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PROPERTIES, GENETIC REGULATION AND APPLICATIONS OF BACTERIOCINS

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ABSTRACT

Bacteriocin is a term that refers to the proteinaceous substances produced by Gram-positive and Gram-negative organisms that bears antimicrobial properties. Bacteriocins are notably different from antibiotics by their structural features and activity. Since bacteriocins are proteins, they are ribosomally synthesized and exhibit narrow-spectrum activity and works on the same or near related species. Antibiotics are secondary metabolites produced through complex pathways catalysed by varieties of enzymes and demonstrate a broad spectrum of antimicrobial activity. *Lactobacillus* sp. is found to be major producers of bacteriocin which is most commonly used in the food industry. Nisin is an example of bacteriocin that is approved and worldwide accepted for utilization in the food industry. Looking at the currently applied aspect of bacteriocin, it is not limited to one or two industrial sectors. In addition to the food industry, bacteriocins are also found to have potential in health care especially skincare to treat acne. Bacteriocins that inhibit DNA synthesis can also have promising applications in cancer therapy due to their mode of action, which does not allow the growth of other carcinogenic cells.

Keywords: Bacteriocin, LAB, Lantibiotic, Nisin, Antibiotics, Peptide antibiotic

INTRODUCTION

We are surrounded by a plethora of microorganisms that can synthesize antimicrobial compounds like bacteriocins,

which have a killing or inhibiting effect on other microorganisms. Studies have proven that nearly all species of bacteria can

synthesize bacteriocins. Bacteriocins are made up of an immense number of ribosomally synthesized peptides that possess antimicrobial activity against strains that are directly connected to producer strain and rarely across genera [1].

In recent years, bacteriocins and their derivatives have drawn attention because they have the potential to destruct many bacterial species including drug resistance species. It can also find application in many fields such as analeptic, food industry, clinical expanse etc. In the food industry, bacteriocins synthesized by Lactic Acid Bacteria (LAB) is in greatest demand as natural preservatives. In past studies, it has been demonstrated that bacteriocins are generally produced by *Lactobacillus* species and some other species too. Apart from this, past studies also manifest that bacteriocins producing species broadly belong to *Bacillus* sp. Few Gram-positive, as well as Gram-negative bacteria, also form bacteriocins like substances. One or more bacteriocins contribute to the defence mechanism of particular species [2].

The nature of bacteriocins may be bactericidal or bacteriostatic. Numerous bacteriocins are produced by Gram-positive bacteria shows broad-spectrum inhibition activity. Whenever a product is not thermally sterilizable, bacteriocin is used instead. Bacteriocins isolated from LAB

such as *Lactococcus* sp., *Streptococcus* sp., *Pediococcus* sp., *Lactobacillus* sp. are used in fermented food products and are Generally Recognized As Safe (GRAS) [3, 4]. The key merits of bacteriocins over antibiotic are that they have the nature of primary metabolites and have simple biosynthetic mechanisms than antibiotics which is secondary metabolites in nature. Due to such remarkable nature, bacteriocins are easily controllable via genetic engineering to increase their specificity and activity towards target microbes [5].

Nowadays nisin and pediocin PA-1AcH are the individual bacteriocins that are useful in the food industry. Their application in the clinical field is restricted to animals only and not for human health. In clinical fields, numerous research studies have been conducted for the development of bacteriocins through the genetic engineering process that enhances the bioactivity against the pathogen and their widespread use as therapeutic agents [1].

BRIEF HISTORY:

Bacteriocins were first discovered by Gratis in 1925. He was in curiosity to find another way to destroy bacteria. Suddenly he observed that a few *E. coli* strains were inhibited by some antimicrobial compound and he named that compound colicin V which is released in that medium by *E. coli* V strains (virulent strains). Later this colicin V was identified as a thermo-stable

& dialyzable peptide compound. In the last few years, many bacteriocins like substances are being reported and characterized [6, 7]. Bacteriocins are proteinaceous compounds from the heterogeneous group which may differ in various parameters such as molecular weight, genetic origin, mode of action, antimicrobial activity spectrum, biochemical properties etc. Their proteinaceous nature is found common in all types of bacteriocins or mixed group substances. Lipids and carbohydrates are also the part of bacteriocin complex structure. There are two types of bacteriocin; the first one is either being cell-bound and the second one is released as extracellular particles into the cytoplasm that may be formed at the early or late stage of the life cycle. Bacteriocins compounds are exposed to proteases enzymes and have different stability at various pH and temperatures [7].

