Antibacterial peptides from thermophilic bacteria

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Abstract— *It is becoming interestingly apparent that innovations of the classical antibiotics are not effective, that induces need for novel drugs. Peptide antibiotics exhibit a group of secondary metabolites with hydrophobic and cyclic structures containing d-amino acidc like compounds with more resistant to proteolytic degradation. Bacterial peptides can possess bactericidal, fungicidal, metal chelating and immunomodulation activities. Several bacteriocins are active as food preservation, resulting in foods with more naturally preserved and rich in nutritional properties. Antimicrobial peptides used against infections are isolated mainly from mesophilic bacterial species. Novel antibacterial peptides from thermophilic species are more stable at higher temperatures and pH, and can be improved by variation of cultivation conditions. These cells can growth either autotrophically or heterotrophically. Under mixotrophic conditions can utilize pyruvate or hydrogen with thiosulfate. The present review provides a general overview on primary structure of selected antibiotic peptides and their potential for industrial purposes as well as environmental and biotechnological applications.*

Keywords— antibacterial peptides, novel drugs, metabolites, hydrophobic structure, immunomodulation.

I. INTRODUCTION

The genus Geobacillus contains, more than 25 species, which were detected in thermophilic areas around the world. *Geobacillus thermodenitrificans* N680-2 produces a nisin analogue termed geobacillin I (Fig.1 B). This peptide was produced by heterologous expression in *Escherichia coli*. NMR results showed that geobacillin I incorporates seven thioester cross-lings and demonstrates increased stability compared with nisin. Antimicrobial activity of geobacillin I is similar to nisin A. The genome of *G.stearothermophilus* NG80-2 contains a gene product with a ring topology distinct from any known lantibiotics. The geobacillin II exhibits antibiotic activity against Bacillus only (Garg et al., 2012). Only bacteriocins type I nisin, mutacin (Fig. 1C) and planeosporin are active against multidrug resistant Gram-positive bacteria (Severina et al., 1998; Fontana et al., 2006). Bacteriocin production is stabile even at 55 °C and is dependent on the time of incubation, pH and concentrations of nitrogen.

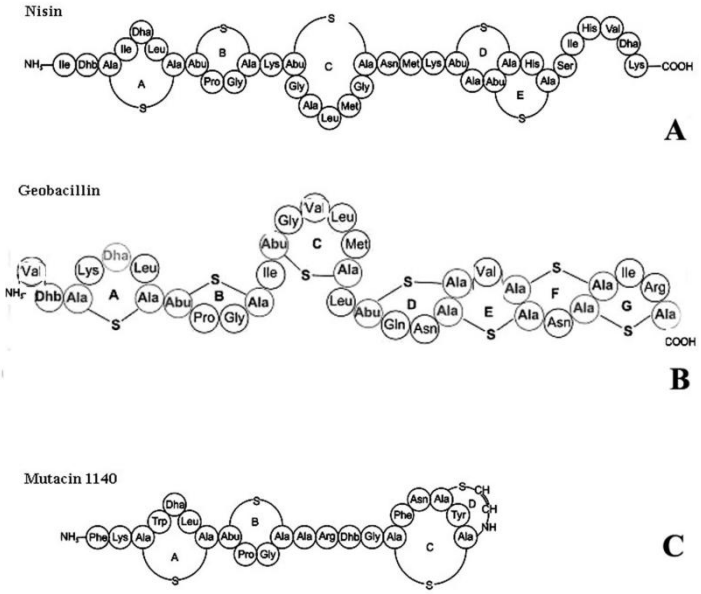

FIG.1. COMPARISON OF NISIN (A), GEOBACILLIN (B) AND MUTACIN (C). LANTIONES ARE THIOESTER-BRIDGES AMINO ACIDS. THEIR STRUCTURES ARE VERY STABLE AND ALLOW A CONFORMATIONAL CHANGES LEADING TO ENHANCED RECEPTOR SELECTIVITY AND PROTECT THE PEPTIDES AGAINST PROTEOLYTIC DIGESTION.

Dhb*- dehydrobutiline;* ***Dha****-dehydroalanine;* ***Abu-*** *aminobutyric acid.*

From thermal areas near to Yellowstone National Park Geobacillus M7 strain was isolated. The cells of this bacterium are globous and they are covered by a capsular layer with bacilliform structures. The bacteria generate petal shaped colonies when grown on nutrient agar at neutral pH and temperatures between 55-65 °C. 16S RNA of M-7 has a 97 % similarity with *G.stereothermophilus*. This strain produces volatile compounds (VOCs) with antibacterial activity such as benzaldehyde, acetic acid, butanol-3-methylbutanoic acid, 2- methyl-butanoic acid, propanoic acid, 2- methyl and benzeneacetaldehyde. These compounds inhibit growth of *Aspergillus fumigatus, Botrytis cinerea, Verticullium dahliae,* and *Geotrichum candidum* after 48h, and cells are killed after 72 h exposure. A mixture of synthetic volatile compounds at the same ratios as those found in the *Geobacillus* M-7 has the same inhibitory effect on activity of the test organism (Ren et al., 2010). *Aeribacillus palidus* SAT4 produses antimicrobial peptide at extreme conditions at pH 5.0, glucose concentration 2%, glutamic acis at 1.5% and under agitation at 100 rpm and 55°C. Antimicrobial compound was isolated from supernatant fluid with precipitation with ammonium sulphate to 50% saturation. Sediment was fractionationed through Sephadex G-75 permeation chromatography. Antibacterial activity was detected against *S.aureus, M. luteus* and *Ps.aeruginose*.

