J. Microbiol. Biotechnol. (2007), **17**(9), 1407–1429

JOURNAL OF MICROBIOLOGY AND BIOTECHNOLOGY

Burkholderia Diversity and Versatility: An Inventory of the Extracellular Products

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Received: July 1, 2007 Accepted: July 31, 2007

Abstract The *Burkholderia* genus consists of over 40 Gram-negative, β-proteobacteria species that occupy remarkably diverse ecological niches. This genus contains species pathogenic to human, animals, and plants, as well as species involved in promoting plant growth and biodegradation of pollutants. This is largely explained by the extraordinary versatility of *Burkholderia*, as reflected by the remarkable diversity of extracellular products released by these bacteria. We exhaustively surveyed the extracellular enzymes, siderophores, toxins, antimicrobials, and other secondary metabolites produced by the members of this very diverse genus. Available information on regulation, especially quorum sensing mechanisms, and secretion is highlighted.

Keywords: *Burkholderia*, enzymes, siderophores, toxins, antimicrobials, quorum sensing

The *Burkholderia* genus, β subdivision of the proteobacteria, comprises more than 40 species that inhabit remarkably diverse ecological niches, as they have been isolated from soil, plant rhizosphere, water, insects, fungus, and hospital environments and from infected humans (Table 1). The genus *Burkholderia* was proposed by Yabuuchi *et al.* [218] to accommodate the former rRNA group II pseudomonads [218]. In fact, confusion with *Pseudomonas* has impeded knowledge progression.

Traditionally, *Burkholderia* species have been known as plant pathogens. *B. cepacia* was first described by Burkholder in 1950 as a plant pathogen causing sour skin of onion [22]. For example, *B. glumae* causes rot of rice grains and seedlings (panicle blight) [88]. Several *Burkholderia* species have developed beneficial interactions with their plant hosts. Somes species are able to fix atmospheric nitrogen, including *B. vietnamiensis*, *B. unamae*, and *B. tropica* [23, 157, 188]. Legumes are also nodulated by several *Burkholderia* species such as *B. mimosarum*, *B. nodosa*, and *B. phymatum* [28, 29, 154]. Several *Burkholderia* species have considerable commercial and ecological importance. Certain species of *Burkholderia* have proved to be very efficient in biocontrol, bioremediation, and plant growth promotion. For example, *B. xenovorans* strain LB400 is one of the most effective polychlorinated biphenyl (PCB) degraders known [27].

In contrast, several *Burkholderia* species are also opportunistic human pathogens. These species include all *Burkholderia cepacia* complex (Bcc) bacteria, *B. gladioli*, and *B. fungorum*. The Bcc contains (at least) nine closely related species or genomovars, which can cause severe respiratory infections in people suffering from cystic fibrosis (CF) or chronic granulomatous disease [39]. All nine species have been recovered from CF patients, but *B. cenocepacia* and *B. multivorans* are the dominant Bcc species [119]. *B. cenocepacia* comprises the most virulent clones and has been associated with higher mortality rates among CF patients [119].

B. pseudomallei and *B. mallei* are the only known members of the genus *Burkholderia* that are primary pathogens in humans and animals. The saprophyte *B. pseudomallei* is the causative agent of melioidosis, a potentially fatal septicemic infection of animals and humans [30]. Melioidosis is endemic in tropical and subtropical areas of Southeast Asia and Northern Australia [30]. *B. pseudomallei* has been classified as a potential biological weapon and has been used by Germany during World War I [160]. *B. mallei* is the etiologic agent of glanders, which is mainly a horse disease but in rare cases affects humans [138]. *B. thailandensis* is closely related to *B. pseudomallei* and is generally considered avirulent [68].

The ecological versatility of *Burkholderia* is likely due to their large genomes, which are often comprised of several large replicons (two to four circular chromosomes or large plasmids). An important variation in genome size from 4.7 to 9 Mb is observed in the *Burkholderia* genus

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Table 1. List of known *Burkholderia* species, with their reported QS systems.

Burkholderia species name	Habitat	Reference	Quorum sensing systems		Alternate name
			Proteins	Signaling molecules	
Complex *cepacia* (Bcc)					
B. cepacia genomovar I	Humans (CF and non-CF), animals, soil, rhizosphere, plants	[218]	CepIR [117]	C_6-HSL, C_8-HSL	*Pseudomonas cepacia*
B. multivorans genomovar II	Humans (CF and non-CF), soil, hospital environment	[200]	CepIR [117]	C_6-HSL, C_8-HSL	
B. cenocepacia genomovar III	Humans (CF and non-CF), animals, soil, rhizosphere, plants	[200]	CepIR [117]CciIR [11,120]	C_6-HSL, C_8-HSL	*Burkholderia cepacia*, *Pseudomonas cepacia*
B. stabilis genomovar IV	Humans (CF and non-CF), hospital environment	[201]	CepIR [41,117]	C_6-HSL, C_8-HSL	
B. vietnamiensis genomovar V	Humans (CF and non-CF), animals, soil, rhizosphere, plants	[66]	CepIR, BviIR	C_6-HSL, C_8-HSL, C_{10}-HSL	
B. dolosa genomovar VI	Humans (CF), rhizosphere	[205]	NI	C_6-HSL, C_8-HSL	
B. ambifaria genomovar VII	Humans (CF), soil, rhizosphere	[38]	BafIR [229]	C_8-HSL	
B. anthina genomovar VIII	Humans (CF), animals, water, soil, rhizosphere	[203]	NI	C_6-HSL, C_8-HSL	
B. pyrrocinia genomovar IX	Humans (CF and non-CF), soil, rhizosphere, plants	[203]	NI	C_6-HSL, C_8-HSL	*Pseudomonas pyrrocinia*
B. andropogonis	Plants	[66]	NI	NI	*Pseudomonas andropogonis*
			NI	NI	*Pseudomonas woodsii*
B. caledonica	Rhizosphere	[37]	NI	NI	
B. caribensis	Soil, root nodules	[2]	NI	NI	
B. caryophylli	Plants	[218]	NI	NI	*Pseudomonas caryophylli*
B. ferrariae	Mines	[199]	NI	NI	
B. fungorum	Humans (CF and non-CF), animals, fungus, soil, plants, water	[37]	NI	NI	
B. ginsengisoli	Soil	[92]	NI	NI	
B. gladioli	Humans (CF and non-CF), plants	[218]	NI	NI	*Burkholderia cocovenenans*, *Pseudomonas antimicrobica*
B. glathei	Plants, rhizosphere	[200]	NI	NI	*Pseudomonas glathei*
B. glumae	Humans (non-CF), plants	[197]	TofIR [51]	C_6-HSL, C_8-HSL	*Pseudomonas glumae*
B. graminis	Plants, soil, rhizosphere	[206]	NI	NI	
B. hospita	Soil	[72]	NI	NI	
B. kururiensis	Water, industrial contaminant	[227]	NI	NI	
B. mallei	Horses, mules, donkeys, humans	[218]	BmaIR 1 and 3 [193]	C_8-HSL, 3-hydroxy-C_8-HSL, C_{10}-HSL, 3-hydroxy-C_{10}-HSL	*Pseudomonas mallei*
B. mimosarum	Root nodules	[28]	NI	NI	

Table 1. Continued.

