Advances in Antibacterial Cyclic Peptides: Post-print

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Abstract

Given the adverse effects of avian bacterial diseases on the healthy development of the poultry industry, there is an urgent need to develop novel sensitive antimicrobial agents to combat bacterial resistance for the treatment of bacterial diseases. Cyclic peptides have emerged as candidates for antimicrobial drugs due to their enhanced bioactivity and pharmaceutical value compared to linear peptides. This review primarily summarizes three aspects: the discovery of natural antimicrobial cyclic peptides, the synthesis of antimicrobial cyclic peptides, and the current application status of cyclic peptide antimicrobial drugs, aiming to provide readers with a comprehensive understanding of the research landscape of antimicrobial cyclic peptides and to facilitate the development of novel antimicrobial cyclic peptide drugs.

Full Text

Research Progress of Antibacterial Cyclopeptides

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Abstract

Given the adverse impact of avian bacterial diseases on the healthy development of the poultry industry, there is an urgent need to develop novel antimicrobial agents that can overcome bacterial resistance for treating these diseases. Cyclic peptides have emerged as promising antibacterial candidates because they possess greater biological activity and medicinal value compared to linear peptides. This review synthesizes current knowledge across three main areas: the discovery of natural antibacterial cyclopeptides, their chemical synthesis, and the clinical application status of cyclic peptide-based antibacterial drugs. We aim to provide readers with a comprehensive understanding of antibacterial cyclopeptide research and offer guidance for developing new antibacterial cyclopeptide therapeutics.

Keywords: cyclic peptides; antibacterial activity; antibacterial mechanism; bacterial diseases; bacterial drug resistance

Introduction

In recent years, expanding poultry farming operations and accelerated product circulation have made bacterial diseases increasingly difficult to treat, posing a serious threat to the poultry industry's healthy development [1]. Common avian bacterial diseases include avian colibacillosis, listeriosis, and campylobacteriosis. Avian colibacillosis, caused by *Escherichia coli*, induces pathological changes such as pericarditis, perihepatitis, airsacculitis, peritonitis, salpingitis, and synovitis. While most *E. coli* strains are non-pathogenic, the O157:H7 serotype is highly pathogenic and represents a primary cause of hemolytic uremic syndrome [2]. Avian listeriosis, also known as avian monocytosis, is a sporadic infectious disease caused by *Listeria monocytogenes*, manifesting as mononuclear cell meningitis, necrotizing hepatitis, and myocarditis. This pathogen also infects livestock and humans, causing abortions or meningitis in immunocompromised patients [3]. Campylobacteriosis can trigger Guillain-Barré syndrome, which has become the most common cause of flaccid paralysis in the United States over the past 50 years [4]. In veterinary medicine, the most important *Salmonella* serotypes include pullorum disease, fowl typhoid, arizonosis, and other serotypes causing salmonellosis and paratyphoid infections [5]. Addressing these complex pathogens through rational antimicrobial use has become a critical challenge for poultry farming, necessitating continuous development of sensitive drugs for disease prevention and treatment.

Cyclic peptides can form constrained conformations that enhance binding affinity to target molecules and receptor selectivity. They exhibit low toxicity, efficient cell membrane penetration, and resistance to exopeptidase and endopeptidase hydrolysis, conferring greater biological activity and medicinal value than linear peptides [6]. Cyclic peptides are classified into two main categories based on their ring formation: homodetic cyclopeptides, composed solely of standard

peptide bonds (with 2,5-diketopiperazine being the smallest member) [7], and heterodetic cyclopeptides (depsipeptides), where the backbone contains standard peptide bonds but the ring closure involves other functional groups. Numerous antibacterial cyclopeptides have been discovered in nature and synthesized in laboratories. As novel antimicrobial agents continue to be developed, several cyclic peptides have found widespread application in treating bacterial infections, demonstrating excellent prospects for treating avian bacterial diseases. This review examines three key aspects: discovery of natural antibacterial cyclopeptides, their synthesis, and clinical applications.

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1. Discovery of Natural Antibacterial Cyclopeptides

Scientific research has identified cyclopeptides in diverse organisms including microorganisms, marine life, and plants [8], with many exhibiting potent antibacterial activity.

