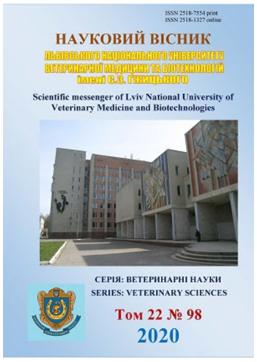


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# Antimicrobial peptides as novel alternatives to antibiotics

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*In recent years, due to the unreasonable use of antibiotics, bacterial resistance has increased, posing a huge threat to human health and the healthy development of the swine industry. Therefore, it is an urgent to look for antibiotic alternatives. Antimicrobial peptides are a class of small molecule peptides, which are the body's first line of defense against the invasion of pathogenic microorganisms. They have small molecular weight, good water solubility, and not easy to produce drug resistance. Therefore, antimicrobial peptides are considered as one of the best alternatives to antibiotics. This review focuses on the mechanism of action of antimicrobial peptides, especially improve performance, improve intestinal inflammation and nutrient digestibility, regulate the intestinal microbiota and enhance the immune function of swine. Overall, AMPs have great potential for application as an alternative to antibiotics in swine industry.*

***Key words:*** *antimicrobial peptide, applications, swine.*

## Introduction

Since the discovery of antibiotics, people have opened the golden age of antibiotic. At present, the World Health Organization has stated that antibiotics are harmful to human and animal health, and animal husbandry has confirmed that the unreasonable use of antibiotics are closely related to antibiotic resistance (Diana et al., 2019). Swine industry used a large number of unreasonable antibiotics to improve swine production performance and immune functions. Up to now, the swine industry has used antibiotics for more than 50 years, increasing bacterial resistance and decreasing quality of meat products. It has brought huge economic losses to swine industry (Xiao et al., 2015; Pérez-Duran et al., 2020). Because of the adverse consequences of antibiotics, they have been banned in many countries. Therefore, it is an urgent to find alternatives to antibiotics.

Antimicrobial peptides come from a wide range of sources, from prokaryotes to humans. Antimicrobial peptides are considered to be ancient weapons against microbial infections. They are an important component of the innate immune system and play an important role in innate immunity. Antimicrobial peptides have become candidates for the design of new antimicrobial drugs due to their good antibacterial activity and not drug resistance. This review focuses on the mechanism of action of antimicrobial peptides, especially improve produce performance and nutrient digestibility, anesis intestinal inflammation, regulate the intestinal microbiota and enhance the immune function of swine.

**Overview of antimicrobial peptides.** Antimicrobial peptide are a kind of small molecule polypeptide, which are the first lines of defense against the invasion of pathogenic microorganisms, and an important component of host innate immunity. They have many biological functions such as antibacterial, antifungal, antiviral and anti-cancer and so on (Forkus et al., 2017; Ramamourthy et al., 2020). Antimicrobial peptide are ubiquitous in nature, they are mainly from plants, mammals, fish, amphibians, birds and humans. Antimicrobial peptide generally consist of 12–100 amino acids, the amino acid sequence is relatively short, amphiphilic, generally carries 40–50 % hydrophobic residues and 2 to 9 positive charges, and its antibacterial activity is closely related to the amount of positive charges (Jenssen et al., 2006; Wang et al., 2019; Zhang et al., 2020). Antimicrobial peptides have good water solubility, broad antibacterial spectrum, low resistance to drug resistance, good heat stability, and resistance to protease and trypsin hydrolysis. In addition, the bactericidal mechanism of antimicrobial peptides is different from antibiotics, which mainly by destroying the cell membranes of bacterial, inhibiting DAN replication of bacterial and bacterial respiration and so on. It indicates that antimicrobial peptides have multiple mechanisms of action. Therefore, antimicrobial peptides are not susceptible to drug resistance (Cederlund et al., 2011; Xia et al., 2018). Compared with antibiotics, antimicrobial peptides have many advantages and become a research hotspot in recent years.