Burkholderia species name	Habitat	Reference	Quorum sensing systems		Alternate name
			Proteins	Signaling molecules	
B. nodosa	Root nodules	[29]	NI	NI	
B. oklahomensis	Human (non-CF)	[69]	NI	NI	Oklahoma strain of *Pseudomonas pseudomallei*
B. phenazinium	Plant, soil	[206]	NI	NI	*Pseudomonas phenazinium*
B. phenoliruptrix	Soil	[40]	NI	NI	
B. phymatum	Root nodule	[202]	NI	NI	
B. phytofirmans	Rhizosphere, soil	[163]	NI	3-Hydroxy-C_8-HSL [163]	
B. plantarii	Plants	[197]	PlaIR [173]	C_6-HSL, C_8-HSL	*Burkholderia gladioli* *Pseudomonas plantarii*
B. pseudomallei	Humans, animals, soil, water	[218]	BpsIR [174], PmiIR, BpmIR2 and 3 [192,198]	C_8-HSL, C_{10}-HSL, 3-hydroxy-C_8-HSL, 3-hydroxy-C_{10}-HSL, 3-hydroxy-C_{12}-HSL, 3-oxo-C_8-HSL, 3-oxo-C_{14}-HSL	*Pseudomonas pseudomallei*
B. sacchari	Soil	[19]	NI	NI	
B. silvatlantica	Rhizosphere, plants (roots, leaves)	[149]	NI	NI	
B. soli	Soil	[224]	NI	NI	
B. sordidicola	Fungus	[111]	NI	NI	
B. terrae	Soil	[220]	NI	NI	
B. terricola	Soil	[72]	NI	NI	
B. thailandensis	Soil	[20]	BtaIR1 to 3 [194]	C_6-HSL, C_8-HSL, C_{10}-HSL	*Burkholderia pseudomallei*-like species
B. tropica	Plants (roots, stem), rhizosphere	[157]	NI	NI	
B. tuberum	Root nodule	[202]	NI	NI	
B. ubonensis	Humans (non-CF)	[218]	NI	NI	
B. unamae	Plants (roots, stem), rhizosphere	[23]	NI	NI	
B. xenovorans	Humans (CF and non-CF), soil, rhizosphere	[72]	BxeB0608, BxeB0610, suggested to be CciIR-related [27,120]	NI	

NI: Not investigated.

[215]. The presence of multiple insertion sequences that confer genome plasticity could also explain the versatility of the genus *Burkholderia* [130].

Burkholderia species secrete a variety of extracellular enzymes with proteolytic, lipolytic, and hemolytic activities. Several strains secrete also toxins, antibiotics, and siderophores. The extracellular products of *Burkholderia* represent admirably the diversity and versatility of that genus. In this review, we present a survey of the extracellular products of *Burkholderia* species and their role in interaction with their hosts. Regulation and secretion of these products are also reported.

Transcriptional Regulation of Exoproducts: Quorum Sensing

Bacteria closely regulate the synthesis and release of extracellular products. Besides environmental and physiological conditions that influence expression of exoproducts, another type of global regulation is widespread among bacterial populations and is called quorum sensing (QS) [156]. Quorum sensing is fundamental to the ability of many bacterial species to create coordinated cell-to-cell interactions. Quorum sensing is a cell-to-cell communication system used by bacteria to perceive and respond to their population

density in order to coordinate gene expression. In Gram-negative bacteria, the most widespread QS mechanism is based on LuxR-type transcriptional regulators and their cognate *N*-acyl-homoserine lactones (AHLs) ligands [63]. These molecules, when they reach a threshold reflecting cell density, activate LuxR-type transcriptional regulators that specifically regulate bacterial gene expression.

Quorum sensing has been well studied among Bcc bacteria, where it was first identified from the clinical isolate *B. cenocepacia* strain K56-2 [108], and comprises the LuxIR-type homologs CepI and CepR (Table 1). The CepI synthase is responsible for the production of two AHLs: *N*-hexanoyl-HSL (C_6-HSL) and the most abundant *N*-octanoyl-HSL (C_8-HSL). The transcriptional regulator CepR responds most efficiently to C_8-HSL [82]. The *cepI* and *cepR* genes have been found in the 9 species comprised in the Bcc [117]. In *B. ambifaria*, the CepIR system has been renamed BafIR [229].

Some Bcc species possess more than one QS circuitry. For example, some *B. vietnamiensis* strains, as well as producing C_6- and C_8-HSLs, display additional AHLs, C_{10}-HSL being the most abundant [41]. In these strains, another QS system is responsible for the production of these additional AHLs, named BviIR. BviI and BviR are only 36% identical to CepI and CepR, respectively. Whether the BviI/BviR system interacts with the CepI/CepR system remains to be investigated. In a particulary virulent strain of *B. cenocepacia* lineage ET12, another QS system is also present and is encoded in a pathogenicity island [11]. It is yet unclear whether this QS system, consisting of the AHL synthase CciI and its cognate receptor protein CciR, operates independently of CepI/CepR.

Although QS has been less studied outside the Bcc, it appears present in every *Burkholderia* strain where it was investigated. In *B. glumae* and *B. plantarii*, QS systems have been identified and named TofIR [93] and PlaIR [173], respectively. These two systems share more than 99% identity, and 75% identity with the CepIR system [173].

Table 2. Extracellular enzymes.

Class	Gene	Regulation	Species	Secretion
Proteases	*zmpA*	CepIR [67,172]	*B. cepacia* *B. cenocepacia* *B. stabilis* *B. ambifaria* *B. pyrrocinia*	Type II secretion pathway [83]
	zmpB	CciIR and CepIR [98,120]	*B. cepacia* *B. cenocepacia* *B. stabilis* *B. ambifaria* *B. pyrrocinia*	Type II secretion pathway [79,83]
	mprA	PmiIR [198]	*B. pseudomallei*	Type II and IV secretion pathways [79]
	ND	Not QS-regulated [194]	*B. thailandensis*	ND
Lipases	*lipA*	ND	*B. cepacia* *B. glumae*	Sec machinery, translocation *via* a chaperone [62,79]
	ND	Not QS-regulated [174,192]	*B. pseudomallei*	Type II secretion pathway [50,59]
	ND	BtaIR 1 to 5 [194]	*B. thailandensis*	ND
	ND	CepIR [108,126]	*B. cepacia* *B. cenocepacia*	Type II secretion pathway [158]
Chitinases	ND	CepIR [5,82,108,109]	*B. cepacia* *B. cenocepacia*	ND
	ND	ND	*B. gladioli*	Type II secretion pathway [33]
Collagenase	ND	ND	*B. pseudomallei*	Type II secretion pathway [50]
Poly galacturonase	*pehA*	CepIR [5]	*B. cepacia* *B. caryophylli* *B. gladioli*	ND
Phospholipases C	ND	Not QS-regulated [194]	*B. thailandensis*	ND
	ND	ND	*B. vietnamiensis*	Type II secretion pathway [59]
	PLC-N	Phosphate and BviIR [212]	*B. cepacia*	ND
	ND	BpsIR [174]	*B. pseudomallei*	ND
	ND	ND	*B. ambifaria* *B. multivorans* *B. cenocepacia*	ND
	PCL1 and 2	Not QS-regulated [192]	*B. pseudomallei*	Type II and IV secretion pathways [50]

ND: Not determined.

Quorum sensing in the pathogens *B. pseudomallei* and *B. mallei* is more complex than in other *Burkholderia* species. Cell-to-cell communication networks in these organisms comprise multiple LuxIR homologs utilizing numerous AHL signal molecules. In various *B. pseudomallei* strains, four LuxI and six LuxR homologs were identified [174, 192, 198]. In *B. mallei*, the QS circuitry consists of two LuxIR-like homologs, but in contrast with *B. pseudomallei*, lacks the BpmIR2, which shares the highest degree of homology with the BviIR system of *B. vietnamiensis* [193].

Although little is known about the regulation of extracellular molecules such as antibiotics and toxins produced by *Burkholderia* spp., multiple extracellular enzymes have been shown to be under the control of QS. In addition, a secretory machinery is needed to export many high molecular weight exoproducts in the extracellular environment. However, only a few studies have focused on their secretion pathways in the *Burkholderia* genus. Regulation and secretion of each category presented here are reported in the different tables within this review.

EXTRACELLULAR ENZYMES

The severity of infections by Bcc strains may be related to their ability to secrete a huge diversity of extracellular proteins. Production of enzymes by environmental strains can also be interesting for industrial purposes. The large variety of enzymes secreted by the *Burkholderia* correlates with the diversity of their ecological niches (Table 2).

