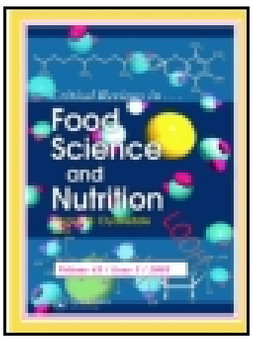

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REVIEW

Cyclic peptide production from lactic acid bacteria (LAB) and their diverse applications

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ABSTRACT

In recent years, cyclic peptides gave gained increasing attention owing to their pH tolerance, heat stability and resistance to enzymatic actions. The increasing outbreaks of antibiotic resistant pathogens and food spoilage have prompted researchers to search for new approaches to combat them. The increasing number of reports on novel cyclic peptides from lactic acid bacteria (LAB) is considered as a breakthrough due to their potential applications. Although an extensive investigation is required to understand the mechanism of action and range of applications, LAB cyclic peptides can be considered as potential substitutes for commercially available antibiotics and bio preservatives. This review summarizes the current updates of LAB cyclic peptides with emphasis on their structure, mode of action and applications. Recent trends in cyclic peptide applications are also discussed.

KEYWORDS

Antibiotics; bio preservative; cyclic peptides; lactic acid bacteria

Introduction

A peptide could be a short chain of amino acids with free amino (NH_2) and carboxyl (COOH-) termini (Nelson and Cox 2004) linked through peptide bonds. Most of the peptides are short with two or more amino acids. A polypeptide could be a single linear chain of the many amino acids (any length), held together by amide bonds. Cyclic peptides are polypeptides with both termini connected by a head-to-tail cyclic backbone. Cyclization of peptides refers to an amide bond formation between amino and carboxy termini. Cyclic peptides are resistant to the action of proteolytic enzymes and also to extreme physiological conditions like pH variation change in temperature etc (Joo et al. 2012). The rigidity of cyclic peptides decreases the entropy term of the Gibbs free energy, therefore allowing the improved binding toward target molecules, or receptor selectivity (Edman 1959; Horton, Bourne, and Smythe 2002). They are immune to both exopeptidases and endopeptidases. They have attracted attention in drug design and pharmacological applications due to their structural rigidity, receptor selectivity and biochemical stability. The natural cyclic peptides are originated from plants, animals, and microbes (Gillon et al. 2008).

Microbial cyclic peptides are produced as secondary metabolites composed of up to 50 amino acid residues among which complex molecules are acylated with fatty acids (lipopeptides) or other substitutes that differ in length and structure (Lee and Kim 2015; Henkel and Hausmann 2019). Their biosynthesis is carried out by multimodular megaenzymes nonribosomal peptide synthetases utilizing both coded and non-proteinogenic amino acids. Each module incorporates a monomeric unit responsible for various traits like epimerization, N-methylation and heterocyclization (Hur, Vickery, and Burkart 2012).

Cyclic peptides from lactic acid bacteria (LAB) have been a field of interest in recent days due to their diversity and the wide spectrum of antibacterial activity making them potential candidates in the food and therapeutic industries. The LAB cyclic peptides are found to be capable of combating gastrointestinal pathogenic bacteria like *Helicobacter pylori*, *Escherichia coli*, and *Salmonella* species. This paper focuses on the various types of LAB cyclic peptides, their mode of action, structure and their possible applications.

General properties of LAB

LAB is Gram-positive and non-sporulating bacteria known for their ability to ferment carbohydrates to lactic acid. This group consists of mainly four genera: *Lactobacillus*, *Pediococcus*, *Streptococcus*, and *Leuconostoc.* Various recent studies reported the addition of new genera collectively *Aerococcus*, *Alloiococcus*, *Carnobacterium*, *Dolosigranulum*, *Enterococcus*, *Globicatella*, *Lactococcus*, *Oenococcus*, *Tetragenococcus*, *Vagococcus*, and *Weissella* (Liu et al. 2009).

LAB obtains ATP from the fermentation of sugars since they cannot synthesize cytochrome and porphyrins. They are usually anaerobic although they can grow in the presence of oxygen too (Michaela et al. 2009). They are catalase negative and have a high tolerance to low pH (Khalid 2011). They are highly used in the food and fermentation industry

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Table 1. Classification of bacteriocins. (Perez et al. 2014)

Class	Features	Examples and references
I	Lantibiotics, small (<5kDa) peptides containing lanthionine and β-methyllanthionine	Nisin Z and Q (Zendo et al. 2003), Enterocin W , Nukacin ISK-1 (Sashihara et al. 2000)
II	Small heat-stable, non-lanthionine-containing bacteriocins	
IIa	Heat stable peptides active mainly against *Listeria monocytogenes*	Enterocin NKR-5-3C , Enterocin A (Sawa et al. 2010), Munditicin , Leucocin A
IIb	Two peptide bacteriocins	Lactococcin Q , Enterocin NKR-5-3AZ , Enterocin X (Hu et al. 2010))
IIc	Circular Bacteriocins	Lactocyclicin Q (Sawa et al. 2009), Leucocyclicin Q (Masuda et al. 2011)
III	Bacteriolysins	Lystostaphin (Bastos, Coutinho, and Coelho 2010)

mainly due to their simple metabolism that prompted their use as cell factories for the production of various food products.

LAB has high applications in the food industry. They have been commercially used in the processing of meats (sausages, hams) (Marshall 1987; Caplice and Fitzgerald 1999; Schlafmann et al. 2002), alcoholic beverages (beer, wine, fortified spirits) and vegetables (Saurkrauts and pickles) (Di Cagno et al. 2013). They also have high applications in the biomedical sector. They have been widely used as adjuvants (Van Overtvelt et al. 2010), immunostimulators (Karamese et al. 2016), for therapeutic drug delivery (Berlec, Ravnikar, and Štrukelj 2012; Wyszyńska et al. 2015; Wang et al. 2016) etc. Recently the various genera of LAB have been exploited for vaccine production (Mercenier, Muller-Alouf, and Grangette 2000). Prototype vaccines using LAB against anthrax (Mohamadzadeh et al. 2010) and rotavirus (Marelli et al. 2011) is under research. The strain *Streptococcus gordonii* has been utilized to develop a prototype vaccine for HIV (Ciabattini et al. 2010) and measles (Szatraj, Szczepankowska, and Chmielewska-Jeznach 2017).

Bacteriocins from LAB

Bacteriocins are proteinaceous or peptidic toxins produced by bacteria to inhibit the growth of similar or closely related bacterial strain(s) (Cotter, Ross, and Hill 2013). They are produced by several Gram positive and Gram negative microbes. Bacteriocins from LAB have gained attention recently due to their broad spectrum of application in food and health sectors.

Bacteriocins produced by LAB possess activity toward closely related Gram-positive bacteria, whereas producer cells are resistant to their bacteriocins (De vyust et al. 1994; Klaenhammer 1988; Cotter, Hill, and Ross 2005). The antibacterial spectrum frequently includes spoilage organisms and food-borne pathogens such as *Listeria monocytogenes,* and *Staphylococcus aureus*. They also contribute the competitiveness of producer cells (Vogel et al. 1993).

Classification of bacteriocins

Bacteriocins from LAB can be classified as follows (Table 1):

Lantibiotics

Lantibiotics are a class of polycyclic peptide antibiotics with a characteristic thioether amino acids lanthionine or methyllanthionine along with the unsaturated amino acids dehydroalanine, and 2-aminoisobutyric acid. Lanthionine is composed of two alanine residues crosslinked on their β-carbon atoms by a thioether (monosulfide) linkage. They are produced on the ribosome as a prepeptide which undergoes extensive post-translational modification to form the biologically active peptide (De Vos et al. 1995; Sahl, Jack, and Bierbaum 1995; Sahl and Bierbaum 1998).

The LAB lantibiotics characterized till date are listed below (Table 2):

Nisin

Nisin was the primary lantibiotic to be discovered with antibiotic properties. It was first isolated in 1933 from a strain of *Streptococcus lactic* (now *Lactococcus lactis*). Nisin is a polycyclic peptide produced by the bacterium *L. lactis* which is widely used as a food preservative.

Nisin is a lantibiotic with 34 amino acid residues including unusual amino acids lanthionine (Lan), methyllanthionine (MeLan), didehydroalanine (Dha), and didehydroaminobutyric acid (Dhb). It shares structural similarities with subtilin and epidermin.

