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Review Article

An Extensive Review on Production, Purification, and Bioactive Application of Different Classes of Bacteriocin

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ABSTRACT
Lactic Acid Bacteria (LAB) synthesize various metabolites during their growth phase and are Generally Recognized as-- Safe (GRAS) and Qualified Presumption of Safety (QPS). Ribosomally synthesized Antimicrobial Peptides (AMP) or Bacteriocins from the genera of Lactic Acid Bacteria and other prokaryotic genera are cationic, heat-stable, amphiphilic and the membrane permeabilizing peptides built with an excess amount of lysyl and arginyl residues. Antimicrobial compounds produced by LAB depend on the physical and biological conditions of microbial culture. Different classes of bacteriocin are produced by both Gram-positive and Gram-negative bacteria. The production of bacteriocin is influenced by various environmental factors. Bacteriocin has a wide variety of applications in various fields. The application spectrum of bacteriocins can be expanded in various domains such as food processing, biomedical, and personal care due to the increase in the number of newly discovered bacteriocins. Bacteriocins acquire a wide spectrum of antimicrobial activity with minimal level of cytotoxicity. In addition, bacteriocins were studied for their anticancer activity against different cancer cell lines. Selective binding of bacteriocins (cationic) towards cancer cells (anionic) increases the cytotoxicity of cancer cells. Bacteriocin peptides initiate necrosis by communicating with the cell surface which selectively targets and kills the cells with tumor formation and does not cause any damage to the normal healthy cells. In this review, the bacteriocins synthesized from lactic acid bacteria along with their interaction with cancer cell lines and other applications are discussed along with a few examples of other bioactive compounds produced by LAB.

INTRODUCTION
Lactic Acid Bacteria (LAB) are gram-positive, non-sporulating, facultative aerobic, cocci or rods which produce lactic acid during fermentation. LAB are most recognized for their employment as starter cultures in the production of acidophilus milk, yogurt, buttermilk, cottage cheese, hard cheeses, and soft cheeses. In addition, they are also used in the processing of meats, alcoholic beverages, and vegetables such as sausage, cured hams, wines, beer, fortified spirits, pickles, sauerkraut, etc. LAB is generally recognized as safe (GRAS) which had sought the attention of industrialists to develop new products. LAB also produces various metabolites such as bacteriocin or bactericidal proteins, organic acids, and vitamins during the fermentation process. Lactic Acid Bacteria consist of diverse genera which are grouped into

homo fermenters and hetero fermenters based on their end products formed during fermentation. Homo fermenters produce lactic acid as the major end product of fermentation from glucose whereas hetero fermenters synthesize several products from the fermentation of glucose besides lactic acid which includes carbon dioxide, acetic acid, and ethanol. Homo fermenters possess the enzyme aldolase which leads to the direct conversion of glucose into lactic acid. Hetero fermenters use an alternate pentose monophosphate pathway and convert six-carbon sugars (hexoses) to five-carbon sugars (pentoses) by the enzyme phosphoketolase, producing in the process both aldehyde and diacetyl-highly desirable aromatic and flavor-enhancing substances which are often used in industries. The genera of homo fermenters include Lactococcus*, Streptococcus, Pediococcous,* and *Lactobacillus*. On the other hand, the genera of hetero fermenters include *Betabacteria* (*Lactobacillus*) and *Leuconostoc* (Carr et al. 2002).

Bacteriocin produced by Gram-positive bacteria was classified into four groups based on the presence of monosulfide and disulfide bond (lanthionine) bonds. Bacteriocins were divided into four categories: (1) antibiotics containing unusual post-translationally modified amino acids such as dehydroalanine, dehydrobutyrine, lanthionine, or -methyl-lanthionine (lantibiotics); (2) antibiotics containing at least one disulfide bridge essential for their activity (cystibiotics); (3) antibiotics to be in active form, compounds with a single -SH residue should be in a reduced form (thiolbiotics); and (4) antibiotics without cysteine residues (Jack et al. 1995). Bacteriocins generated by gram-negative microorganisms were of particular interest.

Optimization of fermentation conditions is necessary for the commercial production of bacteriocin. The strain, medium composition (carbohydrate and nitrogen sources, cations, etc.), fermentation conditions (pH, temperature, agitation, and aeration), as well as the mode of fermentation, influence the yield per unit biomass (batch, fed-batch, and continuous fermentations) (Parente & Ricciardi 1999). Influencing variables may vary with different types of bacteriocin and strains producing bacteriocin. The effects of two key parameters for bacteriocin production include medium compositions and cultivation circumstances (Leroy et al. 2003). Bacteriocin-producing bacteria require complex nutritional requirements to develop, which not only raise manufacturing costs but also complicate bacteriocin purification (Li et al. 2002). An ideal bacteriocin production technique would be one that could be applied to large-scale purification and result in bacteriocin yields of more than 50% and purity of over 90% (Schöbitz et al. 2006). The bacteriocin produced by lactic acid bacteria can be used for various bioactive applications. Cancer is the predominant cause of death worldwide. Cancer-causing risk factors, lifestyle changes, aging, and the building of population are the common cause of cancer incidence and mortality which affect socioeconomic development (Bray et al. 2021). World Health Organization (WHO) reported that cancer is the leading cause of death in 2019 in 112 countries for the people below 70 years. The cancer incidence rate (2006-

2015) was steady in women and decreased by about 2% each year in males, although the cancer death rate (2007-2016) decreased by 1.4 percent and 1.8 percent, respectively, over the last decade of dated from 1991 to 2016, the global cancer death rate fell by a total of 27%, resulting in about 2,629,200 fewer cancer deaths than would have been expected if death rates had maintained at their high. Even though the racial difference in cancer mortality is shrinking, socioeconomic inequalities are rising with the most noteworthy discrepancies occurring in malignancies that are the most preventable. For example, between 2012 and 2016, mortality rates in the poorest regions were 2-fold higher for cervical cancer and 40% higher for male lung and liver cancers when compared to the wealthiest regions (Siegel et al. 2019). In 1940s the generation of Chemotherapy began with the initial usage of nitrogen mustard seeds and antifolate medicines. Since then, cancer medication development has evolved from a low-budget, government-supported research project to a high-stakes, multibillion-dollar enterprise. Although the targeted-therapy revolution has arrived, the concepts and limitations of chemotherapy revealed by the pioneers remain valid. Chemotherapy is widely followed treatment to inhibit the growth of tumor cells. In case of metastasis, the continuation of chemotherapy remains unclear (Chabner & Roberts 2005). Cancer cell resistance and normal cell destruction are other major upcoming problems in cancer treatment (Porta et al. 2015). There is a need for the development of new cancer therapeutics in the future. Nowadays, antimicrobial peptides (AMP) have reported anticancer activity without disturbing the normal cells (Lao et al. 2014). In addition to their broad-spectrum activity and distinct methods of action to traditional antibiotics, antimicrobial peptides (AMPs) have been investigated as potential therapeutic sources of future antibiotics. Although AMPs offer a lot of potential as new generation antibiotics, they still have several drawbacks in terms of clinical and commercial development, such as possible toxicity, protease susceptibility, and expensive peptide synthesis costs. Extensive efforts have been made to overcome those obstacles. To avoid proteolytic breakdown, for example, unique amino acids or peptide-mimetics are used, and the construction of short peptides with antibacterial activity is suggested as a cost-effective approach (Seo et al. 2012). Antimicrobial peptides (AMPs) are a critical component of innate immunity that evolved over 2.6 billion years in most living species to combat microbial assault. These tiny cationic peptides have exhibited direct antibacterial activity against a variety of bacteria, viruses, fungi, and parasites, and are multifunctional as innate immune effectors on the skin and mucosal surfaces (Gordon et al. 2005). Such AMP synthesized by Lactic Acid Bacteria is completely recognized as safe. Bacteriocins are mostly employed in the food processing industry. The application spectrum of bacteriocins can be expanded in various domains such as horticulture, biomedical, and personal care due to the increase in the number of newly discovered bacteriocins.

