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An In Silico Evaluation of the Anti-Wrinkling Potential of Certain Peptides in Relation to the Catalytic Domain of Matrix Metalloproteinase-1

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Abstract

Skin wrinkles are caused by the cleavage of collagen fibers by the major collagenase enzyme matrix metalloproteinase-1 (MMP-1). Peptide-based matrix metalloproteinase-1 inhibitors present a potential new therapeutic strategy to prevent MMP-1-mediated collagenolysis, which is induced by UV-induced MMP-1 overexpression. This in silico study investigated the MMP-1 inhibitory capacity of carefully selected and well-designed hexapeptides. A molecular docking method was employed to screen 14 hexapeptides. The target ligands were observed to interact non-covalently. The LYYYGP peptide sequence was found to form three hydrogen bonds (H-bonds) with amino acid (AA) residues in the catalytic domain of MMP-1. Additionally, hydrophobic interactions between these peptides and the protein were observed at certain sites. The maximum binding affinity was observed for the LYYYGP sequence (binding free energy, ΔG = -9.00 kcal/mol). These sequences exhibited binding energies comparable to those of the LSYYGP sequence (-8.48 kcal/mol) and YSGYYP sequence (-8.27 kcal/mol). The YSGYGY sequence demonstrated a lower binding affinity for the target receptor, with ΔG = -5.59 kcal/mol. This study indicates that specific peptide sequence components are crucial for forming hydrogen bonds that link proteins to peptides. Further investigation, encompassing chemical synthesis and laboratory experimentation, is requisite to substantiate the efficacy of the two hexapeptides.

Keywords: antiphotoaging, matrix metalloproteinase, molecular docking, peptides

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1 Introduction

Skin aging is caused by excessive ultraviolet (UV) radiation that interacts with chromophores, resulting in Reactive Oxygen Species (ROS). Elevated ROS levels initiate cellular damage. This phenomenon can be mitigated through the application of anti-aging care products. Anti-aging products typically contain antioxidant compounds that stimulate skin cell regeneration. These products incorporate compounds containing phenolic hydroxyl groups that interact with ROS and inhibit their activity, thereby potentially decelerating the aging process [1]. The antioxidant activity of a compound is influenced by the number and position of its hydroxyl groups. Hydroxyl groups release hydrogen ions that react with free radicals, thus potentially suppressing free radical activity [2].

Several bioactive peptides have demonstrated promising anti-aging effects [3]. Bioactive peptides are short peptides consisting of 2-20 amino acid residues [4]. Natural bioactive peptides can generally be categorized into two groups: endogenous peptides that are naturally released from precursor proteins and secreted from cells, and exogenous peptides that are produced through enzymatic hydrolysis of proteins or through biosynthesis or organic synthesis [5]. Peptides and proteins are composed of amino acids that are linked to form peptide bonds. The sequence of amino acids that constitute the peptide and protein chains determines the specific functions and characteristics of the proteins they form [6].

Anti-aging bioactive peptides often function in the mechanisms of the aging process. For instance, collagen hydrolysates (CHs) can inhibit the activity of the enzyme matrix metalloproteinase-1 (MMP-1) to reduce the degradation of collagen fibers. Active peptides can reduce skin photoaging by counteracting free radicals [3]. One of the active peptides that exhibits anti-aging activity is the linear hexapeptide short chain peptide LSGYGP (Leucine-Serine-Glycine-Tyrosine-Glycine-Proline). This peptide was isolated from tilapia fish skin gelatin hydroxylate [7]. This short-chain peptide was developed using a molecular docking approach. The role of molecular docking is significant in the selection of target compounds for synthesis. Through the design process, researchers can simulate multiple compound structure designs using a molecular docking approach through ligand-receptor binding, thus potentially conserving time, chemicals, and research costs compared to the trial-and-error method of synthesis-bioactivity testing.