BACTERIOCINS FROM LACTIC ACID BACTERIA (LAB):

Bacteriocins are proteinaceous and antimicrobial by nature which is supposed to be safe for ingestion and easily degradable by a proteolytic enzyme present in the human gastrointestinal tract. Most bacteriocins are isolated from lactic acid

bacteria (LABs) and are naturally found in fermented food mainly in dairy products [8]. LABs are extracted from nutrient-rich habitats such as carbohydrates, vitamins and proteins containing foods e.g., meat, milk, fruits and vegetables etc. LABs are also found in the wastewater, intestinal tract and mucous membrane of all mammals [9].

Major applications of LABs can be observed in the food industry given the fact of their nutritional benefits, organoleptic characteristics. The function of LABs is to produce a rapid and large amount of organic acid like lactic acid in the raw material being used for the fermentation process. In addition to lactic acid, they also form ethanol, acetic acid and aromatic compounds. The industrial application of LABs mostly includes its utilization as a starter culture for the fermentation process. LABs bears the ability to inhibit the growth of other microbes which restrict the whole process and also provide antimicrobial properties for the preservation and safety of food. LABs also possess health-promoting properties and are used as probiotics, having the potential to fight against gastrointestinal pathogens like *E. coli*, *Helicobacter pylori*, *Salmonella* sp. etc. [10].

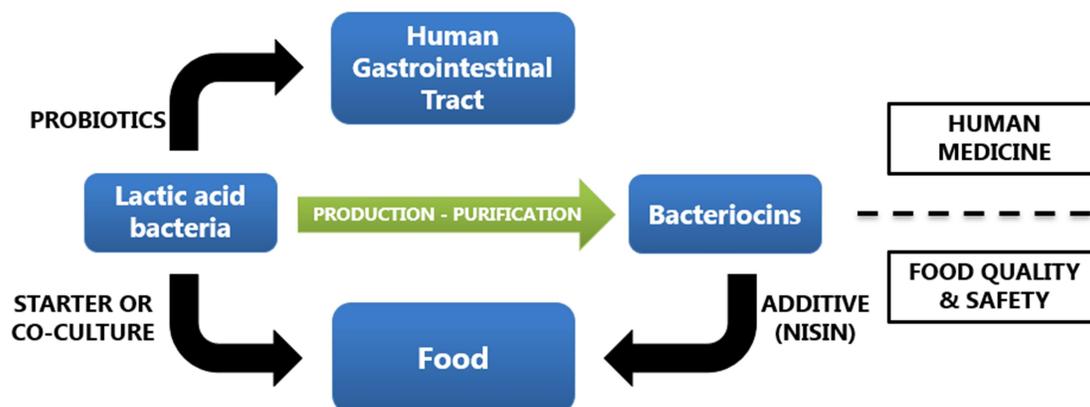


Figure 1: Application potential of bacteriocin produced by LAB [10]

CLASSIFICATION OF BACTERIOCINS:

According to different authors, bacteriocins are classified on different bases such as mechanism behind killing (pore formation, murrain production, inhibition etc.), molecular weight and method of production involved (genetic, chemistry and post ribosomal modification). Bacteriocins are categorized into four groups on basis of different criteria (Klaenhammer classification) like thermostability, mode of action, enzymatic sensitivity, molecular mass and presence of the post-translationally modified amino acids [11]. The major distinguishing factor between these groups is the occupancy of sulfide and disulfide bonds. Classes of bacteriocin are explained below [12].

a. Class I Bacteriocins:

This group of bacteriocins contain lantibiotics with a molecular mass lesser than 5 kDa. The most widely recognized

bacteriocin of this class is Nisin [13]. Lantibiotics are Lanthionine (polycyclic thioester which is post-translationally modified) or 3- Methyllanthionine containing peptide antibiotics. It also contains other unsaturated amino acids, 2-aminoisobutyric acid and dehydroalanine. Several Gram-positive bacteria belonging to *Streptomyces* sp. and *Streptococcus* sp. produce lantibiotics which will attack other Gram-positive bacteria [11]. A covalent bond is formed between amino acid residues resulting in the emergence of the internal ring or cyclic structure which is responsible for the stability of the entire molecule [1]. On basis of structural characteristics and mode of inhibition, lantibiotics are also categorized into two subgroups, Ia and Ib. Ia lantibiotics contain hydrophobic, screw-shaped, small cationic peptides which contain about 34 amino acids.

