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DISCLOSE PRODIGIOSIN: CHEMISTRY, BIOLOGY AND INDUSTRIAL APPLICATION

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Abstract

The red tripyrrole pigment known as prodigiosin (PG), which belongs to the prodigiosin family, is an interesting substance that has attracted the attention of scientists due to its versatility. Thanks to its striking red pigment and distinctive chemical characteristics, prodigiosin has caught the attention of researchers seeking new solutions across a variety of disciplines. *Serratia marcescens* and other bacteria like *Hahella chejuensis*, *Vibrio gazogenes*, *Pseudoalteromonas rubra*, *Janthinobacterium lividum*, *Actinomadura madurae*, and *Streptomyces coelicolor* produce prodigiosin, a red pigment that functions as secondary metabolite. Prodigiosin has shown promising activity as an antibacterial agent in numerous experiments. Prodigiosin is a promising treatment for combating antibiotic-resistant strains and increasing effectiveness of current antibiotic treatments in the face of increasing environmental antibiotic resistance. Furthermore, numerous studies have shown that this natural pigment possesses anticancer characteristics through growth inhibition and spread of cancer cells by the induction of programmed cell death in cancer cells without seriously harming healthy cells. PG have antiviral, antiprotozoal, antifungal, and many applications in food industry. This study aims to elucidate chemical and biological properties of the dye and to assess its potential as a biotherapeutic alternative to conventional antibiotics in the treatment of pathogenic bacteria, fungi, and parasites. Furthermore, it explores the dye's prospective role in cancer therapy and its application within the food industry as a natural colorant and preservative offering a safer substitute for synthetic additives known to have adverse effects on human health.

Keywords: *prodigiosin, Secondary metabolites, nature pigment, Serratia marcescens, anticancer.*

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Introduction

Although virtually every organism is capable of synthesizing some pigments in its system, plants and microorganisms are the major cellular factories capable of producing large quantities of dyes and food colorings for commercial production (1,2). Natural plant-derived pigments exhibit diverse properties, including sensitivity to temperature or pH, photostability, poor solubility in polar solvents, and year-round availability (3). In contrast, pigments made from microorganisms are remarkably stable at high temperatures or pH and are soluble in a variety of solvents (1,4). Furthermore, fermentation techniques facilitate the cultivation of microorganisms in laboratories and large-scale reactors, and subsequent processing is simple and straightforward. In the quest to find safe and bio-compatible alternatives to drugs that have been chemically synthesized, long-term research has been conducted on bacterial secondary metabolites. Bacterial pigments are colorful and diverse substances produced via microorganisms and are one of the intriguing chemical groups with a variety of the pharmacological characteristics. (2) These chemicals have long captured the curiosity of scientists due to their possible medical applications. Because of their unique physiological characteristics, such pigments—which are produced through different bacterial species—make intriguing candidates for a range of biomedical study fields (1). Recently, there has been a notable increase in using natural pigments in a variety of commercial areas, such as cosmetics, food, and health (4). As substitutes for synthetic pigments which can have negative side effects, such pigments are promoted. A lot them were phased out of the business because of severe environmental issues as well as evidence regarding their carcinogenic effects (5,6). With the chemical formula $C_{20}H_{25}N_{30}$, prodigiosin is considered a natural dye. It is a well-known secondary metabolite as well as a red linear tripyrroline-based dye accumulating in the intracellular granules and cell membranes of Gram-negative as well as Gram-positive bacteria.(7) These bacteria can be found in certain places, including *Serratia marcescens*, marine bacteria, *Pseudomonas magnesiorubera, Streptomyces griseoviridis,* actinomycetes, and *Vibrio* species (8,9). Various biological effects are exhibited by such metabolite, including anticancer, antiviral, antibiofilm, antibacterial, and antiparasitic qualities (3,5). Prodigiosin has been shown to have antialgal activity against the hazardous algal blooms (HABs) in oceanography (10). There has been a global shift toward minimally processed and natural alternatives due to growing worries about the hazards regarding chemical-based cancer therapies, antibiotics, along with the emergence regarding resistant microbial strains, as well as the negative health consequences of synthetic food colorants. Prodigiosin is one of them that has garnered a lot of interest because of its wide range of biological activity and possible uses in the healthcare and food sectors. In order to emphasize prodigiosin's potential as a promising natural substitute for numerous synthetic compounds, the presented work will look at its essential characteristics, biological impacts, and chemical composition.

