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REVIEW

Bacilli as sources of agrobiotechnology: recent advances and future directions

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ABSTRACT

The group bacilli represent the Gram-positive ubiquitous spore-forming bacteria. Their diversity, versatility and the ability of producing diverse secondary metabolites including enzymes created enormous potential for applications in agriculture, biotechnology, environment and medicine. The bacilli are considered as one of the most studied groups of bacteria providing plant growth-promotion and biocontrol of multiple diseases reflecting their vital role in enhancing plants' tolerance to biotic and abiotic stresses. Some of the *Bacillus* species are available commercially as phytostimulants, biopesticides, and biofertilizers. Genetically engineered plants such as maize, cotton, brinjal with endotoxins producing genes from *Bacillus thuringiensis* (Bt) has revolutionized agriculture. Many of these applications have been widely adopted in various fields as viable and environmentally friendly alternatives of synthetic chemical fertilizers and pesticides. A better understanding of the biology, ecology, and mechanisms of action of the beneficial strains of bacilli are needed for the development of products to support green biotechnology in agriculture and industries. This report comprehensively reviewed the applications of bacilli in agriculture and industry and discussed their potentials for the development of new products of biotechnological implications.

- The *Bacilli* are considered as one of the most studied groups of plant growth-promoting and biocontrol bacteria that promote plants' tolerance to biotic and abiotic stresses.

- Genetically engineered plants such as maize, cotton and brinjal with endotoxins producing genes from *Bacillus thuringiensis* [Bt] has revolutionized agriculture.

- Better understanding of the biology, ecology, and mechanisms of action of the beneficial strains of *Bacilli* are needed for the development of commercially available products to support green biotechnology in agriculture and other industries.

- This report comprehensively reviewed the applications of *Bacilli* in agriculture and industry, and discussed their potentials for the development of new green biotechnologies.

1. Introduction

Bacillus species are widely distributed in a wide range of environmental (including extreme) conditions such as water, dead insects, plants, soil, marine environment, the gut of animals and food samples (1, 2). They are aerobic endospore-forming bacteria that can survive in the harshest climatic and edaphic conditions. Members of the genus *Bacillus* produce a vast array of bioactive metabolites that have potential applications in agriculture, fisheries, medical, and veterinary sciences (3–5). In addition, Bacillus-produced enzymes, antibiotics and other metabolites have been utilized in medical, agricultural and pharmaceutical industires (5). Mass production

of metabolites such as cyclicpeptides (6), polyketides (7), and bacteriocin (8) by the species of *Bacillus* is an attractive area of research with enormous potential of commercialization (4). One of the promising applications of bacilli in agricultural sector is their use as a biological control agent of biotic diseases (9, 10). *Bacillus* alone is estimated to account for half of the commercially available bacteria-based biological control agents. They belong to one of the most studied microorganisms that have been used as antagonists of phytopathogenic bacteria, fungi, oomycetes, nematodes, and insects (10, 11). Currently, there is an urgent need for intensifying agricultural production to keep pace with the rapid

increase of global population. This elevated production target compelled agricultural community to use synthetic products such as fertlizers and pesticices making the whole agro-ecosystem more unsustainable than ever. Therefore, there are growing appeals for the use of environmentally safe and sustainable pest control agents such as *Bacillus* spp. to support 'Zero hunger' the second most important sustainable development goal (SDG) set by the UNO. In this regard, several strains of the genus *Bacillus* have demonstrated the potential to be used as plant growth-promoting bacteria (PGPB) and proved to have antagonistic activities against several phytopathogenic microorganisms (12).

According to estimates of the Food and Agriculture Organization (FAO), the world population would reach 9.7 billion by the year 2050 (13). This necessitates substantial increase in agricultural production to feed a population of such magnitude. Besides, climate change is also posing a challenge to worldwide crop production. Much of the arable land may no longer be usable due to increase in salinity, drought or pest attack. These problems can't be solved by the use of chemicals. Therefore, there is an urgent need to look for a sustainable way to maximize agricultural production. In this regard, the role of *Bacillus* species in controlling plant pathogens, enhancing their tolerance to various biotic and abiotic stresses thereby increasing production would be an exciting area of research. T he discovery of the elite strains of *Bacillus* spp. has high potentials for commercialization and management of abiotic and biotic stresses to improve crop production. Recent advances in genomics and postgenomics analyses have shed light on the molecular mechanisms of biocontrol of plant diseases by the *Bacillus* species (14, 140). Insecticidal toxins produced in commercially available transgenic plants is originated from the soil bacterium *Bacillus thuringiensis* (Bt). Although Bt strains show differing specificities of insecticidal activity toward pests, they constitute a large reservoir of genes encoding insecticidal proteins, which are accumulated in the crystalline inclusion bodies produced by the bacterium on sporulation (Cry proteins, Cyt proteins) or expressed during bacterial growth (Vip proteins)(15). Development of insect-resistant crops is one of the major successes of plant genetic engineering technology by inserting *B. thuringiensis* genes in many agriculturally important crops. Some of the success stories of Bt technology include cotton (*Gossypium hirsutum*) resistant to lepidopteran larvae (caterpillars) and maize (*Zea mays*) resistant to both lepidopteran and coleopteran larvae (rootworms) that have been widely used in global agriculture resulting in reductions in pesticide usage and lower production costs (16, 17). A recently introduced Bt-brinjal in Bangladesh dramatically

reduced synthetic pesticide application and increased farmers' income (18). However, the use of Bt GM crops comes with various challenges that are to be addressed. Some insects have developed resistance to Bt GM crops creating new economic or agronomic challenges. Additional scientific efforts were made to stack Bt genes in certain crops or new agronomic practices were introduced to prevent insects from developing resistance. For example, farmers need to plant a certain amount of conventional plants alongside Bt plants in 'refuge' areas. Several reviews have been published on bioactive compounds from terrestrial and marine bacilli, their biosynthetic pathways and engineering plants using Bt genes (4, 14, 15, 19–24). However, there is no comprehensive review published on baccili as source of agrobiotechnology. This comprehensive review updates our understanding of the applications of bacilli in agriculture and industry, and discusses their promise for the development of new agrobiotechnology.

2. *Bacillus* spp. as biocontrol agents

2.1. Bacillus *spp. as antagonists of phytopathogens*

Phytopathogens pose a great challenge to world food security (25, 11, 10). They diminish the annual yield by a significant amount that could otherwise feed millions of people (25). Thus, they cause huge economic losses to both developing and developed economies. Various studies have established the potential use of *Bacillus* spp. in controlling plant pathogens (26, 27). Antagonistic activities of these bacilli take place primarily through the production and secretion of various bioactive secondary metabolites (11, 14, 28–32) and lytic enzymes (33–36). Verschuere et al. (37) argued that among bacteria-based antagonists, *B. subtilis* is one of the most studied and used bacteria with a wide range of activities against phytopathogens. On the other hand, *B. thuringiensis* (Bt) accounts for over 90% of all marketed biological control agents with millions of dollars of annual sales.

The emergence of fungal diseases in plants increased remarkably in the last few decades, and they are posing a serious threat to future food and nutritional security (11, 38). From many years of research, a large body of literature is now available on the biological activities of the bacilli against fungal and other phytopathogens. A strain of *B. subtilis* has shown more than 80% suppression of *Rhizoctonia solani,* the causative agent of damping-off of tomato seedlings (39). In a similar study, Ji et al. (40) isolated a strain of *B. amyloliquefaciens* from the

Republic of Korea and tested the strain against various fungal plant diseases. It displayed activities both in laboratory and greenhouse settings against cucumber scleotiorum rot. It also showed antagonistic activity in laboratory setting against tomato gray mold and powdery mildew disease in cucumber. Similarly, a strain *B. velezensis* isolated by Toral et al. (41) demonstrated the potential for protecting tomatoes, grapes, and strawberries from various phytopathogens including *B. cinerea*. The strain produces various lipopeptides with activities against *B. cinerea* and has the potential to trigger an antioxidant activity in fruit. Novel linear lipopeptides produced by a marine *B. subtilis* strain 109GGC020 significantly suppressed oomycete phytopathogens (42).

The filamentous fungus, *Fusarium graminearum* causes *Fusarium* head blight (FHB) on wheat and barley leading to massive economic loss to the growers (43). It is also known to cause seedling blight on maize. Gu et al. (44) investigated a strain of *B. amyloliquefaciens*'s potential to suppress *F. graminearum*. Results from their study showed that the strain produces bacillomycin D, which causes morphological changes in the plasma membrane and cell wall of *F. graminearum*, induces accumulation of reactive oxygen species, and ultimately causes cell death in the pathogen. Araujo et al. (45) isolated strains of *Bacillus* from soil samples of Paraná State, Brazil, to investigate their potential as biological control agents of soybean seed pathogens. They identified strains of *B*. subtilis with promising antagonistic activities against several fungal phytopathogens, e.g. *R. solani, Colletotrichum truncatum, Sclerotinia sclerotiorum, Macrophomina phaseolina,* and *Phomopsis* spp. On the other hand, Zalila-Kolsi et al. (46) have shown that co-application of *B. amyloliquefaciens*, *B. subtilis*, and *P. polymyxa* bacterial cells led to the highest protection against several phytopathogenic fungi *in vivo* in wheat. *B. subtilis* Ch-13, an industrial strain was shown to have a wide spectrum of antagonistic activities against phythopathogens. It produces various metabolites with the potentials to protect plants against fungal pathogens and promote their growth (47).

