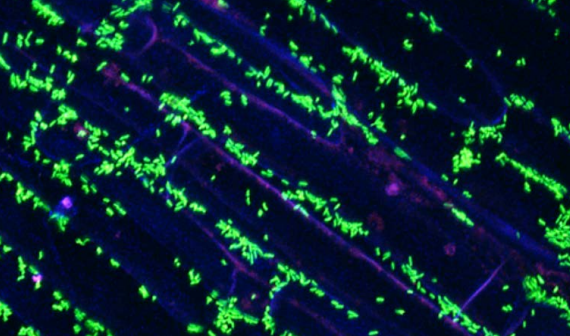


The use of *Bacillus* spp. as bacterial biocontrol agents to control plant diseases

Adrien Anckaert, Anthony Arguelles Arias and Grégory Hoff, Gembloux Agro-Bio Tech, ULiege (University of Liège), Belgium; Maryline Calonne-Salmon and Stéphane Declerck, UCLouvain (University of Louvain-la-Neuve), Belgium; and Marc Ongena, Gembloux Agro-Bio Tech, ULiege, Belgium



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1 Introduction

Biological control of plant diseases, involving the use of (micro-)organisms or compounds of biological origin, is now considered one of the most promising alternatives to the use of chemical pesticides. Sales of so-called biocontrol

agents (BCAs) are expected to reach *circa* 10% of the overall global crop protection market in the near future with an annual growth rate estimated between 15% and 20% (Parnell et al., 2016; Nishimoto, 2019; Zaki et al., 2020). Biocontrol can provide plant protection against many diseases and is environment friendly. Since it often involves several modes of action to restrict the growth of microbial pathogens, biocontrol may limit the development of resistance mechanisms in pathogens but further studies are needed to assess their durability (Geiger et al., 2010; Bardin et al., 2015; Borel, 2017; Kim et al., 2017).

BCAs may act against pathogens via a number of mechanisms: competition for space and nutrients, parasitism, antibiosis and/or by stimulating the host plant defences (Köhl et al., 2019). Biocontrol organisms are natural enemies of plant pathogens including viruses, bacteria, fungi, insects and nematodes. Non-living agents of biological origin include semiochemicals (pheromones, plant volatiles) and biochemical products mainly secreted or extracted from plants and microorganisms (Raymaekers et al., 2020).

Microbial products currently dominate the BCA market, particularly bacteria such as *Bacillus thuringiensis* which is widely used as a bio-insecticide. Selected beneficial bacteria naturally living in close association with plants, and referred to as plant growth-promoting rhizobacteria (PGPR), are also used as BCAs against plant pathogens (Savary et al., 2019). PGPRs constitute a diverse group of bacteria isolated from the rhizosphere and belonging mainly to the genera *Pseudomonas*, *Streptomyces*, *Acetobacter*, *Azospirillum*, *Paenibacillus*, *Serratia*, *Burkholderia*, *Herbaspirillum*, *Rhodococcus*, *Rhizobium* and *Bacillus* (Backer et al., 2018).

Like other PGPR, some *Bacillus* spp. can improve plant growth by nitrogen fixation, phosphate solubilization, phytohormone production or by mitigating the impact of some abiotic stress factors (Kumar et al., 2011; Saxena et al., 2020). This genus includes species that are particularly effective in controlling plant diseases, representing some of the most popular BCAs with global sales of US\$ 160 million in 2016 (Chen, 2017).

Even though reduction of insect and nematode infection has also been occasionally reported (Mnif and Ghribi, 2015; Engelbrecht et al., 2018; Ruiu, 2020), the biocontrol activity of *Bacillus* species has been mainly established against plant diseases. This chapter illustrates the diversity of pathosystems in which BCA based on *Bacillus* spp. have proved effective. It describes the mechanisms underpinning this biocontrol activity via the production of a wide range of enzymes, proteins and small-size bioactive secondary metabolites (BSMs). As these BSMs are clearly involved in pathogen control, we emphasize the importance of understanding the ecological factors influencing their production. In the last part of the chapter, we highlight the potential interactions between *Bacillus* spp. and other soil microorganisms in developing consortia

of biocontrol agents combining species with synergistic activities for plant health improvement.

2 *Bacillus* spp. as biocontrol agents (BCAs)

Most of the *Bacillus* spp. reported as effective BCAs have been isolated from the rhizosphere, occasionally from the phyllosphere, and belong to the so-called *Bacillus subtilis* complex (Cawoy et al., 2011; Fan et al., 2017a). These bacteria may be very competitive in their natural niche. They form populations on plant tissues, as illustrated by *B. velezensis* FZB42, and are able to colonize roots of different monocot and dicot species (Fan et al., 2011, 2012). Root colonization ability contributes to the secretion of antimicrobial compounds and plant resistance elicitors. This metabolite secretion allows to combat a diverse range of bacteria, viruses and fungal pathogens with different lifecycles and modes of virulence (biotrophic, hemibiotrophic or necrotrophic) as illustrated via selected examples in Table 1 (Fira et al., 2018; Miljaković et al., 2020). *Bacillus* spp. biocontrol efficacy has been demonstrated in greenhouse (Fousia et al., 2016; Beris et al., 2018) and field conditions (Matzen et al., 2019; Cucu et al., 2020), as well as at the post-harvest stage for fruit diseases (Punja et al., 2016; Gava et al., 2019).

The ability of *Bacillus* spp. to antagonize Gram-negative bacteria and reduce diseases caused by these pathogens has been established mainly *in vitro* and under controlled conditions (Table 1). A single strain can act against several bacterial pathogens. For example, *B. velezensis* LS69 has been shown to display antibacterial activities against *Erwinia carotovora* and *Ralstonia solanacearum* (Liu et al., 2017). Species can counteract Gram-positive bacterial pathogens such as *Clavibacter michiganensis* by *B. amyloliquefaciens* S1 (Gautam et al., 2019) and *Streptomyces scabies* by *B. amyloliquefaciens* Ba01 (Lin et al., 2018).

Bacillus spp. have been shown to exhibit antagonistic activity against most economically important fungal plant pathogens (Dean et al., 2012) such as *Botrytis cinerea* (Jiang et al., 2018), *Magnaporthe oryzae* (Rahman et al., 2015), *Fusarium graminearum* (Ntushelo et al., 2019), *Fusarium oxysporum* (Elanchezhian et al., 2018), *Blumeria graminis* (Matzen et al., 2019), *Zymoseptoria tritici* (Kildea et al., 2008) or *Colletotrichum acutatum* (Wang et al., 2020b). A single strain can antagonize different fungi, such as *B. velezensis* Y6 and F7 which inhibit both *F. oxysporum* and *Colletotrichum gloeosporioides* *in vitro* (Cao et al., 2018). Antagonism of *Bacillus* strains against oomycetes such as *Pythium aphanidermatum* (Zouari et al., 2016) and *Phytophthora infestans* (Caulier et al., 2018) has also been demonstrated.

Several *Bacillus* spp. have also been reported to control diseases caused by viruses. This has been illustrated on different pathosystems including

Table 1 Selected examples of published studies showing the versatility action of *Bacillus* genus against phytopathogens with different lifecycles or distinct structural features

Pathogen group	Structural feature or lifecycles	Pathogen species	Disease	Biocontrol <i>Bacillus</i> species	Crop(s)	Experimental set-up	Reference
Bacteria	Gram+	<i>Streptomyces scabies</i>	Common scab	<i>B. amyloliquefaciens</i>	Potato	<i>In vitro</i> , Pot assays, Field	(Lin et al., 2018)
		<i>Clavibacter michiganensis</i> subsp. <i>michiganensis</i>	Bacterial canker	<i>B. amyloliquefaciens</i>	Tomato	<i>In vitro</i> , Pot assays	(Gautam et al., 2019)
	Gram-	<i>Rhizobium radiobacter</i>	Crown gall	<i>B. subtilis</i> / <i>B. amyloliquefaciens</i>	Tomato	<i>In vitro</i> , <i>In vivo</i>	(Frikha-Gargouri et al., 2017)
		<i>Erwinia amylovora</i>	Fire blight	<i>B. amyloliquefaciens</i>	Pear/Apple	<i>In vitro</i> , Field	(Ait Bahadou et al., 2018)
Fungi	Biotrophic	<i>Pseudomonas syringae</i>	Leaf spot	<i>B. amyloliquefaciens</i> / <i>B. pumilus</i>	Sugar beet	<i>In vitro</i> , <i>In vivo</i>	(Nikolić et al., 2019)
		<i>Xanthomonas axonopodis</i> pv. <i>vesicatoria</i>	Bacterial leaf spot	<i>B. amyloliquefaciens</i>	Tomato/Pepper	<i>In vitro</i> , <i>In vivo</i>	(Medeot et al., 2020)
		<i>Cladosporium fulvum</i>	Tomato leaf mold	<i>B. subtilis</i>	Tomato	<i>In vitro</i> , Pot assays	(Wang et al., 2018)
		<i>Blumeria graminis</i>	Powdery mildew	<i>B. velezensis</i>	Winter wheat/Spring barley/Oats/Triticale	Field, Greenhouse	(Matzen et al., 2019)
	Hemibiotrophic	<i>Plasmopara halstedii</i>	Downy mildew	<i>Bacillus</i> spp.	Sunflower	Field, Greenhouse	(Nandeeshkumar et al., 2008)
		<i>Plasmopara viticola</i>	Downy mildew	<i>B. subtilis</i> / <i>B. pumilus</i>	Grapevine	<i>In vitro</i> , Field	(Zhang et al., 2017a)
		<i>Mycosphaerella graminicola</i> (<i>Zymoseptoria tritici</i>)	Leaf blotch	<i>B. megaterium</i>	Winter wheat	<i>In vitro</i> , <i>In vivo</i>	(Kildea et al., 2008)