They act on the cytoplasmic membrane of the target cell by depolarization. Subgroup Ib lantibiotics are negatively charged globular peptides and contain up to 19 amino acids [13]. Nisin and epidermin are grouped as Ia bacteriocins while mersacidin is the example of group Ib bacteriocin [11].

b. Class II Bacteriocins:

Class II bacteriocins are non-lantibiotics, thermostable, unmodified peptides which have smaller molecular mass (<10 kDa) [11]. It contains 30 to 60 amino acids. They are thermostable and do not possess or undergo extensive post-translational modifications [14]. The Class II bacteriocins are additionally categorized into four subgroups [15]. Class IIa are characterized by exhibiting remarkable inhibitory activity towards highly pathogenic foodborne microorganism *Listeria monocytogenes* and the presence of marked conserved sequence YGNGV in the N-terminal region. This group of bacteriocin is often called pediocin [1]. Class IIb is also known as two peptide bacteriocin because its activity relies on the co-action of two different peptides [13]. They display a remarkable spectrum of activity against Gram-positive bacteria. Class IIc bacteriocins (circular bacteriocins) contain two types of bacteriocin, one is with one/two cysteine

residues (thiolbiotics and cystibiotics respectively) while the other is without cysteine residue (lactococcin A) [11]. Class IId bacteriocins include other bacteriocins containing single peptides that lack typical pediocin signature and are not modified post-translationally [1]. The best example of class IId bacteriocin is aureocin A53 that exhibit high stability against high temperatures and acidic conditions and is not affected by the action of protease [16, 17].

c. Class III Bacteriocins:

Class III Bacteriocins are peptides having a molecular mass greater than 30 kDa. They are thermolabile proteins containing three domains designated as receptor binding, translocation and lethal domain [13]. Microbes belonging to *Lactobacillus* sp. are the major producer of this bacteriocin. For example, helveticin-M and helveticin-J were produced by *Lactobacillus acidophilus* and *Lactobacillus helveticus* respectively [18, 19].

d. Class IV Bacteriocins:

Class IV bacteriocins are compound proteins consisting of lipid or carbohydrate (glycoprotein) portion that is an essential non-protein part for their action [12]. Leuconocin-S and lactocin-27 are major examples of class IV bacteriocins [13].

BACTERIOCINS PRODUCED BY GRAM-POSITIVE BACTERIA

Many bacteriocins produced by Gram-positive bacteria are cationic and amphiphilic by nature. These antimicrobial peptides with a broad spectrum of action are made by assembling as few as 60 amino acids and also may contain membrane permeabilizing peptides too [20]. Production of bacteriocin is not a lethal event because the biosynthesis of bacteriocin in Gram-positive bacteria is self-regulated and a phenomenon of self-protection is demonstrated by the producer strain against its own antibacterial peptide [21]. Some bacteriocin produced by Gram-Positive bacteria has been proposed to have some additional roles, such as communication molecules in bacterial consortia and chemical mediators in quorum sensing. Quorum sensing is one of the detailed systems which are included in bacteriocin gene control. For control of bacteriocin expression, LAB often uses quorum sensing to prevent the development and attack the competitor strain. In the search of bacteriocin of Gram-positive bacteria, a landmark was observed in which there is stated that *Lactococci* & Group N *Streptococci* shows the inhibitory action towards other LAB are because of molecule known as Group N inhibitory substance (proteinaceous antimicrobial) or Nisin [22].

BACTERIOCINS PRODUCED BY GRAM-NEGATIVE BACTERIA

Moreno and Kolter introduced a classification scheme because they were interested in bacteriocins produced by Gram-Negative bacteria and this classification distinguished heat-stable bacteriocins, lantibiotics, non-lantibiotics, microcins and colicins. Microcins and colicins are defined based on molecular size and they include the compounds being a part of the *Enterobacteriaceae* family that are working against Gram-Negative microorganisms. The first discovered bacteriocin is colicins and they are characterized by their narrow antibiotic spectrum which interacts with specific membrane receptors by displaying bactericidal activity. Some bacteriocins are different because their biosynthesis is controlled by SOS dependent mechanism. Microcins and class II bacteriocins are having the same structure, of molecular size less than 10 kDa and they are produced in the secondary phase and does not undergo SOS control. Two various members of bacteriocin of this class are Colicin V and microcins C7, which is reviewed as the smallest antibiotic peptides [6].