The review article mainly focuses on the different types of bacteriocins produced by lactic acid bacteria during fermentation, and their application to

anticancer agents that have been previously reported by the original authors. It also focuses on the various application of classes of bacteriocins. In addition, the article also discusses the other bioactive compound produced by lactic acid bacteria.

BACTERIOCIN

Bacteriocins are low molecular weight (10 KDa) antimicrobial compounds biologically synthesized from the ribosomes of Lactic Acid Bacteria during the primary phase of their growth. Lactic acid bacteria create a wide range of antagonistic factors, including metabolic end products, antibiotic-like compounds, and bacteriocins (bactericidal proteins). Bacteriocins from lactic acid bacteria have a large range of inhibitory action, inhibiting a diverse spectrum of Gram-positive microorganisms, or a narrow range of inhibitory activity, inhibiting only those strains that are closely related to the producer organism. Bacteriocins are bactericidal proteins or protein complexes that target bacteria that are usually closely related to the producer bacterium. Genetic determinants and transfer mechanisms for bacteriocin production and immunity are expected to play an important role in the development and the use of genetic technologies for lactic acid bacteria in this area (Lao et al. 2014). In comparison to peptide antimicrobials produced by eukaryotic cells which typically have 10^2-10^3-fold lower activities, most bacteriocins are extraordinarily active, demonstrating antimicrobial activity at nanomolar concentrations. Surprisingly, the producer cells are impervious to the bacteriocins that they make. The bacteriocin is produced in multiple microbial environments which are used to eliminate other unwanted microbes. Initially, the antimicrobial activity was restricted particularly to the strains of the same species but later they exhibited a broad range spectrum (both gram-positive and gram-negative bacterium). The degradation of bacteriocins by the enzyme proteases makes it safe for human utilization. Bacteriocins are cationic, heat-stable, amphiphilic, and membrane permeabilizing peptides that contain an excess amount of lysyl and arginyl residues (Chu et al. 2015). They act on the targeted cells by interacting with specific surface receptors. They do not affect the normal commensal of the environment. Bacteriocins and other products from LAB are recognized as safe and Qualified Presumption of Safety (QPS) (Carr et al. 2002).

DIFFERENT CLASSES OF BACTERIOCINS

Bacteriocins of gram-positive bacteria can be divided into four main classes which include classes: 1, 2, 3 & 4 shown in Figure 1. The classifications are made according to their differences in size or molecular weight, primary structure, genetic characters, post-translational modifications, and physicochemical characteristics (Rodr et al. 2000). All the classes show good antimicrobial activity even at low concentrations.

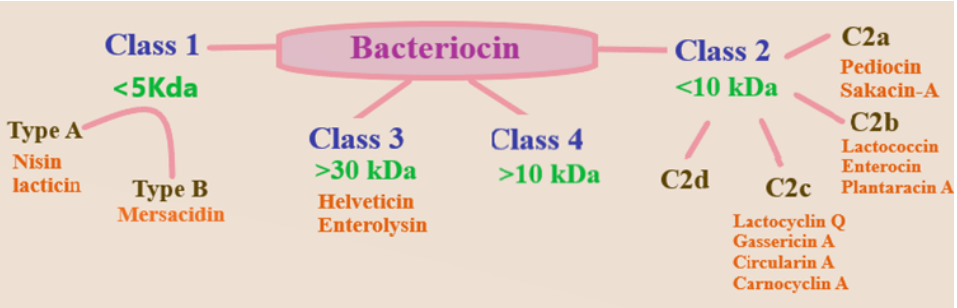

Figure 1. Represents the classification of Bacteriocins.

Class 1

The class 1 bacteriocins are a lantibiotic class of small, heat-stable peptides (<5 kDa) build with methyllanthionine, dehydroalanine, and 2 amino isobutyric acids (unsaturated amino acids). Based on the structural similarities and net charge, lantibiotics are further divided into two types. Type A is amphipathic and positively charged screw-shaped lantibiotics with a molecular mass of 2 to 4 kDa which acts through membrane depolarization and pore formation in the cytoplasmic membrane. The depolarization occurs due to the binding of N- terminal domain bacteriocin with the precursor of peptidoglycan called lipid II. C terminal region also plays an important role in pore formation and membrane destruction. Nisin and lacticin 3147 are the major representatives of this type (Rodríguez et al. 2003; Zacharof & Lovitt 2012). Type B lantibiotics are globular tertiary structures with a molecular mass of 2 to 3 kDa with no net charge or a net negative charge which interferes with cellular enzymatic reactions (Alvarez-Sieiro et al. 2016). The type B bacteriocin also inhibits peptidoglycan synthesis. Example: Mersacidin

Class 2

Non-lantibiotic class 2 bacteriocins (<10 kDa) are built with heat-stable membrane-active peptides (Shaw 2021). The transporter is required for their maturation rather than other enzymes. The non-lantibiotics do not undergo post-translational modification at the peptide chain. So, they can be determined as lanthionine or β-lanthionine (Cotter et al. 2005). They possess a helical structure which is very helpful for depolarization and cell death. Cell death or depolarization occurs by the insertion of a helical structure into the membrane of the target cell (Cleveland et al. 2001). The class 2 bacteriocins are classified into four subclasses C2a, C2b, C2c, and C2d. Subclass C2a is a monomer constructed with a consensus N-terminal sequence. They have antimicrobial activity at a higher rate (Example: pediocin and sakacin-A) (Patton & Donk 2003). Subclass C2b has two independent heterodimeric bacteriocin peptide codings for short-chain amino acids which work in collaboration to exhibit antimicrobial activity. They exhibit antimicrobial activity by forming cation or anion-specific pores (Example: Lactacin, lactococcin, Enterocin, and Plantaracin A) (Deegan et al. 2006). Subclass C2c is circular. The structure is formed by a covalent bond linking the C and N terminal regions of the peptide (Cintas et al. 2001). They have a very stable structure

with one or two cysteine residues at the leader peptide sequence. They contain two transmembrane channels that induce antimicrobial activity by forming pores in the target cells. (Example: Lactocyclin Q, gassericin A, circularin A, and carnocyclin A) (Ovchinnikov et al. 2016). The subclass C2d contains various bacteriocins that contain a single linear peptide but are not similar to pediocin. With pediocin-like Listeria active peptides such as pediocin PA1 and leucocin A as examples, Class 2a is attracting attention in food preservation. Fermented meat, fermented vegetables, dairy products, smoked salmon, and the human gastrointestinal tract have all yielded over 50 different types of class 2a bacteriocins. Plantaricin A and enterocin X are examples of Class IIb bacteriocins that require the synergistic activity of two complementary peptides to exhibit antibacterial activity. Although some of these peptides have antibacterial activity by themselves, the presence of the corresponding peptide dramatically increases this activity. The complementary peptide pair is active at nanomolar to picomolar concentrations. Class 2b bacteriocins are predominantly cationic and comprise amphiphilic and hydrophobic areas. The genes that code for the two peptides are genetically related and encoded in the same operon (Mokoena 2017).

