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RESEARCH ARTICLE

BACTERIOCINS: POTENTIAL USAGES AND MECHANISM OF ACTION

Samanwita Banerjee*, Anil Kanaujia[1], Suruchi Malik[2], Surbhi Sharma[3]

*Assistant manager microbiology R&D, Ayurvet Research Foundation, village Chidana, district Sonipat, Haryana-131306; [1]Head R&D, R&D, Ayurvet Research Foundation, village Chidana, district Sonipat, Haryana-131306; [2,3]Microbiologist, Ayurvet Research Foundation, village Chidana, district Sonipat, Haryana-131306.

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ABSTRACT

Bacteriocin has established significant efficacy as a therapeutic agent. Its discovery has been a breakthrough in the combat against antibiotic resistance, which includes both multidrug-resistant and chronic bacterial infections. They are mainly bactericidal, antibiotic-like compounds produced by many bacteria that kill strains of the same or nearly related species and are differ from other (classical) antibiotics due to their restricted specificity of action and protein composition. It inhibits target organisms from proliferating by forming pores in the cell membrane, inhibiting cell wall component manufacturing, affecting autolytic enzyme activity, and preventing the development of bacterial spores. According to reports, bacteriocins are used as preservatives, probiotics, medications, plant growth promoters, oral, dental, and skin diseases, women's healthcare, and anticancer therapy in agriculture, veterinary medicine, food, and pharmaceutical industries.

INTRODUCTION

Antibiotic-resistant bacteria are becoming more ubiquitous, while the discovery of new antibiotic classes is faltering. These are both serious public health concerns. In the case of the former, long-term usage of antibiotics has caused infectious organisms to adapt to antibiotics, reducing their effectiveness. Furthermore, the transmission of antibiotic-resistant bacterial strains from person to person or from non-human sources in the environment, such as livestock or food animals treated with antibiotics similar to those used to treat human infection, has been a major factor in the spread of antibiotic resistance. Researchers are now under eager to ensure new types of medicinal compounds and techniques due to the lack of efficacy of existing antibiotics[(1,2).] Bacteriocin has established significant efficacy as a therapeutic agent. Its discovery has been a breakthrough in the combat against antibiotic resistance, which includes both multidrug-resistant and chronic bacterial infections [(3).] They are mainly bactericidal, antibiotic-like compounds produced by many bacteria that kill strains of the same or nearly related species and are differ from other (classical) antibiotics due to their restricted specificity of action and protein composition [(4).] Bacteriocins are antimicrobial peptides (AMPs), or proteins produced by bacteria. In order to compete for space and resources, microbial synthesis of a range of bacteriocins is triggered by a lack of nutrients in the environment. They are abundant, diverse, and their genes encode ribosomally produced antimicrobial peptides or proteins that kill other microbiota species [(1,2,5).] It has been observed that bacteriocin-producing cells frequently create self-immunity proteins or use efflux pumps, or both, to protect themselves from being destroyed by their own bacteriocins. The majority of these compounds are made up of non-biologically active precursor peptides with an N-terminal leader sequence. Before cleavage of the leader region and export outside the cell, these precursors may undergo post-translational modifications (PTMs) [(2,5).] Its biosynthesis genes are typically grouped and encoded on plasmids, chromosomes, and/or transposons, with the bare minimum of genetic machinery consisting of structural homologous immunity genes. These are typically made from physiologically inactive pre peptides with an N-terminal leader peptide connected to a C-terminal pro peptide. The leader peptide shows different functionality such as (i) it acts as a recognition site for the pre peptide, directing it to maturation and transport proteins, (ii) provides protection the producer strain by keeping the bacteriocin in an inactive state while inside the producer strain, and (iii) interacts with the pro peptide domain to ensure that it is in a suitable conformation for enzyme-substrate interaction of the modification machineries [(6).] In this review, we focus on the importance of bacteriocins, its classification, mode of action and potential applications as probiotics, preservatives, medicines, growth promoter in food industries, human and livestock healthcare and agriculture.

HISTORY

Bacteriocins were identified about a century ago and have been discovered to be produced by a wide range of bacteria and archaea [(1,2,4,7-10).] In the 1950s, François Jacob introduced the name "bacteriocin".

Some researchers such as Tagg (1976) and Klaenhammer (1988) used it to describe proteinaceous substances of bacterial origin that were harmful to bacteria other than the one that produced them[11]. It has a long history that began with Belgian scientist André Gratia. Gratia characterized the activity of colicin, the first known bacteriocin, in 1925 as an early consequence of a research for microorganisms with antimicrobial capabilities ([1,4,5,12]. It inhibited the growth of another E. coli strains [11]. This occurred at the same time as Alexander Fleming's 1928 description of the antibiotic penicillin, as well as Frederick Twort's 1915 and Félix d'Hérelle's 1917 observations of bacteriophage activity [1,4,5,12].
It did not receive the same amount of attention as antibiotics due to a lack of understanding of their biology, which has resulted in production challenges and inconsistent microbial growth control. For the rest of the twentieth century and into the present, chemically manufactured broad-spectrum antibiotics dominated. It has garnered a lot of interest as antibacterial chemicals in recent decades. Although it has traditionally been used as food preservatives, they are now being investigated as potential clinical antimicrobials and immune-modulating agents [12].

CLASSIFICATION OF BACTERIOCINS

Both gram positive and gram-negative bacteria produce bacteriocins. The classification differs amongst the genera. Several hundred bacteriocins have been identified to date. Its categorization is constantly evolving as new information about their structure, amino acid sequence, and acknowledged mode of action becomes available (13). Gram-positive bacteria produce a wide range of bacteriocins. Ribosomal peptides produced by gram positive bacteria are known as "bacteriocins," whereas the same produced by gram negative microorganisms are known as "colicins" and "microcins" (14). Apart from gram positive and gram-negative bacteria, Archaea is another domain of bacteria which produced bacteriocins at extreme environmental condition (13).

