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

Elma L Leite, Alberto Oliveira Jr, Fillipe L.R. Do Carmo, Nadia Berkova, Debmalya Barh, Preetam Ghosh, Vasco Azevedo

An Acad Bras Cienc (2020) 92(Suppl. 2): e20201216 DOI 10.1590/0001-3765202020201216
Anais da Academia Brasileira de Ciências | *Annals of the Brazilian Academy of Sciences*
Printed ISSN 0001-3765 I Online ISSN 1678-2690
www.scielo.br/aabc | www.fb.com/aabcjournal

BIOLOGICAL SCIENCES

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

ELMA L. LEITE, ALBERTO F. DE OLIVEIRA JR, FILLIPE L.R. DO CARMO, NADIA BERKOVA, DEBMALYA BARH, PREETAM GHOSH & VASCO AZEVEDO

Abstract: *Staphylococcus aureus* (*S. aureus*) is a highly versatile Gram-positive bacterium that is carried asymptomatically 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 *in vitro*)	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 actives. 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 *bla*R1 and *bla*I 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 *Bla*R1. This interaction leads to the autocatalytic activation of *Bla*R1 to *Bla*R2 (or *Bla*R1 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 b-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 impends the synthesis of bacterial cell walls. It inhibits cross-linkage between the linear peptidoglycan polymer chains s, 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

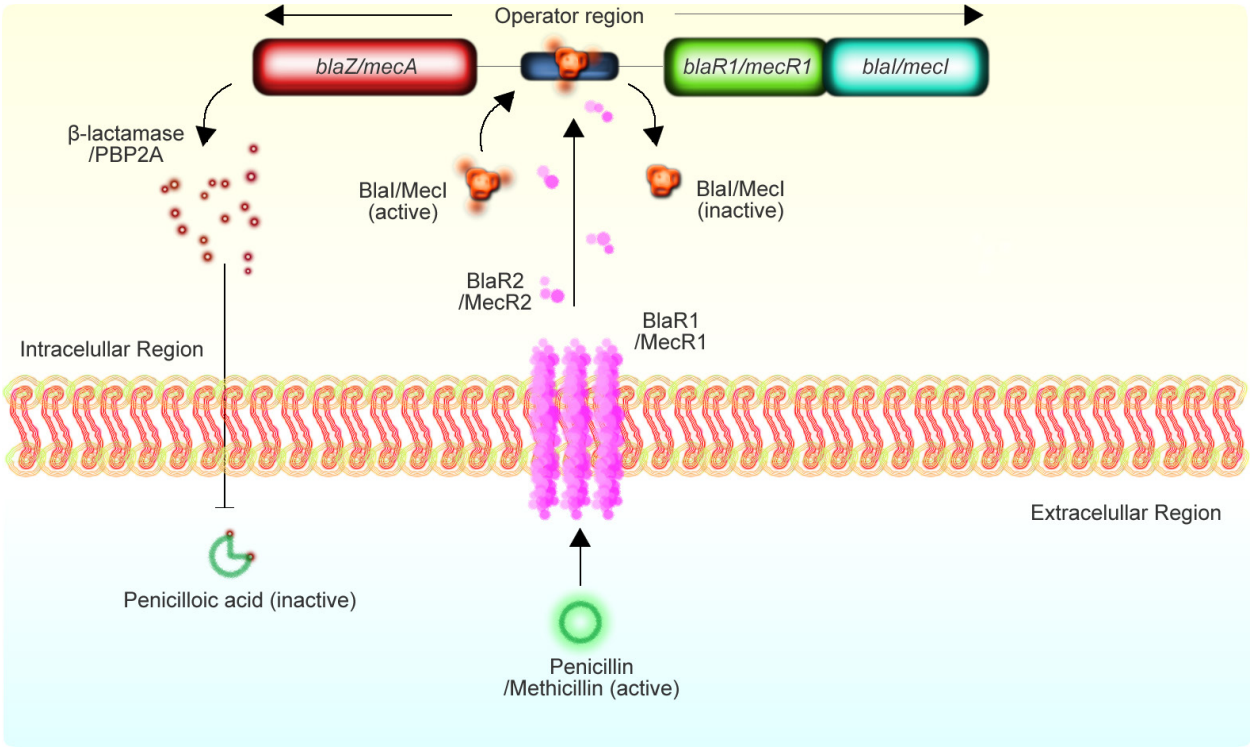

Figure 1. Scheme of Penicillin/Methicillin resistance. The active penicillins can promote the cleavage of the transmembrane protein (BlaR1 or MecR1) that leads the inactivation of the repressor protein on the operator region, allowing the expression of *bla*Z/*mec*A that synthesize the proteins capable 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 *mec*A 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 *mec*A (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 (*van*A) 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 *van*A 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