Class 3

Bacteriocins with large-molecular weight (greater than 30 kDa) synthesize antimicrobial compounds composed of different domains with bacteriolytic activity. The enzymatic activity presented in them is linked with the antibiotic which induces lysis in the target cell. The synthesized bacteriocins can be destroyed when exposed to high temperatures (heat-labile) (Example: helveticin and enterolysin) (Ross et al. 2002). This group of bacteriocin is not well characterized.

Class 4

Bacteriocins of this class contain higher molecular weight peptides. They usually combine with carbohydrates or lipids. The antimicrobial activity is exhibited by disturbing the cell membrane of the targeted microorganism (Jeevaratnam et al. 2005).

PRODUCTION OF BACTERIOCIN FROM NOVEL SOURCES

Initiation and biosynthesis of LAB antimicrobial compounds depend on the physical and biological condition of microbial culture. The operon clusters containing plasmids are responsible for the bacteriocin-producing and immunity-building genes. They can be found on mobile genetic components including chromosomes and transposons, as well as plasmids. Initially, inactive bacteriocin peptides with N-terminal sequence are synthesized ribosomal where the modification is done into active peptides before they are exported out of the cell by a macromolecular protein compound. Serine and threonine residues dehydrate to add cysteines on unsaturated amino acids by thioether cross-links called lanthionine.

Biosynthesis of lantibiotics which belongs to class-I shown in Figure 2 starts with the formation of prebacteriocin which is then qualified by the enzymes (LanB and LanC), where2, 3 –di dehydro alanine along with 2, 3-di dehydro butyrine are yielded as the result of removal of hydroxyl amino acids, serine and threonine, catalyzed by the enzyme LanB and LanC . The mature peptide holds some desiccated amino acids without cysteine residues; whereas the intramolecular Michael addition reaction leads to the synthesis of thioether bridges by the initiation of double bond interaction between thiol groups of neighboring cysteine residues and didehydroamino acids. Serine protease (LanP) modifies the synthesized prebacteriocin and ABC-transporter (LanT) translocates the prebacteriocin which ends with the release of matured bacteriocin (Sugrue et al. 2019). The released matured bacteriocin is sighted by Histidine protein kinase (HPK) which transfers phosphoryl group (p) to response regulator (RR) through the process called autophosphorylation. Phosphorylated regulators will initiate transcription along with LanI, LanFEG, and ABC-transport proteins (immunity proteins), to protect their cells against the synthesized bacteriocin. LanI protein plays an important role in protecting the cell membranes from forming pores and also by retarding back the synthesized bacteriocin molecules (Example: nisin, epidermin, subtilin, and Pep5). Lantibiotics of class II use LanM enzyme for modification and the process is mediated by LanT (P) transporter (Example: cytolysin, lacticin 481, and mersacidin).

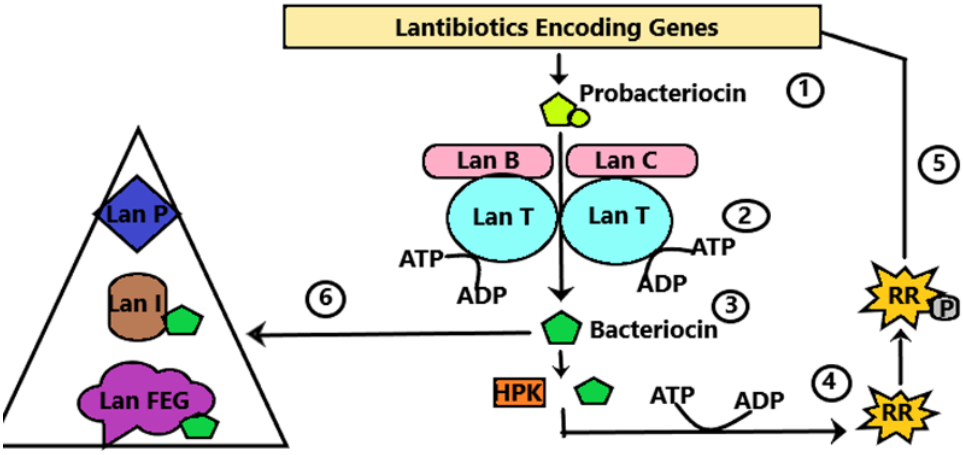

Figure 2. Schematic representation for the biosynthesis of lantibiotics (Class I Bacteriocin). (1) prebacteriocin production (2) LanB, LanC, LanT (ABC- transporter), and LanT (Processor) modifies the produced bacteriocin to release mature bacteriocin (3) Histidine protein kinase (HPK) is autophosphorylated (4) Transfer and addition of phosphoryl group (P) to subsequently response regulator (RR) (5) The transcripted (RR) response regulator activates regulated genes (6) immunity proteins are synthesized..

Unlike lantibiotics, picturized in Figure 3 the modification process is not initiated in bacteriocins of class II. The elimination of leader peptide along with synthesized prebacteriocin export is done by a transporter (ABC)

along with supplementary protein (Van Kraaij et al. 1999; Dufour et al. 2000; Rodali et al. 2013).

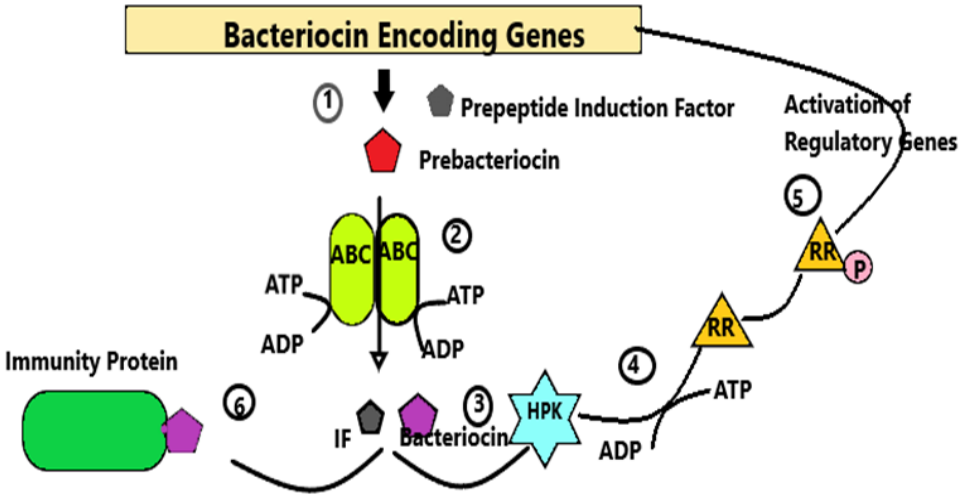

Figure 3. Diagrammatic representation for class II bacteriocins biosynthesis (1) prebacteriocin and induction factor (IF) is formed (2) prebacteriocin translocation and release of mature bacteriocin by a transporter called ABC along with processor (IF) (3) Histidine protein kinase (HPK) autophosphorylate (4) Addition of phosphoryl group (P) to RR (5) regulated genes are activated by the transcription of RR (6) Regulation of immunity producing proteins.