GRAM-POSITIVE BACTERIA'S BACTERIOCIN

In 1993, Klaenhammer classified the first bacteriocins produced by Gram-positive bacteria. These are classified according to their fundamental structures, molecular weights, post-translational modifications, and genetic features [15]. The classification evolves over time, in response to research into their structure, amino acid sequence, and known mode of action [16]. However, no universally accepted classification scheme available[15]. There were four major bacteriocin classes in the Klaenhammer categorization scheme. The Cotter approach, on the other hand, is based on only two major divisions: Class I (lantibiotics) and Class II (antibiotics) (the non-lantibiotic bacteriocins). Klaenhammer classes IIc and IV were reduced to Class IIc since they are unverified phenomena [17]. According to the universal scheme of bacteriocin classification, there are four major divisions i.e., Class I (lantibiotics), Class II (unmodified peptides), Class III (Heat-labile peptides) and Class IV (Cyclic peptides). The researchers also advised that Class IV be eliminated. As a result, researchers have recently revised the classification of gram-positive bacteria from four to three classes [5,15,18], with minor discrepancies in the descriptions of sub-classes across authors [15,18].

Class I (lantibiotics): Lantibiotics or thermostable peptides with a molecular weight less than 5 kDa are classified as Class I.
They're modified once they've been translated. Lanthionine (Lan), methyllanthionine (MeLan), dehydroalanine (Dha), dehydrobutyrine (Dhb), and D-alanine are among the unusual amino acids found in them (D-Ala). Lantibiotics were split into two groups: type A and type B lantibiotics, which have different structural and functional features. Type A lantibiotics are linear peptides with a positive charge that operate by permeabilizing the cytoplasmic membrane in sensitive cells [1,5,14,16]. The bacteriocin N-terminal domain binds to lipid II, which is a precursor of peptidoglycan, inhibiting cell wall formation. In addition, the C-terminal domain aids in the creation of holes that cause membrane potential to be violated whereas type B lantibiotics are globular molecules with a negative charge or no charge that function in a variety of ways. It's thought that type-B attaches to lipid II through an N-terminal segment, after which the C-terminal domain establishes a link with the membrane and the disulfide-containing area creates a hairpin-like shape, causing bilipid layer integrity to be compromised [13]. Nisin, generated by specific strains of *Lactococcus lactis,* is the most well-known bacteriocin of class I [1,5,14,16]. Lipolantins are a newly discovered category of lantipeptides that also have antibacterial properties. The presence of avionin residue and the N-terminal guanidino fatty acid distinguishes this family of molecules. Microvionin is an example bacteriocin produced from *Microbacterium arborescens* 5913 culture extracts that is efficacious against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae* [13].

Another bacteriocin, Thiopeptides that belongs to the Class I category. It contains a central pyridine, dihydropyridine or piperidine as well as heterocycles [19]. It possesses antibacterial, antiviral, antiparasitic, and immunosuppressive properties, among others. By attaching to the 50s ribosomal unit or elongation factors, it normally prevents protein synthesis. They are normally active in the nanomolar range, but their poor water solubility and limited bioavailability prevent them from being tested in humans [13]. Modified thiazole/oxazole-microcins-boromycins are a class of bacteriocins that resemble thiopeptides in structure. Macrocyclic amidine, decarboxylated C-terminal thiazole, and multiple unusual -methylated amino acid residues are some of their distinguishing characteristics. Botromycins also inhibit protein synthesis by interacting with bacterial 50S ribosomal subunit. Linear azole-containing peptides are also included in the modified thiazole/oxazole-microcins family (LAPs). Plantazolicin and Goadsporin are the only two drugs in this category that have been structurally identified so far and have selective antibacterial activity against closely related strains or genus [13]. Sactibiotics are a subclass of bacteriocins that include cysteine sulphur to -carbon links that are mediated by post-translational modifications. In comparison to the most widely investigated lantibiotics, they represent a minor subclass of bacteriocins. Thuricin CD, subtilosin A, thurincin H, and propionicin F are the sactibiotics that have been widely explored thus far [20]. Lasso peptides are another sub class of bacteriocin which have the lasso structure. are a class of bioactive ribosomally synthesized and post-translationally modified peptides (RiPPs), with a threaded knot structure that is formed by an isopeptide bond attaching the N-terminus of the peptide to a side chain carboxylate (21). Cyclic bacteriocins constitute a group of ribosomally synthesized antimicrobial peptides

characterized by their N-to-Cterminal covalent linkage, forming a structurally conserved circular peptide backbone. Circular bacteriocins generally exhibit broad-spectrum antimicrobial activity, including against common food-borne pathogens, such as *Clostridium and Listeria spp*. These peptides are further known for their high pH and thermal stability, as well as for resistance to many proteolytic enzymes, properties which make this group of bacteriocins highly promising for potential industrial applications and their biosynthesis of particular interest as a possible model system for the synthesis of highly stable bioactive peptides [22]

Class II non-lantibiotic bacteriocins: These are small heat-stable peptides (less than 10 kDa) with no lanthionine, a leader sequence of 14–30 amino acids, a conserved processing site, and little posttranslational modification beyond the removal of a leader peptide and the formation of a conserved N-terminal disulfide bridge. They have an amphiphilic helical shape that permits them to penetrate the target cell's membrane, causing depolarization and death.

Subclass IIa: Bacteriocins of the subclass IIa family, such pediocin PA-1 and sakacin A, are monomers with a Tyr-Gly-Asn-Gly-Val-Xaa-Cys consensus sequence at the N-terminus. Against *Listeria monocytogenes*, they're quite effective. They have substantial sequence homology (38–80 percent amino acid sequence similarity), especially in the N-terminal region of their molecules. The C-terminal region, on the other hand, is more hydrophobic and distinct [5,6,16].

Subclass IIb: These subclass IIb peptides' antibacterial activity is accomplished by a collaborative interaction between two peptides. Dipeptide bacteriocins belong to the IIb subclass. They have a single disulfide bridge and may or may not have the YGNGVXC N terminal sequence. Lactococcin G from *Lactobacillus lactis*, lactacin F from *Lactobacillus johnsonii*, and plantaricin F from *Lactobacillus plantarum* are used as examples [5,16].

Subclass IIc: Cyclic peptides, which have the N-terminal and C-terminal portions covalently connected, belong to the IIc subclass. They have a single disulfide bridge but no YGNGVXC sequence at the N-terminus. This group's model is enterocin AS-48 [16]. The IIc subclass includes circular bacteriocins such gassericin A, circularin A, and carnocyclin A. Two transmembrane regions are included in these peptides, which aid in the formation of holes in target cells [5].