Nisin variations arise from modifications of DNA sequences. Among the natural variants of nisin, nisins Z, Q, and F are produced by *Lactococcus* species. *L. lactis* NIZO 2218 produces a natural variant of nisin (nisin Z) encoded by nisZ gene. Nisin Z contains an asparagine at position 27 instead of histidine as in nisin A. (O'Connor et al. 2015). *L lactis* F10 produces nisin F encoded by a plasmid (De Kwaadsteniet, Ten Doeschate, and Dicks 2008). It differs from nisin A at two amino acid positions: Asparagine instead of Histidine at position 27 and valine instead of isoleucine at position 30. Nisin Q is produced by *L. lactis* 61-14 and differs from nisin A at four amino acid positions: Valine instead of alanine at position 15, Leucine instead of methionine at position 21, Asparagine instead of Histidine at position 27 and valine instead of isoleucine at position 30 (Harris, Fleming, and Klaenhammer 1992; Zendo et al. 2003). There are also few bioengineered variants of nisins

Table 2. Major lantibiotics from lactic acid bacteria.

Lantibiotic	Producing strain	References
Nisin A	*L. lactis* NIZOR5, 6F3, NCFB894, ATCC11454	Gross and Morell 1971
Nisin Z	*L. lactis* N8, NIZO22186	De Vos et al. 1993
Lacticin 481	*L. lactis* CNRZ481, ADRIA85LO30	Piard et al. 1993, van den Hooven et al. 1996
Lacticin 3147	*L. lactis* DPC3147	Ryan et al. 1999
Lactocin S	*L. sake* L45	Mørtvedt et al. 1991
Plantaricin W	*Lactiplantibacillus plantarum*	Holo et al. 2001
Plantaricin C	*Lactiplantibacillus plantarum* L441	Gonzalez et al. 1994
Plantaricin ZJ314	*Lactiplantibacillus plantarum*ZJ316	Chen et al. 2018

such as A K22T, A N20P, A M21V, A K22S, S29A, S29D, S29E, and S29G (Field et al. 2012; Field et al. 2015).

Nisin has a unique pore-forming activity against bacteria which is enhanced by lipid II molecule (Breukink et al. 1999; Wiedemann et al. 2001; Prince et al. 2016). Lipid II molecule incorporates the peptidoglycan monomer from the bacterial cytoplasm into the growing peptidoglycan network in the bacterial cell wall. Binding of nisin to lipid II prevents incorporation of the peptidoglycan monomer into growing peptidoglycan network. Nisin also binds to the carbohydrate-pyrophosphate moiety of lipid II through N-terminal binding motif. This permits the insertion of the C-terminal segment of nisin into the cell membrane. Several nisin-lipid II complexes assemble to make a stable pore with a diameter of 2 nm in the plasma membrane of target cells. This pore formation in the plasma membrane may cause an increase in membrane permeability which can lead to the dissipation of the membrane potential, an efflux of small cytoplasmic contents like amino acids, nucleotides and ions from the damaged cells (Scherer et al. 2015).

Nisin interacts with anionic components of the bacterial cell wall (techoic acid, phospholipids) through hydrophobic or electrostatic interactions to enter into the target cell (Kramer et al. 2008; Punyauppa-Path, Phumkhachorn, and Rattanachaikunsopon 2015). Another bactericidal mechanism of nisin involves segregation and loss of lipid (Hasper et al. 2006). When combined with Pep5 nisin induces autolysis of *Staphylococcal* species (Shin et al. 2016) (Figure 1).

Nisin is widely used for the preservation of milk, processed cheeses, meat and canned soups and vegetables. Nisin can also be used to complement other preservation treatments. Addition of nisin to heat pasteurization treatments in canned foods successfully counters heat resistant spores of flat-sour thermophilic bacteria. Reports also suggest that the antibacterial activity of nisin is more potent in a liquid medium (Delves-Broughton 2005).

Nisin inhibits the action of *Clostridium botulinum* spores and *Listeria monocytogenes* in cheese (Cleveland et al. 2001; Zapico et al. 1998). Addition of nisin to milk has been effective against a broad spectrum of organisms like *Staphylococccus aureus, Cronobacter* spps, *Kocuria rhizophila, Streptococcus thermophilus, Listeria innocua, Lactobacillus* and *Lactococcus* (Soares Pinto et al. 2011; Al-Nabulsi et al. 2009; Chollet et al. 2008; Kykkidou et al. 2007; Garde et al. 2004; Bhatti, Veeramachaneni, and Shelef 2004). Various literature works suggest its inhibitory activity against pathogens that spoil meat such as *Brochotrix thermosphacta, Bacillus cereus, Clostridium perfringens* and *Clostridium*

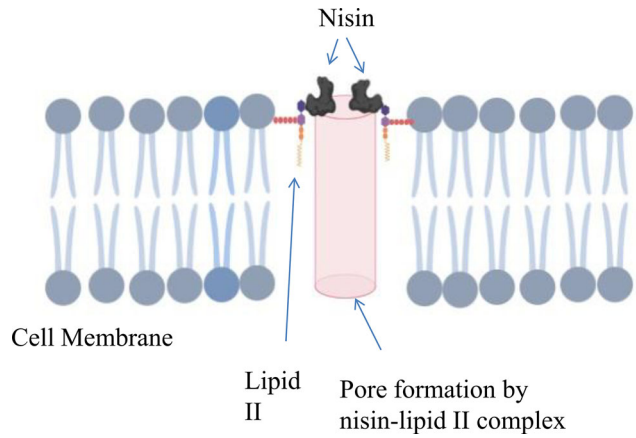

Figure 1. Mode of action of nisin.

sporogenes (Tu and Mustapha 2002; Paik et al. 2006; Wijnker et al. 2011). In fermentation industries such as breweries, addition of nisin can prevent contamination by LAB that competes with yeast for substrate. Reports also suggest that addition of nisin to fermentation mash increased the alcohol content of distillate by 10% (Delves-Broughton 2005). Antimicrobial packaging, incorporating nisin/chitosan have showed effective activity against foodborne pathogens (Guo et al. 2014; Muriel-Galet et al. 2012).

Numerous studies have been published regarding the efficacy of nisin as an antimicrobial therapeutic (Piper et al. 2009; Dosler and Gerceker 2011; Okuda et al. 2013; Singh, Prabha, and Rishi 2013; Ahire and Dicks 2015). Nisin has been reported as a potential candidate against Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *enterococci* (VRE) either by itself or in combination with conventional antibiotics, such as vancomycin or ciprofloxacin (Dosler and Gerceker 2011). Incorporation of nisin with 2,3dihydroxybenzoic acid in nanofibers inhibited the formation of MRSA biofilms (Ahire and Dicks 2015). The antimicrobial effects of nisin against mastitis, respiratory, gastrointestinal, and skin infections have also been reported. Nisin with a purity of 95% or more has been reported to have high bactericidal activity against *C. difficile* (Bartoloni et al. 2004). Nisin tableted with a pectin/HPMC mixture provides an enzymatic controlled delivery system for drug delivery (Ugurlu et al. 2007).

Tong et al. (2011) reported the inhibitory activity of nisin against Gram positive oral organisms like *Streptococcus sanguinis, Streptococcus sobrinus* and *Streptococcus Gordon*. Shin et al. (2015) demonstrated that highly purified nisin Z can inhibit the growth of Gram-negative oral colonizing pathogens, including *Porphyromonas gingivalis, Prevotella*

intermedia, Aggregatibacter actinomycetemcomitans and Treponema denticol. When worked synergically with oral gingival cells, nisin Z provided greater resistance against *C. albicans* infections (Akerey et al. 2009).

Literature works suggest the possible use of nisin as cancer therapeutic. The ability of nisin to block head and neck squamous cell carcinoma (HNSCC) tumorigenesis was reported by Joo et al. (2012). Highly purified nisin A together with doxorubicin decreased tumor severity in skin carcinogenesis in mice (Preet et al. 2015).

Pure nisin Z modulates the innate immune response in human peripheral blood mononuclear cells by inducing chemokine synthesis and suppressing LPS-induced proinflammatory responses (Kindrachuk et al. 2013).

Lacticin 481

Lacticin 481 is isolated from *L. lactis* CNRZ481 which contains dehydrobutyrine formed by dehydration of a threonine residue together with thioether-bridging residues. Dehydration of serine and a threonine to make dehydroalanine and dehydro- butyrine resulted in the formation of lanthionine and 3-methyllanthionine respectively, followed by thiol group addition of cysteine to the α, β-unsaturated residue (Chatterjee et al. 2005).

