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CLASSIFICATION AND MECHANISM OF BACTERIOCIN INDUCED CELL DEATH: A REVIEW

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ABSTRACT

Multidrug resistance and toxicity associated with antimicrobial agents among pathogenic bacteria leading to a surge in morbidity and mortality in humans need bold proclamation in the area of research and development of new biological agents. The maximum propitious possibility we can see in the area of bacteriocins. Bacteriocins are ribosomally synthesized peptides produced by gram-positive and gram-negative bacteria which evince wide and narrow antimicrobial activity spectrum. They can survive in a highly competitive microbial environment. Bacteriocins attack their targeted bacterial cells through different mechanisms. Understanding different mechanisms that induced cell death will enable researchers to develop methodologies to limit this life-threatening problem. Therefore, in this study, we provide the updated information on the number of bacteriocins produced, their potential producers and different mode of action against relevant pathogenic bacteria.

Keywords: Antimicrobial, toxicity, bacteriocins, mechanisms, pathogenic bacteria

INTRODUCTION

Today, the world suffers from a number of infectious diseases, which are mainly caused by pathogenic organisms. Pathogenic organisms inhibit the production of antimicrobial peptides inside the body and caused several life-threatening diseases (**Sharma *et al.*, 2016; Singh *et al.*, 2021**). The important part of natural immunity in human is the production of antimicrobial peptides which protects various disease-causing organisms like bacteria, fungi, yeast viruses and cancer cells (**Reddy *et al.*, 2004**; **Kaushik *et al.*, 2017**). Bacteria itself release some antimicrobial peptides which are the biologically extra-cellular product of ribosomal synthesis (**Klaenhammer, 1993**; **Pirzada *et al.*, 2004**). They are produced by both gram-positive and gram-negative bacteria including some archaea (**Zheng *et al.*, 2015**). A large portion of bacteriocins from gram-negative bacteria resembles defensins which are the eukaryotic antimicrobial peptides (**Baindara *et al.*, 2018**). Many bacteria are known for producing bacteriocins in humans, plants and various food products where they have a valuable place e.g. *E. coli*, *Lactic acid bacteria* (LAB), *Weissellaconfusa*, *Streptococcus mutans*, *Streptococcus salivarius*, *Bacillus subtilis* etc. Out of which LAB described as GRAS (generally regarded as safe) for human consumption (**Balciunas *et al.*, 2013; Kaushik and Arora, 2017; Indumathi et al. 2015; Sing, 2021**). The bacteriocins show inhibitory action on food deterioration and foodborne pathogenic microorganisms, additionally, the bacteriocins from lactic acid microorganisms widely known for both food preservative and therapeutic potentials (**Kumari *et al.*, 2018; Mittal *et al.*, 2020, Sharma *et al.*, 2016**). Bacteriocins from different species of bacteria, in contrast to all other antibiotics, show killing action on the same or closely related species (**Peter R, 1965**). Each species of bacteria produces tens or even hundreds of different kinds of bacteriocins (**Bindiya *et al.*, 2016**). Bacteriocins are a heterogeneous group of particles with different morphological and biochemical entities. They range from simple and low molecular weight protein to complex and high molecular weight protein. Moreover, the bacteriocins are non-immunogenic, biodegradable substances and possess cancer-cell specific toxicity (**Kaur *et al.*, 2015**). They also act as the competitive agents between the microbial communities (**Chao *et al.*, 1981, Majeed *et al.*, 2013, Riley *et al.*, 1999**). Researchers had conducted a deep study on various aspects of bacteriocins like the methods for their detection, characterization, purification and identification of genetic determinants from gram-positive and gram-negative micro-organisms (**Catherine *et al.*, 1993**).

BACKGROUND OF THE REVIEW

Colicin is the very first bacteriocin discovered by Belgian scientist **Gratia, (1925)** a heat-liable product where he observed that *Escherichia coli* V inhibits *Escherichia coli* S during his search for the ways to kill the bacteria. The inhibition of one bacterial strain by another had been observed many times by Gratia. But the importance of bacteriocin can't explore much at that time due to the lack of knowledge about its structure and production which led to the dominance of chemically synthesized broad-spectrum antibiotics (Syngulon.com). **Fredericq, (1946)** revealed the proteinaceous nature of colicin and demonstrated that the inhibitory activity of bacteriocin was due to the presence of specific surface receptors of sensitive cells. After a long period, it is verified that a large number of bacteria produced some common molecules which inhibit the growth of other strains or species, these molecules were named bacteriocins (**Jacob *et al.*, 1953**). Bacteriocins have been detected in all major lineages of eubacteria and some members of Archaebacteria and recently it becomes a viable alternative to conventional antibiotics (**Torrebranca *et al.*, 1995; Gillor *et al.*, 2008; Cotter *et al.*, 2013**).