Prodigiosin: characteristic features.

Throughout microbial metabolism, prodigiosins (PGs), physiologically active pigment molecules, are created. This family includes microorganisms like *Serratia marcescens*. Prodigiosins have been isolated as well as structurally characterized in the 1930s, but it wasn't until the 1960s that their full elucidation and structure have been determined (11). Bacterial prodigiosins can be classified as either cyclic or linear. While cycloprodigiosin, streptotropin B, and cyclononylprodigiosin are instances regarding cyclic derivatives, undecylenylprodigiosin and prodigiosin are examples of linear derivatives. The red dye can be defined as a tripyrrole molecule made up of 2-methyl-3-amylpyrrole (ring C) and pyrrole (ring A), 3-methoxypyrrole (ring B). Its IUPAC nomenclature is 5[3-methoxy-5-pyrrole-2-ylidene-pyrrole-2-ylidene(-methyl)-2methyl-3-pentyl-1H-pyrrole. Rings B and A are linked to a dipyrrole unit, whereas rings C and B are linked to a dipyrene compound (2). Consequently, the existence regarding a pyrrole-dipyrrolemethine structure with a 4-methoxy, 2,2-dipyrrole ring system (6) could be the distinctive sequence regarding such compounds.

The molecular formula of PG from S. marcescens is C20H25N3O(2,5), and it has linear tripyrrole structure (2methyl-3-pentyl-6-methoxyprodigenine). According to electrospray ionization mass spectrometry, PG's molecular weight is 323.4g/mol, the logarithmic p-value is 4.7, and the maximum absorption is at 535nm in acidic ethanol (pH 3) (1). PG is well soluble in acetone, acetonitrile, methanol, ethanol, hexane, DMSO, and chloroform, but poorly soluble in water (5,12). Prodigiosin is structurally similar to prodigiosin R1 and undecyl-prodigiosin; those molecules are known as prodigiosin due to their distinctive tertiary pyrrole structure (2). *Streptomyces coelicolor* A3 was found to produce a cyclic derivative that is called butyl-metacyl-heptyl-prodigiosin in a 2:1 ratio, as well as a tertiary pyrrole called undecylprodigiosin, which has structural similarity to prodigiosin.

Similarly, 2-(phenhydroxybenzyl)prodigiosin and cycloprodigiosin are known to accumulate in *Pseudoalteromonas* species. Interestingly, prodigiosin accumulation has not been observed in actinomycetes identified with undecylprodigiosin, and similarly, γ-proteobacteria strains accumulating prodigiosin have not been found to accumulate undecylprodigiosin (2).

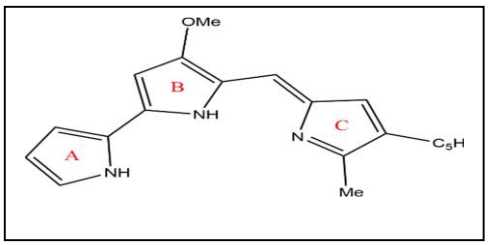

Figure 1.Prodigiosin structure (5)

The quorum sensing system, along with other nutrient sensors, regulates prodigiosin production by *Serratia marcescens* during the stationary phase when glucose levels are low (6). The presence of ATP, glucose, or phosphate in the medium leads to the inhibition of

prodigiosin production. Environmental temperature also affects production; prodigiosin is not generated at 37°C (11), and is most optimum between 25 and 30°C. In *Serratia species*, the majority of the pigment remains cell-bound, while a small fraction is released into the medium (13). The bacteria from which prodigiosin was initially isolated were *Bacillus progious*, this bacterium was later renamed *Serratia marcescens* (5,12,14).

Prodigiosin biosynthesis

Progiosin-producing microorganisms were cloned into heterologous hosts, such as *Serrati*a sp. ATCC39006 (S39006) and *S. marcescens* ATCC274 (Sma274), and their genes were sequenced and expressed by Harris et al. in 2004. Then, in 2006 and 2010, respectively, the genes of *Hahella chejuensis* strain KCTC2396 and *Janthinobacterium lividum* BR01 (JliBR01) have been sequenced (3). A complex regulatory network of N-acyl-L-homoserine quorum-sensing and N-acyl-L-homoserine-independent pathways regulates progiosin production (6). There are 13–15 genes associated with PG synthesis in different microorganisms (4), while the porcine Serratia 39006 group contains 15 porcine (A-O) synthesis genes that are transcribed as polycistronic mRNA (2)..

