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Multidrug resistant bacteria and the role of bacteriocins in resolving the global problem as a new generation of antimicrobials.

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Abstract:
The emergence of serious multidrug resistance problems has been recognised in recent years as a major public health issue impacting humans around the world. Multidrug-resistant species are now also occurring in community settings, in addition to appearing in the hospital environment, suggesting that reservoirs of antibiotic-resistant bacteria are present outside the hospital.Almost all competent infecting agents have used elevated levels of multidrug resistance (MDR) with increased morbidity and mortality. Currently, the World Health Organization has listed antibiotic resistance as one of the three most severe public health problems of the 21st century. The key mechanisms of antibiotic resistance are achieved by reducing the drug's intake, altering the drug's goal, inactivating the drug and activating the drug's efflux.The danger posed by multiple multidrug resistant (MDR) species to public health can be addressed by stimulating the detection, production, and redesign of new antibacterial agents with a broad inhibition range. Interestingly, bacteriocins are a common bacterial protection mechanism against other bacterial agents, removing the potential opponents of the former and increasing the amount of nutrients available in the atmosphere for their own growth.The healthy profile and antimicrobial mechanisms of bacteriocin are much superior to antibiotics that differentiate them from conventional broad-spectrum antibiotics, allowing them to be candidates for potential antibiotic substitution. In the crisis of multi-antibiotic resistant bacteria, bacteriocins have the ability to become the next generation of antibiotics for use.

Keywords:

Antimicrobials, Bacteriocins, Alternative Therapeutic Approach, Global Problem, Resistance to Multi-drugs.

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Introduction:

Antimicrobials, including antibiotics, antivirals, antifungals and antiparasites, are a class of pharmaceuticals that play a crucial role in keeping humans, animals and plants free of disease. Antimicrobial resistance (AMR) evolves when bacteria, viruses, fungi, and parasites adapt over time and no longer react to drugs that make infections more difficult to treat and increase the risk of disease spread, severe illness, and death. Antibiotics and other antimicrobial drugs are ineffective due to drug resistance, and infections are becoming more difficult or impossible to treat (Soltani *et al.*,2021;WHO,2020). Nonetheless, antibiotics have become one of the most important medical steps needed to boost complex health procedures, including cutting-edge surgery, transplantation of solid organs, and patient treatment for cancer. Sadly, the marked increase in antimicrobial resistance among common bacterial pathogens now challenges this therapeutic achievement., jeopardizing the promising results of critically ill patients. An increasing challenge to the effectiveness of these agents is antibiotic resistance, and the morbidity and mortality of those seeking care are high. Worldwide, bacterial resistance to chemical antibiotics has reached such a high degree that it endangers public health. The adoption of alternative strategies that facilitate the removal from the environment of resistant microbial strains is currently of utmost importance (Rios *et al*., 2016) . The antibiotic resistance epidemic can be attributed in recent years to inadequate, self-medicated and unnecessary worldwide prescription of antibiotics all over the world. (Carlet *et al.*, 2012). The development of new antibiotics is a slow process which leaves us with inadequate means of fighting microbial infections. Alternative treatment methods to ensure that resistant microorganisms are excluded from our living space are imperative.

Bacterial resistance and propagation arise:

Through the improper usage of excessive antibiotic intake (Goossens,2009), as well as contributing to numerous drug resistance, resistant bacterial microorganisms have been acquired by humans, effectively identifying the resistant species of normal flora. Apart from excessive consumption, the number of improper prescriptions of antimicrobial agents is also troubling. (Griffith *et al*.,2012). To promote bacterial phenotypic variations and build up resistance to bacterial infections, sub-therapeutic doses of antibiotics have been identified. (Viswanathan, 2014). Another part of the question is the consumption of animal meat. Antibiotics have been used for many years in the farming of food animals to cure or avoid disease. Animal feed also includes antibiotics at concentrations ranging from below therapeutic to full therapeutic levels, and the antibiotics used are the source of most antimicrobial groups present in humans . Evidence supports the idea that feeding animals with antibiotics may contribute to the production of antimicrobial resistant organisms and that those resistant organisms may be passed on to humans who consume those animals (Landers *et al.*,2012).Such bacteria undergo gene-level modifications that play a role in antibiotic resistance development (Vijayakumar &Muriana, 2017; Costa, *et al.*, 2019).

Mechanism of antimicrobial activity:

Antimicrobial agents may be split into classes on the basis of the mechanism of antimicrobial activity. The key groups are: agents that inhibit cell wall synthesis, depolarize the cell

membrane, inhibit protein synthesis, inhibit nucleic acid synthesis, and inhibit metabolic bacterial pathways (Table 1).

