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BIOLOGICALLY ACTIVE METABOLITES OF *Bacillus subtilis* AND THEIR ROLE IN THE CONTROL OF PHYTOPATHOGENIC MICROORGANISMS

(review)

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Abstract

The use of nonpathogenic soil bacteria living in association with the roots of higher plants enhances the adaptive potential of the hosts, stimulates their growth and serves as a promising alternative to chemical pesticides (V.K. Chebotar' et al., 2015). The bacterium *Bacillus subtilis* is recognized as a powerful biocontrol tool because of suppression of a wide range of phytopathogens due to the ability to produce a variety of secondary metabolites of different chemical nature, e.g. cyclic lipopeptides, polypeptides, proteins and nonpeptidic compounds (T. Stein, 2005). Information on the structure of bioactive metabolites of bacterial antagonists of phytopathogens, as well as mechanisms of their biological activity promotes targeted selection of strains for the development of microbiological products. *B. subtilis* is widely distributed due to the ability to form biofilms (A.L. McLoon et al., 2011). The chemical composition of compounds produced by the bacteria is determined by genetic characteristics and physical and chemical conditions of the environment. The cyclic lipopeptide surfactin exhibits antimicrobial (antibacterial, antiviral, antifungal) activity, causing lysis of the cell, and also contributes to a decrease in the production of mycotoxins by microorganisms (M. Mohammadipour et al., 2009). The structure of another peptide metabolite, rizocticin, promotes penetration into the microbial cell and inhibition of protein synthesis (K. Kino et al., 2009). *B. subtilis* can produce various hydrolytic enzymes which lyse the phytopathogenic fungus cell wall (C.P. Quardros et al., 2011). Among the metabolites synthesized by bacteria, lantibiotics play important role, their structure allows the synthesis of peptidoglycan which contributes to the formation of pores in cytoplasmic membrane (J. Parisot et al., 2008). A large family of polyketones exhibits antimicrobial activity due to the ability to collect multifunctional polypeptides into large pesticide complexes. The phospholipid antibiotic bacilizycin, which is produced immediately after the growth ceases and before the formation of thermostable spores, exhibits fungicidal activity against some fungi (A. Hamdache et al., 2011). Some strains of *B. subtilis* synthesize polyene antibiotics with conjugated double bonds, for example, hexaenes which inhibit growth of phytopathogenic fungi (E.B. Kudryashova et al., 2005). Several soil microorganisms, including strains of *B. subtilis*, can synthesize gibberellins and gibberellin-like substances that stimulate plant growth (R. Aloni et al., 2006). Proteins, lipopeptides, polysaccharides and other compounds associated with the *B. subtilis* cell wall can trigger the protective mechanism of the plant, that is, act as elicitors (M. Ongena et al., 2007). Thus, research aimed at studying biologically active metabolites of *B. subtilis*, which possess the properties of biopesticides or inducers of plant resistance to diseases, opens new prospects for the development of environmentally friendly technologies for protection against phytopathogens.

Keywords: biological control, *Bacillus subtilis*, metabolites, antimicrobial activity, biopreparation, phytopathogens, system resistance

Biological control by microorganisms is a promising alternative to an extend use of expensive pesticides, that accumulate in plants with adverse effects on humans health. Pesticides can also be lethal to beneficial soil inhabitants and cause emergence of pathogen strains resistant to fungicides. They have a short-term inhibitory effect of phytopathogenic microorganisms, whereas bioagents

affect negatively on phytopathogens during the whole growing season [1-5].

Non-pathogenic soil bacteria associated with the roots of higher plants enhance their adaptive potential of the hosts, and promote their growth. In 1980 J.M. Kloepper called them plant growth promoting rizobacteria (PGPR). One of the plant rhizosphere characteristics, reflecting its colonization by microorganisms, is a rhizosphere/soil quantitative parameter (R/S). In most rhizobacteria, the R/S value varies from 2 to 25 [6]. Rhizobacteria can act as biocontrol agents due to ability to compete with phytopathogens for ecological niche [7], to produce different antibacterial compounds [8-10], to affect plant defense system, to promote plant growth by increasing availability of nutrients (nitrogen, phosphorus, amino acids) from soil [11].

The purpose of this paper is to data about biologically active metabolites of *Bacillus subtilis* which is recently considered a powerful biocontrol tool.

B. subtilis can contact with higher plants and promotes their growth. *B. subtilis* species is better than other agents of the genus *Bacillus* and more suitable as biocontrol agent because of host wide range, ability to form endospores and to produce different antibiotics [12]. *B. subtilis* has suppressive activity in vitro against more than 20 phytopathogens due to the ability to produce a variety of secondary metabolites, e.g. cyclic lipopeptides, polypeptides, proteins and non-peptidic compounds [13, 14]. These agents, mainly peptides, are of ribosomal or non-ribosomal origins [15].

The main antibiotics of *B. subtilis* which suppress phytopathogens are peptide derivatives, mainly lipopeptides, synthesized non-ribosomally [15]. Lipopeptide antibiotics are produced by binding β-hydroxyl residues or β-amino groups with fatty acids. The length and branching of fatty acids chains and amino acid redisues determine the product properties [16].

