Discovery of a novel tetrapeptide as glucose homeostasis modulator with bifunctionalities of targeting DPP-IV and microbiota

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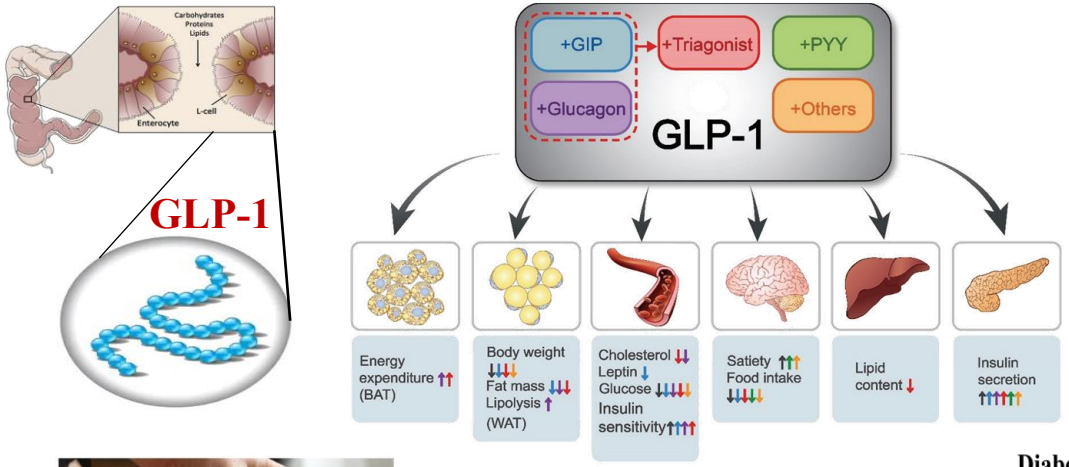
Background

Physiological function of GLP-1



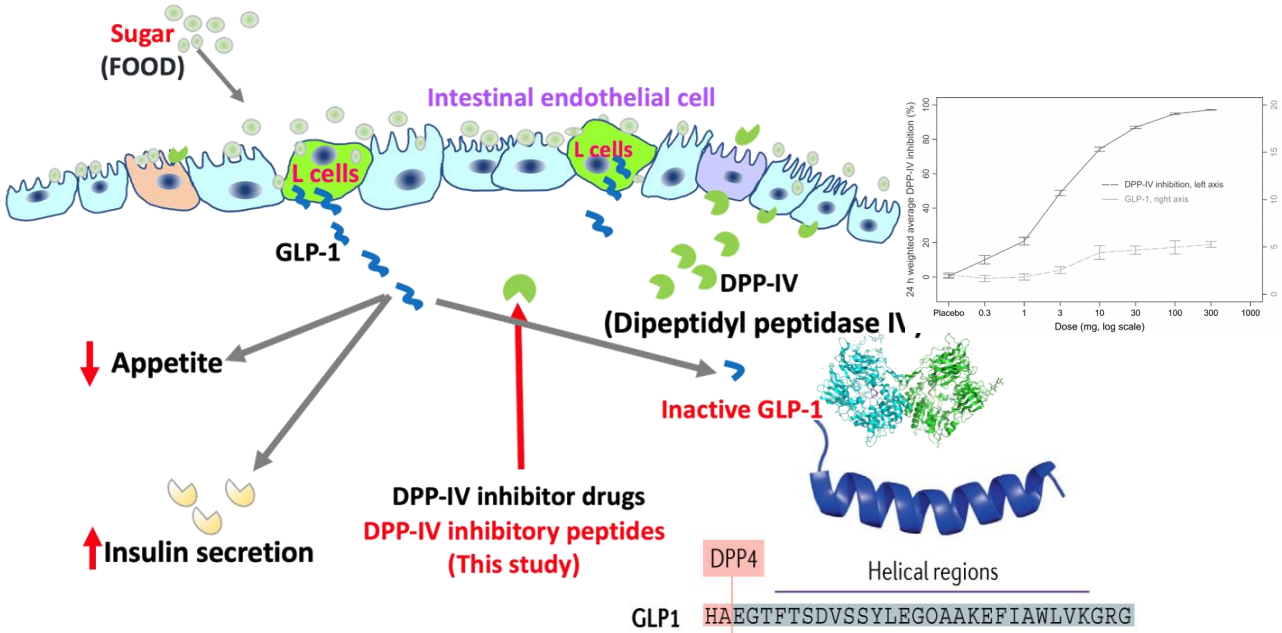
Nature, 2025

Anti-obesity **Anti-diabetes**

Diabetes
- Semaglutide
- Liraglutide
- Lixisenatide
- Albiglutide
- Dulaglutide
- Pramlintide

GLP-1:

- GLP-1 is secreted by intestinal L cells and play a critical role in glucose homeostasis by inducing insulin secretion;
- GLP-1 have lots of health benefits, including inhibit gastric emptying, reduce intestinal peristalsis, control food intake and reduce body weight, etc.
- **GLP-I analogues (agonists)** developed as important drug for diabetes treatment and weight control



DPP-IV:

- DPP IV synthesized by intestinal L cells mediates the GLP-1 degradation and slows down insulin secretion;
- Promising target for DPP-IV inhibitory drug and nutraceutical development

DPP-IV inhibitors:

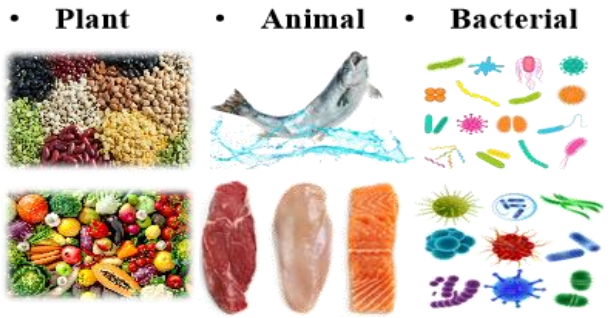
- Prolongs the half-life of GLP-1, improved glucose tolerance and glucose homeostasis.
- Few peptide inhibitors commercialized