Prodigiosin biosynthesis involves two parallel cytoplasmic pathways including the production of 2-methyl-3-pentylpyrrole (MAP) and 4-methoxy-2,2′-bipyrrole-5-carbaldehyde (MBC) respectively. These intermediates are then condensed by the enzyme Pig C to form the final prodigiosin molecule.(6,15)

Analysis of prodigiosin and derivatives

While quantitative analysis is carried out with the use of UV–Vis spectroscopy and chromatography approaches, qualitative analysis of prodioscin and its derivatives has been determined using a variety of approaches, which include UV–Vis spectroscopy, high-performance liquid chromatography, nuclear magnetic resonance, thin-film liquid chromatography, gas–liquid chromatography, and Fourier transform infrared techniques (14,16,17). According to UV-vis spectrophotometer, the maximum absorption of prodigiosin dissolved in methanol ranged between 460nm to 540nm, depending on solvent pH (17, 18). The change in maximum absorption value under alkaline pH is a result of the deprotonation of nitrogen atoms in the pyrrole rings. Similarly, the methanolic extract of undecylprodigiosin and cycloprodigiosin was found to achieve maximum absorption values at wavelength values of 530 and 533nm, respectively. *Vibrio spartina* produced a new pigment called isoheptylprodigiosin 3.6, which exhibited maximum absorption at 537nm (18). Which is why, crude red pigments with linear or cyclic derivatives exhibit the highest absorption between 530 and 540 nm (2,19). Prodigiosin in potassium bromide derived from *Serratia marcescens* exhibited maximum absorption at wavelengths of 3.375, 2.951, 1.646, and 1.556 nm, according to a Fourier transform infra-red (FTIR) study of prodigiosin pigments in the frequency range 4000–400 cm−1 (18,14). High-performance liquid chromatography (HPLC)

that can provide qualitative and quantitative analysis in presence of UV-vis and mass spectrometry as detectors, is commonly used for the analysis of prodigiosin pigments (17). The one-hydrogen nuclear magnetic resonance (1H-NMR) spectrum of prodigiosine shows a number of peaks associated with different chemical shifts. (19)

Factors influencing Prodigiosin production

A secondary metabolite called prodigiosin is typically produced during successive substages of bacterial growth. Many factors, including temperature, pH, ambient conditions, inorganic phosphate availability, and medium composition, influence prodigiosin formation (2, 5). For prodigiosin synthesis, several differential and selective media options were developed. Nutrient broth (0.52mg/ml) and peptone-glycerol broth (0.302mg/ml) are among the few basic media components proven effective for prodigiosin synthesis (2, 17). An experimental study, when *Serratia marcescens* was grown using ground sesame seeds in water, nutrient broth, and peptone-glycerol broth, showed significant improvement (3, 20). Ground sesame seeds showed the highest prodigiosin production in nutrient broth at 28°–30°C among the three low-cost sources tested: peanut oil, coconut oil, and sesame oil. Furthermore, a significant amount of prodigiosin was formed in ground peanut broth incubated at 37°C, comparable to the production of pigmentation that is observed in nutrient broth at 30°C (20). According to published research, prodigiosin production is inhibited by the presence of inorganic nitrogen sources, like urea and ammonium salts such as (NH4)2SO4, NH4Cl, and NH4NO3. Peptone, a cheap organic nitrogen source, may be an excellent alternative in this particular case because it contains a variety of amino acids (4, 20). and casein (6). Prodigiosin production in these strains is significantly influenced by carbon sources. When various carbon sources, including dextrin, maltitol, sucrose, lactose, citrate, starch, glucose, and glycerol, were examined for *Serratia marcescens'* growth, glucose was found to be the most effective source, as evidenced by a 38% increase in prodigiosin concentration compared to control conditions (2, 4, 5, 6). Several studies have shown that *Serratia* sp. requires a pH between 5.5 and 8 for optimal growth and prodigiosin production (5, 4, 6). Another critical factor affecting prodigiosin synthesis is temperature. For example, *Serratia marcescens* produced less prodigiosin when the temperature was raised from 30 to 37°C, while decreased expression levels of the prodigiosin operon were observed when the temperature was lowered to below 22°C (17, 20,21).

