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Review Article

Antimicrobial peptides as a feed additive alternative to animal production, food safety and public health implications: An overview

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ABSTRACT

In the last few years, feed additives have been used in animal nutrition to improve nutrient utilization, health parameters and animal performance. However, the use of antibiotics as feed additives has allowed the occurrence of antimicrobial resistance (AMR), which can bring as a consequence, an increase in the morbidity and mortality of diseases that were previously treatable with antibiotics. In this context, antimicrobial peptides (AMP) have appeared as a promising strategy because they have multiple biological activities and represent a powerful strategy to prevent the development of resistant microorganisms. Despite the small number of studies applied in vivo, AMP appear as a potent alternative to the use of antibiotics in animal nutrition, due to an increase in feed efficiency and the prevention/treatment of some animal diseases. This review discusses the problems associated with antimicrobial resistance and the use of AMP as a strong candidate to replace conventional antibiotics, mainly in the animal industry.

1. Introduction

According to the Food Outlook 2020, disclosed by The Food and Agricultural Organization (FAO, 2020), world meat demand increased 119 million metric tons. However, a reduction in pig meat production is anticipated due to the impact of African swine fever disease. In contrast, the same report shows an expansion of poultry and ovine meat production due to the increased demand. In the dairy sector, milk production is expected to experience an improvement of 1.4%, producing 860 million metric tons of milk per year.

Brazilian companies lead the world beef market, which moves more than 7 million metric tons per year between exports and imports. Since 2005, this country has internationalized the sector, purchasing large processing plants abroad. In 2018, Brazil became the major exporter, trading more than 2 million metric tons of meat, and was followed by Australia, which exported approximately 1.5 million metric tons (ABIEC, 2019). Therefore, countries need to improve the feed safety, health and process certification and quality of origin (traceability) aspects of the herd to avoid the possible serious risk of losing the positive results already achieved in international markets (Morgan et al., 2016; Conchon and Lopes, 2012).

The production of poultry meat in the world is led by the USA, China, and Brazil, which is responsible for a high economic value (FAO, 2020). In recent years, consumers have changed their perspectives when purchasing food products, focusing mainly on food safety (Heneghan, 2015). This factor is related to nutritionally adequate usage and safe foods (Coleman-Jensen et al., 2020), with safe foods being those that do not affect consumer health (Chassy, 2010).

Various techniques have been employed in animal production to maximize food production. To achieve this, research needed to change from being solely focused on animal nutrition, replacing food nutritional value studies with an understanding of animal physiological processes and the factors that affect them (Wallace, 1994). In recent years, research has sought to manipulate and

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improve fermentative patterns and ruminal metabolism with additives in the diet (Meyer et al., 2009; Moya et al., 2009; Possenti et al., 2008), aiming to improve animal feed efficiency.

However, institutes such as the World Health Organization (WHO) and FAO have demonstrated concerns about the use of antibiotic additives in some situations, among them animal nutrition. Because of that, this research has been undertaken with the aim of finding some replacements for the usual additives.

2. Antimicrobial resistance (AMR)

AMR is considered to be one of the great challenges of the human health system. Every year, about 700,000 people die from uncontrolled infections (World Health Organization (WHO), 2019). If no changes in the approaches are taken, by 2050 AMR will kill more people than cancer diseases (O'Neill, 2014). The WHO defines AMR as “the microorganism which has the capacity of stopping antimicrobial activities”. AMR makes conventional treatments inefficient and infections impossible to be cured. AMR has increased in recent years and 6 pathogens are highlighted that exhibit high multidrug resistance and virulence: *Enterobacter* spp., *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterococcus faecium* (ESKAPE). These pathogens form the ESKAPE group, a dangerous pathogen group, which takes its name from the members of the group (Mulani et al., 2019). One of the main problems related to AMR is the lack of innovation, i.e., the development of new health technologies or treatments cannot keep up with the speed that these microorganisms can readapt. The main consequences of this phenomenon are an increase in diseases' morbidity and mortality, in diseases that were previously treatable with antibiotics and even with herbal antimicrobials. In addition, AMR has also resulted in the reappearance of infectious and opportunistic diseases, such as yellow fever, Chagas disease and tuberculosis, because microorganism mutations have caused greater resistance of parasites and agents. These issues represent serious public health problems, especially in most socioeconomically vulnerable populations (Estrela, 1998–2018).

Nowadays, 80% of animals used in food production are treated with drugs at some point in their lives (Chiesa et al., 2020). As a result, products from these animals – such as meat, milk, and eggs – can contain residues from these medicines. This has become a public health problem because these residues can affect the treatment of diseases due to AMR. In the milk industry, for example, the use of antibiotics such as chloramphenicol, β-lactams, streptomycins, sulfonamides, tetracyclines and quinolones is quite common. Their residues in milk can often cause allergies, which increases the development of resistant bacteria in humans (Chiesa et al., 2020). In 1997, the WHO determined that “antimicrobial overuse leads to the selection of resistant forms of bacteria in the ecosystem of use” and recommended that if an antibiotic was essential to human treatments, it should not be used as a growth promoter in animals. This is because after the antibiotic administration, some residues can remain in the animal product (Menkem et al., 2019) and lead to resistance development.

In 1955, a strain of *Shigella dysenteriae* resistant to 4 different antibiotics was isolated in Japan during an outbreak of bacterial dysentery. Ten years later, half of all Japanese *Shigella* infections were caused by multidrug resistant variants (Russell and Mantovani, 2005; Shiga, 1898), which showed how fast the resistance evolves and spreads in the environment. While the transference of antibiotic resistant bacteria between human and animals is not fully understood, we do know that animals fed with antibiotics have more antibiotic resistant bacteria than the free antibiotic fed animals. Further, farm workers carry more antibiotic resistant bacteria than people who live in urban environments (Wang et al., 2021). Research conducted by Abbas et al. (2008) tested the drug sensitivity in *Eimeria tenella* against some anticoccidials used in broiler chicks – salinomycin, maduramicin and clopidol. They found partial resistance in chickens against all 3 anticoccidials. Other additives such as tylosin and virginiamycin are well known for cross resistance to lincosamidines, macrolides and streptogramines (Witte, 2007). In addition, in Germany evidence was found of resistance in chickens to a streptothricin antibiotic, which had only been used in animal feeds (Witte, 2007).

As a consequence of AMR problems, international organizations, countries, academia, productive and technological sectors have been mobilizing on different levels of performance to tackle this obstacle. In 2015, the “Global Action Plan to Combat Antimicrobial Resistance” was launched because of a partnership between the FAO and the WHO, with the aim of keeping the treatment of infectious diseases effective and safe. In the fields of agriculture and animal production, the use of antibiotics to accelerate animal growth for human consumption, and their possible consequences of AMR, is a matter of great relevance due to its high economic impact. However, since 2016, the use of antimicrobial compounds as growth promoters has been banned by the European Union, considered the largest food importer in the world. Therefore, the recent call to combat AMR has led some countries to outline strategies for developing new and effectiveness antimicrobial molecules.

3. Antimicrobial peptides (AMP)

AMP are molecules with low molecular weight, belonging to a diverse and abundant group of biomolecules. AMP are produced in several types of animal and plant cells, with vast biological activity against bacteria, viruses, and fungi (Lai and Gallo, 2009). AMP are part of the natural innate immune system of animals and, in plants, form a defense system similar to the innate immunity observed in animals, protecting them from pathogens and pests (Lehrer et al., 1993; Gabay, 1994; Boman, 1995; Hultmark 1993; Shewry and Lucas, 1997; Gallo et al., 2002). AMP often share a common feature: the presence of even-numbered cysteine residues connected by disulfide bridges, which gives them high stability (Broekaert et al., 1997). In addition, their amino acid composition, amphipathicity, helicity, cationicity and size make them able to become inserted into lipid membranes, leading the target microorganism to death (Lorenzon et al., 2012; Brogden, 2005; Vicente et al., 2013; Izadpanah and Gallo, 2005). The continuous increase of multidrug resistant microorganisms' appearance has led research to shed light on these molecules, allowing the development of new therapeutic agents (Duin and Paterson, 2016; Gallo et al., 2002). Appreciation of the therapeutic potential of AMP is due to their ability to rapidly kill many microorganisms such as fungi, viruses, and bacteria, mainly those which have become resistant to multiple conventional drugs.

Despite conventional antibiotics that usually have the mechanism of action through a high affinity for a defined target in the microorganism, AMP perform multiple antimicrobial functions, which acts as a powerful strategy to prevent the development of resistance by microorganisms (Peschel and Sahl, 2006). Further, they can act on different targets in the cells such as DNA, RNA, regulatory enzymes, and other proteins (Maria-Neto et al., 2015). Specifically, their main advantage is the property to still kill multidrug-resistant bacteria. Zhang and Sack (2012) demonstrated that AMP can inhibit the methicillin-resistant bacteria *Streptococcus aureus* and *P. aeruginosa*, the latter being resistant to conventional antimicrobials, causing severe hospital infections. Unlike direct attacks against microorganisms, AMP may offer protection by different mechanisms, such as attacking unspecific targets (i.e., plasmatic membranes), maintaining normal gut homeostasis or modulating host inflammatory responses (Wang et al., 2015; Cespedes et al., 2012; Lai and Gallo, 2009). Current studies are not enough to fully support the synergies between conventional antibiotics and AMP, although insights could be revealed by exploring different AMP together (Magana et al., 2020). In human medicine, scientists already have published studies testing the capacity of AMP to reverse drug resistance. Teng et al. (2020) tested some AMP as anticancer drugs to reverse the cells resistance to regular drugs that have been used. Interestingly, they have found, for the first time, an antimicrobial peptide that could reverse cell resistance.