Subclass IId: Bacteriocins classified in subgroups IId have structures, secretion mechanisms, and modes of action that are diverse from those classified in subgroups IIa–IIc. These bacteriocins catalyzed by thiol groups such as Lactococcin B, are included in subclass IId. Enterocins L50 (EntL50A and EntL50B), generated by *Enterooccus faecium* L50, are one example. Subclass IId is rejected by several taxonomies [16].

Class III bacteriocins: Bacteriolysins, non-lytic big bacteriocins, and tailocins are the third group of bacteriocins generated by Gram-positive bacteria. The latter are string-like and functional homologues of Gram-negative bacteria's phage tail-like bacteriocins [13]. Class III bacteriocins are large (>30 kDa) peptides. Heat-labile lytic bacteriocins and heat-labile nonlytic bacteriocins are two types of heat-labile bacteriocins. Bacteriolysins have two essential domains: the N-terminal catalytic domain and the C-terminal recognition domain, which are linked by a linker helix. The catalytic domain is a hydrolytic protease that specifically targets peptides and peptidoglycan cross-links. The substrate recognition domain serves as an anchor for the catalytic domain's migration along the peptidoglycan chain in addition to its primary function [13]. In general, lytic bacteriocins are endopeptidase peptides that enzymatically lyse the cell wall of bacteria. Apart from lytic bacteriocins, heat-labile, high-molecular-weight bacteriocins without a lytic mode of action have also been discovered, such as helveticin J from *Lactobacillus helveticus 481*, dysgalacticin from *Streptococcus dysgalactiae subsp. equisimilis W2580*, lysostaphin produced by *Staplyococcus aureus* and Streptococcin A-M57 from *Strepto dysgalacticin's* mechanism of action has been investigated [23]. Non-lytic large bacteriocins exhibit features analogous to bacteriolysins, but their activity is not premised on cell wall lysis. Non-lytic bacteriocins are reported to inhibit glucose from being absorbed and incorporated into cellular macromolecules. Carbohydrate deprivation causes the target cell to shrink in a non-lytic manner [13].

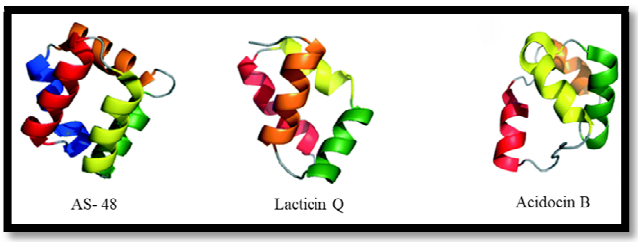

Fig. 1. Some of the gram positive bacteriocins [24]

GRAM-NEGATIVE BACTERIA'S BACTERIOCIN

Gram-negative bacteria's bacteriocins are classified into four groups: colicins, colicin-like, phage-tail-like, and microcins [13].

Colicins: Gram-negative bacteria's bacteriocins, colicins, are the most researched. Many E. coli strains produce these high-molecular-mass bactericidal proteins (30–80 kDa) when they are stressed. Because of the continuous synthesis of a lysis protein, co-expressed with the colicin, colicin production is fatal for the producing cells [13]. Colicins are divided into three domains: an amino-terminal translocation (T) domain that is involved in translocation across the outer membrane via the translocator protein; a central receptor-binding (R) domain that binds to a bacterial outer membrane receptor; and a carboxy-terminal cytotoxic (C) domain that has antibacterial activity [1]. Colicin like bacteriocin share the structural and functional features with colicin, but generated by other Gram-negative bacteria. The central R-domain is responsible for binding to the receptor, the N-terminal T-domain for translocation and bacteriocin penetration into the cell, and the C-terminal C-domain for bacteriocin cytotoxicity [13]. *Pseudomonas aeruginosa*, a Gram-negative opportunistic pathogen, produces colicin-like bacteriocins known as S-type pyocins, similar to E. coli [25]. Colicins E1, A, B, K, Ia, Ib, and N are typical pore-forming colicins; those with DNase activity are E2, E7, and E9; those with RNase activity (transfer RNA (tRNA) and 16S RNA) are D, E5, E3, E4, and E6; and colicin M blocks peptidoglycan formation [14].

Tailocins: (phage tail-like bacteriocins) are bigger protein structures (20–100 kDa) made up of eight to fourteen

polypeptide subunits that resemble bacteriophage tail modules. A cluster of genes greater than 40 kbp encodes tailocins in the genomes of bacteria. Genes producing structural proteins, assembly enzymes, chaperones, regulatory genes, and lysis cassettes, which release bacteriocins into the environment, are all found in this locus [26,27]. This sort of bacteriocin is classified into two groups: R and F. R-type tailocins are evolutionarily related to the tails of Myoviridae phages and form a long shell-encircled tube with a complicated basal plate with receptor-binding proteins at one end (RBP). F-type bacteriocins belonging to the tails of phages in the Siphoviridae family do not have a shell [13].

Microcins: It is the third class of bacteriocin generated by Gram-negative bacteria. These are peptides with a low molecular weight (less than 10 kDa) that are involved in competitive interactions between *Enterobacteriaceae* members [13]. The term "microcin" was coined after their discovery because of its small size [28]. Proteases, extreme pH, and temperature values are typically resistant to these bacteriocins. Microcin-encoding genes are found in plasmids and, less frequently, genomic DNA. They contain a diverse set of genes, but they always follow a similar pattern: open reading frames encoding a microcin precursor, secretion proteins, immunological components, and, in some cases, post-translational modification enzymes [13]. Microcins, like most bacteriocins, are active against enteropathogenic *Klebsiella*, *Shigella, Salmonella*, and *E. coli*, which are known for their ability to acquire antibiotic resistance and are considered major and urgent threats by the CDC [28]. Microcins differ from Gram-positive bacteriocins in that they have a significant structural heterogeneity among a small number of known and well-characterized examples. Researchers proposed a generally accepted classification based on peptide size and degree of posttranslational modification. Microcins are classified into two classes: class I, which has molecular masses below 5 kDa and has substantial posttranslational modification, and class II, which has molecular masses between 5 and 10 kDa and can be modified or not. Microcins are divided into two groups based on their molecular weights, disulfide bonds, and post-translational modifications. Class I microcins, including as microcin B17, C7-C51, D93, and J25, are post-translationally modified peptides with a low molecular weight (5 kDa). Class II microcins have a higher molecular weight (5–10kDa) than class I microcins. Class II microcins are further separated into two subclasses: class IIa and class IIb. To synthesis and assemble functional peptides, Class IIa microcins like microcin L, V, and N require three distinct genes. Microcins in class IIb, such as E492, M, and H47, are linear peptides with or without C-terminal post-translational modifications [1,11].