COMMERCIALY AVAILABLE BACTERIOCINS:

For the utilization of bio-preservatives on a business scale, it needs to satisfy certain

necessities of being nontoxic, stable, not influencing the organoleptic properties of food items, acknowledged by recognized authorities and utilized in low concentration etc. Bacteriocin of different types i.e., subtilin, plantaricin etc., has been specified from various bacteriocin producing bacteria. Till now, only nisin (*Lactococcus lactis*) and pediocin (*Pediococcus acidilactiti*) are commercially produced bacteriocins and other bacteriocins are still under the process of getting marketable GRAS status to be used as bio preservatives in the food industry. Nisin has only been given the GRAS status by FDA (Food and Drug Administration). In canned foods and dairy products, Nisin is extremely effective to prevent food spoilage and it also increases the shelf life. Every Gram-positive bacteria in food is inhibited by Nisin [23].

MODE OF ACTION OF BACTERIOGIN:

Bacteriocin can affect various essential functions of cells [DNA replication, cell wall biosynthesis, translation, transcription etc.] [6]. The mechanism of different bacteriocins on their target cell is much diverse and it can be divided into. Bacteriostatic action stops the growth of the cells but does not cause cell death while bactericidal effect causes the death of the cells without lysing the cells. Bacteriolytic action causes dissolution of the bacterial

cell wall [8, 13]. Formation on membrane pores and thereby channels by the action of bacteriocin ends up the sensitive cells with the destruction of energy potential [13]. Gram-Positive bacteria have a different mode of action in various types of bacteriocin. Nisin (group Ia bacteriocin according to Klaenhammers classification) is the most studied bacteriocin according to the mode of action.

Structurally, bacteriocin consists of two domains named cationic domain and hydrophobic loop domain. The interaction between the target membrane of a bacterial cell and hydrophobic parts of bacteriocin generate the ionic channels; such formation helps to induce high transmembrane potential and the presence/absence of anionic and cationic liquid [24]. The cationic part of the bacteriocin interacts with the bacterial cell membrane which is negatively charged where it neutralizes the phospholipids molecule present in the cell membrane. Additionally, it also reduces the fluidity of the membrane. Now, membrane generated pore which allows the passive emanation of ions like K^+ & Mg^+ ; amino acids such as glutamic acid, lysine and ATP; but do not allow large cytoplasmic proteins. As a result membrane potential is lost directly affecting proton motive force and is followed by a cell death [6, 23, 25].

Class IIa bacteriocin has an anti-listeria activity due to the presence of a YGNGV

sequence in their N terminal region. This specific sequence is called the “leader” sequence. The hypothetical receptor is responsible for the recognition of the YGNGV anti-listerial motif present in the leader peptide [6, 23]. The large bacteriolytic protein, like lysostaphin (class

III bacteriocin) acts on Gram-Positive target cells & cause cell lysis or death by directly acting on the cell walls. Except for the nisin, other bacteriocin affects gene expression especially inhibiting protein synthesis and killing their target cells [8].