1.1 Antibacterial Cyclopeptides from Microorganisms Gramicidin S (GS), a cyclic decapeptide produced by soil bacteria *Bacillus brevis*, was discovered in the 1940s. In 1944, British chemist Richard Synge demonstrated via paper chromatography that this compound was both an antibiotic and a peptide. Subsequent work by Dorothy Hodgkin and Gerhard Schmidt determined its crystal structure through derivatization and co-crystallization, establishing GS as the first cyclic peptide antibiotic in history [9,10]. In 1969, researchers revealed that GS synthesis was catalyzed by non-ribosomal peptide synthetases rather than through mRNA templates and tRNA carriers [11].

Following GS, many natural antibacterial cyclopeptides were isolated. Polymyxins, discovered in the 1940s, are cyclic lipopeptide antibiotics [12] produced by various *Paenibacillus* species [13]. Vancomycin, isolated in 1952 from microbial fermentation products of Borneo soil, exhibits activity against penicillin-resistant strains. Its structure features an asymmetric dimer that can link different glycopeptide strains by docking two D-Ala-D-Ala peptides in opposite orientations, with aromatic amino acids forming ether bonds through hydroxyl groups to create a seven-peptide core [14]. Vancomycin' s antibacterial mechanism involves binding the N-terminus to D-alanine-D-alanine residues at the C-terminus of peptidoglycan precursor UDP-N-acetylmuramoyl pentapeptide. Since peptidoglycan precursors reside on the outer surface of the bacterial cytoplasmic membrane, this binding blocks transpeptidation in bacterial cell wall synthesis [15], effectively inhibiting cell wall formation by preventing addition of peptidoglycan precursors via transglycosylase inhibition [16].

Daptomycin, extracted from *Streptomyces roseosporus* fermentation broth in the 1980s, inhibits Gram-positive bacteria [17] and effectively treats left-sided endocarditis caused by MRSA and *Streptococcus mutans* without side effects [18]. Pogliano J proposed that daptomycin' s antibacterial mechanism involves mem-

brane interaction, inserting into the cell membrane in a phosphatidylglycerol-dependent manner. Aggregation of daptomycin alters membrane curvature, creating ion channels that dissipate membrane potential and inhibit protein, DNA, and RNA synthesis, ultimately causing bacterial cell death [19,20].

Paenibacterin, a cyclic lipopeptide produced by *Paenibacillus thiaminolyticus* OSY-SE, comprises 13 amino acids and a C15 fatty acyl chain, affecting viability of both Gram-negative and Gram-positive human pathogens [21]. Its positive charge enables binding to negatively charged endotoxins in vitro and inhibits drug-resistant *Pseudomonas aeruginosa* in vivo [22]. Laterocidin from *B. laterosporus* shows moderate antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* with MIC values of 16-32 g/mL [23]. Using genome mining, Issara Kaweewan et al. [24] isolated a novel antibacterial cyclopeptide (1) and its analog dechloromycin (2) from *Streptomyces flavidofuscus* (NBRC 12761T) and *Streptomyces niger* (NBRC 15452T). Comparative antimicrobial activity studies revealed that chlorine in compound 1 is essential for antibacterial activity.

Microbial cyclopeptides also demonstrate important antifungal activity. Iturin, an antifungal cyclic lipopeptide produced by *Bacillus* spp., serves as a valuable biocontrol agent against plant pathogens in agriculture [25].

1.2 Antibacterial Cyclopeptides from Marine Organisms Marine species account for approximately 50% of global biodiversity, and researchers have discovered many cyclopeptides with potent antibacterial activity in marine organisms [26]. Antibacterial cyclopeptides from sponges have been particularly well-documented.

