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Review Article

Secondary metabolite production by bacterial antagonists

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ABSTRACT: Secondary metabolites are low molecular weight compounds, less than 2.5 KDa produced during the idiophase of bacterial growth. Bacteria belonging to *Pseudomonas*, *Bacillus* and *Streptomyces* are prolific producers of secondary metabolites that include a wide array of naturally produced compounds viz., peptides, polypeptides, cyclic lipopeptides, polyketides, pyrroles, phenazines, phloroglucinols, lantibiotics, bacteriocins, lactones, macrolactone, anthracyclines, alkaloids, quinones, polyenes, pyrone, quinolones, isoquinoline, aminoglycosides, macrolides, bithiazoles, isocoumarins, aminosugars, phospholipids, siderophores and volatiles. These metabolites exhibit remarkable antimicrobial, plant growth regulatory, plant enzyme inhibitory, herbicidal, insecticidal and anti-parasitic properties. All these biological properties paved way for the use of these secondary metabolites as biocontrol agents in agriculture. Use of microbial antagonists and their secondary metabolites in agriculture in the place of agrochemicals could alleviate pollution hazard.

KEY WORDS: Secondary metabolites, bacterial antagonists, *Pseudomonas*, *Bacillus, Streptomyces*

INTRODUCTION

Agriculture accounts for nearly 14.2% of the gross domestic product (GDP) of India during 2010-11, according to the Central Statistical Organization (CSO). Urbanization and growing population had shrunken the cultivable land and increased the demand for food which necessitates adoption of modern farming techniques such as introduction of high yielding- non-native varieties, monocropping of commercially important crops, overlapping of cropping seasons and plant protection techniques. Excessive use of chemical fertilizers resulted in pest and diseases outbreak. Recent survey shows that loss of total yield due to pests and diseases accounts to nearly ₹15,000 crore annually according to Technology Information, Forecasting and Assessment Council (TIFAC). In order to combat the losses due to pest and diseases, attempts have been made to use agrochemicals and this in turn had polluted the environment leading to 'biological droughts' posing threat to environment and human health. 'Food Safety and Security' is the need of the hour and "Sustainable Agriculture" is the only solution. The U.S. National Research Council (1989) defined sustainable agriculture as 'those alternative farming systems and technologies incorporating natural processes, reducing the use of inputs of off-farm sources, ensuring the long term sustainability of current production levels and conserving soil, water, energy and farm biodiversity'. Such sustainable farming can be achieved by the use of organic fertilizers which are rich in microbes that have plant growth promoting and plant disease suppressing potential. Microbial metabolites such as antibiotics, volatile compounds, enzymes and other toxic substances are the key factors responsible for biocontrol potential apart from microbial competition.

Secondary metabolites by bacterial antagonists are low molecular weight compounds which are less than 2.5 KDa. They are produced during the idiophase when bacterial growth is limited by the exhaustion of any one of the essential nutrient source. These metabolites are not essential for microbial growth and reproductive metabolism. These compounds are chemically and functionally diverse with remarkable antimicrobial, plant growth regulatory, plant enzyme inhibitory, herbicidal, insecticidal and antiparasitic activities. Due to their remarkable biological activities they are widely used in the field of agriculture, medicine, and veterinary sciences (Barrios-Gonzalez *et al*., 2005). Wide range of bacterial antagonists such as *Pseudomonas*, *Bacillus* and *Streptomyces* that produce an array of antimicrobial secondary metabolites have been used as biological control agents in agriculture, as well as in human therapy. Apart from direct use in biological control of plant diseases,

they are also used as lead compounds for chemical synthesis of new analogs or as templates in the rational drug design (RDD) studies. A total of 3800 bioactive secondary metabolites, which accounts to nearly 17% of the total microbial metabolites, are produced by bacteria (Janos Berdy, 2005). This review provides an overview of origin, structure and significance of biologically active secondary metabolites produced by bacteria belonging to *Pseudomonas*, *Bacillus* and *Streptomyces.*

SECONDARY METABOLITES BY PSEUDOMONADS

Pseudomonads are Gram-negative, motile, aerobic, non-enteric, straight or slightly curved rods belonging to γ – Proteobacteria (Galli *et al*., 1992). This group of bacteria inhabits soil, water and phyllosphere, but, is predominant in plant rhizosphere due to the exudation of organic acids, sugars and amino acids (Lugtenberg and Dekkers, 1999). Among pseudomonads, specific group of fluorescent pseudomonads have been widely used as bacterial antagonists. Fluorescent pseudomonads produce secondary metabolites that exhibit wide range of antimicrobial potential (James and Gutterson, 1986; Gutterson *et al*., 1988; Thomashow *et al*., 1990). This particular trait makes fluorescent pseudomonads as promising group of plant growth-promoting rhizobacteria (PGPR) involved in the biocontrol of plant diseases of economically important agricultural crops. Secondary metabolites produced by fluorescent pseudomonads includes phenazines (Gurusiddaiah *et al*., 1986; Thomashow and Weller, 1988; Pierson and Thomashow, 1992; Chin-A-Woeng *et al.,* 1998), phenolics (Keel *et al*., 1990, 1992; Vincent *et al*., 1991), pyrrole-type compounds (Homma and Suzui, 1989; Pfender *et al*., 1993), polyketides (Nowak-Thompson *et al*., 1994; Kraus and Loper, 1995) and peptides (Nielsen *et al*., 1999, 2000; Sorensen *et al*., 2001).