2.2. Biocontrol of plant diseases

The term biological control was first used a century ago to describe the introduction of exotic species to suppress pests. However, its application is much older than the term itself (48). While the use of chemical-based pesticides increased agricultural productivity, their lasting consequence on the environment urges the use of safe and effective alternatives. In this regard,

the use of a biological control agent is an increasingly successful and widespread strategy to decrease plant pathogens and the negative effects of agricultural practices on the environment. Likewise, biological control of phytopthogens has received considerable attention and involves the use of bacteria or fungi with antagonistic activities against plant pathogens (49, 50). A large body of literature suggests that elite strains of bacilli protect plants from the phytopathogens (Table 1). Some of the strains alone or in the consortium have been commercialized as biocontrol and/or phytostimulants. Application of *B. amyloliquefaciens* together with commercial fungicides significantly reduces branch canker disease in tea plants under field conditions (51). In a related study, the use of *B. amyloliquefaciens* together with other microorganisms has been shown to improve the strain's biocontrol potential (52).

While biological control is often seen as the safest, most environment-friendly, and cost-effective method, there are challenges related to its application from a practical point of view. Waage et al. (48) argued that the primary challenge with the use of biological control comes from conflicts of interest with the conservation of native species. Lack of consistent efficacy under different environmental conditions and longer registration time are also some of the hindrances that limit the use of *Bacillus* as biological control of plant pests (53).

One important mechanism by which *Bacilli* may inhibit fungal pathogens that cause diseases in plants is through enhancing the host plant defence mechanisms by stimulating their immune systems. Surfactants are among the molecules that induce significant protective effects against diseases caused by fungal pathogens (54). This has been demonstrated in maize through the treatment of the roots with a suspension of *B. subtilis* strain capable of inducing defence genes (55).

A substantial amount of literature is available on the mechanisms of bacilli biocontrol. Genomics and postgenomics study also elucidated the mechanisms in biocontrol of phytopathogens (19). Inhibition of hyphal growth, induction of cell death, competition for space and nutrients, direct effects on mycotoxin biosynthesis and stability, and promotion of host immunity are some of the modes of actions of the *Bacillus* antagonists (59, 87). While biological control has several merits over chemical fungicides, there are also disadvantages if not applied properly. The misuse of biocontrol in terms of dose and frequency, for example, should be avoided.

2.3. Bacillus *as insecticides*

While plants and insects have coexisted for millions of years, their relationship is not confined to mutual

Table 1. Biocontrol of plant pathogens by *Bacillus* spp.

Bacillus species with strain	Targeted phytopathogen	Controlled plant disease	References
B. amyloliquefaciens NJN-6	*Fusarium oxysporum*	Fusarium wilt	(56)
	Clavibacter michiganensis	Stem canker and leaf wilt	(57)
B. cereus IB311	*Pseudomonas syringae*	Kiwifruit canker	(58)
B. cereus AR156	*Agrobacterium tumefaciens*	Crown gall	
B. firmus DS-1	*Ralstonia solanacearum*	Bacterial wilt	(59)
	Meloidogyne incognita	Root-knot nematode	(60)
B. halotolerans	*Fusarium oxysporum*	Fusarium wilt	(61)
B. subtilis B-1323	*Phaeoacremonium aleophilum*		(62)
	Botrytis cinerea	Gray mold	
	Rhizoctonia solani	Damping off, stem lesions, stem rot, root rot, crown rot, and aerial web blighting	(63)
	Colletotrichum gloeosporioides	Anthracnose	
	Phytophthora capsici	Stem and fruit rot	
B. licheniformis BC98	*Magnaporthe grisea*	Rice seedling blight	(64)
B. licheniformis MH48	*Botrytis cinerea*	Gray mold	(65)
	Pestalotiopsis karstenii	Smut	
	Pestalotia diospyri	Leaf spot	
	Glomerella cingulata	Bitter rot of fruits	
B. licheniformis MH48	*Botrytis cinerea*	Gray mold of tomato caused	(66, 67)
B. methylotrophicus N1	*Fusarium moniliforme*	Seedling blight of corn	(68)
	Aspergillus awamori	Black mold	
	Penicillium sp.	Mold	
	Aspergillus niger	Black mold	
B. pumilus	*Fusarium oxysporum*	Fusarium wilt	(69)
B. pumilus HN-10	*Trichothecium roseum*	Fruit rot of tomato, orange, and apple	(70)
B. pumilus AR03	*Altenaria alternata*	Leaf spot	(71)
B. pumilus AR03	*Erysiphe cichoracearum*	Powdery mildew	(71)
B. subtilis 30B-B6	*Phytophthora infestans*	Late blight	(72)
B. pumilus SS-10.7 and *B. amyloliquefaciens* (SS-12.6 and SS-38.4)	*Pseudomonas syringae*	Blossom blast and spur dieback	(73)
B. subtilis 30VD-1	*F. oxysporum*	Fusarium wilt	(74, 75)
B. subtilis SPB1	*F. solani*	Root rot	(76)
B. subtilis strain 168	*Zymoseptoria tritici*	Wheat leaf blotch	(77)
B. velezensis B. velezensis A2	*F. oxysporum*	Root rot	(78, 79)
B. velezensis XT1 CECT 8661	*Botrytis cinerea*	Gray mold	(41)
	Clavibacter michiganensis	Potato	(80)
	Ralstonia solanacearum	Bacterial Wilt	
	Xanthomonas campestris	Black rot	
	Xanthomonas euvesicatoria	Bacterial spot	
	Alternaria solani,	Early blight of tomato and potato	
	Cochliobolus carbonum,	Northern leaf spot and ear rot	
	Fusarium oxysporum	Vascular wilt	
	Fusarium solani	Soft rot	
	Gibberella pulicaris	Potatoe dry rot	
	Gibberella zeae	Fusarium head blight	
	Monilinia fructicola	Brown rot	
	Pyrenochaeta terrestris	Pink-root	
	Rhizoctonia solani	Damping-off	
B. velezensis NRRL B-23189	*Penicillium roqueforti*		(81, 82)
	F. graminearum	Fusarium head blight	
B. mojavensis A21	*Ralstonia solanacearum*	Moko disease of banana and brown rot of potato	(83)
	Fusarium oxysporum	Fusarium wilt	
Lacto Bacillus plantarum CC100	*Pseudomonas syringae* pv. actinidiae;	Bacterial canker of kiwifruit	(84)
	Xanthomonas arboricola pv. Pruni	Bacterial spot of stone fruits	
	Xanthomonas fragariae	Leaf spot of strawberry	
Paenibacillus polymyxa NSY50	*F. oxysporum*	Fusarium wilt	(85, 86)

benefits such as pollination but also involves insect predation of plants. Therefore, insect pests are one of the challenges plants face in the environment. Farmers lose a sizeable amount of agricultural production due to various insect pests every year (88). Moreover, the rapid increase of the world population intensified the use of synthetic insecticides that has enabled doubling of worldwide grain production in the last century (89).

However, this progress came with undesirable environmental and ecological impacts. Therefore, there is a growing appeal for alternatives with natural and non-synthetic molecules (90). In this regard, *Bacillus*-based pest control has attracted much attention and has been a subject of increased investigation for last couple of decades. Strains of *B. thuringiensis* are arguably the most used species as biological control of insect

Table 2. Insecticidal proteins/toxins produced by the starins of *Bacillus thuringiensis*.

Strain	Targeted insect/worm	Insectididal proteins	References
B. thuringiensis strain AB1	*Plutella xylostella*	Cry toxins	(93)
B. thuringiensis var. *israelensis*	*Anopheles gambiae*	Cry toxins	(94)
B. thuringiensis israelensis (Bti)	*Aedes aegypti*	ATP-binding proteins (ABP)	(95)
B. sthuringiensis Vip1	*Holotrichia parallela* larvae	Vegetative insecticidal proteins	(96)
*B. thuringiensis*various	Caterpillars	Cry 1 C insecticidal protein	(51)
	Spodoptera frugiperda	Cry1Da_7 and Cry1B.868 proteins	(97)
	Spodoptera eridania	Vegetative insecticidal proteins (Vips) Vip3Ab1-740	(98)
	Spodoptera frugiperda,	Vegetative insecticidal proteins (Vips) Vip3Ab1-740	(98)
	Helicoverpa zea	Vegetative insecticidal proteins (Vips) Vip3Ab1-740	(98)
	Pseudoplusia includens	Vegetative insecticidal proteins (Vips) Vip3Ab1-740	(98)
	Anticarsia gemmatalis	Bt toxins	(99)
	Leucinodes orbonalis	Cry1Ac (EE-)	(18)

pests as they produce various metabolites that possess wide-spectrum insecticidal properties (91).

