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MINI-REVIEW

Antimicrobial peptides used as growth promoters in livestock production

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Abstract

Antibiotic growth promoters (AGPs) have been administered in livestock for decades to improve food digestion in growing animals, while also contributing to the control of microbial pathogens. The long-term and indiscrimate use of AGPs has generated genetic modifications in bacteria, leading to antimicrobial resistance (AMR), which can be disseminated to commensal and pathogenic bacteria. Thus, antimicrobial peptides (AMPs) are used to replaced AGPs. AMPs are found in all domains of life, and their cationic characteristics can establish electrostatic interactions with the bacterial membrane. These molecules used as growth promoters can present benefits for nutrient digestibility, intestinal microbiota, intestinal morphology, and immune function activities. Therefore, this review focuses on the application of AMPs with growth promoting potential in livestock, as an alternative to conventional antibiotic growth promoters, in an attempt to control AMR.

Key points

- *The long-term and indiscriminate use of AGPs in animal food can cause AMR.*
- *AMPs can be used as substitute of antibiotics in animal food suplementation.*
- *Animal food suplementated with AMPs can provied economic efficiency and sustainable livestock production.*

Keywords Antibiotics · Antimicrobial resistance · Public health · Livestock farming · Food production

Introduction

Antibiotics have been of vast importance to human health and are also employed in farm animal health to control disease and as growth promoters. Antibiotic growth promoters (AGPs) have been administered in sub-therapeutic doses with the role of eradicating or inhibiting pathogenic bacteria (Hugues and Heritage 2004). AGPs are administered in livestock to improve the animals' digestion, so that they get the highest benefit from foodstuffs and grow into strong and healthy individuals (NOAH 2001; U.S. Food and Drug Administration 2015). Although the AGP mechanism of action is unclear, it is supposed that AGPs inhibit the sensitive populations of bacteria in the intestines, and decrease energy loss with fermentative processes (Jensen 1998). AGPs also act in reducing the frequency and severity of subclinical infections (George et al. 1982; Brennan et al. 2003); they decrease microbial use of nutrients, and boost nutrient absorption, due to intestinal wall thinning (Snyder and Wostmann 1987; Feighner and Dashkevicz 1987; Knarreborg et al. 2004; Huyghebaert et al. 2011). Thus, by regulating the microbial population and controlling microbial nutrients, energy is transformed into animal growth (Hugues and Heritage, 2004).

AGPs have been employed to improve the development of farm animals since the 1950s (Jones and Ricke 2003; Brown et al. 2017; Ronquillo and Hernandez 2017). Over the years, several antibiotics have been administered in livestock as GPs (Table 1). This use helped to produce meat on an industrial scale (Van Boeckel et al. 2015). However, the indiscriminate use of AGPs for decades caused genetic modifications in bacteria and has led to antimicrobial resistance (AMR), which can be disseminated to commensal and pathogenic bacteria (Aslam et al. 2018; Founou et al. 2016; Innes et al. 2020; Li

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Table 1 Antibiotics employed as growth promoters in livestock

Class	Antibiotic	Spectrum	Growth promotion
Aminoglycosides	Neomycin	Narrow spectrum	Cattle
	Gentamicin	Broad spectrum	Cattle, Swine
	Spectinomycin		Sheep
	Streptomycin		Chickens, Swine, Sheep, Cattle
Penicillins	Penicillin G potassium	Broad spectrum	Chickens
	Penicillin G procaine		Chickens, swine
Ionophores	Lasalocid sodium	Broad spectrum	Cattle
	Salinomycin		Cattle, Swine
	Narasin		Swine
	Monesin		Cattle
Macrolides	Erythromycin	Broad spectrum	Chickens
	Tylosin	Broad spectrum	Swine
	Tilmicosin	Narrow spectrum	Chickens
Streptogramins	Virginiamycin	Broad spectrum	Chickens, swine
Tetracyclines	Oxytetracycline	Broad spectrum	Chickens, swine, sheep, cattle
	Chlortetracycline		
B-lactam	Amoxicillin	Narrow spectrum	Chickens, swine, sheep, cattle
	Ampicillin	Broad spectrum	
	Penicillin V	Narrow spectrum	Swine
Bacitracin	Polypeptides	Narrow spectrum	Bovine

Adapted of Brown et al., 2017; Ronquillo and Hernandez, 2017

et al. 2018). AGPs are therefore the subject of controversy associated with their risks and advantages.

