REGULATION OF BACTERIOCIN PRODUCTION: THE ROLE OF GENES, QUORUM SENSING AND ENVIRONMENTAL FACTORS (THE REVIEW)

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Introduction. Bacteriocins are antimicrobial peptides produced by bacteriocinogenic bacteria. They suppress or kill closely related and even unrelated competing species, thereby giving their producer a competitive advantage in the microbial community [1–4]. The biosynthesis of bacteriocins requires high metabolic costs, so bacteria have developed regulatory mechanisms for their generation only upon necessity and in response to specific signals [4–6].

The aim of current review was to analyze the data of scientific literature concerning the study of the mechanisms regulating the production of bacteriocins and environmental factors influencing it.

Bacteriocin production is regulated by genetic factors, intricate quorum sensing (QS) systems and various environmental stimuli (Fig. 1) [7,8].

Genetic regulation. The production of bacteriocins is regulated by genes and depends on their expression levels and interactions [9,10]. Genes encoding bacteriocins are usually clustered in operons, which can be located on chromosomes, plasmids, or sometimes integrated into chromosomes via transposons [11]. A schematic representation of gene clusters involved in the biosynthesis of bacteriocins of different classes (class I, class II, class III and class IV) is presented in the work of Sharma et al. [12].

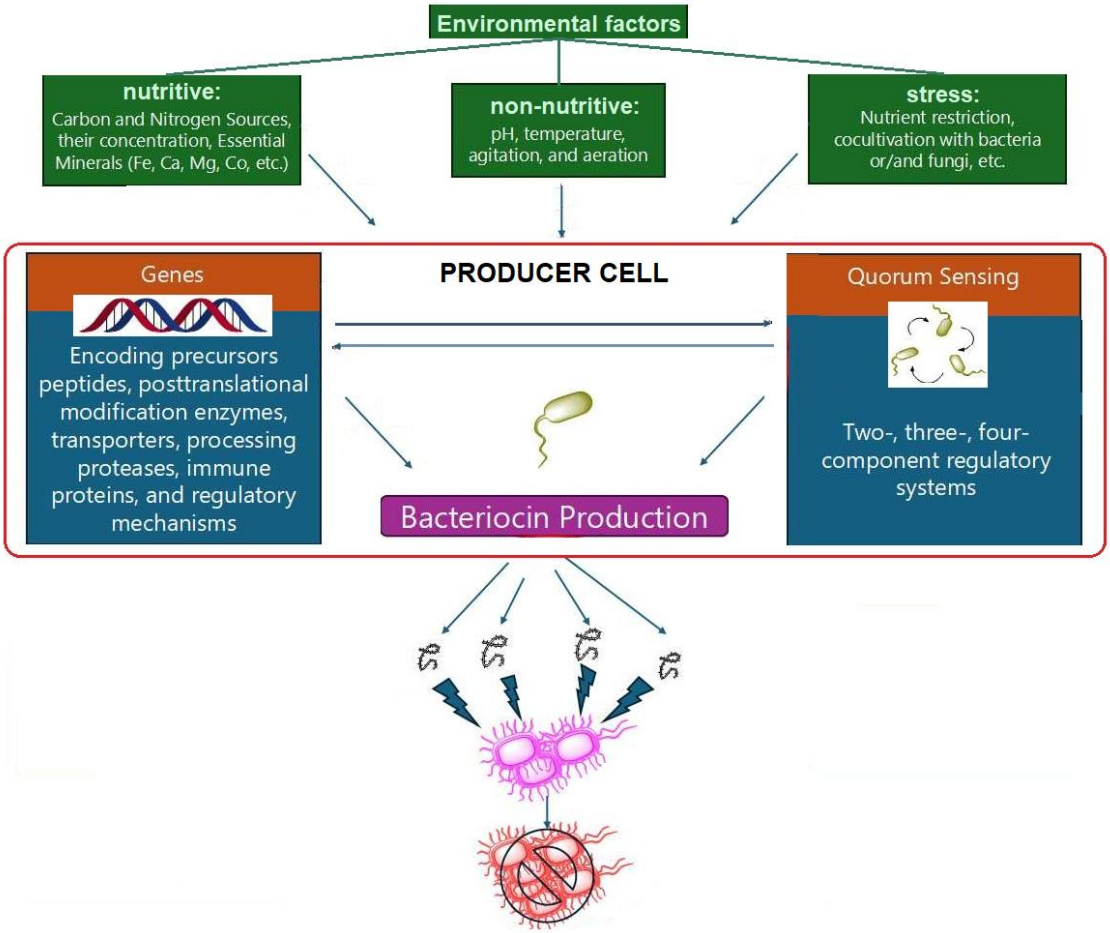

Figure 1. Regulation of bacteriocin production.

