



BIOLOGICAL SCIENCES

Bacteriocins as an alternative in the treatment of infections by *Staphylococcus aureus*

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Abstract: *Staphylococcus aureus* (*S. aureus*) is a highly versatile Gram-positive bacterium that is carried asymptotically by up to 30% of healthy people, while being a major cause of healthcare-associated infections, making it a worldwide problem in clinical medicine. The adaptive evolution of *S. aureus* strains is demonstrated by its remarkable capacity to promptly develop high resistance to multiple antibiotics, thus limiting treatment choice. Nowadays, there is a continuous demand for an alternative to the use of antibiotics for *S. aureus* infections and a strategy to control the spread or to kill phylogenetically related strains. In this scenario, bacteriocins fit as with a promising and interesting alternative. These molecules are produced by a range of bacteria, defined as ribosomally synthesized peptides with bacteriostatic or bactericidal activity against a wide range of pathogens. This work reviews ascertained the main antibiotic-resistance mechanisms of *S. aureus* strains and the current, informative content concerning the applicability of the use of bacteriocins overlapping the use of conventional antibiotics in the context of *S. aureus* infections. Besides, we highlight the possible application of these biomolecules on an industrial scale in future work.

Key words: *Staphylococcus aureus*, antibiotic resistance, bacteriocins, biotechnology use of bacteriocins.

INTRODUCTION

The Gram-positive bacterium *Staphylococcus aureus* (*S. aureus*) is immobile, non-spore-forming, produces coagulase, and is often unencapsulated or has a limited capsule (Acedo et al. 2018, Vestergaard et al. 2019). *S. aureus* is both a human commensal and opportunistic pathogen. Mammal's skin is the primary environment to the colonization of members of the *Staphylococcus* genus in which can facilitates infection in immunologically suppressed individuals (Otto 2010, Weisser et al. 2010). Specifically, *S. aureus* is the main trigger of several diseases such as osteomyelitis (Hatzenbuehler & Pulling 2011), septic arthritis (Deesomchok & Tumrasvin 1990, Ryan et al. 1997,

Shirtliff & Mader 2002), bacteremia (Mylotte et al. 1987, Shurland et al. 2007), endocarditis (Watanakunakorn & Burkert 1993, Cabell et al. 2002, Petti & Fowler, 2002), pneumonia (Watanakunakorn 1987, González et al. 2003, De la Calle et al. 2016), and mastitis (Tenhagen et al. 2009, Deb et al. 2013, Gomes & Henriques 2016). It is noteworthy that this bacterium is also the principal causal agent of numerous implant infections (Arciola et al. 2018). Bacterial infections have been treated by the use of antibiotics since the beginning of the '40s. Still, their efficiency tends to decrease due to the high rate of antibiotic resistance developed by several microorganisms, such as *S. aureus* (Ventola 2015a). The inappropriate use of antibiotics, particularly their overuse, has been

considered one of the factors contributing to multidrug resistance in bacteria. This constitutes a severe global public health problem since the frequency of established and emerging infectious diseases has increased because of the ineffectiveness of antibiotics. This issue brings us a warning about the risk of the inefficacy of our current drug arsenal and pushes us to look for new strategies in the struggle against bacterial infection (Ventola 2015b).

The World Health Organization (WHO) has been treating the case as a danger of worldwide alert since the mechanisms of resistance are emerging and spreading around the world faster than is usual. To prevent and control antibiotic resistance, the WHO advises the healthcare industry to invest in the development of new antibiotics and novel strategies to treat bacterial infections. At the same time, it is estimated that close to 80% of all antibiotics sold just in the United States are intended for animal use (Martin et al. 2015). In 2015, it was estimated that the global average annual consumption of antibiotics per kilogram of animals produced using cattle, chicken, and pigs would increase by 67% from 63.151 ± 1.560 tons to 105.596 ± 3.605 tons (Van Boeckel et al. 2015). These data show that there is the uncontrolled use of antibiotics favoring an exponential multidrug resistance acquired by bacteria and associated with the challenges in the development of new antibiotics that make this situation alarming. In contrast to pathogenic microorganisms and their pathogenic factors, the small molecules produced by certain bacteria called bacteriocins appear to be a different strategy and strong candidates to overlap/replace the role of conventional antibiotics. Bacteriocins are mainly defined as proteins and peptides which inhibit the growth or kill another related and unrelated microorganisms (Klaenhamme 1988, Balciunas

et al. 2013, Chikindas et al. 2018, Lopetuso et al. 2019).

This review gathers recent information about the possible use of bacteriocins replacing antibiotic treatment during *S. aureus* infection, considering the advantages offered by these natural compounds, as well as the differences and comparisons between them.

MECHANISMS OF ANTIBIOTIC RESISTANCE IN *S. aureus*

S. aureus is a highly adaptive and versatile Gram-positive bacterium that can cause a wide range of infectious diseases in humans and animals. The success as a pathogen relies on the combination of diverse virulence factors, invasiveness, and antimicrobial resistance (Le Loir et al. 2003, Rozemeijer et al. 2015). Besides, *S. aureus* is capable of surviving in different environmental conditions (Mäder et al. 2016). The first case of resistance to penicillin by *S. aureus* was reported in mid of the '20s. After this, several cases of antibiotic resistance to these bacteria have been reported (Humphreys & Mulvihill 1985, Kaiser, 2000, Andriole 2005). Table I shows a broad class of antibiotics resistance and the targets of the mechanisms of actions of antibiotics utilized by *S. aureus*.

