Ann. Anim. Sci., Vol. 24, No. 2 (2024) 379–391 *DOI: 10.2478/aoas-2023-0058*

sciendo

EXPLORING THE BIOGENIC PEPTIDE'S POTENTIAL IN COMBATING BACTERIAL ZOONOSIS: APPLICATION AND FUTURE PROSPECT – A REVIEW

Saleha Tahir[1], Rao Zahid Abbas[2], Warda Qamar[2]♦, Muhammad Imran Arshad[1], Mughees Aizaz Alvi[3], Muhammad Shahid Mahmood[1], Tean Zaheer[2]

[1]Institute of Microbiology, University of Agriculture, Faisalabad, Pakistan
[2]Department of Parasitology, University of Agriculture, Faisalabad, Pakistan
[3]Department of Clinical Medicine and Surgery, University of Agriculture, Faisalabad, Pakistan
♦Corresponding author: wardaqamar17@gmail.com

Abstract

Worldwide, microbial infections have a serious impact because they cause infectious diseases, death, and significant economic losses. Zoonosis is now a major public health issue on a global scale because of the fast expansion of human exploitation of nature and animal husbandry. Notably, in the past 30 years, over 30 novel human infections have been discovered, 75% of which fall under the category of zoonosis. Resistant strains have emerged as a result of improper use of antibiotics and insufficient infection management posing a serious risk to both public health and the global economy. As alternatives, antimicrobial peptides are showing good results. The majority of living things use antibacterial peptides (ABPs) as a key part of their natural defenses against invading infections. These peptides are cationic, amphipathic, and relatively tiny with varied sequences, structures, and lengths. For the delivery of these efficacious biological peptides, nanoparticles are providing opportunities for effective, safe, and viable delivery. An innovative method of treating infectious diseases is demonstrated by nanoparticles and antibacterial peptides. When ABPs are combined with carrier nanoparticles to optimize distribution, their half-life may be increased, allowing for lower dosages and ultimately lower toxicity. For biological applications, ABPs and nanoparticle conjugates have become effective methods, enabling the treatment, prevention of disease, and detection. More than 50 peptide medications have been made available for purchase on the market as of 2018. Around 25 billion USD is spent on peptide medications each year, including ABPs. But still, there is a gap in the distribution of these ABPs as an alternative to synthetic antibiotics. It might be due to the high cost of these goods. Thus, scientists, researchers, and commercializing companies should work together so that these ABPs with a safe delivery system should be available in the market to combat resistant strains of bacteria. In doing so, we draw attention to the significant advancements made in the field as well as the difficulties still encountered in developing imaging species, active therapies, and nano-drug delivery systems that are functionalized with peptides and proteins for clinical use.

Key words: antibacterial peptides, bacterial zoonosis, antimicrobial resistance, nanoparticles, nanomedicine

Microbial infections have a serious impact throughout the world as they lead to death, disorders, and major economic losses (Abbas et al., 2020). According to the World Health Organization, infectious diseases caused by pathogens such as bacteria, viruses, parasites, and fungi constitute the second biggest cause of death globally (Maniam et al., 2019). Bacterial pathogens cause acute infection which is followed by the appearance of clinical symptoms (Ogunbayo et al., 2022). Some pathogens can use a different mechanism to evade the host immune system and generate persistent infections which may result in latent illnesses that last a lifetime (Drexler, 2010). Antimicrobial drugs have been playing an effective role as the main pillar for the control of microbial pathogens (Becker, 2013). Antimicrobial drugs bind to the cellular target and alter the life cycle and normal functions of bacterium leading to cell death. The drugs also have a strong enough affinity for their target and accumulate to a level where it has an impact on organism function (Jelliffe and Neely, 2017). However, with the passage of time, their extensive and irrational use has resulted in the emergence of resistance against most of the commercially available drugs (Ahmad et al., 2022). Antimicrobial-resistant pathogens generate significant economic losses, higher rates of morbidity and mortality, and high expenses for the healthcare system, and are expected to overtake all other causes of death by the year 2050 (Humphreys and Fleck, 2016). Antibiotic residues from livestock manure applied to the ground could affect the composition and function of microbial populations and enhance the expansion of antibiotic resistance genes (ARGs) and antibiotic-resistant organisms (ARO) (Menz et al., 2019). Wastewater treatment plants (WWTPs) also encourage the emergence of antibiotic resistance (Harris et al., 2012).

Above mentioned constraints associated with chemical control of microbial infections have motivated the scientific community to find out safe, effective, and environment-friendly alternatives for microbial pathogens. One of the alternatives, antimicrobial peptides (AMPs)

has become the more popular and prospective treatment of pathogen infections as a result of growing public health issues and the rapid spread of drug-resistant pathogens. AMPs show their broad-spectrum efficiency against bacteria, viruses, and fungi (Lei et al., 2019).

Small peptides known as antibacterial peptides (ABPs) play an important role in the innate immune systems of various animals and are found in abundance in nature (Ageitos et al., 2017; Nasr et al., 2021). A selection of food ingredients having proteins is essential for the supply of biogenic peptides. Major sources of protein include foods like milk, egg, and meat from animals and fish as well as grains like wheat and soy (Hartmann and Meisel, 2007). Antimicrobial or host defense peptides were first identified in the 1980s. Due to contaminated food and feedstuffs, gut poisoning causes serious health issues in infants, humans, and young animals. AMPs can suppress a wide variety of bacteria, fungi, parasites, and viruses (Bagheri, 2015).

The majority of ABPs, which are the host defense peptides, are cationic and amphiphilic α-helical peptide molecules. Cationic ABPs are a type of peptide that interacts with bacterial cell membranes differently than traditional antibiotics by neutralizing the charge. They penetrate through bacterial membranes and cause bacterial death, lowering the risk of bacterial drug resistance (Som et al., 2008). Peptides show their advantages over the traditional antibiotic with their broad-spectrum antifungal, antibacterial, antiviral activities (Mahlapuu et al., 2016). Widespread interest has been generated by the application of ABPs as a potential intervention to restrict the use of antibiotics in the production of food and animal operations (Yu et al., 2017 a). Peptides first identified as anti-bacterial have shown defensins and cathelicidins activity which has received the most attention (Niyonsaba et al., 2006).

Cationic ABPs are a type of peptide, these ABPs interact with bacterial cell membranes differently than traditional antibiotics by neutralizing the charge. They then pass through bacterial membranes and cause bacterial death, lowering the risk of bacterial drug resistance (Som et al., 2008). ABPs can be harvested from vertebrates, invertebrates, plants, and microbes (Reddy et al, 2004). Peptides from microbes are quite different from the vertebrate ABPs because they can be synthesized from non-ribosomal peptide synthase (Bahar and Ren, 2013). They are also effective with quick bactericidal capacity and low bactericidal concentration, even efficient against traditional antibiotic-resistant strains, and even work in synergy with conventional antibiotics to neutralize endotoxins (Bahar and Ren, 2013).

Based on their activity, AMPs can also be categorized as antimicrobial, anticancer, insecticidal, anti-parasitic, and antiprotozoal substances (Kang et al., 2019). A wide range of proteins is also found in human skin including certain enzymes, neuropeptides, and enzyme inhibitors, which naturally have antibacterial activity. These peptides act by affecting mammalian cells when used over an extended period of time. They also have hemolytic activity, and toxicity and cause immunogenicity against microbes.

The first AMPs were derived from specific sources like purothionin from wheat flour, defensins from rabbit, gramicidin D from *Bacillus brevis,* and cecropin from *Hyalophota cecropia* (Hultmark et al., 1980). Among all the sources, marine animals, wild plants, weeds, and the black soldier fly are some of the most valuable sources of ABPs with potential for the present studies (Thomas et al., 2010; Panteleev et al., 2018). For the treatment of microbial infections through intravenous or topical administration AMPs can be potentially used. Therefore, for the effective delivery of ABPs development of a suitable drug delivery system is necessary.

Nanotechnology is a current and effective way of delivering those peptides in the body (Tan et al., 2021). Due to their distinctive qualities and efficiency in delivering therapeutic substances for the treatment of a variety of illnesses, nanomaterials have drawn a lot of attention against bacteria and other microbes. Nanomaterials are used widely because of their unique properties, including size (in the nanoscale range), surface characteristics, targetability, inborn antibacterial capabilities, and ease of application (Gera et al., 2021). Commercial formulations based on nanoparticles are available for the delivery of antibacterial, microbial diagnostics and in medical equipment (Thakur et al., 2022).

Structure and characteristics of ABPs

Antibacterial peptides have four different structural types, containing α-helices, β-sheets, loop forms, and extended forms (Nguyen et al., 2011; Narayana and Chen, 2015). Natural-derived ABPs divided into peptides with α-helix, β-sheets, peptides with long lengths, and cyclic peptides. α-helix and β-sheet are abundant in nature (Harmouche et al., 2017). Some structural aspects of ABPs have been shown in Figure 1.

α-helix ABPs are unstructured in an aqueous solution, but when they interact with trifluoroethanol, detergents over the critical micellar concentration like SDS micelles, and liposomes, they form amphipathic helices. The two members of this group are (i) LL3, an inactive precursor of the 18 kDa human cathelicidin antimicrobial protein, which is generated in neutrophils and epithelial cells, (ii) exocrine secretions and milk contain human lactoferricin (Legrand, 2011). LL3 is the only member of the ABP family to have been found in a human which has 37 amino acids and two leucine residues at its N-terminus (Kościuczuk et al., 2012).

Disulfide linkages and cysteine are abundant in β-sheet peptides. These linkages make peptides more stable and less susceptible to proteolytic enzyme degradation (Dhople et al., 2006). In both the membrane environment and the aqueous condition, β-sheet ABPs maintain a stable structure (Lee et al., 2016).