Discodermin A, isolated from the marine sponge *Discodermia kiiensis* in 1985, was later expanded to variants B-D, all showing significant antibacterial activity. Further studies revealed that Discodermin A affects plasma membrane permeability, likely due to six consecutive hydrophobic amino residues at its N-terminus compared to other known peptides with similar activity. Discodermins F-H additionally exhibit antibacterial, antifungal, and cytotoxic properties [27,28]. Auroomycin A-C from *Streptomyces sp.* CNS-575 show antibacterial activity [29], while vancomycin, a glycopeptide antibiotic isolated from marine *Streptomyces* sp. BW2-7, also possesses a cyclic structure [30]. Rakicidin F, a new cyclic depsipeptide, and the known compound rakicidin C were isolated from the fermentation broth of a marine sponge-derived actinomycete strain *Streptomyces sp.* GKU 220. Structural determination via HRFABMS and NMR spectroscopy confirmed rakicidin F' s bacterial growth inhibition [31]. Four novel cyclopeptides—ogipeptins A, B, C, and D—were isolated from the marine bacterium *Pseudoalteromonas sp.* SANK 71903, demonstrating antibacterial activity against *E. coli* with minimum inhibitory concentrations ranging from 0.25 to 1 g/mL [32].

Other marine cyclopeptides exhibit antifungal activity, including halicylin-

dramides (A-C), antifungal cyclic oligopeptides isolated from the marine sponge *Halichondria cylindrata* in the early 1990s [33]; microscleromin from *Microscleroderma herdmani*; and theonellamide G, an antifungal cyclic glycopeptide from the Red Sea sponge *Theonella swinhoei* with the molecular formula $C_{75}H_{97}BrN_{16}O_{27}$ [34]. X. Zhang et al. [35] investigated the antifungal activity of microsclerodermins J, K, A, and B against *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* using amphotericin B as a positive control in CLSI broth microdilution assays, demonstrating potent activity.

1.3 Antibacterial Cyclopeptides from Plants Some cyclopeptides have been isolated and purified from plants, particularly from Caryophyllaceae and Rubiaceae families, though few exhibit significant antibacterial activity. BL-4 from *Arabidopsis thaliana* floral leaves shows only weak antibacterial activity against *Staphylococcus aureus* [36].

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2. Synthesis of Antibacterial Cyclopeptides

Cyclopeptides exhibit diverse physiological activities. Studies indicate that antibacterial cyclopeptides must possess three fundamental characteristics: (1) a large, sheet-like flexible cyclic structure; (2) simultaneous polar and nonpolar surfaces; and (3) multiple positively charged side chains extending from this plane. These features provide theoretical guidance for rational design of cyclic peptide antibiotics [37]. Beyond typical biosynthesis, cyclopeptides can be synthesized via chemical synthesis, combinatorial synthesis, and genetic engineering. A comparison of selected synthetic methods is presented in .

Numerous antibacterial cyclopeptides have been designed and developed, demonstrating excellent pharmacological efficacy, high stability, and resistance to degradation.

2.1.1 Biosynthesis of Antibacterial Cyclopeptides Kohli et al. [39] first synthesized the linear precursor of tyrocidine A on PEGA resin, then cyclized the peptide using the purified thioesterase domain TycC TE to obtain tyrocidine A. This method employs compounds beyond the 20 standard amino acids, using non-ribosomal peptide synthetases as the key catalyst rather than mRNA templates or tRNA carriers [38], demonstrating that bacteria and fungi can synthesize important peptides via non-ribosomal systems.

2.1.2 Solid-Phase Synthesis of Antibacterial Cyclopeptides Cyclopeptide synthesis essentially involves repeated amino acid addition followed by cyclization. While early peptide synthesis was performed in solution, Merrifield pioneered solid-phase chemistry in 1963. Solid-phase synthesis avoids intermolecular dimerization and polymerization, allows control of resin loading capacity, and reduces polymerization—advantages unattainable with traditional liquid-phase synthesis.

Principle: The carboxyl group of the C-terminal amino acid is covalently linked to an insoluble polymer resin. Using this resin-bound amino acid as the amino component, the protecting group is removed and the free amino group reacts with an excess of activated carboxyl component to form peptide bonds. This cycle repeats until the desired peptide length is achieved, after which the peptide is cleaved from the resin, oxidized, folded, and purified.

Process: The synthesis consists of repeated cycles: (1) Deprotection: Fmoc-protected columns and monomers require removal of amino protecting groups with a basic solvent (piperidine); (2) Activation and coupling: The carboxyl group of the next amino acid is activated and reacts with the free amino group to form a peptide bond, using large excesses of highly concentrated reagents to drive the reaction to completion. These two steps are cycled until synthesis is complete. (3) Cleavage and deprotection: The peptide is cleaved from the resin, and protecting groups are removed using a deprotecting agent (TFA).