β -lactam resistance in *S. aureus* strains

S. aureus can acquire resistance to β -lactam antibiotics like penicillin and methicillin (Fuda et al. 2005) (Figure 1). Penicillin, which was discovered by Alexander Fleming in 1929, was the first antibiotic used to fight *S. aureus*-mediated infections. Penicillin inhibits peptidoglycan formation (PG) cross-links in the bacterial cell wall, which generate a three-dimensional structure around the cell, and ensures bacterial integrity. Thus, the penicillin binds to

Table I. Description of the key events on the developing antibiotic resistance by *S. aureus* and the target of the mechanism of action utilized by this bacterium.

| Drug | Year drug introduced | Years to reported of resistance | Mechanism of action |
|---------------|----------------------|--|--|
| Penicillin | 1941 | 1943 | Cell envelope |
| Methicillin | 1961 | 1962 | |
| Vancomycin | 1956 | 1997 | |
| Ceftaroline | 2010 | 2011 | |
| Daptomycin | 1980 | 1988 (resistance rates <i>in vitro</i>) | Disruption of bacterial plasma membrane function |
| Ciprofloxacin | 1985 | 1990 | DNA replication |
| Linezolid | 2000 | 2001 | Protein synthesis |

DD-transpeptidase, an enzyme responsible for the formation of PG cross-links, and prevents its catalytic activity, as part of PG synthesis is inhibited by penicillin, while that the hydrolases and autolysins, bacterial enzymes involved in PG, remain active. Thus, the activity of penicillin that causes an imbalance between PG synthesis and degradation weakens PG and leads to cell death. (Fleming 1929). Only two years after its introduction, *S. aureus* penicillin-resistant strains appeared. These strains contained an enzyme, β -lactamase, able to destroy penicillin (Dietz & Bondi 1948). The *blaZ* gene with *blaR1* and *blaI* genes are the genetic determinants of *S. aureus* resistance to penicillin. The code for the β -lactamase enzyme, the presence of penicillin sensor, and a transcriptional repressor of *blaZ* expression respectively, β -lactamase acts on penicillin outside the cell by changing its molecular structure to an inactive form, penicilloic acid by the hydrolysis of its β -lactam ring. The expression of *blaZ* is controlled by external penicillin availability. Penicillin interacts with the transmembrane

protein *BlaR1*. This interaction leads to the autocatalytic activation of *BlaR1* to *BlaR2* (or *BlaR1* in the active form) that can promote the inactivation of the *BlaI* repressor and, therefore *blaZ* to synthesize enzyme. The three genes are located on a transposable element of a large *S. aureus* plasmid called β -lactamase-encoding transposon Tn552 that it shows to be persistent over time and be geography spread.

Furthermore, it was described as well as carry cadmium resistance genes, which can strengthen the role of resistance by attributing greater persistence among strains that carry this genetic content (Shearer et al. 2011). Like the other β -lactams, methicillin impedes the synthesis of bacterial cell walls. It inhibits cross-linkage between the linear peptidoglycan polymer chains, which composes a significant component of the cell wall of gram-positive bacteria by binding to and competitively inhibiting penicillin-binding proteins (PBPs). These PBPs molecules also are called transpeptidases (D-alanyl-alanine). The mechanism that describes the methicillin-resistance *S. aureus* (MRSA) proceeds