Thus, antimicrobial peptides (AMPs) are being used to replace AGPs (Jenssen et al. 2006; Cheng et al. 2014; Zhao et al. 2016). AMPs are found in all domains of life, present chemical diversity and structure, and usually present cationic and amphipathic properties (Cardoso et al. 2020; Gomes et al. 2018; Spohn et al. 2019; Brogden 2005; Jenssen et al. 2006). The cationic characteristics of AMPs can establish electrostatic interactions with the bacterial membrane, which is commonly composed of negatively charged phospholipids (Hancock and Chapple 1999; Shai 2002). AMPs can interact with the outer membrane, disturbing its physical integrity, and may also be translocated across the membrane and act on internal targets (Hancock and Sahl 2006). AMPs exhibit activity against bacteria, fungi, viruses, and cancer (Cardoso et al. 2020; Hwang et al. 2011; Oshiro et al. 2019; Rodrigues et al. 2019; Saido-Sakanaka et al. 2004). In addition, these peptides can act indirectly by stimulating the host's immune system (Ageitos et al. 2017; Hancock 2001; Ward et al. 2013; Wang et al. 2016; WHO 2014). Therefore, this review summarized the application of AMPs as growth promoters with potential for livestock, as an alternative to traditional antibiotics, in an effort to control AMR.

Concern about growth promoters in livestock

As mentioned, the most common growth promoters applied in livestock are antibiotics (AGPs). However, the excessive use of antimicrobials has already contributed to the emergence of global public health problems, such as antimicrobial resistance, hypersensitivity responses, and damage to normal bacterial biota (Ronquillo and Hernandez 2017; Bacanlı and Başaran 2019). Thus, concern about the risks associated with AGPs in livestock and the consequences for human health has been increasing (Hughes and Heritage 2004; Marquardt and Li 2018; Tona 2018; Ma et al. 2020).

AMR development generally occurs through mutations (vertical AMR acquisition) and gene horizontal transfer (horizontal AMR acquisition) (Nadeem et al. 2020; Vidovic and Vidovic 2020). Occurrence of vertical AMR acquisition may be related with the exposure of bacterial populations to antibiotics, even in low concentrations. In this situation, any mutation that confers partial or full resistance against these antibiotics can be positively selected and transferred to subsequent generations, and this resistance may be against a specific antibiotic or a whole class (Tenover 2006; Davies and Davies 2010; Vidovic and Vidovic 2020). Horizontal AMR acquisition may occur by transference of resistant genetic elements such as plasmids or transposons, by horizontal transfer such as conjugation, transduction, or other mechanisms. Such processes can provide resistance against several antibiotic classes (Fig. 1) (Tenover 2006; Medina et al. 2020; Nadeem et al. 2020; Vidovic and Vidovic 2020).

Some studies estimated that approximately 90% of antibiotics applied in farm animals can be excreted by urine and/or feces. Furthermore, a number of antibiotics applied