2 Methods

2.1 Three-dimensional structure optimization of hexapeptides

The hexapeptides three-dimensional (3D) structure was created using Chemaxon Marvinsketch. Avogadro was used to optimise the structures. In order to optimise the three-dimensional structure of the hexapeptides with their hydrogen atom, the General AMBER Force Field (GAFF) computational approach was utilised.

2.2 Protein preparation

The MMP-1 protein (PDB code: 966C) was obtained from https://www.rcsb.org/. MMP-1 was prepared by isolating it from its natural

ligand, N-hydroxy-2-[4-(4-phenoxy-benzenesulfonyl)-tetrahydro-pyran-4-yl]-acetamide (RS2) and use Discovery Studio software to remove the water molecules.

2.3 Molecular docking validation

The molecular docking was validated using the Autodock Tools application (Autodock 4.2 and Autogrid), which involved redocking the natural ligand on the produced MMP-1 protein. Grid box coordinates (x, y, and z dimensions) were specified, with the grid centre at X = 9.166 Å, Y = -10.353 Å, Z = 38.398 Å and grid size at X = 50 Å, Y = 40 Å, Z = 40 Å. The molecular docking validation parameter was based on an RMSD value of ≤ 2.0 Å.

2.4 Docking the hexapeptides to MMP-1 protein

The optimized hexapeptides were subsequently docked to the generated MMP-1 protein utilizing the Autodock 4.2 software, employing the same grid box dimensions used for validation. The results yielded hexapeptides with the lowest energy conformation. Visualization of the molecular docking outcome was accomplished through Discovery Studio.

2.5 Data analysis

The binding energy and hydrogen bonding between hexapeptides and MMP-1 proteins were determined by the molecular docking procedure. The lower binding energy indicates that the relationship is stronger. The amino acid residues in MMP-1's pocket for interacting with hexapeptides were found to be identical to the natural ligand.

3 Results and Discussions

The legitimacy of the docking process was established by comparing the redocked ligand's position and bond alignment with those observed during the crystallisation process, as supported by an RMSD value of two [8]. According to the validation criteria (RMSD ≤ 2.0 Å), the chosen conformation had the lowest RMSD value. The variation in protein-ligand interactions in the crystal structure prior to and following docking is described by the RMSD parameter. A lower RMSD value indicates that the docked natural ligand's conformation is closer to the target protein binding site [9]. Redocking RS2 validated the use of the AutoDock4 application by forming hydrogen bond connections with residues Asn180, Leu181, Ala182, Ala184, and Glu219. This interaction profile further demonstrates how well and consistently the AutoDock4 tool replicates the binding configuration of RS2 with the MMP-1 receptor's active site.

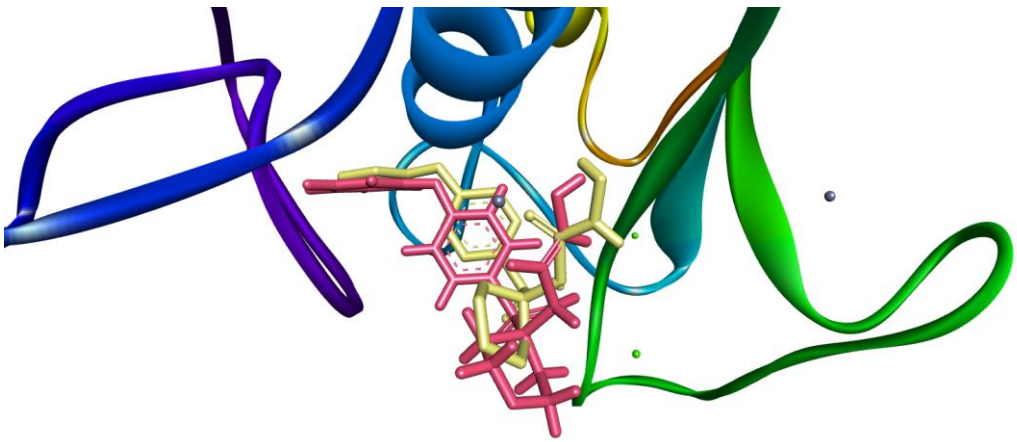

Figure 1. Superimpose of redocked ligand (yellow) and native ligand (pink).