The genes involved in lantipeptide biosynthesis are usually assembled into gene clusters encoding precursor peptides (LanA), post-translational modification enzymes (LanBC), transporters (LanT), processing proteases (LanP), immune proteins (LanIFEG), and regulatory mechanisms (Lan RK) [12–14]. For example, **nisin** biosynthesis involves 11 gene clusters interacting with each other (Fig. 2).

The *nisA* gene encodes the pre-nisin peptide (NisA), which consists of leader peptide (N-terminal, important for recognition by modification enzymes) and core peptide (C-terminal, contains the active antimicrobial region). The *nisB* and *nisC* genes encode modification enzymes.

DOI: 10.5281/zenodo.17922805

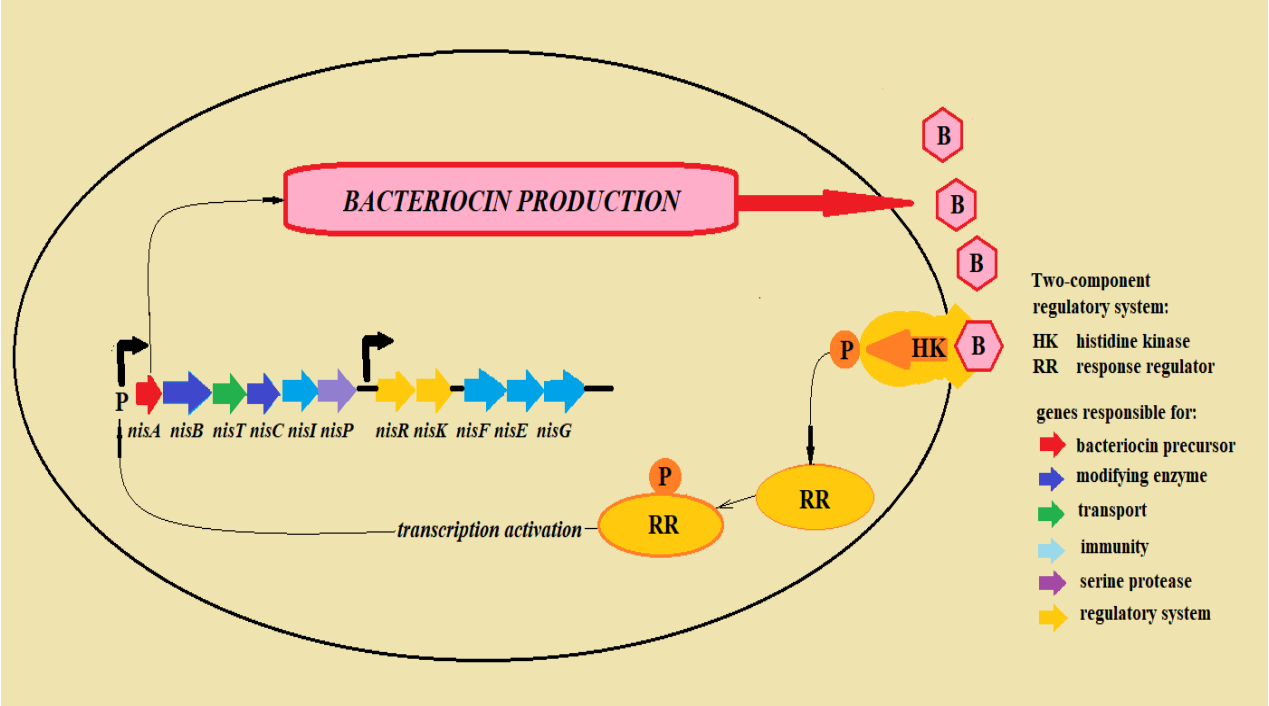

Figure 2. Regulation of nisin production.

