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(REVIEW ARTICLE)

A review of Prodigiosin pigment production, gene expression, extraction and medical important from Serratia marcescens

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Abstract

The Gram-negative bacillus *Serratia marcescens* (*S. marcescens*) belongs to the Enterobacteriaceae family. *S. marcescens* was once thought to be a nonpathogenic saprophytic organism that appeared on decomposing organic matter, animals, plants, and foods, water, and soil. However, it has evolved into an opportunist pathogen that causes nosocomial infections, where it is linked to a variety of hospital-acquired infections, including conjunctivitis, septicemia, wound, and eye infections, pneumonia, meningitis, osteomyelitis, and endocarditis, in addition to respiratory tract and urinary tract infections (UTI). Chitinase, protease, nuclease, lipase, and hemolysin are among the products released by *S. marcescens* strains, and many of these compounds are probably virulence factors in human infections caused by this disease. Prodigiosin pigment is a natural red produced by *S. marcescens* which exhibits anticancer, and immunosuppressive properties furthermore to antimicrobial activities. This bacterium has been identified as an opportunistic pathogen that may harbor multidrug resistance mechanisms that complicate treatment, many *S. marcescens* strains are resistant to a wide range of antibiotics. There are two categories of *S. marcescens* strains: non-pigmented (white), and pigmented (red). Two stages are involved in the biosynthesis of prodigiosin. The bipyrrole moiety 4-methoxy-2,2-bipyrrole-5-carbaldehyde (MBC) and the monopyrrole moiety 2-methyl-3-n-amyl-pyrrole (MAP) are produced in the first step, which is also referred to as the cytoplasmic step. The condensation of the terminal products of the two parallel routes, MBC and MAP, to generate prodigiosin is the second step in the final biosynthetic process. The aim of this research is to study and know the use of prodigiosin in an applied and medical field and the method of extracting and purifying prodigiosin and the possibility of genetic manipulation of *S. marcescens.*

Keywords: *Serratia Marcescens*; Prodigiosin; Multidrug Resistance; Antimicrobial Activity

1. Introduction

Serratia is a genus of gram-negative rods bacterium that are 0.9–2.0 µm in length, and 0.5–0.8 µm in diameter. It belongs to the *Enterobacteriaceae* family and has 14 known species*: S. ficaria, S. fonticola*, *S. grimesii*, *S. marcescens, S. liquefaciens*, *S. entomophila*, *S. odorifera*, *S. proteamaculans*, *S. quinivorans*, *S. rubidaea*, *S. plymuthica*, and *S. ureilytica* [1]. *Serratia* is facultatively anaerobic, has peritrichous flagella for motility, reduces nitrate and chlorate anaerobically, and doesn't need growth factors. The colonies on nutrient agar are pink, white, or red in color and have an opaque, somewhat iridescent appearance. At pH 5-9, the growth temperature range is 10-37 ˚C [2]. The three unique enzymes that *Serratia* produces—DNAase, Lipase, and Gelatinase set it apart from other genera. Additionally, the mol G+C% content of prokaryote genomic DNA estimated by sequencing globally conserved genes is 52–60%, with a mean value of 58.4%. Among enteric bacteria, S. marcescens has the greatest G+C concentration [3]. The red pigment was initially identified as prodigosin by Kraft in 1902. It is a linear chemical complex (Tripyrrole cycles) composed of two pyrrole compounds (2-methyl-3-amylpyrrole). The secondary metabolic product prodigiosin pigment, which is formed during the stationary phase, weighs around 323.4 dalton [4]. Other volatile chemicals include MBC (4-methyl-2,2-bipyrrole-5-

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carboxyaldehyde) and this pigment, which are created by different types of bacteria as *Serratia rubidaea*, *Vibrio gazogenes*, *Vibrio psychroerythreus*, *Serratia plymuthica*, and *Pseudomonas magnesiorubra*, *Hahella chejuensis* [5]. Prodigiosin is a diffusible pigment that is extracted from the outer membrane of bacteria using a variety of solvents, including ethyl acetate, acetone, methanol, and chloroform [3]. It is then purified using a variety of techniques, including gel filtration [6], thin layer chromatography (TLC) [7], and high performance liquid chromatography (HPLC) [8].

