

Serratia A Novel Source of Secondary Metabolites



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Abstract

For many years' microorganisms have been a fascinating area of study. Researchers have realized the importance of these tiny microbes for their ability to produce various useful natural metabolites and compounds with uncultured bacterial species being a rich source of bioactive molecules. Natural metabolites represent an enormous group of organic compounds that do not play essential roles in the normal growth and development of the producing microorganisms but merely confer a selective advantage in complex microbial communities as a biological defense mechanism against predators. The biosynthesis of bacterial secondary metabolites involves multiple enzymatic pathways and reactions brought about by structural diversity which contribute to their highly specific mechanisms of action. Secondary metabolites include isoprenes, oligosaccharides, peptides, polyketides, β -lactam rings and aromatic compounds. Natural environments are untapped resources of metabolites and encompasses an enormous level of rich ecological biodiversity.

Microbial secondary metabolites are attracting attention due to the rise of antibiotics resistance and the growing demand for finding new antibiotics to combat infectious diseases. These compounds are characterized by antibacterial, anticoagulant, anti-inflammatory, anti-fungal, antihelmintic, antiplatelet, antiprotozoal and antiviral activities and act on the cardiovascular, immune and nervous systems with promising possibilities in marine biochemistry, microbiology and biotechnology as well as in pharmaceutical industry, drug development and research. Strains of the genus *Serratia* inhabit diverse environmental niches with numerous strains considered a reservoir of structurally unique and biologically significant novel secondary metabolites with potent activities. The production of some *Serratia* secondary metabolites is due to the presence of PKSs genes.

Introduction

The genus *Serratia*

Serratia species of the family Enterobacteriaceae are rod shaped opportunistic Gram-negative bacteria of the c subclass of Proteobacteria and are motile, psychrophilic and facultatively anaerobic [1,2]. They are named after the Italian physicist Serafino Serrati. They are ubiquitous; inhabit a variety of different environmental niches such as; water, soil, plants as well as insects and animals with some associated with food spoilage. Some examples of *Serratia* include, *S. fonticola*, *S. plymuthica*, *S. marcescens* and *S. grimesii* [3,4]. In laboratory settings, *Serratia species* can grow on solid media at temperatures ranging from 20 °C to 37 °C while, in liquid media from 5 °C to 40 °C with optimum pH values of 5-9. *Serratia* grow in many complex growth media, these include LB, PDA and NA [5-8].

The production of antimicrobial compounds by *Serratia* is carbon source dependent and highly induced in the presence of nutrients like organic acids and sugars and temperature-regulated with enhanced production at lower temperatures since seasonal variations are a major factor in influencing bacterial metabolic activity [9,10]. Some strains of *Serratia*, in particular *S. marcescens* are human pathogens and the causative agents of contamination in hospital medical devices. *S. marcescens*

associated with nosocomial infections cause pneumonia, septicemia, meningitis, endocarditis and urinary tract infections [11-13].

The red pigment prodigiosin

For many years now, natural pigments from microbial sources have been studied for their various biological activities. These include anti-oxidants, antifungal and immunosuppressive properties. Prodigiosin is a red non-diffusible, water-insoluble pigment bound to the bacterial cell envelope of some strains of *Serratia* such as *S. plymuthica*, *S. marcescens* and *S. rubideae*. However, the pigment is soluble in organic solvents such as methanol [14-16]. Prodigiosin is an alkaloid secondary metabolite with colours ranging from dark red to pale pink notably on nutrient agar. The majority of reported *S. marcescens* isolates are of clinical origins and appear non-pigmented in comparison to environmental strains. It is strongly believed that it is temperature related since the optimal temperature for the production of prodigiosin is 28 °C [4,17,18].

