CLASSIFICATION AND MECHANISM OF BACTERIOCIN INDUCED CELL DEATH: A REVIEW

Kajal Sharma1, Sandeep Kaur2, Rajat Singh3 and Naveen Kumar*

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 resemble 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), Weissella sp., Streptococcus mutans, Streptococcus salivarius, Bacillus subtilis etc. Out of which LAB described as GRAS (generally regarded as safe) for human consumption (Balcunas 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 (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-labile 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 Archaeabacteria 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 (lanthionine) 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 microcin. 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 (Ranu 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 bacteriocylins. It was also suggested by the authors that class IV should be extinguished (Yumbarski 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 subclasses (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) (Osčárie et al., 2001; Singh et al., 2013). However, the presence of some enzymes like proteasome 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-Hartung 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; Kumaříček 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).
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 (Tweetsen et 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-helical 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 cytolyis (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 stains 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 lead 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 Nis (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 (Hesper 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 (Rocelet et al., 2012). In eukaryotic cells, cell membrane acts as the main target of bacteriocin 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 (Breunink 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. Lactococcus 972 (Leu972) is the first unmodified, bacteriocin that binds to the cell wall precursor lipid II to inhibit the septum biosynthesis in Lactococcus lactis (Martinez 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 PLNC8a and PLNC8b 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. monocytyogenes*, 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 | Ghequiret 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         | Ruminococcus gnarus E1  | Active against pathogenic *Clostridia* and multidrug-resistant strains | Chiumento et al., 2019 |
| Acidophalin 801        | Lactobacillus acidophilus IBB 801 | Have a bactericidal effect on *Lactobacillus* strains and also effective against some gram-negative bacteria | Zamfiri et al., 2007, 2009 |
| Cytolytin A            | Escherichia coli (pathogenic strain) | Cause hemolytic phenotype of several *E. coli* strains | Fahei 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 Q5    | 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. monocytyogenes, B. subtilis* | McAuliffe et al., 1998 |
| Pediocin PA-1          | Pediococcus acidilactici PAC1.0 | Active against the relative strains forms hydrophilic pores | Chikindas 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 *L. 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 *Porphyromonas gingivalis* infections | Pangsomboon et al., 2006 |
| Pediocin PD-1          | Pediococcus damnosus NCFB 1832 | Inhibits the growth of several food spoilage bacteria, including malolactic bacteria isolated from wine, highly active against the cells of *Oenococcus oeni* | Bauer et al., 2005 |
| Lacticin 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. *dermatisdihensis* | Chehimi et al., 2010 |
| Cerein 8A             | Bacillus cereus | Antibacterial to closely related species also includes *E. coli* and *Salmonella enteritidis, L. monocytyogenes* | 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 disinorgranized the outer membrane of gram negative bacteria. Active against S. aureus, S. supraphylococcus and Enterobacter cloacae | Sun et al., 2018 |
| Colicin M (29.5kDa) | Escherichia coli | Kills susceptible E. coli cells and other related strains | Barretoeu et al., 2012 |
| BacC1 | Enterococcus faecium C1 | Inhibit the growth of selective food spoilage bacteria | Goh & Philip, 2015 |
| PLNCS (f)(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 | Lazzis, 2020 |
| Nisin | Lactococcus lactis | Kills vegetative cells of gram-positive bacteria | Jozala et al., 2015 |
| Lysostaphin | Staphylococcus simulans bv. staphylofticus | Effective against S. aureus and may other related 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 IB | Lactobacillus acidophilus GP1B | Active against LAB and other pathogens including gram negative bacteria | Han et al., 2007 |
| Butyrin 7423 | Clostridium butyricum NCIB 7423 | 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 |
| Pin 149 (amphiphatic o-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 |
| Millercin B | Streptococcus milleri NMSCC 061 | Active against broad spectrum of gram positive bacteria except B. subtilis W23 and E. coli ATCC 486 | Beukes et al., 2000 |
| NAI-107 (microbisporicin) | Microbispora s. ATCC PTA-5024 | Active against multi-drg 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 PR52 | Inhibit membrane of Listeria ivanovii CIP 12510 without pore formation and of Listeria innocua CIP 12511 with pore formation | Jasniwerski et al., 2008 |

Nucleic acid activity inhibition/protein inhibition

Generally, the nucleic 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 nucleic 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 nucleic 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 (Cascaleset 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 nucleic 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 nucleic colicins may be dissociated at the cell surface in a pmf-dependent step (Sharp et al., 2017). The nucleic bacteriocin delivered to the cytoplasm of a targeted cell which involves the DNA chromosomal cleavage randomly led to the cell death. Many nucleic 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; Chakel 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 cleavage with a single divalent metal ion (Klein et al., 2016). Walker et al., (2007) showed that the toxic action of nucleic colicins depends upon functional Fe3, 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. coliand is a key membrane component of cellular secretion machinery offered a chaperon-like function for the penetration of several nucleic bacteriocins into a target cell in addition to this it was also reported as the necessary component of machinery hijacked by the iRNase 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 16S 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 mesenterocin 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 (Chirowu 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 (McEntree 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 effux of phosphate through the channels (Guilhard et al., 2010).
inhibition of ATP synthesis either as a primary or as a secondary action of these antimicrobials.

| 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 rRNAs | 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 cells | Sensitive to Mks-A TU-7 | 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* AP41 | In vivo, inhibits DNA synthesis | Sensitive to *P. aeruginosa* strains | Konisky, 1982 |
| Carocin S2 | *Pectobacterium carotovorum* | Cause exhaustingly supplying 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 et al., 1979 |
| Staphylococcus 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. monocytogenes* | 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 |
| Lactostreptacin 5 | *Lactococcus lactis* subsp. cremoris 202 | Inhibits synthesise 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 marcescens* HY | Inhibit DNA, RNA, protein synthesis, also degrades DNA & RNA | Active against strains of *S. marcescens & E. coli* | Eichenlaub et al., 1974 |
| Marcescin B | *Serratia marcescens* 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 | Inhibition spectrum restricted to strains of *E. faecalis* | 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 saccharoperbutylicum* | Synthesis of DNA, mRNA and mononucleotides, moderately effects the lipid, mRNA and protein synthesis | Actively 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 |
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  | Membrane depolarization | Cause decrease in intracellular ATP level without affecting the respiration of sensitive cells | Uratani et al., 1984 |
| Linencin OC2           | Brevibacterium linensOC2 | 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 | Boucabelle 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 |
| Pisciecin CSS26        | Carnobacterium piscicola CSS26 | 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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