Table 1: Classes of antimicrobials based upon mechanisms of action:

Action process	Groups of antimicrobials
Inhibit the synthesis of cell walls	B-lactams Carbapenemes-Cephalosporins-Monobactams-Penicillins-Glycopeptides
Cell Membrane Deployment	Lipopeptides
Inhibit Synthesis of Proteins	Binds to 30S Ribosomal Subunit: Aminoglycosides-Tetracyclines Binds to 50S Ribosomal Subunit: ChloramphenicoLincosamides-Macrolides-Oxazolidiones-Streptogramins
Inhibit Synthesis of Nucleic Acid	Quinolones -Floroquinolones
Inhibit Metabolic Pathways	Sulfonamides-Trimethoprimes

Overuse of many popular antimicrobial drugs, improper prescription of antimicrobial medications, such as the initial prescription of excessively broad-spectrum drugs, contributes to the development of resistant organisms (Goossens,2009). In addition, prior antimicrobial drug use puts a patient at risk of being contaminated with a drug-resistant infection, and those with the highest antimicrobial exposure are the patients most often infected with resistant bacteria (Griffith *et al*.,2012). Bacteria may also acquire resistance genes from other related organisms and, depending on the species and genes, the degree of resistance can vary (Martinez,2014). Before discussing the various aspects of antimicrobial resistance, it would be beneficial to distinguish between natural and acquired resistance.

Resistance, natural and acquired:

Natural resistance can be innate (always expressed in the species) or induced (genes naturally occur in bacteria but are only expressed at resistance levels after exposure to the antibiotic). Genetic material that confers resistance can be acquired by all the key routes through which bacteria acquire any genetic material: transformation, transposition, and conjugation (all called horizontal gene transfer-HGT); plus, the bacteria may have their own chromosomal DNA mutations (Reygaert ,2018).

The genetic basis of resistance to antimicrobials:

Bacteria have an excellent genetic plasticity that helps them to adapt, including the existence of antibiotic molecules that can threaten their survival, to a wide variety of environmental threats. Bacteria sharing the same ecological niche with antimicrobial-producing organisms have evolved ancient mechanisms to withstand the effect of the harmful antibiotic molecule and, thus, their inherent resistance helps them to thrive in its presence. In bacteria, either of the two mechanisms may develop multidrug resistance. First, these bacteria may accumulate multiple genes within a single cell, each coding for resistance to a single drug. This accumulation normally happens on resistance plasmids (R). Second, the increased expression of genes that code for multidrug efflux pumps can also contribute to multidrug tolerance by extruding a wide range of drugs. (Nikaido,2009). First, it is important for us to briefly review the processes of resistance commonly encountered.

Resistance to Mutational:

By means of mutations which make the target protein less susceptible to the agent, bacteria may become resistant. In this case, in the presence of an antimicrobial molecule,a subset of bacterial cells originating in a susceptible population produce gene mutations that affect the action of the drug, resulting in the survival of preserved cells. The antibiotic destroys the susceptible population until a resistant mutation develops and the resistant bacteria predominate.. Mutations that result in antimicrobial resistance typically modify the antibiotic's function through one of the following mechanisms: (1) limiting uptake of a drug; (2) modifying a drug target; (3) inactivating a drug; (4) active drug efflux.