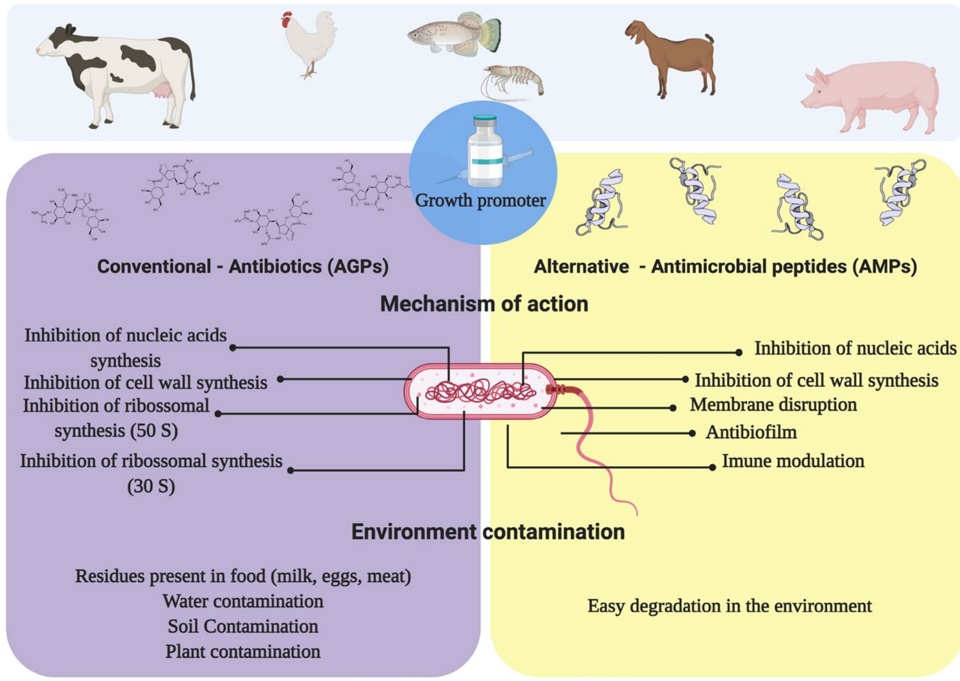

Fig. 1 Mechanism of action of antibiotics and antimicrobial peptides used as growths promoters

in animals can be stored in tissues such as muscle, milk, eggs, and fat. These residues can be dispersed by water and waste-water systems, or by fertilizers that employ manure, and cause the contamination of soil and consequently affect the soil microbiota, water, and plants (Ronquillo and Hernandez 2017; Iwu et al. 2020). Humans can be contaminated by AGPs in different ways, by ingestion in food, including milk, eggs, and meat, or by consuming water with residues of AGPs (Ben et al. 2019; Kraemer et al. 2019).

In this context, regulatory agencies, such as the European Commission and the US Food and Drug Administration (FDA), have established limits for antibiotic residues in animal foods (European Commission 1998; FDA 2016; FAO 2018). In 2006, the use of AGPs was completely banned in the European Union countries, and the use of antibiotics is permitted only for veterinary purposes (ten Doeschate and Raine 2006). In recent years, countries such as Canada, India, China, and Malaysia have restricted the use of AGPs in livestock, but many countries do not present any formal restrictions on AGPs (Brown et al. 2017; Ronquillo and Hernandez 2017; Salim et al. 2018; Bacanlı and Başaran 2019; Ben et al. 2019).

Thus, in recent years, the use of AGPs has been reduced and gradually replaced by effective dietary supplements, such as probiotics and/or prebiotics, enzymes, and novel antimicrobial peptides. In addition, the application of antibiotics in livestock requires control and prudence (Ma et al. 2020; Magnusson 2020; Patel et al. 2020).

Antimicrobial peptide growth promoters

Antimicrobial peptides (AMPs) display a broad spectrum of activity against bacteria, fungi, viruses, and cancer, and these characteristics have already been widely discussed (Cardoso et al. 2020; Hwang et al. 2011; Rodrigues et al. 2019; Saido-Sakanaka et al. 2004). Normally, the activity of AMPs can be related to bacterial membrane interaction. This interaction can occur associated with ion channel/pore formation and/or detergent-like effect, indicating the molecular basis of their attraction to membranes (Brogden 2005; Nguyen et al. 2011). Furthermore, AMPs display different modes of action, like membrane disruption, increased membrane permeability, and/or disturbances in key cellular processes by interacting with intracellular targets (Yeaman and Yount 2003; Nguyen et al. 2011; Wimley and Hristova 2011; Sani and Separovic 2016). Besides, the use of AMPs as a growth promoter has demonstrated beneficial effects on nutrient digestibility, the intestinal microbiota, intestinal morphology, and immune function activities (Fig. 1) (Liu et al. 2008; Xiao et al. 2015; Gadde et al. 2017).

