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Review

Biosynthesis and Production of Class II Bacteriocins of Food-Associated Lactic Acid Bacteria

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Abstract: Bacteriocins are ribosomally synthesized peptides made by bacteria that inhibit the growth of similar or closely related bacterial strains. Class II bacteriocins are a class of bacteriocins that are heat-resistant and do not undergo extensive posttranslational modification. In lactic acid bacteria (LAB), class II bacteriocins are widely distributed, and some of them have been successfully applied as food preservatives or antibiotic alternatives. Class II bacteriocins can be further divided into four subcategories. In the same subcategory, variations were observed in terms of amino acid identity, peptide length, pI, etc. The production of class II bacteriocin is controlled by a dedicated gene cluster located in the plasmid or chromosome. Besides the pre-bacteriocin encoding gene, the gene cluster generally includes various combinations of immunity, transportation, and regulatory genes. Among class II bacteriocin-producing LAB, some strains/species showed low yield. A multitude of fermentation factors including medium composition, temperature, and pH have a strong influence on bacteriocin production which is usually strain-specific. Consequently, scientists are motivated to develop high-yielding strains through the genetic engineering approach. Thus, this review aims to present and discuss the distribution, sequence characteristics, as well as biosynthesis of class II bacteriocins of LAB. Moreover, the integration of modern biotechnology and genetics with conventional fermentation technology to improve bacteriocin production will also be discussed in this review.

Keywords: bacteriocins; lactic acid bacteria; biosynthesis; genetic regulation; genome mining

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1. Introduction

Lactic acid bacteria (LAB) constitute a ubiquitous bacterial group that is widespread in niches of fermented food and gastrointestinal tracts of humans and many animals [1]. LAB are especially known for their ability to produce lactic acid as the main end-product. These microorganisms also possess the ability to synthesize a wide variety of bioactive metabolites, belonging to different classes of chemicals including diacetyl, hydrogen peroxide, antibiotics, and bacteriocins. Bacteriocins are ribosomally synthesized, extracellularly released bioactive peptides which have a bactericidal or bacteriostatic effect on other closely related species [2]. Bacteriocins from LAB have been used as food preservatives due to their heat stability and safety. Nisin is the most famous and best-studied bacteriocin, and it has high antibacterial activity against a wide range of Gram-positive bacteria. Nisin has received considerable attention in the food industry because it is the only purified bacteriocin approved for food use by the FDA and EU. However, several restrictions to the efficacy of nisin limit its range of practical applications. For instance, nisin has weak inhibition activity against Gram-negative bacteria, and its biological activity is reduced at an elevated pH. Moreover, spontaneous nisin resistance may occur in target bacteria.

Consequently, lots of researchers seek to find novel bacteriocins with different targeting spectra and biochemical properties.

Bacteriocins produced by LAB are classified into two main classes: class I, containing heavily modified (lanthionine-containing) peptides called lantibiotics; and class II, containing non-modified peptides or peptides with minor modifications [3]. Class II bacteriocins are typically small (<60 amino acids) and heat-stable, and often synthesized as pre-bacteriocins containing an N-terminal leader sequence that is cleaved during secretion [4]. The class II bacteriocins are perhaps the best characterized and the most distributed group in food-associated LAB.

A typical gene cluster involved in the biosynthesis of class II bacteriocins consists of genes that encode a bacteriocin precursor peptide, an immunity protein, and an ATP-binding cassette (ABC) transporter. In some class II bacteriocins, an accessory protein is required for proper transportation [5]. The gene-encoded nature of bacteriocins makes them easily amenable through bioengineering to either increase their activity or specify target microorganisms. Concomitantly with the discovery of new bacteriocins, several interesting aspects of the biosynthetic mechanisms of class II bacteriocins have been revealed. These include regulation of the production, immunity (self-protection), and extracellular transportation.

Given the extensive fundamental and industrial importance of class II bacteriocins of LAB, the understanding of their distribution, biosynthesis, and genetics is beneficial for both scientific and industrial purposes. In this review, we investigate the distribution of class II bacteriocins in food-associated LAB. We then summarize the current understanding of the biosynthesis process of class II bacteriocins and the structure of their biosynthetic gene clusters. We also discuss the fermentation and genetic engineering strategies that can improve the yields of class II bacteriocins.

2. Classification of LAB Bacteriocins

There are several classification schemes based on the biochemical and structural features of LAB bacteriocins. In 1993, Klaenhammer et al. suggested a classification system that divides LAB bacteriocins into four groups [6]. The class I bacteriocins are lantibiotics, which are small membrane-active peptides (<5 kDa) containing uncommon amino acids such as lanthionine, β-methyl lanthionine, and dehydrated residues. Class II includes small heat-stable peptides without lanthionine residues. Class III comprises large heat-labile proteins, while class IV is composed of large peptides complexed with carbohydrates or lipids. Cotter et al. (2005) performed a thorough modification of Klaenhammer's classification scheme and they grouped bacteriocins into just two categories: lantibiotics (class I) and non-lanthionine-containing bacteriocins (class II). They also suggested that the high-molecular weight thermolabile peptides (previously class III) should be designated as "bacteriolysins", and the previous class IV should be extinguished [7]. Cotter's classification scheme was broadly accepted for a long time, and has continuously been modified by researchers, since the repertoire of bacteriocins is rapidly growing [8–10].

In general, class I bacteriocins are produced as precursor peptides that undergo extensive post-translational modifications. The mature peptides contain unusual amino acids, such as 2,3-didehydroalanine, D-alanine, and 2,3-didehydrobutyrine, as well as characteristic lanthionine rings that result from thioether formation between the side chains of cysteine and serine or threonine. Class Ia bacteriocins, which include nisin, consist of cationic and hydrophobic peptides that form pores in target membranes and have a flexible structure compared to the more rigid class Ib. Class Ib bacteriocins, which are globular peptides, have no net charge or a net negative charge. Class Ic is a growing class of two-component lantibiotic systems that utilize two peptides that are each posttranslationally modified to an active form and act in synergy to provide antibacterial activity. More detailed information on the structure and biosynthesis of lantibiotics is presented in previous reviews [11–13].

Class II bacteriocins are a class of small non-lanthionine-containing peptides. Unlike the lantibiotics described above, class II bacteriocins are less modified; a disulfide bridge and some N-terminal modifications are known to exist in some class II bacteriocins. Class

II bacteriocins are divided into four subclasses, IIa, IIb, IIc, and IId. Subclass IIa bacteriocins are the most thoroughly studied. They are also known as pediocin-like peptides with antilisterial activity [14]. The class IIb bacteriocins (two-peptide bacteriocins) require two different peptides for optimal activity [15]. Class IIc bacteriocins are referred to as circular bacteriocins whose ring structure is formed in a head-to-end fashion [16]. Class IId bacteriocins are categorized as bacteriocins that have no significant sequence similarity to the other class II bacteriocins [17].

3. Sequence Properties of Identified Class II Bacteriocins

Class II is the largest group of bacteriocins and includes a range of small peptides with antimicrobial activity. Great efforts have been made to identify the sequence of class II bacteriocins that LAB can produce and to further recognize the bases of their antibacterial activity. Nonetheless, sequence diversification can be found among class II bacteriocins. On the one hand, some motifs are conserved throughout evolution, such as the "YGNGV" motif in class IIa and the "GXXXG-like" motif in class IIb (Table 1). On the other hand, class IIc bacteriocins have poor sequence similarity but share similar structural patterns of globular arrangement of four or five helices (Table 1 [18]).

Table 1. Amino acids sequences of class II bacteriocins.

Name of Bacteriocins	Sequence	Producer Species	Strain	Reference
ClassIIa				
Acidocin A	MISMISSHQKTLTDKELALISGGKT YYGTNGVHCTKRSLWGKVRLKNVI PGTLCRKQSLPIKQDLKILLGWATGA FGKTFH	*Lactobacillus acidophilus*	TK9201	[19]
Bacteriocin 31	MKKKLVICGIIGIGFTALGTNVEAATATY YGNGLYCNKQKCWVDWNKASREIGKIIV NGWVQHGPWAPR	*Enterococcus faecalis*	YI717	[20]
Bacteriocin BM1	MKSVKELNKKEMQQINGGAISYGNGVYC NKEKCWVNKAENKQAITGIVIGGWASSLA GMGH	*Carnobacterium piscicola*	LV17B	[21]
Bacteriocin B2	MNSVKELNVKEMKQLHGGVNYGNGVS CSKTKCSVNNGQAFQERYTAGINSFVSGVA SGAGSIGRRP	*Carnobacterium piscicola*	LV17B	[21]
Bacteriocin T8	MKKKVLKHCVILGILGTCLAGIGTGIKVDAA TYYGNGLYCNKEKCWVDWNQAKGEIGKIIV NGWVNHGPWAPRR	*Enterococcus faecium*	T8	[22]
Carnobacteriocin B2	MNSVKELNVKEMKQLHGGVNYGNGVSCSK TKCSVNWGQAFQERYTAGINSFVSGVA SGAGSIGRRP	*Carnobacterium piscicola*	LV17	[23]
Carnobacteriocin BM1	MKSVKELNKKEMQQIIGGAISYGNGVYCNK EKCWVNKAENKQAITGIVIGGWASSLAGMGH	*Carnobacterium piscicola*	LV17B	[21]
Curvacin A	MNNVKELSMTELQTITGGARSYGNGVYCNN KKCWVNRGEATQSIIGGMISGWASGLAGM	*Latilactobacillus curvatus*	LTH1174	[24]
Divercin V41	MKNLKEGSYTAVNTDELKSINGGTKYYGNGV YCNSKKCWVDWGQASGCIGQTVVGGWLGGA IPGKC	*Carnobacterium divergens*	V41	[25]
Enterocin A	MKHLKILSIKETQLIYGGTTHSGKYYGNGVYCT KNKCTVDWAKATTCIAGMSIGGFLGGAIPGKC	*Enterococcus faecium*	CTCA92/T136	[26]

Table 1. *Cont.*

Name of Bacteriocins	Sequence	Producer Species	Strain	Reference
Enterocin CRL35	MKKLTSKEMAQVVGGKYYGNGVSCNKKGCSV DWGKAIGIIGNNSAANLATGGAAGWKS	*Enterococcus faecium*	CRL 35	[27]
Enterocin HF	MEKLTVKEMSQVVGGKYYGNGVSCNKKGCSV DWGKAIGIIGNNAAANLTTGGKAGWKG	*Enterococcus faecium*	M3K31	[28]
Enterocin P	MRKKLFSLALIGIFGLVVTNFGTKVDAATRSYGN GVYCNNSKCWVNWGEAKENIAGIVISGWASGL AGMGH	*Enterococcus faecium*	P13	[29]
Enterocin SE-K4	MKKKLVKGLVICGMIGIGFTALGTNVEAATYYG NGVYCNKQKCWVDWSRARSEIIDRGVKAYVN GFTKVLG	*Enterococcus faecalis*	K-4	[30]
Leucocin A	MMNMKPTESYEQLDNSALEQVVGGKYYGNG VHCTKSGCSVNWGEAFSAGVHRLANGGNGFW	*Leuconostoc gelidum*	UAL 187	[31]
Mesentericin Y105	MTNMKSVEAYQQLDNQNLKKVVGGKYYGNG VHCTKSGCSVNWGEAASAGIHRLANGGNGFW	*Leuconostoc mesenteroides*	Y105	[32]
Mundticin KS	MKKLTAKEMSQVVGGKYYGNGVSCNKKGCSVD WGKAIGIIGNNSAANLATGGAAGWKS	*Enterococcus mundtii*	NFRI 7393	[33]
Pediocin PA-1	MKKIEKLTEKEMANIIGGKYYGNGVTCGKH SCSVDWGKATTCIINNGAMAWATGGHQGNHKC	*Pediococcus acidilactici*	PAC 1.0	[34]
Piscicolin 126	MKTVKELSVKEMQLTTGGKYYGNGVSCNKNGCT VDWSKAIGIIGNNAAANLTTGGAAGWNKG	*Carnobacterium piscicola*	JG126	[35]
Plantaricin 423	MMKKIEKLTEKEMANIIGGKYYGNGVTCGKHSCS VNWGQAFSCSVSHLANFGHGKC	*Lactiplantibacillus plantarum*	423	[36]
Sakacin A	MNNVKELSMTELQTITGGARSYGNGVYCNNKK CWVNRGEATQSIIGGMISGWASGLAGM	*Latilactobacillus sakei*	706	[37]
Sakacin P	MEKFIELSLKEVTAITGGKYYGNGVHCGKHSCTV DWGTAIGNIGNNAAANWATGGNAGWNK	*Latilactobacillus sakei*	MI401	[38]
Sakacin G	MKNTRSLTIQEIKSITGGKYYGNGVSCNSHGCSV NWGQAWTCGVNHLANGGHGGVC	*Latilactobacillus sakei*	2512	[39]
Bacteriocin L-1077	TNYGNGVGVPDAIMAGIIKLIFIFNIRQGYNFG KKAT	*Ligilactobacillus salivarius*	1077	[40]
Bavaricin MN	TKYYGNGVYCNSKKCWVDWGQAAGGIGQTVVX GWLGGAIPGK	*Lactobacillus bavaricus*	MN	[41]
Bavaricin A	KYYGNGVHCGKHSCTVDWGTAIGNIGNNAAAN XATGXNAGG	*Latilactobacillus sakei*	MI401	[42]
Bifidocin B	KYYGNGVTCGLHDCRVDRGKATCGIINNGG MWGDIG	*Bifidobacterium bifidum*	NCFB 1454	[43]
Lactococcin MMFII	TSYGNGVHCNKSKCWIDVSELETYKAGT VSNPKDILW	*Lactococcus lactis*	MMFII	[44]
Leucocin C	KNYGNGVHCTKKGCSVDWGYAWTNIANNSV MNGLTGGNAGWHN	*Leuconostoc mesenteroides*	TA33a	[45]
Mundticin	KYYGNGVSCNKKGCSVDWGKAIGIIGNNSAAN LATGGAAGWSK	*Enterococcus mundtii*	ATO6	[33]
Piscicocin VIa	KYYGNGVSCNKNGCTVDWSKAIGIIGNNAAANL TTGGAAGWNKG	*Carnobacterium piscicola*	V1	[46]
Plantaricin C19	KYYGNGLSCSKKGCTVNWGQAFSCGVNRVATA GHGK	*Lactiplantibacillus plantarum*	C19	[47]
plantaricin LPL-1	VIADKYYGNGVSCGKHTCTVDWGEAFSCSVSHL ANFGHGKC	*Lactiplantibacillus plantarum*	LPL-1	[48]