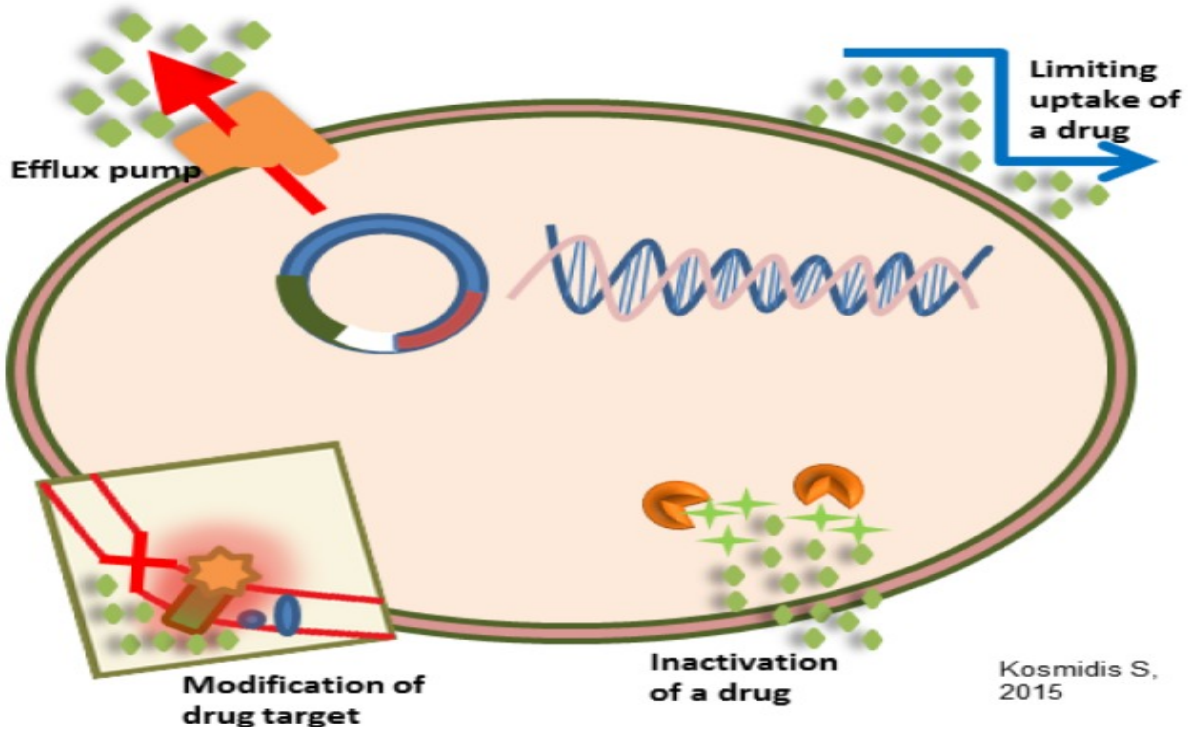

Fig 1: **General antimicrobial resistance mechanisms**

Bacterial species are constantly attacked within a particular host by the host's immune system, and it is important that they adapt and cope with these difficult circumstances in order to sustain themselves in unique biological niches. In order to prevent the killing of antimicrobial molecules, bacteria have developed advanced drug resistance mechanisms, a process that has definitely taken place over millions of years of development.. Multiple biochemical pathways can usually achieve resistance to one antimicrobial class, and one bacterial cell can withstand the effect of an antibiotic using a system of resistance mechanisms.

1-Limiting uptake of the drug:

There is a natural variation in the ability of bacteria to restrict the absorption of antimicrobial agents. A barrier to certain kinds of molecules is provided in Gram negative bacteria, by the structure and functions of the LPS layer. This gives these bacteria innate resistance to large antimicrobial agents in some classes (Blair *et al*.,2014). There is a high-lipid outer membrane in mycobacteria, and hydrophobic drugs such as rifampicin and fluoroquinolones have better cell access, but hydrophilic drugs have less cellular access. (Kumar & Schweizer ,2005). Bacteria lacking a cell wall, such as Mycoplasma and related organisms, are therefore naturally immune to all drugs, including beta-lactams and glycopeptides, that attack the cell wall (Bébéar & Pereyre, 2005). There is no outer membrane for Gram positive bacteria, and limiting drug access is not as prevalent. Recently, by constructing a thickened cell wall, *Staphylococcus aureus* has developed vancomycin resistance that makes it difficult for the drug to enter the cell and provides intermediate resistance to vancomycin. These strains are designated as strains of the VISA (Miller *et al*.,2014).

2-Antimicrobial target modifications (decreasing drug affinity):

In both gram-negative and gram-positive bacteria, a well-known mechanism of acquired antibiotic resistance is the addition of complex chemical moieties (enzymes) to the compound that can introduce chemical modifications to the antimicrobial molecule. Several types of enzyme modification have been identified: i) acetylation (aminoglycosides, chloramphenicol, streptogramins), ii) phosphorylation (aminoglycosides, chloramphenicol) and iii) adenylation (aminoglycosides, lincosamides) are the most frequent biochemical reactions to be catalysed (Wilson,2014) or destroying the molecule itself, the bacteria generate enzymes that inactivate the drug, making the antibiotic unable to interact with its target. The degradation of these compounds by the action of β-lactamases is the main mechanism of β-lactam resistance. These enzymes sever the amide bond of the β-lactam ring, which renders the antimicrobial ineffective. (D'Costa *et al*.2011).

3- Inactivation of the drug:

Inhibiting the antibiotic's action by interfering with its target location is a popular technique for bacteria to develop antimicrobial resistance. Bacteria have developed different strategies to accomplish this, including the protection of the target (preventing the antibiotic from reaching its binding site) . The protein Qnr of quinolone resistance, which is a plasmid-mediated fluoroquinolone resistance determinant often found in clinical isolates, is an example of target protection. Mentioned initially in a clinical isolate of *K. pneumoniae* . Qnr

