Bacillus licheniformis

Bacillus licheniformis produces several classes of antimicrobial substances, including bacteriocins, which are peptides or proteins with different structural composition and molecular mass: ribosomally synthesized by bacteria (1.4–20 kDa), non-ribosomally synthesized peptides and cyclic lipopeptides (0.8–42 kDa) and exopolysaccharides (>1000 kDa). Different bacteriocins act against Gram-positive or Gram-negative bacteria, fungal pathogens and amoeba cells.

1. Introduction

The spread of bacterial strains that cause severe infectious diseases but are now resistant to known antibiotics necessitates the search for and development of new approaches to combat these diseases [1]. The most known and medically important example that illustrates this problem is the growing number of cases of multidrug-resistant strains of *Mycobacterium tuberculosis* (*Mtb*), which is the causative agent of tuberculosis. In addition to drug resistance, *Mtb* is able to asymptomatically persist in the host organism for many years, causing latent forms of tuberculosis. In this dormant state, *Mtb* cells are also resistant to known antibiotics [2][3][4].

The search for and study of substances that have bactericidal or bacteriostatic properties against human and animal pathogens are also required for the development of new antibiotic therapy or disinfectants for objects and surfaces that have been in close contact with patients and therefore may carry pathogenic bacteria. Currently, in addition to the synthesis of new chemical substances, considerable attention has focused on the analysis of the potential of natural products from different origins as antimicrobials. The discovery of antibiotics with activity against human pathogens is often based on the observation of the interaction between microorganisms, called antagonism. This antagonism manifests through the synthesis and release of substances that inhibit or completely suppress the growth of other species. Under natural conditions, a microorganism-secreted substance(s) that inhibits the growth of another organism gains a competitive advantage in the struggle for environmental resources. Most of the antibiotics used for medical applications are secreted products or derivatives of microorganisms belonging to the order *Actinomycetalis* (among them, the most well-known are *Streptomyces*). The bacterial world represents a huge reservoir of not-yet-discovered and used substances that have antibacterial potential. In this regard, representatives of the genus *Bacillus* are known as producers of many enzymes and antimicrobial compounds. For example, *Bacillus amyloliquefaciens* is a source of the natural antibiotic barnase (ribonuclease), alpha-amylase, which is used in starch hydrolysis; protease subtilisin, which is used in combination with detergents; and the restriction enzyme, BamH1, used in DNA research [5]. *Bacillus subtilis* produces 66 derived antimicrobials, and *Bacillus brevis* produces 23 peptide antibiotics [6]. There is a growing interest in considering these substances, including bacteriocins, as alternative antimicrobials for the treatment of human and animal infections [7][8][9][10][11].

Currently, the use of bacterial probiotic strains and their metabolic products is considered a new approach for the control and prevention of various infectious diseases [12]. Animal studies have demonstrated that probiotics from the *Bacillus* genus have antimicrobial properties. This conclusion also applies to humans [13][14]. The use of bacteriocins and antimicrobial peptides produced by probiotic strains is a suitable alternative to antibiotics because their production is inexpensive and resistance to them is rare [15]. They exhibit a broad spectrum of activity against many Gram-positive and Gram-negative bacteria and fungi. Owing to the efficacy and cost-effectiveness of many of these compounds, they are attractive for clinical use [16]. A few natural peptides have shown potential because of their desirable therapeutic properties, including antimicrobial, antiviral, anticancer, and contraceptive activities. Additionally, they have been shown to protect against topical and systemic infections in combination with conventional antibiotics [17].

Among the organisms belonging to the *Bacillus* genus, *Bacillus licheniformis* is a unique specie that which produces wide variety of antimicrobial substances. This bacterium shows promise for use as a probiotic in the treatment of dysbacteriosis, which is caused by various diseases [13]. The effectiveness of *B. licheniformis* as a probiotic is associated

with its ability to produce a large amount of substances with antimicrobial, antioxidant and immunomodulatory activities [13], for example, a phosphorus-containing triene antibiotic called proticin [18][19]. *B. licheniformis* shows a protective effect in zebrafish (Danio rerio) against *Vibrio parahaemolyticus* infection. Due to the antagonistic activity of this probiotic, the complete survival of infected fish was observed in contrast with untreated fish [20]. This probiotic, in combination with *Bifidobacterium breve*, significantly inhibited the adhesion of the pathogen *Kocuria rhizophila* in vitro [21] and showed antivibrio activity against *Vibrio parahaemolyticus* [22]. The use of a crude extract from *B. licheniformis* resulted in marked antiviral activity against porcine epidemic diarrhea virus in Vero cells and reduced virus shedding in piglets [23]. After the administration of fermented *B. licheniformis* products, the number of pathogenic bacteria including *Clostridium perfringens* significantly decreased in cats with chronic diarrhea [24]. In piglets, *B. licheniformis* treatment showed positive effects against *Salmonella* [25]. Probiotic *B. licheniformis* produces antimicrobial substances and has a strong ability to auto- and coaggregate against pathogenic bacteria [26]. Approaches are being developed to combat bacterial biofilms using silver nanoparticles and the probiotic *B. licheniformis* [27].

The bacteriocins from *B. licheniformis* are being considered as natural preparations as a preservative in the food industry [28][29].

In general, bacteriocins are a group of antimicrobial peptides that represent a potential alternative to classical antibiotics in the fight against antimicrobial resistance in pathogenic microorganisms. Several reports have been published in the literature about numerous bacteriocins, many of which currently remain undiscovered due to the wide variety of their natural sources; hence, further research in this area is required [11].

Considering the medical and industrial application of *Bacillus licheniformis*, a thorough description and characterization of the variety of antimicrobial compounds produced and their use against resistant pathogens, such as mycobacteria, are required.