CLASSIFICATION OF BACTERIOCINS

Bacteriocins can be classified based on their molecular weight, thermostability, enzymatic sensitivity, mode of action and presence of post-translationally modified amino acids (**Klaenhammer, 1993**). **Jack *et al.* (1995)** reported that the presence of the number of disulfide and monosulfide (lanthione) bonds not only forms the basis of classification but also affects the activity spectrum of bacteriocins. Furthermore, based on molecular weight gram-negative bacteria are divided into two classes namely colicins and microcins. Most bacteriocins of gram-negative bacteria are isolated from *E. coli* and other enterobacteria (**Hassan *et al.*, 2012**). The bacteriocins of gram-positive bacteria are divided into four classes (Class I, II, III, IV) which are broadly described in previous literature. These classes from gram-negative and gram-positive bacteria are further subdivided into their respective sub-groups (**Ramu *et al.*, 2015**). However, Cotter *et al*. classified the

bacteriocin produced from LAB (gram-positive bacteria) into two main classes, lantibiotics (class I), not containing lanthionine lantibiotics (class II) whereas class III was individually designated as bacteriolysins. It was also suggested by the authors that class IV should be extinguished (**Tumbarski *et al.*, 2018**). So, recently authors have altered the classification of gram-positive bacteria from four classes to three, while different authors have used a somewhat different description of sub-classes (**Mokoena, 2017**). **Yang *et al*. (2014)** mentioned that microcin E492 derived from gram-negative bacterial sp. *Klebsiella pneumonia*, so class II should be categorized under microcins of gram-negative bacteria. Moreover, the bacteriocins are currently used in agro-food as a food preservative however it may be considered as potential candidates for further development and used in health contexts. The different classification and applications of bacteriocins are enlisted in Figure 1 and 2.

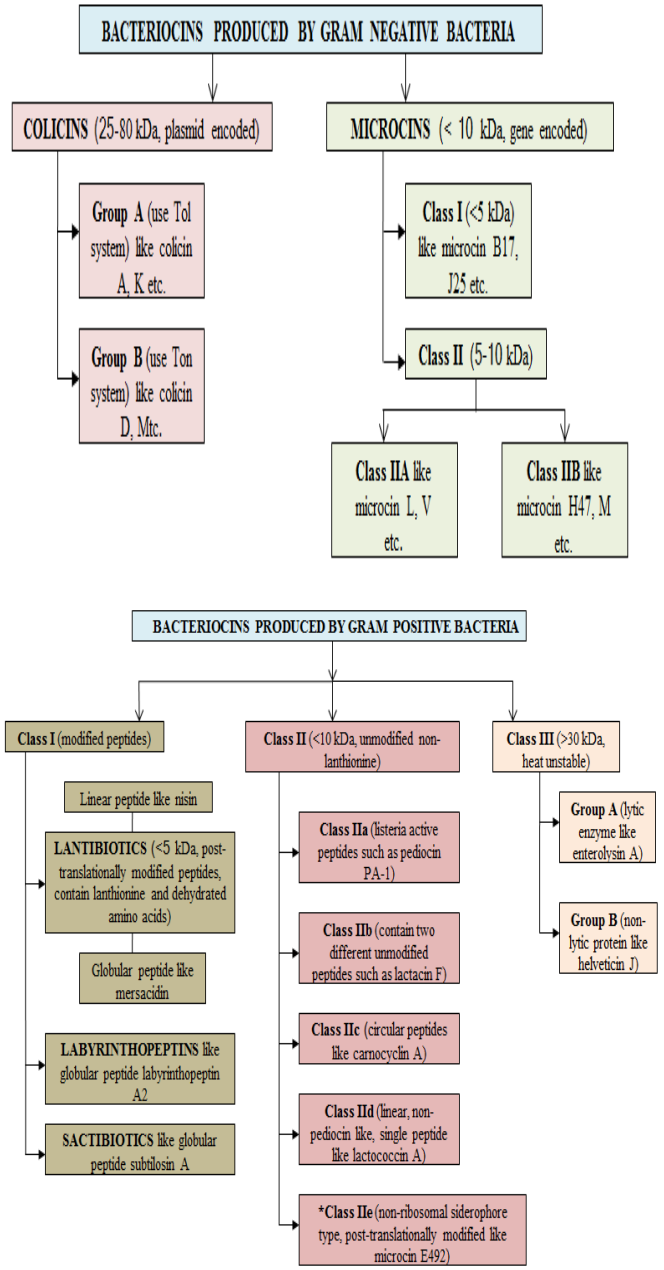

Figure 1 Classification of gram-negative and gram-positive bacteriocins **(Yang *et al*., 2014)**

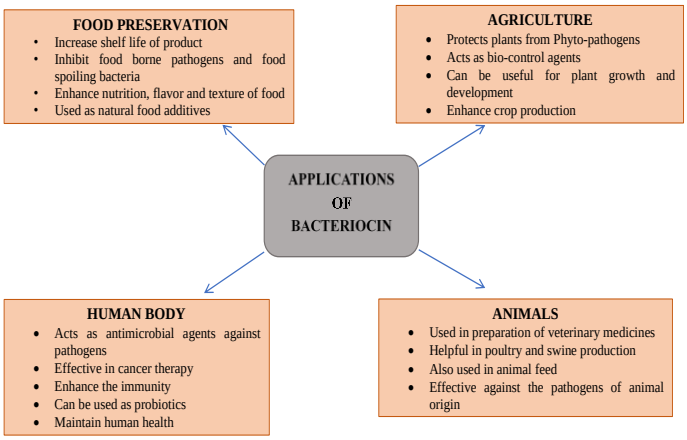

Figure 2 Schematic representation of various applications of bacteriocins in different sectors