The NisB dehydrates specific serine and threonine residues into dehydroalanine (Dha) and dehydrobutyrine (Dhb). The NisC catalyzes the formation of lanthionine (Lan) and methyllanthionine (MeLan) rings by linking these dehydrated residues with cysteines. Post-translational modification confers stability and biological activity to nisin. The *nisT* gene encodes an ATP-binding cassette (ABC) type transporter protein (NisT), which exports the modified pre-nisin across the membrane. The *nisP* gene encodes a serine protease (NisP), that cleaves the leader peptide outside the cell, releasing active nisin. The *nisI* and *nisFEG* genes encode immunity proteins to protect the producer against its own bacteriocin. The NisI is membrane-associated immunity lipoprotein consisting of a functionally specialized two-domain protein, the N-terminal domain interacts with membranes, and the C-terminal domain specifically binds to nisin. The NisFEG is an ABC transporter system that actively pumps out nisin. The *nisRK* genes encode the regulatory two-component system, that mediate signal transduction for nisin autoregulation. The PnisA, PnisR, and PnisE promoters drive the transcription of the entire gene cluster. Different individual modules (enzymes) are responsible for different biosynthetic steps in the biosynthetic gene clusters [9].

Lantibiotic **subtilin**, natively produced by *Bacillus subtilis* ATCC6633, is encoded in a gene cluster *spaBTCSIFEGRK* (*spa*-locus) consisting of four transcriptional units: *spaS* (subtilin prepeptide structural gene), *spaBTC* (gene encodes modification enzymes and transporter), *spaIFEG* (immunity genes) and *spaRK* (genes of the two-component regulation system) [15].

The gene clusters of the lantibiotics **epidermin** and **gallidermin** in *S. epidermidis* and *S. gallinarum* strains have the same organization. They consist of 11 genes localized on plasmids. The genes are organized in transcription units according to their function. These are structural genes of prepeptides (*epiA* and *gdmA*), genes responsible for modification (*gdmBCD* and *epiBCD*), immunity (*gdmFEG* and *epiFEG*), transport and export (*gdmTH, epiT'T"H*), genes of specific serine proteases (*gdmP* and *epiP*) and genes of the key positive regulator that activates the production of epidermin and gallidermin (*gdmQ*) [16].

Class II bacteriocins (non lantibiotics) of different subtypes (IIa, IIb, IIc and IId) have similar operon structures, but the gene organization differs in each subtype [12,17,18]. The operon responsible for the biosynthesis of **pediocin** (IIa subtype) contains four genes located on a plasmid pSRQ11: the structural gene *pedA* for the bacteriocin prepeptide, *pedB* for an immunity protein, and *pedC* and *pedD* encoding proteins required for processing, cleavage and export of the mature bacteriocin (Fig. 3).

Supernatants of strains lacking any of the three genes (*pedA*, *pedC*, *pedD*) do not exhibit pediocin activity. The *pedB* gene is not required for pediocin production. Changing the gene order by moving *pedACg* to the end of the operon (*pedCDACg*) or adding a second copy of *pedACg* (*pedAACDCg*) results in a decrease in the antimicrobial activity of the supernatants of the corresponding strains [19]. The production of **plantaricin** EF (IIb subtype) is regulated by operons *plnABCD*, *plnEFI* and *plnGHSTUVW* of *pln locus* in *L. plantarum* [20]. The *plnABCD* operon encodes a QS system. The *plnA* gene encodes autoinducing peptide (AIP, also known as PlnA in *L. plantarum*); the *plnB* gene encodes a membrane-located histidine protein kinase (HPK, also known as PlnB in *L. plantarum*); the *plnC* and *plnD* genes encode response regulator (RR). In addition to the structural genes, the *plnEFI* operon contains the *plnI* gene, which encodes a

DOI: 10.5281/zenodo.17922805

cognate immune protein. The operon *plnGHSTUVW* codes for an ABC-transport system, which is responsible for the secretion and processing of peptides employing a double-glycine leader [20,21]. Transcriptomic data analysis results showed that genes of TCSs and other genes of *pln* locus interact with each other [20]. The *pln* locus also contains the *plnXY* operon (encoding a pair of proteins with strong homology to the plasmid maintenance systems), the *plnorf3orf5orfZ3* operon (encoding a bacteriocin, an immunity protein and a putative protein with unknown function) [20].