2. Antibacterial Substances Secreted by *Bacillus licheniformis*

The endospore-forming bacterium *Bacillus licheniformis* is capable of producing a large amount of substances with different structures and different antibacterial activities [30] (**Figure 1**). When grown on identical media, different strains of *B. licheniformis* produce different sets of substances with antibacterial activities [31]. It is plausible that all strains of *B. licheniformis* potentially are able to produce variety of antimicrobial substances, however, the synthesis and production of particular substance can be differently regulated on the transcriptional or translational level for certain strains grown in identical media. As a result, the amount of secreted antimicrobial compounds may substantially vary from strain to strain allowing to consider them as unique producers of defined set of antimicrobials. The secreted antimicrobial substances have molecular masses ranging from 1.4 to 20 kDa [28][29][32][33][34][35][36][37][38].
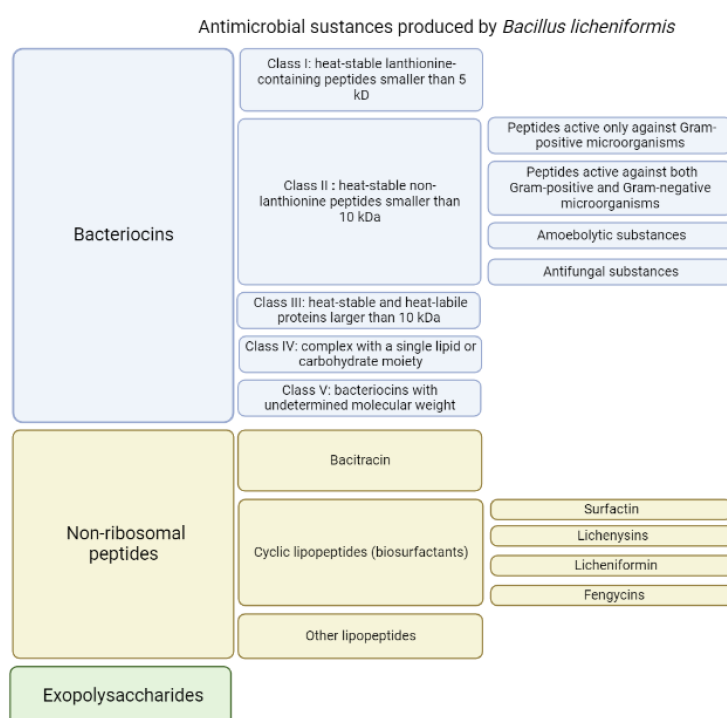

Figure 1. Antibacterial substances produced by *Bacillus licheniformis*.

Changing the composition of the medium used for *B. licheniformis* growth results in the alterations in the secreted substances. Thus, on media containing iron, *B. licheniformis* can synthesize the red pigment pulcherrimin [39]. When grown on a medium with lactate and a high ratio of nitrogen and carbon, *B. licheniformis* strain N.C.T.C. 7072 produces licheniformins; when grown on a medium with glucose and a low nitrogen/carbon ratio, this strain produces bacitracins [37]. Several substances synthesized by *B. licheniformis* have been investigated as antibiotics against various types of bacteria. They are listed and characterized below. Some of them (bacitracin) are used in combined antibacterial preparations intended for topical use. Others are used as oral antibiotics, but only in animals due to their toxic effects.

Among the antimicrobial components (**Figure 1**) produced by various strains of *B. licheniformis* in a nutrient medium, several groups differ in properties and structure.

2.1. Bacteriocins

Bacteriocins are substances represented by an amino acid sequence (peptides or proteins) that act against other strains of bacteria or closely related species. They demonstrate both bactericidal and bacteriostatic effects. Bacteriocins are natural antimicrobial peptides that are ribosomally synthesized by bacteria [10][11][40]. Genes whose expression leads to the synthesis of bacteriocins are organized into clusters of operons and can be located in the genome, plasmids, or other mobile genetic elements. These genes are inducible; peptide secretion and accumulation outside the cell are required for their induction. More details regarding bacteriocins biosynthesis are described in the review by Nishie et al. [9]. Bacteriocins are heterogeneous substances that demonstrate various biochemical properties, molecular weights, inhibitory spectra and mechanisms of action [10][41]. Due to the wide spectrum of antagonistic activity inherent to the bacteriocins of some strains of microorganisms, they have the potential to be used as a component of antibacterial drugs. The resistance to enzyme activity of the antimicrobial peptides produced by *Bacillus* spp. differs with stability over a wide range of pH and temperature. Most of these peptides have high specificity against microbial pathogens and low cytotoxicity against human cells [42]. The related bactericidal mechanisms include the pore-forming type, nuclease type with DNase and RNase functions, and the peptidoglycanase type [10] (**Figure 2**).
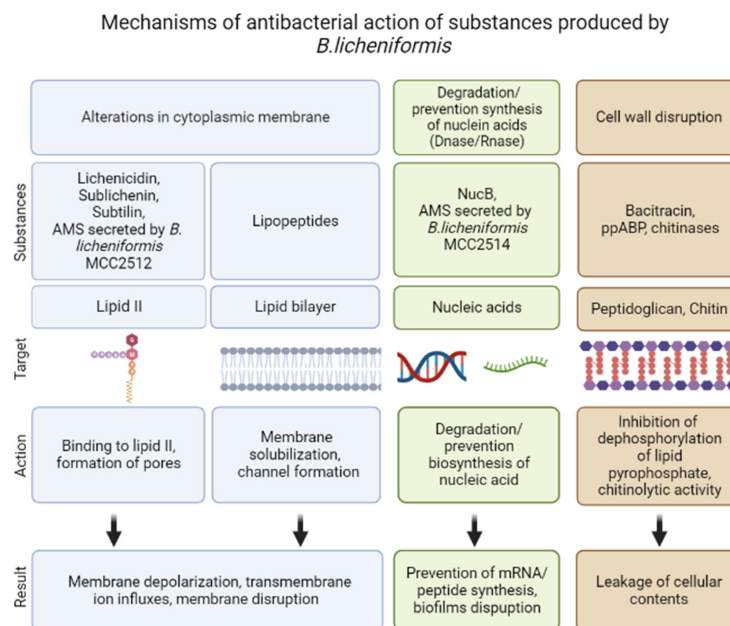

Figure 2. Mechanisms of antibacterial action of substances produced by *Bacillus licheniformis*.

As a result, pores are formed, which leads to the rapid removal of small cytoplasmic molecules, ions from target cells, and the collapse of the protonmotive force, leading to the death of bacterial cells [9][43]. However, other antimicrobial mechanisms of bacteriocins were also identified [11]. Despite the recent popularity of research on the properties of bacteriocins and their use in medicine, veterinary sciences, and food industry [10][11], many bacteriocins have not yet been studied.

The production of several bacteriocin-like substances with different characteristics and a wide spectrum of activity against pathogenic bacteria was recorded in the strains of *B. licheniformis* [44]. For example, *B. licheniformis* SMIA-2, a thermophilic and thermostable enzyme-producing strain, is active against some strains of *Staphylococcus aureus* and *Bacillus* sp. The genome annotation of this strain detected gene clusters responsible for antimicrobial component production (lichenysin, fengycin, lichenicidin and bacillibactin biosynthetic gene clusters) [45].