Phenazines are intensely colored nitrogen containing heterocyclic pigments (Leisinger and Margraff, 1979; Budzikiewicz, 1993; Stevans *et al*., 1994). A total of 50 different phenazines have been described so far. Some strains of fluorescent pseudomonads synthesize more than 10 different phenazine derivatives (Turner and Messenger, 1986; Mavrodi *et al*., 1998). Phenazine nucleus is formed by the symmetric condensation of 2 molecules of chorismic acid (Chang and Blackwood 1969; Herbert *et al*., 1976) wherein, N of the heterocyclic ring is derived from the nitrogen of glutamine. Phenazines exhibit broad-spectrum activity against both bacterial and fungal pathogens (Sunish Kumar *et al*., 2005: Ayyadurai *et al*., 2006, 2007; Ravindra Naik and Sakthivel, 2006; Ravindra Naik *et al*., 2008) and involve microbial competition in the plant rhizosphere (Mazzola *et al*., 1992). Phenazine-1-carboxylic acid (PCA) has been reported from *P. fluorescens* (Gurusiddaiah *et al*., 1986), *P. chlororaphis* (Pierson and Thomashow, 1992), *P. aeruginosa* (Anjaiah *et al*., 1998) and *P. putida* (Pathma *et al*., 2010). PCA has been reported to inhibit fungal pathogens such as *Gaeumannomyces graminis* var. *tritici*, *Pythium* sp., *Rhizoctonia solani*, *Polyporus* sp., *Sarocladium oryzae, Macrophomina phaseolina, Pestalotia theae* and various species of *Colletotrichum* etc. and bacterial pathogens, *Actinomyces viscosus*, *Bacillus subtilis* and *Erwinia amylovora* etc. (Gurusiddaiah *et al*., 1986; Sakthivel and Gnanamanickam, 1987; Ayyadurai *et al*., 2007; Thomashow *et al*., 1990; Pathma *et al*., 2010). In addition to PCA, *P. aeruginosa* and *P. chlororaphis* have been reported to produce phenazine-1-carboxamide (PCN) which differs from PCA with a carboxamide ($CONH_2$) group replacing the carboxyl (COOH) group at the first position of the phenazine core (Chin-A-Woeng *et al*., 1998; Mavrodi *et al*., 2001; Sunish Kumar *et al*., 2005). PCN is more stable than PCA and exhibits antifungal activities even in alkaline pH (Chin-A-Woeng *et al*., 1998). The broad-spectrum of antifungal activity of PCN against *Pythium, Fusarium oxysporum* f.sp. *radicipersici, S. oryzae* and *R. solani* have been documented (Chin-A-Woeng *et al*., 1998; Sunish Kumar *et al*., 2005). Pyocyanin (1-hydroxy-5-methyl-phenazine) is predominantly produced by *P. aeruginosa* (Demange *et al*., 1987). This bluish coloured compound, is toxic to a wide range of fungi including *Septoria tritici* and bacteria (Baron and Rowe, 1981; Flaishman *et al*., 1990; Hassan and Fridovich, 1980).

Phloroglucinols, another important group of metabolites of fluorescent pseudomonads exhibit antimicrobial activity. They are known to induce systemic resistance (ISR) in plants and serve as specific elicitor of phytoalexins and other similar defense molecules (Dwivedi and Johri, 2003). Production of 2,4-diacetylphloroglucinol (DAPG) a phenolic antibiotic, has been reported from *P. fluorescens* strains such as Pf-5, CHA0, Q2-87, F113, Q8r1-96. DAPG-producing strains are effective against black root rot of tobacco, root rot of tomato, *Pythium* damping-off of cucumber and sugar beet, cyst nematode and soft rot of potato and take-all of wheat (Howell and Stipanovic, 1980; Vincent *et al*., 1991; Fenton *et al*., 1992; Harrison *et al*., 1993; Pierson and Weller, 1994; Rosales *et al*., 1995; Cronin *et al*., 1997; Raaijmakers and Weller, 1998; Duffy and Defago, 1999). Apart from antifungal activity, DAPG is found to exhibit antibacterial and antihelmenthic activities (Keel *et al*., 1992; Levy *et al*., 1992; Harrison *et al*., 1993; Nowak-Thompson *et al*., 1994; Bangera and Thomashow, 1996).

In addition, DAPG also exhibits herbicidal activity similar to 2,4-dichlorophenoxyacetic acid a commonly used post-emergence herbicide for the control of many

annual, broad-leaved weeds of cereals, sugarcane and plantation crops. The broad-spectrum antimicrobial activity of DAPG against phytopathogens has drawn great attention in agriculture (Keel *et al.,* 1992; Thomashow and Weller, 1988; Duffy and Defago, 1997; Duffy *et al*., 2004).

Pyrrolnitrin (PRN) (3-chloro-4-(2'-nitro-3'-chlorophenyl) pyrrole), a broad-spectrum antifungal metabolite first described by Arima *et al*. (1964) has been reported from *P. aureofaciens* (Elander *et al*., 1968) and *P. fluorescens* (Kirner *et al*., 1998). PRN was found to be active against a wide range of fungi belonging deuteromycota, ascomycota and basidiomycota. Hence, PRN is widely used as fungicide in agriculture. PRN producing *P. fluorescens* BL915 has been reported as bacterial antagonists that suppress *R. solani* in cotton (Ligon *et al*., 2000) and *Burkholderia cepacia* 5.5B showed a broad-spectrum antifungal activity towards phytopathogenic fungi including *R. solani* (Cartwright *et al*., 1995). Variants of PRN viz., isopyrrolnitrin, oxypyrrolnitrin from *Pseudomonas* spp. (Hashimoto and Hattori, 1966a, b) and monodechloropyrrolnitrin from *P. pyrrolnitrica* with lower antifungal activity have been also reported (Hashimoto and Hattori, 1968).