belongs to the family of pentapeptide repeat proteins and serves as a homologue of DNA vying for the DNA gyrase and topoisomerase IV DNA binding site. This decrease in DNA gyrase-DNA interaction is thought to decrease the quinolone molecule's ability to shape and stabilise the gyrase-cleaved DNA-quinolone complex that is lethal to the cell. (Rodríguez *et al*.,2011), or by the implementation of improvements to the target site . These target changes can include i) point mutations in the target site encoding genes. An example of antibiotic resistance occurring due to mutational changes is oxazolidinone resistance (linezolid and tedizolid). These drugs are synthetic bacteriostatic antibiotics that exert their mechanism through interaction with bacterial ribosomes at the A site with large gram-positive activity. Such an interaction precludes protein synthesis by interfering with the positioning of aminoacyl-tRNA. Linezolid is the most widely used antibiotic in this class, as tedizolid has only recently been licenced for clinical use. (Mendes *et al*.,2014) (ii) Enzymatic binding sites modifications (e.g. addition of methyl groups),. One of the best described examples of resistance by enzymatic modification of the target site is the methylation of the ribosome catalysed by an enzyme encoded by the erm genes (erythromycin ribosomal methylation) that results in macrolide resistance. These enzymes are capable of mono- or dimethylating the 23rRNA domain V adenine residue of the 50S ribosomal subunit at the A2058 position. Because of this biochemical transition, the binding of the antimicrobial molecule to its target is disrupted. (Leclercq, 2002) and/or (iii) initial target site replacement or bypass . Using this approach, bacteria are able to set new targets that achieve the original target's similar biochemical functions but are not inhibited by the antimicrobial moleculeThe most significant clinical examples include resistance to methicillin in *S.aureus* . The acquisition of exogenous PBP (PBP2a) and vancomycin resistance in enterococci through modifications of peptidoglycan structure mediated by the van gene clusters (Courvalin,2006). As stated, The final result is always the same, regardless of the form of modification, with a reduction in the affinity of the antibiotic to the target site.

4- Reduced penetration and efflux of antibiotics:

Many of the antibiotics used in clinical practise for Gram-negative bacteria have bacterial intracellular targets or are found in the cytoplasmic membrane (the inner membrane). In order to exert its antimicrobial influence, the compound must thus penetrate the outer and/or cytoplasmic membrane. To prevent the antibiotic from reaching its intracellular or periplasmic target, Etracyclines have evolved permeability reduction mechanisms and some fluoroquinolones are particularly affected by changes in the permeability of the outer membrane (Pages *et al*., 2008) ,or by creating a complex bacterial machinery capable of extruding a toxic compound from the cell, the concept of an efflux mechanism capable of pumping tetracycline from the cytoplasm of *E.coli* may also lead to antimicrobial resistance. (McMurry *et al*.,2008).

MDR bacteria and antibiotic resistance :

Evaluation of MDR bacteria and antibiotic resistance by the World Health Organization in 2020 confirmed that high rates of antibiotic resistance have been observed, predominantly used to treat urinary tract infections, sepsis, sexually transmitted infections, and some types of diarrhoea, indicating that effective antibiotics are not available. Fluoroquinolone's

antibiotic resistance in *E. Coli*, used for urinary tract infection treatment, is common. Colistin is the only last resort treatment for life threatening infections caused by carbapenem-resistant Enterobacteriaceae (i.e. *E.coli, Klebsiella*, etc). In several nations and regions, colistin-resistant bacteria have also been reported, causing infections for which there is currently no successful antibiotic treatment. Our skin flora includes *Staphlylococcus aureus* bacteria and is a frequent source of both environmental and health care infections. People with *Staphylococcus aureus* (MRSA) methicillin-resistant infections are 64 percent more likely than individuals with drug-sensitive infections to die. The treatment and regulation of *N.gonorrhoea* has affected sulphonamides, penicillins, tetracyclines, macrolides, fluoroquinolones and early generation cephalosporins, and resistance has grown rapidly. An increasing problem of antibiotic resistance and Clostridium difficile infections worldwide has been developed by the use of potent broad-spectrum antibiotics. A substantial number of hospital-acquired infections account for multidrug-resistant infections that have a direct impact on health conditions and costs.

Drug-resistant illnesses lead to death:

Drug-resistant diseases cause at least 700,000 people to die each year, according to a report released by the UN in April 2019. Multidrug-resistant infection of *Tubercle bacilli* leads to an additional 230,000 deaths. In the modern sense of the word, sexually transmitted diseases, urinary tract infections and serious respiratory tract infections are not treatable.. Life-saving therapies have become dangerous and there is growing confusion about industrial food systems. The "One Health" policy of the United Nations suggests that countries combat antimicrobial resistance and ensure the success of vital medicines by implementing strategic implementation methods, such as supporting and organising awareness campaigns on the prudent use of antimicrobials. It focuses on investing in new R&D technologies in the fight against antimicrobial resistance. (Chaib *et al.*,2019) .

