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Lorena Kröner[1], Jutta Meier[2], Marie-T. Hopp[1]

Bioactive Skin Peptides from Caudate Amphibians: Structural and Functional Insights

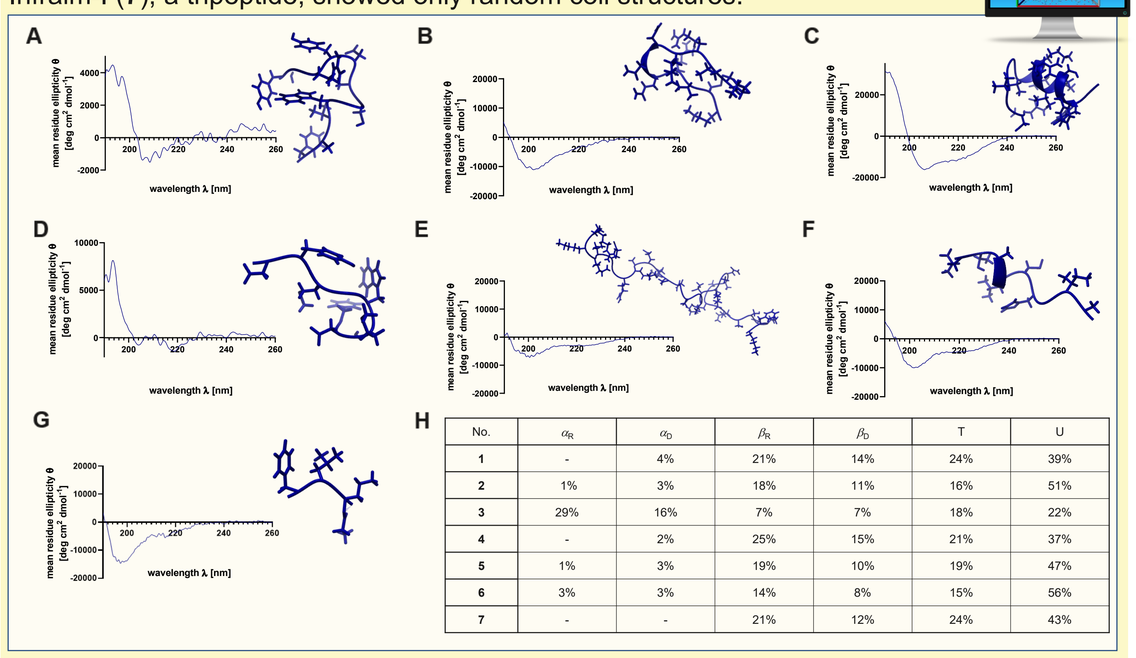
Background

Bioactive peptides from amphibian skin comprise a spectrum of molecules that are highly diverse in terms of both their structure and function, resulting in their essential role in the discovery and development of **novel therapeutic agents**. While skin peptides from Anura (i.e., frogs and toads) have been extensively studied over the past decades, the order Caudata (i.e., salamanders and newts) remains comparatively underexplored, although previous studies of caudate amphibian skin peptides reported promising bioactivities, like antimicrobial, wound-healing, and antiinflammatory effects.[1,2] To address this gap, seven currently known **caudate amphibian skin peptides** (3-34 mer) were synthesized and systematically compared.[3] Peptide synthesis was performed via standard Fmoc-based solid-phase peptide synthesis, incorporating native post-translational modifications, like C-terminal amidation, disulfide bond formation, and N-ethylation.[3] Analytical characterization was conducted by means of RP-HPLC, thin layer chromatography, and mass spectrometry.[3]

Results

Secondary structure analysis based on *in silico* studies and electronic circular dichroism (ECD) spectroscopy

Secondary structures of salamandrin-I (**1**), tylotoin (**2**), and andricin-I (**5**) unfolded during the course of the molecular dynamics (MD) simulation.[3] These **observations are coherent with the ECD analysis**: salamandrin-I (**1**) showed highest proportion in disordered regions, the β-sheet of tylotoin (**2**) is proportionally considerably lower than predicted (~29%), and in case of andricin-I (**5**) only a small proportion of helical elements (~4%) was observed (**Fig. 1**).[3] Ramosin (**3**) showed **highest proportions of α-helix**, which was substantiated by ECD spectroscopy (~45%) and MD simulation (~41%). Infraim-I (**7**), a tripeptide, showed only random coil structures.[3]



