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MINI-REVIEW

Bacillus thuringiensis: a successful insecticide with new environmental features and tidings

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Abstract *Bacillus thuringiensis* (*Bt*) is known as the most successful microbial insecticide against different orders of insect pests in agriculture and medicine. Moreover, *Bt* toxin genes also have been efficiently used to enhance resistance to insect pests in genetically modified crops. In light of the scientific advantages of new molecular biology technologies, recently, some other new potentials of *Bt* have been explored. These new environmental features include the toxicity against nematodes, mites, and ticks, antagonistic effects against plant and animal pathogenic bacteria and fungi, plant growth-promoting activities (PGPR), bioremediation of different heavy metals and other pollutants, biosynthesis of metal nanoparticles, production of polyhydroxyalkanoate biopolymer, and anticancer activities (due to parasporins). This review comprehensively describes recent advances in the *Bt* whole-genome studies, the last updated known *Bt* toxins and their functions, and application of *cry* genes in plant genetic engineering. Moreover, the review thoroughly describes the new features of *Bt* which make it a suitable cell factory that might be used for production of different novel valuable bioproducts.

Keywords Anticancer · Antagonistic effect · *Bacillus thuringiensis* · Bioacaricide · Bioremediation · Nanoparticle biosynthesis · Plant growth-promoting rhizobacteria (PGPR) · Whole genome

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Introduction

The use of environmental-friendly microbial insecticides as substitutes for harmful chemical pesticides is an alternative for mass control of destructive crop pests. The global market for biocontrol agents (macro and micro) is about 3.5 billion USD with 16% annual growth, which consists approximately 8% of the global pesticides trade (50 billion USD). The share of microbial insecticides is about 807 million USD (BCC Research Report 2015; Lacey et al. 2015; Velivelli et al. 2014).

Bacillus thuringiensis (*Bt*) is an aerobic, spore-forming, gram-positive, and entomopathogenic bacterium that produces parasporal crystal proteins or δ-endotoxins (Cry). These Cry proteins are toxic to a wide variety of insect pests, such as Lepidoptera, Coleoptera, and Diptera (Salehi Jouzani et al. 2008a,b). *Bt* has been considered as the most successful bioinsecticide during the last century. Currently, it consists of more than 98 (424 million USD) of formulated sprayable bacterial pesticides (Lacey et al. 2015). The species *Bt* commonly consists of a large family of different subspecies which are categorized in different subspecies with different phylogenetic and serotyping features (such as *Bt* subsp. *kurstaki*, *Bt* subsp. *aizawai*, *Bt* subsp. *tenebrionis*, *Bt* subsp. *Israelensis*, etc.). In addition, each *Bt* subspecies consists of different strains and serotypes (Seifinejad et al. 2008). *Bt* is known as a fast-acting and host-specific bioinsecticide, so its adverse effects on non-target organisms are very limited. Moreover, its production (upstream and downstream processes) and application (conventional spraying or genetically modified (GM) *Bt* crops) are easy and cheap (Jain et al. 2016; Lacey et al. 2015). Accordingly, *Bt* has been efficiently used as the source of *cry* genes in plant genetic engineering to make transgenic crops resistant to different pests (Melo et al. 2016; Salehi Jouzani et al. 2008c; Tohidfar and Salehi Jouzani 2008; Tohidfar et al. 2013; Jain et al. 2016) and also has potential to be used as a nematicide to control plant

pathogenic nematodes (Iatsenko et al. 2014a,b, Salehi Jouzani et al. 2008b). Moreover, recent studies have confirmed more new potentials of different *Bt* strains. These new features are including plant growth promoting (Armada et al. 2015a,b), bioremediation of heavy metals and other chemicals (Aceves-Diez et al. 2015; Dash et al. 2014; Melo et al. 2016), anticancer activities (Periyasamy et al. 2016), polymer production (Singh et al. 2013), and antagonistic effects against plant and animal pathogenic microorganisms (Gutiérrez-Chávez et al. 2016; Roy et al. 2013) (Fig. 1).

In spite of publication of some review papers focused on different aspects of *Bt* during the last years (e.g., De la Fuente-Salcido et al. 2013; Hu and Aroian 2012; Jisha et al. 2013; Melo et al. 2016), there is no comprehensive review presenting an integrated package of data on biotechnological applications (as insecticide and gene source for plant genetic engineering), insecticidal proteins, whole-genome structure, and also recent explored potential applications of *Bt* in the last 5 years. Accordingly, the objective of the present paper is to comprehensively review the recent advances in new features and potential applications of *Bt* strains.

Recent advances in the *Bt* genome studies

Various studies during the last century resulted in the detection and characterization of a dozen different genes encoding insecticidal bioactive substances in *Bt* strains isolated from different regions of the world. However, the conventional methods often fail to obtain a comprehensive understanding of those genes and insecticidal active substances, as they are very diverse, and their encoded proteins have a relatively short half-life. Recent advances in the next-generation sequencing and new "omics" technologies, such as genomics, transcriptomics, proteomics, and transcriptomics, have enhanced deep insights into genome diversity among *Bacillus* species and also among different *Bt* subspecies and strains. *Bt* genome projects have been expected to increase and accelerate detection of novel pathogenic genes and related regulatory factors. Moreover, a combination of genomics, transcriptomics, proteomics, and metabolomics could be used to study *Bt* toxin proteins with different characteristics and activities (Dong et al. 2016).

Until now, whole and partial genome sequences of more than 60 *Bt* strains (about 30 complete sequences) have been submitted to the GeneBank. The full-length genome (including one to multiple plasmids) of the studied *Bt* strains spans from 5.3 to 6.87 Mb. The number of genes in the studied *Bt* strains varies from 5343 to 7227, and the number of plasmids ranges between 1 and 13. The guanine-cytosine content (GC) of the *Bt* genomes is between 31.4 and 35. 48% (Table 1). Accordingly, these reports confirm the vast genetic diversity among the studied strains, and therefore, by exploring new strains, novel toxin genes and proteins most probably will be detected.

Bt insecticidal genes and their host specificity: an update

Bt constitutes a large family of subspecies which recognized as entomopathogens and found in various habitats.

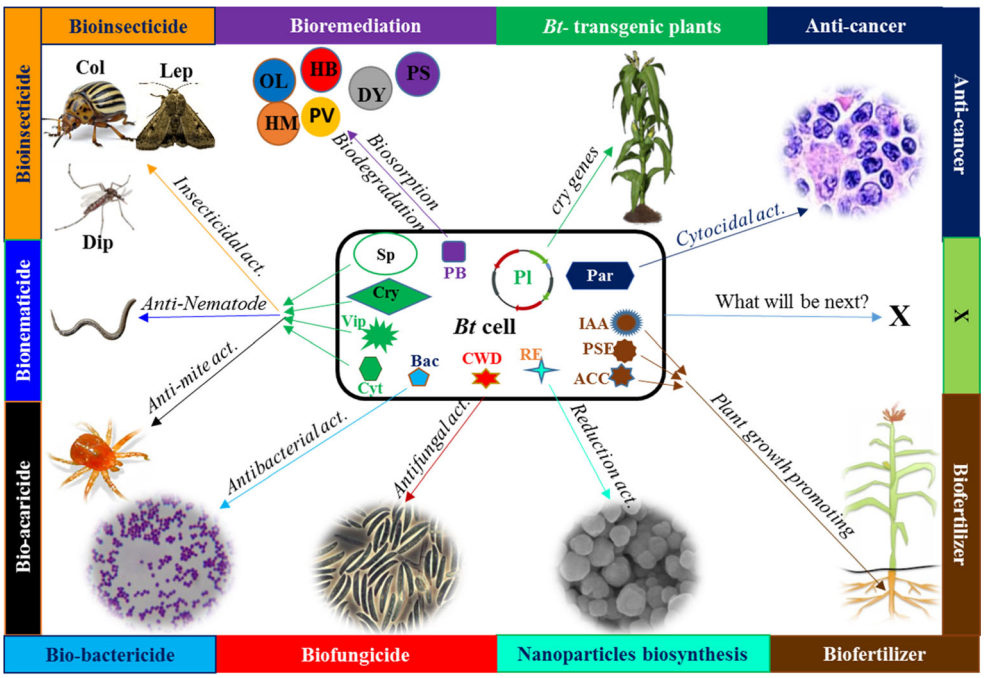

Fig. 1 *Bt* cell factory potentials. *ACC* ACC deaminase, *Bac* bacteriocin, *CWD* cell wall-degrading enzymes, *Col* Coleoptera, *Cry* crystal proteins (δ-endotoxins), *Cyt* cytolytic proteins, *Dip* Diptera, *DY* dyes, *HP* herbicides, *HM* heavy metals, *IAA* indole-3-acetic acid, *Lep* Lepidoptera, *OL* oil (petroleum), *Par* parasporin, *PB* bioremediation involving proteins, *Pl* plasmid, *PS* pesticide, *PSE* phosphate solubilization enzymes, *PV* plastics, *RE* reducing enzymes, *Sp* spore, *Vip* vegetative insecticidal proteins

Table 1 Features of *Bt* strain genomes (chromosome and plasmids)