To attain a good quantity of bacteriocin the physical and chemical composition of the culture medium is essential for *in-vitro* production. The highest bacteriocin activity was achieved in De Man Rogosa and Sharpe Agar, LAPTg Agar, and M17 Agar (lactic *streptococci*) improved by the addition of inconsistent carbohydrates. The optimization of physiological conditions is the principal part of bacteriocin production. This review aims at experiments as examples that were conducted by the original author. A good amount of antimicrobial compound synthesized from *Lactobacillus plantarum* was obtained under different physiochemical conditions (temperature-22 to 27°C, NaCl - 2.3 to 2.5%, inoculum size- 107.3 to 107.4 CFU/ml, glucose concentration - 2%) under anaerobic incubation (Leal-Sánchez et al. 2002). Bacteriocin synthesized from *Lactobacillus acidophilus* at pH of 6.0, under the temperature of 34 °C, incorporated with 4% phenyl acetamide (Mahrous et al. 2013). (Onwuakor et al. 2014) reported that *Lactococcus lactis, L. fermentum, L. casei*, and *L. plantarum* exhibited good bacteriocin activity after adding 2 percent of sodium chloride at pH ranging from 5 to 6 when incubated at 35° C for 72 hours. The addition of cysteine and glycine into the production medium induced bacteriocin production after 20 hours of incubation at 37° C. Adding 1 % of glycerol and pyruvic acid in the production medium increased the concentration of bacteriocin. Sometimes, bacteriocins on their initiative the process of biological synthesis after the addition of bacteriocin compound in to the production medium (Yi et al. 2013).

FACTORS INFLUENCING THE PRODUCTION OF BACTERIOCINS

Production of Bacteriocins in Distinct Broths

The production of four different types of bacteriocin (AU ml-l) was determined by growing a strain from an individual genus in Tryptone Glucose Extract (TGE) broth. In another study, the impact of the addiction to broth with the increased concentration of supplements such as tryptone (1.5%), glucose (2%) and yeast extract (1·5%) or pantothenic acid, niacinamide, and biotin (each 0·5 μg ml-l) was analyzed on the production of bacteriocins. The strains used for the production of pediocin AcH (chimeric protein) were *P. acidilacti* B42-923, for nisin *L. lactis* sp. ATCC 11454, *L. carnosum* for leuconocin Lcml and *L. sake* B 706 for sakacin.A 1% level overnight culture was inoculated in both 1L GE and TGE buffer broths. The degree of pediocin AcH production differed little across *P. acidi lactici* strains, the level of nisin and leuconocin Lcm1 production varied significantly. The study results specified that for a large scale and economical production an increased producer strain must be selected.

Significant Effect of Media Composition on Bacteriocin Production

Bacteriocin Pediocin AcH was produced in high quantity by strain *P.acidilactici* B42-923 in TGE broth than in TGE buffer broth. It has been found that a buffered medium produces less pediocin AcH and that high pediocin production requires a pH of 3.6 to 3.7. It was suggested that pediocin AcH was initially produced as a secondary metabolite. Prepediocin to active pediocin AcH post-translation processing was found to be efficient at pH levels below 5.0 in recent investigations. The production of bacteriocins such as nisin, leuconocin LCM1, and sakacin A was reduced in TGE broth when compared to TGE buffer broth. This was due to the demand for an increase in pH for the production of the three bacteriocins. Different researchers have found increased nisin synthesis by *L. lactis* strains by increasing glucose or sucrose concentrations and adding acetate, citrate, phosphate, and pantothenic acid to various complex broths.

Effect of Final pH on the Production of Bacteriocin

At an initial pH of 6.8, the strain was grown in broth and the final pH of broth was varied. The production varied accordingly to the pH of different broths. The growth and the production of bacteriocin varied greatly concerning their pH. The maximum pH for the production of pediocin AcH was 3.7, and the maximum production of leuconocin Lcm1 was at pH 5, followed by nisin at pH 5.8 and pH 4.5 for sakacin A production. Because the final pH for optimum bacteriocin production varies, a producer strain should be cultivated in a broth at the pH where bacteriocin production is highest for economical production (Yang & Ray 1994).

PURIFICATION OF BACTERIOCIN

Bacteriocin biosynthesis occurs inside the fermentation medium, where crude extract contains media components. A few purification steps carried out by different authors are reviewed. Initially, the purification is carried out by the ammonium sulfate precipitation method to precipitate the proteins secreted into the culture medium (Carolissen-Mackay et al. 1997). Since this method does not allow a greater level of purification multiple chromatographic techniques such as ion exchange hydrophobic interaction method (Beaulieu et al. 2006), gel filtration technique (Martínez et al. 1998), and reversed-phase high-pressure liquid chromatography (RP-HPLC) are adopted (Abriouel et al. 2003). In addition, a simple protocol has been developed for purification which includes extraction using chloroform or methanol followed by extraction or precipitation. Finally, the RP-HPLC technique is adopted for purification (Callewaert et al. 1999). In addition, crude bacteriocins are purified by expanded bed adsorption chromatography and hydrophobic gel interaction chromatography by adjusting the pH of the crude fermentation medium by maximizing the bioavailability of bacteriocin through titer analysis (Callewaert & De Vuyst 1999). Pediocin PA-1 yielded 110% by Cation-exchange chromatography (81% yield) followed by Reverse-phase HPLC (RP-HPLC).

ANTICANCER ACTIVITY OF BACTERIOCIN

The quantity of positively charged amino acids in bacteriocins, hydrophobicity, and the ability to form amphipathic structures and oligomers may all influence their cytotoxicity and potential to harm cancer cells. Bacteriocins are thought to primarily target the cytoplasmic membrane of eukaryotic cells. Bacteriocins have been shown to kill organisms that are close to the bacterium that produces them. Because they are active against bacteria of the same or phylogenetically related species which include cancer cells, bacteriocins have a relatively narrow spectrum of activity. Induction of apoptosis and/or depolarization of the cell membrane leads to alterations in permeability, which are examples of cytotoxicity mechanisms. Some of them can produce necrosis and apoptosis in the same cell.

Studies of membrane potential show that a sensitive eukaryotic cell's surface is depolarized and its permeability increases within seconds of interacting with cytotoxic bacteriocin, resulting in cell death. Cytotoxic bacteriocin's rapid degradation may imply a non-receptor mechanism of action. Bacteriocins are advantageous as therapeutic agents since they are short peptides that are not immunogenic. Second, they are simple amino acids that are quickly hydrolyzed. Bacteriocins are advantageous as therapeutic agents since they are short peptides that are not immunogenic (Ankaiah et al. 2017).

Second, they are simple amino acids that are quickly hydrolyzed. The loss of stability in the intestines or human tissues is one of the major drawbacks of employing bacteriocins as medications. Chemically synthesizing peptides using D-amino acids which are less sensitive to proteolytic cleavage

in the stomach, has been attempted. Lactococcin G analogs were made by replacing the N- and C-terminal residues with D-amino acids which have a lower sensitivity to exopeptidases but did not affect activity. Changes in salivaricin P trypsin recognition sites resulted in a stable molecule with a minor alteration in activity. Such research is justified to improve the stability and efficiency of anticancer bacteriocins. Furthermore, functional carriers for the targeted and regulated distribution of bacteriocins can improve their in vivo stability (Soltani et al. 2021).

