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In Silico Study of the YAKRCFR Peptide Structure and Its Interaction with Human Peroxiredoxin-5

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ABSTRACT

The identification of bioactive peptides with therapeutic potential is an emerging focus in drug discovery. In this study, we evaluated the structural stability and binding affinity of the oyster-derived peptide YAKRCFR through molecular modeling and docking simulations against the human peroxiredoxin receptor. Structural prediction using the PEP-FOLD4 server revealed a consistent α-helical conformation across all models, stabilized by key intramolecular hydrogen bonds and favorable sOPEP energy values. Molecular docking was validated with a root mean square deviation (RMSD) of 0.273 Å, confirming the reliability of the docking protocol. The YAKRCFR peptide exhibited a strong binding affinity with the 1HD2 receptor (ΔG = −8.1 kcal/mol), outperforming both ascorbic acid (−6.1 kcal/mol) and the native ligand (−4.862 kcal/mol). Detailed interaction analysis indicated that YAKRCFR forms stable hydrogen bonds and van der Waals interactions with critical residues such as ILE A119 and PHE A120, contributing to its thermodynamic stability and binding specificity. These findings suggest that YAKRCFR holds promise as a lead compound for further development in peptide-based therapeutic strategies, particularly for targets involving the human peroxiredoxin receptor.

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INTRODUCTION

Peptides derived from natural sources, particularly marine organisms, have attracted increasing attention due to their diverse bioactivities and potential applications in health and pharmaceutical fields [1,2,3]. Among these, antioxidant peptides have shown promise as therapeutic agents capable of neutralizing reactive oxygen species (ROS), which are implicated in various oxidative stress-related diseases such as cancer, neurodegeneration, and cardiovascular disorders[4, 5]. Oysters, as a rich source of bioactive compounds, have been widely studied for their nutritional and functional properties. Recent studies have identified several antioxidant peptides from oyster (Crassostrea rivularis) protein hydrolysates, including a heptapeptide with the sequence YAKRCFR that consists of seven amino acids: tyrosine (Y), alanine (A), lysine (K), arginine (R), cysteine (C), phenylalanine (F), and arginine (R) (tyr-ala-lys-arg-cys-phe-arg), which has demonstrated notable free radical scavenging activity in vitro[6].

Oxidative stress plays a critical role in the development of various chronic diseases, including neurodegenerative disorders, cancer, and cardiovascular diseases. One of the key cellular antioxidant mechanisms involves Peroxiredoxin-5 (PRDX5), a thiol-specific peroxidase found in mitochondria, peroxisomes, the cytosol, and the nucleus, which reduces hydrogen peroxide and other peroxides to water, thus maintaining redox homeostasis . Impaired PRDX5

function has been linked to multiple pathological conditions, such as protecting dopaminergic neurons from oxidative damage in Parkinson's disease models , preventing neuronal apoptosis induced by amyloid-β oligomers in Alzheimer's disease [7] , inhibiting TGF-β-induced fibrosis in kidney fibroblasts [8], and exacerbating cardiac hypertrophy through oxidative stress–mediated MAPK activation when PRDX5 expression is reduced[9] . Due to its pivotal role in oxidative stress–related pathology, PRDX5 represents a promising molecular target for therapeutic intervention.

YAKRCFR exhibits a direct free radical scavenging mechanism, primarily through its ability to donate hydrogen atoms or electrons. This antioxidant property is largely influenced by the specific amino acid residues within its sequence. Aromatic amino acids such as tyrosine (Tyr) and phenylalanine (Phe), both present in YAKRCFR, are known to contribute electrons to neutralize reactive free radicals, converting them into more stable, non-reactive molecules. These residues stabilize the resulting radical intermediates through resonance, preserving molecular integrity and enhancing overall antioxidant capacity. Such structural features make YAKRCFR a promising peptide for mitigating oxidative stress through direct radical neutralization [6,10].

