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BACKGROUND: Bee venom therapy has been officially incorporated into “TCM diagnosis and treatment system” in China since 2007. Due to its complex composition and varying toxicity, wasp venom has emerged as a promising drug resource. Therefore, it is crucial to analyze the peptide components of wasp venom and their pharmacological activities for novel drug discovery and the industrial development of bee venom. **METHODOLOGY:** In this study, venoms from four wasp species (*Vespa mandarinia*, *Vespa velutina*, *Vespa basalis*, *Provespa barthelemyi*) were collected using electrical stimulation, and their peptide components were analyzed by liquid chromatography-tandem mass spectrometry. BLAST searches on the UniProt protein database were performed to identify homologous proteins of endogenous peptides in wasp venom, with the closest homologous protein considered as the putative source of each peptide. Bioinformatics analysis was then conducted to identify potential bioactive peptides. **Results and CONCLUSIONS:** A total of 681 peptides were identified from four types of wasp venom, with nearly 90% being novel peptides. The protein sources of most peptides in wasp venom remained unidentified, likely due to the limited representation of wasp proteins and peptides in current databases. The identified protein sources of the remaining peptides primarily included Mastoparan-B, Mastoparan-X, Mastoparan-V, Phospholipase A1, Vespakinin-M, and Hyaluronidase B. Bioinformatics analysis revealed that 291 peptides exhibited high bioactivity, including ACE inhibition, DPP4 inhibition, and antioxidant properties, suggesting that wasp venom may serve as a potential resource for the development of drugs targeting hypertension and diabetes. **Practical implications:** This study elucidates the peptide composition of wasp venom with potential therapeutic value, providing a scientific foundation for precision medicine and novel drug development. The constructed peptide library serves as an initial screening platform for drug discovery, facilitating the efficient utilization of wasp venom resources and promoting their medical development.

Diversity and Therapeutic Potential of Endogenous Peptides in Wasp Venoms

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Outline



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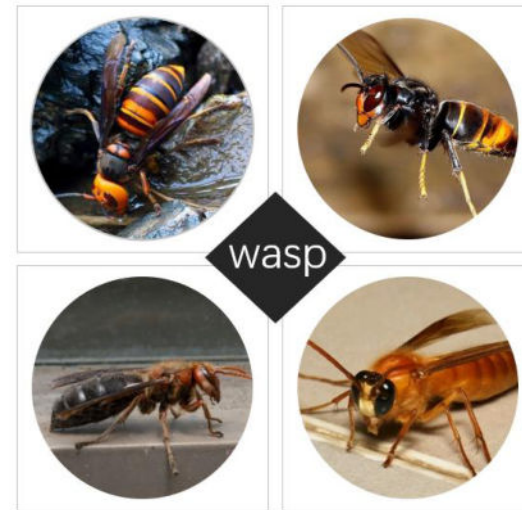
Background

- Bee venom therapy is widely used in traditional Chinese medicine and modern rehabilitation.
- Wasp venom is largely unexplored, partly due to rearing difficulties.
- This study provides the first systematic peptidome analysis of four wasp venoms.
- Findings offer resources for drug discovery and potential venom-based applications.