Lancet Diabetes Endocrinol, 2017; Diabetes, Obesity and Metabolism, 2008

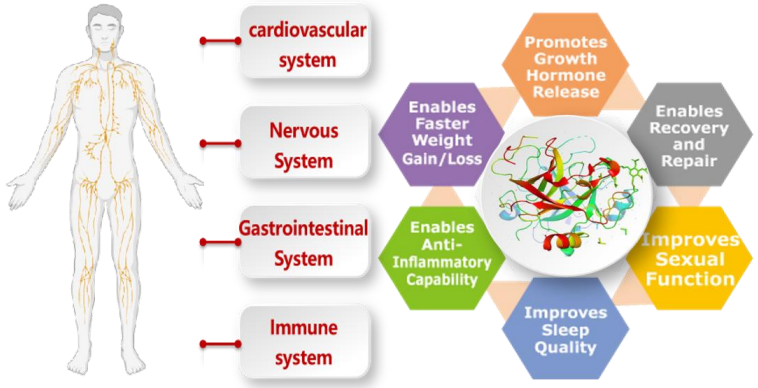
Background

Bioactive peptide mining methods and bottlenecks

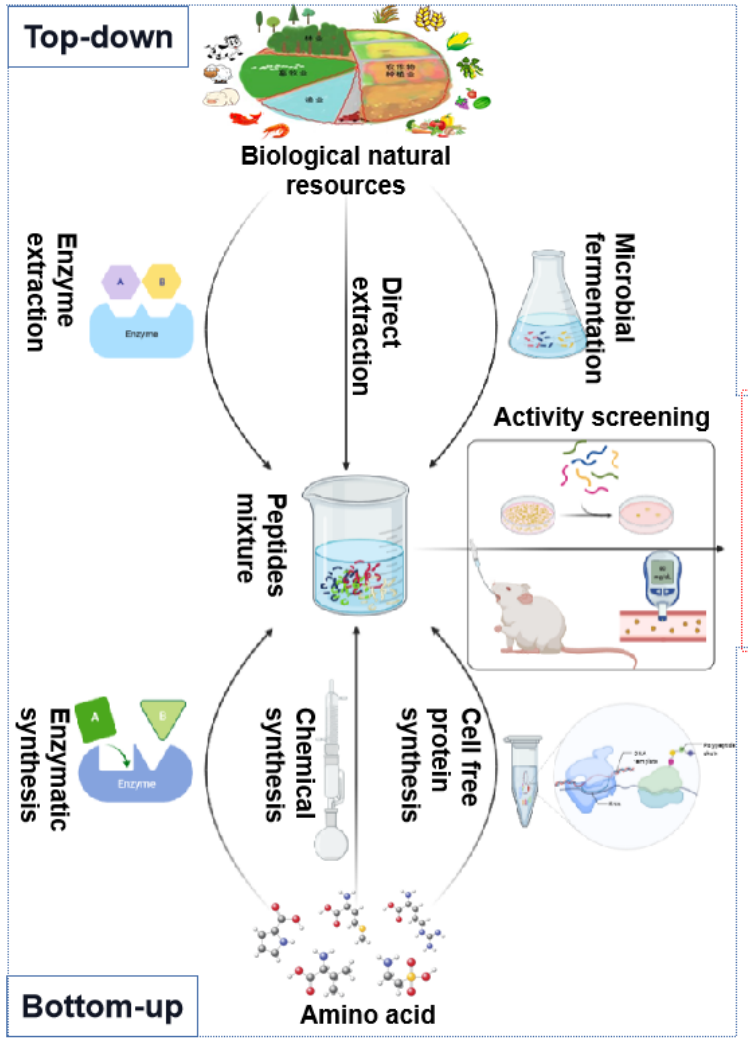
■ Natural protein sources



■ Health benefits of peptides



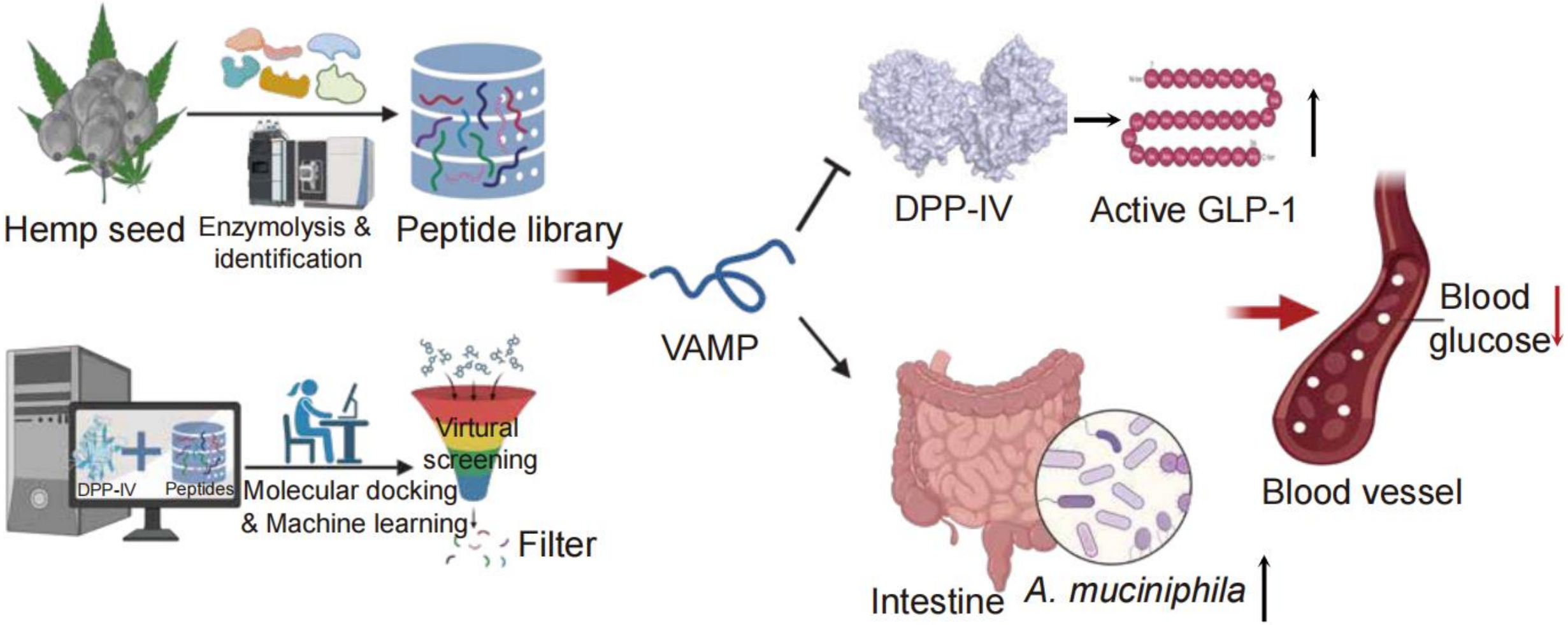
Method for the mining of bioactive peptides