Understanding the structure of bioactive peptides is crucial for elucidating their mechanism of action and for optimizing their biological efficacy. However, due to the limitations of experimental techniques such as NMR or X-ray crystallography especially for small, flexible peptides computational structure prediction tools offer a valuable alternative. One such tool is PEP-FOLD4, a widely used web-based platform capable of generating accurate three-dimensional (3D) models of linear peptides based solely on their amino acid sequences[10,11]. These predicted structures can serve as the basis for molecular docking studies, which simulate the interaction between peptides and target proteins, offering insights into their binding behavior and potential biological effects.

In the context of antioxidant activity, human peroxiredoxin 5 (PRDX5) is a key intracellular enzyme involved in the reduction of hydrogen peroxide and organic hydroperoxides, thereby playing a vital role in cellular redox homeostasis[12,13]. By evaluating the interaction between YAKRCFR and PRDX5 through molecular docking, it is possible to assess the peptide's potential antioxidant mechanism at the molecular level. This study aims to predict the 3D structure of the oyster-derived peptide YAKRCFR using PEP-FOLD4 and to investigate its binding affinity and interaction profile with human peroxiredoxin 5 using AutoDock Vina. Reference ligands, including the native ligand of PRDX5 and ascorbic acid, were included for comparative purposes. The findings are expected to contribute to a deeper understanding of the structure of antioxidant peptides and their potential therapeutic applications.

RESEARCH METHODS

The three-dimensional structure of the peptide YAKRCFR was predicted using the PEP-FOLD4 web server, a well-established tool for de novo modeling of linear peptides ranging from 5 to 50 amino acids [10]. The peptide sequence, Tyrosine (Y), Alanine (A), Lysine (K), Arginine (R), Cysteine (C), Phenylalanine (F), and Arginine (R) was entered in Fasta format into the input form of the PEP-FOLD4 server, which is accessible at https://bioserv.rpbs.univ-paris-diderot.fr/services/PEP-FOLD4/. The prediction was carried out using default parameters, which typically generate five representative 3D models based on coarse-grained force field simulations and a fragment assembly approach [14].

After submission, the server processed the sequence and returned five predicted models along with corresponding structural data, including sOPEP energy scores, which reflect the estimated stability of each model and clustering information to indicate structural similarities among the conformations. The model with the lowest energy score or that appeared most

frequently across clusters was selected as the most representative structure. The resulting PDB files were downloaded and further analyzed using BIOVIA Discovery Studio Vizualizer 2025 for detailed visualization of the peptide's secondary structure and hydrogen bonding interactions. This structural data was then submitted to in silico molecular docking with human peroxiredoxin 5.

The peptide YAKRCFR was further analyzed through molecular docking to evaluate its potential interaction with the human peroxiredoxin 5 enzyme (PDB ID: 1HD2). The docking simulation was performed using AutoDock Vina, a widely used tool for predicting binding affinity and orientation of ligands within a receptor's active site [15]. Before docking, the 3D structure of the target protein was obtained from the Protein Data Bank and prepared by removing water molecules, adding polar hydrogens, and assigning Gasteiger charges using AutoDock Tools (ADT). The predicted 3D structure of YAKRCFR from PEP-FOLD4 was energy-minimized and converted to PDBQT format to ensure compatibility with the docking software.

The docking grid was centered on the known active site of peroxiredoxin 5, and its size was adjusted to cover the entire binding pocket adequately. The grid box size is 40 x 40 x 40 Å, and the grid space is 0.375 Å. Two reference ligands were used for comparison: the native ligand co-crystallized with 1HD2 and ascorbic acid, a known antioxidant compound. These references provided baseline binding affinities and interaction patterns for evaluating the docking performance of the peptide. Upon completion of the docking simulations, the binding affinities (expressed as binding energy in kcal/mol) and interaction profiles were analyzed. Visualization and interpretation of binding modes, hydrogen bonds, and hydrophobic contacts were conducted using BIOVIA Discovery Studio Vizualizer 2025.

