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Prodigiosin from *Serratia*: Synthesis and potential applications

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ABSTRACT

Prodigiosin is a red pigment with a pyrrolylpyrromethane skeleton. It is mainly produced by bacterial strains belonging to the *Serratia* genus, but also by some other genera, including *Streptomyces* and *Vibrio*. Within the genus *Serratia*, the pigment is generally produced as a virulence factor. However, it also has many important beneficial biological activities such as immunosuppressive and anti-proliferative activities. Moreover, the pigment has many industrial applications in textile and cosmetics. In this mini-review, we discuss the genetic and molecular mechanisms supporting prodigiosin synthesis and production from the *Serratia* genus, as well as its potential applications.

KEYWORDS: Prodigiosin; *Serratia*; Synthesis; Metabolites; Biological activities; Applications; Antimicrobial; Anti-proliferative

1. Introduction

Among natural products, secondary metabolites are obtained from two main sources: plants, and microorganisms. As secondary metabolites, they are generally classified as low molecular weight products that have generally little or no proven function in cell vital metabolisms. Secondary metabolites produced and secreted by microorganisms are of great interest. Certainly, these metabolites have numerous pharmaceutical properties, which will benefit human health and nutrition as well as add economical value. Biopigments, produced either by microorganisms or plants, are among the most abundant classes of secondary metabolites[1]. As a result of their stability and year-round availability, biopigments from microorganisms have been preferred over those from plants. Conversely, plant biopigments suffer from many disadvantages, such as being unstable to heat and light. Prodigiosin is one of these microbial biopigments[1]. Prodigiosin is considered an important molecule since it has been applied in various fields and represents a promising area of research. Prodigiosin belongs to a family of natural red pigments (prodiginins) of low molecular weight (323.4 Daltons) that appear only in the later stages of bacterial growth called idiophase. Prodigiosin ($C_{20}H_{25}N_3O$) is produced by many strains of *Serratia* spp. It is associated with extracellular vesicles or found in intracellular granules[1].

Prodigiosin is a member of the prodiginines[2]. It is a hydrophobic compound with a Log POW of 5.16[3] and has been reported as responsible for cell surface hydrophobicity in various *Serratia* strains[4]. The prodigiosin group belongs to the tripyrrole family, which contains a 4-methoxy, 2-2 bipyrrole ring. Its biosynthesis is a two-step process in which the mono- and bipyrrole precursors are first synthesized as two distinct units and then combined to form the final product, prodigiosin (Figure 1)[5]. In this review, we investigate the exact mechanism of prodigiosin production, including structural pathways, molecular regulation in *Serratia* strains, and potent biological activities of this versatile compound. Moreover, the recent advances in large-scale production of prodigiosin are also discussed.

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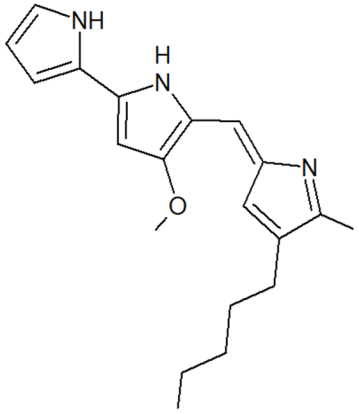

Figure 1. Chemical structure of prodigiosin.

2. Prodigiosin-producing microorganisms

Prodigiosin has long been a subject of research interest because of its many potential beneficial properties. It belongs to the family of prodiginins (Figure 2). This metabolite is secreted by several microorganisms such as *Vibrio ruber*[6], *Hahella chejuensis*[7], *Zooshikella* sp.[8], *Streptomyces coelicolor*[9], *Streptomyces griseoviridis*[10], *Serratia nematodiphila*[11], *Serratia rubidaea*[12] and *Serratia marcescens* (*S. marcescens*)[13]. The most widely known source is *S. marcescens*[14].

3. Prodigiosin synthesis

As shown in Figure 3, the biosynthesis of prodigiosin results from the condensation of two key intermediates, 2-methyl-3-*n*-amylpyrrole (MAP) and 4-methoxy-2-2'-bipyrrole-5-carbaldehyde (MBC)[15].