B. licheniformis produces various bacteriocins ranging in molecular weight from 1.4 to 55 kDa, but the expression of a particular antimicrobial agent may depend on environmental conditions, growth period, and the specific bacterial strain [28] [32][33][36][46].

In general, based on their thermostability, size and chemical moieties, bacteriocins are classified into four major groups [47]: class I, heat-stable lanthionine-containing peptides smaller than 5 kDa; class II, heat-stable non-lanthionine peptides smaller than 10 kDa; class III, heat-labile proteins larger than 30 kDa; and class IV, complex with a single lipid or carbohydrate moiety [48]. To describe the antimicrobial substances produced by different strains of *B. licheniformis*, Cotter's classification is used, with a slight modification: heat-stable and heat-labile proteins larger than 10 kDa are assigned to class III, and class V was added, which includes proteins with undetermined molecular weight (**Figure 1**).

2.1.1. Class I: Heat-Stable Lanthionine-Containing Peptides Smaller Than 5 kDa

Lantibiotics are antimicrobial peptides that undergo post-translational modification. They contain non-standard amino acids: lanthionine, β-methyl lanthionine and dehydrated residues (dehydrated amino acids) [49]. Their molecular weight does not exceed 5 kDa. Lantibiotics are active at low concentrations and are therefore attractive antimicrobials. They mainly target lipid II. A number of lantibiotics interact with the cell wall precursor lipid II (undecaprenyl-pyrophosphoryl-MurNAc-(pentapeptide)-GlcNAc), which prevents cell wall biosynthesis and contributes to the destruction of the bacterial membrane [50]. Thus, the most well-studied lantibiotic nisin interacts with the pyrophosphate fragment of lipid II. Critical to this binding are the two N-terminal rings of the lantibiotic [51]. The formation of the pore complex results in cell membrane permeabilization and dissipation of the proton motive force [50].

In general, lantibiotics are synthesized and secreted by Gram-positive microorganisms, and their activity is most often manifested in connection with closely related Gram-positive bacteria. For Gram-negative bacteria, their activity is rather limited [49] because the cell wall of Gram-negative bacteria is an effective permeability barrier due to the presence of an outer membrane, which prevents access to the peptidoglycan layer (localization of lipid II) and the cytoplasmic membrane (**Figure 2**). Moreover, the anionic cell surface of Gram-negative bacteria promotes the binding of cationic lantibiotics, where such an interaction potentially increases the stability of the outer membrane through electrostatic interactions [52].

The first one is sublichenin, which is a subtilin-like lantibiotic of probiotic bacterium *Bacillus licheniformis* MCC 2512 that has a molecular weight of 3.348 kDa and the succinylated form has a molecular weight of 3.448 kDa [31][53]. Subtilin is a natural variant of nisin that refers to linear pentacyclic class I antibiotics [54]. The sublichenins from *B. licheniformis* are almost identical to the JS-4 subtilin from *B. subtilis*. Subtilin JS-4 retained >90% and 86.1% of its antibacterial activity even after a 30 min exposure to 80–100 °C and 121 °C, respectively, indicating considerable thermostability. Subtilin JS-4 was also rapidly inactivated by proteolytic enzymes including proteinase K, trypsin, papain and pepsin [55]. It also showed a broad antimicrobial spectrum against Gram-positive bacteria. Subtilin JS-4 inhibited the growth of foodborne bacterium *L. monocytogenes* by increasing cell membrane permeability, triggering pore formation and K^+ leakage, and damaging cell membrane integrity, which eventually disrupted the membrane and cellular structure [55] (**Figure 2**).

The second antibiotic is lichenicidin, a dipeptide lantibiotic consisting of a synergetic lantibiotic pair, Licα (3.251kDa) and Licβ (3.021 kDa), which was described for *B. licheniformis* DSM 13. This substance demonstrated activity against the growth of Gram-positive bacteria, such as *Bacillus subtilis*, *Micrococcus luteus*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Staphylococcus simulans* and *enterococci* but neither caused hemolysis nor inhibited the growth of Gram-negative bacteria. Lichenicidin is associated with the cell surface and shows stability against trypsin, chymotrypsin, and proteases [56]. Moreover, lichenicidin can be produced by other strains of *B. licheniformis*, and the structure of its peptides may differ depending on the strain. Lichenicidin was not cytotoxic to human erythrocytes and fibroblasts [57]. *B licheniformis* strain ATCC 14580 produced lichenicidin with activity against a range of pathogenic microorganisms including *Listeria monocytogenes*, *Staphylococcus aureus*, vancomycin-resistant enterococci, *Bacillus cereus*, *Streptococcus pneumoniae* and *Streptococcus* mutants [58]. Lichenicidin has been produced by *B. licheniformis* strain VK21 [59], and WIT 562, 564 and 566 [60]. Additionally, lichenicidin production was found in *B. licheniformis* isolates (isolated from retail infant milk formulae): strains IMF20, IMF66, IMF69 and IMF80. These strains demonstrated antimicrobial activity against target Gram-positive organisms. No activity was observed against the Gram-negative bacteria *E. coli* or *S. typhimurium* [61]. For Lchα and Lchβ, lichenicidin subunits produced by VK21 strain, described tertiary structures and details of mode of action [59].

Another variant of lichenicidin comprises two mature peptides, Bliα and Bliβ, produced by the I89 strain; their synergistic activity is required for full activity [62][63].

Lichenicidin acts through a dual mode of action that involves the α subunit recognition of lipid II, providing specificity and stability for the interaction of β subunit, which induces leakage of the intracellular contents of bacteria [64][65] (**Figure 2**).

2.1.2. Class II: Heat-Stable Non-Lanthionine Peptides Smaller Than 10 kDa

B. licheniformis Secreted Peptides Active Only against Gram-Positive Microorganisms

Because antagonism provides a survival advantage in the suppression of related species of microorganisms, most bacteriocins secreted by different strains of *B. licheniformis* are active only against Gram-positive bacteria. Peptides may be insensitive or sensitive to the action of proteolytic enzymes. However, the vast majority of the identified bacteriocins that are active only against Gram-positive microorganisms are sensitive to the action of proteinases.