2.1.3 Combinatorial Synthesis of Antibacterial Cyclopeptides High-throughput synthesis strategies in combinatorial chemistry have become important for new drug development, with approaches including parallel synthesis, split-and-pool synthesis, and pooled synthesis. While cyclopeptides were historically synthesized in parallel, this method cannot achieve the diversity obtainable through genetic approaches. Split-and-pool synthesis enables large-scale preparation of peptide libraries, and studies have successfully generated multiple libraries for biological screening. Tyrocidine A, an antibiotic cyclic decapeptide from *Bacillus brevis*, forms a β-sheet conformation under physiological conditions and kills bacteria by disrupting cell membranes—a mechanism that makes resistance development difficult. However, tyrocidine A also affects mammalian cell membranes, whereas clinical applications require high microbial selectivity. To improve the therapeutic index, researchers used split-and-pool synthesis to generate and screen tyrocidine A analogs [40], producing a library of 1,716 variants for antibacterial activity screening in 96-well plates.

2.2.1 Cationic Amphiphilic Antibacterial Cyclopeptides Cationic amphiphilic peptides are effective membrane-active agents [41]. Some cyclic antimicrobial peptides (AMPs) and amphiphilic cyclic cell-penetrating peptides (CPPs) exhibit both amphiphilic and cationic properties. Cyclic AMPs are attractive as novel antimicrobials and represent promising next-generation therapies for multidrug-resistant infections. Gramicidin S is a small amphiphilic cationic cyclopeptide containing hydrophobic and charged amino acids. Researchers have modified its structure to develop new antibacterial cyclopeptides with reduced hemolytic activity. For example, GS10 was synthesized by replacing two positively charged lysine residues with two ornithine residues and two phenylalanine residues with two tyrosine residues, resulting in enhanced antibacterial activity. Darin L. Lee and colleagues demonstrated that increasing the ring size to 14 residues enhances antibacterial activity [42]. CPPs serve dual functions as antibiotics and molecular transporters. Building on the superior an-

tibacterial activity of cyclic peptides over linear counterparts, Donghoon Oh et al. [43] synthesized several amphiphilic cyclic CPPs and analogs, which exhibited antibacterial activity against MRSA in the range of 2.67-9.75 g/mL. The cyclic peptide [R_4W_4] (1) showed the strongest activity with a minimum inhibitory concentration of 2.67 g/mL. Furthermore, amphiphilic cyclic CPPs combined with antibiotics such as tetracycline demonstrated enhanced efficacy against multidrug-resistant pathogens. Additionally, amphiphilic cyclic D,L-peptides with self-assembling and membrane-disrupting mechanisms show potential for systemic administration and treatment of other antibiotic-resistant infections.

2.2.2 De Novo Designed Cyclopeptides from Defensins Annarita Falanga et al. [44] employed a de novo design strategy to create a 17-amino acid cyclic β-defensin mimetic containing a single disulfide bond, inspired by cyclic -defensins [45]. This molecule (AMC) combines the internal hydrophobic domain of HBD1 with the C-terminal charged region of HBD3, retaining antimicrobial activity from both parent molecules while demonstrating enhanced stability in human serum.

2.2.3 Cyclic Peptide Nanotubes First synthesized by the Ghadiri group in 1993, cyclic peptide nanotubes are formed when amino acids link head-to-tail to create planar ring structures, which then assemble into hollow tubular structures via intermolecular hydrogen bonding between C=O and N–H groups in a β-sheet antiparallel arrangement [46]. These nanotubes have attracted significant attention as drug carriers and antibacterial agents. Cyclic peptides with even numbers of alternating D,L-α-amino acid residues can self-assemble into organic nanotubes, enhancing protease stability, improving bacterial membrane selectivity and permeability, and exerting antimicrobial activity against *Staphylococcus aureus*. Clark et al. [47] first proposed self-assembling peptide nanotubes as antibacterial agents, and Fernandez-Lopez et al. [48] subsequently developed peptide nanotube-based antimicrobials with significantly enhanced bacterial membrane permeability.