3.1. Biosynthesis of MAP fragment

The original precursor to this pyrrole is oct-2-enal, which can be obtained by fatty acid transformations. When oct-2-enal reacts with pyruvate in the presence of thiamine pyrophosphate, it produces CO_2 and 3-acetyloctanal (Figure 4). In the presence of amino acid, an aminotransferase produces the cyclic imine H_2MAP. This imine is eventually oxidized by a flavin (flavin adenine dinucleotide) to MAP[16] (Figure 4).

3.2. Biosynthesis of MBC fragment

The first step in the synthesis of MBC is the conversion of proline to a pyrrole *via* a thioester intermediate. ATP activates and transfers it to a thiol of a PCP transport protein (peptidyl carrier protein) (Figure 5). This compound undergoes double oxidation with flavin adenine dinucleotide, to lead to the pyrrole core. The pyrrole moiety is transferred to an active site of cysteine and then to a

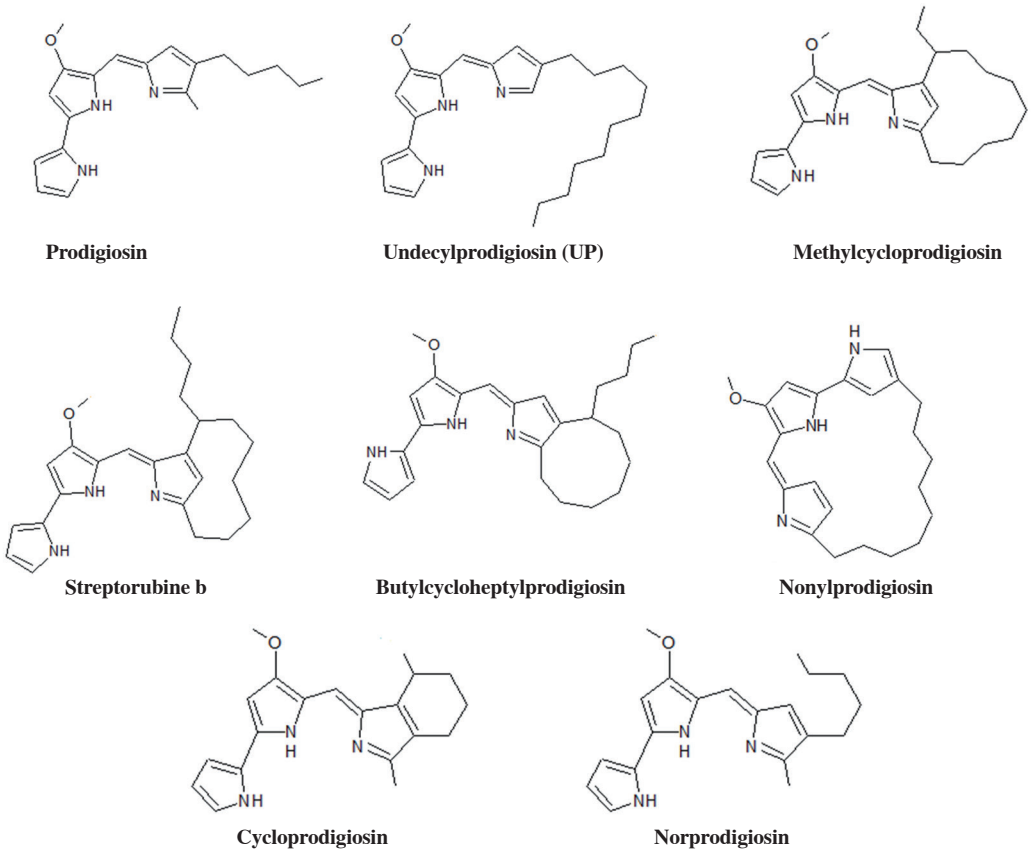

Figure 2. Structures of prodiginins.

malonyl group. The latter has been previously decarboxylated and is derived from the malonyl-CoA complex. Thus, the pyrrolyl-β-ketothioester is formed. Condensation of a serine gives 4'-hydroxy-2,2'-bipyrrole-5-methanol by transamination. The primary alcohol in 4'-hydroxy-2,2'-bipyrrole-5-methanol is oxidized to carboxaldehyde. Methylation occurs with a methyltransferase from S-adenosylmethionine (AdoMet) to provide the MBC fragment[16] (Figure 5).

