New antimicrobial peptides on the horizon: comprehensive investigation of bioactive peptaibols for future practical application

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PEPTAIBOL

Peptide, rich in special non-proteinogenic amino acids, like α-aminoisobutyric acid (**Aib**), and containing **aminoalcohol** group at C-terminal.

WHY ARE PEPTAIBOLS IMPORTANT?

Peptaibols are **bioactive, small peptides** produced by the filamentous fungal *Trichoderma* species. Peptaibols aggregate and **form ion channels** in the cell membrane and exert **strong antibiotic effect** on other microorganisms. In the future, they may play an **important role in agriculture**, biological plant protection, and we are exploring further areas of possible benefits. Their **comprehensive investigation** is essential for their future practical application.

DETERMINATION OF PEPTAIBIOM

- Each *Trichoderma* strain produces a characteristic **mixture of peptaibiotics** - compound of short and long peptaibols or lipopeptaibols
- **Peptaibiome** → total peptaibol production of a *Trichoderma* strain
- Preparation of the peptaibol extracts and determination of the total peptaibiom by **mass spectrometry (HPLC-MS)** (*Figure 1*)
- **Comprehensive investigation** of their characteristic properties is fundamentally important to facilitate their future application in agriculture and biotechnology

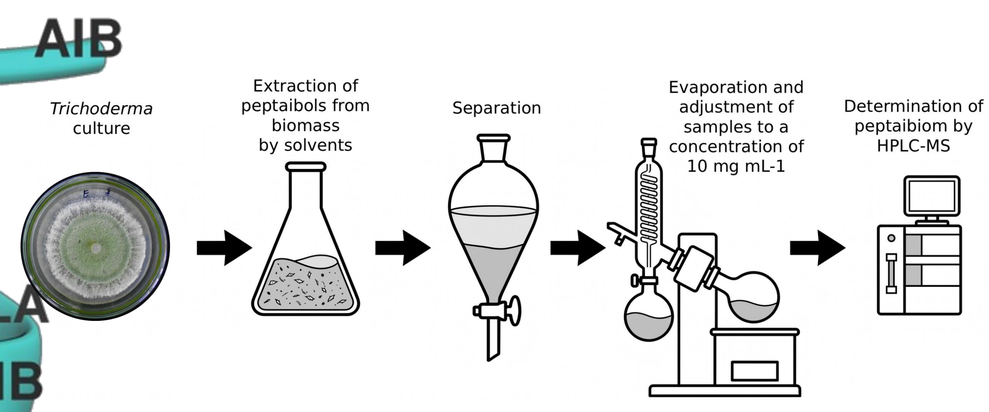


Figure 1. The process of the extraction and determination of peptaibiome

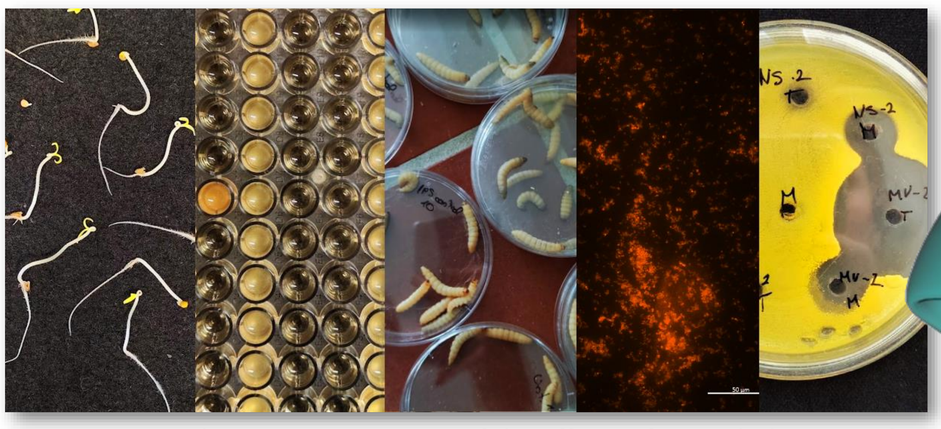


Figure 2. Comprehensive investigation of the effects of peptaibol extracts from various perspectives

COMPREHENSIVE STUDY OF BIOACTIVITY

- Exploring their biological effects against Gram-positive and -negative bacterial and fungal species
  - ➢ Most of the investigated peptaibol extracts inhibit Gram-positive, and several Gram-negative bacterial and phytopathogenic fungal species **between the concentration of 10 and 0.156 mg ml^{-1}**
  - ➢ Further studies on **plants, model organisms, biofilm-forming bacteria**, and **ecotoxicological studies** for safe and effective practical application (*Figure 2*)

COMPUTATIONAL SIMULATIONS

- For **computational investigations** of the most produced peptaibol sequences 1 microsecond long **accelerated molecular dynamics (aMD)** simulations were performed
- Dihedral-angle based principal component analysis (dPCA) method was used to cluster the trajectory based on their **internal motions and obtain lowest energy representative structures** (*Figure 3*)
- The various structural properties and folding characteristics have been summarized