3.1. AMP activity

The most studied classes of AMP are those with antibacterial activity. Most AMP can interact with bacterial membranes and there are at least 9 hypotheses of mechanisms of action: 1) electroporation; 2) carpet model, 3) membrane thinning or thickening, 4) non-lytic membrane depolarization, 5) toroidal pore, 6) oxidized lipid targeting, 7) barrel stave, 8) disordered toroidal pore, and 9) non-bilayer intermediate (Magana et al., 2020).

There are several databases where most AMP are compiled and registered. The Antimicrobial PeptideDatabase (APD - http://aps.unmc.edu/AP/main.php) have 3,201 AMP from 6 kingdoms (357 bacteriocins/peptide antibiotics from bacteria, 5 from archaea, 8 from protists, 20 from fungi, 352 from plants, and 2,377 from animals, including some synthetic peptides) with a large variety of activity (Wang et al, 2009, 2016c; Wang and Wang 2004). A second database is the Data Repository of AntiMicrobial Peptides (DRAMP - http://dramp.cpu-bioinfor.org/), an open-access and manually curated database harboring diverse annotations of AMP including sequences, structures, activities, physicochemical, patent, clinical and reference information with 20,434 entries, 5,619 of which are general AMP (containing natural and synthetic AMP), 14,739 AMP patents and 76 AMP in drug development (Kang et al., 2019; Liu et al, 2017, 2018; Fan et al., 2016). Finally, the DBAASP (acronym for DataBase of Antimicrobial Activity and Structure of Peptides - https://dbaasp.org/) was developed to provide information and analytical resources for the scientific community, to help in developing antimicrobial compounds with a high therapeutic index (Pirtskhalava et al., 2016). To date, there are many other databases and resources for AMP research described elsewhere (Magana et al., 2020).

Antimicrobial peptides isolated from insects are the largest group of known AMP (Wang et al., 2016a). Among the antibacterial peptides, cecropins were extensively studied and represent an important component of insect defense systems against bacterial infection (Hoffmann, 1995). Synthetic cecropins exhibit a powerful inhibitory efficacy against *Escherichia coli, P. aeruginosa, Bacillus megatherium* and *Micrococcus luteus* (Andreu et al., 1985) and these classes of peptides act to destroy the bacterial membrane integrity (Silvestro et al., 2000). Another highlighted insect AMP group is the defensins (Hoffmann and Hetru, 1992), which act against Gram-positive bacteria and participate in the antibacterial defense reactions in insects (Wang et al., 2016a).

Another group of animals that presents a rich arsenal of AMP to defend against noxious microorganisms are the amphibians (Simmaco et al., 2004). The magainins were isolated from an African frog's skin and its synthetic peptide form displayed antibacterial activity against numerous Gram-positive and Gram-negative bacteria such as *E. coli, S. aureus* and *Klebsiella pneumonia*. The synthetic limnochariin, a peptide from amphibians' skin, showed antimicrobial activity against Gram-positive and negative bacteria (Wang et al., 2016b). Also, the synthetic hylaranins, an amphibian AMP extracted from an Oriental frog, showed antibacterial activity against *E. coli* and *S. aureus* (Lin et al., 2014). Finally, the hylins and ceratotoxin-Ha (Ctx-Ha) are cytolytic peptides isolated from the arboreal South American frog *Hypsiboas albopunctatus* that present a broad biological activity against bacteria and fungi (Castro et al., 2009; Cespedes et al., 2012; Vicente et al., 2013). From mammals, defensins and cathelicidins (CATH) are the main classes of AMP that have been identified. Defensins show a broad range of antimicrobial activity against bacteria that have demonstrated resistance to antibiotic treatments (Verma et al., 2007) and CATH exert antibacterial activity against Gram-positive and Gram-negative bacteria via electrostatic interactions with the bacterial cell membrane (Dean et al., 2011).

One of the interesting types of AMP studied are bacteriocins (Russell and Mantovani, 2005), which are ribosomal peptides released into the extracellular medium by Gram-positive and Gram-negative microorganisms and which have specific bactericidal or bacteriostatic action (Collins et al., 2010; De Vuyst and Leroy, 2007). The first bacteriocin was initially identified as an antimicrobial protein produced by *E. coli*, called colicin (Gratia, 1925).

In 1969, studies in bacteriocins produced by lactic acid bacteria aroused more interest in nisin, the first commercially applied bacteriocin. Nisin was added to the European list of food additives in 1983 and authorized for use in processed cheeses by the Food and Drug Administration (FDA) in 1988. Since then, the research field on this biomolecule has extensively increased, allowing the discovery and detailed characterization of many bacteriocins in recent decades (Rolhion et al., 2019; Hwanhlem et al., 2017; Collins et al., 2010). Recently, this compound has received great attention due to its high potential for application in the food industry — being used as natural preservatives — as well as being suggested to reduce the indiscriminate use of antibiotics in food products for humans and animals (Sabo et al., 2014). The production of bacteriocins occurs initially as a response mechanism to stimuli or environmental stress generated by microbial competition. They are usually synthesized as inactive pre-peptides with a precursor sequence in the N-terminal region (Xie and van Der Donk, 2004) and transported to the cell surface during the exponential phase and catalyzed into the active form (Aucher et al., 2005).

Bacteriocins are also widely used in the clinical field, e.g., in the treatment of topical dermatitis (Valenta et al., 1996), stomach ulcers and colon infections and respiratory tract infections (Dicks et al., 2018). Nisin, combined with conventional antibiotics, effectively helped the membrane permeabilization of an enteric multidrug-resistant *Salmonella* strain (Singh et al., 2013). This combination of antibiotics with AMP represents a way to decrease the use of conventional antibiotics in medical applications and help to reduce resistant bacteria (Naghmouchi et al., 2011). Kamarajan et al. (2015) demonstrated that nisin ZP (a naturally occurring variant) reduced tumorigenesis in vivo. In addition, a long-term treatment with nisin ZP extended survival and induced apoptosis dose-dependently in human umbilical vein endothelial cells (HUVEC), with concomitant decrease in vascular sprout formation in vitro and reduction of intratumoral microvessel density in vivo.

Over 70,000 distinct fungi have been identified and some of these can cause serious damage to human health (Li et al., 2012). Since the AMP have pleiotropic functions, i.e., a single molecule has several characteristics that are often unrelated, they can exert strong antifungal activity and could be useful in addressing fungal infections. In addition, many AMP are viral inhibitors (Jenssen et al., 2006). This antiviral activity can be related to the direct interaction with the virus or is a result of an indirect effect through interactions with potential target cells. Moreover, there are some studies that show the effects of some AMP against influenza virus and human immunodeficiency virus (HIV) (Tripathi et al., 2013; Barlow et al., 2011).

4. AMP utilization in animal feed

Antibiotics have been used in the animal industry for more than 50 years (Xiao et al., 2015). Although its use brings benefits, the misuse has caused some problems, including the emergence of bacteria resistant to antibiotics and drug residues in meat products (Bacanli and Basaran, 2019).

4.1. Swine

In the swine industry, post weaning diarrhea is a serious problem for production, due to increased mortality and reduced growth performance. Approximately, 50% of piglet mortality due to diarrhea is caused by enterotoxigenic *E. coli* (ETEC) (Cutler et al., 2007). According to United States Department of Agriculture (USDA, 2018), 95.5% of swine farms in United States include subtherapeutic concentrations of antibiotics in young pigs' diets. Despite that, farmers still reported a large occurrence of diarrhea, an unsurprising fact since very often they have seen a broad spectrum of antibiotic resistance among ETEC strains (Lanz et al., 2003; Maynard et al., 2004).

A potential alternative to conventional antibiotics is the colicins, a class of bacteriocins produced by and effective against *E. coli*, killing bacteria by disrupting the ionic gradient (FAO, 2020). Recent studies have demonstrated that colicins are effective against ETEC strains from pigs in vitro (Cutler et al., 2007) and against a wide range of *E. coli* strains (Murinda et al., 1996; Lanz et al., 2003). The colicins are not related to any antibiotic used in human medicine and do not leave any kind of traces in the animals (Cutler et al., 2007). Cutler et al. (2007) tested 2 doses of colicins (11.5 and 16.5 mg of colicin/kg of diet) on weaning pigs and observed a 40% higher weight gain and a 7% lower feed efficiency in the higher dose group compared to the control group (no colicin) showing that the animals have a better performance with colicin even when a small dose was used. Also, the authors did not observe any signs of post weaning diarrhea in the pigs in the higher dose group.

Other types of AMP that have been used are the synthetic AMP A3 and P5 (Yoon et al., 2012 a,b; 2014). Yoon et al. (2012a) evaluated different increasing levels of AMP A3, which were 0, 60 and 90 mg/kg of diet, as an alternative to conventional antibiotics. The study analyzed the growth performance, coefficient of total tract apparent digestibility (CTTAD) of nutrients and intestinal aspects of weanling pigs. A linear improvement on final body weight and an average daily gain, with no effect on average daily feed intake and feed efficiency were found. In addition, they observed a linear improvement on CTTAD of dry matter and crude protein, and no differences were observed between ileal total anaerobic bacteria, *Clostridium* spp. and coliform populations of pigs feed with AMP A3 compared to conventional antibiotics. Therefore, the results showed that AMP A3 is a potential molecule to replace antibiotics used as growth promoters in pigs.