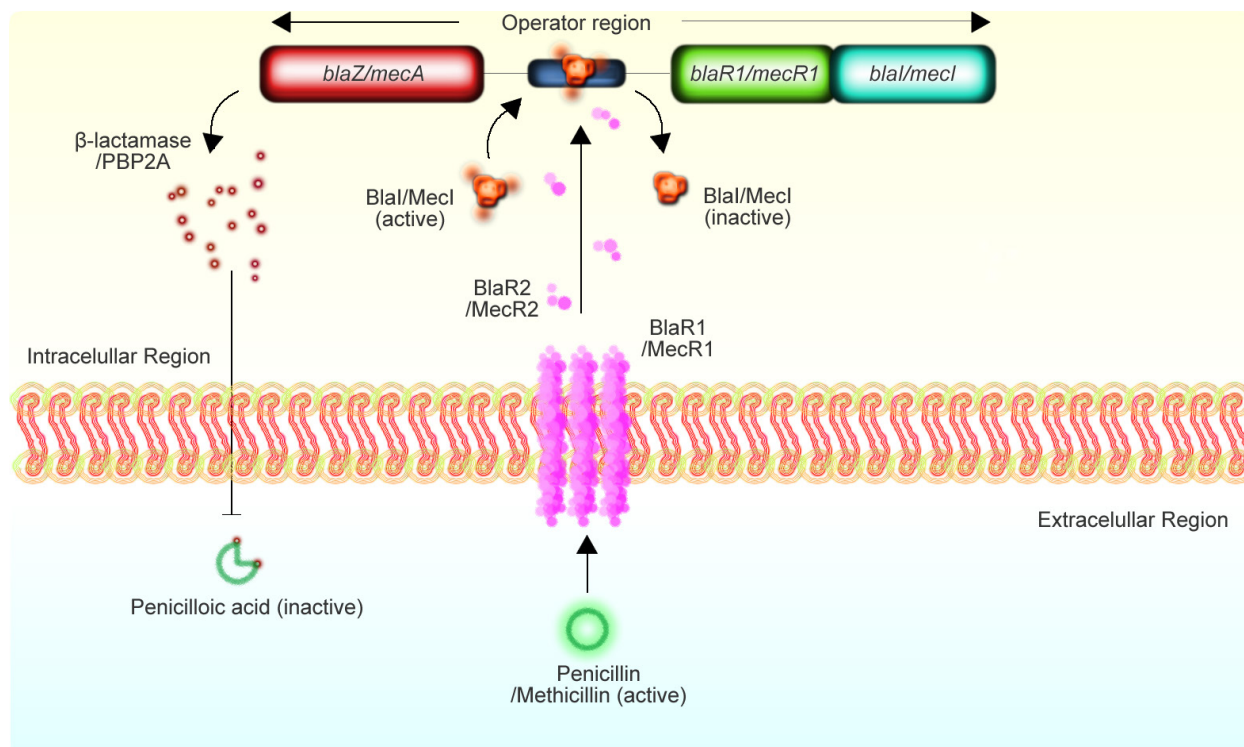


Figure 1. Scheme of Penicillin/Methicillin resistance. The active penicillins can promote the cleavage of the transmembrane protein (BlaR1 or MecR1) that leads the inactivation of the repressor protein on the operator region, allowing the expression of *blaZ/mecA* that synthesizes the proteins capable of breaking the β -lactam ring in the various penicillins forming penicillanic acid derivatives, also inactive (Lowy 2003).

in a similar way to Penicillin. However, several works have discussed that the *mecA* gene that is responsible for methicillin resistance may be a mobile genetic element (MGE), which confers the ability to respond to environmental stresses. β -Lactams triggers the autolytic activation of the intracellular metalloproteinase domain (MPD), which is controlled by the integral-membrane zinc-dependent sensor (MecR1) a sensor protein and a transcriptional repressor (MecI) in the operator region to the expression of *mecA* (Peacock & Paterson 2015).

Vancomycin resistance in *S. aureus*

Vancomycin is classified as one glycopeptide antibiotic susceptible to *S. aureus*-resistance (Walters et al. 2015). Currently, are known four *S. aureus* strains are identified as vancomycin-resistant: Vancomycin-sensitive *S. aureus*

(VSSA), Vancomycin-resistant *S. aureus* (VRSA), Vancomycin-intermediate *S. aureus* (VISA) and heterogeneous VISA (hVISA) (McGuinness et al. 2017). Vancomycin alters the peptidoglycan density in the cell wall, being capable of interacting with it forming non-covalent hydrogen bonds, in the exposed D- D-Ala-D-Ala peptides (Hanaki 1998), which inhibits cell wall synthesis in the VSSA strains. Therefore, the mechanism of resistance can be associated with the presence of an enterococcal plasmid (*vanA*) or by the transposition of elements related to (Tn1546) (Zhu et al. 2010). Thus, the affinity of vancomycin to the polypeptide is heavily reduced due to the *vanA* operon provided by the conjugation of the plasmid in the VRSA strains, which can produce the different polypeptides D-Ala-D-Lac (Figure 2).

Fluoroquinolone-resistant *S. aureus*

S. aureus has been reported as resistant to the quinolone class of antibiotics (Tanaka et al. 2000, Oizumi et al. 2001, Lowy 2003). This resistance is achieved due to specific mutations in two chromosomal genes: *grlA* coding for a subunit of DNA topoisomerase IV, the primary quinolone target reported (Ferrero et al. 1994), and *gyrA* coding for DNA gyrase A subunit (Figure 3). The two proteins are intimately associated with the over-lapping and opening of the double DNA strand during DNA replication. Specific mutations in *grlB* and *gyrB* also cause

resistance to quinolones (Andriole 2005). Both proteins have also been described as having the B subunit (*grlB* and *gyrB*) intrinsically associated with resistance in *S. aureus*. These mutations stand out in a region known as the quinolone-resistance determining region (QRDR), which trigger several codon alterations in synonymous and non-synonymous amino acid mutations (Tanaka et al. 2000). Mutations reduce the affinity of the enzyme-DNA complex for quinolones.

Linezolid resistance in Staphylococci

Considering the oxazolidinone class, the resistance of *S. aureus* to linezolid has also