Proteases

A majority of Bcc isolates produce extracellular proteases. In a study on exoenzymes production in CF isolates of *B. cenocepacia*, *B. multivorans*, *B. ambifaria*, and *B. vietnamiensis*, only *B. ambifaria* and *B. cenocepacia* had proteolytic activity on BHI-milk agar [26]. A 34 kDa protease formerly named PSCP (*Pseudomonas cepacia* protease) was purified from *B. cenocepacia* strain Pc715j supernatant [127]. This protease, now known as ZmpA, is a zinc metalloprotease. Expression of *zmpA* was detected in *B. cepacia, B. cenocepacia, B. stabilis, B. ambifaria*, and *B. pyrrocinia*, which correlated with a strong protease activity when tested on BHI-milk agar. Strains in which the *zmpA* gene was absent (*B. multivorans*, *B. vietnamiensis*, *B. dolosa*, and *B. anthina*) showed no proteolytic activity. *B. cepacia* genomovar I type strain ATCC 25416, an onion pathogen, shows proteolytic activity and expresses ZmpA [4,67]. ZmpA is important for extracellular protease activity in Bcc strains [67]. The mature ZmpA is proteolytically active against hide powder azure, type IV collagen, fibronectin, neutrophil alpha-1 proteinase inhibitor, alpha(2)-macroglobulin, and gamma interferon [97]. The impact of ZmpA on persistence was investigated. A *zmpA*$^-$ mutant of *B. cenocepacia* K56-2 was less able to persist in the lungs of infected rats [42]. However, in *B. cenocepacia* Pc715j, the same mutation caused no difference in persistence when compared with the parent strain [42]. Quorum sensing *cepI*- and *cepR*-mutants of this strain showed less proteolytic activity than the parent strain [4]. ZmpA expression also seems to be controlled by the CepIR QS system in *B. cenocepacia* K56-2 and, accordingly, a possible Cep box is found in the promoter region [181].

A second metalloprotease called ZmpB was identified in the same species carrying ZmpA. ZmpB has proteolytic activity against α-1 proteinase inhibitor, α_2-macrogobulin, type IV collagen, fibronectin, lactoferrin, transferrin, and immunoglobulins [98]. *zmpB*$^-$ mutants and *zmpA*$^-$*zmpB*$^-$ double mutants show no proteolytic activity against casein and are less virulent in the agar bead rat lung infection model, indicating that proteolytic activity is involved in virulence of the bacteria. *zmpB* expression is controlled by CepIR and CciIR quorum sensing systems in *B. cenocepacia* [98].

Most *B. pseudomallei* isolates show protease activity on BHI-milk agar [9, 50]. Strains deficient in protease production are less virulent than the parental strain in diabetes-induced Sprague-Dawley rats, a lung infection model [164]. However, Gauthier *et al.* [64] reported no correlation between virulence and proteolytic activity when human isolated *B. pseudomallei* ATCC 23353 was injected intraperitoneally in SWISS mice, although this strain is a low protease producer [64, 107]. In addition, a deficiency in the type II secretion pathway inhibits protease activity but does not affect virulence of a *B. pseudomallei* mutant in Syrian hamsters, which are usually very susceptible to *B. pseudomallei* infections [50].

The *mprA* gene, encoding a metalloprotease expressed by *B. pseudomallei*, was cloned and sequenced [107]. An *mprA*$^-$ mutant has very low protease activity compared with wild type, indicating production of MprA is essential to *B. pseudomallei*'s proteolytic activity [198]. The SWISS mice were used to test the *mprA*$^-$ mutant's virulence compared with parental strain *B. pseudomallei* 008. No significant differences were noted, indicating that MprA did not act as a virulence determinant in this model. [198]. The PmlIR QS system downregulates expression of MprA during the stationary phase in *B. pseudomallei* [198]. *B. thailandensis*, although closely related to *B. pseudomallei*, does not seem to regulate its proteolytic activity by QS, as shown by Ulrich *et al.* [194].

Lipases

Many bacterial species produce lipases, enzymes that catalyze the hydrolysis and synthesis of esters of glycerol with long-chain fatty acids. Lipases of microbial origin have found great application in many industrial sectors since they are able to catalyze a large variety of reactions.

Ten *B. cepacia* (originally *P. cepacia*) isolates from the sputum of CF patients were tested for their lipolytic

activity against various substrates. All of them produced variable activities when substrates of different chain lengths were used [113]. A similar screening was performed on various Bcc CF isolates of *B. cenocepacia*, *B. ambifaria*, *B. vietnamiensis*, and *B. multivorans*. All the strains were lipolytic against various substrates, although the activity from *B. multivorans* was the strongest [26].

A 25-kDa lipase has been purified by gel filtration from the clinical isolate *B. cepacia* 90ee supernatant and tested on the lungs of rats [114], resulting in a large amount of proteinaceous exudates, accumulation of polymorphonuclear leucocytes and red blood cells, and disorganization of the alveolar structure [114]. *B. cepacia* DSM3959 produces an extracellular lipase, LipA [89], whose activity depends on the presence of the chaperone, LimA [1, 79]. An extracellular 37-kDa cholesterol esterase was purified from *B. cepacia* strain ST-200, which shows 87% similarity to LipA from *B. cepacia* DSM3959 and preferentially hydrolyzes long-chain fatty acid esters of cholesterol, except cholesteryl palmitate. This enzyme also displays lipolytic activity toward various *p*-nitrophenyl esters [184]. *B. glumae* strain PG1, a rice pathogen, also produces a LipA lipase [60, 158]. The chaperone LipB is essential for folding of the LipA precursor into an active enzyme and acts on LipA stability by protecting it against proteolysis [55, 61, 62]. the presence of hexadecane and Tween 80 in the medium was shown to enhance LipA production and activity, depending on the carbon source [18].

In *B. pseudomallei*, lipase activity was detected in 96% of strains investigated for their extracellular production [9]. Quorum sensing seems not to control lipase production in this bacterium [192]. However, in *B. thailandensis*, which is genetically closely related to *B. pseudomallei*, lipase production is positively regulated by LuxIR homolog BtaIR2 and negatively regulated by BtaIR1 and BtaIR3. Mutations in *luxR* homologs *btaR4* and *btaR5* increase lipase production when compared with the wild-type strain [194]. A study on Tn*5* mutants of *B. pseudomallei* showed that *gspC*, a centrally located gene of a genetic locus implicated in secretion, is essential for exoproduction of protease, lipase, and phospholipase C, suggesting this bacterium secretes these products by the same pathway [50].

Chitinases

Chitin is a homopolymer of *N*-acetyl-D-glucosamine (GlcNAc) residues linked by β-1,4 bonds, found in the exoskeletons of arthropods, coelenterates, nematodes, protozoa, and molluscs and in the cell walls of many fungi [222]. Chitosan is a deacetylated derivative of chitin. Low-molecular-weight chitosan oligomers are studied for their beneficial biological activities such as their antifungal and antibacterial potentials. Chitinases are able to hydrolyze the 1,4-beta-linkages of chitin [151, 222].

B. cepacia KH2, a strain isolated from the bed log of Shiitake mushrooms, secretes a 34-kDa chitinase. This enzyme exhibits higher activity against 62% deacetylated chitosan (Chitosan 7B) and colloidal chitin than toward highly deacetylated chitosan substrates such as Chitosan EL, 10, 9B, and 8B [139]. *B. gladioli* can be found in many CF patients' lungs [34, 216] or in some chronic granulomatous disease (CGD) cases [159], but is primarily known as a plant pathogen responsible for infection of Gladioli [125]. Two chitosanases (I and II), which have respectively 37 and 30 kDa, were purified from *B. gladioli* CHB101 cultures [165]. Most bacterial chitosanases are induced by the presence of chitosan in the medium, although these two enzymes are produced in a constitutive manner. They are responsible for 90% of the chitolytic activity in the medium when chitosan (D.A. 30%) is used as a substrate. More recently, a third chitosanase (chitosanase A) with a molecular mass of 28 kDa and strong activity against chitosans with a low degree of acetylation (D.A. between 0 and 30%) was purified from the same strain. However, it has no activity against colloidal chitin and carboxymethyl cellulose [166]. Chitosanase A can fully hydrolyze chitosan (D.A. 0%), chitopentaose, and chitohexaose, whereas chitosanases I and II cannot. Chitosanase A seems to be responsible for the degradation and utilization of GlnN oligomers produced by the action of chitosanases I and II on partially acetylated chitosan [166]. Chitinase activity is also detected in *B. cenocepacia* H111 supernatant, and it seems to be regulated by the QS CepIR system [83, 181].