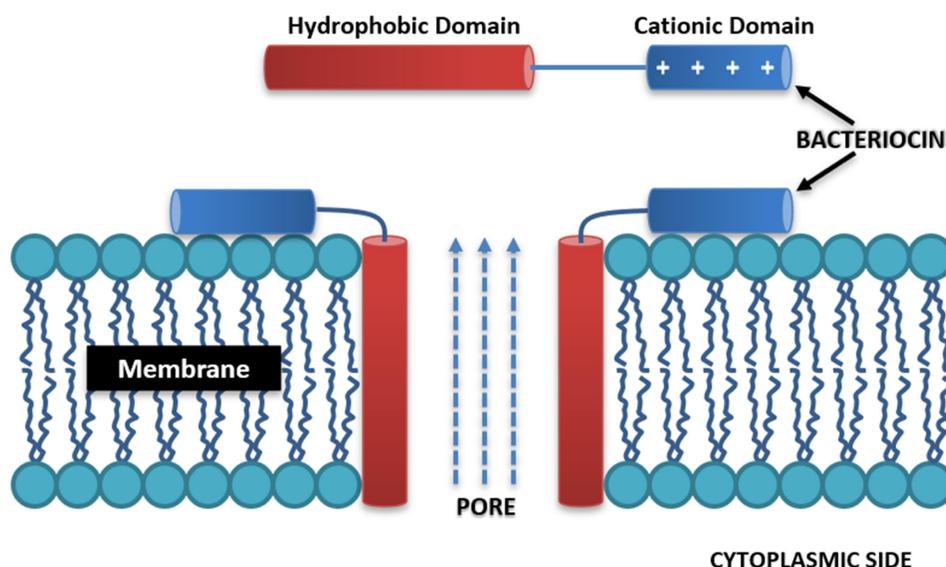


Figure 2: Mechanism of killing by Class IIc bacteriocin [6]

Biosynthesis of bacteriocin:

Rather than being secondary metabolites like antibiotics, bacteriocins are simple primary metabolites. Hence, the mechanism of their biosynthesis is very simple. Coding genes of bacteriocin are found to be encoded on plasmids [5]. Gene related to the biosynthesis of bacteriocins are usually clustered with the lowest genetic machinery including structure genes and cognate immunity genes. Bacteriocin is synthesized in the form of a biologically inactive peptide that can act as precursors of active

protein. It may contain an N-terminal leader peptide that adheres to the C-terminal. After going through enzymatic cleavage of precursor, mature and active bacteriocin can be observed.

There are three major functions of leader peptide. First, the leader peptide helps to recognize the binding site for the proteolytic enzyme for the maturation process and allows the transport of the enzyme to the extracellular space. Secondly, it protects producer strains from inhibitory action of bacteriocin by

maintaining bacteriocin in the core of the producer cell at the dormant stage. Third, in the enzyme-substrate interaction suitable confirmation is required for the leader peptide while the enzyme interacts with a potential domain of the precursor's peptide. The gene clusters are used in the synthesis of bacteriocin which encodes biosynthetic machinery and is responsible for modification, transport, immunity and regulation of production [1].

Considering an example, Nisin A is ribosomally synthesized as an inactive peptide. NisA protein consists of N-terminal leader sequences and is attached to the remaining part that is known as 'propertied'. Thereafter pre-peptide undergoes modification, followed by translocation of the modified pre-peptide across the cytoplasmic membrane and proteolytic cleavage of leader peptide by a specific enzyme. NisB and NisC are modification enzymes that dehydrate and cyclize the propertied. The ABC transporter called Nis T; translocate the precursor peptide into the extracellular space. NisP is

a protease enzyme, which is present outside the cell in membrane-bound form. It cleaves the leader peptide and releases the mature nisin A. NisI is a membrane-bound lipoprotein exposed to the extracellular side which provides immunity to the producer cell from the action of nisin-A. A multiprotein transporter complex called NisFEG is a combination of two units of NisF and one unit of each NisE and NisG. The role of this complex is to expel nisin-A molecule from the producer and protect the cell from the inhibitory action of nisin-A. NisK is a histidine kinase that acts as a response regulator along with NisR that controls the production of the bacteriocin. The NisK, a membrane-bound protein is responsible for sensing nisin-A molecule surrounding the cell. Nisin-A binding to NisK results in autophosphorylation of NisK which in turn phosphorylates NisR present in the cytoplasm. Phosphorylation results in activation of NisR that positively regulates transcription of nis genes as directed in **Figure 2** [1, 5, 26].