P. fluorescens Pf-5 produces pyoluteorin (PLT), a chlorinated antifungal metabolite of mixed polyketide/ amino acid origin (Maurhofer *et al*., 1992; Maurhofer *et al*., 1994; Kraus and Loper, 1995; Nowak-Thompson *et al*., 1997). PLT is found to be more effective against the damping-off disease causing oomycete, *P. ultimum* (Maurhofer *et al*., 1992). The mode of action is by the selective inhibition of bacterial isoleucyl-tRNA synthetase (Bennett *et al*., 1999). Mupirocin, also known as pseudomonic acid, is a naturally occurring polyketide antibiotic of fluorescent pseudomonads. Mupirocin produced by *P. fluorescens* NCIMB 10586 is highly active against *Staphylococcus aureus* and a variety of Gram-positive organisms (El-sayed *et al*., 2003). Mupirocin is also used as a tropical and intranasal antibiotic (Carcanague, 1997). Another polyketide, 2,3-deepoxy-2,3-didehydrorhizoxin (DDR) produced by *P. chlororaphis* MA342 is effective against several phytopathogenic fungi, including net blotch of barley caused by the fungus *Drechslera teres* (Tombolini *et al*., 1999). Through the insertional mutagenesis and subsequent metabolite profiling in *P. fluorescens* Pf-5, five analogs of rhizoxin, a 16-member macrolides with antifungal activity were identified as products synthesized from a hybrid polyketide synthase or nonribosomal peptide synthetase gene clusters. The rhizoxin analogs were reported to show differential toxicity towards *Botrytis cinerea* and *Phytophthora ramorum*.

Cyclic lipopeptides (CLPs) produced by fluorescent pseudomonads have been considered as effective bio-control metabolites. Viscosinamide, a cyclic lipopeptide produced by *P. fluorescens* DR54 (Nielsen *et al*., 1999) shows prominent antifungal and biosurfactant properties (Nielsen *et al*., 2000; Thrane *et al*., 2000; Nielsen *et al*., 2002) and is highly effective against *R. solani* (Thrane *et al*., 2001). Tensin, a cyclic lipodecapeptide, produced by *P. fluorescens* 96.578 (Nielsen *et al*., 2000) effectively inhibited *R. solani* in sugar beet (Nielsen *et al*., 2000). The activity is proposed to be in synergism with chitinolytic or cell wall degrading enzymes produced by *P. fluorescens* 96.578 (Nielsen and Sorensen, 1999; Nielsen *et al*., 2000). A close analogue of the cyclic lipopeptides tensin and polipeptin, the Amphisin synthesised non-ribosomally by *Pseudomonas* sp. DSS73 is a lactone, linking Thr4 Oã to the C-terminal (Nielsen *et al*., 2000; Sorensen *et al*., 2001). The primary structure is â-hydroxydecanoyl-D-Leu-D-Asp-D-*allo*-Thr-D-Leu-D-Leu-D-Ser-L-Leu-D-Gln-L-Leu-L-Ile-L-Asp. Amphisin provides better antifungal activity compared to other fluorescent pseudomonad peptide antibiotics such as tensin and viscosinamide (Nielsen *et al*., 2002). *Pseudomonas* spp. also produces another cyclic lipopeptide antibiotic, the massetolides. Massetolide A biosynthesis in *P. fluorescens* strain SS101 involves three genes and it plays an essential important role in biofilm formation and swarming motility of *P. fluorescens* SS101 (de Bruijn *et al*., 2008).

Hydrogen cyanide (HCN), a volatile antimicrobial secondary metabolite (Castric, 1981) produced by *Pseudomonas* helps in disease suppression (Bagnasco *et al*., 1998; Rodriguez and Fraga, 1999; Siddiqui, 2006; Voisard *et al*., 1981; Sacherer *et al*., 1994). HCN and CO_2 are formed from glycine and catalysed by HCN synthase (Castric, 1994). HCN in *P. fluorescens* CHA0 played an indispensible role in suppression of black root rot of tobacco caused by the fungus *Thielaviopsis basicola* (Voisard *et al*., 1981) and take-all disease of wheat caused by *G. graminis* var. *tritici*.

Siderophores are low molecular weight iron chelating agents synthesized and secreted by fluorescent pseudomonads to solubilize iron (Neilands, 1981; Abd- Alla, 1998). Microbial siderophores sequester the limited iron supply available in the rhizosphere making it unavailable to harmful pathogenic fungi and thereby, suppressing fungal growth (Keel *et al*., 1992). Siderophores reported from pseudomonads so far include pyoverdines, pyocheline, quinolobactin, ornicorrugatin. A number of pyoverdines comprising of a shared dihydroxy-quinoline chromophore joined to an acyl (carboxylic acid or amide) group and a 6-12 amino acid type-specific peptide have been characterized (Budzikiewicz, 1993; Meyer, 2000; Lamont and Martin, 2003). Pyoverdines and pseudobactins