Advantages of bioactive peptides and key issues:

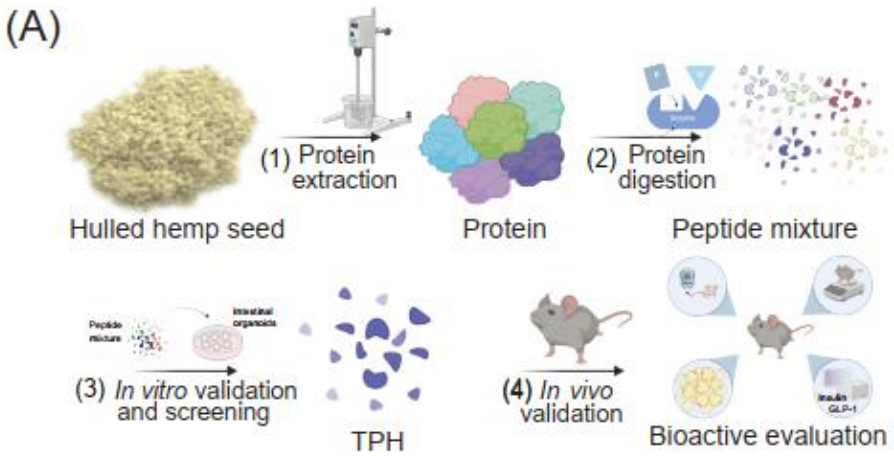
- One of the important strategies receiving increasing attention is to mine food-derived bioactive peptides from the abundant natural food protein sources for developing DPP-IV bioinhibitors.
- The lack of genomic and proteomic information for many natural protein-containing bioresources also hinders the efficient mining of new DPP-IV inhibitory peptides.
- The Traditional approaches for the mining of DPP-IV inhibitory peptides are labour-, time-, and cost-intensive.
- New startegies for mining of functional peptides are needed.

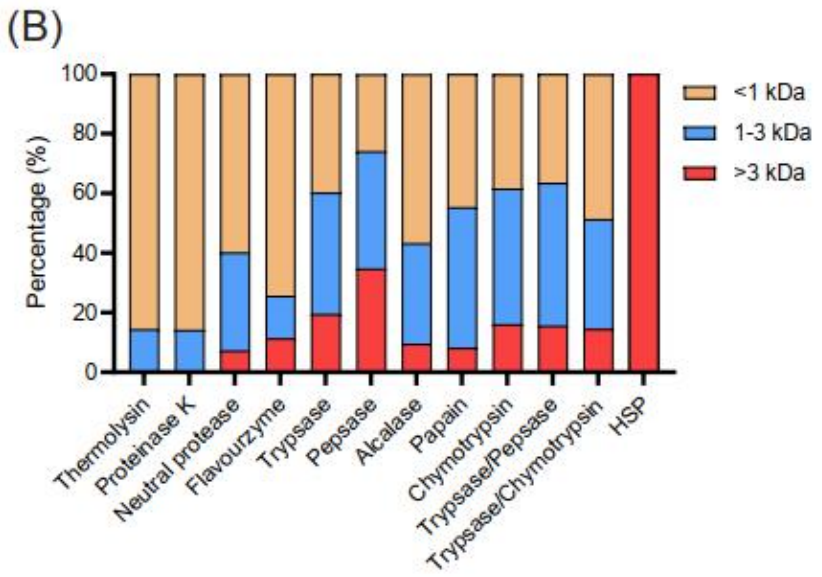
Construction of a DPP-IV inhibitory peptide mining system and mechanistic analysis of the hypoglycemic effects of active peptide VAMP