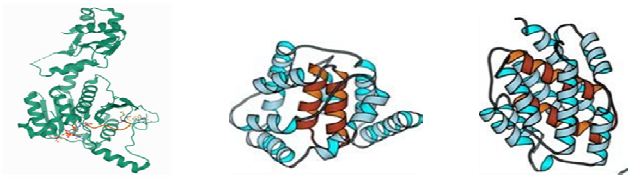

Fig 2: Some of the Gram negative bacteriocin (Dong. *Et al*, 2019; Stanyslav *et al*, 2004)

MECHANISM OF ACTION

Bacteriocins can be bactericidal or bacteriostatic in action, determining death or log phase prolongation, respectively It exhibits multiple antibacterial mechanisms based on their physicochemical characteristics and the presence or absence of post-translational modification [2].

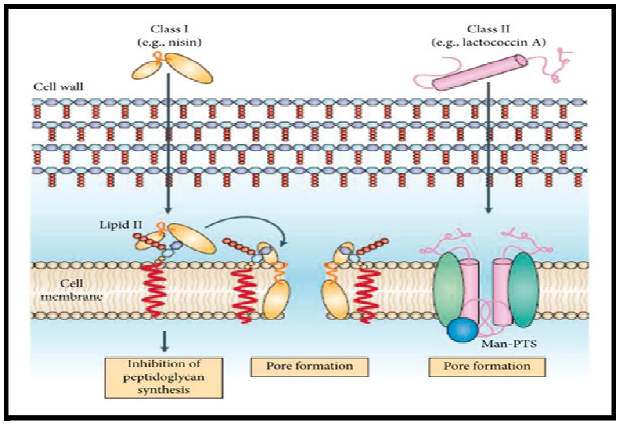

Fig. 4. Mechanism of action of bacteriocin on gram positive bacteria [31]

They have mainly four ways of antibacterial activities i.e. bactericidal activity caused by the formation of pores in the cell membrane, inhibition of cell wall component biosynthesis, effect on autolytic enzyme activity, and inhibition of bacterial spore formation [16]. Electrostatic interactions between a positively charged bacteriocin molecule and negatively charged phospholipids in the cytoplasmic membrane of a sensitive cell cause the first contact of bacteriocin with a sensitive cell. The local disruption of the ordered bilayer structure is caused by peptide entry between the double phospholipid layer. Then Bacteriocin reacts with the membranous peptide glycate precursor, lipid II, which acts as an anchoring molecule and allows lantibiotics to adhere to sensitive bacteria's cell membrane as shown in fig.4. It works by forming a temporary pore and ion channel combination in the cytoplasmic membrane of sensitive bacteria. A passive outflow of tiny molecules, including as potassium, magnesium, and phosphorus ions, amino acids, and ATP, is also evident. The proton pump's function is inhibited as a result of the disruption in membrane potential and pH gradient. DNA, RNA, protein, and polysaccharide production are all inhibited when there is a low level of ATP and an ion deficit in the cell.

The bacterial cell finally dies as a result of this [2]. Few bacteriocins use the carpet or barrel stave mechanism to permeabilize the membrane via pore creation. Individual peptides align parallel to the membrane surface and interact with no aggregation formation in the carpet model. A local and transient perforation comes from a temporary disturbance of the membrane bilayer structure. Hydrophilic portions of amphipathic a-helical peptides form pores in the cell membrane in the barrel stave model. A-helices' outer hydrophobic regions interact with fatty acid chains to produce phospholipids. Mannose Such kind of interaction has been established in LAB class IIa bacteriocins. The bacteriocins' lethal activity is due to a disturbed ionic balance and the loss of inorganic phosphates, which escape from the cells through the created pores. In addition, intracellular ATP levels plummet due to increased ATP consumption, which is essential for maintaining electric potential, and an inability to build ATP due to phosphate leakage from the cell. phosphotransferase (membrane receptors) elements have a mediating role in this binding [2]. They also have the ability to cause bacterial cell lysis, which is another mechanism of action. Bacteriocins interact with teichoic, lipoteichoic, and teichuronic acids,

which are components of the cell membrane, to cause this reaction. Autolytic enzymes associated to the acids are released and activated, resulting in cell autolysis [(2).] Bacteriocins belonging to the lantibiotics class may also disrupt cell wall production processes. They prevent the formation of peptidoglycan during the transglycosylation stage, without disrupting DNA, RNA, or protein biosynthesis. Mersacidin, a lantibiotic, inhibits peptidoglycan formation by interacting with the peptidoglycan precursor, lipid II (Fig 4). In few instances, it was observed that it works by interfering with DNA, RNA, and protein metabolism to destroy their target cells. For example, MccB17, is transported across the inner membrane by SbmA (an inner-membrane peptide transporter) and then works by interfering with DNA replication by preventing DNA gyrase-mediated supercoiling [(31)] (Fig 3). Some of them acts as transcription inhibitors. The iron siderophore receptor on the outer membrane recognizes the lasso bacteriocin MccJ25, but it requires TonB and SbmA on the inner membrane to enter the cell. MccJ25 suppresses transcription by inhibiting the secondary channel of RNA polymerase after entering the cell wheras MccC7-C51 passes through the inner layer of the E. coli cell wall via the YejABEF transporter, after which it is digested by one of the broad-specificity cytoplasmic aminopeptidases to produce modified aspartyl-adenylate. This, in turn, inhibits aspartyl-tRNA synthetase, thus blocking mRNA synthesis [(2)] (Fig 3). Bacteriocins like Nocathiacins, thiostrepton, thiazomycin, and a variety of other thiopeptides attach to the 23s rRNA of the 50S ribosomal subunit and target the bacterial ribosome whereas Bottromycins work by preventing the binding of aminoacyl-tRNA to the 50S ribosome. Some thiopeptides, like GE2270 A, bind to the bacterial chaperone elongation factor Tu (EF-Tu) and prevent protein synthesis [(2)] (fig 3).