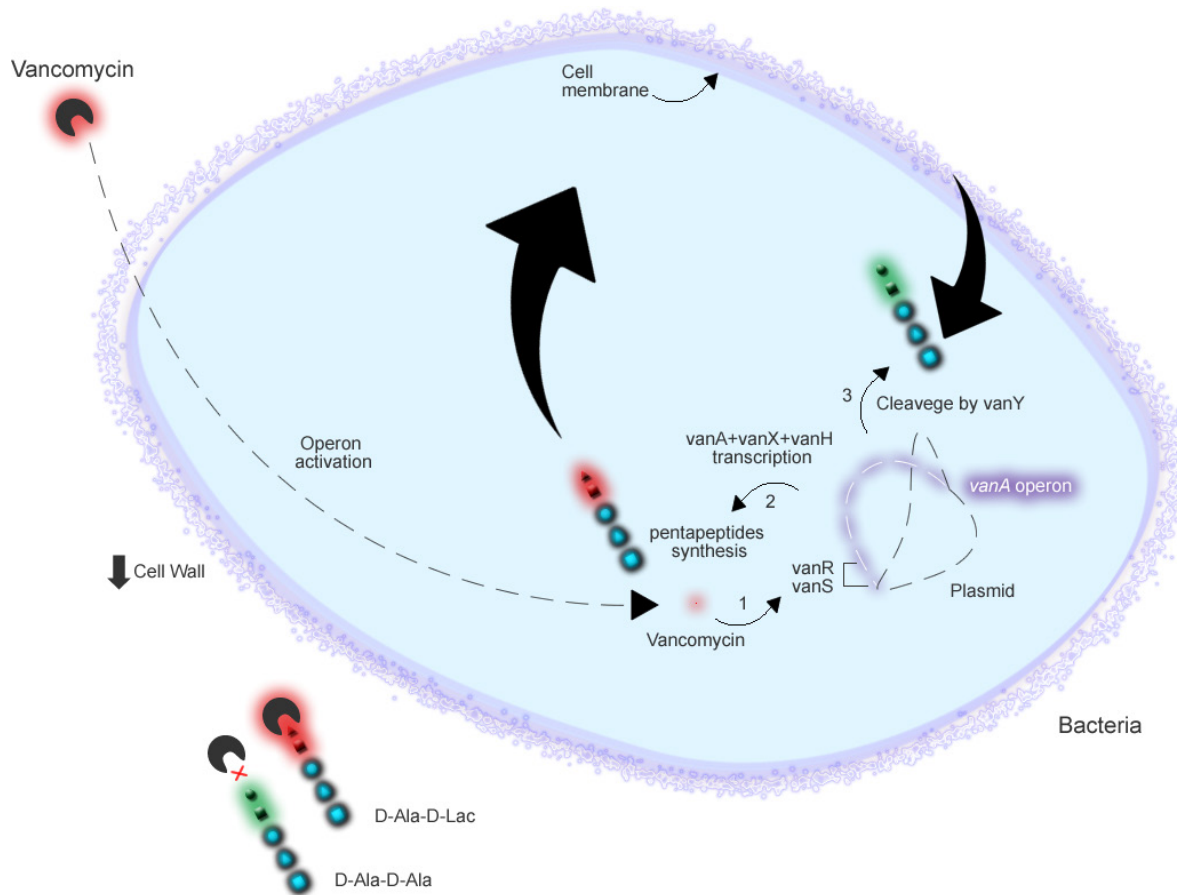


Figure 2. Scheme of Vancomycin resistance. The main factor in the resistance role of Vancomycin is the *vanA* operon acquired by conjugal transfer. Initially, it is controlled by *vanS* and *vanR*, which are sensitive to the presence of vancomycin and active within the transcription of the operon. The genes *vanA*, *vanH*, and *vanX* are functionally associated with D-Ala-D-Lac synthesis and are responsible for the vancomycin resistance phenotype. Finally, *vanY* is described as being associated with the peptidase function, which cleavage the D-Ala-D-Ala that already were attached. The function of *vanZ* is still unclear and is not entirely understood.

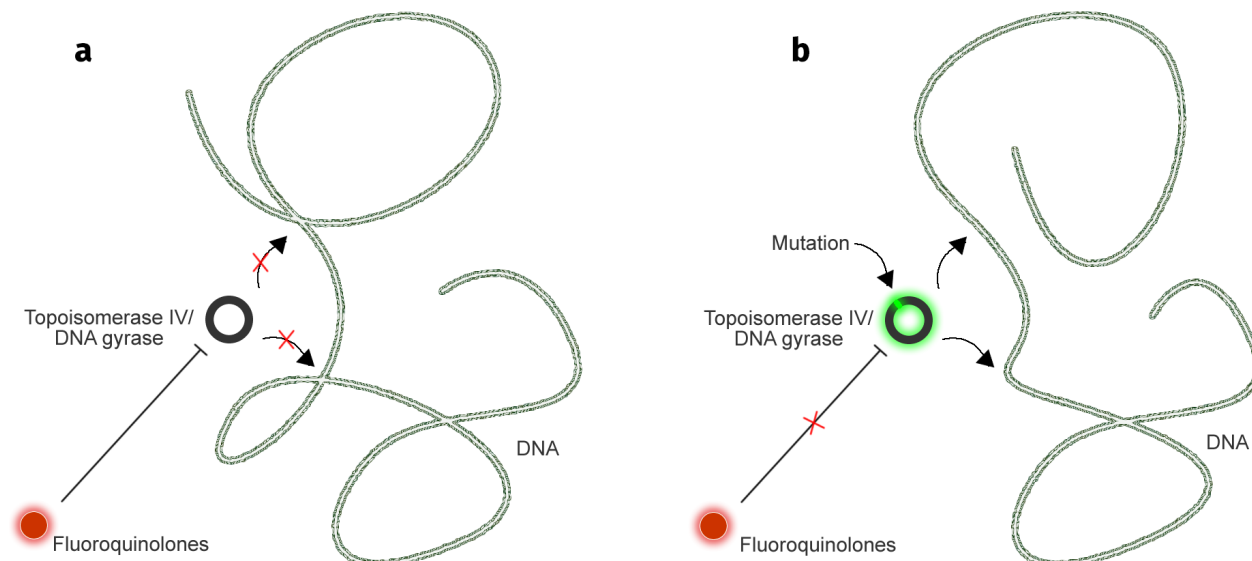


Figure 3. Scheme of quinolones resistance. (a) The fluoroquinolones can inhibit the topoisomerase IV and DNA gyrase, preventing remodeling of the DNA molecule when it undergoes torsion due to the DNA replication, leading to cell death. (b) Mutations on Topoisomerase and DNA gyrase avoid fluoroquinolones activity, which confer antimicrobial activity allowing bacterial growth.