Collagenase

When comparing the secretomes from genetically closely related *B. thailandensis* and *B. pseudomallei*, a 65-kDa protein was identified as being a collagenase. Its absence in the *B. thailandensis* profile was suggested to contribute to the virulence of *B. pseudomallei* [153].

Polygalacturonase

Pectic substances are found in the cell walls of plants. Plant pathogens secrete a variety of cell wall-degrading enzymes responsible for the breakdown of polysaccharides that compose cell walls, which helps them invade plant tissues [123, 210]. Polygalacturonase are pectin-degrading enzymes. *B. cepacia* gen. I-induced maceration of the onion is possibly related to polygalacturonase secretion, which is known to be implicated in onion disease development [4, 71]. Polygalacturonase activity was detected in *B. cepacia* ATCC 25416 supernatant in the presence of polygalacturonic acid [71, 123]. A *cepIR*$^-$ mutant shows diminished production of polygalacturonase, and this correlates with attenuated maceration of onion [4]. Polygalacturonase production was also found in *B. gladioli* and *B. caryophylli* [71].

Phospholipase C

Phospholipases of the C type (PLC) are enzymes that cleave the phosphodiester bond of phospholipids to yield

diacylglycerol and a water-soluble phosphate ester. PLC are present in both Gram-positive and Gram-negative bacteria [175]. Two types of PLC can be distinguished: hemolytic and nonhemolytic. For example, in *P. aeruginosa*, the hemolytic PLC lyzes red blood cells, hydrolyzing phosphatidylcholine and sphingomyelin. The nonhemolytic PLC hydrolyzes phosphatidylcholine and phosphatidylserine, but not sphingomyelin [142]. PLC might be important for interaction with the phospholipids of eukaryotic cell membranes during infections [175].

B. cenocepacia, *B. multivorans*, *B. ambifaria*, and *B. vietnamiensis* isolates from CF patients produce PLC [26]. A 54-kDa nonhemolytic PLC was purified from *B. cepacia* strain Pc224c [213]. Expression of this PLC was repressed by high phosphate concentrations [212]. Two nonhemolytic PLC (Plc1 and Plc2) have been characterized in *B. pseudomallei* K96243. These PLC are able to hydrolyze phospholipid phosphatidylcholine and sphingomyelin [100]. Plc1, together with Plc2, contributes to the plaque formation assay used to detect cell-to-cell spread. *B. pseudomallei* K96243 requires Plc2 for cell cytotoxicity, but not Plc1 [100]. They have no effect on induction of apoptosis [100]. These two PLC present on chromosome 1 share strong homology with the two PLC from *B. thailandensis* [99, 100]. Only a gene homologous to *plc1* is present in the *B. mallei* genome [100]. The published *B. pseudomallei* K96243 genome sequence reveals a third PLC on chromosome 2 (Plc3) [80,100]. In *B. pseudomallei* 1026B, this PLC is involved in virulence in the hamster model of acute melioidosis, as *pcl3* is strongly upregulated in several infected hamster organs [191]. Quorum sensing mutants of *B. pseudomallei* 1026B are not altered in PLC production [192]. However, PLC production by *B. pseudomallei* KHW is dependent on the growth phase and is positively regulated by the BpsIR QS system [174]. On the other hand, disruption of the *B. thailandensis* QS system had no effect on PLC activity [194].

There are few reports on the hemolytic PLC activity in *Burkholderia*. Two genes (with one gene that shares homology with PLC from *P. aeruginosa*) from *B. cepacia* PC-69 are required for expression of hemolytic and PLC activities (when only one gene is expressed, hemolytic and PLC activities are not detected) [204]. The phospholipase activity of *B. cepacia* does not correlate with hemolytic activity. Nagazawa *et al.* [137] reported that 70% of *B. cepacia* strains produce lecithinase but only 4% produce hemolysin.

HEMOLYTIC ACTIVITY

Hemolytic activity is very often found in *Burkholderia* [15, 26]. Bevivino *et al.* [15] reported that several strains belonging to the Bcc exhibit hemolytic activity, *B. ambifaria* and *B. pyrrocinia* being the species with the highest percentage of strains positive for this activity [15]. Surprisingly, in that study, a much higher percentage of environmental than clinical isolates showed hemolytic activity [15]. Hemolytic activity is also reported in *B. pseudomallei*, but *B. mallei* and *B. thailandensis* are normally negative (see Rhamnolipids section) [9]. *B. cenocepacia* J2315 secretes a lipopeptide with a hemolytic activity against horse and human erythrocytes [84]. At low concentration, this toxin is able to induce apoptosis in human neutrophils. At high concentration, this toxin induces degranulation of mammalian phagocytes [84].

SIDEROPHORES

Iron is one of the most abundant element on Earth and one of the most important nutrients of bacteria. However, in the presence of oxygen and at neutral pH, Fe^{2+} is rapidly oxidized to Fe^{3+}, which is not readily available to bacteria. Bacteria have developed ways to scavenge iron with high affinity by producing siderophores, low-molecular-weight chelating molecules that sequester iron from other iron-containing molecules present in the surroundings. For example, in animal hosts, little free iron is available to bacteria as it is bound by lactoferrin, transferrin, and heme

Table 3. Siderophores.

Class	Gene	Regulation	Species	Secretion
Salicylic acid	ND	Iron [207]	*B. cenocepacia*	Efflux pump [136]
Pyochelin	*pch*	Not QS-regulated [109]	Bcc	ND
Ornibactin	*pvd*	CepIR [5,82,108,109], Fur [3]	*B. cenocepacia* *B. cepacia* *B. ambifaria* *B. vietnamiensis*	ABC transporter OrbE [3]
Malleobactin	*mbaA, mbaF*	Fur (iron) [115]	*B. pseudomallei*	ND
Cepabactin	ND	ND	Bcc	ND
Cepaciachelin	ND	ND	*B. ambifaria*	ND

ND: Not determined.

[211]. Members of the *Burkholderia* genus produce many kinds of siderophores which, depending on the chemical structure of their chelating group, are mostly classified into hydroxamates (based on hydroxamic acid) and catecholates (containing a catechol ring) [155, 186] (Table 3).

Salicylic Acid

Salicylic acid, or 2-hydroxybenzoic acid, which serves as a precursor for many siderophores such as pyochelin, was initially identified in many *B. cepacia* isolates and was then called azurechelin [170]. It has iron-binding properties and appears to promote iron uptake as well as growth of many bacteria in iron-limiting conditions, including *B. cenocepacia* [171]. Its production is regulated by the availability of iron [170]. In *B. cenocepacia*, salicylate was found to induce an antibiotic efflux pump, conferring resistance to chloramphenicol, trimethoprim, and ciprofloxacin [136]. Since very low iron is present in CF lungs, it was proposed that salicylate might induce efflux-mediated resistance, even in the absence of antibiotic selective pressure, and then contribute to the virulence of this bacterium [136]. The role of salicylate as a siderophore is often questioned. Bacteria that produce salicylate but no other siderophore are negative in the standard CAS plate assay, even when it is overproduced or when a shuttle between the dye complex and the siderophore is added [171]. Moreover, mutants producing salicylate as the sole potential siderophore are growth limited under iron-restrictive conditions [3, 49].

Pyochelin

The siderophore pyochelin was first described in studies on *P. aeruginosa* grown under iron-limiting conditions [46]. It is derived from the condensation of two molecules of cysteine with salicylic acid, which requires the presence of non-ribosomal peptide synthetases (NRPS), PchE and PchF. PchE is necessary for the synthesis of the first intermediate, and PchF is responsible for synthesis of the core structure. These two enzymes are coded by the *pchEFGHI* operon, which is regulated by iron-regulated repressor Fur and by PchR, an AraC family transcriptional regulator [77, 116]. Details on the biosynthesis and regulation of pyochelin have been recently reviewed [186].

Pyochelin is produced by some members of the Bcc, including *B. cepacia* strains (*e.g.*, ATCC 25416 and ATCC 17759) [129]. However, in a study screening Bcc clinical isolates, about 50% produced little or no pyochelin [47, 169]. Strain K56-2, now confirmed to be *B. cenocepacia*, produces negligible amounts of pyochelin, whereas the clinical isolate Pc715j produces significant amounts [209]. The *pch* genes coding for the biosynthesis machinery and transport of pyochelin are found in both *B. pseudomallei* and *B. thailandensis*, but not in *B. mallei* [138]. *B. cenocepacia* Tn*5* mutants were screened for the inability to produce pyochelin. Two mutants were identified. In both mutants, the transposon had integrated into the *cysW* gene coding for a component of the sulfate/thiosulfate transporter. Both mutants were also defective in sulfate transport, and the ability to produce pyochelin was restored in the presence of cysteine, a bioprecursor of pyochelin [58].