Bee venom therapy widely used

VS



Wasp venom largely unexplored

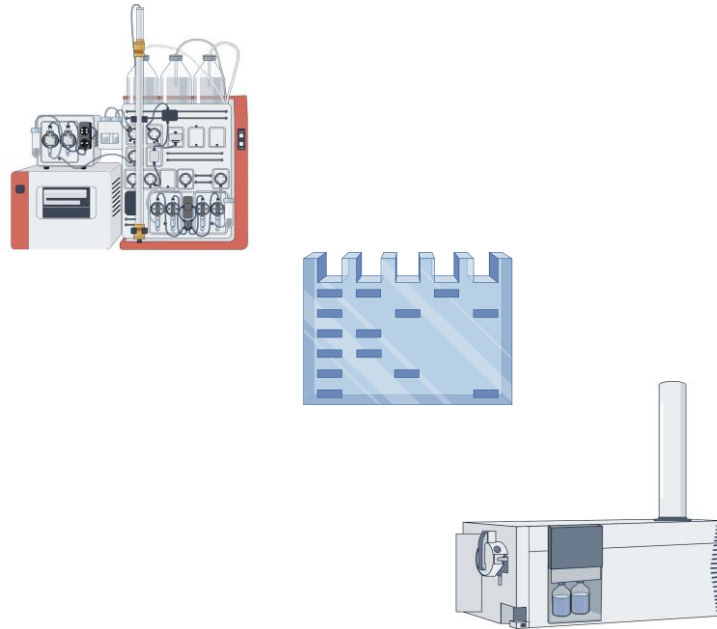
Methods

Experimental Workflow for Wasp Venom Peptidome Analysis

Wasp Venom Collection



Fractionation & Identification



Bioinformatics & Discovery

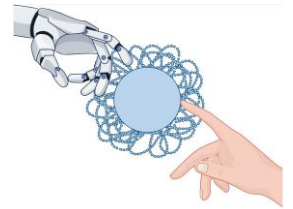


Sequence similarity / clustering

Protease cleavage motifs

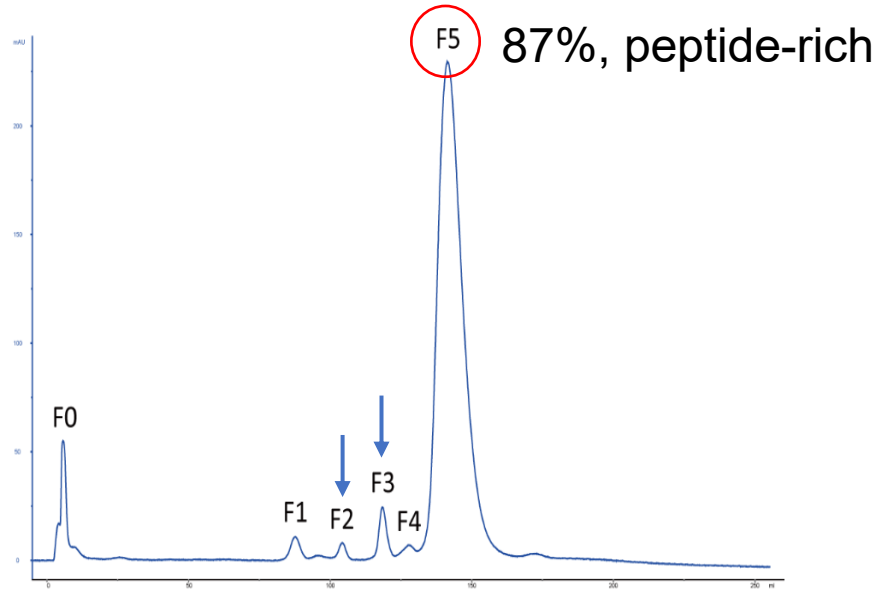
Bioactivity prediction

Discovery of novel cryptides

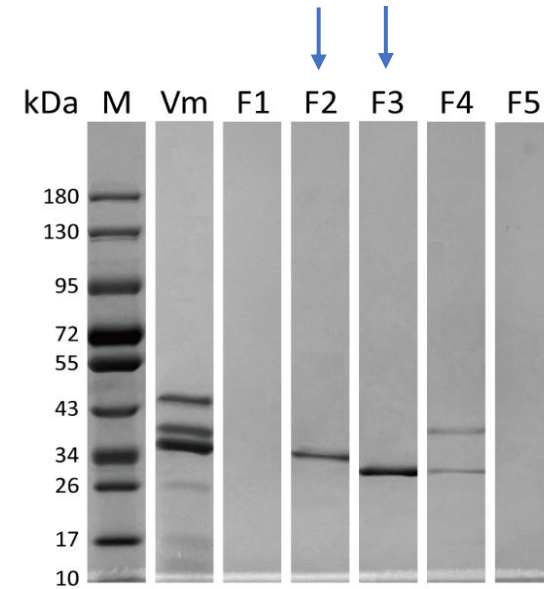


Results· Venom Protein and Peptide Separation

Vespa mandarinia (Vm)



Vm F5, with high response, was identified as peptide-rich and collected for peptidome analysis.

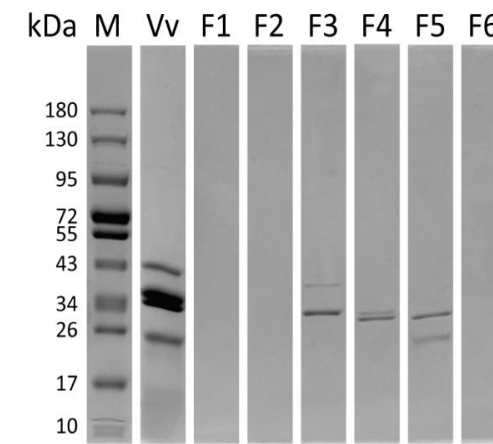
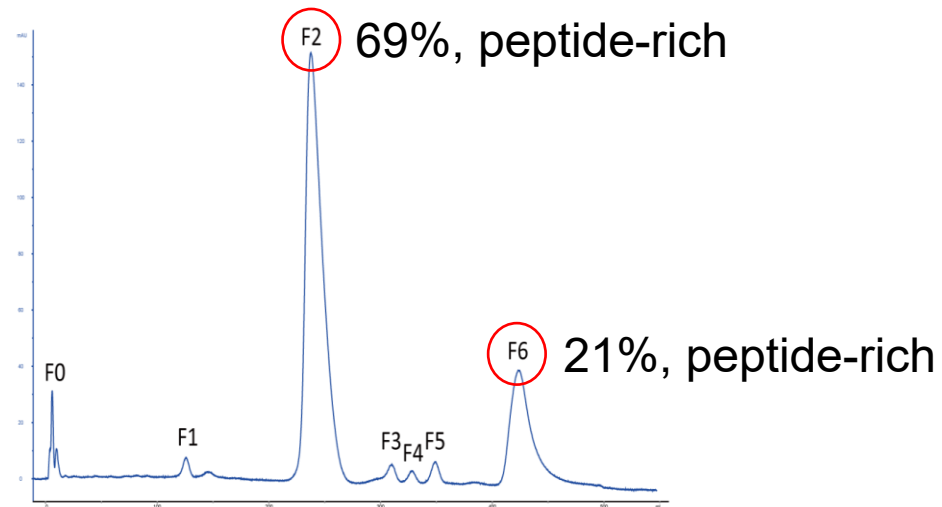