Extraction& Purification of Prodigiosin

To extract prodigiosin, various extraction techniques have been used, including homogenization, ultrasound, freeze-thaw, heat treatment, organic solvents, and inorganic acids (4).Centrifugation is used to separate cells after fermentation. Because prodigiosin is insoluble in water, it is typically separated using an organic solvent extraction technique (2).

The resulting pigment is reconstituted in ethanol after drying in a vacuum dryer. Liquid chromatography is an excellent choice for the quantification of prodigiosin, using a glass column and silica gel (6). In column chromatography (3,4), the sorbent is coated with an ethanol-suspended dye, obtained from the final stage of the extraction process. The sorbent surface is coated with the ethanol-dissolved dye, which is subsequently eluted from the column at a 3:1 hexane-acetone ratio:acetone. Hexane-ethyl ether-acetic acid (70:30:1) is then used in preparative thin-layer chromatography on silica gel 60 F254 glass plates to further purify the dye (6). After removing the individual dye bands from the plates, the dye has been extracted from silica gel with the use of 96% ethanol, acetone, and chloroform, in that order (2,3). With a pure propylene glycol extraction rate of 98.1 ± 1.7%, ultrasound is a potentially promising approach for expanding commercial use. Freezing and thawing produced the lowest extraction rate, 31.80 ± 3.80% (4).

Biological activities of Prodigiosin

1.Anti-bacterial Activity

Gram-positive as well as Gram-negative bacteria are sensitive to potent antibacterial activity of PG. Several researchers have proposed three ways to explain the antibacterial activity of PG: cell cycle inhibition (17,22), pH modification (2,23), and bacterial DNA cleavage (by inhibiting target enzymes like DNA gyrase and topoisomerase IV) (2,4,3). Furthermore, reactive oxygen species (ROS) production and phototoxicity are considered possible pathways (5). The antimicrobial properties of PG are believed to be not limited to the destruction of specific cellular targets; rather, they may also have pleiotropic effects on bacterial physiology, like disrupting outer membrane integrity, causing plasma membrane leakage, activating cellular enzymes, and cell lysis (23). The growth phase has been found to influence the induction of cell lysis, with the mid-logarithmic growth phase showing maximum lytic activity, while the stationary phase produces bacteriostatic activity (14). Strong antibacterial activity against *S. aureus* was shown by the potent bactericidal chemical prodigiocin. Following 48 hours, prodigiocin considerably reduced *S. aureus*-induced skin infections in in vivo animal tests. The results regarding the histopathological analysis revealed better tissue quality as well as the appearance regarding infection-free, healthy tissue when comparing control group and *S. aureus* group with S. aureus + prodigiocin group. Prodigiosin is one of the possible microbial metabolites that is effective against the *S. aureus* infection, according to histopathological results. Exchange analysis in in-vivo studies has verified the antibacterial results (24,25). The potential application of prodigiosin (PG) as natural biocide was investigated; this is particularly true in the case when paired with biological surfactants, which increase PG's antibacterial activity as well as lessening the requirement for synthetic antibiotics. The significance regarding such natural substances in the development of alternative therapeutic approaches is underscored by the growing worry over antibiotic resistance (26,27).