Ornibactin

Ornibactin is a linear hydroxamate-hydroxycarboxylate siderophore, related in its peptide structure to pyoverdine, which is produced by *P. aeruginosa* and *P. fluorescens* [129, 176]. It is composed of a conserved tetrapeptide, L-Orn^1(N^δ-OH,N^δ-acyl)-D-*threo*-Asp(β-OH)-L-Ser-L-Orn^4(N^δ-OH,N^δ-formyl)-1,4-diaminobutane and it provides three bidentate metal chelation groups. These three groups (two hydroxamates and one α-hydroxycarboxylate) are obtained by modification of the side chains of the N- and C-terminal ornithines, and the D-aspartate found in the peptide. Depending on the chain length of the acid binding to Orn^1, three species of ornibactin are generated: ornibactin-C_4, ornibactin-C_6, and ornibactin-C_8 [176]. During a study on clinical Bcc strains, ornibactin was shown to be produced by 87% of tested isolates [47]. It has been isolated from culture supernatants of *B. vietnamiensis* and was also identified in *B. ambifaria* PHP7, in two clinical strains of *B. cepacia* (ATCC 17759 and ATCC 25416), and in many other Bcc strains including *B. cenocepacia* [12, 129]. Ornibactin appears to be the most prevalent siderophore among the *Burkholderia*. The genes required for ornibactin biosynthesis and transport have been identified in *B. cenocepacia* K56-2 and shown to be negatively regulated by the QS system CepIR, in contrast to pyochelin and salicylic acid [109, 171]. In a proposed synthesis pathway model, precursors are modified by the products of *pvdA*, *pvdF*, *orbG*, *orbK*, and *orbL* genes and assembled into ornibactin by NRPSs OrbI and OrbJ. *PvdA* encodes for L-ornithine N^5-oxygenase, an enzyme responsible for catalyzing the hydroxylation of the δ-amino group nitrogen of ornithine, the first step in the formation of a hydroxamate siderophore [208]. *B. cenocepacia* K56-2 *pvdA*$^-$ mutants display no siderophore activity, but can be restored by addition of the precursor L-N^5-OH-Orn. The *pvdA*$^-$ mutants are less virulent than the parent strain in chronic and acute models of respiratory infection in rats [171]. Details about the biosynthesis and transport of ornibactin across the cytoplasmic membrane for Bcc members were recently reviewed [186]. *B. cenocepacia* Pc715j produces both ornibactin and pyochelin [47, 109, 209]. When *orbA*, a gene encoding for the outer membrane receptor of ferric-ornibactin, is inactivated, the mutant strain shows less virulence than the parent strain in a rat agar bead lung infection model [209]. The *orbA*$^-$ mutant is cleared from the lungs, showing that pyochelin uptake cannot compensate for the ornibactin system. However, a *ptaA*$^-$ mutant from the same *B. cenocepacia*

strain, which is deficient in ferric-pyochelin uptake, persists in the lung in the same animal model, showing that ornibactin uptake is able to compensate a deficiency in the pyochelin system. Both mutants can grow in iron-starvation conditions *in vitro* and produce smaller amounts of the corresponding siderophore [209].

Malleobactin

Malleobactin, a hydroxamate siderophore purified from *B. pseudomallei* K96243 presents similarities with ornibactins. MbaA, a putative ornithine-N^5-oxygenase, and MbaF, a putative NRPS, are involved in its biosynthesis, whereas *fmtA* is coding for the malleobactin receptor and is involved in the uptake [7]. These genes are part of an operon with *mbaJ* and *mbaI*, which are under the control of the sigma factor MbaS [7]. Malleobactin is able to acquire iron from both transferrin and lactoferrin. Because *B. pseudomallei* initiates infection at the mucosal surface, its ability to take iron from lactoferrin could play an important role in infections, as it is found in most secretions bathing mucosal surfaces [219]. The FmtA receptor can also recognize ornibactin (not produced by *B. pseudomallei*), and *B. cenocepacia*'s purified ornibactins can cross-feed *mbaA*$^-$ mutants [7].

Cepabactin

Cepabactin, or 1-hydroxy-5-methoxy-6-methyl-2(1H)-pyridinone, is a cyclic hydroxamate siderophore that was first identified as a metal-binding antibiotic secreted in the culture medium of *Pseudomonas alcaligenes* NCIB11492 [128]. Some Bcc clinical strains (ATCC 17759 and ATCC 25416 gen. I) were shown to produce cepabactin, although it never was the only siderophore produced [47, 128]. In fact, cepabactin is not widely produced among *Burkholderia* strains, clinical or environmental, which does not preclude its utilization.

Cepaciachelin

Another siderophore, cepaciachelin, was isolated from a culture supernatant of *B. cepacia* PHP7 (now *B. ambifaria*) grown under iron-limiting conditions [12]. Cepaciachelin seems to represent the third subunit of protochelin, a siderophore identified in *Azotobacter vinelandii* [12, 44]. This type of siderophore is among the most effective because it contains three complexing sites for Fe^{3+}. The other two subunits of protochelin are azotochelin and aminochelin and have not yet been reported in *Burkholderia* species.

Rhamnolipids

Rhamnolipids are extracellular glycolipidic surface-active molecules produced by many bacteria. Rhamnolipids have several potential biotechnological applications owing to their tensioactive properties [168].

A rhamnolipid was detected in the supernatant of *B. pseudomallei* cultures. This rhamnolipid is composed of two molecules of rhamnoses and two molecules of β-hydroxytetradecanoic acid to give 2-O-α-L-rhamnopyranosyl-α-L-rhamnopyranosyl-β-hydroxytetradecanoyl-β-hydroxytetradecanoate (Rha-Rha-C_{14}-C_{14}). At high concentrations, this rhamnolipid is toxic to nonphagocytic and phagocytic cell lines and displays hemolytic activity on erythrocytes from different species [75]. The hemolytic and cytotoxic activities of the *B. pseudomallei* rhamnolipid are probably due to its detergent-like properties. At low concentrations, this rhamnolipid changes the cell morphology with modifications of the cytoskeleton organization [76]. *B. thailandensis* synthesizes a rhamnolipid that is structurally analogous to the *B. pseudomallei* rhamnolipid [194]. Disruption of the *B. thailandensis* QS system results in hyper-beta-hemolysis of erythrocytes, which was suggested to result from increased rhamnolipid production [194]. Genes involved in rhamnolipid synthesis have not yet been identified.

Toxins

Phytopathogenic *Burkholderia*

Phytopathogenic bacteria produce phytotoxins that are toxic to plant cells and influence symptoms development.

Toxoflavin

B. glumae causes rot of rice grains and seedlings (panicle blight) and is a limiting factor of rice yield throughout rice-growing countries (United States, Japan, the Philippines, and Korea) [45, 182]. Moreover, *B. glumae* can also cause wilting symptoms in solanaceous crops [88]. *B. glumae* produces bright yellow pigments, identified as toxoflavin {1.6-dimethylpyrimido[5,4-e]-1,2,4-triazine-5,7(1*H*,6*H*)-dione} and fervenulin (a tautomeric isomer of toxoflavin), which are essential for the pathogenicity of rice seedling rot and grain rot [93, 182]. A toxoflavin-deficient mutant fails to cause disease symptoms in plants. Toxoflavin also has antibacterial, antifungal, and herbicidal activities [135]. Recently, toxoflavin was identified as a potential novel anticancer agent by its action against Polo-like kinase (involved in signal transduction) [70]. Toxoflavin acts in various microorganisms and cell extracts as an electron carrier between NADH and oxygen, and it can produce hydrogen peroxide or superoxide anion [102]. Toxoflavin is also produced by several strains of *B. gladioli* [196].