Table 1. *Cont.*

Name of Bacteriocins		Sequence	Producer Species	Strain	Reference
Class IIb					
ABP-118	118α	MMKEFTVLTECELAKVDGGKRGPNCVG NFLGGLFAGAAAGVPLGPAGIVGGANL GMVGGALTCL	*Ligilactobacillus salivarius*	UCC118	[49]
	118β	MKNLDKRFTIMTEDNLASVNGGKNGY GGSGNRWVHCGAGIVGGALIGAIGGPW SAVAGGISGGFTSCR			
Amylovorin L	amyLa	MSKGEVLNEDELTAVVGGSKGKGRNNW AGNTIGIVSSAATGAALGSAICGPGCGFV GAHWGAVGWTAVASFSGAFGKIRK	*Lactobacillus amylovorus*	DCE 471	[50]
	amyLb	MKQLNSEQLQNIIGGNRWTNAYSAALG CAVPGVKYGKKLGGVWGAVIGGVGGA AVCGLAGYVRKG			
Acidocin LF221B	LF221B	MIEKVSKNELSRIYGGNNVNWGSVAGSC GKGAVMEIYFGNPILGCANGAATSLVLQ TASGIYKNYQKKR	*Lactobacillus gasseri*	LF221	[51]
	LF221β	MALKTLEKHELRNVMGGNKWGNAVIGA ATGATRGVSWCRGFGPWGMTACALGGA AIGGYLGYKSN			
Brevicin 174A	174A-β	MEKFAVLSLSDLVDIQGGKKKKKYTGPN YRCMVKSGGGLVSGAIGGSPFGVG GIVGGGMAGLVGGAISCLNNK	*Levilactobacillus brevis*	174A	[52]
	174A-γ	MYKELTVDELALIDGGKKKKKKVACTWG NAATAAASGAVKGILGGPTGALAGAIWG VSQCASNNLHGMH			
Carnobacteriocin XY	CbnX	MKSVKELNVKEMQQTIGGWGWKEVVQ NGQTIFSAGQKLGNMVGKIVPLPFG	*Carnobacteria*		[53]
	CbnY	MNKEFKSLNEVEMKKINGGSAILAITLG IFATGYGMGVQKAINDRRKK			
Enterocin X	EntXα	MQNVKEVSVKEMKQIIGGSNDSLWY GVGQFMGKQANCITNHPVKHMIIPGY CLSKILG	*Enterococcus faecium*	KU-B5	[54]
	EntXβ	MKKYNELSKKELLQIQGGIAPIIVAGLGY LVKDAWDHSDQIISGFKKGWNGGRRK			
Enterocin 1071	Entα	MKQYKVLNEKEMKKPIGGESVFSKIGNA VGPAAYWILKGLGNMSDVNQADRINR KKH	*Enterococcus faecalis*	FAIR-E 309	[55]
	Entβ	MKNIKNASNIKVIEDNELKAITGGGPGK WLPWLQPAYDFVTGLAKGIGKEGNKNK WKNV			
Gassericin S	GasA	MKVLNECQLQTVVGGKNWSVAKCGGT IGTNIAIGAWRGARAGSFFGQPVSVG AGALIGASAGAIGGSVQCVGWLAGGGR	*Lactobacillus gasseri*	LA327	[56]
	GasX	MIEKVSKNELSRIYGGNNVNWGSVAGSC GKGAVMGIYFGNPILGCANGAATSLVLQ TTSGIYKNYQKKR			

Table 1. *Cont.*

Name of Bacteriocins		Sequence	Producer Species	Strain	Reference
Gassericin T	GatA	MKNFNTLSFETLANIVGGRNNWAANIG GVGGATVAGWALGNAVCGPA CGFVGAHYVPIAWAGVTAATGGFGKIRK	*Lactobacillus gasseri*	LA327	[56]
	GatX	MALKTLEKHELRNVMGGNKWGNAVIGA ATGATRGVSWCRGFGPWGMTACGLGGA AIGGYLGYKSN			
Mutacin IV	nlm A	MDTQAFEQFDVMDSQTLSTVEGGKVSG GEAVAAIGICATASAAIGGLAGATLVTPY CVGTWGLIRSH	*Streptococcus mutans*	UA159	[57]
	nlm B	MELNVNNYKSLTNDELSEVFGGDKQAA DTFLSAVGGAASGFTYCASNGVWHPYILA GCAGVGAVGSVVFPH			
Lactococcin G	LcnGα	MKELSEKELRECVGGGTWDDIGQGIGRV AYWVGKAMGNMSDVNQASRINRKKKH	*Lactococcus lactis*		[58]
	LcnGβ	MKNNNNFFKGMEIIEDQELVSITGGKKW GWLAWVDPAYEFIKGFGKGAIKEGNK DKWKNI			
Lactococcin Q	LcnQα	MKELSEKELRECVGGSIWGDIGQGVGKA AYWVGKAMGNMSDVNQASRINRKKKH	*Lactococcus lactis*	QU4	[59]
	LcnQβ	MKNNNNNFFKDMEIIEDQELVSITGGKK WGWLAWVEPAGEFLKGFGKGAIKEGNK DKWKNI			
Lactocin 705	705α	MESNKLEKFANISNKDLNKITGGGFWGG LGYIAGRVGAAYGHAQASANNHHSPING	*Lacticaseibacillus casei*	CRL 705	[60]
	705β	MDNLNKFKKLSDNKLQATIGGGMSGYIQ GIPDFLKGYLHGISAANKHKKGRLGY			
Plantaricin NC8	PlnC8α	MDKFEKISTSNLEKISGGDLTTKLWSSWG YYLGKKARWNLKHPYVQF	*Lactiplantibacillus plantarum*	NC8	[61]
	PlnC8β	MNNLNKFSTLGKSSLSQIEGGSVPTSVYT LGIKILWSAYKHRKTIEKSFNKGFYH			
Plantaricin S	Plsα	MNNALSFEQQFTDFSTLSDSELESVEGGR NKLAYNMGHYAGKATIFGLAAWALLA	*Lactiplantibacillus plantarum*	LPCO10	[62]
	Plsβ	MDKIIKFQGISDDQLNAVIGGKKKKQSW YAAAGDAIVSFGEGFLNAW			
Plantaricin EF	PlnE	MLQFEKLQYSRLPQKKLAKISGGFNRG GFNRGGYNFGKSVRHVVDAIGSVAGI RGILKSIR	*Lactiplantibacillus plantarum*	C11	[63]
	PlnF	MKKFLVLRDRELNAISGGVFHAYSARGV RNNYKSAVGPADWVISAVRGFIHG			
Plantaricin JK	PlnJ	MTVNKMIKDLDVVDAFAPISNNKLNG VVGGGAWKNFWSSLRKGFYDGEA GRAIRR	*Lactiplantibacillus plantarum*	C11	[64]
	PlnK	MKIKLTVLNEFEELTADAEKNISGGRRSR KNGIGYAIGYAFGAVERAVLGGSRDYNK			
Salivaricin P	SalPα	MMKEFTVLTECELAKVDGGKRG PNCVGNFLGGLFAGAAAGVPLGPAGIVG GANLGMVGGALTCL	*Ligilactobacillus salivarius*	DPC6005	[65]
	SalPβ	MKNLDKRFTIMTEDNLASVNGGKNG YGGSGNRWVHCGAGIVGGALIGAIGGP WSAVAGGISGGFASCH			

Table 1. *Cont.*

Name of Bacteriocins		Sequence	Producer Species	Strain	Reference
Thermophilin 13	ThmA	MNTITICKFDVLDAELLSTVEGGYSGKDC LKDMGGYALAGAGSGALWGAPAGGV GALPGAFVGAHVGAIAGGFACMGG MIGNKFN	*Streptococcus thermophiles*	SPi13	[66]
	ThmB	MKQYNGFEVLHELDLANVTGGQINWG SVVGHCIGGAIIGGAFSGGAAAGVGCLV GSGKAIINGL			
Uncharacterized	LSEI_2392	MYTMTNLKDKELSQITGGFAFGIPVAA ILGFLASDAWSHADEIAGGATSGWSLA DKSHSL	*Lacticaseibacillus casei*	ATCC 334	[67]
	LSEI_2393	MQQFMTLDNSSLEKIAGGENGGLWSIIG FGLGFSARSVLTGSLFVPSRGPVIDLVK QLTPKN			
Uncharacterized	LSEI_2405	MISKEVGITLKQHDLVLIQGGAKRRNK PSGCIVSTIGGAVAGAAGLNPFTTVAGAA IGLSLPRLQ	*Lacticaseibacillus casei*	ATCC 334	[67]
	LSEI_2406	MSYNYRQIDDFQLSGVSGGKKKFDCAATF VTGITAGIGSGTITGLAGGPFGIIGGAVVG GNLGAVGSAIKCLGDGMQ			
Class IIc					
Carnocyclin-A		MLYELVAYGIAQGTAEKVVSLINAGLTV GSIISILGGVTVGLSGVFTAVKAAIAKQG IKKAIQL	*Carnobacterium maltaromaticum*	UAL307	[68]
Enterocin NKR-5-3B		MKKNLLLVLPIVGIVGLFVGAPMLTANL GISSYAAKKVIDIINTGSAVATIIALVTAVVG GGLITAGIVATAKSLIKKYGAKYAAAW	*Enterococcus faecium*	NKR-5-3	[69]
Enterocin AS-48		MVKENKFSKIFILMALSFLGLALFSASLQ FLPIAHMAKEFGIPAAVAGTVLNVVEAG GWVTTIVSILTAVGSGGLSLLAAAGRESIK AYLKKEIKKKGKRAVIAW	*Enterococcus faecalis*	S-48	[70]
Garvicin ML		MFDLVATGMAAGVAKTIVNAVSAGMD IATALSLFSGAFTAAGGIMALIK KYAQKKLWKQLIAA	*Lactococcus garvieae*	DCC43	[71]
Leucocyclicin Q		MFLVNQLGISKSLANTILGAIAVGNLAS WLLALVPGPGWATKAALATAETIVKHEG KAAAIAW	*Leuconostoc mesenteroides*	TK41401	[72]
Lactocyclicin Q		MFLIDHLGAPRWAVDTILGAIAVGNLAS WVLALVPGPGWAVKAGLATAAAIVKHQ GKAAAAAW	*Lactococcus* sp.	QU 12	[73]
Plantaricyclin A		MLSAYRSKLGLNKFEVTVLMIISLFILL FATVNIVWIAKQFGVHLTTSLTQKALDL LSAGSSLGTVAAAVLGVTLPAWAVAAAG ALGGTAA	*Lactiplantibacillus plantarum*	NI326	[74]
Plantacyclin B21AG		MLSAYRSRLGLNKFEVAILMIISLFILL FATVNIVWIARQFGVHLTTKLTQKALD LLSSGASLGTVAAVILGVTLPGWAVAA AGALGGTAA	*Lactiplantibacillus plantarum*	B21	[75]
Uberolysin		MDILLELAGYTGIASGTAKKVVDAIDK GAAAFVIISIISTVISAGALGAVSASADFI ILTVKNYISRNLKAQAVIW	*Streptococcus uberis*	42	[76]