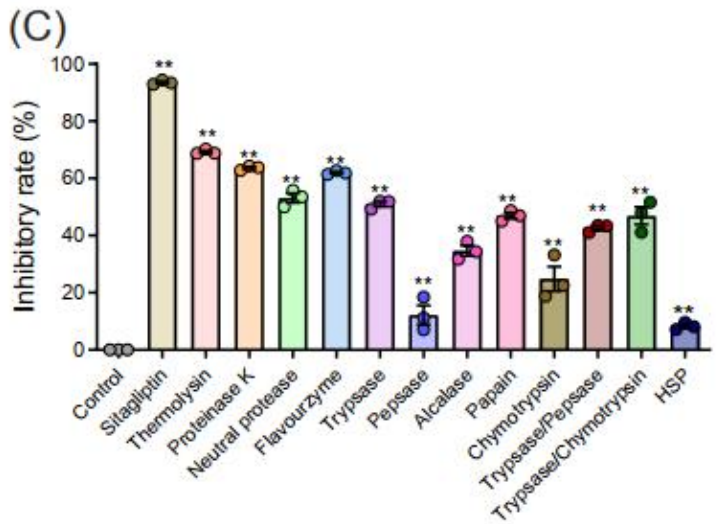


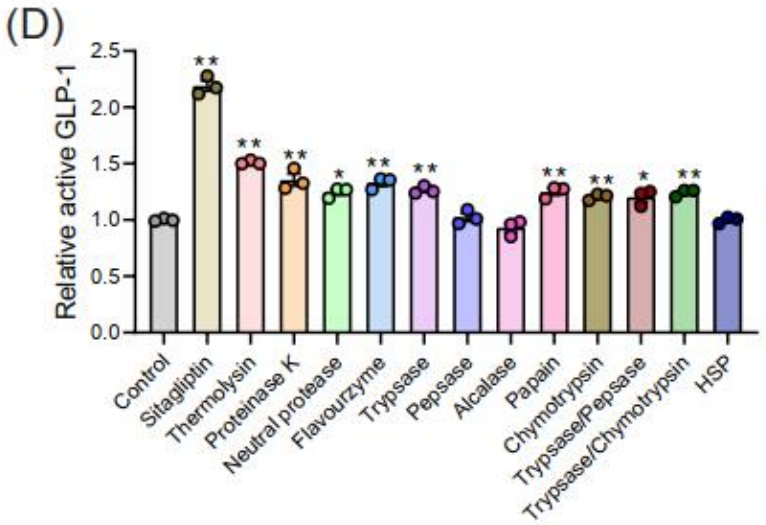
Screening of DPP-IV-inhibiting peptides from HSP

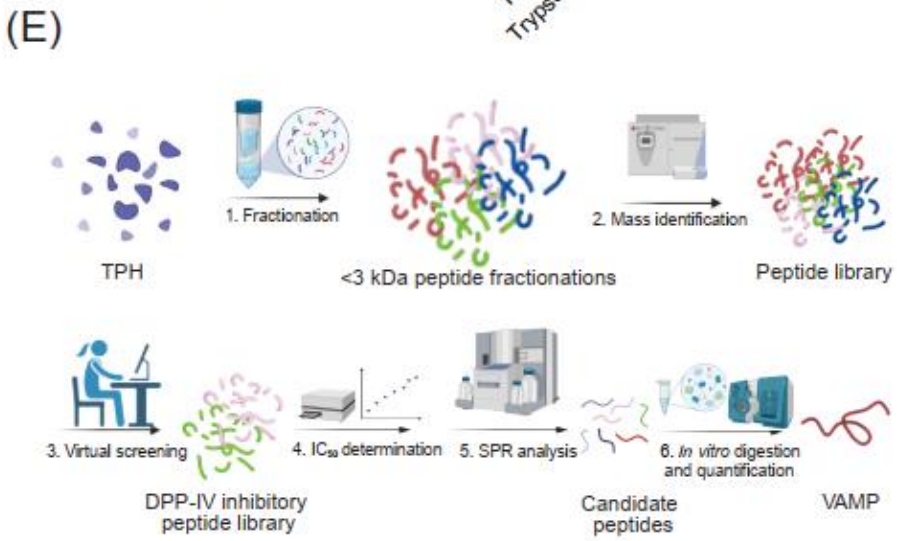
By molecular docking-, machine learning-, enzymomics-, proteomics-, and intestinal organoid based-strategy, we developed a high throughput screening platform for mining and evaluation of bioactive peptides from food resources