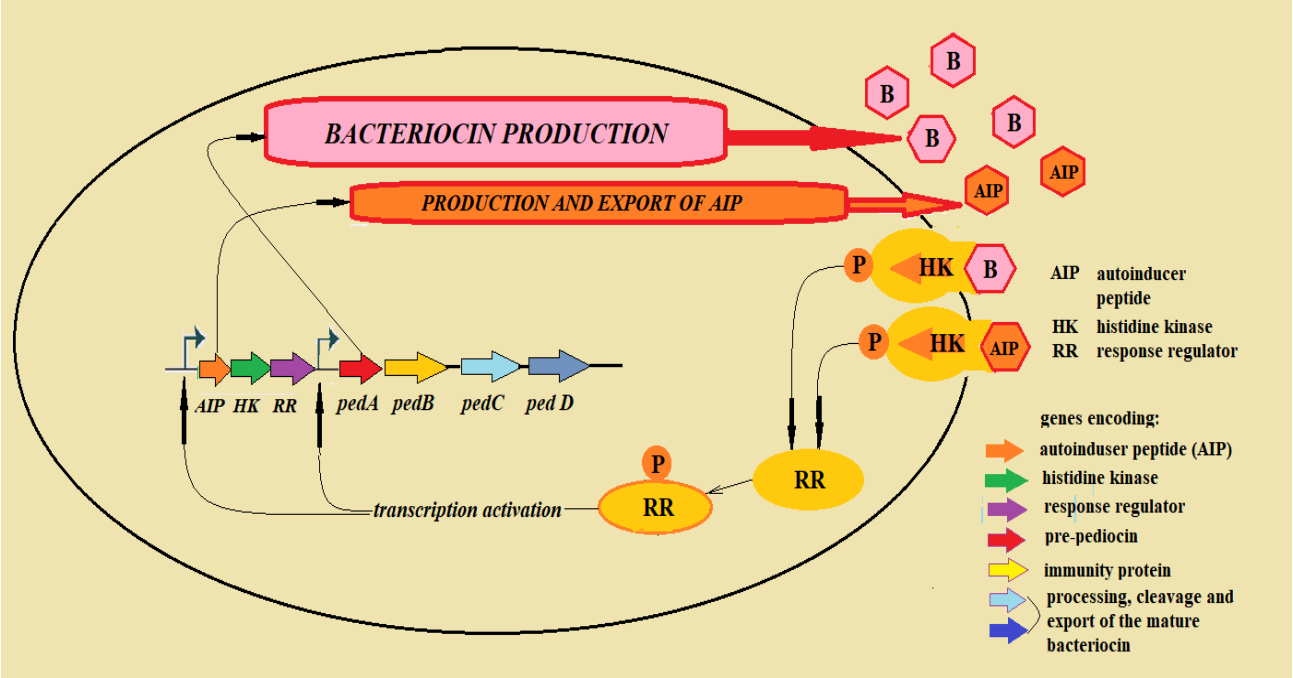

Figure 3. Regulation of pediocin production

Genes *pfs* and *luxS* encode the AI-2 synthase [22]. Deletion of the *plNC8-plNC8HK-plnD* and *plnBCD* genes from *L. plantarum* NC8 and WCFS1, respectively, resulted in the loss of the bacteriocin-generating potential of these strains when co-cultured with inducer strains [22].

The genes involved in the production of class III bacteriocins show high variability in their clusters encoding structure, immunity, regulation, transport and processing [12,23]. The genes encoding class IV bacteriocins are also clustered and include structural genes (sometimes for multiple bacteriocins), transport and secretion, immunity and regulatory genes. For example, enterocins biosynthesis is encoded by structural genes, located in close proximity to each other, an ABC transporter gene (enkT), immunity genes (enkIaz and enkIc), and regulatory genes (a response regulator (*enkR*), and a histidine protein kinase (*enkK*) [12,24].

Regulation via quorum sensing. Quorum sensing (QS) is a cell communication mechanism that plays a crucial role in regulating various physiological activities of microorganisms, including the production of antimicrobial substances [25,26]. The QS mechanism of regulation of bacteriocin production allows bacteria to coordinate gene expression based on population density through direct cell-to-cell contact or the production/detection of signaling molecules [25].