2. Antifungal Activity

Among other fungal diseases, prodigiosin has antifungal activity against dermatophytes as well as plant pathogenic fungi(23). Prodigiosin, for instance, efficiently suppresses dermatophyte spores, like *Microsporum cookie*, *M. ajelloi*, and *Trichophyton longfeuseus* (14, 28). *Trichoderma viroidea, Aspergillus niger, Microsporum canis*, *Penicillium chrysogenum*, *Fusarium moniliforme*, *Candida albicans*, *Trichophyton trichinella*, *Trichophyton rubrum*, *Aspergillus flavus*, *Fusarium oxysporum*, with minimum inhibitory concentration of 8, 10, and 21 µg mL−1 respectively (1, 2, 4). Purified prodigiosin has been shown by other studies to be efficient against significant plant pathogens, including *Coccleopulus meabenus*, *Phytophthora capsicum*, *P. altemum*, and *Pythium spinosum*, indicating that it may find application in agricultural settings. It was previously been demonstrated that the plant-pathogenic fungus *Fusarium* and *Alternaria* are strongly inhibited by purified PG(1). *S. marcescens* produces prodigiosin, which has been utilized to investigate spore germination inhibition. The germination rate decreased by one-third in the case when 10 µg/ml of PG has been added (4). Antifungal qualities are directly related to its capacity to damage fungal cell membranes and cause oxidative stress, which reduces the cells' capacity to survive (14, 28). The efficacy regarding PG against the amphipathogenic bacterium *Batrachochytrium dendrobatidis*, was confirmed, indicating its potential as one of the bioactive substances in the treatment regarding fungal infections. PGs wide range of antifungal properties makes it one of the promising candidates for developing novel antifungal drugs without making patients resistant to traditional antifungal treatment (1).

3. Antiparasitic Activity

Progigiocin's ability for treating neglected diseases like amebiasis, malaria, and Chagas disease has been shown in many studies (4). The antimalarial activity regarding progigiocin as well as its derivatives against the *Plasmodium falciparum* D6 was investigated with the use of chloroquine as reference drug (1, 2, 23). In a direct comparative evaluation regarding their antimalarial activity, progigiocin (1), undecylprodigenin (2), metacycloprodigenin (3), and streptotropin B (4) have been found to have very strong antimalarial activity against *P. falciparum* D6, with extremely low IC50 values (8nmol, 7.70nmol, 1.70nmol, and 7.80nmol, respectively). They also found to be marginally more active compared with chloroquine (11 nmol) (29). Furthermore, it was discovered that such dyes work well against *Entamoeba histolytica*, *Schitosoma*, *Trypanosoma cruzi*, and *T. brucei* (2). The effects regarding PG and benznidazole, a drug utilized for treating Chagas disease, have been contrasted in one research. Two distinct strains of *T. cruzi* exhibited lower IC50 values compared to benznidazole after being exposed to PG. Oxygen uptake as well as mitochondrial membrane potential tests showed the anti-*T. cruzi* effect, which is a behavior that is comparable to PG-induced apoptosis (30,6).

This pigment's antiamoebic qualities were researched for a long time. Tests on two distinct strains—one linked to a mixture of bacteria and the other only to *Aerobacter aerogenes*—were the first to demonstrate PG's direct effectiveness against the *Entamoeba*

histolytica. In vitro, the two strains demonstrated cytotoxic effects. Since PG treatment was linked to changes in pH and redox potential, the authors of this study came to the conclusion that PG has direct and substantial impact on *E. histolystica.*

Additionally, PG demonstrated a cytotoxic effect against *E. histolytica* strains resistant to the antibiotic metronidazole (MNZ), which is currently utilized in order to treat amebiasis. Furthermore, a significant effect was observed on larger mature cysts compared to MNZ, suggesting that PG may be an effective therapeutic option in cases of clinical resistance to MNZ (31).

4. Anticancer

Prodigiosin action mechanism affects cancer cell death as well as immune responses. PG dye can be specified as a promising application since it could inhibit the proliferation of the cells of cancer while having no negative impact on health tissues. Prodigiosin is a preferred option for the production regarding pharmaceutical drugs for treating cancer because of its harmful impact on cancer cells (1). Various research have examined its capacity to prevent cancer cell growth in vitro and tumor progression in vivo (2). Through cell-specific mechanisms, like Wnt/β-catenin inhibition (in cells of breast cancer), cyclin D1 decrease (in breast cancer cells), and p53 tumor suppressor activity (in stem cells of the colorectal cancer), about 60 cancer cell lines have shown anti-cancer activity of PG. Additionally, cell lines from hepatocellular carcinoma and melanoma have shown anticancer activity (1, 3, 5). Human epidermal laryngeal carcinoma (HEp-2), mucoepidermoid lung carcinoma (NCIH-292), human myeloid leukemia (HL-60), and mammary adenocarcinoma (MCF-7) have all been investigated for toxicity against prodigiocin, which is produced from *Serratia marcescens* strain UFPEDA 398. The research results have shown that prodigiosin had an IC50 value of 3.4µg/ml-1 in NCHI292, HL60, and Hep2 cell lines, while MCF-7 cell lines had a higher IC50 value of 5.10µg/ml-1 (2,32). PG apoptotic activity has been investigated using the human gastric cancer cell line (HGT-l), and the findings consistently demonstrated apoptosis-induced reductions in cell viability. Furthermore, morphological evidence—like chromatin condensation and cell shrinkage—was discovered that suggests the Prodigiosin is apoptotic factor. Both in vivo, utilizing tumor-bearing JEG-3 and PC-3 nude mice, and in vitro, utilizing human choriocarcinoma (JEG3) and prostate cancer (PC3) cell lines, prodiosin's anticancer properties were examined. In line with its anticancer properties in vitro, bacterial prodiosin caused JEG3 cells to undergo apoptosis. The proliferation regarding JEG3 as well as PC3 cells was markedly suppressed; the inhibitory efficacy varied with time and dose(7).