**The mechanism of action of antimicrobial peptide.** Due to the special properties of AMPs, such as amino acid composition variability, net charge, spatial conformation and structure, the mobility of amphiphilic modules and membranes is considered to have a special mechanism of action, and the antibacterial mechanism of several antimicrobial peptides is studied. The most scholars mainly agree that there are two kinds of mechanism of antimicrobial peptide, one is that the antimicrobial peptide destroy the cell membrane of the bacteria, forms a cavity, and causes the contents of the bacteria to leak out, leading to bacterial death. The other one is that antimicrobial peptide breaks the membrane after that enter into the bacteria body and combines with other substances in the cell, causing the bacteria die.

**The membrane sterilization mechanism of antimicrobial peptide.** At first, antimicrobial peptide aggregates on the surface of the bacterial cell membrane and inserted into the bilayer of the bacterial cell membrane phospholipid in a multimeric manner to form a channel. The external water molecules and ions use the channel to enter the interior of the bacteria, eventually leading to bacterial death (Jenssen et al., 2006). It can form a transmembrane potential after the antimicrobial peptide interacts with the bacterial cell membrane, thereby destroying the acid-base balance of the cell membrane, affecting the osmotic pressure of the bacteria, and inhibiting the bacterial respiration (Pandey et al., 2011). Su Jin Ko et al., 2017 used the circular dichroism to determine the structure of the antimicrobial peptide Macropin in the membrane simulation environment, and found that the antimicrobial peptide Macropin combined with LPS by destroying the bacterial cell membrane, resulting in bacterial death. Domenyuk V. et al., 2013 found that membrane labeled of antimicrobial peptides could against Staphylococcus aureus (UAB637) infection which mainly by destroying the bacterial cell membrane. It can be seen that the antimicrobial peptide exert bactericidal action by destroying the bacterial cell membrane.

**Intracellular bactericidal mechanism of antibacterial peptides.** In addition to destroying the cell membrane to produce bactericidal action, antimicrobial peptide can also enter the bacteria body and combine with other substances, and produce better bactericidal effect at a lower concentration (Wang et al., 2016). Dev K. Ranjit et al., 2010 used the hexamer peptide isolated from the laboratory to study its bactericidal mechanism and found that the antimicrobial peptide WRWYCR caused bacterial death by inhibiting bacterial DNA protein repair. Antimicrobial peptides cause bacterial death by inhibiting the respiration of mycobacterium tuberculosis, depolarizing membranes and releasing bacterial ATP (Hurdle et al., 2011). Hernandez-Gordillo V. et al., 2014 found that the dimeric peptide CAPH increased the antimicrobial activity against Escherichia coli and Staphylococcus aureus by nearly 60 times at high concentrations by inducing beta-galactosidase release. Porcine antimicrobial peptide PR-39 caused the death of Bacillus globospores and Escherichia coli by releasing bacterial ATP and membrane damage (Veldhuizen et al., 2014). Hassan Mahmood Jindal et al., 2017 found that the antimicrobial peptide RN7-IN8 released ATP after destroying the bacterial cell membrane, and inhibited bacterial DNA synthesis at a concentration of 62.5 mg/ml, leading to bacterial death. The results showed that antimicrobial peptide causes the bacteria to die by interacting with the intracellular substance of the bacteria.

**Application of antimicrobial peptides in swine industry.** Up to now, the widespread use of antimicrobial peptides is added to foods as food additives to preserve food (Wang et al., 2016). However, as study continues to deepen, it has been found that antimicrobial peptides have multiple functions in the swine industry. therefore, it has become the focus of the swine industry. Various antimicrobial peptides have been reported to play an important role in improving swine production performance, intestinal morphology, regulating intestinal flora and improving immune function.