Table 1. *Cont.*

Name of Bacteriocins		Sequence	Producer Species	Strain	Reference
Acidocin B		MVTKYGRNLGLSKVELFAIWAVLV VALLLATANIYWIADQFGIHLATGTAR KLLDAVASGASLGTAFAAILGVTLPAWAL AAAGALGATAA	*Lactobacillus acidophilus*	M46	[77]
Gassericin A		MVTKYGRNLGLNKVELFAIWAVLVVAL LLTTANIYWIADQFGIHLATGTARKLLD AMASGASLGTAFAAILGVTLPAWALAA AGALGATAA	*Lactobacillus gasseri*	LA39	[78]
Reutericin 6		MVTKYGRNLGLNKVELFAIWAVLVVAL LLTTANIYWIADQFGIHLATGTARKLLD AMASGASLGTAFAAILGVTLPAWALA AAGALGATAA	*Limosilactobacillus reuteri*	LA 6	[79]
Class IId (leaderless)					
Bacteriocin LS2		TNWKKIGKCYAGTLGSAVLGFGAMGP VGYWAGAGVGYASFC	*Ligilactobacillus salivarius*	BGHO1	[80]
Enterocin EJ97		MLAKIKAMIKKFPNPYTLAAKLTTYEI NWYKQQYGRYPWERPVA	*Enterococcus faecalis*	EJ97	[81]
Enterocin Q		MNFLKNGIAKWMTGAELQAYKKKYG CLPWEKISC	*Enterococcus faecium*	L50	[82]
LsbB		MKTILRFVAGYDIASHKKKTGGYP WERGKA	*Lactococcus lactis*	BGMN1-5	[83]
Lacticin Q		MAGFLKVVQLLAKYGSKAVQWAWANK GKILDWLNAGQAIDWVVSKIKQILGIK	*Lactococcus lactis*	QU 5	[84]
Lacticin Z		MAGFLKVVQILAKYGSKAVQWAWANK GKILDWINAGQAIDWVVEKIKQILGIK	*Lactococcus lactis*	QU 14	[85]
Lactolisterin BU		MWGRILGTVAKYGPKAVSWAWQHKWE LINMGDLAFRYIQRIWG	*Lactococcus lactis*	BGBU1-4	[86]
Weisselicin Y		MANIVLRVGSVAYNYAPKIFKWIGEGVS YNQIIKWGHNKGWW	*Weissella hellenica*	QU 13	[87]
Weisselicin M		MVSAAKVALKVGWGLVKKYYTKVMQF IGEGWSVDQIADWLKRH	*Weissella hellenica*	QU 13	[87]
Enterocin L50	L50A	MGAIAKLVAKFGWPIVKKYYKQIMQFIG EGWAINKIIEWIKKHI	*Enterococcus faecalis*	L50	[88]
	L50B	MGAIAKLVTKFGWPLIKKFYKQIMQFIGQ GWTIDQIEKWLKRH			
Enterocin MR10	MR10A	MGAIAKLVAKFGWPIVKKYYKQIMQFIGE GWAINKIIDWIKKHI	*Enterococcus faecalis*	MRR 10-3	[89]
	MR10B	MGAIAKLVAKFGWPFIKKFYKQIMQFIG QGWTIDQIEKWLKRH			
Garvicin KS	KS-A	MGAIIKAGAKIVGKGVLGGGASWLGW NVGEKIWK	*Lactococcus garvieae*	KS1546	[90]
	KS-B	MGAIIKAGAKIIGKGLLGGAAGG ATYGGLKKIFG			
	KS-C	MGAIIKAGAKIVGKGALTGGGVWLAEK LFGGK			

Table 1. *Cont.*

Name of Bacteriocins	Sequence	Producer Species	Strain	Reference
ClassIId (non-pediocin liner bacteriocins)				
Bovicin 255	MNTKTFEQFDVMTDEALSTVEGGGKG YCKPVYYAANGYSCRYSNGEWGYVVTK GAFQATTDVIANGWVSSLGGGYFGKP	*Streptococcus bovis*	LRC 0255	[91]
Enterocin 96	MLNKKLLENGVVNAVTIDELDAQFGG MSKRDCNLMKACCAGQAVTYAIHSLL NRLGGDSSDPAGCNDIVRKYCK	*Enterococcus faecalis*	WHE 96	[92]
Garvieacin Q	MENKNYTVLSDEELQKIDGGEYHLMNG ANGYLTRVNGKYVYRVTKDPVSAVFGVIS NGWGSAGAGFGPQH	*Lactococcus garvieae*	BCC 43578	[93]
Garvicins A	MENNNYTVLSDEELQKIDGGIGGALGN ALNGLGTWANMMNGGGFVNQWQVYA NKGKINQYRPY	*Lactococcus garvieae*	21881	[94]
Lactococcin 972	MKTKSLVLALSAVTLFSAGGIVAQAEGT WQHGYGVSSAYSNYHHGSKTHSATVVN NNTGRQGKDTQRAGVWAKATVGRNLTE KASFYYNFW	*Lactococcus lactis*	IPLA 972	[95]
Lactococcin A	MKNQLNFNIVSDEELSEANGGKLTFIQST AAGDLYYNTNTHKYVYQQTQNAFGA AANTIVNGWMGGAAGGFGLHH	*Lactococcus lactis*	LMG 2130	[96]
Lactococcin B	MKNQLNFNIVSDEELAEVNGGSLQYVM SAGPYTWYKDTRTGKTICKQTIDTASYTF GVMAEGWGKTFH	*Lactococcus lactis*	9B4	[97]
Enterocin B	MQNVKELSTKEMKQIIGGENDHRMPN ELNRPNNLSKGGAKCGAAIAGGLFGIPK GPLAWAAGLANVYSKCN	*Enterococcus faecium*	T136	[98]
Carnobacteriocin A	MNNVKELSIKEMQQVTGGDQMSDGVN YGKGSSLSKGGAKCGLGIVGG LATIPSGPLGWLAGAAGVINSCMK	*Carnobacterium piscicola*	LV17A	[99]

Gray letters represent leader sequence.

The leader is almost exclusively a so-called double-glycine type with exceptions for some bacteriocins that use a common Sec signal sequence for secretion [100] (Table 1). It is reported that the interaction of the positively charged amino acids of class II bacteriocins and negatively charged phospholipid molecules on the cell membrane is crucial for their bactericidal activity [14]. It is noteworthy that some newly identified class II bacteriocins have net zero or negative charges, e.g., lactococcin MMFII produced by Lc lactis, mutacin IV produced by *Streptococcus mutans* (Table 2 [18]). In most class IIa, class IIb, and class IId bacteriocins, small amino acids including glycine, alanine, and serine are present in high amounts, which increase the conformational freedom of bacteriocins. The high content of non-polar and aromatic amino acids will facilitate the interaction of bacteriocins with the cell membrane of the target bacteria (Table 2).

Table 2. Characteristics of the amino acid sequence of class II bacteriocins of LAB.

Bacteriocin	Number of Amino Acids	PIa	Net Charge	Ratio of Amino Acid Group					Most Enriched Amino Acids	Amino Acids Absent
				Polar	Non-Polar	Aromatic	Acidic	Basic		
Class IIa										
Acidocin A	58	10.8	10.1	41% (24)	24% (14)	10% (6)	2% (1)	22% (13)	K(8)G(7)L(7) T(6)	ME
Bacteriocin 31	43	9.7	4	40% (17)	23% (10)	16% (7)	5% (2)	16% (7)	G(5)N(4)W(4)K(4)	FM
Bacteriocin BM1	43	8.9	2	47% (20)	28% (12)	9% (4)	5% (2)	12% (5)	G(7)A(5)I(4)K(4)I(4)	PFDR
Bacteriocin B2	48	10	3.9	42% (20)	38% (18)	8% (4)	2% (1)	10% (5)	G(8)S(7)V(5)N(5)	LMWDH
Bacteriocin T8	44	9.4	3	41% (18)	20% (9)	16% (7)	7% (3)	16% (7)	G(6)N(5)K(4)W(4)	FMS
Carnobacteriocin B2	48	10	3.9	42% (20)	35% (17)	10% (5)	2% (1)	10% (5)	G(8)S(7)V(5)N(4)	LMDH
Carnobacteriocin BM1	43	8.9	2	47% (20)	28% (12)	9% (4)	5% (2)	12% (5)	G(7)A(5)I(4)N(4)K(4)	PFDR
Coagulin	44	8.7	3.1	36% (16)	36% (16)	9% (4)	2% (1)	16% (7)	G(8)T(5)A(4)C(4)K(4)	LPFER
Curvacin A	41	9.6	2.9	44% (18)	34% (14)	10% (4)	2% (1)	10% (4)	G(8)A(4)S(4)N(4)	PFDH
Divercin V41	43	8.7	2.8	47% (20)	28% (12)	14% (6)	2% (1)	9% (4)	G(10)V(4)C(4)K(4)	MFERH
Enterocin A	47	9.1	3.9	43% (20)	32% (15)	9% (4)	2% (1)	15% (7)	G(9)T(6)K(6)A(4)C(4)	QWER
Enterocin CRL35	43	9.8	3.9	49% (21)	28% (12)	9% (4)	2% (1)	12% (5)	G(9)A(6)K(5)N(5)	EFHMPQR
Enterocin HF	43	10	4.9	49% (21)	26% (11)	9% (4)	2% (1)	14% (6)	G(10)K(6)A(5)N(5)	PMQFERH
Enterocin P	44	8.3	1	45% (20)	30% (13)	11% (5)	5% (2)	9% (4)	G(8)A(5)Q(5)S(4)	PQFD
Enterocin SE-K4	43	9.7	3.9	37% (16)	23% (10)	16% (7)	7% (3)	16% (7)	G(5)V(5)Y(4)K(4)	HMP
Leucocin A	37	9	2.1	41% (15)	27% (10)	16% (6)	3% (1)	14% (5)	G(8)N(4)A(3)V(3)	IPMQD
Mesentericin Y105	37	9	2.1	43% (16)	27% (10)	14% (5)	3% (1)	14% (5)	G(8)A(4)N(4)S(3)	PMQD
Mundticin KS	43	9.8	3.9	49% (21)	28% (12)	9% (4)	2% (1)	12% (5)	G(9)A(6)N(5)K(5)	PMQFERH
Pediocin PA-1	44	8.7	3.1	36% (16)	36% (16)	9% (4)	2% (1)	16% (7)	G(8)A(4)C(4)N(4)T(4)K(4)	LPFER
Piscicolin 126	44	9.5	2.9	48% (21)	32% (14)	9% (4)	2% (1)	9% (4)	G(9)N(7)A(6)K(4)	PMQFERH
Plantaricin 423	37	8.7	3.1	32% (12)	38% (14)	14% (5)	0% (0)	16% (6)	G(6)S(5)C(4)K(3)	IPMDER
Sakacin A	41	9.6	2.9	44% (18)	34% (14)	10% (4)	2% (1)	10% (4)	G(8)A(4)S(4)N(4)	PFDH
Sakacin P	43	9	2.1	44% (19)	30% (13)	12% (5)	2% (1)	12% (5)	G(9)N(7)A(6)K(3)	LPMQFER
Sakacin G	38	7.9	1.1	42% (16)	37%(14)	11% (4)	0% (0)	11% (4)	G(9)N(5)C(4)V(4)	IPMFDER
Unbericin A	49	9.5	3	37% (18)	41% (20)	10% (5)	2% (1)	10% (5)	N(8)G(8)T(5)K(3)	DFP
Bacteriocin L-1077	37	10.2	3	51% (19)	22% (8)	14% (5)	3% (1)	11% (4)	G(6)I(6)N(4)K(3)F(3)	CEHSW
Bavaricin MN	42	9.3	3	51% (21)	22% (9)	15% (6)	2% (1)	10% (4)	G(10)K(4)V(4)W(3)A(3)	EFHMR
Bavaricin A	39	8.3	1.1	49% (19)	31% (12)	8% (3)	3% (1)	10% (4)	G(9)N(6)A(6)T(3)	EFLMPQR
Lactococcin MMFII	37	7	0	32% (12)	32% (12)	11% (4)	11% (4)	14% (5)	S(4)K(4)T(3)G(3)N(3)	FMQR
Leucocin C	43	9	2.1	37% (16)	37% (16)	12% (5)	2% (1)	12% (5)	N(8)G(8)K(3)V(3)	EFPQR
Mundticin	41	9.5	2.9	49% (21)	28% (12)	9% (4)	2% (1)	12% (5)	G(9)A(6)K(5)N(5)	EFHMPQR
Piscicocin VIa	44	9.5	2.9	48% (21)	32% (14)	9% (4)	2% (1)	9% (4)	G(9)N(7)A(6)K(4)	EFHMPQR
Plantaricin C19	36	9.9	5	39% (14)	33% (12)	11% (4)	0% (0)	17% (6)	G(7)K(4)N(3)A(3)	DEIMP
plantaricin LPL-1	41	7.1	0.1	37% (15)	29% (12)	12% (5)	7% (3)	15% (6)	G(6)V(4)C(4)H(3)	MPQR
Class IIb										
ABP-118 118α	45	9.1	1.9	76% (34)	16% (7)	4% (2)	0% (0)	4% (2)	G(13)A(7)L(6)V(4)	SQYWDEH
ABP-118 118β	46	9.8	3	63% (29)	20% (9)	9% (4)	0% (0)	9% (4)	G(15)A(5)S(4)I(4)	MQDE
Acidocin LF221B LF221B	53	9.7	3.9	47% (25)	32% (17)	9% (5)	2% (1)	9% (5)	G(8)N(6)A(6)S(4)	DH
Acidocin LF221B LF221β	48	10	3.9	56% (27)	23% (11)	13% (6)	0% (0)	8% (4)	G(12)A(8)W(3)T(3)	DEHQ