4. Genetic organization of the group of biosynthetic genes of prodigiosin

The pig cluster comprises 14 genes and is 20960 bp in size. These genes are arranged in the order of *pigA*, *pigB*, *pigC*, *pigD*, *pigE*, *pigF*, *pigG*, *pigH*, *pigI*, *pigJ*, *pigK*, *pigL*, *pigM* and *pigN* (Figure 6)[16]. The function of each corresponding protein is listed in Table 1. The green arrows indicate the genes involved in the biosynthesis of the monopyrrole fragment, MAP, while the blue arrows represent the genes involved in the synthesis of the bipyrrole group, MBC. The red arrow is the gene that encodes for the terminal condensation enzyme, *pigC*. Transcriptional regulators of prodigiosin expression are indicated by yellow arrows (Figure 6). *PigG* and *pigA* are involved in the early steps of MBC biosynthesis[17]. *PigJ* and *pigH* are involved in the biosynthesis of MBC[16]. All genes encoded for known proteins except *pigK* for which no assigned function is known[16,18]. Indeed, in *Serratia*, deletion of *pigK* has no effects on prodigiosin production. It was suggested that *pigK* may have a role in assisting the folding of one or more of the *Pig* enzymes involved in the later stages of MBC biosynthesis[18].

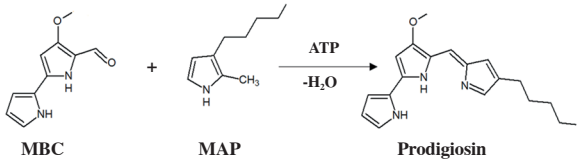

Figure 3. Final step of prodigiosin biosynthesis. MAP: 2-methyl-3-*n*-amylpyrrole, MBC: 4-methoxy-2-2'-bipyrrole-5-carbaldehyde, ATP: adenosine triphosphate.

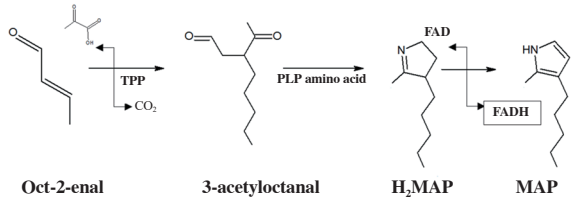

Figure 4. Biosynthesis of MAP fragment. H_2MAP: dihydroMAP, MAP: 2 methyl-3-*n*-amylpyrrole, TPP: thiamine pyrophosphate, PLP: pyridoxal 5′-phosphate, FAD/$FADH_2$: flavin adenine dinucleotide.

Table 1. Function of *pig* genes involved in prodigiosin biosynthesi[16].

Genes	Pathway	Protein
pigA	MBC	*L*-prolyl-PCP dehydrogenase
pigB	MAP	H_2MAP dehydrogenase
pigC	Condensation	Enzyme condensation (MAP et MBC) phosphotransferase
pigD	MAP	2-acetyloctanal synthase
pigE	MAP	2-acetyloctanal aminotransferase
pigF	MBC	HBC *O*-methyl transferase
pigG	MBC	Peptide carrier protein
pigH	MBC	HBM synthase
pigI	MBC	*L*-prolyl-AMP ligase
pigJ	MBC	Pyrrolyl-β-cetoacyl ACP synthase
pigK	MBC	No assigned function
pigL	MBC	4'-Phosphopantetheinyl transferase
pigM	MBC	HBM dehydrogenase
pigN	MBC	Oxidoreductase

MBC: 4-methoxy-2-2'-bipyrrole-5-carbaldehyde, MAP: 2 methyl-3-*n*-amylpyrrole.

5. Control of prodigiosin production by quorum sensing

Generally, prodigiosin production is controlled by the quorum-sensing regulatory system, which controls biofilm formation and virulence factor production in *Serratia* and other bacterial genera.

