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REVIEW

# Antimicrobial peptides produced by *Brevibacillus* spp.: structure, classification and bioactivity: a mini review

**Xu Yang[1] · Ahmed E. Yousef[1,2]**

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## Abstract

Species that are currently listed under the genus *Brevibacillus* (formerly, *Bacillus brevis* cluster) have been a rich source of antimicrobial peptides for many decades. The first known peptide antibiotic, gramicidin, is presumed to be produced by a *Brevibacillus* sp. Members of the genus are widely spread in nature. They can be found in a variety of environments including intestinal tracts of animals, seawater, and soil. Some *Brevibacillus* strains have been used commercially as probiotics. Bioactive peptides produced by *Brevibacillus* spp. include antibacterial, antifungal and anti-invertebrate agents. *Brevibacillus* antimicrobial peptides are synthesized through ribosomal or nonribosomal pathway; these two groups can be further categorized based on specific structural features such as cyclization and presence of lipid chain. Some of the antimicrobial compounds produced by this genus share structural similarities that were overlooked previously. For example, the structural similarity between BT peptide, brevibacillin, and bogorol was revealed only recently. Here we review and classify *Brevibacillus* antimicrobial peptides and summarize their bioactivities and potential applications.

**Keywords** *Brevibacillus* · Antimicrobial peptides · Ribosomally-synthesized peptides · Nonribosomally-synthesized peptides

## Introduction

*Brevibacillus* spp. have been found in almost all environmental habitats, including plants, animal intestinal tract, seawater, soil and many food products (Ruiu 2013). Members of the genus have been applied as probiotics for a long time (Sanders et al. 2003). *Br. laterosporus* BOD strain, in particular, has been used as a commercial human probiotic since 1989 (O'donnell 1995). *Br. laterosporus* isolated from honeybees digestive tract was reported to have probiotic effect and can promote growth of the host (Khaled et al. 2017). *Brevibacillus* spp. have not been associated with health hazards to humans, but some species caused spoilage of foods, especially milk (Gopal et al. 2015). In China, *Br. borstelensis* was isolated from whole and skim milk powders (Yuan et al. 2012).

*Brevibacillus* spp. are rod-shaped gram-positive or gram-variable firmicutes, and members of the genus are mostly strict aerobes (Logan and De Vos 2009). The genus was reclassified in 1996 from *Bacillus brevis* cluster, based on its 16S rRNA gene sequence and further phylogenetic analysis. According to Shida et al. (1996), the genus *Brevibacillus* included ten previous *Bacillus* species (the *B. brevis* cluster), which were *Brevibacillus agri, B. borstelensis, B. brevis, Brevibacillus centrosporus, Brevibacillus choshinensis, Brevibacillus formosus, B. laterosporus, Brevibacillus parabrevis, Brevibacillus reuszeri*, and *Brevibacillus thermoruber*. Currently, there are 20 species under the genus *Brevibacillus* (Hatayama et al. 2014; Panda et al. 2014).

Before its genetic reclassification, members of *B. brevis* cluster served as a rich source of antimicrobial peptides (AMPs), including gramicidin A and gramicidin S, the first linear and cyclic peptide antibiotics used clinically, respectively (Wang et al. 2016). After reclassifying *B. brevis* cluster into *Brevibacillus*, the genus remained a reliable source for novel AMPs. In this mini-review, AMPs produced by *Brevibacillus* spp. (and the previous *B. brevis* cluster),

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were classified based on biosynthesis pathway and structural traits. Here, we define AMP as the antimicrobial agent that contains a peptide chain as the main building block, regardless its linear or cyclic configuration, or if it contains nonproteinogenic amino acids (e.g., D-amino acids) or non-proteinaceous composition (e.g., a lipid chain or polyamine structure).

## Classification of antimicrobial peptides

AMPs can be classified using different criteria. When the producing organism is considered, there are bacterial, fungal, plant and animal AMPs. Considering the biosynthetic pathways, AMPs may be divided into ribosomally- and nonribosomally-synthesized categories. Ribosomal synthesis involves translating mRNA into polypeptide chains based on genetic code. Post-translational modification can occur in many ribosomally-synthesized peptides leading to amino acids having non-proteinogenic structure (McIntosh et al. 2009). Nonribosomal synthesis involves non-ribosomal peptide synthetases (NRPSs), which are multi-enzymatic, multi-domain megasynthases. NRPSs function like an assembly line where one enzymatic module integrates one amino acid into the polypeptide chain (Huang et al. 2014). In most cases, each enzymatic module contains adenylation (A), thiolation (T), and condensation (C) domains (Ansari et al. 2004). If the mechanism of action is the classification criterion, two groups are recognized: (i) AMPs that target cell-surface components, i.e., cell wall, membrane and membrane-bound protein, and (ii) AMPs that target intracellular components such as ribosomes, and the synthesis machinery for DNA and RNA (Sadredinamin et al. 2016). Recently, Wang (2015) proposed a classification based on the covalent bonding patterns of AMPs. The researcher divided all AMPs into four groups: linear polypeptide, sidechain-linked, sidechain-backbone linked, and backbone–backbone linked circular group.