Moreover, advances in genetic engineering techniques have enabled the production of transgenic pest-resistant crops by using the genes discovered in *B. thuringiensis* (92). Maize, potato, brinjal, and cotton were engineered for the expression of the entomocidalδ-endotoxins from various strains of *B. thuringiensis* (Table 2). These toxins have provided efficient suppression of lepidopteran and coleopteran insects, and remarkably increased yield and reduced the application of insecticides (15, 18). The worldwide application of Bt technologies remarkably reduced the application of hazardous chemical insecticides and increased the yield and income of the farmers. Increased yield alone, however, can not offset costs associated with genetically engineered seeds and, therefore, requires other considerations such as environmental stewardship and sustainability factored in.

Transgenic Bt-crops expressing *cry* genes from *B. thuringiensis* are protected against not only insect pests but also pathogenic microbes vectored by those insects. Bt-corn, although not very effective in aflatoxin mitigation, has been shown to reduce fumonisins (FUMs) and deoxynivalenol contamination (100). *Aspergillus flavus* and *A. parasiticus* invade the seed through silk and are vectored mainly by insects that are not controlled by Bt-corn (101). Lower mycotoxin levels in Bt-corn have been shown from the feeding damage caused by the European corn borer but not the corn earworm. *B. thuringiensis* may have additional biocontrol effects. For example, seed treatment with a chitinase from *B. thuringiensis*-controlled *Fusarium* infection in soybean (102). Brown plant hopper (BPH; *Nilaparvata lugens* Stål) is one of the most destructive insect pests, which reduce rice yield remarkably in many rice-growing areas. Based on a high-throughput transcriptome analysis, Rashid et al. (103) demonstrated that systemic resistance induced by *B. velezensis* YC7010 against BPH is linked with activation of salicylic acid (SA) – and jasmonic acid (JA)-dependent pathways

in rice. Furthermore, the authors confirmed that bacterial metabolites, bacillopeptin A, B and X were found to be involved in the induction of systemic resistance in rice (103).

2.4. Reduction of mycotoxin in agricultural produce

Mycotoxins are toxic secondary metabolites produced by various filamentous fungi. They have medical and veterinary importance. The toxins consist of low molecular weight fungal metabolites. Fungi of the genera *Aspergillus*, *Fusarium*, and *Penicillium* are responsible for the production of most mycotoxins reported (104). Bennett (105) describes mycotoxins as natural products that trigger a toxic response in animals, plants, and microorganisms. At present, hundreds of them have been identified and investigated from various fungal species. One of the highly toxic groups of mycotoxins is aflatoxins, which are produced by *Aspergillus* spp. The *Aspergillus* infects wheat, walnut, corn, cotton, peanuts, and tree nuts. Consumption of aflatoxin-contaminated food for a while leads to health complications. Liver cancer, a decline in the immune system, malnutrition, and retarded child growth are some of the health impacts caused by aflatoxin consumptions (106). Acute toxicity can lead to liver failure and subsequent death associated with the ingestion of higher amounts of aflatoxin through contaminated foods (107, 108). Other groups of mycotoxins such as ochratoxins, fumonisins, deoxynivalenol, patulin, zearalenone (ZEA), and trichothecenes have also been associated with acute or chronic toxicity. Moreover, they are ubiquitous and pose a significant threat to human and animal health (109). Ringot et al. (110) argued that ochratoxin A (OTA) as one of the most harmful metabolites produced by toxigenic fungi has the potential to contaminate products such as cereals, figs, grapes, spices, coffee beans, cocoa beans, pork meat and dried vine fruits. According to Peraica et al. (111) mycotoxicosis has been a threat for millennia basically from the consumption of contaminated food.

Few examples, 'St. Anthony's fire' caused by toxins from the ergot fungus, *Claviceps purpurea*, the 1891 cardiac beriberi in Japan, and alimentary toxic aleukia (characterized by nausea, vomiting, diarrhea, leukopenia, hemorrhaging, skin inflammation, and sometimes death) was another example of mycotoxicosis outbreak that occurred during the World War II in Russia and associated with the *Fusarium* toxin T-2. In addition to the health impact of mycotoxins on humans and animals, they account for a loss of about a quarter of global crop productions leading to the loss of billions of dollars.

While preventing contamination of crops from mycotoxin producing strains is one of the best approaches to curb their effects on humans and animals' health, degrading the toxins to their harmless state is also a potential method of controlling the damage they cause. While approaches such as the use of chemicals and physical techniques to degrade mycotoxins have been widely described, they are indicated to be unsafe and usually impractical. Hence, one of the methods to mitigate mycotoxin contamination is through biological detoxification in which the toxins are degraded into lesser or nontoxic metabolites (112–116). The application of bacilli as agents of biocontrol of mycotoxin producing fungi is a promising approach for solving this critical problem. A report by Fu et al. (117) showed that a strain of *B. licheniformis* degrades zearalenone in feed and reduces its toxicity in piglets. Similarly, fengycin producing *B. amyloliquefaciens* FZB42 controls *Fusarium graminearum* and significantly reduces mycotoxins such as deoxynivalenol (DON), 3-acetyldeoxinivalenol (3-ADON), 15-acetoxydeoxinivalenol (15-ADON) and zearalenone (ZEN) (125). Biocontrol of mycotoxins in the agricultural produce by the application of *Bacillus* spp. has been reviewed (118). Moreover, these approaches have received increased attention as they are safe and effective than the use of chemicals for mycotoxin contamination control (110).

2.5. Mechanisms of biocontrol

The members of the genus *Bacillus* use various mechanisms to suppress phytopathogens. Competing with the pathogen for resources, secretion of secondary metabolites that inhibit the growth of pathogens, and stimulation of the systemic resistance in the host plants are some of the reported mechanisms of biocontrol of plant pests by the bacilli (10).

2.5.1. Antibiosis

Antibiosis as a mechanism of biocontrol of plant pathogens by the *Bacillus* spp. has extensively been explored. A study published in weekly Nature in 1948 documented the isolation of an antibiotic subtilin from a freeze-dried *B. subtils* culture (119). *Bacillus* species have also been hailed as sources of antifungal compounds that have effectively suppressed various pathogens. Table 3 and Figure 1 presents some major antibiotics produced by various strains of *Bacillus* species. Cyclic lipopeptides (CLPs) from *Bacillus* have received much attention in recent years as potential class of antifungal compounds (4). They are rings of amino acids with fatty acid side chains and exhibit remarkable heterogeneity. These structural diversities endowed CLPs with a broad-spectrum and environmentally-stable antimicrobial (120). While CLPs belong to three families, surfactin, iturin, and fengycin, a single *Bacillus* strain can make one or more of them (121). Although surfactins are characterized as poor antagonists of some pathogenic fungi,

Table 3. Secondary metabolites or antibiotics produced by the strains of *Bacillus* species.

Bacillus species	Metabolite	Chemical nature	Bioactiviy	References
B. subtilis (unidentified marin starin)	Bacilotetrins	Cyclic-lipotetrapeptides	Antimicrobial	(42)
B. amyloliquefaciens AP183	Bacillusin	Macrocyclic polyene	Antimicrobial	(135)
B. subtilis (unidentified marin starin)	Gageotetrins	Linear lipopeptides	Antimicrobial, anticancer	(133)
B. subtilis DSM 16696	Macrolactin	Macrolides	Antimicrobial	(136)
	Plipastatin A	Lipopeptides	Antifungal	(137)
B. subtilis MTCC 10403	Furanoterpenoids	Polyketide	Antimicrobial	(138)
Unidentified *Bacillus* strain	Turnagainolides	Depsipeptides	Activation of *SHIP1*	(139)
B. subterraneus 11593	Bacilsubteramide A	Alkaloid		(140)
B. cereus RKHC-09	Cereusitin A	Cyclic tetrapeptide	Antifungal	(141)
B. amyloliquefaciens HAB-2	Bacillomycin	Cyclic lipopeptide	Antifungal	(142)
Bacillus sp. FS8D	Pseurotin A	Spirocyclic	Anticancer	(143)
B. coagulans 14	Coagulin	Peptide	Antibacterial	(144)
B. thuringenesis	Bacthurucin f4	Peptide	Antifungal	(145)
B. cereus	Cerein	Peptide	Antibacterial	(146)
B. megaterium	Megacin	Peptide	Antibacterial	(147)
B. thuringenesis S	Thuricin	Peptide		(148)
B. licheniformis	Halobacillin 5b	Hemolytic, cytotoxic		(149)
B. amyloliquefaciens GSB272	Bacilysin 1	Antifungal, antibacterial		(150)
B. subtilis 168	Bacilysocin	Fungicidal, antibacterial		(151)