Bacillocin 490, a bacteriocin with a low molecular mass (2 kDa) and produced by a thermophilic strain (*B. licheniformis* 490/5) isolated from dairy foods, shows high thermal stability, with 46.4% residual activity after 1 h of exposure to 100 °C. This bacteriocin was inactivated by pronase E and proteinase K. Bactericidal activity was maintained during storage at 4 °C and was remarkably stable over a wide pH range. The activity range of bacillocin 490 was limited to some Gram-positive bacteria. The highest antimicrobial activity was observed against *Bacillus stearothermophilus*, *B. smithii*, *B. subtilis* and *B. anthracis*. Moderate inhibition of *B. cereus*, very low inhibition of *Listeria innocua* and *S. aureus*, and no inhibition of *B. thuringensis* and *Streptococcus thermophilus* were noted. This activity spectrum shows that bacillocin 490 is principally active against species phylogenetically related to the producer strain. The incubation of *B. smithii* in the presence of bacillocin 490 resulted in 96% death in 30 min, indicating that bacteriocin has a bactericidal effect [28].

The supernatant of thermophilic strain *B. licheniformis* H1 exhibited antagonistic activity against various species of Gram-positive bacteria, such as *Listeria monocytogenes* but not against Gram-negative bacteria, except for *Pseudomonas fluorescens*. The inactivation of this bacteriocin-like activity by a-chymotrypsin, trypsin, and papain was highly significant. No significant decrease was found in antimicrobial activity after the incubation of a bacteriocin-containing supernatant from *B. licheniformis* H1with pepsin or lipase. The bacteriocin-like substance was stable at temperatures up to 75 °C for 60 min, but activity was lost after being autoclaved at 121 °C for 15 min. Concentrated antimicrobial activity was found in the protein fraction obtained with 60% ammonium sulfate saturation. The results of sodium dodecyl sulfate–polyacrylamide electrophoresis analysis of concentrated partially purified supernatants collected after resting bacterial cells at 55 °C revealed a bacteriocin-like protein with a molecular mass of approximately 3.5 kDa [66].

B. licheniformis AnBa9 produced antibacterial bacteriocin-type peptides with a molecular mass of <10 kDa. The production of these peptides was 25-fold higher under optimized conditions for producer growth compared with nonoptimized condition. The level of bacteriocin production and its specific activity gradually decreased with increasing concentrations of lactose and NH_4NO_3. F high concentration of yeast extract, an alkaline pH and an elevated temperature improved the production of antibacterial peptides by *B. licheniformis* AnBa9. *B. licheniformis* AnBa9 inhibited several Gram-positive bacteria, including *Staphylococcus aureus*, *Bacillus cereus*, *Staphylococcus epidermidis*, *Kurthia gibsonii*, *Micrococcus luteus*, *Streptococcus mitis*, *Bacillus subtilis*, *L. lactis*, *Bacillus smithii*, *Lactobacillus acidophilus*, *Pediococcus acidilactici*, and *Leuconostoc mesenteriodes*. However, these bacteriocins did not inhibit *Listeria* strains or Gram-negative bacteria. The loss of antibacterial activity of the permeate after treatment with proteinase K, pronase E, and trypsin, suggested that these bacteriocins are sensitive to proteolytic enzymes. They were resistant to temperature up to 100 °C for 30 min and over a wide range of pH from 4 to 12 [35].

Under anaerobic conditions, *B. licheniformis* 26L10/3RA produced an inhibitory bacteriocin-like component called lichenin. This peptide was purified to homogeneity, and the molecular mass was estimated at approximately 1.4 kDa. Lichenin was found to be hydrophobic, was sensitive to atmospheric oxygen, retained biological activity even after boiling for 10 min, and was active over a pH range of 4.0–9.0. It was active against *Streptococcus bovis*, *Ruminococcus albus*, *Ruminococcus avefaciens*, and *Eubacterium ruminantium*. The biological activity of this peptide was completely inactivated by proteinase K treatment, but this peptide was resistant to trypsin. Heat treatment at 80 °C and boiling for 10 min at pH 4.0 and 9.0 resulted in a significant reduction in biological activity. Lichenin production was observed only upon *B. licheniformis* anaerobic growth, the antibacterial activity of which was also demonstrated for the reference strains grown under anaerobic conditions only. The inability of lichenin to inhibit aerobically grown bacteria was explained either by its inactivation by atmospheric oxygen or the target bacteria due to oxidative respiration. No N-terminal block was observed in the sequence and the peptide did not show any characteristics of cyclicity. However, the seventh amino acid residue could not be identified and it did not belong to any of the natural amino acids [32].

Strain BTHT8, identified as *B. licheniformis*, inhibited the growth of Gram-positive test organisms. The active component, labeled as bacteriocin BL8, was purified from the supernatant of *B. licheniformis* strain BTHT8. The molecular mass was

determined as 1.4 kDa. The results of N-terminal amino acid sequencing of BL8 identified a 13 amino acid sequence stretch. Bacteriocin BL8 was stable even after boiling at 100 °C for 30 min and over a wide pH range of 1–12 [67].

A bacteriocin from *B. licheniformis* cy2, named BSCY2, was stable at pH 2.5–9.5, showing activity against *B. subtilis*. BSCY2 was stable below 40 °C and retained its antimicrobial activity during long tern storage at −20 °C and −70 °C. BSCY2 was inactivated after 15 min exposure to temperatures over 80 °C and lost 50% of its antimicrobial activity within 2 h at 70 °C. BSCY2 was inactivated by proteinase K treatment, which indicated its proteinous nature. The direct detection of the BSCY2 band showing antimicrobial activity on Tricine–SDS-PAGE suggested an apparent molecular mass of about 6.5 kDa [68].

In contrast to the above-mentioned bacteriocins of this group, some bacteriocins retain their activity after treatment with proteolytic enzymes.

B. licheniformis strain VPS50.2 produced bacteriocin licheniocin 50.2 (molecular mass of approximately 3.25 kDa) and was effective against Gram-positive bacteria, including *Listeria monocytogenes*, methicillin-resistant *Staphylococcus aureus*, and b-haemolytic streptococci. Bacteriocin activity was insensitive to lysozyme and proteinase K, being heat stable after incubation at 100 °C for 30 min and over a wide range of pH (2–12). The inhibitory spectrum considered in this study was limited to Gram-positive bacteria only. The maximum antagonistic activity was found in the precipitate with 60% saturation of ammonium sulfate [69].

Despite the varying degrees of sensitivity to the action of proteolytic enzymes, bacteriocins of this group are resistant to elevated temperatures and wide pH values, so they are especially suitable for medical applications.

B. licheniformis Secreted Peptides Active against Both Gram-Positive and Gram-Negative Microorganisms

The bacteriocins secreted by *B. licheniformis* that show activity against both Gram-positive and Gram-negative microorganisms are common and are sensitive to the action of proteolytic enzymes but resistant to elevated temperatures. They show different sensitivities to a wide range of pH values. All bacteriocins of this sub-group are sensitive to the action of proteinases.