Ribosomally-synthesized AMPs (i.e., bacteriocins) have been grouped based on whether they are produced by gram-positive or gram-negative bacteria (Rea et al. 2011; Rebuffat 2011). Bacteriocins produced by gram-positive bacteria may have been post-translationally-modified or unmodified. The latter refers to bateriocins that are not subjected to extensive post-translational modifications during biosynthesis. Cotter et al. (2005) classified the bacteriocins of gram-positive bacteria into lanthionine-containing, non-lanthionine-containing, and bacteriolysin classes.

Considering that *Brevibacillus* AMPs are only a subset of the larger antimicrobial agents spectrum, and that some members of this subset share interesting structural similarities, a customized classification scheme is proposed. *Brevibacillus* AMPs are first classified based on biosynthetic pathway, into ribosomally-synthesized and nonribosomally-synthesized peptides (Fig. 1). Since the majority of currently-known *Brevibacillus* AMPs are nonribosomally-synthesized, this subgroup is further categorized into peptide and lipopeptide, depending on the presence of a lipid

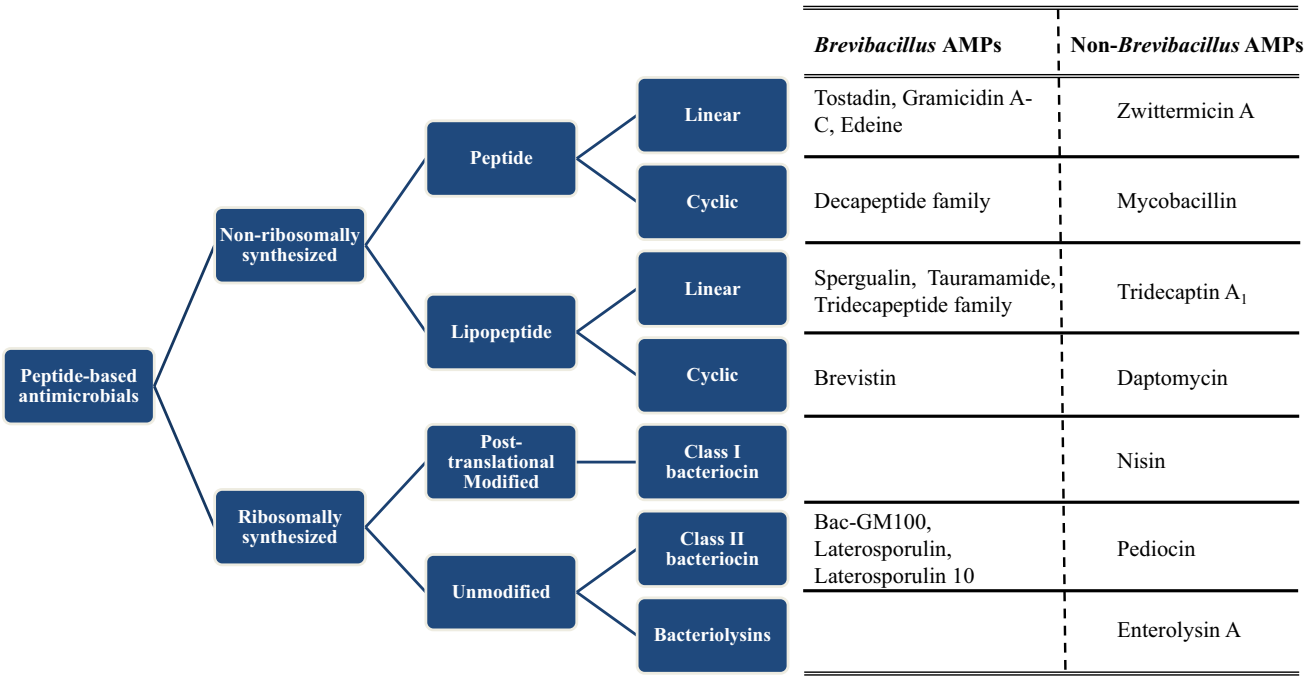


**Fig. 1** Classification of antimicrobial peptides (AMPs) isolated from *Brevibacillus* spp. based on biosynthetic pathway and structural trait

chain acylating the *N*-terminal. Peptides and lipopeptides are divided further based on structural configuration into linear and cyclic categories. Despite the limited number of ribosomally-synthesized AMPs known to be produced by *Brevibacillus* spp., the classification of this category by Cotter et al. (2005) will be included in our proposed scheme (Fig. 1).