In *Serratia* sp. ATCC 39006, prodigiosin production is regulated by the *SmaI/SmaR* quorum-sensing system and its cognate *N*-acylhomoserine lactones, *N*-butanoyl-*L*-homoserine lactone (C_4-HSL), and *N*-hexanoyl-*L*-homoserine lactone (C_6-HSL), the former being the more abundant molecule[19]. *SmaR* is a repressor of Pig when the levels of *N*-acyl-*L*-homoserine lactones, produced by *SmaI*, are low[17]. At low cell density, transcription of the *pig* cluster is repressed by *SmaR*, whereas at high cell density, binding of C_4-HSL/C_6-HSL to *SmaR* derepresses transcription. In addition, the production of prodigiosin also depends on quorum sensing system within the strain of *S. marcescens* SS-1. The regulation of prodigiosin production is coordinated by two *LuxI/LuxR* homologues which are *SpnI/SpnR*. Autoinducers involved in this regulation were identified as 3-oxo-C_6HSL, C_6-HSL, C_7-HSL, and C_8-HSL[20]. More recent investigations showed that a *PigP* has a significant regulatory role in *Serratia* sp. ATCC 39006 and acts by binding to DNA (transcriptional regulator). It also seems that environmental conditions mainly phosphate availability could regulate prodigiosin synthesis[21].

6. Medical, pharmaceutical, and industrial applications of prodigiosin

Prodigiosin has recently received great attention for its wide range of biological activities, including antimalarial, antifungal, and antibiotic activities. Moreover, it also has anti-cancer, and anti-metastatic properties and is best known for its ability to trigger

apoptosis in cancer cells. However, the molecular mechanisms responsible for these abilities are not fully understood[22]. Some of these activities and applications are detailed below.

6.1. Antimicrobial activity

6.1.1. Antibacterial activity

The antibacterial activity of prodigiosin is higher against Gram-positive bacteria such as *Staphylococcus aureus*, *Staphylococcus saprophyticus*, *Bacillus subtilis*, *Enterococcus avium*, and *Streptococcus pyogenes* compared to Gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, and *Klebsiella aerogenes*[22,23]. Prodigiosin has also been shown to be effective against *Borrelia burgdorferi*, the causative agent of Lyme disease[24]. Hage-Hülsmann *et al*. reported the minimum inhibitory concentration (MIC) value of prodigiosin against *Corynebacterium glutamicum* of 2.56 μg/mL which was improved in the presence of *N*-myristoyltyrosine to 0.005 μg/mL[25]. It has been demonstrated that the antibacterial activity of prodigiosin arises from its ability to cross the outer membrane and inhibit target enzymes such as DNA gyrase and topoisomerase Ⅳ, thus blocking cell growth by generating reactive oxygen species (ROS) that damage biological molecules[16]. Furthermore, other studies by Kimyon *et al*.[26] showed that the mechanism of action of prodigiosin is a nonspecific mechanism of procaryotes that involves RNA and DNA fragmentation, ROS generation, and expression of protein with caspase-like substrate specificity in bacterial cells. and activation of the programmed cell death[16,26].

Moreover, prodigiosin can be used in certain textile applications, particularly in hospitals to reduce nosocomial infections. A recent study showed that this attractive color pigment, which was extracted from *Serratia rubidaea* RAM-Alex and used for dyeing various