Table 2. *Cont.*

Bacteriocin		Number of Amino Acids	PIa	Net Charge	Ratio of Amino Acid Group					Most Enriched Amino Acids	Amino Acids Absent
					Polar	Non-Polar	Aromatic	Acidic	Basic		
Brevicin 174A	174A-β	55	10.6	7.9	58% (32)	22% (12)	5% (3)	0% (0)	15% (8)	G(16)K(7)V(5)S(4)	QWDEH
	174A-γ	53	10.7	7.1	55% (29)	25% (13)	4% (2)	0% (0)	17% (9)	A(11)G(9)K(7)V(3)T(3)	FYDER
Carnobacteriocin XY	CbnX	33	10.3	2	52% (17)	24% (8)	12% (4)	3% (1)	9% (3)	G(6)V(4)K(3)Q(3)	CYDRH
	CbnY	29	10.9	4	52% (15)	21% (6)	7% (2)	3% (1)	17% (5)	A(4)I(4)G(4)K(3)	PCWEH
Enterocin X	EntXα	40	9	2.1	43% (17)	33% (13)	10% (4)	3% (1)	13% (5)	G(5)I(4)L(3)K(3)S(3)N(3)	ER
	EntXβ	37	10.3	3.1	51% (19)	11% (4)	11% (4)	8% (3)	19% (7)	G(6)I(5)K(4)A(3)	CMTE
Enterocin 1071	Entα	39	10.3	3.1	44% (17)	23% (9)	8% (3)	8% (3)	18% (7)	G(4)A(4)N(4)K(4)	CT
	Entβ	35	10.4	4	49% (17)	14% (5)	14% (5)	6% (2)	17% (6)	G(6)K(6)L(3)P(3)N(3)W(3)	SCMRH
Gassericin S	GasA	64	11.4	4.9	64% (41)	20% (13)	8% (5)	0% (0)	8% (5)	G(17)A(11)V(5)I(5)	DEHMY
	GasX	53	10	4.9	47% (25)	34% (18)	9% (5)	0% (0)	9% (5)	G(9)N(6)A(5)K(4)	DEH
Gassericin T	GatA	57	10.2	4	65% (37)	16% (9)	11% (6)	0% (0)	9% (5)	G(13)A(12)V(6)N(4)	DEMQS
	GatX	48	10	3.9	56%(27)	23% (11)	13% (6)	0% (0)	8% (4)	G(13)A(7)N(3)W(3)	DEHQ
Mutacin IV	nlm A	44	8.3	1	66% (29)	20% (9)	5% (2)	2% (1)	7% (3)	A(9)G(8)I(4)T(4)	DFMNQ
	nlm B	49	6	−0.9	57% (28)	20% (10)	12% (6)	4% (2)	6% (3)	A(9)G(8)V(6)F(3)	EMR
Lactococcin G	LcnGα	39	10.6	4.1	38% (15)	26% (10)	8% (3)	8% (3)	21% (8)	G(6)K(4)A(3)V(3)I(3)N(3)	LPCFE
	LcnGβ	35	10.2	4	40% (14)	6% (2)	20% (7)	11% (4)	23% (8)	K(8)G(5)W(4)A(3)I(3)	SCMQTRH
Lactococcin Q	LcnQα	39	10.8	5.1	38% (15)	28% (11)	8% (3)	5% (2)	21% (8)	G(5)K(5)A(4)V(3)I(3)S(3)Q(3)T(3)	LPCTFE
	LcnQβ	35	10.2	4	43% (15)	6% (2)	17% (6)	11% (4)	23% (8)	K(8)G(6)W(4)A(3)E(3)	SCMQTYRH0
Lactocin 705	705α	33	9.6	1.3	58% (19)	18% (6)	12% (4)	0% (0)	12% (4)	G(8)A(6)H(3)N(3)	CMTDEK
	705β	33	10.3	4.2	48% (16)	15% (5)	12% (4)	3% (1)	21% (7)	G(7)K(4)Y(3)I(3)L(3)	VCTWE
Plantaricin NC8	PlnC8α	29	10.3	4.1	31% (9)	21% (6)	24% (7)	3% (1)	21% (6)	L(4)K(4)Y(3)W(3)	ICME
	PlnC8β	34	10.4	5.2	32% (11)	24% (8)	18% (6)	3% (1)	24% (8)	K(5)S(4)I(3)Y(3)	CMQD
Plantaricin S	Plsα	27	10.4	3.1	56% (15)	15% (4)	15% (4)	0% (0)	15% (4)	A(7)L(4)G(3)K(2)	VPSCQDE
	Plsβ	26	10	2	42% (11)	15% (4)	19% (5)	8% (2)	15% (4)	A(5)K(4)G(3)S(2)	PCMTRH
Plantaricin EF	PlnE	33	12	5.1	52% (17)	15% (5)	9% (3)	3% (1)	21% (7)	G(6)R(4)V(4)I(4)	CEMPQTW
	PlnF	34	10.6	3.2	50% (17)	15% (5)	15% (5)	3% (1)	18% (6)	A(5)V(5)G(4)S(3)R(3)	CELMQT
Plantaricin JK	PlnJ	25	11.4	4	36% (9)	12% (3)	20% (5)	8% (2)	24% (6)	G(4)R(4)A(3)W(2)K(2)	CHMPQTV
	PlnK	32	10.9	5	47% (15)	13% (4)	13% (4)	6% (2)	22% (7)	G(6)R(5)A(4)Y(3)	CHMPQTV
Salivaricin P	SalPα	45	9.1	1.9	76% (34)	16% (7)	4% (2)	0% (0)	4% (2)	G(13) A(7)L(6)V(4)	DEHQSWY
	SalPβ	46	9.1	2.1	65% (30)	17% (8)	9% (4)	0% (0)	9% (4)	G(15)A(6)S(4)I(4)	DEMQT
Thermophilin 13	ThmA	62	8.3	1	66% (41)	15% (9)	10% (6)	3% (2)	6% (4)	G(18)A(12)V(3)F(3)	EQRT
	ThmB	43	8.3	1	72% (31)	19% (8)	5% (2)	0% (0)	5% (2)	G(13)I(6)A(6)V(4)	DEMPRTY
Uncharacterized	LSEI_2392	42	4.4	−2.8	55% (23)	17% (7)	12% (5)	10% (4)	7% (3)	A(9)S(6)G(5)L(4)	CMNQRY
	LSEI_2393	44	10.6	2	55% (24)	23% (10)	9% (4)	5% (2)	9% (4)	G(7)L(6)S(5)V(4)	CHMY
Uncharacterized	LSEI_2405	44	12.2	5	64% (28)	23% (10)	2% (1)	0% (0)	11% (5)	A(8)G(7)L(4)T(3)	DEHMWY
	LSEI_2406	58	9.1	1.9	64% (37)	21% (12)	5% (3)	3% (2)	7% (4)	G(16)A(7)I(6)T(5)	EHRWY
Class IIc											
Carnocyclin A		60	10.5	4	67% (40)	20% (12)	3% (2)	2% (1)	8% (5)	A(9)G(9)V(8)I(8)	DCHMPRW
Enterocin NKR-5-3B		64	10.3	5	64% (41)	19% (12)	6% (4)	2% (1)	9% (6)	A(14)I(9)G(7)T(6)K(6)V(6)	PCMQFERH
Enterocin AS-48		70	10.6	6	60% (42)	14% (10)	6% (4)	6% (4)	14% (10)	A(12)G(9)K(8)V(8)	DCHQ