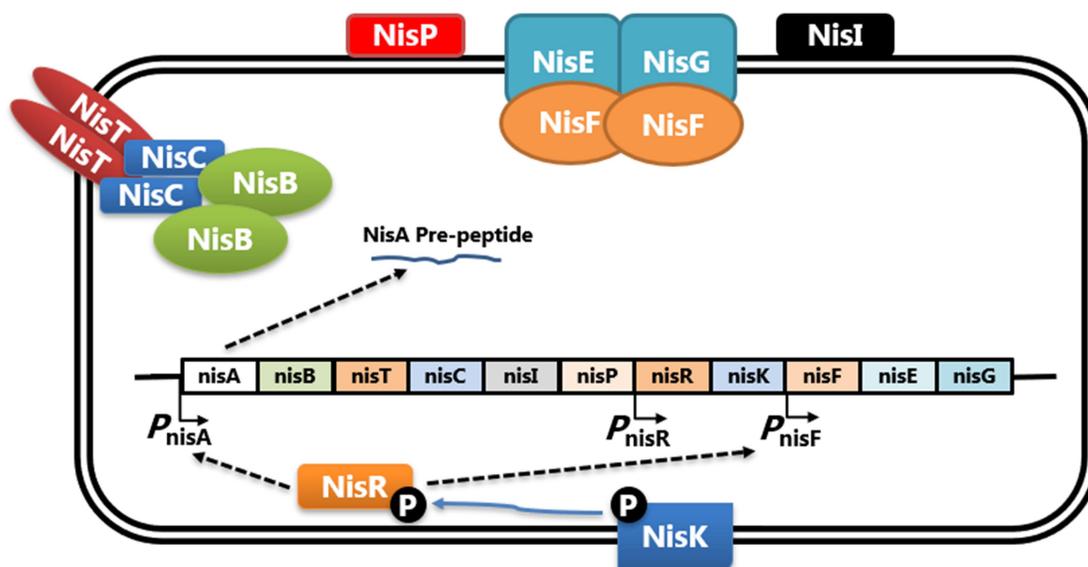


Figure 3: Biosynthesis of Nisin A [1]

Comparative analysis of similarity/differences between bacteriocin and antibiotics:

Proteinaceous toxins or peptide antibiotics that are produced by bacteria to obstruct the growth of directly related bacterial strains are known as bacteriocin whereas antibiotics are the type of antimicrobial substances which are active against bacteria. Contrasts between bacteriocins and antibiotics can be listed as:

(i) The bacteriocins are broadly applied in the industry as well as in clinical fields, while antibiotics are purely clinically used [27]. (ii) Synthesis of antibiotics occurs as secondary metabolites while bacteriocins are ribosomally synthesized like every protein in the cell [5]. (iii) Considering the bioactivity spectra, bacteriocin exhibits a narrow spectrum as compared to antibiotics

displaying wide or broad range [28, 29].

(iv) Bacteriocin are active at nano to micromolar range in the terms of potency where at the same aspects, antibiotics are active at micro to millimolar range. (v) Due to the proteinaceous nature, there is a possibility of proteolysis for bacteriocin as compared to antibiotics. (vi) Bacteriocin may possess high thermal stability whereas many antibiotics bear thermolabile nature. (vii) Antibiotics need a specific pH range or low pH range where bacteriocin need a comparatively higher pH to work efficiently. (viii) Antibiotics have their unique taste, odour and colour whereas bacteriocin has no taste, no odour and no colour. (ix) Amenability to bioengineering is one of the remarkable properties while considering the case of bacteriocin which is not possible with antibiotics. (x)

Bacteriocin have no toxicity towards eukaryotic cells whereas antibiotics are capable of exerting toxicity to eukaryotic cells [27]. (xi) The bacteriocin and antibiotic vary in the mode of action too where bacteriocin causes pore formation on the cell membrane as well as indirectly inhibits the biosynthesis of the cell wall. Antibiotics have intracellular targets to exert an effect as well as can directly inhibit the biosynthesis of the cell membrane [30].

Purification of bacteriocin:

Bacteriocin requires to be purified before its utilization for various purposes. Conventionally, it can be purified through a multi-step process comprising precipitation using ammonium sulphate followed by various chromatographic methods such as ion exchange, gel filtration and RP-HPLC (Reversed-Phase High-Pressure Liquid Chromatography). Along with the conventional method, bacteriocin can also be purified by a three-step process where the purification is carried out stepwise through ammonium sulphate precipitation, chloroform/methanol extraction/purification and RP-HPLC respectively [31]. The third method for isolation of bacteriocin use distinctive unit operation, i.e. firstly maximizing the bioavailable bacteriocin titer via pH adjustment of crude fermentation medium and then expanded bed adsorption is carried

out using hydrophobic interaction gel [7, [10, [26, 32]. The two-step purification system was developed earlier that was based on desorption/adsorption on a cation exchange resin and phase partitioning. This method is effective in mesenterocin Y105 and nisin recovery. In the fermentation broth, bacteriocins can be adsorbed by using ingestible porous silica compound [26].