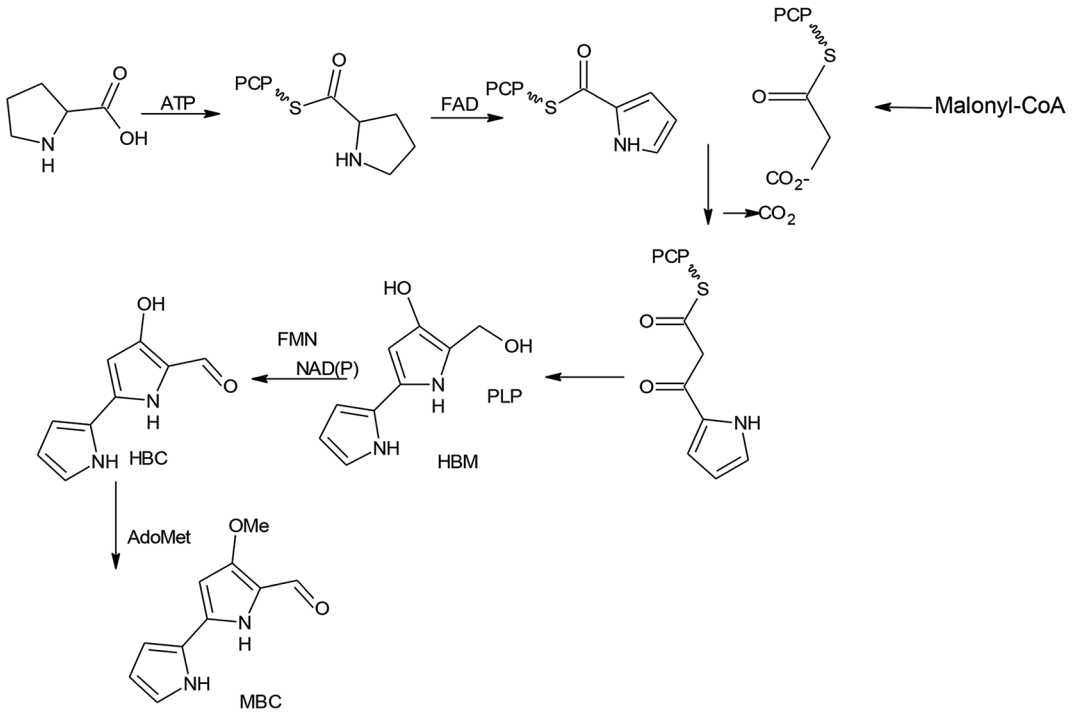

Figure 5. Biosynthesis of MBC fragment. PCP: peptidyl carrier protein, HBM: 4 hydroxy-2-2-bipyrrol-5-methanol, NAD(P): nicotinamide adenine dinucleotide (phosphate), FMN: flavin mononucleotide, AdoMeth: S-adenosylmethionine, MBC: 4-methoxy-2-2'-bipyrrole-5-carbaldehyde; PLP: pyridoxal phosphate.

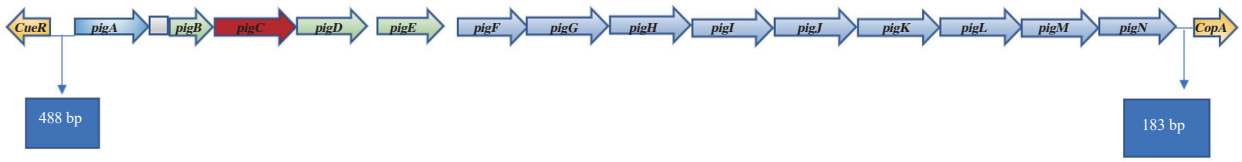

Figure 6. Biosynthetic genes for prodigiosin biosynthesis. The blue arrows represent the genes involved in the synthesis of the bipyrrole group, MBC; the green arrows indicate the genes involved in the biosynthesis of the monopyrrole fragment, MAP; the red arrow is the gene that encodes for the terminal condensation enzyme and the yellow arrows indicate transcriptional regulators of prodigiosin expression.

textile fabrics, had both good dyeing performance and antibacterial activity against *Escherichia coli* ATCC8739 and *Staphylococcus aureus* ATCC25923 strains[27].

MIC and minimum bactericidal concentration values of prodigiosin against some Gram-positive and Gram-negative bacteria are represented in Table 2.

6.1.2. Antifungal activity

The prodigiosin pigment is also renowned for its antifungal activity against several fungal strains. Suryawanshi *et al*. demonstrated that prodigiosin inhibited the growth of fungal strains *Fusarium oxysporum*, *Aspergillus flavus*, and *Penicillium notatum* with MICs of 8, 10, and 21 μg/mL, respectively[28]. Other studies have demonstrated the antifungal activity of prodigiosin against several fungal strains including *Epidermophyton floccosum* (MIC = 41.5 μg/mL), *Trichophyton* spp. (MIC = 5.8-13.5 μg/mL), *Microsporum* spp. (MIC = 2.0-5.6 μg/mL)[29], *Botrytis cinerea* (MIC = 100 μg/mL)[30] and *Didymella applanata* (IC_{50} = 0.8 μg/mL)[31]. Recently, inhibition of the human fungal pathogen *Mucor irregularis* was reported by Hazarika *et al*. where prodigiosin, produced by the *S. marcescens* D1, induced increasing permeability in fungal cell membrane that helps the bacterium to invade fungal hyphae[32].