ABPs often have a composition that is high in cationic and hydrophobic amino acids and show the prop-

erties of both amphiphilic and cationic because these ABPs have a high concentration of hydrophobic groups and both hydrophobic and hydrophilic regions (Mirski et al., 2017). These peptides' hydrophobicity and number of cationic net charges both correlate with the antibacterial and hemolytic activities, respectively. ABPs are also important constituents of innate immunity and have broad-spectrum antimicrobial properties (Som et al., 2008).

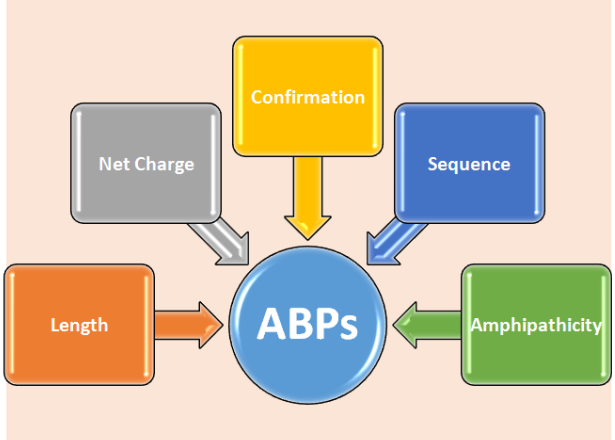


Figure 1. Structural aspects in antibacterial peptides (ABPs)

Cathelicidins and defensins: two broad groups of ABPs

ABPs are derived from mammals (Kościuczuk et al., 2012). The cathelicidins and defensins are the peptides that have drawn the most attention since they were first identified for their ability to kill bacteria (Zaiou and Gallo, 2002; Agier et al., 2015).

Cathelicidins

Small, cationic ABPs called cathelicidins are present in humans and farm animals (chicken, rabbit, in some species of fish cattle, sheep and goats) (Kościuczuk et al., 2012). Cathelicidins were first identified in mammals in bone marrow myeloid cells (Valdez-Miramontes et al., 2021). Two functional domains of cathelicidins are present: 1 – C-terminus cationic peptide and 2 – N-terminal signal peptide. Cathelicidin was first discovered in the skin when examining the components of wound fluid in search of molecules that could facilitate the induction of extracellular matrix proteoglycans to aid wound repair (Cao et al., 2018). Proline and arginine (PR)-39, a peptide that had been isolated in pig intestine and neutrophil azurophilic granules was purified and sequenced to indicate that it might work in pig skin to kill bacteria and promote wound healing (Cardoso et al., 2019).

Only one cathelicidin gene (CAMP) is recognized in humans and its protein product is most usually known as hCAP18/LL-37. Although more recently it was discovered that hCAP18/LL-37 is also constitutively produced in eccrine glands and specialized keratinocytes like those of the nail or in neonatal skin. It was initially discovered that the expression of hCAP18/LL-37 directly in human skin keratinocytes was only detected at sites of inflammation (Yang et al., 2020). Human cathelicidin functions as a direct and indirect antibacterial agent, promotes the healing of wounds, and can alter adaptive immunity (Mookherjee et al., 2020).

Defensins

The family defensins are small, cationic ABPs with β-sheet structure having three disulfide bonds. The first mammalian defensin, also known as microbicidal cationic protein, was identified in 1980 from rabbit lung macrophages (Das et al., 2022). Mammalian defensins are divided into three subfamilies based on disulfide topology: α-, β-, and θ-defensins. In humans only α- and β-defensins are present (Zhai et al., 2023).

α-Defensins

Arginine serves as the main cationic residue in the non-glycosylated cationic peptides known as mammalian defensins. They include 6 cysteine residues that create 3 intramolecular disulfide bridges and have molecular weights of 3.56 kDa (Ganz, 2005; Su et al., 2018). The 3 disulfide bridges connecting residues 1–6, 2–4 and 3–5 are located between the 29–35 amino acids that make up an α-defensin. Four human α-defensins (HNP 1–4) have been isolated from neutrophils (Amerikova et al., 2019). The azurophilic granules contain all four α-defensins. The HNP 1, 2, and 3 make up 50% of the azurophilic protein content, while HNP 4 is only found in small amounts (Gao et al., 2021). In the epithelial cells of the female genitourinary tract and the Paneth cells of the small intestine, two more human defensins 5 and 6 are expressed (Xu and Lu, 2020).

α-defensins are kept in Paneth cells as propeptides. In human monocytes stimulated by *Staphylococcus aureus*, human neutrophil peptides 1 to 3 upregulate the production of TNF-alpha and IL-1b (Chaly et al., 2000). Additionally, defensins exhibit strong antiviral action, particularly in the case of adenoviruses (Ahmed et al., 2019).

β-Defensins

β-defensins have been recognized in numerous cell types including neutrophils and epithelial cells from the lungs and trachea (Solanki et al., 2021). Certain β-defensins are expressed when stimulated with pro-inflammatory cytokines or bacterial component and this suggests that these peptides are crucial for host defense against infection or inflammation (Zhu and Gao, 2013). The 3 disulfide bridges seen in β-defensins connect residues 1–5, 2–4, and 3–6, producing peptides with triple-stranded β-sheet structures and β-hairpin loops carrying positively charged molecules (Cid-Uribe et al., 2020).

HBD-1 was first human β-defensin discovered from hemofiltrate of dialysis patients (Ghosh et al., 2019). HBD-2 was the second human β-defensin initially discovered from psoriatic skin. Bone marrow, leukocytes and epithelia (gut, lungs, skin, pancreas and urogeni-

tal system) all have high levels of HBD-2 expression (Amira et al., 2021). HBD-2 encourages prostaglandin D2 synthesis in mast and histamine release. HBD-3 is expressed by the tonsils and skin (Du et al., 2023). Many tissues produce HBD-4 although testes and stomach antrum express it most strongly (Gao et al., 2021). As a bridge between adaptive and innate immune responses, β-defensins may be significant in the beginning of the Th1 response.

The mechanisms of action of antibacterial peptides

The mechanism of ABPs depends on a variety of physiochemical characteristics such as the charge, structure, order of amino acid, particularly secondary structure and amphipathic property (Mojsoska and Jenssen, 2015).

ABPs mechanism of action is different from other synthetic drugs. Different mechanisms of action of peptides are present including intracellular bactericidal mechanism, damage to cell membrane, suppression of the production of macromolecules, inhibition of enzyme activity, damage to organelles that cause DNA fragmentation and antimicrobial effect through participating in immune regulation (Som et al., 2008). The majority of AMPs affect microorganisms by making cytoplasmic membranes more permeable. These peptides primarily target bacteria rather than mammalian cells, mostly because of the difference in membrane composition (Rathinakumar and Wimley, 2008).

The interaction of cationic charged ABPs with the surfaces of anionic charged bacterial membranes through electrostatic forces is the initial step in the mechanism of membrane permeability. The membrane damage caused by the development of pores in microbial membranes eventually results in metabolite leakage, membrane-coupled respiration blockage, biosynthesis inhibition, metabolite leakage and the death of microorganisms by ion leakage (Guo et al., 2018).

For the creation and design of peptide-based antibiotics, knowing the mechanism of action of ABPs is essential (Heath et al., 2018). Electrostatic interactions between cationic ABPs and negatively charged cell membranes result in membrane binding and structural modification. After peptides bind to the cell membrane, they can complete their action using a variety of processes including the carpet model, barrel stave model and the toroidal pore model (Park and Hahm, 2005). The mechanism of action of these three models has been shown in Figure 2 and 3.

Barrel-stave model

Toroidal and barrel-stave models are within the category of pore creation mechanisms (Zhang et al., 2018). The barrel-stave model describes a situation in which ABPs accumulate vertically to the bilayer, increasing cell lysis. The hydrophobic regions of the AMPs attach to cell membrane's surface and create a porous structure within the membrane causing the fluids of the bacterial cell to overflow and the death of bacteria occurs. In barrel-stave model the size of the pore depends on the peptide to lipid molar ratio (Lei et al., 2019).

Carpet model

The carpet model is also called as detergent model. According to this hypothesis, ABPs must be adsorbed at a crucial concentration parallel to the lipid membrane (Brady et al., 2019). The molecules in the carpet model are positioned at the membrane's surface and are approximately parallel to the lipid membrane plane and completely cover the cell surface to create the carpet. This results in detergent like model which results in micelle formation (Rozek et al., 2000). The insertion of peptide would cause cell death and membrane distortion by lowering the order parameter, disrupting lipid ordering, and making it easier for water molecules to pass through the membrane (Bogdanova et al., 2020).