<i>Pyricularia oryzae</i>	Rice blast	<i>Bacillus</i> spp.	Rice	<i>In vitro</i> , Greenhouse	(Rais et al., 2016)
<i>Bipolaris sorokiniana</i>	Wheat spot blotch	<i>B. subtilis</i>	Wheat	<i>In vitro</i> , <i>In vivo</i>	(Villa-Rodríguez et al., 2019)
<i>Colletotrichum acutatum</i>	Anthraxnose	<i>B. amyloliquefaciens</i>	Loquats	<i>In vitro</i> , <i>In vivo</i>	(Wang et al., 2020b)
Necrotrophic					
<i>Botrytis cinerea</i>	Gray mold	<i>B. velezensis</i>	Pepper	<i>In vitro</i> , Greenhouse	(Jiang et al., 2018)
<i>Fusarium oxysporum</i>	Wilt	<i>B. velezensis</i>	Tomato	Greenhouse, Field	(Elanchezhian et al., 2018)
<i>Rhizoctonia solani</i>	Damping-off	<i>B. subtilis</i> / <i>B. amyloliquefaciens</i>	Tomato	<i>In vitro</i> , Greenhouse, Field	(Solanki et al., 2015)
<i>Sclerotinia sclerotiorum</i>	White mold	<i>B. velezensis</i>	Tomato	<i>In vivo</i> , Greenhouse	(Farzand et al., 2019)
<i>Pythium aphanidermatum</i>	Damping-off	<i>B. amyloliquefaciens</i>	Tomato	<i>In vivo</i>	(Zouari et al., 2016)
<i>Phytophthora infestans</i>	Late blight	<i>B. subtilis</i>	Potato	<i>In vitro</i> , Pilot field	(Caulier et al., 2018)
Tomato yellow leaf curl virus (TYLCV)		<i>B. velezensis</i> / <i>B. amyloliquefaciens</i>	Tomato	<i>In vivo</i> , Pot assays	(Guo et al., 2019)
Cucumber mosaic virus (CMV)		<i>B. amyloliquefaciens</i>	Pepper/ <i>Nicotiana benthamiana</i>	<i>In vivo</i> , Field	(Lee and Ryu, 2016)
Oomycete					
Virus					

tomato plants infected by the tomato yellow leaf curl virus counteracted by *B. amyloliquefaciens* Ba13 (Guo et al., 2019) or pepper and tobacco plants infected by the cucumber mosaic virus and controlled by *B. amyloliquefaciens* 5B6 (Lee and Ryu, 2016).

These bacilli have been commercially used as BCAs partly because of their ability to combat disease and partly because of technological advantages (Table 2). Species belonging to the so-called *B. subtilis* complex are, for example, considered GRAS ('generally regarded as safe') (Schallmey et al., 2004) and can be produced at an industrial scale. These bacteria are aerobic with relatively high growth rates, low nutritional requirements and are able to grow on various nutrient sources. They usually produce a range of enzymes (cellulases, amylases, proteases) degrading various substrates derived from naturally abundant sources such as lignocellulose, starch, proteins, hydrocarbon and biofuels (Chen et al., 2018; Elisashvili et al., 2019). This allows their cultivation in low-cost media such as plant raw materials in industrial bioreactors or in solid-state fermentation (Khardziani et al., 2017; Berikashvili et al., 2018). An important advantage of *Bacillus* spp. is their ability to form endospores which make them particularly resistant to abiotic stresses such as heat and drought (Piggot and Hilbert, 2004; Mutlu et al., 2020). The endospore allows the formulation of *Bacillus*-based products with good long-term storage due to resistance to industrial processing (lyophilization or spray drying of the spore suspensions collected from the fermentation broth) and the ability to mix endospores with appropriate additives, adjuvants or surfactants (Schisler et al., 2004; Stamenkovic-Stojanovic et al., 2019). Products can either be sprayed on aerial parts of the plants, delivered into soil or coated on seeds according to the disease targeted and farmers needs (Rahman, 2016; Toral et al., 2020).

3 The diversity of *Bacillus* spp. metabolites involved in biocontrol

The biocontrol activity of *Bacillus* species has mainly been linked to their ability to produce a wide range of chemically diverse compounds (Fig. 1). Comparative genomics has revealed that species of the *B. subtilis* group, including plant-associated clades, are particularly rich in biosynthetic gene clusters (BGCs) encoding bioactive secondary metabolites (BSMs) (Grubbs et al., 2017; Harwood et al., 2018). Up to 12% of the genome is devoted to the synthesis of those compounds (Chowdhury et al., 2015a; Molinatto et al., 2016; Liu et al., 2017; Pandin et al., 2018). Some BGCs are widespread across species in the *B. subtilis* group while others seem to be more species-specific. *B. velezensis* has the highest number of different genes coding for BSMs (Fan et al., 2018), making this species one of the most efficient and commonly used bacilli in biocontrol (Ye et al., 2018; Rabbee et al., 2019). Other species of the

B. subtilis group produce fewer BSMs in terms of diversity, for example, *B. amyloliquefaciens* and *B. subtilis* (Harwood et al., 2018; Andrić et al., 2020). Many of the commercialized strains have been registered as *B. subtilis* or *B. amyloliquefaciens*. However, according to recent re-classification based on phylogenetic analyses at the whole genome level, most of these strains actually belong to *B. velezensis* species (Dunlap et al., 2016). This is the case for the strains GBO3, MBI600, QST713, FZB42 or D747 mentioned in Table 2 (Fan et al., 2017a; Dunlap, 2019).

BSMs formed by *Bacillus* spp. originate either from classical ribosomal synthesis or from non-ribosomal synthesis involving mega-enzymatic complexes. *Bacillus* species are able to synthesize both ribosomal peptides that can be post-translationally modified (RiPPs) and non-ribosomal metabolites (Fig. 1) (Arguelles Arias et al., 2011).

Among RiPPs, *B. subtilis* and related species produce bacteriocins, including lantibiotics, (Abriouel et al., 2011; Lajis, 2020) such as plantazolicin, subtilin, ericin, mersacidin, amylolysin, subtilosin and amylocyclicin (Abriouel et al., 2011; Scholz et al., 2011, 2014; Arguelles Arias et al., 2013). Some antimicrobial peptides such as LCI peptides are also considered bacteriocin-like inhibitory substances because their structure has not been elucidated yet, or they cannot be classified in an existing group (Abriouel et al., 2011; Salazar et al., 2017).

Unlike RiPPs, non-ribosomally synthesized molecules seem to be much more conserved within the species. These molecules are synthesized by large modular enzymatic complexes (non ribosomal peptide synthetases and polyketides synthetases) which are classified into two different types: non-ribosomal peptides (NRPs) and polyketides (PKs) (Dutta et al., 2014; Winn et al., 2016; Bozhüyük et al., 2019). These molecules are synthesized using amino acids (for NRPs) and carboxylic acids (for PKs) as building blocks (Chen et al., 2009a; Winn et al., 2016).

There are three main types of PKs produced by species of the *B. subtilis* group: bacillaene, difficidin and macrolactin (Chen et al., 2006; Caulier et al., 2019). Structural variants can often be coproduced by the same strain. For example, transcription of the difficidin operon results in the production of difficidin and its oxidized form oxydifficidin (Caulier et al., 2019). Cyclic lipopeptides (cLPs) of the iturin, surfactin, and fengycin families are the best-studied compounds among NRPs. These share amphiphilic properties due to a similar structure composed of a peptidic moiety (seven amino acids for iturins and surfactin, and ten amino acids in fengycin) linked to a fatty acid tail (ranging from 12 to 19 carbons) (Ongena and Jacques, 2008).

cLPs biosynthesis allows great structural diversity such as the incorporation of non-proteogenic amino acids or *D*-amino acids. Variants exhibiting differentiations in fatty acid chain length, branching type or amino acids

Table 2 Examples of *Bacillus*-based biocontrol agents commercialized for plant disease control (Lakshmanan et al., 2014; Fira et al., 2018; Rabbee et al., 2019; Borriss, 2020)

Product	<i>Bacillus</i> strain (species assignment)	Pathogens	Crops	Company
Amylo-X® WG	<i>B. amyloliquefaciens</i> D747	<i>Pseudomonas syringae</i> , <i>Monilinia</i> spp., <i>Sterphylium</i> spp., <i>Botrytis cinerea</i> , <i>Sclerotinia</i> spp, <i>Pezizula alba</i>	Vegetable cultivation, arboriculture, grapevine, mushroom, fruit trees	Certis EUROPE
DOUBLE NICKEL 55™	<i>B. amyloliquefaciens</i> D747	<i>Sphaerotheca fuliginea</i> , <i>Erysiphe cichoracearum</i> , <i>Phytophthora capsici</i> , <i>B. cinerea</i> , <i>Alternaria solani</i> , <i>Sclerotinia minor</i> , <i>Sclerotinia sclerotiorum</i> , <i>Rhizoctonia solani</i>	Cucumber, fruiting vegetable, grapevine, lettuce, potatoes	Certis USA, LLC
Eco-Shot	<i>B. amyloliquefaciens</i> D747	<i>Colletotrichum gloeosporioides</i> , <i>Podospaera fuliginea</i> , <i>S. sclerotiorum</i> , <i>B. cinerea</i> , <i>Erysiphe polygoni</i> , <i>A. solani</i> , <i>Phyllosticta citricarpa</i> , <i>Cryptosporiopsis perennans</i>	Grape, citrus, vegetables, legumes	IHARA
Serifel®	<i>B. amyloliquefaciens</i> MBI 600	<i>B. cinerea</i> , <i>Sclerotinia</i> spp.	Grapes, tomato, lettuce, strawberry, mushroom, pepper, tobacco	BASF, Germany
Integral® Pro (SUBTILEX®)	<i>B. amyloliquefaciens</i> MBI 600	<i>Phoma</i> spp.	Rapeseed, Brassicaceae	BASF, Germany
FZB24® liquide	<i>B. amyloliquefaciens/velezensis</i> FZB42	<i>Rhizoctonia</i> spp., <i>Oidium</i> spp., <i>B. cinerea</i> , <i>Sclerotinia</i> spp, <i>Bremia</i> spp., <i>Fusarium</i> spp.	Potatoes, lettuce	Bayer Crop Science/ ABITEP
Taegro®	<i>B. amyloliquefaciens</i> FZB42	<i>Oidium</i> spp., <i>B. cinerea</i> , <i>Sclerotinia</i> spp., <i>Bremia</i> spp.	Strawberry, chicory, cucumber, lettuce, corn, salad, grapevine	Syngenta