6.2. Antimalarial activity

Prodigiosin is characterized by its antimalarial activity, which was firstly studied by Castro in 1967. Papireddy *et al*. studied the antimalarial activity of the pigments prodigiosin and undecylprodigiosin which showed interesting activities against *Plasmodium falciparum* (*P. falciparum*) with IC_{50} of 8 and 7.7 nM, respectively[33]. *P. falciparum* was also sensitive to the action of metacycloprodigiosin with an IC_{50} of 12 nM[34]. Newly synthesized prodigiosin derivatives exhibited asexual blood-stage antiplasmodial activity at low nanomolar concentration against a panel of *P. falciparum* parasites[35].

6.3. Antiparasitic activity

Prodigiosin pigment is also recognized for its antiparasitic activities. The effects of prodigiosin against several parasites *Entamoeba*

Table 2. Antibacterial activities of prodigiosin against some Gram-positive and Gram-negative bacteria.

Source strains	Antibacterial activities	Reference
Serratia marcescens	*Staphylococcus aureus* (MIC 3 μg/mL; MBC 20 μg/mL) *Bacillus subtilis* (MIC 5 μg/mL; MBC 50 μg/mL) *Bacillus cereus* (MIC 4 μg/mL; MBC 50 μg/mL)	[32]
Serratia marcescens UFPEDA 398	Oxacillin-resistant *Staphylococcus aureus* strains (MIC from 1, 2 and 4 μg/mL; MBC from 2, 4, 8 and 16 μg/mL)	[80]
Serratia marcescens 2170	*Staphylococcus aureus* ATCC 2921, *Staphylococcus aureus* ATCC 700698 (MIC 4 μM) *Bacillus subtilis*, *Bacillus pumilus*, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922 (MIC 2 μM) *Pseudomonas aeruginosa* ATCC 27853 (MIC 8 μM)	[38]
Serratia marcescens	*Pseudomonas aeruginosa* MG (MIC 16 μg/mL; MBC 16 μg/mL) *Pseudomonas aeruginosa* PG30 (MIC 4 μg/mL; MBC 4 μg/mL) *Staphylococcus aureus* (MIC 8 μg/mL; MBC 16 μg/mL) *Chromobacterium violaceum* (MIC 16 μg/mL; MBC 16 μg/mL)	[81]
Serratia nematodiphila darsh1	*Bacillus cereus* MTCC 1272, *Staphylococcus aureus* MTCC 96, *Pseudomonas aeruginosa* DT CT1, *Escherichia coli* MTCC 729 (MIC from 5 to 30 μg/mL) *Bacillus cereus* MTCC 1272 (MBC 12 μg/mL) *Staphylococcus aureus* MTCC 96 (MBC 9 μg/mL) *Pseudomonas aeruginosa* DT CT1 (MBC 16 μg/mL) *Escherichia coli* MTCC 729 (MBC 20 μg/mL)	[22]
Serratia marcescens CMST 07	*Alteromonas* sp (MIC 6.75 μg/mL; MBC 12.5 μg/mL)	[82]
Serratia marcescens DSM12481	*Corynebacterium glutamicum* (MIC and MBC 2.56 μg/mL)	[25]
Serratia marcescens	*Borrelia burgdorferi* (MIC ≤ 0.21 μg/mL)	[24]
Serratia marcescens	*Enterococcus faecalis* S1 (MIC<0.75 mg/mL; MBC 1.5 mg/mL)	[83]
Vibrio ruber DSM14379	*Escherichia coli* MG1655 [MIC (103.4 ± 6.3) μg/mL] *Bacillus amyloliquefaciens* FZB42 [MIC (6.1 ± 1.2) μg/mL] *Bacillus licheniformis* ATTC9445A [MIC (6.9 ± 2.2) μg/mL] *Bacillus mycoides* (MIC 1.2 μg/mL) *Bacillus subtilis* NCIB3610 [MIC (5.2 ± 1.4) μg/mL] *Bacillus subtilis* ATCC6051 (MIC 5.9 μg/mL) *Bacillus subtilis* PS-216 (MIC 5.9 μg/mL)	[6]
Serratia marcescens sma 274	*Staphylococcus aureus* (MIC 10 μg/mL) *Staphylococcus aureus* MRSA (MIC > 10 μg/mL) *Enterococcus faecalis* (MIC 10 μg/mL) *Escherichia coli* (MIC 10 μg/mL)	[23]

MIC: minimum inhibitory concentration, MBC: minimum bactericidal concentration.