Fractions	Protein name
BandVmF2	Probable phospholipase A1 magnifin isoform X2 [<i>V. mandarinia</i>]
BandVmF3	Phospholipase A1 1 [<i>V. mandarinia</i>]

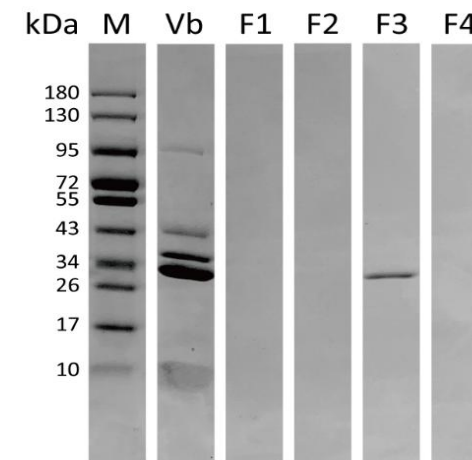
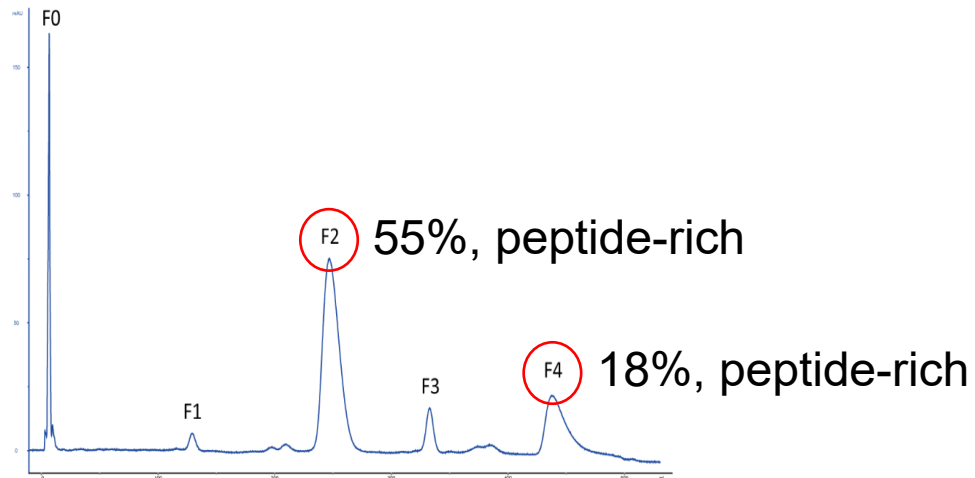
First experimental evidence in *V. mandarinia* venom (previously genome-predicted only)

Results · Venom Protein and Peptide Separation

Vespa velutina (Vv)