Bacteriocins:

The ongoing development of multi-drug resistant pathogens has sparked an interest in finding alternative therapeutic options. One such route is antimicrobial combinatorial therapy. To bypass the development of antimicrobial resistance and/or improve antimicrobial potency, a number of experiments, including combinations of bacteriocins with other antimicrobials, were performed. These bacteriocin-antimicrobial combinations may have significant advantages in terms of reducing the risk of developing resistance because of the existence of two distinct mechanisms of antimicrobial action. In addition, synergistic antimicrobial interactions can also have financial implications in terms of lowering treatment costs by reducing the concentration of a costly antimicrobial agent and using it in combination with inexpensive therapy. Furthermore, combinatorial therapy with bacteriocin can extend the antimicrobial spectrum and/or decrease the concentration of antibiotics needed for effective therapy to the degree that they can minimize or eliminate potentially harmful or adverse side effects. (Mathur *et al.*,2017). A promising infection control technique can be bacteriocins taken alone or in combination with antibiotics and can also reduce the risk of food contamination. (Dittu *et al.*,2014).

Bacteriocin :Updated Classification:

Because of the considerable variation in structure and behaviour, the classification of bacteriocins has been a problem to date, and recent work has classified bacteriocins into various groups, based on a variety of variables, such as their size, molecular composition and structure or modification method, (Simons *et al*.,2020):

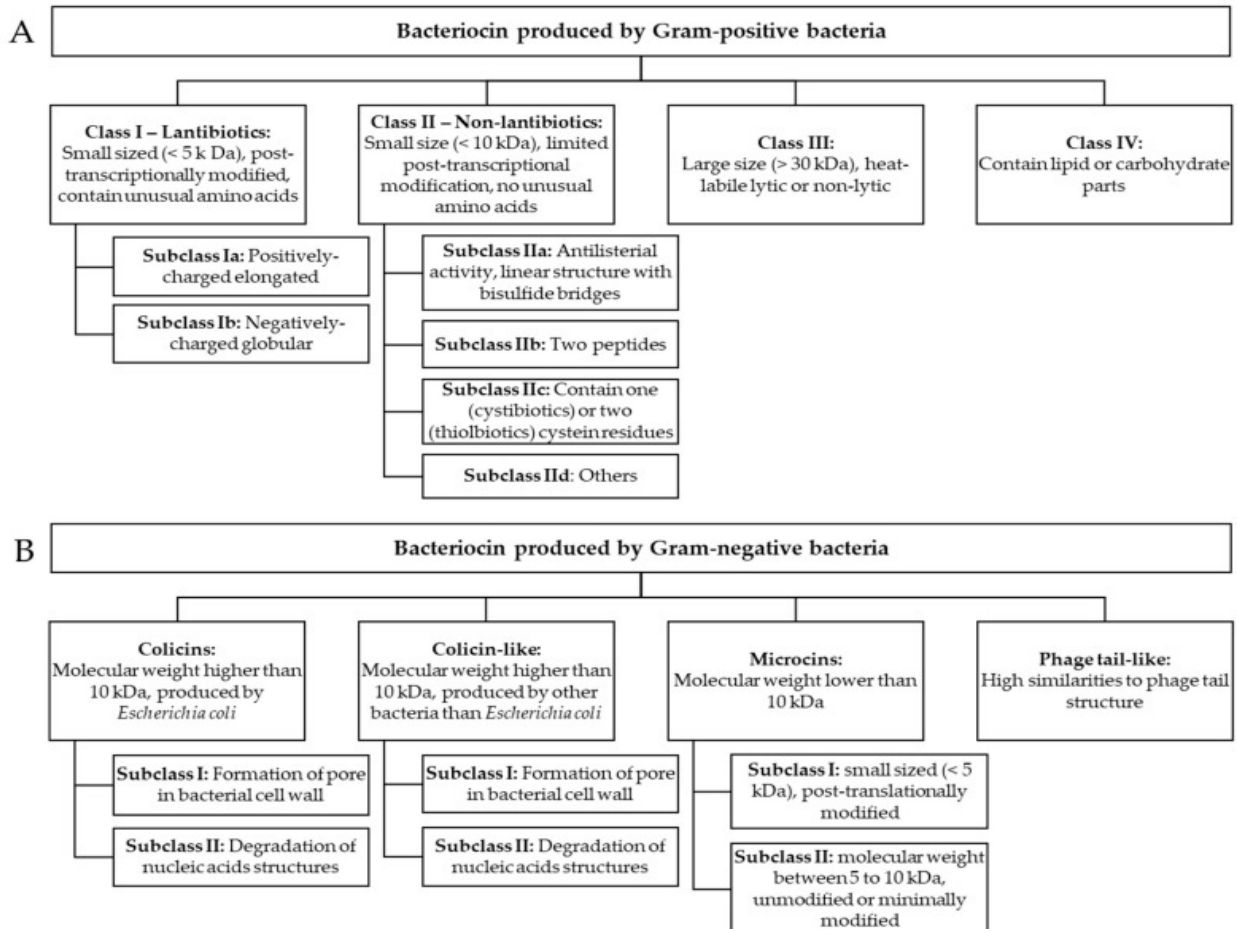

Fig 2: Classification of Gram-positive (A) and Gram-negative (B) bacteria formed by bacteriocins.