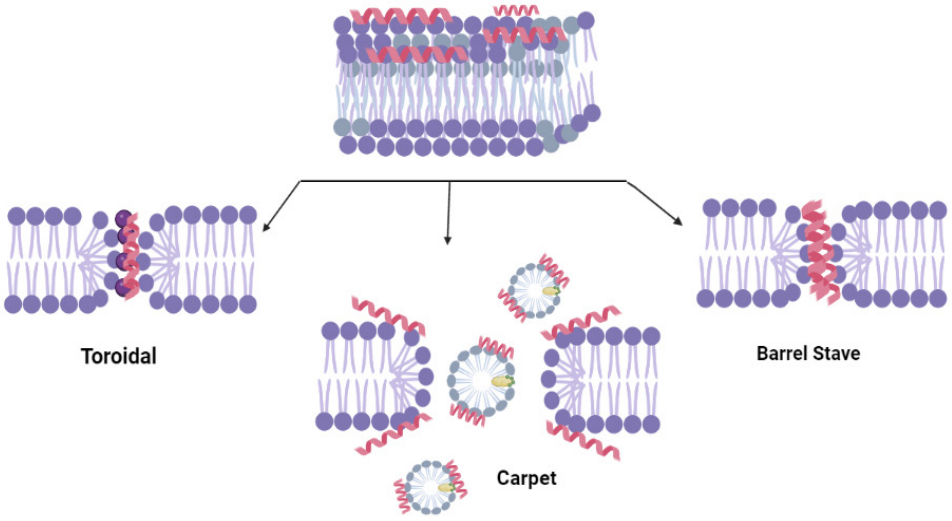


Figure 2. Mechanism of action of three models (retrieved from bio render)

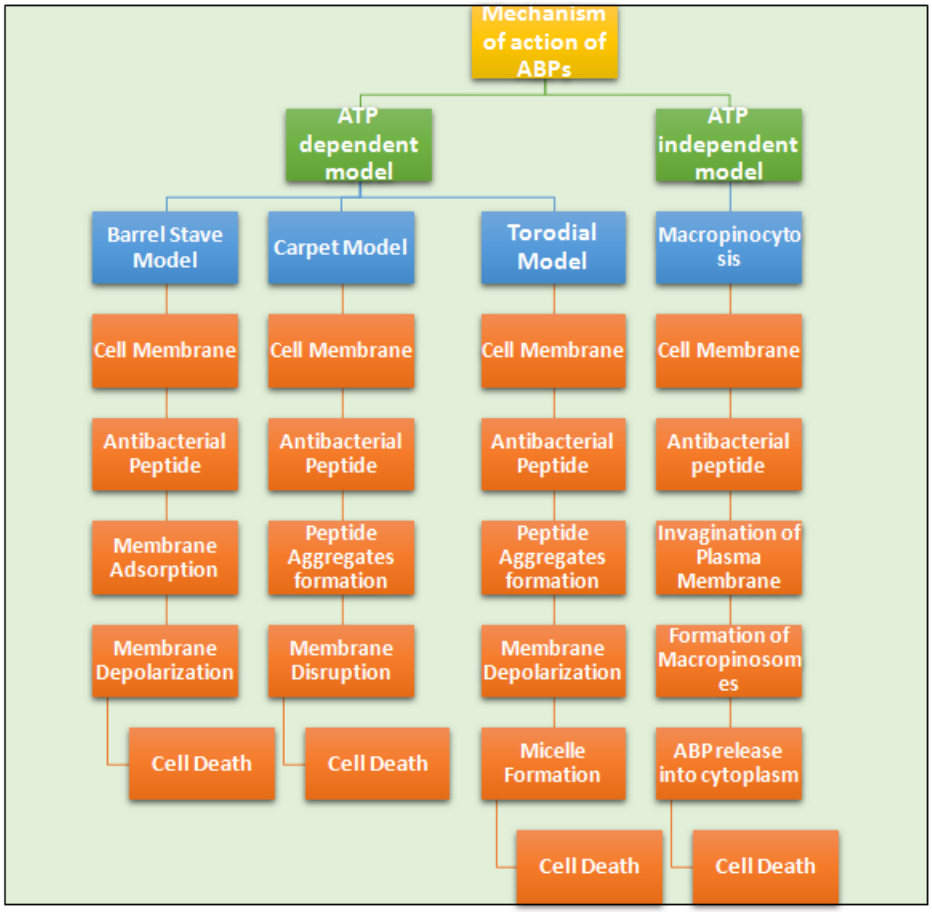


Figure 3. Mechanism of action of antibacterial peptide models

Toroidal pore model

In this model peptides are arranged with the double-layered membrane in the same direction. Although ABPs are introduced vertically into the lipid membrane, no peptide-peptide interaction is created (Wimley, 2010). In this arrangement the helical hydrophilic head is positioned toward the hydrophilic portion of lipids, the aqueous phase is outside the membrane and the hydrophobic head is positioned in the membrane's hydrophobic center (Gaspar and Castanho, 2016). In the toroidal model, the arrangement of hydrophilic and hydrophobic regions in the bilayer membrane is changed and damaged. Aurein 2.2, magainin 2, melittin and lacticin Q proved toroidal pores (Cheng et al., 2009; Lee et al., 2016).

Intracellular bactericidal mechanism

ABPs disrupt bacterial physiological activity by entering the cytoplasm and binding to DNA in addition to damaging bacterial cell membranes and ultimately causing cell death in Gram-positive and Gram-negative bacteria (Moravej et al., 2018).

Bacterial zoonosis

Humans face a serious risk from foodborne zoonotic illnesses (Jamil et al., 2022). *Campylobacter* species (mostly *C. coli*, *C. jejuni*, and *C. lari*) cause campylobacteriosis, a condition that is frequently spread by infected bird meat and is characterized by diarrhea, fever, nausea and stomach pain (Kaakoush et al., 2015; Mbindyo et al., 2023).

Salmonellosis is commonly transmitted through the ingestion of eggs, cattle, meat, and dairy products. *Salmonella* serotypes (*S.* Typhimurium, *S.* Newport, *S.* Enteritidis, and *S.* Heidelberg) cause food contamination (Nupur et al., 2023). Symptoms include diarrhea, stomachache, fever, muscular pain, and nausea (Hassan et al., 2021).

In yersiniosis, the causative agent is *Yersinia enterocolitica*. The infection can be spread through plants, milk and dairy products, pork, contaminated water, and seafood ingestion. The symptoms include mimicking appendicitis, bloody diarrhea, and fever (Chlebicz and Śliżewska, 2018).

A bacteria called Shiga-toxin-producing *Escherichia coli* (STEC) possesses the genes needed to express Shiga toxin types 1 (Stx1) and 2 (Stx2) (Wang et al., 2021). Transmission occurs through beef, milk, and water. The classical manifestation of STEC are abdominal cramping, diarrhea, headache, and fever (Hunt, 2010). ABPs can also be used as valid strategies for targeting bacterial zoonoses mentioned in Table 1.

Table 1. ABPs against bacterial zoonosis

AMPs	Target microorganisms	Mechanism of action	References
ABPs derived from bovine lactoferrin	*Yersinia enterocolitica*	Bactericidal effect	Sijbrandij et al., 2017
Puroindoline A	*Listeria monocytogenes*	Bacterial membrane disruption	Talukdar et al., 2021
Cap-18 derivatives	*Salmonella*	Inhibiting the growth of bacteria	Hassan et al., 2021
Hexapeptide WRWYCR	*STEC*	Reducing STEC survival	Lino et al., 2011
Puroindoline A	*Campylobacter*	Disrupting bacterial cellular membranes to prevent the growth of the bacteria	Talukdar et al., 2021
Css54	*Listeria monocytogenes*	Inhibition of *L. monocytogenes* biofilm formation by Css54	Park et al., 2020
Css54	*Campylobacter jejuni*	Strong antibacterial activity	Park et al., 2020
Css54	*Streptococcus suis*	Strong antibacterial activity	Park et al., 2020
Css54	*S. typhimurium*	Disruption of the outer membrane of *S. typhimurium*	Park et al., 2020
Allomyrinasin	*S. pseudintermedius*	Elimination of established biofilms and inhibition of the sessile cells	Tang et al., 2021
Andricin B	*S. pseudintermedius*	Microbicidal effects	Tang et al., 2021
Pinipesin	*S. cohnii*	Bactericidal effects	Tang et al., 2021
Nigrocin-HLM	*S. cohnii*	Inhibitory effect on biofilm formation	Tang et al., 2021

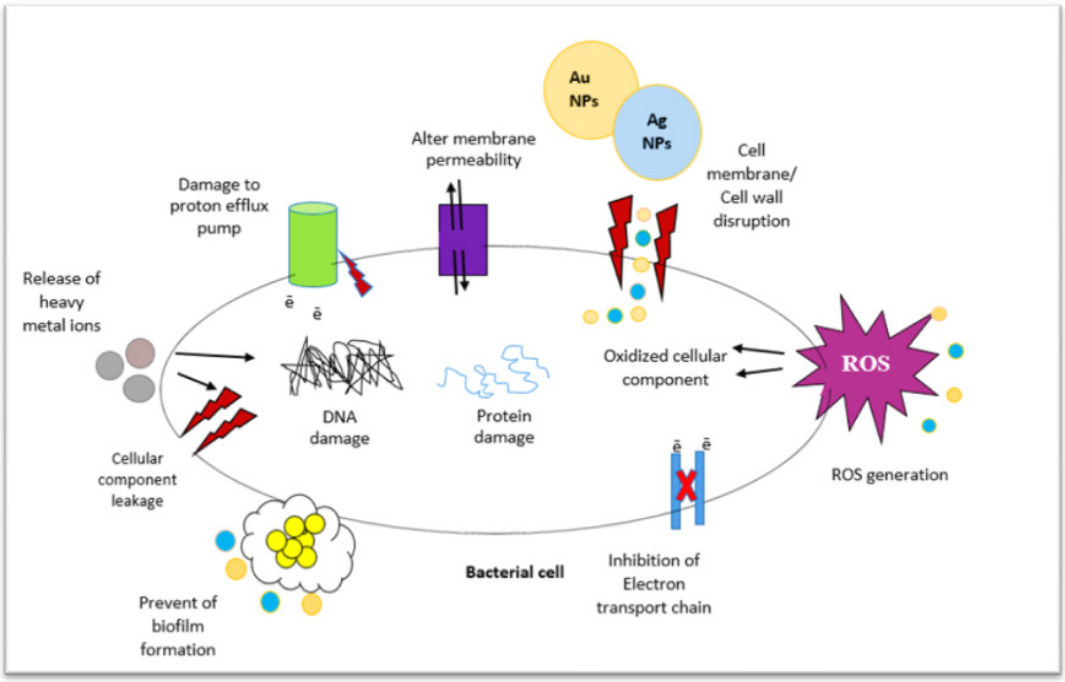


Figure 4. Schematic representation of the mechanism of metallic nanoparticles (retrieved from bio render)

Nanoparticles for ABP delivery

Nanoparticles represent a potential solution to tackle multidrug-resistant bacteria (Sharif et al., 2021). Nanoparticles have been shown to exhibit antibacterial properties and operate in a variety of ways as mentioned in Figure 4. Adaptation to nanoparticle immobilization may also aid due to the fact that nanoparticles are good target-specific drug delivery methods, several of the ABPs' intrinsic limitations, such as susceptibility to proteases and limited penetration across biological membranes, have been eliminated (Salama, 2022).