**Antimicrobial peptides improve swine performance.** In recent years, studies have found that adding antimicrobial peptides to swine diets can significantly improve swine production performance. Adding 0.5, 1.0, and 2.0 mg/kg of antimicrobial peptide MccJ25 to the diet of weaned piglets, the average daily weight gain (ADG), average daily feed intake (ADFI), the incidence of diarrhea and the average daily weight gain/average daily feed intake (G:F) of piglets in 0 to 14 days significantly reduce the diarrhea rate, increase ADG, ADFI and G:F, and the effect is the same as the dosage of antimicrobial peptide MccJ25 positive correlation (Yu et al., 2017). Shi Jiankai et al., 2018 added 400 mg/kg antimicrobial peptide CAP to the diet of weaned piglets, which significantly increased the average daily weight gain of the piglets and reduced the diarrhea rate. The weight and feed intake of the piglets are reduced after E. coli infection, while adding 400 mg/kg cecropin AD to the diet, the weight and feed intake of the piglets are increased and the diarrhea rate of the piglets is reduced (Wu et al., 2012). Adding 10 mg/kg antimicrobial peptide AP to the piglet diet significantly increased ADG and ADFI, compared to the normal diet, reduced the rate of diarrhea in piglets (Wang et al., 2011). Consecutive injecting 0.6 mg/kg antimicrobial peptide CWA to clinical diarrhea piglets for 4 days can effectively relieve the diarrhea index of piglets and increase the weight of piglets (Yi et al., 2016). The above results indicate that antimicrobial peptides are expected to become antibiotic alternative in improving swine growth performance.

**Antimicrobial peptides improve intestinal inflammation and increase digestibility of nutrients of swine.** Toxins produced by pathogenic bacteria in the intestinal tract cause inflammation of the intestinal mucosa, changing the length of the intestinal villi and the depth of crypts (Burkey et al., 2009). Antimicrobial peptides change the intestinal morphology by reducing the expression of inflammatory factors. Adding colicin E1 to the diet of weaned piglets can reduce the E. coli titer in feces and ileum and diarrhea rate, and significantly reduce the expression levels of proinflammatory cytokines IL-1β and TNF-α in the ileum, thereby alleviating intestinal inflammation in piglets, improving intestinal morphology (Cutler et al., 2007). The study found that cecropin A can down-regulate the mRNA expression of TNF-α, IL-6 and IL-8 in swine intestinal. In addition, crocetin A can increase the transmembrane resistance (TER) of porcine jejunal epithelial cells, while reducing the permeability of the IPEC-J2 monolayer cell barrier (Zhai et al., 2018). Antimicrobial peptide CWA down-regulated the expression of TLR4-, MyD88- and NF-κB, thereby inhibiting the inflammatory response and alleviating diarrhea in piglets. In addition, antimicrobial peptide CWA improved the intestinal state by increasing the height of villi and microvilli, and increased the intestinal barrier function by increasing the expression of tight junction protein (TJ) in the small intestine and increasing wound healing ability (Yi et al., 2016).

Study found that antimicrobial peptides improving the growth performance of swine is closely related to improving the digestibility of swine nutrients. Antimicrobial peptides isolated from potatoes can increase the apparent digestibility of dry matter in weaned piglets (Jin et al., 2008). Antimicrobial peptides A3 and P5 have important functions in increasing dry matter, crude protein and total energy digestion of weaned piglets (Choi et al., 2013; Yoon et al., 2013). After adding 400mg/kg cecropin AD to the piglet diet, the feed conversion rate and nitrogen content in the feed were improved (Wu et al., 2012). The results shows that antimicrobial peptides have important function in improving swine intestinal morphology and improving nutrient digestibility.

