Mini Review

Bacteriocin-like protein produced Brevibacillus laterosporus that can inhibit the growth of drug resistant bacteria

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Abstract

This minireview contains a compendium of bacteriocin or bacteriocin-like proteins produced from Brevibacillus laterosporus that can inhibit the growth of drug resistant bacteria. A good number of bacterial secondary metabolites/bacteriocin/bacteriocin-like proteins are reported to have anti-drug resistant bacteria activity or anti-cancer activity comparable to the existing chemical synthesis antimicrobial drugs or sometimes even better. Information regarding the mode of action of bacteriocin leads to insight into their activity relationship and potency. A further well defined strategy is required to exploit these active molecules used as anti-drug resistant bacteria drugs.

Introduction

Currently, resistance of pathogenic organisms to approved antibiotics has become a worldwide problem with serious consequences on the treatment of infectious diseases [1-2]. The increased use/misuse of antibiotics in a treatment of infectious diseases is mainly causing to the phenomenon and/or pathogenic bacteria develop mechanism of antibiotic resistance [2]. There is an alarming increase of antibiotic resistance of bacteria that cause either community infections and/or hospital-acquired infections. Of particular interest are the multidrug resistant pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant MRSA, penicillin-resistant Streptococcus pneumoniae (PRSP) and vancomycin-resistant Enterococcus (VRE) [3]. Including, ESBLs (extended-spectrum beta-lactamases)-producing strains such as Klebsiella pneumoniae, Pseudomonas aeruginosa and E. coli etc., which can be transferred antibiotic-resistant gene to the other species by conjugation [4]. In many multidrug resistant pathogens, MRSA and ESBLs-producing strains are the most serious pathogens because they are a major cause of nosocomial infections and non-hospital acquired infections that associated morbidity and mortality. In many years past, the emergence of MRSA strains resistant to all beta-lactam antibiotics. Since the discovery, development and drug administration approval of vancomycin in the 1950s, this antibiotic is a mainstay for the treatment of infections caused by MRSA. However, because of the development of new anti-staphylococcal antibiotics, several researches reported vancomycin failure [5-6]. The MRSA, ESBLs-producing strains and some multidrug resistant pathogen has multi-mechanism resistance such as 1) modification of the bio-molecular target of antibiotics 2) enzymatic inactivation of antibiotic, e.g. beta-lactamases which hydrolyze beta-lactams 3) reduction of the intracellular antibiotic concentration in bacteria, by its efflux outside from the cell through bacterial trans-membrane efflux pumps. As a result, the development of novel antibiotics increases [2-3,7].

The several researches reported antibacterial/antimicrobial peptides or bacteriocins were applied as model for the production of novel antibiotics [8-9] because of the mode of action of antibacterial/antimicrobial peptides or bacteriocins are inhibit cell wall synthesis of MRSA strains with efficiency equal to that reported for vancomycin, which leaves the option...
of using the two substances in combination [8]. According to the research report in 2008, the partially bioactive compounds, which expected as bacteriocin, produced by Brevibacillus laterosporus strain SA14 inhibit the growth of clinical strain of MRSA [10]. Whereas, the non-specific on targets of the bioactive compounds and/or partially bioactive compounds is a major disadvantage. The several researches reported the bioactive compounds and/or partially bioactive compounds produced by many strains of Brev. laterosporus, which are major proteins, were used to control Musca domestica, Aedes aegypti, Coleoptera, parasitic nematodes ova/larvae and mollusks [11-12].

Brevibacillus laterosporus

Brev. laterosporus, previously classified as Bacillus laterosporus (B. laterosporus) [13], is a Gram-positive bacilli and an aerobic spore-forming bacterium characterized by the production of a typical canoe-shaped parasporal body (CSPB) which remains firmly attached to one side of the spore after lysis of the sporangium. As a pathogen against invertebrates, its toxic activities against parasitic nematodes ova/larvae [11]. It has been found as a secondary invader during European foulbrood, which is a serious infectious disease of honey bees [14]. The Brev. laterosporus can produce different virulence factors: parasporal crystalline, extracellular protease [15] and lipopeptide antibiotics [16]. Including, the secretion of short-sequence peptides (bacteriocin) with broad antibiotic spectra, such as laterosporulin [17], lolotain A [18].