B. licheniformis strain IITRHR2 produced a bacteriocin-like inhibitory substance (~1.2 kDa), which was thermostable (up to 80 °C but showed decreased activity at higher temperatures) and pH-resistant but lost activity when subjected to proteinase treatment (proteinase K and pronase E). This bacteriocin inhibited various Gram-positive bacterial strains, such as *B. subtilis*, *B. cereus*, *Streptococcus thermophilus*, *Pediococcus pentosaceus*, *Leuconostoc mesenteroides*, *L. monocytogenes*, *Bifidobacterium bifidum*, and *Enterococcus faecalis*. The growth of Gram-negative bacteria *Shigella flexneri*, *Shigella sonnei* and *Pseudomonas aeruginosa* was also inhibited by this compound [70].

A culture supernatant of *B. licheniformis* MKU3 exhibited bacteriocin-like activity against several type strains of Gram-positive bacteria, such as *Bacillus subtilis*, *Bacillus smithii*, *Staphylococcus epidermidis*, *Micrococcus luteus*, *Leuconostoc mesenteriodes* and *Pediococus acidilactici*, *B. cereus*, *B. megaterium*, *K. gibsonii*, *Staphyloccus* sp., *Streptococcus* sp., and *Micrococcus caseolyticus* but not *Listeria* sp. However, Gram-negative bacteria, such as *Serratia marcescens* and *Pseudomonas fluorescens* B10 were not inhibited by this bacteriocin, excluding *Escherichia coli*. The extract showed strong activity against different fungi including *Aspergillus niger*, *A. versicolor*, *A. fischeri*, and *A. fumigatus* and the yeast *Candida albicans*. The active substance apparently is a bacteriocin-like protein with a molecular mass of 1.5 kDa. The activity of this bacteriocin was stable at pH 3.0–10.0 and temperatures up to 100 °C for 60 min but was inactivated by proteinase K, trypsin or pronase E. The bacteriocin lost its activity after incubation at 121 °C for 15 min. The composition of the medium affected the production of this bacteriocin [34].

B. licheniformis strain B116 showed strong antimicrobial activity against *Staphylococcus aureus* and *Salmonella enterica ser. Pullorum*. Bacteriocin was precipitated by ammonium sulfate, and its molecular mass was determined as ~4 kDa. The culture supernatant of this strain exhibited antimicrobial activity against both Gram-positive and Gram-negative bacteria, including *Bacillus cereus*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Micrococcus luteus*, *Escherichia coli*, *Streptococcus equi*, and *Salmonella* spp. The bacteriocin was resistant to heat, acid, and alkaline treatments. The activity of this bacteriocin was totally lost after digestion by pronase and activity was partially lost after digestion by papain and lipase. The inactivation by lipase indicated that this bacteriocin may have contained a lipid moiety [71].

B. licheniformis MCC 2016 (strain was also named Me1) produced the antibacterial peptide ppABP that was completely abolished by proteinase K. The culture, which was isolated from milk, was able to produce a proteinaceous antibacterial peptide with a low molecular weight between 3.0 and 3.5 kDa. It exhibited a broad spectrum of inhibitory activity and was

stable over a wide range of temperature and pH. ppABPs were found to be thermally stable for 15 min at 80 °C. The SN of this strain exhibited inhibitory activity against both Gram-positive and Gram-negative food-borne and human pathogens [72][73]. Films activated with ppABP from *B. licheniformis* Me1 showed a zone of inhibition that was not confined to the film area, indicating that the ppABP diffused from the films into the medium [74].

B. licheniformis strain N.C.T.C. 7072 produced licheniformins, which are antibacterial agents, with in vitro bacteriostatic activity against many organisms, including *Mycobacterium tuberculosis*. In addition to inhibiting the growth of mycobacteria, they showed efficacy against *Staphylococcus aureus* and *Escherichia coli* [75]. The peptides had a molecular mass of 3.8, 4.4 and 4.8 kDa, respectively [37].

B. licheniformis strains MCC2512 and MCC2514 exhibited inhibitory activity against *Micrococcus luteus*, *Staphylococcus aureus*, *Klebsiella* sp., and *Aeromonas hydrophila*. In addition to these pathogenic strains, B. *licheniformis* strain MCC2512 also showed inhibitory activity against *Listeria monocytogenes* and *Salmonella typhimurium*. The activities of the bacteriocins from both cultures were completely lost upon exposure to proteinase K, indicating the proteinaceous nature of the compounds. After treating the sample with trypsin and pepsin, 100% of the activity was retained; however, with a-amylase, 50% of the activity was lost. The isolated bacteriocins varied in their mechanisms of action and stability. The molecular weights of the inhibitor components from MCC2514 and MCC2512 were 6.5 and 3.5 kDa, respectively. *B. licheniformis* MCC2512 produced a subtilin-type antimicrobial compound that acted on cell wall synthesis. Strain MCC2514 inhibited RNA synthesis [31]. The active substance produced by *B. licheniformis* MCC2512 was identified as sublichenin [53] (**Figure 2**).

B. licheniformis Peptide Activity against Fungal Pathogens

An important characteristic of some bacteriocins is antifungal activity, which substantially expands the horizons of their application in medicine, agriculture, and the food industry.

The cell-free supernatant of *B. licheniformis,* ZJU12, isolated from soil exhibited pronounced antibacterial (for Gram-positive bacteria) activity. The bacteriocin-like peptides produced by *B. licheniformis* ZJU12 showed no activity against Gram-negative bacteria, but exhibited activity against fungi (*Xanthomonas oryzae pv.oryzae*, *Alternaria brassicae*, *Fusarium oxysporum*, and others). After treatment with proteinase K and trypsin, the antagonistic activity was completely lost. The molecular mass estimated via Tricine–SDS-PAGE of the antagonistic compound was approximately 3 kDa. These characteristics indicated that the antagonistic substances produced by this strain had the property of bacteriocin. The activity was stable following exposure up to 100 °C for 30 min but was completely lost at 121 °C for 15 min. The maximum antagonistic activity was found in the resolved precipitate of supernatant with 60% saturation of ammonium sulfate. The toxicity of the substance was low because no adverse effects on mice were detected at a dose of up to 0.8 mg/20 g in acute toxicity tests [33].