The structural gene for Lacticin 481 is *lct* gene.Lacticin 481 share a bridging pattern with mutacin II. Lacticin is synthesized on ribosome as a LctA which is a prepeptide and later modified posttranslationally into its mature form. These posttranslational modifications include dehydration of serine and threonines, along with the intramolecular addition of cysteine to the unsaturated amino acids to generate cyclic thioethers. This results in breakage of eight chemical bonds and formation of six new bends catalyzed by LctM enzyme. Maturation depends on modification enzyme (LanM) that creates unusual residues and protease/transporter LanT. The final structure of lacticin 481 has a globular C –terminal part, unbridged N-terminals with 2 lanthionine, one 3-methyllanthionine, one dehydroalanine and S-[(2)-2-aminovinyl]-D-cysteine (Chatterjee et al. 2005).

Studies show that lacticin 418 interacts with artificial lipid monolayers. It has a higher affinity for zwitterionic lipids than anionic lipids. It has few positively charged residues (K and/R) at the N-terminal (Demel et al. 1996). The membranes are targetted by electrostatic interaction with lipids like nukacin-ISK 1(Asaduzzaman et al. 2006) and also through binding of lipid II molecules. The mode of action in the latter might include inhibition of cell wall biosynthesis (Wiedemann et al. 2001; Wiedemann, Böttiger, Bonelli, Schneider, et al. 2006). But experimental evidence is not yet available for confirming these hypotheses (Dufour et al. 2007).

The major applications of lacticin 418 are against other LAB. This property has been utilized to accelerate the ripening of cheese by lysing starter cells resulting in intracellular enzymes like aminopeptidases (Oumer et al. 2001; Garde, Carbonell, et al. 2002; Garde, Tomillo, et al. 2002, 2006; O'Sullivan, Ross, et al. , 2003; Ávila, Garde, Gaya, et al. 2005; Ávila, Garde, Medina, et al. 2005). Incorporation of lacticin 481 to cheeses subjected with high pressure treatments was found to have a profound effect on the spoilage organisms like *Listeria monocytogenes, Staphylococcus aureus* and Gram negative *E. coli* O157: H7 (Arqués, Rodríguez, Gaya, Medina, Guamis, et al. 2005; Ávila, Rodríguez, Gaya, Medina, Guamis, et al. 2005; Rodriguez et al. 2005). High pressure increases the sensitivity of microbial cells to lacticin 481. They damage the outer membrane of *E.coli*/cause changes in membrane fluidity facilitating the entry of lacticin 481 into the cytoplasmic membrane (Rodriguez et al. 2005). It has inhibitory activity against *Clostridium tyrobutyricum, Lactobacillus lactis* and *Streptococcus thermophilus* (Dufour et al. 2007).

Transconjugant lactococcal starters that produce lacticin 481 and lacticin 3147 generated through conjugation of plasmids were reported to be effective at killing *Limosilactobacillus fermentum* and inhibiting the growth of *Listeria monocytogenes* than the single bacteriocin (O'Sullivan, Ross, et al. 2003).

Lacticin 481 is reported as a food grade selectable, marker to facilitate the introduction of advantageous traits to starter cultures for industrial food fermentation especially in large scale cheddar cheese manufacture (Mills et al. 2002).

They can create in vitro dehydrated and (Me) Lan residues using lacticin 481 synthase enzyme, LctM (Xie et al. 2004). This enzyme can modify mutated/partially deleted prelactin 481 which can pave way for engineering a novel (Me) Lan containing peptide with therapeutic abilities. Their stability can be increased further by thioether bridges. (Xie et al. 2004; Chatterjee et al. 2005; Cotter, Hill, and Ross 2005; Kluskens et al. 2005).

Lacticin 3147

It is a two component lantibiotic that acts through synergistic activity of peptides LtnA1 (30 amino acids) and Ltn A2 (29 amino acids). The lanthionine bridging pattern of Lactin 3147 A1 resembles globular type B mersacidin while A2 peptide belongs to type A lantibiotic class (Martin et al. 2004).

The antibiotic activity of Lacticin 3147 is due to the synergic interaction of LtnA1 and Ltn A2 in the nanomolar concentration range. LtnAl has been identified as the lipid II binding component. It interacts with the lipid II of the bacterial cytoplasmic membrane. But LtnA1 cannot inhibit cell wall synthesis on its own. The LtnA1-Lipid II complex recruits LtnA2 which leads to inhibition of cell wall biosynthesis and pore formation (Weidemann et al. 2006). These pores are found to be selective for small molecules like K^+ ions and inorganic phosphate leading to dissipation of membrane potential and hydrolysis of internal ATP finally resulting in the collapse of pH gradient and eventually cell death (McAuliffe et al. 1998; Wiedemann, Böttiger, Bonelli, Wiese, et al. 2006; Suda, Cotter, et al. 2012) (Figure 2).

The ability of lacticin 3147 to inhibit non starter LAB (NSLAB) has been utilized in the manufacturing of cheese. The addition of lacticin 3147 as a starter culture inhibited

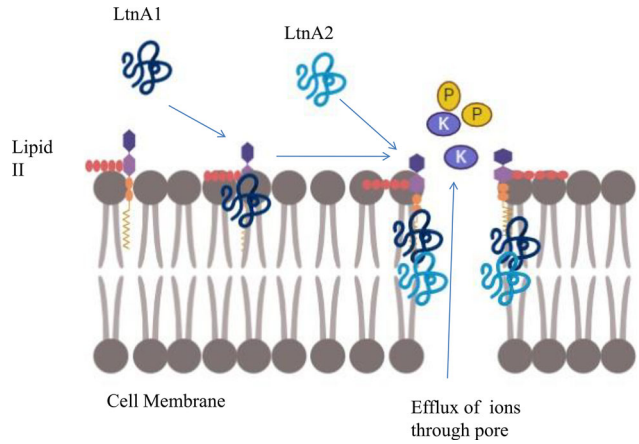

Figure 2. Mode of action of lacticin 3147.

NSLAB and improved the quality and flavor of the final product (Ryan et al. 1996). Lacticin 3147 can also lyse cells resulting in the release of intracellular enzymes from NSLAB that can accelerate the ripening of cheese (Fallico et al. 2009). Reports also suggest an improvement in flavor attributed to increased branched chain amino acid transamination due to cell permeabilisation. Cell permeabilisation permits free diffusion of amino acids into the cell and cell lysis resulting in increased accessibility of the enzymes to their substrate (Martínez-Cuesta, Requena, and Peláez 2002). There has been also reporting on improvement of cheese flavor and aroma due to increase in volatile compound 2-methylbutanal (de Palencia et al. 2004; Martínez-Cuesta, Requena, and Peláez 2006).

Lacticin 3147 has been also employed to inhibit the growth of *Listeria monocytogenes* in cottage cheese (McAuliffe, Hill, and Ross 1999). It is also used as a bio protectant to control this pathogen in smear ripened cheese (O'Sullivan et al. 2006).

Lacticin 3147 producing strains *L. lactis* DPC4275 has been used as a viable alternative to *Lactobacillus sake* and *Staphylococcus carnosus* as a starter for salami manufacture (Coffey et al. 1998). A considerable amount of reduction in *L.innocua* and *Staphylococcus aureus* was observed in sausage samples in the presence of *L.lactis* DPC4275 (Scannell et al. 2001). Incorporation of Lacticin 3147 incorporated whey powder also decreased the incidence of *Listeria monocytogenes* in cottage cheese and natural yoghurt. Soup incorporated with this powder observed 80% reduction in *Bacillus cereus* contamination (Morgan et al. 2001).

Lacticin 3147 has been often used with other antimicrobial treatments to increase the efficiency of pathogen inhibition. Treatment of milk and whey with a combination of high pressure and lacticin 3471 resulted in an increased reduction of *Staphylococcus* and *Listeria* (Morgan et al. 2000). Lacticin in combination with sodium citrate or sodium lactate is reported as an effective alternative to sodium metabisulphite for the preservation of pork sausages (Scannell et al. 2000).

