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Review

Molecular and genetic insights into quorum-sensing-driven bacteriocin production in Gram-positive bacteria

Hafsa Kaleem[1,†], Abrar Hussain[1,†], Mushtaq Hussain[1,2], Syed Ghulam Musharraf[3] and Syed Abid Ali[1,*]

[1] Third World Center for Science and Technology, H.E.J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, Karachi-75270, Pakistan
[2] Present address. Dow College of Biotechnology, Dow University of Health Sciences, Ojha Campus, Karachi, Pakistan
[3] H.E.J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, Karachi-75270, Pakistan

* **Correspondence:** Email: abid.ali@iccs.edu; Tel: +00922199261720.

† These two authors contributed equally.

Abstract: Quorum sensing (QS) is a cell density-dependent regulatory mechanism that controls various cell-to-cell communication and metabolic processes in bacteria. This mechanism regulates many important functions, including capsule synthesis, antimicrobial peptide production, biofilm formation, and virulence-related traits. In Gram-positive bacteria, these coordinated responses are mediated by the production, release, and detection of extracellular signaling molecules, commonly referred to as autoinducers (AIs). As the bacterial population increases, these signals are typically detected by a two-component regulatory system, mainly consisting of a membrane-bound histidine kinase and a response regulator, which activates specific gene expression, or by a three-component system comprising an extracellular induction peptide, a membrane-bound histidine kinase, and a response regulator. In lactic acid bacteria, QS tightly regulates bacteriocin production, which is typically induced only under specific environmental or physiological conditions. Many class-I bacteriocins employ a two-component regulatory system for their regulation, in which the mature lantibiotic or a processed signaling peptide acts as an extracellular signaling pheromone to induce the expression of bacteriocin-associated genes. The production of several class-II bacteriocins relies on a

three-component regulatory mechanism involving an extracellular peptide, membrane-bound histidine kinase, and a response regulator. In contrast, class-III bacteriocins are diverse; some class-III bacteriocins are regulated by specific induction peptides, whereas in some cases, the mature bacteriocins themselves directly function as autoinducing peptides. The broad potential applications of bacteriocins as food preservatives and potential therapeutics have accelerated research into their regulatory systems. Therefore, insights into these regulatory pathways may facilitate the development of effective strategies for bacteriocin production and their potential use in food and healthcare applications. This review provides a concise overview of genetic insights related to bacteriocin regulation and expression, focusing on the cell density-dependent regulatory system and the external signals that induce bacteriocin production.

Keywords: bacteriocins; enterocins; cross-talks; lactic acid bacteria; lantibiotics; quorum sensing; antimicrobial peptides

1. Introduction

Intercellular communication plays a pivotal role in the physiology of living organisms, including microbial species. Many bacterial species, once thought to exist as single cells, have been found to exhibit population-dependent physiological and/or metabolic responses. This population-dependent phenotypic expression is termed quorum sensing (QS) [1,2]. Bacteriocins and their associated proteins, such as immunity, transporter proteins (e.g., ABC transporters), and expression regulators, are regulated by QS [3]. Bacteria involved in QS produce low-molecular-weight signal molecules that are released into the environment when a sufficient level, or quorum, of bacteria is established. These signal molecules bring out the expression or halting of gene(s) [4–6]. Hence, it seems plausible to state that the QS phenomenon could be considered a cell-to-cell communication strategy that allows microorganisms to behave in a multicellular way by allowing sensing of cell density and population-wide synchronization as a function [7]. On that basis, it could be reasonable to conclude that QS provides new insights into the evolutionary studies of the transition from prokaryotic to multicellular origin.

Bacteriocins are a diverse group of ribosomally synthesized antimicrobial peptides or proteins that inhibit the growth of other bacteria [8]. The potential application of bacteriocins as natural biopreservatives in food systems includes the direct incorporation of purified bacteriocins into food products as well as the use of bacteriocin-producing strains as starter or protective cultures to enhance food safety, prolong shelf life, and hinder the growth of spoilage and other pathogenic microbes [5,9]. The remarkable rise of antibiotic resistance against common pathogens warns researchers to search for alternative options. In this regard, the use of bacteriocins as a novel candidate attracts great interests [10,11].

Bacteriocins are produced by both Gram-positive and Gram-negative microorganisms [12,13]. However, bacteriocins from Gram-positive organisms, especially lactic acid bacteria (LAB), are more noteworthy for their industrial applications because they are generally recognized as safe (GRAS) and have qualified presumption of safety (QPS) status [14,15]. Additionally, they are distinguished from Gram-negative bacteriocins in two ways: First, bacteriocin production in Gram-positive organisms is not necessarily lethal because of the release of inactive, premature bacteriocin, which is further

processed by dedicated transport machinery [16–19]. Second, bacteriocin-specific regulation is synchronized by the bacteriocin itself [16,20] or mostly by dedicated, similar but not identical peptides. In contrast, the Gram-negative bacteriocins rely solely on host regulatory networks via aminoacyl homoserine lactone (AHL) [21]. However, exceptional deviations are always present, as autoinducer type B (furanosyl borate diester) is found both in Gram-positive and Gram-negative bacteria as a signal molecule [6,22]. Furthermore, QS cross-talk across different biological kingdoms has been reported between *Escherichia coli* O157 and human cells, demonstrating the ability of bacterial signaling molecules to influence host cellular responses [23].

In most cases, bacteriocin production is considered an unstable trait because bacteriocin and immunity-associated genes are commonly located on extrachromosomal elements such as plasmids or on transposable elements, which may be lost during cell division or under stress conditions [24,25]. Bacteriocin production in lactic acid bacteria is influenced not only by QS and cell density but also by the physiological state of the producer and the surrounding culture conditions [26]. The onset of bacteriocin gene expression may occur during different stages of growth, including early, mid-, or late-exponential phase, depending on the producer strain, bacteriocin regulatory architecture, signal accumulation, and environmental conditions. Consequently, the relationship between cell density and bacteriocin production should not be considered strictly linear. QS signaling can provide a cell-density-dependent regulatory input, whereas growth rate, nutrient availability, and cellular stress can modify the responsiveness of the regulatory system and the metabolic capacity required for bacteriocin biosynthesis [27,28].

Culture medium is an important determinant of bacteriocin production because carbon and nitrogen sources, peptide availability, mineral composition, and nutrient limitation can affect both biomass formation and expression of bacteriocin-associated genes. Likewise, pH, temperature, acidity, osmotic conditions, and other environmental stresses can alter cellular physiology, QS signal accumulation or stability, regulatory protein activity, and bacteriocin synthesis [29–31]. In some LAB, environmental stress may also activate regulatory pathways that interact with bacteriocin-associated two-component or multicomponent systems, thereby modifying the timing or magnitude of production. These effects emphasize that QS should be interpreted within the broader physiological context of the growing culture rather than as an isolated determinant of bacteriocin expression [32].

However, environmental conditions can influence bacteriocin production in different ways. For instance, in *Enterococcus faecium* RZS C5, oxidative stress did not significantly affect cell growth or bacteriocin activity, whereas salt stress reduced cell growth and specific bacteriocin production. Interestingly, moderate NaCl concentrations increased bacteriocin activity by allowing bacteriocin production to remain active at higher biomass levels [33]. In contrast, bacteriocin production in *Lactobacillus plantarum* 17.2b was highly influenced by temperature, pH, NaCl concentration, and carbon and nitrogen sources. The factors associated with maximum bacteriocin production differed from those affecting bacterial growth [34].

Similarly, carnocin KZ213 production by *Carnobacterium piscicola* 213 strongly depended on temperature, pH, culture medium, and carbon source. Notably, conditions favorable for bacterial growth were not necessarily associated with bacteriocin production [35]. Variation among these studies suggests that apparently contradictory results may be attributed to differences in producer strain, the regulatory system mediating bacteriocin production, physicochemical conditions, and the methods used to assess bacteriocin production [33–36]. Therefore, bacteriocin production should be distinguished from extracellular stability and antimicrobial activity, as the same factors can affect each of these processes differently.

In addition, metal-ion availability is also an important determinant of bacteriocin production. In *Lactobacillus gasseri* SBT2055, elevated concentrations of certain metal ions such as Mg^{2+}, Fe^{2+}, Ca^{2+}, Zn^{2+}, and Mn^{2+} reduced gassericin T production to the point that it was almost undetectable at 200 mM despite continued bacterial growth. The restoration of production following the addition of trisodium citrate highlights the importance of divalent cation availability for gassericin T production [36].

Importantly, the timing of bacteriocin production is strain- and regulator-system-dependent and may vary across stages of growth. For instance, in *E. faecium* RZS C5, enterocin production is restricted to the very early growth phase and is switched off upon reaching a defined cell density [37]. In contrast, bacteriocin production in *Streptococcus thermophilus* is regulated by the *Blp* QS system, with bacteriocin production varying with growth phase and the concentration of the BlpC signaling peptide. In *Carnobacterium piscicola* 213, carnocin KZ213 production is affected by medium composition, glucose availability, pH, and temperature [35].

It is worth mentioning that QS, although providing an important cell- density-dependent mechanism for regulating bacteriocin production in many LAB, is not a universal prerequisite for bacteriocin expression. Certain bacteriocin-producing LAB, particularly strains belonging to genera such as *Carnobacterium* and *Leuconostoc*, have been reported to produce active bacteriocins during the early exponential phase, when population density remains relatively low, and classical QS signal accumulation may not yet have reached the threshold required for autoinduction. Such early production may reflect strain-specific regulatory mechanisms and the integration of growth-phase, nutritional, temperature, and stress-related signals with bacteriocin gene expression [38,39]. Low temperature and nutrient-limited conditions can further influence bacteriocin production and may favor early antimicrobial activity. This phenotype is particularly relevant to protective cultures used in refrigerated foods, where bacteriocin production at low temperature and before high cell densities are reached may provide an early competitive advantage against foodborne or spoilage microorganisms [40,41]. These observations highlight the regulatory diversity of bacteriocin systems and indicate that QS-dependent regulation should be considered as one component of a broader network integrating cell density, growth physiology, environmental conditions, and microbial interactions.

Furthermore, bacteriocin production is an important trait for selecting probiotic strains. Although their precise ecological role remains incompletely defined, bacteriocins may contribute to probiotic efficacy through several mechanisms. They may facilitate colonization by providing the producer with a competitive advantage among coexisting microbial populations [42]. Their antimicrobial activity in the gut may additionally suppress the proliferation of competitive and/or pathogenic microorganisms, thereby favoring gut microbial balance. Moreover, they also serve as signaling peptides and participate in QS-mediated intracellular signaling, interspecies communication, and cross-kingdom signaling [43,44]. The regulatory system governing bacteriocin production also regulates the expression of immunity proteins and ABC transporters, as well as its own expression. Such coordinated regulation provides several advantages to the producer: (i) it ensures that the concentration of bacteriocin reaches a sufficient threshold to suppress competing cells; (ii) upon encountering microbial competition, bacteriocin concentration may rapidly increase to effective levels, potentially reducing the likelihood of resistance development; and (iii) it minimizes the expenditure of cellular energy by preventing bacteriocin production under conditions where antimicrobial activity is not advantageous [32,45].

This review aims to provide molecular insights into bacterial cross-talk and the signaling molecules involved in their mechanisms of action. It further discusses QS-driven bacteriocin

production in Gram-positive bacteria. Additionally, it summarizes the genetic regulatory systems involved in bacteriocin production, with particular emphasis on population-dependent regulation and structural diversity.

2. Searching strategy

A comprehensive literature survey was conducted to identify relevant studies related to mechanistic insights into QS and bacteriocins. Different databases, including Google Scholar, ScienceDirect, Web of Science, PubMed, and Scopus, were systematically searched using a combination of keywords and phrases such as quorum sensing, bacterial cross-talk, QS in bacteria, quorum sensing in LAB, quorum sensing in Gram-positive bacteria, bacterial communication, bacteriocins, bacteriocin classification, classes of bacteriocins, factors affecting QS, mechanisms of bacteriocin action, QS mechanisms, and bacterial communication mechanisms. Other relevant literature was identified through manual screening of reference lists from selected articles.