Different Types of Bacteriocin against Cancer Cell

The surface variations provide selective action among the cancer cells and normal cells. The inner and outer surface of normal mammalian cells is distributed with phospholipids as a bilayered phospholipid membrane. Normal cells contain sphingomyelin and phosphatidylcholine as neutral choline-containing zwitter ionic phospholipids on their outer surface whereas the interior layer contains amino phospholipids such as phosphatidyl serine and phosphatidyl ethanol amine. In the case of cancer cells, the phospholipids are loosely bound with the asymmetric structure where the cell membrane carries anionic phosphatidyl serine along with O-glycosylated mucins, gangliosides, and heparin sulfates at a greater quantity than imparts predominantly negative charge on cancer cells (Schweizer 2009; Riedl et al. 2011). Whereas the bacteriocin is structured with a cationic cell surface which gets easily attracted to anionic cell surfaces rather than neutral cell surfaces (normal cells) (Dobrzyńska et al. 2005; Hoskin & Ramamoorthy 2008). The fluidity nature of cancer cell membranes is quite high rather than normal cells for this reason the facilitation becomes easy for bacteriocins to provoke a destabilization of membranes (Sok et al. 1999). In addition, cancer cells are structured with a high number of microvilli which paves the way for easy attachment of bacteriocins rather than normal cell structures with less amount of microvilli on their cell surface (Chan et al. 1998). For the above-mentioned reasons, bacteriocin peptides start to communicate with the cell surface which selectively targets and kills the cells with tumor formation and does not cause any damage to the normal healthy cells. Interestingly, such factors may facilitate the bacteriocins that initiate the pathway of cell lysis (apoptosis) by disrupting the quality of mitochondria, particularly on their surfaces, and releasing cytochrome (Smolarczyk et al. 2010). In addition, the results also found that necrosis occurs through cell membrane damage (Maher & McClean 2006; Vaucher et al. 2010).

The mechanism behind the suppression of cancer cells such as HNSCC, SW480, LS180, HT29, Caco2, SW1088, A375, and IMR-32 by bacteriocins starts with apoptosis (Schenkel & Bakovic 2014). Apoptosis index Bax/BCL-2 is initiated after the treatment of cancer cells with bacteria. After the initiation of the apoptosis index, the cell cycle becomes eventually arrested finally it inhibits the proliferation and migration of cancer cells by bringing down the expression genes such as *cea, ceam6, and mmp2f* (Kim et al. 2006).

Bacteriocin also disturbs the cell membrane and releases LDH (Lactate Dehydrogenase) and leads to the rapid accumulation of ROS (Reactive Oxygen Species) as shown in Figure 4. As a result of such reactions cancer cells completely loses their energy by inhibiting mitochondrial responsibilities (Maher & McClean 2006; Ahmadi et al. 2017). I hereby discussed the anticancer activity of some bacteriocins synthesized from lactic acid bacterium against different types of cancer cell lines that have been previously reported by the original author which gives a perspective view of the development of bacteriocins as a cancer drug. Anticancer activity of different classes of bacteriocin is given in Table 1.

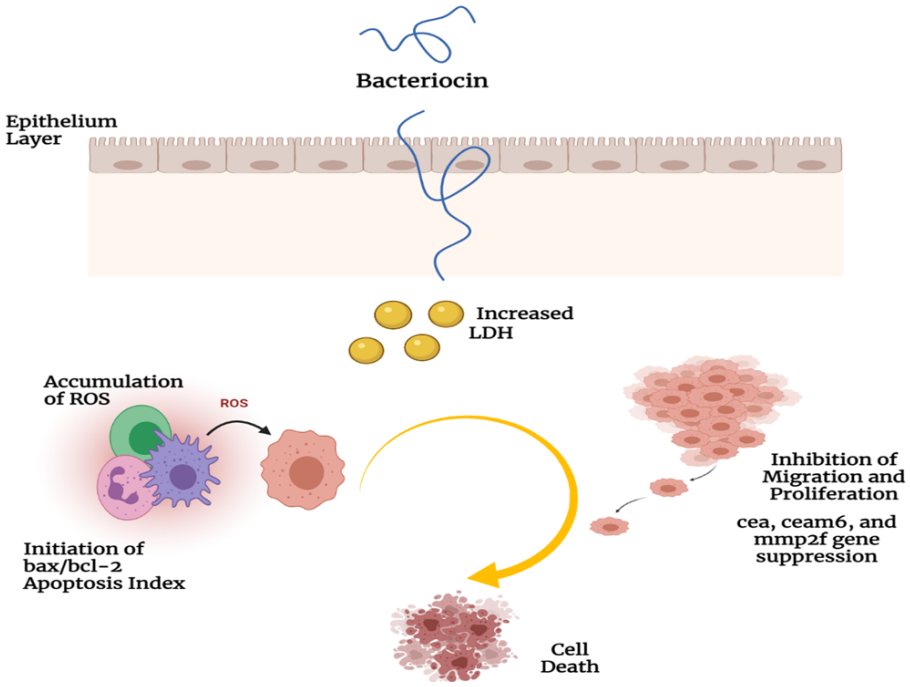

Figure 4. Pictorial representation of cell death initiation by bacteriocin**.** Bacteriocin exhibits anticancer activity by increasing the LDH, Accumulating the ROS, initiating the Apoptosis index followed by inhibiting cell proliferation and migration. The picture is created in biorender, https://biorender.com/

Nisin

Nisin is a 3.49 kDa lantibiotics bacteriocin synthesized by *Lactococcus lactis*, composed of 34 amino acids that exhibit a broad spectrum of antimicrobial activity by inhibiting gram-positive and negative bacteria. Nisin A and Nisin

Table 1. Anticancer activity of bacteriocin

S.no	Bacteriocin	Organism	size (kda)	Cancer cell line	Reference
1	Pediocin K2a2-3	*P.acidilacti* PAC1.0	3.5	DLD-1, A549	(Beaulieu et al. 2005)
2	Microcin E492	*K.pnuemoniea*	7.9	RJ2.25, HeLa, Jurkat,	(Hetz et al. 2002)
3.	Colicin E3	*E.coli*	9.8	P388, HS913T HeLa,	(Fuska et al. 1979)
4	Pediocin K2a2-3	*P.acidilacti* K2a2-3	4.6	HeLa HT2a,	(Villarante et al. 2011)
5	Nisin	*L. lactis*	3.5	HepG2, MCF7	(Paiva et al. 2011)
6	Pyosin S2	*Pseudomonas aeruginosa* 42A	74	mKS-A ,HepG2, HeLa, AS-II, TU-7	(Abdi-Ali et al. 2004)
7	Plantaricin A	*L.plantarum* C11	2.4	PC12, Jurkat, GH4, Reh,	(Zhao et al. 2006)