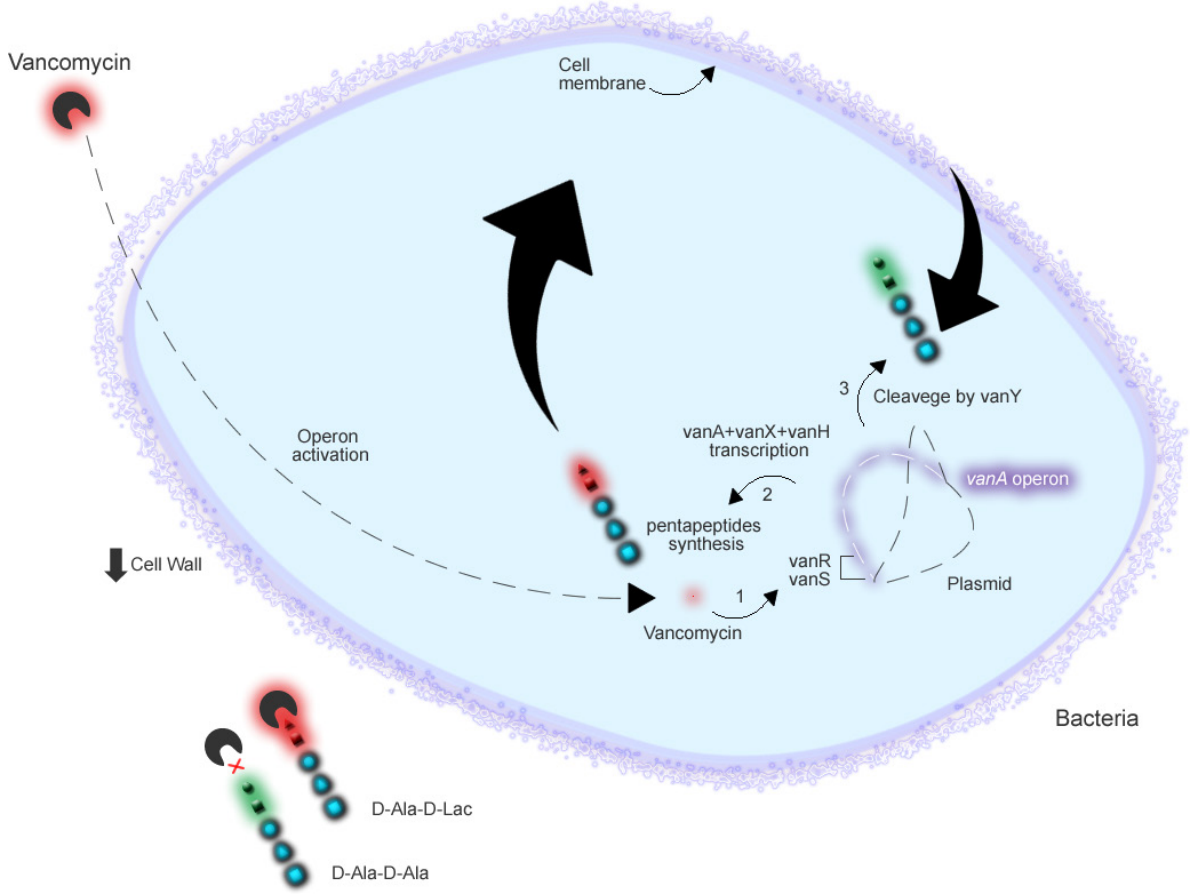

Figure 2. Scheme of Vancomycin resistance. The main factor in the resistance role of Vancomycin is the *vanA* operon acquired by conjugal transfer. Initially, it is controlled by *vanS* and *vanR*, which are sensitive to the presence of vancomycin and active within the transcription of the operon. The 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.

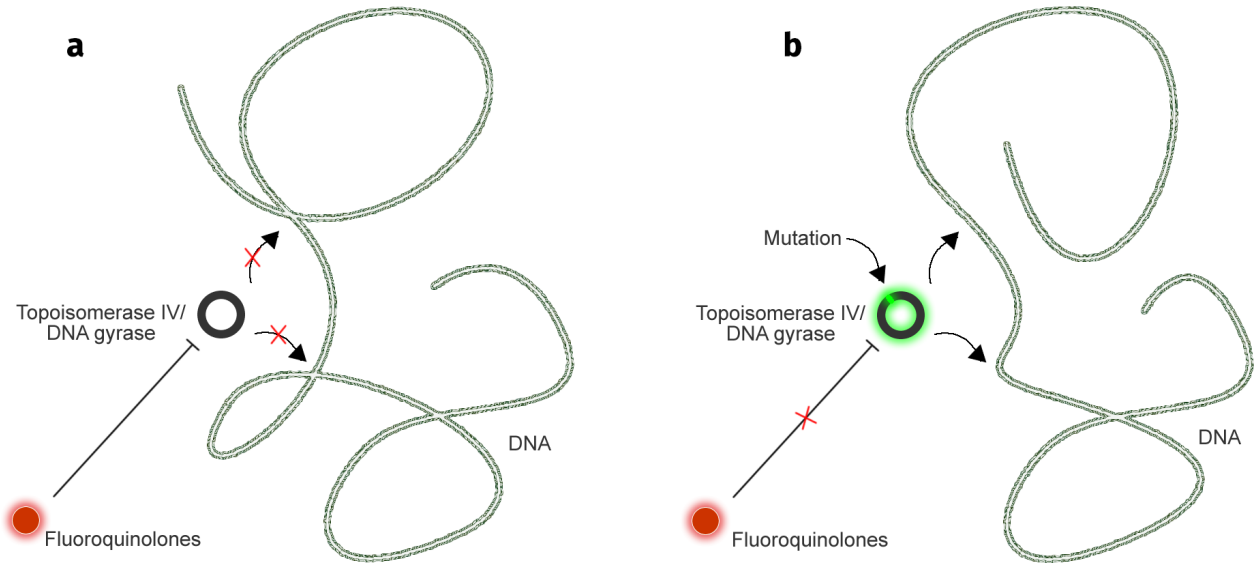

Figure 3. Scheme of quinolones resistance. (a) The fluoroquinolones can inhibit the topoisomerase IV and DNA gyrase, preventing remodeling of the DNA molecule when it undergoes torsion due to the DNA replication, leading to cell death. (b) Mutations on Topoisomerase and DNA gyrase avoid fluoroquinolones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