PROPERTIES OF BACTERIOCIN FOR INHIBITION

Bacteriocins have some special features which make them lethal towards pathogenic organisms. They must have a cationic (mostly at pH 7.0) and highly hydrophobic nature to be lethal as observed for the most bacteriocins belonged to Class I and II. They must be active at a wide range of pH, as found in the case of numerous small size bacteriocins where they show antibacterial activity at different pH ranging from 3.0 to 9.0. Their high isoelectric point promotes the interaction at physiological pH with the anionic surface of bacterial membranes which cause the insertion of hydrophobic moiety into the bacterial membrane which finally build up a trans-membrane pore that led to cell death due to gradient dissipation (**Jack *et al*., 1995**). They are diffusible toxins that do not require contact between bacteria like type six secretion system (T6SS) and contact-dependent inhibition (CDI) (**Sharp *et al*., 2017**). Bacteriocins are potent even at the pico to nanomolar concentration as compared to eukaryotic AMPs which acts at a micromolar concentration (**Hassan *et al*., 2012**). Low molecular protein must be heat stable to show the killing action on related pathogenic strains. The stabilization of secondary structures accompanies by the complex pattern of monosulfide and disulfide intramolecular bonds which acts to reduce the number of possible unfolded structures (entropic effect) (**Oscáriz *et al*., 2001, Singh *et al*., 2013**). However, the presence of some enzymes like proteinase K, trypsin, proteases, pronase and other proteolytic enzymes inhibitor may lead to the complete reduction of the killing action of bacteriocins produced by different bacterial species (**Sharma *et al*., 2009; Jabeen *et al*., 2009; Pirzada *et al*., 2004; Todorov and Dicks, 2005; Tolincki *et al*., 2010**). The way, they kill the sensitive cells is called"quantal" killing rather than "molar" cooperative killing action of classical antibiotics (**Mayr-Harting *et al*., 1972**).

MECHANISMS OF BACTERIOCINS

Bacteriocins kill the pathogenic bacteria in several ways, like pore-forming inhibition of cell wall, nucleic acid and protein synthesis (Figure 3). Usually, they have a narrow killing spectrum as they are limited to the inhibition of closely related species and simultaneously they may have broad-spectrum activity against distantly related bacterial species (**Singh *et al*., 2013**; **Klaenhammer, 1993**; **Adams and Moss, 2008**; **Kumariya *et al*., 2019**) and plays a defensive role by inhibiting the invasion of other strains or by limiting the growth of neighbouring cells (**Riley and Wertz, 2002b**). The production of bacteriocins seems to be a hereditary feature associated with cytoplasmic genes i.e. bacteriocinogenic factors. Their mode of action varies greatly from one species to another (**Daw and Falkiner, 1996**).

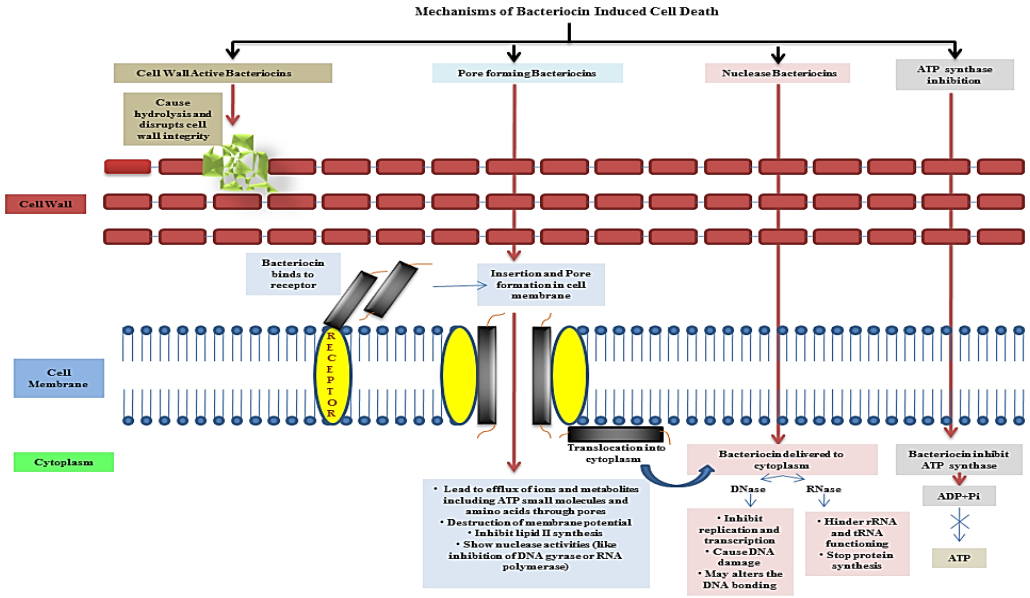

Figure 3 Schematic diagram of mechanisms of bacteriocin induced cell death

INHIBITION BY PORE FORMATION

Pore formation is the well-known mechanism in which these antibacterial proteins binds to the specific receptors on cells and forms pores in the membrane which is also called as cell permeability and thus cause the death of pathogenic microorganism (**Preciado *et al*., 2016**). These antibacterial proteins are also called c PFTs are one of the wide categories of virulence factors as they constitute 25-30% of cytotoxic bacterial proteins (**Alouf, 2003**; **Gonzalez *et al*., 2008**). The diameter of the pore formed by these proteins varies from one species to another, ranging between 1-50 nm consisting of 6-50 or more units of PFPs (**Peraro and van der Goot, 2016**). The largest pores found in cholesterol-dependent cytolysins (CDCs) whose diameter ranges from 25-40 nm (**Twetene*t al*., 2015**). Generally, PFPs are genetically encoded large proteins (α-toxin) or small cationic peptides which are delivered to the targeted cell for production and insertion into the membrane (**Panchal *et al*., 2002**). Based on the secondary structure of the region that allows the formation of the pore by penetrating the host cell, PFPs are divided into two main classes: α-PFPs and β-PFPs which forms pores by bundles of α-helicals or by trans-membrane β-barrels respectively (**Anderluh*et al*., 2008, Ostolaza*et al*., 2019**). These antibacterial proteins are water-soluble monomers that bind to the lipid membrane of the cell and oligomerize to form structural assemblies called pre-pores. These pre-pores exposed the hydrophobic surface of the cell by undergoing some conformational changes that lead to the insertion into the lipid bilayer which forms a pore that causes the permeabilization of the cell membrane (**Omersa *et al*., 2019**). This mechanism is followed by β-PFPs while in the case of α-PFPs the insertion into the membrane is associated with a sequential oligomerization which then forms a partial or complete pore and the pore remains active in both cases. The β-pores are structurally more stable in comparison to α-pores due to the inter-chain interactions between the hydrogen bonds (**Ostolaza*et al*., 2019**). The formation of oligomers is a common characteristic of PFPs that pierce the cell membrane of the pathogen (**Cosentino *et al*., 2016**). Pore-forming proteins disrupt the maintenance of the osmotic balance of the cell which leads to the cytolysis (**Alouf, 2003**). They make the path for the passage of ions, proteins or other constitutes through the targeted membrane. The loss of potassium and magnesium ion has been implicated as the primary cause of cell death (**Konisky, 1982**). Pore formation also causes rapid dissipation of transmembrane electrostatic potential which lead to the rapid death of bacterial cells (**Prince *et al*., 2016**).