EcoGuard™ BIOFUNGICIDE	<i>B. licheniformis</i> SB3086	<i>Sclerotinia homoeocarpa</i> , <i>Pyricularia grisea</i> , <i>P. oryzae</i> , <i>Gloeocercospora sorghi</i> , <i>Puccinia graminis</i> , <i>Alternaria</i> spp., <i>Typhula</i> spp., <i>Microdochium nivale</i> , <i>Drechslera poae</i> , <i>Puccinia</i> spp., <i>Uromyces</i> spp., <i>Calletatrachium graminicola</i> <i>Oidium</i> spp.	Turf, ornamental plants	Novozymes Biologicals, Inc.
Sonata®	<i>B. pumilus</i> QST 2808		Vegetable cultivation, tobacco, grapevine, fruit bush	Bayer Crop Science, previously AgraQuest
Ballad®	<i>B. pumilus</i> QST 2808	<i>Alternaria brassicae</i> , <i>oidium</i> spp., <i>Rhizoctonia oryzae</i> , <i>Xanthomonas</i> spp., <i>Puccinia sorghi</i> , <i>Erysiphe graminis</i> , <i>Puccinia</i> spp., <i>Xanthomonas</i> spp., <i>Sphaerotheca</i> spp., <i>Pseudomonas syringae</i> , <i>Cercospora</i> spp.	Oil seed crops, cereal grains, grass seed, sweet corn	Bayer Crop Science, previously AgraQuest
BSF4®	<i>B. subtilis</i> BSF4	<i>Erwinia amylovora</i> , <i>B. cinerea</i>	Pear, apple, strawberry, tomato, ornamental plants, lettuce	Agribiotech, Italy
Cease®	<i>B. subtilis</i> QST 713	<i>Peronospora belbahrii</i> , <i>B. cinerea</i> , <i>E. cichoracearum</i>	Ornamental plant, tomato, lettuce, celery, strawberry, tropical fruit, cannabis	BioWorks®
BIOBAC® WP	<i>B. subtilis</i> BSY 1336	<i>B. cinerea</i> , <i>Sclerotinia</i> spp., <i>Leveillula tarurica</i>	Tomato, grapevine, cherry, strawberry, pepper	Kuanghwa Chemical Co. Ltd., Taiwan
BACSTAR®	<i>B. subtilis</i> D747	<i>E. amylovora</i> , <i>B. cinerea</i> , <i>P. capsici</i>	Apple, pears, citrus, grapes, kiwifruit, strawberry, lettuce, onions, ornamental plant, turf	Certis USA, LLC

(Continued)

Table 2 Examples of *Bacillus*-based biocontrol agents commercialized for plant disease control (Lakshmanan et al., 2014; Fira et al., 2018; Rabbee et al., 2019; Borriss, 2020) (Continued)

Product	<i>Bacillus</i> strain (species assignment)	Pathogens	Crops	Company
Companion®	<i>B. subtilis</i> GB03	<i>Sclerotinia</i> spp., <i>Rhizoctonia</i> spp., <i>Fusarium</i> spp., <i>Aspergillus</i> spp.	Pod vegetable, cotton, peanuts, soybean, wheat, barley, corn, strawberry, grapes, tomatoes	Growth Products Ltd., USA
Kodiak™	<i>B. subtilis</i> GB03	<i>Rhizoctonia</i> spp., <i>Fusarium</i> spp., <i>Alternaria</i> spp., <i>Aspergillus</i> spp.	Seed treatment, cotton, soybean, wheat, barley,	Bayer Crop Science, previously Gustafsson LLC
Serenade® ASO	<i>B. subtilis</i> QST 713	<i>B. cinerea</i> , <i>Oidium</i> spp., <i>Golovinomyces cichoracearum</i> , <i>Podosphaera</i> spp.	Fruit bush, vegetable cultivation, tomato, pepper	Bayer Crop Science, previously AgraQuest
Serenade® SOIL	<i>B. subtilis</i> QST 713	<i>Fusarium oxysporum</i> , <i>Pythium</i> spp., <i>Rhizoctonia</i> spp.	Root vegetables, bulb vegetables, leafy vegetables, <i>Brassicaceae</i> , fruiting vegetable, cucurbits	Bayer Crop Science, previously AgraQuest
Serenade® OPTI	<i>B. subtilis</i> QST 713	<i>Botrytis cinerea</i> , <i>Sclerotinia</i> spp. G. <i>cichoracearum</i> , <i>Podosphaera</i> spp., <i>Albugo candida</i> , <i>Oidium</i> spp., <i>Phytophthora</i> spp., <i>Peronospora</i> spp., <i>E. amylovora</i>	Stone fruits, garden beet, tomatoes, arboriculture, vegetable cultivation, fruit bush	Bayer Crop Science, previously AgraQuest
Serenade® MAX	<i>B. subtilis</i> QST 713	<i>B. cinerea</i> , <i>Oidium</i> spp., <i>Colletotrichum</i> spp., <i>Glomerella</i> spp.	Avocado, banana, mushroom, cucumber, ornamental plant, arboriculture, lettuce, melon, tomato, grapes	Bayer Crop Science, previously AgraQuest
Rhapsody®	<i>B. subtilis</i> QST713	<i>B. cinerea</i> , <i>Sclerotinia</i> spp., <i>Rhizoctonia</i> spp., <i>Fusarium</i> spp., <i>Pythium</i> spp., <i>Oidium</i> spp., <i>Monilinia</i> spp.	Vegetable cultivation, grapevine, fruit bush, ornamental plant, potatoes	Bayer Crop Science, previously AgraQuest

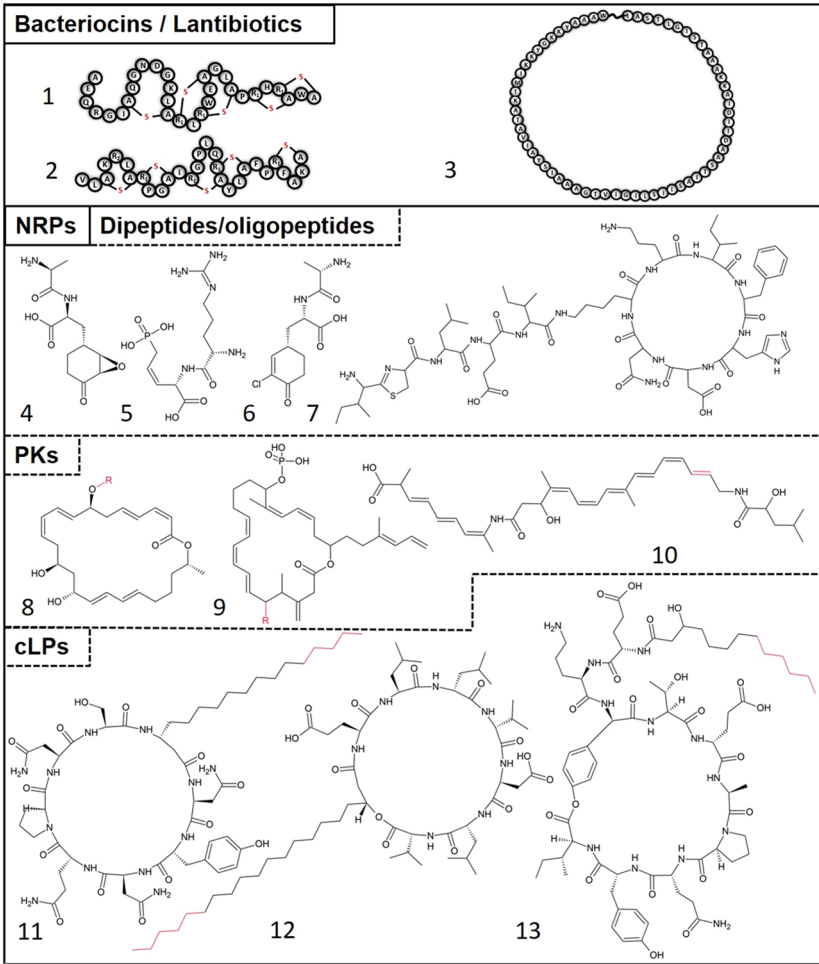


Figure 1 Overview of bioactive secondary metabolites (BSMs) produced by the *Bacillus subtilis* complex. The antimicrobial compounds can be synthesized by the classical ribosomal synthesis, such as the lantibiotics amylylosin (1, R1: aminobutyrate) or ericin A (2, R2: 2,3-didehydroalanine) and the cyclic bacteriocins amylocyclin (3). Besides, some are produced by a non-ribosomal biosynthesis, the non-ribosomal peptides (NRPs), as the unusual peptides (dipeptides and oligopeptides), the cyclic lipopeptides (cLPs), and the polyketides (PKs). The dipeptides and oligopeptides include bacilysin (4), rhizocticin (5), chlorotetain (6), and bacitracin (7). The three main polyketides are synthesized by this genus, macrolactin A, R: H or COCH₂COOH or COCH₂CH₂COOH), diffidicin (9, R: H or OH for oxydiffidicin) and bacillaene (10, unsaturated or bacillaene glycosylated or dihydrobacillaene glycosylated). Likewise, the three main families of cLPs produced by *Bacillus* sp. are iturin (11, iturin A, C13 to C17), surfactin (12, surfactin, C12 to C16) and fengycin (13, fengycin A, C14 to C19).

substitution can also be coproduced by the same strain. Surfactin is the only cLP that can be found in all species of the *B. subtilis* group. Some lipopeptides such as lichenysin or pumilacidin are specific to the producing species (*B. licheniformis* and *B. pumilus*, respectively). This structural diversity is also present in the iturin family, regrouping peptidic variants such as bacillomycin, iturin and mycosubtilin, or in the fengycin family that includes fengycin A, fengycin B and plipastatin (Ongena and Jacques, 2008; Raaijmakers et al., 2010; Caulier et al., 2019). Unlike surfactin, these two cLPs families are not produced by all members of the *B. subtilis* group and structural variants do not seem to be linked to the species (Andrić et al., 2020).