B. licheniformis strain MGrP1 produced antibiotics in liquid media containing soyabean meal and mannitol that inhibited the growth of plant fungal pathogens of agricultural importance, namely *Colletotrichum lindemuthianum* (bean anthracnose), *Colletotrichum kahawae* (coffee berry disease), *Fusarium oxysporum f.sp. phaseoli* (fusarium yellow), and *Alternaria solani* (early blight). The results of paper chromatography combined with bioautography revealed two thermostable active compounds whose activity was optimal at pH 6. Low pH ranges and autoclaving temperatures significantly reduced the activities of the antibiotics [76].

Fungicin M-4, produced by *B. licheniformis* M-4, is composed of 34 amino acid residues of 7 different amino acids, including 4 residues of ornithine per molecule. The same strain showed inhibitory activity against the human pathogenic amoeba *Naegleria fowleri*. Purified fungicin M-4 demonstrated antifungal activity against the pathogenic fungi *Sporothrix schenckii* and *Microsporum canis.* Fungicin M-4 was resistant to proteolytic enzymes and lipase. Its antifungal activity was fairly resistant to heat, although incubation at 80 °C for 30 min caused 30% inactivation. The activity was stable in the pH range from 2.5 to 9.0. Its molecular weight was 3.6 kDa. Attempts to deduce an amino acid sequence were unsuccessful, suggesting that fungicin may be a cyclic peptide or it is blocked at its amino-terminal end [77].

Peptide A12-C from *B. licheniformis* A12 showed a pronounced antifungal effect, being an acidic hydrophilic peptide with a mass of 0.77 kDa, containing only six different amino acids. Peptide A12-C was resistant to proteolytic enzymes, such as trypsin, pronase, and proteinase K, as well as to carboxypeptidase A, alkaline phosphatase, lipase, lysozyme, β-glucosidase, and β-glucuronidase. Peptide A12-C showed resistance to heat (100 °C for 30 min at pH 7.0) and incubation at room temperature under acidic conditions (pH 2.5), but 75% of the activity was lost after incubation at pH 9.5 for 30 min at room temperature. Peptide A12-C was active against several fungi (*Microsporum canis*, *Mucor mucedo*, *M. plumbeus*,

Sporothrix schenckii, and *Trichophyton mentagrophytes*) and bacteria (*Bacillus megaterium*, *Corynebacteriurn glutamicum*, *Sarcina* and *Mycobacterium phlei*) [46].

B. licheniformis NCIMB 8874 produced peptide ComX with antifungal activity against the fungal leaf pathogen *Alternaria alternata*. ComX comprises 13 amino acid residues: Glu-Ala-Gly-Trp-Gly-Pro-Tyr-Pro-Asn-Leu-Trp-Phe-Lys [78].

Amoebolytic Substances from *B. licheniformis*

Bacteriocins with amoebolytic activity have been identified, all of which showed resistance to the action of proteolytic enzymes and elevated temperatures.

B. licheniformis A12 produced two amoebolytic substances (amoebicins A12-A and A12-B) in liquid media during sporulation. Both substances were heat- and protease-resistant peptides containing aspartic acid, glutamic acid, serine, proline, and tyrosine in a molar ratio of 5:2:2:2:2. No fatty acids or carbohydrates were detected. Both amoebicins retained 100% of their activity after being heated at 100 °C for 30 min at pH 7.0. They were also resistant to incubation at room temperature under acidic conditions (pH 2.5) but lost 75% of their activity upon incubation at pH 9.5 for 30 min. The crude supernatants, as well as the purified substances, retained 100% of their activity after storage for 1 month at 4 °C or for 6 months at −20 °C. Amoebicins A12-A and A12-B were resistant to the enzymes trypsin, pronase, proteinase K, alkaline phosphatase, lipase, lysozyme, α-glucosidase, and 3-glucuronidase. They were also resistant to carboxy peptidase A, suggesting that a free carboxyl terminus was not present. Their molecular weight was found to be 1.43–1.60 kDa. Purified amoebicins A12-A and A12-B exhibited amoebolytic action against *Naegleria fowleri*. They also exhibited antibiotic action against yeasts (*Saccharomyces heterogenicus* and *Cryptococcus neoformans*) and several fungal species (*Aspergillus niger*, *Microsporum canis*, *Mucor plumbeus*, and *Trychophyton mentagrophytes*). Their antibacterial spectrum appears to be restricted to *Bacillus megaterium*, *Corynebacterium glutamicum*, and *Sarcina* sp. The amoebolytic effect was studied via electron microscopy. At 10 min after addition, the characteristic shape of the cells changed. First, they developed abnormal globular pseudopodia, and then they became rounded. After 30 min of incubation, the cell membrane ruptured, with the release of the cytoplasmic material. All of this was followed by complete cellular destruction within 1 h [79].

B. licheniformis M-4 produced three antibiotic peptides (m4-A, m4-B, and m4-C) with amoebolytic activity. They were active against human pathogenic and non-pathogenic strains of *Naegleria fowleri*, which is the causative agent of primary amoebic meningoencephalitis. The amoebicidal activity of these peptides was resistant to the actions of trypsin, proteinase K, and carboxypeptidase A. They were cyclic peptides with molecular weights ranging from 3.0 to 3.2 kDa. These peptides were composed of six different amino acids (Asp, Glu, Ser, Thr, Pro, and Tyr), and they differed only in the number of Asp residues. The three amoebicins had a broad antifungal spectrum, although peptide m4-C showed a two-fold higher specific activity against a variety of fungi and yeasts than others. The three peptides showed a narrow antibacterial spectrum, but *Bacillus megaterium* (not spores) was highly sensitive [80]. The amoebicins from *B. licheniformis* M-4 differ from those produced by strain A12 in molecular weight, in their amino acid composition (A12-A and A12-B contained threonine), in the number of residues per molecule, and in their solubility in water (A12-A and A12-B are not water-soluble) [79][80].

B. licheniformis D-13 produced three hydrophobic peptides (amoebicins d13-A, d13-B, and d13-C) that showed anti-amoebic activity against human-pathogenic and non-pathogenic species of Naegleria and had a broad spectrum of antibacterial activity. The three amoebicins showed the same amino acid composition and molecular weight of 1.87 kDa. The three amoebicins were stable at pH 2.5 to 9.5, and they retained 100% of their activity after being heated at 100 °C for 30 min and after being stored at −20 °C for 6 months. Because the purified amoebicins were not soluble in aqueous buffers, a mixture of partially purified amoebicins in 20 mM Tris-HCl (pH 7.2) was tested for sensitivity to various enzymes. The mixture retained 100% of its activity after being treated for 1 h with proteases (trypsin, pronase, and proteinase K), lipase, or β-glucuronidase. Amoebicin d13-B caused the lysis of amoebae through the disorganization of the cell membrane (**Figure 2**). No amino acid residues were detected after the N-terminal sequence of amoebicin d13-B, suggesting that this peptide is cyclic or blocked at its amino terminus [81].