produced by a single strain have the same peptide but differ in the nature of acyl group. Fe^{3+} binding sites of pyoverdine are present in the quinoline chromophore and the peptide chain (Budzikiewicz, 1993). Pyoverdines effectively suppress *Pythium*-induced damping-off disease of tomato (Buysens *et al*., 1996). *P. aeruginosa* produce pyochelines (Cox *et al*., 1981) and pyocheline frequently accompany pyoverdines and is responsible for second iron transport system. Pyochelines similar to pyoverdines minimizie availability of iron to other microorganisms deleterious to plants and thereby inhibit their growth. *P. fluorescens* ATCC 17400 has shown to produce quinolobactin siderophore in addition to pyoverdine, which itself results from the hydrolysis of the unstable molecule thioquinolobactin. *P. fluorescens* ATCC 17400 actively suppresses the oomycete, *Pythium* sp., by competing for iron, suggesting the involvement of siderophores (Matthijs *et al*., 2007). Ornicorrugatin, a new class of lipopeptidic siderophore, was reported from a pyoverdine-negative mutant of *P. fluorescens* AF76. It is structurally similar to *P. corrugata* siderophore except for the replacement of one Dab unit by Orn (Matthijs *et al*., 2008). However, it is generally suggested that siderophores of fluorescent pseudomonads do not play a role in bio-control in iron rich soils (Campbell *et al*., 1986). Secondary metabolites of fluorescent pseudomonads, their source of origin and biological activity are presented in Table 1.

SECONDARY METABOLITES BY BACILLI

Bacilli are Gram-positive, rod-shaped, aerobic bacteria, capable of resisting stressful conditions by forming endospores. Over 200 peptide antibiotics have been produced by the bacilli (Vining, 1990; Cherif *et al*., 2001; Lisboa *et al*., 2006). Secondary metabolites by bacilli can be broadly classified as bacteriocins, lantibiotics and miscellaneous antibiotics based on their structure. Production of bacteriocins takes place after 10–16 h of bacterial population growth, in the stationary phase, both in solid and broth media (Khalil *et al*., 2009). Bacteriocins produced by different *Bacillus* spp. with remarkable bactericidal, fungicidal properties reported until date are presented in Table 2. Bacteriocins are reported to be the precursors of antibiotics (Sansinenea and Ortiz, 2011), as biopreservatives in food and beverages, and biocontrol agents in agriculture (Bais *et al.,* 2004). Bacteriocins such as thuricin, thuricin 7, thuricin S, thuricin CD 19, thuricin 439A and thuricin 439B, bacthuricin F4, tochicin, kurstakin 18 and entomocin have been reported. Kurstakin 18 exhibits antifungal activity against *Stachybotrys charatum* (Hathout *et al*., 2000). Entomocin differs from the other bacteriocins by molecular mass, biochemical and physical properties, spectrum of activity, and production kinetics (Cherif *et al*., 2003).

Lantibiotics are peptide antibiotics with an inter-residual thioether bonds and are usually secreted in the mid-growth phase. Based on structural variation lantibiotics are classified as Type A and Type B lantibiotics exhibiting a linear and globular structure respectively. Subtilin is the well-characterized 32-amino-acid pentacyclic lanti-biotic derived from *B. subtilis* and its production depends upon the growth phase and culture density as well, a quorum sensing mechanism in which subtilin plays a pheromone type role (Stein *et al*., 2002). Bacilysin 1, is a non-ribosomally synthesized dipeptide composed of L-alanine and L-anticapsin (an unusual amino acid) shows biocontrol property against *Erwinia amylovora* (Arguelles-Arias *et al*., 2009). Its antibiotic activity depends on the anticapsin moiety, which becomes released by peptidases (Chmara *et al*., 1982). Sublancin 168 is an unusual lantibiotic, with two disulphide bridges and an unusual â- methyllanthionine bridge (Paik *et al*., 1998), effective against Gram-positive bacteria. Subtilosin A is also another unusual lantibiotic with a macrocyclic structure containing three inter-residual thioether bonds between cysteine sulphurs and amino acid alpha-carbons (Kawulka *et al*., 2004) effective against a variety of Gram-positive bacteria, including *Listeria* (Zheng *et al*., 1999). Mersacidin is a type B lantibiotics with a globular structure showing antibacterial activity by inhibiting peptidoglycan biosynthesis and in turn affecting cell wall biosynthesis by complexing lipid II (Brotz *et al*., 1997). The lantibiotic ericin based on structure is classified as ericin S and ericin A. Ericin S differ from subtilin only by four amino acid residues, thus similar anti-microbial properties. Ericin A has a different ring organization and 16 amino acid substitutions compared with ericin S (Stein, 2005).

Surfactin, a lipoheptapeptide is a powerful bio-surfactant which exerts a detergent-like action on biological membranes (Carrillo *et al*., 2003). It has remarkable antibacterial, anti-viral, anti-mycoplasma, emulsifying and foaming activities, but its usage is limited due to its high production cost (Das *et al*., 2008). The variations in the lipid portion and/or the amino acid composition have led to origin of several isoforms of surfactin 5. viz., bacircine 5a, halo- and isohalobacillin 5b, lichenysin A/G 5c, daitocidin 5d and pumilacidin 5e. Pumilacidins 5e A, B, C, D, E, F and G are cyclic acylheptapeptide composed of a â -hydroxy fatty acid, two L-leucine, two D-leucine, L-glutamic acid, L-aspartic acid and L-isoleucine (or L-valine) (Kalinovskaya *et al*., 2002; Naruse *et al*., 1990). The iturin family comprises of closely related cyclic lipoheptapeptides that contains one â-amino fatty acid and seven á-amino acids and includes mycosubtilin 6 (Moyne *et al*., 2004), the iturines 7 and bacillomycins 9. Iturin family peptides are capable of forming ion-conducting pores and this is the reason for their biological effects