Table 2. *Cont.*

Bacteriocin	Number of Amino Acids	PIa	Net Charge	Ratio of Amino Acid Group					Most Enriched Amino Acids	Amino Acids Absent
				Polar	Non-Polar	Aromatic	Acidic	Basic		
Garvicin ML	60	10.6	5	60% (36)	22% (13)	7% (4)	2% (1)	10% (6)	A(15)L(6)G(6)K(6)	CEHPR
Leucocyclicin Q	61	10.2	2.1	66% (40)	18% (11)	5% (3)	3% (2)	8% (5)	A(14)L(9)G(6)I(5)	DCFMRY
Lactocyclicin Q	61	10.3	2.2	72% (44)	8% (5)	7% (4)	3% (2)	10% (6)	A(17)L(7)G(7)V(6)	CMFYE
Plantaricyclin A	58	9.9	1.1	67% (39)	21% (12)	5% (3)	2% (1)	5% (3)	A(14)L(9)G(7)V(6)	CEMNRY
Plantacyclin B21AG	58	10.6	2.1	67% (39)	19% (11)	5% (3)	2% (1)	7% (4)	A(12)L(9)G(8)V(6)T(6)	CEMNY
Uberolysin	70	10.1	3	60% (42)	20% (14)	7% (5)	4% (3)	9% (6)	A(14)I(11)S(7)V(7)	CEHMP
Acidocin B	58	7.7	0.1	69% (40)	14% (8)	9% (5)	3% (2)	5% (3)	A(18)L(8)G(7)T(5)	CEMN
Butyrivibriocin AR10	58	3.7	−2	62% (36)	17% (10)	14% (8)	5% (3)	2% (1)	A(13)I(8)G(6)V(5)	CHR
Gassericin A	58	7.7	0.1	67% (39)	16% (9)	9% (5)	3% (2)	5% (3)	A(18)L(8)G(7)T(5)	CEN
Reutericin 6	58	7.7	0.1	67% (39)	16% (9)	9% (5)	3% (2)	5% (3)	A(18)L(8)G(7)T(5)	CEN
Class IId (leaderless bacteriocins)										
Bacteriocin LS2	41	9.4	2.9	56% (23)	20% (8)	17% (7)	0% (0)	7% (3)	G(10)A(6)K(3)Y(3)V(3)	DEHQR
Enterocin EJ97	44	10.3	4	39% (17)	20% (9)	18% (8)	5% (2)	18% (8)	K(6)A(5)Y(5)P(4)	DCHS
Epidermicin NI01	51	10.7	8.1	39% (20)	22% (11)	18% (9)	2% (1)	20% (10)	K(9)A(6)L(5)I(5)	DCPR
Enterocin Q	34	9.8	3.9	35% (12)	26% (9)	15% (5)	6% (2)	18% (6)	K(6)L(3)G(3)A(3)	DHRV
LsbB	30	10.6	5.1	40% (12)	13% (4)	13% (4)	7% (2)	27% (8)	K(5)G(4)A(3)Y(2)	CNQ
Lacticin Q	53	10.6	6	53% (28)	17% (9)	11% (6)	4% (2)	15% (8)	K(8)A(7)L(6)G(5)V(5)I(5)	CEHPRT
Lacticin Z	53	10.4	5	53% (28)	15% (8)	11% (6)	6% (3)	15% (8)	K(8)A(7)I(7)G(5)V(5)	CHPRT
Lactolisterin BU	43	10.6	4.1	44% (19)	16% (7)	19% (8)	5% (2)	16% (7)	W(5)G(5)I(4)A(4)R(3)	C
Weisselicin Y	42	10.3	4.1	45% (19)	19% (8)	19% (8)	2% (1)	14% (6)	I(5)G(5)N(4)V(4)K(4)	DCT
Weisselicin M	43	10.2	4.1	44% (19)	16% (7)	14% (6)	7% (3)	19% (8)	V(6)K(6)G(4)W(3)	CNP
Enterocin L50 L50A	44	10.5	6.1	48% (21)	11% (5)	16% (7)	5% (2)	20% (9)	I(9)K(8)G(4)A(4)	DCRST
Enterocin L50 L50B	43	10.7	6.1	40% (17)	19% (8)	16% (7)	5% (2)	21% (9)	K(7)I(6)G(4)Q(4)	CNS
Enterocin MR10 MR10A	44	10.5	6.1	48% (21)	11% (5)	16% (7)	5% (2)	20% (9)	I(9)K(8)G(4)A(4)	CRST
Enterocin MR10 MR10B	43	10.7	6.1	40% (17)	16% (7)	19% (8)	5% (2)	21% (9)	K(7)I(6)G(4)F(4)Q(4)	CNS
Garvicin KS KS-A	34	10.7	4	65% (22)	9% (3)	9% (3)	3% (1)	15% (5)	G(9)K(5)A(4)I(4)	DCFHPQRTY
Garvicin KS KS-B	34	10.8	5	74% (25)	6% (2)	6% (2)	0% (0)	15% (5)	G(11)A(6)I(5)K(5)	DCEHNPQRSVW
Garvicin KS KS-C	32	10.7	4	69% (22)	6% (2)	6% (2)	3% (1)	16% (5)	G(9)A(5)K(5)I(3)L(3)	DCHNPQRSY
Class IId (non-pediocin liner bacteriocins)										
Bovicin 255	56	9.2	2.9	45% (25)	23% (13)	20% (11)	4% (2)	9% (5)	G(11)Y(7)V(5)A(5)	HM
Enterocin 96	48	8.5	2.9	38% (18)	33% (16)	4% (2)	8% (4)	17% (8)	C(5)A(5)S(4)K(4)D(4)	EFW
Garvieacin Q	50	9.7	2.2	48% (24)	22% (11)	14% (7)	4% (2)	12% (6)	G(9)V(6)Y(4)N(4)	C
Garvicin A	43	10.2	3	49% (21)	30% (13)	14% (6)	0% (0)	7% (3)	G(9)N(7)A(4)L(3)Q(3)Y(3)	SCDEH
Lactococcin 972	66	10	4.4	30% (20)	33% (22)	15% (10)	5% (3)	17% (11)	G(8)T(7)S(6)A(6)N(6)	CIMP
Lactococcin A	54	9.3	1.3	43% (23)	31% (17)	15% (8)	2% (1)	9% (5)	A(8)G(8)T(6)N(5)	CEPR
Lactococcin B	47	9.3	2	30% (14)	34% (16)	17% (8)	6% (3)	13% (6)	T(8)G(5)Y(4)K(4)	N
Enterocin B	53	9.6	3	53% (28)	23% (12)	6% (3)	6% (3)	13% (7)	G(8)A(8)N(7)L(5)	QT
DivergicinA	46	9.8	2.9	70% (32)	22% (10)	2% (1)	0% (0)	7% (3)	G(14)A(6)L(4)K(3)I(3)	SYWDERH
Carnobacteriocin A	53	9	1.9	58% (31)	26% (14)	4% (2)	4% (2)	8% (4)	G(13)S(6)L(5)A(5)	FERH
Garvicins A	43	10.2	3	49% (21)	30% (13)	14% (6)	0% (0)	7% (3)	G(9)N(7)A(4)L(3)Q(3)	SCDEH

4. Distribution of Class II Bacteriocins in Food-Associated LAB

4.1. Approaches for Studying Bacteriocin Diversity

Bacteriocins must be obtained in their purified form to be studied and characterized. To develop novel food preservatives, many class II bacteriocins were purified and characterized from food-associated LAB strains, which have been isolated from a variety of food products of industrial and natural origins: mainly from meat and dairy products, but also vegetables. LAB in the family of *Lactobacillus* spp., *Enterococcus* spp., *Pediococcus* spp., *Leuconostoc* spp., were frequently identified as producers of class II bacteriocin. However, it is well known that establishing a purification system for bacteriocins can be expensive, time-consuming, and tedious. Moreover, in many cases, these systems often identify previously reported bacteriocins [101]. Another obstacle with the conventional approach is that bacteriocin production is often an unstable trait. The instability can be explained by the loss of plasmid-encoded traits, gene inactivation by transposition, or complex regulatory mechanisms that are affected by environmental factors [102].

It has been shown that the gene content and organization of bacteriocin are conserved among phylogenetically different bacteria. For instance, most class II bacteriocin precursors have the double-glycine motif in their leader sequence. This motif serves as a processing site by dedicated downstream transport machinery to cleave off the leader peptide concomitant with transport [103]. Thus, putative bacteriocins can be identified by comparing new genome sequences against well-characterized biosynthetic genes or gene clusters. This "genome mining" approach allows for the discovery of potentially novel bacteriocins in a complete culture-independent fashion, with the potential to reduce the rediscovery rate of known molecules [104]. Various powerful tools with broad databases have been created for the automated screening of bacteriocin gene clusters. BAGEL4 (http://bagel4.molgenrug.nl/) (accessed on 15 January 2022) is a versatile fast genome-mining tool valid for modified- and non-modified bacteriocins [105]. BAGEL4 uses DNA nucleotide sequences as the input, which are analyzed in parallel via two different approaches; one is the context of bacteriocin- or RiPP (ribosomally synthesized and post-translationally modified peptides) gene-based mining, the other is the precursor (structural gene)-based mining directly by Glimmer, which increases the success rate and lowers the need for the manual evaluation of results [105]. By genome mining of 1011 LAB strains (including WGS and complete genomes) of 82 species using BAGEL4, we shed light on the diversity of food-associated LAB that processes biosynthetic genes of class II bacteriocin at the species level (Table 3, Supplementary Table S1).

4.2. In Silico Prediction of the Distribution of Class II Bacteriocins in LAB

4.2.1. Carnobacteria

Carnobacteria are ubiquitous LAB occurring in different foods. Three sepicies, *Carnobacterium piscicola*, *Carnobacterium divergens*, and *Carnobacterium maltaromaticum*, have been frequently isolated from various meat and dairy products [106]. *C. piscicola* produces bacteriocins, namely piscicocin V1a and piscicocin V1b of molecular weights 4416 Da and 4526 D [107]. *C. piscicola* 213 produces carnocin KZ213 with strong antilisterial activity [108]. In *C. maltaromaticum*, 43.75% of investigated strains possess class IIa bacteiocins, which mainly include carnobacteriocin_BM1 and carnobacteriocin_B2 (Supplementary Table S1). A dry-formulated live culture of *C. maltaromaticum* CB1 which produces carnobacteriocin BM1 has been commercially used as a biopreservative against *L. monocytogenes* in meat [109].

Table 3. Distribution of class II bacteriocin in some food associated LAB.

Species (Number of Strains Analyzed)	Percentage of Strains Harbor Class II Bcteriocin				Number of Class II Bacteriocins Identified			
	IIa	IIb	IIc	IId	IIa	IIb	IIc	IId
Carnobacterium divergens (1)	0	0	0	0	0	0	0	0
Carnobacterium maltaromaticum (16)	43.75%	0	6.25%	18.75%	12	0	1	3
Enterococcus faecalis (32)	56.25%	3.13%	3.13%	31.25%	20	1	1	10
Enterococcus faecium (30)	83.33%	46.66%	13.33%	76.66%	33	16	4	31
Enterococcus avium (5)	0	0	0	20%	0	0	0	1
Enterococcus gallinarum (10)	0	0	0	30%	0	0	0	5
Enterococcus durans (12)	50%	25%	0	8.33%	10	3	0	1
Enterococcus casseliflavus (12)	0	8.33%	8.33%	25%	0	2	1	7
Enterococcus mundtii (16)	31.25%	0	0	56.25%	5	0	0	9
Enterococcus sulfureus (1)	0	0	0	0	0	0	0	0
Lactobacillus acidophilus (18)	94.44%	100%	0	100%	17	20		53
Amylolactobacillus amylotrophicus (1)	0.00%	0	0	0	0	0	0	0
Lentilactobacillus buchneri (5)	0	0	0	0	0	0	0	0
Levilactobacillus brevis (26)	0	0	0	11.54%	0	0	0	5
Lacticaseibacillus casei (14)	92.86%	21.43%	0	100%	15	3	0	77
Lactococcus chungangensis (1)	0	0	0	0	0	0	0	0
Secundilactobacillus collinoides (2)	0	0	0	0	0	0	0	0
Loigolactobacillus coryniformis subsp. *torquens* (1)	0	0	0	0	0	0	0	0
Loigolactobacillus coryniformis subsp. *coryniformis* (3)	0	0	0	0	0	0	0	0
Lactobacillus crispatus (22)	36.36%	50%	0	72.73%	17	11	0	27
Companilactobacillus crustorum (3)	0	0	0	0	0	0	0	0
Lactobacillus delbrueckii subsp. *bulgaricus* (14)	0	0	0	0	0	0	0	0
Lactobacillus delbrueckii subsp. *indicus* (2)	0	0	0	0	0	0	0	0
Lactobacillus delbrueckii subsp. *sunkii* (1)	100%	0	0	0	1	0	0	0
Lactobacillus delbrueckii subsp. *lactis* (5)	0	0	0	80%	0	0	0	4
Lactobacillus delbrueckii subsp. *delbrueckii* (5)	0	0	0	0	0	0	0	0
Lapidilactobacillus dextrinicus (1)	0	0	0	0	0	0	0	0
Lactobacillus equicursoris (2)	0	0	0	0	0	0	0	0
Lactococcus fujiensis (1)	0	0	0	0	0	0	0	0
Fructilactobacillus fructivorans (4)	0	0	0	0	0	0	0	0
Lactobacillus gasseri (23)	39.13%	34.78%	39.13%	52.17%	9	8	12	26
Lactobacillus helveticus (27)	0	0	0	0	0	0	0	0
Lactobacillus iners (17)	0	0	0	0	0	0	0	0
Lactobacillus johnsonii (22)	72.73%	54.55%	0	31.82%	27	12	0	7
Apilactobacillus kunkeei (10)	0	0	0	0	0	0	0	0
Lacticaseibacillus paracasei (20)	100%	35%	0	100%	21	7	0	94
Schleiferilactobacillus perolens (1)	0	0	0	0	0	0	0	0
Lactiplantibacillus plantarum (50)	0	80%	4%	80%	0	72	2	73
Limosilactobacillus reuteri (31)	0	6.45%	0	6.45%	0	2	0	2
Lacticaseibacillus rhamnosus (30)	100%	20%		100%	32	6	0	76
Furfurilactobacillus rossiae (1)	100%	0	0	100%	1	0	0	1