In a parallel work, Yoon et al. (2012b) evaluated the increasing levels of AMP P5 on growth performance, CTTAD and intestinal aspects of weanling pigs as an alternative to conventional antibiotics. They noted a similarity between the groups fed with a conventional antibiotic and with the AMP P5 on average daily gain, also presenting CTTAD with greater results than the negative control group. The same behavior was observed for fecal coliform concentration. As in the previous work, results also showed that the AMP P5 is a possible potential molecule for replacement to conventional antibiotics used as growth promoters to pigs. Finally, in an association analysis, Yoon et al. (2014) tested both AMP A3 and P5 with a negative control (no antibiotic) and a positive control (a conventional antibiotic). They found that both AMP have potential to improve growth performance, nutrient digestibility, intestinal morphology and to reduce pathogenic bacteria in weanling pigs and could be an alternative to the usual antibiotics used in the swine industry.

Cecropin, an AMP isolated from silkworm *Hyalophora cecropia*, have also been tested on pigs. Wu et al. (2012) evaluated the cecropin AD – a chimeric cecropin AD peptide, which has the first 11 residues from *H. cecropia* cecropin A and the last 26 residues from *H. cecropia* cecropin D (Wu et al., 2012) – and a conventional antibiotic on pigs challenged with *E. coli* to investigate whether dietary alteration with AMP application could improve performance, immune defenses and reduce intestinal inflammation. The results indicated that animals fed with a diet containing the AMP cecropin AD improved the performance and reduced the incidence of diarrhea, a similar effect to what they observed from the treatment with conventional antibiotics.

As can be seen, there are some proven strategies with AMP to replace the use of antibiotics as growth promoters. However, further studies are needed to identify the precise in vivo mechanism of the action of these AMP to allow for safer utilization in animal nutrition.

4.2. Cattle

The rumen is an essential organ for nutrient fermentation due its capacity to produce end-products, particularly short chain fatty acids (SCFA) and microbial protein, the major energy and protein source to ruminants, respectively (Kristensen et al., 2005). Therefore, the more efficient the rumen is, the more end-products are synthetized. For this reason, in recent years, studies in rumen manipulation have widely increased. Antibiotics can increment the rumen efficiency; however, as occurred in swine industry, long-term usage may not be beneficial for ruminants and consumers (Cheema et al., 2011). Therefore, attempts have been made to replace them with better and safer alternatives.

Ruminants, as other animals, produce many AMP that act as natural innate barriers, limiting microbial infectious diseases and, therefore, have different sizes and mechanism of actions (Brogden et al., 2003). Ruminants present 2 AMP groups, available in different tissues, macrophages, mucosal epithelial cells and polymorphonuclear leukocytes, as follows: 1) anionic peptides – a small group rich in aspartic and glutamic acids, with activity against Gram-negative and Gram-positive bacteria, and 2) cationic peptides – rich in proline and cysteine, with activity against Gram-positive and Gram-negative bacteria (Brogden et al., 1996, 1997). These peptides have also antiviral and antifungal activities (Jenssen et al., 2009; Lee-Huang et al., 1999; Arnold et al., 1980).

Some ruminal Gram-positive bacteria can produce bacteriocins, an inhibitor of other bacteria species (Kalmokoff et al., 1996). A lantibiotic, bovicin HC5, was identified and isolated from *Streptococcus bovis* HC5 by Mantovani et al. (2001) with a large antibacterial activity and no bacterial adaptation demonstrated (Mantovani et al., 2001, 2002). Lee et al. (2002) tested the effects of bovicin HC5 on ruminal methane production in vitro and demonstrated that it can inhibit methane production at pH 6.7. Another study found that bovicin HC5 is even more effective in 5.5 pH, showing that the molecule can be more effective in animals fed grain rather than forage (Mantovani et al., 2002). The same study also tested the capacity of bovicin HC5 to inhibit methane production in a successive fashion. In addition, it was found that microorganisms, which received bovicin HC5, gradually lose their activity, i.e., the methanogen archaea did not adapt to the molecule. Lima et al. (2009) investigated if bovicin HC5 could inhibit the deamination of mixed ruminal bacteria and evaluated if bovicin HC5 and monensin affected the same types of ammonia producing ruminal bacteria. Interestingly, they found that bovicin HC5 and monensin have activity against the same types of bacteria.

4.3. Broilers and layers

In the poultry industry, the greatest problem raised is based on the presence of *Salmonella* sp., which also affects human public health (Narushin et al., 2020). The defense mechanisms of both broilers and laying hens have been studied for several years. As a result, it has been possible to identify AMP and classify them into 2 large families, defensins and CATH (Akbari et al., 2008).

Defensins are composed of between 18 and 45 amino acids, predominately comprised of cystines, cationic and hydrophobic residues. They present antimicrobial activity against bacteria, some fungi, protozoa, and even viruses (Sugiarto and Yu, 2004), immunomodulatory, anti-inflammatory, and intermediaries in regeneration of skin wounds (Xiao et al., 2020; Akbari et al., 2008). They are subdivided into α, β and θ, which are differentiated by the disulfide bridge position, size (kDa), and structure (β-sheet dimer or cyclic). Furthermore, in previous studies, it was revealed that chickens, as well as cattle, pigs and humans have β-defensins, but not α- or θ-defensins (Sugiarto and Yu, 2004). Avian β-defensins (AvD) are produced by the activation of encoded genes in response to an external or environmental factor and thus achieve homeostasis. These genes remain inactivated when chickens are not strained or are totally healthy, which is directly related to the presence of pathogenic microorganisms such as *Salmonella* sp. (Narushin et al., 2020; Akbari et al., 2008).

In laying hens, white eggs have been demonstrated to possess antimicrobial proteins and β-defensins. Also, a wide variety of cationically active AMP such as gallinacins, which can interact with pathogens cell membrane, have also been found. In addition, many of these AMP were identified as anti-biofilms that could eliminate microorganisms (Arena et al., 2020). A large list of AMP and other peptides related to anticancer, anti-inflammatory, antihypertensive and antiviral effects were also identified in chicken yolk plasma (Arena and Scaloni, 2018). Gallinacin 11 has demonstrated an effective response against *S. typhimurium* and *Listeria monocytogenes* in chickens (Higgs et al., 2005).

Some ceratotoxins, such as the cationic AMP, Ctx (Ile^{21})-Ha are a promising peptide applied against *S. enteritidis* and *S. typhimurium*, it also showed great activity against multidrug-resistant bacteria (Roque-Borda et al., 2021a). Innovative systems such as microparticles were successfully applied to control systemic infection caused by *Salmonella* (Roque-Borda et al., 2021b). Likewise, it was reported that these microparticles would be able to reduce the mortality rate of the chicks during the first days of post-infection life and increase their weight with the passing of days (Roque-Borda et al., 2021c).

A previous study has shown that the regulation of AMP was influenced by the presence of probiotics in chickens, because their relationship was inversely proportional (Ma et al., 2020). The gene expression of AMP decreased as the probiotic concentration increased, which indicates that AMP may not be entirely necessary in the presence of probiotics. However, there are still gaps to be studied in this relationship (Schlee et al., 2008; Akbari et al., 2008; Wehkamp et al., 2004). Another important regulator could be yeast culture (YC), where the expression of genes encoding AMP is increased, such as those expressing the AvD 1, 4 and 7 peptides and CATH 1 and 3. These molecules presented beneficial results for aged laying hens, demonstrating how beneficial this combination supplemented with YC can be, and the impact it has with the age of the chickens (Zhang et al., 2020).

In recent published studies on broilers, the AMP Microcin J25 was used against *Salmonella* sp. and *E. coli.* This peptide, showing antimicrobial activity, promoted animal growth performance, which improved the fecal flora composition and intestinal structure, as well as an induction of an efficient immune response (Wang et al., 2020). Another important agent used was potato proteins, which reduced the presence of coliform bacteria and improved broiler production performance (Ohh et al., 2009). Lactobacillins (Xu et al., 2020), which are polypeptides with antimicrobial activity produced by lactic acid bacteria (LAB), were also studied. *Lactobacillus* bacteriocin plantaricin K (PlnK) is part of this group and was expressed in vitro by genetic engineering. This peptide is particularly selective because it does not eliminate Gram-positive bacteria and exclusively eliminates pathogenic bacteria from the body. In addition to not altering the intestinal flora diversity, this peptide is a specific promoter of intestinal microbial control and has become an option for studies of selective AMP (Xu et al., 2020). A recombinant peptide, plectasin, complements the positive results already mentioned, and has exhibited an increase in duodenal lipase yield and trypsin activity, which are important for the digestion process in broilers (Ma et al., 2020).

Some studies based on broilers have also integrated the use of sublancin, from *Bacillus subtilis* 168, which was shown to have a great biological effect against *Clostridium perfringens*, *S. aureus* and *P. aeruginosa*, also helping the proliferation and count of LAB (Özcan et al., 2019). This recombinant AMP has also been shown to generate immunological memory (e.g., humoral, and cellular) by increasing the lymphocyte T content (CD4^{+}-to-CD8^{+} ratio), and Newcastle disease antibodies. Therefore, due to these results, a highly effective vaccine could be generated using this AMP as immunity stimulators (Liu et al., 2019).