APPLICATIONS:

- 1. Food Industry:** In addition to other preservation methods, bacteriocin takes a leading part in maintaining the good quality and safety of food. Sometimes LAB culture and bacteriocin which is formed by those bacteria are used as a protective system to prevent the food from spoilage pathogen. Bacteriocin is found in many food products e.g. dairy products, meat, alcoholic beverages, mayonnaise, fruits **Figure 2** [1, 5, 26], vegetables, sauces, baby food etc. [23]. *Lactococcus lactis* produces nisin and it was the first bacteriocin used in the agro-food industry and now it is marketed as Nisaplin™ as a commercial bacteriocin [13].
- 2. Aquaculture:** In wastewater, various pathogenic bacteria are found as causative agents of hazardous diseases. To prevent these diseases, antibiotics are used in aquaculture to prevent the lives of aquatic animals. But because of

overconsumption of antibiotics, various undesirable effects are manifested in fish and other aquatic animals. Now, researchers have initiated a new alternative for disease control that gives healthy life to aquatic animals [23]. In aquaculture, the application of bacteriocins is now most commonly documented as disease resistance. Different LAB such as *Enterococcus* sp., *Lactococcus* sp., *Lactobacillus* sp. etc. has been studied on various species of fish concerning immunomodulatory effects [13].

3. **Skin Care:** Skin's microflora and skin's immune system modulation can be carried out by certain probiotics which will lead to the maintenance of skin homeostatic (fact-based and scientific report-based assumption) [9]. ESL5, a bacteriocin produced by *Enterococcus faecalis* SL-5 strain has been used as a lotion in some patients reported to have proactive acne lesions produced by *Propionibacterium acnes*, and compared to placebo lotion. This may remarkably reduce agitative lesions and pimples [33].

4. **Cancer Therapy:** Applications of bacteriocin can also be extended for cancer therapy due to its mode of action where it inhibits the DNA synthesis along with the synthesis of membrane proteins which results in cytotoxicity or

apoptosis in tumour cells. For therapy of head and neck squalors cell carcinoma (HNSCC), a significant role of CHAC1 (ChaC Glutathione Specific Gamma-Glutamylcyclotransferase 1, a pro-apoptotic cation transport regulator) is reported under the treatment of nisin. Here, nisin can serve as a new potential therapeutic agent by playing role in the activation of CHAC1, causing the increase in Ca^{2+} influx and inducing cell cycle arrest that promotes preferential programmed cell death and decreased cell expansion in HNSCC cells [34]. A naturally occurring variant of nisin (nisin ZP) is found to be exerting a higher antitumor effect in HNSCC cells in vivo and in vitro. Nisin ZP decreased clonogenic capacity, cell proliferation level and sphere formation in HNSCC cells thereby increasing the level of apoptosis and decreasing level of clonogenic capacity, cell proliferation and sphere formation [35]. Susceptibility testing of 10 kDa bacteriocin produced by *Enterococcus mundtii* strain C4L10 against various cancer cell lines such as H1299 (lung cancer), MCF7 (breast cancer), HCT116 (colon cancer), and HSC3 (oral cancer) proved its potential in vitro as an anti-proliferative agent in controlling cancer [33, 36].

CONCLUSION:

Bacteriocins have different kinds of mechanisms for killing pathogens and it is regulated via a few genes that are either plasmid-borne or chromosomally encoded. Advantages of bacteriocins are in great demand with the food industry because they are granted as safe for human health and also used as bio-preservatives. Class I bacteriocins are extracted from LAB which is known as lantibiotics, and it has a wide spectrum of applications in various sectors such as the food industry, medical fields, aquaculture and pharmaceutical industry. Till now, the antimicrobial activity of bacteriocin is widely studied, but their safety, toxicity, potentiality and efficacy related *in vivo* and *in vitro* data is insufficient; therefore, different assays are necessary to perform further confirmation and investigation of bacteriocin. In a concentrated form, bacteriocin can be encapsulated into nano-particles to minimize its side effects and increase its effectiveness. In addition, recombinant DNA technology based approaches such as the construction of vectors carrying novel bacteriocin genes for expression and regulation of heterologous protein in favourable hosts to achieve overproduction can bring revolution in the food industry. Pediocin steadiness is important in a multiplex environment of the food and in

the hydrophobic residue rich amount of pediocin should be developed.

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