Thermophilic strain of *B.licheniformis* synthetised bacillosin 490. The peptide was inactivated by pronase E and proteinaseK. The peptide is good antibacterial agent, stabile to heath treatment and wide pH range (Martirant et. al, 2002).

Several Archae can synthetized a small peptides (archeocins) with potential interest to biotechnology (Charlesworth and Burns, 2015). *Sulfolobus islandicus* produce peptide sulfolobicin at pH from 2-4 and temperatures between 65 °C and 85 °C. Halocins are produced from halophilic rods (Torroblance et. al, 1994). Halocins forms two groups based on size. Microhalocins are about 3.6 kDa and higher halocins of 35 kDa. Some halocins are able to inhibit growth of *S.solfataricus*.

II. PEPTIDES STRUCTURALLY RELATED TO NISIN

Structurally similar substances to nisin were found in many bacteria. Subtilin is 32amino acids pentacyclic lantibiotic (Fig. 2A) was identified in *Lactobacillus lactis* (Ross et al., 2002). The cluster for subtilin contains specifies genes for subtilin peptide SpaS, posttranslational lantoin formation SpaBC, and translocation gene Spa T for modified species. Proteases (AprE) WprA and Vpr are involved in processing of subtilin (Corvey et al., 2003). Subtilin self-protection is mediated by ABC-translocator Spa FEG and lipoprotein Spa I (Klein and Entian 1994; Stein et al., 2003b). Biosynthesis of subtilin is regulated by sensor histidine kinase SpaK and regulatory protein SpaR that binds to spa-box of DNA, supporting expression of the genes for subtilin biosynthesis spaS, spa BTC and self protection protein Spa FEG (Stein et al., 2003b; Kleerebezem, 2004). Expressions of SpaRK are regulated by sporulation specific factor SigH, which is repressed during exponential growth by regulator AbrB (Fawcett et al., 2000). These data indicate that production of subilin is under dual control by culture density in quorum sensing mode, where subtilin response to the growth phases is directed by the Abrb/SigH (Stein et al., 2002b).

Ericin S (Fig. 2B) is closely related to the subtilin cluster. Subtilisin differs from ericin in four amino acid residues only, but their antibiotic activity is comparable. Ericin A (Fig. 2C) has different amino acid composition and ring organization with ericin S. Although ericin A is fully matured and is produced in equal quantities as ericin S, single synthetases EriC catalyses the development of two different products: ericin A and S. Requirements for single synthetase (EriBC) indicate flexibility of the lantibiotic biosynthetic route.

Mersacidin (Fig. 2D) is comprised of three melane rings along with dehydroalanine and aminovinylmethylcysteine residues. The peptide is synthesized at the beginning of the stationary phase of growth (Guder et al., 2002). Connection between cellular regulatory systems of *B. subtilis* and the mersacidin regulatory network is not known, but Mrsd the Flavin-containing cysteine decarboxylase (HFCD) catalyses oxidative decarboxylation of the C-terminal cysteine of mescacidin pro-peptide. Introduction of amino acids to mersacidin rings exhibits a loss of activity.

Sublancin 168 (Fig. 2E) contains two disulphide bridges and a β-methyllananthionine bridge. A hybridization probe based on the peptide sequence was used to clone the pre-sublancin gene, which encoded a 56-residue polypeptide consisting of a 19-residue leader segment and a 37-residue mature segment. The mature segment contained one serine, one threonine, and five cysteine residues. The sublancin leader was similar to the known type AII lantibiotics, containing a double-glycine motif that is typically recognized by dual-function transporters. A protein encoded immediately downstream from the sublancin gene possessed features of a dual-function ABC transporter with a proteolytic domain and an ATP-binding domain. The antimicrobial activity spectrums of sublancin were like other lantibiotics, inhibiting Gram-positive bacteria but not Gram-negative bacteria; and like the lantibiotics, nisin and subtilin, are able to inhibit both bacterial spore outgrowth and vegetative

growth. Sublancin is an extraordinarily stable lantibiotic, showing no degradation or inactivation after being stored in an aqueous solution at room temperature for two years (Paik et al., 1998).