Antagonistic compounds produced by bacteria from the genus Brevibacillus have also been studied [19]. The strains of Brevibacillus laterosporus are well known produced antibacterial and antifungal agents [10, 20–22]. The recently characterized Brev. laterosporus OSY-11 produces brevibacillin, a 1583 Da antimicrobial lipopeptide with a linear structure containing 13 amino acids and a C6 fatty acid at the N-terminus [23]. Brevibacillin shows strong antimicrobial activity against some pathogenic and food-spoilage Gram-positive bacteria, particularly MRSA, Listeria monocyctogenes and Bacillus cereus. In addition, some strains of Brev. laterosporus also produced the medically important substance such as spergualin, which is a new antitumor antibiotic [13], and bacitracins A, B and C [14].

Bacteriocin and Bacteriocin produced by Brevibacillus sp.

Bacteriocins, antibacterial peptides, which are produced by bacteria as a defense mechanism in complex environments [17]. It is short-sequence peptides that categorized into different classes based on structural and functional characteristics as follows 1) the class I bacteriocin (molecular weight <5 kDa) called as lantibiotics, are well studied with wide applications in both therapeutic and preservation of food products at industrial scale [24–25] 2) the class II bacteriocin (molecular weight <10 kDa) are further divided into different sub-classes, including antilisterial one-peptide pediciocin like bacteriocin as sub-class IIA [26–29], the two-peptide bacteriocin as sub-class IIB [24,27–30], the sec-dependent bacteriocin as sub-class IIC 3) the class III bacteriocin (molecular weight >30 kDa) containing cyclic and heat-labile protein bacteriocin 4) the class IV bacteriocin (large protein) composed of one-peptide, lipid(s) and carbohydrate(s) in bacteriocin molecule [25, 28, 30–31]. The mode of action of bacteriocins is most likely based on its amphiphilic nature and the ability of the cationic amino acids to interact with the negatively charged phospholipids of the cell membrane, causing the disruption and depolarization of the membrane [23]. A similar mechanism was observed in the case of paenibacterin, a broad-spectrum antimicrobial lipopeptide produced by Paenibacillus thiamolyticus [32]. In addition, it was found that the marine bacterial isolate Brevibacillus laterosporus PNG-276 showed broad-spectrum antibiotic activity (producing polyketides the basiliskamides A and B and non-ribosomal peptides: lolotain A–D and bogorol A–E) against the human pathogens MRSA, VRE, Mycobacterium tuberculosis, Candida albicans, and Escherichia coli [33].

The laterosporulin, a novel bacteriocin produced by Brevibacillus laterosporus strain GI-9 [34], which are class IId bacteriocin because of molecular weight of peptide to be of 5.6 kDa. The open reading frame (ORF) encoding laterosporulin were identified a 4 kb region from the draft genome sequence of GI-9. The 4 kb region contained the putative structural gene encoding laterosporulin and its flanking genes (transcriptional regulator, hypothetical protein, ABC transporter and alkyl hydroperoxide reductase). The ORF of 153 nucleotides followed the putative Shine–Dalgarno sequence most likely codes for the bacteriocins [17]. Laterosporulin is active against both Gram-positive and Gram-negative bacteria and was found to be resistant to a range of proteolytic enzymes. Structural studies revealed that the peptide consists of twisted Antimicrobials from new Brevibacillus laterosporus strains [https://doi.org/10.1371/journal.pone.0216773; 35]. β-sheet and includes three disulfide bonds [36]. Laterosporulin is relatively rich in cysteine and polar amino acids, which is atypical for bacteriocins in general, whereas its structure showed similarities with mammalian defensins. More recently, laterosporulin 10, produced by the strain Brevibacillus sp. SKDU10 was characterized [37] and, while considered similar, shows only 57.6% identity with laterosporulin. In addition, this novel bacteriocin has a different antimicrobial spectrum to laterosporulin as activity is limited to Gram-positive bacteria. However, laterosporulin 10 has also proven to be a promising new anti-cancer molecule that exhibits a cytotoxic effect on cancer cells [38].