The biosynthesis of prodigiosin is controlled by numerous environmental and physicochemical factors including temperature, oxygen and pH with maximum production yields achieved in the absence of light. The availability of nutrients in

media composition like carbon, nitrogen, inorganic phosphate and salts can influence the production of prodigiosin and a number of selective broth media are used for the production of the pigment. These include marine broth, nutrient broth, peptone glycerol broth and sesame seed broth [16,19]. The structure of prodigiosin includes three pyrrole rings with two linked together and the third ring attached to a methene forming a pyrrolopyrrole-ethene linkage [20,21]. The production of prodigiosin is controlled by a cluster of operonic genes called pigA-O [22].

Prodigiosin appears in the later stages of bacterial growth with no obvious physiological function. Nevertheless, studies speculated on the true biological functions of prodigiosin. These include, acting as an overflow for metabolic cellular waste products in the producing strains, contributing to surface adherence and enhancing bacterial dispersal while other studies claim that it might act as a sink for excess proline such as in *Streptomyces* [23,24]. The pigment displays anti-malarial, anti-protozoal, anti-fungal activities and a promising potential as an anti-cancer agent due to its potent apoptotic activity in T and B lymphocytes but low cytotoxicity towards normal cells [18,25,26]. Prodigiosin shows bacteriostatic effects with anti-bacterial activity against numerous pathogenic strains. These include, *E. coli*, *E. faecalis*, *S. pyogenes* and *Acinetobacter species* [27,28]. Prodigiosin extracts purified from *S. marcescens* IBRL USM 84, *Serratia marcescens* B₂ and *S. marcescens* B10 VKM are active against *S. aureus*, *P. aeruginosa*, *B. subtilis*, *B. cereus*, salmonella, Shigella, *C. albicans*, *C. utilis*, *Cryptococcus* as well as algal blooms [29,30].

The commercial biotechnological applications of Serratia

Serratia produce commercially important compounds and enzymes such as lipases, serralysin, chitinases, nucleases, protease, haemolysin and amylases. Some strains of *Serratia marcescens* secrete chitinase B which is characterized by high thermal stability. It is strongly believed that enzymatic production in *Serratia* is due to their ability to inhabit various environmental habitats [2,31,3]. There is a great interest in the role of *Serratia* as cost-effective and environmental-friendly bioremediation agents. *S. marcescens* B742 synthesizes protease and chitosanase and hydrolyzes the proteinsin SSP protein produced by shrimp shell wastes into water-soluble protein hydrolysates [32,33]. *Serratia* isolated from soil and water samples encompass unique enzymatic activity and can degrade carboxylic acids (nitriles). *Serratia sp.* ISTVKR1 biodegradable activity include various chemical compounds and contaminants including organophosphorus pesticides, methyl parathion and p-nitrophenol [34]. *Serratia* strains isolated from petroleum-contaminated sites in Norway coastline produce hydrocarbon-degrading activity with great biotechnological potential in the remediation of oil and petroleum spills.

A novel non-pigmented strain of *Serratia* isolated from a

river in India can hydrolyse urea to ammonia [11, 35]. There are numerous studies regarding the important role of *Serratia* as bio-control agents in agricultural crops management including strawberry, cauliflower and olives. *S. plymuthica* A30 shows potent activity against the bacterium pathogen *Dickeya solani* that cause blackleg and soft rot in potato [36-38]. *Serratia* strains used as environmental bio-control agents include, *S. proteamaculans* and *Serratia sp.* ANU101 which produce various compounds including the antifungals haterumalides which were the first polyketides to be discovered in *Serratia* [10,5,39].

The novel strain *Serratia marcescens* B4A produces potent antifungal compounds and inhibit the growth of insects and plant pathogens such as *Rhizoctonia solani* and *Alternaria raphanin*. The following strains of *Serratia*, *Serratia marcescens*, *Serratia plymuthica*, *Serratia sp.* SY5, *Serratia fonticola* AU-P3 and *Serratia fonticola* DSM 4576T are plant growth promoting bacteria. They enhance crop yields and ecological balance in the agroecosystem by facilitating the uptake of nutrients from the environment. They also produce secondary metabolites such as siderophores and phytohormone and protect the plants against pathogenic infections [39-41]. Some strains of *Serratia* including, *Serratia plymuthica* HRO-C48 produce the halogenated secondary metabolite pyrrolnitrin which is a promising agricultural fungicide [42-44]. *Serratia nematodiphila* DSM 21420T is a biological pest control agent and produce potent insecticidal Sep proteins (SepA, SepB, SepC).