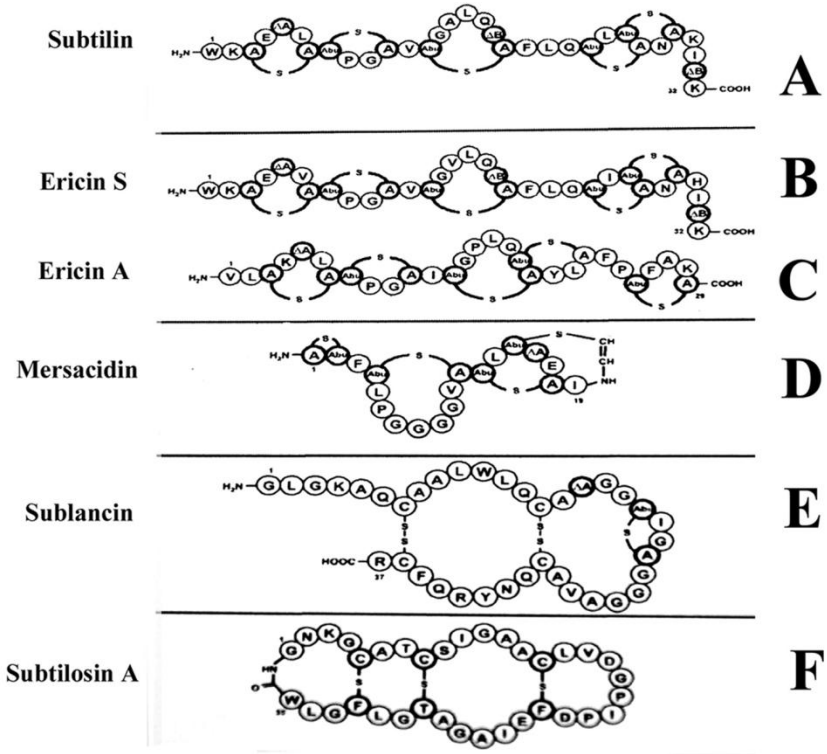

FIG.2. PENTACYCLIC LANTIBIOTICS -SUBTILIN (A); ERICIN S (B); ERICIN A (C). UNUSUAL LANTIBIOTICS WITH MACROCYCLIC STRUCTURE AND WITH ONE MERSACIDIN (D); TWO–SUBLANCIN (E) ; AND THREE INTER-RESIDUAL LINKAGES SUBTILOSIN A (F).

Subtilolisin A (Fig. 2F) has a macrocyclic structure with three inter-residual linkages (Marx et al., 2001) and is produced by B. subtilis (Zheng et al., 1999; Stein et al., 2004). In the processing of subtilolisin AlbF (YwhN) protein and immunity proteins AlbB-D (YwhQPO) are included (Zheng et al., 2000). It has been shown that inter-residual connection is mediated by the thioester bond between cysteine sulphur and alfa amino acid carbons (Kawulka et al., 2004). Subtilolisin is active against Gram-positive bacteria including Listeria (Zheng et al., 1999). The Antilisterial bacteriocin cluster encodes AlbA (YwiA) protein which is probably involved in post-translational modification of pre-subtilosin. Expression of the anti-listerial bacteriocin (sbo-alb) is under AbrB control (Zheng et al., 1999) and under stress conditions (Nakano et al., 2000).

From municipal solid waste a strain of Brevibacillus borstelensis RH 102 was isolated a component with good activity against G+ bacteria (M. flavus, S .aureus, B. subtilis and Difzia K44). Antibiotics produced at 60 °C that are soluble in methanol and water suggests a polar nature of their active components (Venugopalan et al., 2013).

III. TWO COMPONENT LANTIBIOTICS

Lacticin 3147 (Fig. 3A) contains two melan and two lan rings D-alanine, and two Dhb residues (Ryan et al., 1996). Lacticin 3147 was identified in a supernatant solution of Lactococcus lactis (DPC3147). This bacteriocin is very active against Listeria monocytogenes and resistant strains of Staphylococcus aureus, vancomycin resistant Enterococci, penicillin resistant Pneumococcus and Streptococcus mutant strains (McAuliffe et al., 1999). Lacticin 3147 is an effective protective agent in the production of cheese. Solid phase peptide synthesis was used in examination of the role of lan and melan residues in lactin 3147. Three ring analogues were synthesized. When thioester of lan or melan is oxidized, the peptide loses its antibacterial activity. Lactococcus lactis also produces lactin 481 containing one melan, andthe two lan rings with one Dhb residue. Each ring can exist as lan or melan, and the peptide remains active. When the ring was opened the peptide lost activity (Rince, 1994).

Haloduracin β (Fig. 3B) is a two-component lantibiotic comprising α-globular peptide and elongated β–peptide. This peptide was identified in *Bacillus halodurans*. Haloduracin α consists of one lan, one cysteine, two melan rings and three Dhbs.

Haloduracin β contains one lan, three melan groups and three Dhbs. Haloduracin is more stable at pH 7 than nisin. Ring A has a small effect on activity in contrast to rings C and D that are important for activity. N-terminal cysteine of peptide is not essential for activity. Haloduracin synthesis is accompanied by sporulation and stationary cultures and spores containing haloduracin peptides were collected. Two products with 2.332 Da and 3.046 Da were identified (McClerren et al., 2006).