## Nonribosomally-synthesized peptides produced by *Brevibacillus* spp.

Nonribosomally-synthesized peptides are secondary metabolites synthesized through peptide synthetases (Stachelhaus et al. 1999). As reviewed by Finking and Marahiel (2004), and modified in the current manuscript, presence of any of the following structural features in an AMP is suggestive of the nonribosomal synthesis origin: (i) fatty acid acylation at peptide's *N*-terminal (e.g., fengycin), (ii) nonproteinogenic amino acids, such as D-amino acids (e.g., gramicidin S), (iii) dihydroxybenzoate (e.g., enterobactin), and (iv) glycosylation (e.g., vancomycin). As indicated earlier, the classification of *Brevibacillus* nonribosomally-synthesized AMPs will take into account the presence of a fatty acid chain and linearity or cyclization of the molecule.

### Nonribosomal linear peptides

This category of peptides has linear configuration; i.e., lacks any ring structure. These peptides are synthesized through NRPSs, thus, may contain non-proteinogenic amino acids and fatty acid chains.

#### Tostadin

Tostadin was produced by *Br. brevis* XDH, a strain isolated from soil. Structure of tostadin was elucidated using mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy. Results revealed tostadin as a linear AMP containing nine amino acids: $Ser^{1}$-$Leu^{2}$-$Tyr^{3}$-$Lys^{4}$-$Leu^{5}$-$Thr^{6}$-$Cys^{7}$-$Lys^{8}$-$Phe^{9}$. The presence of nonproteinogenic D-configuration amino acids ($Lys^{4}$ and $Phe^{9}$) indicated that tostadin is synthesized nonribosomally. Tostadin exhibited antimicrobial activity against both gram-positive and gram-negative bacteria (Song et al. 2012).

#### Gramicidin A–C (linear gramicidin)

Gramicidins are structurally diverse compounds. Gramicidin A–C are linear pentadecapeptides while gramicidin S is cyclic decapeptide. Hotchkiss and Dubos (1940) discovered linear gramicidin from *Br. brevis* (previously *B. brevis*). The linear gramicidin contains 15 amino acid residues in either L- or D- configuration and the entire compound forms a β-helix-like structure. Both terminals of linear gramicidins are modified; –CHO at the *N*-terminus and $–NHCH_2CH_2OH$ at the *C*-terminus. Linear gramicidin is biosynthesized by NRPS, which has four multimodular structure containing 16 adenylation domains, with the last A-domain responsible for *C*-terminal modification (Kessler et al. 2004). Linear gramicidins are active against gram-positive bacteria (including *Streptococcus pyogenes, S. aureus* and *B. subtilis*) with no inhibitory effect against the gram-negative *Escherichia coli* (Wang et al. 2012). Gramicidin antimicrobial action is attributed to its ability to create transmembrane channels, which lead to membrane lysis (Wang et al. 2012). These channels allow the diffusion of intracellular component (e.g., potassium ions) out of the cell, leading to cell dysfunction. In general, membrane active AMP carries positively charged amino acid residues at cell's physiological pH. These cationic amino acids can bind to negatively charged cell membrane to disrupt its integrity (Yeaman and Yount 2003). Interestingly, when lysine residues were replaced by leucines in gramicidin A, the minimum inhibitory concentration (MIC) values were essentially identical, indicating the cationic amino acids of gramicidin A may have no role in its pore-forming activity (Wang et al. 2012).

Linear gramicidin is the first AMP used clinically (Wang et al. 2016). However, linear gramicidin has low solubility in water (< 50 nM) and could lead to hemolytic reaction to human cells at compound's bactericidal concentration. As a result, clinical use for linear gramicidin was limited to topical applications. For example, drugs containing linear gramicidin have been commercialized in Canada as antibiotic ointments (Wang et al. 2012). In addition, linear gramicidin is used commercially as one of the active ingredients in topical medications such as neosporinand polymicin B and gramicidin (U.S. Food and Drug Administration 2017).