Bt subspecies/strain	Activity	Total genome length	No. of genes	Chromosome genome length (bps)	Chromosome GC (%)	No. of chromosomal genes	No. of plasmids	Plasmids size (×1000 bp)	No. of tRNAs and rRNAs	Accession number	Reference
Galleriae HD-29	Lep/Col	6,741,233	6904	5,701,188	34.9	5890	10	8423–426,282	115 and 42	CP010089-99	Zhu et al. (2015a)
HS18-1	Lep/Col	6,403,499	6126	5,292,526	35.43	5382	9	7386–509,170	106 and 42	CP012099-108	Li et al. (2015a)
Hailuosis YWC2-8	Dip/Lep active	6,227,942	6253	5,674,369	35.29	5692	6	8512–250,706	94 and 45	CP013055-61	Zhu et al. (2016)
Fitimus (CTC)	S-layer protein production	5,352,926	5565	5,327,397	35.4	5397	1	25,529	93 and 34	CP0130273-274	Dong et al. (2016)
HD521	Col and antifungal	6,190,688	6310	5,429,688	35.28	5538	6	7000–310,000	138 RNA	CP010106-112	Li et al. (2015b)
147	Dip/Lep	6,167,994	6457	5,337,997	34.90	5602	6	6759–357,957	138 RNA	LFXM00000000	Barbosa et al. (2015)
Tenebrionis-44A1	Col active (Cry8Ga)	6,179,896	6574	5,652,292	35.3	6337	6	4845–232,994	98 and 39	SRP041917	Gao et al. (2015)
Israelensis, HD-789	Encoding 7 Cry and 3 Cyt	6,334,630	6626	5,495,278	35.26	5697	6	6824–349,599	121 and 42	CP003763-69	Doggett et al. (2013)
Kurstaki, HD73	Lep	6,600,000	6169	5,646,799	31.4	5892	7	8000–77,000	104 and 36	CP004069-76	Liu et al. (2013)
Thuringiensis-IS5056	Lep	6,800,000	6755	5,491,935	35.4	5617	14	6880–328,151	85 and 39	CP004123-37	Murawska et al. (2013)
407 Cry	Lep	6,134,344	6635	5,500,501	35.4	5714	9	2062–501,911	138 and 42	CP003889-98	Sheppard et al. (2013)
Tolworthi	Lep	6,870,591	7044	5,896,839	–		8	7812–437,451	112 and 36	AP014864-72	Kanda et al. (2015)
BR58	Dip/Col active	5,980,291	7227	5,578,174	35	6286	1	402,117	173 RNAs	LIIT00000000	Zorzetti et al. (2015)
KB1	Antibacterial and antifungal	5,748,443	5783	4,594,360	35	5666	ND	Total 1,154,083	117 RNAs	LSNJ01000000	Jeong et al. (2016)
Al Hakam	–	5,310,000	5537	52,600,000	35	4969	1	50,000	104 and 42	CP000485-86	Challacombe et al. (2007)
BMB171	GE model	5,640,000	5760	5,330,000	35.3	5088	1	310,000	102 and 42	CP001903-4	He et al. (2010)
Chinensis CT-43	Lep/Dip	6,150,000	6270	5,486,830	35.38	5596	10	6880–281,231	85 and 39	CP001907.1-17.1.	He et al. (2011)
Finitimus-YBT-020	Crys are adhered to spore	5,682,383	5826	5,355,490	35.3	5477	2	187,880–139,013	107 and 42	CP002508-10	Zhu et al. (2011)
Sichuansis-MC28	Lep/Dip	6,680,000	6557	5,414,461	35.41	5279	7	7826–429,674	75 and 45	CP003687-94	Guan et al. (2012)
Kurstaki HD1	Lep	6,767,044	6928	5,631,672	35.3	5864	13	Combined 1,135,000	95 and 41	CP004870-83	Zhu et al. (2015b)
YBT-1520	Lep	6,580,536	6720	5,602,565	35.3	5830	11	Combined 978	99 and 39	CP004858-69	Zhu et al. (2015b)

Table 1 (continued)

Bt subspecies/strain	Activity	Total genome length	No. of genes	Chromosome genome length (bps)	Chromosome GC (%)	No. of chromosomal genes	No. of plasmids	Plasmids size (×1000 bp)	No. of tRNAs and rRNAs	Accession number	Reference
YBT-1518	Nematicidal	6,672,911	6738	6,002,284	35.4	6025	6	17,706–240,661	94 and 15	CP005935-40	Wang et al. (2014)
Al.Hakam	General	5,676,963	–	–	36	–	6	–	–	CP009645-51	Johnson et al. (2015)
97-27	General	5,312,686	–	–	35	–	1	–	–	CP010087-88	Johnson et al. (2015)
Morrisoni HD 600	Col	6,916,808	–	–	35	–	7	–	–	JTHH00000000	Johnson et al. (2015)
HD-571	General	5,312,179	–	–	35.41	–	1	–	–	CP009599-600	Johnson et al. (2015)
HD-682	General	5,291,389	–	–	35.48	–	3	–	–	CP009717-20	Johnson et al. (2015)
Thuringiensis HD 1002	General	6,572,702	–	–	35	–	7	–	–	CP009344-51	Johnson et al. (2015)
HD1011	General	6,093,375	–	–	35.15	–	4	–	–	CP009332-36	Johnson et al. (2015)
Kurstaki HD 1	Lep	6,859,374	–	–	35		14	–	–	CP009998-012	Johnson et al. (2015)
97-27	–	5,314,794	5343	5,237,682	35.36	–	1	–	105 and 41	–	Han et al. (2006)

According to *Bt* flagellar antigens, 72 antigenic groups (serotypes) have been distinguished (Blackburn et al. 2013; Lecadet et al. 1999; Lecadet 2013). Crickmore et al. (2016) have designed an especial database for *Bt* toxins with links to information on host insects, which is continually updated (www.lifesci.sussex.ac.uk/Home/Neil_Crickmore/*Bt*/). Based on the last updated data in this database (June 2016), about 952 toxin genes, encoding different entomopathogenic proteinaceous toxins, have been identified and characterized in the *Bt* strains isolated from different regions of the world. Most of these toxins are parasporal inclusions, produced during the sporulation phase. Parasporal inclusion bodies contain crystalline proteins known as delta-endotoxins and classified into two families: Cry and Cyt proteins. Based on the amino acid sequence similarities, up to now, 74 *cry* gene families (*cry1–cry74*) with 770 different *cry* genes and three *cyt* families (*cyt1–cyt3*) consisting of 38 *cyt* genes have been characterized. Other insecticidal proteins are vegetative insecticidal proteins (Vips) produced during the vegetative phase of growth. Up to now, about 138 different *vip* genes categorized into four groups (*vip1–vip4*) have been identified and characterized (Table 2). Based on the Cry, Cyt, and Vip protein contents, each strain may be specifically active towards lepidopteran, dipteran, coleopteran, or hymenopteran pests and even other invertebrates, such as mites and nematodes (Abdelmalek et al. 2015; Salehi Jouzani et al. 2008a,b). The *cry1* family contains 14 subfamilies (*cry1A–N*) which contain 275 *cry* genes. The majority of the *cry1* genes are active against lepidopteran pests. The *cry1b* and *cry1I* genes from this family are active also against coleopteran pests (Nazarian et al. 2009). The *cry2* family is placed in the second rank with about 82 genes, and their activity is mostly against lepidopteran or dipteran pests. The *cry3* family contains 19 genes, which the majority of them are active against coleopteran insects (Table 2). In more details, the *cry1*, *cry9*, *cry15*, *cry20*, *cry51*, *cry54*, *cry59*, and *vip* genes are mainly active against the lepidopteran pests. The *cry2*, *cry4*, *cry10*, *cry11*, *cry16*, *cry17*, *cry19*, *cry24*, *cry25*, *cry27*, *cry29*, *cry30*, *cry32*, *cry39*, *cry40*, *cry44*, *cry47*, *cry48*, *cry49*, *cry52*, and *cyt* genes are active against dipteran pests, whereas the *cry3*, *cry7*, *cry8*, *cry14*, *cry18*, *cry22*, *cry23*, *cry26*, *cry28*, *cry34*, *cry35*, *cry366*, *cry37*, *cry38*, *cry43*, and *cry55* are coleopteran-specific genes (Table 2). Also, during the last two decades, it has been proved that some *cry* genes, such as *cry5*, *cry6*, *cry12*, *cry13, cry14*, *cry21*, and *cry55* have toxicity against plant and animal nematodes (Ruan et al. 2015; Salehi Jouzani et al. 2008b). However, it should be taken into account that some reported nematicidal activities of Cry proteins have been observed when high concentrations of them were used.

Bt and plant genetic engineering

Recent years have witnessed rapid advancements in the application of modern biotechnology, especially in the agriculture. The global acreage of GM crops across the world has dramatically increased during the last 20 years due to their socioeconomic and environmental advantages and reached to 179.7 million ha in 2015 (Salehi Jouzani et al. 2008c; Salehi Jouzani 2012; Tohidfar and Salehi Jouzani 2008; James 2015). The most widely used traits in the plant genetic engineering are herbicide and pest resistance. *Bt* toxin genes have been extensively used to enhance resistance to pests in crops. In 2015, the acreage of *Bt* transgenic crops was about 75 million ha (58.5 million ha stacked *Bt*/herbicide tolerance and 18 million ha *Bt* crops). These GM crops contain one or more different *cry* genes for resistance to lepidopteran and/or coleopteran pests (James 2015). The *Bt* crops have enhanced pesticide application reduction of more than 583 million kg throughout 1996–2014 (Brookes and Barfoot 2015; James 2015).

