeing properties, antifungal activity against blast fungus, Magnaporthe grisea, and antibacterial properties against blight of rice, Xanthomonas oryzae [262]. Micrococcus sp.’s yellow pigment showed excellent wound healing and anti-inflammatory property in albino rats [263]. Bacterioruberin carotenoids of halophilic bacteria have significant antioxidant and antibacterial activities [264]. Microbial pigments (Actinorhodin, carotenoids, flexirubin, melanin, phycocyanin, phycoerythrin, blue pigment) are also used to synthesize various nanoparticles with biological properties like antioxidant, antimicrobial, anticancer activities [265].

Fungal pigments were reviewed to have a wide range of applications in food colorants [266,267], bioactive properties, and textile dyeing [40,268–270]. In contrast, bacterial pigments like prodigiosin and violacine are used to color papers, candles, soaps, ink, clothes [271], and textile dyeing [272]. Monascus pigment or anthocyanin pigment are employed as noninvasive dye indicators in safe cell viability assay for Paramecium [273], Euglena [274], and breast cancer cells [275]. Microbes isolated from cryosphere environments also produced various pigments with multifaceted applications [269,276,277], including anticancer activities [278].

Carotenoids of archaea [100] and Thraustochytrids [279,280] have potential nutraceutical applications. However, pigments from marine archaea and protists remain the least studied groups. Red algae extracts are used to make L’Oreal Paris Pure Clay Mask for skin glow and smoothening. Similarly, other commercial cosmetic products have been developed from cyanobacteria and microalgae [281]. Phycobiliproteins from cyanobacteria and algae demonstrated cosmetic, dye, nutraceutical, and bioactive applications [282–284]. Marennine, a blue pigment produced by diatoms, Haslea species, promises antimicrobial, antiviral, anticancer, and antioxidant activities [285].
Figure 5. Chemicals structures of synthetic pigments.
Figure 6. Chemical structures of important microbial pigments.
11. Photo-Pigment Therapy

The combinations of light and pigments were found to be an effective strategy in antimicrobial assays. A study found that the bactericidal effect of blue light irradiated intracellular black pigment (protoporphyrin IX) on *Porphyromonas gingivalis* [286]. Likewise, flavin mononucleotide activated by blue light resulted in inhibition of *Staphylococcus aureus* biofilm [287]. Such strategies may be adopted and employed to increase the bioactive effectivity of microbial pigments against various pathogens.

12. Market Demand for Microbial Pigments

In recent times, people around the world have come to know the harmful effects of synthetic colorants in foods (Figure 7). Thus, demand on natural pigments is increasing over artificial colorants. In 1971, the United States spent around 1 billion US dollars to increase the supply of natural colorants from various natural resources [288]. There are inadequate or scarce data on the global market value of food-grade microbial pigments. Very few pigments such as β-carotene, astaxanthin, and monascus are available in the market. Lack of surveys and literature on microbial pigments’ cost and demand are becoming hurdles to estimate the actual global market demand on microbial pigments.

Figure 7. An illustration explaining the requirement of natural colorants over synthetic colorants.

Monascus pigments are traditional food colorants widely used in southeast Asian countries, which had an estimated market value of $12.0 million dollars during 1992 [289]. Monascus pigments are prohibited in the United States and Europe due to the presence of mycotoxins [290]. The global commercial market value for carotenoids reached $1.2 billion in 2010, $1.5 billion in 2014, and is expected to reach $2.0 billion by 2022 [228,291,292], with an annual growth rate of 5.7% for the period 2017–2022 [293]. Prodigiosin and violacein (chemical standards) are fetching about $5000 × 10^5 per kg in the market [271]. Natural carotenoids (24%) are gaining a high market value of $350 to 7500 kg⁻¹ than synthetic carotenoids (76%) with a value of $250–2000 kg⁻¹ [294]. Astaxanthin and β-carotene are the highly demanded pigments globally with an expected market value of $225 and $309 million dollars by 2018, respectively [295]. Lutein is a xanthophyll pigment expected to gain a $308 million market value by 2018 [296]. The global market value of carotenoids is projected to reach up to 2.0 billion by 2026 [297]. According to the global phycobiliproteins market research report, market demand for phycobiliproteins is expected to rise by 2026.
Currently, the phycobiliproteins (10 mg) price in Merck ranges from $200 to $270. A recent report has estimated the expected global dyes and pigments market value of $33.2 to 49.1 billion dollars by 2027 [298]. Indeed, 80 to 90% of the carotenoids supply in the market is fulfilled via chemical synthesis [299]. However, due to synthetic colorants’ side effects and the expensive pigment source of plants, microbial pigments have been gaining high demand in recent times. Therefore, finding potential promising microbes became a research interest in food and drug industries. For instance, yeast carotenoids’ market value has declined due to low dry weight production (0.40%) compared to algae, Haematococcus sp. (3.0%) [295]. In the current global population rise scenario, demand for edible microbial pigments as food colors is expected to rise to fulfill the food industry requirements [300].

Microbial species with high biomass and pigment yield, including the genetically modified microbes, are highly interested in the current research. On the other hand, in view of the side effects posed with synthetic colorants [31,36,301], the scientific community has to reach the public through various social programs to make awareness about the importance of natural pigments and negative impacts of synthetic colorants on health. These awareness programs would save many lives from various health disorders, including life-threatening cancer.

13. Future Perspective

Microbial pigments demonstrated a wide variety of applications in food, drug, and textiles. These natural pigments can replace synthetic colorants and fulfill the emerging need on food colors in the global market. Microbial pigments play an indirect role in the conservation of plants and animal resources by substituting them from pigment resources. Many researchers are restricted to pigments like prodigiosin, violacein, monascin, astaxanthin, lutein, and phycobiliproteins. Therefore, exploring other microbial pigments from different environments would offer novel and potential known pigment molecules for multifaceted applications. Research on microbial pigments would ultimately reveal the evolutionary lineages of origin of life and the dispersal of various chromophore-based phenomena in all lineages. Isolation and chemical characterization of microbial pigments are easier than non-pigmented microbes, whose compounds’ characterization is arduous and time-consuming. Thus, focusing on microbial pigments would garner more attention to research and development and their economic demand in various industries.

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