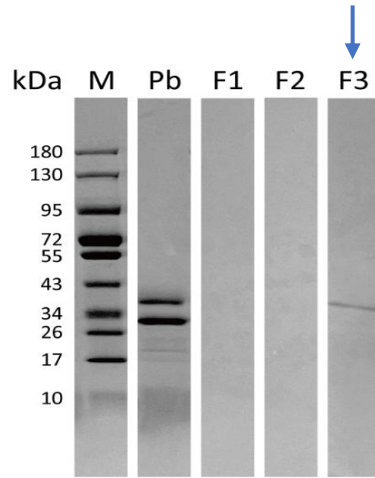
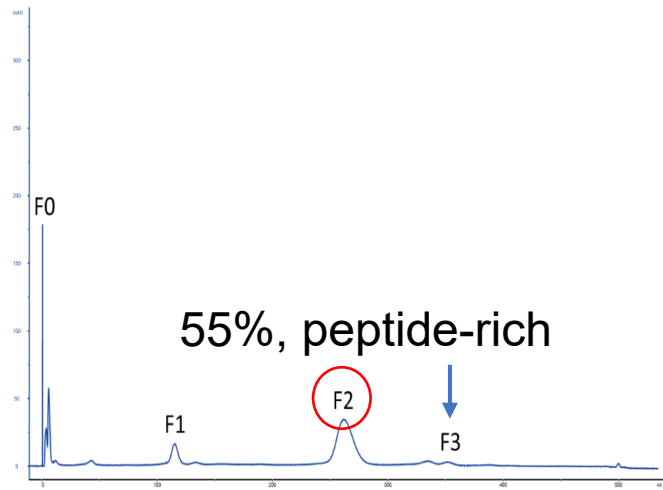


Vespa basalis (Vb)



Results· Venom Protein and Peptide Separation

Provespa barthelemyi (Pb)

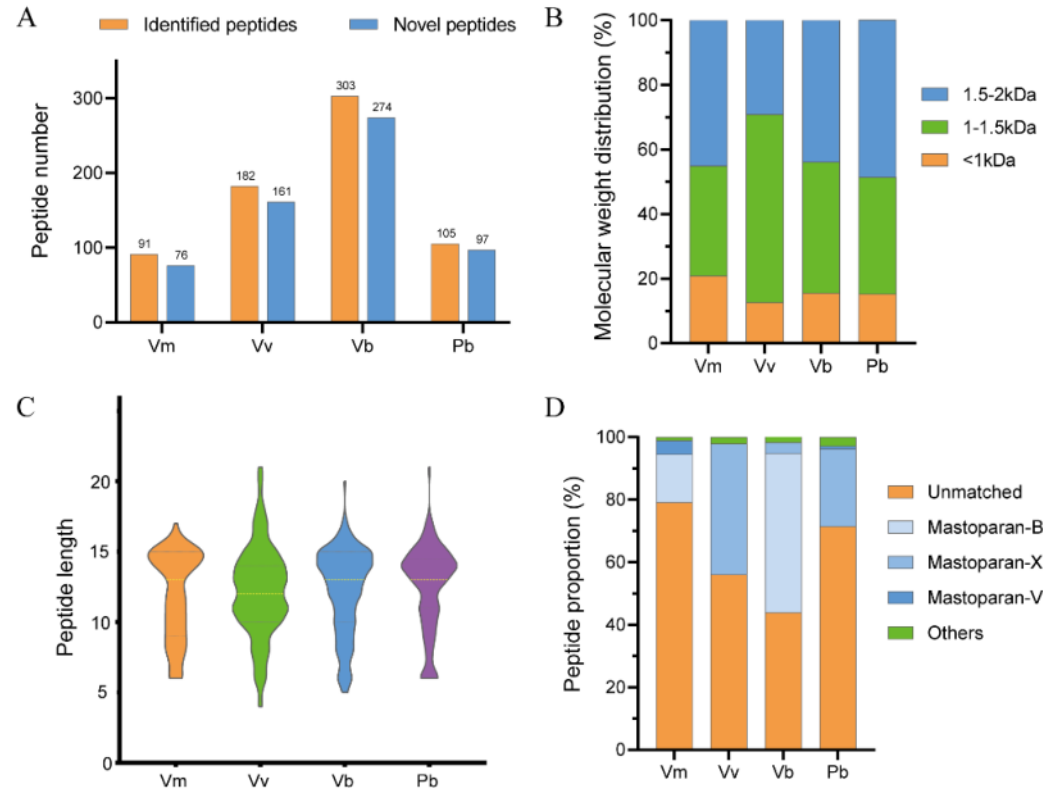


Fractions	Protein name
BandPbF3	Phospholipase A1 1 [<i>V. mandarinia</i>]

First experimental evidence of a PLA1-like protein in *P. barthelemyi* (previously unreported; no gene/protein record in databases).

Peptide-rich fractions were consistently obtained from all four wasp venoms for downstream peptidome analysis.