been observed for the last decade (Besier et al. 2008). The main feature of the mechanism of action describes the linezolid interaction with the 50S subunit of prokaryotic ribosomes, which prevents initiation factors such as formylmethionyl-tRNA from acting to form the complex with the 30S subunit. This disruption precludes the formation of the 70S complex, which sequentially disrupts protein synthesis (Figure 4) (Swaney et al. 1998). However, some cases of bacteria resistant to linezolid bearing point mutations at the specific targets in the 50S, more precisely in the 23S ribosomal portion, have been reported (Meka et al. 2004, Afşar et al. 2012). Furthermore, a new mechanism of linezolid resistance, which was first explored by the presence in a plasmid that included the gene *cfr*, was detected (Schwarz et al. 2000). Several years ago, a novel variant of the phenicol resistance transposon Tn558 was detected on the plasmid pSCFS6 suggesting the ability of horizontal transfer between staphylococci (Kehrenberg et al. 2007). The transcription of the

cfr gene produces a methyltransferase protein, which catalyzes the methylation of 23S rRNA at position A2503 offering resistance to some antibiotics such as chloramphenicol, florfenicol, and clindamycin (Kehrenberg et al. 2005), and later to linezolid (Toh et al. 2007).

Regarding all the information explored here, the broad spectrum of antibiotics capable of inhibiting bacterial growth has been gradually decreasing over the last 70 years. All mechanisms of the bacterial resistance to the action of antibiotics are embedded in the complexity of interactions among genes and its mobile elements but mainly considering the bacterial hosts too. Moreover, the misuse of antibiotics by humans intensifies the selection pressure, making the resistance struggle even harder.

Bacteriocins against *S. aureus* infections

Bacteriocins are molecules usually produced by bacteria that can be used with biopreservative applications (Bali et al. 2016) but mainly in an antibiotic role (Egan et al. 2017). These