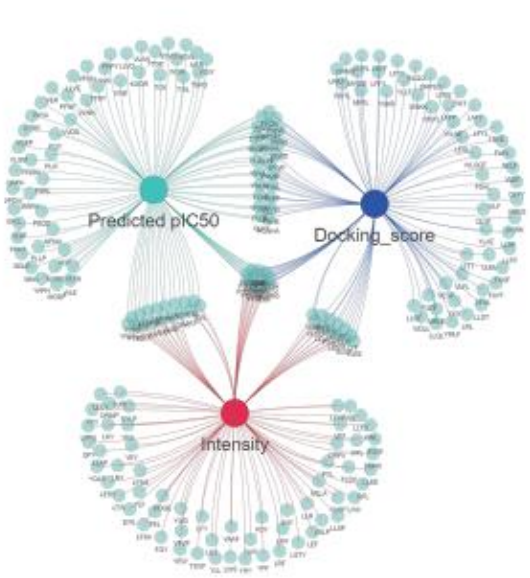






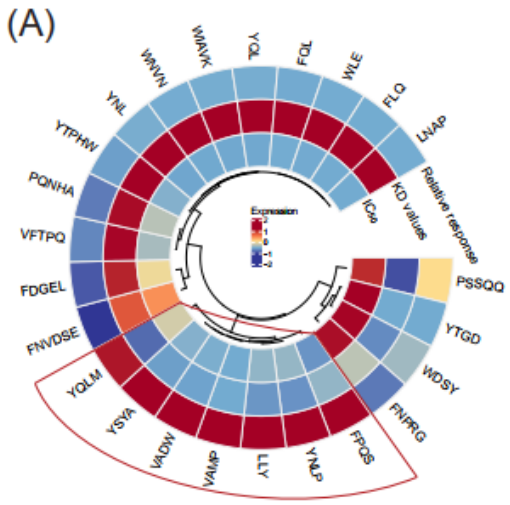


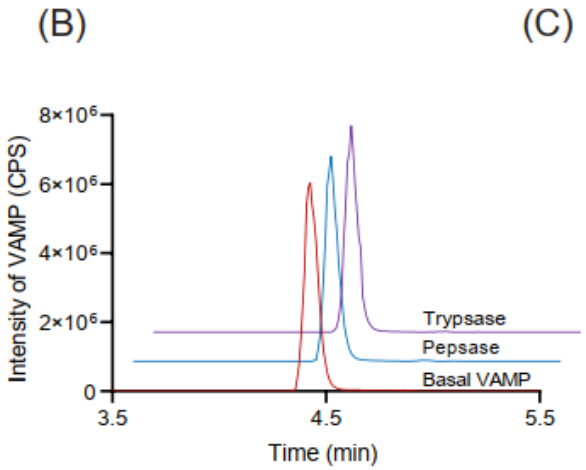


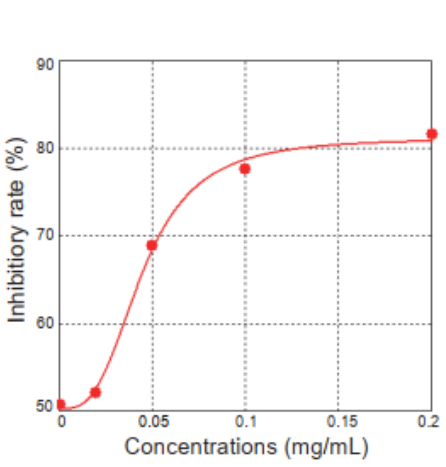


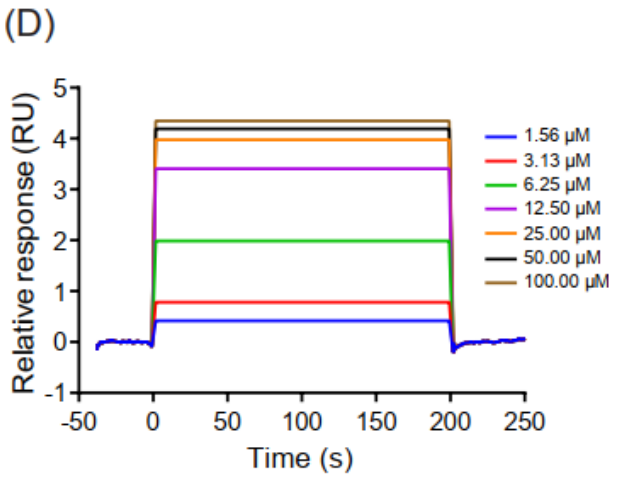
VAMP inhibits DPP-IV

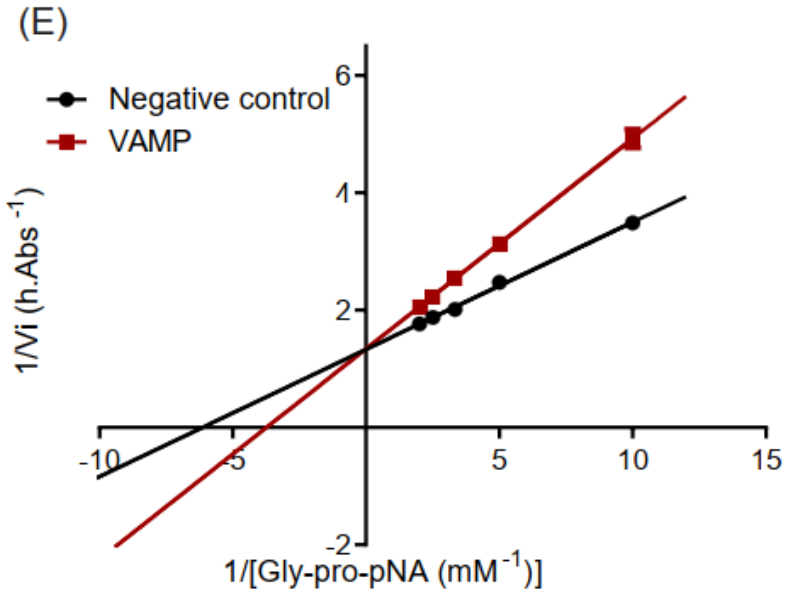
Mechanism of DPP-IV inhibition by active peptide VAMP