Table 1. Secondary metabolites produced by fluorescent pseudomonads and their biological potential

Secondary metabolites	Producer strains	Biological effects	References
Phenazines			
Phenazine-1-carboxylic acid	*P. fluorescens* 2-79 *P. aureofaciens* 30-84 *P. chlororaphis* *P. putida P15*	Antifungal Antibacterial Antifungal Antifungal	Gurusiddaiah *et al*. (1986); Thomashow *et al*. (1990); Pierson and Thomashow (1992); Pathma *et al*. (2010)
Dimer of phenazine-1-	*P. fluorescens* Pf23	Antimicrobial Anticancer	Sakthivel and Sunish Kumar (2008) carboxylic acid
Phenazine-1-carboxamide	*P. aeruginosa* PUPa3	Antifungal	Sunish Kumar *et al*. (2005)
2-hydroxyphenazine carboxylic acid	*P. chlororaphis* PCL1391 *P. fluorescens* 2-79RN$_{10}$	Antifungal	Chin-A-Woeng *et al*. (1998); Weller (1983)
Pyocyanin	*P. aeruginosa* PAO1	Antifungal, Antibacterial	Baron *et al*. (1997)
Phloroglucinols			
2,4-diacetylphloroglucinol	*P. fluorescens* Pf-5, Q2-87, CHAO, PFM2, Q8r1-96, F113	Antifungal, antibacterial, antihelmenthic, Herbicidal	Howell and Stipanovic (1979); Vincent *et al*. (1991); Shanahan *et al*. (1992); Keel *et al*. (1992); Levy *et al*. (1992); Flaishman *et al*. (1990); Raaijmakers and Weller (2001)
Pyrrols			
Pyrrolnitrin	*P. fluorescens* BL914, BL915 *P. aureofaciens* A10338.7 *P. cepacia* 5.5B	Antifungal	Kirner *et al*. (1998); Ligon *et al.* (2000) Elander *et al*. (1968) Cartwright *et al*. (1995)
Isopyrrolnitrin	*Pseudomonads* sp.	Antifungal	Hashimoto and Hattori (1966a)
Oxypyrrolnitrin	*Pseudomonads* sp.	Antifungal	Hashimoto and Hattori (1966b)
Monodechloropyrrolnitrin	*P. pyrrolnitrica*	Antifungal	Hashimoto and Hattori (1968)
Polyketides			
Pyoluteorin	*P. fluorescens* Pf-5, CHA0	Antifungal	Howell and Stipanovic (1979); Keel *et al*. (1992)
Mupirocin	*P. fluorescens* NCIMB10586	Antibacterial	El-Sayed *et al*. (2003)
2,3-deepoxy-2,3-didehydro rhizoxin	*P. borealis* MA342	Antifungal	Tombolini *et al*. (1999)
Rhizoxin analogs	*P. fluorescens* Pf-5	Antifungal	Loper *et al*. (2008)
Peptides			
Viscosinamide	*P. fluorescens* DR54	Antifungal	Nielsen *et al*. (1998)
Tensin	*P. fluorescens* 96.578	Antifungal	Nielsen *et al.* (2000)
Amphisin	*Pseudomonas* sp. DSS73	Antifungal	Sorensen *et al*. (2001)
Masstolides A	*P. fluorescens* SS101	Biofilm formation, swarming motility	de Bruijn *et al*. (2008)
Siderophores			
Pyoverdine	*P. fluorescens* 3551 *P. fluorescens* CHAO *P. putida* WCS358	Competitive inhibition of phytopathogens	Loper (2008) Maurhofer *et al*. (1994) Van Wees *et al*. (1997)

Table 1. Secondary metabolites produced by fluorescent pseudomonads and their biological potential (contd. ..)

Secondary metabolites	Producer strains	Biological effects	References
Pyochelin	*P. aeruginosa* PAO-1 *P. fluorescens* CHAO *P. aeruginosa* 7NSK2	Competitive inhibition of phytopathogens	Cox *et al*. (1981) Buysens *et al*. (1996)
Pseudomonine	*P. stutzeri* KC *P. fluorescens* ATCC 17400 *P. fluorescens* WCS374	Competitive inhibition of phytopathogens	Lewis *et al*. (2000) Mossialos *et al.* (2000) Mercado-Blanco *et al.* (2001)
Quinolobactin	*P. fluorescens* ATCC 17400		Matthijs *et al*. (2007)
Ornicorrugatin	Pyoverdin-negative mutant of *P. fluorescens* AF76	Antifungal	Matthijs *et al.* (2008)
Volatiles			
Hydrogen cyanide	*P. fluorescens* Pf-5, P5, P7, P8, P21 *P. pseudoalcaligenes* P4	Antifungal	Voisard *et al*. (1981) ; Ayyadurai *et al*. (2007)

(Maget-Dana and Peypoux, 1994). They exhibit strong antifungal and hemolytic activities as well as limited antibacterial activity (Stein, 2005). Iturin A 7 (Yu *et al*., 2002; Pyoung *et al*., 2010) and bacillomycin L 9 causes hemolysis and releases potassium from erythrocytes (Aranda *et al*., 2005). Iturin A 7 contains the heptapeptide Asn1-Tyr2-Asn3-Gln4-Pro5-Asn6-Ser7. Mycosubtilin 6, that was isolated from *B. subtilis*, has slight variation in the amino acid residues in heptapeptides Asn1-Tyr2-Asn3-Gln4-Pro5- Ser6-Asn7. The cyclic lipopeptide Fengycin 8 (synonymous to plipastatin) (Jacques *et al*., 1999) is a combination of several exceptional structural properties: cyclization, branching and unusual constituents and is specifically active against filamentous fungi (Stein, 2005). Apart from fungicidal and haemolytic properties, Iturin A 7 and Fengycin 8 play different roles in the development and survival of *Bacillus* strains in their natural habitat viz., motility, biofilm formation, quorum sensing, increasing bioavailability of hydrophobic water-insoluble substrates, heavy metal binding, bacterial pathogenesis, etc (Sansinenea and Ortiz, 2011).