H

No.	α_R	α_D	β_R	β_D	T	U
1	-	4%	21%	14%	24%	39%
2	1%	3%	18%	11%	16%	51%
3	29%	16%	7%	7%	18%	22%
4	-	2%	25%	15%	21%	37%
5	1%	3%	19%	10%	19%	47%
6	3%	3%	14%	8%	15%	56%
7	-	-	21%	12%	24%	43%

Fig. 1. Secondary structure elements of caudate amphibian skin peptides. ECD spectra and structures after 100 ns MD simulation of peptide **1** (**A**), peptide **2** (**B**), peptide **3** (**C**), peptide **4** (**D**), peptide **5** (**E**), peptide **6** (**F**), and peptide **7** (**G**) are represented.[3] Secondary structure proportions based on deconvolution analysis of peptide **1-7** are displayed (**H**).[3] ECD spectra were recorded in 50% TFE in 10 mM phosphate buffer (pH 7.4).[3] α_R, regular α-helix; α_D, distorted α-helix; β_R, regular β-sheet; β_D, distorted β-sheet; T, turns; U, unordered.[3]

Determination of antioxidant capacity

The **ABTS$^{\bullet+}$ radical scavenging assay**, based on the decolorization of the radical, was used to assess the antioxidant capacities (**Fig. 2**).[3] Peptides and reduced glutathione (GSH; as a positive control) were tested in the range of 1 nM to 100 μM.[3] The **strongest antioxidant activity** was exhibited by salamandrin-I (**1**) and CCK-TV (**4**) with EC_{50} of ~4.07 μM and ~4.94 μM, while GSH achieved an EC_{50} of ~11.43 μM.[3] Ramosin (**3**) showed an antioxidant effect with an EC_{50} of ~6.39 μM, followed by andricin-I (**5**) with an EC_{50} of ~25.14 μM.[3] Weak or no antioxidant effects were observed for tylotoin (**2**), Ad-Cath (**6**), and infraim-I (**7**).[3]

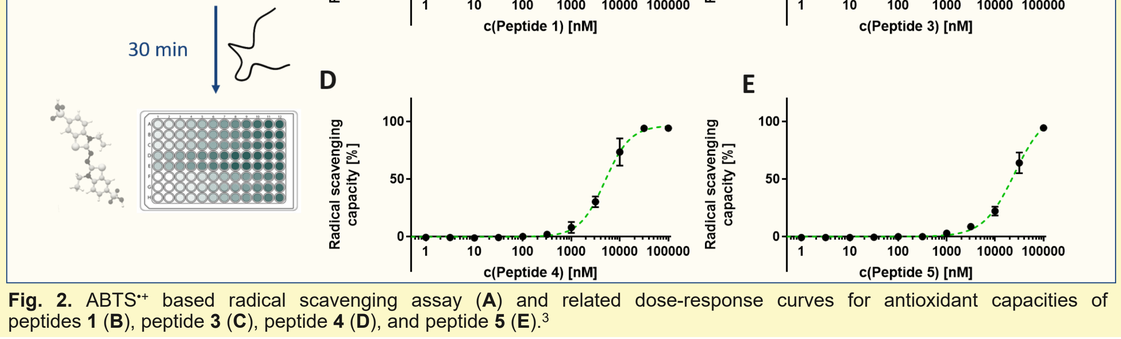


Fig. 2. ABTS$^{\bullet+}$ based radical scavenging assay (**A**) and related dose-response curves for antioxidant capacities of peptides **1** (**B**), peptide **3** (**C**), peptide **4** (**D**), and peptide **5** (**E**).[3]