Several oligopeptides are known to be produced by non-ribosomal synthesis pathways, including bacilysin, chlorotetain, bacitracin and rhizoctin. These are not synthesized by the NRPS machinery and *de facto* are referred to as unusual peptides (Konz et al., 1997; Ming and Epperson, 2002; Rajavel et al., 2009).

4 *Bacillus* spp. biocontrol mechanisms: root colonization

The effectiveness of *Bacillus* spp. as a BCA relies on three main mechanisms that are (i) establishment on plant tissues, mainly roots, that prevent or reduce colonization of pathogens via competition, (ii) antibiosis towards microbial pathogens, (iii) induction of systemic resistance in the host plant.

Various approaches (comparative studies of strains with very different patterns, specific knock-out mutants, tests of purified molecules) have been used to understand the roles of the molecules involved in these mechanisms (Fig. 2).

4.1 Chemotaxis

Plant roots that provide physical support and nutrients via exudates are colonized by a plethora of microbes. As with other members of this root-associated microbiome, a successful *Bacillus* spp.-plant association is based on a fine-tuned molecular 'dialogue'. This is driven by root exudates, the composition which varies according to plant genotype and growth stage (Van Overbeek and Van Elsas, 2008; Zhang et al., 2013; Sasse et al., 2018). The proximity of the root is first sensed by the bacterium which moves towards root tissues via chemotaxis (Yssel et al., 2011; Sourjik and Wingreen, 2012). *B. velezensis* FZB42, for example, is attracted by root exudates of maize which act as a chemoattractant and facilitate motility and biofilm formation (Jin et al., 2019).

The presence of pathogens modifies root exudates, increasing their attractiveness for *Bacillus* spp. In cucumber plants infected by *F. oxysporum*

f. sp. *cucumerinum*, the proportion of chemoattractant compounds (citric acid and fumaric acid) is higher compared to non-infected plants, resulting in enhanced root colonization by *B. velezensis* SQR9 (Liu et al., 2014b, 2020). Better colonization of *B. velezensis* 32 on *Rhizobium radiobacter*-infected tomato roots has also been reported compared to uninfected seedlings, correlated with changes in root exudate composition (Abdallah et al., 2020). *Arabidopsis thaliana* foliar infection by *Pseudomonas syringae* also induced root secretion of L-malic acid, attracting *B. subtilis* FB17 and stimulating biofilm formation (Rudrappa et al., 2008). So far, up to ten specific chemoreceptors/chemoattractants of root exudate compounds, such as amino acids, organic acids or sugars, have been characterized in *B. subtilis* NCIB 3610 and *B. velezensis* SQR9 (Tan et al., 2013; Zhang et al., 2013; Allard-Massicotte et al., 2016; Feng et al., 2019).

4.2 Motility and biofilm formation

Biofilm formation capacity is widely distributed through the *Bacillus* genus. Biofilms can be defined as a multicellular community encased within an extracellular matrix of self-produced polymers such as exopolysaccharides and proteins (e.g. TasA or BslA) (Vlamakis et al., 2013; Pandin et al., 2017). Exopolysaccharides promote mobility and nutrient capture. This form of communal life constitutes a divergent lifestyle of planktonic cells in which metabolism remodelling occurs through a complex regulatory network (Kearns et al., 2005; Pisithkul et al., 2019). Biofilms are composed of heterogeneous subpopulations organized through this regulator network. Different communities of cells are present in the same biofilm, including matrix-producing cells, surfactin-producing cells, flagellated motile cells and sporulated cells.

Biofilms provide a strong ecological advantage for *Bacillus* spp., promoting migration (Vlamakis et al., 2013; Flemming et al., 2016). They allow *Bacillus* spp. to colonize and survive on the surface of plant roots. *Bacillus* spp. have been shown to form biofilms on plant roots, for example, *B. velezensis* FZB42 on *Zea mays*, *A. thaliana* and *Lemna minor* plantlets (Fan et al., 2011). The plant stimulates biofilm formation both through root exudates and the presence of polysaccharides derived from the plant cell wall which act as signal molecules. Maize and cucumber root exudates, or individual exudate compounds such as glucose, fructose, citric acid, malic acid and fumaric acid, have been shown to stimulate biofilm formation in *B. velezensis* SQR9 and in *B. velezensis* S3-1 (Zhang et al., 2015; Jin et al., 2019; Liu et al., 2020). Biofilm establishment is also triggered in the presence of pectin and arabinogalactan, two important plant polysaccharides, in *B. amyloliquefaciens* S499 and SQY 162, and *B. subtilis* NCIB 3610 (Beauregard et al., 2013; Debois et al., 2015; Wu et al., 2015a).

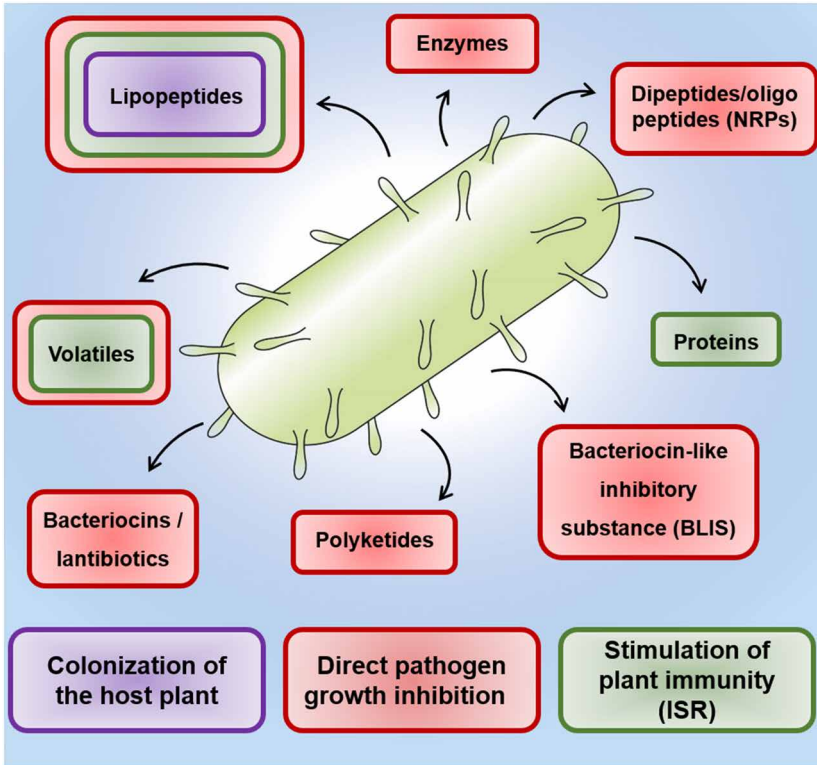


Figure 2 Implication of the different bioactive secondary metabolites (BSMs) in the three main mechanisms of plant protection: by colonization and competition for ecological niche/substrate (in purple), by direct growth inhibition (in red) and/or as an elicitor of induced systemic resistance (ISR) (in green).

Some small-size BSMs, particularly those belonging to the lipopeptide family (especially surfactin), are essential in reducing surface tension and acting as a wetting agent. Surfactin helps to organize cells in bundles to increase biofilm surface area. When deprived of surfactin, for example, mutants of *B. subtilis* 6051 and OKB120 and *B. atrophaeus* ATCC 9372 show impaired biofilm formation (Bais et al., 2004; Aleti et al., 2016). Surfactin plays an important role in the ecological fitness of *Bacillus* spp. for root colonization, both as a surfactant and as a quorum-sensing (QS) molecule (Kearns et al., 2004; Chen et al., 2013; Aleti et al., 2016). Iturin and, to a lesser extent, fengycin have also been reported to facilitate biofilm formation. *In vitro* studies of *B. velezensis* Y6 have shown that these two lipopeptides play important roles in cell motility (Cao et al., 2018). In the case of *B. subtilis* 916, it has been suggested that bacillomycin L (a variant of the iturin family) and surfactin can synergistically contribute to biofilm formation and so to the ecological fitness of *Bacillus* spp.

(Luo et al., 2015). However, a recent study has shown that surfactin production is not required for biofilm formation by *B. subtilis* 3610 (Thérien et al., 2020). The lipopeptide arsenal of *B. subtilis* 3610 is less diverse and contains only surfactin. The involvement of surfactin in biofilm formation may be more complex than expected and could be linked to the lipopeptidome richness of each *Bacillus* species.

Biofilm lifestyle also allows *Bacillus* spp. to resist the presence of other microorganisms. Biofilms act as a fortress to block antimicrobials produced by other competitors (Flemming et al., 2016). The biofilm extracellular matrix has been shown to protect *B. subtilis* 3610 colonies from infiltration by competitors such as *Pseudomonas chlororaphis* (Molina-Santiago et al., 2019). Biofilm formation can also be boosted by the presence of other microorganisms. In *B. subtilis* ATCC6051, the expression of *sinR* and *tasA* genes involved in biofilm formation is modified in contact with the pathogen *Fusarium culmorum*, stimulating matrix multicellular production (Khezri et al., 2016). Biofilm formation also promotes the production of compounds involved in many biocontrol activities (Vlamakis et al., 2013; Pandin et al., 2019; Pisithkul et al., 2019). The biofilm extracellular matrix improves the competitiveness of *Bacillus* spp. in the rhizosphere and thus its biocontrol capability (Pandin et al., 2017). Deficiency in matrix production has been associated with a decrease in biocontrol efficacy by *B. subtilis* 3610 on tomato root against *R. solanacearum* (Chen et al., 2013) and by *B. subtilis* 6051 against *P. syringae* on *A. thaliana* (Bais et al., 2004).

5 *Bacillus* spp. biocontrol mechanisms: antagonistic activity

Bacillus spp. have great potential to control infection through direct inhibition of pathogen growth via antibiosis and/or by interfering with pathogen fitness, notably via quorum quenching (QQ). *Bacillus* spp. antimicrobial potential is related to the synthesis of different classes of metabolites, enzymes, and low-molecular-weight compounds including RiPPs, PKs, NRPs and volatiles (Fig. 2).