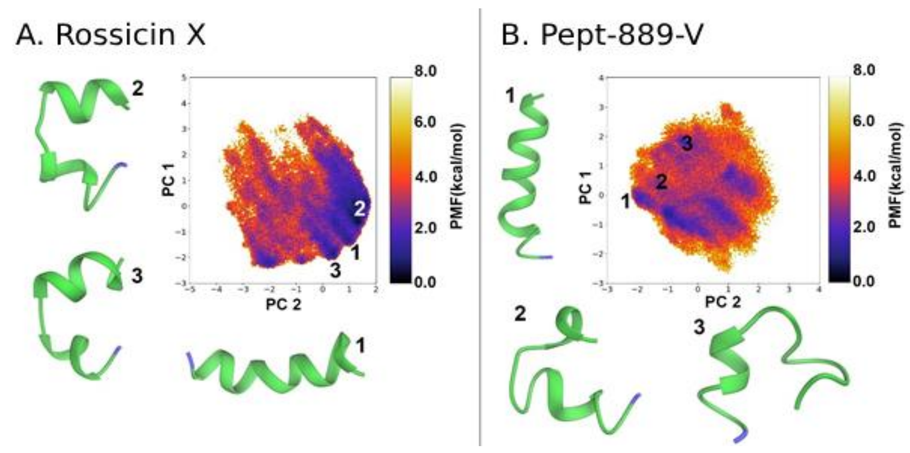


Figure 3. dPCA performed with the selected, most produced peptaibol sequences

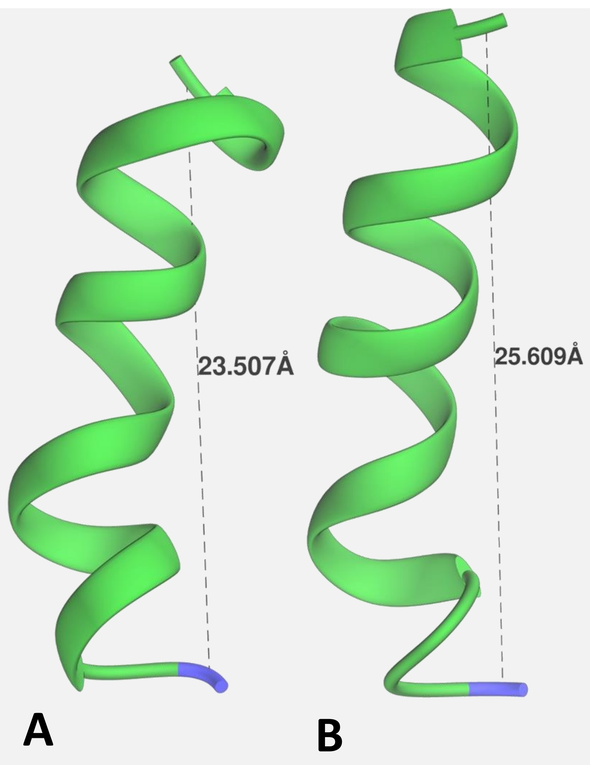


Figure 4. The length of Rossicin X (A) and Pept-889-V (B)

STRUCTURE-ACTIVITY RELATIONSHIPS

The search for connections between the amino acid compositions, structural dynamics changes and characteristics and their exerted bioactivites

➢ AMINO ACID MOTIFS

- Characteristic motif allows more defined folding process and less stable states, which provides the forming of ion channels.

➢ AMINO ACID CONTENT

- The sequences with more Aib form 3^{10} helix structure more often, which allows the tighter incorporation of amino acids with larger side chains. This process leads to the elongation of peptaibol chains.

➢ LENGTH OF PEPTAIBOLS

- Based on the results of bioactivity tests, the longer peptaibols (with 19-and 20-residue sequences) are more active against microorganisms (*Figure 4*).

➢ HYDROPHOBIC AND HYDROPHILIC REGIONS

- The different hydrophobic and hydrophilic regions cluster on the same side of the peptaibols. The position of regions may affect their bioactivity (*Figure 5*).

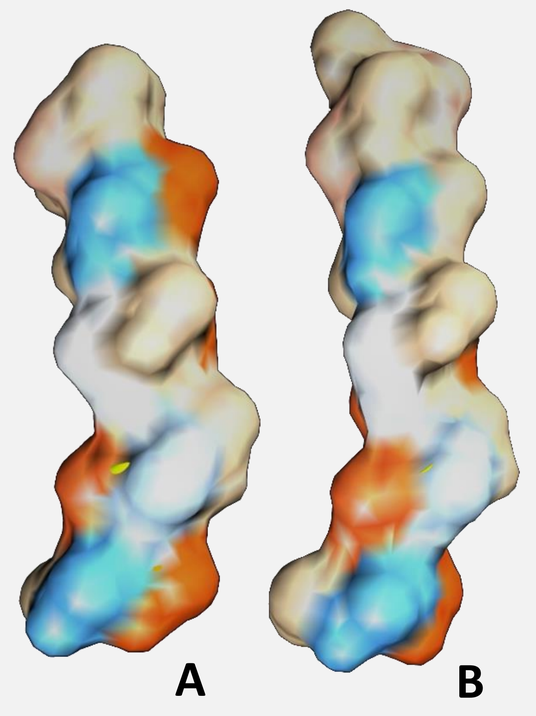


Figure 5. The hydrophobic and hydrophilic regions of Rossicin X (A) and Pept-889-V (B)

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