Lacticin 3147 consolidated powder formulations have been successful against oral bacteria like *Streptococcus mutans* (O'Connor et al. 2006). Addition of food-grade milk based lacticin 3147 containing powder at concentrations between 1280 and 5000 AU/mL was effective in the reduction of *Clostridium difficile*, causative agent of diarrhea along with other pathogens like *Lactobacillus* sp. and *Bifidobacterium* sp (Rea et al. 2007). The antimicrobial activity of lacticin 3147 against methicillin resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis* (VRE) was also reported (Piper et al. 2009). A relative investigation of the inhibitory activity of nisin and lacticin 3147 reported that lacticin 3147 has been more dynamic against VRE than nisin. Lacticin 3147 is also a potent inhibitor against *Mycobacterium* as compared to nisin (Draper et al. 2010). Lacticin 3147 at a concentration 200 μg/ml was accounted to have spermicidal activity against horse/pony, bovine, and rat sperm. It is the only lantibiotic with a capability of immobilizing the sperm within 30 seconds (Silkin et al. 2008).

Lacticin 3147 has been reported as a potential agent for the treatment of bovine mastitis. An oil based teat seal product containing lacticin 3147 provided a physical barrier for the infection. Addition of Tween 80 prior to mixing of lacticin 3147 increased the efficacy of the treatment(Ryan et al. 1998). The approach of dipping teats coated with a mastitis causing pathogen with lacticin 3147 caused a reduction in the levels of *Staphylococcus* species by 80%, *Streptococcus dysgalactiae* by 97% and *Streptococcus uberis* by 90% (Klostermann et al. 2010).

Lactocin S

Lactocin S is a lantibiotic produced by *Lactobacillus sakei*45.It is a 37 residue amino acid out of which 50% are non-polar amino acids alanine, valine and leucine. Near the 25 residues, there are three unidentified aminoacids which are believed to be modified residues of cysteine/amino acids associated with cysteine similar to that in the lanthionine residues in nisin. It shares partial homology with pectate lyase B precursor, Bacteriorhodopsin and 6-aminohexanoate-dimer hydrolase (Mørtvedt et al. 1991). Reports conclude the presence of D_alanine at positions 7, 11 and 9. Lactocin S is the longest and only known lantibiotic of prokaryotic origin that contains D-aminoacid (Skaugen, Abildgaard, and Nes 1997). The instability of N-terminally situated 2,3,didehydro-aminoacid suggests the presence of 2-oxopropionyl group in N terminus (Skaugen et al. 1994). It also has positively charged (Lys) and two negatively charged (Glu and Asp) amino acids. The two histidine residues determine the total effective charge of the peptide (Mørtvedt et al. 1994).

Lactocin S operon (lasA-W) comprises of a 9 open reading frame (ORF) with pre-lactocin encoding gene (las A), a gene for peptide export (lasT), dehydration-thioether bridge formation (lasM) and prepeptide gene (lasP) (Skaugen, Abildgaard, and Nes 1997). A second operon lasXY upstream of the lasA-W operon is also reported to be associated in lactocin S production (Skaugen et al. 2002).

The plasma membrane is the suggested target of lactocin S due to its hydrophobicity and homology with signal

sequences (Mørtvedt et al. 1991). It has no bactericidal activity above pH 6. It has a neutral PI (7.1). The biological activity of lactocin S is due to the presence of histidine residues (Nes et al. 1994).

Lactocin S is reported to have a narrow spectrum of inhibitory activity against microbes (Rawlinson, Nes, and Skaugen 2002). They exhibit both bacteriostatic and slow bactericidal effect against target organisms (Mørtvedt et al. 1995). It has inhibitory activity against *Lactobacillus*, *Leuconostoc*, and *Pediococcus acidalactici* (Gonzalez and Kunka 1987).

Plantaricin C

Plantaricin C (Pln C) is isolated from *Lactiplantibacillus plantarum* L441 (Gonzalez et al. 1994). It is a 27 amino acid residue molecule with two distinct regions\: a linear N terminal comprising six residues out of which four are lysine and a second globular domain due to the thioether bond between residues 7 and 27. According to the reports the N-terminal section will be mobile whereas the rest of the molecule will be rigid and compact because of the 7–27 bridge and presence of the β-methyl-lanthionine bridges between residues 12–15, 13–18, and 23–26 (Turner et al. 1999).

Plantaricin C is a pore-forming bacteriocin functioning in a voltage-independent manner without the requirement of a specific target protein receptor. Reports point that plantaricin C act primarily on the permeability barrier of the cytoplasmic membrane. It interferes with the proton motive force requiring processes (like ion and metabolite accumulation, lowering of pH which reduced the glycolytic rate which in turn lowered the ATP production) by dissipating transmembrane proton motive potential. It stimulates the release of intracellular molecules like ATP, glutamate and CF.This release of ATP results in depletion of intracellular ATP pool leading to inhibition and gradual death of the bacteriocin sensitive strains. Several plantaricin molecules may combine to form a multi peptide pore complex that allows passage of hydrophilic solutes. In proteoliposomes, plantaricin C dissipates the transmembrane electrical potential, and in liposomes, it elicits efflux of entrapped carboxyfluorescein (Gonzalez et al. 1996).

The distribution of charge may be a crucial factor in the mode of action of Plantaricin C. The N-terminal has positive charge due to the presence of four lysine residues (Gonzalez et al. 1996). The first interaction of plantaricin C depends on this charge since it attracts negatively charged phospholipids. After the binding of phospholipids, the globular domain will integrate into the membrane matrix since it is uncharged. Out of the 21 residues in the globular domain, 15 are nonpolar, 2 are polar, without charge, 3 are negatively charged and one has a positive charge. This results in the insertion of hydrophobic domain of plantaricin C into the membrane, while the N terminal remains connected to the heads of phospholipids (Turner et al. 1999).

Besides pore formation, lipid II plays a major role in the antimicrobial activity of plantaricin C. The pore-forming activity of the lantibiotic involves shielding the lipid II on the cell surface. The bacteriocin was found to inhibit lipid synthesis and Fem X reaction (Addition of first Gly to the first pentapeptide side chain of lipid II) (Wiedemann, Böttiger, Bonelli, Wiese, et al. 2006).

Apart from being bactericidal plantaricin C is also reported to induce lysis in some instances. Since lysis is observed only in few bacteriocin sensitive strains, it is believed to be a secondary effect of bacteriocin. Lysis is followed by immediate cessation of macromolecule synthesis and release of uridine previously accumulated in the cytoplasm of susceptible cells (Gonzalez et al. 1994).

Plantaricin activity was lost completely when treated with pronase, trypsin, and α-chymotrypsin. Bacteriocin activity was found stable at acidic and neutral pH. At alkaline pH, the bacteriocin becomes inactivated although its activity can be restored by switching to acidic pH. It is also stable in various conditions like heating and organic acid treatment (Gonzalez et al. 1994).

Plantaricin C has antagonistic activity against various Gram positive and Gram negative microbes. It has been used against its competitors like *Leuconostoc, Pediococci, Streptococcus thermophilus, Lactobacillus* and food spoilage bacteria like *Enterococcus faecalis, Propionobacterium*and *Clostridium tryobutyricum*.The inhibition of spore outgrowth was not reported.

The lysis activity of Plantaricin C was reported, being preceded by the depolymerization of the peptidoglycan layer. Literature reports suggest that this might be due to the activation of autolysins (Bierbaum and Sahl 1985; Gálvez et al. 1990). The lytic of Pln C is observed only for certain sensitive strains like *Lactobacillus sakei* and *Limosilactobacillus fermentum.* This property could be potentially applied for accelerating the cheese ripening by facilitating the realease of cytosolic enzymes (Gonzalez et al. 1996).

The antagonistic activity of Pln C can be utilized in the treatment of bacteriemia by *leuconostoc* strains that are resistant to standard antibiotics like vancomycin and teicoplanin. Its pore forming activity can be utilized for food preservations and fermentation. The temperature stability of the bacteriocin also makes it a convenient food preservative. Its bacteriocin activity at neutral pH constitutes an advantage over the normally used food preservatives like nisin (whose maximum activity decreases with an increase in pH above 2).