#### Edeine

Edeine was discovered in 1959 as a metabolite of *Br. brevis* Vm4 (previously *B. brevis* Vm4), a soil isolate. Edeine is composed of five amino acid residues; four of them are nonproteinogenic, indicating that the AMP was synthesized through NRPS (Westman et al. 2013). Edeine contains a spermidine-polyamine structure at the *C*-terminus and a tyrosine residue at the *N*-terminus. Edeine has been reported to be broad spectrum, and it is active against bacteria and fungi (Czajgucki et al. 2006; Hill et al. 1994). Mode of action of edeine seems to be concentration dependent. Edeine inhibited DNA synthesis at < 15 µg/ml (Kurylo-Borowska and Szer 1972) while the antimicrobial compound became broad inhibitor (DNA synthesis, protein translation and synthesis) when its concentration exceeded 150 µg/ml (Cozzarelli 1977; Dinos et al. 2004).

### Spergualin

Spergualin is an AMP produced by *Br. laterosporus* (previously *B. laterosporus*). The AMP has a unique structure: a guanidino group acylating the *N*-terminus and a polyamine linked to *C*-terminus. Spergualin was reported to have broad-spectrum antimicrobial activity, i.e., active against both gram-positive and gram-negative bacteria (Takeuchi et al. 1981). Spergualin also was investigated as an antitumor compound, which significantly prolonged the survival of mice inoculated with leukemia cells with dosage at 6.25 mg/kg/day (Takeuchi et al. 1981). In addition, spergualin was reported to have low toxicity: 80 mg/kg of intravenous injection was not lethal to mice (Takeuchi et al. 1981).

## Nonribosomal cyclic peptides

A group of nonribosomal AMPs produced from *Brevibacillus* share structural similarities; they are cyclic in nature and consist of ten amino acids, thus, they are classified as nonribosomal cyclic decapeptides. Members of cyclic decapeptide group are gramicidin S, tyrocidine A–C, laterocidin and loloatins A–D. As shown in Table 1, the structural formula and discrepancies can be summarized as: Cyclo (Phe/Tyr$^{1}$- Pro$^{2}$- Val/Phe/Trp$^{3}$- Orn/Phe/Trp$^{4}$- Leu/Asn$^{5}$- Phe/Asp/Gln$^{6}$- Pro/Tyr/Trp/Leu$^{7}$- Val$^{8}$- Orn$^{9}$- Leu$^{10}$). Residues 8–10, which corresponding to Val-Orn-Leu, are conserved among all nine members of this cyclic decapeptide family. This conserved sequence has been reported to contribute to the amphiphilicity of gramicidin S, due to the positively-charged and hydrophilic ornithine side chain, projecting on one side, and the hydrophobic Leu/Val side chains projecting on the opposite side. These side chain structures seem to be critical for the antimicrobial efficacy of gramicidin S analogues (Prenner et al. 1999). In addition to the conserved amino acid sequence, subtle changes in structure among the variants may affect the antimicrobial spectrum and efficacy. For instance, within loloatins A–D, an additional hydroxyl group on Pro$^{2}$ residue of loloatin D leads to a four-fold decrease in its antimicrobial activity, compared to loloatin A–C (Gerard et al. 1999). In addition, the tryptophan on residue 3 of loloatin C provides the compound with antimicrobial activity against both gram-negative and gram-positive bacteria whereas the other loloatins are effective against gram-positives only (Scherkenbeck and chen 2002). The following is a description of the cyclic decapeptide family members; these are also depicted in Table 1.

### Gramicidin S

Soviet gramicidin (gramicidin S) was discovered in 1942 by Russian scientists in a culture of *B. brevis* strain (Gause and Brazhnikova 1944). According to several researchers, the producer of gramicidin S was reclassified to *B. migulanus* (Takagi et al. 1993), which was reclassified later as *Aneurinibacillus migulanus* (Shida et al. 1996; Berditsch et al. 2007; Mogi and Kita 2009). Other researchers still hold the opinion that gramicidin S was produced from a *Brevibacillus* sp. (Edwards and Seddon 2001; Chandel et al. 2010; Wang et al. 2010; Li et al. 2005).

As shown in Table 1, gramicidin S is a cyclic decapeptide molecule which consists of two identical pentapeptides (Val-Orn-Leu-Phe-Pro-). Gramicidin S molecule differs in 5–6 amino acids compared to other members of cyclic decapeptide (tyrocidine A–C, laterocidin and loloatins A–D). Gramicidin S is potent against gram-positive, gram-negative and fungi in liquid media (Prenner et al. 1999), but it also possesses high hemolytic activity (Scherkenbeck and chen 2002). It was proposed that gramicidin S compromises the integrity of lipid bilayer of cytoplasmic membrane, leading to cell death (Prenner et al. 1999).