Polyketides are the other major family of secondary metabolites next to peptides. Difficidin 10, bacillaene 11 and macrolactin produced by *B. amyloliquefaciens* FZB42 and GA1 comes under this group. Difficidin 10 is an unsaturated 22-membered macrocyclic polyene lactone phosphate ester with broad spectrum antibacterial activity. It inhibits protein biosynthesis and acts effectively against *Erwinia amylovara*, (Arguelles-Arias *et al*., 2009). Bacillaene 11, with the empiric formula $C_{35}H_{48}O_7$, is an inhibitor of prokaryotic protein synthesis. Macrolactins 12, the polyketide with macrolid-like structure, contain three separated diene structure elements in a 24-membered lactone ring. Macrolactin 12, was originally detected in an unclassified deepsea marine bacterium (Jaruchokta-weechai *et al*., 2000). A total of 17 macrolactins have been described and one among them, 7-O-malonyl macrolactin A, was found to be effective against Gram-positive bacterial pathogens (Romero Tabarez *et al*., 2006). Bacitracin is a mixture of related cyclic polypeptides produced by organisms of the licheniformis group of *Bacillus*. Bacitracin is synthesised via nonribosomal peptide synthetases (NRPSs), and it interferes with bacterial cell wall synthesis and is primarily active against the Gram-positive bacteria viz., *Streptococcus aureus* and *Streptococcus* spp. but inactive against Gram-negative organisms and yeasts.

Bacillibactin 15 is a 2, 3-dihydroxybenzoyl-Gly-Thr trilactone siderophore produced by members of *B. cereus* group, *B. thuringiensis, B. subtilis* and *B. licheniformis.* Synthesis bacillibactin 15 depends upon functional Ppant-transferase (Sfp) (Chen *et al*., 2009). *B. anthracis* and *B. cereus* produce petrobactin 16, which was first isolated from the marine bacterium *Marinobacter hydrocarbono-clasticus* and contains two 3,4-catecholate moieties and a citrate-based backbone. Members of a family of proteins termed nonribosomal peptide synthetase-independent siderophore (NIS) synthases are responsible for bio-synthesis of petrobactin 16 (Koppisch *et al*., 2008a). 3,4-dihydroxybenzoic acid (3,4-DHB) 17, a petrobactin precursor is produced by *B. thuringiensis, B. anthracis* and *B. cereus* and its biosynthesis is through early shikimate intermediates (Koppisch *et al*., 2008b).

â-exotoxin I 13, termed as thuringiensin 13 from *B. thuringiensis* is a non-proteinaceous, non-specific toxin. Unlike Vip and Cry toxins it is active against dipteral, coleoptera, lepidoptera, and few nematode species. â-exotoxin affects the insect metamorphosis by inhibiting the synthesis of RNA, by competing with ATP for binding sites, and causes teratogenic effects at sublethal doses (Espinasse *et al*., 2002, 2004).

Zwittermicin A 14 produced by *B. thuringiensis* and *B. cereus* is a linear aminopolyol antibiotic (Silo-Suh *et al*., 1998) and has an unusual chemical structure which includes a D-amino acid, ethanolamine, glycolyl moieties, and terminal amide that is generated from the modification of the nonproteinogenic amino acid ureidoalanine. It has a potent antibiotic property. It has ability to suppress damping-off disease incited by *Phytophthora medicaginis* in alfalfa. In addition, zwittermicin A enhances the activity of the *B. thuringiensis* endotoxin against insects (Zhou *et al*., 2008). Other antibiotics also include an antimicrobial phospholipid bacilysocin (Tamehiro *et al*., 2002), an aminosugar antibiotic 3,3'-neotrehalosadiamine (NTD) 3 structurally 3,3'- diamino-3,30-dideoxy-a,b-trehalose (Inaoka and Ochi, 2007), and amicoumacin 4 (Pinchuk *et al*., 2002). The microbial source of origin of the above mentioned secondary metabolites and their importance are presented in Table 2.

Table 2. Secondary metabolites produced by *Bacillus* spp. and their biological potential