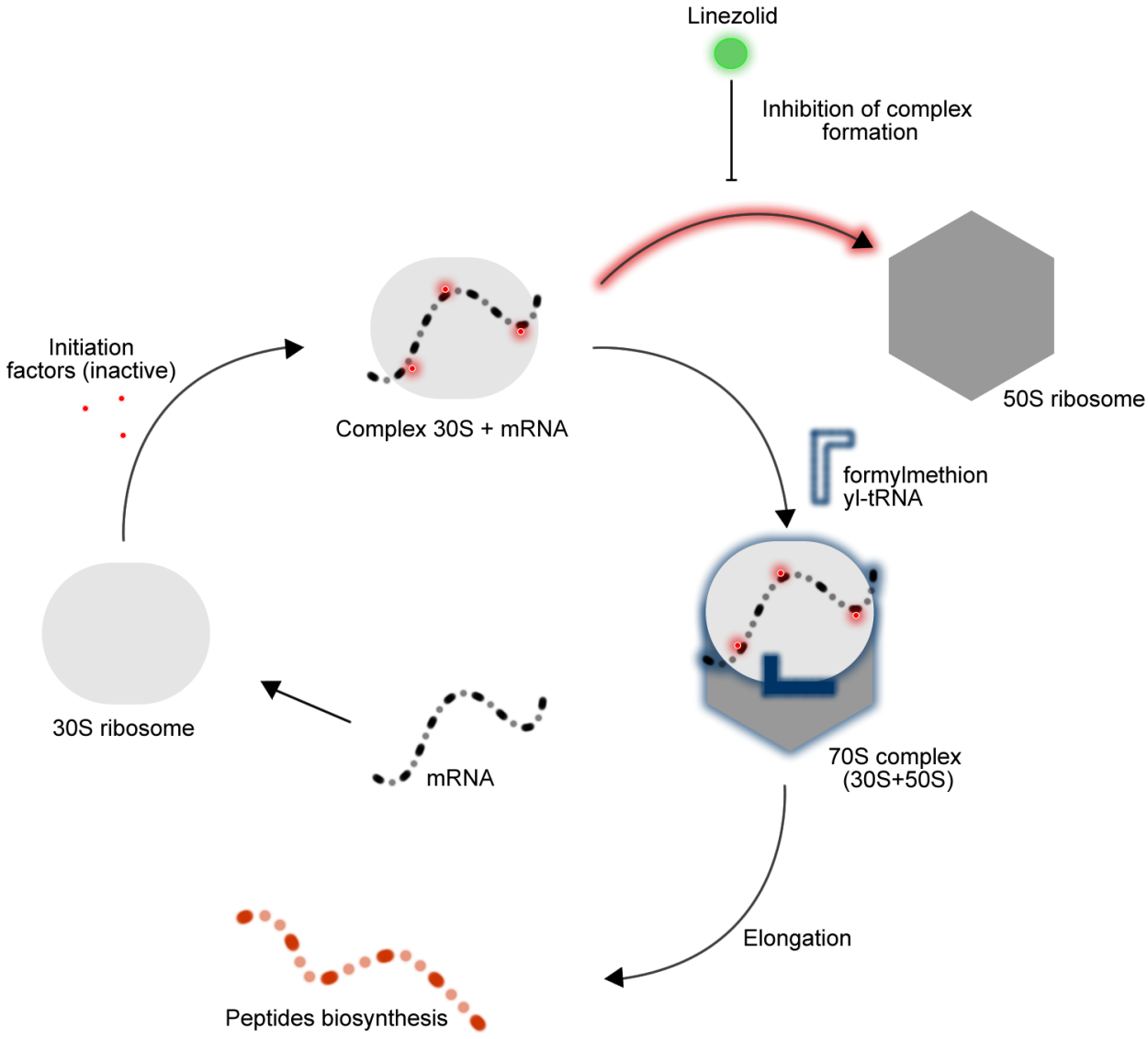

Figure 4. Mode of action of Linezolid. Description mechanism of the common peptides biosynthesis processes in prokaryotes. The complex formation of the 30S and 50S ribosomes to 70S formation and the inhibiting of protein biosynthesis by Linezolid action.

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%) (Lívio 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 µg ml-1 compared to the usually used bacteriocin nisin, which was 15.6 to 500 µg 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	Quinolenes
Membrane perturbers	Geobacillin I, bac-GM17, plantaricins, dysgalacticin, 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	*Staphylococcus aureus* and *Staphylococcus epidermidis*	(Lívio Varella Coelho et al. 2017)
Morricin 269, Kurstacin 287, Kenyacin 404, Entomocin 420 and Tolworthcin 524	II	*Bacillus thuringiensis*	(Barboza-Corona et al. 2009)
Lysostaphin	III	*Staphylococcus simulans* biovar *staphylolyticus*	(Schindler & Schuhardt 1964, Lívio Varella Coelho et al. 2017)
Epidermicin NI01		Staphylococcus epidermidis	(Sandiford & Upton 2012)
Pediocina PA-1	II	*Lactococcus lactis*	(Rodríguez et al. 2005)
Nisin A, lacticin Q, and Nukacin ISK-1	I	*Lactococcus lactis QU 5* and *Staphylococcus warneri ISK-1*	(Okuda et al. 2013)
Lacticin 3147	I	*Lactococcus lactis subsp. lactis*	(Twomey et al. 2000)
Enterocin CCM 4231	II	*Enterococcus faecium CCM 4231*	(Lauková & Czikková 1999)
E 50-52 and OR-70	II	*Enterococcus faecium* NRRL B-30746 *and Lactobacillus salivarius* NRRL B-30514	(Svetoch et al. 2008, Hanchi et al. 2017)
Duracin 61A and Reuterin		*Enterococcus durans* 61A and *Lactobacillus reuteri*	(Hanchi et al. 2017)
Pentocin JL-1	I	*Lactobacillus pentosus*	(Jiang et al. 2017)
TA6	II	*Pseudomonas aeruginosa* 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.