APPLICATION OF BACTERIOCINS

Food Preservation: There has been a lot of concern in recent years regarding the prospect of using microbe-produced compounds like bacteriocins to extend the shelf life of food. The compounds offer a number of desirable qualities, including the lack of flavour, odour, or colour, as well as their ability to easily penetrate the structure of food. In contrast to chemical preservation agents, they are absolutely safe for the human body. Bacteriocin can be used to preserve food in three different methods.

- The addition of purified bacteriocins to food products; the inoculation of a food product with LAB, which will produce bacteriocin in the product itself;
- The use of an ingredient in food processing that has previously been fermented with bacteriocin-producing bacterial strains [(16).]
- Bacteriocins operate as bactericidal barriers, reducing the numbers of contaminating bacteria while biostatic measures, such as modified atmospheric packing or water reduction, prevent the remnant population from multiplying. They can also be used in conjunction with other antibacterial agents. Many Gram-positive cells are lysed by lysozyme, an animal-derived protein that is utilized in some cheeses to prevent gas generation [(32).]

Lacticin 3147 and lacticin 481 are two bacteriocins that have showed promise as natural preservatives and flavour enhancers. [(5).] Bacteriocins are gene-encoded peptides or proteins that Gram-positive or Gram-negative bacteria can utilise as natural preservatives in food. Unrecognizable bacteriocins may be digested by proteases that are sensitive to bacteriocins, resulting in the digestion of non-functional short peptides and amino acids. After consumption, bacteriocins are thus regarded to be rather safe food additives. Bacteriocins are natural food additives that have been discovered in a wide range of foods since ancient times, including cheeses, yoghurts, and Portuguese fermented pork [(1).] Nisin is an antimicrobial peptide that was first found in *Lactococcus lactis* and is employed in food technology. It's also known as Nisaplin, a commercial bacteriocin intended to prevent microbial contamination in food. Animal faeces can easily contaminate milk used in the production of numerous dairy products, such as traditional European cheeses [(1).] Enterocin AS-48, which is used to prevent microbiota contamination in cider, fruit and vegetable juices, and canned vegetables, and Enterocin CCM4231 and EJ97, which are used to prevent microbiota contamination in soya milk and zucchini purée, can be used as starter cultures or co-cultures to reduce microbiota contamination [(1).] Bacteriocins produced by lactic acid bacteria are presently the sole ones used to preserve food, and they have a number of advantages over antibiotics or other chemical food preservatives [(13).]

Pure and mixed cultures of lactic acid-producing bacteria, as well as bacteriocin prepatars like nisin, acidocin, and propionicin, are used as antibacterial agents against bacteria and pathogens that cause food spoilage, and to preserve and stabilise a variety of foods, including fermented milk products, mayonnaise spreads, cream, cheese products, meat, and vegetable compositions [(13).] Secondary cultures with bactericidal properties can also aid in the maturation of dairy products. Early lysis and release of intracellular enzymes from the beginning culture, as well as early cheese maturation, are aided by the addition of lactococcin ABM. Employing pure and concentrated bacteriocins as food supplements is preferable to using cultures that can produce bacteriocins due to the slowdown development of bacteria or the production of bacteriocins at a late stage of the life cycle [(13).] Bacterial contamination of wheat dough used in the production of various baked products creates problems in bread, including an increase in enterotoxin levels. Bacteriocins are effective against *B. subtilis, B. licheniformis, B. cereus, and B. pumilus* vegetative cells at low concentrations, but greater doses (23 u/g) are required to destroy endospores. Bacteriocin AS48 is effective against *S. aureus, B. cereus, and L. monocytogenes* when added to baking cream, soy sweets, and gelatin puddings [(13).] To prevent *Listeria* infection in hot dogs, the gelatinous form of pediocin, a bacteriocin of the IIa class, is recommended [(5,13).] Strains of *L. monocytogenes* can be found in nature as well as in ready-to-eat meat (Maria *et al*, 2020). Bacteriocins produced by lactic acid bacteria are known to inhibit or limit their growth during the preparation of meat products [(13).]Gassericin A, a food preservative derived from *Lactobacillus gasseri LA39*, has previously been found to be stable at 4 degrees Celsius for three months, 37 degrees Celsius for two months, 60 degrees Celsius for five hours, and 100 degrees Celsius for 30 minutes [(23).] Bacteriocins from *Klebsiella pneumoniae, Klebsiella ozaenae, and Klebsiella rhinoscleromatis* have been demonstrated to be active against *Klebsiella, Enterobacter, Escherichia, Shigella, Proteus, and Pseudomonas*. These bacteriocins have also been reported to be capable of protecting corn and tomato seeds from contamination with *Erwinia* [(33).] Nisin (100 and 300 IU/g) significantly reduced the number of *L. monocytogenes, S. aureus, and C. sporogenes* thermal spores in cold pack cheese

spreads [34]. In some Western European nations, natamycin (pimaricin) is allowed for cheese surface preservation and as a cheese coating additive. Fruit, fruit juices, cottage cheese, poultry items, and sausage have all been treated with it to prevent yeast and mould deterioration [35]. Another concern in the cheese making process is *Clostridium*-associated butyric acid fermentation. Nisin is often used to suppress *Clostridium tyrobutyricum* spores in pasteurised processed cheese spreads [34]. Bacteriocins are being investigated by researchers as a way to enhance the shelf life of their products. The effects of nisin Z, carnocin UI49, and a crude bavaricin were investigated. A study was conducted on the shelf life of brined shrimp. Carnocin UI49 had no effect when compared to the control (10-day shelflife), whereas bavaricin A had a 16-day shelflife and Nisin Z had a 31-day shelf life [34].