Peer-reviewed original research articles, review papers, book chapters, and meta-analyses relevant to the scope of the review were included. Non-peer-reviewed sources, conference abstracts lacking sufficient details, commercial reports, and other forms of grey literature were excluded. The retrieved literature was screened and critically evaluated, and the extracted information was synthesized to provide a comprehensive overview of the interplay between QS and bacteriocin production, their underlying mechanisms, and their applications in microbial ecology, food biotechnology, and human health.

3. Overview of bacteriocins and their classification

Bacteriocins are ribosomally synthesized antimicrobial peptides or proteins produced by bacteria that suppress the growth of closely related or competing microorganisms, thereby contributing to microbial competition and ecological fitness. To avoid self-destruction, producer strains possess specific immunity mechanisms, often mediated by dedicated immunity proteins. Owing to their natural origin, targeted antimicrobial activity, and generally recognized safety, bacteriocins have emerged as promising alternatives or complements to conventional antibiotics, with diverse applications in food preservation, medicine, and biotechnology [46,47]. In 1993, for the first time, Klaenhammer presented the classification of bacteriocins produced by *Lactobacillus* [48]. However, advances in our understanding of bacteriocin diversity and biosynthesis have progressively revised the classification. The current classification categorizes bacteriocins into three major classes (Figure 1). This modern classification is defined based on the molecular weight, structural characteristics, biological activities, post-translational modification, and the mechanism involved in their biosynthesis [49,50]. These classes are briefly classified in the following section.

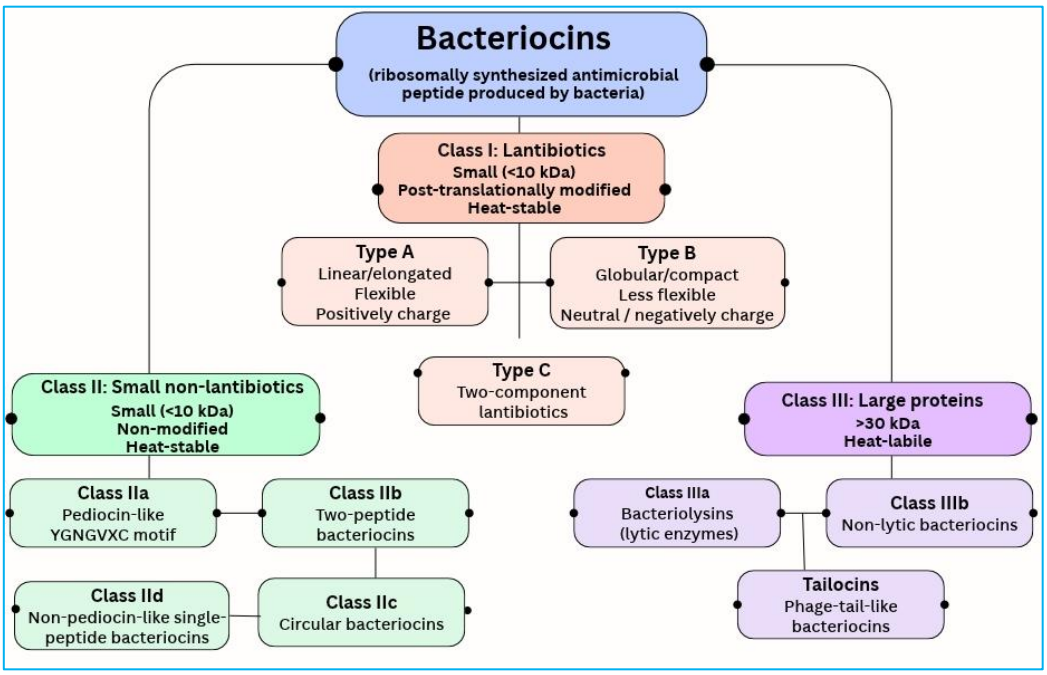


Figure 1. Classification of bacteriocins based on structural characteristics, molecular size, post-translational modifications, and physicochemical properties.

3.1. Class I (lantibiotics)

Lantibiotics are characterized by small-sized (<5 kDa) peptides and the presence of the uncommon amino acids lanthionine (Lan) and β-methyl lanthionine (MeLan), and post-translationally modified amino acids such as 2,3-didehydroalanine (Dha) and 2,3-didehydrobutyrine (Dhb) [11,50,51]. A total of 17 unusual amino acid residues have been reported in lantibiotics, arising from extensive post-translational modifications [52]. Lantibiotics are produced as precursors that undergo extensive post-translational modifications, which provide structural stability and enhance the antimicrobial activity of these peptides [53]. Predominantly, two hydroxyl side chain-containing amino acids, serine (Ser) and threonine (Thr), and their sulfhydryl analogue, cysteine (Cys), are the targets of such post-translational modification. However, in a few cases, lysine (Lys), aspartic acid (Asp), and isoleucine (Ile) are also reported to be modified [11]. The cascade begins with selective dehydration of serine and threonine in the lantibiotic prepeptide sequence, yielding α,β-unsaturated amino acids: Di-dehydroalanine (Dha) and didehydrobutyrine (Dhb). Subsequently, cysteine reacts with the didehydro residue to form the characteristic thioether amino acids lanthionine (Lan) and 3-methyl lanthionine (MetLan) [54,55].

Various other modifications in the last step of the post-translational modification have also been reported, such as Cys at the C-terminus in some lantibiotics being oxidized and decarboxylated before being a component of the lanthionine ring. This consecutive oxidation and decarboxylation of Cys residues results in the formation of S-Amino-Vinyl-D-cysteine (AviCys) or S-amino-vinyl-3-Methyl-D-cysteine, respectively. In addition to these modified amino acids, others such as lysinoalanine, erythron-3-hydroxyaspartate, D-alanine, allo-isoleucine, and 2-oxypyruvate are also reported to be the primary structural components of various lantibiotics [11]. These extensive post-translational modifications might contribute significantly to their structural stability, resistance to proteolytic

degradation, and biological activity [56]. Lantibiotics were initially classified into two types: Type A and type B. However, some classifications have introduced two-peptide type-C lantibiotics [57].

Type A: Type-A lantibiotics are elongated, positively charged, and flexible peptides, typically adopting an α-helical or screw-like conformation. They are generally composed of fewer than 34 amino acid residues and are often encoded by genes with relatively low G+C content [11,34]. The antimicrobial mode of action of type-A bacteriocins is attributed to pore formation and subsequently altering the permeability of the cytoplasmic membrane [58,59]. Type-A lantibiotics include nisin (*Lactococcus lactis*) [60], epidermin (*Staphylococcus epidermidis*) [61], subtilin (*Bacillus subtilis* ATCC 6633) [62], and Lacticin 481 (*Lactococcus lactis*) [63].

Type B: Type-B lantibiotics are compact, globular, and relatively rigid peptides that generally possess neutral or negative net charges. They typically contain fewer than 19 amino acid residues in their primary structure. In many cases, type-B lantibiotics are produced by bacteria with relatively high genomic G+C content [11,50]. Type-B lantibiotics show activity by acting as enzyme inhibitors, especially the biosynthetic enzymes related to cell wall, DNA, and RNA synthesis [51,59]. Mersacidin (*Bacillus subtilis* HIL Y-85,54728) [64], planosporicin (Planomonospora alba) [65], deoxyactagardine B (DAB) (*Actinoplanes liguriae* NCIMB 41362) [66] and cinnamycin (*Streptomyces cinnamoneus* DSM 40005/DSM 40646) [67] are well-characterized members of type-B lantibiotics.

Type C: Type-C lantibiotics are characterized by two-peptide components that act synergistically to exert their antimicrobial effect. A prominent example of type-C lantibiotics is lacticin 3147, produced by *Lactococcus lactis* [57,68]. Lacticin 3147 comprises two peptides, A1 and A2; the A1 peptide acts as the lipid II-binding component, and the A2 peptide is involved in membrane pore formation [57]. The A1 peptide contains a specific lanthionine-bridging pattern that resembles mersacidin (a globular type-B lantibiotic). In contrast, A2 belongs to the elongated type-A lantibiotic class. Nuclear magnetic resonance (NMR) spectroscopy further revealed that the A1 peptide has a similar conformation to mersacidin, whereas A2 has an α-helical conformation [68]. Other examples of type-C lantibiotics include lichenicidin VK21, staphylococcin C55, haloduracin, *Sh*-lantibiotic α/β, and plantaricin W [57]. Furthermore, Enterocin W produced by *Enterococcus faecalis* NKR-4-1 also possesses two peptides named Wα and Wβ, which work in a synergistic manner. Enterocin W also has structural similarity to plantaricin W [69].

3.1.1. Genetic organization and insights into lantibiotic gene(s)

Lantibiotics are produced as precursor peptides containing an N-terminal leader peptide and a C-terminal propeptide domain that, after undergoing modifications, are converted into a biologically active lantibiotic peptide [70,71]. In general, prepeptides are encoded by the structural gene (*lanA*) clusters with the gene(s) required for modification (*lanB*, *lanC*, *lanM*), proteolytic protein (*lanP*), transport protein (*lanT*, *lanH*), immunity protein (*lanI*, *lanFEG*), and regulation [11,56,72]. These structural, regulatory, transport, processing, and immunity gene clusters of bacteriocin are located on chromosomes, as in subtilin and mersacidin [70,73]. There is evidence for the presence of bacteriocin and its related genes on mobile genetic elements like plasmids, as exemplified by epidermin [74] and lacticin 3147 [75,76] and transposons, as in nisin and its variants [77].

Interestingly, in strains capable of producing cytolysin, the operon is typically located on the pathogenicity island (PAI) encoded on the chromosome or on a pheromone-responsive conjugative plasmid like pAD1 [78]. In addition, evidence for the presence of unrelated metabolic genes, along

with bacteriocin genes, is reported in the form of sucrose metabolism genes in the nisin biosynthetic gene cluster [79]. Assemblage of the genes in the operon of some well-characterized lantibiotics is schematized in Figure 2.

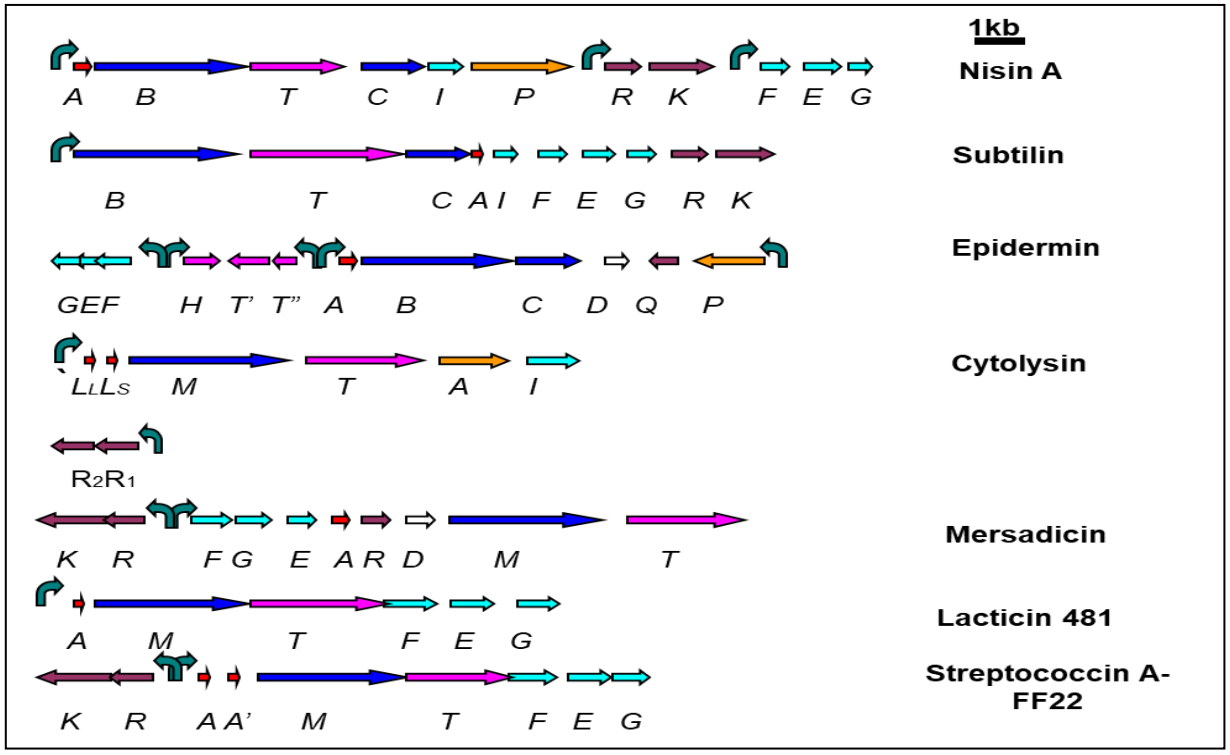


Figure 2. Genetic clusters of the producers (blue arrow), proteolytic processing and modification (brown arrow), regulatory (cyan), immunity (pink), transport (green), promoters (red), lantibiotic (white), and unknown open reading frame (ORF). Note that the alphabetical nomenclature remains the same for the set of operons.