Bacilotetrin A

Cereusitin A

*Bacillus*in A

Plipastatin A

Macrolactin

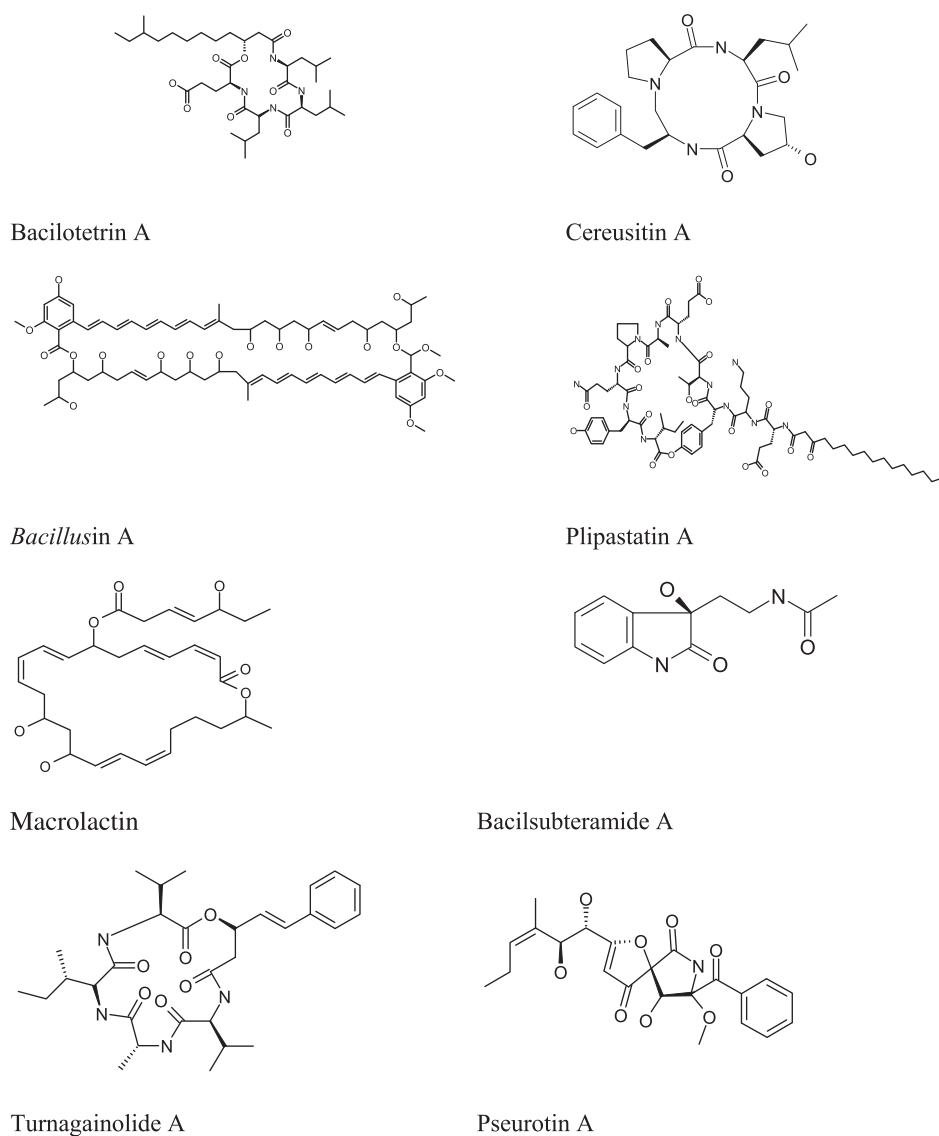Bacilsubteramide A

Turnagainolide A

Pseurotin A

Figure 1. Structures of the few representatives of antimicrobial metabolites discovered from various species of *Bacillus*.

they have received attention because of their ability to induce systemic resistance in host plants (122; 56). Fengycins on the other hand, are known to inhibit most filamentous fungi and species such as *F. verticilloides* (123–125). Their mode of action ranges from disrupting the membrane integrity to organelle dysfunction leading to cell death. The group iturins are also reported to have strong antagonistic activities against *A. flavus* (126) and *F. graminearum* (127). Besides, both surfactins and iturins are promoters of biofilm formation (128).

Romero et al. (130) reported that iturin and fengycin families of lipopeptides play a major role in the antagonism of *B. subtilis* against *Podosphaera fusca* (129). The surfactin – and fengycin-type lipopeptides can act as bacterial determinants in plant cells by initiating the immune response through the stimulation of ISR (induced systemic resistance) (77). Lipopeptides of

B. subtilis S499 proved to be effective triggers of ISR in tobacco and bean plants (77). Comparison of the level of production of antibiotic substances with different strains showed the advantages of *B. subtilis* species. For example, concentrations of lipopeptides in the culture medium of the most active strain of *B. subtilis* IB-54 exceeded those of active *Pseudomonas. ehimensis* and *P. polymyxa* by 10–100 times. Differences between *B. subtilis* strains were also observed both in an individual activity level and in the spectrum of the lipopeptides formed. It has been established that the main components of *B. subtilis* lipopeptide complex are iturin, surfactin, and related compounds (129, 130). It was also identified that antifungal peptides produced by *B. subtilis* AU195 show similarity with bacillomycin (group iturin A) and exhibit strong antagonistic activity against *Aspergillus flavus* and other plant
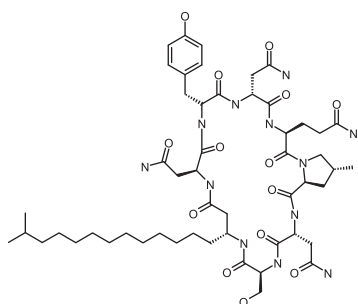
B. amyloliquefaciens

Bacillomycin
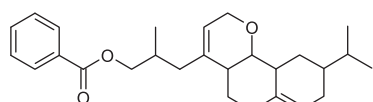
Cereusitin A
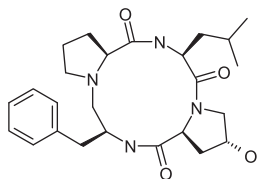
Gageotetrin
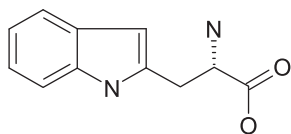
Isotryptophan
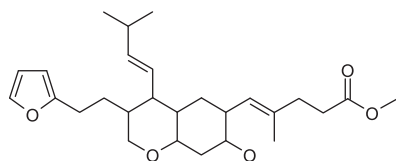
Turnagainolide B

Furanoterpenoids

iturin F1
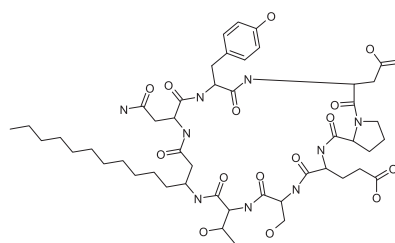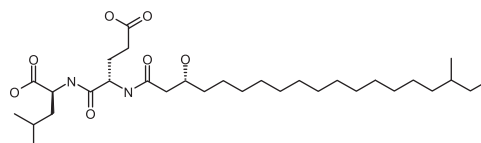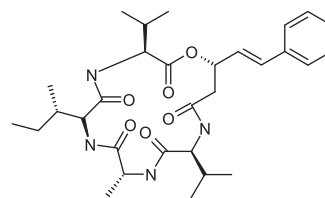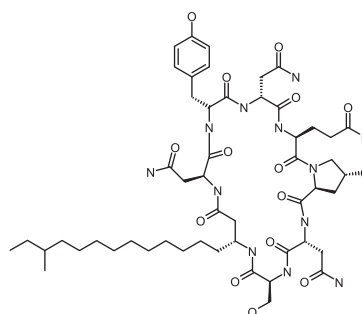
iturin F2