The strains of Brev. laterosporus have been sequenced and their genomes deposited in Genbank. These include LMG 15441 (under accession number AFRV000000000, [39]), GI-9 (under accession numbers CAGD01000001 to CAGD01000061, [40]), B9 (under accession numbers CP011074–CP011076, [41]), Lak 1210 (under accession number NDIP00000000, [42]), OSY-11 (under accession number NOLX00000000, [43]), and SA14 (accession number KF718856.1, [https://www.ncbi.nlm.nih.gov/nuccore/KF718856.1]).

Unfortunately, the manufacturing of important substances (bioactive compound, anticancer/antimicrobial–peptides and/or bacteriocins) used the high cost and time-consuming. Nevertheless, it can be produced very less amounts which cannot industrial use. However, the advancement of genetic engineering was used to solve the above problems. The novel
bacteriocin-encoding genes will be inserted into appropriate shuttle / expression plasmid vector. The recombinant plasmids containing bacteriocin gene will be transferred to host cell-free protein expression system for introduce the novel bacteriocin production. With the hope, the constructed shuttle plasmid vector may be high segregational stability which can be introduce the novel bacteriocin production in large scale for industrial use.

Conclusion

It will be difficult to treat the drug resistant bacteria without increased funding for drug discovery. Bacteriocin producing bacteria are applicable used for treatment of infectious disease caused from drug resistant microorganisms. Though anti-drug resistant microorganisms MIC of bacteriocin is higher but they derived drugs can help in fighting the drug resistance. Unfortunately, there is no bacteriocin derived molecule either in market or under trial for treatment of drug resistant infections. Majority of studies focused on identification of bacteriocin structures or extracts with anti-drug resistant microorganisms properties and has not been extended to identification of bioactive-compound metabolites. Therefore, an integrated approach of identification of secondary metabolites/bacteriocin with anti-drug resistant microorganisms activity followed by identification of bioactive metabolites will speed up the research and development of bacteriocin derived drug molecules for drug resistant microorganisms infections.

Acknowledgement

We acknowledge the staff and members of Medical Technology, School of Allied Health Sciences, Walailak University, Thailand for their kind assistance and support.