Plantaricin W

Plantaricin W is a two-peptide lantibiotic isolated from *Lactiplantibacillus plantarum.* It is a two peptide bacteriocin. The two peptides are PlWα (comprising of 29 residues) and PlWβ (comprising of 32 residues). The two peptides work in a 1:1 ratio. Reports show that both these peptides are lantibiotics but Plwα has two unmodified cysteines and two serine residues while Plwβ contains one cysteine modified serine and threonine residues. Plwβ also has three α,β-unsaturated amino acid residues and three Lan/MeLan cross-links. Plwα has the same number of thioether residues, & three Lan/Melan residues but no α,β-unsaturated amino

acid residues. Plw shows sequence similarities with staphylococcin C55 and lacticin 3147. PlWα and Plwβ form 31% and 32% homology to Staphylococcin C55 and 40% and 26% homology to lacticin 3147, respectively (Holo et al. 2001). The final structural model reported by Holo et al mentions that each peptide has a central lanthionine and two overlapping thioether bridges close to their C-terminal.

Plantaricin W isolated from the fermented fish product has been reported to have an inhibition spectrum against Gram positive bacteria, and pathogenic strains like *Bacillus*, *Staphylococcus*, *Enterococcus* and *Listeria*.

Plantaricin ZJ316

Plantaricin ZJ316 is isolated from *Lactiplantibacillus plantarum*ZJ316. It is a 22 amino acid residue bacteriocin. The N terminal sequence of the peptide was S (Serine)-L (Leucine)-P (Proline)-Q(Glutamine)-N(Aspartic acid). Chen et al. have reported that no homologs identical to plantaricin ZJ316 were found in the NCBI database. Dehydroalanine and dehydrobutyrine residues are reactive enough to be part of lanthionine. They may produce unknown signals that are not vulnerable to Edman's degradation (Holtsmark et al. 2006; Kellner et al. 1988).

The exact mode of action of plantaricin ZJ316 is yet to be investigated. The genomic analysis of *Lactiplantibacillus plantarum* ZJ316 indicated that the organism has several genes that help in defence mechanisms, cell wall/membrane envelope biogenesis, outer membrane amino acid transport and metabolism. This can be a possible factor behind the adaptation of plantaricin ZJ316 within the gastrointestinal Tract of various animals (Li et al. 2016). Suo et al. (2012) reported that the culture supernatant of *Lactiplantibacillus plantarum*Z J316 was not antimicrobial against the probiotic species like *Limosilactobacillus fermentum. Lactobacillus lactis* and *Saccharomyces cerevisiae* suggesting the possibility of *Lactiplantibacillus plantarum* ZJ316 being a probiotic strain.

Plantaricin ZJ316 has a wide spectrum of activity against both Gram positive and Gram negative organisms. The Gram positive organisms sensitive to plantaricin ZJ316 include *Staphylococcus aureus, Enterococcus faecalis, Micrococcus luteus* and *Bacillus subtilis.* The Gram negative organisms sensitive to plantaricin ZJ316 include *Pseudomonas aeroginosa, Pseudomonas putida, E.coli, Acetobacter aceti, Salmonella enteric* and *Vibrio parahemolyticus.* It also shows strong antibacterial activity against *Listeria monocytogens* and *Listeria welshimeri*. Its wide antibacterial spectrum can be utilized in food preservation and also as an alternative antibiotic (Chen et al. 2018).

Although the application of plantaricin ZJ314 in other areas is yet to be investigated, few literary works suggest their potential application in fodder preparation and animal growth.

Plantaricin ZJ314 can be included in the preparation of fodder additives. Its application has two possible advantages: 1) it can prevent the contamination from contaminants like *Salmonella.* 2) It can prevent harmful pathogens within the animal intestine.

Table 3. Circular bateriocins.

Subgroup	Bacteriocin	Producer organism
I	Garvicin ML	*Lactococcus garvieae*
I	AS-48	*Enterococcus faecalis*
I	Uberolysin A	*Streptococcus uberis*
I	Carnocyclin A	*Carnobacterium maltaromaticum*
I	Amylocyclin A	*Bacillus amyloliquefaciens*
I	Leucocyclicin Q	*Leuconostoc mesenteroides*
I	Circularin A	*Clostridium beijerinckii*
I	Lactocyclicin Q	*Lactococcus sp*
II	Gassericin A/Reutericin A	*Lactobacillus gasseri/ Limosilactobacillus reuteri*
II	Butyrivibriocin A	*Butyrivibrio fibrisolvens*

The role of plantaricin ZJ314 in improving animal growth and the quality of meat is also a topic under research. Previous studies have reported that feeding of *Lactobacillus* sps and its metabolites to rats can improve their growth (Foo et al. 2003). Studies also indicate that usage of *Lactobacillus* and their metabolites can improve chicken growth (Thanh et al. 2009). Suo et al. (2012) reported that *Lactiplantibacillus plantarum* ZJ316 improved pig growth and meat quality. The mechanism was related to the metabolites of *Lactiplantibacillus plantarum* that inhibited the growth of opportunistic pathogens and increases the villus height.

As compared to other bacteriocins with similar activity, plantaricinZJ314 has few advantages. Bacteriocins like Lin33 lose their antimicrobial activity at a pH 10 but the activity of plantaricin ZJ314 remains stable at a pH range of 2.0–10.0. Bacteriocins from *Lactobacillus curvatus*P99 have antimicrobial activities against *Listeria monocytogens* but it is inactive against *Pseudomonas aeroginosa, E.coli,* and *S.entericus* (de Lima Marques et al. 2017). Bacteriocin by *Lactiplantibacillus plantarum* ST2202ch also has antilisterial activity but only in the presence of NaCl and low temperature. Bacteriocins like nisin show reduced activities in neutral and alkaline conditions (Sobrino-López and Martín-Belloso 2008) whereas plantaricin ZJ314 being thermostable is active even under acidic conditions. These properties can be advantageous on a commercial and industrial scale of applications (Chen et al. 2018)

Circular bacteriocins

Circular bacteriocins are peptides with antimicrobial activity that are ribosomally synthesized and characterized by their N to C terminal covalent linkage leading to a circular peptide backbone. Their leader sequence is cleaved during maturation (Martínez-Bueno et al. 1998). They are produced mainly by Gram positive bacteria especially LAB. They are known for their broad antimicrobial spectrum and thermal stability. They are hydrophobic and membrane-associated with a typical structure consisting of two α-helical segments(Kawai et al. 2009; Gabrielsen, Brede, Nes, et al. 2014). Till date, about ten circular bacteriocins have been identified. They are listed in the Table 3:

Lactocyclicin Q

Lactocyclicin Q (LycQ) is isolated from *Lactococcus* sp. strain QU12. It is a bacteriocin with 61 amino acid residues. It has a short leader peptide with two amino acid residues. This leader sequence is believed to be cleaved off during cyclization which indicated that propeptide mature to yield cyclization of N-terminal leucine to C-terminal tryptophan with dehydration by a peptide bond. Lyc Q has K-X-X-X-X-X-W sequence at C-terminal end. This is a common feature of all circular bacteriocins. LycQ consists of four α helical segment: α_1 helix (Ala^{11} to Ala^{18}), α_2 helix (Gly^{22} to Leu^{29}), α_3 helix (Ala^{41} to Ala^{48}) and α_4 helix (Ala^{57} to His^{4}). LycQ has the highest hydrophobic aminoacid ratio (78%) among the circular bacteriocins (Sawa et al. 2009).

The exact mode of action of most circular bacteriocins has not been determined. The mechanism of action was believed to be due to their ability to directly interact with bacterial cell membranes that would cause permeation resulting in ion leakage, dissipation of membrane potential, and cell death. The positive charge of bacteriocins might facilitate their interaction with the negatively charged bacterial membranes (Perez, Zendo, and Sonomoto 2018). Combining the data from various studies, it can be concluded that these bacteriocins are concentration dependent on the nonspecific activity at higher bacteriocin concentrations and specific activity at lower bacteriocin concentrations (Gabrielsen et al. 2014). LycQ is normally more active against Gram positive organisms but at higher concentrations, they are effective against Gram negative organisms (Sawa et al. 2009).

Lactocyclicin Q shows high antimicrobial activity against *Bacillus. Lactococcus lactis, Lactobacillus raffinolactics, Lactobacillus sakei, Pediococcus, Enterococcus,* and *Listeria.* Lyc Q is found to be resistant to heat and actions of proteolytic enzymes like α-chymotrypsin. This can make them a potential candidate in the food industry to prevent spoilage. It is also found to have inhibitory action against Gram positive organisms like *Weisseria ciberia, Pediococcus pentasaceus, Bacillus subtilis* etc. (Van Belkum, Martin-Visscher, and Vederas 2011).