Application of gramicidin S can be traced back to World War II, as the first cyclic antimicrobial peptide used clinically. In 1942, the same year gramicidin S was discovered, Soviet military hospitals had applied this antibiotic to treat infected wounds, and by 1943, the antimicrobial compound was used at the battlefront (Gause and Brazhnikova 1944; Gall and Konashev 2001). Subsequently, use of gramicidin S

**Table 1** Nonribosomally-synthesized cyclic antimicrobial decapeptide produced by *Brevibacillus* spp.

| Peptide | Chemical Structure | Reference |
|---|---|---|
| Gramicidin S | cyclo (**Phe-Pro**-Val-Orn-Leu-Phe-Pro-**Val-Orn-Leu**) | Gause and Brazhnikova, 1944 |
| Loloatin A | cyclo (Tyr-**Pro**-Phe-**Phe-Asn**-Asp-**Tyr-Val-Orn-Leu**) | Gerard et al. 1999 |
| Loloatin B | cyclo (**Phe-Pro**-Phe-**Phe-Asn-Gln-Trp-Val-Orn-Leu**) | Gerard et al. 1996 |
| Loloatin C | cyclo (**Phe-Pro**-Trp-**Phe-Asn-Gln-Trp-Val-Orn-Leu**) | Gerard et al. 1999 |
| Loloatin D | cyclo (**Phe**-Pro(OH)-Phe-**Phe-Asn-Gln-Trp-Val-Orn-Leu**) | Gerard et al. 1999 |
| Tyrocidine A | cyclo (**Phe-Pro**-Phe-**Phe-Asn-Gln-Tyr-Val-Orn-Leu**) | Lipmann et al. 1941 |
| Tyrocidine B | cyclo (**Phe-Pro**-Trp-**Phe-Asn-Gln-Tyr-Val-Orn-Leu**) | Lipmann et al. 1941 |
| Tyrocidine C | cyclo (**Phe-Pro**-Trp-**Trp-Asn-Gln-Tyr-Val-Orn-Leu**) | Lipmann et al. 1941 |
| Laterocidin | cyclo (Tyr-**Pro**-Phe-Phe-**Asn**-Asp-Leu-**Val-Orn-Leu**) | Xu et al. 2010 |

Conserved amino acid residues within the group are bold

was limited to topical applications due to its high hemolytic activity (Waki and Izumiya 1990; Xu et al. 1995). Considering the rapid bactericidal action of gramicidin S, Berditsch et al. (2016) reported that gramicidin S was applied successfully to treat infected root canals of patients.

#### Tyrocidines (tyrocidine A–C)

Tyrocidine was isolated from *B. brevis* which has been reclassified as *B. aneurinolyticus* (Spathelf and Rautenbach 2009; Munyuki et al. 2013). Interestingly, some species of *Brevibacillus* also may serve as producers of tyrocidine. Nakai et al. (2005) reported that an American Type Culture Collection strain, *Br. parabrevis* ATCC 8185, is capable of producing tyrocidine.

Tyrocidine exhibited bactericidal effect against gram-positives and antifungal activity (Munyuki et al. 2013; Vosloo et al. 2013; Scherkenbeck and chen 2002). Similar to gramicidin S, tyrocidine is a cytoplasmic membrane-active compound, which exerts bactericidal efficacy through membrane disruption (Munyuki et al. 2013). Tyrocidine is biosynthesized by NRPS. A thioesterase domain from tyrocidine NRPS gene cluster have been independently engineered to cyclize novel substrates and to generate new compounds (Trauger et al. 2000).

Feasibility of medical application of tyrocidine increased when combined with linear gramicidins, and this mixture is known as tyrothricin (Katz and Demain 1977). According to Lang and Staiger (2016), tyrothricin is active against bacteria, fungi and some viruses. The mixture has useful topical applications. For example, application of tyrothricin component in a wound gel system was reported to improve significantly wound healing in 33 healthy volunteers, especially with an earlier healing onset time (Wigger-Alberti et al. 2012). Tyrothricin did not induce resistances in targeted cells, thus it may serve as next generation antibiotics (Lang and Staiger 2016).