It has been shown that there is no homogeneity in the arrangement of the genetic components of the bacteriocin. Even with the higher sequence identity in the subtilin and nisin operon, in contrast to nisin, the structural gene for subtilin *spaS* is located in the middle of the operon [4,80]. Little variation is also observed in the cytolysin operon system because of the presence of two peptides with antimicrobial activity. The gene cluster involves the $cylL_L$ and $cylL_s$ genes for the structural unit of the operon, which is post-translationally modified by the product of the *cylM* gene [81]. For the transport of the respective precursor lantibiotics, the cylB gene codes for the ABC transporters, and the *cylA* gene codes for the extracellular serine protease responsible for cleaving the leader peptide from the lantibiotics. The collective action of all such genes results in the production of mature and active cytolysin molecules, that is, $CylL_L$ and $CylL_S$ [78,81]. But the most interesting fact is the presence of a two-component regulatory system (i.e., cylR1 and cylR2) involved in the regulation of cytolysin [82]. Additionally, genomic analysis of agalacticin, a streptococcin produced by *S. agalactiae* ATCC 13813, showed strong homology to nisin, including the presence of a leader peptide. Moreover, the gene cluster of agalacticin comprises genes for modification (agaBC), transport (agaT), immunity (agal and agaFEG), regulation (agaRK), and the processing of the leader peptide [83,84].

3.1.2. Regulation and quorum sensing

Experimental evidence for mature lantibiotics functioning as peptide pheromones is primarily established for nisin and subtilin, which regulate their own biosynthesis through QS. The genetic arrangement of numerous other lantibiotics indicates a similar form of regulation [85,86]. Biosynthesis of several lantibiotics has been shown to depend on the growth phase of the producers. Usually, lantibiotics start appearing in the culture at the late log and reach their maximum in the early stationary phase [87,88]. Genetic analysis also revealed that lantibiotic synthesis is a complex trait controlled by a two-component response regulatory system that functions as a signal transduction system [89]. Furthermore, the two-component regulatory systems involved in the regulation of nisin and subtilin belong to the EnvZ-OmpR family [87,90]. Apparently, in connection with a two-component signal transduction system, lantibiotics are found to contribute to QS [91]. The two components involved in the mentioned regulation and population-dependent expression of the gene(s) are a membrane-bound histidine kinase (HK) and a response regulator [90].

3.1.3. Histidine kinase

A membrane-bound histidine kinase (LanK) is the first component of the regulatory system that comes into contact with its respective signal molecule [92]. Histidine kinase is a 380–480 residue protein and is reported to be auto-phosphorylated at its conserved histidine residue located at the C-terminus of the cytoplasmic domain. This autophosphorylation process occurs concomitantly with the recognition of a specific signaling molecule by the extracellular sensing domain of the receptor [93]. It is worth noting that direct biochemical evidence for the interaction of nisin and subtilin with their respective sensor kinases remains limited. However, studies employing chimeric SpaK-NisK sensor kinases have provided strong evidence for such interactions, demonstrating that replacement of the nisin-sensing domain with the subtilin-sensing domain, and vice versa, can alter ligand specificity and signal recognition. The same experiment also indicates that the binding site lies on the N-terminal extracellular domain of the kinase [94,95]. Upon activation and autophosphorylation, the sensor kinase transfers the phosphate group to its cognate response regulator. The phosphorylated response regulator then binds to specific promoter regions within the operon, thereby activating transcription and subsequent expression of the target gene(s) [96].

Interestingly, the nature of signaling molecules varies considerably among different lantibiotic-producing bacteria and across different classes of lantibiotics. For most lantibiotic producers, the lantibiotic itself performs the task of an autoregulator for its synthesis; for example, both nisin A and Z act as autoregulators (like pheromones) for their operons; despite this similarity in the nisin A gene cluster, operons *nisABTCIP* and *nisFEG* are only induced by nisin, whereas *nisRK* is expressed constitutively [97–99]. In contrast, nisin Z can induce the expression of both the nisRK and nisABTCP operons. During autoinduction, residues 1–11 of mature nisin are involved in binding to the membrane-associated sensor kinase NisK, thereby enabling nisin to function as an autoinducing pheromone. Although HK-mediated phosphorylation is generally species-specific, several studies have reported heterologous expression and signaling across closely related species, indicating a degree of interspecies compatibility [95,100].

Several studies suggest that basal transcription of the nisin biosynthetic genes occurs continuously at low levels, resulting in the gradual accumulation of nisin A in the culture supernatant. Once nisin A

reaches a threshold concentration as the bacterial population increases, it is sensed by the producer cells through the NisRK two-component regulatory system, thereby triggering autoinduction and enhanced expression of nisin biosynthetic genes [101]. A 4-bp deletion in the structural nisA gene led not only to the loss of nisin production but also to the complete cessation of operon transcription, providing evidence that nisin-mediated autoinduction is essential for activation and maintenance of nisin operon expression. Furthermore, the transcription products are retrieved after the addition of exogenous nisin A at a sub-inhibitory concentration. Such observations suggest that nisin not only confers the expression of its own respective gene but also the associated genes, like immunity, transport, processing, and regulation [97]. Mutational analyses of the operons encoding cytolysin, salivaricin A, streptococcin, subtilin, and mersacidin have revealed similar regulatory mechanisms governing the biosynthesis and expression of these lantibiotics, as understood from genetic studies [87,102].

In addition, major contributions in responding to cell density for bacteriocinogenesis are the kinases, which make the bacteria susceptible/resistant to certain antimicrobial agents. Mutational studies in *Listeria monocytogenes* have demonstrated that a Δ*lisK* mutant, lacking the LisK histidine kinase sensor component, exhibits significantly enhanced resistance to the lantibiotic nisin. In addition, the mutant exhibits markedly increased sensitivity to cephalosporins and a significant reduction in the expression of three genes encoding a putative penicillin-binding protein, a second HK, and a protein of unknown function [103,104].

3.1.4. Response regulator

In lantibiotic regulatory systems, autophosphorylation of the HK is followed by phosphotransfer to the response regulator, which subsequently binds to promoter regions and regulates the expression of genes that play a role in lantibiotic biosynthesis, immunity, and transport. Subsequently, the autophosphorylated HK transfers the phosphoryl group to a conserved aspartate (Asp) residue located in the N-terminal receiver domain of the response regulator (LanR/RR). This phosphorylation induces a conformational change in the C-terminal DNA-binding domain, enabling the response regulator to bind to promoter or operator sequences of target genes and thereby activate or repress transcription [11,105]. Likewise, the response regulator of lacticin 3147 (LtnR) has been shown to function primarily as a transcriptional repressor of its own regulatory genes and immunity-associated genes. However, LtnR does not appear to directly regulate the biosynthetic genes responsible for lacticin 3147 production. It has also been observed that LtnR has a high degree of homology to the PBSX(Xre) family of transcriptional repressors [106].

DNA sequence alignment deciphers penta-nucleotide direct repeats (PDR) in the promoters of nisin and subtilin operons, which are separated by hexa-nucleotides. It has been experimentally validated that this region is crucial for the binding of the phosphorylated response regulator to the promoter site [107]. Figure 3 presents representative nucleotide sequences of bacteriocin-associated genes to illustrate sequence-level features relevant to their genetic organization and regulation. The entA, entQ, bac31, and ent1071 sequences represent genes associated with class-II bacteriocins, whereas the plnC18 and plnA sequences are associated with plantaricin production by *Lactiplantibacillus plantarum* and likewise do not represent lantibiotics [108]. In particular, plantaricins are predominantly classified among the non-lantibiotic bacteriocins, with their regulatory and biosynthetic systems differing from the post-translational modification pathways characteristic of class-I lantibiotics.

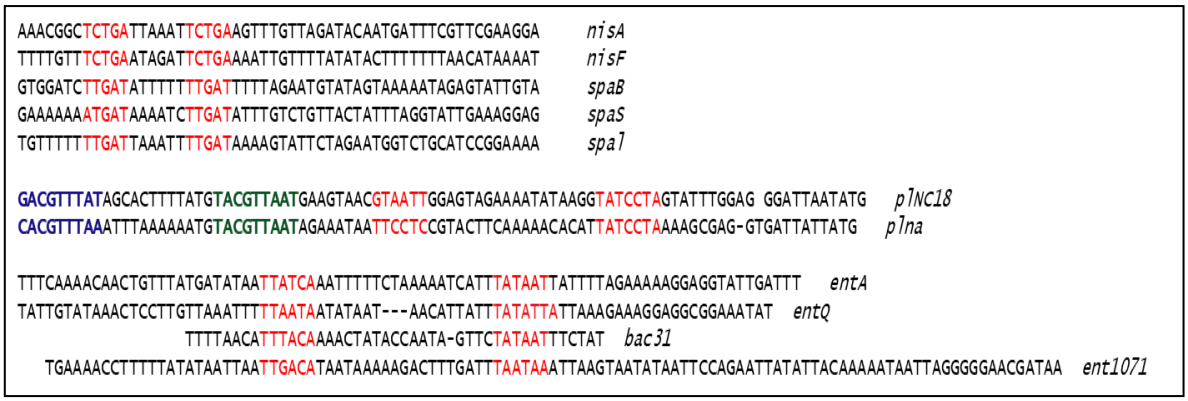


Figure 3. Reported nucleotide sequences of *nisA*, *nisF*, *spaB*, *spaS*, and *spaI* promoters indicating penta-nucleotide direct repeats (PDR) at the −35 region of the operon (marked in red), the possible binding site for the phosphorylated response regulator. *plnC18* and *pln3* have an L repeat (marked blue) and an R repeat (marked green) as an RR binding site, while subsequently representing the red colored −35 and −10 sequences. The rest of the sequences are of the RR binding site (marked red) of bacteriocins produced by *Enterococcus.* Sequences were obtained from the GenBank database at NCBI (www.ncbi.nlm.nih.gov/).

A fascinating trait has been observed in the regulation and QS mechanism of the lantibiotic epidermin, where, despite the absence of the respective kinase, a response regulator-like protein, EpiQ, is present. It also functions as a response regulator but lacks the ubiquitous Asp residue [12,109]. Multiple sequence alignment also shows the similarity of EpiQ with the other response regulator of its own producer, *Streptococcus epidermidis*. However, further investigation revealed that EpiQ directs the biosynthesis of epidermin, which is subsequently phosphorylated by an intrinsic histidine kinase (Figure 4). EpiQ activates transcription of the epiA promoter by binding to inverted repeat sequences (ANAATTACNGTAATTNT) located immediately upstream of the promoter region. Notably, similar inverted repeat motifs have also been identified throughout other regions of the epidermin gene cluster, suggesting a broader role for EpiQ in the regulation of epidermin biosynthesis [110]. A similar sort of regulation of the immunity protein, but not the lantibiotic mersacidin gene clusters, by three regulatory genes, *mrsR1*, *mrsR2*, and *mrsK2*, has been reported [70]. Likewise, *orf239* within the lactosin S gene clusters has some significant identity (22%) to tryptophan repressor-binding protein A (WrbA), which is a regulator of the *trp* operon in *Escherichia coli* [111].