Results • Peptidome Overview



- A total of 681 peptides identified; ~90% novel
- All peptides < 2 kDa; species-specific MW/length distributions
- Protein origin: most unmatched; matched mainly mastoparan-like proteins
- Built an in-house venom peptide library for drug prediction and development

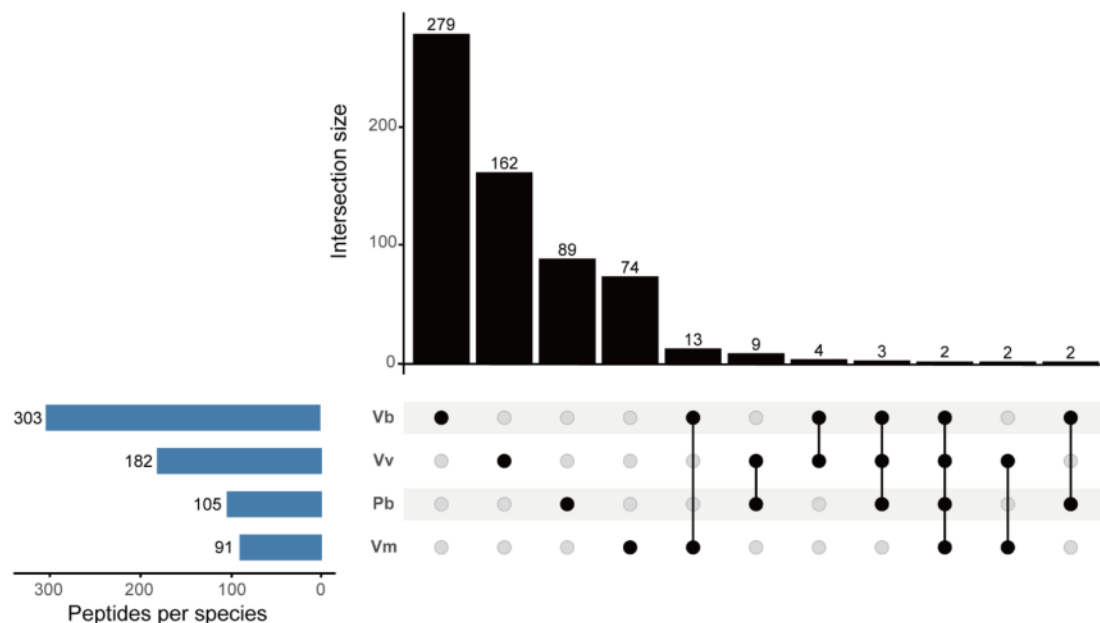
Vm: *V. mandarinia*,
Vb: *V. basalis*,

Vv: *V. velutina*,
Pb: *Pro. barthelemyi*

Results · Shared vs. Species-specific Peptides

Unique & Shared Venom Peptides (Exact sequence match)

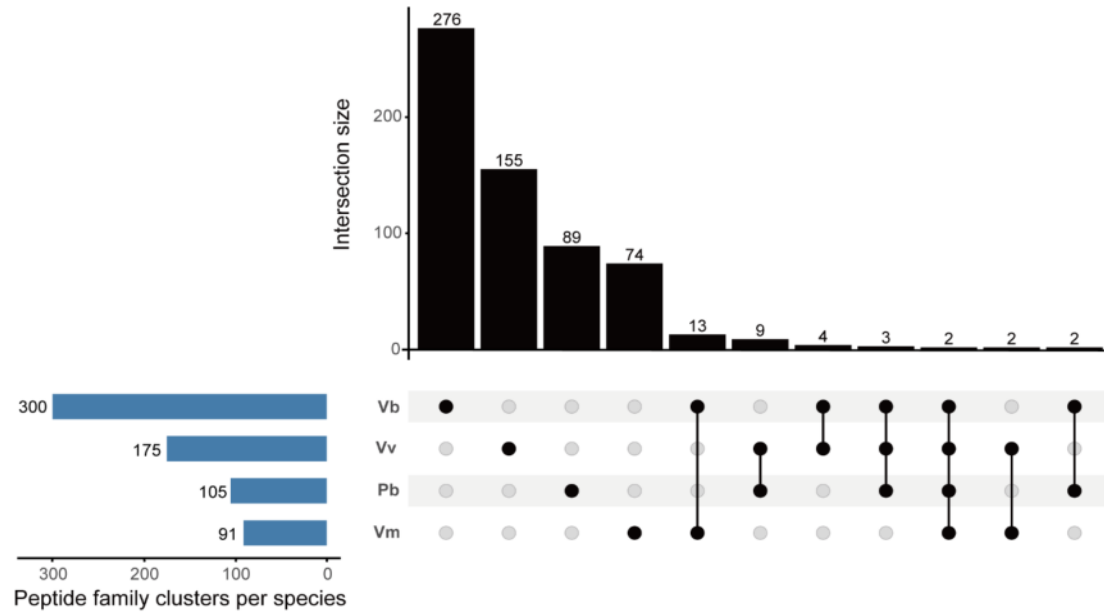
- Vast majority of peptides species-specific
- Only 2 peptides conserved across all 4 species
- Small number peptides shared between 2–3 species
- High compositional diversity and species specificity



Vm: *V. mandarinia*
Vv: *V. velutina*
Vb: *V. basalis*
Pb: *Pro. barthelemyi*

Results · Shared vs. Species-specific Peptides

Venom Peptide Family Clusters (90% similarity)