References

1. Alanis AJ (2005) Resistance to Antibiotics: Are We in the Post-Antibiotic Era? J Archives of Medical Research 36: 697-705. Link: https://bit.ly/2KJztWx0
2. Gancea S, Stoia M (2010) Antibiotic resistance of bacterial pathogens: the magnitude of the problem from two perspectives-Romanian and worldwide. Journal of Romanian Biotechnological Letters 15: 5519-5529. Link: https://bit.ly/2Y2bt6r
3. Alexshun MN, Levy SB (2007) Molecular mechanisms of antibacterial multidrug resistant. Journal of cell 128: 1037-1050. Link: https://bit.ly/2XjdB89
4. Pitout JDD, Nordmann P, Laupland KB, Poirel L (2005) Emergence of Enterobacteriaceae producing extended-spectrum β-Lactamase (ESBLs) in the community. Journal of Antimicrobial Chemotherapy 56: 52–59. Link: https://bit.ly/3dMhwUZ
5. Hiramatsu K, Hanakia H, Inob T, Yabutab K, Oguric T, et al. (1997) Methicillin-resistant Staphylococcus aureus clinical strain with reduced vancomycin susceptibility. Journal of Antimicrobial Chemotherapy 40: 135-146. Link: https://bit.ly/3eATxqO
6. Chang S, Sievert DM, Hageman JC, Boulton ML, Tenover FC, et al. (2003) Infection with Vancomycin-Resistant Staphylococcus aureus containing the van A Resistance Gene. Journal of medicine 348: 1342-1347. Link: https://bit.ly/2XJAIink
7. Gould IM (2009) Antibiotic Resistance: The Perfect Storm. Int J Antimicrob Agents. 34: 2-5. Link: https://bit.ly/3gDRJyd
8. Kruzweska D, Sahl HG, Bierbaum G, Pag U, Hynes SO, et al. (2004) Mersacidin eradicates methillin-resistant Staphylococcus aureus (MRSA) in a mouse rhinitis model. Journal of Antimicrobial Chemotherapy 54: 648-653. Link: https://bit.ly/3eA94X2
9. Dicks LMT, Heunis TDJ, Staden DA, Brand A, Sutyak NK, et al. (2011) Medical and personal care applications of bacteriocins produced by lactic acid bacteria. Journal of Prokaryotic Antimicrobial Peptides from Genes to Applications. 391. Link: https://bit.ly/3c5SNP
10. Chawawisit K, Lertcanawanichakul M (2008) Minimum inhibition concentration (MIC) of crude preparations of Brevibacillus laterosporus SA14 bioactive material compared to vancomycin and oxacillin, against clinical isolates of methicillin-resistant Staphylococcus aureus. Journal of Microbiology and Biotechnology 24: 2199-2204. Link: https://bit.ly/36Q3qxp
11. Ruiu L, Floris I, Satta A, Ellar DJ (2007) Toxicity of a Brevibacillus laterosporus strain lacking parasporal crystals against Musca domestica and Aedes aegypti. Journal of Biological control 43: 136-143. Link: https://bit.ly/3cnItuI
12. De Oliveira EJ, Rabinovitch L, Monnerat RG, Passos LKJ, Zahner V (2004) Molecular characterization of Brevibacillus laterosporus and its potential use in biological control. Journal of Applied Environmental Microbiology 70: 6657-6664. Link: https://bit.ly/3gC0qHE
13. Umezawa K, Takeuchi T (1987) Spergualin: A new antitumor antibiotic. Journal of Biomedical Pharmacotherapy 41: 227-232. Link: https://bit.ly/3dsPUE
14. Kaniymaya T, Umino T, Nakamura Y, Itezo Y, Sawari S, et al. (1994) Bacidthrocins A, B and C, novel thrombin inhibitors. Journal of Antibiotic 47: 959-968. Link: https://bit.ly/2MiSwEN
15. Shida O, Takagi H, Kadowski K, Komagata K (1996) Proposal for two new genera, Brevibacillus gen. nov. and Aneurinibacillus gen. nov. Journal of systematic bacteriology 46: 939-946. Link: https://bit.ly/3eHx2jj
16. Forsgren E (2010) European foulbrood in honey bees. Journal of Invertebrate Pathology 103: 5–9. Link: https://bit.ly/2ZNPym
17. Huang X, Tian B, Niu Q, Yang J, Zhang L, Zhang K (2005) An extracellular protease from Brevibacillus laterosporus G4 without parasporal crystals can serve as a pathogenic factor in infection of nematodes. Journal of Research Microbiology 156: 719-727. Link: https://bit.ly/2XM1hyx
18. Desjardine K, Pereira A, Wright H, Matainaho T, Kelly M, Andersen RJ (2007) Tauramamide, a lipopeptide antibiotic produced in culture by Brevibacillus as a biological tool: a short review. Antonie Van Leeuwenhoek 90: 623–639. Link: https://bit.ly/2ZX2gPo
19. Singh PK, Ashish C, Sharma V, Patil PB, Korpole S (2012) Identification, Purification and Characterization of Laterosporulin, a Novel Bacteriocin Produced by Brevibacillus sp. Strain GI-9. Journal of PLoSONE 7: 1-8. Link: https://bit.ly/2MiW3Fa
20. Krachkovskii SA, Sobol AG, Ovchinnikova TV, Tagaev AA, Yakimenko ZA, et al. (2002) Isolation, biological properties, and spatial structure of antibiotic lolatin A. Journal of Bioorganism Chemistry 28: 269-273. Link: https://bit.ly/2ZK2qPo
21. Yang X, Yousef AE (2018) Antimicrobial peptides produced by Brevibacillus spp.: structure, classification and bioactivity: a mini review. World Journal of Microbiology and Biotechnology 34: 57. Link: https://bit.ly/3gCA5uZ
22. Panda AK, Bisht SS, DeMondal S, Kumar SN, Gurusubramanian G, et al. (2011) Brevibacillus as a biological tool: a short review. Antonie Van Leeuwenhoek 105: 623–639. Link: https://bit.ly/2Bm6Zt
23. Jiang H, Wang X, Xiao C, Wang W, Zhao X, et al. (2015) Antifungal activity of Brevibacillus laterosporus JA-5 and characterization of its antifungal components. World Journal of Microbiology and Biotechnology 31: 1605-1618. Link: https://pubmed.ncbi.nlm.nih.gov/26265360/
24. Hassi M, Guendouzi SE, Haggoud A, David S, Ibnoussida S, et al. (2012) Antimycobacterial activity of a Brevibacillus laterosporus strain isolated from a Moroccan soil. Brazilian Journal of Microbiology 43: 1516-1522. Link: https://bit.ly/3eGB8hN