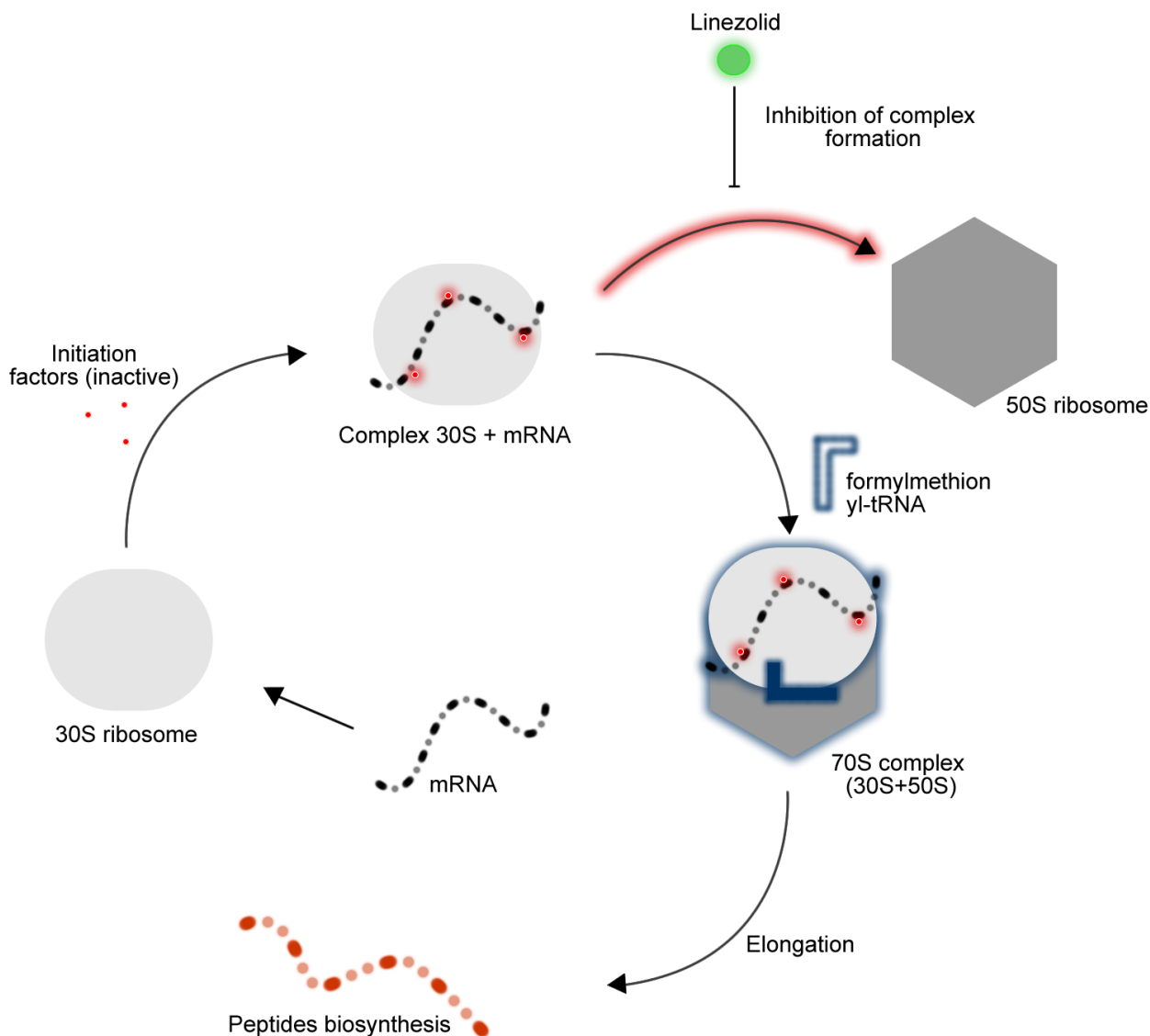


Figure 4. Mode of action of Linezolid. Description mechanism of the common peptides biosynthesis processes in prokaryotes. The complex formation of the 30S and 50S ribosomes to 70S formation and the inhibiting of protein biosynthesis by Linezolid action.

biomolecules can be differently classified over the Gram-positive and Gram-negative bacteria (Table II). Most of them have low molecular mass (from less than 5kDa to 90 kDa), high isoelectric point, and contain hydrophilic and hydrophobic regions (Lopetuso et al. 2019).

It is suggested that the primary function of bacteriocins regarding their killing ability is directly associated with maintaining the population around to reduce the number of

nutritional competitors in the environment. The targets for bacteriocins may have a broad spectrum of action similar to those of antibiotics (Table III), blocking several biologically important phases to the cell. Some recently characterized bacteriocins appear to have a common mechanism of action in which they dissipate proton-motive force (MPF), with modifications in membrane potential ($\Delta\psi$) and H⁺ concentration gradient (ΔpH) which consequently lead to the

Table II. Classification of bacteriocins produced by Gram-positive (Bierbaum & Sahl 2009, Lívio Varella Coelho et al. 2017) and Gram-negative bacteria (Rebuffat 2011).

| | Classification | Features | Subclasses |
|---------------|--|---|---|
| Gram-positive | Class I | Small, heat-stable peptides (<5 kDa), containing modified amino acids (lanthionine, 3-methyl-lanthionine, dehydrated amino acids, S-aminovinyl-cystein, among others) | Type A (linear) |
| | | | Type B (globular) |
| | | | Type C (two components) |
| | | | Type D (reduced antimicrobial activity) |
| | Class II | Small, heat-stable peptides (<10 kDa), containing no modified amino acids | IIa (linear; pediocin-like) |
| | | | IIb (linear; two components) |
| | | | IIc (cyclic peptides) |
| | | | IId (linear) |
| | | | IIe (linear; more than two components) |
| | Class III | Large, heat-labile proteins | Type IIIa (bacteriolysins) |
| | | | Type IIIb (non-lytic) |
| Class IV | Small (<10 kDa), circular peptides without posttranslationally modified amino acids and with an amide bond between the N- and C-terminal | - | |
| Class V | Small (<5 kDa), linear or circular peptides containing extensively posttranslationally modified amino acids with thioether bridges formed between α -carbon of other amino acid residues and the thiol groups of Cys residues | - | |
| Gram-negative | Colicins | High molecular mass modular proteins (30–80 kDa) | - |
| | Microcins | Low molecular mass peptides (between 1 and 10 kDa) | - |

formation of pores in the cytoplasmic membrane (Cleveland et al. 2001, Perez et al. 2018).

Concerning the increased rate of *S. aureus* resistance, bacteriocins show great potential as candidates that can overlap the function of a large number of antibiotics (Table III) (Cavera et al. 2015, Ceotto-Vigoder et al. 2016).

Several studies have described the bacteriostatic activity of bacteriocins that inhibits the growth of *S. aureus*, as observed in (Table IV). One work (Varella Coelho et al. 2017) described the inhibitory activity of seven bacteriocins in 165 strains of *S. aureus* in cases of bovine mastitis, showing a potent inhibition by epidermin (>85%) and a medium inhibition by aureocin A53 (>67%) (Livio Varella Coelho et al. 2017), however, the combination of aureocin 70 and A53 showed a more significant inhibitory potential when compared to previous results (>91%). Still exploring cases of bovine mastitis, another study (Barboza-Corona et al. 2009) highlighted five bacteriocins derivate from *Bacillus thuringiensis* that were tested against 50 strains of *S. aureus* recovered from

the milk of lactating cows. The results of the study presented data on the resistance of these strains to penicillin, dicloxacillin, ampicillin, and erythromycin. However, all strains were susceptible to the five tested bacteriocins, showing them to be useful as an alternative approach to control bovine mastitis. Currently, one bacteriocin has shown strong relevance in the treatment of bovine mastitis (Ceotto-Vigoder et al. 2016). The bacteriocin lysostaphin shows a minimal inhibitory concentration of 3.9 to 50 $\mu\text{g ml}^{-1}$ compared to the usually used bacteriocin nisin, which was 15.6 to 500 $\mu\text{g ml}^{-1}$. This study concludes that treatment using lysostaphin alone or associated with nisin was efficient in promoting bacterial cell lysis. Other studies investigating the role of biofilm formation in methicillin-resistant *S. aureus* (MRSA) strains, which has been observed to be able to alternate the resistance phenotype and thus attenuate the virulence (Pozzi et al. 2012), noted the effects of three bacteriocins. In this study, nisin A showed the highest bactericidal activity against planktonic and biofilm cells,