Colloidal particles known as metal-based nanoparticles (MNPs) exhibit distinctive properties such as electrical conductivity, optical behavior, and great thermal and chemical durability. MNPs, in particular, gold (Au) and silver (Ag) nanoparticles (NPs) have substantial an-

tibacterial properties and can be preferentially absorbed by cancer cells without harming healthy cells (Wang et al., 2012).

Gold nanoparticles (AuNPs)

Gold (Au) is one of the metallic nanoparticles that has received extensive research as a nano-carrier system, diagnostic tool, and treatment (Hu et al., 2020). Reactive oxygen species (ROS) are generated which lead to oxidative stress in the microbial cells, gold nanoparticles produce antibacterial effects (Mohamed et al., 2017). Powerful bactericidal effects of gold nanoparticles have been reported against multiple drug resistant (MDR) bacteria as mentioned in Table 2 (Casciaro et al., 2017; Wadhwani et al., 2017). Significant biomedical use of AuNps in the creation of preventative and therapeutic vaccines to regulate the immune system. Depending on their properties, gold nanoparticles can serve as immunogens or as a delivery system for adjuvants and antigens (Tapia et al., 2020; Mwafy et al., 2023). Energy metabolism and transcription inhibition are two of the processes through which AuNPs carry out their antibacterial activity (Ferrando et al., 2020). AuNPs prevent the ATPase, which causes ATP levels to decrease and the membrane potential to drop (Cui et al., 2012).

Silver nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) have strong antimicrobial properties and potential mechanisms include the release of silver ions, interactions with bacteria and damage to their DNA, the generation of free radicals and cell membrane damage (Durán et al., 2016; Umair et al., 2022). In order to increase the contacts of the peptides with bacterial membranes and release silver ions for toxicity activation in bacteria for combinatorial antibacterial activities, silver nanoparticles and ABPs can be conjugated (Morales-Avila et al., 2017). The stability of nanoparticles can be improved, and their aggregation prevented through peptide linkage (Pal et al., 2019).

Applications of ABPs

ABPs have been used in different fields such as agriculture, the pharmaceutical industry, the food industry, aquaculture, etc. (Meng et al., 2010). Antibacterial peptides have different biological functions e.g., anticancer, immune-modulating, anti-biofilm, angiogenesis, anti-inflammatory, and wound-healing activities shown in Table 3 (Hilchie et al., 2019; Liang et al., 2020).

Antibiotics are those medications that are frequently used to manage and treat bacterial diseases worldwide. Antibiotic resistance could occur if antibiotics are used wisely and continuously over an extended period of time [110] (Mehmood et al., 2020). The pharmaceutical industry is a significant area where ABPs are used, particularly given the severe antibiotic resistance**.** To direct antibacterial activity these peptides take part in a variety of cellular processes including wound healing, chemotaxis, and the selection of the color of the canine coat.

Table 2. Gold nanoparticle-based and silver nanoparticle-based ABP delivery

ABP delivery	ABPs	Target microorganisms	Treatment purpose	Outcomes	References
1	2	3	4	5	6
Gold nanoparticle based	Vancomycin	Vancomycin resistant *E. coli* and *S. aureus*	*In vitro* study	Vancomycin's MIC was reduced by 4–6 fold	Mohammed Fayaz et al., 2011
	LL37	MRSA	Mouse model of an infected diabetic wound	With a single dose of medication, wound microorganisms are reduced by >99	Wang et al., 2018
	Surfactin	*E. coli*	Wound infection treatment	Bacterial membrane disruption	Chen et al., 2015
	Surfactin	*S. aureus, B. subtilis*	Wound infection	Antibacterial activity	Chen et al., 2015
	Anti-apoptotic peptide	*K. pneumoniae*	Cancer treatment	Modulation of the anti-cancer effects of chosen peptides	Akrami et al., 2016
	Vancomycin	Vancomycin resistant *E. coli*	*In vitro* study	8–32 fold decrease in vancomycin's MIC	Gu et al., 2003
	Cecropin-melittin derivative	*E. coli*	Systemic infection	Cecropin-melittin's MIC was reduced by four times.	Rai et al., 2016
	PEP	*Staphylococcus aureus*	NA	One dose of medication killed >99% of the bacteria.	Peng et al., 2016
	A3-APOHis	*S. typhimurium*	*In vivo* study	Total bacterial colonization inhibition	Yeom et al., 2016
	1018K6	*L. monocytogenes*	In mouse model	Complete inhibition of pathogenic bacteria	Palmieri et al., 2018
	Pep-H motif of (HNP-1	*Mycobacterium tuberculosis*	*In vitro* study	Bacteria inside cells have decreased by over 90%.	Sharma et al., 2019

Table 2 – contd.

1	2	3	4	5	6
Silver nanoparticle based	Andersonin-Y1	*E. coli* and *P. aeruginosa*	*In vitro* study	MIC is reduced by 3–10 fold when the peptide has a cysteine residue.	Pal et al., 2019
	G3R6TAT	*B. subtilis* and *E. coli*	*In vitro* study	Ag-biocidal pep's effectiveness increased by 10 and 50 times against *E. coli* and *B. subtilis*, respectively	Liu et al., 2013
	PAs	*E. coli*	Wound infection treatment	*E. coli* bacterial growth suppression	Pazos et al., 2016
	MBP-1	*S. aureus*	Infected wounds in a mouse model	Synergistic bactericidal effect of silver nanoparticles and MBP-1	Salouti et al., 2016
	Polymixin B	*E. coli*	NA	Antibacterial effect of silver nanoparticles	Ruden et al., 2009
	LL37	*S. epidermidis*	*In vitro* study	Bactericidal effects of Ag NPs	Vignoni et al., 2014
	LL37	*E.coli*	*In vitro* study	Bactericidal effects of Ag NPs	Vignoni et al., 2014
	LL37	*P. aeruginosa*	NA	Antibacterial effects of Ag NPs	Vignoni et al., 2014
	Bacitracin	*B. amyloliquefaciens*	Infected rat wound model	Similar to silver sulfadiazine or silver nitrate in potency, AgNP's bactericidal properties were maintained	Mei et al., 2013
	Bacitracin	*P. aeruginosa*	NA	A 10-fold increase in antibacterial activity	Mei et al., 2013
	Polymyxin E	*S. aureus*	Infected wound	Up to 10-fold increase in the bactericidal activity	Mei et al., 2013
	Polymyxin E	*P. aeruginosa*	NA	NA	Mei et al., 2013
	Andersonin-Y1	*K. pneumonia*	*In vitro* study	Up to a 10-fold increase in antibacterial activity without an increase in bacterial resistance	Pal et al., 2019
	Andersonin-Y1	*S. typhimurium*	*In vitro* study	Enhanced antibacterial effects when AgNPs are conjugated Bactericidal effects	Pal et al., 2019
	Ampicillin	*E. coli*	NA	AgNPs and ampicillin are conjugated using polymersomes to produce synergistic effects	Geilich et al., 2015
	T 359	*S. aureus* and *S. pyogenes*	NA	Strong antibacterial activity was shown by TP359	Chaudhari et al., 2016
	T 359	*S. typhimurium* and *E. coli*	NA	Antibacterial effect against gram-negative bacteria	Chaudhari et al., 2016

ABPs have demonstrated promise as treatments against cancer when directed selectively at tumor cells. Even further research has shown that the bound ABP can lyse liposomes, trigger apoptosis *in vitro*, and significantly shrink tumor growth in *in-vivo* mice tests (Lee et al., 2011).

Scientists have examined the *in vitro* activities of ABPs (cecropin, indolicidinmelittin A amide [CAMA], and nisin) against the standard and clinical MRSA biofilms both on their own and in combination with antibiotics (teicoplanin, linezolid, ciprofloxacin, daptomycin, and azithromycin) demonstrating that ABPs increase the *in vitro* PK efficiency of traditional antibiotics (Dosler and Mataraci, 2013).

The challenges and future prospects of antibacterial peptides

The majority of peptides have very few clinically useful druggable properties. For scientists to create new cationic peptide medications, they need to understand the mode of action and interaction between the structure and activity of these antimicrobial peptides. Although cationic ABPs display variability in structure and sequence the distinctive properties of these peptides, or amphipathicity and cationic must be taken into consideration when designing synthetic cationic AMPs (Moravej et al., 2018).