Figure 1 *Continued.*

pathogenic fungi. The iturin and fengycin from *B. subtilis* strains UMAF6614, UMAF6616, UMAF6639, and UMAF8561 were involved in the suppression of cucurbit disease caused by *Podosphaera fusca* (77). The analysis of culture filtrate, along with the recovery of inhibitory components (fengycin, surfactin, and iturin A or bacillomycin) from melon leaves inoculated with *B. subtilis* UMAF6614 and *B. subtilis* UMAF663, strongly supported the evidence of in situ production of these antimicrobials. Bais et al. (131) reported that protective action of surfactin produced by *B. subtilis* against infection caused by *Pseudomonas syringae* in *Arabidopsis*

iturin A$_9$ Koranimine
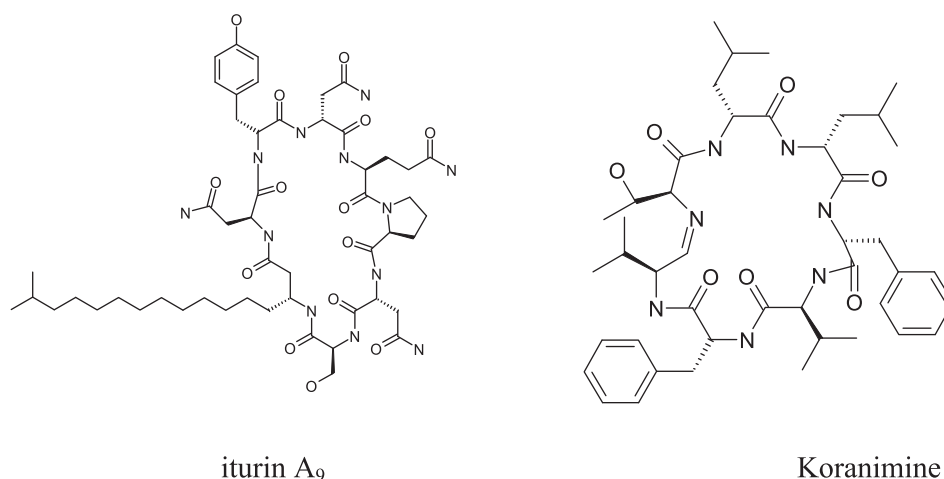
Figure 1 *Continued.*

thaliana and suggested that surfactin was necessary for both root colonization and protection of the plant against the pathogen. Ahmad et al. (130) observed that endophytic *B. subtilis* 330–2 enhanced rice and maize plant growth (ranging 14–37%) and tolerance to biotic/abiotic stresses, regulate the expression of different non-ribosomal polyketide synthases (NRPSs) including surfactin (*srfAA*), fengycin (*fen*), and bacillaene (*bae*). In addition to NRPS, *B. subtilis* 330–2 triggered the production of secondary metabolites, including antibiotics such as macrolactin (*mln*), difficidin *(dfn)*, iturin A (*ituA*), bacillibactin (*dhbF*), penicillin-binding protein 2B (*pbpB*) and beta-lactamase (*penP*), which are important manifestations of a plant's defence mechanism to cope with competing microorganisms and inhibit the growth of phytopathogenic fungi or bacteria. It should be noted that only 10% of all 114 genes of *B. subtilis* 330–2 were involved that differentially expressed for antibiotic production (130).

Bacteriocins produced by *Bacillus* species also display various biological activities that are heat-stable antimicrobial peptides and ribosomally synthesized.

Versatility in their structure and function made bacteriocins potential candidates for antimicrobial study (132). These peptides are active against a wide range of microorganisms, including bacteria, fungi, oomycetes, and viruses. The linear non-cytotoxic lipopeptides, e.g. gageotetrins A-C produced by a marine *B. subtilis* effectively controlled oomycete *Phytophthora capscisi* that has a broad host range (133), and the most destructive wheat killer fungus *Magnaporthe oryzae Triticum* (134).

2.5.2. Production of lytic enzymes

Bacillus species are also good sources of various enzymes. Particularly, the production of hydrolytic enzymes by the species has attracted attention in the last decades. Keratinases, for example, from *B. licheniformis* and other microorganisms, have been extensively used in a variety of industrial applications such as feed, fertilizer, detergent, and leather industries, as well as for pharmaceutical and biomedical applications (152). The bacilli also serve as a source of vital enzymes such as proteases, lipases, β-glucanases, L-asparaginase and cellulases (Table 4). The use of *B. subtilis* keratinolytic ability to recycle feathers and helped to reduce the environmental impact of the poultry industry. This is an interesting application as keratin contains a significant number of amino acids containing sulphur-forming disulphide bridges which present mechanical stability and resistance to common proteolytic enzymes (153). There are other several classes of enzymes produced by *Bacillus* spp. with potential industrial and biotechnological applications. A group multi-copper oxidoreductase enzyme, laccases (E.C.1.10.3.2; benzenediol: oxygen-oxidoreductase) with broader substrate affinity to compounds such as phenolic, aniline, aromatic, amines, and some environmental pollutants have been used for decolorization of textile dyes, polymer synthesis, wine and beverage stabilization, detoxification of industrial effluents and

Table 4. Lytic enzymes produced by *Bacillus* spp.

Bacillusspecies	Enzyme	References
B. megaterium Ti3	Biolytic extraction of poly (3-hydroxybutyrate)	(156)
	Cortex lytic enzymes	(157)
B. cereus KCCM40133	LysB4	(158)
B. subtilis ATCC 11774	Endolysin (endopeptidase)	
	Chitinase	(34)
	Nattokinase (NK)	(35)
	Cortex-lytic enzymes	(33)
B. thuringiensis	Endolysin PlyBt33	(56)
B. cereus ATCC 14579	LysBC17	(36)
B. licheniformis	Chitosanase	(159)
B. tequilensis	L-asparginase	(21)

biodegradation of environmental pollutants, in production of anti-cancerous and antibiotic drugs, ingredients for cosmetics, and hair coloring (21,154). Chitinolytic activity of some *Bacillus* spp. plays an important role in the biocontrol of *A. parasiticus* and show varied level of antifungal activity (155).

They induce cell death by actively degrading fungal cell walls (160). Jayaraj et al. (161) inoculated rice plants with a strain of *B. subtilis* capable of producing β-1-3-glucanases and thaumatin and have shown their protective capabilities against sheath blight disease. In a related study, an endophytic *B. subtilis* has shown protective effects against fungal pathogens. The strain produced β-1,3-glucanase, β-1,4-glucanase, and proteases that could degrade the fungal cell wall composition (130).

2.5.3. Induction of systemic resistance in plants

Plants use various strategies to defend against pathogens and stressors. with, which induced systemic resistance (ISR) mediated by *Bacillus* spp. have been reported in several studies (162). This defence mechanism is effective against fungi, bacteria, viruses, and insect herbivores (163). Moreover, co-evolution between plants and their pathogens plays a role in the activation of plants' innate immune system (164). Bais et al. (133) has demonstrated that surfactin and iturin producing *Bacillus* spp. have successfully reduced infection by *Pseudomonas syringae* in *Arabidopsis*. A study by Toure et al. (165) involving inoculation of *B. subtilis* endospore to apple pulp has demonstrated *in vivo* synthesis of lipopeptides which have a strong protective effect against the gray mold of apple fruits. Induced systemic resistance and promotion of plant growth by *Bacillus* spp. have been reviewed (162). A potential bioinsecticidal *B. thuringiensis* inoculum suppressed gray mold disease through induction of systemic resistance in tomato plants (166). Biocontrol of plant disease by endophytic *Bacillus* species through induced systemic resistance has also been reviewed recently (167).

2.5.4. Quorum sensing and biofilm formation

Quorum sensing (QS) is a process by which bacteria communicate. It involves detection and mounting of response to extracellular signaling molecules (autoinducers) through secretion of antibiotics, biofilm formation, and production of virulence factors. It allows bacteria to share information about cell density and adjust gene expression accordingly. This process enables bacteria to express energetically expensive processes as a collective only when the impact of those processes on the environment or a host will be maximized. Among the many traits controlled through quorum sensing, one is the expression of virulence factors by pathogenic

bacteria (168). This communication process among the cells involves the production, detection, and response to extracellular signaling molecules. As bacterial population density increases, extracellular signaling molecules or autoinducers (AIs) accumulate in the environment. It helps them monitoring the information and track changes in their cell numbers leading to gene expression. The QS controls genes that dictates beneficial activities when performed by groups of bacteria in synchrony. The processes that are controlled by QS include bioluminescence, sporulation, competence, antibiotic production, biofilm formation, and secretions related to virulence factor.

Studies show all known QS systems depend on three basic principles: first, members of the community produce AIs, which are the signaling molecules. At low cell density (LCD), AIs diffuse away present at concentrations below the threshold required for detection. At high cell density (HCD), the cumulative production of AIs leads to a locally high concentration, enabling detection and response (169). Second, AIs are detected by receptors that exist in the cytoplasm or the membrane. Third, in addition to activating the expression of genes necessary for cooperative behaviors, detection of AIs results in activation of AI production (170, 171). This feed-forward autoinduction loop presumably promotes synchrony in the population.

Microorganisms come together and form a community that is attached to a surface forming biofilms. Biofilm formation is a common phenomenon among bacteria (172). Several lines of evidence show that plant growth-promoting rhizobacteria (PGPR) such as *B*. subtilis form beneficial biofilms on plants root (172). They have been reported to protect the host plant from infections. Production of antimicrobial compounds such as surfactin in the biofilm matrix plays a major role in biocontrol. A study by Bais et al. (131) demonstrated that biofilm formed on the roots of *Arabidopsis* by a strain of *B. subtilis* in Murashige and Skoog medium has led to protecting effect against *P. syringae*. The genetic regulatory circuit that governs biofilm formation has been well studied in *Bacillus* species (173).