Table III. Biological functions affected by the action of bacteriocins and antibiotics.

| Targeted biological functions | Bacteriocins | Antibiotics |
|-----------------------------------|--|---|
| Cell envelope | Nisin A, nukasin ISK-1, NAI-107 | β -lactams, glycopeptides |
| DNA Replication and Transcription | Microcin B17, colicins, carocin S2 | Quinolones |
| Membrane perturbers | Geobacillin I, bac-GM17, plantaricins, dysgalactin, lactococcin, pediocin-like bacteriocins, mesentericin Y105, lacticin Q, nisin A, Uberolysin, AS-48 Bacteriocin | Lipopetides |
| Protein Synthesis | Colicins, cloacin DF13 | Aminoglycosides, tetracyclines, chloramphenicol, macrolides |
| Septum Formation | Garvicin A, lactococcin 972 | Benzamide derivade, N-heterocycles, phenols/polyphenols, carboxylic acids |
| Metabolism | - | Sulfonamides |

while Lacticin Q showed lower activity. However, the Nukacin ISK-1 just showed bacteriostatic activity against planktonic cells. Despite this, the results show that the bacteriocins used to stand out as potent molecules effective in the treatment of MRSA infections (Okuda et al. 2013). Recently, cases of MRSA have been achieving prominence in the search for new bacteriocins.

Jiang et al. (2017) observed the role of pentocin JL-1 bacteriocin showing effectiveness in both gram-negative and positive bacteria (Jiang et al. 2017). Moreover, the authors also explored the ability of this bacteriocin to target the cell membrane of MRSA strains leading to cell death. At the same time, another study devoted to the investigation of the pattern of bacterial strains

Table IV. Role of bacteriocins on preventing and control of the *S. aureus* growth.

| Bacteriocins | Class | Organism source | Reference |
|---|----------|---|--|
| Aureocins A70, A53 and 215FN (aureus) Pep5, Epidermin K7 and Epicidin 280 (epidermidis) | II and I | <i>Staphylococcus aureus</i> and <i>Staphylococcus epidermidis</i> | (Lívio Varella Coelho et al. 2017) |
| Morricin 269, Kurstacin 287, Kenyacin 404, Entomocin 420 and Tolworthcin 524 | II | <i>Bacillus thuringiensis</i> | (Barboza-Corona et al. 2009) |
| Lysostaphin | III | <i>Staphylococcus simulans</i> biovar <i>staphylolyticus</i> | (Schindler & Schuhardt 1964, Lívio Varella Coelho et al. 2017) |
| Epidermicin NI01 | | <i>Staphylococcus epidermidis</i> | (Sandiford & Upton 2012) |
| Pediocina PA-1 | II | <i>Lactococcus lactis</i> | (Rodríguez et al. 2005) |
| Nisin A, lacticin Q, and Nukacin ISK-1 | I | <i>Lactococcus lactis</i> QU 5 and <i>Staphylococcus warneri</i> ISK-1 | (Okuda et al. 2013) |
| Lacticin 3147 | I | <i>Lactococcus lactis</i> subsp. <i>lactis</i> | (Twomey et al. 2000) |
| Enterocin CCM 4231 | II | <i>Enterococcus faecium</i> CCM 4231 | (Lauková & Czikková 1999) |
| E 50-52 and OR-70 | II | <i>Enterococcus faecium</i> NRRL B-30746 and <i>Lactobacillus salivarius</i> NRRL B-30514 | (Svetoch et al. 2008, Hanchi et al. 2017) |
| Duracin 61A and Reuterin | | <i>Enterococcus durans</i> 61A and <i>Lactobacillus reuteri</i> | (Hanchi et al. 2017) |
| Pentocin JL-1 | I | <i>Lactobacillus pentosus</i> | (Jiang et al. 2017) |
| TA6 | II | <i>Pseudomonas aeruginosa</i> TA6 | (Arumugam et al. 2019) |

that are capable of exhibiting antibacterial activity against MRSA revealed one bacteriocin-like protein with a molecular mass of ~10 kDa produced by *P. aeruginosa* TA6 strain (Arumugam et al. 2019). Several analysis has highlighted the fact that, in addition to resistance to high temperature and various chemical compounds, it is a potent antimicrobial efficient against MRSA and a strong candidate for higher-yielding and enhancement of bacteriocin production.