The genus *Lactococcus* is regarded as one of the safest and most important microbes to humans. This indicates about their possible usage in the manufacturing of therapeutics. More information regarding the mechanism of action and biosynthesis of lycQ has to be elucidated to identify its possible uses in other areas (Van Belkum, Martin-Visscher, and Vederas 2011).

Leucocyclicin Q

Leucocyclicin Q was isolated from *Leuconostoc mesenteroides* TK41401. It has two amino acid leader sequences. The N and C termini of the cleavage peptide are flanked by leucine and tryptophan respectively. Cyclization was observed between L3 and W63. It possesses a KXXXXXW sequence. Leucocyclicin shows homology to the precursor of LycQ, the circular bacteriocin produced by *Lactococcus* sps (Masuda et al. 2011).

The exact mode of action of leucocyclicin Q is not discovered. Circular bacteriocins act by disrupting the membrane integrity of target cells (Van Belkum, Martin-Visscher, and Vederas 2011). Leucocyclicin Q belongs to subgroup I of circular bacteriocins. All circular bacteriocins within this group share a common mechanism of action. Few works regarding the difference in the mode of action of the widely studied bacteriocins of this group namely enterocin AS-48 (Gálvez et al. 1991) and Carnocyclin (Gong et al. 2009) have been also reported.

Leucocyclicin Q has strong antimicrobial activity against *Lactobacillus sakei* and *Bacillus coagulans* and weak activity against Gram negative bacteria. The other bacteria sensitive against leucocyclicin Q include *Pediococcus dextrinicus, Enterococcus, Streptococcus, Weissella paramesenteroides,* and *Leuconostoc.* It has no activity against *Staphylococcus aureus* (Masuda et al. 2011).

The producer strain of leucocyclicin Q has been reported to be isolated from several fermented vegetables such as Japanese pickles and sauerkraut (Ogier et al. 2008). Leucocyclicin is stable at a pH range of 3–9 ions. Reports indicated about the resistance of leucocyclicin Q to the action of various enzymes and bacterial peptidases. It was not resistant to α-chymotrypsin and pepsin and has no susceptibility to carboxypeptidase Y that digests peptides from C-terminal residues (Masuda et al. 2011).

Due to its activity against *Bacillus coagulants* which is a major contaminant in pickles, leucocyclicin Q can be used as a potential bio preservative (Masuda et al. 2011).

With more knowledge and insight into mechanism and mode of action, their uses in other fields, such as using them as scaffolds in the therapeutic drug designing, can be explored.

Garvicin

Garvicin (GarML) is isolated from *Lactococcus garvieae* DCC43. It is a 60 amino acid residue that shares 30% identity with carnocyclin A (CclA) (Martin-Visscher et al. 2008) and 28% identity with enterocin AS-48 produced by *Enterococcus faecalis* S-48 (Gálvez et al. 1986). Literature works suggest that GarML folds into a compact globular bundle with four conserved α-helices enclosing a hydrophobic core (Borrero et al. 2011). It has a cluster of amino acids like Lys^{46}, Lys^{47}, Lys^{52}, Lys^{53} and Lys^{56} residues that impart a positive charge on peptide surfaces (Martin-Visscher et al. 2009). Gene cluster contains four transcriptional units: gar A (bacteriocin precursor), garX(transmembrane protein), garBCDE (immunity protein and putative transport complex) and garFGH (putative ABC transporter) operons (Gabrielsen, Brede, Nes, et al. 2014). It is postulated that cyclization takes place between N-terminal Leu^{4} and C-terminal Ala^{13} by a peptide bond.

The highly purified form of GarML shows a higher antibacterial spectrum and broader activity due to removal of antimicrobial inhibitors, disaggregation of bacteriocin/ changes in the conformation of bacteriocin in hydrophobic solvent. Reports suggest that the mode of action of GarML

may be different from other circular bacteriocins since no activity was observed against Gram negative strains (Borrero et al. 2011).

GarML has been found to have activity against other *L. garvieae* strains. *L.garviae* is an etiological agent of Lactococcosis which is an emerging disease that affects aquaculture (Vela et al. 2000; Algöet et al. 2009; Fortina et al. 2007). Several strategies like bacteriocins, probiotics and vaccines are being developed against this hemorrhagic septicemia (Brunt, Newaj-Fyzul, and Austin 2007; Gatesoupe 2008). The activity of GarML against *L. garvieae* can be utilized in the treatment of lactococcosis. The possible usage of GarML against other pathogenic bacteria and its potential as a probiotic against other infections are yet to be explored (Borrero et al. 2011).

Gassericin A

Gassericin A (GA) is isolated from *Lactobacillus gasseri* LA39. It is a 58 amino acid residue bacteriocin with the N and C terminal linked by a covalent bond (Kawai et al. 2004). GA shows 98% identity with acidocin B and 45% identity with butyrivibriocin AR10. N-terminal begins with isoleucine followed by a sequence IYWIADQFGIHLATGTARKLLDAMASGASLGTAFAAILG-VTLPAWALAAAGALGATAA. It's highly hydrophobic with mostly α-helical structure. It has a section that exhibits hydrophilic properties after attachment to target membrane. The putative leader peptide sequence of GA has three residues and it does not have the Gly-Gly motif normally observed in class II bacteriocins (Pandey et al. 2013). Its production is encoded by 7 genes BCADITE.

GA was believed to act in the cytoplasmic membrane of target cell causing the death of the cell via efflux of potassium ions (Kawai, Ishii, et al. 2004). It does not cause efflux of ATP through the cytoplasmic membrane of susceptible strains ie it does not cause lysis/leakage of substances with a molecular weight of more than 507. They have a mode of action different from that of the other hydrophobic and low molecular weight bacteriocins (Moll, Konings, and Driessen 1999).

Gassericin A is reported to be heat stable and pH tolerant (pH 2–12). It shows high bactericidal activity against several LAB and food pathogenic *Listeria monocytogenes, Bacillus cereus* and *Staphylococcus aureus* (Toba et al. 1991). According to various literature works, GA has potential bio preservative properties. Few studies report that the growth of spoilage bacteria was inhibited by a combination of GA and glycine in commercially available custard creams (Arakawa et al. 2009). But this procedure requires 10%–25% of culture concentrate of *Lactobacillus gasseri*LA39 for inhibition. This high quantity may have undesired effects on the flavor and texture of foods. Nakamura et al. (2013) employed a cross-filtration device to use GA as a preservative. The GA concentrate so formed with glycine (0.5% w/w glycine and 5% w/w GA-containing concentrate) inhibited several microbes like *Achromobacter denitrificans, Pseudomonas fluorescens, Bacillus cereus*AK1124, *Lactococcus lactis* subs. *Lactis* AK1155. The inhibitory activity of GA is concentration dependent, since at a concentration of 2%, its effects were comparatively weak. Custard creams prepared using GA concentrates were reported to have better flavor and texture. The combinatorial usage of glycine and GA can be effective in inhibiting both Gram positive and Gram negative organisms in various foods. The GA-containing concentrate can be prepared at low cost and low heat load. Their heat stability and less effect on flavor and texture of foods, suggest their potential applications in food industry and animal hygiene.

Lactobacillus gasseri is a widely used probiotic strain. Therefore further research regarding the possible use of GA against various medical conditions like vaginosis and gastrointestinal infections have to be explored. The ability of GA to reduce cholesterol and induce γ-interferon production can be explored further, since its producer strains have several similar therapeutic applications (Baltova and Dimitrov 2014).

Reutericin 6

Reutericin 6 (R6) is produced by *Limosilactobacillus reuteri* LA6. R6 and GA were isolated within a two month interval from feces of the same human infant. They cannot be distinguished by molecular weight/primary structure (Kawai et al. 2001). The only difference found between these bacteriocins, is the presence of one (GA)/two (R6) D-alanine residues in their molecules. This L-alanine to D-alanine conversion was found to be the reason behind their different mode of action and secondary structure (Kawai, Ishii, et al. 2004). But Arakawa et al. (2010) reported that GA and R6 are chemically identical and consist of exclusively L-amino acid residues.

R6 has a mode of action similar to that of GA. They act in the cytoplasmic membrane of target cell causing the death of cell by potassium ion efflux (Kawai, Ishii, et al. 2004). This activity is influenced by substances on the surface of indicator cells which may cause the time lag in the mode of action and low efflux pattern (Kawai, Ishii, et al. 2004; Maqueda et al. 2008). At higher concentration (50 AU/mL) it shows a bacteriolytic action (Toba et al. 1991). Kabuki et al. (1997) indicated a drop in optical density of indicator strains treated with R6 and also an increase in β-galactosidase activity in the medium.