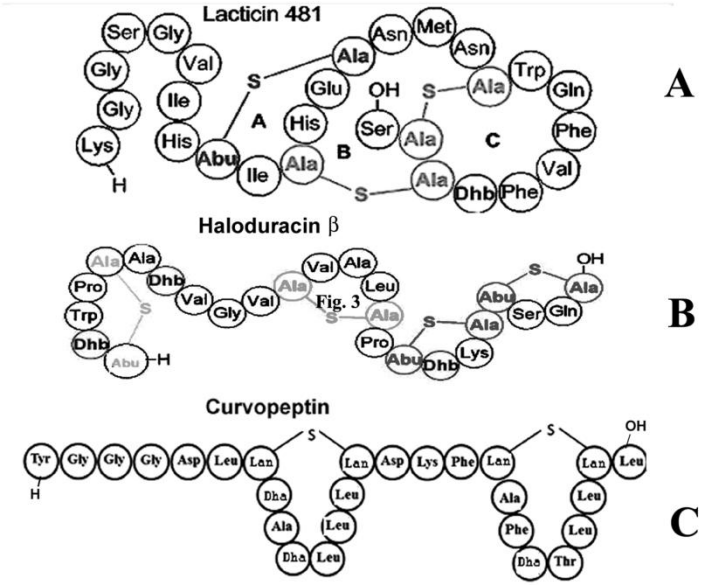

FIG.3. THE TWO-PEPTIDE LANTIBIOTICS DESCRIBED AMONG BACILLI HALODURACIN (FIG. 3B) AND LICHENICIDIN ARE CLOSELY RELATED TO TWO-PEPTIDE LANTIBIOTICS PRODUCED IN OTHER BACTERIA SUCH AS LACTICIN (FIG. 3A) PRODUCED BY *L. LACTIS* DPC3147. CURVOPEPTIN (FIG. 3C) FROM THERMOMONOSPORA CURVATA IS THE FIRST CLASS III LANTIBIOTIC OF THERMOPHILIC ORIGIN.

Thermomonospora curvata synthetizes Curvopeptins (Fig. 3C), that is labionin-carbocyclic variant of lantione (Krawczyk et al., 2012). Enzymatic studies with a precursor peptide mutant allowed the assignment of all dehydration sites. Curvopeptin biosynthesis of nine intermediates was studied by high-resolution mass spectrometry combined with deuterium-labeling. This approach makes it possible to create a model of three post-translational modification reactions: phosphorylation, elimination, and cyclization. These data support the characterizetion of the modifying enzyme CurKC, and in particular its specificity toward phosphorylation co-substrates. The enzyme accepted NTPs and dNTPs although the purine nucleotides ATP/dATP and GTP/dGTP were the preferred co-substrates. These data give important mechanistic insights into the processing and directionality of the multifunctional class III modifying enzymes (Jungmann et al., 2014).

Bacillus thermoleovorans S-II and *B. thermoleovorans NR-9* produce bacteriocins: thermoleovorin-S2 and thermoleovorin-N9, respectively. The bacteriocins are stable at pH from 3 to 10 and at temperatures 70-80°C. Thermoleovorins are produced during log-phase growth and are inhibitory to actively growing cells, they are effective against *Salmonella typhimurium, Branhamella catarrhalis, Streptococcus faecalis, and Thermus aquaticus.* The bacteriocins are digested by protease type XI and pepsin. Thermoleovorin-S2 was more thermostable than thermoleovorin-N9 at 70 and 80 °C. Thermoleovorins-S2 and -N9 apparently act by binding to susceptible organisms, resulting in lysis of the cell. Thermoleovorins-S2 has an estimated M(r) of 42,000, while thermoleovorin-N9 has M(r) of 36,000. (Novotny and Perry, 1992). The ability of thermoleovorins to inhibit *Salmonella typhimu*num, *Branhamella catarrhalis*, and *Streptococcus faecalis* was an unexpected finding. The antimicrobial effect on *Salmonella typhimurium* permits further investigation and may provide a use for these bacteriocins either in the food industry or as a feed additive for poultry. From composts thermophilic bacteria sensitive to penicillin G were isolated. Facultative autotrophic strains isolated from hot composts were Gram-variable rods with terminal endospores. Optimum temperature for growth was between 65-70 °C. These cells can growt either autotrophically or heterotrophically with hydrogen, or can oxidize thiosulfate. Under mixotrophic conditions they can utilize pyruvate or hydrogen with thiosulfate. DNA content and DNA: DNA homology of these strains had more than 75% with a reference strain of *Bacillus schlegelii.* Strains with inhibitory effects against pathogenic bacteria were isolated from cow manure compost. These bacteriocin-like components were thermal unstable (Abdel-Mohsein et al., 2003). Supernatant solutions of *Bacillus licheniformis* H1 inhibit growth of various Gram negative bacteria, e.g. *Listeria monocytogenes* ATCC 19111, but with the exception of *Pseudomonas fluorescents* ATCC11251, bacteriocin(s) are inactivated by proteolytic enzymes (chymotrypsin,

trypsin and papain) and are stable under pH from 3 to 9 and temperatures up to 75 °C. Using SDS-polyacrylamide gel electrophoresis of partially purified supernatant an active protein with M_r approximately 3.5 kDa was identified. *Streptococcus thermophilus* producing bacteriocin that lost antibacterial activity after incubation 1h at 60 °C was isolated from raw milk. When co-cultured with *Lactobacillus delbruecki* susp. *Lactis*, the production of bacteriocin was enhanced. The isolated bacteriocin termophilin T (Aktypis et al., 1998) from *S.thermophilus* ACA-DC 0040 inhibits both lactic acid bacteria and clostridia. The inhibition of clostridia was also described for acidocin B (tenBring et al., 1994) and pedocins (Daeschel, 1989; Ray et al., 1989). Thermophilin T regulates population dynamics in the yogurt production and hard cheeses. Since proteolytic enzymes and α-amylase inactivate thermophilin T, this indicates that bacteriocin is glycoprotein.