REFERENCES

ACEDO JZ, CHIOREAN S, VEDERAS JC & VAN BELKUM MJ. 2018. The expanding structural variety among bacteriocins from Gram-positive bacteria. FEMS Microbiol Rev 42: 805-828. doi:10.1093/femsre/fuy033.

AFŞAR I, BARIŞ I, SENE AG, KÖKSAL V & DEMIRCI M. 2012. [Linezolid-resistant Enterococcus faecium: the first G2576T mutation in Turkey. Mikrobiyol Bul 46: 516-518.

ALTAY F, KARBANCIOGLU-GÜLER F, DASKAYA-DIKMEN C & HEPERKAN D. 2013. A review on traditional Turkish fermented non-alcoholic beverages: Microbiota, fermentation process and quality characteristics. Int J Food Microbiol 167: 44-56. doi:10.1016/j.ijfoodmicro.2013.06.016.

ANDRIOLE VT. 2005. The Quinolones: Past, Present, and Future. Clin Infect Dis 41: S113-S119. doi:10.1086/428051.

ARCIOLA CR, CAMPOCCIA D & MONTANARO L. 2018. Implant infections: adhesion, biofilm formation and immune evasion. Nat Rev Microbiol 16: 397-409. doi:10.1038/s41579-018-0019-y.

ARUMUGAM T, DHANAM S. RAMESHKUMAR N, KRISHNAN M & KAYALVIZHI N. 2019. Inhibition of Methicillin Resistant Staphylococcus aureus by Bacteriocin Producing *Pseudomonas aeruginosa*. Int J Pept Res Ther 25: 339-348. doi:10.1007/s10989-018-9676-y.

BALCIUNAS EM, CASTILLO MARTINEZ FA, TODOROV SD, FRANCO BDG DE M, CONVERTI A & OLIVEIRA RP DE S. 2013. Novel biotechnological applications of bacteriocins: A review. Food Control 32: 134-142. doi:10.1016/j.foodcont.2012.11.025.

BALI V, PANESAR PS & BERA MB. 2016. Trends in utilization of agro-industrial byproducts for production of bacteriocins and their biopreservative applications. Crit Rev Biotechnol 36: 204-214. doi:10.3109/07388551.2014.947916.

BARBOZA-CORONA JE, DE LA FUENTE-SALCIDO N, ALVA-MURILLO N, OCHOA-ZARZOSA A & LÓPEZ-MEZA JE. 2009. Activity of bacteriocins synthesized by Bacillus thuringiensis against *Staphylococcus aureus* isolates associated to bovine mastitis. Vet Microbiol 138: 179-183. doi:10.1016/j.vetmic.2009.03.018.

BESIER S, LUDWIG A, ZANDER J, BRADE V & WICHELHAUS TA. 2008. Linezolid Resistance in Staphylococcus aureus: Gene Dosage Effect, Stability, Fitness Costs, and Cross-Resistances. Antimicrob Agents Chemother 52: 1570-1572. doi:10.1128/AAC.01098-07.

BIERBAUM G & SAHL H-G. 2009. Lantibiotics: mode of action, biosynthesis and bioengineering. Curr Pharm Biotechnol 10: 2-18.

BLANDINO A, AL-ASEERI ME, PANDIELLA SS, CANTERO D & WEBB C. 2003. Cereal-based fermented foods and beverages. Food Res Int 36: 527-543. doi:10.1016/S0963-9969(03)00009-7.

CABELL CH, JOLLIS JG, PETERSON GE, COREY GR, ANDERSON DJ, SEXTON DJ, WOODS CW, RELLER LB, RYAN T & FOWLER JR VG. 2002. Changing patient characteristics and the effect on mortality in endocarditis. Arch Intern Med 162: 90-94. doi:10.1001/archinte.162.1.90.

CAVERA VL, ARTHUR TD, KASHTANOV D & CHIKINDAS ML. 2015. Bacteriocins and their position in the next wave of conventional antibiotics. Int J Antimicrob Agents 46: 494-501. doi:10.1016/j.ijantimicag.2015.07.011.

CEOTTO-VIGODER H, MARQUES SLS, SANTOS INS, ALVES MDB, BARRIAS ES, POTTER A, ALVIANO DS & BASTOS MCF. 2016. Nisin and lysostaphin activity against preformed biofilm of *Staphylococcus aureus* involved in bovine mastitis. J Appl Microbiol 121: 101-114. doi:10.1111/jam.13136.

CHIKINDAS ML, WEEKS R, DRIDER D, CHISTYAKOV VA & DICKS LM. 2018. Functions and emerging applications of bacteriocins. Curr Opin Biotechnol 49: 23-28. doi:10.1016/j.copbio.2017.07.011.

CLEVELAND J, MONTVILLE TJ, NES IF & CHIKINDAS ML. 2001. Bacteriocins: safe, natural antimicrobials for food preservation. Int J Food Microbiol 71: 1-20. doi:10.1016/S0168-1605(01)00560-8.

COYNE B, FARAGHER J, GOUIN S, HANSEN CB, INGRAM R, ISAK T, THOMAS LV & TSE KL. 2014. Composition comprising a bacteriocin and an extract from a plant of the Labiatae family. Available at: https://patents.google.com/patent/ES2481167T3/en [Accessed March 6, 2020].

DE LA CALLE C, MORATA L, COBOS-TRIGUEROS N, MARTINEZ JA, CARDOZO C, MENSA J & SORIANO A. 2016. *Staphylococcus aureus* bacteremic pneumonia. Eur J Clin Microbiol Infect Dis 35: 497-502. doi:10.1007/s10096-015-2566-8.