2. Historical review of *Serratia marcescens*

In 1819, Italian scientist Bartolomeo Bizio discovered that *S. marcescens* was responsible for the red blood coloration of maize flour in Pauda City. Because of the quick deterioration of its stain, Bizio named this organism Serratia in honor of the scientist Serafino Serratia, who discovered steamboats. The adjective *marcescens* means rotting in Latin [9].

2.1. General features of Serratia

Serratia marcescens, can grow in a temperature range of 20 to 37 ºC, *S. plymuthica* and *S. odorifera* in a temperature range of 4 to 50 ºC, *Serratia* in a pH range of 5 to 9, and it was shown that *S. marcescens* grow in the presence of (0.5%) NaCl [2]. Microscopically straight rods with rounded ends. Hekton-Enteric medium displays colorless colonies of *Serratia* spp., MacConkey agar displays late lactose fermentation, and *S. marcescens* produces red pigment on nutrient agar as seen in figure (1), particularly if the plate is kept at 25 °C. Similar to other *Enterobacteriaceae* species, they may thrive in aerobic environments on a variety of medium [10]. With the exception of *S. nematodiphila*, which has a only one polar flagellum, the common of strains are motile and have peritrichous flagella. These bacteria can exhibit movement swimming in broth media using their peritrichous flagella, but they are unable to do so on solid culture medium. *S. marcescens* exhibits movement swarming, in semi-solid medium with a little percentage of agar, 0.7-0.8% approximately [11].

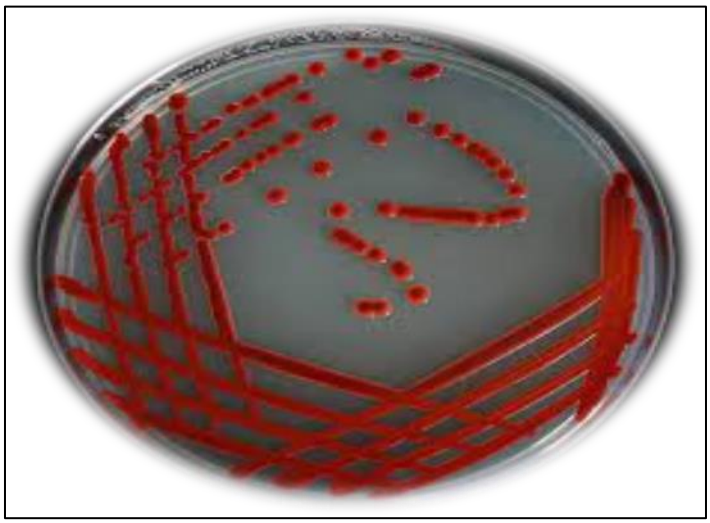

Figure 1 *Serratia marcescens* pigment on nutrient agar [12]

3. Prodigiosins pigments

Prodigiosin is a red pigment that dissolves in chemical solvents like alcohol and chloroform but is insoluble in water. The biosynthesis of prodigiosin, a linear tripyrrole, is thought to follow a bifurcated pathway that results in the enzymatic condensation of the terminal products of the two pathways: the volatile monopyrrole moiety 2-methyl-3-namyl-pyrrole (MAP) and the stable bipyrrole moiety 4-methoxy-2, 2-bipyrrole-5carbaldehyde (MBC) [13]. The linear tripyrrole prodigiosin, which is the archetypal pigment in this family, serves as the basis for classification. Produced by other bacterial taxa, related chemicals with complex side chains and alterations are commonly referred to as prodiginines. The word "prodigiosins" is often used to refer to the pigments collectively and informally. Prodigiosin and related pigments may be identified by taking use of their distinctive absorption spectra in acidified ethanol, which have a characteristic shoulder -35 nm lower and absorption maxima between 510 and 570 nm [14]. The chemical formula for prodigiosin is $C_{20}H_{25}N_{3}O$. It has an apparent pka of 7.6 in aqueous dioxane and 8.25 in aqueous ethanol. It appears pink in acidic environments and yellow in alkaline ones. Recent research has shown that the prodigiosin's proton affinity

is controlled by the presence of two geometrical isomers (α and β forms) with a modest molecular weight of 323.4 Dalton and dramatically differing apparent pka values (pkα = 8.23, pkβ = 5.4) [15] and [16].