Since 1996, 198 *Bt* GM varieties and lines of eight plants, including corn, cotton, potato, soybean, tomato, poplar, rice, and eggplant have been approved for commercial release (Fig. 2). Corn, cotton, and potato with 115, 42, and 30 varieties and lines are the most approved *Bt* GM crops, respectively (ISAAA's GM Approval Database 2016). Seven anti-lepidopteran *cry* and *vip* genes, including *cry1Ab*, *cry1A.105*, *cry1Ac*, *cry1F*, *cry2Ab*, *cry2Ae*, and *vip3A*, have been used to enhance resistance to lepidopteran genes. The *cry1Ab*, *cry1F*, and *cry1Ac* are the most used genes to produce lepidopteran-resistant crops, which have been used in 61, 51, and 32 GM varieties, respectively (Fig. 3). Some *Bt* crops contain more than one *cry* or *vip* genes (two or three). These gene-pyramiding systems have been developed to postpone the potential pest resistance to *Bt* toxins produced in transgenic plants. The number of approved *Bt* varieties containing anti-coleopteran genes is about 111, some of them also contain anti-lepidopteran pests. Four anti-coleopteran *cry* genes, including *cry3Aa*, *cry3B*, *cry34Ab1*, and *cry35Ab1*, have been used to enhance resistance towards coleopteran pests. Two *cry34Ab1* and *cry35Ab1* have been used as a hybrid gene. The *cry3A* and *cry34Ab1–cry35Ab1*, as the most used genes to produce coleopteran pests' resistant crops, have been used in 60 and 34 GM varieties, respectively (Fig. 4).

Nevertheless, commercial transgenic crops containing *cry* genes with activity against other insect orders and also against nematodes have not released yet; therefore, more research and development projects should be performed to achieve nematode-resistant crops at commercial level. In addition, in spite of the mentioned advantages, some potential risks on human health and environment have been taken into account for transgenic crops, including *Bt* crops. Typical categories of risks of *Bt* crops include possible unintended negative effects on human and animal health, the possible evolution of

Table 2 The summarized list of *Bt* toxin genes and their activities (last updated: June, 2016)

Gene family	Numbers	Toxicity against	Gene family	Numbers	Toxicity against	Gene family	Numbers	Toxicity against	Gene family	Numbers	Toxicity against
cry1(A–N)	275	Lep or Col	*cry23(A)*	1	Col	*cry45(A–B)*	2	ND, AC	*cry67(A)*	2	ND
cry2(A–B)	82	Dip or Lep	*cry24(A–C)*	3	Dip	*cry46(A)*	3	ND, AC	*cry68(A)*	1	ND
cry3(A–C)	19	Col	*cry25(A)*	1	Dip	*cry47(A)*	1	Dip	*cry69(A)*	3	ND
cry4 (A–C)	17	Dip	*cry26(A)*	1	Col	*cry48(A)*	5	Dip	*cry70(A)*	3	ND
cry5 (A–E)	13	Nem	*cry27(A)*	1	Dip	*cry49(A)*	5	Dip	*cry71(A)*	1	ND
cry6(A–B)	4	Nem	*cry28(A)*	2	Col	*cry50(A–B)*	3	ND	*cry72(A)*	1	ND
cry7 (A–L)	37	Col	*cry29(A–B)*	2	Dip	*cry51(A)*	2	Lep	*cry73(A)*	1	ND
cry8 (A–T)	59	Col	*cry30(A–G)*	13	Dip	*cry52(A–B)*	2	Dip	*cry74(A)*	1	ND
cry9(A–G)	37	Lep	*cry31(A)*	12	ND, AC	*cry53(A)*	2	ND	*cyt1(A–D)*	13	Dip
cry10(A)	5	Dip	*cry32(A–W)*	31	Dip	*cry54(A–B)*	5	Lep	*cyt2(A–C)*	24	Dip
cry11(A–B)	8	Dip	*cry33(A)*	1	ND, AC, AB	*cry55(A)*	3	Col and Nem	*cyt3(A)*	1	Dip
cry12(A)	1	Nem	*cry34(A–B)*	11	Col	*cry56(A)*	4	ND	*vip1(A–D)*	15	Lep
cry13(A)	1	Nem	*cry35(A–B)*	11	Col	*cry57(A)*	2	ND	*vip2(A–B)*	20	Lep
cry14(A)	2	Col or Nem	*cry36(A)*	1	Col	*cry58(A)*	1	ND	*vip3(A–C)*	102	Lep
cry15(A)	1	Lep	*cry37(A)*	1	Col	*cry59(A–B)*	2	Lep	*vip4(A)*	1	Lep
cry16(A)	1	Dip	*cry38(A)*	1	Col	*cry60(A–B)*	6	ND	*other*	6	
cry17(A)	1	Dip	*cry39(A)*	1	Dip	*cry61(A)*	3	ND			
cry18(A–C)	3	Col	*cry40(A–D)*	4	Dip	*cry62(A)*	1	ND			
cry19(A–C)	3	Dip, Lep	*cry41(A–C)*	5	ND, AC	*cry63(A)*	1	ND, AC			
cry20(A–B)	4	Lep,	*cry42(A)*	1	ND	*cry64(A–C)*	3	ND, AC			
cry21(A–H)	10	Nem, Dip	*cry43(A–C)*	7	Col	*cry65(A)*	2	ND, AC, AB			
cry22(A–B)	7	Col	*cry44(A)*	1	Dip	*cry66(A)*	2	ND			

AB antibacterial, *AC* anticancer, *Col* Coleoptera, *Dip* Diptera, *Lep* Lepidoptera, *ND* no known invertebrate target, *Nem* nematodes

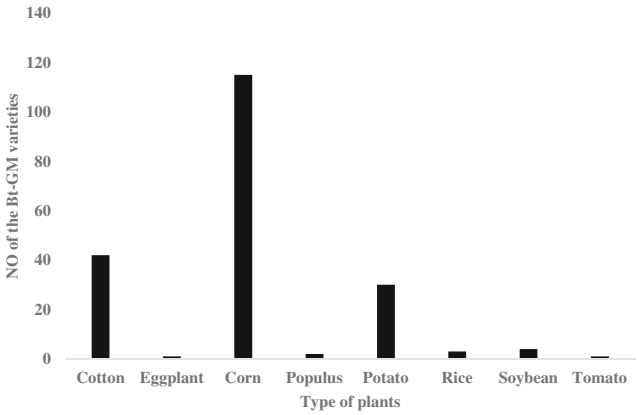

Fig. 2 The list of approved *Bt* crops for release

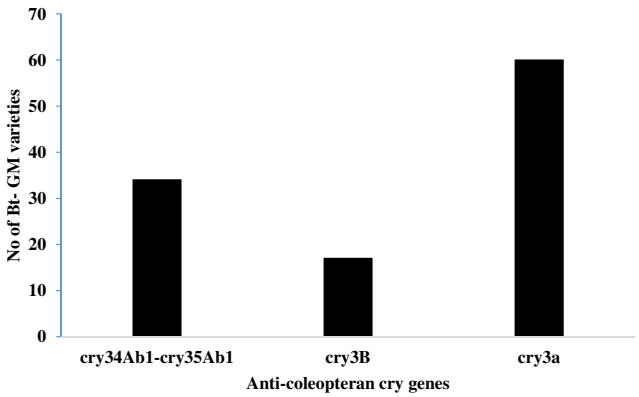

Fig. 4 The list of *cry* genes used in the approved coleopteran-resistant *Bt* crops

resistance in the targeted pest populations, possible effects on non-target organisms, and the transgene escape and expression in a different organism as result of transgene flow (Craig et al. 2008; Raybould 2006; Salehi Jouzani 2012). However, during the last 20 years after commercial production of *Bt* crops, no significant harm has been proved for them.

Bt as biological nematicide

Plant-parasitic nematodes, including cyst nematodes (*Heterodera* and *Globodera* spp.) and root-knot nematodes (*Meloidogyne* spp.), are piercing/sucking pests causing severe damage to different crops. These nematodes cause annual yield loss of approximately $125 billion globally (Chitwood 2003; Yu et al. 2014, 2015; Zhang et al. 2012). Moreover, animal parasitic nematodes, by increasing the cost of veterinary services, delaying in animal growth and even causing death, are known as one of the most important factors interfering with animal production (Sinott et al. 2012). Although chemical nematicides remain the most current means of controlling root-knot nematodes, the growing concerns of environmental safety and public health lead to the withdrawal or restricted usage of these kinds of nematicides (Yu et al. 2015).

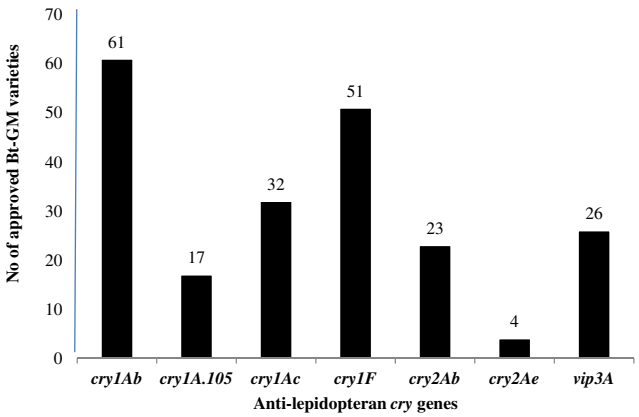

Fig. 3 The list of *cry* and *vip* genes used in the approved lepidopteran-resistant *Bt* crops

Some *Bt* strains can infect, germinate, and replicate inside the digestive system of nematodes (Ruan et al. 2015). *Bt* strains, containing one or many families of crystal proteins, i.e., *cry5*, *cry6*, *cry12*, *cry13*, *cry14*, *cry21*, and *cry55*, have been documented to have nematicidal activities (Guo et al. 2008; Luo et al. 2013a,b; Salehi Jouzani et al. 2008b; Yu et al. 2015; Zhang et al. 2012) (Figs. 1 and 5). Moreover, these Cry proteins have synergistic effects on nematodes when present in the *Bt* strains (Yu et al. 2014). Accordingly, the expression of recombinant nematode-active Cry proteins expressed in the plants provides protection against plant-endoparasitic nematodes (Li et al. 2007, 2008).