histolytica, *Giardia lamblia*, *Naegleria fowleri*, *Acanthamoeba castellanii*, *Balamuthia mandrillaris* (trophozoites), *Balamuthia mandrillaris* (cysts), *Cryptosporidium parvum*, *Schistosoma mansoni*, and *Trypanosoma brucei* were observed with IC_{50} values of 0.7, 3.8, 6.4, 2.2, 4, 3.8, 0.09, 1 and 0.03 μM, respectively[36]. Another study reported by Rahul *et al*. showed that prodigiosin, produced by *Serratia nematodiphila*, inhibited the growth of *Trypanosoma brucei gambiense* and *P. falciparum*, with IC_{50} values of 0.158 and 1.1 μg/mL, respectively[37]. Moreover, prodigiosin PG 3, produced by *S. marcescens* 2170, exhibited strong antiparasitic activity against *Trypanosoma cruzi* (souche CL, clone B5) with an IC_{50} of 0.6 μM in comparison with the current drug benznidazole with an IC_{50} of 18.9 μM[38]. Additionally, prodigiosin treatment led to severe membrane damage in *Trypanosoma cruzi* epimastigotes, accompanied by a change in parasite cell height and the surface roughness[38].

6.4. Insecticidal activity

Several studies demonstrated the efficacy of prodigiosin as an insecticidal pigment[39–41]. Sree *et al*. reported insecticidal activity and confirmed the efficacy of prodigiosin to kill various household pests. Indeed, total death of *Periplaneta americana* (Cockroaches) and *Solenopsis geminata* (tropical ants) was observed after treatment with prodigiosin, while 71%-85% mortality was observed against *Dorymyrmex insanus* (pyramid ants) and *Isoptera* (termites)[42].

6.5. Antioxidant activity

The antioxidant activity of prodigiosin was evaluated using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis 3-ethylbenzthiazoline-6-sulfonic acid (ABTS) assays. The IC_{50} values recorded for DPPH and ABTS assays were 235 and 115 μg/mL, respectively in comparison to alpha-tocopherol with IC_{50} values of 24.3 and 12.7, respectively[43]. On the other hand, Arivizhivendhan *et al*. studied the antioxidant potential of prodigiosin, which was examined by DPPH and ABTS radical scavenging assays. Antioxidant activity was assessed *via* UV-visible, electron spin resonance, cyclic voltammetry, and excitation-emission spectra. The DPPH and ABTS radicals were completely scavenged by prodigiosin at the concentration of 10 mg/L[44].

6.6. Anticancer activity

Cancer is a global scourge. According to the World Health Organization, there were 19 million newly diagnosed cancer cases and 10 million cancer-related deaths globally in 2020. Cancer tends to be the leading cause of death in Western countries. It is a serious disease that can occur in any organ and at any age. Due to its severity, cancer causes profound anxiety and fear in most people. In view of this awareness, it is, therefore, necessary to find new anti-tumor agents that ideally have specific targets in the affected cells. Boger *et al*. demonstrated the anticancer effects of prodiginins[45]. Their results showed that prodigiosin has a significant *in vitro* cytotoxic effect on leukemic embryonic stem cells (IC_{50} = 3.7 × 10^{-4} μg/mL). Subsequent studies have demonstrated the effect of prodiginins on human leukemia cells (IC_{50} = 0.11 μM)[46], colon cancer (IC_{50} = 0.27 μM)[47], breast cancer (IC_{50} = 2.1 μM)[48], and hepatocellular carcinoma (IC_{50} = 0.27-0.59 μM)[49]. Many researches also focused on other tumor cell lines such as gastric cancer[50], hematopoietic cancer[51], and lung cancer[52]. Although the molecular targets of prodigiosin are not clearly defined, prodigiosin can target various signaling pathways that induce double-stranded DNA breaks and/or neutralize pH gradients, leading to changes in the cell cycle[53]. Another possible mechanism of prodigiosin action against cancer cells is the inhibition of protein phosphatase activity[54]. In 2016, Wang *et al*. reported that prodigiosin and its analogue obatoclax block Wnt signaling at nanomolar concentrations by preventing the Dishevelled phosphorylation. Cyclin D is an established target of Wnt signaling, and elevated cyclin D levels are a characteristic of advanced breast cancer. In a Wnt-driven murine transgenic model of breast cancer, prodigiosin decreased the levels of cyclin D and inhibited tumor growth[55]. In another study, it has been demonstrated that prodigiosin could induce apoptosis in HeLa cells. Apoptosis may be associated with the upregulation of Bax and caspase 3, the concomitant downregulation of Bcl-2 levels, and the activation of the extrinsic apoptotic signaling pathway[56]. These results provide a rationale for the introduction of prodigiosin analogues in advanced breast cancer clinical trials[55].