- Strong species-specific signature at both peptide & family levels → may reflect shared evolutionary / functional pressures

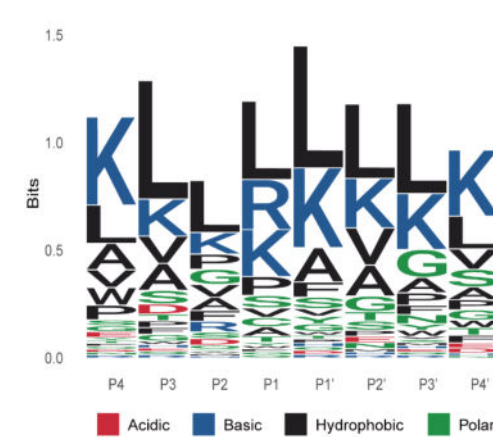
Vm: *V. mandarinia*,
Vb: *V. basalis*,

Vv: *V. velutina*,
Pb: *Pro. barthelemyi*

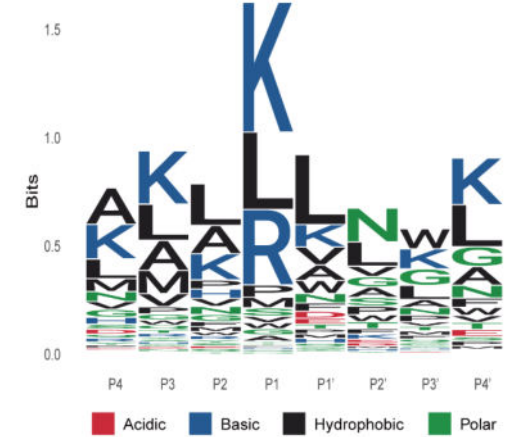
Results • Venom Peptide Formation Mechanism

P4–P4' Cleavage Site Motif Analysis

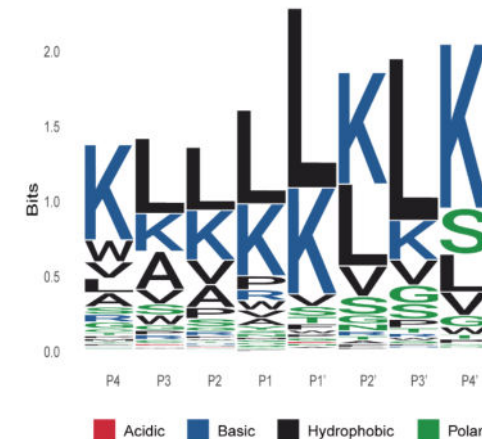
- Non-random processing
Strong residue bias →
not random,
but enzyme-mediated maturation.
- Enzyme preference
P1 enriched in L; R/K moderate →
suggests metalloproteases
+ trypsin-like serine proteases.