Table 3. ABPs applications in various fields

Peptide	Route of administration	Applications of ABPs as therapeutic agents	References
TD-1792	Topical	Skin and soft tissue infections	Felício et al., 2017
C16G2	Topical	Dental caries	Felício et al., 2017
LL-37	Solution for administration in the wound bed	Hard-to-heal venous leg ulcers	Roudi et al., 2017
PAC-113	Mouth rinse	Oral candidiasis in HIV seropositive patients	Roudi et al., 2017
Iseganan	Oral solution	Oral mucositis in individuals getting radiation for head and neck cancer	Fjell et al., 2012
Lytixar	Topical hydrogel	Gram-positive skin infections that are not too serious, impetigo, and nasal colonization with *S. aureus*	Mohamed et al., 2016
Peptide	**Devices**	**Applications of ABPs on medical devices development**	**References**
Esc (1–21)	Contact lens	Disrupt the bacterial biofilm	Casciaro et al., 2018
OP-145	Polymer-Lipid Encapsulation MatriX	Inhibiting biofilm and effective in killing *S. aureus*	De Breij et al., 2016
GL13K	TiO_2 nanotubes	Kill both *P. gingivalis* and *F. nucleatum*	Li et al., 2017
RRWRIVVIR-VRRC	Catheter	Gram-negative and gram-positive bacteria were both stopped from adhering by the ABPs covering up to 99.9% and planktonic bacteria were also prevented from growing up to 70%	Yu et al., 2017 b
FK-16	Titanium surface	Inhibiting biofilm and anti-adhesion capabilities against both *E. coli* and *S. aureus*	Mishra and Wang, 2017
ABPs	**Activity against bacteria**	**Applications in food industry**	**References**
Lactococcus lactis produce nisin	Inhibitory effects on *Staphylococcus aureus*, *Pseudomonas aeruginosa, E. faecalis*, *E. coli*, *Listeria monocytogenes* and *S. typhimurium*	A potential food preservative in dairy products and starter cultures during fermentation	Tanhaeian et al., 2020
Thurincin	*B. cereus*	Promote discomposure in the spore-forming microbe cell membrane	Wang et al., 2014

However, a number of issues, including poor absorption, distribution, metabolism, excretion, and bulky size, have prevented the therapeutic adoption of ABPs (Chih et al., 2019). Many ABPs were unsuccessful or declined permission in Phase III clinical trials including Omiganan for catheter infections, Iseganan (IB-367) for mouthwash to avoid infection in chemotherapy patients, and Pexiganan (MSI-78) for the treatment of impetigo and diabetic foot ulcers. The past failures have not stopped attempts to utilize this product line in real-world applications. With an expanding range of possible uses for both humans and animals, a larger number of ABPs are being evaluated (Magana et al., 2020).

It is uncommon to see resistance phenotypes since ABPs have a broad spectrum of activity and do not bind with particular receptors. However, several instances have already been reported including *Staphylococcus aureus* developing resistance to dermicidin and other bacteria developing reduced sensitivity to cationic ABPs (Ageitos et al., 2017).

Natural ABPs are difficult to isolate due to their poor yield and undesirable contaminants, hence synthetic peptides are being used in research more frequently (Diehnelt, 2013). Peptide design enables alterations to amino acid residues, enhancing their antibacterial and immunomodulatory potential or possibly enhancing their resistance to breakdown (Riedl et al., 2011).

The development of nanobiotechnology has made it possible for various nanostructures to function as an effective method to reduce the negative properties of both natural and synthesized ABPs (Umerska et al., 2017). It has been reported that peptides in nanostructures have been shown to have lesser cytotoxicity, less degradation, and more effectiveness at the desired target (Sun et al., 2017; Wang et al., 2017).

Conclusion

The focus on avoiding and managing zoonotic infections is constantly expanding in the context of the present pandemic. In fact, in both global populations and scientific communications, antimicrobial agents known as ABPs are considered to be among the most effective medication possibilities for treating infections. They have unique modes of action and show biological activities such as biomarkers, signaling molecules, and tumoricidal chemicals. However antibacterial peptides exhibit some drawbacks in terms of their bioavailability and safety. Due to a number of problems, including their interaction with body components, their solubility, susceptibility to environmental variables other than proteases, and a lack of targeted and controlled release of peptides, even sta-

ble ABPs cannot be delivered as a solution. Incorporation of AMPs into nanomaterials is a highly attractive and practical way to improve these constraints (e.g., gold and silver nanoparticles). Nano-drugs can cause inflammation because they are foreign compounds to the body. To avoid the potential risk, safety information for prolonged therapy or repeated dosing is required. It has been suggested that biodegradable nanoparticles can lower the risk of toxicological effects both *in vivo* and *in vitro*. The creation of nanomedicine-based formulations for AMP distribution can make use of the combination of peptide assemblies and AMP-loaded nanoparticles. Different nanoparticle systems each have special characteristics and features that make them good candidates for AMP delivery. By altering the nanoparticles for efficient AMP loading and delivery, it is essential to enhance the benefits of such systems and address the problems with nanoparticle stability, toxicity, and therapeutic efficacy. One of the obstacles to the successful deployment of these goods is the price and mass manufacture of nanomaterials. Therefore, the scientific community should focus on creating accessible approaches so that patients can access nanotechnology.

References

Abbas R.Z., Zaman M.A., Sindhu D., Sharif M., Rafique A., Saeed Z., Rehman T., Siddique F., Zaheer T., Khan M.K., Akram M.S., Chattha A.J., Fatima U., Munir T., Ahmad M. (2020). Anthelmintic effects and toxicity analysis of herbal dewormer against the infection of *Haemonchus contortus* and *Fasciola hepatica* in goat. Pak. Vet. J., 40.

Ageitos J.M., Sánchez-Pérez A., Calo-Mata P., Villa T.G. (2017). Antimicrobial peptides (AMPs): Ancient compounds that represent novel weapons in the fight against bacteria. Biochem. Pharmacol., 133: 117–138.

Agier J., Efenberger M., Brzezińska-Błaszczyk E. (2015). Cathelicidin impact on inflammatory cells. Cent. Eur. J. Immun., 40: 225–235.

Ahmad S., Rasheed U., Naz I., Ali S., Ali N., Aziz A. (2022). Antimicrobial resistant pattern of isolates from intensive care unit of tertiary care hospital. Advance. Life Sci., 9: 32–35.

Ahmed A., Siman-Tov G., Hall G., Bhalla N., Narayanan A. (2019). Human antimicrobial peptides as therapeutics for viral infections. Viruses, 11: 704.

Akrami M., Balalaie S., Hosseinkhani S., Alipour M., Salehi F., Bahador A., Haririan I. (2016). Tuning the anticancer activity of a novel pro-apoptotic peptide using gold nanoparticle platforms. Sci. Rep., 6: 1–12.

Amerikova M., Pencheva El-Tibi I., Maslarska V., Bozhanov S., Tachkov K. (2019). Antimicrobial activity, mechanism of action, and methods for stabilisation of defensins as new therapeutic agents. Biotech. Biotechnol. Equipment, 33: 671–682.

Amira M., Rateb A.A., Hammad R.A.E., Faisal N.E.D., Salama D.M., Khalda S.M. (2021). Human b-2 defensin in tinea versicolor and tinea circinata. Med. J. Cairo Univ., 89: 1141–1145.

Bagheri M. (2015). Cationic antimicrobial peptides (AMPs): thermodynamic characterization of peptide–lipid interactions and biological efficacy of surface-tethered peptides. Chem. Open, 4: 389–393.

Bahar A.A., Ren D. (2013). Antimicrobial peptides. Pharmaceuticals, 6: 1543–1575.

Becker D.E. (2013). Antimicrobial drugs. Anesthesia Progr., 60: 111–123.

Bogdanova L.R., Valiullina Y.A., Faizullin D.A., Kurbanov R.K., Ermakova E.A. (2020). Spectroscopic, zeta potential and molecular dynamics studies of the interaction of antimicrobial peptides with model bacterial membrane. Spectrochim. Acta A Mol. Biomol. Spectros., 242: 118785.

Brady D., Grapputo A., Romoli O., Sandrelli F. (2019). Insect cecropins, antimicrobial peptides with potential therapeutic applications. Int. J. Mol. Sci., 20: 5862.

Cao X., Wang Y., Wu C., Li X., Fu, Z., Yang M., Yang X. (2018). Cathelicidin-OA1, a novel antioxidant peptide identified from an amphibian, accelerates skin wound healing. Sci. Rep., 8: 1–15.

Cardoso M.H., Meneguetti B.T., Costa B.O., Buccini D.F., Oshiro K.G., Preza S.L., Franco O.L. (2019). Non-lytic antibacterial peptides that translocate through bacterial membranes to act on intracellular targets. Inter. J. Mol. Sci., 20: 4877.

Casciaro B., Moros M., Rivera-Fernández S. (2017). Gold-nanoparticles coated with the antimicrobial peptide esculentin-1a (1–21) NH_2 as a reliable strategy for antipseudomonal drugs. Acta Biomat., 47: 170–181.

Casciaro B., Dutta D., Loffredo M.R., Marcheggiani S., McDermott A.M., Willcox M.D., Mangoni M.L. (2018). Esculentin-1a derived peptides kill *Pseudomonas aeruginosa* biofilm on soft contact lenses and retain antibacterial activity upon immobilization to the lens surface. Peptide Sci., 110: e23074.

Chaly Y.V., Paleolog E.M., Kolesnikova T.S., Tikhonov I.I., Petratchenko E.V., Voitenok N.N. (2000). Neutrophil alpha-defensin human neutrophil peptide modulates cytoline production in human monocytes and adhesion molecule expression in endothelial cells. Eur. Cyto. Net., 11: 257–266.

Chaudhari A.A., Kate K., Dennis V., Singh S.R., Owen D.R., Palazzo C., Arnold R.D., Miller M.E., Pillai S.R. (2016). A novel covalent approach to bio-conjugate silver coated single walled carbon nanotubes with antimicrobial peptide. J. Nanobiotechnol., 14: 1–15.