In addition, it has also been shown that mixed-formulations of AMP and other compounds could have promising effects, such as those that use marine algae-cecropin, when *Laminaria japanica* powders were used as a feed supplement, showing a high growth performance and immune protection (Bai et al., 2019); This mixed effect could be key to the development of new antimicrobial additives as a food source for chickens.

There are other AMP such as magainin (Wang et al., 2016b), nisin (O'Connor et al., 2020), camel lactoferrin "36" and "chimera" (Daneshmand et al., 2019a,b) that are described in literature. These molecules have shown results like those already mentioned in this section. For all these reasons, AMP are essential for the survival and animal protection and become an interesting and valuable alternative for poultry production improvement.

5. Food preservatives

AMP have been applied in food preservation for more than 25 years. The most studied AMP were the bacteriocins produced by the LAB family, as they have potential application in food preservation (as shown in their application in broilers) (Kareem and Razavi, 2020). Among the most studied, plantaricins showed a high rate of microbial inhibition and activity against *S. enteritidis*, *E. coli*, *L. monocytogenes*, *C. perfringens* and *B. cereus*, among others (Thakur, 2017). Regarding the plantaricin family, some molecules have special features, such as: plantaricin A, inducer of production of other plantaricins (E/F and J/K); plantaricin C, applied in conservation and preservation of cheese and plantaricin S, extracted from fermented green olives (Kareem and Razavi, 2020).

The use of natural preservatives in replacement of chemical agents is an important strategy to increase shelf life of minimally processed fruits and vegetables (da Costa et al., 2019; Przybylski et al., 2016). In Brazil, with the approval of nisin in 1996, the first AMP/bacteriocin was used commercially by the Health Department as a cheese preservative. In addition, pediocin peptide, isolated from *Pediococcus* spp., is mainly used as a preservative for meat products, which protects from heat treatment due to its stability over a wide pH range (2 to 8) and high temperatures (maximum at 121 °C) (da Costa et al., 2019).

A new peptide recently isolated from broccoli, known as broccoli napin, has revealed a protective activity against pathogenic fungi, such as *Fusarium culmorum* and *Penicillium expansum*, being one of the most problematic pathogens in the agricultural sector. Moreover, the molecule has shown thermal stability, anti-tumor activity, and presented no hemolysis, protecting mainly crops and cereal-based products (Thery et al., 2020).

The α137–141 peptide was obtained from hemoglobin hydrolysis of blood residues of slaughterhouses, a residual by-product of beef production. This peptide has shown a high rate of microbial inhibition and potential antioxidant capacity. Thus, these functions together are interesting for their application in the food industry (Przybylski et al., 2020). Other AMP, such as those isolated from the house fly (*Musca domestica pupae*) (Md-AMP), which are used to preserve pork (chilled pork), have been found to destabilize the cell membrane and bind to DNA (Dang et al., 2020). The application of some AMP in the food industry has been tested through pilot trials of innovative containers, such as polyethylene terephthalate with the mitochondrial-targeted peptide 1. This molecule was evaluated in meat and dairy foods, demonstrating satisfactory results, corroborating a great progress and efficiency of AMP (Gogliettino et al., 2020). Therefore, these recent discoveries could lead to a promising alternative for food additives.

6. Cattle disease treatments with AMP

As mentioned, AMP have been considered a new source of biomolecules in several fields of scientific research, given their potential against many pathogenic microorganisms. In addition, the increase of microorganisms' resistance to antibiotics and the inability to discern the mechanisms of inhibition of these microorganisms have become a matter of concern, receiving immediate attention from the pharmaceutical industry to governmental and academic institutions (Lima et al., 2009). Many pathologies associated with animal production are related to the presence of bacteria, fungi, and viruses. However, they have already been evaluated as a method of prevention and treatment. In this section, AMP applications with successful results in cases of diseases caused by several types of microorganisms in cattle production are described.

Trichomonas foetus and *T. vaginalis* are parasites that generate enormous economic problems due to their high morbidity rates. These microorganisms can also be transmitted by humans through sexual contact. To overcome this problem, the D-hecate peptide was evaluated, proving to be highly effective against these microorganisms at a concentration of 10 μmol/L, by promoting a serious rupture in plasma membrane (Mutwiri et al., 2000). It also exhibited a great activity in cancer cells, appearing as an alternative in this type of disease in cattle production (Leuschner and Hansel, 2004). Some food additives, such as sodium bicarbonate, helped tritrpticin, also an AMP with high biological effectiveness, against *T. vaginalis* (Infante et al., 2011).

The bovine respiratory syncytial virus is considered a serious risk disease due to economic losses. This virus was counteracted by CATH LL-37 peptide, which is exceptionally attractive for monoclonal antibodies, due to their specificity and ability to induce immunity (Caskey et al., 2019). In vitro studies were carried out with this AMP in human cells and the molecule induced direct damage to the viral envelope, modifying the viral structure and decreasing the binding and interaction with epithelial cells. In addition, studies with murines indicated that an exogenous application would help in the eradication of post-infection disease (Armiento et al., 2020; Currie et al., 2016). Therefore, it is possible to use AMP with antiviral activity when applied in cattle, with possible efficient results.

Bovine respiratory disease complex (BRDC) is one of the most common illnesses in animal production caused by *Mannheimia haemolytica, Histophilus somni* and *Pasteurella multocida.* Bovines have as a natural defense mechanism, the tracheal antimicrobial peptide (TAP), that is affected and inhibited due to the stress generated by hormonal regulation in animal production (Siracusa, 2018; Vulikh et al., 2019). Synthetic TAP was used to evaluate its direct dosage effect via the nasal route. However, results showed no effects and no variance, explained by the amount of mucosa present in the nasal passage, which could be related to peptide instability and degradation (Vulikh et al., 2019). In this way, the current challenge is to use carriers or formulations for peptide interaction with the target pathogenic bacteria, with no destabilization or degradation. Another study evidenced the antimicrobial activity of bovine NK-lysine (natural killer cell origin and lytic properties) derived peptides, such as NK1, NK2A, NK2B and NK2C exhibiting activity against BRDC, which demonstrated excellent results, modifying the structure of the cell membrane, and causing a cytosolic effusion (Dassanayake et al., 2017).

In summary, these studies indicate that the use of peptides in animal models or in vitro studies could be taken as a reference for the development of novel and safer molecules for the improvement of livestock production.

7. Public health implications and future implications

The discovery of antibiotics in 1928, by Alexander Fleming, helped to improve the life expectancy of humankind (Hu et al., 2020). Following the increasing use of antibiotics over time, antimicrobial resistance became a severe public health problem. In recent years, antibiotics used against some diseases such as *K. pneumoniae* and *E. coli* are no longer effective in at least 50% of treated people (Peleg and Hooper, 2010; Shaikh et al., 2015). Moreover, the last option for gonorrhea medical treatment has failed in at least 10 countries (World Health Organization (WHO), 2019). The lack of policies to control the use of antibiotics, their misuse by humans and in livestock production have helped to achieve this threatening scenario.

Since 2015, AMR has become a worldwide priority. The WHO created the "Global Action Plan on Antimicrobial Resistance" to encourage a wise use of antibiotics and some strategies to reduce their consumption. This plan of action identified that some common medical conditions, such as tuberculosis, HIV, malaria, sexually transmitted diseases, urinary tract infections, pneumonia, blood-stream infections, and food poisoning have become resistant to a large number of conventional antibiotics (Roque-Borda et al., 2021d). Consequently, this fact has forced medical practitioners to use so-called "last-resort" drugs, which are expensive and mostly unavailable in poor countries.

Therefore, the urgent need for the development of new antimicrobials, mainly natural ones, is a powerful strategy to minimize the indiscriminate use of conventional antibiotics and could help treat and overcome some diseases, thus improving our quality of life.

8. Conclusions

Advances in animal production have demanded the increase of use of additives for productivity and to avoid mortality by pathogens. However, the increasing application of antibiotics and other growth promoters has revealed unfortunate "side effects": the appearance of AMR, multidrug resistant bacteria, and hazardous risks for human health. To tackle this broad-spectrum problem at different levels, this review presents and discusses an interesting alternative among several researched molecules: the AMP. These compounds, which have been proven to be efficient and promising, have shown biological activity and applicability against several microorganisms, mainly in the areas of animal production, as well as being suitable for food preservation. The multiple properties of AMP make them optimistic and powerful candidates to replace conventional drugs. Moreover, the development of new natural peptide-based antimicrobials for livestock, swine and poultry can help to reduce the antimicrobial problem without affecting either animal production or human health, nor leaving any pharmacological residues that generate environmental impact issues.

Conflict of interest

We declare that we have no financial and personal relationships with other people or organizations that might inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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References

Abbas RZ, Iqbal Z, Sindhu ZD, Khan MN, Arshad M. Identification of cross-resistance and multiple resistance in Eimeria tenella field isolates to commonly used anticoccidials in Pakistan. J Appl Poultry Res 2008;17:361–8. https://doi.org/10.3382/japr.2008-00027.

ABIEC (Associação Brasileira das Indústrias Exportadoras de Carne). Beef report 2019. Available on, http://abiec.com.br/publicacoes/beef-report-2019/; 2019.