Previous research has demonstrated that elevated ROS generation can influence MMP levels [10]. It is of interest to determine whether the hexapeptides exhibit direct interactions with MMP-1's active sites that could potentially inhibit MMP-1 activity. The structural

architectures of MMPs are similar, with primary variations occurring in the S1 pocket. The S1′ pocket of MMP-1 is characterized by its short and thin structure [11]. Molecular docking simulation can be employed to investigate the molecular interactions between MMPs and hexapeptides. Our findings indicated that hexapeptides could access the S1′-subpocket of MMP-1 and interact strongly with the enzymes. The optimized hexapeptides were docked into the MMP1 protein. The conformation exhibiting the lowest binding energy to the MMP-1 target protein formed the strongest and most stable connection. Table 1 presents the binding energies of hexapeptides to the MMP-1 protein. The lowest binding energy observed in this investigation was attributed to LYYYGP, which exhibited a binding energy of -9.00 kcal/mol.

Table 1. Bond energy and interactions of hexapeptides against MMP-1

No.	Compounds	Bond Energy (kcal/mol)	Hydrogen Bond	Hydrophobic Interactions
1	LSGYGP	7.34	ASN180, TYR210, SER239, TYR240, HIS218, GLY179, GLU219, PRO238	LEU181
2	YSGYGP	7.85	ASN180, LEU181, ALA182, TYR240, PRO238, HIS228	HIS218, HIS228, PRO238, LEU181
3	LYGYGP	7.89	ALA182, PRO238, THR241	HIS218, TYR210, HIS218, LEU181
4	LSYYGP	8.48	LEU235, TYR237, SER239, GLU219	ARG214, LEU235, VAL246
5	LSGYYP	8.12	ASN180, HIS218, ALA182, GLU219	HIS222, HIS228
6	LSGYGY	6.74	TYR240, SER239	LEU181, TYR210
7	YYGYGP	7.58	GLU219, THR241, TYR240	TYR240, VAL215, LEU181
8	YSYYGP	7.99	ASN180, LEU181, ALA182, TYR240, GLY179, HIS228	SER239, TYR240, HIS222, HIS228, LEU181, PRO238
9	YSGYYP	8.27	ASN180, LEU181, ALA182, TYR240, GLY179, PRO238, GLU219	TYR240, PRO238
10	YSGYGY	5.59	LEU181, ALA182, HIS228, GLU219, LEU235, TYR237, PRO238	LEU181, HIS218
11	LYGYGY	6.09	PRO238, ASN180, ARG214, GLU219, HIS218	HIS228, TYR240, PRO238, LEU181, ARG214, LEU235
12	LSYYGY	6.08	SER239, ALA182, ASN180, TYR237	HIS218, LEU181, ARG214, LEU235, PRO238
13	LSGYYY	6.19	ASN180, VAL215, TYR240, ALA182, ALA234, LEU235	HIS218, HIS228
14	LSYYYP	7.88	TYR210, TYR240, VAL215	LEU181, TYR237, PRO238, ALA182, VAL215
15	LYYYGP	9.00	ASN180, TYR237, ALA182	LEU181, PRO238
16	RS2 (Native Ligand)	11.06	ASN180, LEU181, ALA182, ALA184, GLU219	LEU181, ALA182, VAL215, ARG214