**Antimicrobial peptides regulate swine intestinal microbiota.** Previous studies found that antimicrobial peptides were mainly reducing the number of harmful bacteria in swine intestines and increasing the number of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* to maintain intestinal health (Wang et al., 2016). Compared with the control group, lactoferrin significantly reduced the total viable count of Escherichia coli and Salmonella in swine small intestine, and increased the number of lactobacilli and bifidobacteria (Wang et al., 2007). Adding antimicrobial peptide CWA to the diarrhea piglet diet significantly reduced the ratio of *E. coli* to total bacteria in the feces, and increased the ratio of lactobacilli to total bacteria, indicating that the antimicrobial peptide CWA has a positive effect on the regulation of intestinal microbiota (Yi et al., 2016). Adding potato protein to the diet of weaned piglets can significantly reduce the number of E. coli and bacteria in the contents of feces, cecum, colon and rectum (Jin et al., 2008).

**Antimicrobial peptides enhance the immune function of swine.** Antimicrobial peptides are an important part of the host's defense system, and are also the effector molecules of the innate immune system mediate immune function (Levy, 2000). Weaned piglets were fed antimicrobial peptides with different concentrations (250 mg/kg; 500 mg/kg; 1000 mg/kg) for 28 days, and blood samples were collected at 32, 39, 46, and 53 days of age for testing. The levels of IgG, IgM, IgA, classical swine fever virus antibody (CSF-Ab) and total serum complement (CH50) in the blood are increasing with dose-dependent (Yuan et al., 2015). Adding antimicrobial peptides(10 mg/kg) to the diet of weaned piglets can reduce the diarrhea rate, and significantly increase IgG levels and peroxide dismutase activity, and reduce the total cholesterol concentration (Wang et al., 2011). Adding antimicrobial peptide HDP to the diet of weaned piglets can improve the digestibility of nutrients, intestinal morphology and growth performance of weaned piglets, and increase the concentration of serum IgA, IgG or IgM. PFM105 isolated from the rectum of healthy sows can improve growth performance of weaned piglets, reduce diarrhea rate, increase intestinal health indicators, and significantly increase serum IgM, IL-10, TGF-β and SCFAs levels in the colon (Wang et al., 2019). porcine defensins are mixed with antimicrobial peptides derived from flies to the diet of weaned piglets, and found that the mixed antimicrobial peptides can increase the T cell population and significantly enhance the proliferation of T cells. It indicates that addition of antimicrobial peptides to the grain significantly enhances the immune function of swine (Ren et al., 2015). Artificially synthesized lactoferrin can enhance the proliferation of peripheral blood and splenic lymphocytes and increase the levels of IgG, IgA, IgM and IL-2 in the serum of weaned piglets (Shan et al., 2007). The piglets treatment with 100 mg/kg antimicrobial peptide cipB-LFC-LFA after enterotoxigenic *E. coli* infection can significantly increase the levels of IgA, IgG and IgM in serum (Tang et al., 2009). The above results indicate that antimicrobial peptides have important functions in enhancing the immune function of swine.

## Conclusion

Antimicrobial peptides are expected to become one of the best alternatives to antibiotics with its unique antibacterial mechanism and immunomodulatory function. It has been proved that many antimicrobial peptides have huge application potential in the swine industry. Antimicrobial peptides provide the swine industry with functions such as improved growth performance and nutrient digestibility, improved intestinal health, regulation of intestinal microbiota and immune regulation. Antimicrobial peptides improve swine growth performance and are closely related to antibacterial and immunomodulatory functions. However, the studies on antimicrobial peptides exerting immunomodulatory functions and metabolism in vivo are relatively weak, and further studies are needed. With the continuous development of science and technology, the study on antimicrobial peptides will be more and more in-depth. Eventually, antimicribail peptides become growth promoters and therapeutic agents of the swine industry by virtue of their antibacterial and immunomodulatory effects.

## Author's contributions

All authors participated in this review design. Xueqin Zhao participated and performed writing and data collection. All authors read and approved the final manuscript. All authors contributed to the draft of the manuscript. All authors gave final approval for publication.

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## Conflict of interest

Author does not report any financial or personal connec tions with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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