Hanchi and collaborator, in a different study trying to comprise the synergy of antimicrobial, a group of bacteriocins and some antibiotics were evaluated considering the two subtypes to understand the efficacy of bacteriocins vs. antibiotics, these results show the effectiveness of bacteriocins nisin Z, pediocin pa-1, duracin 61 and reuterin as well, evidenced inhibition of MRSA (Hanchi et al. 2017). However, in the set of antibiotics used, only vancomycin displays effects against MRSA. Evaluation of synergistic activities of antimicrobial agents was showed that the combination of duracin with nisin or pediocin are a strong strategy in the control of growth bacterial, thus demonstrating the important role of duracin 61A as an active bacteriocin against clinical drug-resistant MRSA (Hanchi et al. 2017). Staden and collaborators show that nisin F-loaded self-setting brushite cement can control infection with *S. aureus* Xen 36 in mice model for 7 days (van Staden et al. 2012). This study shows that the possibilities are bright for the use of bacteriocins to control infections.

BACTERIOCINS AS A BIOTECHNOLOGY TOOL IN THE TREATMENT BY *S. aureus* INFECTIONS

Interest in bacteriocins, as well as their production, has been growing over the years due

to their use in food preservation, which exhibits antimicrobial activity as being an alternative to the use of chemical preservatives. Given the vast amount of methods capable of purifying these biomolecules, two approaches have been gaining more interest and becoming more effective in purifying bacteriocins: the Aqueous two-phase system (ATPS) and the Aqueous micellar two-phase system (AMTPS) (Jamaluddin et al. 2018). These systems can be formed by mixing in a solution with various components. ATPS are generally formed when two polymers that are inconsistent, *i.e.*, polyethyleneglycol (PEG) and dextran or sodium sulfate, are diluted in water (Peters 1987, Hatti-Kaul 2001, Grilo et al. 2016). There are other types including, ionic liquids and short-chain alcohols. The result of purification from ATPS displays a higher yield (~70%) (Md Sidek et al. 2016) compared to the conventional method, for example, the single gel filtration chromatography (~1.0%). Interest has grown around this approach in the academic world, and recent studies have shown better results when the PEG / salt-based ATPS type is used, reaching yield values around 93% (Sabo et al. 2018). Besides, the AMTPS results trying to improve the nisin extraction in the presence of electrolytes, show the advances in using the approach compared to conventional methods (Jozala et al. 2013). Hence, the potential of ATPS and AMTPS as primary recovery methods for bacteriocins from a complex fermentation broth can be explored on an industrial scale, considering the easy handling and speed in obtaining these biomolecules, compared to the production stages already developed in the research laboratory.

Recent research on fermented vegetable extract is a good strategy and new application in the use of bacteriocins (Feng et al. 2017). Receiving the name of Fermented Plant Extract (FPE), this approach - most commonly performed as plain

liquid manure or plant extract can be used as a tool that assists in obtaining active substances providing a diversity of health benefits (Altay et al. 2013, Marsh et al. 2014). Some plants of the *Labiatae* family, which contain a diversity of herbs shown to have antimicrobial activity (Mahboubi et al. 2014). FEP is also described as being fermented microorganisms, which include yeast and bacteria (Blandino et al. 2003, Manzanilla et al. 2006). This gives scope for the conclusion on the specific use of bacteria and plants, which may constitute a synergy in the antimicrobial treatment and a better understanding of the control by bacteriostatic phenotypes. The approach describing a composition comprising a bacteriocin and an extract from a plant is described in a patent of Coyne et al. (Coyne et al. 2014). This kind of strategy has been gaining strength and evidencing in numerous cases where the interruption of bacterial growth appears to be ineffective due to the use of these vegetable broths in conjunction with specific microbiotas (Marbun et al. 2016). Besides, extracts of tea and soybean showed dose-dependent growth inhibition of pathogens (Zhao & Shah 2015). This study used phenolic-enriched milk (PEM), fermented with lactic acid bacteria (LAB) and ultra-filtered, concluding that multiple agents, such as bacteriocins secreted by LAB, may exhibit synergistic antibacterial activity. This evidence on the role of FPE reveals the importance of their applicability, not only considering their use for health, thus presenting a new approach in treatments for *S. aureus* infections, but also the production on an industrial scale, and amongst other considerations, the environment.

CONCLUSIONS

Our work concludes that bacteriocins are becoming increasingly important in the fight against infections by several microorganisms, especially *S. aureus*. The mechanisms of resistance to antibiotics explored here show the need to obtain new strategies to combat this pathogen. Several bacteriocins having a latent action spectrum against *S. aureus* are shown to be as effective as or even more so than conventional antibiotics have been disclosed herein. Besides, although bacteriocins have great potential for functional overlap of some antibiotics, it is noteworthy that even these biomolecules are so susceptible to bacterial resistance as well as the common antibiotics. Thus, we believe that the information discussed here is remarkably important for animal and human health, as well as to provide a means of production on an industrial scale and new possibilities for future applications such as therapeutic methods.

Acknowledgments and funding

The authors would like to acknowledge the INRA - Institut National de la Recherche Agronomique for the support of this work and CAPES – Brazil. This work was supported by Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and, Finance Code 001 and by grants from INRA - Institut National de la Recherche Agronomique, France.

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How to cite

LEITE EL, DE OLIVEIRA JR AF, DO CARMO FLR, BERKOVA N, BARH D, GHOSH P & AZEVEDO V. 2020. Bacteriocins as an alternative in the treatment of infections by *Staphylococcus aureus*. *An Acad Bras Cienc* 92: e20201216. DOI 10.1590/0001-3765202020201216.

Manuscript received on July 30, 2020;
accepted for publication on August 18, 2020

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