IN HUMAN AND ANIMAL HEALTH

As Probiotics: Probiotics are strains of bacteria that are non-pathogenic and non-toxic to the host animal that can survive and maintain metabolic activity in the gut environment while remaining stable and alive for lengthy periods of time [2]. *Lactobacillus bulgaricus, L. acidophilus, L. casei, L. helveticus, L. lactis, L. salivarius, and L. plantarum* strains have been found to have probiotic qualities. Lactobacillus rods create an unfriendly environment for pathogenic bacteria, such as *Clostridium difficile, Shigella, Salmonella, and enterotoxic strains of E. coli or rotaviruses*, by creating pH-lowering chemicals in the gastrointestinal tract and preventing neighbouring bacteria's growth [16]. *Lactobacillus murinus* DPC6002 and *DPC6003*, *Lactobacullus pentosus DPC6004, Lactobacillus salivarius DPC6005,* and *Pediococcus pentosaceus DPC6006* were found to improve the clinical and microbiological outcomes of *Salmonella* infection in pigs. Lactobacillus populations were much higher in mice given Bacteriocinogenic *E. Faecium* than in non-producing mice, according to a study, implying that bacteriocinogenic *Enterococci* may serve to manage the indigenous microbiota in a favourable way [36]. *Lactic acid bacteria, non-pathogenic E. coli strains, Bacilli,* and *yeast* are currently employed as probiotics in everyday life [2].

Treating Ulcers*:* Bacteriocins produced by *Pediococcus acidilactici BA28* inhibit *Helicobacter pylori,* the bacteria that causes pectic ulcers, gastric ulcers, and duodenal ulcers. It is caused by an imbalance between the gastroduodenal mucosa's defensive systems and the harmful force of stomach acid and pepsin, as well as overlapping lesions caused by environmental or immunological factors (5). A *Lactococcus lactis* strain that generates nisin to promote *Bifidobacterium* growth in rats' intestines while suppressing *Enterococci* and *Streptococci* reproduction in the duodenum, ileum, caecum, and colon (2).

Used Against Dental, Oral and Respiratory Infection: Some *Lactobacillus* probiotic strains have antagonistic effects on periodontopathogens like *Aggregatibacter actinomycetemcomitans, Prevotella intermedia*, and *Porphyromonas gingivalis*, and the presence of H2O2-producing *Lactobacillus* strains in periodontal pockets helps to prevent chronic periodontitis (16,23). Microbes like *Haemophilus influenzae, Moraxella catarrhalis, S. aureus, Enterobacteriaceae, Pseudomonas aeruginosa, S. pyogenes, Neisseria meningitidis, Pasteurella multocida*, and Mycobacterium tuberculosis are important pathogens causing respiratory diseases such pneumonia, otitis, rhinitis (TB). When given at a dosage of 8192 AU, the bacteriocin nisin F inhibits *S. aureus* in non-immunosuppressed and immunosuppressed Wistar rats without causing any damage to the lungs, bronchi, trachea, or haematology [23]. Mersacidin, a peptide antibiotic made from the *Bacillus* strain and containing beta-methyllanthionine, has been proven to be particularly efficient against *Staphylococcal* infection [16,37]. Regardless of the colonisation period or number of inoculations, this bacteriocin was able to entirely destroy MRSA from the mouse's nasal epithelium [36]. Bacteriocins Salivaricin A2 and B. Salivaricins produced by *Streptococcus anginosus* salivaricins were effective against *Streptococcus pyogenes*, which causes pharyngitis and S. salivarius K12 was able to inhibit halitosis caused by *Atopobium parvulum* ATCC33793, *Eubacterium sulci ATCC35585, Eubacterium saburreum ATCC33271, Parvimonas micra ATCC33270, Solobacterium moorei CCUG39336, Streptococcus anginosus T-29, and Micromonas micros* [5]. Nisin S, Nisin T, and Nisin V a) were found to have effective inhibitory action against Mycobacterium tuberculosis (H37Ra), *Mycobacterium kansasii (CIT11/06), Mycobacterium avium subsp. hominissuis (CIT05/03), and Mycobacterium avium subsp. paratuberculosis (CIT05/03*), according to (ATCC 19698). Lacticin 3147, a membrane-permeabilizing bacteriocin found inside macrophages, has been shown to inhibit *M. Kansasii* (MIC90, 60 mg/L) and *M. Tuberculosis H37Ra* (MIC90, 7.5 mg/L) bacteria [23].

Used against skin infection and vaginosis*: S. aureus, Propionibacterium acnes, Staphylococcus epidermidis, B. cereus, B. subtilis, and L. monocytogenes* are bacteria that cause skin and soft-tissue infections. Nisin and its derivatives have been reported to be beneficial in the treatment of various skin disorders. Apart from nisin, other bacteriocins such as hiracin JM79 from *Enterococcus hirae DCH5* and lactocyclicin Q from *Lactococcus subsp. QU12*, as well as subpeptin JM4B from *Bacillus subtilis JM4* have been successfully tested in vitro against *Staphylococci, Enterococci, Lactobacilli, P. aeruginosa, Salmonella* [23]. In a patient with inflammatory acne lesions caused by *Propionibacterium acnes, ESL5*, a bacteriocin generated by *Enterococcus faecalis SL-5*, was used as a lotion, which drastically reduced the inflammatory lesions and pimples when compared to a placebo lotion. Similarly, Infectious pathogens such *G. vaginalis, Mycoplasma hominis, Prevotella bivia, and Mobiluncus curtisii* are also widespread in millions of women. The *Bacillus amyloliquefaciens* bacteriocin lactocin 160 and subtilin A activity against *G. vaginalis* was found to be effective [23].

As Spermicidal Agents: Bacteriocins have the ability to influence sperm motility, making them potential spermicidal agents [13]. *Lactobacillus fermentum HV6b MTCC 10770* produces fermenticin HV6b, a class iia antimicrobial peptide identified from the human vaginal ecosystem. *Gardnerella vaginalis, Mobiluncus, Staphylococci, and Streptococci,* which cause vaginal infections in humans, can be inhibited by it. Fermenticin HV6b possesses a sperm immobilisation and spermicidal action that is unique. A new formulation including *Lactobacillus fermentum HV6b* or fermenticin HV6b can be used alone or in combination with the creation of vaginal creams to protect the human vagina against microbial infections while simultaneously serving as contraception [5]. Bacteriocins Subtilin and Lacticin 3147 from *B. Subtilis* have been tested as a safe contraceptive in both animals and humans. As a result, subtilosin appears to have a lot of potential as a contraceptive [23].