Paracin 1.7 is peptide produced by *Lactobacillus paracasei* HD1-7 from sauerkraut juice. The molecular mass of Parecin 1.7 was about 10 kDa. The N-terminal structure was similar to that of an ABC-oligopeptide transport system. Paracin 1.7 was sensitive to protease K, had antimicrobial activities at a broad pH range (3.0-8.0), and was heat resistant (121 °C for 20 min). Paracin 1.7 from *Lactobacillus paracasei* HD1-7 is a novel bacteriocin that has potential applications in food preservation. Paracin 1.7 shows a broad spectrum of activities against various strains in the genera of Proteus, Bacillus, Enterobacter, Staphylococcus, Escherichia, Lactobacillus, Micrococus, Pseudomonas, Salmonella and Saccharomyces, some of which belong to food borne pathogenic bacteria (Ge et al., 2016)

Amylocyclin is a circular bacteriocin produced by *Bacillus amyloliquefaciens* FZB 42 (Scholz et al., 2014) which is released into cultivation medium. Amylocyclin with molecular mass of 6. 381 Da is synthetized on ribosomes. Self-protections against drug produced is directed by small cationic peptides AcnC, AcnO, AcnE and AcnF. The drug inhibits Gram-positive cells only. Amylocyclicin is released into the culture medium by wild-type strain *B. amyloliquefaciens* FZB42 and *sfp* mutants derived from there. It can be obtained from ammonium sulfate precipitation of the supernatants, followed by extraction of the pellet with methanol. In addition, the bacteriocin is attached in an appreciable amount to the outer surface of the bacterial cells, from where it can be extracted with a 50% aqueous acetonitrile–0.1% trifluoroacetic acid. Such surface extracts are the source of choice for further purification and characterization of the bacteriocin.

IV. NON-RIBOSOMAL SYNTHESIS OF PEPTIDE ANTIBIOTICS

Large multienzymes non-ribosomal peptide synthetases (NRPSs) contain domains that catalyse ordered selections and polymeration of amino acid residues (Sieber and Marahiel 2003; Finking and Marahiel, 2004). Elongation steps in peptide biosynthesis need three core domains: i) The 350 amino acid residues of adenylation domain, are required for recognition of cognate amino acid, which resembles the acylation of tRNA synthetases during ribosomal peptide synthesis. ii). The peptidyl carrier domain containing 4'phosphopantheine group accepting adenylated amino acid under thioesterification and release of AMP. The 4'phosphopantheine cofactor serves as a transporter of intermediates between various catalytic domains. Peptidyl carrier proteins are posttranslationally modified from inactive apoforms to holoforms by 4´phosphopantheine-transferases (Lambalot et al., 1996). iii) Condensation domains (450 aa), which are located between pair of adenylation and peptidyl carrier domains catalysing formation of peptide bonds (Herbst et al., 2013). Biosynthesis is terminated by cyclization of the peptide (Kohli and Walsh, 2003) and such reactions are catalysed by thioesters-part of C-terminus. Lipopeptide antibiotics with β-hydroxyl or β amino fatty acids are synthetized in *Bacillus subtilis*.The branching and length of the chains of amino and fatty acids participate in microheterogeneity (Kowall et al., 1998). The most-well known lipopeptide surfactin (20nM) causes a decrease in tension of water from 72 to 27 $mMm,^{-1}$and it is an efficient detergent on cell membranes (Carrillo et al., 2003). PCR screening for the presence of nonribosomal synthetase and polyketide synthetase show a role of antibiotic lipopeptides as a potential resource of novel therapeutic drugs (Palomo et al., 2013).

Rhizovital is a lipopeptide antibiotic produced by *B. amyloliquefaciens* FZB42 (Sylla, et al., 2013) and the product requires sfp-dependent 4´phosphopanteinyl transferase to transmit 4´phosphopanteinyle from coenzyme A onto peptidyl carrier protein. RhizoVital 42 fl. suppresses *Botrytis cinerea* infections.

Surfactin (Fig. 4A) catalyse the three peptide synthetases Srf A-C. The thioesterase/acyltransferase enzyme SrtD initiates the process (Steller et al., 2004). The excretion of surfactin by passive diffusion across the cytoplasmic membrane is anticipated. Resistance to surfactin is acquired by the YerP multidrug efflux pump (Tsuge et al., 2001a). Production of surfactin is regulated by the 4´phosphopantheine transferase Sfp that transmit inactive apoform of surfactin and fengycin synthetase to active holoform (Lambalot et al., 1996; Mootz et al., 2001). The transfer of native *stp* allel into *Bacillus subtilis* induces the production of surfactin (Nakano et al., 1992) and fengycin (Tosato et al., 1997). Biosurfactant from certain strains of Bacillus and Pseudomonas are mixtures of different lipopeptides or isoforms (Naruse et al., 1990; Abalos et al., 2001; Vater et al.,