Akbari MR, Haghighi HR, Chambers JR, Brisbin J, Read LR, Sharif S. Expression of antimicrobial peptides in cecal tonsils of chickens treated with probiotics and infected with Salmonella enterica serovar typhimurium. Clin Vaccine Immunol 2008;15(11):1689–93. https://doi.org/10.1128/CVI.00242-08.

Andreu D, Merrifield RB, Steiner H, Boman HG. N-terminal analogues of cecropin A: Synthesis, antibacterial activity, and conformational properties. Biochemistry 1985;24:1683–8. https://doi.org/10.1021/bi00328a017.

Arena S, Scaloni A. An extensive description of the peptidomic repertoire of the hen egg yolk plasma. J Agric Food Chem 2018;66(12):3239–55. https://doi.org/10.1021/acs.jafc.8b01183.

Arena S, Renzone G, Scaloni A. A multi-approach peptidomic analysis of hen egg white reveals novel putative bioactive molecules and food markers of storage. J Proteom 2020:103646. https://doi.org/10.1016/j.jprot.2020.103646.

Arnold RR, Brewer M, Gauthier JJ. Bactericidal activity of human lactoferrin: sensitivity of a variety of microorganisms. Infect Immun 1980;28:893–8.

Armiento V, Hille K, Naltsas D, Lin JS, Barron AE, Kapurniotu A. The human cathelicidin LL-37 is a nanomolar inhibitor of amyloid self-assembly of islet amyloid polypeptide (IAPP). Angew Chem 2020. https://doi.org/10.1002/ange.202000148.

Aucher W, Lacombe C, Héquet A, Frère J, Berjeaud J. Influence of amino acid substitutions in the leader peptide on maturation and secretion of mesentericin Y105 by leuconostoc mesenteroides. J Bacteriol 2005;187:2218–23. https://doi.org/10.1128/JB.187.6.2218-2223.2005.

Bacanli M, Basaran N. Importance of antibiotic residues in animal food. Food Chem Toxicol 2019;125. https://doi.org/10.1016/j.fct.2019.01.033.

Bai J, Wang R, Yan L, Feng J. Co-supplementation of dietary seaweed powder and antibacterial peptides improves broiler growth performance and immune function. Braz J Poultry Sci 2019;21. https://doi.org/10.1590/1806-9061-2018-0826.

Barlow PG, Svoboda P, Mackellar A, Nash AA, York IA, Pohl J, Davidson DJ, Donis RO. Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. PloS One 2011;6:e25333. https://doi.org/10.1371/journal.pone.0025333.

Boman HG. Peptides antibiotics and their role in innate immunity. Annu Rev Immunol 1995;13:61–92. https://doi.org/10.1146/annurev.iy.13.040195.000425.

Broekaert WF, Cammue BPA, De Bolle MFC, Thevissen K, De Samblanx G, Osborn RW. Antimicrobial peptides from plants. Crit Rev Plant Sci 1997;16: 297–323. https://doi.org/10.1080/07352689709701952.

Brogden KA, Mark A, McCray PB, Tack BF. Antimicrobial peptides in animals and their role in host defences. Int J Antimicrob Agents 2003;22:465–78. https://doi.org/10.1016/S0924-8579(03)00180-8.

Brogden KA, Ackermann M, Huttner KM. Small, anionic, and charge-neutralizing propeptide fragments of zymogens are antimicrobial. Antimicrob Agents Chem 1997;41:1615–7.

Brogden KA, De Lucca AJ, Bland J, Elliott S. Isolation of an ovine pulmonary surfactant-associated anionic peptide bactericidal for Pasteurella haemolytica. Proc Natl Acad Sci USA 1996;93:412–6.

Brogden KA. Antimicrobial peptides: pore formers or metabolic inhibitors in bacteria? Nat Rev 2005:238–50. https://doi.org/10.1038/nrmicro1098.

Caskey M, Klein F, Nussenzweig MC. Broadly neutralizing anti-HIV-1 monoclonal antibodies in the clinic. Nat Med 2019;25:547–53. https://doi.org/10.1038/s41591-019-0412-8.

Castro MS, Ferreira TCG, Cilli EM, Crusca Jr E, Mendes-Giannini MJS, Sebben A, Fontes W. Hylin a1, the first cytolytic peptide isolated from the arboreal South American frog *Hypsiboas albopunctatus* (“spotted treefrog”). Peptides 2009;30: 291–6. https://doi.org/10.1016/j.peptides.2008.11.003.

Cespedes GF, Lorezón EN, Vicente EF, Mendes-Giannini MJS, Fontes W, Castro MS, Cilli EM. Mechanism of action and relationship between structure and biological activity of Ctx-Ha: a new ceratotoxin-like peptide from *Hypsiboas albopunctatus*. Protein Pept Lett 2012;19. https://doi.org/10.2174/092986612800494011.

Chassy BM. Food safety risks and consumer health. N Biotech 2010;27:534–44. https://doi.org/10.1016/j.nbt.2010.05.018.

Cheema UB, Younas M, Sultan JI, Iqbal A, Tariq M, Waheed A. Antimicrobial peptides: an alternative of antibiotics in ruminants. Adv Agric Biotechnol 2011;2: 15–21.

Chiesa LM, DeCastelli L, Nobile M, Martucci F, Mosconi G, Fontana M. Analysis of antibiotic residues in raw bovine milk and their impact toward food safety and on milk starter cultures in cheese-making process. LWT (Lebensm-Wiss & Technol) 2020;131:109783. https://doi.org/10.1016/j.lwt.2020.109783.

Coleman-Jensen A, Rabbitt MP, Gregory CA. USDA ERS - measurement. Econ Res Serv 2020. https://www.ers.usda.gov/topics/food-nutrition-assistance/food-security-in-the-us/measurement.aspx. [Accessed 22 October 2020].

Collins B, Cotter PD, Ross RP. Applications of lactic acid bacteria-produced bacteriocins. In: Mozzi F, Raya RR, Vignolo GM, editors. Biotechnology of lactic acid bacteria: novel applications; 2010. p. 89–109.

Conchon FL, Lopes MA. RASTREABILIDADE E SEGURANÇA ALIMENTAR. Boletim Técnico - n. 91 -. Lavras/MG: GOVERNO DO BRASIL; 2012. p. 1–25.

Currie SM, Findlay EG, McFarlane AJ, Fitch PM, Böttcher B, Colegrave N, Davidson DJ. Cathelicidins have direct antiviral activity against respiratory syncytial virus in vitro and protective function in vivo in mice and humans. J Immunol 2016;196:2699–710. https://doi.org/10.4049/jimmunol.1502478.

Cutler SA, Lonergan SM, Cornick N, Johnson AK, Stahl CH. Dietary inclusion of colicin e1 is effective in preventing postweaning diarrhea caused by F18-positive Escherichia coli in pigs. Antimicrob Agents Chemother 2007;51: 3830–5. https://doi.org/10.1128/AAC.00360-07.

Dassanayake RP, Falkenberg SM, Briggs RE, Tatum FM, Sacco RE. Antimicrobial activity of bovine NK-lysin-derived peptides on bovine respiratory pathogen Histophilus somni. PLoS One 2017;12:e0183610. https://doi.org/10.1371/journal.pone.0183610.

Daneshmand A, Kermanshahi H, Sekhavati MH, et al. Antimicrobial peptide, cLF36, affects performance and intestinal morphology, microflora, junctional proteins, and immune cells in broilers challenged with E. coli. Sci Rep 2019a;9:14176. https://doi.org/10.1038/s41598-019-50511-7.

Daneshmand A, Kermanshahi H, Sekhavati MH, Javadmanesh A, Ahmadian M, Alizadeh M, Aldavoodi A. Effects of cLFchimera, a recombinant antimicrobial peptide, on intestinal morphology, microbiota, and gene expression of immune cells and tight junctions in broiler chickens challenged with C. perfringens. bioRxiv 2019:871467. https://doi.org/10.1101/871467.

Dang X, Zheng X, Wang Y, Wang L, Ye L, Jiang J. Antimicrobial peptides from the edible insect Musca domestica and their preservation effect on chilled pork. J Food Process Preserv 2020;44:e14369. https://doi.org/10.1111/jfpp.14369.

da Costa RJ, Voloski FL, Mondadori RG, Duval EH, Fiorentini ÂM. Preservation of meat products with bacteriocins produced by lactic acid bacteria isolated from meat. J Food Qual 2019. https://doi.org/10.1155/2019/4726510.

Dean SN, Bishop BM, van Hoek ML. Susceptibility of pseudomonas aeruginosa biofilm to α-helical peptides: D-enantiomer of LL-37. Front Microbiol 2011;2: 128. https://doi.org/10.3389/fmicb.2011.00128.

De Vuyst L, Leroy F. Bacteriocins from lactic acid bacteria: production, purification, and food applications. J Mol Microbiol Biotechnol 2007;13:194–9. https://doi.org/10.1159/000104752.

Dicks L, Dreyer L, Smith C, van Staden AD. A review: the fate of bacteriocins in the human gastro-intestinal tract: do they cross the gut-blood barrier? Front Microbiol 2018;9:2297. https://doi.org/10.3389/fmicb.2018.02297.

Duin D, Paterson D. Multidrug resistant bacteria in the community: trends and lessons learned. Infect Dis Clin 2016;30:377–90. https://doi.org/10.1016/j.idc.2016.02.004.

Estrela TS. Resistência antimicrobiana: enfoque multilateral e resposta brasileira. In: Saúde e Política Externa: os 20 anos da Assessoria de Assuntos Internacionais de Saúde (1998-2018); 2018. p. 307–27.