5.1 Enzymes

Antagonistic activities of enzymes rely on several modes of action, such as QQ or cell lysis. QQ is an important strategy in plant disease suppression by interfering with QS molecules used by most Gram-negative pathogens. As an example, lactonases, which interfere with the well-known QS molecules N-acyl-L-homoserine lactones (AHL), have been found in numerous *Bacillus* spp. and are considered as QQ enzymes (Dong et al., 2002; Chandra Kalia et al., 2011; Raafat et al., 2019). By blocking cross-talk (via degradation of AHL by QQ) of *P. syringae*, *B. cereus* INT1c reduces pathogen motility, leading to inefficient root

colonization (Ananda et al., 2019). QS interference by several *Bacillus* spp. has also been reported to decrease the hypersensitivity response of tomato plants caused by *P. syringae* due to degradation of pathogen AHLs (Jose et al., 2019).

A second enzymatic mode of action involves cell-wall-degrading enzymes. These include chitinases, which degrade chitin (a major component of fungal cell walls) and other enzymes such as chitosanases, glucanases, cellulases and lipases (Caulier et al., 2019; Miljaković et al., 2020). These lytic enzymes have been reported to reduce plant pathogen growth. Chitinase produced by *B. subtilis* ATCC1774 and *B. cereus* CRS7 decreases the growth of *Rhizoctonia solani* (Saber et al., 2015) and *B. cinerea*, respectively (Kishore and Pande, 2007). Alkaline protease purified from *B. amyloliquefaciens* SP1 and heterologously expressed in *Escherichia coli* has been reported to inhibit *F. oxysporum* growth (Guleria et al., 2016).

5.2 Bacteriocins and lantibiotics

Several RiPPs produced by *Bacillus* spp. are effective as antibacterial agents. Bacteriocins exhibit a broad spectrum of antibacterial activity acting by cell lysis, pore formation or inhibition of cell wall biosynthesis (Abriouel et al., 2011; Lajis, 2020). Bacteriocin activity has been occasionally reported against Gram-positive and Gram-negative bacterial plant pathogens. Amylocyclicin, produced by *B. velezensis* FZB42, appears to exhibit activity against *C. michiganensis*, while Bac IH7 and Bac14B inhibit the growth of *R. radiobacter* (formerly called *Agrobacterium tumefaciens*), and *Pseudomonas* spp., *E. carotovora* and *Alternaria solani* (Hammami et al., 2009, 2012; Scholz et al., 2014). LCI peptide, purified from *B. subtilis* A014 and considered as bacteriocin-like inhibitory substances, have antibacterial activities against *Xanthomonas campestris* and *R. solanacearum*. The APC2 protein, a so-called LCI-like peptide produced by *B. amyloliquefaciens* FS6, has been shown to prevent *Fusarium solani* infection (Gong et al., 2011; Fan et al., 2018; Saikia et al., 2019; Wang et al., 2020a).

5.3 Non-ribosomal metabolites

The activity of dipeptides and oligopeptides against plant pathogens has been little studied. Dipeptide bacilysin, a non-ribosomal synthesized molecule produced by *B. velezensis* FZB42, has been reported to inhibit growth of bacteria such as *Erwinia amylovora*, *Xanthomonas oryzae* and oomycete *P. infestans* (Chen et al., 2009b; Wu et al., 2015b; Caulier et al., 2018). PKs are known for their antibacterial activity. A mutant, for example, of *B. velezensis* FZB42, impaired in difficidin, has been found to inhibit *E. amylovora* (Chen et al., 2009b) and *X. oryzae* (Wu et al., 2015b) less than the wild-type strain. Purified macrolactin has also been reported to be active against *R. solanacearum* and *F.*

oxy Sporium (Yuan et al., 2012a). Bacillaene has been shown to protect *Bacillus* spp. cells against the degrading-enzymatic activity caused by competitors (*Streptomyces* sp. Mg1 and *Myxococcus xanthus*) (Barger et al., 2012; Müller et al., 2014, 2015). *Bacillus* PK type difficidin also shows antimicrobial activity, depending on the structure. The oxydifficidin derivative is approximately three times more active against *R. solanacearum* as compared to difficidin (Im et al., 2020) showing the importance of structural variations among *Bacillus* spp. BSMs.

The antimicrobial activity of lipopeptides is mainly related to members of the fengycin and iturin family. These two families have been reported to damage hyphae and conidia of several fungal pathogens including *F. graminearum* (Gu et al., 2017; Hanif et al., 2019) and *Monilinia fructicola* (Liu et al., 2011). The effects of lipopeptides depend on their amphiphilic nature and chemical structure. Fengycins are active against filamentous fungi such as *Rhizopus stolonifera* (Tao et al., 2011), *Magnaporthe grisea* (Zhang and Sun, 2018) or *R. solani* (Guo et al., 2014). Iturins are efficient not only against filamentous fungal pathogens such as *C. gloeosporioides* (Jin et al., 2020) and *Aspergillus flavus* (Gong et al., 2014) but also against the oomycete *P. infestans* (Wang et al., 2020c). Fengycin can also inhibit damaging mycotoxin synthesis produced by *F. graminearum* (Hanif et al., 2019). Iturins and fengycins are mainly active against fungi. However, the antibacterial activity of iturins and fengycins has also been occasionally reported against *X. campestris* and *Pectobacterium carotovorum* (Zerouh et al., 2011) and *Xanthomonas axonopodis* pv. *vesicatoria* (Medeot et al., 2020) or *R. solanacearum* (Villegas-Escobar et al., 2018). Mode of actions of iturins and fengycins are still partially unknown but are most probably related to their capacity to disrupt fungal pathogens plasma membranes by forming pores, leading thus to cell death (Deleu et al., 2008; Wise et al., 2014; Zakharova et al., 2019). Small structural variations can impact bioactivity. Different homologues of bacillomycin D have thus different antimicrobial activities against the same pathogen according to the physiological stage of the fungi (Tanaka et al., 2015; Luna-Bulbarela et al., 2018). Differential activities of these variants can be viewed as a strategy by *Bacillus* spp. to increase the antibiotic spectra of one molecule family.

Surfactin has been found to have antimicrobial activity but in the 50–200 µM range, a higher concentration than in natural conditions (Jourdan et al., 2009; Raaijmakers et al., 2010; Debois et al., 2014; Liu et al., 2014a; Fan et al., 2017b; Sarwar et al., 2018). The inhibitory effect of surfactin is probably not due to direct antagonism but rather the interference with the colonization process of pathogens such as *P. syringae* (Bais et al., 2004) and *R. solanacearum* (Almoneafy et al., 2014). Even if surfactin cannot be considered as an antimicrobial molecule, it still has the ability to interact with biological membranes to induce structural modifications (Deleu et al., 2013). Its antimicrobial activity can be linked to a synergistic effect

with other cLPs. The combination of surfactin with bacillomycin D or mycosubtilin leads to more efficient control of *F. oxysporum* f. sp. *iridacearum* (Mihalache et al., 2018) and *B. cinerea* (Tanaka et al., 2015). Combining surfactin and fengycin is effective against *F. oxysporum* f. sp. *iridacearum* (Mihalache et al., 2018) and *P. infestans* (Wang et al., 2020c). Co-production of two antifungal compounds (i.e. iturins and fengycins) by *Bacillus* improves its antifungal properties since these antifungal compounds are active against different pathogens.

5.4 Volatiles

The antimicrobial activities of *Bacillus* spp. are also linked to volatiles. The most relevant group of volatiles are volatile organic compounds (VOCs) including alcohol, aldehydes, ketones, hydrocarbons, acids and terpenes. The majority of VOCs are derived from *Bacillus* spp. metabolic pathways such as 2-nonanone produced by β -oxidation of fatty acid (Korpi et al., 2009; Fincheira et al., 2017). Some of these metabolites have been reported to affect motility and biofilm formation of bacterial pathogens (Raza et al., 2016) and/or decrease fungal spore germination and growth (Yuan et al., 2012b). Antimicrobial activities of VOCs have been extensively studied (Caulier et al., 2019; Kai, 2020), including against fungal pathogens such as *Sclerotinia sclerotiorum* (Lim et al., 2017), *B. cinerea* (Jiang et al., 2018), *A. solani* (Zhang et al., 2020) or *M. fructicola* (Liu et al., 2018a). VOCs synthesized by *Bacillus* spp. also display antimicrobial activity against *R. solanacearum* such as 2-nonanone and 2-undecanone (Raza et al., 2016).

The BSM arsenal of *Bacillus* species such as *B. velezensis* includes many antimicrobials with broad-spectrum activity. However, recent studies strongly suggest no marked and durable effect of these bacteria on the microbiome of the treated crop (Correa et al., 2009; Chowdhury et al., 2013; Kröber et al., 2014; Qiao et al., 2017). Those bacilli thus provide protection to their host plant but have no detrimental effect on the microbiome, which is of prime interest for future application as BCAs.

6 *Bacillus* spp. biocontrol mechanisms: induced-systemic resistance

Bacillus spp. can protect plants by triggering an immune response which is systemically expressed in all organs of the host plant called induced systemic resistance (ISR) (Yu et al., 2017; Ranf, 2018; Schellenberger et al., 2019). ISR involves activation of a latent defence process called priming and characterized by activation of defence responses only after infection. Priming provides an enhanced level of protection and a faster/stronger activation of defences by the whole plant (Pieterse et al., 2014). ISR activated by *Bacillus*

spp. protects plants against a broad spectrum of pathogens (Köhl et al., 2019; Miljaković et al., 2020). ISR can, *de facto*, complement resistance induced by pathogen attack such as recognition of pathogen- or microbial-associated molecular patterns (PAMPs or MAMPs, respectively) (Van Wees et al., 2000). *Bacillus* spp. are not generally a source of MAMPs, even though some *Bacillus* spp. can trigger ISR in host plants (Vanthana et al., 2019; Rajamanickam and Nakkeeran, 2020). BSM induction of ISR by *Bacillus* spp. involves different types of metabolites, degradation products due to bacterial activity or secreted molecules and volatiles (Pršić and Ongena, 2020). However, the molecular mechanisms driving recognition of these elicitors of *Bacillus* spp., especially for BSMs, are poorly understood.