Z are the two variant natural polypeptides. They differ from each other in the 27th position by single amino acid. Nisin A contains histidine in the 27th position whereas Nisin Z contains asparagine in the 27th position (Norouzi et al. 2018). Nisin was accepted by FDA and WHO as a food preservative in 1988, with promising therapeutic applications (Zainodini et al. 2018). The potential anti-tumor activity of nisin Z was analyzed using different HNSCC cell lines, where oral keratinocytes served as a control. The cytotoxic activity occurred by apoptosis and cell growth arrest at the G2 phase during the cell cycle through a significant increase in calcium influx. In addition, an Affymetrix gene microarray was used to analyze the HNSCC cells treated with nisin Z on 39,000 genes which resulted in four-fold upregulation of apoptosis, regulation of cation transporter, and CHAC1. The *in vivo* study reported that injection of nisin for three weeks at the dosage of 200 mg per kilogram resulted in a significant reduction of a tumor with no evidence of fibrosis, necrosis, or inflammation. The long-term ingestion of nisin Z increased the rate of survival (Lewies et al. 2018). Nisin A and Z were analyzed for cytotoxic effects on HNSCC cells *in vitro* and *in vivo* method showed decreased proliferation in cells at different doses ranging from 100 to800 μg/ml (Kamarajan et al. 2015). Also, oral gavage of Nisin A and Z were tested for their properties along with their body weight for 3 weeks at the dosage of 800 mg/kg. The result signified a 3- and 17-fold reduction of the tumor. (Preet et al. 2015) tested the effect of nisin in combination with doxorubicin in a mice model. The individual compound analysis of nisin and doxorubicin showed mean tumor reduction after 4 weeks of treatment with volumes ranging from 14 to 51.3%. whereas 66.82 % reduction in tumor volume was reported by using nisin combined with doxorubicin due to chromatin condensation and marginalization of nuclear material when compared to the untreated group which may be due to apoptosis in tumor tissues. Nisin also exhibited a cytotoxic effect in HepG2 along with MCF-7. The inhibitory concentration of half of the cells (IC50) values for MCF-7 and HepG2 cell lines resulted at 105.46 and 112.25 μM, at the high concentration of 140 μM, both the cell lines' viabilities were less than 20%. Microscopic observations showed shrinkage in a cell, cytoplasm vacuolization along with condensation, lateralization, and cell detachment at concentrations above IC50 (Paiva et al. 2012). In another study, IC50 cytotoxicity test results were seen to be 225μM in Jurkat cell lines treated with nisin where no apoptosis was observed in the cancer cell line (Begde et al. 2011). Adenocarcinomas of the colon (HT29) and colorectum (Caco-2) human cell lines showed significant cytotoxic activity with IC50 values of 89.9μM and115μM when administered with nisin (Maher & McClean 2006). Also, evaluated the cytotoxic activity of nisin against SW480 (colon cancer cells) which resulted in anti-proliferative impact and increased apoptotic index. In addition, (Ahmadi et al. 2017) reported the intrinsic apoptotic pathway which is responsible for the cytotoxicity of nisin. A recent study also reported that nisin has an antitumor and antiproliferative effect with decreased cyclin D1 in colon cancer cell lines SW480 (Kamarajan et al. 2015).

The other recent work has been done by combining Thioridazine and Nisin as an antitumor drug against hepatocellular carcinoma cell lines (HepG2). The result indicated PI3K/AKT proliferation pathway inhibition, ROS induction, and angiogenic inhibition against hepatocellular carcinoma cell lines (HepG2). From the existing reports, Nisin has an anti-cancer activity by inducing apoptosis and arresting the cell cycle. However, the mechanism of antitumor activity remains unclear. Furthermore, potential analysis is required for the clinical application of nisin as cancer therapeutics.

Plantaricin

Plantaricin A (plnA) with 2.4kDa is a class II antimicrobial bacteriocin synthesized by *Lactobacillus plantarum* which can act as a hormone. They exhibit 3 variants that contain Plantaricin gene derived from the residues of 48 precursor genes. Plantaricin exhibited antimicrobial activity at the pH ranging 4.0–6.5 against lactic acid bacteria of closely related species by forming a hole in the cell membrane of target bacteria due to the amphiphilic nature of plnA that results in its oligomerization. In addition, different glycosylation patterns intake activities against different cell types including cancerous cells (Sand et al. 2010; Andersland et al. 2010; Sand et al. 2013). The Cytotoxicity of plantaricin at a rate of 25 μM at 20°C was determined against the human T cell leukemia (Jurkat) under in vitro conditions. It caused a 75% loss in the cell viability, whereas at 37◦C it decreased to 55%. The reason behind the loss of cell viability is apoptosis along with necrosis by fragmentation of cancer cells in cell nuclei and plasma membrane which was induced by Plantaricin with the increasing impact on intracellular concentration of caspase-3 in cancerous cells. In addition, plnA binds with negatively charged phospholipids (phosphatidylserine) by the formation of the amyloid-like fibrils which effectively concentrate on the targeted cell membrane (Zhao et al. 2006). Similar reports on plnA exposure with phosphatidylserine on the various cancer cell surface. The permeability study of Plantaricin A towards normal cell and GH4 cancerous cell lines was analyzed by whole-cell patch-clamp recordings and microfluorimetry. Interestingly, plnA was able to concentrate on all cancerous cells within a few seconds at a rate of 1 mM concentration, on the other hand, plnA was not able to permeabilize into normal cells even at the concentration of 1 Mm (Sand et al. 2007). Highlighted that membrane permeabilizing activity of plnA towards eukaryotic cell membranes is significantly due to the negative surface charge which is imparted by glycosylated membrane proteins. Plantaricin C belongs to a class of lantibiotics with 3.5 Kilo Dalton synthesized by *Lactobacillus plantarum*. The cytotoxic effects completely changed when a high concentration of plnC was used (Turner et al. 1999). In addition, plnC did not show any cytotoxic activity against HT29 and HeLa cell lines at variable concentrations (Martín et al. 2015).

Pediocin

Pediocin (class IIa bacteriocins) are small (>5 kDa), thermostable, cationic

encoded antimicrobial peptides built from 44 amino acids synthesized by the genera of *Pediococcus* (Papagianni 2003). The pediocins are assembled with the N terminal region by a conserved motif known as a "pediocin box" which forms a β-sheet structure built with conserved cysteines connected by Disulfide Bridge. The β-sheet region at a cationic site with N-terminal initiates binding whereas the hairpin-like C-terminal region initiates to enter inside the target cell surface in the hydrophobic sector leading to membrane leakage (Fimland et al. 2005). Cell lines including lung carcinoma and colorectal adenocarcinoma reported inhibition by recombinant pediocin PA-1 pideocin (*Pediococcus acidilactici* PAC1). Pediocin synthesized by *Pediococcus acidilactici* showed a cytotoxic reaction in different cell lines such as human liver carcinoma cell lines, cervical cancer cell lines, and mammalian gland adenocarcinoma cell lines.

Enterocin

Enterocin (65 kDa) is a heat-stable antimicrobial peptide synthesized by "*Enterococcus* sp." which shows activity at a wide range of pH and temperatures. Enterocin exhibits a broad spectrum of antimicrobial activity against gram-positive and gram-negative bacteria. Antimicrobial peptides act on the cytoplasmic membrane by creating pores and destroying the transmembrane channel which leads to cell damage. Antitumor activity of some enterocins has been reported by (Fimland et al. 2005) observed anticancer activity of enterocin-A by late apoptosis mechanism, cell cycle arrest at sub-G, G1 phase against HeLa, HT-29, Caco-2 cancer cell lines without showing any disturbance towards normal intestinal cell lines (INT-407). In addition (Drider et al. 2006) reported *in-vitro* anticancer activity of enterocin LNS18 against HepG2 cells at low concentrations with induction of ROS and cell cycle arrest at the G0 phase. According to the data provided, enterocin poses antitumor activity. Furthermore, therapeutic analysis can provide a solution for the findings.