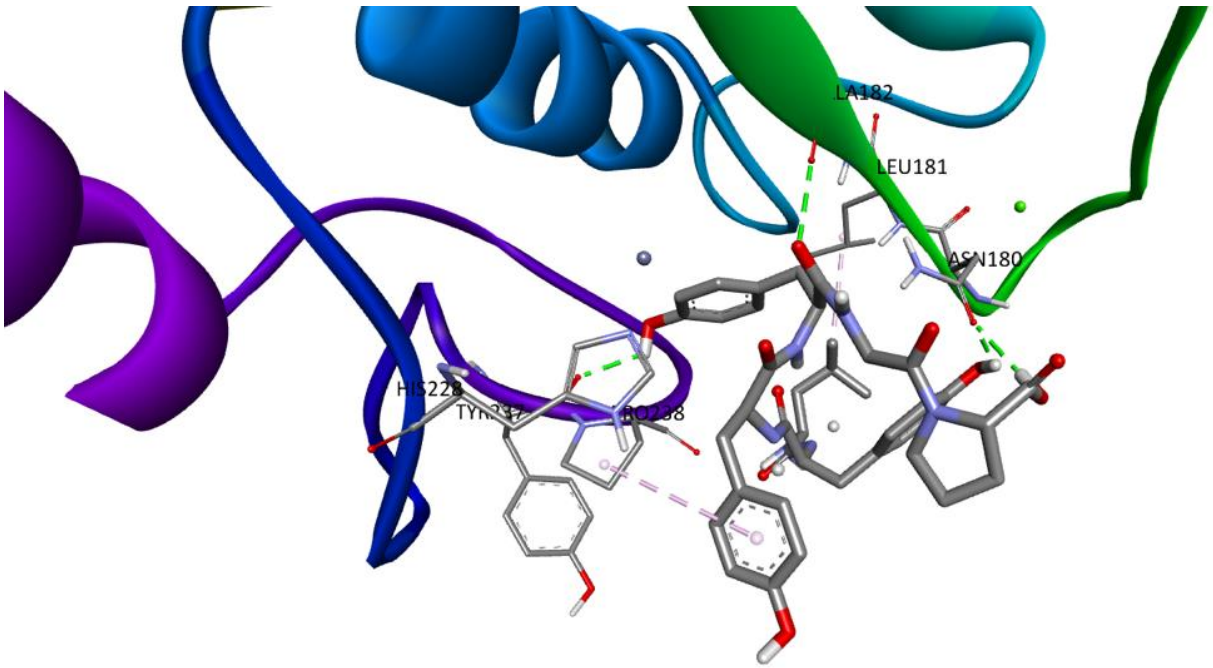

Figure 2. LYYYGP pose interaction against MMP-1

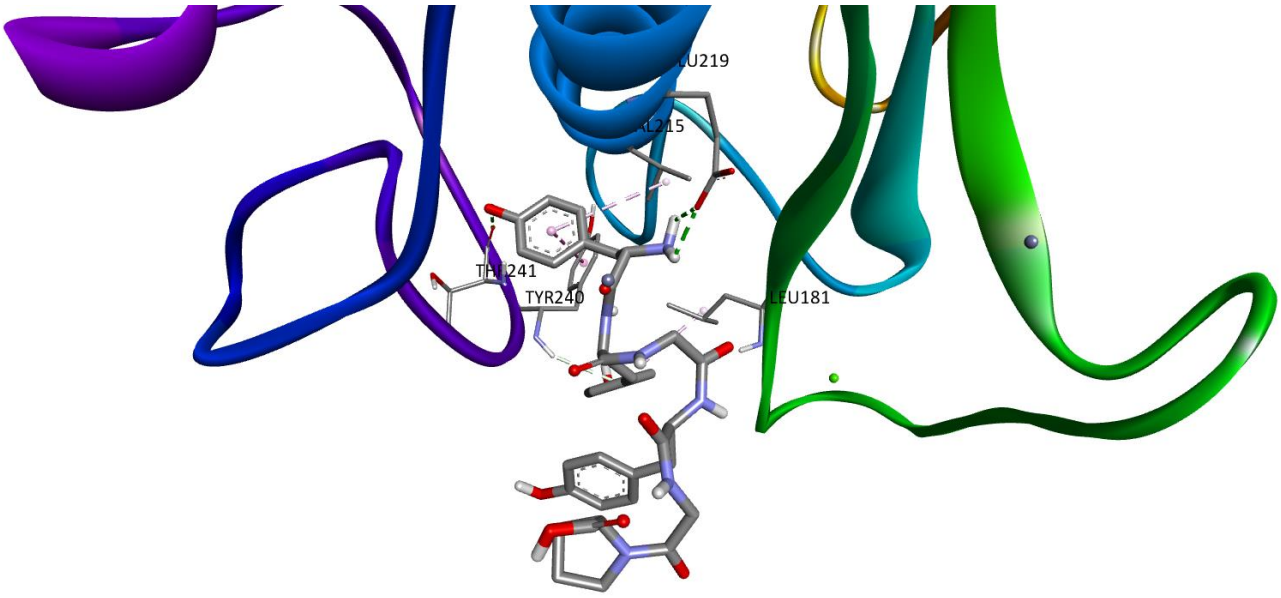

Figure 3. YYGYGP pose interaction against MMP-1

Hydrogen bond interactions play a pivotal role in molecular docking, exerting significant influence on the binding affinity and stability of ligand-protein complexes. These interactions can substantially impact the outcomes of docking studies, as they contribute to the overall energy landscape of the binding process. The binding of LYYYGP and YYGYGP to the active sites of MMP-1 was shown in Figure 2 and Figure 3. Both hexapeptides accessed the tight S1′-subpocket and interacted strongly with the enzymes. The docking simulation of LYYYGP and YYGYGP at MMP-1 active sites in the presence of Zn(II) yielded the optimal docking pose, with total scores of 9.00 and 7.58, respectively (Table 1). Table 1 displayed all conceivable direct hydrogen bond interactions. After docking, the hexapeptide LYYYGP formed hydrogen connections with MMP-1 residues such as ASN180, TYR237, and ALA182. Meanwhile, the hexapeptide YYGYGP shows hydrogen interactions with amino acid residues GLU219, THR241, and TYR240 as well as hydrophobic interactions with residues TYR240, VAL215, and LEU181.

The flexible-hydrogen interaction model in molecular docking accounts for hydrogen bond flexibility by discretizing interaction spheres of donors and acceptors, optimizing hydrogen alignment, and evaluating tautomeric states, enhancing the accuracy of ligand placement and scoring during docking processes [12]. The contact force of hydrogen bonds is vital in stabilising docking