Moreover, a few of other *Bt* compounds, such as thuringiensin (Devidas and Rehberger 1992; Sánchez-Soto et al. 2015), chitinase (Zhang et al. 2014), and metalloproteinase (Luo et al. 2013b), show nematicidal activities (Fig. 5). Other genes encoding nematicidal factors, including lantibiotics, enterotoxins, hemolysins, and proteases mostly controlled by the transcriptional activator PlcR, has been confirmed (Ruan et al. 2015; Zhou et al. 2014). Peng et al. (2016) proved that the presence of metalloproteinase ColB (collagenase protein) is very necessary to enhance nematicidal activities of Cry5 and Cry6 proteins. Ruan et al. (2015) have proposed two other alternative mechanisms (necrotrophism and phoresis) for *Bt* interactions with nematodes. Recent sequencing projects have confirmed that the genes involved in the necrotrophic life stage are under the control of the NprR (a transcriptional factor whose activity depends on the NprX signaling peptide and involves in the necrotrophism mechanism) regulator (Dubois et al. 2012). Three proteins, keratinolytic proteinase, collagenase (regulated by a pleiotropic transcriptional factor (PlcR)), and immune inhibitor A, enable a necromenic lifestyle of *Bt.* The keratinolytic proteinase digests collagen contents in the nematode cuticle. The second alternative mechanism is phoresy, in which *Bt* is carried by the nematode, either on its surface or within its intestinal tract without killing the host (Ruan et al. 2015).

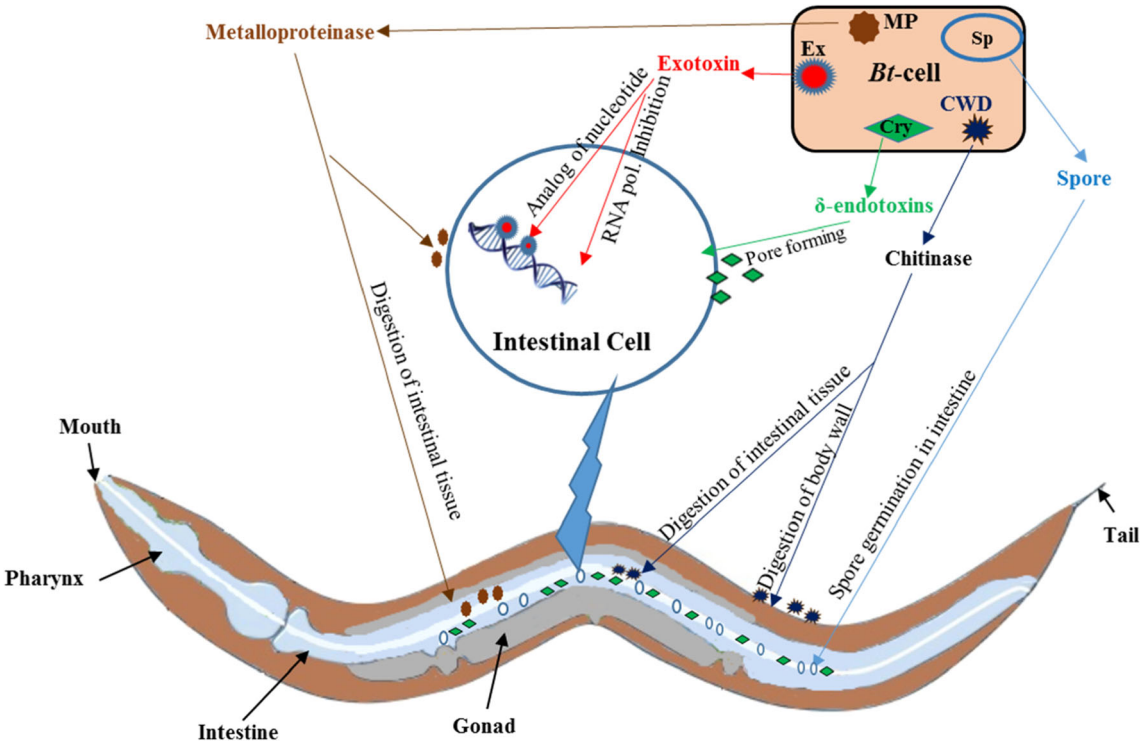

Fig. 5 Mode of action of *Bt* against nematodes. The crystal proteins destroy the intestine following spore germination. Multi-pathogenic factors, such as chitinase, metalloproteinase, and exotoxin, which produced during *Bt* cell growth, can act synergistically with crystal proteins. *CWD* cell wall-degrading enzymes (chitinase), *Cry* crystal proteins (δ-endotoxins), *Ex* exotoxin (thuringiensin), *Mp* metalloproteinase, *Sp* spore

The nematicidal activities of *Bt* strains have been tested against different free-living nematodes, such as *Caenorhabdita elegans*, *Pristionchus pacificus*, and *Chiloplacus tenuis* (Devidas and Rehberger 1992; Iatsenko et al. 2014a; Luo et al. 2013a,b; Salehi Jouzani et al. 2008b), animal parasitic nematodes, such as *Ascaris suum*, *Distolabrellus veechi*, *Haemonchus contortus*, *Trichostrongylus* sp., and *Ostertagia circumcincta* (Kotze et al. 2005; Sinott et al. 2012; Urban et al. 2013), and plant parasitic nematodes, such as *Meloidogyne incognita*, *Meloidogyne halpa*, *Pratylenchus scribneri*, *Tylenchorhynchus* sp., *Ditylenchus destructor*, and *Aphelenchoides* sp. (Guo et al. 2008; Khan et al. 2010; Mohammed et al. 2008; Salehi Jouzani et al. 2008b; Yu et al. 2015; Zhang et al. 2012; Zi-Quan et al. 2008). The recent studies on nematicidal activities of *Bt* strains or their Cry proteins are summarized in Table 3. As it is clear in the Table 3, the LC_{50} of the Cry proteins/spores for nematodes in the most of the reports was quite low. This raises hope for future application *Bt* strains as bionematicide. However, in spite of proving nematicidal activity of some *Bt* strains, there is no commercial *Bt*-based nematicide product in the world at the moment. This limited application may be because of ambiguity in mechanisms of nematicidal activity or low efficiency of some *Bt* strains.

Acaricidal effects of *Bt*

Some mite and tick species colonize humans and animals directly and also act as vectors for disease transmission or cause allergenic diseases. Although information concerning the effect of *Bt* on mites is rare, a few in vitro and in vivo studies have reported the acaricidal activity of some *Bt* strains (Erban et al. 2009; Dunstand-Guzmán et al. 2015; Alquisira-Ramírez et al. 2014). In the first reports, Hassanain et al. (1997) evaluated the acaricidal activities of three *Bt* subspecies *(kurstaki, israelensis*, and *thuringiensis*) against the soft tick *Argas persicus* and the hard tick *Hyalomma dromedarii*. The *Bt. var. kurstaki* and *Bt* var. *israelensis* showed the highest toxicity, respectively. The acaricidal effect of the *Bt.* var. *kurstaki* against the black-legged tick, *Ixodes scapularis* Say, which acts as a vector for several animal and human diseases, has been also confirmed (Zhioua et al. 1999). In another study, *Bt* var. *tenebrionis* producing Cry3A toxin showed high toxicity (LC_{50} 25 to 38 mg/g) against the mites *Acarus siro* L., *Tyrophagus putrescentiae*, *Dermatophagoides farinae*, and *Lepidoglyphus destructor* (Erban et al. 2009). Alquisira-Ramírez et al. (2014) isolated and characterized some *Bt* strains with high acaricidal activity from mite *Varroa destructor* (Acari: Varroidae), an ectoparasitic mite that feeds on the hemolymph of bee *Apis mellifera* (Hymenoptera: Apidae). Another group firstly reported the