Anticancer Properties: Bacteriocins have the potential to be used in cancer therapy because they inhibit the synthesis of DNA and membrane proteins in tumour cells, causing apoptosis or cytotoxicity. Nisin, as compared to primary keratinocytes, produces selective apoptosis, cell cycle arrests, and inhibits cell proliferation in HNSCC cells, making it a new potential therapy for the treatment of head and neck squamous cell carcinoma (HNSCC). The anticancer effect of Nisin ZP, which has a content of 95%, has been reported. *Enterococcus mundtii* strain C4L10 could be exploited as an antibacterial and antiproliferative agent in the fight against cancer. HSC3 oral cancer, MCF7 breast cancer, H1299 lung cancer, and HCT116 colon cancer cell lines were found to be susceptible to bacteriocins [(5).] *Lactobacillus fermentum HV6b MTCC 10770* has the potential to be used as part of anticancer medication therapy because it has been shown to generate apoptosis in cancer cells and rec-pediocin CP2, which has considerably higher cytotoxicity activity and causes chromosomal DNA damage in cell lines. [(5).]

***Used As Plant Growth Promoter*:** Some bacteriocins are important in nodulation competitiveness against certain bacteria. Many bacteriocins, such as cerein8A from *B. subtilis*, are found in the rhizosphere such as H4, IH7, and Bac14B from *Bacillus subtilis, Bac-GM17 from Bacillus clausii GM17* [(26).] In comparison to controls, *Bacillus thuringiensis* NEB17 and BF4 produce bacteriocins thuricin 17 and bacthuricin F4, respectively, and *Bacillus cereus UW85* secretes bacteriocin C85, which increase the leaf area of tomato, corn, and soyabean plants on spraying, resulting in a 6% increase in photosynthesis, a 15% increase in plant dry weight, and a 21% increase in [(5).] Thuricin 17 also aids plant growth and development by reducing the population of root-associated plant-bacterial pathogens, resulting in more vigorous growth. Another benefit of extracellular PGPR (ePGPR) is demonstrated by the bacteriocin-producing *B. thuringiensis NEB17*, which has been shown to have no harmful effects on nodulating rhizobia including *Serratia proteomaculans* 1-102, 2-68, *Pseudomonas putida*, and *Bacillus species* such as *Bacillus licheniformis Alfa-Rhi* [(26).]

Pseudomonas fluorescens SF39a, isolated from the wheat rhizosphere that limit the growth of phytopathogenic *Pseudomonas and Xanthomonas strains*, has been shown to have the ability to excrete bacteriocins. *Bradyrhizobium japonicum* and other slow-growing rhizobia produce bacteriocin-like compounds, as do some rhizobial strains linked with Medicago and *Rhizobium leguminosarumbv. viciae. R. leguminosarum* strains have also been shown to have the symbiotic plasmid pRL1J, which contains critical nodulation and nitrogen fixation genes as well as determinants for secretion of small, medium, and large bacteriocins [(26)] Other bacteriocins with antimicrobial activity have been explored, including Cerein 8A, Bac-GM17, putidacin, Bac 14B, and amylocyclicin. Bac IH7 encourages the growth of tomato and musk melon plants [(38).] Bac-GM17 bacteriocin produced from the rhizosphere bacteria *Bacillus clausii GM17* having bactericidal effect on *Agrobacterium tumefaciens C58* and fungistatic effect on *Candida tropicalis R2 CIP203*. B. subtilis strain IH7 produces a bacteriocin Bac IH7 which is reported to be a plant growth promotor. In Tomato and muskmelon, it showed enhanced germination percentage and increased shoot weight and height and root lengths; it also served as a biocontrol for *Alternaria solani* and other seed borne pathogens [(38).] It has been observed in an experiment, the effective concentration of bacteriocin for enhanced plant growth and production, which makes it economically viable and reduce the use of energy-based fertilizers and chemicals used in agricultural crop production systems [(38).]

***Used In Veterinary Medicine*:** AMR (Antimicrobial resistance) is a global issue that impacts both human and veterinary medicine. This problem has prompted a "One Health" approach to better coordinate efforts and halt the spread of drug-resistant bacteria. Bacteriocins or antimicrobial peptides have been shown to be effective in vitro and in vivo against a variety of infections, including those resistant to many traditional antibiotics. Antimicrobial peptides are now used in veterinary goods like udder disinfection for dairy cows and dermatological medicated wipes for dogs, cats, and horses. However, there are other possible uses for companion and production animals in the veterinary industry to investigate. In veterinary medicine, nisin has been approved by the Food and Drug Administration (FDA) for use as an udder disinfectant in dairy cattle (Wipe Out®) [(39).] In dairy cattle, this formulation is used to prevent intramammary bacterial infections caused by *S. aureus, Streptococcus uberis, and Streptococcus dysgalactiae*. In addition, another nisin-based formulation (Preva®) containing 25 g/mL API was recently released to the Veterinary market in the United States, and it is indicated for topical treatment on dogs, cats, and horses with dermatological diseases linked with bacterial infections [(27).] *E. coli, Salmonella enteritidis, Clostridium perfringens, Streptococcus equisubsp. zooepidemicus, Streptococcus aureus, and Pasteurella multocida* were all suppressed by Bacteriocin LFB 112, which was derived from *Bacillus subtilis*. In addition, enterocin E-760, a protein isolated from chicken cecum, has been shown to inhibit the growth of a variety of Gram positive and Gram-negative bacteria [(27).] One of the primary goals of bacteriocin research in the veterinary medicine field is pathogens associated with bovine mastitis. Lacticin 3147, generated by *Lactis lactis subsp*. Lactis DPC 3147, inhibited twenty-four strains of *Staphylococcus aureus and Streptococci (S. agalactiae, S. dysgalactiae, and S. uberis)* isolated from mastitic illnesses. In her investigation, one of the researchers discovered that distinct *Staphylococcus strains* produce aureocin A70, aureocin A53, aureocin 215FN, Pep5, epidermin, epilancin K7, and epicidin 280 showed in vitro activity against *S. aureus* and *S. agalactiae* isolated from clinical mastitis udder [(27).] There are some other potential anti-mastitis bacteriocins such as nisin U, uberolysin , bacteriocin ST91KM, morricin 269, kurstacin 287, kenyacin 404, entomocin, Pep5, epidermin, epilancin K7, epicidin 280 and aureocins A70, A53 and 215FN against S. *aureus* and *S. agalactiae* involved in the control of bovine mastitis [(39).] Macedocin ST91KM, generated by *Streptococcus gallolyticus subsp. macedonicus ST91KM*, was also added to a teat seal preparation and was found to be effective against *S. agalactiae. AP-CECT7121*, another putative anti-mastitis peptide, demonstrated bactericidal efficacy against MRSA and *vancomycin-resistant E. faecium (VRE)* isolated from mastitic cows [(27).] The efficacy of combining nisin and enterocin DD14 with colistin on eradicating planktonic and biofilm cultures of susceptible and resistant strains of *E. coli* from swine origins has also been effectively reported among swine pathogens [(27).] Another antimicrobial peptide isolated from *Bacillus subtilis subsp. Spizezinii (ATCC 6633)* suppressed the growth of *Haemophilus parasuis*, which causes Glasser's illness in young pigs (Laureano *et al*, 2020). *P. pentosaceus* produces pediocin, a broad-spectrum class IIa bacteriocin. Significantly reduced