2002; Mukherjee and Das 2005). Surface tension or antimicrobial properties of lipopeptides are dependent on its molecular structure. Branching and length of the chains of amino and fatty acids participate in microheterogeneity (Kowall et al., 1998). The antimicrobial part of the biosurfactant is formed by lipopeptides. The biosurfactant and surfactin showed overlapping patterns in IR spektra, characteristic of lipopeptides (Lin et al., 1994). The iturin family includes cyclic lipopeptides mycosubtilin (Fig. 4B), iturins (Fig.4C), and bacillomycins (Fig. 4D). These compounds are antifungal and haemolytic, but their antibacterial activity is low (Thimon et al., 1995). The synthesis of these peptides catalyses similar nonribosomal peptide synthetases: mycosubtilin (Duitman et al., 1999), iturin (Tsuge et al., 2001b) and bacillomycin synthetases (Moyne et al., 2004). Fengycin (plipastatin) (Fig. 4E) inhibits growth of filamentous fungi (Vanittanakom et al., 1986) and contains β-hydroxy fatty acids ligated to the N-terminus of a decapeptide including four D-amino acids. C terminal residue of the peptide part is connected to the tyrosine residue, forming branching points of acylpeptide and cyclic lactone. Fengycin is synthesized by a complex of fengycin synthetases (Fen1-Fen5) (Steller et al.,1999) that are regulated with *fen* operon, catalysing different properties as cyclization, branching and unusual constituents. For fenglycin biosynthesis, the UP element between -55 and -39 position in *feng* DNA of *B. subtilis* is important. Other factors than UP may regulated the transcription of fengycin. More detailed analysis must be conducted as to how these factors operate in biosynthesis of fengycin.

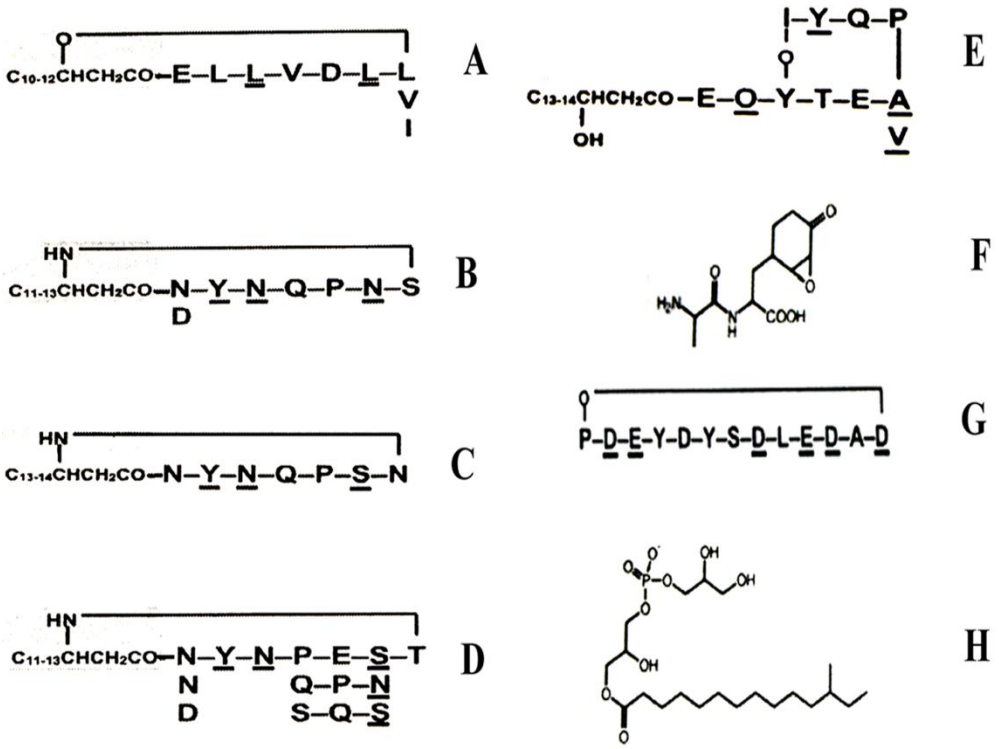

FIG.4. NON-RIBOSOMALLY GENERATED PEPTIDE ANTIBIOTICS. SURFACTIN (FIG.4A); ITURIN (FIG. 4B); MYCOSUBTILIN (FIG.4C); BACILOMYCIN (FIG.4D), FENGYCIN (FIG.4E); BACILYSIN (FIG. 4F); MYCOBACILLIN (FIG.4G) AND RHIZOCTICIN (FIG. 4H).

Taromycin A is a lipopeptide antibiotic produced by marine actinomycete *Saccharomonospora* CNQ-490. Taromycin gene *tar* is similar to the antibiotic daptomycin from *Streptomyces raseosporus*, but there are differences in the three amino acids and a lipid side chain (Yamanaka et al., 2014). *Streptomyces roseosporus* produced an acidic lipodepsipeptide antibiotic Daptomycin by a nonribosomal peptide synthetase (NRPS) mechanism *(*Walsh and Fischbach, 2010). Daptomycin is composed of a 13-member peptide, cyclized to form a 10-member ring and a 3-member exocyclic tail, to which is attached a decanoic acid side chain to the N terminus of l-Trp_1. In the biosynthesis of daptomycin by *S. roseosporus* three nonribosomal peptide synthetases: DptA, DptBC, and DptD are involved.