RESULTS AND DISCUSSION

The structural prediction of the peptide YAKRCFR was performed using the PEP-FOLD4 server, yielding four representative models shown in Table 1. The quality and stability of each predicted conformation were assessed based on their sOPEP energy scores, secondary structure features, and key intramolecular hydrogen bonding interactions.

Table 1. Simulation results of the YAKRCFR peptide structure using PEPFOLD4

Model result	sOPEP	Peptide structure	Hydrogen Bonding distance (Å)		
			Tyr1:O-Cys5:H	Ala2:O-Phe6:H	Lys3:O-Arg7:H
1	-8.58555	α-heliks	1.952	1.871	1.911
2	-8.57978	α-heliks	1.952	1.870	1.888
3	-8.57134	α-heliks	1.952	1.892	1.895
4	-8.56773	α-heliks	1.952	1.875	1.902

All models demonstrated a consistent α-helical folding pattern, indicating that the peptide adopts a stable secondary structure in silico. The calculated sOPEP energy values ranged from −8.58555 (Model 1) to −8.56773 (Model 4). Among them, Model 1 exhibited the lowest energy, suggesting that it represents the most thermodynamically favorable structure (Figure 1). However, the energy differences between the models were relatively small, which reflects structural consistency and supports the reliability of the predictions. A detailed analysis of hydrogen bonding patterns revealed three recurring interactions that contribute to the peptide's structural stability: Tyr1:O – Cys5:H, Ala2:O – Phe6:H, and Lys3:O – Arg7:H. These hydrogen bonds were found across all four models with bond lengths ranging from 1.870 Å to 1.952 Å, which fall within the optimal distance for stable hydrogen bonding. Notably, the Tyr1–Cys5 interaction was conserved across all models with an identical bond distance of 1.952 Å, indicating a robust interaction at the N-terminal segment of the peptide. Minor variations in the other bond lengths

were observed but remained within acceptable ranges, further supporting the peptide's conformational stability. Collectively, these results suggest that the oyster-derived peptide YAKRCFR adopts a compact and stable α-helical structure, reinforced by consistent intramolecular hydrogen bonding. This conformation may play a key role in its biological activity, particularly its potential antioxidant function[16,17,18].

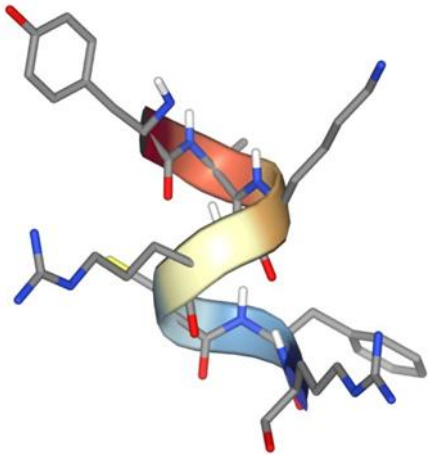

Fig 1. Peptide structure of YAKRCFR based on PEPFOLD4 simulation

Validation of the docking process was carried out between the test receptor and the native ligand to obtain the RMSD (Root Mean Square Deviation) value. The RMSD value indicates the extent of structural changes in the ligand before and after the docking process. The result obtained for receptor 1HD2 was 0.273 Å. A good RMSD value is ≤ 2, so the result meets the validation criteria, and the method used is considered valid (Figure 2)[19]. The smaller the RMSD value, the better the match between the docked ligand structure and the original structure. Once the docking method is validated, molecular docking simulations can proceed.

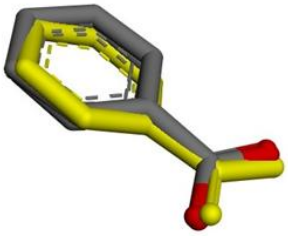

Fig 2. Position of native ligand after redocking

The molecular docking results showed that the YAKRCFR peptide and ascorbic acid interacted with the 1HD2 receptor, but with different interaction profiles in terms of both binding strength and the types of residues involved. These differences reflect the varying potential biological activities of each ligand toward the target protein. The docking results between the receptor and the test ligands produced Gibbs free energy (ΔG) values, which serve as indicators of how stable the bond or conformation is between them. The lower the ΔG value of a molecule, the more stable the molecule. The ΔG values resulting from the interactions between the YAKRCFR peptide and ascorbic acid with the 1HD2 receptor are shown in Table 2.