Fan L, Sun J, Zhou M, Zhou J, Lao X, Zheng H, Xu H. DRAMP: a comprehensive data repository of antimicrobial peptides. Sci Rep 2016;14:24482. PMID: 27075512.
FAO. Gateway to poultry production and products. Food Agric Organ United Nations; 2020. http://www.fao.org/poultry-production-products/production/en/. [Accessed 22 October 2020].
Gallo RL, Murakami M, Ohtake T, Zaiou M. Biology and clinical relevance of naturally occurring antimicrobial peptides. Colicins Annu Rev Microbiol 2002;110: 823–31. https://doi.org/10.1067/mai.2002.129801.
Gabay JE. Ubiquitous natural antibiotics. Science 1994;264:373–4. https://doi.org/10.1126/science.8153623.
Gogliettino M, Balestrieri M, Ambrosio RL, Anastasio A, Smaldone G, Proroga YT, Palmieri G. Extending the shelf-life of meat and dairy products via PET-modified packaging activated with the antimicrobial peptide MTP1. Front Microbiol 2020;10:2963. https://doi.org/10.3389/fmicb.2019.02963.
Gratia A. Sur un remarquable example d'antagonisme entre deux souches de colibacille. Compt Rend Soc Biol 1925;93:1040–2. Referred from: Gratia, J.P. (2000) Andre Gratia: A Forerunner in Microbial and Viral Genetics. Genetics, 156, 471-476.
Heneghan C. Food safety top concern for consumers: survey. Food Dive 2015. https://www.fooddive.com/news/food-safety-top-concern-for-consumers-survey/407395/. [Accessed 22 October 2020].
Hultmark D. Immune reactions in Drosophila and other insects: a model for innate immunity. Trends Genet 1993;9:178–82. https://doi.org/10.1016/0168-9525(93)90165-e.
Hu X, Logue M, Robinson N. Antimicrobial resistance is a global problem—a UK perspective. Eur J Integr Med 2020;36:101136. https://doi.org/10.1016/j.eujim.2020.101136.
Higgs R, Lynn DJ, Gaines S, et al. The synthetic form of a novel chicken β-defensin identified in silico is predominantly active against intestinal pathogens. Immunogenetics 2005;57:90–8. https://doi.org/10.1007/s00251-005-0777-3.
Hoffmann JA. Innate immunity of insects. Curr Opin Immunol 1995;7:4–10. https://doi.org/10.1016/0952-7915(95)80022-0.
Hoffmann J, Hetru C. Insect defensins: inducible antibacterial peptides. Immunol Today 1992;13:411–5. https://doi.org/10.1016/0167-5699(92)90092-L.
Hwanhlem N, Ivanova T, Biscola V, Choiset Y, Hartlé T. Bacteriocin producing Enterococcus faecal isisolated from chicken gastrointestinal tract originating from Phitsanulok, Thailand: isolation, screening, safety evaluation and probiotic properties. Food Contr 2017;78:187–95.
Infante VV, Miranda-Olvera AD, De Leon-Rodriguez LM, Anaya-Velazquez F, Rodriguez MC, Avila EE. Effect of the antimicrobial peptide tritrpticin on the in vitro viability and growth of trichomonas vaginalis. Curr Microbiol 2011;62: 301–6. https://doi.org/10.1007/s00284-010-9709-z.
Izadpanah A, Gallo RL. Antimicrobial peptides. J Am Acad Dermatol 2005;52: 381–90. https://doi.org/10.1016/j.jaad.2004.08.026.
Jenssen H, Robert EW, Hancock RE. Antimicrobial properties of lactoferrin. Biochimie 2009;91:19–29. https://doi.org/10.1016/j.biochi.2008.05.015.
Jenssen H, Hamill P, Hancock RE. Peptide antimicrobial agents. Clin Microbiol Rev 2006;19:491–511. https://doi.org/10.1128/CMR.00056-05.
Kamarajan P, Hayami T, Matte B, Liu Y, Danciu T, Ramamoorthy A, Worden F, Kapila S, Kapila Y, Nisin ZP. A bacteriocin and food preservative, inhibits head and neck cancer tumorigenesis and prolongs survival. PLoS One 2015;10:e0131008. https://doi.org/10.1371/journal.pone.0131008. PMID: 26132406; PMCID: PMC4489501.
Kang X, Dong F, Shi C, Zheng H, et al. DRAMP 2.0, an updated data repository of antimicrobial peptides. Sci Data 2019;6:148. PMID:31409791.
Kareem AR, Razavi SH. Plantaricin bacteriocins: as safe alternative antimicrobial peptides in food preservation—a review. J Food Saf 2020;40:e12735. https://doi.org/10.1111/jfs.12735.
Kristensen NB, Huntington GB, Harmon DL. Chapter 17 Splanchnic carbohydrate and energy metabolism in growing ruminants11Approved as publication No. 02-07-97 by the Kentucky Agricultural Experiment Station. In: Burrin DG, Mersmann HJ, editors. Biology of Growing Animals, vol. 3; 2005. p. 405–32. https://doi.org/10.1016/S1877-1823(09)70024-4.
Lai Y, Gallo RL. AMPed up immunity: how antimicrobial peptides have multiple roles in immune defense. Trends Immunol 2009;30:131–41. https://doi.org/10.1016/j.it.2008.12.003.
Lanz R, P K, Boerlin P. Antimicrobial resistance and resistance gene determinants in clinical Escherichia coli from different animal species in Switzerland. Vet Microbiol 2003;91:73–84. https://doi.org/10.1016/S0378-1135(02)00263-8.
Lee SS, Hsu J, Mantovani HC, Russell JB. The effect of bovicin HC5, a bacteriocin from *Streptococcus bovis* HC5, on ruminal methane production in vitro. FEMS (Fed Eur Microbiol Soc) Microbiol Lett 2002;217:51–5. https://doi.org/10.1111/j.1574-6968.2002.tb11455.x.
Lee-Huang S, Huang PL, Sun Y, Kung HF, Blithe DL, Chen HC. Lysozyme and RNases as anti-HIV components in beta-core preparations of human chorionic gonadotropin. Proc Natl Acad Sci Unit States Am 1999;96:2678–81.
Lehrer RI, Lichtenstein AK, Ganz T. Defensins: antimicrobial and cytotoxic peptides of mammalian cells. Annu Rev Immunol 1993;11:105–28. https://doi.org/10.1146/annurev.iy.11.040193.000541.
Leuschner C, Hansel W. Membrane disrupting lytic peptides for cancer treatments. Curr Pharmaceut Des 2004;10:2299–310. https://doi.org/10.2174/1381612043383971.
Li Y, Xiang Q, Zhang Q, Huang Y, Su Z. Overview on the recent study of antimicrobial peptides: origins, functions, relative mechanisms and application. Peptides 2012;37:207–15. https://doi.org/10.1016/j.peptides.2012.07.001.
Lima JR, Ribon AOB, Russel JB, Mantovani HC. Bovicin HC5 inhibits wasteful amino acid degradation by mixed ruminal bactéria invitro. FEMS (Fed Eur Microbiol Soc) Microbiol Lett 2009;292:78–84. https://doi.org/10.1111/j.1574-6968.2008.01474.x.