25. Yang X, Huang E, Yuen C, Zhang L, Yousef AE (2016) Isolation and structural elucidation of brevibacillin, an antimicrobial lipopeptide from Brevibacillus laterosporus that combat drug-resistant Gram-positive bacteria. Applied and Environmental Microbiology 82: 2763-2772. Link: https://bit.ly/2Bmi0G7

26. Cotter PD, Hill C, Ross RP (2005a) Bacterial antibiotics: strategies to improve therapeutic potential. Journal of Current Protein Peptides Science 6: 61–75. Link: https://bit.ly/3cm1A1Mz

27. Cotter PD, Hill C, Ross RP (2005b) Bacteriocins: developing innate immunity for food. Journal of Natural Review Microbiology 3: 777-788. Link: https://bit.ly/3cjykX9

28. Svetoa EA, Stern NJ, Eruslanov BV (2005) Isolation of Bacillus circulans and Penibacillus polyxyma strains inhibitory to campylobacter jejuni and genomic sequence comparison with Bacillus subtilis. Journal of Nucleic Acid Research 28: 4317-4331. Link: https://bit.ly/2BIBiGO

29. Drider D, Finland G, Hechard Y, McMillen LM, Prevsr H (2006) The continuing reinfection and of Brevibacillus laterosporus strain B9, a biological control strain isolated from Zhejiang, China. Journal of Applied Microbiology 103: 1621-1631. Link: https://bit.ly/27UqXkX

30. Nissen-Meyer J, Rogne P, Emanuelsen L, Kristiansen PE (2007) Structure-function relationships of non-lanthionine containing peptide (class II) bacteriocins produced by gram positive bacteria. Journal of Current Pharmacology Biotechnology 10: 19-37. Link: https://bit.ly/3yRmRgN

31. Oppegard C, Rogne P, Emanuelsen L, Kristiansen PE, Finland G (2007) The two-peptide class II bacteriocins: structure, production and mode of action. Journal of Molecular Microbiology Biotechnology 13: 210-219. Link: https://bit.ly/3cm3J6

32. Le Marrec C, Hyronimus B, Bressollier P, Verneuil B, Urdaci MC (2000) Biochemical and genetic characterization of coagulin, a new antilisterial bacteriocin in the pediocin family of bacteriocins, produced by Bacillus coagulans I4. Journal of Applied Environment Microbiology 66: 5213-5220. Link: https://bit.ly/2TUqXkX