Bacillus spp. can produce some protein elicitors of plant defence. The AMEP 412 protein in the *Bacillus* genus triggers ISR in tobacco against *P. syringae* pv. *Tomato* (Shen et al., 2019). The PeBA1 protein from *B. amyloliquefaciens* NC6 induces resistance in tobacco against infection by *B. cinerea* and by the tobacco mosaic virus (Wang et al., 2016).

cLPs are key ISR elicitors in a range of pathosystems. Surfactin and, to a lesser extent, iturin or fengycin, are powerful inducers of plant systemic resistance (Crouzet et al., 2020). Application of surfactin at the root level decreases disease severity due to the necrotrophic fungus *B. cinerea* on bean, tomato and *A. thaliana* leaves (Ongena et al., 2007; Debois et al., 2015). A comparative analysis using different *Bacillus* strains revealed a strong correlation between the amounts of surfactin and its ability to trigger defence immunity in a plant (Cawoy et al., 2014). Studies with *B. velezensis* FZB42 surfactin deficient mutant demonstrated the importance of this lipopeptide in the induction of plant defences in lettuce against *R. solani* (Chowdhury et al., 2015b). ISR activation by surfactin has been reported for several other pathosystems such as melon/*Podosphaera fusca* (García-Gutiérrez et al., 2013) and wheat/*Z. tritici* (Le Mire et al., 2018). Several iturin variants have also been shown to trigger ISR in different pathosystems, such as strawberry/*C. gloeosporioides* (Yamamoto et al., 2015), chili pepper/*Phytophthora capsica* (Park et al., 2016) or wheat/*Z. tritici* (Mejri et al., 2018). The iturin variant mycosubtilin has been reported to induce an immune response in grapevine against *B. cinerea* (Farace et al., 2015). Fengycin has been shown to trigger ISR in tomato against *B. cinerea* (Ongena et al., 2007), and more recently in grapevine and in tomato against *Plasmopara viticola* and *S. sclerotiorum*, respectively (Farzand et al., 2019; Li et al., 2019).

Lipopeptide activity has been shown to be plant and even organ-dependent (Pršić and Ongena, 2020). Surfactin is more efficient on dicots than on monocots (Ongena et al., 2007; Rahman et al., 2015; Mejri et al., 2018). Iturin treatment is more efficient when applied on leaves rather than roots (Han et al., 2015; Yamamoto et al., 2015). Iturin and surfactin have been shown to trigger

an immune response by interacting with plant membrane lipids, but the precise mechanism remains unclear (Henry et al., 2011; Deleu et al., 2013; Fiedler and Heerklotz, 2015; Balleza et al., 2019). It appears that surfactin activity is related to plant plasma membrane composition and is also affected by lipopeptide structure. Structural changes in fatty acid chain length (long chains are more efficient), as well as the substitution in the peptidic cycle, modulate their ability to trigger ISR (Jourdan et al., 2009; Kawagoe et al., 2015).

Volatiles produced by *Bacillus* are also involved in the induction of plant immunity. Exposure of roots of *A. thaliana* seedlings to VOC mixtures, produced by *B. subtilis* GBO3 or by *B. amyloliquefaciens* IN937a, resulted in fewer lesions from the pathogen *E. carotovora* subsp. *carotovora* due to immune resistance induction (Ryu et al., 2004). The majority of cases showing VOCs as inducers of systemic resistance relate to acetoin and 2,3-butanediol (Ryu et al., 2004; Rudrappa et al., 2010; Peng et al., 2019). Commercially available compounds such as 3-pentanol are involved in the induced resistance in pepper plants against *X. axonopodis* pv. *vesicatoria* (Choi et al., 2014).

7 Factors influencing the production of bioactive secondary metabolites: cellular regulation

The conditions under which optimal production of BSMs is achieved by *Bacillus* spp. are still poorly understood and studied in a restricted number of metabolites. Evidence for efficient *in situ* production of these metabolites by *Bacillus* spp. inoculants mainly concerns lipopeptides. Surfactin and/or iturin have been recovered in biologically relevant quantities from cucumber roots inoculated with *B. velezensis* strain QST713 (Kinsella et al., 2009) and from the tomato rhizosphere after treatment with *B. subtilis* BGS3 (Ongena et al., 2007; Nihorimbere et al., 2009) and strain RB14-C (Asaka and Shoda, 1996). Surfactin synthesis *ad planta* by *B. velezensis* FZB42 has been demonstrated in Lemna plantlets (Fan et al., 2011) and in lettuce together with fengycin and bacillomycin (Chowdhury et al., 2015b). Fengycins and iturins have also been detected on leaves and in fruits, illustrating that these plant tissues may also support cLP biosynthesis (Touré et al., 2004; Romero et al., 2007; Zerriouh et al., 2011, 2014; Debois et al., 2015). This limited research on the production of BSMs under natural conditions reflects the inherent difficulties in detecting and quantifying these small-size compounds in complex environments like soil. These molecules can be chemically unstable, degraded by other (micro)organisms or adsorbed on the surface or within soil particles. Whether BSMs accumulate to biologically efficient concentrations in the rhizosphere is, therefore, still a matter of debate. However, it is crucial to measure such concentrations in order to better understand the real impact of these molecules in eliciting plant defences and/or in the direct biocontrol of pathogens.

Recent studies mainly on *B. subtilis* suggest that regulation of the expression of BGCs at the cellular level is quite complex, at least for NRP/PK products. It involves a range of pleiotropic regulators or transcription factors driving developmental processes such as QS, biofilm formation or sporulation. Natural conditions are also far from *in vitro* cultural conditions in artificial media. Root-associated bacteria feed almost exclusively on plant exudates, cross-communicate with other organisms (with positive or negative outcomes) and have to face multiple abiotic factors in the soil. Production of BSMs may, therefore, also be modulated by multiple ecological parameters.

The regulation of lipopeptides biosynthesis at the cellular level has been quite well studied. Two QS regulatory systems; that is, ComQXPA (Lopez et al., 2009) and Rap-Phr (Auchtung et al., 2006), are key players in surfactin regulation. Phosphorylated ComA is required to initiate *urfA* gene transcription, while the Rap phosphatases dephosphorylate ComA act as repressors. Additional transcription factors such as Spx (Zhang et al., 2006) or *codY* (Coutte et al., 2015) interfere with the role of ComA (Han et al., 2015) and others, such as ClpX/P, (Nakano et al., 2000) display a chaperone activity to facilitate ComA DNA binding. DegU, another master regulator, has also been shown to have a positive effect on surfactin production (Ogura, 2001). The AbrB/Abh system seems to affect lipopeptide synthesis in a more specific manner depending on the physiology of the cell (Zhi et al., 2017).

Environmental factors such as phosphate limitation or oxidative stress also have an impact on surfactin regulation via transcription factors such as PhoP and PerR (Ogura, 2001; Hayashi et al., 2005). The regulation of iturin and fengycin shares some regulators with surfactin. DegU, ComA, AbrB and GlnR, which are involved in glutamine synthesis (Koumoutsis et al., 2007; Zhang et al., 2017b; Xu et al., 2020), regulate iturin biosynthesis together with YczE, presumably acting at the post-transcriptional level (Koumoutsis et al., 2007; Dang et al., 2019). DegQ, PhoP and AbrB drive fengycin synthesis (Wang et al., 2015; Lu et al., 2016; Guo et al., 2018). Two extra-factors LutR and SinR, both involved in cellular mechanisms, are also positive regulators (İrigül-Sönmez et al., 2014).

The regulation of lantibiotics is determined by cell density. They act as autoinducing peptides via a typical two-component regulatory system composed of a sensor (histidine kinase) and a response regulator (LanRK) present in their operon (Kleerebezem et al., 2004; Schmitz et al., 2006).

The complexity of BSM regulation in *Bacillus* spp. is illustrated in the case of the dipeptide bacilysin. It involves several pleiotropic regulators depending on the physiological state of the cells in culture. In *B. subtilis*, bacilysin biosynthesis is under the control of the ComQXPA and PhrC QS system (Yazgan et al., 2001; Yazgan Karata et al., 2003). ComA binds directly to the promoter region of the *bac* operon and initiates a basal expression of this BGC (Köroğlu et al., 2011). The LutR regulon and the two interconnected regulators (DegU and DegQ) also

regulate bacilysin synthesis (Köroğlu et al., 2008; Mariappan et al., 2012). ComA may also act indirectly on bacilysin production by influencing DegU through DegQ activation. AbrB acts as a repressor of *bac* during the exponential growth phase, but its negative regulatory effect is silenced by Spo0A (Köroğlu et al., 2011). The other transcription factors CodY and ScoC also negatively regulate bacilysin production by binding directly to the promoter region.

Less information is available regarding PKS regulation. In *B. subtilis*, expression of the *bae* operon, which is the only PK cluster conserved among species of the *B. subtilis* complex (Fan et al., 2018), is under the control of several transcriptional regulators. Full expression of this operon requires ComA, DegU, the ScoC regulon and CodY, which binds multiple sites in the cluster (Belitsky and Sonenshein, 2013; Vargas-Bautista et al., 2014). The *dfn* and *mIn* operons, responsible for the synthesis of the two other PKs (difficidin and macrolactin, respectively) are only present within the *B. velezensis* species, explaining the low number of studies dealing with their regulatory pathways. The antiterminator *LoaP*, encoded by a gene positioned directly upstream of the *dfn* operon, has been shown to regulate the transcriptional readthrough of termination sites located within the *dfn* and *mIn* operons in *B. velezensis* (Goodson et al., 2017). Upon *loaP* deletion, the production of both difficidin and macrolactin is abolished, but bacillaene synthesis is fully conserved (Goodson et al., 2017). Difficidin production is also impaired in mutants not expressing the DegU regulator (Mariappan et al., 2012).

8 Factors influencing the production of bioactive secondary metabolites: biofilm formation

Agitated liquid cultures are commonly used to assess the effect of a given factor on secondary metabolite synthesis. However, the physiology of planktonic cells, when undergoing fast 'latence-exponential-stationary' growth typically observed in batch cultivation, does not reflect the physiology of bacteria developing in the close vicinity of roots. PGPR form biofilm-structured multicellular communities at the surface of roots in nutritionally limited conditions very different from the optimized laboratory conditions. The inoculated strain establishes on plant tissues as biofilm-structured patches. Biofilm formation is associated with the diversification of the cell community into sub-populations with distinct roles and activities (metabolically active vegetative cells, matrix producers, cannibals and spores). This formation results in phenotypic heterogeneity that may influence the synthesis of secondary metabolites (Nihorimbere et al., 2009).