the growth of dangerous bacteria, such as clostridia and coliforms, and boosted the metabolic activity of cellulolytic bacteria in the small and large intestines of pigs, demonstrating efficacy on microbial metabolism [39].

Staphylococcus pseudintermedius is an opportunistic canine pathogen that causes skin and soft tissue infections in small animals. A nisin derivate (nisin I4V) that exhibited great activity against a multi-drug resistant strain of *S. pseudintermedius* could be a prospective therapeutic alternative [27]. Enteric infections are a major concern in the poultry industry since they cost a lot of money. *C. perfringens* colonises the digestive system of chickens and is the cause of necrotic enteritis, making it one of the most studied bacteriocins [27,39]. A strain of *C.perfringens* isolated from a chicken with necrotic enteritis produces perfrin, which is effective against other type A *C. perfringens* strains [39]. In comparison to the infected control group, supplementation with B. subtilis reduces intestinal lesion score and considerably lowers intestinal *C. perfringens* numbers in broiler chickens infected with *C. perfringens*. The addition of pediocin A, produced by *Pediococcus pentosaceus FBB61*, to the food of broiler chickens exposed to *C. perfringens* increased growth performance during the challenge and allowed for optimal growth over a 4-day period (Laureano *et al*, 2020). Bacteriocins diversion generated by *Carnobacterium divergens* and albusin B produced by *Ruminococcus albus* a were found to have a similar regulating effect on the microbiota of the gastrointestinal tract by reducing *Bacteroides* and *Enterobacteriaceae* numbers [39]. The impact of nisin on poultry physiology, production, and the microbiota of the gastrointestinal tract (GIT) has been studied extensively. Nisin supplementation boosted broiler development performance in a dose-dependent manner, functioning similarly to salinomycin when employed as a growth promoter, according to the researchers. Nisin boosted body weight gain while lowering bacterial counts in the ileal digesta, including *Enterobacteriaceae, Clostridium perfringens*, *and Lactobacillus spp./Enterococcus spp*[27,40]. In rabbits and horses, enterocin M, a thermostable short peptide generated by *E. faecium*, was found to have positive benefits. It boosted phagocytic activity in blood samples and decreased the count of *coliform bacteria, S. aureus, and enterococci* in faeces samples in rabbits, and it decreased the count of *coliform bacteria, S. aureus, and enterococci* in horse faeces samples [27,40]. Furthermore, Nisin Z generated by *L. lactis subsp. cremoris* protects rainbow trout from lactococcosis. *Lactococcus garvieae, Streptococcus iniae, Carnobacterium maltaromaticum, and Aeromonas salmonicida* are among the pathogens that *Pediococcus acidilactici L-14* produces Pediocin PA-1 bacteriocin, which has been shown to have antimicrobial activity against *Lactococcus garvieae*, *Streptococcus iniae, Carnobacterium*[40]. Other research suggests *that Lactobacillus pentosus HC-2 and E. faecium NRW-2*, which have antibacterial action against *Vibrio harveyi* and *Vibrio parahaemolyticus (ATCC 17802)*, could be employed in the shrimp diet [40]. Nisin's immunomodulatory action can be shown in non-immune cells as well. Nisin enhances intracellular lysozyme and even releases it into the extracellular environment in bovine mammary epithelial cells. Bacteriocins have been proven to have anti-inflammatory activities in injured or infected tissue when used as immune modulators. Nisin protects bovines from endometritis caused by an experimental infection with *S. aureus*. Bacteriocins reduce proinflammatory cytokines while increasing anti-inflammatory cytokines in this illness. Bacteriocins produced by *Lactobacillus rhamnosus L34 and Lactobacillus rhamnosus (ATCC 53103)* have been proven to minimise postoperative effects such as inflammation in tissue injuries such as fractures. LAB *Pediococcus pentosaceus (SL001)* was also found to express the bacteriocin coagulin in one of the tests. *P. pentosaceus* supplementation improved grass carp immunity by raising IgM and C3 (complement 3), while lowering IL-8 levels [40].

Conclusion

In 21st century, antimicrobial resistance is a fervent issue that impacts both human and livestock. This problem has prompted a "One Health" approach to better coordinate efforts and halt the spread of drug-resistant bacteria. Bacteriocins are antimicrobial peptides (AMPs), or proteins produced by bacteria. They are abundant, diverse, and their genes encode ribosomally produced antimicrobial peptides or proteins that kill other microbiota species. Bacteriocins operate as bactericidal barriers, reducing the numbers of contaminating bacteria while biostatic measures, such as modified atmospheric packing or water reduction, prevent the remnant population from multiplying. They can also be used in conjunction with other antibacterial agents. There are few commercially available bacteriocins such as nisin, pediocin PA, etc. Researchers are continually struggling with the availability, potency, and specificity of new bacteriocins for treating MDR infections. To enhance the effectiveness, it is required to developed more novel bacteriocins with promising properties. design is very realistic for the future of the automotive industry as well as our education.

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