Secondary metabolites	Producer strains	Biological effects	References
Bacteriocins			
Thuricin	*B. thuringiensis* HD2	Bacteriolytic	Favret and Yousten (1989)
Tochicin	*B. thuringiensis* HD868	Bactericidal	Paik *et al*. (1997)
Kurstakin 18	*B. thuringiensis* BMG1.7	Fungicidal	Hathout *et al*. (2000)
Coagulin	*B. coagulans*	Bactericidal, bacteriolytic	Le Marrec *et al*. (2000)
Thuricin 7	*B. thuringiensis* BMG1.7	Bactericidal, bacteriolytic	Cherif *et al*. (2001)
Lichenin	*B. licheniformis* 26-103RA	Bactericidal, bacteriolytic	Pattnaik *et al*. (2001)
Polyfermenticin SCD	*B. polyfermenticus*	Bactericidal, bacteriolytic	Lee *et al*. (2001)
Thuricin 439A/ B	*B. thuringiensis* B439, *B. anthracis*	Bactericidal, bacteriolytic	Ahern *et al*. (2003)
Entomocin	*B. thuringiensis* subsp., entomocidus HD9	Bactericidal	Cherif *et al*. (2003)
Bacthuricin F4	*B. thuringiensis* subsp. kurstaki BUPM4	Fungicidal	Kamoun *et al*. (2005)
Cerein	*B. cereus*	Bactericidal, bacteriolytic	Torkar and Matijasic (2003); Bizani *et al*. (2005a, b)
Megacin	*B. megaterium*	Bactericidal, bacteriolytic	Lisboa *et al*. (2006)
Thuricin S	*B. thuringiensis*	Bactericidal, bacteriolytic	Chehimi *et al*. (2007)
Thuricin CD 19	*B. thuringiensis* DPC 6431, *B. anthracis*	Bactericidal, bacteriolytic	Rea *et al*. (2010)
Lantibiotics			
Subtilin	*B. subtilis* ATCC6633	Antibacterial	Stein *et al*. (2002)
Ericin	*B. subtilis* A1/3	Antibacterial	Stein (2005)
Mersacidin	*B. subtilis* HIL Y-85, 54728	Antibacterial	Stein (2005)
Sublancin	*B. subtilis* 168	Antibacterial	Stein (2005)
Subtilosin A	*B. subtilis* 168, ATCC6633	Antibacterial	Stein (2005)
Cyclic lipoheptapeptide			
Pumilacidin 5e	*B. pumilus*	Antiulcer activity	Naruse *et al*. (1990)
Lichenysin 5c	*B. licheniformis*	Hemolytic, cytotoxic	Grangemard *et al*. (2001)
Bacircine 5a	*B. subtilis, B. amyloliquefaciens, B. pumilus*	Hemolytic, cytotoxic	Kalinovskaya *et al*. (2002)
Halobacillin 5b	*B. licheniformis*	Hemolytic, cytotoxic	Kalinovskaya *et al*. (2002)
Isohalobacillin5b	*B. licheniformis*	Hemolytic, cytotoxic	Kalinovskaya *et al*. (2002)
Daitocidin 5d	*Bacillus sp.*	Hemolytic, cytotoxic	Kalinovskaya *et al*. (2002)
Surfactin 5	*B. subtilis*	Hemolytic, cytotoxic	Carrillo *et al*. (2003)
Mycosubtilin 6	*B. subtilis*	Hemolytic, fungicidal	Moyne *et al*. (2004)
Iturin 7	*B. amyloliquefaciens* B94, FZB42	Antifingal, haemolytic	Yu *et al*. (2002); Aranda *et al*. (2005)
	B. subtilis,		Han *et al*. (2005)

Table 2. Secondary metabolites produced by *Bacillus* spp. and their biological potential (contd. ..)

Secondary metabolites	Producer strains	Biological effects	References
Fengycin 8	*B. subtilis, B. amyloliquefaciens*	Antifungal	Koumoutsi *et al*. (2004)
Bacillomycin D 9	*B. amyloliquefaciens* FZB42, *B. subtilis*	Antifingal hemolytic	Koumoutsi *et al*. (2004); Aranda *et al*. (2005); Ramarathnam *et al*. (2007)
Polyketides macrolactone			
Difficidin 10	*B. amyloliquefaciens* FZB42, GA1	Antibacterial	Arguelles-Arias *et al*. (2009)
Bacillaene 11	*B. amyloliquefaciens* FZB42, GA1	Antibacterial	Chen *et al*. (2009)
Macrolactin 12	*B. amyloliquefaciens* FZB42, GA1	Antibacterial	Jaruchoktaweechai *et al*. (2000)
Phospholipid			
Bacilysocin 2	*B. subtilis*	Fungicidal, antibacterial	Tamehiro *et al*. (2002)
Aminosugar			
NTD 3	*B. subtilis, B. pumilus, B. circulans*	Antibacterial	Tsuno *et al*. (1986); Inaoka and Ochi (2007)
Bacillibactin 15	*B. subtilis, B. licheniformis, B. thuringiensis, B. cereus, B. anthracis*	Iron chelation	Arguelles-Arias *et al*. (2009)
Petrobactin 16	*B. thuringiensis, B. cereus, B. anthracis*	Iron chelation	Zawadzka *et al*. (2009)
3,4-DHB 17	*B. thuringiensis, B. cereus, B. anthracis*	Iron chelation	Zawadzka *et al*. (2009)
Adenine nucleotide analog			
â-exotoxin 13	*B. thuringiensis*	Insecticidal	Espinasse *et al*. (2002)
Polyacetilene derivative			
Melanin	*B. thuringiensis*	Photoprotective	Espinasse *et al*. (2002)
Aminopolyol Antibiotic			
Zwittermicin 14	*B. thuringiensis, B. cereus*	Antifungal	Silo-Suh *et al*. (1998)
Dipeptide			
Bacilysin 1	*B. subtilis* 168*, B. pumilus* *B. amyloliquefaciens* GSB272,	Antifungal, antibacterial	Chmara *et al*. (1982); Steinborn *et al*. (2005)
Isocoumarin			
Amicoumacin 4	*B. subtilis, B. pumilus*	Antibacterial, anti-inflammatory	Pinchuk *et al*. (2002)

SECONDARY METABOLITES BY STREPTOMYCES

Streptomyces are high G+C, Gram-positive predominant soil dwelling organisms forming the largest genus of actinobacteria. They are versatile producers of secondary metabolites and they include a wide array of compounds which exhibit potent antimicrobial, anthelmintic, antiproliferative, immunosuppressive and insecticidal compounds which are of immense use in human medicine as well as agriculture. The first antibiotic, actinomycin from *Streptomyces* in 1940, followed by streptomycin in 1943 by Selman Waksman and his co-worker Woodruff was reported earlier.