Compared to other circular bacteriocins, R6 has a narrow spectrum of inhibition. It has inhibitory activity against *Lactobacillus acidophilus* JCM2125, *Lactobacilus delbrueckii* subsp. *Lactis* JCM1248 and JCM1148. It is not effective against heterofermentative lactobacilli (Toba et al. 1991).

Limosilactobacillus reuteri was reported to have probiotic properties. It has been effective in combating various inflammatory diseases. They are also reported to have neuromodulatory capabilities. The therapeutic potential of *Limosilactobacillus reuteri* has been an area of research that has provided promising results. It has been found to be efficient in improving symptoms of systemic lupus erythematosus. *L.reuteri* also has immunomodulatory effects. The

Table 4. Cyclic Peptides and their potential applications.

Cyclic peptide	Producer organism	Potential applications	Reference
Nisin	*L. lactis*	Preservation of meat, Dairy products and Canned food	Delves-Broughton 2005
Lacticin 481	*L. lactis* CNRZ481, ADRIA85LO30	Starter culture for cheddar cheese manufacture	Mills et al. 2002
Lacticin 3147	*L. lactis* DPC3147	Prevention spoilage of cheese, sausage, milk and whey	O'Sullivan et al. 2006
Lactocin S	*L. sake* L45	Inhibition of other Lactic Acid Bacteria	Rawlinson, Nes, and Skaugen 2002
Plantaricin W	*Lactiplantibacillus plantarum*	Inhibition of food borne pathogens	Holo et al. 2001
Plantaricin C	*Lactiplantibacillus plantarum* L441	Acceleration of cheese ripening; food preseravtive	Gonzalez et al. 1996
Plantaricin ZJ314	*Lactiplantibacillus plantarum*ZJ316	Fodder preparation	Chen et al. 2018
Lactocyclicin Q	*Lactococcus sp*	Therapeutic applications	Van Belkum, Martin-Visscher, and Vederas 2011
Leucocyclicin Q	*Leuconostoc mesenteroides*	Biopreservative; therapeutic scaffolds for drug designing	Masuda et al. 2011
Reutericin A	*Limosilactobacillus reuteri*	Probiotic	Mu, Tavella, and Luo 2018
Garvicin ML	*Lactococcus garvieae*	Treatment of lactococcosis	Borrero et al. 2011
Gassericin A (GA)	*Lactobacillus gasseri* LA39	Cholesterol reduction; biopreservative	Baltova and Dimitrov 2014
Plantaricyclin A (PlcA)	*Lactiplantibacillus plantarum*N1326	Clinical applications	Borrero et al. 2018
Plantaricyclin B21AG	*Lactiplantibacillus plantarum*B21	Not yet explored	Golneshin et al. 2020

antimicrobial and immunomodulatory effects of the bacterium are often linked to their metabolite production. The effect of R6 synthesis against various gastrointestinal infections and disorders is a promising area of research (Mu, Tavella, and Luo 2018).

Plantaricyclin A

Plantaricyclin A (PlcA) is produced by *Lactiplantibacillus plantarum*N1326. PlcA has a 58 amino acid residue with 67% similarity to GA and 68% similarity to acidocin B. The cleavage site of the signal peptide from mature peptide is predicted to be between amino acids N33 and I34. It has a fully conserved asparaginyl cleavage site which is common for all subgroup II circular bacteriocin. It consists of a 7 ORF cluster downstream of PlcA encoding gene (PlcA). The gene cluster includes PlcA (Precursor), PlcD (unknown function), PlcI (Immunity), PlcT and PlcC (unknown functions) (Borrero et al. 2018).

The mode of action of PlcA has been not yet reported. Compared to the other circular bacteriocins in subgroup II, PlcA has a high isoelectric point (8.6) and net charge of +1 (Gasteiger et al. 2005). The initial speculation of PlcA may be due to their circular structure and hydrophobic interactions between the target strains.

PlcA is active against *Alicyclobacillus acidoterrestris, Lactobacillus bulgaricus*UCC, *Pediococcus onopinatus* 1011 and *Lactococcus lactis. Alicyclobacillus acidoterrestris* is a food and beverage spoilage microorganism. Previous reports indicate that bacteriocins like nisin A and enterocin AS-48 is effective against *Alicyclobacillus acidoterrestris* (Tianli, Jiangbo, and Yahong 2014). PlcA is pH tolerant (2–10) and heat stable. The narrow spectrum of activity of this bacteriocin can be quite advantageous. PlcA could be used to specifically target *Alicyclobacillus acidoterrestris* without inhibiting desirable microbes in beverages and foods. More research has to be done to explore the uses of PlcA in food and clinical applications (Borrero et al. 2018).

Plantaricyclin B21AG

Plantaricyclin B21AG is isolated from *Lactiplantibacillus plantarum*B21. Reports suggest that the N-terminal sequence of peptide started with sequence PGWAVAAAGALG and AAVILGV sequence nearer to C-terminus. Mature bacteriocin is 58 amino acid residues long showing 86% similarity to PlcA (Borrero et al. 2018), 67% similarity to pentocin KCA1 and 65% similarity with GA (Kawai et al. 1998) and acidocin B (Leer et al. 1995). The amino acid analysis showed the lack of cysteine residues (which is shared by all known circular bacteriocins) in Plantaricyclin B21AG. The absence of cysteine pairs indicates that the CN terminal litigation is responsible for the unique characteristics of Plantaricyclin B21AG. It also consists of two tryptophan and one Phenylalanine residues (Golneshin et al. 2020).The mode of action of Plantaricyclin B21AG has not been reported.

Plantaricyclin B21AG is active against foodborne pathogens *Clostridium perfringens* and *Listeria monocytogenes* and closely related *Lactobacillus* species. They could be used for food preservation. Further research is necessary to explore the range of applications of Plantaricyclin B21AG (Golneshin et al. 2020) (Table 4).

Cyclic dipeptides from LAB and their biological applications

Cyclic dipeptides or cyclodipeptides (CDPs) also known as 2, 5-diketopiperazines are the smallest cyclic peptides mainly synthesized from microbes (Prasad 1995). The nitrogen atoms of a piperazine 6-membrane ring in CDPs form amide linkages. The CDP scaffold is generated by the condensation of two α-amino acids. The nomenclature of CDPs is indicated by the three letter code for each of the two amino acids, and a prefix to designate the absolute configuration, e.g., cyclo (L-Xaa-L-Yaa). CDPs predominantly exhibit cis transfiguration (Eguchi and Kakuta 1974). According to various literature works, almost 90% of the available cyclic dipeptides are bacterial type (Giessen at al. 2014; Mishra et al. 2017).

Lactic acid bacterial strains have been reported to produce cyclic dipeptides with various biological functions.*Lactiplantibacillus plantarum* produced various cyclic dipeptides (cis-cyclo (Leu-L-Pro), cis-cyclo(L-Phe-L-

Pro) and cis-cyclo(L-Val-L-Pro)) with antiviral and anitifungal properties (Gänzle et al. 2000).

Biological applications

Due to their cyclic structure and ability to resist extreme pH and enzymatic digestion, cyclic dipeptides have a range of biomedical and industrial applications.

Cyclo (Gly-Leu) from *Lactiplantibacillus plantarum*VTTE 78,076 has been reported to have antifungal activity against plant pathogen *Fusarium avenaceum* VTT-D-80,147 (Niku-Paavola et al. 1999). Cyclo (Phe-Pro) and Cyclo (Phe-trans-4-OH-Pro) from *Lactiplantibacillus plantarum*MiLAB393 have been reported to have antifungal activities (Strom et al. 2002). *Lacticaseibacillus casei*AST8 produces cyclo (Leu-Pro) which is active against *Pencillium* species (Li et al. 2012). Cis-cyclo (L-Val-L-Pro) and cis-Cyclo (L-Phe-L-Pro) from *Lactiplantibacillus plantarum*LBP-K10 were active against plant pathogen *Ganoderma boninense.* Cyclo (L-Phe-L-Pro) exhibited inhibitory spectrum against *Candida albicans* (Kwak et al. 2014). Cyclo (L-Tyr-L-Pro) and Cyclo (L-Phe-L-Pro) from *Limosilactobacillus reuteri* were reported to inhibit staphylococcal quorum sensing system *agr* repressing expression of TSST-1 in *Staphylococcus aureus* (Liu et al. 2009). Cyclo (His-Pro) was reported to have a potential therapeutic effect in neurological and peripheral inflammatory diseases (Bellezza, Peirce, and Minelli 2014). Cis-Cyclo (L-Val-L-Pro), cis-Cyclo (L-Tyr-L-Pro), cis-Cyclo (L-Ser-L-Pro), cis-Cyclo (L-Leu-L-Pro) and cis-Cyclo (L-Phe-L-Pro) have antifungal activities (Liu 2017).