Table 3 The list of *Bt* strains with nematicidal activities

Bt strain	Gene/protein	Nematicidal activities against	Host	Nematicidal efficiency	Reference
YBT-021	ND	*Meloidogyne hapla*	Vegetables	LC_{50} 35.62 μg/ml	Zi-Quan et al. (2008)
		Pratylenchus scribneri	Ramie	LC_{50} 75.65 μg/ml	
		Tylenchorhynchus sp.	Ramie	LC_{50} 94.31 μg/ml	
		Ditylenchus destructor	Sweet potato	LC_{50} 215.21 μg/ml	
		Aphelenchoides sp.	Different plants	LC_{50} 128.76 μg/ml	
ND	Exotoxin	*Meloidogyne incognita*	Vegetable	10 mg/kg soil	Devidas and Rehberger (1992)
		Caenorhabdita elegans	Free living	15.6 μg/ml	
BMB171-15	*cry6Aa2*	*Caenorhabdita elegans*	Free living	LC_{50} 7.43 μg/ml	Luo et al. (2013a)
BMB0224	*cry55Aa1*	*Meloidogyne hapla*	Vegetables	LC_{50} 23.2 μg/ml	Guo et al. (2008)
BMB0250	*cry6Aa2*			LC_{50} 23.9 μg/ml	
BMB0215	*cry5Ba2*			LC_{50} 18.1 μg/ml	
DB27	Cry21Fa1	*Caenorhabdita elegans*	Free living	LC_{50} 13.6 μg/ml	Iatsenko et al. (2014a,b)
	Cry21Ha1			LC_{50} 23.9 μg/ml	
*Bt*7 and *Bt*7N	–	*Meloidogyne incognita*	Vegetables	LC_{50} 34–37 μg/ml	Mohammed et al. (2008)
Bt-64	–	*Meloidogyne javanica*	Vegetables	51% mortality	Khan et al. (2010)
YD5 and KON4	–	*Meloidogyne incognita*	Vegetables	81% mortality	Salehi Jouzani et al. (2008a,b,c)
		Chiloplacus tenuis	Free living	77% mortality	
		Acrobeloides enoplus	Free living	71% mortality	
BMB171-15	Cry6Aa2	*Meloidogyne hapla*	Vegetables	LC_{50} 71.08 μg/ml	Yu et al. (2015)
*Bt*010	Chitinase	*Caenorhabdita elegans*	Free living	48.4% mortality (48 h)	Zhang et al. (2014)
Bt. osvaldocruzi	–			47.5%	Sinott et al. (2012)
Bt. kurstak	–	*Haemonchus contortus*	Sheep	33.2%	
Bt. israelensis	–			14.1%	
Bt WA 3.4.9	Cry5A, Cry5B, and Cry13	*Haemonchus contortus*	Animals	LC_{50} 26 ng/ml	Kotze et al. (2005)
		Trichostrongylus sp.	Animals	LC_{50} 47 ng/ml	
		Ostertagia circumcincta	Animals	LC_{50} 81 ng/ml	
Bt L366	Cry5A, Cry5B, and Cry13	*Haemonchus contortus*	Animals	LC_{50} 41 ng/ml	Kotze et al. (2005)
		Trichostrongylus sp.	Animals	LC_{50} 127 ng/ml	
		Ostertagia circumcincta	Animals	LC_{50} 10 ng/ml	
–	Cry5B	*Ascaris suum*	Animals	100% mortality (25 ng/kg)	Urban et al. (2013)
–	Metalloproteinase *ColB* (collagenase)	*Caenorhabdita elegans*	Free living	Significantly improved toxicity of Cry5 and Cry6	Peng et al. (2016)

acaricidal activity of the *Bt* strain GP532 (LC_{50} 1.3 mg/ml and LT_{50} 68 h) on the mite *Psoroptes cuniculi*, known as a common ectoparasite of rabbit ear (Dunstand-Guzmán et al. 2015). Recently, a novel *Bt* strain (BPU5) was isolated from the rumen of Malabari goat, which was efficiently toxic to *Tetranychus macfarlanei* (LC_{50} 8 mg/ml), a sucking mite infesting different crops and ornamentals (Neethu et al. 2016). Ahmed et al. (2016) reported the acaricidal activities of *Bt* var. *israelensis* (81.22% mortality) and *tenebrionis* (90.91% mortality) against *T. putrescentiae* (Schrank), a mold mite *which is* a cosmopolitan pest of stored food products, at the rate of 32 mg/kg after 4 weeks.

In spite of confirmation of acaricidal activity of *Bt* strains against different ticks and mites, the mechanism of action of *acaricidal Bt* strains is unknown yet. However, the presence of enzymes like trypsin, alkaline phosphatase, and some aminopeptidases on the digestive system of the studied mites, suggests that alterations in the intestinal cells of the mites may be due to activation of *Bt* protoxins (Dunstand-Guzmán et al. 2015). Exploring the mechanism of action of *Bt* in the mite digestive system is one of the subjects which should be taken into account for the future studies on *Bt*. However, to have high acaricidal activity, high doses of Cry proteins/spores (mg/ml) are required which make it impractical to use

Bt as bioacaricide at commercial level. At the moment, there is no commercially available *Bt* products for control of mite and tick species in the world. Therefore, it will be necessary to explore new *Bt* strains with more powerful acaricidal activity in the future.

Bt as plant growth-promoting bacteria

Commonly, bacterial strains with beneficial effects on plant growth and development are referred to as plant growth-promoting rhizobacteria (Mishra et al. 2009a). Some strains of *Bt* colonize plant roots and have plant growth-promoting characteristics. These *Bt* strains have potentials to be used solely or in mixture with other microorganisms as biofertilizer in the agriculture (Armada et al. 2015a,b; Bai et al. 2003; Mishra et al. 2009a,b). Bai et al. (2003) confirmed that the *Bt strain* NEB17 significantly enhance soybean nodulation, growth, and yield parameters compared to *Bacillus subtilis* strains when they co-inoculated with *Bradyrhizobium japonicum* onto soybean plants. Co-inoculation of an IAA-producing *Bt strain* KR1 with *Rhizobium leguminosarum*-PR1 could significantly promote the growth of field pea and lentil compared to inoculation of *R. leguminosarum*-PR1 solely (Mishra et al. 2009a). The co-inoculation of *Bt*-KR1 with *B. japonicum*-SB1 also promoted the growth of soybean plants and provided a significant increase in nodule number, shoot weight, root weight, root volume, and total biomass compared to rhizobial inoculation and control (Mishra et al. 2009b).

Many *Bt* strains produce some metabolites which enhance plant growth at abiotic stress conditions. These compounds include ACC deaminase, indole-3-acetic acid (IAA), proline,

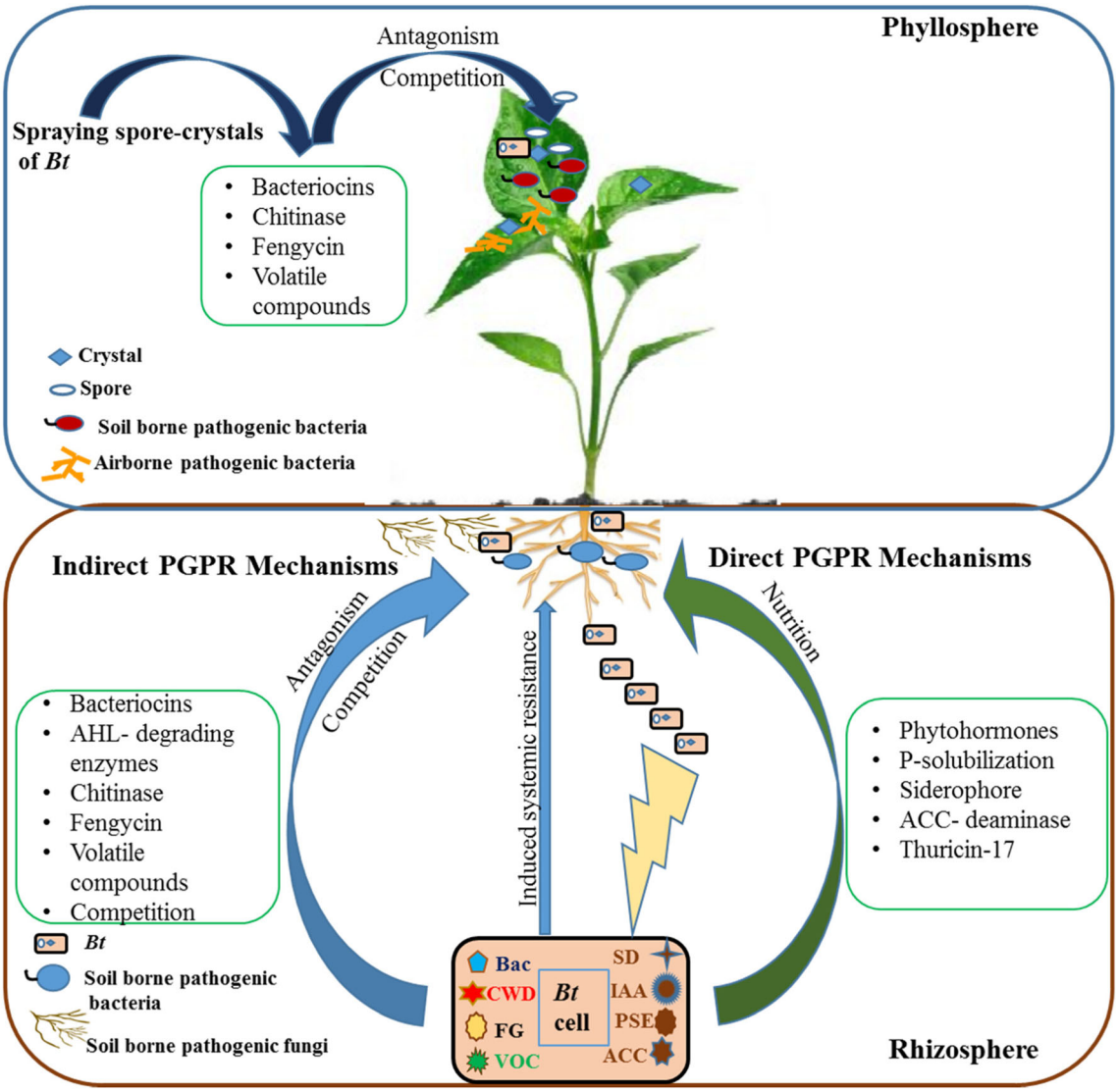

Fig. 6 Mechanisms of *Bt* as PGPR and antagonist of plant pathogenic bacteria and fungi. *AHL* *N*-acylhomoserine lactone, *ACC* ACC deaminase, *Bac* bacteriocin, *CWD* cell wall-degrading enzymes, *FG* fengycin, *IAA* indole-3-acetic acid, *PSE* phosphate solubilization enzymes, *Sp* spore, *VOCs* volatile compounds