DEB R, KUMAR A, CHAKRABORTY S, VERMA AK, TIWARI R, DHAMA K, SINGH K & KUMAR S. 2013. Trends in diagnosis and control of bovine mastitis: a review. Pak J Biol Sci 16: 1653-1661.

DEESOMCHOK U & TUMRASVIN T. 1990. Clinical study of culture-proven cases of non-gonococcal arthritis. J Med Assoc Thai 73: 615-623.

DIETZ CC & BONDI A. 1948. The Susceptibility of Penicillinase-producing Bacteria to Penicillin: II. The Effect of Sodium Azide. J Bacteriol 55: 849-854.

EGAN K, ROSS RP & HILL C. 2017. Bacteriocins: antibiotics in the age of the microbiome. Emerging Topics in Life Sciences 1: 55-63. doi:10.1042/ETLS20160015.

FENG Y, ZHANG M, MUJUMDAR AS & GAO Z. 2017. Recent research process of fermented plant extract: A review. Trends Food Sci Technol 65: 40-48. doi:10.1016/j.tifs.2017.04.006.

FERRERO L, CAMERON B, MANSE B, LAGNEAUX D, CROUZET J, FAMECHON A & BLANCHE F. 1994. Cloning and primary structure of Staphylococcus aureus DNA topoisomerase

IV: a primary target of fluoroquinolones. Mol Microbiol 13: 641-653. doi:10.1111/j.1365-2958.1994.tb00458.x.

FLEMING A. 1929. On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to their Use in the Isolation of B. influenzæ. Br J Exp Pathol 10: 226-236.

FUDA CCS, FISHER JF & MOBASHERY S. 2005. β-Lactam resistance in *Staphylococcus aureus*: the adaptive resistance of a plastic genome. Cell Mol Life Sci 62: 2617-2633. doi:10.1007/s00018-005-5148-6.

GOMES F & HENRIQUES M. 2016. Control of Bovine Mastitis: Old and Recent Therapeutic Approaches. Curr Microbiol 72: 377-382. doi:10.1007/s00284-015-0958-8.

GONZÁLEZ C, RUBIO M, ROMERO-VIVAS J, GONZÁLEZ M & PICAZO JJ. 2003. Staphylococcus aureus bacteremic pneumonia: differences between community and nosocomial acquisition. Int J Infect Dis 7: 102-108. doi:10.1016/s1201-9712(03)90004-x.

GRILO AL, RAQUEL AIRES-BARROS M & AZEVEDO AM. 2016. Partitioning in Aqueous Two-Phase Systems: Fundamentals, Applications and Trends. Sep Purif Rev 45: 68-80. doi:10.1080/15422119.2014.983128.

HANAKI H. 1998. Activated cell-wall synthesis is associated with vancomycin resistance in methicillin-resistant *Staphylococcus aureus* clinical strains Mu3 and Mu50. J Antimicrob Chemother 42: 199-209. doi:10.1093/jac/42.2.199.

HANCHI H, HAMMAMI R, GINGRAS H, KOURDA R, BERGERON MG, BEN HAMIDA J, QUELLETTE M & FLISS I. 2017. Inhibition of MRSA and of *Clostridium difficile* by durancin 61A: synergy with bacteriocins and antibiotics. Future Microbiol 12: 205-212. doi:10.2217/fmb-2016-0113.

HATTI-KAUL R. 2001. Aqueous Two-Phase Systems. Mol Biotechnol 19: 9.

HATZENBUEHLER J & PULLING TJ. 2011. Diagnosis and management of osteomyelitis. Am Fam Physician 84: 1027-1033.

HUMPHREYS H & MULVIHILL E. 1985. Ciprofloxacin-resistant *Staphylococcus aureus*. The Lancet 326: 383. doi:10.1016/S0140-6736(85)92510-3.

JAMALUDDIN N, STUCKEY DC, ARIFF AB & FAIZAL WONG FW. 2018. Novel approaches to purifying bacteriocin: A review. Crit Rev Food Sci Nutr 58: 2453-2465. doi:10.1080/10408398.2017.1328658.

JIANG H, ZOU J, CHENG H, FANG J & HUANG G. 2017. Purification, Characterization, and Mode of Action of Pentocin JL-1, a Novel Bacteriocin Isolated from Lactobacillus pentosus, against Drug-Resistant *Staphylococcus aureus*. BioMed Res Int 2017: 1-11. doi:10.1155/2017/7657190.

JOZALA AF, LOPES AM, DE LENCASTRE NOVAES LC, MAZZOLA PG, PENNA TCV & JÚNIOR AP. 2013. Aqueous Two-Phase Micellar System for Nisin Extraction in the Presence of Electrolytes. Food Bioprocess Technol 6: 3456-3461. doi:10.1007/s11947-012-1008-1.

KAISER C. 2000. Pharmaceutical Innovation. Revolutionizing Human Health Edited by Ralph Landau, Basil Achilladelis, and Alexander Scriabine. Chemical Heritage Press, Philadelphia. 1999. ISBN 0-941901-21-1. $44.95. J Med Chem 43: 1899-1900. doi:10.1021/jm000120h.

KEHRENBERG C, AARESTRUP FM & SCHWARZ S. 2007. IS21-558 Insertion Sequences Are Involved in the Mobility of the Multiresistance Gene cfr. Antimicrob Agents Chemother 51: 483-487. doi:10.1128/AAC.01340-06.