Table 3. *Cont.*

Species (Number of Strains Analyzed)	Percentage of Strains Harbor Class II Bcteriocin				Number of Class II Bacteriocins Identified			
	IIa	IIb	IIc	IId	IIa	IIb	IIc	IId
Latilactobacillus sakei (25)	32%	16%	0	56%	10	4	0	20
Ligilactobacillus salivarius (30)	0%	50%	3.33%	56.67%	0	16	1	31
Paucilactobacillus vaccinostercus (1)	0	0	0	0	0	0	0	0
Lactococcus garvieae (19)	0	0	5.26%	26.32%	0	0	1	7
Lactococcus lactis subsp. *cremoris* (21)	0	0	0	85.71%	0	0	0	37
Lactococcus lactis subsp. *hordniae* (2)	0	0	0	0	0	0	0	0
Lactococcus lactis subsp. *lactis* (20)	0	0	0	50%	0	0	0	18
Lactococcus lactis subsp. *tructae* (1)	0	0	0	100%	0	0	0	4
Lactococcus piscium (4)	25%	0	0	50%	1	0	0	3
Lactococcus raffinolactis (4)	50%	0	25%	100%	2	0	1	5
Leuconostoc carnosum (1)	0	0	0	0	0	0	0	0
Leuconostoc citreum (9)	0	0	0	0	0	0	0	0
Leuconostoc fallax (1)	0	0	0	0	0	0	0	0
Leuconostoc gelidum (11)	27.27%	0	0	72.73%	3	0	0	14
Leuconostoc kimchi (1)	0	0	0	100%	0	0	0	1
Leuconostoc lactis (7)	0	0	0	71.43%	0	0	0	5
Leuconostoc mesenteroides (40)	5%	0	0	37.50%	2	0	0	17
Leuconostoc pseudomesenteroides (23)	0	0	0	0	0	0	0	0
Oenococcus oeni (40)	0	0	0	0	0	0	0	0
Pediococcus pentosaceus (12)	58.33%	0	0	8.30%	12	0	0	1
Pediococcus acidilactici (22)	4.50%	0	0	4.50%	2	0	0	1
Pediococcus damnosus (11)	100%	0	0	18.18%	12	0	0	2
Pediococcus parvulus (1)	0	0	0	0	0	0	0	0
Pediococcus inopinatus (2)	0	0	0	100%	0	0	0	2
Streptococcus thermophilus (42)	0	9.52%	0	100%	0	5	0	189
Weissella confusa (4)	0	0	0	0	0	0	0	0
Weissella cibaria (15)	0	0	0	0	0	0	0	0
Weissella kandleri (1)	0	0	0	0	0	0	0	0
Weissella koreensis (1)	0	0	0	0	0	0	0	0
Weissella oryzae (1)	0	0	0	0	0	0	0	0
Weissella viridescens (2)	0	0	0	0	0	0	0	0

4.2.2. Enterococci

The genus *Enterococcus* is the most controversial group of LAB that comprises both pathogenic and commensal microorganisms; some strains of *Enterococcus* spp. are highly adapted to several food systems, and they are also involved in the fermentation activity of traditionally manufactured cheese, dry sausages, and olives [110]. The production of bacteriocins by enterococci is well documented. Our analysis shows that *Enterococcus faecium* and *E. faecalis* are predominant species that producing class II bacteriocins, which is in accordance with previous reports [111]. *E. durans* and *E. mundtii* also have great potential for class II bacteriocin screening. More than 50% of investigated strains have at least one bacteriocin encoding genes (Table 3).

4.2.3. Lactobacilli Group

The genus *Lactobacillus* used to comprise over 200 species, making it the largest and most diverse genus of LAB [112]. In 2020, a taxonomic reorganization of the lactic acid bacteria reclassified the genus *Lactobacillus* into 25 genera. The lactobacilli group occupies a variety of niches, including milk and plant surfaces, as well as the gastrointestinal tract of humans and animals [113]. *Lactobacillus* spp. has been deployed and studied extensively as fermentation starter cultures and as probiotics, of which bacteriocin production has been considered an important trait. However, the ability to produce class II bacteriocins varied among different species. Notably, almost all *L. acidophilus* strains contain IIa, IIb and IId bacteriocins. *L. casei*, *L. paracasei* and *L. rhamnosus* stand out as rich sources of IIa and IId bacteriocin.

4.2.4. Lactococci

Due to their particular ability to ferment lactose, members of the genus *Lactococcus* are widely used as starter cultures in the dairy industry. Some strains of lactococci of human and milk origin are reported to have probiotic properties [114]. This genus is well known for its ability to produce class I bacteriocin nisin. Our analysis showed that some species also have considerable potential for class II bacteriocin. Specifically, 85% of tested *Lc. lactis* subsp. *cremoris* strains and 50% of tested *Lc. lactis* subsp. *lactis* strains harbor class IId bacteriocin. Class IIa and IId bacteriocins were found in some *Lc. piscium* and *Lc. raffinolactis* strains.

4.2.5. *Leuconostoc* Spp.

The genus *Leuconostoc* naturally exists in vegetables and some fermented dairy products [115]. Some species of this genus were considered major microorganisms responsible for food spoilage [116]. Class II bacteriocin genes were mainly detected in *L. gelidum*, *L. lactis*, and *L. mesenteroides*, of which the class IId was the dominant subgroup (Table 3). The genus *Pediococcus* has a negative role in the spoilage of beer/wine and a positive role in many fermented foods. Most species of this genus are used in the food industry as probiotic products and starter cultures for fermentation [117].

4.2.6. Pediococci

The genus *Pediococcus* consists of eight species and various species and strains differ in tolerance to oxygen, pH, temperature, and NaCl [118]. *P. acidilactici* and *P. pentosaceus* take place in food fermentations either as indigenous microflora or in starters, and both have been used in natural and controlled fermentations of vegetables and sausages. Studies have shown that non-starter and adjunct *Pediococcus* spp. impart desirable attributes to cheese [119]. *P. pentosaceus*, *P. damnosus*, and *P. acidilactici* are major species of this genus that are capable of producing class II bacteriocins, especially pediocin and other class IIa bacteriocins.

4.2.7. Others

Streptococcus thermophilus is the only streptococcal species widely used in food fermentations, especially for yogurt manufacturing [120]. Several *S. thermophiles* strains can produce thermophilin 13, a two-peptide class IIb bacteriocin. Most *S. thermophiles* strains contain genes encoding bacteriocin-like peptide (blp), which was also frequently detected in other pathogenic streptococci strains [121]. The genus *Oenococcus* plays an important role in wine fermentation, while the species *Weissella* have been described to be associated with vegetable fermentations [122]. However, no class II bacteriocin encoding genes were detected in these two genera.

5. Biosynthesis and Genetics

5.1. IIa

Class IIa bacteriocin is first ribosomally synthesized as a prebacteriocin, which contains an N-terminal leader sequence to keep the peptide inactive (Figure 1). The leaders contain 15 to 30 residues, most of which are featured for the double-glycine residues upstream of the cleavage site. The leader is believed to serve as a signal sequence for the processing and secretion of bacteriocins by a dedicated system comprising an ABC transporter and an accessory protein. ABC-transporter protein contains the C-terminal ATP-binding domain and the N-terminal transmembrane domain embedded in the membrane bilayer. The N-terminal region can cleave the leader peptide at the double-glycine motif. The binding of prebacteriocin with N-terminal proteolytic domain triggers the ATP hydrolysis and subsequent conformational changes of the transporter, resulting in leader cleavage and translocation of the mature bacteriocin across the membrane [14]. The accessory proteins are postulated to facilitate the membrane translocation and/or help in the processing of the leader peptide [14]. For some class IIa bacteriocins, the accessory protein ensures the formation of correct disulfide bond formation [123]. However, not all class IIa bacteriocins are transported via ABC-transporter. Some bacteriocins including enterocin P, bacteriocin 31, enterocin SE-K4 lack the double-glycine motif in their leaders and are exported by sec-dependent translocation system [20,29,124]. These bacteriocins have a hydrophobic N-terminal sec-dependent leader to direct the secretion of the prebacteriocins. The leader was removed by a signal peptidase during translocation.

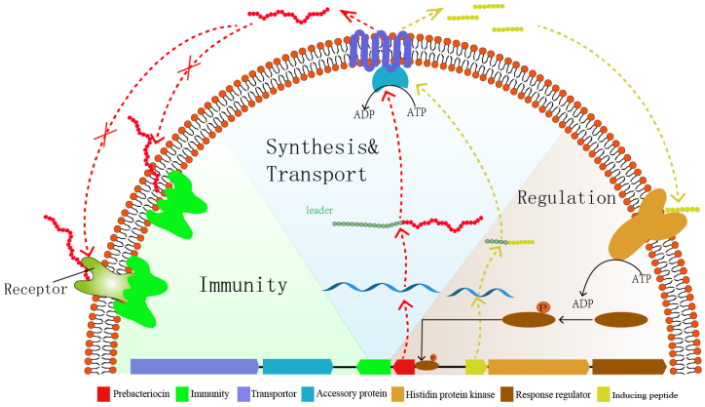

Figure 1. A schematic diagram of the biosynthesis of class IIa bacteriocins.

The synthesis of class IIa bacteriocins is typically regulated by a quorum sensing (QS) system that consists of three components, an inducing peptide, a membrane-associated histidine protein kinase (HPK) and a cytoplasmic response regulator (RR). The inducing peptide is initially synthesized as a prepeptide with N-terminal leader sequence, which is cleaved upon secretion by the ABC-transporter. The concentration of inducer peptide increased along with cell growth. An excess in inducer peptide concentration activates the three-component system by triggering the autophosphorylation of HPK, which transfers a phosphate group to its cognate RR. The phosphorylated RR acts as a transcriptional

activator and activates the expression of biosynthetic gene clusters (Figure 1). Moreover, environmental parameters may influence the production of class IIa bacteriocin by acting on the bacteriocin regulatory system or affecting the binding of the induction peptide to HPK [125].

The bacteriocin-producing bacteria avoid killing by their own bacteriocins through the co-expression of immunity proteins. Immunity proteins for the class IIa bacteriocins range from 81 to 115 amino acids in length and display substantial variation in their sequences. The C-terminal region is involved in specific recognition of their related bacteriocins. However, "cross-immunity" against other class IIa bacteriocins was observed [126]. The immunity protein folds into a globular protein in an aqueous solution and contains an antiparallel four-helix bundle [127]. There are currently two models being proposed regarding the mechanism of immunity protein: (i) the immunity protein directly interacts with the bacteriocin to obstruct pore formation; (ii) the immunity protein binds to the cytoplasmic side of the receptor and blocks the receptor's ability to interact with the bacteriocin (Figure 1). Although direct evidence of contact between the immunity protein and bacteriocin has not been obtained, there are experimental data to support the first model. The expression of MunC protein (enterocin CRL35 immunity protein) in *E. coli* is sufficient to prevent the lethal effects of the hybrid suicide probe EtpM-enterocin CRL35. *E. coli* is naturally insensitive to enterocin CRL35, since it does not express the receptor. These results prove that the immunity protein MunC can protect bacterial cells in the absence of the receptor [27]. The second model of "indirect immunity protein and bacteriocin binding" was recently proved experimentally. When the bacterocin targets the membrane from the outside, it gets locked onto the receptor by its immunity protein by forming a ternary complex. For pediocin PA-1, both IIC and IID components of the man-PTS play an important role in the specific recognition between the bacteriocin-receptor complex and the immunity protein PedB [128].

Production of class IIa bacteriocins is often associated with the presence of a plasmid. In some cases, the biosynthetic gene clusters could be located in the chromosome, as exemplified by enteriocin A, divercin V41, sakacin P and canobacteriocin B2, etc. The genetic organization of this class shows considerable conservation. The gene cluster encoding class IIa bacteriocins usually also contain an operon that encodes ABC-transporters and their accessory proteins. The bacteriocin structural genes are generally located in a small operon with the immunity genes, with the exception of divercin V41, mundicin KS and mundicin L (Figure 2). For most class IIa bacteriocins, three genes encoding the regulatory system are located in the same operon, in which the two genes encoding HPK and RR follow the gene encoding the inducing peptide (Figure 2). Intriguingly, the sakacin G gene cluster contains duplicated structural genes skgA1 and skgA2 that encode essentially identical bacteriocin. The leader sequence of SkgA1 and SkgA2 differed only by three residues [39].

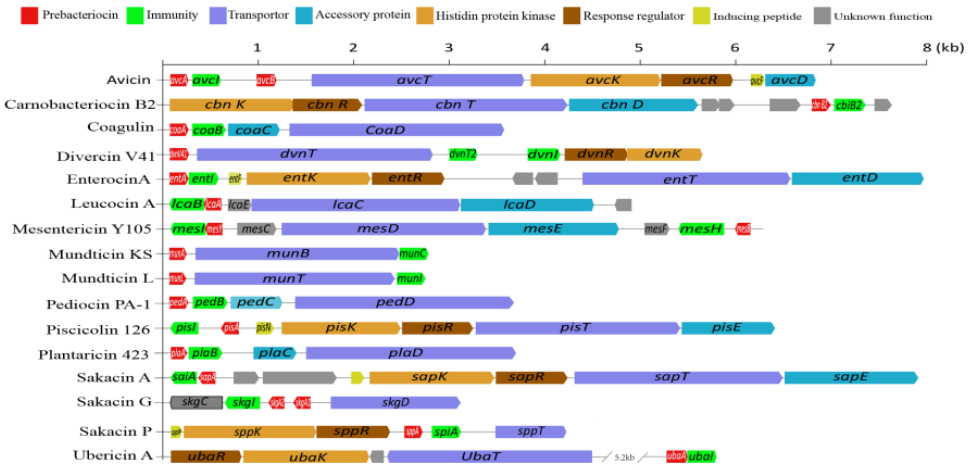

Figure 2. Organization of biosynthetic gene clusters of class IIa bacteriocins of LAB.