Fusion Protein

The cloning of different bacteriocin peptides results in the formation of fusion proteins. The fusion protein has been developed to identify new cancer drugs. (Villarante et al. 2011), reported that the fusion of three different bacteriocins such as Enterocin A- R type Pyocin- Lactocin induced apoptosis in gastric cancer cell lines (AGS) at a concentration of 80 µg/ml. the recombinant fusion protein activates apoptosis which leads to death internally. Similar way different bacteriocins can be fused to develop promising cancer therapeutics.

OTHER APPLICATIONS OF BACTERIOCIN

Bacteriocin-a possible substitute for antibiotics

Emerging antibiotic-resistant bacteria, as well as the fact the application of broad-spectrum antibiotics would reduce the normal commensal of human

microbiota (Laxminarayan et al. 2013). Bacteriocins could be a viable alternative to antibiotics. Peptides, which are produced by various bacteria, can be bioengineered and have high potency and low toxicity. They can also be created in situ by probiotics. Bacteriocins can be broad-spectrum or narrow-spectrum. Bacteriocins work through a variety of processes that are often not the same as those used by antibiotics. Bacteriocins are divided into two types: those that target the cell membrane and those that target DNA, RNA, and protein metabolism within the cell (Lopetuso et al. 2019). Many bacteriocins have characteristics that suggest they could be useful in clinical situations. To date, however, the primary focus of their use has been on animal health rather than human health (Hanchi et al. 2018).

To fight against intestinal infections, bacteriocins can be produced in situ by the probiotic bacteria that are present in the gut. The bacteriocins namely lantibiotics and thiopeptides the class I bacteriocins act against gram-positive pathogens (Osbelt 2020). Nisin type of lantibiotics, planosporicin, Pep5, epidermin, gallidermin, mutacin B-Ny266, lacticin 3147, and actagardine (and their bioengineered derivatives) have a significant *in vitro* activity opposing pathogen that is clinically essential which include *Streptococcus pneumoniae, staphylococci* (including methicillin-resistant Staphylococcus aureus (MRSA)), *vancomycin-resistant enterococci* (VRE), various mycobacteria, *Propionibacterium acnes* and *Clostridium difficile. C. difficile*-associated diarrhea (CDAD) is an excellent illustration of this situation because the disease is frequently caused by and treated with drugs that can modify the resident gut microbiota (Van Staden 2015).

Application of bacteriocin in meat

LAB are found most commonly in meat, bacteria that produce bacteriocin are isolated and studied. Many bacteriocins that are isolated from food-related LAB are not the most effective in all food systems. But under appropriate conditions, many bacteriocins have an effective role in food applications (Deegan et al. 2006). One of the best examples and well-studied is the usage of nisin in meat systems**.** To prevent clostridial growth in meat, nitrates are used mostly. Based on safety the food industries are looking out for an alternative preservation method. Nisin or its compound along with the smaller number of nitrates can be used as a preservative to prevent the growth *of Clostridium.* Sausage is a commonly studied subject because its deterioration is often caused by lactic acid bacteria that can be found in the environment where the bacteriocins are the inhibitors (Vandenbergh 1993).

In other research, nisin is used in combination with Latic acid showed an increased effect on the growth of gram-negative bacteria. When used in a cold meat-binding system, nisin is also effective at inhibiting *Brochothrix thermosphacta.* In another investigation, pediocin AcH A-1 successfully inhibited the growth of *L. monocytogenes* in raw chicken. After 28 days of storage at 58^0C, the chickens treated with 2,400 AU/g pediocin had 2.8 log cfu/g *L.*

monocytogene but the control chickens had up to 8.1 log cfu/g (Branen & Davidson 2004).

Application in the food system

The use of bacteriocins in food systems, particularly nisin, has been examined. The bacteriocin's activity can be influenced significantly by the chemical composition and physical circumstances of the diet (Ghanbari & Jami 2013). At pH 2, for example, nisin is 228 times more soluble than at pH 8. Lactic acid bacteria are widely utilized as starter cultures in food fermentations, and researchers looked at using bacteriocin makers (Gillor et al. 2008). Inoculating Manchego cheese with a bacteriocin-producing *Ent. faecalis* strain reduced the organism's survival by 6 logs in 7 days, whereas the organism's survival in cheese prepared with a commercial starting culture was unaffected (Silva et al. 2018). Similarly, when a naturally contaminated salami sausage was inoculated with the bacteriocin producer *L. plantarum* MCS1, the amount of *L. monocytogenes* that survived was reduced (Ndlovu et al. 2013). Although the majority of commercial beginning cultures do not create bacteriocins, a few bacteriocin-producing meat starter cultures are currently available. A commercial *L. lactis* starter culture for Gouda cheese was developed using transposon-encoding nisin production and immunity (Roberts & Zottola 1993). Because *Pediococcus* sp. isn't used as cheese starting cultures, the plasmid-encoded pediocin was expressed in *Lac. lactis* to aid in the preservation of cheddar cheese and to ensure the microbiological quality of the fermentation process. According to the findings, the control cheese prepared from milk spiked with 106 CFU /ml was superior to the cheese created from milk spiked with 106 cfu /ml. After 2 weeks of ripening, *L. monocytogenes* had 107 cfu/g, but cheese prepared with the pediocin-producing strain had only 102 cfu/g. *Streptococcus thermophilus*, a key bacterium in dairy fermentations, has also been found to express pediocin PA-1 (Bagenda & Yamazaki 2007).

Another study found that *Lac. lactis* co-expressed pediocin PA-1 and nisin, two separate families of bacteriocins that have both been proved to be safe and effective (Reddy 2008). Even though the transformed cells produced only 11.8 percent of the pediocin produced by the control pediocin producer, the co-production of bacteriocins could have significant implications for food safety and reducing the chance of resistant organisms (Ahmad et al. 2017) Pediocin PA-1 has also been found to be expressed in the yeast *Saccharomyces cerevisiae* which aids in the preservation of wine, bread, and other yeast-containing foods, and the United States, it is approved as a food additive for this purpose (Van Reenen et al. 2003). Various applications of bacteriocin in food are given in Table 2.

OTHER BIOACTIVE COMPOUNDS PRODUCED BY LACTIC ACID BACTERIA

Antimicrobial compounds such as organic acid, hydrogen peroxide, CO_2, ethanol, fatty acid, Diacetyl, ethanol, reuterin, and bacteriocin are commonly

Table 2. Application of bacteriocin in food.

No	Bacteriocin	Organism	Target Pathogens	FoodProcessing	Reduction (Log Cfu G^{-1})	Reference
1	AcH Pediocin	*Lactobacillus plantarum*	*L. monocytogenes*	Cheese	1.0-2.0	(Loessner et al. 2003)
2	Enterocin	*Enterococcus faecium* *Enterococcus faecalis*	*L. monocytogenes* *S. aureus*	Milk Sausage	2.0 5.3	(Elotmani et al. 2002) (Ananou et al. 2005)
3	Nisin	*Lactococcus lactis*	*Brochothrix thermosphacta* *L. monocytogenes*	Pork Fermented milk	3.5 6.0	(Nattress et al. 2001)
4	Nisin Z	*Lactococcus lactis*	*S. aureus*	Afuega'l pitu cheese	2.0	(Rilla et al. 2004)
5	Aureocin A70	*Staphylococcus aureus A70*	*L. monocytogenes*	Skim milk	5.5	(Fagundes et al. 2016)

produced by Lactic Acid Bacteria (Ross et al. 2002). They tend to inhibit the growths of microflora as well as bacteria and pathogens causing spoilage (Jeevaratnam et al. 2005).