KEHRENBERG C, SCHWARZ S, JACOBSEN L, HANSEN LH & VESTER B. 2005. A new mechanism for chloramphenicol, florfenicol and clindamycin resistance: methylation of 23S ribosomal RNA at A2503: Drug resistance by methylation of A2503 in 23S rRNA. Mol Microbiol 57: 1064-1073. doi:10.1111/j.1365-2958.2005.04754.x.

KLAENHAMMER TR. 1988. Bacteriocins of lactic acid bacteria. Biochimie 70: 337-349. doi:10.1016/0300-9084(88)90206-4.

LAUKOVÁ A & CZIKKOVÁ S. 1999. The use of enterocin CCM 4231 in soy milk to control the growth of Listeria monocytogenes and *Staphylococcus aureus*. J Appl Microbiol 87 : 182-186. doi:10.1046/j.1365-2672.1999.00810.x.

LE LOIR Y, BARON F & GAUTIER M. 2003. *Staphylococcus aureus* and food poisoning. Genet Mol Res 2: 63-76.

LÍVIO VARELLA COELHO M, FREITAS DE SOUZA DUARTE A & DO CARMO DE FREIRE BASTOS M. 2017. Bacterial Labionin-Containing Peptides and Sactibiotics: Unusual Types of Antimicrobial Peptides with Potential Use in Clinical Settings (a Review). Curr Top Med Chem 17: 1177-1198.

LOPETUSO LR, GIORGIO ME, SAVIANO A, SCALDAFERRI F, GASBARRINI A & CAMMAROTA G. 2019. Bacteriocins and Bacteriophages: Therapeutic Weapons for Gastrointestinal Diseases? Int J Mol Sci 20. doi:10.3390/ijms20010183.

LOWY FD. 2003. Antimicrobial resistance: the example of *Staphylococcus aureus*. J Clin Invest 111: 1265-1273. doi:10.1172/JCI18535.

MÄDER U ET AL. 2016. Staphylococcus aureus Transcriptome Architecture: From Laboratory to Infection-Mimicking Conditions. PLoS Genet 12: e1005962. doi:10.1371/journal.pgen.1005962.

MAHBOUBI A, KAMALINEJAD M, AYATOLLAHI AM & BABAEIAN M. 2014. Total Phenolic Content and Antibacterial Activity of Five Plants of Labiatae against Four Foodborne and Some Other Bacteria. Iran J Pharm Res 13: 559-566.

MANZANILLA EG, NOFRARÍAS M, ANGUITA M, CASTILLO M, PEREZ JF, MARTÍN-ORÚE SM, KAMEL C & GASA J. 2006. Effects of butyrate, avilamycin, and a plant extract combination on the intestinal equilibrium of early-weaned pigs. J Anim Sci 84: 2743-2751. doi:10.2527/jas.2005-509.

MARBUN T ET AL. 2016. Analysis of Antibacterial, Antioxidant, and In Vitro Methane Mitigation Activities of Fermented *Scutellaria baicalensis* Georgi Extract*. Korean J Org Agric 24: 735-746. doi:10.11625/KJOA.2016.24.4.735.

MARSH AJ, HILL C, ROSS RP & COTTER PD. 2014. Fermented beverages with health-promoting potential: Past and future perspectives. Trends Food Sci Technol 38: 113-124. doi:10.1016/j.tifs.2014.05.002.

MARTIN MJ, THOTTATHIL SE & NEWMAN TB. 2015. Antibiotics Overuse in Animal Agriculture: A Call to Action for Health Care Providers. Am J Public Health 105: 2409-2410. doi:10.2105/AJPH.2015.302870.

MCGUINNESS WA, MALACHOWA N & DELEO FR. 2017. Vancomycin Resistance in *Staphylococcus aureus*. Yale J Biol Med 90: 269-281.

MD SIDEK NL, TAN JS, ABBASILIASI S, WONG FWF, MUSTAFA S & ARIFF AB. 2016. Aqueous two-phase flotation for primary recovery of bacteriocin-like inhibitory substance (BLIS) from Pediococcus acidilactici Kp10. J Chromatogr B 1027: 81-87. doi:10.1016/j.jchromb.2016.05.024.

MEKA VG, PILLAI SK, SAKOULAS G, WENNERSTEN C, VENKATARAMAN L, DEGIROLAMI PC, ELIOPOULOS GM, MOELLERIN JR RC & GOLD HS. 2004. Linezolid Resistance in Sequential *Staphylococcus aureus* Isolates Associated with a T2500A mutation in the 23S rRNA Gene and Loss of a Single Copy of rRNA. J Infect Dis 190: 311-317. doi:10.1086/421471.

MYLOTTE JM, MCDERMOTT C & SPOONER JA. 1987. Prospective study of 114 consecutive episodes of *Staphylococcus aureus* bacteremia. Rev Infect Dis 9: 891-907. doi:10.1093/clinids/9.5.891.

OIZUMI N, KAWABATA S, HIRAO M, WATANABE K, OKUNO S, FUJIWARA T & KIKUCHI M. 2001. Relationship between mutations in the DNA gyrase & topoisomerase IV genes and nadifloxacin resistance in clinically isolated quinolone-resistant Staphylococcus aureus. J Infect Chemother 7: 191-194. doi:10.1007/s101560100034.

OKUDA K, ZENDO T, SUGIMOTO S, IWASE T, TAJIMA A, YAMADA S, SONOMOTO K & MIZUNOE Y. 2013. Effects of bacteriocins on methicillin-resistant *Staphylococcus aureus* biofilm. Antimicrob Agents Chemother 57: 5572-5579. doi:10.1128/AAC.00888-13.

OTTO M. 2010. Basis of virulence in community-associated methicillin-resistant *Staphylococcus aureus*. Annu Rev Microbiol 64: 143-162. doi:10.1146/annurev.micro.112408.134309.