Metabolites avermectins, bialaphos, wuyiencin and coumarrins produced by Streptomyces have been reported (Burg *et al*., 1979; Kondo *et al*., 1973; Zhong *et al*., 2004). Screening of *in vivo* inhibitory activity of *Streptomyces* against nematodes and coccids paved way for the discovery of avermectins. Avermectins isolated from *S. avermitilis* are 16-membered macrocyclic lactone derivatives with potent anthelmintic and insecticidal properties. Ivermectin, selamectin, doramectin and abamectin are derivatives of avermectins antihelmintic property. Avermectins are effective against arthropod pests but lack antimicrobial activity. Bialaphos, chemically (L-alanyl-L-alanyl-phosphinothricin), a tripeptide composed of alanine and phosphinothricin isolated from *S. hygroscopicus* and *S. viridochromogenes* finds importance in agriculture as a herbicide (Kondo *et al*., 1973). *Streptomyces* sp. TK-

VL_333 which produced metabolites such as 2,3-dihydroxy-5-(hydroxymethyl) benzaldehyde, 4-(4-hydroxyphenoxy) butan-2-one, acetic acid-2-hydroxy-6- (3-oxobutyl)-phenyl ester and 8-methyl decanoic acid effectively inhibited Fusarium wilt (Kavitha *et al*., 2010). Wuyiencin produced by *S. hygroscopicus* var. *wuyiensis* inhibited the germination of *Botrytis cinerea* conidia (Zhong *et al*., 2004). Wuyiencin showed broad spectrum activity against other bacterial and fungal phytopathogens and effectively controlled gray mold, leaf mold and powdery mildew etc (Cui *et al.,* 2010). Secondary metabolites *viz.,* 5,7-dimethoxy-4-p-methoxylphenylcoumarin and 5,7-dimethoxy-4 phenylcoumarin produced by *S. aureofaciens* CMUAc 130 effectively inhibited phytopathogenic fungi (Taechowisan *et al*., 2005b). Brief description of different secondary metabolites from *Streptomyces* sp., their source of origin, structural class, and their biological properties are presented in Table 3.

Table 3. Metabolites produced by Streptomyces and their biological potential

Secondary metabolites	Producer strains	Biological effects	References
Lipopeptide			
Daptomycin	*S. roseosporus*.	Antibiotic, effective against Gram-positive bacteria	Woodworth *et al*. (1992)
Tripeptide			
Bialaphos	*S. hygroscopicus*, *S. viridochromogenes*	Herbicidal	Kondo *et al*. (1973)
Depsipeptides			
Salinamide A and B	*Streptomyces sp.*	Antibiotic, anti-inflammatory	Trischman *et al*. (1994
Cyclic Peptides			
Cyclomarins	*S. arenicola*	Anti- inflammatory	Renner *et al*. (1999)
Glycopeptide			
Bleomycin	S. *verticillus* *S. mobaraensis* ATCC 15003	Antibiotic	Radwan *et al*. (2011)
Aminoglycoside			
Streptomycin	*S. griseus*	Prokaryotic protein synthesis inhibitor; bactericidal	Singh and Mitchison (1954)
Neomycin	*S. fradiae*	Antibacterial	Waksman and Lechevalier (1949)
Istamycins A and B	*S. tenjimariensis*	Antibiotic	Okami *et al*. (1979)
Macrocyclic lactones			
Avermectin	*S. avermitilis*,	Anthelmintic, insecticidal properties	Burg *et al*. (1979)
Tacrolimus	*S. tsukubaensis* *S. hygroscopicus*	Immunosuppressor Immunosuppressor antiproliferative, antifungal	Sirolimus (rapamycin) Vezina *et al*. (1975)
Ionophore			
Aplasmomycin	*S. griseus*	Antibiotic	Okami *et al*. (1976)
Carbapenem			
Thienamycin	*S. cattleya* I	Inhibits peptidoglycan biosynthesis	Kahan *et al*. (1979)
Quinones			
Marinone	*Streptomyces* sp.	Antibiotic	Pathirana *et al*. (1992)
Komodoquinone A	*Streptomyces* sp. KS3	Neutritogenic	Itoh *et al*. (2003)
Others			
Rifamycin	*S. arenicola*	Antibiotic	Kim *et al*. (2006)
Clavulanic acid	*S. clavuligerus*	β-lactamase inhibitor	Brown (1986)
Platensimycin	*S. platensis*	Antibacterial	Wang *et al*. (2006)

CONCLUSION

Secondary metabolites from bacterial antagonists have served as important sources of antimicrobial agents which are of great use in the field of medicine and agriculture. New scientific approaches such as use of metagenomics would serve to explore the potential of numerous silent, unculturable microbial consortia that might produce novel metabolites which in turn could possibly serve in the field of agriculture as bio-pesticides, bio-fungicides and bio-weedicides. Bioantagonists and their metabolites enable us to do better organic farming and reap higher yields without polluting or depleting the environment.

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