Nisin belongs to the lantibiotic family, an amphiphilic and cationic bacteriocin (3.4kDa) isolated from the different strains of *Lactococcus lactis* subsp. *lactis*, is one of the widely studied bacteriocins. It is an FDA approved and GRAS peptide with recognized potential for clinical use (**Shin *et al*., 2016**). It acts on the targeted cells through pore formation by the use of "Docking Molecule" mediated by cell wall precursor lipid II which forms stable pores of around 2-2.5 nm diameter (**Wiedemann *et al*., 2004**). Nisin binds to lipid II with the two lanthionine rings at the N-terminus, forming a pyrophosphate cage around the head group of lipid II and flexible hinge region cause the insertion of C-terminus in a transmembrane orientation which led to the formation of a stable pore (**Prince *et al*., 2016**). **Kraaij *et al*., (1998)** demonstrated the importance of translocation of the C-terminal region in pore formation. However, the C- terminus of NisI (immunity protein of *Lactococcus lactis*) found to inhibiting the nisin mediated pore formation by protecting the lipid II (**Alkhatib *et al*., 2014**). Further, nisin use all lipid II molecules to form the pore complex which uniformly consists of 8 nisin and 4 lipid-II molecules. These pores were able to resist the solubilization of the membrane environment by mild detergents (**Hasper*et al*., 2004**). The micromolar concentrations are necessary in the absence of lipid II while nanomolar concentrations are sufficient to form a pore in the presence of lipid II (**Christ, 2007**). Nisin also acts as an anionic selective carrier during the absence of anionic membrane phospholipids and forms nonselective, wedge-like, multistate, water-filled pores in the presence of anionic phospholipids which results from the bending of lipid surface due to co-insertion of the surface-bound aggregate to it (**Moll *et al*., 1996**). The bacteriocins that kill the pathogens by pore formation are enlist in Table 1.

CELL WALL BIOSYNTHESIS INHIBITION

The antimicrobial peptides involved in the inhibition of biosynthesis of cell wall either by inhibiting peptidoglycan synthesis or by binding to the lipid II or may impair the cell wall functions are called as cell-wall active or membrane-active bacteriocins. This mechanism may involve a concerted action with pore formation as observed in nisin, a well-known bacteriocin widely used in food preservation. This mechanism is followed by both gram-negative and gram-positive bacteria. It comprises a wide variety of structures like lipid II-binding bacteriocins, two peptide lantibiotics and non-modified bacteriocins (**Rocese*t al*., 2012**). In eukaryotic cells, cell membrane acts as the main target of bacteriocins where they enhance the expression of negatively charged cell surface molecules on the cancer cells makes them prone to the cytotoxic activity of bacteriocins (**Kaur *et al*., 2015**). Nisin is the first example of a membrane-targeted lantibiotics (**Breukink*et al*., 2003**). However, **Tol *et al.* (2015)** suggested that nisin variants that cluster lipid II kill L-form bacteria without involving the delocalization of peptidoglycan synthesis which is the primary killing mechanism of these lantibiotics. Lactococcin 972 (Lcn972) is the first unmodified, bacteriocin that binds to the cell wall precursor lipid II to inhibit the septum biosynthesis in *Lactococcus lactis* (**Martínez *et al*., 2008**). **Scherer *et al*., (2015)** revealed that an increase in the size of the nisin-lipid-II complex also plays a role in the inhibition of cell wall synthesis and also induce vesicle budding in the targeted cell membrane. However in some cases, the destabilization of the cell wall or outer membrane is brought by stress condition such as treatment of targeted cell with chemicals or by inducing some physical stress conditions like pH, heating, freezing etc., which may increase the sensitivity of targeted cell as observed for gram-negative bacteria (**Costa *et al*., 2019**). Besides all this, plantaricin NC8, a two-peptide non-lantibiotic class IIb bacteriocin composed of PLNC8α and PLNC8β and derived from *Lactobacillus plantarum* ZJ316 has been found to show antimicrobial activity against *Micrococcus luteus* 1.193 by following the mechanism of cell membrane disruption without targeting lipid II (**Jiang *et al*., 2018**). The bacteriocins that follow the cell wall inhibition mechanism for killing of pathogens are listed in Table 2.