Chen W.Y., Chang H.Y., Lu J.K., Huang Y.C., Harroun S.G., Tseng Y.T., Li Y.J., Huang C.C., Chang H.T. (2015). Self-assembly of antimicrobial peptides on gold nanodots: against multidrug-resistant bacteria and wound-healing application. Adv. Funct. Mater., 25: 7189–7199.

Cheng J.T., Hale J.D., Elliot M., Hancock R.E., Straus S.K. (2009). Effect of membrane composition on antimicrobial peptides aurein 2.2 and 2.3 from Australian southern bell frogs. Biophys. J., 96: 552–565.

Chih Y.H., Wang S.Y., Yip B.S., Cheng K.T., Hsu S.Y., Wu C.L., Yu H.Y., Cheng J.W. (2019). Dependence on size and shape of non-nature amino acids in the enhancement of lipopolysaccharide (LPS) neutralizing activities of antimicrobial peptides. J. Colloid Interface Sci., 533: 492–502.

Chlebicz A., Śliżewska K. (2018). Campylobacteriosis, salmonellosis, yersiniosis, and listeriosis as zoonotic foodborne diseases. Int. J. Environ. Res. Public Health, 15: 863.

Cid-Uribe J.I., Veytia-Bucheli J.I., Romero-Gutierrez T., Ortiz E., Possani L.D. (2020). Scorpion venomics: a 2019 overview. Expert Rev. Proteom., 17: 67–83.

Cui Y., Zhao Y., Tian Y., Zhang W., Lü X., Jiang X. (2012). The molecular mechanism of action of bactericidal gold nanoparticles on *Escherichia coli*. Biomaterials, 33: 2327–2333.

Das S., Pradhan C., Pillai D. (2022). β-Defensin: an adroit saviour in teleosts. Fish Shellfish Immunol., 123: 417–430.

De Breij A., Riool M., Kwakman P.H.S., De Boer L., Cordfunke R.A., Drijfhout J.W., Moriarty T.F. (2016). Prevention of *Staphylococcus aureus* biomaterial-associated infections using a polymer-lipid coating containing the antimicrobial peptide OP-145. J. Control. Release, 222: 1–8.

Dhople V., Krukemeyer A., Ramamoorthy A. (2006). The human beta-defensin-3, an antibacterial peptide with multiple biological functions. Biochim. Biophys. Acta Biomembranes, 1758: 1499–1512.

Diehnelt C.W. (2013). Peptide array based discovery of synthetic antimicrobial peptides Front. Microbiol., 4: 402.

Dosler S., Mataraci E. (2013). *In vitro* pharmacokinetics of antimicrobial cationic peptides alone and in combination with antibiot-

ics against methicillin resistant *Staphylococcus aureus* biofilms. Peptides, 49: 53–58.
Drexler M. (2010). How infection works. In: What you need to know about infectious disease. National Academies Press (US).
Du Y., Yang Y., Zhang W., Yang C., Xu P. (2023). Human β-defensin-3 and nuclear factor-kappa B p65 synergistically promote the cell proliferation and invasion of oral squamous cell carcinoma. Transl. Oncol., 27: 101582.
Durán N., Durán M., De Jesus M.B., Seabra A.B., Fávaro W.J., Nakazato G. (2016). Silver nanoparticles: A new view on mechanistic aspects on antimicrobial activity. Nanomedicine: Nanotechnol. Biol. Med., 12: 789–799.
Fayaz A.M., Girilal M., Mahdy S.A., Somsundar S.S., Venkatesan R., Kalaichelvan P.T. (2011). Vancomycin bound biogenic gold nanoparticles: a different perspective for development of anti VRSA agents. Process Biochem., 46: 636–641.
Felício M.R., Silva O.N., Gonçalves S., Santos N.C., Franco O.L. (2017). Peptides with dual antimicrobial and anticancer activities. Front. Chem., 5: 5.
Ferrando R.M., Lay L., Polito L. (2020). Gold nanoparticle-based platforms for vaccine development. Drug Discov. Today Technol., 38: 57–67.
Fjell C.D., Hiss J.A., Hancock R.E., Schneider G. (2012). Designing antimicrobial peptides: form follows function. Nat. Rev. Drug Discov., 11: 37–51.
Ganz T. (2005). Defensins and other antimicrobial peptides: a historical perspective and an update. Comb. Chem. High Throughput Screen, 8: 209–217.
Gao X., Ding J., Liao C., Xu J., Liu X., Lu W. (2021). Defensins: The natural peptide antibiotic. Advanced Drug Deliv. Rev., 179: 114008.
Gaspar D., Castanho M.A. (2016). Anticancer peptides: prospective innovation in cancer therapy. Host defense peptides and their potential as therapeutic agents. Springer, Cham., pp. 95–109.
Geilich B.M., van de Ven A.L., Singleton G.L., Sepúlveda L.J., Sridhar S., Webster T.J. (2015). Silver nanoparticle-embedded polymersome nanocarriers for the treatment of antibiotic-resistant infections. Nanoscale, 7: 3511–3519.
Gera S., Kankuri E., Kogermann K. (2021). Antimicrobial peptides – unleashing their therapeutic potential using nanotechnology. Pharmacol. Therapeut., 232: 107990.
Ghosh S.K., McCormick T.S., Weinberg A. (2019). Human beta defensins and cancer: contradictions and common ground. Front. Oncol., 9: 341.
Gu H., Ho P.L., Tong E., Wang L., Xu B. (2003). Presenting vancomycin on nanoparticles to enhance antimicrobial activities. Nano Lett., 3: 1261–1263.
Guo Y., Xun M., Han J. (2018). A bovine myeloid antimicrobial peptide (BMAP-28) and its analogs kill pan-drug-resistant *Acinetobacter baumannii* by interacting with outer membrane protein A (OmpA). Medicine (Baltimore), 97: 12832.
Harmouche N., Aisenbrey C., Porcelli F., Xia Y., Nelson S.E., Chen X., Raya J., Vermeer L., Aparicio C., Veglia G., Gorr S.U. (2017). Solution and solid-state nuclear magnetic resonance structural investigations of the antimicrobial designer peptide GL13K in membranes. Biochemistry, 56: 4269–4278.
Harris S.J., Cormican M., Cummins E. (2012). Antimicrobial residues and antimicrobial-resistant bacteria: impact on the microbial environment and risk to human health – a review. Human Ecol. Risk Asses.: Interna. J., 18: 767–809.
Hartmann R., Meisel H. (2007). Food-derived peptides with biological activity: from research to food applications. Curr. Opin. Biotech., 18: 163–169.
Hassan M., Ali A., Ahmad A., Saleemi M.K., Wajid M., Sarwar Y., Iqbal M. (2021). Purification and antigenic detection of Lipopolysaccharides of *Salmonella enterica* serovar Typhimurium isolate from Faisalabad, Pakistan. Pakis. Vet. J., 41: 1.
Heath G.R., Harrison P.L., Strong P.N., Evans S.D., Miller K. (2018). Visualization of diffusion limited antimicrobial peptide attack on supported lipid membranes. Soft Matter, 14: 6146–6154.
Hilchie A.L., Hoskin D.W., Power Coombs M.R. (2019). Anticancer activities of natural and synthetic peptides. Adv. Exp. Med. Biol., 1117: 131–147.
Hu X., Zhang Y., Ding T., Liu J., Zhao H. (2020). Multifunctional gold nanoparticles: a novel nanomaterial for various medical applications and biological activities. Front. Bioeng. Biotech., 8: 990.
Hultmark D., Steiner H., Rasmuson T., Boman H.G. (1980). Insect immunity. Purification and properties of three inducible bactericidal proteins from hemolymph of immunized pupae of *Hyalophora cecropia*. Eur. J. Biochem., 106: 7–16.
Humphreys G., Fleck F. (2016). United Nations meeting on antimicrobial resistance. WHO. Bulletin of the World Health Organization, 94: 638.
Hunt J.M. (2010). Shiga toxin-producing *Escherichia coli* (STEC). Clin. Lab. Med., 30: 21–45.
Jamil T., Kalim F., Aleem M. T., Mohsin M., Hadi F., Ali K., Hussain J. (2022). Rodents as reservoirs and carriers of different zoonotic diseases. Cont. Vet. J., 2: 1–14.
Jelliffe R.W., Neely M. (2016). Editors. Individualized drug therapy for patients: basic foundations, relevant software and clinical applications. Academic Press, pp. 157–179.
Kaakoush N.O., Castaño-Rodríguez N., Mitchell H.M., Man S.M. (2015). Global epidemiology of *Campylobacter* infection. Clin. Microbiol. Rev., 28: 687–720.
Kang X., Dong F., Shi C., Liu S., Sun J., Chen J., Li H., Xu H., Lao X., Zheng H. (2019). DRAMP 2.0, an updated data repository of antimicrobial peptides. Sci. Data, 6: 1–10.
Kościuczuk E.M., Lisowski P., Jarczak J., Strzałkowska N., Jóźwik A., Horbańczuk J., Krzyżewski J., Zwierzchowski L., Bagnicka E. (2012). Cathelicidins: family of antimicrobial peptides. A review. Mol. Biol. Rep., 39: 10957–10970.
Lee S.J., Schlesinger P.H., Wickline S.A., Lanza G.M., Baker N.A. (2011). Interaction of melittin peptides with perfluorocarbon nanoemulsion particles. J. Phys. Chem. B., 115: 15271–15279.
Lee T.H., Hall N., Aguilar M.I. (2016). Antimicrobial peptide structure and mechanism of action: a focus on the role of membrane structure. Curr. Topics Med. Chem., 16: 25–39.
Legrand D. (2011). Lactoferrin, a key molecule in immune and inflammatory processes. Biochem. Cell. Biol., 90: 252–268.
Lei J., Sun L., Huang S., Zhu C., Li P., He J., Mackey V., Coy D.H., He Q. (2019). The antimicrobial peptides and their potential clinical applications. Am. J. Transl. Res., 11: 3919–3931.
Li T., Wang N., Chen,S., Lu R., Li H., Zhang Z. (2017). Antibacterial activity and cytocompatibility of an implant coating consisting of TiO_2 nanotubes combined with a GL13K antimicrobial peptide. Int. J. Nanomed., 12: 2995.
Liang X., Zhang X., Lian K., Tian X., Zhang M., Wang S., Chen C., Nie C., Pan Y., Han F., Wei Z. (2020). Antiviral effects of bovine antimicrobial peptide against TGEV *in vivo* and *in vitro*. J. Vet. Sci., 21.
Lino M., Kus J.V., Tran S.L., Naqvi Z., Binnington B., Goodman S.D., Segall A.M., Foster D.B. (2011). A novel antimicrobial peptide significantly enhances acid-induced killing of Shiga toxin-producing *Escherichia coli* O157 and Non-O157 serotypes. Microbiology, 157: 1768–1775.
Liu L., Yang J., Xie J., Luo Z., Jiang J., Yang Y.Y., Liu S. (2013). The potent antimicrobial properties of cell penetrating peptide-conjugated silver nanoparticles with excellent selectivity for Gram-positive bacteria over erythrocytes. Nanoscale, 5: 3834–3840.
Magana M., Pushpanathan M., Santos A.L., Leanse L., Fernandez M., Ioannidis A., Giulianotti M.A., Apidianakis Y., Bradfute S., Ferguson A.L., Cherkasov A. (2020). The value of antimicrobial peptides in the age of resistance. Lancet Infect. Dis., 20: e216–e230.
Mahlapuu M., Håkansson J., Ringstad L., Björn C. (2016). Antimicrobial peptides: an emerging category of therapeutic agents. Front. Cell Infect. Microbiol., 6: 194.
Maniam R., Salleh A., Mohd Z.S., Firdaus Abdullah J. F., Zunita Z. (2019). A study of aetiology and risk factors of bacterial septicaemia of cats. Pak. Vet. J., 39.
Mbindyo S.N., Kitaa J., Abuom T.O., Aboge G.O., Muasya D.W., Muchira B.W., Mulei C.M. (2023). Prevalence and risk factors of *Campylobacter* species infection of puppies in the Nairobi Metropolitan Region, Kenya. Int. J. Vet. Sci., 12: 389–394.
Mehmood K., Bilal R.M., Zhang H. (2020). Study on the genotypic and phenotypic resistance of tetracycline antibiotic in *Escherichia*