Rhizosphere colonization by plant growth-promoting rhizobacteria (PGPR) along plant roots facilitates the ability of PGPR to promote plant growth and health. Xu et al. (122) provided evidence that the major wall teichoic acid (WTA) biosynthetic enzyme GtaB is involved in both biofilm formation and root colonization. The deficiency in biofilm formation of the ΔgtaB mutant may be due to an absence of UDP-glucose, which is necessary for the synthesis of biofilm matrix exopolysaccharides (EPS). Therefore, these observations provide insights into the root colonization process by a plant-beneficial *Bacillus* strain,

which will help improve its application as a biofertilizer. The contribution of bacillomycin D in *Bacillus amyloliquefaciens* SQR9 to antifungal activity and biofilm formation has been reported (122).

3. Plant growth promotion, quality improvement, and yield increase

A considerable amount of literature is available on the effects of plant growth-promoting rhizobacteria (PGPR) on plant growth and development (174,175). These PGPRs are closely associated with plant roots and promote plants' defence against pathogens. There is a growing interest in root-colonizing bacteria as supplements or alternatives to chemicals to increase crop productivity in agriculture as they can influence plants' growth and development through production of phytohormones such as auxins, gibberellins, and cytokinins. They also play a protective role against harmful microorganisms through competition and activation of plant defence mechanisms. Several experimental reports proved these roles of beneficial microorganisms in plant growth and development. A strain of *B. megaterium* has been shown to promote the growth of *A. thaliana* and *Phaseolus vulgaris* plants *in vitro* and in soil. Inoculation of *B. Megaterium* to the root system of *A. thaliana* inhibited primary root growth followed by an increase in lateral root number growth, and root hair length mediated by phytohormones (176). In a similar study, the root-colonizing *B. subtilis* strain has been reported to suppress soil-borne disease thereby fostering the growth of tomato plants (177). Seed treatment with *B. amyloliquefaciens* resulted in maximum enhancement of germination (84.75%), seedling vigor (1423.8) and an increase in vegetative growth parameters. Significant protection (71%) against anthracnose disease was observed in plants pretreated with *B. amyloliquefaciens* (178). Besides production of phytohormones, *Bacillus* spp. such as *B. licheniformis* promotes plant growth through fixing atmospheric nitrogen and solubilizing phosphorus.

In addition to ISR, many BCBs also promote plant growth (179), by producing phytohormones that are related to growth conditions (180). For example, plants treated with *B. aryabhattai* showed greater tolerance to heat stress and produced more abscisic acid, the stress hormone that controls stomatal closure (180). Heat and drought stresses are known to exacerbate mycotoxin synthesis and also insect damage (105). Species such as *B. megaterium* and *Paenibacillus polymyxa* can be used as biofertilizers since they can fix nitrogen and solubilize phosphate (181).

Strawberry is an excellent source of natural antioxidants with a high capacity for scavenging free radicals. Rahman et al. (175) demonstrated that application of *B. amyloliquefaciens* BChi1 not only remarkably increased (43% over control) fruit yield but also enhanced contents of phenolics, carotenoids, flavonoids, anthocyanins and total antioxidants of strawberry fruit over untreated control. However, the mechanism of the quality improvement of fruits by the application of *B. amyloliquefaciens* is unknown. Further study is needed to elucidate the underlying mechanism of strawberry fruit quality improvement by the *B. amyloliquefaciens* strain BChi1.

3.1. Production of phytohormones

Plant associated microbes of different genera and species produce vital phytohormones (182). *Bacillus* strains such as *B. amyloliquefaciens*, *B. megaterium*, *B. licheniformis, B. pumilus*, and *B. subtilis* are some of the species associated with crops. They reside in the rhizosphere and positively influence plants' growth and development (162). Phytohormones are also known as plant growth regulators (PGRs) that are produced at a very low concentration but play an important role in plants' growth and development. Stress tolerance (112), seed dormancy, formation of floral organs, lateral shoot growth (183), cellular proliferation and differentiation, inhibition of premature leaf senescence (184,185), and promotion of heavy metal tolerance are some of the roles they play. Auxins, cytokinins, abscisic acid, gibberellic acid, and salicylic acids are well studied and functionally characterized phytohormones. They also function as signaling molecules enabling plants to mobilize responses to abiotic and biotic stresses (186). A *B. Aryabhattai* strain isolated from rhizospheric soil of a soybean collected in South Korea for example has shown to significantly promote growth and heat tolerance of the plant through production of abscisic acid, indole acetic acid, cytokinin and different gibberellic acids (187). *Bacillus* spp., as one of the phytohormone producing bacteria positively impact plants'

Table 5. Phytohormone production by *Bacillus* spp.

Bacillius species	Phytohormone	Reference
B. licheniformis	IAA	(191)
B. subtilis	IAA	(192–194)
B. subtilis	CK	(195)
B. amyloliquefaciens	ABA	(196)
B. licheniformis	ABA	(196)
B. aryabhattai	IAA, GA, ABA	(187)
B. megaterium	IAA	(74)
B. cereus	IAA	(197)

IAA, indole acetic acid; GA, giberallic acid; ABA, abscisic acid; CK, citokinin.

growth and development in many ways. They either improve the bioavailability of nutrients or influence phytohormone concentrations (188–190). Table 5 listed various phytohormones produced by some *Bacillus* species.

3.2. Solubilization of nutrients

Rhizobacteria play a role as biofertilizers that enhance plant growth and development. Biofertilizers involve live microorganisms that have potential applications in stimulating plant growth and development (198). They are preferred to chemical fertilizers as they are environmentally benign, support sustainability and may also be less expensive. Examples are phosphate and potassium solubilizing and N_2 fixing bacteria. Phosphorus, one of the most important nutrients needed for plant growth and development has limited availability in soluble forms. To alleviate this challenge, either soil should be supplemented with artificial fertilizer, rich in phosphate or phosphate solubilizing microorganisms (PSMs) should be introduced. Various *Bacillus* spp. have demonstrated phosphate solubilizing potential. Bacilli such as *B. circulans*, *B. megaterium*, *B. pulvifaciens*, and *B. sircalmous* are few examples (199). Likewise, the role of bacilli in N_2 fixation has been known for a long time. The work of Wahab (200) has demonstrated the potential of *Bacillus* as nitrogen-fixing species. A study by Pramanik et al (201) has also demonstrated that a strain of *B. pseudomycoides* can be used as a Potassium-solubilizing biofertilizer.

4. Enhancement of stress tolerance

Plants are exposed to adverse environmental conditions known as abiotic stressors in their natural habitats. These stressors include salinity, drought, heat, cold, flooding, heavy metals, and UV radiation that pose serious threats to the sustainability of crop yields. Due to global climate change, the impacts of abiotic stresses on crop production are increasing. Studies have shown that losses to major crops due to abiotic stressors have increased at an alarming rate in recent years posing serious threats to food security (202, 203). Since abiotic stresses are major constraints for crop production, finding biorational approaches to enhance stress tolerance is crucial to increase crop production and achieve food security. A large body of literature indicates that application of elite strains of *Bacillus* spp. enhances tolerance of plants to abiotic stresses (204). Microbial genes providing beneficial effects to plants have been characterized (204, 205). The Food and Agriculture Organization of the United Nations (FAO) predicts that current agricultural production should be increased by more than 70% (206, 207) to feed the rapidly increasing world population.

4.1. Drought tolerance

As one of the most damaging abiotic stresses, drought affects agricultural productivity worldwide. Reports show that it inhibits growth and development of plants resulting a reduction in yield (206, 208). The current trend in climate change shows drought is affecting a wide range of crop-producing countries posing a significant amount of threat to food security. Its effect, however, ranges from moderate and short to extremely severe and prolonged duration. Plants employ various adaptations and mitigation strategies to stand drought stress. They initiate a series of physiological reactions to reduce water loss through the closure of stomata, ABA accumulation, photosynthetic rate reduction, expression of aquaporins and vacuolar H^+-pyrophosphatases for maintaining cell turgor through osmotic adjustments, accumulation of compatible osmolytes, and reactive oxygen species (ROS) enzymes, which result in cell integrity, functionality and survival of plants (209–211).

Plants partly rely on soil microorganisms to mitigate stress caused by drought. Plants use microbial molecules such as exopolysaccharides (EPS), phytohormones, and 1-aminocyclopropane- 1-carboxylate (ACC) for drought tolerance. These molecules play a role in plant's osmoregulation by decreasing electrolyte leakage and promoting the production of metabolites such as amino acids and sugars.