With respect to its regulatory mechanism, cytolysin, a lantibiotic-like virulence factor produced by *Enterococcus faecalis*, is controlled by a complex regulatory system. In addition to the promoter located upstream of the cylLLLSMBAI operon, two regulatory genes, *cylR1* and *cylR2*, together with their associated promoter, have been identified as key repressors of cytolysin expression [82]. Autoinduction of cytolysin is mediated by the small lantibiotic subunit CylLS (also referred to as CylS), which functions as a signaling molecule. As its extracellular concentration increases with cell density, it activates the cytolysin regulatory pathway, thereby establishing a QS mechanism that controls the expression of cytolysin biosynthetic genes [78,112]. As mentioned, a set of repressor genes is also present; these genes act as negative regulators and include cylR1, which codes for a cylR1 transport protein, and cylR2, which codes for a DA-binding protein [113].

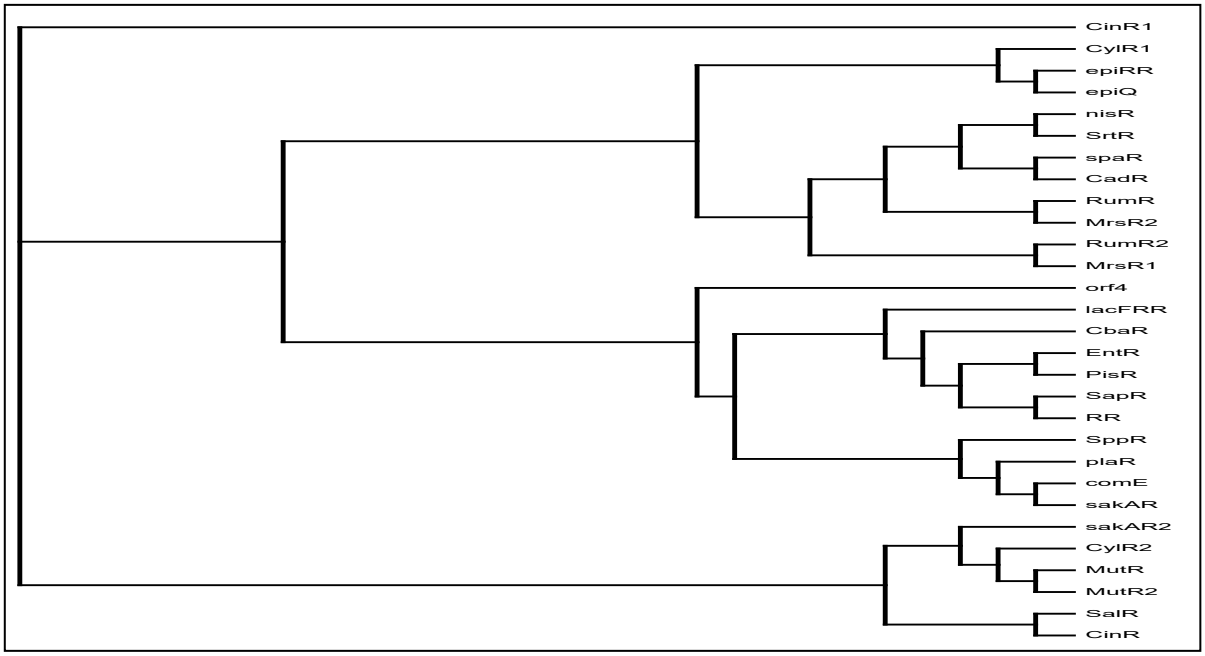


Figure 4. Phylogenetic intimacy between the response regulators of various bacteriocins, especially showing the close homology between the epidermin (epiRR) response regulator and its putative unorthodox response regulator EpiQ. Ostensible and conspicuous segregation between the lantibiotic and non-lantibiotic response regulators is also evident. Protein sequences were obtained from the Protein Data Bank at NCBI (www.ncbi.nlm.nih.gov/), multiple sequence alignment was performed using Clustal X, and the dendrogram was plotted using TreeView.

Structural predictions have not yet elucidated the precise mechanism of action of CylR1. Nevertheless, computational analyses indicate that CylR1 likely possesses three transmembrane α-helical domains, suggesting its involvement in membrane-associated signal transduction or regulatory processes [78], whereas CylR2 has three non-globular, α-helical domains with a helix-DNA-binding motif and belongs to the helix-turn family of proteins, which are distinguished by their DNA-binding tendency. Neither of these molecules will be found to have any resemblance to any protein of the signal transducers or any other protein in the database. It has been proposed that the interaction of R1 and R2 holds R2 in the repressing conformation. Concomitantly, it has been revealed that CylS interacts with CylR1 on the membrane surface, owing to its hydrophobic composition. CylR1 binds to the DNA, and CylR2 inhibits transcription [81,114]. Figure 5 summarizes the main events in the production, processing, and cell-dependent regulation of the cytolysin and associated protein/peptides. It also facilitates the establishment of a general view regarding cell-to-cell communication in bacteriocinogenesis.

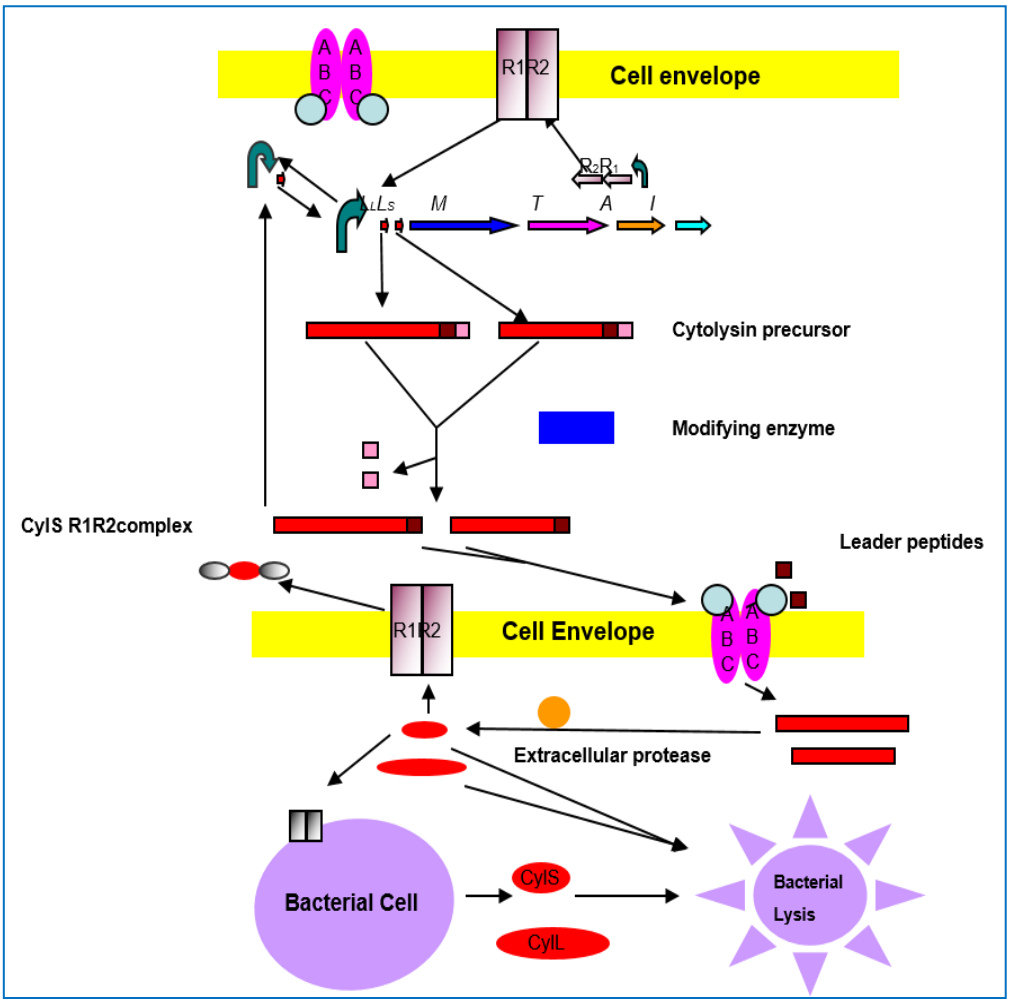


Figure 5. The regulatory genes *R1* and *R2* synthesize the regulatory proteins R1 and R2 on the membrane, which suppress the promoter (green, truncated). Constitutively expressed structural genes *CylL* and *CylS* synthesize the respective precursor proteins CylL and CylS of the lantibiotic cytolysin. *CylM* produces a protease that post-translationally modifies both units of cytolysin, which is further modified by the ABC transporter encoded by *CylB* by removing the leader peptide (brown square). Extracellular protease produced by *CylA*. The cumulative action of *CylL* and *CylS* kills the competitive bacteria (purple star), while only CylS (small red oval) interacts with the promoter (green), which induces the expression of the operon not intrinsically but also in the other bacteria. The genes and their product are colored with their respective color.

3.2. Clas-II bacteriocins

Class-II bacteriocins constitute the largest and most diverse group of bacteriocins. They are generally small, heat-stable peptides, typically with molecular masses below 10 kDa, and are predominantly cationic and non-lanthionine-containing in nature. Their antimicrobial activity is primarily attributed to the potential to form a pore in the plasma membrane of susceptible cells, leading to increased membrane permeability, dissipation of ion gradients, and ultimately cell death [54,115,116]. Sequence-based analyses have further revealed considerable diversity within this subgroup. Fimland et al. (2005) proposed a subdivision of

class-IIa bacteriocins into three sequence-related groups (groups 1–3) based on similarities and differences in their amino acid sequences [117]. This sequence-based organization highlights the molecular diversity within the pediocin-like group rather than representing three independent bacteriocin classes. This classification illustrates that class-IIa bacteriocins, despite sharing common structural and functional characteristics, are not a homogeneous group [118]. Class-II peptides can be further segregated into four subgroups based on their structural characteristics [119].

Class IIa: Class-IIa or pediocin-like bacteriocins are characterized by the presence of a conserved sequence motif (YGNGVxCxK/NxxC) at the N-terminal site [120]. It is one of the most extensively studied groups of class-II bacteriocins and includes leucocin A [121] and mesentericin Y105 [122], both of which differ at amino acid positions (positions 22 and 26). However, besides the similarity of the N-terminal half, the C-terminal end of such sequence similarity is feeble but still considered significant enough for segregating the group into subgroups [123,124].

Besides the mentioned sequence identity, the anti-listerial activity of class-IIa bacteriocins is also an omnipresent attribute. The heat stability of class-IIa bacteriocins is a function of the presence of a cysteine residue in the N-terminal half of the bacteriocin. Moreover, divercin V41, plantaricin 423, sakacinG, pediocin PA-1/AcH, and enterocin A have an extra second pair of cysteine residues, enabling them to form an extra disulfide bond in the C-terminus, hence providing more stability [123]. These disulfide bonds play a crucial role in stabilizing the β-sheet within the N-terminal β-hairpin structure of class-IIa bacteriocins. The C-terminal region is predicted to adopt an amphipathic α-helix that functions as a transmembrane segment during pore formation in susceptible target cells [118].

Class IIb: These bacteriocins have cationic, amphipathic, and/or hydrophobic properties [115]. The antimicrobial spectrum of class-IIb bacteriocins depends on the complementary activity of two peptides, which may or may not give any antibacterial activity alone, but clear synergistic antibacterial activity has been reported [125]. In this connection, it is noteworthy that the two-peptide bacteriocins refer only to that set of peptides whose genes are present in the same operon [126].