6.7. Anti-inflammatory activity

Cyclooxygenases (COX) or prostaglandin-endoperoxide synthases are the key enzymes in the synthesis of prostaglandins, the main mediator of inflammation, pain, and increased body temperature (hyperpyrexia). The body produces two forms of COX protein, COX1, and COX2. COX1 is involved in pain, blood clots, and stomach protection[57], whereas COX-2 is involved in pain by inflammation and plays a major role in prostaglandin biosynthesis in inflammatory cells and the central nervous systems[58]. The *in silico* anti-inflammatory activity of prodigiosin has been proven. Using molecular docking, the prodigiosin ligand revealed the highest fitness, score in comparison with the standard drug rofecoxib, suggesting that it may be an effective COX-2 inhibitor[59].

7. Large-scale production of prodigiosin

Several biological activities have been reported for prodigiosin such as antibacterial, antifungal, antiparasitic, insecticidal, anticancer, antioxidant, and anti-inflammatory activities. This product is gaining

more and more attention for its wide application in several medical, cosmetic, environmental, and food fields. Han *et al*. emphasize the importance of producing this pigment at a large scale while minimizing production costs[60].

Recently, several studies have been devoted to the optimization of prodigiosin production through the optimization of culture conditions, medium composition, and fermentation methods. The composition of the medium plays a critical role in the production of prodigiosin. In some studies, researchers have found that yeast extract or peptone and sucrose are important nitrogen and carbon sources for the production of prodigiosin by the *S. marcescens* strain[61–63]. On the other hand, glycerol has been proven by some researchers as an important source of carbon promoting better production of prodigiosin[64].

The prodigiosin synthesis pathway requires the amino acids proline, serine, and methionine as synthesis precursors. Adding these amino acids can stimulate the synthesis of the MBC precursor and enhance the production of the prodigiosin pigment[65].

In addition, the other precursor of prodigiosin 2-octenal, which is the initiator of MAP synthesis, is obtained essentially from the oxidation of fatty acids. Subsequently, the addition of oils such as olive oil[66], sunflower oil[67], palm oil[68], and peanut powder[69] could improve the production of prodigiosin. Several studies have been devoted to the search for low-cost substrates to minimize the cost of prodigiosin production, including kitchen waste[70], squid pen powder[41], and α-chitin from shrimp shells[71].

The production yield of prodigiosin is also affected by cultural conditions such as pH, temperature[63], oxygen levels[72], agitation[73], illumination[74], and the presence of salts[75]. Large-scale production of prodigiosin is achieved through the fermentation process. All biological, physical, and chemical conditions must be present to maximize production yield. The fermentation process for prodigiosin production has been studied using liquid and solid fermentation cultures[76,77], foam flotation method for continuous fermentation[78], and immobilized culture[79].

8. Prospects and conclusion

The synthesis of secondary metabolites by microorganisms in response to environmental stress is an important source of bioactive molecules. Indeed, secondary metabolites can serve as bioactive molecules in a variety of industries including medicine, food, or environmental fields. Biopigment prodigiosin is useful for numerous applications in a wide range of fields. The mechanism of prodigiosin synthesis is complex and involves many genes. It is regulated by quorum sensing system within the species *S. marcescens* and even with other microorganisms.

Studies are being conducted to lower the costs of prodigiosin production on a large scale through the use of economic media and to develop innovative downstream processing strategies for this compound. Moreover, the pharmacodynamic, pharmacokinetic and toxic information of prodigiosin in animals needs further investigation. Current works are also oriented towards the development of new prodigiosin derivatives which will certainly display more potent activity than the parent compound.

Conflict of interest statement

The authors declare that they have no competing interests.

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Authors' contributions

SM and MJ were responsible for writing and original draft preparation, BB and SA reviewed and edited the manuscript. All authors read and approved the final manuscript.

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