5. Antiviral Activity

Herpes simplex virus (HSV), Bombyx mori nuclear polyhedron virus (BmNPV), and the new coronavirus (SARS-CoV-2) are only a few of the viruses that PG exhibits strong antiviral effects against. (1)

Targeting virus-infected cells selectively, disrupting the viral replication, and inhibiting the transcription of viral genes are the mechanisms behind its antiviral effect (33). Laboratory

studies showed that PG could particularly destroy BmNPV-infected cells, stopping the virus's early replication. This is accomplished by limiting viral membrane fusion, necessary for viral entrance into host cells, and through suppressing the transcription of viral genes, with an emphasis on early genes, like ie-1 (34). The capacity of PG of inducing selective cytotoxicity in infected cells while preserving healthy cells had demonstrated its potential as one of the therapeutic agents in anti-viral technology. PG was demonstrated to have inhibitory effects towards enterovirus (33).

Another study had demonstrated that obatoclax, a derivative of PG, has antiviral properties against alphaviruses. The researchers hypothesized that the antiviral effect of obatoclax results from changes in the pH of the endosome, preventing virus fusion with the cell (34). Subsequent anti-viral studies of SARS-CoV2 by using obatoclax showed that viral replication was inhibited in epithelial cell cultures. This inhibition mechanism has been again linked to endosome acidification and the inhibition of furin and cathepsin (1,34).

6. Algilicidal Activity

Due to excess nutrients, these algae can cause fish kills, oxygen depletion, and disruptions to marine food chains. Fishing and tourism losses resulting from beach closures and water quality problems are included in the economic impact (5). To mitigate these negative impacts, effective management and control techniques must be implemented (10). Among the algal species effectively controlled by are *Prorocentrum donghaiense*, the red-tide dinoflagellates, *Heterosigma akashiwo, Phaeocystis globosa*, and *Microcystis aeruginosa* (35). This dye, depending on its concentration, has shown high algal control efficacy against some red-tide phytoplankton, including *H. akashiwo, H. circleisquama*, *C. polykrikoides, G. impudica,* and *A. tamarense* (6). The PG have effect on harmful algae *Phaeocystis globose* different concentrations have been added into *P. globosa* cultures and 5µg/mL presented a better algicidal effect/ dose-response. Following 72 hrs of treatment, 84% of algal vigor was attained. Furthermore, the median lethal dose (LD50) regarding PG throughout a 24-hour period has been 2.24 µg/ml. Examining the morphological consequences after PG treatment, plasmolysis as well as cell shrinkage were found. Furthermore, with the increase of exposure time, algal cells dissolved and disintegrated. Additionally, the treatment reduced the motility of normal cells by causing them to lose their flagella. Lipid peroxidation and generation of ROS are caused by such treatment's inhibition of the life cycle of dangerous algal cells (4,5).

Prodigiosin For Industrial Biotechnology

Known as "industrial biotechnology," such developing economic sector capitalizes on biological materials' capacity to create a variety of products, like food, chemicals and drink, vitamins, medications, bio-fuels, and raw materials. With regard to industrial biotechnology, bioactive compounds are not only produced from living organisms but are used as additives to increase product functionality as well as technological features (1). It was demonstrated that PG has enormous potential for use in a variety of industries, like the cosmetics, food, and textile sectors (36,37).

Prodigiosin as Industrial Colorant.