Cis-Cyclo (L-Leu-L-Pro), cis-Cyclo (L-Phe-L-Pro) and cis-Cyclo (L-Val-L-Pro) from *Lactiplantibacillus plantarum*LBP-K10 have been reported to have activity against influenza virus (H3N2) (Kwak et al. 2013). Cis –cyclo (L-Leu-L-Pro) was active against several Gram negative and Gram positive bacteria such as *Bacillus subtilis, Staphylococcus aureus, Listeria monocytogenes, Streptococcus pneumonia, Salmonella typhimurium, E.coli* and *Shigella dysentrii* (Liu 2017). Cyclo (L-Phe-L-Pro) was active against *Fusarium sporotrichoidesor* and *Aspergillus fumigates*. Reports also suggested that the combination of CDPs exhibit higher antibiotic activity against several types of pathogens compared to single CDPs.

CDPs from *Lactiplantibacillus plantarum*LBP-K10 induced breast cancer cell apoptosis. Cyclo (Phe-Pro) impaired cancer cell viability and tumor formation ability. Cyclo (His-Phe) is reported to be an active agent for oral, cavity, vaginal, intestinal tract and skin infections and also for prevention of infections like endocarditis, septicemia, kidney and lung infections (Liu 2017).

Recent trends in applications of cyclic peptides

Incorporation of cyclic peptides from LAB with probiotic potential was found to be an excellent alternative in health promotion. Probiotic bacterial cyclic peptides can interact more with sensitive organisms within the intestine (Gillor, Etzion, and Riley 2008). A reduction in diarrhea by *Salmonella* was observed when milk was supplemented with probiotic bacteriocin producing strains of LAB (Walsh et al. 2008). Plantaricin producer strains *Lactiplantibacillus plantarum* influenced expression level of cytokine IL-10 secreted by peripheral blood mononuclear cells (van Hemert et al. 2010). Genes involved in plantaricin production and secretions were also found to have immunomodulatory effects (Meijerink et al. 2010). Peptide engineering can be employed to generate more potent cyclic peptides (Rossi et al. 2008).

Incorporation of cyclic peptides in packages can be employed to prevent the reduction of antimicrobial activity of cyclic peptides (Guerra et al. 2005). Combination of nisin with polyethylene (PE), low density polyethylene (LDPE), cellophane, chitosan and soy protein/essential oils have shown a reduction in the activity of *Listeria monocytogenes, B. thermosphacta, Enterobacteriacea* etc in raw meat, sliced ham and ground beef (Ye, Neetoo, and Chen 2008; Emiroğlu et al. 2010; Kuorwel et al. 2011; La Storia et al. 2013). Incorporation of cyclic peptides to cellulose packages has also inhibited *Listeria monocyctogenes* in various meat products (Ming et al. 1997; Santiago-Silva et al. 2009). Incorporation of cyclic peptides to alginate, zein, and polyvinyl alcohol-based biodegradable films reduced the incidence of spoilage microbes (Marcos et al. 2007). A Cyclic peptide mix can also be considered, since target cells resistant to one cyclic peptide would be inactivated by others. Synergistic activity of *Lactobacillus sakei* and *Lactobacillus curvatus* was found to be effective against *Listeria monocytogenes* in beef (Dortu et al. 2008).

Bacteriocin nano-capsules obtained through nanoemulsions, nanoliposomes, nanoparticles, and nanofibers can be employed for food and medical applications. Nanoemulsion with cyclic peptides in combination with curcumin, carvacrol and cymene were effective against *Listeria monocytogenes, Salmonella typhimurium, Candida albicans* and *E.coli* (Zhang et al. 2014; Aznar et al. 2015; Ndoti-Nembe et al. 2013). Nanovesicles encapsulating nisin, pediocin, and BLISP34 were effective against *Listeria monocytogenes* (de Mello et al. 2013). Nanofibres with ethylene oxide and poly D, L-lactic acid including nisin/plantaricin was incorporated in deep wounds caused by *Staphylococcus aureus* (Dicks et al. 2011; Brand, Smith, and Dicks 2013). Significant reduction of infection by *Pseudomonas aeroginosa* was observed after the incorporation of *Lactiplantibacillus plantarum* immobilized with calcium alginate films in burn wounds in rats. Further investigation is necessary regarding the efficacy of immobilization and freeze-drying of cyclic peptides producing strains against infection in human burns (Brachkova et al. 2011).

Various cyclic peptides of LAB have been employed as delivery systems in combination with polymers. Salmaso et al. (2004) reported the inhibition of *L. Bulgarucus* using nisin encapsulated poly L-lactide nano particles. Nisin-containing nanofiber wound dressings have been successful in reducing *S. aureus* induced skin infections (Heunis, Smith, and Dicks 2013). Plantaricin 423 encapsulated in polyethylene oxide (PEO) electrospun nanofibers were reported to have inihibitory activity against *Lactobacillus sakei* and

Enterococcus faecium (Heunis, Smith, and Dicks 2013). Reports also indicated that the cellulose nanofibers prepared with the 2,2,6,6-tetramethylpiperidine-1-oxyl radical–mediated oxidation system showed viable release of plantaricin and this property can be utilized for the probiotic delivery in gastrointestinal tract (Luan et al. 2018). Gassericin encapsulated with polyvinyl alcohol electrospun nanofibers exhibit high biocompatibilty indicating its possible application in food industry (Amna et al. 2013). *L. plantarum* encapsulated in electrospun fructooligosaccharides was reported to have increased viability and hence an effective method for the development of probiotic supplements (Feng et al. 2018)

Cyclic peptides conjugated with fluorescein have been found to have positive effects for tumor-targeted imaging (Shan et al. 2012). Cyclic peptides capable of fibrin binding are employed for targeting thrombosis (Rezaeianpour et al. 2017). Recently bicyclic peptides were reported to improve cell membrane permeability compared to monocyclic peptides (Lian et al. 2014). Bicyclic peptides were also found to be effective in disrupting protein-protein interactions in oncogenic K-Ras mutant protein (Trinh et al. 2016). The potential application of cyclic peptides in imaging and diagnostics require further investigation.

Possible usage of cyclic peptides to inhibit HIV-Tat transactivating response element (TAR) RNA essential for viral replication is under development (Lalonde et al. 2011). Synthesis of cyclic peptides that can mimic proteins taking part in viral translation too is a method to increase the usage of cyclic peptides against viruses (Manna et al. 2013). Reports also indicate that the development of a cyclic peptide inhibitor can modulate pre mRNA splicing by targeting U2AF homology motifs (Jagtap et al. 2016).

Approaches like phage display, combinatorial chemistry technology, etc. can be typically used for the preparation of cyclic peptides to enhance their drug-like properties (Choi and Joo 2020). The usage of stapled peptides and bicyclic/tricyclic peptides can also represent an advantageous approach toward understanding the extensive range of cyclic peptides.

Conclusion and future perspectives

Cyclic peptides are of great research interest in recent times due to the increased search for new alternatives for commercial antibiotics. More insight is required to fully characterize the diversity of cyclic peptide, their mode of action, genetics and possible applications. Role of cyclic peptides in areas other than the food industry has to be explored. So far the efficacy of cyclic peptides in the biomedical field has been restricted mostly to probiotic strain interactions and gut health. There is still more to discover about cyclic peptides. Fortunately the growing concern of Multiple Drug Resistant pathogens and the decreasing antibiotics to combat them, has forced researchers to look for alternatives. Due to their pH tolerance, heat stable and enzyme resistant characteristics, cyclic peptides can be employed to combat MDR organisms. The cyclization mechanism of cyclic peptides could open up new ways to engineer cyclic peptides to increase their stability. There is also a necessity to search for new novel cyclic peptides with promising properties.

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