In many regions, agricultural production is adversely affected by a variety of abiotic stresses such as drought, salinity, extreme temperatures, and toxic metals resulting in a significant reduction of crop productivity (201, 212). Abiotic stresses are often interrelated and induce general signaling pathways for the regulation of cellular responses aimed at plant adaptation causing similar morphological, physiological, biochemical, molecular, and genetic changes (213–215). Many studies have shown that various strains of *B. subtilis* contribute to the protection of different host plants against diverse abiotic stresses leading to the increase of plant growth and productivity (130, 197, 216, 217). Investigations on the mechanisms mediated by *B. subtilis* on plant stress tolerance are of the most urgent scientific demand in modern plant biology due to the fact that *B. subtilis*-induced responses against stresses could range from diverse to very specific (130,218). The comparative physiological and metabolic analysis revealed that a complex metabolic change in

plants is associated with enhanced drought tolerance (219). Application of *B.subtilis*, *B. thuringiensis*, and *B. megaterium* significantly enhanced drought tolerance through increased accumulation of riboflavin, L-asparagine, aspartate, glycerol, nicotinamide, 4-hydroxy methylglycine and 3-hydroxy-3-methylglutarate in the leaves of chickpea (219). Another important aspect associated with the enhancement of drought tolerance in plants by *Bacillus* spp. is the ability of biofilm formation on plants' surfaces. In a recent report, Wang et al. (220) demonstrated that *B. amyloliquefaciens* 54 inoculation in tomato exerts drought tolerance in plants through enhanced expression levels of stress-responsive genes, such as *lea*, *tdi65*, and *ltpg2* in the treated plants. Enhancement of drought tolerance was also linked to the enhancement of survival rate, relative water content and root vigor in tomato. It was also found that *B. amyloliquefaciens* 54 induced stomatal closure through the abscisic acid pathway. Biofilm forming ability of *Bacillus* bacteria was positively correlated with plant root colonization. Interestingly, plants inoculated with hyper-robust biofilm-forming (ΔabrB and ΔywcC) mutants were better able to resist drought stress compared to defective biofilm mutants (220). Although a large body of literature is available on the enhancement of drought tolerance in plants by plant-associated bacilli, precise mechanisms of their beneficial actions in plants are still poorly understood. Further genomics and postgenomics studies are needed to clarify the mode of actions of the elite strains of bacilli associated with plants.

4.2. Salinity tolerance

Disturbed water balance and ion homeostasis lead to soil salinity imposing deleterious effects on plant growth and development (215, 221). This leads to a loss in crop yield. Salinity causes oxidative stress, water deficit (222) and deficiency of essential nutrients. It also affects lipid metabolism, protein synthesis, and biomass accumulation (215). This also impacts the process of photosynthesis leading to perturbations in carbon and nitrogen assimilatory pathways (223). It has also been associated with the accumulation of toxic ions such as Na^+ and Cl^- in cells resulting in immediate stress. To mitigate the effects of salt stress, plants employ strategies that regulate water status and have osmoregulatory functions. They initiate the expression of genes coding for various enzymes and accumulation of metabolites such as amino acids, sugars, and betaines (224).

Harnessing the potential of beneficial microorganisms present in the rhizosphere is an alternative strategy for improving plant stress tolerance. Promising results

have been reported in areas where saline irrigation of crops is practiced. A handful of studies revealed that some elite strains of plant-associated bacilli enhance plants' tolerance to salinity (204, 205). In the Sinai region of Egypt, a strain of *B. subtilis* was field-tested and reported to promote salt tolerance in two cultivars of eggplant and pepper in saline soil (225). *B. subtilis* has been reported to enhance the production of phytohormones: auxin, IAA, CKs, and giberellines in crops such as wheat thereby increasing their salinity tolerance (225–227). In a similar study, Bochow et al. (225) described that plants in saline soil that grew from *B. subtilis* FZB2 treated seeds showed a multi-fold increase in yield. In a similar study, endophytic strain *B. subtilis* NUU4 improved symbiotic performance of host plant (*Cicer arietinum* L.) with rhizobia by uptaking more nutrients, which resulted in a significant increase in growth parameters (roots and shoots) and yield under salinity compared to non-inoculated control plants (197). This strain is known to produce IAA, HCN, siderophores, cell wall degrading enzymes, and demonstrated antagonistic activity against *F. oxysporum*, *F. solani*, *F. culmorum*, *B. cinerea*, and *A. alternata*. Most of the common osmoprotectants are low molecular weight metabolites such as amino acids that show no toxicity towards plant tissues when present in higher concentrations (228). The amino acid proline is known to enable plants to cope with osmotic stress (229). An important mechanism of rhizobacteria-induced salt tolerance in plants is the production of enzyme 1-aminocyclopropane-1-carboxylic acid (ACC) deaminase, which acts by degrading ACC (230). The enzymatic activity of ACC deaminase results in the production of alpha-ketoglutarate and ammonia, which, by lowering ACC levels, prevents excessive increases in the synthesis of ethylene and enhances plants tolerance to salt stress.

Rhizobacteria exert beneficial functions to plants through induction of gene expression in the interacting plants. For example, *B. amyloliquefaciens*-SN13 induced changes in expression of a considerable number of photosynthesis, hormone, and stress responsive genes in rice under salt stress as compared to salt stress or SN13 inoculation alone, indicating its potential role in reducing harmful effects of salinity (204). Functional expression of rice genes *OsNAM* and *OsGRAM* in yeast showed enhanced tolerance to various abiotic stresses including salinity. (204). Likewise, expression analysis of *OsGRAM* genes in rice roots subjected to salt stress with or without *B. amyloliquefaciens* SN13 inoculation revealed significant differential expression patterns suggesting their crucial role in beneficial plant-rhizobacteria interactions under salinity (205). Further study using mutants of *OsGRAM* would precisely elucidated

the role of these genes in salt tolerance induction in rice by SN13. Findings of these and other studies demonstrate that *Bacillus* spp. has the potential to induce gene expression in plants associated with salt tolerance. Bacteria that enhance salt tolerance in plants are recruited by root exudate secreted from the roots of the host plants. The secreted organic acids are 2-methylbutyric acid, stearic acid, palmitic acid, palmitoleic acid, and oleic acid. Precise molecular cross-talks between roots and rhizobacteria are needed to be elucidated for getting better benefit from the elite strains of bacteria that exert salt tolerance to plants.

4.3. Low temperature tolerance

Cold stress can affect plant distribution, development, and productivity thereby threatening food security by limiting crop yield. Plants activate various physiological and molecular processes in response to cold stress (220). In particular, *Bacillus* spp. has demonstrated the capability of increasing plant's tolerance against cold. They have genetic features that enable them to initiate a physiological response to cold stress including synthesizing of cold shock proteins, initiation of signal transduction pathways, osmotic regulation, membrane transportation, and antioxidant enzymes (231, 232).

Advancement in biotechnology has enabled the identification of genes associated with stress tolerance. While this opens opportunities to improve cold tolerance by gene transformation or altering multigenic traits, challenges do exist in understanding the changes in cellular, biochemical and molecular mechanisms that occur in response to cold stress (233)

Members of the *Bacillus* genus are among the most naturally abundant plant growth-promoting rhizobacteria (PGPR) in the soil. As *Bacillus* spp. are among the most naturally abundant PGPR capable of producing phytohormones such as AUX, CK, and GA, they can also increase plant growth by reducing their susceptibility to stressors such as cold (205). They cause alterations in metabolic and physiological activities leading to production of metabolites, abundant proteins with protective properties during cold stress. Zubair et al. (232) demonstrated that inoculation of cold-tolerant *Bacillus* strains aided in inducing stress responses in wheat by regulating abscisic acid, lipid peroxidation and proline accumulation pathways in a beneficial manner.

5. Bioremediation of heavy metals and contaminated soils

The discharge of untreated industrial wastewater containing biotoxic substances of heavy metals in the ecosystem is one of the most important environmental and health challenges society facing today. Hence, there is a growing need for the development of a novel, efficient, eco-friendly, and cost-effective approach for the remediation of toxic metals (Cr, Hg, Cd, and Pb) released into the environment and to safeguard the ecosystem. In this regard, recent advances in microbe-based heavy metal bioremediation have propelled a prospective alternative to conventional techniques. Bioremediation is a process that involves all methods and activities for the reduction of environmental pollutants with the help of biological entities. Bioremediation offers a promising means to reclaim such contaminated soil in an economical and eco-friendly way (234). Metal toxicity is of great environmental concern because of its bioaccumulation and non-biodegradability in nature (235). Bioremediation is employed to transform toxic heavy metals into a less harmful state using microbes. Species of *Bacillus* isolated from solar salterns were shown to have a potential of detoxifying the heavy metals such as lead, chromium, and copper by biosorption (236).