complexes and catalytic processes. Following docking, the peptide YYGYGP made three hydrogen bonds and three hydrophobic contacts with MMP-1 residues. Tyr 240 and Thr 241 were previously identified as important hydrophobic and polar amino acids in MMP-1's S1 pocket [13]. Our results demonstrated that only YYGYGP may form hydrogen bonds with MMP-1 Tyr 240 and Thr 241. The findings indicated that YYGYGP successfully interacted with the active sites of MMPs, perhaps increasing its inhibitory MMP actions. Furthermore, LYYYGP and YYGYGP contained a hydrophobic amino acid (Pro) at the carboxy terminus, an aromatic group in Tyr, and side chains of Gly and Leu. Tyrosin aromatic group may accommodate the S1′ pocket of MMP-1, increasing the inhibitory MMPs' capability [14].

4 Conclusions

Molecular docking results of the fifteen hexapeptides showed different results. Energy affinity approach and essential interaction approach showed that the hexapeptide sequences LYYYGP and YYGYGP may have potential as inhibitors of MMPs enzymes, especially MMP-1. Further evidence, such as

organic synthesis and in vitro tests, are needed to confirm the activities of the two hexapeptides.

5 Declarations

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5.3 Authors Contribution

A.R, H.A, S.S, and D.D.R.T: conceptualization, methodology, conducting the research and writing the original article, field data collection, data analysis, and revision. I. T., N.Y.P.O, and M.R: Field data collection, data analysis and revision.

5.4 Conflict of Interest

The authors declare no conflicts of interest.

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