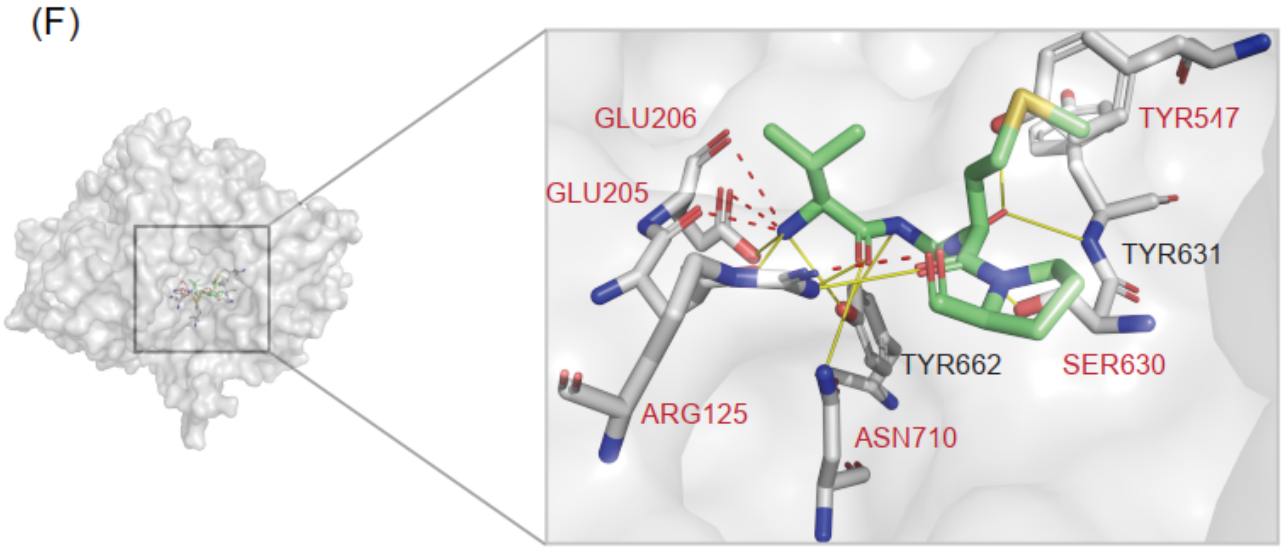






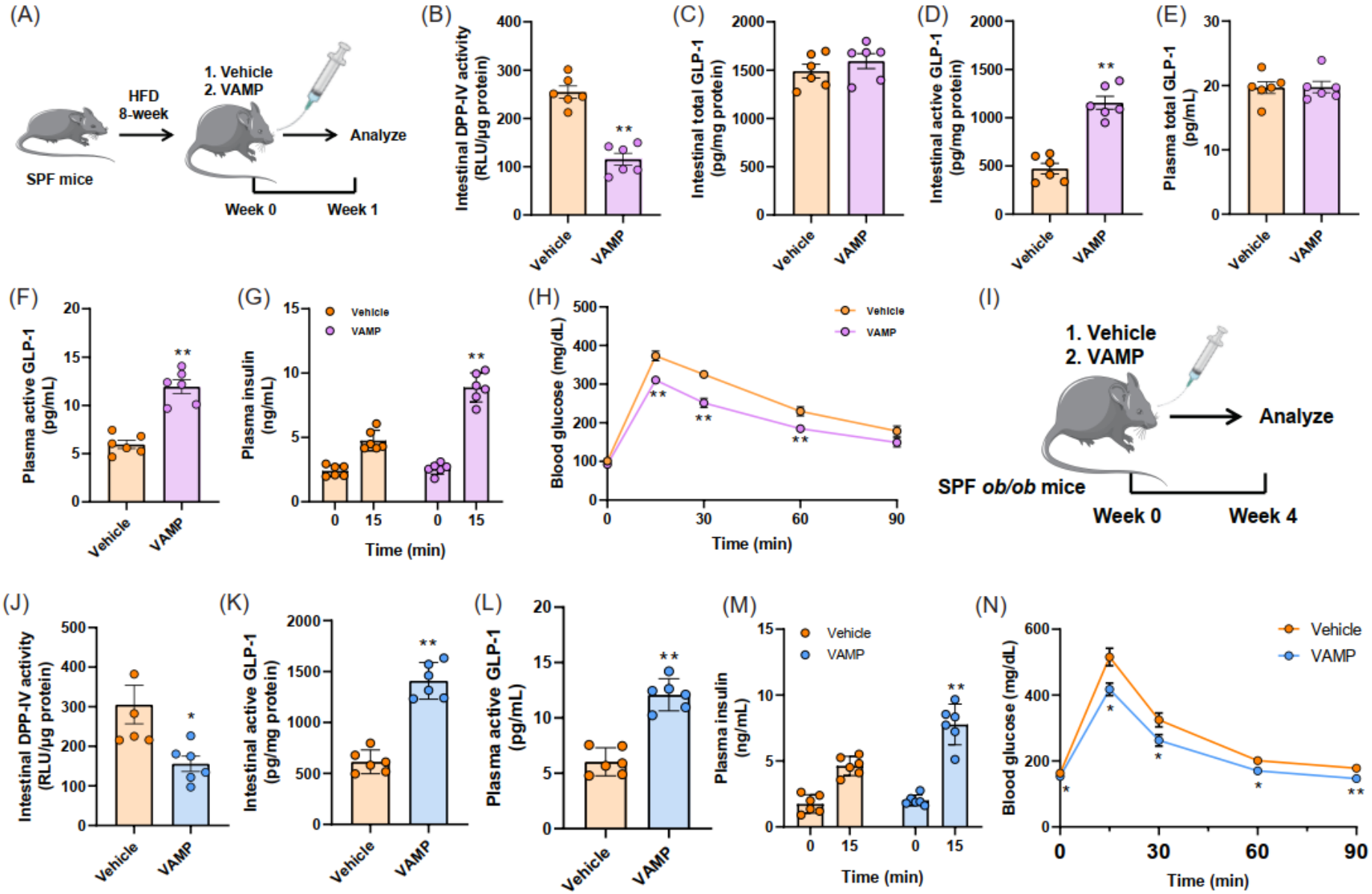






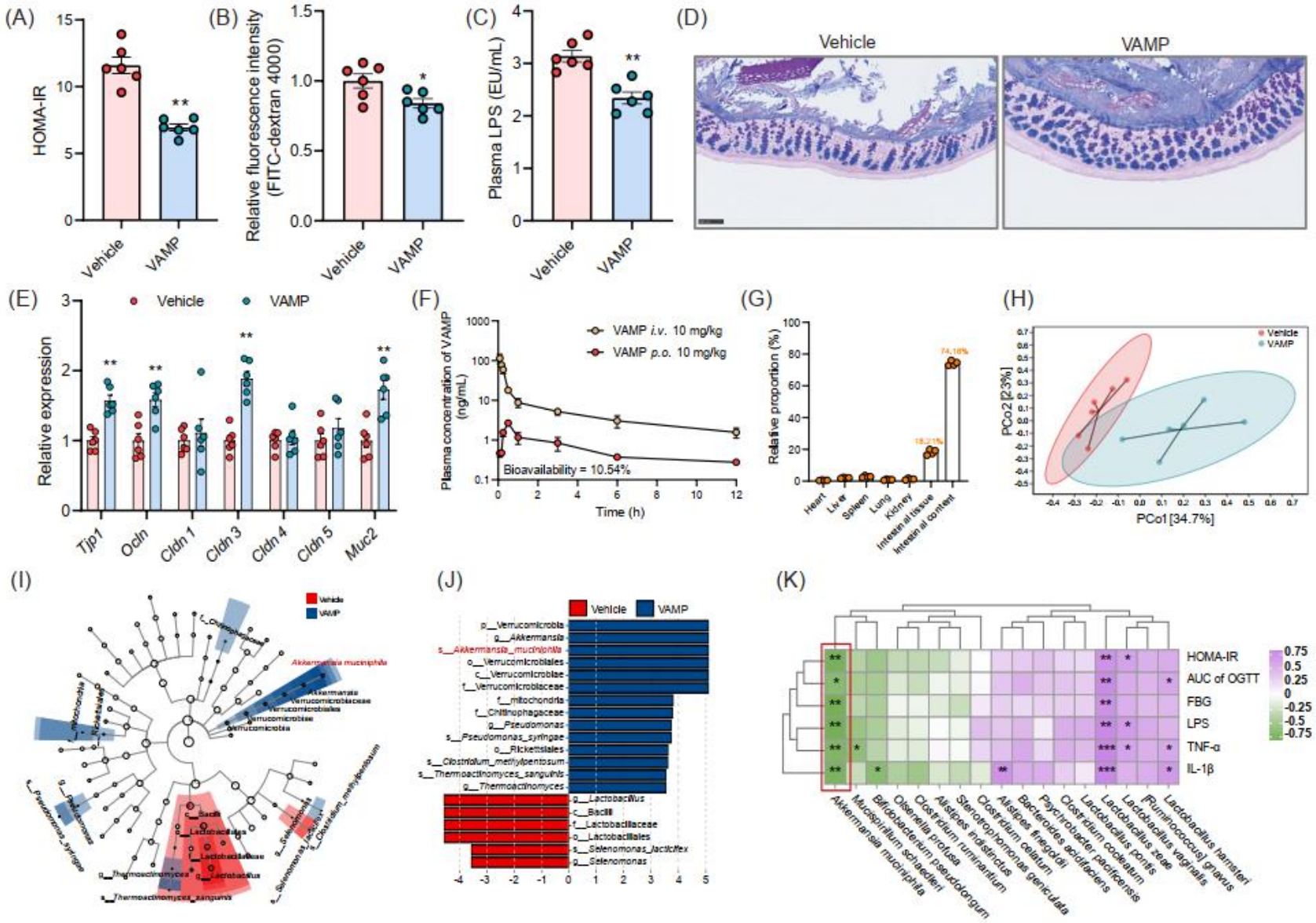
VAMP regulates glucose metabolism by inhibiting intestinal DPP-IV