Class IIc: Class-IIc bacteriocins, also called circular bacteriocins, are ribosomally synthesized antimicrobial peptides. They are characterized by the presence of a conserved circular backbone, which results from covalent bond formation between N- and C-terminal amino acid residues. Other significant features of these bacteriocins are their stability at high temperatures and different pH levels and resistance to proteolytic degradation because of the presence of their compact and circular structural features [79]. Well-known class-IIC bacteriocins include enterocin AS-48 (*E. faecalis*) and gassericin A (*L. gasseri*) [127].

Class IId: They are a diverse, miscellaneous subgroup of small, linear, non-modified (or lightly modified) antimicrobial peptides produced by LAB. This subclass does not possess the pediocin box motif and lacks sequence similarity to other class-II bacteriocins [128,129]. According to the earlier classification, they were named as class-IId bacteriocins, which also encompassed leaderless antimicrobial peptides. Bacteriocins of this class are highly heterogeneous, displaying diversity in antimicrobial spectrum, organization of genetic clusters, primary sequences of peptides, and mechanism of action [130,131]. Representative LAB bacteriocins assigned to this subgroup include acidocin J113, produced by *Lactobacillus acidophilus* JCM 1132, and *lactococcin* 972, produced by *Lactococcus lactis* IPLA 972. These bacteriocins illustrate the structural and functional diversity of unmodified LAB antimicrobial peptides and differ from the precursor-modified bacteriocins included in class I and other modified-peptide groups [132,133].

3.2.1. Genetic organization of class-II bacteriocins

Before discussing the regulation and population-dependent induction of class-II bacteriocins, it is important to briefly review their genetic organization. Similar to lantibiotics, the genes involved in the biosynthesis, regulation, immunity, and transport of class-II bacteriocins may be located on either plasmids or chromosomal DNA, depending on the producer strain. The gene(s) related to class-II bacteriocin production and associated protein production are usually assembled within operon clusters, which may be transcribed divergently [108,128]. Class-IIa bacteriocin genetic makeup has significant conservation in its architecture and arrangement [120]. The structural gene produces the prepeptide equipped with the leader peptide with characteristics of two glycine residues at its C-terminus, which may serve as a recognition sequence for the ABC transporter [128]. For several bacteriocins, such as lactococcin G, the same operon containing genes encoding precursor peptides and immunity proteins also comprises an ABC transporter and accessory proteins. However, exceptions are available, as exemplified in enterocin 1071, plantaricin E/F, and plantaricin J/K, where the genes responsible for the ABC transporter and accessory proteins are located in separate operons, different from the one that contains genes for precursor peptides and immunity proteins [126,134,135].

Class-IIb bacteriocins have two complementary peptides that are generally required for optimal antimicrobial activity. Representative LAB members include several carnobacteriocins, enterocin 1071, and the plantaricins PlnE/F and PlnJ/K. Plantaricin E/F and plantaricin J/K are class-IIb bacteriocin systems produced by *Lactiplantibacillus plantarum* and should be distinguished from lantibiotic plantaricin systems, which belong to class I and undergo post-translational modification. Similarly, the carnobacteriocins and enterocin 1071 represent non-lantibiotic-containing peptide bacteriocins and illustrate the structural and functional diversity of class-IIb systems. Their production and regulation may involve dedicated precursor, processing, transport, immunity, and regulatory genes, with some systems being associated with QS-dependent regulatory circuits [126,128].

Most class-IIa bacteriocin genetic arsenal is also composed of two operons encoding ABC transporters and accessory proteins, responsible for the proteolytic processing and transport of the bacteriocins. In addition to that, some not entirely characterized ORFs are also found to be part of the ABC transporter operon. Most of the class-II bacteriocins are found to possess additional ORFs for the population-dependent regulatory response of the bacteriocin, which code for the three-gene operon (Phe), HK, and response regulator (RR) [136,137]. The architecture of the different class-IIa bacteriocins is summarized in Figure 6.

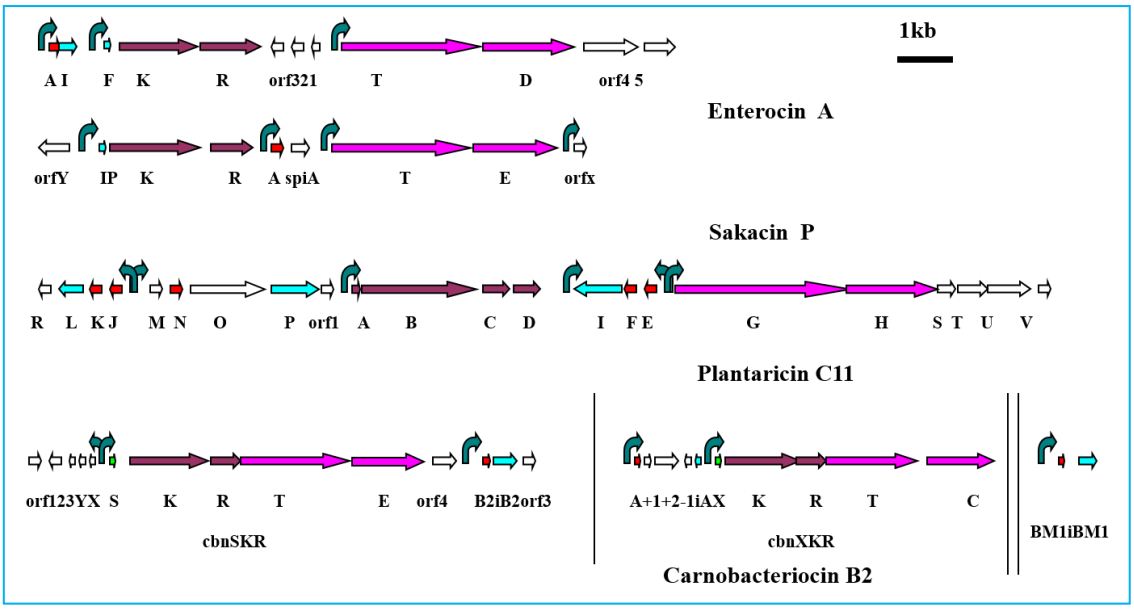


Figure 6. Genetic clusters of the producers (brown arrow), regulatory (fluorescent green), pheromone precursors (Indigo), immunity (pink), transport (green), promoters (red), structural genes (white), and unknown open reading frame (ORF).

3.2.2. Regulation of bacteriocin and quorum sensing

The production of class-II bacteriocins in LAB is regulated by a signal transduction system analogous to those governing bacterial responses to environmental cues, including competence development and virulence. This cell density-dependent regulation is mediated by a three-component regulatory system comprising an induction peptide, a membrane-bound histidine kinase, and a cognate response regulator [128]. With some exceptions, three-component regulatory systems work almost in the same manner as two-component regulatory systems of class-I lantibiotics [5,18]. Moreover, the expression of the enterocin O16 gene *ef1097* is tightly regulated by the *Fsr*-mediated QS response regulator FsrA [112]. Furthermore, it has been proven that class-IIa bacteriocin, e.g., divercin V41, is regulated by two-component regulatory systems [138,139]. The presence of the dedicated peptide in the shape of a pheromone makes the regulation of class-II bacteriocin distinct from the regulatory mechanism of lantibiotics, in which the role of pheromone is performed by the bacteriocin itself [140,141].

The pheromone accumulates gradually; when the cell population reaches a certain size, they induce bacteriocinogenesis by being recognized by an HK. This leads to its phosphorylation and then to the response regulator. The phosphorylated regulator then binds to the promoter of the respective operon to induce the synthesis of the respective bacteriocins, hence establishing density-dependent regulation, or QS, in the regulation [18,59,87,118]. To facilitate a clearer understanding of QS-mediated regulation of bacteriocin production, the major regulatory components should be considered individually. Figure 7 provides a comparative schematic representation of the principal regulatory components associated with lantibiotic and class-II bacteriocin production, highlighting the organization of signaling, sensing, and response elements involved in bacteriocin regulation. Importantly, the bacteriocins produced by *Carnobacterium* are structurally diverse and should not be collectively regarded as lantibiotics. For example, carnobacteriocins B2 and BM1 are well-

characterized class-IIa bacteriocins, whereas carnobacteriocin A is a circular bacteriocin generally classified as class IIc. These bacteriocins therefore differ from lanthionine-containing class-I lantibiotics in their structural characteristics and biosynthetic pathways [142,143].

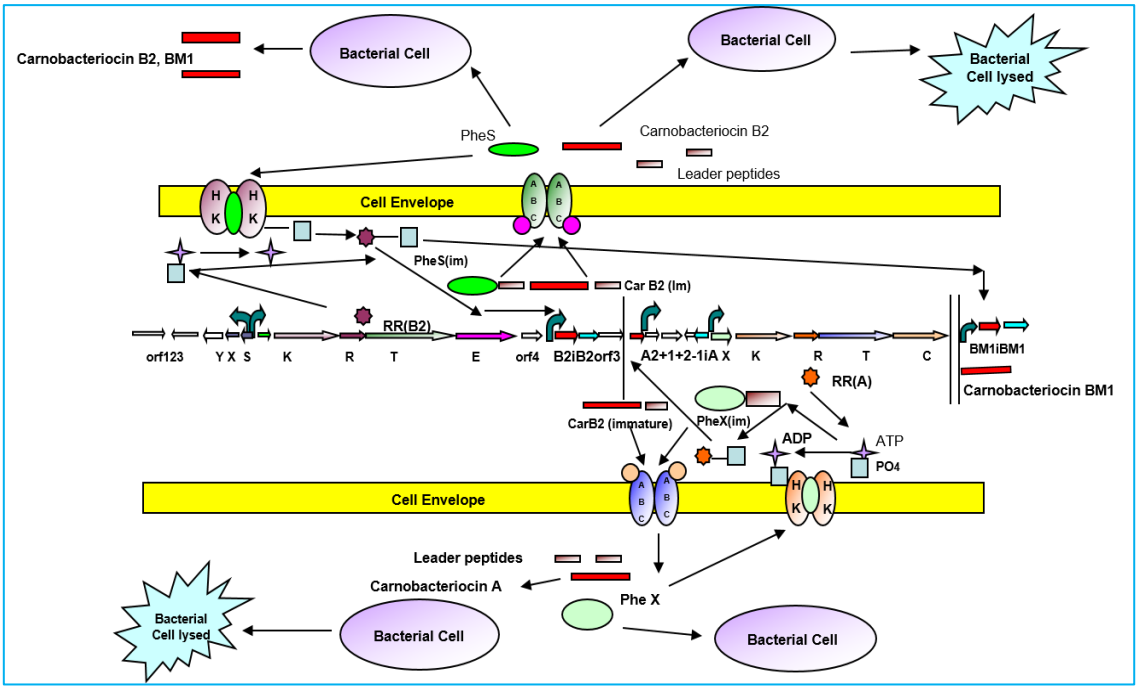


Figure 7. The cbnSKR plasmid-located operon (first) produces pheromone S precursor (PheSim) coded by cbnS. The bacteriocin B2 precursor (CarB2(Im)), coded by the B2 gene, the ABC transporter (shaded green ABC), coded by the T gene, and the accessory protein (pink oval), coded by the E gene, are also envolved. Mature pheromone (PheB2) and bacteriocin (carnobacteriocin B2) are released. Bacteriocin B2 kills the competing cell. Pheromone induces synthesis of bacteriocins by binding to the histidine kinase (shaded brown oval HK) coded by the K gene on the cell envelope, leading to autophosphorylation by ATP, in turn converting ATP into ADP. Later on, the phosphate group (cyan square) is transferred to the response regulator (RR(B2)) coded by the R gene, which ultimately binds to the promoters (green curved arrow) of the B2 and BM1 operon (third operon) and induces its expression. The same phenomenon occurs with the chromosomally located middle operon cbnXKR. Its cbnX codes for pheromone X precursor (PheX (Im)). This precursor is processed along with the bacteriocin A precursor coded by the A gene (CarB2(Im)), by the ABC transporter (shaded blue ABC) coded by the T gene and an accessory protein (orange) coded by the E gene. Mature pheromone (PheA) and bacteriocin (Carnobacteriocin A) are released. Bacteriocin A kills the competitive cell. Pheromones induce the synthesis of bacteriocins both intrinsically and extrinsically. The pheromone binds to HK (shaded orange oval, HK) coded by the K gene on the membrane, leading to autophosphorylation by ATP. As a result, ATP is converted into ADP. Later on, the phosphate group (cyan square) is transferred to the response regulator (dark orange star) coded by the R gene, which binds to the promoter of the cbnXKR operon, hence leading to auto-induction. The genes are of the same color.