Lin Y, Hu N, Lyu P, Ma J, Wang L, Zhou M, Guo S, Chen T, Shaw C. Hylaranins: prototypes of a new class of amphibian antimicrobial peptide from the skin secretion of the oriental broad-folded frog. Hylarana Lataouchii Amino Acids 2014;46:901–9. https://doi.org/10.1007/s00726-013-1655-1.
Liu Y, Zhang J, Wang S, Guo Y, He T y, Zhou R. Una nueva "sublancina" adyuvante mejora la respuesta inmune en pollos de engorde específicos libres de patógenos inoculados con la vacuna contra la enfermedad de Newcastle. J Immunol Res 2019. https://doi.org/10.1155/2019/1016567.
Liu S, Bao J, Lao X, Zheng H. Novel 3D structure based model for activity prediction and design of antimicrobial peptides. Sci Rep 2018;25:11189. PMID:30046138.
Liu S, Fan L, Sun J, Lao X, Zheng H. Computational resources and tools for antimicrobial peptides. J Pept Sci 2017;23:4–12. PMID:27966278.
Lorenzon EN, Cespedes GF, Vicente EF, Nogueira LG, Bauab TM, Castro MS, Cilli EM. Effects of dimerization on the structure and biological activity of antimicrobial peptide Ctx-Ha. Antimicrob Agents Chemother 2012;56:3004–10.
Ma JL, Zhao LH, Sun DD, et al. Effects of dietary supplementation of recombinant plectasin on growth performance, intestinal health and innate immunity response in broilers. Probiotics Antimicrob Proteomics 2020;12:214–23. https://doi.org/10.1007/s12602-019-9515-2.
Magana M, Pushpanathan M, Santos AL, Leanse L, Fernandez M, Ioannidis A. The value of antimicrobial peptides in the age of resistance. Lancet Infect Dis 2020;20:e216–30. https://doi.org/10.1016/S1473-3099(20)30327-3.
Mantovani HC, Hu H, Worobo RW, Russell JB. Bovicin HC5, a bacteriocin from Streptococcus bovis HC5. Microbiology 2002;148:3347–52.
Mantovani HC, Kam DK, Ha JK, Russell JB. The antibacterial activity and sensitivity of *Streptococcus bovis* strains isolated from the rumen of cattle. FEMS (Fed Eur Microbiol Soc) Microbiol Ecol 2001;37. https://doi.org/10.1016/S0168-6496(01)00166-0. 223±229.
Maynard C, Bekal S, Sanschagrin F, Levesque RC, Brousseau R, Masson L, Lariviere S, Harel J. Heterogeneity among virulence and antimicrobial resistance gene profiles of extraintestinal *Escherichia coli* isolates of animal and human origin. J Clin Microbiol 2004;42:5444–52. https://doi.org/10.1128/JCM.42.12.5444-5452.2004.
Maria-Neto S, De Almeida KC, Macedo MLR, Franco OL. Understanding bacterial resistance to antimicrobial peptides: from the surface to deep inside. Biochim Biophys Acta Biomembr 2015;1848:3078–88. https://doi.org/10.1016/j.bbamem.2015.02.017.
Menkem ZE, Ngangom BL, Tamunjoh SSA, Boyom FF. Antibiotic residues in food animals: public health concern. Acta Ecol Sin 2019;39:411–5. https://doi.org/10.1016/j.chnaes.2018.10.004.
Meyer NF, Erickson GE, Klopfenstein TJ, Greenquist MA, Luebbe MK, Williams P, Engstrom MA. Effect of essential oils, tylosin, and monensin on finishing steer performance, carcass characteristics, liver abscesses, ruminal fermentation, and digestibility. J Anim Sci 2009;87:2346–54. https://doi.org/10.2527/jas.2008-1493.
Morgan A, Winck CA, Gianezinim M. A influência da rastreabilidade na cadeia produtiva brasileira de carne bovina. Espacios 2016;37:20.
Moya D, Calsamiglia S, Ferret A, Blanch M, Fandiño JI, Castillejos L, Yoon I. Effects of dietary changes and yeast culture (*Saccharomyces cerevisiae*) on rumen microbial fermentation of Holstein heifers. J Anim Sci 2009;87:2874–81. https://doi.org/10.2527/jas.2008-1446.
Mulani MS, Kamble EE, Kumkar SN, Tawre MS, Pardesi KR. Emerging strategies to combat ESKAPE pathogens in the era of antimicrobial resistance: a review. Front Microbiol 2019;10:539. https://doi.org/10.3389/fmicb.2019.00539.
Murinda SE, Roberts RF, Wilson RA. Evaluation of colicins for inhibitory activity against diarrheagenic *Escherichia coli* strains, including serotype O157:H7. Appl Environ Microbiol 1996;62:3196–202. PMC168116.
Mutwiri GK, Henk WG, Enright FM, Corbeil LB. Effect of the antimicrobial peptide, D-hecate, on trichomonads. J Parasitol 2000;86:1355–9. https://doi.org/10.1645/0022-3395(2000)086[1355:EOTAPD]2.0.CO,2.
Naghmouchi K, Lay C, Baah J, Drider D. Antibiotic and antimicrobial peptide combinations: synergistic inhibition of Pseudomonas fluorescens and antibiotic-resistant variants. Res Microbiol 2011;163:101–8. https://doi.org/10.1016/j.resmic.2011.11.002.
Narushin VG, Laptev GY, Yildirim EA, Ilina LA, Filippova VA, Kochish II, et al. Modelling effects of phytobiotic administration on coherent responses to Salmonella infection in laying hens. Ital J Anim Sci 2020;19:282–7. https://doi.org/10.1080/1828051X.2020.1733445.
O'Connor PM, Kuniyoshi TM, Oliveira RP, Hill C, Ross RP, Cotter PD. Antimicrobials for food and feed, a bacteriocin perspective. Curr Opin Biotechnol 2020;61: 160–7. https://doi.org/10.1016/j.copbio.2019.12.023.
Ohh SH, Shinde PL, Jin Z, Choi JY, Hahn TW, Lim HT, Chae B. J. Potato (Solanum tuberosum L. cv. Gogu valley) protein as an antimicrobial agent in the diets of broilers. Poultry Sci 2009;88:1227–34. https://doi.org/10.3382/ps.2008-00491.
O'Neill J. The Review on Antimicrobial Resistance. "Tackling a crisis for the health and wealth of nations". 2014. London, UK.
Özcan MA, Gülüm L, Midilli M, Gören M. The using of antimicrobial peptides in broiler feeding. Turk J Agric Food Sci Technol 2019;7:1–6. https://doi.org/10.24925/turjaf.v7i1.1-6.1275.
Peleg Y, Hooper DC. Hospital-acquired infections due to Gram-negative bacteria. N Engl J Med 2010;362:1804–13. https://doi.org/10.1056/nejmra0904124.
Peschel A, Sahl HG. The co-evolution of host cationic antimicrobial peptides and microbial resistance. Nat Rev Microbiol 2006;4:529–36. https://doi.org/10.1038/nrmicro1441.