B. subtilis bacteria are common in the environment, because many wild strains are able to form biofilm on the plants roots surface [17, 18]. Cyclic lypopetide surfactin contains carboxylic acid (3-hydroxy-13-methyltetradecanoic acid) and seven aminoacids. The molecule contains heptapeptide associated with the β-hydroxy fatty acid through lactonic bound [19, 20]. Another surfactin analogues are pumilacidin, bacircin and lihenizin [21]. Surfactin is one of the most active biosurfactants [13, 21], famous as simulator of biofilms formation. Partly, it is due to activation of membrane-sensitive histidine kinase [17, 22, 23].

Exopolymeric compounds play an important role in biofilm formation, and their chemical composition affects biofilm properties and quality [24, 25]. Biofilms promote the colonization of roots by bacteria and thereby increase the local antibiotics concentration [26]. Also its formation enhances antimicrobial resistance [27-29]. Surfactin has antibacterial, antiviral, antifungal, insecticide, herbicidal activities [30-34], stimulates resistance to the pathogen penetration affecting on protective plant mechanism [35, 36]. Biocontrol of the phytopathogenic fungus *Aspergillus flavus* by surfactin reduces plant contamination by mycotoxins (37).

Many authors group mycosubtilins, iturin and bacillomycin, the cyclic lipoheptapeptides which are similar in structure and show powerful antifungal and hemolytic features but limited antibacterial activity, under the general title iturins. Antifungal effect is manifested in interacting with the cytoplasmic cells membrane with formation of ion-permeable pores [38, 39]. In China, a new strain of *B. subtilis* has been isolated, which can produce jiean-peptide, an antibiotic similar in structure to iturin [40]. Jiean-peptide manifests fungicidal properties against various plant pathogens [41, 42]. The strain can produce this biofungicidal compound provided that the bacterial cells are adsorbed on wood pieces.

Fengycin (synonym plipastatin) combines several compounds of unusual

structure, i.e. cyclic, branched components and rare substances [43]. It contains β-hydroxy fatty acid associated with the N-terminal decapeptide, which includes four β-amino acids residues and rare L-ornithine amino acid. The C-end residue of the peptide is partially linked with the tyrosine residue at position 3, with branching point of acyl peptide and the 8-membered lactone ring also persisting [15]. Fengycin has antifungal activity against some thread like fungi [44]. This compound is successfully used to control *Fusarium moniliforme*, due to inhibition of mycelia growth and spore formation. A possible mechanism of fungicin antifungal activity involves interaction of the styrene molecules and phospholipid membrane which disrupts target cell membrane structure [45-47].

Rhizocticin is a phosphonate oligopeptides antibiotic produced by the gram-positive *B. subtilis* ATCC 6633 strain [48]. This is di- and tripeptide, containing arginine amino acid and L-2-amino-5-phosphono-3-pentenoic amino acid, not found in proteins. Rhizocticins penetrate into the fungal cell through the oligopeptide transport system. As a result, the non-protein phosphate-containing amino acid peptidase releases which inhibits protein synthesis. Phosphonate compounds are common among biologically active substances mainly due to their ability to influence the carboxy- and phosphate-containing metabolites [46].

Lantibiotics (lanthionine-containing peptide antibiotics) are ribosomally synthesized peptide antibiotics with unique features. Lanthionine is produced by ribosomal synthesis or by modification (serine dehydration and subsequent binding with thiol cysteine groups) [49]. Properties of various types of lantibiotics depend on their structure and, thence, differ. Lantibiotics of A type (21-38 amino acid residues) have more linear secondary structure and destroy gram-positive target cells, forming pores in the cytoplasmic membrane.

Subtilin is a 32-amino acid pentacyclic lantibiotic structurally similar to nisin of *Lactococcus lactis* which is widely used in biocontrol [50]. Both cell density and sporulation can regulate synthesis of lantibiotics. The lantibiotics produced by gram-positive bacteria inhibit synthesis of peptidoglycans and shorten the peptidoglycan molecule, which facilitates the pores formation [51]. Serine proteases also participate in the subtilin synthesis. High lipopeptide mycosubtilin content (880 mg/g) is found in the *B. subtilis* strain with antagonistic effect on *Candida* sp. [18].

Ericin S differs from subtilis only in four amino acids, that is, the antimicrobial properties of both lantibiotics should be comparable. However, ericin A differs from erysin S in the ring structure and the position of 16 amino acids [16]. The lantibiotic mersacidin refers to type B lantibiotics which have a larger molecule size and a diverse structure.

Subtilomycin is synthesized by *B. subtilis* MMA7 isolated from the marine sponge *Halilona simulans*. Several strains of *B. subtilis* synthesize subtilosin A which has a macrocyclic structure with three intermediate bounds, including both ether bonds between cysteine sulfate and α-carbon of amino acids [15]. Sublancine 168 with β-methyllanthionine bridge and two disulfides bonds rare for lantibiotics is active mainly against gram-positive bacteria.