Fusaricidins are a group of lipopeptide antibiotics produced by *Paenibacillus polymyxa* (formerly *Bacillus polymyxa*) and consist of a guanidinylated β-hydroxy fatty acid linked to a cyclic hexapeptide containing four amino acid residues in the d-configuration (Kajimura and Kaneda, 1996, Kajimura and Kaneda, 1997). In most peptides epimerization of l-amino acids requires a specialized domnain. An l-amino acid is activated, and the epimerization (E) domain then catalyzes l-to-d

racemization of the thioester-bound amino acid. In the lipopeptide arthrofactin, there are no E domains detected in any of the 3 arthrofactin synthetases, although 7 of the 11 amino acids are in the d-configuration. Additional analyses demonstrated that A domains in modules corresponding to d-amino acids were specific for activation of l-isomers, and epimerase activity was supported by a new type of C domain with dual epimerization and condensation functions. A third strategy for incorporation of d-amino acids involves the direct activation of d-isomers by the A domains.

Bacilysin (Fig. 4F) the epoxy-modified amino acid anti-capsin (l-alanine [2.3-epoxycyclohexane-4] l-alanine), depend on the *ywfBCDEFGH* cluster (Inaoka et. al., 2003) Nonribosomal synthesis of dipeptide is synthesized by *Bacillus amyloliquefaciens* FZB42 and is independent of Sfp. The genes *basDE*(*ywfEF)* encode the function of amino acid ligation as well as bacilysin self-protection (Steinborn et al., 2005). Bacilysin is negatively regulated by GTP via the transcription regulation *AbrB* and *Cod Y*. Positive regulation is directed by guanosine-5-diphosphate-3-diphosphate (Inaoka et al., 2003) and a quorum sensing mechanism utilizing peptide PhrC (Yazgan et al., 2003). Bacilysin- has anticyanobacterial activity and thus could be used to moderate the detrimental algal effects (Wu et al., 2014). Bacilysin caused apparent changes in the algal cell wall and cell organelle membranes, and this resulted in cell lysis. Meanwhile, there was downregulated expression of *glmS*, *psbA1*, *mcyB*, and *ftsZ*—genes involved in peptidoglycan synthesis, photosynthesis, microcystin synthesis, and cell division, respectively.

Mycobacillin (Fig. 4G) is produced by *Bacillus subtilis* B_3. The molecule is formed with cyclic peptide composed of 13 residues of 7 different amino acids (Majumdar and Bose, 1960; 1996), and it is an exclusively antifungal antibiotic. Enzyme complex mycobacillin synthetase was created by the hydroxyapatite column chromatography and sucrose-density-gradient centrifugation; each of the fractions contained migrates as a single component in SDS/polyacrylamide-gel electrophoresis and gel electrofocusing. The Mr of the enzyme fractions A, B and C by gel filtration is 260 000, 190 000 and 105 000 and this, by SDS/polyacrylamide-gel electrophoresis, is 252 000, 198 000 and 108 000, respectively. None of the enzyme fractions appears to possess a subunit structure.

Kocurin: Despite the broad distribution of *Micrococcaceae* in sponges, very little is known about the occurrence of the natural products biosynthetic pathways and the production of bioactive compounds, especially by species of the sponge-associated genera *Kocuria* and *Micrococcus*. The production conditions of kocurin by the *Kocuria* strain F-276,345 were analyzed with a time course study monitoring the growth and kocurin production over 4 days. Kocurin is closely related to two known thiazolyl peptide antibiotics with a similar mode of action, produced by a soil strain of *Streptomyces* and *Planobispora rosea*. The strains were PCR screened for the presence of secondary metabolite genes encoding nonribosomal synthetase and polyketide synthases (Palomo et al., 2013), a new member of the thiazolyl peptide family of antibiotics, as a resource for novel drugs.

Rhizocticin (Fig. 4H): Rhizocticins are dipeptide or tripeptide antibiotics and commonly possess l-arginyl-l-2-amino-5-phosphono-3-cis-pentenoic acid. Rhizocticins are produced by the Gram-positive bacterium *B. subtilis* ATCC6633. Rhizocticin A is l-arginyl-l-2-amino-5-phosphono-3-cis-pentenoic acid (Arg-APPA); rhizocticin B is-valyl l-arginyl-l-2-amino-5-phosphono-3-cis-pentenoic acid (Val-Arg-APPA); and rhizocticin C and D are the same as rhizocticin B but Val is substituted with l-isoleucine (Ile) and l-leucine (Leu), respectively. Rhizocticins enter the target fungal cell through the oligopeptide transport system (Kugler et al., 1990) and then are cleaved by host peptidases to release(Z)-l -2-amino-5-phosphono-3-panteonic acid (APPA), which inhibits threonine synthase, catalyzing the pyridoxal 5′-phosphate (PLP)-dependent conversion of phosphohomoserine to l-threonine (Laber et al., 1994). APPA interferes with the biosynthesis of threonine and related metabolic pathways, initially affecting protein synthesis and leading to growth inhibition. The antifungal effect of rhizocticin A was neutralized by the presence of oligopeptides and amino acids. Phosphinothricin (PT) is the only known phosphinic acid natural product, a non-proteinogenic amino acid found in a number of peptide antibiotics. In *Streptomyces viridochromogenes* were discovered the compound as a component of a tripeptide antibiotic (PT-Ala-Ala) produced by (phosphinothricin-tripeptide, PTT) or *Streptomyces hygroscopicus* (bialaphos PT), later it was found as a component of phosalacine, a PT-Ala-Leu tripeptide produced by *Kitasatospora phosalacina* and trialaphos (PT-Ala-Ala-Ala), which is a tetrapeptide produced by *Streptomyces hygroscopicus* KSB-1285 (Higgins et al., 2005; Omura et al., 1984). PT is a structural analog of glutamate and a potent inhibitor of glutamin synthetase. As a free amino acid, PT has relatively poor antibiotic activity, probably due to ineffective transport. Many organisms utilize the peptide versions that are hydrolyzed by cytoplasmic peptidases, releasing the active component. Because glutamine synthetase plays an essential role in pH homeostasis in plants, PT is an outstanding herbicide and both the tripeptide and synthetic versions of the monomer are widely used in agriculture (Thompson and Seto 1995).