The effect of biofilm formation on the pattern of lipopeptides produced by *B. amyloliquefaciens* has been assessed by growing the bacterium in static liquid cultures conducted in wells of microtiter plates. In these conditions, cells

readily aggregate to form pellicles at the liquid-air interface. LC-MS profiling of the secreted lipopeptides revealed clear differences compared to agitated cultures with enhanced production of surfactin production but not iturins and fengycins. The proportions of the three lipopeptide families were similar to those secreted after root colonization and clearly differed from planktonic cells secreting much higher amounts of iturins and fengycins (Nihorimbere et al., 2012; Debois et al., 2014). The formation of biofilm is accompanied by metabolic changes under the control of regulators such as SpoOA. These transcriptional modifications may also influence the production of BSMs like the *bacABCDEF* and *sbo-alb* operons coding, respectively, for bacilysin and subtilosin A that are up-regulated during biofilm formation (Pisithkul et al., 2019). The production of other BSMs under biofilm conditions has not yet been investigated.

The formation, organization and functioning of this complex multi-cellular structure have been extensively studied in *B. subtilis* and related species but almost exclusively *in vitro* by forming macrocolonies on gelled media or as pellicles developing at the air-liquid interface. However, biofilm formation on plant tissues is very different compared to an inert surface, taking into account interactions with the host. In natural conditions, *Bacillus* cells evolve in the middle of other microbes and interactions with other microbial species can modulate motility and biofilm formation (Andrić et al., 2020) (see below). Biofilm formation and functionality have been poorly investigated *in planta*, including all these biotic parameters that may interfere with this process. There is a need to develop new cultivation methods in the lab to mimic biofilm formation by bacterial cells colonizing roots or influenced by plant factors. This initially requires gnotobiotic conditions where the bacterium and the plant interact under controlled physico-chemical settings such as temperature and pH. Population diversification and phenotypic heterogeneity should be studied using fluorescent transcriptional reporters designed to highlight the phenotype of interest using confocal laser-scanning or other microscopy techniques. The use of flow cytometry on microbial cells extracted from biofilm structures may also provide a dynamic view of the microbial population of interest.

9 Factors influencing the production of bioactive secondary metabolites: abiotic factors

The potential of BCAs such as *Bacillus* spp. to produce BSMs has been, in most cases, evaluated *in vitro* using optimal growth conditions for key parameters such as temperature, pH and oxygen availability. However, these conditions fluctuate in soil and may significantly influence BSMs production *in planta*. Research so far has mainly focused on the impact of these abiotic factors on lipopeptide production.

Oxygen depletion is common in the rhizosphere due to consumption by roots and microbes (Dubern and Bloemberg, 2006). Under oxygen-starvation conditions, surfactin production remains unchanged, suggesting that a low oxygen level is not detrimental for surfactin synthesis in the rhizosphere (Nihorimbere et al., 2009, 2012). A positive effect of O₂ limitation has even been reported for surfactin production but under bioreactor conditions (Yeh et al., 2006; Yi et al., 2017). In contrast, expression of iturin and fengycin operons is O₂-dependent (Guez et al., 2008; Nihorimbere et al., 2012; Rangarajan et al., 2015).

Temperature stress is a key factor affecting basal and secondary metabolism production in microbes, significantly affecting the survival and effectiveness of plant-associated microbes used as microbial inoculants. Little is known about the effects of low or fluctuating temperature on the production of BSMs by *Bacillus* spp. Several studies have reported an increase in lipopeptide production with decreasing temperatures (Fickers et al., 2008; Pertot et al., 2013; Pereira Monteiro et al., 2016; Chen et al., 2019). Growth at low temperatures (15°C) led to a marked increase in surfactin production in comparison to high temperatures (>35°C) (Pertot et al., 2013). Low temperatures may affect the expression of ComK and further down-regulate genes coding for the RapF and RapH repressors of surfactin gene expression (Budde et al., 2006; Jacques, 2011). Enhanced production at low temperature may also rely on post-transcriptional events, such as NRPS protein turn-over or modifications in the lipopeptide export process (Fickers et al., 2008). Data from *in planta* assays performed in greenhouses have also suggested that enhanced surfactin production at low temperature may counter-balance the reduced growth of *B. amyloliquefaciens* S499 on roots, maintaining its ISR triggering potential under cold conditions (Pertot et al., 2013). The effect of cold/heat on the production of other *Bacillus* spp. lipopeptides has been little investigated but enhanced iturin synthesis by lowering the temperature from 37°C to 25°C has been observed (Ohno et al., 1995; Jacques et al., 1999; Fickers et al., 2008). The consequences of temperature fluctuations on cLP production seem to vary between strains. Results obtained for surfactin in *B. velezensis* S499 and FZB42 could not be confirmed for *B. velezensis* QST713 (Pertot et al., 2013). It has also been shown that increased temperature can cause a higher production of surfactin in *B. velezensis* FJAT-46737 (Chen et al., 2020). Further investigation covering a wider range of temperatures and evaluating the impact on the whole secreted metabolome is required to better appreciate its impact on the production of BSMs.

The effect of pH on BSMs production is poorly documented. Surfactin production has been reported to be inhibited at pH 5 (Yi et al., 2017). Efficient synthesis of lipopeptides is favoured in mild-acidic to neutral environments, which is often the case for rhizosphere due to multiple processes related notably to plant exudation and root/microflora activity (Cosby et al., 1998; Akpa et al., 2001; Hinsinger et al., 2009; Wang et al., 2020a).

10 Factors influencing the production of bioactive secondary metabolites: biotic factors

10.1 Interactions with the host plant

Root exudates are primarily used as nutrients by plant-associated bacteria to sustain growth but may also stimulate flagella motility, chemotaxis and biofilm formation. They are, therefore, essential for rhizosphere establishment (Kierul et al., 2015; Pandin et al., 2017). The chemical nature of these exudates also influences the production of BSMs.

cLPs production is impacted both qualitatively and quantitatively by changes in exudate components. Carbon (C) sources in root exudates support *B. amyloliquefaciens* S499 growth. Surfactin secretion (but not iturin or fengycin) has been shown to be significantly higher in the presence of organic acids as compared to sugars (Nihorimbere et al., 2012). The relative proportions of different homologues may vary in relation to carbon sources. The synthesis of C₁₅ surfactins is promoted in the presence of organic and amino acids compared to sugars.

In response to maize root exudates, the expression of genes involved in the synthesis of bacillaene, difficidin, macrolactin, fengycin and surfactin was up-regulated in *B. velezensis* FZB42 and in *B. velezensis* SQR9 (Fan et al., 2012; Zhang et al., 2015). Root exudates of *Eruca sativa* (rocket salad) have been shown to induce *pks* operon expression, responsible for bacillaene synthesis in *B. subtilis*, allowing the bacterium to attack other root-associated bacteria (Ogran et al., 2019). In *B. velezensis* SQR9, comparative proteomic analysis revealed that PKs, fengycin and surfactin were overproduced upon colonization of cucumber roots (Qiu et al., 2014).

Physical contact with the root surface and, more specifically, perception of plant polymers may initiate processes such as biofilm formation in *Bacillus* species. It has been shown that polymers of the plant cell wall (xylan, pectin) also act as cues for triggering the synthesis of surfactin (Beauregard et al., 2013; Debois et al., 2015; Wu et al., 2015a). The *srfAA* gene is induced when *Bacillus* spp. are placed in contact with rice seedlings (Xie et al., 2015). As surfactin is involved in swarming motility and biofilm formation, improved production may contribute to spread on root tissues and aggregation in biofilm-related multicellular communities.

10.2 Interactions with microbial pathogens

Bacillus spp. have to compete with other microorganisms in the rhizosphere. *Bacillus* spp. thus have to adapt and improve their ecological fitness by modulating BSM production in response to fungal and bacterial competitors. The presence of chitin or S-glucan has been found to increase the production of fungal cell wall

degrading enzymes such as chitinase and glucanases by *B. subtilis* JF419701, (Alamri, 2015). It has been shown that co-cultures between plant beneficial bacilli and oomycetes or fungi (including *P. aphanidermatum*, *F. oxysporum* or *S. sclerotiorum*) increase iturin and fengycin production, both known for their antifungal properties (Cawoy et al., 2015; Farzand et al., 2020). Fengycin synthesis by *B. velezensis* S499 has also been reported to be upregulated in the presence of *Rhizomucor variabilis*, suggesting that the bacterium is able to perceive some molecular trigger(s) emitted by the pathogen (Zihahirwa Kulimushi et al., 2017).

In addition to these two antifungal cLPs, surfactin production has also been induced when *Bacillus* spp. are confronted to *Phytophthora parasitica*, *R. solani*, *F. solani*, *S. sclerotiorum*, *R. stolonifera*, *Fusarium sambucinum* and *Trichoderma aggressivum* (Chowdhury et al., 2013; DeFilippi et al., 2018; Pandin et al., 2019). Surfactin overproduction could promote competition for nutrients and space (Molina-Santiago et al., 2019; Andrić et al., 2020). Surfactin is involved in QS, stimulates biofilm formation, and contributes to plant root colonization (Kinsinger et al., 2003; Lopez et al., 2009; Raaijmakers et al., 2010). The isoform profile of cLPs changes depending on the competitor pathogen (Cao et al., 2018; DeFilippi et al., 2018). This suggests that bacteria modulate BSM synthesis depending on signals emitted by specific fungal pathogens (Frey-Klett et al., 2011).