In *B. glumae*, the biosynthesis and transport of toxoflavin involve, respectively, the *toxABCDE* and the *toxFGHI* operons, which are regulated by the LysR family regulator ToxR, with toxoflavin acting as a co-inducer [93]. The TofI-TofR(C_8-HSL) QS system regulates toxoflavin production and transport *via* the transcriptional activator ToxJ [93]. In

B. glumae, a *tofI* mutant fails to produce phytotoxins and causes much less severe panicle blight than that produced by the wild type. Kim *et al*. [93] suggested that since toxoflavin production consumes large amounts of energy, *B. glumae* cells must ensure that they reach a critical cell density before they start to produce it [93]. This is the only study demonstrating that QS is involved in the pathogenicity of phytopathogenic bacteria by regulating a phytotoxin production. Toxoflavin production is also dependent on growth temperature, which is maximal at 37°C [124].

Tropolone

B. plantarii (also known as *Pseudomonas plantarii*), a rice phytopathogen, is often co-isolated with *B. glumae*, suggesting that they may share similar transmission paths and life cycle [36, 197]. *B. plantarii* and *B. glumae* induce similar symptoms on rice. The virulence of *B. plantarii* was associated with production of the phytotoxin tropolone, which is also produced by some other *Pseudomonas* and *Burkholderia* spp. including *B. glumae*. Tropolone is a non-benzenoid aromatic compound that has properties characteristic of phenol and acids. Tropolone causes root growth inhibition and wilting of seedlings, symptoms that are typically caused by the pathogen itself [10]. Its activity is inhibited by the presence of iron [10]. This compound is toxic to rice seedlings but also exhibits antimicrobial and antifungal activities, especially against *Pythium aphanidermatum* [133, 189]. Tropolone displays strong insecticidal activity on *Tyrophagus putrescentiae* (mould mite) and *Dermatophagoides farinae*. This activity is even higher than that of *N*, *N*-diethyl-*m*-toluamide [133].

The PlaI-PlaR QS system plays an important role in the ability of *B. plantarii* to cause rice seedling blight disease: a *plaI* mutant is less virulent than the wild type. However, it is not known whether QS regulates tropolone synthesis [173].

Rhizobitoxine

Rhizobitoxine, an enol-ether amino acid [2-amino-4-(2-amino-3-hydroxypropoxy)-*trans*-but-3-enoic acid] is synthesized by the legume symbiont *Bradyrhizobium elkanii* and the plant pathogen *B. andropogonis* [131]. These strains also produce dihydrorhizobitoxine [131]. *B. andropogonis* causes chlorotic symptoms in corn and sorghum, presumably as a result of rhizobitoxine production *in planta* [131]. Rhizobitoxine also plays a positive role in establishing symbiosis between *B. elkanii* and host legumes [53]. Rhizobitoxine inhibits cystathionine-β-lyase in methionine biosynthesis and 1-aminocyclopropane-1-carboxylate (ACC) synthase in the ethylene biosynthesis pathway [225]. ACC synthase is the rate-limiting enzyme in the ethylene biosynthesis pathway in plants [118]. Inhibition of ethylene biosynthesis by rhizobitoxine enhances the nodulation process and nodulation competitivenes [53]. *B. andropogonis* probably produces rhizobitoxine to inhibit ethylene biosynthesis and reduce defence reactions by the host plants [141]. However, in *B. elkanii*, it was shown recently that rhizobitoxine-induced foliar chlorosis is the result of methionine deficiency due to inhibition of cystathione-β-lyase [141].

The genes involved in rhizobitoxine biosynthesis have been identified in *B. elkanii* as *rtxA* and *rtxC* [221]. However, these genes have not been isolated from *B. andropogonis*.

Rhizoxin

Rhizoxin, a macrocyclic polyketide, is the causative agent of the rice seedling blight. This phytotoxin exerts its effect by binding to rice β-tubulin, which results in inhibition of mitosis and cell cycle arrest [96]. The blockage of microtubule formation has been observed in many other eukaryotic cells, including human and murine tumor cells. Additionally, rhizoxin can depolymerize assembled microtubules [183]. Rhizoxin demonstrates broad antitumor activity *in vitro* [187, 190]. Rhizoxin has undergone extensive clinical trials as a potential antitumor drug candidate [101]. For many years, the fungus *Rhizopus microsporus* was assumed to synthesize rhizoxin. However, recent evidence indicate that it is instead produced by a symbiotic bacteria of the genus *Burkholderia* residing within the fungal mycelium [146]. Curing the fungus of the bacteria with an antibiotic treatment, which resulted in a nonproducing phenotype, unequivocally established the role of the rhizoxin. In pure culture, the endosymbiont produces rhizoxin, and the re-inoculation of the cured fungal strain with the symbiotic *Burkholderia* re-establishes a rhizoxin-produced fungal bacterial symbiosis. The name *Burkholderia rhizoxina* was proposed for this symbiotic bacterium [148]. Novel rhizoxin derivatives isolated from a scaled-up fermentation of the cultured *B. rhizoxina* strain are 1,000 times more active than rhizoxin in antimitotic bioassays [162]. A gene cluster encoding rhizoxin biosynthesis has been isolated in the genome of *B. rhizoxina* [148]. Recently, Partida-Martinez *et al*. [147] found that rhizonin is also produced by an endosymbiont *Burkholderia* (see below).

OTHER TOXINS

Bongkrek Acid

Tempe bongkrek is an Indonesian food made by fermentation of coconut. Consumption of *tempe bongkrek* is associated with a foodborne human intoxication and significant numbers of mortalities. The main symptom is a strong hyperglycemia followed by hypoglycemia [78]. The causative organism *B. gladioli* pathovar *cocovenenans* (also referred to as *Pseudomonas cocovenenans* and *B. cocovenenans*) produces two toxins, toxoflavin (discussed above) and bongkrekic acid (also commonly referred to as bongkrek acid) [36]. Bongkrekic acid is an inhibitor of adenine

nucleotide translocase, which is a component of the mitochondrial permeability transition pore complex [78]. It is also an inhibitor of apoptosis by preventing a number of phenomena: generation of reactive oxygen species, chromatin condensation, and cytoplasmic vacuolization [78, 122]. *Pseudomonas farinofermentans* strains isolated from acase of food poisoning caused by the consumption of fermented corn flour in China are now know to be *B. gladioli* pathovar *cocovenenans* [228].

Rhizonin

Rhizonins A and B were known as mycotoxins from *Rhizopus microsporus*, a fungus that is traditionally used in many food fermentations; for example, for soybean *tempeh* production in Indonesia [87]. Rhizonins A and B have a strong hepatotoxic activity [217]. In animal tests, rhizonins cause hepatic lesions and induce acute and chronic failure of the liver [217]. However, this toxin, like rhizoxin, is not produced by the fungus but by bacteria that reside within the fungal mycelium. Phylogenetic analyses revealed that this symbiont belongs to the genus *Burkholderia* [147]. Pure rhizonin A can be isolated from a scaled-up culture of this *Burkholderia* strain [147].

Antifungals and Other Antimicrobials

Organisms such as *Burkholderia* produce a wide range of antifungals and other compounds that are able to suppress many soilborne plant pathogens (*e.g.*, *R. solani*, *Pythium* spp., *Fusarium* spp.) and in doing so improve plant health. For example, *B. ambifaria* LMG 19182 (*B. ambifaria* AMMD) is very effective in controlling phytopathogenic *Pythium* species and *Aphanomyces euteiches* [38]. Various strains of *Burkholderia* have been reported to produce a large variety of antifungals such as altericidins, pyrrolnitrin, and xylocandins (also called cepacidines) [16, 54, 94].

Pyrrolnitrin

Pyrrolnitrin [3-chloro-4-(2'-nitro-3'-chlorophenyl)-pyrrole] is a secondary metabolite derived from tryptophan, first isolated from *B. pyrrocinia* (originally *Pseudomonas pyrrocinia*) [8]. It is produced by several strains of *Pseudomonas* and *Burkholderia* [21, 56] and also *Enterobacter agglomerans*, *Serratia plymuthica*, and *Myxococcus* isolates [31, 65, 143].