In gram-negative bacteria, the role of signaling molecules is performed by acylated homoserine lactones (AHLs), synthesized by LuxI-type synthetases and, usually, together with LuxR transcription regulators, controlling the expression of downstream genes. In gram-positive bacteria, signaling molecules are small peptides that are elements of a two-component regulatory system, which will be discussed below. A third molecule, autoinducer-2 (AI-2), is involved in interspecies communication. QS regulation system ensures that bacteriocins are produced only when the number of bacteria reaches a threshold sufficient to provide a competitive advantage [25].

To date, the QS mechanism for regulating the production of class I (lantibiotics) and class II bacteriocins has been described. The production of class I bacteriocins is regulated by a two-component system consisting of a histidine kinase and a response regulator. The mature lantibiotic acts as an inducer. It binds to the producer's transmembrane sensor histidine kinase KI/KT and activates it. This leads to phosphorylation and activation of the response regulator RR/RO. The latter, in turn, activates transcription of the lantibiotic by binding to the promoter region of the lan-box [25]. For example, production of the lantibiotic **nisin** is regulated by the NisRK two-component system, consisting of the sensor kinase NisK and response regulator NisR (Fig. 2). The NisK detects extracellular nisin or its fragments and the NisR activates the transcription of genes required for nisin biosynthesis and immunity. Nisin production is upregulated in response to cell density [9,27]. The two-component SpaRK system, comprising the membrane sensor histidine kinase SpaK

DOI: 10.5281/zenodo.17922805

and the response regulator SpaR, regulates **subtilin** production. When the threshold concentration of subtilin is reached in the environment, SpaK initiates the phosphorylation of SpaR. SpaR-P activates the transcription of spaI, spaB, spaS, but does not activate spaRK, its own locus region [15].

Biosynthesis of the lantibiotic **epidermin** by *S. epidermidis* Tü3298 is not regulated by autoinduction, but is indirectly controlled by the *agr* (accessory gene regulator) quorum-sensing system. The *agr* system controls epidermin production not at the transcription level, but at the level of its processing through its effect on EpiP. EpiP is a serine protease required to cleave the leader of the EpiA prepeptide, converting it into the active form of epidermin. This is a key step in the maturation of the molecule. Mutants in the *agr* quorum sensing system significantly reduce epidermin production due to disturbances in its post-translational processing [28].

The production of class II bacteriocins is typically regulated by a three-component regulatory system comprising an autoinducing peptide (AIP), a transmembrane histidine kinase and a cytosolic response regulator [25,29]. The AIP is usually encoded close to the structural gene of the bacteriocin, is expressed and exported from the cell constitutively at a low rate [25]. The extracellular concentration of AIP corresponds to the cell density of its producer. When AIP reaches a certain level, it is detected by the extra-cytoplasmic portion of histidine kinase (Fig. 3) [20,25]. Researchers have elucidated how the recognition of the autoinducing peptide PlnA1 by the extra-cytoplasmic domain of histidine kinase PlnB1 and their interaction occur. The Ile-Ser-Met-Leu key motif of the autoinducing peptide PlnA1 binds to the hydrophobic Phe-Ala-Ser-Gln-Phe region of the extra-cytoplasmic loop 2 of PlnB1 via hydrophobic interactions and hydrogen bonds [21]. The extra-cytoplasmic domain of histidine kinase catalyzes the autophosphorylation of the cytoplasmic domain. Following this, the response regulator phosphorylates and attaches to bacteriocin structural genes *plnEF* [20]. Acetate is also an inducer that regulates plantaricin synthesis. It binds to the positively charged region (Arg-Arg-Tyr-Ser-His-Lys) in loop 4 of PlnB1 via electrostatic interaction, and the side chain of Phe143 in loop 4 determines the specificity and affinity of PlnB1 to recognize acetate. PlnA1 activates quorum sensing in the logarithmic growth phase and acetate in the stationary phase to maintain plantaricin synthesis under reduced growth conditions [21].

Recent studies on the quorum-sensing regulation of class II bacteriocin (pediocin and plantaricin) have shown that their synthesis is also regulated by a two-component system [20,29]. It turned out that pediocin AcH, present in the inactivated culture supernatant of *L. plantarum* subsp. *plantarum Zhang-LL* from de Man Rogosa Sharpe (MRS) medium, is an inducer of bacteriocin production by this bacterium in skim milk (SM) medium. After induction by pediocin, the expression of the *papABCD* genes responsible for bacteriocin synthesis and three genes (*ABT40_05745, ABT40_05750* and *ABT40_11975*) encoding components of the two-component system significantly increases [29].