Table 1 List of some bacteriocins that kill the pathogens by pore formation

Name of the bacteriocin	Producing microorganism	Inhibition spectrum	Ref.
Acanthaporin	*Acanthamoeba culbertsoni*	Cytotoxic for human neuronal cells, antibacterial against various bacterial strains	**Michalek *et al*., 2013**
Pentocin MQ1	*Lactobacillus pentosus* CS2	Potent against *M. luteus*, *B. cereus* and *L.monocytogenes*, exhibit high chemical, thermal and pH stability but sensitive to proteolytic enzymes	**Wayah and Philip, 2018**
PmnH	*Pseudomonas* species	Reflects parasitism of the ferrichrome type transporter for the entry into targeted cells under iron-limited growth conditions	**Ghequire*et al*., 2017**
Nisin (3.5kDa)	*Lactococcus lactis*	Antibacterial against gram-positive bacteria, potent against gram-negative bacteria when used at high concentration or when targeted cell have been pretreated with EDTA, also active against spore-forming bacteria	**Parada *et al*., 2007, Abee*et al*., 2003**
Ruminococcin C	*Ruminococcusgnavus*E1	Active against pathogenic *Clostridia* and multidrug-resistant strains	**Chiumento*etal*., 2019**
Acidophilin 801	*Lactobacillus acidophilus* IBB 801	Have a bactericidal effect on *Lactobacillus* strains and also effective against some gram-negative bacteria	**Zamfir*et al*., 2007, 2009**
Cytolysin A	*Escherichia coli* (pathogenic strain)	Cause hemolytic phenotype of several *E. coli* strains	**Fahie*et al*., 2013**
Microcin E492	*Klebsiella pneumonia* RYC492	Exerts antibacterial action on related strains and also has a cytotoxic effect on malignant human cell lines	**Lagos *et al*., 2009**
Lacticin Q	*Lactococcus lactis* QU5	Forms a huge toroidal pore, antibacterial to the targeted cell even at nanomolar range	**Yoneyama*et al*., 2009**
Lacticin 3147	*Lactococcus lactis* subsp. *lactis* DPC3147	Acts on a broad range of gram-positive bacteria including *L. lactis*, *L. monocytogenes*, *B. subtilis*	**McAuliffe *et al*., 1998**
Pediocin PA-1	*Pediococcusacidilactici* PAC1.0	Active against the relative strains forms hydrophilic pores	**Chikinidas *et al*., 1993**
Lactococcin G	*Lactococcus* sp.	Antibacterial to the relative strains where activity depends on the complementary action of two peptides	**Nissen-Meyer *et al*., 1992**
Acidocin J1132	*Lactobacillus acidophilus* JCM 1132	Has narrow inhibitory spectrum	**Tahara *et al*., 1996**
Thermophilin 13	*Streptococcus thermophilus*	Exhibit a non-typical antilisterialporation complex	**Marciset *et al*., 1997**
Bacteriocin AS-48 (Enterocin AS-48)	*Enterococcus faecalis*	Has broad-spectrum antimicrobial activity against gram-positive and gram-negative bacteria, also acts as a leishmanicidal agent	**Cruz *et al*., 2013; Abengózar *et al*., 2017**
Plantaricin MG	*Lactobacillus plantarum* KLDS1.0391	Broad inhibitory activity against gram-positive and gram-negative bacteria including *Listeria monocytogenes* and *Salmonella typhimurium*	**Gong *et al*., 2010**
Lactocin 705	*Lactobacillus casei* CRL705	Active against relative strains of *Lactobacillus* sp.	**Castellano *et al*., 2003**
Bifidocin A	*Bifidobacterium animalis* BB04	Has broad antibacterial spectrum against gram-negative bacteria	**Liu *et al*., 2016**
Lactococcin MMT24	*Lactococcus lactis* MMT24	Has narrow spectrum and possesses a bactericidal effect on closely related species	**Ghrairi *et al*., 2005**
Bacteriocin HL32	*Lactobacillus paracasei*HL32	Active against *Porphyromonasgingivalis* infections	**Pangsomboon *et al*., 2006**
Pediocin PD-1	*Pediococcusdamnosus* NCFB 1832	Inhibits the growth of several food spoilage bacteria, including malolactic bacteria isolated from wine, highly active against the cells of *Oenococcusoeni*	**Bauer *et al*., 2005**
Lactocin 160	*Lactobacillus rhamnosus* (Vaginal strain)	Inhibits the growth of *Micrococcus luteus* ATCC 10420	**Jie *et al*., 2005**
Bovicin HC5	*Streptococcus bovis* HC5	Active against *Staphylococcus cohnii* and *Staphylococcus warneri*, blocked lipid II-dependent pore formation activity of Nisin	**Paiva *et al*., 2011**
Pneumolysin	*Streptococcus pneumonia*	Acts as a key virulence factor against host cells especially toxic to human	**Vögele *et al*., 2019, Rai *et al*., 2016**
Bificin C6165	*Bifidobacterium animalis*	Active against almost sixteen strains of *Alicyclobacillus acidoterrestris*	**Pei *et al*., 2014**
Thuricin S	*Bacillus thuringiensis*	Bactericidal to sensitive cells of *B. thuringiensis* subsp. *dermastadiensis*	**Chehimi *et al*., 2010**
Cerein 8A	*Bacillus cereus*	Antibacterial to closely related species also includes *E. coli* and *Salmonellaenteritidis*, *L. monocytogenes*	**Bizani *et al*., 2005**