3.2.3. Pheromones

Several other terms are regarded as pheromones (Phe), such as auto-inducers (AI) or auto-inducing peptides (IP) [144,145]. Class-II bacteriocins are initially synthesized as inactive prepeptides bearing a leader sequence at the N-terminus, which includes a double glycine proteolytic processing site [146]. The dedicated pheromones or AI are unmodified small cationic, hydrophobic, and heat-stable peptides [147]. They may or may not have any antimicrobial activity, and they are synthesized as bacteriocin-like precursors with N-terminal leader peptides of 16–22 amino acids with the predicted structure of a partly amphiphilic α-helical structure [19].

Pheromones generally perform their task in very low concentrations, from 10^{-7} M (plantaricin A) to 10^{-12} M (ent F). As mentioned previously, pheromone peptides (Phe) possess leader sequences containing the characteristic double-glycine motif found in many bacteriocins. Therefore, it has been proposed that these peptides share common processing and transport machinery with bacteriocins. Specifically, the precursor peptides are exported by dedicated ATP-binding cassette (ABC) transporters, which simultaneously cleave the leader peptide at the double-glycine processing site, thereby converting the inactive precursor into its mature, biologically active form [148]. However, some of the class-IIa bacteriocins, such as enterocins (P and SEK-4), hiracin JM79, and listeriocin 743A, are exported through the Sec-dependent transport system [120]. It is interesting to note that Phe or AI also regulate their own operon [5].

The involvement of AI in the induction of various bacteriocins and their immunity proteins is reported in several Gram-positive bacteria, including strains of *C. piscicola* LV17B, *Lactobacillus plantarum* C11, *Lactobacillus sakei* Lb706, *Lb. sakei* LTH673, *Enterococcus faecium* CTC492, and *E. faecium* DPC1146 [149,150]. Despite sequence similarities between the pheromones of different genera of producers, no cross-induction has been reported, suggesting a high degree of strain specificity in the molecules. However, evidence of heterologous expression is increasing at a rapid pace, as exemplified by the induction of plantaricin NC8 (class IIb) after co-culturing *L. plantarum* with inducing strains of *L. lactis*. Interestingly, the same result has been observed even if the producer is grown with heat-killed *L. lactis*; however, the cell-free suspension failed to induce bacteriocinogenesis [151,152]. The most elusive problem concerning bacteriocin regulation is how this auto-induction mechanism is induced.

Two possible mechanisms have been proposed that unveil the mechanism, based on the principle of QS. The induction factor (IF) is constitutively produced and accumulates in small amounts, but, with reference to the cell population, when IF concentration reaches the threshold level, it will start expressing bacteriocin production. Alternatively, environmental signals or environmental stress may induce the synthesis of IF and subsequent bacteriocin production. The IF acts as an input signal for the signal-transduction system, which binds to the HK and, in subsequent steps, leads to the induction of the synthesis of bacteriocin and associated traits [153,154].

3.2.4. Histidine kinase (HK)

The association between the regulation phenomenon and QS cannot be fully comprehended without describing the role of HK. HK is a membrane-embedded enzyme that senses external stimuli, and a cytoplasm-localized response regulator (RR) controls cellular responses, typically by modulating gene expression. The interaction between these two proteins is mediated by conserved

phosphorylation and dephosphorylation [155]. The N-terminal half of HK contains stretches of hydrophobic amino acids, which facilitate the formation of a transmembrane helix [156]. This N-terminal segment of HK also serves as an input domain with sensor function(s), located at the periplasmic side of the cytoplasmic membrane [157]. The C-terminal region of HK (located on the cytosolic side) that exhibits autokinase activity comprises a homodimeric histidine phosphotransfer (DHp) domain and an ATP-binding catalytic domain (CA). Upon signal detection, the conserved core adopts an asymmetric homodimeric conformation, thereby activating kinase activity in one of the two subunits. As a result, the γ-phosphoryl group of ATP bound to the CA domain lies near the conserved histidine residue of the DHp domain, enabling auto-phosphorylation. Following histidine phosphorylation, the phosphoryl group is transferred to a conserved aspartate residue of the RR [96,158].

3.2.5. Response regulators

Response regulators are also an equally important component of the bacteriocin production system. After the auto-phosphorylation of the HK, the phosphate group is transferred to the response regulator, which binds to the target region in the gene clusters to induce transcription [19,128]. Usually, there is only one gene for response regulator synthesis present in class-II bacteriocins, except for the plantaricin system, which possesses two response regulators, named Pln C, which is a response regulator, and Pln D, which is a repressor. Both response regulators are 59% identical and 76% similar to each other [159]. In the quest for a binding site for the pheromones of various regulators of several bacteriocins, it was found that it consists of two conserved direct repeats of 9 bp separated by a 12-bp spacer region found just upstream of the −35 region [159]. Furthermore, for many bacteriocins, particularly of enterococcal origin, TA-rich −35 and −10 regions themselves are considered a promoter region [140,160]. Plantaricin NC18 response regulator binds to the L repeat and the R repeat region found upstream of the −35 region [152]. Even though PlnC is an activator while PlnD is a repressor, it has been later established that both of these regulators work antagonistically in a dimeric form and tend to bind to the direct repeats of the promoters [159].

As mentioned elsewhere, the QS mechanism of bacteriocin production has some similarities with the competence development in Gram-positive bacteria, but a little contradiction is present in connection with the response regulator, as in *Bacillus subtilis*, the genes for the dephosphorylation of the response regulator of spore formation are present. However, no such genes are reported in the bacteriocin expression operon [6].

3.3. Class-III bacteriocins

The bacteriocins of this group are large and high-molecular-weight (>30 kDa) non-modified proteins. They typically consist of an N-terminal endopeptidase domain and a C-terminal domain that is responsible for the recognition of the substrate [161]. Due to their complex structure, they become inactive at high temperatures of about 100 °C, and thus they are considered heat-labile bacteriocins [50,162]. Class-III bacteriocins, including bacteriolysins, non-lytic high-molecular-weight bacteriocins, and phage-derived tailocins, exhibit regulatory architectures that differ substantially from the relatively well-characterized precursor peptide-receptor systems of many class-I and class-II bacteriocins [12]. Class-III bacteriocins are classified into three subtypes (Figure 8).

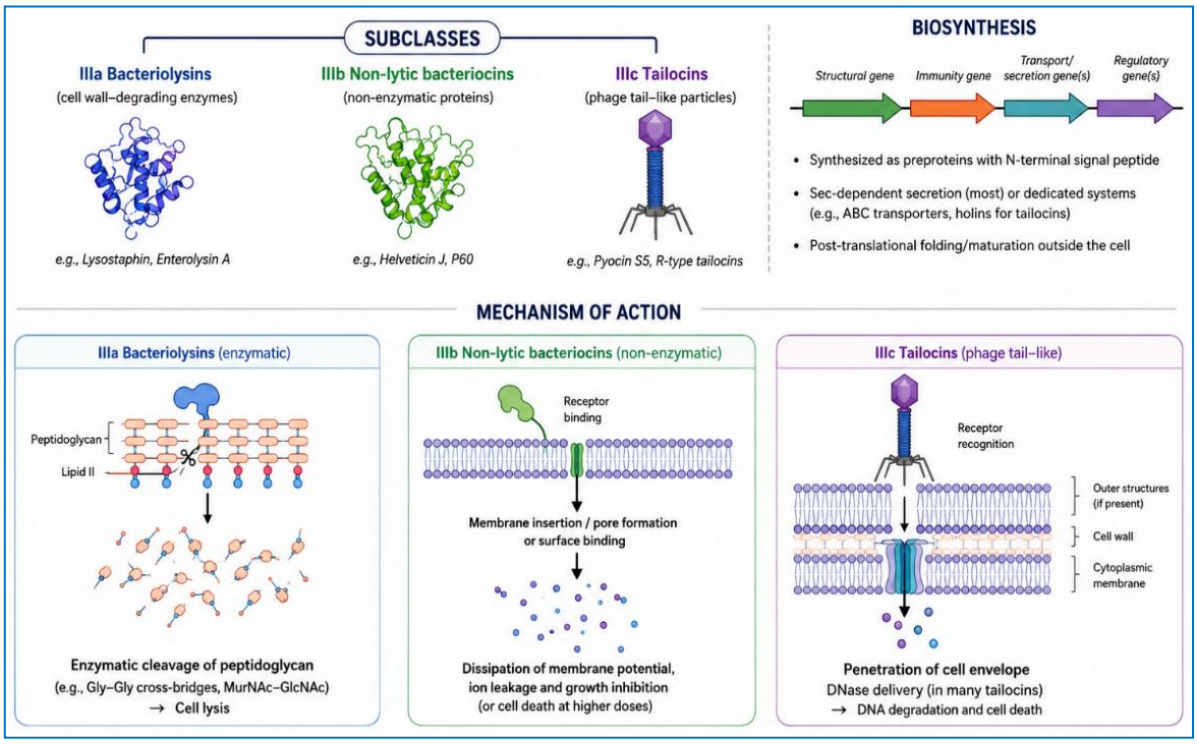


Figure 8. Classification and mechanisms of action of class-III bacteriocins. Class-III bacteriocins are classified into bacteriolysins (IIIa), non-lytic bacteriocins (IIIb), and tailocins (IIIc). Bacteriolysins kill target cells through enzymatic degradation of peptidoglycan, resulting in cell lysis. Non-lytic bacteriocins disrupt membrane integrity, causing ion leakage and membrane depolarization. Tailocins recognize specific cell surface receptors and penetrate the cell envelope, leading to rapid cell death.

3.3.1. Types of class-III bacteriocins

Bacteriolysins (Class IIIa): Bacteriolysins are heat-sensitive, high-molecular-weight polypeptides ranging between 27 and 35 kDa. They are involved in the lysis of the peptidoglycan layer of the target bacteria; thus, they are termed bacteriolysins [14,50]. Furthermore, bacteriolysins comprise an N-terminal catalytic domain and a C-terminal substrate recognition domain. In the known examples, the N-terminal domain is considered to function as a peptidoglycan hydrolase that cleaves the stem peptides and cross-links within the peptidoglycan layer of sensitive bacteria. Examples comprise millericin B, lysostaphin A [130], zoocin A, and enterolysin A [50].

Non-lytic bacteriocins (Class IIIb): Non-lytic bacteriocins are so called due to their inability to perform hydrolase activity [163]. They are high-molecular-weight bacteriocins that reduce glucose uptake or induce carbohydrate starvation in the target cells by disrupting cell membrane integrity, thereby interfering with nutrient uptake and causing the leakage of vital cellular molecules [50]. They may also inhibit carbohydrate transport by affecting membrane transport proteins responsible for the uptake of sugars. Moreover, impaired membrane function reduces ATP synthesis required for carbohydrate metabolism. Therefore, cells activate stress responses that prioritize survival over growth, thereby reducing carbohydrate utilization [162,164]. Examples include Enterolysin A and Helveticin J.

Tailocins: They are also known as phage tail-like bacteriocins due to their close resemblance to

active phages. However, they are mainly composed of a sheath, spike, and tail fibers. Unlike phages, tailocins lack most of the proteins required for the production of a capsid and replication of bacteriophages [165] Still, they have a similar structure and mechanism of action to bacteriophages, as they induce cell death by penetrating the membrane of target bacteria [130]. Based on their morphology and structural similarity to bacteriophage tails, tailocins are generally classified into two major groups:

R-type tailocins: These resemble the contractile tails of myophages (e.g., bacteriophage P2) and consist of a rigid inner tube surrounded by a contractile sheath. Upon recognition of a susceptible target cell, sheath contraction drives the inner tube through the cell envelope, leading to membrane depolarization and cell death [166].