#### Loloatins (loloatin A–D)

The loloatins were discovered in cultures of *Bacillus* sp. MK-PNG-276A, a tropical marine isolate (Gerard et al. 1996). Whole genome sequencing results showed the presence of a loloatin biosynthesis gene cluster in *Br. laterosporus* (Djukic et al. 2011). Loloatins have four variants, A–D, with loloatin B being most abundant in producer culture (Gerard et al. 1999). The loloatins are effective against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and penicillin-resistant *Streptococus pneumonia*. Loloatins have been chemically-synthesized through solid-phase approaches (Ding et al. 2007; Scherkenbeck and chen 2002).

#### Laterocidin

Laterocidin was discovered from *Br. laterosporus* VKPM B-8287, and published in a Russian patent. The antimicrobial compound was active against bacteria, fungi and protozoa. The compound has been chemically-synthesized through solid-phase synthesis method (Xu et al. 2010).

### Nonribosomal linear lipopeptides

These nonribosomally-synthesized antimicrobial compounds have linear peptides that are acylated with lipid moieties at *N*-termini. Compared to other *Brevibacillus* AMPs, members of this group are relatively new and have interesting structural similarities.

#### Linear lipo tridecapeptide family

A number of AMPs produced by *Brevibacillus* spp. can be grouped into a nonribosomal linear lipo tridecapeptide family. Members of this family have linear configuration, a lipid moiety acylating the *N*-terminus of the peptide backbone, which is made of 13 amino acid residues. The family includes bogorol antibiotics (Bogorol A–E), brevibacillin and BT peptide (Table 2). The structural similarities and discrepancies are summarized as the following chemical formula: Bmt/(FA-Dhb)$^{1}$- Met/Met sulfoxide/Val/Leu$^{2}$- Orn$^{3}$- Ile/Val$^{4}$- Val/Ile$^{5}$- Val$^{6}$- Lys$^{7}$- Val$^{8}$- Leu$^{9}$- Lys$^{10}$- Tyr$^{11}$- Leu$^{12}$- valinol$^{13}$. The conserved residues 3, 7, and 10, are cationic amino acids, which grant the family cationic charge at cell's typical physiological pH. These positively charged

**Table 2** Nonribosomally-synthesized linear antimicrobial lipo tridecapeptide produced by *Brevibacillus* spp.

| Peptide | Chemical Structure | Reference |
|---|---|---|
| Bogorol A | FA-Dhb-Leu-**Orn-Ile-Val-Val-Lys-Val-Leu-Lys-Tyr-Leu-valinol** | Barsby et al. 2001 |
| Bogorol B | FA-Dhb-Val-**Orn-Ile-Val-Val-Lys-Val-Leu-Lys-Tyr-Leu-valinol** | Barsby et al. 2006 |
| Bogorol C | FA-Dhb-Val-**Orn-Val-Val-Val-Lys-Val-Leu-Lys-Tyr-Leu-valinol** | Barsby et al. 2006 |
| Bogorol D | FA-Dhb-Met-**Orn-Ile-Val-Val-Lys-Val-Leu-Lys-Tyr-Leu-valinol** | Barsby et al. 2006 |
| Bogorol E | FA-Dhb-Met -**Orn-Ile-Val-Val-Lys-Val-Leu-Lys-Tyr-Leu-valinol** | Barsby et al. 2006 |
| Brevibacillin | FA-Dhb-Leu-**Orn-Ile-Ile-Val-Lys-Val**-Val-**Lys-Tyr-Leu-valinol** | Yang et al. 2016 |
| BT peptide | Bmt-Leu-**Orn-Ile-Val-Val-Lys-Val-Leu-Lys-Tyr-Leu-valinol** | Wu et al. 2005 |

Conserved amino acid residues within the group are bold

molecules permeabilize cytoplasmic membranes to cause leakage of intracellular component (Yang et al. 2017a).

**Bogorols** Bogorol A (Table 2) is a lipopeptide that consists of a $C_6$-fatty acid chain (2-hydroxy-3-methylpentanoic acid) and 13 amino acid residues (Barsby et al. 2001). Bogorol A was first isolated from a marine *Bacillus* spp. but then the source was revised to *Br. laterosporus* by the same group of researchers. The compound is effective against MRSA, VRE and has moderate antimicrobial activity against *E. coli* (MIC of 35 µg/ml).

**BT peptide** In 2005, Wu et al. reported the discovery of BT peptide, an AMP isolated from *Brevibacillus* sp. As shown in Table 2, BT peptide shares high similarity with bogorol A, with the only difference at *N*-terminus structure. Despite the ambiguous structural information reported about the *N*-terminus moiety, Bmt (Wu et al. 2005), there are obvious resemblances between BT peptide and bogorol A (Yang et al. 2016). BT peptide was biosynthesized through NRPS and the genome of the producer microorganism was sequenced. Selected adenylation domains were expressed in vitro to propose the final structure of BT peptide (Wu et al. 2005).