Table 2 List of some bacteriocins that follow the cell wall inhibition mechanism

Name of the bacteriocin	Producing microorganism	Inhibition spectrum	Ref.
Enterolysin A (pH regulated)	*Enterococcus faecalis* LMG 2333	Inhibits the growth of selected enterococci, pediococci, lactococci and lactobacilli	**Nilsen *et al*., 2003**
Helveticin-M	*Lactobacillus crispatus*	Disrupts the cell wall of gram-positive bacteria and disorganized the outer memberane of gram negative bacteria. Active against *S. aureus*, *S. saprophyticus* and *Enterobacter cloacae.*	**Sun *et al*., 2018**
Colicin M (29.5kDa)	*Escherichia coli*	Kills susceptible *E. coli* cells and other related strains	**Barreteau *et al*., 2012**
BacC1	*Enterococcus faecium* C1	Inhibit the growth of selective food spoilage bacteria	**Goh & Philip, 2015**
PLNC8 αβ (two peptide bacteriocin)	*Lactobacillus plantarum* NC8	Effective against periodontal pathogen *Porphyromonas gingivalis* (may form pores causing intracellular leakage)	**Khalaf *et al*., 2016**
Mersacidin	*Bacillus* spp.	Susceptible to gram-positive bacteria	**Lajis, 2020**
Nisin	*Lactococcus lactis*	Kills vegetative cells of gram-positive bacteria	**Jozala *et al*., 2015**
Lysostaphin	*Staphylococcus simulans* bv. *staphylolyticus*	Effective against *S. aureus* and may other relative strains	**Gründling *et al*., 2006**
S.s bacteriocin	*Streptococcus sanguinis*	Effective against *Candida albicans* and *Candida tropicalis*	**Ma *et al*., 2015**
Planosporicin	*Planomonospora* spp.	Active against gram positive pathogens of medical importance, including multi-resistant clinical isolates	**Castiglione *et al*., 2007**
Acidocin 1B	*Lactobacillus acidophilus* GP1B	Active against LAB and other pathogens including gram negative bacteria	**Han *et al*., 2007**
Butyricin 7423	*Clostridium butyricum* NCIB7423	Have non-lytic action on *C. pasteurianum* but bactericidal to other species of *Clostridium*	**Clarke *et al*., 1976**
Halocin H6	*Halobacterial* sp.	Inhibit the growth of other halobacteria	**Torreblanca *et al*., 1990**
Pln 149 (amphipathic α-helical antimicrobial peptide)	*Lactobacillus plantarum* NRIC 149	Active against *S. cerevisiae*, applicable in food industries for disrupting cells as non-enzymatic /non-mechanical process	**Lopes *et al*., 2009**
Millericin B	*Streptococcus milleri* NMSCC 061	Active against broad spectrum of gram positive bacteria except *B. subtilis* W23 and *E. coli* ATCC 486 or against the producer strain itself	**Beukes *et al*., 2000**
NAI-107 (microbisporicin)	*Microbispora s.* ATCC PTA-5024	Active against multi-drug resistant gram-positive pathogens including MRSA and VRE and some gram negative spp.	**Münch *et al*., 2014**
SK 119	*L. plantarum* subsp. *plantarum* SK119	*Listeria* active bacteriocin (also forms pores but researchers insists that cell death associated with damage of cell membrane)	**Botthoulath *et al*., 2018**
Mesenterocin 52A	*Leuconostoc mesenteroides* subsp. *Mesenteroides* FR52	Inhibit membrane of *Listeria ivanovii* CIP 12510 without pore formation and of *Listeria innocua* CIP 12511 with pore formation	**Jasniewski *et al*., 2008**

Nuclease activity inhibition/ protein inhibition

Generally, the nuclease activity involves the breakdown of macromolecules like the disruption of bonds between nucleotides in nucleic acids such as DNA and RNA. Table 3. showed the list of bacteriocins that inhibits protein or nuclease activity of the targeted cell. The bacteriocins which follow this mechanism are also known as nuclease bacteriocins (NBs). Different nuclease bacteriocins are involved in the inhibition of DNA, RNA and protein synthesis together with permease function and show the primary effect on the deployment of energy by the bacterium (**Reeves, 1972**). They usually have a broad range of size, ranges from 178 to777 amino acid (**Bindiya*et al*., 2016**). The colicins, plasmid encoded bacteriocin from *Escherichia coli* also shows nuclease activity. Even the colicin E1 and K inhibits all macromolecule synthesis without the arrest of respiration while others may act by cleaving the precise site of particular nucleic acid (**Cascales*et al*., 2007**). They contain an N-terminal translocation domain, a central receptor binding domain and a C-terminal cytotoxic domain that binds a cognate immunity protein however the location of the translocation and receptor-binding domains in pyocins (bacteriocins from *Pseudomonas aeruginosa*) appears to be reverse (**Atanaskovic *et al*., 2019**). Translocations of nuclease colicins across the outer and inner membrane must be necessary to achieve their target in the cytoplasm (**Cascales *et al*., 2007; de Zamaroczy *et al*., 2011**). During translocation, the immunity proteins of nuclease colicins may be dissociated at the cell surface in a pmf-dependent step (**Sharp *et al*., 2017**). The nuclease bacteriocin delivered to the cytoplasm of a targeted cell which involves the DNA chromosomal cleavage randomly led to the cell death. Many nuclease colicins like colicin E2, E7, E8 and E9 found to exhibit their antimicrobial activity by the action of DNase which involves the non-specific cleavage of genomic DNA (**Schaller *et al*., 1976; Chak*et al*., 1991; Cooper *et al*., 1984**).HNH/ββα-Me motif acts as the catalytic centre of many colicins and pyocins DNases by hydrolyzing the phosphodiester bond through chelation with a single divalent metal ion (**Klein *et al*., 2016**). **Walker *et al*., (2007)** showed that the toxic action of nuclease colicins depends upon functional FtsH, an inner membrane AAA^+ ATPase and protease that dislocates misfolded membrane proteins to the cytoplasm of a targeted cell as to cause cell death. LepB which is an important inner membrane enzyme of *E. coli*and a key membrane component of cellular secretion machinery offered a chaperon-like function for the penetration of several nuclease bacteriocins into a target cell in addition to this it was also reported as the necessary component of machinery hijacked by the tRNase colicin D for its import (**Mora *et al*., 2015**). Colicin like E3, E4, E6 exhibit RNase activity, out of which Colicin E3 is most widely studied, which is known to cleaves the 3' region of 16-S rRNA between A1493 and G1494 (E. coli numbering) in the decoding A-site and decreases the acceptance of cognate aminoacyl-tRNAs (aa-tRNAs) and thus slow down the protein synthesis and finally cause the death of the targeted cell (**Ogawa *et al*., 2016**).