F-type tailocins: These resemble the flexible, non-contractile tails of siphophages (e.g., bacteriophage λ) and lack a contractile sheath. Their antibacterial activity is mediated through receptor-specific interactions with susceptible bacterial cells, although their mechanism of killing is generally less well understood than that of R-type tailocins [167].

3.3.2. Genetic organization and biosynthesis

Class-III bacteriocins are large, heat-labile antimicrobial proteins with molecular weights >10 kDa and are composed of multiple domains. The genes involved in the production of class-III bacteriocins exhibit substantial diversity among structural, immunity, regulatory, transport, and processing genes [153]. Sequence analysis of Enterolysin A, produced by *Enterococcus faecalis*, revealed its similarity to other antimicrobial peptides such as zoocin A and millericin, but it exhibited no similarity to helveticin J. It was also suggested that Enterolysin A contains an N-terminal catalytic domain homologous to M37 metalloproteases, with a conserved histidine residue, suggesting Zn^{2+}-dependent activity and a C-terminal substrate recognition domain. This separate arrangement of the catalytic and binding domains suggests its similarity to lysostaphin, ALE-1, LytM, and zoocin A [168]. In the case of zoocin A, an S-alanyl-L-alanyl endopeptidase, both the zooA structural gene and the immunity gene (zif) are chromosomally encoded but are transcribed divergently. The zooA-zif locus is flanked by two transposon-like elements that exhibit strong sequence similarity to the plasmid-encoded lysostaphin and lysostaphin resistance genes of *Staphylococcus simulans* biovar staphylolyticus [169].

Class-III bacteriocins differ in their synthesis from those of class-I and class-II bacteriocins. Their production is tightly regulated through specific promoters and transcriptional factors [116]. Many bacteriolytic bacteriocins of class III are synthesized by the Sec-dependent pathway. The signal peptide possesses an N-terminal signal peptide comprised of positively charged residues, followed by a hydrophobic core and a polar C-terminal region serving as a cleavage site, typically recognized by Sec-dependent secretion machinery. For instance, enlA, a 343-amino-acid precursor synthesized by *E. faecalis*, contains a 27-amino-acid Sec-signal peptide [170], whereas in zoocin A, the producer cell immunity is mediated by a zoocin A immunity factor, zif [169].

The genetic determinants of class-III bacteriocins are often organized into clusters containing structural genes together with genes involved in processing, secretion, immunity, transcriptional regulation, or cell-envelope-associated functions, while tailocin loci may additionally retain phage-related structural and regulatory elements. In bacteriolysins and non-lytic bacteriocins, production can be influenced by cell-density-dependent signaling, environmental stress, and two-component regulatory systems [171,172]. The direct evidence for classical peptide-mediated autoinduction is considerably less extensive than that available for several class-I and class-II systems.

Consequently, population-dependent regulation of class-III bacteriocins should not automatically be equated with canonical QS [173], in contrast to many class-I and class-II systems, in which accumulation of an extracellular signaling peptide activates a cognate sensor and induces bacteriocin gene expression after reaching a functional threshold.

Class-III regulation may involve more complex combinations of stress-responsive, transcriptional, and prophage-associated regulatory pathways. Tailocins represent a particularly distinct category because their expression can be linked to phage-derived regulatory networks and ecological competition rather than conventional pheromone-mediated autoinduction [174]. Nevertheless, increasing availability of comparative genomics, transcriptomics, and functional genetic approaches provides opportunities to determine whether population density, intercellular signaling, or environmental cues directly regulate these high-molecular-weight bacteriocins [147,175]. Thus, while class-III bacteriocins share the ecological objective of enabling producer cells to compete within microbial communities, their regulatory divergence from class-I and class-II bacteriocins highlights an important knowledge gap. These limitations concern the molecular basis, signal specificity, and autoinduction mechanisms of QS-associated regulation in high-molecular-weight bacteriocin systems [176,177].

4. Quorum-sensing interactions in interspecies and cross-kingdom crosstalk

Quorum-sensing communication among lactic acid bacteria can extend beyond strain-specific signaling, although the extent of heterologous signal recognition is strongly dependent on the structural compatibility between signaling peptides and their cognate receptors [178]. In comparison to intraspecies QS, the signal regulation mechanism of interspecies QS and interkingdom QS is considered more complicated, with a relatively wide distribution of receptors [179]. Autoinducing peptides (AIPs) are generally highly strain- and species-specific because sequence variation, peptide processing, and receptor recognition determine signal activity. Thus, a signal produced by one LAB strain does not necessarily activate the corresponding QS pathway in another species [180]. Nevertheless, co-culture experiments have demonstrated that interspecies interactions can alter bacteriocin production. This suggests that microbial community context can influence bacteriocin-associated regulatory pathways [152].

Beyond bacterial-bacterial communication, bacterial signaling molecules and metabolites may also affect mammalian host cells. This bacterial-host communication, however, can be distinguished from canonical QS and direct QS-mediated bacteriocin regulation. Such interspecies and cross-kingdom interactions may have important ecological consequences in complex environments such as the gastrointestinal tract, where signal exchange can influence microbial competition, bacteriocin production, niche colonization, and community composition [181,182]. Consequently, QS-mediated signal compatibility and interference may contribute to the dynamic balance of gut microbial communities, while the mechanistic basis and ecological significance of many proposed heterologous and cross-kingdom interactions remain important areas for future investigation.

Quorum sensing-mediated bacteriocin regulation involves signaling within and between bacterial populations. Bacterial species may respond to the signals produced by their own QS systems; this interaction is called a cognate interaction and can be studied in the *pln*ABCD signaling system of *Lactiplantibacillus plantarum* C11 [150] and the Ent53D-EnkK-EnkR signaling system of *Enterococcus faecium* NKR-5-3 [183]. Bacteria can also respond to signals produced by another bacterial species; this is called a non-cognate interaction, as demonstrated by BlpC-BlpH-BlpR

signaling between *Streptococcus pneumoniae* strains [184]. Moreover, co-culture-associated induction can also facilitate QS-mediated bacteriocin regulation, as described in the PLNC8IF-PLNC8HK-PlnD signaling system of *L. plantarum* NC8 [152]. Interestingly, these interactions are not limited to bacterial species but can also occur across kingdoms, as exemplified by Sil QS signaling in the interaction between mammalian host cells and Streptococcus pyogenes (GAS) [185]. Such interactions demonstrate how bacteriocin production can be influenced by signals from the cognate system, neighboring bacterial populations, or the host environment. Representative examples and their regulatory mechanisms are summarized in Table 1.

5. Comparative conservation and divergence of QS regulatory networks among non-lactic acid Gram-positive bacteria

The peptide-mediated quorum sensing regulatory system is not restricted to LAB but also occurs in non-LAB Gram-positive bacteria such as *Staphylococcus aureus* and *Listeria monocytogenes*. In these microorganisms, the Agr system coordinates the bacterial response and is activated upon detection of an extracellular signaling peptide [186,187]. The Agr system of *S. aureus* comprises a precursor of AIP called AgrD, which is processed by AgrB, a membrane protein, and a membrane peptidase termed MroQ. Moreover, it also contains a membrane-bound sensor histidine kinase (AgrC) and a response regulator called AgrA [187,188]. AgrD is processed into a mature autoinducing peptide through two sequential steps. First, AgrB promotes the formation of a thiolactone ring, followed by N-terminal cleavage of the precursor peptide by MroQ to convert it into mature autoinducing peptide (AIP) [187,189]. The resulting AIP is detected by AgrC, which in turn activates AgrA and regulates downstream expression of virulence factors such as α-hemolysin and extracellular functions rather than bacteriocin production [190]. Furthermore, there are four Agr-specificity groups (AgrI, AgrII, AgrIII, and AgrIV) in *S. aureus* that share a similar signaling architecture but possess distinct AIP sequences and corresponding AgrC receptor specificity, suggesting molecular diversification within the conserved QS system [191].

Listeria monocytogenes also comprises a similar Agr system in which AgrD serves as a precursor of AIP, which in turn is detected by AgrC and results in the activation of AgrA [192], ultimately mediating the regulation of biofilm formation and virulence-related factors. Additionally, recent studies demonstrated that the Agr system of *L. monocytogenes* can be experimentally manipulated; analogues of AIP can either stimulate or inhibit the Agr system and can affect biofilm formation [193]. Despite conservation of the AgrC-AgrA signaling system, the differences in Agr-dependent regulation and downstream outputs reflect species-to-species regulatory characteristics [194].

Comparison of the Agr systems in non-LAB Gram-positive bacteria reveals both conserved and divergent features. Despite having a similar Agr system, the two species, *S. aureus* and *Listeria monocytogenes,* differ in AIP signaling, receptor recognition, and downstream regulatory outputs, indicating that this conserved QS architecture can vary among species [187,194,195]. Further evidence for QS diversification is evident in *Streptococcus pneumoniae*. The comparative analysis of 4096 pneumococcal genomes identified nine BlpC signal groups and five BlpH receptor groups, indicating considerable diversity in peptide signals and signal–receptor combinations. Such strain-dependent variations result in both cognate and non-cognate interactions among *Streptococcus pneumoniae* strains [184].

Table 1. Representative QS-mediated interactions associated with bacteriocin production in Gram-positive bacteria.

QS interaction type	QS signaling system	Signal-producing strain/host	Signal-responsive strain	Response specificity	Downstream regulatory outcome	Mechanistic significance	Ref.
Cognate	*pln*ABCD	*Lactiplantibacillus plantarum* C11	*L. plantarum* C11	PlnB recognizes the cognate induction peptide IP-C11 derived from PlnA.	PlnC/PlnD signaling regulates bacteriocin-associated genes, including plantaricin EF and JK.	Links accumulation of the cognate peptide signal with activation of plantaricin production.	[150]
	Ent53D-EnkK-EnkR	*Enterococcus faecium* NKR-5-3	*E. faecium* NKR-5-3	Ent53D activates the cognate EnkK-EnkR signaling system.	Promotes expression of multiple enterocin genes, including *ent53A*, *ent53C*, *ent53D*, and *ent53Z*.	Enables coordinated regulation of multiple enterocins through one QS system.	[183]
Non-cognate	BlpC-BlpH-BlpR	*Streptococcus pneumoniae* PMEN-2 (Foxtrot BlpC)	*S. pneumoniae* strain carrying the Charlie-type BlpH receptor (e.g., Hermans-1012)	The Charlie-type BlpH receptor responds to a heterologous Foxtrot BlpC signal.	Activation of BlpH-BlpR signaling and the corresponding bacteriocin-associated promoter.	Demonstrates QS signal-receptor cross-recognition between pneumococcal Blp systems.	[184]
	BlpC-BlpH-BlpR	*S. pneumoniae* PMEN-14 (Charlie BlpC)	*S. pneumoniae* PMEN-18 (Golf/Hotel-type BlpH)	A Golf/Hotel-type BlpH receptor can respond to a heterologous BlpC signal.	Activation of BlpH-BlpR signaling and bacteriocin-associated gene expression.	Illustrates potential QS cross-recognition among pneumococcal QS systems.	[184]
Co-culture-associated	PLNC8IF-PLNC8HK-PlnD	*L. plantarum* NC8; induction occurs during co-culture with specific Gram-positive bacteria, including *Lactococcus lactis* MG1363	*L. plantarum* NC8	Co-cultivation induces the NC8 regulatory system; the NC8-produced PLNC8IF then acts as the autoinducing peptide.	Activation of the regulatory operon induces PLNC8 as well as plantaricin EF and JK production.	Demonstrates that the presence of neighboring bacteria can trigger QS-dependent bacteriocin production through an autoinduction mechanism.	[152]
Cross-kingdom (host-to-bacterium)	Sil QS	Mammalian host cells	*Streptococcus pyogenes* (GAS)	Host-derived L-asparagine is sensed by GAS and promotes SilCR autoinducer production.	SilCR autoinduction propagates through the GAS population and promotes bacteriocin production.	Connects a host-derived metabolic signal with bacterial QS and population-wide bacteriocin production.	[185]

6. Applications of bacteriocins in therapeutics and food preservation

The growing understanding of bacteriocins and their regulatory systems has attracted attention for their potential use in therapeutics and food preservation as an alternative to conventional approaches involving live microorganisms. Some bacteriocins have been reported to possess anticancer activity because of their selective binding to cancer cells. This binding causes the overexpression of anionic surface components on cancer cells, making them more susceptible to the cytotoxic effects of bacteriocins, which can lead to apoptosis and/or cell membrane depolarization, ultimately resulting in changes in membrane permeability [14]. A well-known bacteriocin, i.e., nisin, has demonstrated promising anticancer activity in head and neck squamous cell carcinoma by reducing cell proliferation and inducing selective apoptosis [196,197].