4. Gene expression of Prodigiosin

Assays for the expression of bacteria are interesting teaching aids for several reasons. First, bacteria quickly change how their genes are expressed in response to environmental cues such as cell density, growth medium, and growth temperature. While the stability of eukaryotic transcripts is evaluated in hours, the half-lives of bacterial messenger RNA molecules are often determined in minutes. Second, many bacteria express colors under certain conditions. Spectrophotometric monitoring of pigment expression is easy since most pigments absorb light at a certain wavelength. Third, and perhaps most importantly, germs may easily proliferate in a teaching lab [17]. In the broad process of gene expression known as quorum sensing, which allows bacteria to utilize this information to coordinate gene expression and sense their cell population density, prodigiosin is produced as a secondary metabolite. Bacterial populations can effectively adjust to environmental changes thanks to quorum sensing [18]. As the population grows, diffusible, low molecular mass signal molecules produced by *Serratia* strains build up in their surroundings. In *Serratia*, two types of quorum-sensing systems have been identified: the autoinducer-2 (AI2) /LuxS type and the N-acyl homoserine lactones (AHL)-dependent Lux IR type [19]. AHL-dependent quorum sensing controls a variety of *S. marcescens* characteristics, such as the synthesis of prodigiosin, carbapenem antibiotics, extracellular and cell-associated enzymes, and biofilm development [20]. A membrane-permeable positive regulator of gene expression may be produced at low levels by low cell density growth in liquid culture. The intracellular concentration of the regulator remains low at low cell density because it diffuses across the cell membrane after production. High levels of prodigiosin are only expressed in liquid culture at high cell density; in a closed environment, the intracellular concentration of the regulator increases to a threshold necessary for prodigiosin expression activation. On agar plates, colonies created from single cells behave similarly [21].

5. Prodigiosin production

Prodigiosin pigment is a common secondary metabolite, that only manifests throughout, late stages, or the stationary phase of bacterial growth. Numerous environmental factors, such as the availability of inorganic phosphate, the length of the incubation period, the composition of the media, oxygen contents, temperature, the age of the bacterial colony, pH, and have been shown to affect the production of prodigiosin [17]. Because prodigiosin is light-sensitive, it is kept red in the dark for extended periods of time [22]. *Vibrio gazogenes*, *Vibrio psychreorythrous*, *Serratia marcescens*, *Rugamonas rubra*, *Alteromonas rubra*, *S. rubidaea*, and *Pseudomonas magneslorubra*, a variety of bacterial marine, including *Pseudoalteromonas denitrificans*, as well as Gram-positive Actinomycetes, like *Streptomyces longisporus*, produce it [23]. Due to its reported anti-fungal, anti-bacterial, anti-protozoal/ antimalarial, immunosuppressive, and anti-cancer properties, prodigiosin may be of clinical interest. The pigment's biosynthesis is influenced by a variety of factors, including glucose, NaCl, KCI, ATP, inorganic phosphate, ribose, temperature, streptomycin, and polymyxin B [24].

6. Factors Influence on prodigiosin production

Numerous environmental factors, such as the availability of inorganic phosphate, media composition, temperature, pH, and the number of differential and selective media used for the isolation and production of pigment from *Serratia* spp., have been found to have an impact on the production of prodigiosin, a secondary metabolite that only appears in the later stages of bacterial growth. The liquid media currently utilized to produce prodigiosin are nutrient broth (0.52 mg/mL) and peptone glycerol broth (0.302 mg/mL) [25]. The highest levels of prodigiosin were produced in nutritional broth between 28 and 30 °C. Nevertheless, *S. marcescens* did not develop any color in nutrient broth at 37 °C, and the culture broth was white. The pH of the medium has a significant impact on pigment production and the continuation of the metabolic pathway. The ideal pH range for prodigiosin synthesis is between 8.0 and 8.5, whereas all strains of *Serratia* have been shown to thrive best at pH 7 and to be inhibited at a pH of less than 4.5 [26]. One of the most crucial elements of the culture medium, for that producing microorganism, is the nitrogen source, which can be found in organic sources like proteins and amino acids or inorganic sources like nitrogen salts. These nitrogen sources can be utilized in reduced form (NH_2, NH^{+4}) or oxidized form (NO^{-3}, NO^{-2}). The optimal nitrogen source for *S. marcescens* to produce prodigiosin was found to be 1.5% casein hydrolysate [27].