ATP SYNTHESIS INHIBITION

Many bacteriocins also show their antimicrobial activity by inhibiting the ATP synthesis or by the release of ATP out of the cell. The bacteriocin that showed the ATP inhibition accompanied by other mechanisms is shown in Table 4. The ATP synthesis inhibition accompanied by either cell wall synthesis inhibition or by pore formation which allows the secretion or reduction of ATP along with other ionic molecules as stated by many researchers. There are many examples of bacteriocins that involved in ATP synthesis inhibition like mesentericin Y105 produced by *Leuconostoc mesenteroides* strain which is a pore-forming bacteriocin, had been found to show the effects on cell organelle, where it uncouples the mitochondria by increasing state 4 respiration and decreasing state 3 respiration. It also inhibits the ATP synthase and adenine nucleotide translocase of the organelle (**Maftah *et al*., 1993**). Similarly, microcin J25 also showed inhibition of ATP along with concomitant enhancement of ATP degradation. It was also observed for altering the membrane permeability and inhibiting the enzymatic activity of cytochrome C reductase (complex III) of the respiratory chain (**Chirou *et al*., 2004**). The increased ATPase activity found to be responsible for acid sensitivity of nisin-resistant *Listeria monocytogenes* which cause cell death on the addition of an acid like hydrochloric acid or lactic acid (**McEntire *et al*., 2004**). Sometimes, as a consequence of a shift in the ATP equilibrium, the ATP is hydrolysed into ADP and AMP due to the efflux of phosphate through the channels (**Guihard *et al*.,**

1993). Here, we represent the list of some bacteriocins that involves in the inhibition of ATP synthesis either as a primary or as a secondary action of these antimicrobial proteins.

Table 3 List of bacteriocins that inhibits protein or nuclease activity of targeted cell

Name of the bacteriocin	Producing microorganism	Mode of action	Inhibition spectrum	Ref.
Colicin (E3, E4, E5, E6 and D)	*E. coli* strains	Found to inhibit protein biosynthesis by cleaving 16s rRNA or tRNAs	Active against some other strains of *E. coli* and other related bacteria	**Kaur *et al*., 2015**
Smegmatocin	*Mycobacterium smegmatis*	Inhibits the protein and DNA synthesis	Sensitive to Mks-A TU-7 cells	**Kaur *et al*., 2015**
Colicin E2	*E. coli* K12	Cause specific inhibition of DNA synthesis and induce DNA damage	Active against uropathogenic *E. coli* and other related strains	**Konisky, 1982; Pugsley *et al*., 1985; Trivedi *et al*., 2014**
Colicin L	*Serratia marcescens*	Inhibits the synthesis of proteins, DNA, RNA	Active against certain strains of *E. coli*	**Konisky, 1982**
Butyricin 7423	*Clostridium butyricum* 7423	Inhibit the synthesis of proteins, DNA, RNA, also lowers the ATP levels	Active against *Clostridium pasteurianum*	**Konisky, 1982**
Pyocin AP41	*Pseudomonas aeruginosa* PAF41	In vivo, inhibits DNA synthesis	Sensitive to *P. aeruginosa* strains	**Konisky, 1982**
Carocin S2	*Pectobacterium carotovorum*	Cause exhausting supply of RNA which led to inactivation of protein synthesis	Inhibits the growth of closely related species	**Chan *et al*., 2011**
Bacteriocin (Unclassified)	*Bacteroides fragilis* strain	Inhibits RNA synthesis which led to the inhibition of protein synthesis but has no effect on DNA	Active only against closely related strains	**Mossie *etal*., 1979**
Staphylococcin 1580	*Staphylococcus epidermidis*	Inhibit the synthesis of proteins, DNA, RNA but also have effects on membrane	bactericidal to many gram positive bacteria and stable staphylococcal L-forms	**Jetten and Vogels, 1972**
Bacteriocin (unclassified)	*Bacteroides fragilis*	Inhibit ribonucleic acid polymerase	narrow spectrum of activity	**Mossie *et al*., 1981**
Enterocin E1A & E1B	*Streptococcus faecium* E1	Without degrading DNA or RNA it inhibits the synthesis of proteins, DNA and RNA	Active only against certain strains of *enterococci, S. salivarius*&*L. monocytogens*	**Kramer & Brandis, 1975**
Megacin C	*Bacillus megaterium*	Inhibits DNA synthesis while protein and RNA are little effected	Specific for other strains of species as well as some closely related strains	**Holland, 1965**
Lactostrepcin 5	*Lactococcus lactis* subsp. *cremoris* 202	Inhibits the synthesis of proteins, DNA and RNA, also cause ion leakage and interfere with uridine transport	Antimicrobial against *lactococci*	**Nettles *et al*., 1993**
Agrocin 84	*Agrobacterium radiobacter*	Inhibits DNA synthesis without degrading it	Antimicrobial against oncogenic strains of *A. Tumefaciens*	**Das *et al*., 1978**
Marcescin A	*Serratia marcesens* HY	Inhibit DNA, RNA, protein synthesis, also degrades DNA & RNA	Active against strains of *S. marcescens* & *E. coli*	**Eichenlaub *et al*., 1974**
Mercescin B	*Serratia marcesens* HY	Only inhibits DNA, RNA, protein synthesis	Active only against *E. coli* strains	**Eichenlaub *et al*., 1974**
Lactocin 27	*Lactobacillus helveticus* strain LP27	Inhibits primarily protein synthesis	Bacteriostatic to *L. helveticus* strain LS18	**Upreti *et al*., 1975**
Streptocin A	Group A *Streptococcus strain* FF-22	Inhibit DNA, RNA, protein synthesis, also interfere with the uptake and incorporation of glucose	Has bactericidal effect on Group A *Streptococcus* species	**Tagg *et al*., 1973**
Bacteriocin DF13	*Enterobacter cloacae* DF13	Inhibits primarily protein synthesis had no effect on DNA & RNA synthesis	Has killing action on *Klebsiella edwardsii*	**Graaf *et al*., 1969**
Staphylococcin 462	*Staphylococcus aureus* strain 462	Stop protein synthesis, also inhibits the DNA & RNA synthesis but does not stop it	Active against *S.aureus* 140	**Hale *et al*., 1975**
Bacteriocin Bc-48	*Enterococcus faecalis ssp. Liquefaciens S-48 and its mutant B-48-28(AS-48⁻)*	Inhibits protein synthesis but does not affect amino acid uptake	Inhibition spectrum restricted to strains of *E. faecalis*	**Lopez-Lara *et al*., 1991**
Clostocin O	*Clostridium saccharoperbutylacet-onicum*	Synthesis of DNA, mRNA and mononucleotides, moderately effects the lipid, mRNA and protein synthesis	Active only against closely related strains	**Kato *et al*., 1977**
Pneumolysin	*Streptococcus pneumoniae*	Induce DNA damage and cell cycle arrest	Effective against *S. pneumoniae* infections	**Rai *et al*., 2016**