and phosphate solubilization enzymes (Fig. 6). Armada et al. (2015a) showed that when *Bt* was used solely or mixed with arbuscular mycorrhizal fungi (AMF), it could significantly result in an increase of shoot growth, biomass (more than 20%), and micronutrient elements in the plant shoots. It also could substantially reduce the oxidative stress through increasing antioxidant enzyme activities (superoxide dismutase, catalase, and ascorbate peroxidase) and reduction of the plant oxidative damage of lipids (malondialdehyde). In another study, the combined inoculation of *Bt* and AMF to maize under drought stress could significantly increase the accumulation of nutrients in the plant and decrease the oxidative damage to lipids and accumulation of proline (Armada et al. 2015b). Also, application of autochthonous microorganisms (a consortium of *Bt* and AMF) enhanced a significant increase in water stress alleviation for *Trifolium repens* in a natural arid soil under drought conditions via increasing nutrient contents and the relative water content and decreasing stomatal conductance, electrolyte leakage, proline, and ascorbate peroxidase activity (Ortiz et al. 2015).

Lee et al. (2009) confirmed that the application of bacteriocin (thuricin-17) purified from *Bt* strain NEB17 to leaves (spray) or roots (drench) directly stimulated the growth of both a C3 dicot (soybean) and a C4 monocot (corn) plants. Application of thuricin-17 with the N2-fixing *B. japonicum* under water stress condition could significantly increase plant biomass (17%), root biomass (37%), nodule biomass (55%), root abscisic acid (30%), and total nitrogen amount (17%) (Prudent et al. 2015). Recently, Cherif-Silini et al. (2016) reported the plant growth-promoting rhizobacteria (PGPR) activity for the *Bt* and *B. subtilis* strains isolated from the wheat rhizosphere in different regions of Algeria. These strains showed the maximum biofertilization (phosphate solubilization), biostimulation (IAA production), and biocontrol activities (cyanhydric acid, siderophores, and 2,3-butanediol production and antifungal activity). The possible PGPR mechanisms of *Bt* are summarized in the Fig. 6.

The results of previous studies on PGPR activity of *Bt* strains are very promising. Nevertheless, at the present time, there is no commercially available *Bt*-based PGPR formulation in the biofertilizer market. By finding new *Bt* strains with powerful PGPR activities and exploring details of PGPR activity of those *Bt* strains, commercial production of PGPR *Bt* strains will be available in the near future for different crop systems.

Bt as antagonist of plant and human pathogenic fungi

Commonly, antifungal effects of biocontrol agents are due to various antifungal compounds, such as antibiotics, lipopeptides, siderophores, volatile organic compounds, secondary metabolites, and cell wall-degrading enzymes. The signaling molecules inducing systemic resistance in plants should be taken into account (Gao et al. 2014; Pane et al. 2012; Shrestha et al. 2015). Cry proteins synthesized by *Bt* do not show any antifungal activity. However, some *Bt* strains produce antifungal compounds, including cell wall-degrading enzymes, lipopeptide fengycin, volatile compounds (VOCs), and signaling molecules inducing systemic resistance (Fig. 6). The antifungal activities of *Bt* strains against different plant pathogenic fungi, such as *Fusarium*, *Sclerotium*, *Colletotrichum, Rhizoctonia, and Botrytis,* have been previously confirmed (Akram et al. 2013; Reyes-Ramírez et al. 2004; Sadfi et al. 2001; Shrestha et al. 2015; Tang et al. 2012; Zheng et al. 2013).

Chitinase activity is known as one of the most important antifungal agents detected in *Bt* strains. Chitinase-producing *Bt* strains have showed high antifungal activities against *Fusarium roseum* var. *sambucinum*, the causal agent of the dry rot of potato tubers (Sadfi et al. 2001), *Sclerotium rolfsii* Sacc (Reyes-Ramírez et al. 2004), *Penicillum chrysogenum* (causal agent of human disease), *Rhizoctonia* sp. and *Fusarium oxysporum* (Gomaa 2012), *Sclerotinia minor* and *Sclerotinia sclerotiorum, the causal agents of lettuce drop disease (*Shrestha et al. 2015*), Urocystis tritici*, the causal agent of the wheat flag smut (Tao et al. 2014), *Fusarium verticillioides* (maize pathogen) (Rocha et al. 2014), and *Botrytis cinerea*, the causing agent of mold disease in fruit and crop production (Martínez-Absalón et al. 2014).

Moreover, recent studies have confirmed the systemic resistance induction by *Bt* strains in plants against different fungal pathogens. For instance, when roots of 2-week-old tomato seedlings were primed with vegetative cells of Bt-199 (CFU 10^3) by keeping them in inoculum for 30 min and then transferred into pots, the bacterium could induce systemic resistance in tomato against *F. oxysporum* lycopersici wilt, by a significant increase of the quantity of total phenolics (1.7-fold) and defense-related enzymes, including polyphenol oxidase (1.3-fold), phenyl ammonia lyase (1.8-fold), and peroxidase (1.4-fold). Nevertheless, the mechanism for increase of these metabolites by *Bt* strains is not clear (Akram et al. 2013). In another study, chitinase extracted from Bt-H3 could significantly inhibit mycelial growth of several pathogenic fungi, including *Pyricularia grisea* (72.2%), *Thantephorus cucumris* (*Rhizoctonia solani*) (62.6%), *Fusarium vasinfectum* (44.6%), *Fusarium gramineum* (50.0%), and *F. oxysporum* (55.8%). The strain could significantly increase rice seedlings' defense enzyme activity, including phenylalanine ammonia lyase (PAL) and peroxidase (POD) (Tang et al. 2012).

Another antifungal mechanism of *Bt* is the production of fengycin-like and volatile compounds (Fig. 6). Kim et al. (2004) purified a lipopeptide (fengycin) from *Bt* CMB26 with potent toxicity against phytopathogenic anthracnose fungus *Colletotrichum gloeosporioides, Escherichia coli,* and cabbage white butterfly (*Pieris rapae crucivora*). Another study reported that the *Bt-TB72* produces different volatile compounds, such as

2-nonanone, β-benzeneethanamine, 2-decanone, and thymol. These compounds *could inhibit* 80.07 and 87.06% of the mycelial growth of *C. gloeosporioides* in postharvest mangos at in vitro and in vivo levels, respectively (Zheng et al. 2013).

Many *Bt* strains also can control some human and animal pathogenic fungi, such as *Candida albicans*, *Aspergilus niger* (Roy et al. 2013), and *P. chrysogenum* (Gomaa 2012). For instance, *Bt* strain SM1 produces a fengycin-like lipopeptide with high antifungal activities against *C. albicans* and *A. niger* (Roy et al. 2013). Information about antagonistic effects of *Bt* strains against human and animal pathogenic fungi is less, and accordingly, more detailed research is necessary to be performed in the future to find ways to use these antifungal properties in the plant protection, medicine, and food industries.

Bt as antagonist of pathogenic bacteria

Some *Bt* strains may have antibacterial activities against the plant and human pathogenic bacteria and those bacteria involving in food degradation. The mechanism of antibacterial activities of *Bt* includes the production of bacteriocins (Ahern et al. 2003; Cherif et al. 2001; Paik et al. 1997) and signal interference by *N*-acylhomoserine lactone (AHL)-degrading enzymes (Dong et al. 2004).

Commonly, prokaryotes produce different antimicrobial peptides to enhance their defense against other microorganisms. Bacteriocins are the small thermotolerant antimicrobial peptides with molecular masses between 3 and 12 kDa and are ribosomally synthesized during the stationary phase. They mostly affect the growth and (or) viability of other bacteria (de la Fuente-Salcido et al. 2013). Some studies reported bacteriocin production during the sporulation and Cry synthesis in *Bt* strains (Ahern et al. 2003; Barboza-Corona et al. 2007; Cherif et al. 2001; de la Fuente-Salcido et al. 2013; Kamoun et al. 2011). Recently, de la Fuente-Salcido et al. (2013) have reported a list of different types of bacteriocins synthesized by *Bt* strains. Up to now, 18 different types of bacteriocins have been isolated and purified from *Bt* subspecies (during vegetative growth period), including *morrisoni*, *kurstaki*, *kenyae*, *entomocidus*, *tolworthi*, *tochigiensis*, and *thuringiensis. Bt* bacteriocins may show a wide or narrow bactericidal or bacteriostatic effects (de la Fuente-Salcido et al. 2013).