Jiang et al. (2005) tested BT peptide as an animal feed antibiotic to prevent colibacillosis outbreak in broiler chickens. The experiment was designed to mimic the conditions that are conducive to an outbreak of colibacillosis and BT peptide was used as a medication treatment. There were significant weight gain and feed conversion in BT peptide-treated broilers. The use of BT peptide as medication reduced broilers mortality rate to 0.05%, compared to 13.4% for the unmedicated treatment group. Subsequently, a study was conducted to test BT peptide as a stimulator of the innate immune system for young chicks. The use of BT peptide significantly increased the protection of boiler chicken against *Salmonella enterica* serovar Enteritidis by improving the innate response of the newly-hatched chicks; immunological factors were up-regulated including phagocytosis, oxidative burst and degranulation (Kogut et al. 2007). Further research in 2012 showed that improved boiler chickens' health did not correspond to BT's antimicrobial activity, considering that the concentrations applied were below the MIC of BT against *Salmonella* Enteritidis. Additionally, the researchers found that BT peptide was not absorbed in the intestine but enhanced immunological performance of the tested chicks. When the authors performed a number experiments using in vitro model, they concluded that BT served as an immune modulator in treated chicken (Kogut et al. 2012).

**Brevibacillin** Brevibacillin, a lipopetide active against gram-positive bacteria, was discovered recently and its structure was fully elucidated (Yang et al. 2016). Brevibacillin shares structural similarity with bogorol A, but the two compounds differ in two amino acid residues; valine and leucine at position five and nine in bogorol A were replaced by isoleucine and valine in brevibacillin, respectively. Brevibacillin demonstrated comparable antimicrobial activity with that of vancomycin against a panel of gram-positive bacteria, including several foodborne pathogenic or spoilage bacteria such as *Listeria monocytogenes, Alicyclobacillus acidoterrestris* and *S. aureus* (Yang et al. 2016). Further research indicated that brevibacillin could bind to lipoteichoic acid of *S. aureus* cell wall and exert cytoplasmic membrane permeabilization (Yang et al. 2017a). The genome of the producer strain has been sequenced and brevibacillin biosynthetic gene cluster has been fully identified (Yang et al. 2017b).

#### BL-A60

In 2012, Zhao et al. reported the discovery of a new antimicrobial peptide, BL-A60, from *Br. laterosporus* A60. The structures at both *C* and *N* terminus were not elucidated by the authors, but the partial peptide sequence shares high similarity with bogorol C, with the exception that the sequence order was reversed (Yang et al. 2016; Zhao et al. 2012). Since only liquid chromatography-mass spectrometry (LC–MS) was applied to elucidate BL-A60 structure and no further experiments were designed to confirm Leu residues at position 1, 4 and 9, we did not classify BL-A60 into the linear lipo tridecapeptide family.

#### Tauramamide

Tauramamide is a linear antimicrobial lipopeptide produced from *Br. laterosporus* PNG276 that was isolated from a marine sample collected at Papua New Guinea (Desjardine et al. 2007). Tauramamide is composed of 7-methyloctanoic acid lipid chain esterified on a pentapeptide chain: $C_7$-Tyr-Ser-Leu-Trp-Arg. Tauramamide was reported to have antimicrobial efficacy against *Enterococcus* sp.; however, it did not exhibit efficacy against MRSA nor *Candida albicans* (Desjardine et al. 2007).

### Nonribosomal cyclic lipopeptides

Nonribosomal cyclic lipopeptides consist of a fatty acid chain acylated to an oligopeptide structure. Cyclization usually is formed as a lactone ring either between two amino acid residues or between one amino acid and a hydroxyl group-bearing fatty acid chain (Schneider et al. 2014).

#### Brevistin

Brevistin was discovered in 1975 from *Br. brevis* (previously *B. brevis* 342-14). Brevistin is a cyclic lipopeptide

with 11 amino acids [cyclo ($Thr^{1}$- $Dab^{2}$- $Asp^{3}$- $Gly^{4}$- $Asn^{5}$- $Asp^{6}$- $Gly^{7}$- $Trp^{8}$- Ile/$Val^{9}$- $Dab^{10}$- $Phe^{11}$)] and anteisononanoic acid acylated at residue one, threonine. Brevistin is effective against Gram-positive bacteria including *S. aureus* and *Streptococcus pneumoniae*, and it was reported to have low toxicity to mice (Shoji and Kato 1976).