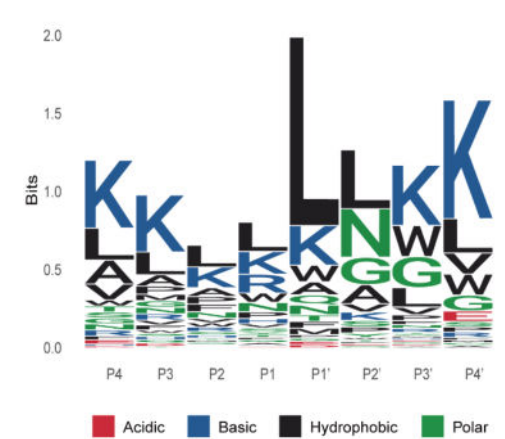
V. mandarinia



V. velutina

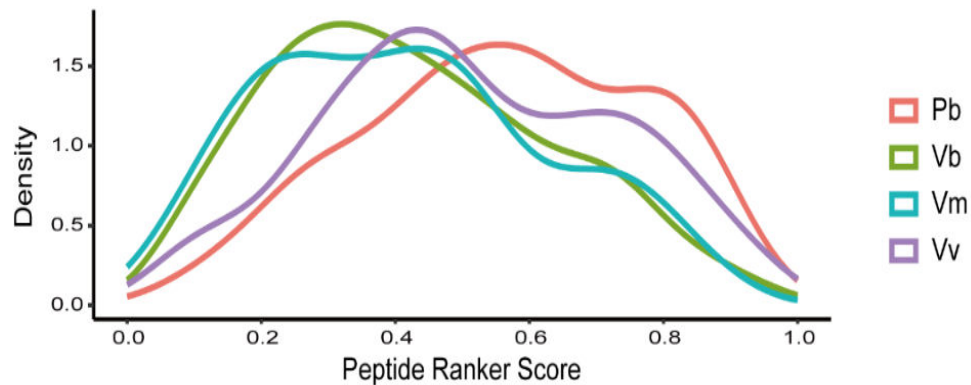


V. basalis



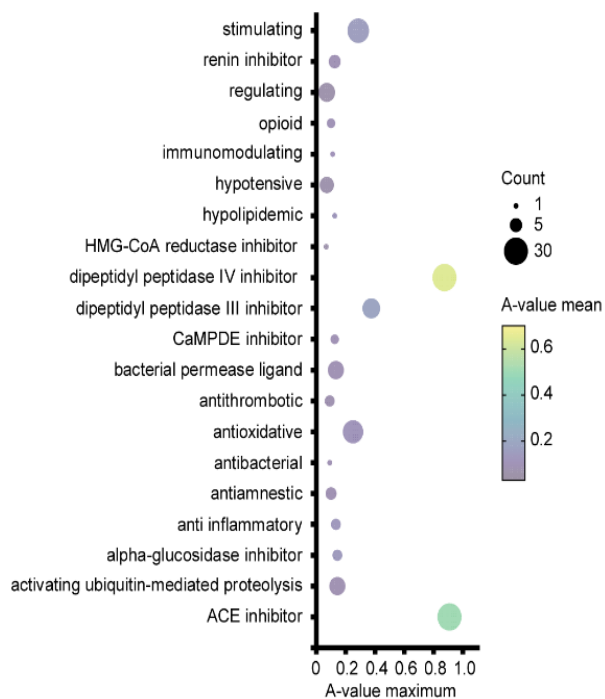
Pro. barthelemyi

Results · Bioactivity Prediction

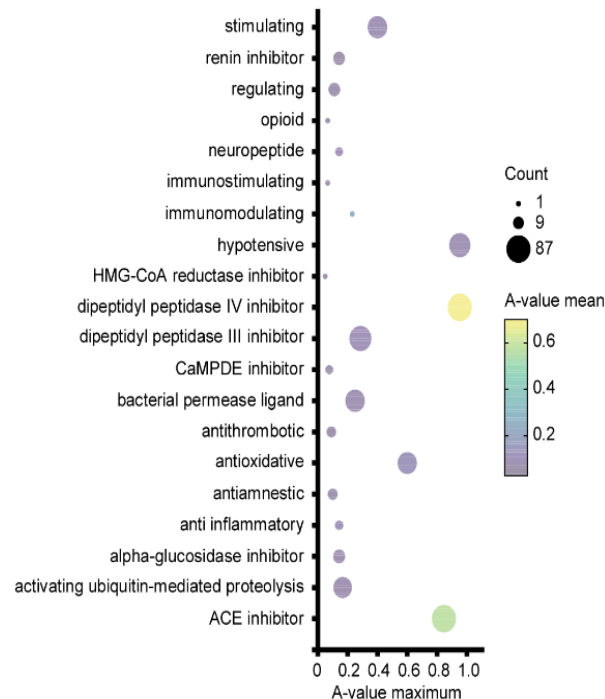


Major predicted activities

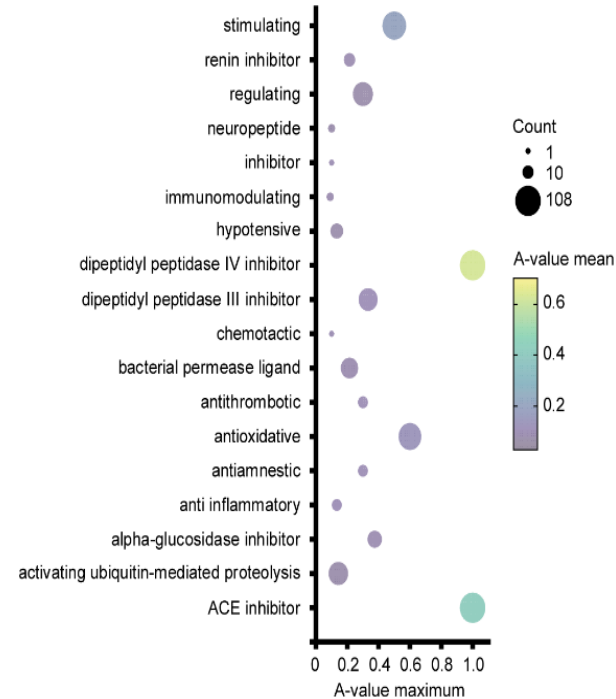
- ACE inhibition
- DPP4 inhibition
- Hypotensive effects