Variation in BSM production in response to bacterial competitors has been poorly studied and mostly limited to transcriptional analyses. Expression of genes belonging to iturin, fengycin and surfactin operons has been shown to be up-regulated in the presence of *R. solanacearum* (Almoneafy et al., 2014; Cao et al., 2018). Expression of lipopeptide operons and bacilysin in *B. velezensis* BK7 has been reported to be significantly upregulated in the presence of *Pseudomonas fuscovaginae* (Kakar et al., 2014). Bacterial competitors also stimulate *B. subtilis* motility and biofilm formation, but the causal link between overproduction of biofilm in the presence of some competitors and surfactin production has not yet been demonstrated (Grau et al., 2015; van Gestel et al., 2015; Liu et al., 2018c).

11 Interactions of *Bacillus* spp. with other beneficial microorganisms and their use in biocontrol

Interactions between *Bacillus* spp. and other microorganisms do not always lead to competition and antagonism but may be compatible and result in synergistic effects. The application of *Bacillus* spp. with other beneficial microbes has thus emerged as a promising biocontrol strategy.

Synergistic effects in protecting plants against pathogens and promoting growth have been reported using combinations of *Bacillus* spp. with *Trichoderma* species (Wu et al., 2018; Karuppiyah et al., 2019; Izquierdo-García et al., 2020), another BCA acting via competition, mycoparasitism, antibiosis

and triggering of ISR (Vinale et al., 2008; Ghorbanpour et al., 2018). Higher production of BSMs, as well as cryptic compounds (depending on specific conditions), has also been reported in liquid co-cultivation of *B. subtilis* 22 and *Trichoderma atroviride* SG3403 as compared with the two microorganisms cultivated individually (Li et al., 2020).

Arbuscular mycorrhizal (AM) fungi are also key microorganisms in soil, forming symbiotic associations with more than 70% of vascular plant species (Brundrett and Tedersoo, 2018). They improve plant nutrition (mainly phosphorus and nitrogen) and water uptake. Plants forming associations with these soil fungi have been found to resist biotic and abiotic stresses better (Bonfante and Genre, 2010; Plouznikoff et al., 2016; Mathieu et al., 2018), partly due to the ability of AM fungi to induce ISR (Gallou et al., 2011, 2012; Fiorilli et al., 2018; Deja-Sikora et al., 2020). Some synergies and improved functionality of PGPR-AM fungi consortia have been reported for plant growth and health (Armada et al., 2018; Zhang et al., 2018; Yadav et al., 2020). Co-inoculation of *B. subtilis* or *B. amyloliquefaciens* with AM fungi did not affect fungal growth but improved resistance to biotic and abiotic stresses due to more efficient nutrient supply in *Artemisia annua* L., *Allium sativum* L. and *Triticum aestivum* L. (Awasthi et al., 2011; Agnolucci et al., 2019; Rashad et al., 2020; Yadav et al., 2020). Metabolism markers such as succinate dehydrogenase and alkaline phosphatase showed a positive impact of *Bacillus* spp. on AM fungi metabolism (Vivas et al., 2003). However, there remains a lack of data demonstrating enhanced biocontrol activity of formulations combining bacilli and AM fungi.

Co-inoculation of *Bacillus* spp. with bacteria belonging to the *Pseudomonas* or *Streptomyces* genera is also promising. These BCA species are competitors, producing antimicrobials affecting *Bacillus* growth. Antagonistic interactions have been reported between *Pseudomonas protegens* PF-5 and *B. subtilis* NCIB3610 (Powers et al., 2015; Molina-Santiago et al., 2019) or between *Streptomyces* sp. MG1 and *B. subtilis* 3610 (Barger et al., 2012; Traxler and Kolter, 2015). However, co-inoculation of *B. licheniformis* B642 and the beneficial *Pseudomonas fluorescens* strain FAP2 may have beneficial effects on the host plant (Ansari and Ahmad, 2019). The combination of these two genera enhanced resistance against *X. campestris* pv. *campestris* compared to their use individually (Mishra and Arora, 2012). The combination of *B. subtilis* GBO3 with *P. fluorescens* CECT 5398 has been shown to improve the control of *F. oxysporum* and *R. solani* in tomato and pepper (Domenech et al., 2006). However, the molecular basis underpinning synergistic effects still remains to be deciphered.

Combining strains belonging to the *Bacillus* genus can also enhance disease suppression. The combination of *B. amyloliquefaciens*, *B. sphaericus*, *B. pumilus* strains or of *B. altitudinis* and *B. velezensis* strains exhibited higher levels of biocontrol against *X. axonopodis* pv. *vesicatoria*, *P. syringae* pv. *tomato*

and *R. solanacearum* on tomato but also against *Pythium ultimum* and cucumber mosaic virus on cucumber compared single bacteria (Jetiyanon and Kloepper, 2002; Liu et al., 2018b). Studies in greenhouses have demonstrated that a mixture of *Bacillus* species (*B. pumilus* and *B. amyloliquefaciens*) significantly improved control of *P. capsici* on squash compared to individual strains (Zhang et al., 2010).

Some products combining other PGPR species with *Bacillus* spp. have been commercialized as BCAs. Products include LS213 by Gustafson Inc. (combining *B. subtilis* strain GB03 and *B. amyloliquefaciens* strain IN937a), Bio Protector by Bacto Agro Culture Care Pvt Ltd (2 strains of *Trichoderma*, *Ps. fluorescens* and *B. subtilis*) or BioYield™ by Bayer Crop Science (*B. amyloliquefaciens* GB99 + *B. subtilis* GB12), though most are described as biofertilizers or biostimulants (Domenech et al., 2006; Woo et al., 2014; Le Mire et al., 2016; Borriss, 2020).

Further research is needed to better understand the molecular dialogue existing between *Bacillus* and other BCAs to evaluate factors that inhibit or enhance synergistic interactions. Interaction-mediated variations in colony morphology, motility, biofilm formation, or sporulation illustrate how soil bacilli can protect themselves from antimicrobials emitted by bacterial competitors. The effect on these developmental processes could be coupled with significant modulation in the production of specific BSMs. These BSMs would then act as antimicrobials or in promoting cooperative interspecies communication processes which do not affect growth (Bleich et al., 2015; Liu et al., 2018c). This understanding would help design combinations of *Bacillus* with other microbes for more efficient biocontrol products.

12 Conclusions and future trends

The potential of some *Bacillus* species to control plant diseases caused by a range of pathogens has been amply demonstrated from lab to field, and selected isolates have been successfully commercialized. However, as for other microorganisms, the success of *Bacillus*-based products has been hampered by their highly variable or poor performance across agro-ecological environments and host plant species. There is a need to optimize/adapt their production and formulation (addition of prebiotics) at an industrial scale. It is also crucial to improve our basic knowledge of the processes influencing the expression of biocontrol traits and their persistence in plants following application in the field.

The biocontrol potential of *Bacillus* species mostly relies on their capacity to synthesize a wide range of BSMs involved in the three processes underpinning biocontrol. Some BSMs viewed as 'specialized' metabolites having a single main function may actually play multiple roles. As illustrated for surfactin, many BSMs may be multifunctional and act as signals or antimicrobials depending on the concentration. It is necessary to combine

approaches such as loss/gain of functions of mutants and the effect of purified BSMs to clearly identify bioactivities, depending on the concentration and the type of microbial pathogen (for antagonism) or plant genotype (for ISR). Better characterization of the molecular mechanisms of key bioactivities compounds acting individually or in combination is required if we want to understand why they inhibit some pathogens but not others or why they can stimulate immunity in some plants but not others. There is a need to combine carefully designed biotests with other approaches such as experimental and *in silico* biophysics to investigate effects on cellular membranes (depending on lipid composition) and thus on the target organism (Deleu et al., 2014; Balleza et al., 2019).

As they can be affected by abiotic factors and multitrophic interactions, we also need to improve our knowledge on the timing, amount and diversity of BSMs when produced *in planta* under natural conditions. This would help to understand whether these BSMs act as signals at sub-inhibitory concentrations or if they can play antimicrobial functions upon reaching threshold amounts at least locally around the plant tissues. It will also help in determining to what extent effects differ according to plant species, age and physico-chemical conditions. We need to develop new *ex vivo* approaches and exploit technologies like imaging mass spectrometry to spatiotemporally resolve the dynamics of production of those small molecules produced upon colonization or during microbial interspecies interactions (Debois et al., 2014; Boughton et al., 2016; Spraker et al., 2020).

Integrating all those data is necessary to predict the pathosystems against which these bacilli would work as BCAs. This will benefit the practical use of *Bacillus*-based products as sprays to treat aerial parts of the plants or as soil inoculants to protect seedlings from attack by soil-borne microbial pathogens. Even if results are promising (Parnell et al., 2016; Meng and Hao, 2017), prophylactic applications such as soil drenching or seed coating to protect crops in the first stage of their development remain a major challenge for large-scale biocontrol, notably for cereals.

B. velezensis is among the best candidate species for the development of biocontrol agents. Several products with different strains of this species are already on the market (Table 2) but all these strains are genetically close and have a similar arsenal of bioactive metabolites. Soil represents an un-tapped reservoir from which new *Bacillus* species/strains forming unknown but highly active compounds can be isolated, based on rationally designed screening procedures (Köhl et al., 2019).

Another attractive alternative is the development of products with *Bacillus* spp. metabolites as active ingredients (Glare et al., 2012; Heimpel and Mills, 2017). Lipopeptides are naturally formed in high amounts by species such as *B. subtilis* and *B. velezensis* and optimization of their production in bioreactors

at pilot scale has been thoroughly investigated (Rangarajan et al., 2015; Motta Dos Santos et al., 2016; Brück et al., 2019). There are methods available for extraction and (semi-)purification, allowing cost-effective processes to obtain bio-sourced products with reasonable purity and good stability (Coutte et al., 2017). If formulated metabolites are developed, their (eco-)toxicological risks need to be carefully assessed in relation to doses used to treat crops and stability in the environment.

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14 Where to look for further information

The International Organisation for biological and integrated control (IOBC) is a very active society headed by (academic) experts in the field who organizes symposia, workshops, and congresses on all aspects of the biocontrol science. The website <https://www.iobc-wprs.org/> also provides valuable information on integrated production and integrated pest management.

For more information about the biocontrol industry and a comprehensive view of biocontrol technologies are used (or being developed) as alternatives to control pests and diseases effectively in an environmental friendly way in agriculture, forestry: <https://ibma-global.org/>.

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