Sublancin	*Bacillus subtilis* 168	Effects DNA replication, transcription and RNA translation	Effective against gram-positive bacteria including MRSA	**Wu *et al*., 2018**

Table 4 List of bacteriocin that shows ATP inhibition accompanied by other mechanisms

Name of the bacteriocin	Producing microorganism	Primary mechanism	Effect on ATP	Ref.
Pyocin R1	*Pseudomonas aeruginosa*	Memberane depolarization	Cause decrease in intracellular ATP level without affecting the respiration of sensitive cells	**Uratani *et al*., 1984**
Linenscin OC2	*Brevibacterium linens*OC2	Acts on cytoplasmic membrane (Membrane depolarization), active against *Listeria innocua*	Cause hydrolysis of internal ATP along with efflux of Pi and cause transient increase in oxygen consumption	**Boucabeille *et al*., 1998**
Enterocin LD3	*Enterococcus hirae* LD3	Cause dissipation of cell membrane (inhibits gram positive and gram negative bacteria including human pathogens)	Loss of internal ATP	**Gupta *et al*., 2016**
Pediocin PA-1	*Pediococcus acidilactici* PAC 1.0	Pore formation	ATP depletion occurs in concentration and time-dependent manner, also induce irreversible K^+ and Pi efflux	**Chen *et al*., 1995; Chikinidas *et al*.,1993**
Nisin A	*Lactococcus lactis* strains	-	Reduced the ATP and cause the leakage of intracellular ATP out of the targeted cell i.e. *Mycobacterium smegmatis*	**Montville *et al*., 1999**
Pentocin 31-1	*Lactobacillus pentosus*	Cause cell membrane permeabilization	Efflux of ATP along with K^+ and Pi	**Zhou *et al*., 2008**
Viridin B	*Streptococcus mitis (mitior)*	Block macromolecule synthesis without causing any degradation	ATP production of targeted cell was slightly enhanced within 1h of exposure to bacteriocin	**Law *et al*., 1978**
Lactacin F	*Lactobacillus johnsonii*	Form poration complex in cytoplasmic membrane	Cause hydrolysis of internal ATP along with loss of cellular K^+	**Abee *et al*., 1994**
Bacteriocin CHQS	*Enterococcus faecalis TG2*	Changes the cell membrane permeability, integrity and proton motive force	Cause massive release of ATP and UV absorbing materials	**Cao *et al*., 2019**
Bacteriocin 2a	*Lactobacillus sake* strain	Pore formation	Reduce the intracellular ATP with no detectable increase in extracellular ATP	**Rosa *et al*., 2002**
Piscicocin CS526	*Carnobacterium piscicola* CS526	Pore formation	ATP level rapidly reduced without leakage of ATP from the cells, indicating ATP depletion	**Suzuki *et al*., 2005**

CONCLUSION

As described above, we can recapitulate that how these bacteriocins are inhibiting the growth of bacteria replacing the hazardous chemical preservatives in agro-food industries and become prominence for society as they involve in the killing of pathogens by following mechanisms. Due to their diversity in various aspects like mode of action, uses and their habitat they may provide new and more advanced pathways for researchers in the area of medical, pharma, agriculture and food biotechnology for the sake of humanity. To overcome, antibiotic-resistant related issue in the medical sector this can warrant an alternative and provide the researchers to remove insurmountable difficulties.

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