Pirtskhalava M, Gabrielian A, Cruz P, Griggs HL, Squires RB, Hurt DE, Grigolava M, Chubinidze M, Gogoladze G, Vishnepolsky B, Alekseev V, Rosenthal A, Tartakovsky M. DBAASP v.2: an enhanced database of structure and antimicrobial/cytotoxic activity of natural and synthetic peptides. Nucleic Acids Res 2016;44:D1104−12.
Possenti RA, Franzolin R, Schammas EA, Demarchi JJAA, Frighetto RTS, Lima MA. Efeitos de dietas contendo *Leucaena leucocephala e Saccharomyces cerevisiae* sobre a fermentação ruminal e a emissão de gás metano em bovinos. Rev Bras Zootec 2008;37:1509−16. https://doi.org/10.1590/S1516-35982008000800025.
Przybylski R, Bazinet L, Firdaous L, Kouach M, Goossens JF, Dhulster P, Nedjar N. Harnessing slaughterhouse by-products: from wastes to high-added value natural food preservative. Food Chem 2020;304:125448. https://doi.org/10.1016/j.foodchem.2019.125448.
Przybylski R, Firdaous L, Châtaigné G, Dhulster P, Nedjar N. Production of an antimicrobial peptide derived from slaughterhouse by-product and its potential application on meat as preservative. Food Chem 2016;211:306−13. https://doi.org/10.1016/j.foodchem.2016.05.074.
Rolhion N, Chassaing B, Nahori MA, et al. A Listeria monocytogenes bacteriocin can target the commensal prevotella copri and modulate intestinal infection. Cell Host Microbe 2019;26:691−701. https://doi.org/10.1016/j.chom.2019.10.016.
Roque-Borda CA, Silva HRL, Junior EC, Serafim JA, Meneguin AB, Chorilli M, et al. Alginate-based microparticles coated with HPMCP/AS cellulose-derivatives enable the Ctx(Ile[21])-Ha antimicrobial peptide application as a feed additive. Int J Biol Macromol 2021a;183:1236−47. https://doi.org/10.1016/j.ijbiomac.2021.05.011.
Roque-Borda CA, Saraiva MDMS, Monte DF, Alves LBR, de Almeida AM, Ferreira TS, et al. Application of HPMCAS-coated Ctx(Ile[21])-Ha peptide microparticles as a potential use to prevent systemic infection caused by Salmonella Enteritidis in poultry. bioRxiv 2021. https://doi.org/10.1101/2021.03.19.436179. 2021.03.19.436179.
Roque-Borda CA, Pereira LP, Guastalli EAL, Soares NM, Mac-Lean PAB, Salgado DD, et al. HPMCP-coated microcapsules containing the ctx(ile[21])-Ha antimicrobial peptide reduce the mortality rate caused by resistant Salmonella enteritidis in laying hens. Antibiotics 2021c;10:616. https://doi.org/10.3390/antibiotics10060616.
Roque-Borda CA, da Silva PB, Rodrigues MC, Azevedo RB, Filippo L Di, Duarte JL, et al. Challenge in the discovery of new drugs: antimicrobial peptides against WHO-list of critical and high-priority bacteria. Pharm Times 2021d;13:773. https://doi.org/10.3390/pharmaceutics13060773. 2021.
Russell JB, Mantovani HC. The bacteriocins of ruminal bacteria and their potential as an alternative to antibiotics. J Mol Microbiol Biotechnol 2005;4:347-355.
Sabo SS, Vitolo M, González JMD, de Souza Oliveira RP. Overview of *Lactobacillus plantarum* as a promising bacteriocin producer among lactic acid bacteria. Food Res Int 2014;64:527−36. https://doi.org/10.1016/j.foodres.2014.07.041.
Schlee M, Harder J, Köten B, Stange EF, Wehkamp J, Fellermann K. Probiotic lactobacilli and VSL# 3 induce enterocyte β-defensin 2. Clin Exp Immunol 2008;151:528−35. https://doi.org/10.1111/j.1365-2249.2007.03587.x.
Shaikh S, Fatima J, Shakil S, Rizvi SM, Kamal MA. Antibiotic resistance and extended spectrum beta-lactamases:Types, epidemiology and treatment. Saudi J Biol Sci 2015;22:90−101. https://doi.org/10.1016/j.sjbs.2014.08.002.
Shewry PR, Lucas JA. Plant proteins that confer resistance to pest and pathogens. Adv Bot Res 1997;26:135−92. https://doi.org/10.1016/S0065-2296(08)60120-2.
Shiga K. Ueber den dysenteriebacillus *(Bacillus dysenteriae)*, *Zentralbl. Bakteriol. Parasitenkd*. Abt I Orig 1898;24:817−24.
Silvestro L, Weiser JN, Axelsen PH. Antibacterial and antimembrane activities of cecropin A in Escherichia coli. Antimicrob Agents Chemother 2000;44:602−7. https://doi.org/10.1128/aac.44.3.602-607.2000.
Simmaco M, Mignogna G, Barra D. Antimicrobial peptides from amphibian skin: what do they tell us? Biopolymers 2004;47:435−50. https://doi.org/10.1002/(SICI)1097-0282(1998)47:6<435::AID-BIP3>3.0.CO,2-8.
Singh R, Yadav AS, Tripathi V, Singh RP. Antimicrobial resistance profile of Salmonella present in poultry and poultry environment in North India. Food Contr 2013;33:545−8. https://doi.org/10.1016/j.foodcont.2013.03.041.
Siracusa L. Mecanismos de la supresión mediada por glucocorticoides de la expresión del péptido antimicrobiano traqueal en células epiteliales traqueales bovinas (disertación doctoral). 2018.
Sugiarto H, Yu PL. Avian antimicrobial peptides: the defense role of β-defensins. Biochem Biophys Res Commun 2004;323:721−7. https://doi.org/10.1016/j.bbrc.2004.08.162.
Teng Q, Luo X, Lei Z, Wang J, Wurpel J, Qin Z, Yang D. The multidrug resistance-reversing activity of a novel antimicrobial peptide. Cancers 2020;12:1963. https://doi.org/10.3390/cancers12071963.
Thakur A. Evaluation of antimicrobial activity of bacteriocin producing lactic acid bacteria isolated from dairy products and to assess their role in enhancing the shelf life of food (Doctoral dissertation, UHF, NAUNI). 2017.
Thery T, Lynch KM, Zannini E, Arendt EK. Isolation, characterisation and application of a new antifungal protein from broccoli seeds−New food preservative with great potential. Food Contr 2020:107356. https://doi.org/10.1016/j.foodcont.2020.107356.
Tripathi S, Tecle T, Verma A, Crouch E, White M, Hartshorn KL. The human cathelicidin LL-37 inhibits influenza A viruses through a mechanism distinct from that of surfactant protein D or defensins. J Gen Virol 2013;94:40−9. https://doi.org/10.1099/vir.0.045013-0.
Valenta C, Bernkop-Schnürch A, Rigler HP. The antistaphylococcal effect of nisin in a suitable vehicle: a potential therapy for atopic dermatitis in man. J Pharm Pharmacol 1996;48:988−91. https://doi.org/10.1111/j.2042-7158.1996.tb06019.x.
Verma C, Seebah S, Low SM, Zhou L, Liu SP, Li J, Beuerman RW. Defensins: antimicrobial peptides for therapeutic development. Biotechnology 2007;2:1353−9. https://doi.org/10.1002/biot.200700148.
Vicente EF, Basso LGM, Cespedes GF, Lorenzón EN, Castro MS, Mendes-Giannini MJS, Cilli EM. Dynamics and conformational studies of TOAC spin labeled analogues of Ctx(Ile[21])-Ha peptide from *Hypsiboas albopunctatus*. PLoS One 2013;8:e60818. https://doi.org/10.1371/journal.pone.0060818.
Vulikh K, Bassel LL, Sergejewich L, Kaufman EI, Hewson J, MacInnes JI, Caswell JL. Effect of tracheal antimicrobial peptide on the development of Mannheimia haemolytica pneumonia in cattle. PloS One 2019;14:e0225533. https://doi.org/10.1371/journal.pone.0225533.
Wallace RJ. Ruminal microbiology, biotechnology, and ruminant nutrition: progress and problems. J Anim Sci 1994;72:2992−3003. https://doi.org/10.2527/1994.72112992x.
Wang Y, Lyu N, Liu F, Liu WJ, Bi Y, Zhang Z, Ma S, Cao J, Song X, Wang A, Zhang G, Hu Y, Zhu B, Gao GF. More diversified antibiotic resistance genes in chickens and workers of the live poultry markets. Environ Int 2021;30. https://doi.org/10.1016/j.envint.2021.106534.
Wang G, Song Q, Huang S, Wang Y, Cai S, Yu H, Zhang J. Effect of antimicrobial peptide Microcin J25 on growth performance, immune regulation, and intestinal microbiota in broiler chickens challenged with Escherichia coli and Salmonella. Animals 2020;10:345. https://doi.org/10.3390/ani10020345.
Wang Y, Zhang Y, Lee WH, Yang X, Zhang Y. Novel peptides from skins of amphibians showed broad-spectrum antimicrobial activities. Chem Biol Drug Des 2016a;87:419−24. https://doi.org/10.1111/cbdd.12672.
Wang S, Zeng X, Yang Q, Qiao S. Antimicrobial peptides as potential alternatives to antibiotics in food animal industry. Int J Mol Sci 2016b;17:603. https://doi.org/10.3390/ijms17050603.
Wang G, Li X, Wang Z. APD3: the antimicrobial peptide database as a tool for research and education. Nucleic Acids Res 2016c;44:D1087−93.
Wang S, Thacker PA, Watford M, Qiao S. Functions of antimicrobial peptides in gut homeostasis. Curr Protein Pept Sci 2015;16:582−91. https://doi.org/10.2174/1389203716666150630135847.
Wang Z, Wang G. APD: the antimicrobial peptide database. Nucleic Acids Res 2004;32:D590−2.
Wehkamp J, Harder J, Wehkamp K, Wehkamp-von Meissner B, Schlee M, Enders C, Schröder JM. NF-κB-and AP-1-mediated induction of human beta defensin-2 in intestinal epithelial cells by Escherichia coli Nissle 1917: a novel effect of a probiotic bacterium. Infect Immun 2004;72:5750−8. https://doi.org/10.1128/IAI.72.10.5750-5758.2004.
Witte W. Impact of antibiotic use in animal feeding on resistance of bacterial pathogens in humans. In: Chadwick DJ, Goode J, editors. Ciba foundation symposium 207 - antibiotic resistance: origins, evolution, selection and spread; 2007. https://doi.org/10.1002/9780470515358.ch5.
World Health Organization (WHO). No time to wait: securing the future from drug-resistant infections. Report to the secretary-general of the United Nations. Available on: https://www.who.int/antimicrobial-resistance/interagency-coordination-group/final-report/en/. [Accessed June 2020].
Wu S, Zhang F, Huang Z, Liu H, Xie C, Zhang J. Effects of the antimicrobial peptide cecropin AD on performance and intestinal health in weaned piglets challenged with Escherichia coli. Peptides 2012;35:225−30. https://doi.org/10.1016/j.peptides.2012.03.030.
Xiao Y, Lyu W, Yang H, Xu X, Zhou C, Lu L, Zhang L. Molecular characterization, mRNA gene expression and antimicrobial activity of two new cathelicidin genes in goose. Poultry Sci 2020. https://doi.org/10.1016/j.psj.2020.03.021.
Xiao H, Xiao H, Wu MM, Tan B, Li T, Ren WK. Metabolic profiles in the response to supplementation with composite antimicrobial peptides in piglets challenged with deoxynivalenol. J Anim Sci 2015;93:1114−23. https://doi.org/10.2527/jas.2014-8229.
Xie L, van Der Donk WA. Post-translational modifications during lantibiotic biosynthesis. Curr Opin Chem Biol 2004;8:498−507. https://doi.org/10.1016/j.cbpa.2004.08.005.
Xu L, Zhou J, Qu G, Lin Z, Fan Q, Wang C, Wang Q. Recombinant lactobacillin PlnK adjusts the gut microbiome distribution in broilers. Br Poultry Sci 2020. https://doi.org/10.1080/00071668.2020.1752911 (just-accepted).
Yoon JH, Ingale SL, Kim JS, Kim KH, Lee SH, Park YK. Effects of dietary supplementation of antimicrobial peptide-A3 on growth performance, nutrient digestibility, intestinal and fecal microflora and intestinal morphology in weanling pigs. Anim Feed Sci Technol 2012a;177:98−107. https://doi.org/10.1016/j.livsci.2013.10.025.
Yoon JH, Ingale SL, Kim JS. Effects of dietary supplementation with antimicrobial peptide-P5 on growth performance, apparent total tract digestibility, faecal and intestinal microflora and intestinal morphology of weanling pigs. J Sci Food Agric 2012b;93:587−92. https://doi.org/10.1002/jsfa.5840.
Yoon JH, Ingale SL, Kim JS, Kim KH, Lee SH, Park YK. Effects of dietary supplementation of synthetic antimicrobial peptide-A3 and P5 on growth performance, apparent total tract digestibility of nutrients, fecal and intestinal microflora and intestinal morphology in weanling pigs. Livest Sci 2014;159:53−60. https://doi.org/10.1016/j.livsci.2013.10.025.
Zhang JC, Chen P, Zhang C, Khalil MM, Zhang NY, Qi DS, Sun LH. Yeast culture promotes the production of aged laying hens by improving intestinal digestive enzyme activities and the intestinal health status. Poultry Sci 2020. https://doi.org/10.1016/j.psj.2019.11.017.
Zhang W, Sack DA. Progress and hurdles in the development of vaccines against enterotoxigenic Escherichiacoli in humans. Expet Rev Vaccine 2012;11:677−94. https://doi.org/10.1586/erv.12.37.