Gram positive bacterium-generated bacteriocin:

Gram-positive bacteriocins are classified into four categories: on the basis of their primary structure, composition, molecular mass, thermostability, enzyme resistance, mechanism of action, post-translation changes and genetic features (Klaenhammer, 1993; Nes *et al*, 2002), although in the classification of sub-classes there are minor differences between different authors.

Lantibiotics:

Class I bacteriocins are known as lantibiotics and are classified as being representative of nisin and lactocin based on their post-translation modification. These are modified extensively after translation, resulting in the synthesis of unusual amino acids and methyllanthionine (Parada *et al*., 2007). Lantibiotics may be further segmented into subclasses. Positively charged elongated peptides are known as subclass Ia (nisin, epidermine, gallidermine) and are commonly associated with pore formation in the bacterial membranes of the cell (Bierbaum & Sahl, 2009). Antimicrobial peptides have been shown to be active in the treatment of bacterial infections and multidrug-resistant bacteria against Vancomycin Resistant Enterococci and Methecillin Resistant *Staphylococcus aureus* strains, such as nisin, pediocin, mersacidin, mutacin and lactacin.(Santos *et al*., 2017; Mathur *et al*., 2018). With respect to subclass Ib, the structure of these bacteriocins is globular and inflexible and these peptides are negatively charged (e.g., lacticin 481, cytolysin, salivaricin). The mechanism of action of this subclass is associated with the inhibition of specific enzymes that are essential to the attacking bacteria.

Non-Lantibiotics:

Bacteriocins in class II are small (< 10 kDa), cationic, hydrophobic, heat sensitive, unmodified peptides.These peptides mainly induce the bacterial membranes to be destabilised and permeabilized or cause pore formation into the membrane. (Fimland *et al.*,2005). Splitting this group into four subclasses is possible. The linear structure of members of subclass IIa reveals bisulfide bridges and a typical antilisterial behaviour known as antilisterial bacteriocinsin (e.g., leucocin A, acidocin A, pediocin PA-1) (Devi &Halami, 2011). Subclass IIb bacteriocins are bacteriocins formed equally by two peptides (α/β) and both are required to demonstrate antibiotic activity (e.g., lactococcin G, lactococcin Q and plantaricin NC8) (Héchard &Sahl,2002). Subclass IIc is a small bacteriocin associated with a leading sequence of peptides which may contain one to two cysteine residues in their structure (named, respectively, cystibiotics and thiolbiotics). This subgroup contains different molecules such as lactococcin A, divergicin A, or acidocin B (Oscáriz & Pisabarro,2001). Finally, subclass IId is used to collect all bacteriocins which have not been included in the different subgroups referred to above that have been included in the category of Class II. Class III bacteriocins are large peptides (>30 kDa) and, in comparison to class I and class II bacteriocins, may be heat-labile lytic or non-lytic bacteriocins such as zoocin A, lysotaphin or helveticin J and V in this category (Joerger & Klaenhammer,1986). The antibacterial activity of these bacteriocins is related to enzymatic activity (e.g. endopeptidase), leading to bacterial cell wall destruction. Class IV bacteriocins containing lipid or carbohydrate parts are characterised by their structure (Savadogo *et al*.,2006) such as plantaricin S (da Silva Sabo *et al.*,2014)or leuconocin S, which interferes with the membrane of bacterial cells. These molecules are susceptible to many enzymes because of this structural feature (i.e., glycolytic or lipolytic enzymes).

Gram-negative bacterium-generated bacteriocins:

Compared with Gram-positive bacteriocins, the narrower spectrum of Gram-negative bacteriocins limits the antimicrobial activity of Gram-negative bacteria (Balciunas *et*