5.2. IIb

Similar to some class IIa bacteriocins, class IIb bacteriocins are initially synthesized as precursor peptides containing N-terminal extensions (leader peptides) which are cleaved off during maturation. All class IIb bacteriocins identified so far contain a double-glycine-type leader. The ATP-binding cassette (ABC) transporter and an accessory protein lead to the cleavage of inactive pre-peptide with the concomitant export of the mature bacteriocin across the cytoplasmic membrane. The accessory protein may be involved in immunity against the bacteriocin or required for secretion of the bacteriocin. However, for some two-peptide bacteriocins such as sakacin T, the processing and secretion are solely dependent on the ABC-transporter since the gene encoding the accessory protein is absent [129].

The production of class IIb bacteriocins was commonly regulated by a three-component regulatory system. The inducing peptide acts as an indicator of the cell density, which is sensed by the corresponding HK, resulting in the activation of the RR, which then activates the expression of all operons necessary for bacteriocin synthesis, transport, and regulation. The best example of such a regulatory system is the production of plantaricin E/F and plantaricin J/K by *L. plantarum* C11. The inducing peptide plantaricin A is secreted at low basal levels, thus enabling the bacterium to sense its own growth. At a certain threshold level of plantaricin A, an autoinduction loop is triggered, which leads to massive production of plantaricin E/F and plantaricin J/K [130]. Notably, there are two RRs encoded by *L. plantarum* C11, PlnC and PlnD. It has been shown that PlnC activates while PlnD represses the genes involved in bacteriocin synthesis [131] (Figure 3). However, truncated versions of the activator PlnC, resulting from the translation from alternative start codons within plnC, were found to exhibit repression on the bacteriocin biosynthesis operon [132]. Moreover, *L. lactis* MG1363 produced supernatants acting as environmental signals which can switch on bacteriocin production in *L. plantarum* NC8 via a quorum-sensing mechanism mediated by the inducing peptide PLNC8IF [133].

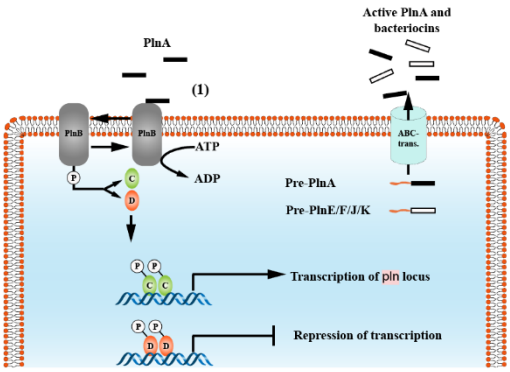

Figure 3. A schematic diagram of the biosynthesis of plantaricinE/F and plantaricinJ/K.

The mechanism of how immunity proteins protect producing cells from class IIb bacteriocins was not fully elucidated. Some immunity proteins, including plnI for plantaricin EF and plnLR for plantaricin JK, show homology to the Abi family of proteins, which are putative membrane-bound metalloproteases characterized by three conserved motifs. These immunity proteins probably function by proteolytically degrading their cognate bacteriocins [134]. Other immunity proteins, including the immunity protein for lactococcin G, likely interact directly both with the bacteriocin and its cellular receptor [135]. So far, all the immunity proteins for class IIb bacteriocins are predicted to contain transmembrane domains (TMD). However, they range in length, number of TMDs, and orientation across the membrane. The smallest immunity protein, CbnZ for carnobacteriocin XY, has just 42 amino acids and contains as few as one TMD, while LagC is a membrane-associated protein with four TMDs [136]. The wide structural variety of immunity proteins may be attributed to the fact that class IIb bacteriocins adopt different receptors as targeting molecules.

A typical gene set for class IIb bacteriocin production comprises five to eight genes (Figure 4) [137–139]. These include two bacteriocin encoding genes, whose closely adjacent gene encodes the immunity protein. The genes encoding a three-component regulatory system may locate up- or downstream of the bacteriocin structural genes. Most class IIb gene clusters also have two genes encoding an ABC transporter complex.

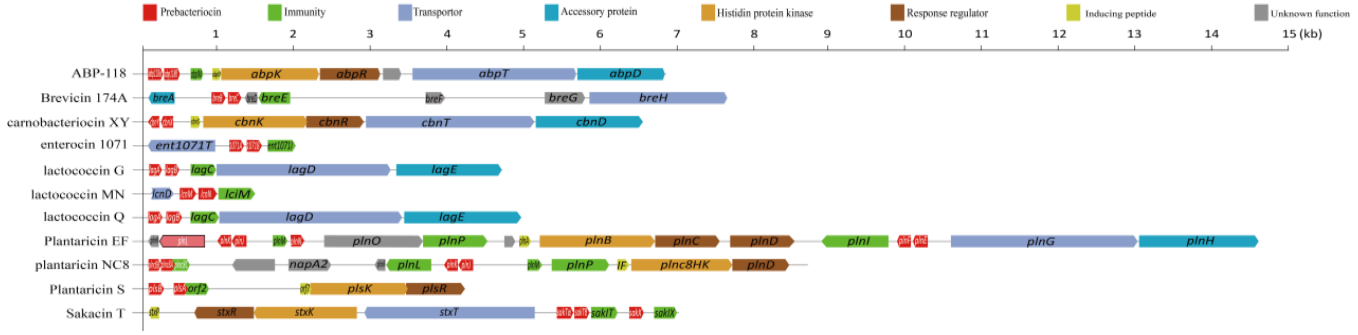

Figure 4. Organization of biosynthetic gene clusters of class IIb bacteriocins of LAB.

5.3. IIc

Three key steps are involved in the biosynthesis of circular bacteriocins: cleavage of the leader, circularization, and exportation of the mature bacteriocin. Leader cleavage is believed to be the first step in the maturation and a requirement for further processing into the mature bacteriocins. The leader peptides ranging between 2 and 35 amino acids share no sequence similarity and the function of the leaders awaits further investigation. Unlike class IIa and IIb bacteriocins, whose leader was generally cleaved at the double-glycine site, there is no common recognition site for leader cleavage of circular bacteriocins. Moreover, the enzymes responsible for the cleavage of the leader peptide have not yet been identified.

The exact mechanism of the circularization reaction for circular bacteriocins is not fully understood. The ligation sites of all circular bacteriocins are located within a helical structure, consisting mainly of stretches of hydrophobic residues. It was suggested that the hydrophobic environment is essential for the circularization reaction [16]. The properties of both the N- and C-terminal residues are critical to the efficiency of the circularization process. In the case of AS-48, the substitution of Met1 to Ala lowered the circularization efficiency significantly, whereas the substitution of Trp70 (last residue) to Ala resulted in the production of both circular and linear forms of the bacteriocin [140]. Mutational analysis at the Leu1 position of enterocin NKR-5-3B revealed that only mutations with helix structure-promoting hydrophobic residues (Ala, Ile, Val or Phe) were able to yield the mature Ent53B derivative [141]. These results highlight the importance of the hydrophobic nature of ligation points for the circularization mechanism. Most of the proteins encoded by the biosynthetic gene clusters contain multiple putative membrane-spanning domains and are probably associated with the membrane (Figure 5). The circularization reaction may be catalyzed by a membrane-located protein complex [142]. Such a complex may be also responsible for exporting circular bacteriocins in a manner of coupling circularization and secretion reactions.

Several proteins have been identified to be involved in immunity to circular bacteriocins. As-48D1, GaaI, and CclI are the dedicated immunity proteins for AS-48, gassericin A, and carnocyclin A, respectively [143–145]. These immunity proteins are small (49–56 amino acids), cationic (high pI), and contain one or two transmembrane domains, suggesting that they may be located in the cell membrane. These immunity proteins can provide a certain level of immunity to their cognate bacteriocins. Full immunity requires the combined activity of several other proteins.

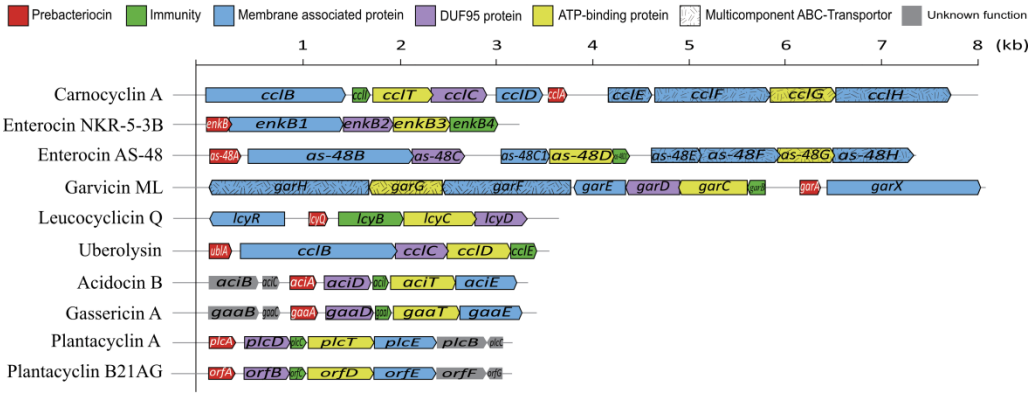

Figure 5. Organization of biosynthetic gene clusters of class IIc bacteriocins of LAB.

Circular bacteriocin gene clusters often consist of overlapping genes, demonstrating a tight organizational structure or genes which depend upon the ribosomal binding site of upstream genes (Figure 5). This indicates that expression is regulated by translational coupling. The minimal set of genes required for bacteriocin production and immunity, in general, comprises 5 to 10 genes [146]. Interestingly, the bacteriocin structural genes are not adjacent to the immunity genes, some of them are located in different operons (Figure 5). The transportation system of class IIc bacteriocins is usually more complex than other class II bacteriocins. They have an accessory operon (cclEFGH, as-48EFGH, garEFGH) encoding an ABC transporter complex, consisting of a permease, an ATPase, and an extracellular protein (Figure 5).

5.4. IId

Most of the leaderless bacteriocins remain to be studied in more detail regarding the biosynthetic mechanism. The leader sequences of other general bacteriocins play an important role in the recognition by transporters. Moreover, the leader sequences keep the precursor peptides inactive during biosynthesis inside the host until the appropriate time for secretion. How leaderless bacteriocins are recognized by transporter protein and secreted remains elusive. A distinguishing feature of leaderless bacteriocins is the presence of a formylated N-terminal methionine residue. Interestingly, lacticins Q expressed in *E. coli* BL21(DE3) has unformylated methionine at the N-terminal. Nevertheless, the peptide demonstrated antimicrobial activity against several of the indicator strains tested [147]. Thus, leaderless bacteriocins may not require a formylated N-terminus for full activity. However, more studies are needed to decipher the importance of the formylated methionine at the N-terminus for the biosynthesis of leaderless bacteriocins. The leaderless bacteriocins are active immediately after their translation process. The transport and immunity of leaderless bacteriocins may be carried out by one protein or protein complex. LmrB, an ABC-type multidrug resistance transporter, has been shown to be involved in both the secretion and self-immunity of this leaderless bacteriocin [148]. The secretion of lacticin Q is strictly controlled by the presence of LnqBCDEF complex, whereas immunity is flexible in that LnqEF (ABC transporter) is the minimal unit required for sufficient immunity and LnqBCD could be considered an accessory protein that supports the activity of LnqEF [149]. This may indicate that leaderless bacteriocins have in common the feature of having one dedicated ABC transporter mediating both secretion and immunity. However, a recent study showed that the ABC transporter is only involved in the transport but not the immunity of enterocin DD14, a leaderless two-peptide bacteriocin. The intracellular enterocin DD14 plays a role in its own immunity system [150].

Similar to class IIa and IIb bacteriocins, the non-pediocin liner bacteriocins are synthesized as biologically inactive pre-peptides consisting of an N-terminal leader peptide. Following synthesis of the pre-peptide, cleavage of the N-terminal leader sequence generally occurs at the double glycine site by means of a dedicated membrane protein from

the ATP-binding cassette transporter family. In addition, a number of non-pediocin liner bacteriocins including lactococcin 972 and divergicinA are secreted through a general sec-dependent pathway and their leaders are cleaved by extracellular signal peptidase. Most LAB have a dedicated immunity protein to protect the cells from their own non-pediocin liner bacteriocins. It is not clear if there is a common mechanism of immunity for non-pediocin liner bacteriocins. For Lactococcin A, its immunity protein LciA has a similar four-helix bundle fold with the immunity proteins of the pediocin-like bacteriocins. Interestingly, LciA and the pediocin-like immunity proteins function in a similar manner. They bind to the bacteriocin–man-PTS complex and prevent membrane leakage [151].