PEACOCK SJ & PATERSON GK. 2015. Mechanisms of Methicillin Resistance in *Staphylococcus aureus*. Annu Rev Biochem 84: 577-601. doi:10.1146/annurev-biochem-060614-034516.

PEREZ RH, ZENDO T & SONOMOTO K. 2018. Circular and Leaderless Bacteriocins: Biosynthesis, Mode of Action, Applications, and Prospects. Front Microbiol 9: 2085. doi:10.3389/fmicb.2018.02085.

PETERS TJ. 1987. Partition of cell particles and macromolecules: Separation and purification of biomolecules, cell organelles, membranes and cells in aqueous polymer two phase systems and their use in biochemical analysis and biotechnology. P-A. Albertsson. Third Edition, 1986, J Wiley & Sons, Chichester, £61.35 pages 346. Cell Biochem Funct 5: 233-234. doi:10.1002/cbf.290050311.

PETTI CA & FOWLER VG. 2002. *Staphylococcus aureus* bacteremia and endocarditis. Infect Dis Clin North Am 16: 413-435, x–xi. doi:10.1016/s0891-5520(01)00003-4.

POZZI C ET AL. 2012. Methicillin Resistance Alters the Biofilm Phenotype & Attenuates Virulence in *Staphylococcus aureus* Device-Associated Infections. PLoS Pathog 8: e1002626. doi:10.1371/journal.ppat.1002626.

REBUFFAT S. 2011. "Bacteriocins from Gram-Negative Bacteria: A Classification?," in Prokaryotic Antimicrobial Peptides (New York, NY: Springer New York), p. 55-72. doi:10.1007/978-1-4419-7692-5_4.

RODRÍGUEZ E, CALZADA J, ARQUÉS JL, RODRÍGUEZ JM, NUÑEZ M & MEDINA M. 2005. Antimicrobial activity of pediocin-producing *Lactococcus lactis* on *Listeria monocytogenes*, *Staphylococcus aureus* and *Escherichia coli* O157:H7 in cheese. Int Dairy J 15: 51-57. doi:10.1016/j.idairyj.2004.05.004.

ROZEMEIJER W ET AL. 2015. Evaluation of Approaches to Monitor *Staphylococcus aureus* Virulence Factor Expression during Human Disease. PLoS ONE 10: e0116945. doi:10.1371/journal.pone.0116945.

RYAN MJ, KAVANAGH R, WALL PG & HAZLEMAN BL. 1997. Bacterial joint infections in England and Wales: analysis of bacterial isolates over a four year period. Br J Rheumatol 36: 370-373. doi:10.1093/rheumatology/36.3.370.

SABO S DA S, LOPES AM, SANTOS-EBINUMA V DE C, RANGELYAGUI C DE O & OLIVEIRA RP DE S. 2018. Bacteriocin partitioning

from a clarified fermentation broth of *Lactobacillus plantarum* ST16Pa in aqueous two-phase systems with sodium sulfate and choline-based salts as additives. Process Biochem 66: 212-221. doi:10.1016/j.procbio.2017.11.018.

SANDIFORD S & UPTON M. 2012. Identification, Characterization, and Recombinant Expression of Epidermicin NI01, a Novel Unmodified Bacteriocin Produced by *Staphylococcus epidermidis* That Displays Potent Activity against Staphylococci. Antimicro. Agents Chemother 56: 1539-1547. doi:10.1128/AAC.05397-11.

SCHINDLER CA & SCHUHARDT VT. 1964. Lysostaphin: A new bacteriolytic agent for the *staphylococcus*. Proc Natl Acad Sci USA 51: 414-421. doi:10.1073/pnas.51.3.414.

SCHWARZ S, WERCKENTHIN C & KEHRENBERG C. 2000. Identification of a Plasmid-Borne Chloramphenicol-Florfenicol Resistance Gene in *Staphylococcus sciuri*. Antimicrob Agents Chemothery 44: 2530-2533. doi:10.1128/AAC.44.9.2530-2533.2000.

SHEARER JES ET AL. 2011. Major Families of Multiresistant Plasmids from Geographically and Epidemiologically Diverse Staphylococci. G3 1: 581-591. doi:10.1534/g3.111.000760.

SHIRTLIFF ME & MADER JT. 2002. Acute septic arthritis. Clin Microbiol Rev 15: 527-544. doi:10.1128/cmr.15.4.527-544.2002.

SHURLAND S, ZHAN M, BRADHAM DD & ROGHMANN M-C. 2007. Comparison of mortality risk associated with bacteremia due to methicillin-resistant and methicillin-susceptible *Staphylococcus aureus*. Infect Control Hosp Epidemiol 28: 273-279. doi:10.1086/512627.

SVETOCH EA ET AL. 2008. Diverse antimicrobial killing by *Enterococcus faecium* E 50-52 bacteriocin. J Agric Food Chem 56: 1942-1948. doi:10.1021/jf073284g.

SWANEY SM, AOKI H, GANOZA MC & SHINABARGER DL. 1998. The oxazolidinone linezolid inhibits initiation of protein synthesis in bacteria. Antimicrob Agents Chemother 42: 3251-3255.

TANAKA M, WANG T, ONODERA Y, UCHIDA Y & SATO K. 2000. Mechanism of quinolone resistance in *Staphylococcus aureus*. J Infect Chemother 6: 131-139. doi:10.1007/s101560070010.

TENHAGEN B-A, HANSEN I, REINECKE A & HEUWIESER W. 2009. Prevalence of pathogens in milk samples of dairy cows with clinical mastitis and in heifers at first parturition. J Dairy Res 76 : 179-187. doi:10.1017/S0022029908003786.