2.1.3. Class III: Heat-Stable and Heat-Labile Proteins Larger Than 10 kDa

This class includes unmodified peptides with a molecular weight larger than 10 kDa. In most cases, these are thermostable membrane-active peptides that are sensitive to proteinase treatment.

B. licheniformis SXAU06 produced a bacteriocin-like substance (BLIS) with an approximate molecular weight of 14 kDa designated as BLIS_SXAU06. It was active against *Escherichia coli*, *Salmonella enterica*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Micrococcus luteus*, and *Listeria monocytogenes.* BLIS_SXAU06 exhibited high resistance to treatment at high temperature, high acidity and alkalinity, and proteinase K, but it was fully inactivated by pronase E and

partially inactivated by trypsin and pepsin. BLIS_SXAU06 was heterologously expressed in *E. coli*, and the recombinant BLIS_SXAU06 exhibited effective antibacterial activity against *S. aureus*, *S. epidermidis*, *M. luteus*, and *L. monocytogenes* [82].

When a tropical marine strain of *B. licheniformis* D1 was grown in Luria–Bertani (LB) broth-containing tryptone medium, it produced a 14 kDa protein BL-DZ1 (BL00275) with antimicrobial activity against pathogenic *Candida albicans* BH, *Pseudomonas aeruginosa* PAO1, and biofouling *Bacillus pumilus* TiO1 cultures. The antimicrobial activity was lost after treatment with trypsin and proteinase K. The protein was stable at 75 °C for 30 min and over a pH range of 3.0 to 11.0. The BL-DZ1 protein was able to inhibit both biofilm growth and disrupt pre-formed biofilms of *C. albicans*, *P. aeruginosa*, and *B. pumilus* [83].

B. licheniformis HS10 produced an antifungal protein with a molecular weight of approximately 55 kDa, identified as carboxypeptidase. It showed significant inhibition activity of eight different kinds of plant pathogenic fungi, and it was stable with strong biological activity at as high as 100 °C for 30 min and in pH values ranging from 6 to 10. The biological activity was negatively affected by protease K. The protein had broad spectrum antifungal activity against seven kinds of plant pathogenic fungi [84].

Isolated from seaweed, *B. licheniformis* produced a protein with antibacterial activity against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and *Listeria monocytogenes.* The antibacterial activity was strongest in cultures grown under shaking at 210 to 230 rpm. No antibacterial activity was found in cultures grown statically or at other rotary shaking speeds. The antibacterial compound was sensitive to proteinase K, pronase, and trypsin, but was not affected by Tween-20, -40, -60, or -80, or a- or b-amylase. Its activity was not adversely affected by heating up to 40 °C or treatment at pH from 5 to 14. The bioactive compound was determined to be associated with a 30.7 kDa protein, that showed homology to the secreted YbdN protein of *B. licheniformis* ATCC 14580 [85].

B. licheniformis MY75 secreted high levels of extracellular chitinase with a molecular weight of 55 kDa and inhibited the growth of pathogenic fungi *Gibberella saubinetii* and *Aspergillus niger.* The secretion of this protein was induced by chitin powder [86]. Chitinase proteins were present in the culture supernatant of *B. licheniformis* Mb-2 [87], *B. licheniformis* TP–1 [88], *B. licheniformis* S213 [89], *B. licheniformis* SSCL-10 [90], *B. licheniformis* B307 [91].

B. licheniformis BS-3 produced an antifungal 31 kDa protein, F2, that inhibited the growth of *Aspergillus niger*, *Magnaporthe oryzae*, and *Rhizoctonia solani.* The F2 protein was moderately resistant to hydrolysis by trypsin and proteinase K. Higher F2 antifungal activity was observed from pH 6.0 to pH 10.0 and at a temperature below 70 °C for 30 min [92].

As in the other cases, this group of bacteriocins contains some proteinase-resistant members. Owing to this property, these proteins may be applicable for administration through the digestive system.

B. licheniformis strain JS produced 16 kDa antimicrobial protein (AMP), which demonstrated more activity against Gram-positive bacteria *Bacillus cereus* and less activity against Gram-negative bacteria (*S. dysenteriae* and *S. typhimurium*). The purified peptide also increased the effectiveness of antibiotics, such as kanamycin, neomycin, and streptomycin. Hence, it could be important because the AMPs produced by *B. licheniformis* may facilitate the entry of these antibiotics inside the pathogens and increase their efficiency. The antimicrobial activity was 100% after AMP incubation between 10 and 90 °C. The trypsin digestion study revealed that AMP retained 100% of its activity [93].

B. licheniformis T6-5 inhibited more than 65% of the 40 *Bacillus* strains and of the sulfate-reducing bacteria *Desulfovibrio alaskensis*. The treatment of the supernatant with organic solvents led to total (acetone, ethanol, and methanol) or partial (chloroform) inactivation of the inhibitor component. The inhibitor probably contained a lipidic portion as a part of its structure. This substance was heat-stable after incubation at 100 °C for 1 h and maintained its activity after being autoclaved at 121 °C for 15 min. It was active in a wide range of pH (3.5–9.5). The inhibitory component was resistant to the action of pronase E, proteinase K, trypsin, RNase, chitinase, b-galactosidase, a-galactosidase, and manosidase. The substance produced by strain T6-5 was estimated via dialysis to be bigger than 12 kDa. According to the results of SDS-PAGE analysis, strain T6-5 showed an inhibitory zone of ca. 20 kDa, corresponding to the molecular weight suggested by the dialysis membrane approach [36]. The substance inhibitory zones of *B. licheniformis* H2O-1 antimicrobial were related to a region of high molecular mass (90–120 kDa) [36]. *B. licheniformis* strains T6-5 and H2O-1 prevented the formation of *B. pumilus* LF4 biofilm and eliminated pre-established LF4 biofilm [94]. The nature and precise structure of the above inhibitory substances are still unclear.