coli strains isolated from free ranging chickens of Anhui Province. China. Agrobiol. Rec., 2: 63–68.
Mei L., Lu Z., Zhang W., Wu Z., Zhang X., Wang Y., Luo Y., Li C., Jia Y. (2013). Bioconjugated nanoparticles for attachment and penetration into pathogenic bacteria. Biomaterials, 34: 10328–10337.
Meng S., Xu H., Wang F. (2010). Research advances of antimicrobial peptides and applications in food industry and agriculture. Curr. Prot. Pept. Sci., 11: 264–273.
Menz J., Olsson O., Kümmerer K. (2019). Antibiotic residues in livestock manure: Does the EU risk assessment sufficiently protect against microbial toxicity and selection of resistant bacteria in the environment? J. Hazar. Mater., 379: 120807.
Mirski T., Niemcewicz M., Bartoszcze M., Gryko R., Michalski A. (2017). Utilisation of peptides against microbial infections – a review. Ann. Agric. Environ. Med., 25: 205–210.
Mishra B., Wang G. (2017). Titanium surfaces immobilized with the major antimicrobial fragment FK-16 of human cathelicidin LL-37 are potent against multiple antibiotic-resistant bacteria. Biofouling, 33: 544–555.
Mohamed M.F., Abdelkhalek A., Seleem M.N. (2016). Evaluation of short synthetic antimicrobial peptides for treatment of drug-resistant and intracellular *Staphylococcus aureus*. Sci. Rep., 6: 29707.
Mohamed M.M., Fouad S.A., Elshoky H.A., Mohammed G.M., Salaheldin T.A. (2017). Antibacterial effect of gold nanoparticles against *Corynebacterium pseudotuberculosis*. Int. J. Vet. Sci. Med., 5: 23–29.
Mojsoska B., Jenssen H. (2015). Peptides and peptidomimetics for antimicrobial drug design. Pharmaceuticals, 8: 366–415.
Mookherjee N., Anderson M.A., Haagsman H.P., Davidson D.J. (2020). Antimicrobial host defence peptides: functions and clinical potential. Nature Rev. Drug Disc., 19: 311–332.
Morales-Avila E., Ferro-Flores G., Ocampo-García B.E., López-Téllez G., López-Ortega J., Rogel-Ayala D.G., Sánchez-Padilla D. (2017). Antibacterial efficacy of gold and silver nanoparticles functionalized with the ubiquicidin antimicrobial peptide. J. Nanomat., 5831959: 29–41.
Moravej H., Moravej Z., Yazdanparast M., Heiat M., Mirhosseini A., Moosazadeh Moghaddam M., Mirnejad R. (2018). Antimicrobial peptides: features, action, and their resistance mechanisms in bacteria. Microb. Drug Resist., 24: 747–767.
Mwafy A., Youssef D.Y., Mohamed M.M. (2023). Antibacterial activity of zinc oxide nanoparticles against some multidrug resistant strains of *Escherichia coli* and *Staphylococcus aureus*. Int. J. Vet. Sci., 12: 284–289.
Narayana J.L., Chen J.Y. (2015). Antimicrobial peptides: possible anti-infective agents. Peptides, 72: 88–94.
Nasr N.Y., El-Dawy K., Ahmed A.I., Alattar R.H. (2021). Ingestive peptides – an emerging tool for diagnostics and therapeutics: a review. Int. J. Vet. Sci., 10: 267–279.
Nguyen L.T., Haney E.F., Vogel H.J. (2011). The expanding scope of antimicrobial peptide structures and their modes of action. Trends Biotech., 29: 464–472.
Niyonsaba F., Nagaoka I., Ogawa H. (2006). Human defensins and cathelicidins in the skin: beyond direct antimicrobial properties. Crit. Rev. Immunol., 26: 545–576.
Nupur M.N., Afroz F., Hossain M.K., Harun-ur-Rashid S.M., Rahman M.G., Kamruzzaman M., Haque M.A. (2023). Prevalence of potential zoonotic bacterial pathogens isolated from household pet birds and their antimicrobial profile in northern Bangladesh. Agrobiol. Rec., 11: 28–38.
Ogunbayo A.E., Mogotsi M.T., Sondlane H., Nkwadipo K. R., Sabiu S., Nyaga M.M. (2022). Pathogen profile of children hospitalized with severe acute respiratory infections during COVID-19 pandemic in the Free State Province, South Africa. Int. J. Envir. Res. Public Health, 19: 10418.
Pal I., Bhattacharyya D., Kar R.K., Zarena D., Bhunia A., Atreya H.S. (2019). A peptide-nanoparticle system with improved efficacy against multidrug resistant bacteria. Sci. Rep., 9: 1–11.
Palmieri G., Tatè R., Goglіettino M., Balestrieri M., Rea I., Terracciano M., Proroga Y.T., Capuano F., Anastasio A., De Stefano L. (2018). Small synthetic peptides bioconjugated to hybrid gold nanoparticles destroy potentially deadly bacteria at submicromolar concentrations. Bioconjug. Chem., 29: 3877–3885.
Panteleev P.V., Tsarev A.V., Bolosov I.A., Paramonov A.S., Marggraf M.B., Sychev S.V., Shenkarev Z.O., Ovchinnikova T.V. (2018). Novel antimicrobial peptides from the arctic polychaeta *Nicomache minor* provide new molecular insight into biological role of the BRICHOS domain. Marine Drugs, 16: 401.
Park J., Oh J.H., Kang H.K., Choi M.C., Seo C.H., Park Y. (2020). Scorpion-venom-derived antimicrobial peptide Css54 exerts potent antimicrobial activity by disrupting bacterial membrane of zoonotic bacteria. Antibiotics, 9: 831.
Park Y., Hahm K.S. (2005). Antimicrobial peptides (AMPs): peptide structure and mode of action. J. Biochem. Mol. Biol., 38: 507–516.
Pazos E., Sleep E., Rubert Pérez C.M., Lee S.S., Tantakitti F., Stupp S.I. (2016). Nucleation and growth of ordered arrays of silver nanoparticles on peptide nanofibers: hybrid nanostructures with antimicrobial properties. J. Am. Chem. Soc., 138: 5507–5510.
Peng L.H., Huang Y.F., Zhang C.Z., Niu J., Chen Y., Chu Y., Jiang Z.H., Gao J.Q., Mao Z.W. (2016). Integration of antimicrobial peptides with gold nanoparticles as unique non-viral vectors for gene delivery to mesenchymal stem cells with antibacterial activity. Biomaterials, 103: 137–149.
Rai A., Pinto S., Velho T.R., Ferreira A.F., Moita C., Trivedi U., Evangelista M., Comune M., Rumbaugh K.P., Simões P.N., Moita L. (2016). One-step synthesis of high-density peptide-conjugated gold nanoparticles with antimicrobial efficacy in a systemic infection model. Biomaterials, 85: 99–110.
Rathinakumar R., Wimley W.C. (2008). Biomolecular engineering by combinatorial design and high-throughput screening: small, soluble peptides that permeabilize membranes. J. Am. Chem. Soc., 130: 9849–9858.
Reddy K., Yedery R., Aranha C. (2004). Antimicrobial peptides: Premises and promises. Int. J. Antimicrob. Agents, 24: 536–547.
Riedl S., Zweytick D., Lohner K. (2011). Membrane-active host defense peptides-challenges and perspectives for the development of novel anticancer drugs. Chem. Phys. Lipids, 164: 766–781.
Roudi R., Syn N.L., Roudbary M. (2017). Antimicrobial peptides as biologic and immunotherapeutic agents against cancer: a comprehensive overview. Front. Immunol., 8: 1320.
Rozek A., Friedrich C.L., Hancock R.E. (2000). Structure of the bovine antimicrobial peptide indolicidin bound to dodecylphosphocholine and sodium dodecyl sulfate micelles. Biochemistry, 39: 15765–15774.
Ruden S., Hilpert K., Berditsch M., Wadhwani P., Ulrich A.S. (2009). Synergistic interaction between silver nanoparticles and membrane-permeabilizing antimicrobial peptides. Antimicrob. Agents Chemother., 53: 3538–3540.
Salama A. (2022). The development of a novel ultrashort antimicrobial peptide nanoparticles with potent antimicrobial effect. Pharmacia, 69: 255–260.
Salouti M., Mirzaei F., Shapouri R., Ahangari A. (2016). Synergistic antibacterial activity of plant peptide MBP-1 and silver nanoparticles combination on healing of infected wound due to Staphylococcus aureus. Jundishapur J. Microbiol., 9: 5.
Sharif M., Tunio S.A., Bano S. (2021). Synergistic effects of zinc oxide nanoparticles and conventional antibiotics against methicillin resistant *Staphylococcus aureus*. Advanc. Life Sci., 8: 167–171.
Sharma R., Raghav R., Priyanka K., Rishi P., Sharma S., Srivastava S., Verma I. (2019). Exploiting chitosan and gold nanoparticles for antimycobacterial activity of *in silico* identified antimicrobial motif of human neutrophil peptide-1. Sci. Rep., 9: 1–14.
Sijbrandij T., Ligtenberg A.J., Nazmi K., Veerman E.C.I., Bolscher J.G.M., Bikker F.J. (2017). Effects of lactoferrin derived peptides on simulants of biological warfare agents. World J. Microbiol. Biotechnol., 33: 3.
Solanki S.S., Singh P., Kashyap P., Sansi M.S., Ali S.A. (2021). Promising role of defensins peptides as therapeutics to combat against viral infection. Microbial Pathogen., 155: 104930.
Som A., Vemparala S., Ivanov I., Tew G.N. (2008). Synthetic mimics of antimicrobial peptides. Peptide Sci., 90: 83–93.
Su J., Wang Y., Si Y., Gao J., Song C., Cui L., Zhou Y. (2018). Ga-