B. subtilis bacteria are applied as producers of amylase, protease, chitinase, xylanase, lipase, gluconase, cellulase, and other enzymez [52, 53]. Bacilli attach to hyphae and lyse fungal cell walls to use lysates as an additive nutrients and energy sources [54].

B. subtilis along with the peptide antibiotics produce polyketones which are active agents for phytopathogens biocontrol. Polyketones are a metabolite family which consists of polyketon synthetase enzymes with antimicrobial activity due to ability to gather multifunctional polypeptides into big pesticide complexes. These are linear molecules with two amide bounds and different residues

and substituent in structure. These metabolites are grouped based on structure and functions [40, 43].

Phospholipid antibiotic bacilysocin is produced by *B. subtilis* 168 just after growth cessation and before thermostable spore formation. Its activity is more pronounced against eukaryotic *Sacharomyces cerevisiae*, and also lower fungi *Candida pseudotropicalis* and *Cryptococus neoformans* characterized by non-filamentary growth [55, 56].

Phospholipids produced by *B. subtilis*, possess antimicrobial activity against gram-negative bacteria (*Escherichia coli*, *Proteus mirabilis* and *Pseudomonas aeruginosa*), gram-positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*), *Actinomyces* sp. and fungi (*Aspergillus niger, Candida albicans*) [57]. It has been found, that their antimicrobial effect is enhanced with rising temperature (up to 50 °C) and pH (up to 10) [58, 59].

Some *B. subtilis* strains produce metabolites of polyene antibiotic groups with conjugated double bonds. Hexaenes of other *B. subtilis* strains inhibit the growth of phytopathogenic *Fusarium culmorum*, *F. sporotrichiella*, *F. oxysporum, Botrytis sorokiniana*, *Alternaria tenui* and *Phytophthora infestans* [60].

Isocoumarins are phenolic compounds that occur in *Bacillus* species as phenylpropanol derivatives. Eleven strains of *B. subtilis* isolated from various geographical and ecological niches, produce amicoumacins classified as antibiotics of the isocoumarin group. Amicoumacin and bacillosarcin extracted from the culture liquid of *B. subtilis* marine bacterium TP-B0611, protect plants from grain moth [43].

Isoprene makes the smallest group of the natural terpenoids. Unlike others bacteria, *B. subtilis* 6051, *B. subtilis* 23029 and *B. subtilis* 23856 produce volatile isoprene at relatively high concentrations [43]. Sporulenes A, B and C are three terpenoids isolated from *B. subtilis* spores, which can protect spores of bacilli from oxidative stress. The biological role of sporulenes is determined by sporulation of *B. subtilis* [43].

Some strains of *B. subtilis* produce gibberellins and gibberellin-like substances [61]. Cytokinins are regulators of cell division and differentiation in various plant tissues. They play an important role in the growth and nodules formation. It is shown that *B. subtilis* cells produce volatile compounds stimulating plant growth, mainly of 3-hydroxybutan-2-one and butane-2,3-diol [46, 57].

Induced plant resistance is due to interaction between plants and microorganisms among which bacteria of rhizosphere, in particular *B. subtilis*, play an important role. Proteins, lipopeptides, polysaccharides and other compounds associated with the cell wall of the *B. subtilis* may be elicitors which trigger plant defense response [61, 62]. Bacterial metabolites trigger cascade of defense processes, including formation of reactive oxygen species, proteins phosphorylation, initiation of phytoimmunity mechanisms, that lead to the development of system resistance [63, 64]. Cyclic lipopeptides, the surfactin, iturin, and fenghin, can influence the signaling cells of plants, that results in initiation of natural immune responses [65].

Compounds released from the cell wall of the phytopathogens by hydrolases of antagonists can function as elicitors of resistance and cause defensive response, e.g. synthesis of phytoalexins, activation of hydrolytic enzymes, lignification etc. For example, *B. subtilis* AF1 strain isolated from the soil suppressive to *Fusarium udum* can induce resistance against *Aspergillus niger* in ground-pea [66]. This strain, being an inducer of resistance, is a stimulant of accumulation of phenylalanine ammonia-lyase and peroxidase. In other systems, significant changes of plants cells defense responses are related to phenol modifications. Treatment of tobacco plants with cell suspension at low surfactin concentration

activates phosphorylation and oxidative reactions, leading to plant cell death and penetration of phytopathogens [67].

So, *Bacillus subtilis* cells produce significant quantity of bioactive metabolites, having different chemical structure: cyclic lipopetides, proteins, polypeptides, ketone, polyenoic compounds etc. Ability to synthesize compounds of a particular structure presumes a specific mechanism of bacterial action on a phytopathogenic organism, and also explains the biological activity of a particular bacterial strain against certain microorganisms. When selecting effective producer strains, it is necessary to pay attention to the structure of their metabolites, since they can be the basis for the development of environmentally friendly technologies for plant protection against phytopathogens.

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