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3. Application Status of Antibacterial Cyclopeptide Drugs

The antibacterial activity of both natural and synthetic cyclopeptides provides strong evidence for their potential to treat avian bacterial diseases. Over 40 cyclic peptide drugs are currently in clinical use [49], demonstrating excellent efficacy as antibacterial agents. Selected approved and developing antibacterial cyclopeptides are listed in .

3.1 Polymyxins Polymyxins are narrow-spectrum antibiotics effective primarily against Gram-negative bacteria. Five main types (A-E) exist, but only polymyxin B and polymyxin E are used clinically, typically as sulfates or

methanesulfonates. Polymyxin methanesulfonate is mainly used for parenteral administration in small animals.

3.2 Vancomycin Vancomycin is a highly active glycopeptide antibiotic against Gram-positive bacteria and has become the most commonly used injectable drug for treating infections caused by methicillin-resistant staphylococci and drug-resistant enterococci [50]. Studies in mice have shown significant reductions in *Staphylococcus aureus* colonies in blood following vancomycin treatment [51]. However, as a last-resort antibiotic in humans, vancomycin is expensive, requires continuous intravenous infusion, and is inconvenient for animal administration, limiting its veterinary applications despite substantial potential [52].

3.3 Glycolipid Cyclopeptide Antibiotics Several cyclic peptides are commercially available internationally and FDA-approved as antibacterial compounds. Telavancin, dalbavancin, and oritavancin are cyclic lipoglycopeptides in the same class as vancomycin and teicoplanin, exhibiting potent activity against vancomycin-resistant *Staphylococcus aureus* and enterococci. Like vancomycin and teicoplanin, they share the same core structure and D-Ala-D-Ala binding site [53]. These three antibiotics contain lipophilic side chains that may increase target residence time by anchoring to the cell membrane or destabilize bacterial membranes; hydrophobic tail interactions with cell membranes and plasma proteins also prolong plasma half-life. To overcome resistance, some drugs are used in combination for synergistic effects. Daptomycin combined with the β-lactam ceftaroline treats MRSA bacteremia [54], and these drugs may also treat bacterial diseases in poultry and other animals.

3.4 POL7080 POL7080 is a *Pseudomonas aeruginosa*-specific cyclic peptide antibiotic currently in Phase II clinical trials. Compared to its precursor, POL7080 exhibits a novel mechanism of action. The compound was derived from iterative peptide library synthesis and screening starting from the naturally occurring peptide protegrin I, which has broad-spectrum antibacterial activity. Using a D-Pro-L-Pro β-turn motif and multiple rounds of amino acid substitution to stabilize the secondary structure, a 14-amino acid peptide was obtained. The target is the membrane protein LptD, characterized by reduced cell lysis capacity but significantly enhanced antibacterial activity and selectivity against *P. aeruginosa* [55].

Outlook

Cyclic peptides have achieved considerable success as therapeutic agents due to their antibacterial activity and are considered a new force for reducing bacterial resistance. As discussed, cyclic peptides inhibit pathogens causing avian bacterial diseases and have found veterinary clinical applications. However, several challenges remain: most sponge-derived cyclopeptides have only been tested in

vitro with limited clinical application; many cyclopeptides exhibit both antibacterial activity and cytotoxicity or strong hemolytic effects; natural abundance is low; and more specialized structures need to be designed for cyclic peptide nanotubes as antibacterial drugs. With increasing bacterial resistance potentially evolving into a global crisis, recent research has focused on structural modification of natural cyclopeptides to optimize antibacterial activity. Strategies include using cell-penetrating peptides as scaffolds with chemical modifications to stabilize α-helical conformations, investigating in vitro evolution of N-methylated peptides, and combining in vitro evolution with de novo design and random peptide library screening. These emerging approaches will powerfully advance development of novel antibacterial cyclopeptide drugs for treating avian bacterial diseases. In conclusion, developing cyclic peptides as antibacterial agents represents a crucial pathway for ensuring the healthy development of the poultry industry.

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Note: Figure translations are in progress. See original paper for figures.