Bt as antagonist of plant pathogenic bacteria

Some *Bt* strains, which produce different types of bacteriocins and AHL-degrading enzymes, can potentially be used as the antagonist in the biocontrol of plant pathogenic bacteria (Fig. 6). The AHL-degrading enzyme (AiiA) produced by some *Bt* strains can attenuate the virulence of pathogenic bacteria, such as *Erwinia carotovora*, the causal agent of soft rot in the root system of the pepper plant. The antibacterial activity of AiiA is due to the quorum-quenching mechanism (Park et al. 2008). The antibacterial activities of the *Bt*-derived bacteriocins against different plant pathogenic bacteria, such as *Agrobacterium tumefaciens* (Bacthuricin F103; Kamoun et al. 2011), *Pseudomonas syringae*, *Pseudomonas savastanoi*, *Paucimonas lemoignei* (Thuricin Bn1; Ugras and Demirbag 2013), and *B. cinerea* have been reported (Hong et al. 2015; Jeong et al. 2016). Moreover, the presence of *Bt* (vegetative cells) in mixtures with other bacterial (*Citrobacter farmer* and *Streptomyces avermectinius*) and fungal (*Paecilomyces variotii*, *Trichoderma parareesei* TPJ-S-1, and *Trichoderma viride* TVJ-S-1) antagonists significantly improved their efficiency to control *Ralstonia solanacearum* in *Naga chilli* (Bora et al. 2015), tomato (Elsharkawy et al. 2015), and eucalyptus (Santiago et al. 2015). Bora et al. (2015) reported that the combination of *Bt*, *T. parareesei*, and *T. viride* shows the maximum antagonistic effect (91.47%) against *R. solanacearum*, compared to other treatments and control. In another study, the treatment of tomato roots with *Bt* CR-371 and *S. avermectinius* suppressed bacterial wilt diseases (caused by *R. solanacearum*) and root-knot nematode diseases (Elsharkawy et al. 2015).

Bt as an agent for control of human and animal pathogenic bacteria

Some *Bt* bacteriocins have high potentials to be used as excellent alternatives for the traditional antibiotic treatment against different human or animal pathogenic bacteria. They also may be used as biodegradable natural and safe food preservatives in food packaging to inhibit the growth of enterotoxigenic bacteria and to extend the shelf life of foods. The combination of *Bt* bacteriocins with nisin can improve their antibacterial activities (Cherif et al. 2008; de la Fuente-Salcido et al. 2008, 2013; Paik et al. 1997).

For instance, a *Bt* fengycin-like lipopeptide showed antibacterial activity against *E. coli* and *Staphylococcus epidermidis* (Roy et al. 2013). Some bacteriocin-like compounds produced by Mexican *Bt* subspecies *morrisoni, kurstaki, kenyae, entomocidus,* and *tolworthi* showed high levels of activity against *Bacillus cereus* and *Vibrio cholerae*, the agents of emetic, diarrheal, and lethal syndromes in humans (Barboza-Corona et al. 2007). Bacthuricin F103, Thuricin S, and Thurincin H show high antibacterial activity against *Listeria monocytogenes* and *B. cereus*, and Thuricin 7 prevented spoilage of raw milk and dairy products caused by *Bacillus weihenstephanensis* (Cherif et al. 2001). Thuricin S has antibacterial activity against a broad spectrum of bacteria, such as *L. monocytogenes*, *B. cereus*, *S. enterica* subsp. *enterica* serovar *cholerae*, and *Pseudomonas aeruginosa*, and accordingly, it is feasible to be used as a natural food preservative in the food industry (Chehimi et al. 2012; de la Fuente-Salcido et al. 2013). Also, Morricin 269, Kurstacin

287, Kenyacin 404, Entomocin 420, and Tolworthcin 524 have a broad effect against foodborne pathogenic bacteria, such as *B. cereus*, *Listeria innocua*, *L. monocytogenes*, *V. cholerae*, *Staphylococcus aureus*, *Staphylococcus xylosus*, *Shigella flexneri*, *Salmonella* spp., *Streptococcus pyogenes*, and *E. coli*, and other human pathogens, including *Klebsiella pneumoniae*, *Proteus vulgaris*, *Enterobacter cloacae*, and *Enterococcus faecium* (Barboza-Corona et al. 2007, 2009; de la Fuente-Salcido et al. 2008, 2013).

Bt bacteriocins also have the potential to be used in apiculture industry. Entomocin 110 is active against *Peanibacillus larvae*, the causal agent of foulbrood disease in honeybee larvae (*A. mellifera*) and other *Apis* spp. (pollinators insect), and therefore could be used as a natural and environmentally safe alternative to antibiotics, such as oxytetracycline, to control *P. larvae* (Cherif et al. 2008; de la Fuente-Salcido et al. 2013).

Bt as a source for biosynthesis of metal nanoparticles

Metal nanoparticles (NPs), due to their advanced physicochemical properties and their wide applications in different industries, have attracted attention. Various biological systems, such as bacteria, fungi, plant extracts, and other biological-based products, have been used for the green synthesis of different metal NPs (Juibari et al. 2011, 2015; Okafor et al. 2013). The synthesized NPs using microbes show significant advantages, like being clean, non-toxic, and eco-friendly, and it is also possible at ambient temperature and pressure. Consequently, several bacterial and fungal strains have been used to produce NPs (Das et al. 2014a,b; Nayak et al. 2016).

Some recent studies have proved the ability of *Bt* strains to produce metal NPs, such as silver (Banu et al. 2014; Jain et al. 2010; Nayak et al. 2016) and cobalt (Marimuthu et al. 2013). Jain et al. (2010) for the first time reported the high efficient silver NP green synthesis using the spore-crystal mixture of *Bt*. The average particle size was about 15 nm with mixed (cubic and hexagonal) structure. The AgNPs were found to be highly toxic to different multi-drug-resistant human pathogenic bacteria, including *E. coli*, *P. aeroginosa*, and *S. aureus*. It has been previously confirmed that some bacteria contain reducing enzymes which involve in reduction of metal ions to nanoparticles. Therefore, it may have concluded that some *Bt* strains contain reducing enzymes for NP biosynthesis. Marimuthu et al. (2013) have reported cobalt nanoparticle biosynthesis (Co-NPs) using a *Bt* strain and confirmed that Co-NPs have high larvicidal activities against malaria vector, *Anopheles subpictus*, and dengue vector, *Aedes aegypti* (Diptera: Culicidae), with LC_{50} values of 3.59 and 2.87 mg/l, respectively. In another study, Banu et al. (2014) confirmed the larvicidal activity of silver nanoparticles (AgNPs) synthesized by *Bt* against *A. aegypti* (LC_{50} 0.10 ppm and LC_{90} 0.39 ppm). Moreover, recently, the protocol to fabricate and purify silver NPs in stable form during *Bt* cell growth was optimized (Nayak et al. 2016).

As the biosynthesis of nanoparticles using microorganisms and plant extracts is costlier than that of mechanical or chemical synthesis, efforts for designing cost-effective process for biosynthesis of NPs will be continued.

Bt as the agent for bioremediation of heavy metals and pollutions

Heavy metals, pesticides, herbicides, and petroleum derivate are known as the principal source of environmental and human health concerns nowadays. These compounds can accumulate readily in the food chain and, consequently, cause hazards to the higher trophic levels (Chen et al. 2015a,b,c; Dash et al. 2014; Huang et al. 2014a,b; Thamer et al. 2013). Some *Bt* strains efficiently degrade some toxic pollutants. These strains can accumulate, degrade, or mineralize toxic heavy metals. Previously, *Bt*-based bioremediation of arsenic, cadmium, lead, copper, nickel, zinc, chromium, mercury, and uranium has been reported (Table 4). Moreover, some *Bt* strains can degrade persistent pesticides and herbicides, such as phenanthrene, imidacloprid (Ferreira et al. 2016), fipronil (Mandal et al. 2013), chlorpyrifos (Aceves-Diez et al. 2015; Wu et al. 2015), cyhalothrin, phenoxybenzoic acid (Chen et al. 2015a), triphenyltin (an organotin herbicide), diphenyltin, and monophenyltin (Huang et al. 2014a). Also, *Bt*-based efficient degradation of petroleum pollutions (diesel fuel and crude oil), polycyclic aromatic hydrocarbons (fluoranthene and pyrene (Kebria et al. 2009; Maiti et al. 2012; Thamer et al. 2013)), dyes (methylene blue (El-Sersy 2007) and acid red 119 (Dave and Dave 2009)), organic wastes (distillery effluent (Kumar and Chandra 2004), malachite green (Olukanni et al. 2013), and melanoidins (Kumar and Chandra 2006)), and also plasticizer materials (dimethyl phthalate (Brar et al. 2009; Surhio et al. 2014)) has been reported (Table 4). Accordingly, these findings confirm that *Bt* strains will find a significant place in bioremediation projects in the future. However, there is no *Bt*-based commercial product for bioremediation purposes, and therefore, it is neccessary to perfom more research and development projects to open way for commercialization of these products.