Active peptide VAMP inhibits DPP-IV to promote insulin secretion

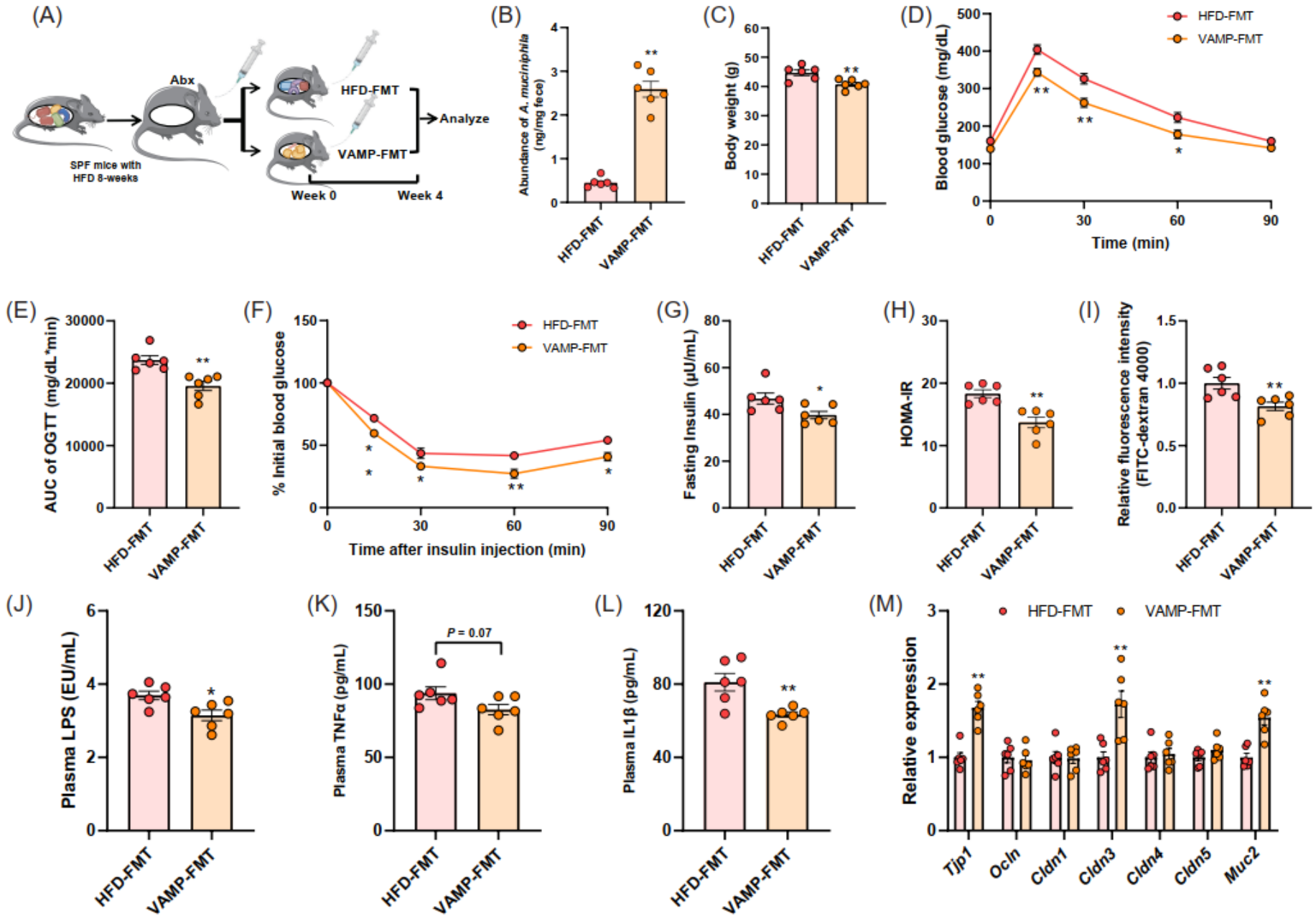


VAMP modulating gut microbiota

VAMP improve gut barrier function by promoting *Akkermansia muciniphila* abundance