The gene clusters for most of the leaderless bacteriocins have been identified. Genes involved in transport and immunity are often closely associated with bacteriocin structural genes (Figure 6). Leader-containing bacteriocins need an accessory protein function together with the cognate ABC transporter to mediate bacteriocin secretion. Such an accessory protein is not required for transporting leaderless bacteriocins. Moreover, genes related to formylase synthesis were not found in the vicinity of the bacteriocin structural gene, indicating that the N-terminal formylation of leaderless bacteriocins may be carried out by a host-encoded formylase that exists outside of the biosynthetic gene cluster [16,152]. Interestingly, the structural genes of two leaderless bacteriocins weissellicin Y and weissellicin M produced by *Weissella hellenica* QU 13 are located in the same locus [87] (Figure 6). The structural genes of multi-peptides leaderless bacteriocins are co-transcribed. For instance, there is only one promoter has been detected upstream of the ddA gene, and a clear processing site motif of 48 bp was detected between the ddB and ddC genes [150]. The genes responsible for regulation were only found in the biosynthetic gene cluster of lacticinQ/Z, whose production was positively regulated by LnqR, a TetR-family transcriptional regulator [153] (Figure 6).

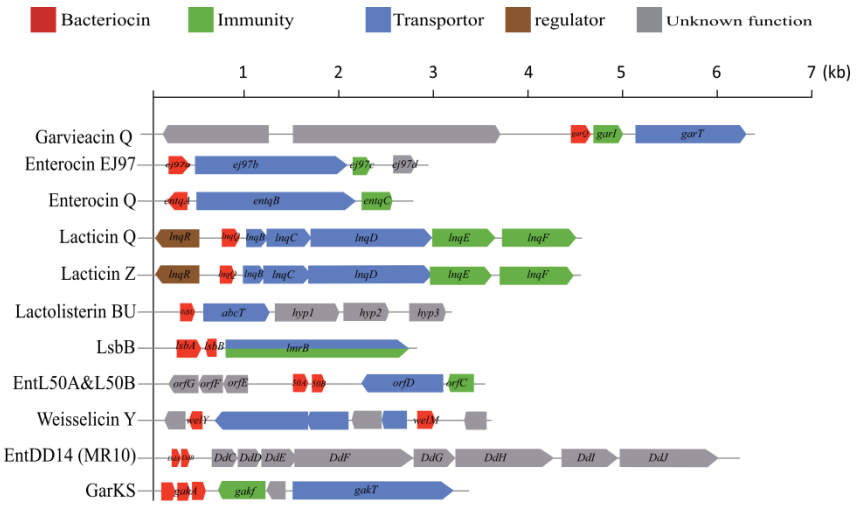

Figure 6. Organization of biosynthetic gene clusters of class IId bacteriocins of LAB.

The regulation of most leaderless bacteriocins was associated with environmental stimuli. The production of Enterocin L50, Enterocin P, and Enterocin Q by *Enterococcus faecium* L50 was temperature-dependent [154]. The production of weissellicin Y and weissellicin M by Weissella hellenica QU 13 was nutrition-adaptive and thiamine addition decreases weissellicin Y production [155]. Pasteurized milk supplemented with tryptone significantly improved the production of garvicin KS [156].

6. Production of Class II Bacteriocins by Microbial Fermentation

The biosynthesis of bacteriocins can be influenced by various culture conditions, such as the composition of the medium, pH, temperature, and growth kinetics of the microorganisms [157]. Fermentation studies on the class II bacteriocin production indicate that it follows primary metabolite kinetics producing the bacteriocin during the growth

phase and declines completely after entering the stationary phase [158]. The commercial availability of bacteriocins is still limited due to the low yield of the product. Moreover, bacteriocin-producing LAB needs complex nutrition to grow, and this not only increases the production cost but also gives rise to the difficulties related to their purification. The efficient use of these compounds requires various approaches to overcome the low yield and the high production costs. In this regard, different studies have examined the effects of various media compositions and culture conditions on the yield of bacteriocins [159]. In recent years, growing knowledge of the genetics and biosynthesis of class II bacteriocins has enabled researchers to quickly manufacture and engineer LAB strains for improved bacteriocin production. LAB strains developed by genetic engineering can not only be used to enhance yields but also for increased tolerance to various biotic and abiotic stresses during fermentation.

6.1. Natural Fermentation

Various media are used to cultivate the bacteriocin-producer such as CM, SM8, M17, and MRS media. These media are good for neutralizing lactic acid and improving cell growth, but do not consider the accumulation of bacteriocin and high content of nitrogen sources, especially proteins and peptides, that may bring about the difficulties of bacteriocin purification [160]. Avonts et al. compared the bacteriocin production of seven *Lactobacillus* strains during fermentation in MRS medium and milk medium [161]. Their results showed that *L. acidophilus* IBB 801 and *L. gasseri* K7 performed better than *L. casei* complex strains including *L. rhamnosus* GG. Although natural fermentation only reached a limited bacteriocin yield, the preservation potential of bacteriocins could be achieved by applying a bacteriocin-producing strain as starter culture.

Most class II bacteriocins are regulated by a quorum sensing (QS) system whose initiation can be induced by environmental factors and other bacterial strains. The production of class IIb bacteriocin plantaricin NC8 by *L. plantarum* NC8 is inducible by co-culture with Gram-positive bacterial strains and requires cell-to-cell contact with the inducer bacteria [61]. This activates the expression of the operon *plNC8IF-plNC8HK-plnD* encoding a three-component regulatory system (TCRS) formed by an autoinducer peptide (PLNC8IF), a histidine protein kinase (PLNC8HK), and a response regulator (PlnD), which is indispensable for bacteriocin production by NC8 and is thought to be involved in quorum sensing [162]. The bacteriocin synthesis of *L. plantarum* NMD-17 in co-cultivation has a close relationship with LuxS-mediated quorum sensing system [163]. Enhanced bacteriocin production in a co-culture system has also been reported in *Pediococcus pentosaceus* and *Enterococcus faecium* [164,165].

6.2. Improving Class II Bacteriocin Production by Optimizing Fermentation Conditions

Similar to other metabolites, the yield of class II bacteriocins was strongly influenced by medium compositions and fermentation factors. The optimization of fermentation conditions is a complex approach but critically essential for high-performance bacteriocin production at a commercial scale [158]. The culture medium is one of the key factors that need to be considered in the enhancement of any fermentation processes. The properties of the growth media including amino acid composition, carbon/nitrogen ratio, pH and lactose levels have a great influence on the change in biomass of the culture and the corresponding change in the level of bacteriocin production. In many cases, the optimal growth medium does not reflect the optimal productivity of bacteriocins by strain producers. The production of bacteriocins by *L. lactis* Gh1 in soytone was 1.28-times higher as compared to that of organic nitrogen sources ($(NH_4)_2SO_4$) [166]. The addition of certain amino acids in the fermentation medium stimulates bacteriocin production. For instance, glycine and cystine could stimulate the production of certain bacteriocins, while no stimulus effect was observed for alanine, tyrosine, and glutamic acid [167].

It was reported that some stressful environments could enhance bacteriocin production. For instance, a downward temperature shift stimulated amylovorin L471 production [168].

Nutrient stress is known to increase the bacteriocin production capability of *L. plantarum* B21 during industrial processing. Further investigation revealed that unstressed *L. plantarum* B21 cells use glucose as their primary energy source with high concentrations of metabolites involved in glycolysis and organic acid synthesis. In contrast, large numbers of metabolites involved in amino acid metabolism were upregulated in glucose-stressed cells, indicating that they were using amino acids as their main source of energy, which may favor the synthesis of bacteriocin [169]. The effects of NaCl on bacteriocin production are controversial. It has been reported that the supplementation of appropriate NaCl could enhance the growth and bacteriocin production of Lactobacillus amylovorus DCE 471 [170], while optimum bacteriocin production by *L. plantarum* 17.2b requires the absence of NaCl [168]. Other inorganic ions including KH_2PO_4, $CaCl_2$ and NH_4PO_4 also have a profound influence on bacteriocin production [171].

Given the high number of influencing factors, the application of an adequate experimental design (optimization) is the best strategy to obtain maximum information with a minimum number of experiments. Response surface methodology is a powerful tool used for building models and evaluating the effects of factors and searching for optimum conditions of factors for bacteriocin production [172]. For *Latilactobacillus curvatus* P99, RSM analysis revealed that the optimum production of bacteriocin was obtained at pH 6.22 and 30.6 °C for 17.9 h. Suganthi and Mohanasrinivasan reported a 20-fold increase in bacteriocin for *Pediococcus pentosaceus* KC692718 by using the RMS tool. The optimum conditions were soytone (1.03%), sucrose (2.4%), pH (5.5) and temperature (34.5 °C) [173].

6.3. Improving Class II Bacteriocin Production by Genetic Engineering

Besides the optimization of fermentation conditions, bacteriocin production can be increased by genetic approaches either by engineering the producer cells or using various heterologous expression systems. The entire *gak* locus including the genes involved in immunity and transport of class IId bacteriocin garvicin KS was cloned into a plasmid and transformed into native producers *Lactococcus garvieae* KS1546. The bacteriocin of the engineered KS1546 in optimized medium is about 2000-fold higher compared to that initially achieved by wild-type strain in GM17 [156]. A green fluorescent protein (*gfp*)-based promoter-trap reporter system was used to screen conditions with enhanced bacteriocin production by *Companilactobacillus crustorum* MN047 [174].

Recombinant bacteriocin production was also widely investigated by using bacteria and yeast cells as hosts. Heterologous expression of three different class II bacteriocins, sakacin P, pediocin PA-1 and piscicolin 61, was successful in *L. sake* Lb790 (pSAK20). Bacteriocin enterocin A and its immune protein Ent I from *E. faecium* T136 were cloned for co-expression under *Lc. lactis* MG1363 Usp45 protein signal peptide [175]. Arbulu et al. reported the use of synthetic genes designed from the published amino acid sequence of the mature bacteriocins SRCAM 602, OR-7, E-760, and L-1077 and with adapted codon usage for successful expression by *Pichia pastoris* [176]. The class IIb two-peptide bacteriocins plantaricin EF (composed of PlnE and PlnF) and plantaricin NC8 (composed of PLNC8α and PLNC8β) were successfully heterologously expressed in *E. coli* BL21 cells to enhance bacteriocin production yield [177]. Yu et al. constructed recombinant plasmids harboring genes encoding bacteriocin lactocinAB and expressed in *E. coli* BL21 cells with high yield [178]. The enterocin P signal peptide was used to facilitate the secretion of the munA-cvaC hybrid bacteriocin in *Lc. lactis* NZ9000. The engineered hybrid bacteriocin was produced in situ in food products to effectively control Gram-negative and Gram-positive foodborne pathogens [179].

7. Conclusions

Class II bacteriocins of LAB with broad-spectrum antibacterial activity are expected to play a major role in many fields. Bacteriocins have great potential for use as biopreservatives, antibiotic alternatives, health-promoting gut modulators, and animal growth promoters [180]. Class II bacteriocins can be directly applied as food preservatives. Moreover,

some bacteriocins, e.g., AS-48, become alternative antibiotics through the development of bacteriocin-based therapies and offer promising revenue to address the problem of antibiotic resistance.

In general, LAB strains have a system to coordinate the production of class IIa and IIb bacteriocins at an adequate stage of growth, which is called a quorum-sensing system. The regulation mechanisms of the genes encoding class IIc and IId bacteriocin biosynthesis need to be investigated further. The potential application of bacteriocin as natural food preservatives depends on the capacity of expression of bacteriocin genetic determinants by genetically modified heterologous host strains at the industrial level. At present, commercial-scale bacteriocin production is still hampered by high costs and low yield. Overcoming this task will be unimaginable without a deep understanding of the bacteriocins' genetics and biosynthesis. In the last few decades, our understanding of bacteriocins' biosynthesis and regulation has considerably increased, which provides opportunities for the development of more advanced systems for the cost-effective production of bacteriocins.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/fermentation8050217/s1: Table S1: Genome mining of class II bacteriocins of food-associated lactic acid bacterial strains.

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