## Ribosomally-synthesized antimicrobial peptides produced by *Brevibacillus* spp.

Bacteriocin is another name for ribosomally-synthesized AMPs produced from bacteria (Martinez et al. 2013). Bacteriocins have been classified, based on structural differences, into two classes (Class I and II) and bacteriolysins (Cotter et al. 2005). Class I refers to lanthionine-containing bacteriocins (e.g., nisin and other lantibiotics), and class II includes non-lanthionine-containing bacteriocins (e.g., pediocin). Class II can be divided into four subgroups: (a) pediocin-like, (b) two-peptide bacteriocin, (c) cyclic bacteriocin, and (d) miscellaneous. Bacteriolysins encompass large, heat-labile proteins (e.g., enterolysin A). *Brevibacillus* spp. produce several bacteriocins including laterosporulin, laterosporulin10 and Bac-GM100. A schematic representation of this classification is shown in Fig. 1.

### Laterosporulin

Laterosporulin is a class IId bacteriocin produced by *Br. laterosporus* GI-9 (Singh et al. 2012). Structure of laterosporulin was initially analyzed by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS) and protein sequencer; this was followed by whole genome sequencing, which provided biosynthetic gene cluster identification and open reading frames analysis (Sharma et al. 2012). The results uncovered that laterosporulin contains 49 amino acid residues and demonstrated broad antimicrobial spectrum against gram-positive and gram-negative bacteria (Singh et al. 2012). Circular dichroism and fluorescence analyses revealed that laterosporulin contained disulfide bonds intramolecularly, resulting in a closed cyclic structure. The disulfide connectivity [$C^{I}$–$C^{V}$, $C^{II}$–$C^{IV}$, and $C^{III}$–$C^{VI}$], along with the tertiary structure of laterosporulin demonstrated striking similarity to human defensins; therefore, the authors proposed that laterosporulin represents a missing link between bacteriocins and mammalian defensins. Laterosporulin is thought to inactivate target cells by disrupting the function of their cytoplasmic membranes (Singh et al. 2015).

### Laterosporulin10

Laterosporulin10 was isolated from *Brevibacillus* sp. SKDU 10 by the same group of researchers who discovered laterosporulin. Antimicrobial laterosporulin10 is a class IId bacteriocin and shares 58% structural homology with laterosporulin. Laterosporulin10 was found active against *S. aureus* and *Mycobacterium tuberculosis*. Interestingly, laterosporulin10 inactivated *M. tuberculosis* residing inside macrophages without antagonistic activity against macrophages. Bactericidal action of laterosporulin10 was attributed to its ability to permeabilize bacterial membrane (Baindara et al. 2016).

### Bac-GM100

Bac-GM100 is a ribosomally-synthesized AMP produced by *Br. brevis* GM100, a strain isolated from the rhizosphere of *Ononis angustissima*, an Algerian plant (Ghadbane et al. 2013). Molecular weight of Bac-GM100 was determined by MALDI-TOF MS and the partial sequence at *N*-terminal was determined by protein sequencer. Results uncovered that Bac-GM100 had molecular weight of 4375.66 Da with its 21 *N*-terminal residues (DWTFANWSCLVCDDCSVNLTY) having 65% homology with thurincin H from *B. thuringiensis*. Based on limited structural information, we suggest that Bac-GM100 is a class IId bacteriocin, since no cyclization was reported, nor it shared structural similarity with pediocin (Cotter et al. 2005). In addition, Bac-GM100 demonstrated broad-spectrum antimicrobial activity against Gram-negatives (e.g., *Pseudomonas aeruginosa*), Gram-positives (e.g., *Enterococcus faecalis*) and fungi (*Candida tropicalis* and *Fusarium* sp.) (Ghadbane et al. 2013).

## Concluding remarks

The genus *Brevibacillus* includes 20 species that are prolific producers of antimicrobial peptides. These AMPs have diverse structures and can be classified based on biosynthesis pathway and structural traits. Among all AMPs isolated from *Brevibacillus*, cyclic decapeptide and linear lipo tridecapeptide are two unique groups. Antimicrobial mode of action for most *Brevibacillus* AMPs is through cytoplasmic membrane damage, and these membrane-active AMPs include linear gramicidin, gramicidin S, tyrocidine, brevibacillin, laterosporulin and laterosporulin10. Exceptions include edeine, which inhibits DNA synthesis, protein translation and synthesis under different concentrations. *Brevibacillus* AMPs can be applied as clinical drugs (particularly for topical applications), feed additives and potentially food preservatives.

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