Table 2. Binding energy affinity from molecular docking with the 1HD2 receptor

Compound	ΔG (kcal/mol)
Native Ligand	-4.862
Ascorbic acid	-6,100
YAKRCFR	-8,100

Molecular docking analysis showed that the YAKRCFR peptide has a higher binding affinity to the 1HD2 receptor compared to ascorbic acid, based on the Gibbs free energy (ΔG) values. The ΔG value obtained for YAKRCFR was -8.1 kcal/mol, wheras ascorbic acid showed a ΔG of only 6.1 kcal/mol. A more negative ΔG value indicates a more stable and thermodynamically favorable interaction, suggesting greater potential as a ligand for the target protein [20].

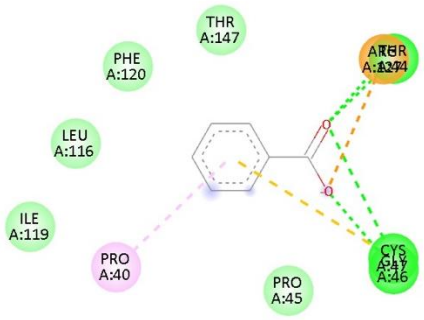

Fig 3.a. Protein and native ligan interaction

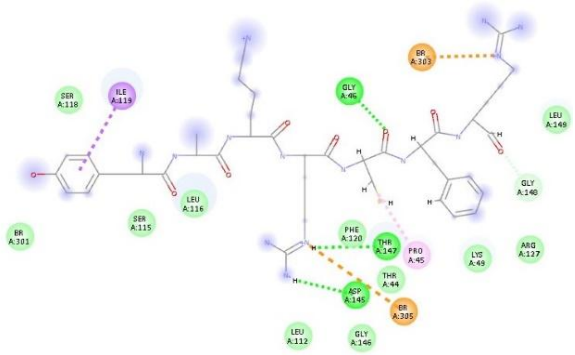

Fig 3.b. Protein and YAKRCFR interaction

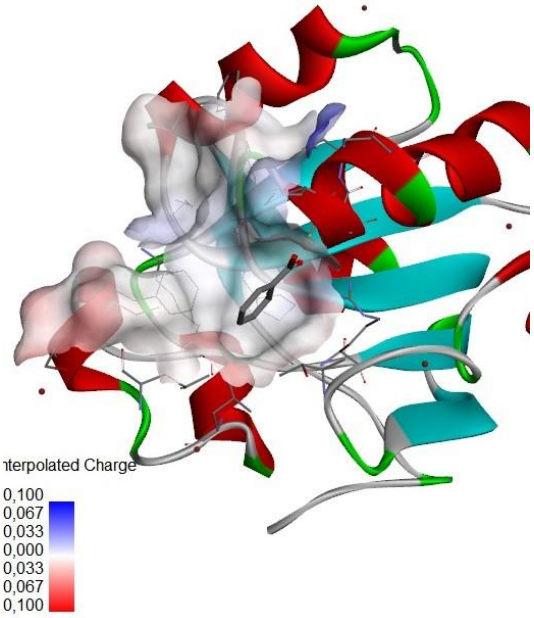

Fig 3.c. Binding site visualization of native ligand

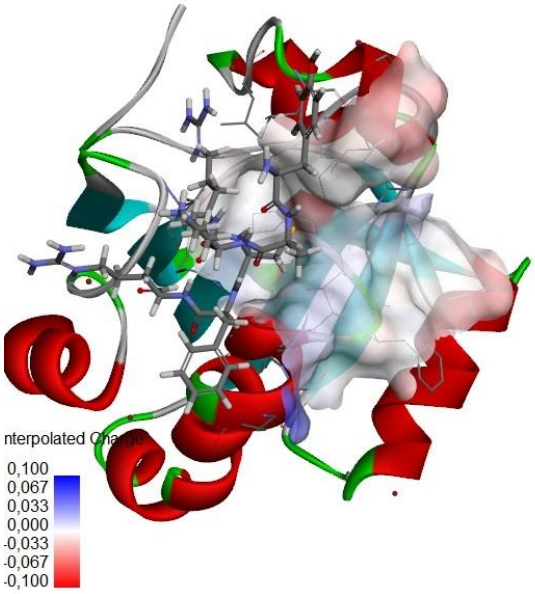

Fig 3.d. Binding site visualization of YAKRCFR

The superior interaction of the YAKRCFR peptide with 1HD2 can be explained by its structural characteristics. This peptide consists of several charged and aromatic amino acids (such as arginine, lysine, and phenylalanine), which allow for various types of interactions, including hydrogen bonding, electrostatic interactions, and van der Waals forces [21]. The peptide's chain length and conformational flexibility also enable deeper penetration into the receptor's active pocket[22]. In contrast, ascorbic acid, while still capable of interacting with the receptor via hydrogen bonds, has a smaller and more rigid molecular structure. This limits the number of interactions that can form and also reduces accessibility to active residues within the binding site. The interactions of ascorbic acid likely occur only at the surface or outer edges of the binding pocket, resulting in a ligand-protein complex that is relatively less stable compared to the YAKRCFR peptide. Based on the comparison of ΔG values and the potential molecular interactions formed, the YAKRCFR peptide can be considered to have better potential as a ligand or active compound candidate for the 1HD2 receptor compared to ascorbic acid. This makes the peptide an attractive subject for further studies in biological activity or peptide-based therapeutic