al.,2013). However, an essential portion of antimicrobial peptides is also expressed by this group of bacteriocins. Most of the Gram negative bacteriocins produced have been isolated from Escherichia coli strains, but many other genera, such as *Pseudomonas* or *Klebsiella*, may also produce antimicrobial peptides. Gram negative bacteriocins are categorised into four different groups. Gram negative bacteriocins are classified into four distinct categories. Colicins are the first group of bacteriocins that are generated by E.coli and have a molecular weight greater than 10 kDa. It is possible to distinguish the mechanism of action of colicins into two classes (Bakkal *et al*.,2010): (i) formation of bacterial cell wall pores (i.e. A, B, E1, Ia, Ib, K, and 5 colicin) and (ii) degradation of nucleic acid-like structures of DNA, RNA, or tRNase) (i.e., colicins E2 to E9. Colicin-like bacteriocins formed by other bacteria (e.g., *Klebsiella* spp.: klebicins; *P. aeruginosa: S-pyocins)* are still similar in structure, size and function to bacteriocins produced by *E.coli* gathered in the second population.. Their colicin-like antimicrobial activity may be due to pore or nuclease activity formation (Michel & Baysse,2002). The third category consists of small peptides forming microcins (<10 kDa) (Duquesne *et al.*,2007). Subclass I is a post-translationally modified bacteriocin with a molecular weight of less than 5 kDa, and subclass II is an unmodified or minimally modified peptide with a higher molecular weight of 5-10 kDa. Two subclasses can be defined. Microcins interact with different cellular targets, resulting in various modes of action such as disruption of the membrane or inhibition of important enzymatic functions such as the complex of ATP synthase, DNA gyrase, RNA polymerase, or aspartyl-t RNA synthetase. Some high molecular peptides have cylindrical structures that are capable of penetrating the bacterial cell membrane and then leading to cell death (Scholl ,2017). These structures are very close to the structure of the phage tail, so these antimicrobial peptides are called Phage Tail-Like bacteriocins.They constitute the fourth party.

Potential uses of bacteriocins:

Because of its wide range of applications in the prevention or management of spoilage and pathogenic microorganisms, as well as in the agricultural and pharmaceutical fields, bacteriocins have great potential for applications in the food industry. (Abbasiliasi *et al.*, 2017), particularly as clinical antimicrobials (van Heel *et al.*, 2011), inhibitory effects against pathogens (Hanchi *et al*. 2017), anticancer activities (Ahmad *et al*.,2017) and as microbial control during fermentation for biopreservation and shelf-life extension (Lee &Kim 2011). Their potential as birth control contraceptives is emphasised by nisin, subtilosin fermenticin and lacticin 3147 (Dicks *et al.* 2018). For use against multidrug resistant (MDR) pathogens in clinical settings, bacteriocins are a good option since these AMPs can work with high specificity at picomolar and nanomolar concentrations. Continuous research may lead to the acquisition of antimicrobial bacteriocins that are more diverse and active. New identification, purification and heterologous protein techniques will make new antibiotics capable of controlling MDRBBB in this situation (Preciado *et al.*,2016).

Bacteriocin's role in the resolution of the global multidrug resistance problem:

Antibiotic-impervious microorganisms have become prevalent and are a global issue that needs to be solved before the health of human life becomes an unmanageable, deadly risk..Recent trends suggest that human life may be threatened if a suitable alternative to

antibiotics is not rapidly discovered. To reduce the risk of universal public health, appropriate antibiotic alternatives need to be created. (Carlet *et al.*,2012;WHO, 2015). Bacteriocins are potent bactericidal peptides that are produced and secreted by a variety of microorganisms that cause death and elimination of pathogenic bacteria producing non-bacteriocinin, including yeast, protozoa, and naturally bacteria (Lopetuso, *et al.,* 2019). In 1925, bacteriocins were first described, but their synthesis, functions and applications in the medical field have recently been explored (Chikindas, *et al.,* 2017). These bacteriocin therapies are generally more effective than antibiotic therapy, since they are natural bioactive peptides without side effects. The ability of bacteriocins must be explored and made available to the medical community as an alternative or adjuvant to antibiotics. This is another significant explanation for studying and harnessing bacteriocins' therapeutic potential to fight drug-resistant bacterial infections.Bacteriocins will soon be used as a preventive agent against MDR bacteria in order to benefit humans. Together with antibiotics, they are being examined as a potential replacement or adjuvant to combat disease-causing pathogens.. The fact that they have an outstanding safety profile and are robust is an additional reason for evaluating them. While they are a therapeutic alternative to chemical antibiotics, they are known as therapeutic supplements because they are highly stable and very low in toxicity. While they are a therapeutic alternative to chemical antibiotics, they are known as therapeutic supplements because they are highly stable and very low in toxicity.

The advantages of treatment with bacteriocin over antibiotic therapy :

Treatment with antimicrobial peptides is a necessary requirement because of the production and dispersal of antibiotic resistance and its many side effects (Chen *et al.,* 2012). Bacteriocins have antibacterial activity against microbial species by directly affecting niche rivalry between commensals, as they control the immune system and inhibit competitive strains. In bacterial cells, bacteriocins are synthesised on the ribosomal surface, whereas antibiotics are secondary metabolites of bacteria . Producers of antibiotics are readily affected by antimicrobials, while producers of bacteriocins are not prone to antimicrobials.(Morisset & Frère, 2002), bacteriocins can be attached anywhere to the target bacterial cell surface, as the target bacterial cell surface does not have any special receptors .The synthesis of cell wall destruction, genomic protein formation and replication processes is accountable for other side chemical antimicrobials (Perez e*t al.,* 2018).