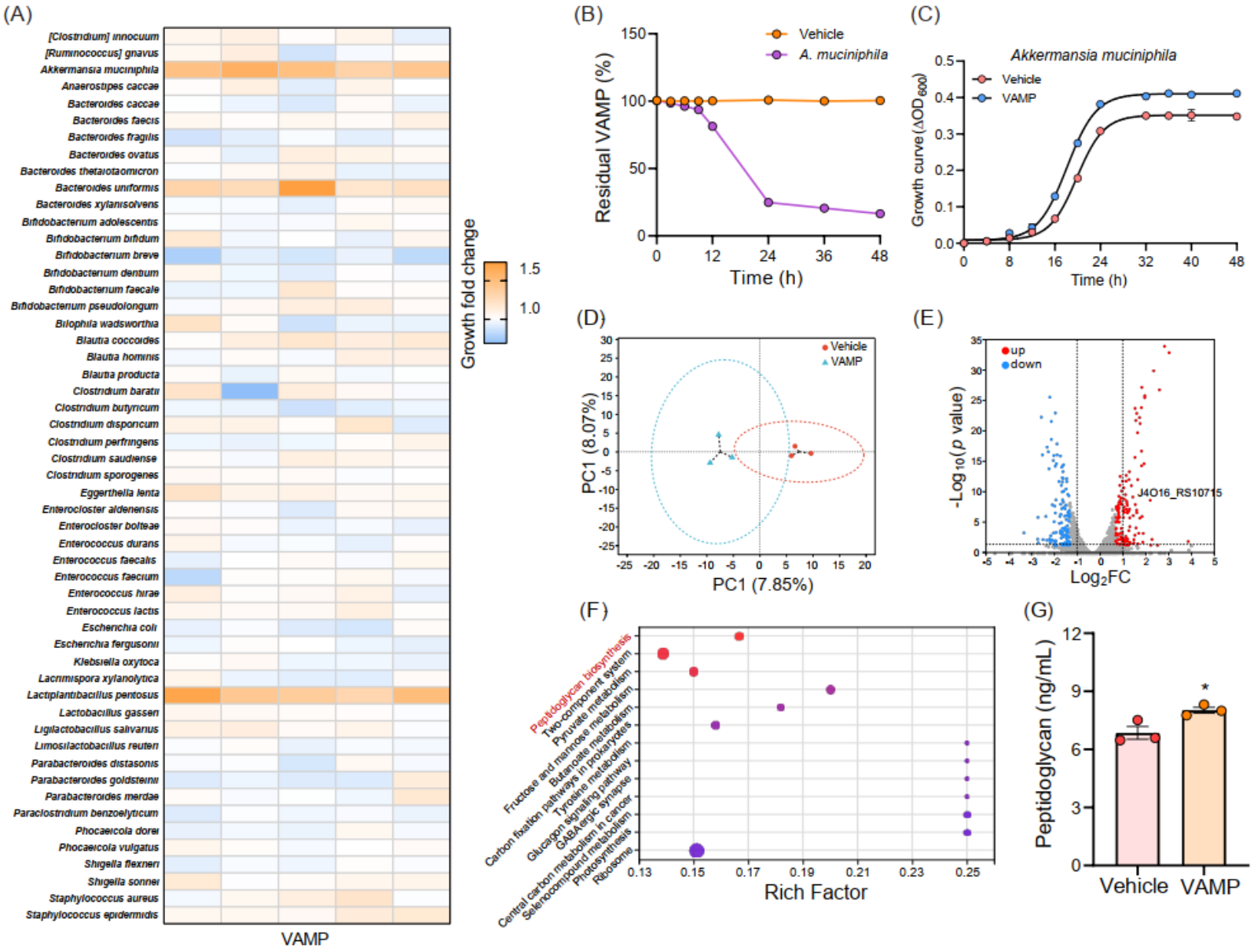


FMT mimics the regulatory effects of VAMP



VAMP promotes peptidoglycan synthesis in *Akkermansia muciniphila*

VAMP promotes *A. muciniphila* by upregulating the expression of gene J4O16_RS10715



Summary

- By molecular docking-, machine learning-, enzymomics-, proteomics-, and intestinal organoid based-strategy, we developed a high throughput screening platform for mining and evaluation of bioactive peptides from food resources.
- Hemp seeds derived VAMP competitively binds to intestinal DPP-IV and increases the active GLP-1 levels to reduce blood glucose level.
- VAMP specifically promoted the growth and abundance of intestinal *A. muciniphila* via up-regulating the expression of gene J4O16_RS10715, which synergitically contributes to regulation of glucose metabolism.

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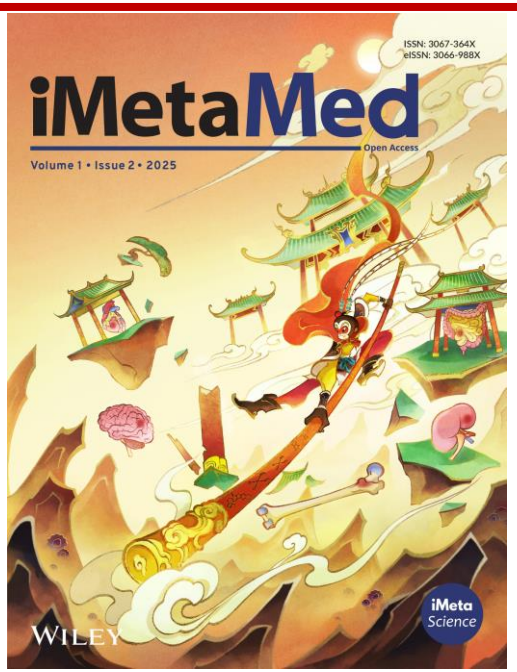

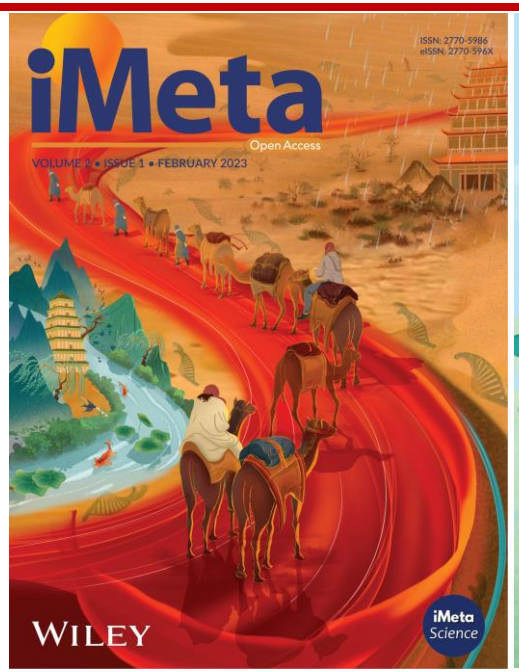

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