In the food industry, bacteriocins are of great interest because of their antimicrobial activity against pathogens and food spoilage microorganisms. For example, pediocin PA-1/AcH and nisin are FDA-approved commercial bacteriocins, widely utilized in the food industry across many developed countries, attributed to their ability to inhibit the growth of certain bacteria, including *Listeria monocytogenes* [50]. Nisin serves as a food preservative worldwide in various food items, such as canned vegetables and cheese, and pediocin PA-1 is used as a food additive in meat products [198]. Recently, it has been documented that the presence of type-III polyketide synthases (T3PKS) can produce bacteriocins, which can contribute to food-related applications [42].

However, the antimicrobial activity of bacteriocins may vary between laboratory conditions and real food matrices because interactions with food components can affect their availability and activity. For example, sakacin P and nisin showed substantial adsorption to food proteins in smoked salmon and chicken products, whereas variations in the composition of model cheese influenced the antimicrobial activity of nisin [199,200]. Although the antimicrobial effects of several bacteriocins have been demonstrated in experimental food models, their efficacy under large-scale food processing and commercial conditions remains insufficiently validated [164,201]. Moreover, acidity and proteolytic degradation in the gastrointestinal environment can potentially compromise bacteriocin stability and bioavailability. Accordingly, encapsulation approaches have been investigated to improve the protection and intestinal delivery of plantaricin EF under gastrointestinal conditions [202]. Nevertheless, studies on the in vivo stability, bioavailability, and biological fate of bacteriocins remain limited [203,204]. Additionally, the industrial application of bacteriocins is challenged by limited production yields, purification requirements, and production costs, emphasizing the need for optimized fermentation, product recovery, and scalable production strategies [31,205].

7. Current limitations

Over the past decades, extensive research has been conducted regarding the bacterial cross-talk and QS-driven bacteriocin/enterocin production in Gram-positive bacteria, and it is still progressing. With the advancement in genomics, molecular biology, and bioinformatics, a large number of antimicrobial peptides of Gram-positive bacteria have been studied, and their two- and three-component regulatory mechanisms have been explored; however, there are still major gaps that need to be explored explicitly. Although these peptides have been extensively investigated using bioinformatic approaches and their presence has been confirmed through PCR-based detection and various phenotypic assays, studies examining their gene expression remain limited. This gap in the

literature raises questions regarding the relationship between gene expression levels and the phenotypic traits observed, as well as the extent to which the detected genes are actively expressed under the conditions evaluated. Another major limitation is the relatively small number of studies that integrate multi-omics approaches, including genomics, transcriptomics, and proteomics, to comprehensively investigate QS systems and their associated traits.

Multi-omics approaches are increasingly providing a systems-level perspective on the relationship between QS, environmental conditions, cellular metabolism, and bacteriocin production in lactic acid bacteria [206]. Transcriptomic analysis of *Lactobacillus paracasei* HD1.7 under acetic acid stress, for example, revealed stress-associated activation of the late bacteriocin regulatory system together with alterations in signal-peptide transport, amino-acid metabolism, and nucleotide metabolism, demonstrating that environmental stress can reshape the regulatory and metabolic context of bacteriocin biosynthesis [207]. Proteomic analysis of *Lactiplantibacillus plantarum* KLDS1.0391 further showed that deletion of *luxS* altered proteins involved in carbohydrate, amino-acid, and fatty-acid metabolism as well as the two-component signaling system. Notably, the sensor histidine kinase AgrC was differentially expressed during co-cultivation, linking QS-associated signaling with broader physiological responses associated with bacteriocin production [208].

Metabolomic studies provide an additional layer of evidence, showing that QS modulation can alter energy, redox, and signaling-related metabolic pathways in LAB. Similarly, comparative metabolomics of co-cultured *Pediococcus acidilactici* CCFM18 and *Bacillus cereus* ATCC11778 demonstrated enhanced bacteriocin production alongside changes in metabolites and pathways related to QS, ABC transport, and amino acid metabolism, highlighting the influence of microbial interactions on bacteriocin-associated metabolism [209]. Collectively, these findings demonstrate the value of integrating genomic potential with transcriptomic, proteomic, and metabolomic capacities. However, fully integrated studies connecting QS signals with regulatory-gene expression, protein abundance, bacteriocin production, and extracellular metabolite changes remain comparatively limited. Such studies are therefore needed to distinguish direct QS-mediated regulation from secondary metabolic responses and to establish causal regulatory networks.

Furthermore, the detection and quantification of QS molecules and QS-regulated phenotypes remain technically challenging due to their low abundance, rapid degradation, and the substantial metabolic cost associated with their production. These factors may compromise the accurate assessment of their biological activity in phenotypic assays. In addition, the structural diversity and strain-specific variation of many QS molecules remain poorly characterized. Overall, research in this field is still largely confined to laboratory settings, and the translation of these findings into industrial, clinical, and biotechnological applications will require more comprehensive mechanistic studies and rigorous validation under real-world conditions.

8. Future perspective

The importance of bacteriocins as alternative therapeutics, food preservatives, probiotics, and starter cultures is well documented. The advent of molecular biology tools will bring new insights into interbacterial cross-talk regarding bacteriocin production. It has been revealed that the cell density-dependent expression of class I, class II, and class III bacteriocins occurs in almost the same manner, with some minor differences in the involvement of auto-induction in the former and a dedicated pheromone system in the latter. However, sequence delving and alignment studies have

augmented the quest to find the homologous regions in the promoters, which opens a new door for understanding the expression of various metabolic traits and their regulation mechanisms in prokaryotes with a great deal of veracity. The involvement of genomics and proteomics in this issue will certainly expand the frontier and spur new horizons in solving the limited efficiency and instability in the expression of bacteriocin traits by providing new insight into the indigenous, homologous, and heterologous expressions. The shorter size and peptidyl nature of the pheromones provide an additional advantage to industries to produce bacteriocins in larger quantities with less input of time and money.

Despite the promising antimicrobial potential of QS-regulated bacteriocins, several practical barriers currently limit their large-scale industrial and clinical translation. Natural bacteriocin production is often relatively low and strongly dependent on strain, growth phase, medium composition, and environmental conditions, increasing production costs and complicating process standardization [210]. Moreover, QS signal molecules and regulatory peptides may degrade or lose activity during food processing, storage, or changes in pH, temperature, and proteolytic conditions. Genetic instability represents another concern, as bacteriocin biosynthetic gene clusters may be located on mobile genetic elements or may be lost, silenced, or rearranged during prolonged cultivation, potentially resulting in reduced production [210,211]. In clinical applications, additional challenges include strain-specific safety assessment, antimicrobial resistance and virulence profiling, toxicological evaluation, pharmacokinetic considerations, immunological responses, dose standardization, and regulatory requirements for therapeutic administration [212,213].

Targeted approaches could help overcome these limitations, including rational engineering of QS-responsive promoters and regulatory circuits to enhance production. Additionally, retaining appropriate biological control, optimizing fermentation and cell- retention or immobilized-cell systems to improve productivity and process stability, and developing controlled-release or encapsulation strategies to protect bacteriocins and signaling components during processing are important [214]. In food applications, combining bacteriocins with mild preservation technologies, such as reduced-intensity heat treatment, organic acids, modified-atmosphere packaging, or other hurdle approaches, may permit lower bacteriocin concentrations while maintaining antimicrobial efficacy and minimizing adverse effects on sensory quality [177,215]. However, genetically modified production strains and engineered QS systems require rigorous assessment of genetic stability, unintended regulatory effects, environmental dissemination, and product safety before industrial implementation [212]. Collectively, integrating QS engineering, optimized bioprocessing, formulation technologies, and evidence-based safety evaluation may provide a more realistic pathway toward the scalable utilization of QS-regulated bacteriocins in food and other applications.

Moreover, the regulatory system itself could serve as a model system for studies of various signal transduction activities involved in a wide range of metabolic and regulatory processes, including the cell division cycle; hence, such a regulatory mechanism, in its recombinant or native form, could potentially inform drug design for overcoming antimicrobial resistance. Furthermore, these purified bacteriocins could be tested as an alternative to antibiotics, replace chemical preservatives in the food industry, and have the potential to be utilized in cosmetics for modulating the skin microbiome. The current use of advanced technologies such as artificial intelligence and its allies (machine learning and deep learning) will also benefit in analyzing large datasets and helping to find patterns.

Artificial intelligence (AI) and machine learning (ML) offer several specific opportunities to accelerate the discovery and mechanistic characterization of QS-regulated bacteriocin systems. ML-based sequence and structure prediction could be used to prioritize potential interactions between

autoinducing peptides and their cognate receptors, thereby narrowing candidate signal–receptor pairs for experimental testing [216–218]. Similarly, genome and metagenome mining can be applied to identify putative bacteriocin biosynthetic gene clusters together with neighboring or functionally associated QS-related genes, regulatory elements, and transport systems. Integration of genomic information with transcriptomic and proteomic datasets could further help predict regulatory relationships by identifying coordinated changes in QS-associated regulators, bacteriocin biosynthetic genes, and downstream proteins under different growth or environmental conditions. Metabolomic data may provide an additional layer for linking QS signaling with changes in cellular metabolism and bacteriocin production. These computational approaches could therefore facilitate the prioritization of novel bacteriocin systems and experimentally testable regulatory hypotheses; however, predicted receptor-ligand interactions, genomic associations, or regulatory relationships should not be considered evidence of direct QS control until validated using appropriate genetic, biochemical, transcriptional, and functional experiments.

9. Conclusions

In conclusion, quorum sensing is a cell-to-cell communication mechanism that enables microorganisms to detect and respond to changes in population density through coordinated regulation of gene expression. The production and accumulation of signaling molecules, known as autoinducers, allow microbial populations to synchronize collective behaviors, including biofilm formation, virulence factor production, bacteriocin synthesis, competence development, and adaptation to environmental changes. Through these coordinated responses, QS plays a crucial role in microbial survival, ecological fitness, and interactions within complex microbial communities. In bacteria, particularly LAB, many of these processes are regulated by bacteriocins through intricate molecular and regulatory pathways. A deeper understanding of these mechanisms will facilitate the broader application of bacteriocins across the food, pharmaceutical, medical, and biotechnological sectors. However, their widespread utilization is still constrained by limited mechanistic understanding of their regulation, biosynthesis, and modes of action. Future research integrating advanced omics technologies, systems biology approaches, and high-throughput analytical tools will provide clearer mechanistic insights, thereby enabling the development of more effective and targeted bacteriocin-based applications.

Use of AI tools declaration

The authors declare that they used the free version of an AI-assisted tool (ChatGPT) to prepare and visually refine Figure 8. The authors used the tool solely to assist with the figure's graphical presentation. The scientific concepts, interpretation, and accuracy of the information presented were reviewed and verified by the authors. The authors take full responsibility for the integrity and accuracy of the final figure and the entire manuscript.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Hafsa Kaleem: Software, Methodology, Investigation, Formal analysis, Data curation. Abrar Hussain: Writing—original draft, Methodology, Visualization, Validation. Mushtaq Hussain: Writing—original draft, Methodology, Investigation, Formal analysis. Syed Ghulam Musharraf: Writing—original draft, Formal analysis. Syed Abid Ali: Writing-review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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