2.1.4. Class IV: Complex with a Lipid Moiety or Carbohydrate Moiety

B. licheniformis BFP011 isolated from papaya (Thailand), produced extracellular antimicrobial substances that were active against some important phytopathogens, pathogenic and spoilage microorganisms, such as *Colletotrichum capsici*, and *Escherichia coli* O157: H7, and *Salmonella typhi* ATCC 5784. The three types of antimicrobial substances (F4, F5, and F6) produced by *B. licheniformis* BFP011 were not sensitive to pronase as revealed in stationary phase cultures. The antimicrobial substances of this bacterium were stable at 37 and 70 °C and partly resistant at 121 °C. Most of the antimicrobial protein substances from the culture supernatant were extracellular compounds having low molecular weights of less than 45 kDa. The antimicrobial substances of *B. licheniformis* BFP011 contained peptides and unsaturated fatty acids; however, the precise structural organizations of these compounds are not known. They exhibited a broad spectrum of antimicrobial activity against both Gram-positive and Gram-negative bacteria and the fungus *C. capsici*. These substances differed from iturin A (commercial), bacitracin (commercial), and a bacteriocin-like substance of *B. licheniformis* P40 [95].

Two glycolipopeptides, ieodoglucomides A and B, were isolated from marine-derived *Bacillus licheniformis* 09IDYM23. They consisted of an amino acid, a new fatty acid, a succinic acid, and a sugar. These glycolipopeptides showed moderate antimicrobial activity when tested against both Gram-positive and Gram-negative bacteria and fungi, such as *S. aureus*, *P. aeruginosa*, *E. coli*, *B. cereus*, and *A. niger.* The molecular formula of ieodoglucomides A and B were assigned as $C_{30}H_{53}NO_{12}$ and $-C_{29}H_{51}NO_{12,}$ respectively [96].

The same strain, 09IDYM23, produced a glycolipopeptide, ieodoglucomide C, and a new monoacyldiglycosylglycerolipid, ieodoglycolipid. These compounds showed antimicrobial activity against fungi *C. albicans*, *A. niger*, *R. solani*, *C. acutatum*, and *B. cenerea* and bacteria *S. aureus*, *B. subtilis*, *B. cereus*, *S. typhi*, *E. coli*, and *P. aeruginosa*. The molecular formulae of each isolated component were determined to be $C_{29}H_{51}NO_{12}$ and $C_{30}H_{56}O_{14,}$ respectively [97].

2.1.5. Class V: Bacteriocins with Undetermined Molecular Weight

A skin isolate of *B. licheniformis* showed the most potent antibacterial activity at pH 7, with an incubation period of 48 h, at an incubation temperature of 25 °C. The antipathogenic metabolites were then detected as bacteriocin-like substances, which demonstrated heat stability up to 80 °C for 30 min. The papain-treated cell-free supernatant did not show any bacteriocin activity, suggesting that the substances were antimicrobial peptides. This bacteriocin inhibited the growth of *Staph. aureus* and *Kl. pneumoniae subsp. Pneumonia* [98].

A skin isolate *B. licheniformis* UpA was observed to produce antimicrobial metabolite that was effective against *Klebsiella pneumoniae subsp. pneumoniae*. It was detected as a bacteriocin-like substance and was further confirmed as an antimicrobial peptide through papain treatment. The produced bacteriocin was stable with heat treatment up to 80 °C for 30 min and up to pH 7 [99].

The supernatant of *B. licheniformis* A-1-5B-AP significantly reduced the growth of oral pathogenic strains *Porphyromonas gulae* 3/H, *Prevotella intermedia* 1/P, and *Streptococcus mutans* ATCC 35668. However, *B. licheniformis* A-2-11B-AP only significantly inhibited the growth of *P. intermedia* 1/P and *S. mutans* ATCC 35668. The enzyme-treated SN of *B. licheniformis* A-1-5B-AP did not lose its antimicrobial effect and significantly inhibited the growth of *Micrococcus luteus* DSM 1790. Proteinase K, lipase, or α-amylase did not affect the antimicrobial activity present in the SN of strain of *B. licheniformis* A-1-5B-AP. The presence of genes associated with the synthesis of lichenysin was detected, although their presence in the medium was not confirmed [100].

B. licheniformis HJ2020 MT192715.1 produced a bacteriocin active against many food spoilage microorganisms. The residual inhibition activity of bacteriocin varied according to the incubation conditions and treatment type. The inhibitory activity was 220 and 360 U mL^{-1} against the clinical isolates of pathogenic strains *Escherichia coli* and *Salmonella typhi*, respectively; the activity was 42, 60, and 80 U/mL against to *B. subtilis*, *B. cereus* and *Candida albican,* respectively [101]. No activity was detected against *Lactobacillus* or *Bifidobacterium*. These results are similar to those reported for *B. licheniformis* P40 [29]. The bacteriocin lost approximately 25–40% of its activity when incubated in acidic pH (between 3 and 5), it lost approximately 80% of its activity at pH 10, and no activity was observed at pH 12. The heat stability of the bacteriocin also was tested, and the results showed that it retained all activity when incubated at 5–35 °C for 30 min. It lost approximately 25–50% of its activity after incubation at 50–80 °C and lost all activity when incubated at 100 °C for 30 min or autoclaved at 121 °C for 15 min at 15 psi. The reduction in bacteriocin activity and the loss of all of its activity at high temperature were attributed to denaturation, indicating the proteinaceous nature of bacteriocin. The results also revealed that the bacteriocin was stable when treated with α-amylase and lipase, pointing to the absence of glycosidic or lipidic residuals [101].

The bacteriocins produced by *B. licheniformis* are characterized by resistance to various pH ranges, thermal stability, and, in some cases, sensitivity to proteolytic enzymes. However, they differ in the spectrum of antibacterial activity for different strains of *B. licheniformis*. For example, a bacteriocin produced by *B. licheniformis* MKU3 isolated from slaughterhouse sediments did not inhibit *L. monocytogenes*, *P. fluorescens* or *S. marcescens*, but inhibited *E. coli* [34]. A bacteriocin-like peptide produced by *B. licheniformis* ZJU12 isolated from soil exhibited antagonistic activity against *S. aureus* [33]; *B. licheniformis* P40 inhibited *E. aerogenes* but did not inhibit *P. fluorescens* [29]. Anaerobiosis specifically expressing lichenin demonstrated a narrow spectrum of activity against ruminal anaerobes [32].

Bacteriocins have different structures and different mechanisms of action against bacteria. Their ability to reach their targets is crucial for their effectiveness. Due to variations in cell wall structure, certain bacteriocins, particularly those designed to target intracellular components, may encounter challenges in penetrating the cell walls of mycobacteria or Gram-negative bacteria. Conversely, pore-forming bacteriocins have demonstrated a broader spectrum of activity against various types of bacteria.

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