Anticancer characteristics of *Bt*

Cry toxins are primarily known as a family of insecticidal toxins produced by *Bt*. However, some *Bt* Cry proteins, such as Cry31A, Cry41A, Cry45A, Cry46A, Cry63A, and Cry64A, called as parasporins (PSs), do not show any insecticidal and hemolytic activity, nevertheless, have strong

Table 4 Ability of *Bt* strains to be used as source of bioremediation of different environmental pollutant materials

Bioremediation activity	Specific activity	Strain	Degradation efficiency	Reference(s)
Heavy metals	Mercury(II), copper, and chromium	*Bt* var. *thuringiensis*, serotype 1	42.7, 18.7, and 8.9% of metals, respectively	Hassen et al. (1998)
	Mercury	*Bt* strain PW05	70–95%	Dash et al. (2014)
	Zinc and lead	*Bt* strain Simi	54% after 4 days	Kumar et al. (2015)
	Cadmium, lead, and copper	*Bt* strain L14	76, 80, and 21%, respectively	Guo et al. (2010)
	Cadmium, chromium, copper, lead, and nickel	*Bt* strain OSM29	Ni (94%), Cu (91.8%), and Cd (87%) of 25 mg/l	Khan and Zaidi (2013)
	Arsenic, copper, lead, nickel, and zinc	*Bt* strain GDB-1	8–77%	Babu et al. (2013)
	Uranium(VI)	*Bt* strain BRC-ZYR3	400 mg U/g biomass (dry weight)	Pan et al. (2015)
	Chromium	*Bt* strain Cr-S1	87.04% within 24 h	Jahan et al. (2016)
	Lead(II)	*Bt* strain 016	Biosorption 164.77 mg/g	Chen et al. (2015a,b,c)
	Nickel	*Bt* strain KUNi1	82% of 2 mM Ni	Das et al. (2014a,b)
	Chromium (Cr)	*Bt* strain BRC-ZYR2	25–75 mg/l after 24	Huang et al. (2014a,b)
Pesticides and herbicides	Phenanthrene and imidacloprid	*Bt* from marine sediment	–	Ferreira et al. (2016)
	Fipronil	*Bt* strain from sugarcane fields	100% after 42 days	Mandal et al. (2013)
	Chlorpyrifos	*Bt* strain *Bts*	More than 83% degradation	Aceves-Diez et al. (2015)
	Cyhalothrin and 3-phenoxybenzoic acid	*Bt* strain ZS-19	100% of 100 μg/ml and 80% of 800 μg/ml within 72 h	Chen et al. (2015a)
	Chlorpyrifos	*Bt* strain BRC-HZM2	88.9% after 48 h	Wu et al. (2015)
	Triphenyltin	*Bt* from contaminated sediments	70–80%	Huang et al. (2014a,b)
Oil pollutions and plasticizers	Diesel fuel	*Bt* strain R	85.20% of diesel fuel	Kebria et al. (2009)
	Light crude oil	*Bt* strain	Up to 80%	Thamer et al. (2013)
	PAH (fluoranthene and pyrene)	*Bt* strain NA2	Up to 70%	Maiti et al. (2012)
	Dimethyl phthalate (DMP)	*Bt* from cotton field soil	99% of 400 mg/l of DMP	Surhio et al. (2014)
	Dimethyl phthalate	*Bt* var. *kurstaki*	97–99% of 500 mg/l DMP	Brar et al. (2009)
Dyes	Acid red 119 and actual azo	*Bt* strain *SRDD*	50–70% decolorization	Dave and Dave (2009)
	Methylene blue	*Bt* strain 4G1	98%	El-Sersy (2007)
	Malachite green	*Bt* strain RUN1	85%	Olukanni et al. (2013)
	Ethidium bromide	*Bt* strain PSU9	Large portion of EtR was degraded	Sukhumungoon et al. (2013)
Organic wastes	Chicken feather waste (keratin)	*Bt israelensis* H14 (IPS-82)	100% of 5 g/l keratin	Poopathi and Abidha (2008)
	Distillery effluent	MTCC 4714	40–50%	Kumar and Chandra (2004)
	Synthetic molasses melanoidins	MTCC 4714	6–50%	Kumar and Chandra (2006)

cytocidal activity against human cancer cells (without affecting normal ones) when digested with proteases (Ammons et al. 2016; Ohba et al. 2009). The Committee of Parasporin Classification and Nomenclature have registered 19 different parasporins, which are grouped in six subclasses (PS1, PS2, PS3, PS4, PS5, and PS6) according to their amino acid sequence homology (Ammons et al. 2016; Ohba et al. (2009); Okumura et al. 2011). Anticancer activities of the parasporins have been confirmed against different cancer cells, such as human cervical cancer cells (HeLa (Brasseur et al. 2015; Katayama et al. 2005; Krishnan et al. 2010; Mizuki et al. 1999) and SiHa (Periyasamy et al. 2016)), murine lymphoma L5178YR cell line (Franco-Molina et al. 2016), human leukemia T cells (MOLT-4 (Hayakawa et al. 2007; Katayama et al. 2005; Mizuki et al. 1999; Okumura et al. 2005)), CEM-SS (Krishnan et al. 2010), human uterus endometrium adenocarcinoma cell lines Hec-1A and KLE (Brasseur et al. 2015), myeloid leukemia cells (HL60) and liver (hepatocyte) cancer

cell (HepG2 (Brasseur et al. 2015; Katayama et al. 2005; Okumura et al. 2005; Yamashita et al. 2005)), human epithelial colorectal adenocarcinoma cell line (CACO-2 (Brasseur et al. 2015; Okumura et al. 2005), endometrial adenocarcinoma (Sawano (Okumura et al. 2005)), adherent human colon cancer cells (HT-29 (Krishnan et al. 2010), HCT-250 (Okumura et al. 2005; Poornima et al. 2010), HCT 116 and SW620 (Periyasamy et al. 2016)), human prostate cancer cell line (PC-3 (Brasseur et al. 2015; Hayakawa et al. 2007)), human histiocytic lymphoma (U-937 (Okumura et al. 2005; Poornima et al. 2010)), and human breast cancer cell lines (MCF-7 and MDA-MB231 (Brasseur et al. 2015) and Jurkat cells (Hayakawa et al. 2007)).

Recently, the significant increase in the incidence of cancer and the limitations of the existing treatment methods have pushed scientists to perform intensive research projects to find new efficient therapeutic agents. Since parasporins are known as potential candidates for targeted anticancer therapy, characterization of their mode of action, which is probably through receptor mediation, is of importance (Periyasamy et al. 2016; Poornima et al. 2010). The known parasporins exhibit a different mode of action against various cancer cell lines (Ekino et al. 2014; Mizuki et al. 1999; Periyasamy et al. 2016; Yamashita et al. 2005). PS-1 induces cancer cell death by activating signals of apoptosis and increasing Ca^{2+} concentration. The beclin-1 in the HeLa cell line acts as the receptor of PS-1 (Katayama et al. 2005). PS-2 is a pore-forming toxin and serves as a cytolysin through targeting on the cancer cell plasma membrane. The structure and function of this parasporin are similar to insecticidal Cry proteins and therefore requires glycosylphosphatidylinositol-anchored proteins for its oligomerization and pore formation on cancer cells (Aldeewan et al. 2014). PS-3 and PS-6 have similar three-domain structure to insecticidal Cry toxins. They may also act as a pore-forming toxin, which affects the cancer cell plasma membrane (Aldeewan et al. 2014; Yamashita et al. 2005). PS4 kills cancer cells through non-specifically binding to the plasma membrane and forming oligomeric complexes in the target cell membranes (Aldeewan et al. 2014; Okumura et al. 2011). At the present time, there is no *Bt*-based pharmaceuticals as anticancer bioproducts in the market, but by exploring the details of *Bt*-parasporin mechanisms of action against different cancers, these proteins may practically be used in the future as the anticancer pharmaceuticals.

Future considerations

Bt has been used for decades as the most successful microbial insecticide in agriculture and medicine sectors, and it is expected that this advancing trend will be well continued in the future. During the last two decades, *Bt* recombinant toxin genes have been widely used to enhance resistance to insect pests in crops. Currently, the share of *Bt* crops, containing one or more different *cry* genes for resistance to lepidopteran and/or coleopteran pests, is a striking part of the global acreage of all transgenic crops, and this adoption trend expected to be increased in the future. One of the promising strategies is pyramiding of *Bt* toxin genes in *Bt* wild-type strains or GM plants to expand their pest control efficacy and range and also to delay pest resistance to bioinsecticide or *Bt* transgenic crops. Besides its broad application as insecticide and gene source for genetic engineering, over the past several years, different studies have confirmed new characteristics which make *Bt* as a suitable candidate for applications in other avenues. These potential applications of *Bt* include biocontrol of plant nematodes and mites, antagonistic effects against plant and animal pathogenic bacteria and fungi, plant growth-promoting activities, bioremediation of different pollutants, biosynthesis of different nanoparticles, and anticancer activities. Among these characteristics, one promising field is the potential for *Bt* proteins to act against cancer cells due to the production of parasporins, toxins that have a cytotoxic effect on the cells changed by some cancers. However, except for application of *Bt* as biopesticide and as source of genes for plant genetic engineering, it has not been commercially used for other mentioned applications, such as bioremediation, biocontrol of plant pathogens, NP biosynthesis, or control of cancer yet.

Knowledge about genome structure, toxin genes, mode of action, and different features of *Bt* has critically advanced during the last decades. Nevertheless, detailed understandings of biochemical and physiological pathways and mode of action of *Bt* especially in the field of novel characterized features have been limited due to lack of functional genomics, proteomics, and metabolomic information. Recent advances in next-generation sequencing, genomics, transcriptomics, proteomics, metabolomics, and genetic engineering technologies profoundly open insights into *Bt* biochemical and physiological pathways at the molecular level, genome structure and function, and their novel characteristics. Such innovations will undoubtedly lead to explore novel *Bt* strains with more potent insecticide activities or novel features which will enhance the implementation of these strains in other medical, agronomical, and industrial avenues. The most promising area of investigation on *Bt* will be the discovery, identification, and validation of novel molecular targets, such as Cry, Cyt, and Vip proteins, cell wall-degrading enzymes, plant growth-promoting compounds, and parasporins to develop new efficient insecticides, nematicides, bactericides, fungicides, biofertilizers, and anticancer pharmaceuticals.

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Compliance with ethical standards

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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