Evaluation of antimicrobial properties

Antimicrobial properties of caudate amphibian skin peptides were determined by optical density growth measurements testing against two **Gram-positive** (*B. spizizenii*, *E. durans*) and two **Gram-negative bacterial strains** (*E. coli*, *P. fluorescens*) as well as yeast (*S. cerevisiae*) as a **fungal representative**.[3] Applied peptide concentrations varied from 100 nM up to 100 μM.[3] Salamandrin-I (**1**) affected the growth of both Gram-positive and Gram-negative bacteria as well as yeast.[3] Tylotoin (**2**) showed no antibacterial effect, but inhibited the growth of *S. cerevisiae*, leading to a prolonged lag phase at highest concentration tested.[3] Ramosin (**3**) has shown the **most potent antimicrobial properties against all selected microorganisms**, which was characterized by declining growth rates (e.g., starting at 10 μM for *E. durans* and 31.6 μM for *P. fluorescens*) or elongating lag phases at higher concentrations (**Fig. 3**).[3] In contrast, CCK-TV (**4**) lead to an increase of the growth rate and the lag phase of *S. cerevisiae* at 316 nM.[3] Andricin-I (**5**), Ad-Cath (**6**), and infraim-I (**7**) did not exhibit any inhibitory effect on the growth of the selected microorganisms.[3]

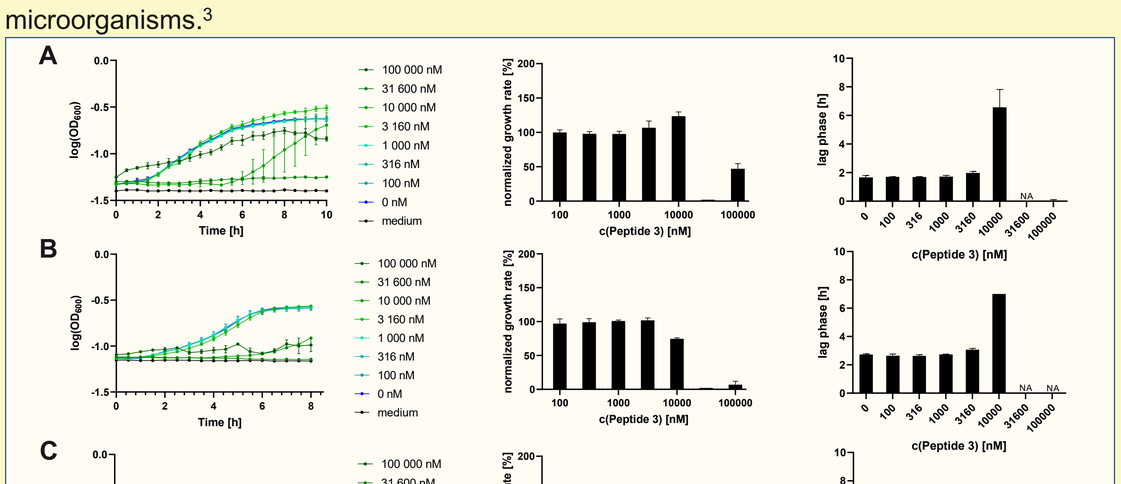


Fig. 3. Dose-dependent growth curves, normalized growth rates, and lag phases of representative bacteria and yeast in presence of selected peptides: Gram-positive *Bacillus spizizenii* DSM 618 in presence of peptide **3** (**A**) and Gram-positive *Enterococcus durans* ATCC 11576 in presence of peptide **3** (**B**).[3] Gram-negative *Escherichia coli* DSM 498 in presence of peptide **3** (**C**) and Gram-negative *Pseudomonas fluorescens* DSM 4358 in presence of peptide **3** (**D**).[3] Fungus *Saccharomyces cerevisiae* DSM 70449 in presence of peptide **1** (**E**) and in presence of peptide **3** (**F**).[3]

Conclusions

Peptides isolated from caudate amphibian skin secretions were synthesized and thoroughly characterized. ⊕ Four peptides exhibit strong antioxidant activity, while another four display distinct antimicrobial effects. ⊕ A correlation between the structural features of these peptides and their respective antimicrobial properties was substantiated. ⊕ The selective antimicrobial properties and antioxidant activities underscore their potential as scaffolds for peptide-based drug development. ⊕ Moreover, ADMET assessments are necessary to support their safe and effective progression toward pharmacological applications.

Contact
Prof. Dr. Marie-T. Hopp, Bioorganic Chemistry, Institute for Integrated Natural Sciences, University of Koblenz, Universitätsstraße 1, D-56070 Koblenz, +49 261 287 2259, mhopp@uni-koblenz.de

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Affiliations
[1] Bioorganic Chemistry, Institute for Integrated Natural Sciences, University of Koblenz, Koblenz, Germany
[2] Microbiology, Institute for Integrated Natural Sciences, University of Koblenz, Koblenz, Germany

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