Exploring Functional Food Protein Hydrolysates as a Source of DPP-IV Inhibitory Peptides via Peptide Analysis and Molecular Docking

李佳佳（5135）

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Abstract

Dipeptidyl peptidase-IV (DPP-IV) is a key enzyme in glucose metabolism, and its inhibition is an established strategy to improve glycemic control in diabetes. Protein-derived peptides have emerged as promising natural inhibitors with potential applications in functional foods. This study evaluated the inhibitory potency of protein hydrolysates, identified bioactive peptide sequences, and elucidated their interaction mechanisms with DPP-IV using an integrated enzymatic, analytical, and computational approach. Enzymatic hydrolysates from multiple protein sources exhibited significant DPP-IV inhibition; one insect-derived hydrolysate demonstrated an IC_{50} of 1.64 mg/mL, with the 1–3 kDa fraction showing the strongest activity. From this source, the peptides LPDQWDWR (IC_{50} = 0.15 mg/mL) and APPDGGFWEWGD (IC_{50} = 1.03 mg/mL) were identified as actives. Gelatin-derived peptides also showed strong inhibition, with purified sequences LGPQR, RGFDQ, RGPVGP, and RLDDVT exhibiting IC_{50} values in the 52–76 μM range. Milk whey protein hydrolysates displayed multi-enzyme inhibition with IC_{50} values of 0.34 mg/mL for DPP-IV, 0.37 mg/mL for α-glucosidase, and 0.72 mg/mL for α-amylase; from this source, SPPEFLR (56.22 μM), LDADGSY (52.16 μM), YPVEPFT (75.7 μM), and FNPTY (62.32 μM) were characterized. Enzyme kinetics indicated competitive or mixed-type inhibition, while molecular docking supported strong binding within the DPP-IV active site mediated by hydrogen bonds, hydrophobic interactions, salt bridges, π–cation contacts, and π–π stacking, consistent with

in vitro activity. These findings define a panel of peptide inhibitors with quantified potencies and clarified mechanisms, supporting their potential as candidates for diabetes management and development of functional ingredients.

References

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