In this regard, studies using lactoferricin-lactoferrin (LF-chimera) were used to supplement piglet feed. The results demonstrated an increase in body weight and in the average daily gain (ADG) of 13.3 and 29.3%, respectively, compared with pigs fed control diets (Tang et al. 2012). Other studies tested the growth and digestive capacity after administering AMPs in poultry and pigs (Wang et al. 2016). The use of synthetic AMPs, such as AMP-A3 and AMP-P5 (both derived from the amino acid substitution of *Helicobacter pylori*-HP and cecropin-magainin2 fusion,

Table 2 Antimicrobial peptides as growth promoters

AMP	Source	Target bacteria	Animal	Reference
Microcin J25	*Escherichia coli*	*E. coli, Salmonella sp.*	Broilers	Wang et al. 2020
Pediocin A	*Pediococcus pentosaceus*	*Clostridium perfringens*	Broilers	Grilli et al. 2009
Plectasin	*Pseudoplectania nigrella*	*E. coli*, *Salmonella* sp.	Broilers	Ma et al. 2019
RSRP	*Oryctolagus cuniculus*-sacculus rotundus	*E. coli*	Broilers	Aguirre et al. 2015
Lactoferrin (bLf)	*Bos taurus*	*E. coli, Salmonella sp.*	Broilers	Cao et al. 2007; Tang et al. 2012; Messaoudi et al.2012
SMXD51	*Lactobacillus salivarius*	*Campylobacter jejuni*	Poultry	Ceotto-Vigoder et al. 2016; Kogut et al. 2013
BT	*Brevibacillus texasporus*	*Salmonella enterica serovar Enteritidis*	Neonatal poultry	Kogut et al. 2012

respectively), increased the efficiency of gain of weanling pigs and broilers, with additional benefits concerning nutrient uptake and intestinal morphology. The maximal AMP concentrations tested were 90 and 60 mg kg^{-1} for AMP-A3 and AMP-P5, respectively. The results showed the effect for both body weight increases and intestinal injury reduction (Choi et al. 2013; Yoon et al. 2012, 2013, 2014). Another study evaluated the response of pig antibacterial peptides (PABP) in growth performance and small intestine mucosal immune responses in broilers. The authors reported that this PABP added to drinking water (20 and 30 mg/L) or supplemented in feed (150 and 200 mg/kg) can enhance growth performance, raise the intestinal ability to absorb nutrients, and improve the mucosal immunity of the intestine (Bao et al. 2009).

A different group used the AMP *Epinephelus lanceolatus piscidin* (EP), heterologously expressed and used as a dietary supplement for *Gallus gallus domesticus*. Treatment groups included control, and EP supplemented the diet at different doses (0.75, 1.5, 3.0, 6.0, and 12%). The results indicated that EP supplementation increased *G. domesticus* weight gain, feed efficiency, IL-10, and IFN-γ production, when compared to control (Tai et al. 2020). The pediocin A from *Pediococcus pentosaceus* FBB61 was tested by Grilli et al. (2009) as feed supplementation, and also tested against the *Clostridium perfringens* proliferation in broilers. The authors used a control group and another group where 80 AU.g^{-1} of pediocin A was added to the feed. The broilers were fed for 21 days, and they were challenged with culture of *C. perfringens* type A, which was administered by mouth on days 14, 15, and 16, twice daily (106 cfu/broiler). According to the authors, supplementation with pediocin A increased broiler growth performance during the challenge with *C. perfringens* (Grilli et al. 2009).

AMPs can also be used as AGPs in aquaculture, as described by Gyan et al. (2020). The application of AMPs can enhance the innate immune system, and boosts growth performance and disease resistance in Pacific white leg shrimp. In this study, different concentrations of AMP were tested in feed supplementation (0% until 1%). The results demonstrated the optimum concentration of AMP is 0.4% (400 g/kg). Researchers also observed that excess AMP in supplementation negatively affected the growth performance and immune system of the shrimp. Other studies which demonstrate efficient results using AMPs as growth promoters in livestock are shown in Table 2.

Concluding remarks and prospects

In the last 70 years, AGPs have been synonymous with productivity in livestock farming. However, the extensive use of these growth promoters has contributed to the development of bacterial strains with antimicrobial resistance. Antimicrobial resistance represents a worldwide problem and is treated with concern by the WHO. Hence, the European Union and the USA have limited the use of antibiotics in animal production. In an attempt to maintain livestock production, studies using AMPs as growth promoters have taken place, showing effective results in animal weight gains, and in some cases improving host immunity.

AMPs can therefore be an excellent way to substitute antibiotics due to characteristics such as a lower risk of inducing antimicrobial resistance, good inhibitory effects, and ease of degradation. Further studies using AMPs will allow a better understanding of the effects on the gastrointestinal ecosystem, and this will enable the best use of antimicrobial peptides for economic efficiency and sustainable livestock production.

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Declarations

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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