33. Sebei S, Zendo T, Bouadoust A, Nakayama J, Sonamoto K (2007) Characterization, N-terminal sequencing and classification of cerein MRX1, a novel bacteriocin purified from a newly isolated bacterium: Bacillus cereus MRX1. Journal of Applied Microbiology 103: 1621-1631. Link: https://bit.ly/22mvo1

34. Huang E, Yousef AE (2014) The lipopeptide antibiotic paenibacterin binds to the bacterial outer membrane and exerts bactericidal activity through cytoplasmic membrane damage. Applied and Environmental Microbiology 80: 2700-2704. Link: https://bit.ly/2XO4uWh

35. Barsby T, Warabi K, Serensen D, Zimmerman WT, Kelly MT, et al. (2006) The bogorol family of antibiotics: template-based structure elucidation and a new approach to positioning enantiomeric pairs of amino acids. Journal of Organic Chemistry 71: 6031–6037. Link: https://bit.ly/3gJa0H

36. Singh PK, Chittapuna A, Sharma V, Patil PB, Korpole S (2012) Identification, purification and characterization of laterosporulin, a novel bacteriocin produced by Brevibacillus sp. strain GI-9. PLoS ONE 7: e31498. Link: https://bit.ly/2TYxKXP

37. Miljkovic MM, Jovanovic S, O’Connor PM, Mirkovic N, Jovicic B, et al. (2019) Brevibacillus laterosporus strains BGSNP7, BGSNP9 and BGSNP11 isolated from silage produce broad spectrum multi-antimicrobials. PLoS ONE 14: e0216773. Link: https://bit.ly/3VDUHa

38. Singh PK, Solanki V, Sharma S, Thakur KG, Krishnan B, et al. (2015) The intramolecular disulfide-stapled structure of laterosporulin, a class IIId bacteriocin, conceals a human defensin-like structural module. FEBS Journal 282: 203-214. Link: https://bit.ly/36LC1g7

39. Baindara P, Singh N, Ranjan M, Nallabelli N, Chaudhry V, et al. (2016) Laterosporulin10: A novel defensin like class IIId bacteriocin from Brevibacillus sp. strain SKDU10 with inhibitory activity against microbial pathogens. Microbiology 162: 1286-1299. Link: https://bit.ly/2XJAq2g

40. Baindara P, Gautam A, Raghaa RHS, Korpole S (2017) Anticancer properties of a defensin like class IId bacteriocin Laterosporulin10. Scientific Reports 7: 46541. Link: https://go.nature.com/365ahi7

41. Djukic M, Poehlein A, Thuermer A, Daniel R (2011) Genome sequence of Brevibacillus laterosporus LMG 15441, a pathogen of invertebrates. Journal of Bacteriology 193: 5535-5536. Link: https://bit.ly/3dnojm2

42. Sharma V, Singh PK, Midha S, Ranjan M, Korpole S, Patil PB (2012) Genome sequence of Brevibacillus laterosporus strain GI-9. Journal of Bacteriology 194: 1279. Link: https://bit.ly/2AHHW3S

43. Li G, Xu J, Wu L, Ren D, Ye W, et al. (2015) Full genome sequence of Brevibacillus laterosporus strain B9, a biological control strain isolated from Zhejiang, China. Journal of Biotechnology 207: 77-78. Link: https://bit.ly/3dIXyOV

44. Prasanna L, Moharan TR, Sheikh N, Arravapalli VR, Kumaraswamy T, et al. (2017) Draft genome sequence of entomopathogenic Brevibacillus laterosporus strain Lak 1210, an alkaliphilic chitin degrader. Genome Announcements 5: e01251-1217. Link: https://bit.ly/2TYaWP3

45. Yang X, Huang E, Yesil M, Xiaoli D, Dudley, et al. (2017) Draft genome sequence of Brevibacillus laterosporus OSY-H1, a strain that produces brevibacillin, which combats drug-resistant Gram-positive bacteria. Genome Announcements 5: e01093-1017. Link: https://bit.ly/2XRZ9Rc8