lectin-13, a different prototype galectin, does not bind β-galactosides and forms dimers via intermolecular disulfide bridges between Cys-136 and Cys-138. Sci. Rep., 8: 980.

Sun L., Zheng C., Webster T.J. (2017). Self-assembled peptide nanomaterials for biomedical applications: promises and pitfalls. Int. J. Nanomed., 12: 73–86.

Talukdar P.K., Turner K.L., Crockett T.M., Lu X., Morris C.F., Konkel M.E. (2021). Inhibitory effect of puroindoline peptides on *Campylobacter jejuni* growth and biofilm formation, Front. Microbiol., 12702762.

Tan P., Fu H., Ma X. (2021). Design, optimization, and nanotechnology of antimicrobial peptides: From exploration to applications. Nano Today, 39: 101229.

Tang Q., Yang C., Li W., Zhang Y., Wang X., Wang W., Ma Z., Zhang D., Jin Y., Lin D. (2021). Evaluation of short-chain antimicrobial peptides with combined antimicrobial and anti-inflammatory bioactivities for the treatment of zoonotic skin pathogens from canines. Front. Microbiol., 12: 684650.

Tanhaeian A., Mirzaii M., Pirkhezranian Z., Sekhavati M.H. (2020). Generation of an engineered food-grade *Lactococcus lactis* strain for production of an antimicrobial peptide: *in vitro* and *in silico* evaluation. BMC Biotechnol., 20: 1–13.

Tapia D., Sanchez-Villamil J.I., Torres A.G. (2020). Multicomponent gold nano-glycoconjugate as a highly immunogenic and protective platform against *Burkholderia mallei*. NPJ Vaccines, 5: 1–11.

Thakur A., Sharma A., Alajangi H.K., Jaiswal P.K., Lim Y.B., Singh G., Barnwal R.P. (2022). In pursuit of next-generation therapeutics: Antimicrobial peptides against superbugs, their sources, mechanism of action, nanotechnology-based delivery, and clinical applications. Int. J. Biol. Macromol., 218: 135–156.

Thomas S., Karnik S., Barai R.S., Jayaraman V.K., Idicula-Thomas S. (2010). CAMP: a useful resource for research on antimicrobial peptides. Nucleic Acids Res. 38(suppl_1): D774–D780.

Umair M., Altaf S., Muzaffar H., Iftikhar A., Ali A., Batool N., Saifur-Rehman B.S.R. (2022). Green nanotechnology mediated silver and iron oxide nanoparticles: Potential antimicrobials. Agrobiol. Records, 10: 35–41.

Umerska A., Cassisa V., Bastiat G., Matougui N., Nehme H., Manero F., Eveillard M., Saulnier P. (2017). Synergistic interactions between antimicrobial peptides derived from plectasin and lipid nanocapsules containing monolaurin as a cosurfactant against *Staphylococcus aureus*. Int. J. Nanomed., 12: 5687–5699.

Valdez-Miramontes C.E., De Haro-Acosta J., Aréchiga-Flores C.F., Verdiguel-Fernández L., Rivas-Santiago B. (2021). Antimicrobial peptides in domestic animals and their applications in veterinary medicine. Peptides, 142: 170576.

Vignoni M., de Alwis Weerasekera H., Simpson M.J., Phopase J., Mah T.F., Griffith M., Alarcon E.I., Scaiano J.C. (2014). LL37 peptide@silver nanoparticles: combining the best of the two worlds for skin infection control. Nanoscale, 6: 5725–5728.

Wadhwani P., Heidenreich N., Podeyn B., Bürck J., Ulrich A.S. (2017). Antibiotic gold: tethering of antimicrobial peptides to gold nanoparticles maintains conformational flexibility of peptides and improves trypsin susceptibility. Biomater. Sci., 5: 817–827.

Wang A.Z., Langer R., Farokhzad O.C. (2012). Nanoparticle delivery of cancer drugs. Annu. Rev. Med., 63: 185–198.

Wang G., Manns D.C., Guron G.K., Churey J.J., Worobo R.W. (2014). Large-scale purification, characterization, and spore outgrowth inhibitory effect of thurincin H, a bacteriocin produced by *Bacillus thuringiensis* SF361. Probiot. Antimicrob. Prot., 6: 105–113.

Wang L., Hu C., Shao L. (2017). The antimicrobial activity of nanoparticles: present situation and prospects for the future. Int. J. Nanomed., 12: 1227–1249.

Wang S., Yan C., Zhang X., Shi D., Chi L., Luo G., Deng J. (2018). Antimicrobial peptide modification enhances the gene delivery and bactericidal efficiency of gold nanoparticles for accelerating diabetic wound healing. Biomater. Sci., 6: 2757–2772.

Wang X., Zhang H., Bi L., Xi H., Wang Z., Ji Y., Zhu W. (2021). Isolation, characterization and genome analysis of a novel virulent *Escherichia coli* bacteriophage vb_ecom_011d4. Agrobiol. Records, 6: 27–35.

Wimley W.C. (2010). Describing the mechanism of antimicrobial peptide action with the interfacial activity model. ACS Chem. Biol., 5: 905–917.

Xu D., Lu W. (2020). Defensins: a double-edged sword in host immunity. Front. Immunol., 11: 764.

Yang B., Good D., Mosaiab T., Liu W., Ni G., Kaur J., Wei M.Q. (2020). Significance of LL-37 on immunomodulation and disease outcome. BioMed Rese. Int., 2020: 8349712.

Yeom J.H., Lee B., Kim D., Lee J.K., Kim S., Bae J., Park Y., Lee K. (2016). Gold nanoparticle-DNA aptamer conjugate-assisted delivery of antimicrobial peptide effectively eliminates intracellular *Salmonella enterica* serovar Typhimurium. Biomaterials, 104: 43–51.

Yu Z., Gunn L., Wall P., Fanning S. (2017 a). Antimicrobial resistance and its association with tolerance to heavy metals in agriculture production. Food Microbiol., 64: 23–32.

Yu K., Lo J.C., Yan M., Yang X., Brooks D.E., Hancock R.E., Kizhakkedathu J.N. (2017 b). Anti-adhesive antimicrobial peptide coating prevents catheter associated infection in a mouse urinary infection model. Biomaterials, 116: 69–81.

Zaiou M., Gallo R.L. (2002). Cathelicidins, essential gene-encoded mammalian antibiotics. J. Mol. Med., 80: 549–561.

Zhai Y.J., Feng Y., Ma X., Ma F. (2023). Defensins: defenders of human reproductive health. Human Reprod. Update, 29: 126–154.

Zhang M., Wang J., Lyu Y., Fitriyanti M., Hou H., Jin Z., Zhu X., Narsimhan G. (2018). Understanding the antimicrobial activity of water soluble γ-cyclodextrin/alamethicin complex. Colloids Surfaces B: Biointerfaces, 172: 451–458.

Zhu S., Gao B. (2013). Evolutionary origin of β-defensins. Develop. Comp. Immun., 39: 79–84.

Received: 20 I 2023
Accepted: 28 IV 2023