Environmental factors (stimuli). The production of bacteriocins depends on a number of environmental factors. Nutritive factors such as the types of carbon and nitrogen sources and their concentration in the medium have a significant impact on bacteriocinogenesis. Lack of essential minerals such as Fe^{2+} and Ca^{2+} can negatively affect bacteriocin production [30]. The production of bacteriocins also depends on the cultivation conditions, in particular, pH, temperature, agitation and aeration of the cultivation medium [30–32]. Stress factors also significantly affect bacteriocin production. For example, nutrient restriction can stimulate it [30]. The presence of additional bacteria in the co-culture may be a signal of stress [33]. Co-cultivation of certain microorganisms can induce bacteriocin production by an inactive bacteriocin-competent strains or boosts bacteriocin production above the baseline level by bacteriocin-producing bacteria [33–35]. Both bacteria and fungi can be inducers of bacteriocinogenesis [35,36]. The mechanisms of enhanced bacteriocin production during co-cultivation remain not fully clarified. However, it has been found that co-cultivation is accompanied by overexpression of differentially expressed genes, significant stimulation of carbohydrate metabolism, membrane transport processes, and metabolism of both amino acids and nucleic acids, and leads to increased production of bacteriocins [34]. It was found that the induction of bacteriocin production during co-cultivation with bacteriocin-inducing bacteria involves elements of a three-component regulatory system (AIP, histidine kinases, and response regulator), as well as the interspecies QS molecule AI-2 and the associated *LuxS* gene [35,36]. Induction of bacteriocin production by fungi occurs both by activating intercellular communication mechanisms and by eliminating the limiting factor in the production of bacteriocins and creating a more favorable environment for their synthesis [35,37,38]. The phenomenon of induction of bacteriocin production by microorganisms has promising applications in the development of co-culture-inducible bacteriocin-producing systems for the creation of new effective antimicrobials, which could be used both in food preservation and in antimicrobial therapy [35].

Conclusions

Currently, the mechanisms of genetic and quorum-sensing regulation of bacteriocin production have been largely elucidated. Factors influencing the ability of bacteria to produce bacteriocins were also identified. Among them, the most important are the media composition (carbon, nitrogen, vitamins, surfactants, etc.), cultivation conditions (temperature, pH, aeration, stirring, etc.), and co-cultivation. It has been experimentally proven that some microorganisms, when co-cultivated, are capable of inducing the production of bacteriocin by inactive bacteriocin-competent strains or enhancing the production of bacteriocin above the baseline level by a bacteriocinogenic strain. Development of co-culture-inducible bacteriocin-producing systems underlies one of

DOI: 10.5281/zenodo.17922805

the promising strategies for the creation of new effective antimicrobials for food preservation and antimicrobial therapy.

Regulation of bacteriocin production: the role of genes, quorum sensing, and environmental factors (the review)

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The biosynthesis of bacteriocins requires high metabolic costs, so bacteria have developed regulatory mechanisms for their generation only upon necessity and in response to specific signals. Bacteriocin production is regulated by genetic factors, intricate quorum sensing (QS) systems and various environmental stimuli. **The aim** of this investigation was to evaluate the current knowledge about the mechanisms of regulation of bacteriocin production. **Scope of review**: The analysis included more than 30 studies, mostly from the last ten years. C**onclusions:** Currently, the mechanisms of genetic and quorum-sensing regulation of bacteriocin production have been largely elucidated. Factors influencing the ability of bacteria to produce bacteriocins were also identified. Among them, the most important are the media composition (carbon, nitrogen, vitamins, surfactants, etc.), cultivation conditions (temperature, pH, aeration, stirring, etc.), and co-cultivation. It has been experimentally proven that some microorganisms, when co-cultivated, are capable of inducing the production of bacteriocin by inactive bacteriocin-competent strains or enhancing the production of bacteriocin above the baseline level by a bacteriocinogenic strain. Development of co-culture-inducible bacteriocin-producing systems underlies one of the promising strategies for the creation of new effective antimicrobials for food preservation and antimicrobial therapy

Keywords: bacteriocin production, genetic regulation, quorum sensing, two/three-component regulatory system, co-cultivation.

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DOI: 10.5281/zenodo.17922805

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DOI: 10.5281/zenodo.17922805