Synthetic dyes, a lot of which are exotic and dangerous substances that pose a major threat to aquatic life, have long been utilized in textile industry (1). Synthetic dyes as well as their residues accumulate and have the potential to cause cancer in future and current generations because of their resistance to microbial degradation. Natural colors are gaining popularity since they are less hazardous to human health, more environmentally friendly, and more biodegradable compared to synthetic dyes (17). Microbial dyes are a possible substitute for other bio-based dyes derived from animals or plants in addition to synthetic dyes. Prodigiosin has drawn more attention as a natural colorant because of its antifungal, antibacterial, and antiparasitic qualities, which could offer further utility. (38,39)

Additionally,PG-dyed paper has shown potential use as a pH indicator (17),also had been applied as one of the natural colorants in candles, soaps, and as a bio-degradable ink (37). In food industry, prodigiosin demonstrates promise as a safe natural colorant, further enhanced by its antioxidant and antimicrobial properties (38,39).

Cosmetics containing prodigiosin

The number of the pigments that are used in cosmetic products is increasing due to the rapid expansion of the cosmetics industry as a global market for companies. The global cosmetic pigment market has been valued at approximately US$700 million in 2022 and is expected to exceed US$1,532.31 billion by 2032 (1). Thanks to its biological functional properties, prodigiosin is a more beneficial color additive than traditional cosmetic colorants. In addition to its role as a UV protector, this bacterial pigment helps extend the shelf life of cosmetic products and reduce unpleasant odors by inhibiting bacterial growth (17). Since lipids or lipophilic substances are commonly used in cosmetics, the lipophilicity of PG qualifies it for use in the cosmetics sector (1). Advantageous properties of the dye in the cosmetics sector include its limited water solubility, a broad range of colors (from pink to orange and red), varying pH saturation, and brightness (17). Researchers used a pouring technique to color soap by adding a specific amount of dye, which demonstrated excellent color stability at different salinity levels.

Given the reduced exposure to hazardous synthetic substances, natural dyes are generally preferred as colorants due to their low toxicity and low incidence of allergic reactions (37, 17). To improve the properties of commercial sunscreens, *Aloe vera* leaf and cucumber fruit extracts were combined with the bacterial pigment prodigiosin (PG) and violacein. The sun protection factor (SPF) regarding the plant extracts rose dramatically to about 3.5 after such bacterial pigments were added, but SPF values of commercial sunscreens that contained 4% (w/w) prodigiosin increased by 20–65% (40). Compared to ascorbic acid, an effective and well-known antioxidant, prodigiosin showed about 30% more antioxidant activity.. These findings demonstrate Prodigiocin antioxidant and antibacterial qualities.This pigment also helped plant extracts and store-bought sunscreens achieve higher SPF ratings (3, 40).

Apart from its bioactivity, PG was investigated as a natural pigment in nail polish and other cosmetic compositions (17).

- **Prodigiosin in the Food Industry**

Both as a preservative and a natural colorant, PG's beneficial qualities enable its use in food sector (3). Its vibrant red hue could give food products a visually appealing appearance, and its antibacterial properties help to prolong their shelf life (39). Because of their low health hazards and low toxicity, marine-derived bacterial bio-pigments (bpBPs), such as PG, are regarded as promising food-grade additives (1). Further lowering any possible safety issues is their strong color saturation, which enables efficient use at low doses. Furthermore, it was proposed that bpBPs be added to ornamental fish diet for promoting growth and improving coloration. The promise of PG generated from marine bacteria, including *Zooshikella* sp., as a sustainable pigment for food applications has been highlighted by its good coloring capabilities and up to three-month shelf stability (1). Agar-based jellies were explored using concentrated and crudePG-like pigments that were isolated from marine bacteria as colorants. To evaluate pigment stability over time, 500 µg of pigment was added to 5% agar jellies, which were then molded, cooled, as well as kept at 4 °C for several months (41, 42). Strong antioxidant and iron-chelating properties have been demonstrated by purified prodigiosin. This is particularly relevant for iron-rich foods such as liver, red meat, and spinach, which may contribute to iron accumulation and ferroptosis, especially in sensitive organs such as the liver. PG has been found to inhibit ferroptosis, reduce intra-cellular iron levels, and modulate genes involved in the metabolism of iron, suggesting its role in maintaining redox balance and protecting against iron-induced oxidative stress (39).