This active metabolite has been used as a clinical antifungal agent to treat humans infected by opportunistic fungi. Phenylpyrrole derivatives (fenpiclonil and fludioxonil) have been developed by Norvatis as agricultural fungicides [185]. Pyrrolnitrin prevents fungal growth by inhibiting the respiratory electron transport system [54].

Pyrrolnitrin produced by *B. cepacia* NB-1 exhibits a broad spectrum of activity against phytopathogenic fungi and Gram-positive bacteria, with a particular efficiency against *Streptomyces*, whereas Gram-negative bacteria, except *Proteus vulgaris*, are resistant [54]. Pyrrolnitrin production by *B. cepacia* NB-1 is influenced by nutritional and environmental factors, with glycerol strongly enhancing the antifungal production [54]. Pyrrolnitrin produced by *B. cepacia* B37w exhibits antifungal activity against the potato dry rot fungus *Fusarium sambucinum* [21].

The *prnABCD* gene cluster encodes the four biochemical steps to produce pyrrolnitrin from tryptophan by *P. fluorescens* [95]. This cluster was identified in *B. cepacia* LT4-12W and in *B. pyrrocinia* [73]. In *P. fluorescens*, *B. pyrrocinia*, and *B. cepacia* LT4-12W, genes are arranged identically and in a linear relationship to the order of the biochemical reactions for pyrrolnitrin synthesis [73]. De Souza and Raaijmakers [48] suggested that the *Burkholderia* pyrrolnitrin synthase gene was acquired from *Pseudomonas* by horizontal transfer.

Regulation of pyrrolnitrin biosynthesis is not well documented in *Burkholderia* strains. It was reported that QS is required for its production in a rhizospheric biocontrol strain of *Serratia plymuthica* [112]. It is therefore possible that QS is required also for production in *Burkholderia* strains.

Xylocandin Complex

Xylocandin (also called cepacidines A and B) is a complex of peptides with potent anticandidal and antidermatophytic

Table 4. Toxins.

Class	Regulation	Species	Secretion
Toxoflavin	TofIR [93]	*B. glumae*	Efflux pump [93], *toxFGHI*
	ND	*B. gladioli*	ND
Tropolone	Iron and temperature [10]	*B. plantarii*	ND
	ND	*B. glumae*	ND
Rhizobitoxine	ND	*B. andropogonis*	ND
Rhizoxin	ND	Endosymbiotic *Burkholderia*	ND
Bongkrek acid	ND	*B. gladioli* pathovar *cocovenenans*	ND
Rhizonin	ND	Endosymbiotic *Burkholderia*	ND

ND: Not determined.

activities that is produced by *B. pyrrocinia* ATCC 39277 (originally *P. cepacia*), a strain isolated from cornfield soil in New Jersey (U.S.A.) [16]. Cepacidine A has been found in culture broth of *B. cepacia* AF2001 (originally *P. cepacia*) and exhibits high *in vitro* antifungal activity against pathogenic fungi, that showing no activity against bacteria [106]. In semi-greenhouse biocontrol assays, this strain displayed excellent biological activity against *Pythium ultimum* on cotton and cucumbers [105]. Moreover, cepacidine A was found to have potent immunosuppressive activity, significantly suppressing the activation of B lymphocytes [104].

B. cepacia BC11 inhibits the growth of *R. solani* and *Sclerotium rolfsii* in soils and enhances the yield of peanuts [91]. This strain produces a lipopeptide, called AFC-BC11, with characteristics of members of the xylocandin family. However, unlike xylocandins, AFC-BC11 is not active against *Candida* spp. Nonetheless, AFC-BC11 is very active against various plant pathogenic fungi [91]. A region of the genome of strain BC11 that is required for production of this antifungal metabolite was characterized. This region encodes proteins involved in the production of a nonribosomally synthesized lipopeptide [91].

Quinoline Derivatives

The phytophthora blight of red pepper is a plant disease caused by *Phytophtora capsici*. *B. cepacia* PCII inhibits the mycelial growth and zoosporangial germination of *P. capsici*. Inoculation of this strain promotes red pepper plant growth [132]. *B. cepacia* PCII produces several 4-quinolinone metabolites (or pseudanes): [2-(2-heptenyl)-3-methyl-4-quinolinone] (HMQ), and 3-methyl-2-(2-nonenyl)-4-quinolinone (NMQ). HMQ exhibits *in vitro* antifungal activity against *P. capsici*, *F. oxysporum*, and *R. solani* [132]. Treatment of red pepper seeds with HMQ resulted in an increase in weight and height of plants after 30 days [132]. HMQ and NMQ are also synthetized by *B. cepacia* RB245, a strain isolated from a lettuce root and showing activity against several fungal pathogens including *Pyricularia oryzae*, and *R. solani*, but relatively limited antibacterial activity [81].

Glidobactins

Burkholderia spp. K481-B101 (originally assigned as *Polyangium brachysporum*) produces glidobactins [161], acylated tripeptides that contain a 12-membered ring consisting in most variants of the two nonproteinogenic amino acids erythro-4-hydroxy-L-lysine and 4(S)-amino-2(E)-pentenoic acid. The ring structure is linked to an L-threonine residue, which in turn is acylated by different variant-specific unsaturated fatty acids [161]. These compounds were also isolated from *B. cepacia* and designated cepafungin [167]. Glidobactins exhibit broad inhibitory action against fungi and yeasts, as well as antitumor activity [140, 167].

A gene cluster (*glbA-glbH*) involved in glidobactin biosynthesis has been identified in *Burkholderia* strain K481-B101. This gene cluster was also found in the ten completely sequenced *B. pseudomallei* strains. Interestingly, in the nine sequenced *B. mallei* strains, this cluster is inactivated by a transposon [161].

CF661

B. cepacia CF66 produces the antifungal compound CF661, which inhibits the growth of some soilborne fungi such as *R. solani, Aspergillus flavus*, and *F. oxysporum* [150]. Strain CF66 exhibits strong antimicrobial activity against yeasts such as *C. albicans*, but no activity against bacteria. CF661 completely inhibits the hyphal growth of *R. solani*. The exact structure of this compound is not known, but based on nuclear magnetic resonance analysis, and GC-MS spectral and infrared spectral data, CF661 is confirmed to have amide bonds, α-metyl fatty acid, bromine, and some structural units such as CH_2CH_2O [150].

Antifungal Compounds from *Burkholderia* Strain MP-1

Burkholderia strain MP-1, isolated from the rhizosphere, exhibits antifungal activities against various filamentous plant pathogenic fungi (*F. oyxsporum*, *R. solani*). This strain produces at least four antifungal substances: phenylacetic acid, hydrocinnamic acid, 4-hydroxyphenylacetic acid, and 4-hydroxyphenylacetate methyl ester [121]. These four substances exhibit antifungal activity against several pathogenic fungi. Phenylacetic acid, a deamination product of phenylalanine, is known as a plant growth regulator (auxin activity) and it displays growth-inhibitory activity towards bacteria and fungi (*R. solani*, *Pythium ultimum*) [85, 134]. It may be involved in defence mechanisms, protecting the producing strain from competing cells.

OTHER ANTIFUNGALS

2-Hydroxymethyl-chroman-4-one

Burkholderia sp. MSSP was isolated from roots of *Mimosa pudica* and secretes an antifungal compound against *R. solani*, *P. ultimum*, and *Botrytis cinerea* [91]. An antifungal compound was identified as 2-hydroxymethyl-chroman-4-one and exhibits activities against several plant pathogenic fungi [91].

Altericidins

Altericidins, a complex of closely related oligopeptides, were isolated from the culture broth of *B. cepacia* KB-1. The altericidin complex inhibits the germination of *Alternaria kikuchiana* conidia (a black spot fungus of pear). It was

proposed that altericidins might act on the cytoplasmic membrane [94].

Cepacins A and B

Cepacins A and B have been isolated from *B. cepacia* SC 11 783 (originally *P. cepacia*). These antibiotics exhibit only antibacterial activity against staphylococci and Gram-negative microorganisms [145].

Cepaciamides A and B

B. cepacia D-202 is a biological control agent against *Botrytis cinerea* and *Penicillium expansum*, which causes beet roots rot in Japan. This strain produces the 3-amino-2-piperidinone-containing lipids cepaciamides A and B, which exhibit an activity against *B. cinerea* [223].