7. Extraction and purification of the prodigiosin

Prodigiosin is separated from other products and materials found in the crude filtrate during the pigment purification process. Since prodigiosin is occasionally attached to proteins, extracts may need to be treated with acid before the pigment is isolated. Mass spectroscopy has identified higher homologs of prodigiosin [28]. The technique was used to remove the color from the bacterial cells. The petroleum ether extract's dry pigment was vacuum-evaporated in the dark at room temperature. The extracted pigments were subjected to ethyl acetate, chloroform, and thin-layer chromatography (TLC), on silica gel, using acetic acid, and A Perkin Elmer model spectrophotometer was used to measure the infrared absorbance of a sample of purified pigment obtained by preparative TLC. Additionally, high performance liquid chromatography (HPLC) technique, was used as a preliminary analysis to distinguish closely related analogs of prodigiosin, as illustrated in Figure (2) [29]. Prodigiosin was also isolated from the bacterial biomass using acidified ethanol until the biomass was completely discolored. The ethanol extract was dried out at 45 to 50 ^{o}C, and the crimson residue was dissolved in chloroform. The resultant solution was emulsified on a magnetic stirrer for one hour at room temperature after being combined with an equivalent amount of a water–ethanol combination. A separating funnel was used to extract the water-soluble impurities from the water-ethanol combination. The resulting pigment was then redissolved in ethanol after being dried in a vacuum dryer. Silica gel was used to perform liquid chromatography on a glass column. After applying the ethanol-dissolved pigment to the sorbent's surface, it was progressively eluted from the column using hexane-acetone and acetone [30].