Thermotolerant actinobacteria, e.g. *Streptomyces tauricus, S.lanatus, S.coeruleorubidis,* were isolated from the desert of Kuwait during the hot season. These cells were found to inhibit the rhizosphere of many plants and exhibit antimicrobial activity, leading to the protection of plants against phytopathogens (Xue et al., 2013). Thermotolerant streptomycetes isolated from the Himalayan Mountains *(Streptomyces phaeoviridis, S.griseoloalbus, S. viridogens*) inhibit methicillin resistant and vancomycin resistant strains of *Staphylococcus aureus.* Strains of *Streptomyces viridogens* and *S. rimosus* inhibit growth of pathogenic fungi (*Fusarium solani, Rhizoctoconia solani, Colletotricum falcatum* and *Halminthosporium oryzae*) (Radhakrishnan et al., 2007), furthermore, many actinobacteria secreted chelating molecules, retaining a solube form of iron in the rhizosphere of plants grown in iron deficient soil.

The zeamines are peptide antibiotics produced by *Serratia plymuthica* RVH1 (Masschelein et al., 2015). They exhibit activity affecting the integrity of cell membranes of a broad range of bacteria, including multidrug-resistant pathogens. The zeamines irritate rapid release of carboxyfluorescein from unilamellar vesicles with various phospholipid compositions, allowing them to interact directly with the lipid bilayer. The zeamine also facilitated the uptake of small molecules, such as 1-N-phenylnaphtylamine, making it possible to permeabilize the Gram-negative outer membrane. Zeamine at concentrations required for growth inhibition, causes lysis of membrane as indicated by microscopy. It is probable that the bactericidal activity of the zeamines derived from permeabilization membranes caused electrostatict interactions with the negatively charged part of the membrane components.

Pyrrolamides (e.g. congocidine, distamycin, kikumycins, pyrronamycins, noformycin), constitute a family of natural products produced by *Streptomyces* or related actinobacteria. They exhibit a variety of therapeutic applications, against viral, bacterial, tumor and parasitic activities (Juguet et al., 2009). Heat-stable antifungal factor (HSAF) is a secondary metabolite produced by the bacterium *Lysobacter enzymogenes* strain C3. The chemical structure of HSAF suggests that the biosynthesis of this molecule could involve both polyketide and nonribosomal peptide mechanisms, as seen in bleomycins and other natural products. HSAF appears to target a group of sphingolipids that are required for polarized growth of filamentous fungi and appears to be absent from mammals and plants (Yu et al., 2007).

Congocidine (netropsin) consists of peptides that bind to the minor groove of DNA and is a pyrrole-amide antibiotic produced by *Streptomyces ambofaciens.* Congocidine does not bind single stranded DNA or double stranded RNA; it protects such regions from DNase I and other endonucleases, and also inhibits topoisomerases. This peptide disrupts the cell cycle, prolonging G and arresting in G. Congocidine is assembled by a nonribosomal peptide synthetase with unusual features (Juguet et al., 2009). Its single adenylation domain acts applicable, and one of its condensation domains preferably uses CoA- as a substrate.A free standing module and the proposed enzyme mechanism may be used to the synthesis of many oligo-pyrrole molecules, and especially distamycin, which comprises three 4-aminopyrrole-2-carbonyl groups.

V. CONCLUSION

The post-genomic era will provide much new information on target sites and interactions of protein-protein and protein nucleic acids interactions. One of ultimate goals is to adopt order structures of molecules that can past through cell membranes and interact with specific targets. Peptide antibiotics from thermophiles are suitable for the handling of the structure and are more resistant to proteolytic degradation. Peptides can be safer and more selective than small molecular drugs. There is no need for chemical purification and subsequent separation of isomers. There are several hundred of polypeptides that are in various steps of clinical development. There is need for new antimicrobial peptides with hydrophobicity and α-helicity for their activity against mycobacteria in the fight against drug resistant tuberculosis. Natural peptides can be used as food preservatives, chemotherapeutics, and efficient detergents.

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