development. In addition to considering Gibbs free energy (ΔG) as an indicator of interaction stability, the presence of specific types of interactions such as van der Waals bonds and the involvement of certain amino acid residues are also important parameters for evaluating the potential biological activity of test ligands[23]. The tested YAKRCFR peptide showed that the hydrogen bond distances with the target protein fall within a favorable range, indicating the formation of strong and stable hydrogen bonds.

Aside from Gibbs free energy (ΔG), the potential biological activity of test ligands can also be assessed based on the types of interactions formed between the ligand and the target receptor (Figure 3). These include hydrogen bonds, van der Waals interactions, and hydrophobic interactions, all of which contribute to the stability of the ligand-protein complex. In particular, van der Waals interactions, although weak, play a key role in maintaining the ligand's position within the binding pocket. When the test ligand forms van der Waals interactions with key amino acid residues that are also involved in interactions with the native ligand, this suggests that the test ligand likely occupies the same binding site and may mimic the native ligand's biological mechanism[24]. The involvement of amino acid residues ILE A119 and PHE A120, which consistently appear in interactions between the protein and ligands by forming van der Waals bonds, is an important indicator in assessing whether a test ligand has the potential to produce similar biological effects. These interactions also reflect binding selectivity and affinity two crucial aspects in drug candidate development.

CONCLUSION

The YAKRCFR peptide, derived from oyster (Crassostrea rivularis), exhibited a stable α-helical structure with strong intramolecular hydrogen bonds, as predicted by PEP-FOLD4 simulations. Molecular docking analysis, validated through an RMSD value of 0.273 Å, confirmed reliable interaction modeling with the 1HD2 receptor. YAKRCFR demonstrated superior binding affinity (ΔG = −8.1 kcal/mol) compared to both the native ligand and ascorbic acid, supported by stable hydrogen bonding and van der Waals interactions, particularly involving key residues such as ILE A119 and PHE A120. These results suggest that YAKRCFR not only adopts a favorable conformation but also possesses promising potential as a bioactive compound or lead peptide in therapeutic development targeting the human peroxiredoxin-5 receptor.

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