TOH S-M, XIONG L, ARIAS CA, VILLEGAS MV, LOLANS K, QUINN J & MANKIN AS. 2007. Acquisition of a natural resistance gene renders a clinical strain of methicillin-resistant *Staphylococcus aureus* resistant to the synthetic antibiotic linezolid: Linezolid resistance through ribosome modification. Mol Microbiol 64: 1506-1514. doi:10.1111/j.1365-2958.2007.05744.x.

TWOMEY DP, WHEELOCK AI, FLYNN J, MEANEY WJ, HILL C & ROSS RP. 2000. Protection against *Staphylococcus aureus* mastitis in dairy cows using a bismuth-based teat seal containing the bacteriocin, lacticin 3147. J Dairy Sci 83: 1981-1988. doi:10.3168/jds.S0022-0302(00)75075-2.

VAN BOECKEL TP, BROWER C, GILBERT M, GRENFELL BT, LEVIN SA, ROBINSON P, TEILLANT A & LAXMINARAYAN R. 2015. Global trends in antimicrobial use in food animals. Proc Natl Acad Sci USA 112: 5649-5654. doi:10.1073/pnas.1503141112.

VAN STADEN AD, BRAND AM & DICKS LMT. 2012. Nisin F-loaded brushite bone cement prevented the growth of *Staphylococcus aureus* in vivo: Inhibition of S. aureus by nisin F in bone cement. J Appl Microbiol 112: 831-840. doi:10.1111/j.1365-2672.2012.05241.x.

VENTOLA CL. 2015a. The antibiotic resistance crisis: part 1: causes and threats. P T 40: 277-283.

VENTOLA CL. 2015b. The antibiotic resistance crisis: part 2: management strategies and new agents. P T 40: 344-352.

VARELLA COELHO M, DE SOUZA DUARTE A & DE FREIRE BASTOS M. 2017. Bacterial Labionin-Containing Peptides and Sactibiotics: Unusual Types of Antimicrobial Peptides with Potential Use in Clinical Settings (a Review). Curr Top Med Chem 17(10): 1177-1198. https://doi.org/10.2174/1568026616666160930144809

VESTERGAARD M, FREES D & INGMER H. 2019. Antibiotic Resistance and the MRSA Problem. Microbiol Spectr 7. doi:10.1128/microbiolspec.GPP3-0057-2018.

WALTERS MS, EGGERS P, ALBRECHT V, TRAVIS T, LONSWAY D, HOVAN G, TAYLOR D, RASHEED K, LIMGAGO B & KALLEN A. 2015. Vancomycin-Resistant *Staphylococcus aureus* — Delaware, 2015. MMWR Morb Mortal Wkly Rep 64: 1056. doi:10.15585/mmwr.mm6437a6.

WATANAKUNAKORN C. 1987. Bacteremic *Staphylococcus aureus* pneumonia. Scand J Infect. Dis 19: 623-627. doi:10.3109/00365548709117196.

WATANAKUNAKORN C & BURKERT T. 1993. Infective endocarditis at a large community teaching hospital, 1980-1990. A review of 210 episodes. Medicine (Baltimore) 72: 90-102. doi:10.1097/00005792-199303000-00003.

WEISSER M, SCHOENFELDER SMK, ORASCH C, ARBER C, GRATWOHL A, FREI R, ECKART M, FLÜCKIGER U & ZIEBUHR W. 2010. Hypervariability of Biofilm Formation and Oxacillin Resistance in a *Staphylococcus epidermidis*

strain Causing Persistent Severe Infection in an Immunocompromised Patient. J Clin Microbiol 48: 2407-2412. doi:10.1128/JCM.00492-10.

ZHAO D & SHAH NP. 2015. Tea and soybean extracts in combination with milk fermentation, inhibit growth, and enterocyte adherence of selected foodborne pathogens. Food Chem 180: 306-316. doi:10.1016/j.foodchem.2015.02.016.

ZHU W ET AL. 2010. Dissemination of an Enterococcus Inc18-Like vanA Plasmid Associated with Vancomycin-Resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 54: 4314-4320. doi:10.1128/AAC.00185-10.

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

ELMA L. LEITE[1,2*]
https://orcid.org/0000-0001-9497-9819

ALBERTO F. DE OLIVEIRA JR[1*]
https://orcid.org/0000-0002-8222-4440

FILLIPE L.R. DO CARMO[2]
https://orcid.org/0000-0003-4405-1013

NADIA BERKOVA[1]
https://orcid.org/0000-0001-6246-5549

DEBMALYA BARH[3]
https://orcid.org/0000-0002-2557-7768

PREETAM GHOSH[4]
https://orcid.org/0000-0003-3880-5886

VASCO AZEVEDO[2]
https://orcid.org/0000-0002-4775-2280

[1]Institut National de la Recherche Agronomique (INRA), 65 Rue de Saint-Brieuc, 35000 Rennes, France

[2]Departamento de Genética, Ecologia e Evolução, ICB/UFMG, Av. Antonio Carlos, 6627, Pampulha, Caixa Postal 486, 31270-901 Belo Horizonte, MG, Brazil

[3]Centre for Genomics and Applied Gene Technology, Institute of Integrative Omics and Applied Biotechnology (IIOAB), Nonakuri, Purba Medinipur, 721172 West Bengal, India

[4]Department of Computer Science, Virginia Commonwealth University, Richmond, VA-23284, USA

Correspondence to: **Alberto F. de Oliveira Jr**
E-mail: afojunior@gmail.com
* Shared co-first authorship

Author contributions

EL and AO developing and writing of draft preparation; FC, NB, DB, PG writing and suggestion of draft preparation, reviewing and editing; VA supervision contributions and provided the final draft of the manuscript.