Hydrogen Cyanide

Several bacterial species are known to produce and excrete hydrogen cyanide (HCN), a potent inhibitor of cytochrome C oxidase [17]. For example, HCN production by strain *P. fluorescens* CHAO suppresses black root rot of tobacco caused by *Thielaviopsis basicola* [17]. The production of HCN has been rarely described in the genus *Burkholderia*. The endophytic plant growth-promoting *Burkholderia* sp. strain MSSP, isolated from root nodules of *Mimosa pudica*, produces HCN, but its role is unknown [144].

Phenazines

Phenazines are naturally occurring pigments produced by bacteria and are known for their antibiotic properties, and antitumor and antiparasitic activities [103]. For example, phenazine-1-carboxylic acid produced by *P. fluorescens* is important for the control of take-all disease of wheat, which is caused by *Gaeumannomyces graminis* var. *tritici* [32]. Phenazine producers have been identified as organisms belonging to a range of species like *Pseudomonads*, members of the *Streptomyces* genus, *B. cepacia*, and *B. phenazinium* (for a recent review see [103]).

B. phenazinium (previously known as *Pseudomonas phenazinium*) produces ten phenazine pigments, predominantly iodinin [13]. *B. cepacia* strain 5.5B, isolated from soil, produces a purple pigment identified as 4,9-dihydroxyphenazine-1,6-dicarboxylic acid dimethyl ester, a phenazine [25]. This compound inhibits *in vitro* the phytopathogenic fungi *R. solani* [25].

Volatile Compounds

Volatile compounds (molecular weight less than 300, low polarity, and a high vapor pressure) can act as antibiotics and affect fungal mycelial growth [86, 214]. *B. cepacia* RJ3 and ATCC 52796 (originally *P. cepacia*) inhibit several fungal plant pathogens. These strains inhibit the fungi by producing unidentified inhibitory volatile compound(s). The volatile compound(s) of *B. cepacia* moderately inhibits the growth of *R. solani* [90].

Unknown Antifungals

The biocontrol strain *B. ambifaria* BC-F exhibits broad-spectrum antifungal activity against important soilborne pathogens and suppresses diseases caused by fungal pathogens on a number of important crop plants [110]. The nature of this antifungal compound is not known. Interestingly, QS deficient mutants of *B. ambifaria* BC-F have decreased antifungal activity [229].

Burkholderia strain 2.2 N isolated from soil is capable of inhibiting the growth of plant-pathogenic fungi, yeasts, and protozoa. An extracellular compound seems to be responsible for this activity [24].

PHYTOHORMONES

Beneficial bacteria that stimulate growth of cereals and grasses are usually referred to as plant growth promoting Rhizobacteria (PGPR), a group that includes different bacterial species belonging to genera such as *Acetobacter*, *Azospirillum*, *Bacillus*, *Pseudomonas*, *Herbaspirillum*, and *Burkholderia* [52]. PGPR exert their beneficial effects on plant growth directly or indirectly through various mechanisms. Indirect effects rely on preventing deleterious functions of pathogenic microorganisms, generally by the production of antibiotics or antifungal compounds or by competing for nutrients like iron [52]. Several strains of *Burkholderia* can antagonize and repress the growth of many soilborne plant pathogens (see above). Direct mechanisms include the synthesis of phytohormones and vitamins, inhibition of plant ethylene synthesis, improved nutrient uptake, solubilization of inorganic phosphate, or mineralization of organic phosphate.

Several *Burkholderia* species exert beneficial effects on their plant hosts. For example, *B. vietnamiensis* is recognized for its abilities to promote rice plant growth: the inoculation of strain TVV75 resulted in a final 13% to 22% increase in grain yield [188]. Similarly, *B. phytofirmans* strain PsJN inoculation stimulates grapevine growth and enhances resistance to cold stress [6]. *B. ambifaria* MCI-7 enhances the growth of *Zea mays* [35].

Bacterial production of phytohormones can explain the changes in root morphology following *Burkholderia* inoculation. The plant hormones auxins and cytokinins are involved in several stages of plant growth and development, such as cell elongation, cell division, tissue differentiation, and apical dominance [226]. However, there are only a few reports on the phytohormone biosynthetic capacities of *Burkholderia*. The most important auxin, indole-3 acetic acid, is produced by several strains of *B. cepacia* isolated from the rhizosphere, by an endophytic

Table 5. Effector proteins.

Class	Genes	Regulation	Species	Secretion
Effector proteins	*bopA*, *bopB*, *bopE*	ND	*B. pseudomallei*	Type III secretion pathway [74]
Autosecreted protein	*bimA*	ND	*B. pseudomallei*	Type V secretion pathway
Plant cytotoxic protein	ND	CepIR [5]	*B. cenocepacia*	ND

ND: Not determined.

Burkholderia isolated from root nodules of *Mimosa piduca,* and by *B. vietnamiensis* MGK3 isolated from rice root [14, 144].

EFFECTOR PROTEINS

Burkholderia Secretion Apparatus: Effector Proteins

B. pseudomallei is a facultative intracellular pathogen; it can invade nonphagocytic host cells and survive and replicate within phagocytes. *B. pseudomallei* contains at least three loci encoding putative type III secretion systems (TTSS) [152, 178]. TTSS, central to the virulence of many Gram-negative pathogens, resembles molecular syringes for the injection of multiple bacterial effector proteins directly into the host cell cytoplasm [43]. Effector proteins subvert host cell processes to the benefit of the invader. For example, the type III protein secretion apparatus BSA (*Burkholderia* secretion apparatus) is required for full virulence of *B. pseudomallei* in mice [177]. The *bsa* locus is also present in *B. mallei* and *B. cenocepacia* genomes [177]. Several effector proteins encoded within the *bsa* locus have been identified in the *B. pseudomallei* genome (BopA, BopB, and BopE) [177] (Table 5).

BopE facilitates the invasion of nonphagocytic epithelial cells. BopE shares sequence homology with the translocated effector proteins SopE and SopE2 of *Salmonella*, proteins that play an important role in *Salmonella* invasion of nonphagocytic intestinal epithelial cells. In eukaroytic cells (HeLa cells), BopE induces rearrangements in the subcortical actin cytoskeleton, likely by acting as a guanine nucleotide exchange factor for RhoGTPases, that regulate the actin network [195]. The *bopE* gene is also present in the *B. mallei* and *B. thailendensis* genomes [177].

BopB contains an amino acid motif (CX5R) that is conserved in the catalytic domains of numerous phosphatases, like the type III secreted protein of *Salmonella* SobB. The latter influences inositol phosphate signalling pathways in eukaryotic cells as well as bacterial invasion [179]. BopA is a homolog of the *Shigella* type III secreted protein IscB, which mediates cell-to-cell spread of *Shigella* [179]. The exact role of BopA is not known, but *B. pseudomallei* is also capable of cell-to-cell spread. In mice, *B. pseudomallei* $bopA^-$ and $bopB^-$ mutants are less virulent than wild type, causing a delay in median time to death [179].

Other Proteins

BimA (*Burkholderia* intracellular motility A), an autosecreted protein, is localized at the pole of the bacteria and is required for actin-based motility in a macrophage-like cell line [180]. Mutation of *bimA* abolishes the actin-based motility of *B. pseudomallei* in a cell line [180].

B. cenocepacia strain K56-2 is capable of causing a plant tissue watersoaking phenotype (ptw) that results from loss of cell membrane integrity and the accumulation of fluids in the intracellular spaces of plant tissue [57]. In strain K56-2, a type IV secretion system is responsible for the secretion of a plant cytotoxic protein, which causes plasmolysis of plant protoplasts [57].

CONCLUSION

The large variety of extracellular products synthesized by *Burkholderia* species correlates with its important ecological diversity and might explain its versatility. Although a lot of information is published on *Burkholderia* secondary metabolites, effectors, and other exoproducts, sequencing of the genomes will improve knowledge on that matter. Studies on regulation of exoproduction in *Burkholderia* will introduce interesting perspectives about the adaptation, survival, and pathogenesis of these bacteria. This will also favor the optimization of production of various enzymes for industrial purposes.

Acknowledgrment

Ludovic Vial and Marie-Christine Groleau contributed equally to this work.

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