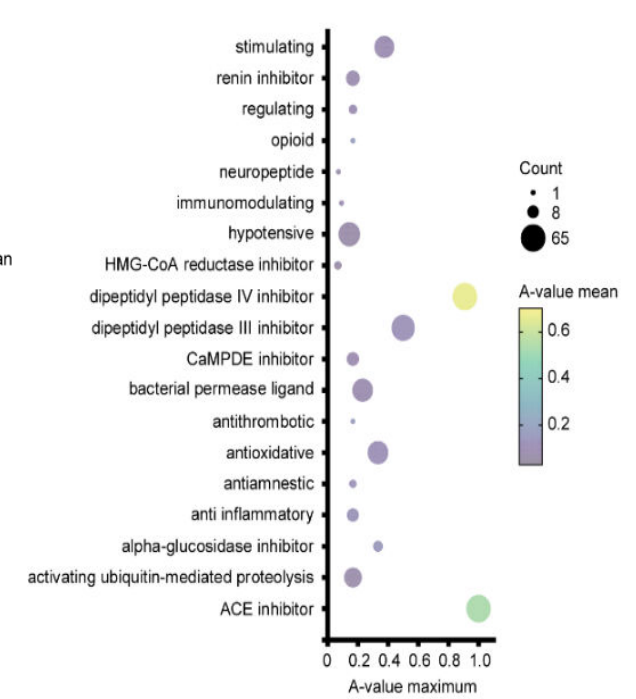
V. mandarinia



V. velutina



V. basalis



Pro. barthelemyi

Results · Bioactivity Prediction

Safety-screened bioactive peptides

8 ACE-inhibitory + 17 DPP4-inhibitory

2 overlap (ACE & DPP4)

→ 23 unique peptides

Safe peptides predicted with ACE/DPP4-inhibitory potential

Peptide_ID	Peptide	Predicted Activity	Length	PeptideRanker Score	A-value	Toxicity	Hemolysis	Allergenicity
Vb_014	GSGGGGGGLGSGEKR	ACE-inhibitor	15	0.65899	1 (ACE)	non	non	non
Vm_082	SSYVLGVGRP	ACE-inhibitor	11	0.554323	0.9091 (ACE)	non	non	non
Vb_098	KRPPGFTLPFR	ACE-inhibitor, DPP4-inhibitor	11	0.89885	0.8182 (ACE) 1 (DPP4)	non	non	non
Pb_068	LNWKGLAAFAKKPK	DPP4-inhibitor	14	0.622539	0.8571 (DPP4)	non	non	non
Vv_140	NNGLLHLHR	DPP4-inhibitor	10	0.511301	0.9 (DPP4)	non	non	non

Results • Novel Cryptides

Cryptides (cryptic peptides)

Functional peptides encrypted within proteins

- **Type I:** Natural cleavage → new, unrelated activity
- **Type II:** Natural cleavage → similar activity (modified features)
- **Type III:** In vitro fragments → novel activity (may not occur naturally)

Results · Novel Cryptides

Novel cryptides from wasp venom

Type I cryptides (9 peptides)

- From mastoparan precursors
- Example: Vb_240 (*V. basalis*)
Parent: Mastoparan-B (antimicrobial, mast cell degranulating, membranolytic)
Predicted: DPP4 inhibitor → divergent function

Type II cryptides (1 peptide)

Example: Vb_099 (from Vespakinin-X)

Parent: vasodilatory/hypotensive

Predicted: ACE & DPP4 inhibitory → related function

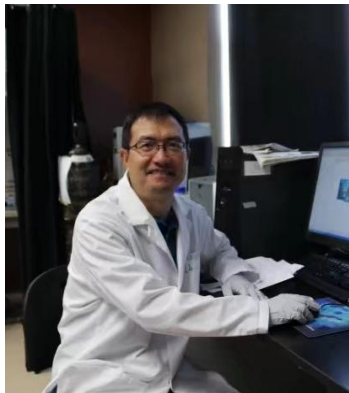
Conclusion

- Built an in-house venom peptide library.
- Wasp venom peptides are mostly species-specific, with only a minimal conserved core across four species.
- Venom peptides are processed by specific proteases, generating structural and functional diversity.
- Several peptides are predicted as safe ACE- and DPP4-inhibitors.
- Novel Type I and Type II cryptides were identified with divergent functions.
- This study provides a foundation for venom utilization and drug discovery.

● Significance

- **For beekeepers / industry:** Understanding wasp venom composition → enabling industrial & therapeutic applications
- **For science & drug discovery:** Rich peptide resource compiled as an in-house venom peptide library; predicted safe ACE/DPP4 inhibitors; novel cryptides
- **Scientific insight:** Highlights peptide diversity, species-specificity, and protease-mediated peptide maturation
- **Novelty:** Provides the first comprehensive and comparative peptidome analysis of four wasp venoms

Acknowledgements & Contact



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Thank you for your attention!