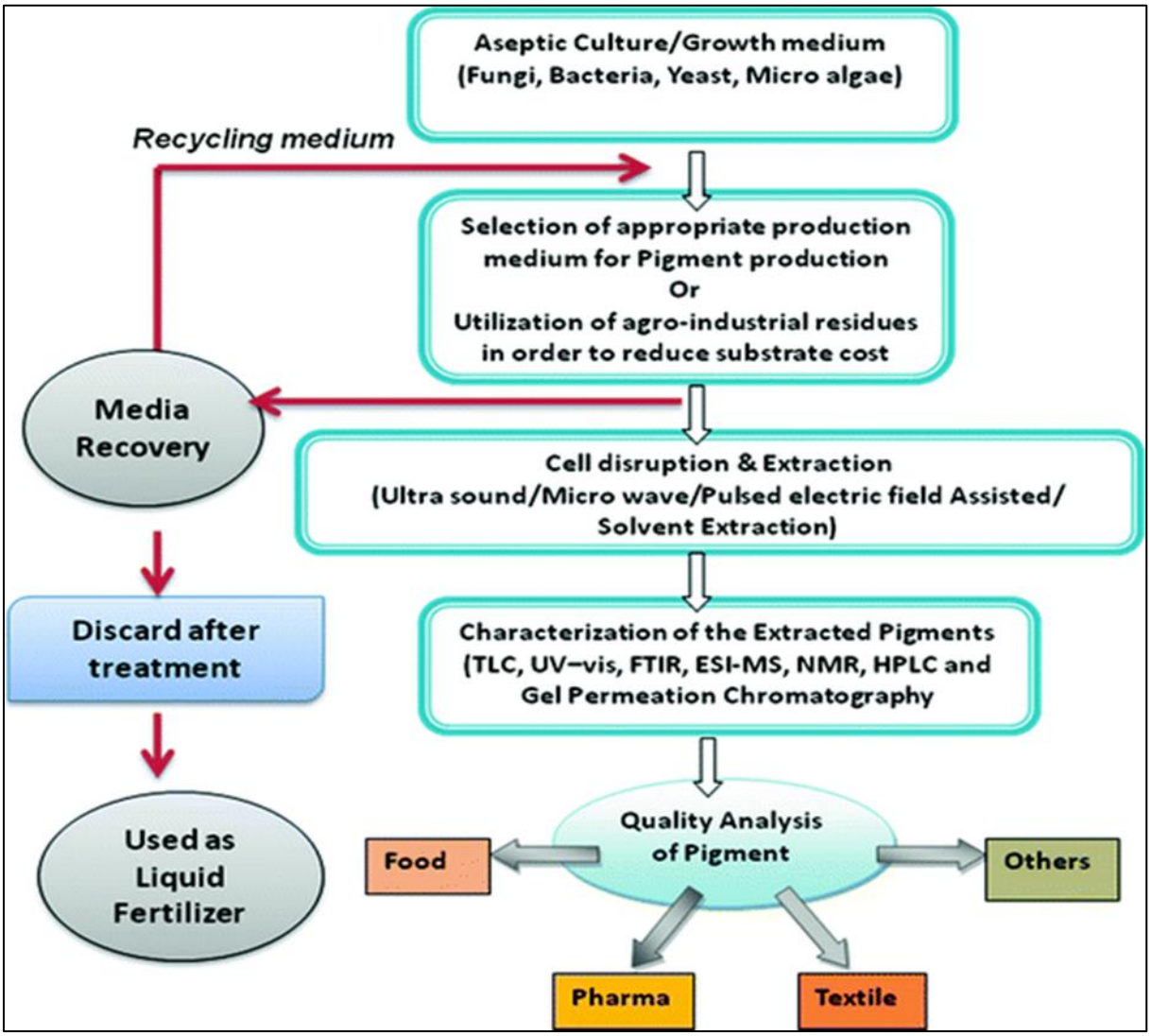

Figure 2 Method of Extraction and purification of the prodigiosin pigment [29]

8. Medical important of prodigiosin

Numerous research has assessed prodigiosin and found that it has numerous advantageous qualities that make it a prospective therapeutic option. Bacterial pigments have been reported to have antimicrobial activities against both Gram-positive and Gram-negative bacteria due to their high inhibition activity against Gram-positive bacteria. Numerous studies have been conducted to find new antimicrobial agents, and pigments are one good alternative, e.g. *Staphylococcus aureus,* while showed little inhibition activity against gram negative bacteria e.g. *Klebsiella pneumonia, Proteus vulgaris*, *Streptococcus pyogenes, Enterobacter faecalis* and oxacillin resistant *S. aureus* (ORSA) [31]. Prodigiosin has been shown to be a powerful antibacterial agent through three mechanisms: bacterial DNA breakage, cell cycle suppression, and pH regulation [32]. Prodigiosin primarily targets the bacterial plasma membrane. Prodigiosin is a chaotropic stressor that damages the bacterial plasma membrane and causes the loss of vital intracellular substances like sugars, amino acids, proteins, and K+ ions from bacteria treated with it. A recent study revealed that prodigiosin causes programmed cell death (PCD) in *B. cereus*, *Pseudomonas aeruginosa*, *S. aureus*, and *E. coli* as well as inhibits the motility of *B. cereus* and *E. coli*. Prodigiosin has been shown to have antimalarial properties against both in vitro and in vivo strains of *P. falciparum* D6 (sensitive to chloroquine) and Dd2 (resistant to several drugs) [33]. Prodigiosin exhibits larvicidal action against the *P. falciparum* vectors, *Aedes aegypti* and *Anopheles stephensi*, according to a significant discovery. Prodigiosin is therefore a viable option for both post-infection therapy and the elimination of the parasite's carriers [34]. Numerous pathogenic fungi, including the filamentous fungus Cryptococcus sp. and *Aspergillus niger*, *Candida parapsilosis*, *Penicillium glaucum*, *Candida albicans*, and *Didymella applanata*, are also inhibited by prodigiosin. It has also been shown that prodigiosin causes apoptotic cell death. The idea that DNA cleavage is proapoptotic activity would be supported by prodigiosin proapoptotic action in the cell's nucleus [35].

9. Conclusion

An opportunistic pathogen that causes nosocomial infections is *S. marcescens*. The capacity of non-pigmented *S. marcescens* to withstand antibiotics makes them more harmful than those that develop pigment. Gram negative, and Gram-positive bacteria, as well as fungi have been shown to create prodigiosin, a secondary metabolite. Casein hydrolysate (1.5%), Olive oil (1.5%), incubation at 28ºC, and KH_2PO_4 at pH 8.0, were the ideal conditions for *S. marcescens* to produce prodigiosin. It has been discovered that the biosynthesis of prodiginines proceeds through a bifurcated route that ends with the concentration of MBC (4-methoxy-2-2-bipyrrole-5 carbaldehyde), with amonopyrrole, which is mediated by an enzyme. Prodigiosin is created by condensing MBC with 2-methyl-3-pentylpyrrole (MPP). Prodigiosin pigment contains immunosuppressive, antibacterial, antifungal, and anticancer properties.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

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