Organic Acid

Fermentation decreases usable carbohydrates and produces a variety of tiny molecular mass organic compounds with antibacterial activity, the most prevalent of which are lactic, acetic, and propionic acid (Pereira Da Costa & Conte-Junior 2015). The amount and kind of organic acids produced during fermentation are determined by the organisms' species, culture composition, and growth circumstances (Güzel-Seydim et al. 2000). The major metabolite of LAB is lactic acid. Many bacteria, fungi, and yeasts are poisonous to the undissociated form of lactic acid, which is present at low pH. Other organic acids generated by LAB through heterofermentative routes include acetic and propionic acids (Caplice & Fitzgerald 1999). Due to the high pKa values (lactic acid 3.08, acetic acid 4.75, and propionic acid 4.87), acetic acid and propionic acid have an effective antimicrobial activity.

Carbon dioxide

Carbon dioxide is mostly produced during hexoses heterofermentative LAB. Its antibacterial action's precise mechanism is still unknown. However, CO_2 generation creates an anaerobic environment, which inhibits enzymatic decarboxylation, and CO_2 accumulation in the membrane lipid bilayer which may result in permeability dysfunction. Many food spoilage germs, particularly Gram-negative psychotropic bacteria, can be efficiently inhibited by carbon dioxide whereas, in LAB, some yeasts exhibited significant tolerance. Various microorganisms have different levels of carbon dioxide resistance. Some food spoilage-causing bacteria are inhibited by carbon dioxide concentrations greater than 50% the inhibition of microorganisms rises linearly with increasing carbon dioxide concentration, depending on the food and microflora (Caplice & Fitzgerald 1999).

Hydrogen Peroxide (H_2O_2)

In the presence of oxygen, LAB produces hydrogen peroxide by the activity of flavoprotein oxidases or nicotinamide adenine hydroxy dinucleotide (NADH) peroxidase. The antibacterial activity of hydrogen peroxide is due to the oxidation of sulfhydryl groups which causes denaturation of several enzymes, as well as the peroxidation of membrane lipids which results in enhanced membrane permeability. It is used as a precursor for bactericidal free radical production which includes superoxide and hydroxyl radicals that damages the DNA. A study found that *Lactobacillus* and *Lactococcus* strains produced H_2O_2 which inhibited *Staphylococcus aureus*, *Pseudomonas* sp., and other psychotropic microbes in food (Caplice & Fitzgerald 1999).

Diacetyl

Some species and strains of the genera *Streptococcus, Leuconostoc, Lactobacillus*, and *Pediococcus*, as well as other microbes, generate diacetyl. Since the 1930s, diacetyl has been known to have antibacterial properties. It inhibits Gram-negative bacteria growth by interfering with arginine utilization by reacting with the arginine-binding protein. Gram-negative bacteria, yeasts, and mold are more sensitive to diacetyl than Gram-positive bacteria, and its mode of action is thought to be related to interference with arginine use by reacting with Gram-negative bacteria's arginine-binding proteins. It has a limited application as a food preservative (Caplice & Fitzgerald 1999).

Reuteri

Lb. reuteri, a heterofermentative species that live in the gastrointestinal tracts of humans and animals produce reuterin. It is formed during the *Lb. reuteri's* anaerobic growth on a mixture of glucose and glycerol or glyceraldehydes. 3-hydroxypropanal (β-hydroxypropionaldehyde), a highly soluble pH-neutral molecule in equilibrium with its hydrated monomeric and cyclic dimeric forms, has been chemically discovered.

(Olaoye & Ntuen 2011) have indicated that when natural preservative techniques are used, probiotics food may be acquired while food-borne pathogens and spoilage pollutants can be reduced. They also described how bacteriocins' inability to permeate the outer membrane of Gram-negative bacteria prevented them from acting on the bacteria. The principal dangers associated with spoilage and pathogenic bacteria found in fresh and processed aquatic foods subjected to short-term storage, as well as the biological techniques that can be employed to reduce their proliferation, were also underlined. (Parada et al. 2007) emphasized that bacteriocin has been proposed as a bio preservative agent capable of reducing the growth of some contaminating bacteria in meat and meat products. However, commercial availability is restricted and expensive. They also looked into selecting *Lactobacillus* sp. isolates with the ability to produce bacteriocins to inhibit the growth of *E. coli, Salmonella typhimurium, and Listeria monocytogenes*, as well as optimizing the bacteriocin production process. (Onwuakor et al. 2014) has demonstrated the

separation, identification, and investigation of physical and cultural aspects of the bacteriocins produced by LAB from traditional Indian fermented foods. Bacteriocin-producing *Lactobacillus lactis* strains derived from maritime environments were investigated and found to have a wide spectrum of antibacterial activity against some of the most common food-borne infections. Their research found that bacteriocin can be used as a food preservative and the *L. lactis* strain can be used as a probiotic.

Bacteriocin-like inhibitory compounds (Bt-BLIS) produced by Mexican *Bacillus thuringiensis* strains had a mild to a wide range of antibacterial activity, being harmful to clinically significant Gram-positive and Gram-negative bacteria, such as common causative agents of human diseases such as strep throat and scarlet fever, septicemia, pneumonia, urinary tract infection, and staph infections. The discovery of a bacteriocin-like inhibitory substance (BLIS) produced by a soil isolate of *Lactobacillus* animalis with a broad inhibitory spectrum against Gram-positive bacteria was the first. An antimicrobial peptide produced by a bacterium isolated from a cattle abattoir's effluent pond was extracted and characterized (Rodali et al. 2013). *Geobacillus stearothermophilus* strains isolated from oil wells in Lithuania developed four novel heat-stable bacteriocin-like compounds. The secretion of the examined bacteriocins began during initial logarithmic growth and abruptly decreased once the culture reached its stationary phase. After pretreatment with proteolytic enzymes, the bacteriocins' antibacterial activity on sensitive indicator cells vanished, demonstrating that they are proteinaceous. The biotechnology sector is interested in bacteriocins with the interaction between various spectra, especially antipathogenic activity because they could be employed as antimicrobial agents in medicine, agriculture, and food item.

CONCLUSION

LAB produce biologically active byproducts as a result of fermentation. The bacteriocins produced by LABs have gained attention due to its non-toxicity. In addition, to antimicrobial property bacteriocins also posses' anticancer activity. Nisin, plantaricin, pediocin, enterocin and fusion proteins had shown sufficient anticancer property against different cell lines. The production, purification and the factors affecting the production of bacteriocins should be considered for pharmaceutical aspects. During the fermentation process LABs also synthesize other chemical compounds such as organic acid, carbon dioxide, hydrogen peroxide and diacetyl which also contributes for the benefits of human. In this regard, the utilization of chemical compounds produced by LAB will pave the way to meet the need for natural requirements. However, much research is needed for the industrial application of bacteriocin and other compounds.

AUTHORS CONTRIBUTION

M.V. collected and analyzed the data and wrote the manuscript, T.S. designed and supervised.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding this manuscript.

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