Pollution of soils with heavy metals (HM) has become a common phenomenon throughout the world due to the increase in the scale of anthropogenic activities. The plants growing on HM contaminated soils are characterized by a decreased growth rates and yields (237). Some of the direct toxic effects caused by high concentrations of HM include inhibition of cytoplasmic enzymes and damage to cellular structures due to the development of oxidative stress (238). An example of an indirect toxic effect is the replacement by HM of cations in the functional groups of various bioorganic compounds (239). Moreover, the negative influence of HM on the activity of soil microorganisms can indirectly affect plant growth. The decrease in the number of beneficial soil microorganisms due to the high concentration of metal can lead to a decrease in the decomposition of organic matter, which in turn can cause a decrease in the content of certain nutrients in the soil. The PGPB, including *B. subtilis*, can grow in HM-contaminated environment and protect plants against toxicity of HM (240). Beneficial microorganisms have different mechanisms for HM tolerance through mobilization, immobilization, and transformation to less toxic forms. Such mechanisms include exclusion, extrusion, active removal, biotransformation, biosorption, precipitation or bioaccumulation of metals both in external and intracellular spaces of plants (237). Naseem et al. (241) demonstrated that inoculation of wheat with *Bacillus* sp. AMP2 caused a reduction in the Cr uptake of seedlings both at 10 and 20 $\mu g \ mL^{-1}$ chromium salts ($CrCl_3$, K_2CrO_4 and $K_2Cr_2O_7$) when compared with non-inoculated plants. Moreover, increased levels

of acid phosphatase and PA were recorded in bacterial inoculated plants compared to the control (241). In a related study, inoculation of wheat plants with *B. subtilis* QM3 promoted their growth in the presence of Pb (240) with concurrent increase of antioxidant enzymes like superoxide dismutase (SOD, EC 1.15.1.1), ascorbate peroxidase (APX, EC 1.11.1.1), and catalase (CAT, EC 1.11.1.6) in plant tissues and decrease of metal concentration in the roots in comparison with non-inoculated control plants (240). It was shown that endophytic strains of *B. subtilis*26D and 11VM improves tolerance of *S. alba* to the toxic effect of Cd and Ni and reduces manifestation of oxidative stress in the presence of higher levels of metal ions in the above-ground part of plants (242). Treesubsuntorn et al. (243) showed that *B. subtilis* inoculation of rice (*Oryza sativa* L.) can highly reduce Cd accumulation in every part of rice roots and shoots (45 days), and grains (120 days). *B. subtilis* can effectively absorb Cd compared to *B. cereus*, which might be the main mechanism to reduce Cd transportation in rice plants. Interestingly, plants that were inoculated with bacterial species individually, harbored higher calcium (Ca) and magnesium (Mg) accumulation; *B. subtilis*-inoculated plants had the highest levels of Ca and Mg compared to plants inoculated with *B. cereus*. Moreover, *B. subtilis* could increase the dry weight of the rice plant and protect them from Cd stress due to the ability to produce IAA, solubilize phosphate, and control ethylene levels by ACC-deaminase activity (243).

Arguably one of the environmental challenges we face today is soil contamination of our environment. A petroleum waste causes an imbalance between carbon, nitrogen, and phosphorus ratio in soil affecting all forms of life (244). As cleaning is costly and labor-intensive, companies show less interest in the use of physicochemical methods. On the other hand, bioremediation is attracting attention as an alternative to physicochemical methods of cleaning an oil-contaminated environment (245). The use of microorganisms that have the potential to degrade pollutants (Bioaugmentation) can be employed to degrade petroleum wastes (246). Microorganisms produce various biosurfactants. These molecules play a significant role in reducing surface tension and critical micelle dilution. This favors the creation of micro-emulsion formation leading to the solubilization of hydrocarbons in water (247). Application of biosurfactants as bioremediation in an oil-contaminated environment has an advantage over the use of synthetic surfactants as they are less toxic and more biodegradable (248). Moreover, biosurfactants show efficiency, high selectivity, and versatility (pH and salinity) (245).

Some members of the microbial community might have the ability to secrete important degradative enzymes and growth factors, whereas others can exhibit the potential of biosurfactant production leading to the enhanced solubilization of hydrophobic hydrocarbons for their better utilization by microbes (249). Ubiquitous presence of cypermethrin as a contaminant in surface stream and soil necessitates developing potential bioremediation methods to degrade and eliminate this pollutant from the environment. *B. subtilis* has been found efficient in biodegradation and detoxification of cypermethrin (250). Enhanced degradation of cypermethrin by *B. thuringiensis* strain SG4 has also been reported (251). The β-glalactosidase generated by *B. subtilis* catalyzes the hydrolysis of o-nitrophenyl-β-D-galactopyranoside (ONPG) to produce o-nitrophenol (ONP), which can be detected at 420 nm and used to evaluate acute biotoxicity of heavy metal ions that inhibit the activity of the enzyme (252). This *B. subtilis*-based bioassay is a sensitive, economically feasible, simple and promising alternative for acute biotoxicity assessment. Generally, remediation of heavy metal using microbes has several advantages. It is eco-friendly and considered to be a long-term solution compared to the physical and chemical methods. However, shortcomings like slowness of the process, difficulty in controlling the treatment, specificity of the microbes towards a particular metal contaminant, and problem with large-scale applications are the areas that need improvement.

6. *Bacillus* as a reservoir of novel genes for engineering

B. thuringiensis is ubiquitous in nature. It produces insecticidal crystal proteins (Cry) on sporulation. The most widely known toxins of *B. thuringiensis* include the δ-endotoxins; Cry and Cyt toxins. Cry proteins consist of various groups based on their structure (253). Strains of *B. thuringiensis* are recognized as one of the most used biocontrol agents. Crystal proteins produced by the species are commercially available for pest control. They show larvicidal activities against larvae of hymenoptera, homoptera, lepidopteran, dipteran, coleopteran etc (254). Recent advancements in the omics technology has created an opportunity to mine for potential gene cluster to increase bioactive metabolites discovery. Moreover, the host-specific toxicity of Bt proteins has attracted researchers' attention to the search for genes potentially coding for novel toxins within the group. Selective solubility of Bt crystal and their specificity for their hosts have gained worldwide attention as an alternative to chemical insecticides. The

usefulness of these insecticidal proteins has also motivated researcher to explore new Bt isolates from the most diverse habitats in order to identify and characterize new insecticidal proteins with different specificities. Some of these isolates exhibit novel and unexpected toxic activities against organisms other than insects, suggesting a pluripotential nature of some toxins. Bt corn, cotton, brinjal etc. that have been genetically modified to express insecticidal toxins derived from the bacterium *B. thuringiensis* to kill lepidopteran pests feeding on these plants. Genetically modified Bt corn has lower levels of mycotoxins compared to non-Bt (255). On farm field trials revealed that Bt cotton technology substantially reduces pest damage and increases yields (256). Discussions and debates of environmental risks and benefits of adopting genetically engineered Bt technology in corn, cotton and brinjal are highly polarized between pro – and anti-biotechnology groups (257). Nonetheless, the current state of our knowledge is frequently overlooked in this debate. While organic and conventional crops' value could be jeopardized if genes from GE crops flow to non-GE varieties through cross-pollination or seed mingling, a survey of existing scientific literature reveals that key experiments on both the environmental risks and benefits are lacking (257). However, the number of genes present in various species of *Bacillus* that encode insecticidal toxins are great resources for future research and judicious introgression in different crops.

7. *Bacillus* spp. as a source of carotenoids

Carotenoids represent one of the most abundant pigments available in nature. They have considerable industrial applications in biotechnology, food processing, and pharmaceuticals (258). They are also currently receiving attention as studies indicate that they can be used to prevent the incidence of cancers, cardiovascular diseases, and some degenerative diseases (259–262). This prompted an interest in the commercial production of carotenoids. Few studies have reported bacilli as potential sources of carotenoids. Sy et al. (263) recovered two *Bacillus* species, *B. indicus* and *B. firmus* capable of producing carotenoids from a marine environment. A strain of *B. megaterium* has also been characterized as a potential producer of carotenoids (264).

8. Concluding remarks and future perspectives

The genus *Bacillus* represents spore-forming Gram-positive bacteria. They are ubiquitous in the environment. They produce diverse secondary metabolites that have applications in the fields of biotechnology and agriculture. They are good sources of bioactive compounds, enzymes, vitamins, and other several secondary metabolites that could be used for industrial applications. Members of the genus have also been known for their effect on plant growth and development. They improve crop yield through enhancing plant stress tolerance, disease defence, and through facilitating minerals and water uptake. Moreover, the current trend in the rapid increase of the world population together with climate unpredictability urges immediate and effective strategies to increase crop productivity. This subsequently involves the use of synthetic chemicals and fertilizers that may make the whole production system unsustainable with unwanted environmental consequences. Therefore, developing biological control against pests and plant pathogens, biofertilizers, and stress-tolerant crop varieties are the areas of future research. Despite their immense potential, bacilli are not fully utilized in the fields of agriculture and biotechnology. Therefore, research on bacilli should aim at (i) searching for novel bioactive metabolites that could be used as lead compounds in developing effective remedy against plant pathogens; (ii) developing biofertilizers that have minimal adverse impact on the environment; (iii) selecting strains that have the potential of stimulating plant defence mechanisms and improve yield; and (iv) applying bacilli species as a source of plant growth hormones.

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