Bacteriocins used in resistant multidrug therapy:

Enterococcus faecalis developed bactofencin A or bacteriocin 21 can remove multidrug-resistant bacteria and help manage niche competition in the gut between bacteria. (Kommineni *et al.,* 2015). In 2017, Umu *et al* stated that the therapeutic potential of the above findings against *Staphylococcus aureus, Salmonella enteritidis* and *Listeria monocytogenes* was assessed by LAB bacteriocins. Bacteriocin 'Sonorensin' was shown to be effective against antibiotic-resistant Staphylococcus aureus biofilms and other gram-positive and gram-negative bacteria by Indian researchers at the CSIR Institute of Microbial Technology, Chandigarh (Chopra *et al.,* 2019). One of the five peptides, the Indian Institute of Science, has succeeded in mice against carbapenem and tigecycline-resistant *Acinetobacter baumanniii* (Nagarajan *et al*., 2019). The Indian Institute of Science has shown that *Acinetobacter baumaniii* is effective against drug-resistant nosocomial infections in China (Peng, *et al.,* 2019). A research team at MIT has successfully developed and optimised several forms of this peptide and tested its effectiveness in antibiotic-immune mice infected

with *Pseudomonas areuginosa*. The bactericidal activity of *Lactobacillus fermentum* bacteriocins was investigated in 2018 by Prakash *et al.*, successfully inhibiting *Escherichia coli* immune to antibiotics and *Salmonella typhi* bacteria immune to drugs. A bacteriocin developed by lactobacillus was described by Bonhi and Imran (2019), which is very effective against methicillin-resistant .Multi-resistant Gram-negative bacteria are the primary driver of nosocomial infections . To demonstrate their efficacy in treating nosocomial infections, a number of bacteriocins that are active against Gram-negative bacteria have been reported in recent years. While more research is still needed before it is possible to more clearly identify the possibilities for bacteriocins in clinical practise. (Ghodhbane *et al*.,2015).

Future perspectives:

As a preventive agent against human illnesses, the use of bacteriocins is still in the production process and is a cause for great optimism in both the scientific and medical communities. To achieve this goal, a significant and sustained effort is required to resolve the MDR threat in the shortest possible time. A mixture of bacteriocins with different spectrums of action may be as potent as a wide variety of antibiotics. Without compromising the effectiveness but decreasing the undesirable side effects of antibiotic treatment, bacteriocins may be combined with an antibiotic. It would also help prevent the development of both antibiotic and bacteriocin-resistant pathogens (Antonio *et al*., 2019). For bacteriocins as treatment agents, the theoretical outlook is rather positive (Kim et al., 2019). Experts have estimated that by 2060, the problem of antibiotic resistance would require more than 20 new groups of antibiotics (Li &Webster, 2018). To date, only a few antimicrobial peptides have been licenced by the FDA and EMEA due to high development costs. (Cattoir &Felden., 2019) .

Conclusion:

Owing to a number of safety and clinical trials, including studies of susceptibility to antimicrobial action, allergies and immune system effects in hosts, method for approval of newly produced medicines, including bacteriocins and antimicrobial peptides, has been sluggish. Bacteriocins can be used because of their variety and availability to prevent infections, combat antibiotic resistance and treatment. As a therapeutic tool against multidrug resistant bacteria, bacteriocins are a promising alternative that is being investigated for potential use. A great deal more work is needed in order to develop new effective bacteriocins that effectively target complex bacterial structures such as cell membranes. In addition, we highlight nanotechnology's contribution to the optimization of bacteriocins in terms of their antimicrobial activity, controlled release and proteolysis safety. Recent development of new detection, purification and heterologous protein techniques will allow for the control of MDRBBB by new antibiotics in this case. Continuous research can contribute to more varied and powerful antimicrobial bacteriocins being acquired.

Abbreviations:

MDR :Multiple drug resistance

AMR: Antimicrobial resistane

HGT :Horizontal-gene transfer

LPS : Lipopolysaccharides

Qnr : Prevalence of plasmid mediated quinolone resistance determinants

Erm genes: Erythromycin ribosomal methylation

PBP : Penicillin-binding proteins

MRSA :Methicillin-resistant *Staphylococcus aureus*

R&D technology : Research &Development technologies

AMP's : Adenosine monophosphate

VISA :Vancomycin-resistant *Staphylococcus aureus*

FDA: Food and drug administration

EMEA : Europe, the Middle East and Africa

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