Antifouling Agent

Marine bio-fouling has become a significant challenge for industries operating in maritime environments. The accumulation of biofilms and marine organisms on ship hulls such as in dreadnought-class vessels—increases surface roughness, thereby elevating frictional resistance and energy consumption (1). As an environmentally friendly alternative to conventional toxic, metal-based antifouling agents, natural antifoulants derived from bacterial bioactive metabolites have been proposed as promising candidates (26). In vitro, prodigisin has demonstrated antibiofilm activity against drug-resistant *Pseudomonas aeruginosa* and *Staphylococcus aureus,* primarily through inhibition of the growth of extracellular polysaccharides and pyocyanins. The ability of PG to produce antiscalc layers with minimal leakage into seawater is enhanced by its hydrophobic properties (27). Prodigiosin derived from *Serratia marcescens* CMST07 also demonstrated antiscalcification properties against *Alteromonas* and *Gallionella*, two marine sediment-causing bacteria. In addition, PG prevented *Bacillus* and *Pseudomonas* from forming biofilms and inhibited the adhesion of *Cyanobacteria* to glass surfaces (43).

Dye-sensitized solar cells

Bacterial dyes have significantly contributed to the development of dye-sensitized solar cells (DSSCs) and microbial fuel cells in recent years (1). PG is an ideal choice for solar cell applications due to its chemical richness, which features pi electrons and electron-donating pyral nitrogens. This bacterial dye can assist in the electron transfer activities necessary to produce short-circuit current in solar cells by forming coordination complexes with metal ions.

Additionally, the use of agricultural and industrial wastes to produce excess prodigiosin provides a sustainable and economical method for adding this dye to dye-sensitized solar cells (44).

Limitations

Prodigiosin has many uses in biotechnology, antimicrobial activity, and selective activity against cancer cells, but it is difficult to produce on a large scale for commercial use and enter the market as a possibly beneficial pharmaceutical product for a number of reasons. Mammals suffer from a number of dangerous illnesses brought on by *Serratia marcescens*, the most prevalent strain regarding Enterobacteriaceae which makes PG.

This strain presents a serious problem for medical practice in the form of hospital infections. Newborns under such strain may experience serious illness or even death, particularly if they are admitted to intensive care units for an extended period of time. In addition, it could result in surgical wound infections, pneumonia, conjunctivitis, keratitis, sepsis, and more. In addition, using disinfectants like chlorhexidine might make this microbe more aggressive. Consequently, it is important to remember that hospital-acquired infections are more frequently caused by non-pigmented strains (4,14). One of the main obstacles to industrial production regarding PG is the high cost of natural dyes as well as using costly production medium components in labs (2).

Conclusions

Serratia marcescens as well as other related bacterial species are the main producers of prodigiosin (PG), which is considered as a multipurpose secondary metabolite pigment. PG, a member of tripyrrole family, has drawn more interest lately as a result of its wide range of biological activities and its uses in a variety of industrial fields, like cosmetics, food, and medicines.

PG has a broad range of bioactivities in pharmaceutical industry, including antifungal, antiviral, antiprotozoal, antibacterial, and anticancer properties. With strong inhibitory activity against a variety of Gram-negative bacteria and Gram-positive, also pathogenic fungi, its antimicrobial efficacy was thoroughly reported. In contrast to traditional antibiotics, PG mainly targets the membranes of microorganisms, causing damage to the membranes and

ultimately cell death. PG is a prospective option for the development regarding next-generation antimicrobial medicines because of its distinct method of action, which could help lower the likelihood that pathogenic microorganisms would evolve resistance. Moreover, numerous in vivo and in vitro investigations have shown that PG has strong anticancer potential. It spares healthy, non-transformed cells while preferentially causing apoptosis in malignant cells. Its promise as agent in targeted cancer therapy is highlighted by its selective cytotoxicity, which provides a more secure and efficient substitute for conventional chemotherapeutic medications. As a natural pigment with inherent antimicrobial qualities, PG is being investigated in the food sector to be used as a dual-purpose ingredient that could be used as a coloring agent as well as a preservative. Yet, unless thorough toxicological analyses and regulatory approval are obtained to guarantee its safety for human consumption, its use in food systems is still restricted.

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