A full genome sequence of the strain showed gene clusters encoding enzymes contributing to antimicrobial production [45]. The following strains of *Serratia* including, *S. plymuthica* 4Rx13, *S. marcescens* Db11, *S. odorifera* DSM 4582 and *S. plymuthica* PRI-2C produce volatile organic compounds VOCs including dimethyl trisulfide, sodorifen and methanethioland terpenoids [46,17,47]. These compounds have cytotoxic broad bacteriostatic inhibitory activity against various pathogenic bacteria and fungi, fruit flies and nematodes [48,49].

Serratia a novel source of antimicrobial compounds

Serratia produce secondary metabolites with potent antibacterial, anti-fungal as well as anticancer activities [9]. Some strains of *Serratia* have a highly species-specific secretion-system (type VI) also known as T6SS which enables the production of broad-spectrum bioactive compounds. This system facilitates the production of antibacterial toxins and self-protecting bacteriophage contained proteins that contribute to virulence against competitors and even related *Serratia* strains [36,50,51]. The production of bioactive secondary metabolites in *Serratia* is due to Quorum Sensing (QS) [52,17]. QS regulates gene expression in many Gram-negative bacteria in response to environmental selective pressure like the depletion of nutrients and influences population density by the production of N-Acyl Homoserine Lactone (AHL) molecules [29,53]. AHL are intercellular auto-inducer diffusible signaling molecules biosynthesized by the enzyme LuxI and regulates the production

of antimicrobials, antibiotics, enzymes and plant growth promoting compounds as well as contributing to motility, sporulation, virulence and biofilm formation [4,54].

There are various studies regarding the antimicrobial metabolites of *Serratia*. The culture supernatant of *Serratia marcescens* 2170 have strong cytotoxic activity against cancer cell lines [55]. Also, *Serratia sp.* strain American Type Culture Collection 39006 produces the broad spectrum β -lactam antibiotic Carbapenem. *S. marcescens* 274 and *Serratia* 39006 secrete haemolysin, prodigiosin [56,24]. Some strains of *S. marcescens* such, as *S. marcescens* strain NSK-1 and *S. marcescens* IBBPo15 produce the lipopeptide compounds, serrawettins synthesized by polyketide synthases. Serrawettins are broad spectrum antibacterial bio-surfactants and potent anticancer agents against T-cell leukemia and Burkitt's lymphoma [17]. Recent research regarding *S. plymuthica* A153 and *S. marcescens* MSU97 revealed the production of the antifungal compound antioomycete, the anticancer agent haterumalide and the antibiotic andrimid.

The latter inhibits the growth of *Salmonella enteritidis*, *Yersinia enterocolitica*, *Vibrio harveyi* and *Enterococcus* [41,13]. *S. grimesii* and *S. proteamaculans* produce anti-cancer metabolites active against human larynx carcinoma [9]. Some *Serratia* produce the exoenzymes oocydin A and bacteriocins [54]. *S. marcescens* Db10 secretes the antibacterial toxins Ssp1 and Ssp2 and produces self-resistance proteins as a protection mechanism from its own toxins [42,37]. Strains of *Serratia* such as *S. plymuthica*, *Serratia sp.* strain V4 and *S. plymuthica* RVH1 produce zeamine antibiotics which have broad spectrum bactericidal activity against multidrug resistant bacteria and yeast. Zeamines cause membrane permeabilization through hydrophobic interactions with phospholipid layers and have cyto-toxic activities against human cancer cell lines [57-61].

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