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REVIEW

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In silico molecular docking of lutein as anti-photoaging agent

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Abstract: The accumulation of UV exposure resulted in the loss of skin elasticity, and the appearance of wrinkles on the skin is commonly known as photoaging. Matrix metalloproteinase-1 (MMP-1) is an enzyme that degrades type I and III fibrillar collagen. This study aims to determine the mechanism of MMP-1 inhibition by lutein, a carotenoid compound with high antioxidant activity, using *in silico* molecular docking. This study was conducted by optimization of lutein structure using HyperChem 8, preparation of MMP-1 (PDB ID: 966C) using Chimera 1.10.1, validation of the method, and docking lutein against MMP-1 using Autodock 4.2. The results showed lutein had binding energy of -12.28 kcal/mol, lower than RS2 native ligand (-10.83 kcal/mol). The hydrogen bond formed between lutein and MMP-1 through HIS 228 residue. To conclude, lutein may be developed as an anti-photoaging agent by inhibiting the MMP-1.

Keywords: lutein, MMP-1, molecular docking, photoaging

Introduction

Excessive sunlight can damage the skin's epidermal tissue, causing the loss of skin elasticity and the appearance of wrinkles as a marker of photo-aging on the skin [1]. Wrinkles on the skin are one of the characteristics of decreased skin cell function due to proteolytic extracellular matrix (ECM) degradation [2]. ECM plays a role in forming the outermost part of the skin, consisting of fibroblasts and proteins such as collagen. Collagen degradation is regulated by matrix metalloproteinase (MMPs). Increased MMP activity is an essential factor contributing to age-related changes in the skin. The MMP in the dermis is responsible for the activity of the ECM collagen fiber network. The photo-aging mechanism due to UV exposure can cause increased MMP-1 activity, degrading collagen types I and III [3].

MMP-1 induction alters the balance of the ECM components; therefore, an MMP-1 inhibitor is needed. MMP-1 inhibitors are commonly used in a variety of cosmetics. However, synthetically formulated MMP-1 inhibitors may negatively impact their long-term application [4]. The utilization of natural resources, such as lutein, can protect the skin from light exposure.

Lutein is a carotenoid group with antioxidant effects (Figure 1). Lutein acts as an antioxidant by scavenging singlet oxygen compounds and other free radicals. Lutein in the skin also acts as a photo protector that can absorb blue light to protect the skin from UV rays and visible rays [5]. Potential anti-photoaging activity can be further identified for lutein by *in silico* molecular docking, a method to predict the interaction of a ligand and a protein [6]. Therefore, this study aims to check the interaction between lutein and MMP-1 through *in silico* molecular docking.

Methods

Three-dimensional structure optimization of lutein

The lutein's three-dimensional (3D) structure of the lutein (PubChem CID: 5281243) downloaded from https://pubchem.ncbi.nlm.nih.gov/ was optimized using the HyperChem 8 program. The 3D structure optimization of the lutein with its hydrogen atom was carried out using the AM1 semi-empirical computational method, as well as single point calculations and geometry optimization.

Protein preparation

The MMP-1 protein (PDB ID: 966C) was downloaded from https://www.rcsb.org/. The MMP-1 preparation process was carried out by separating

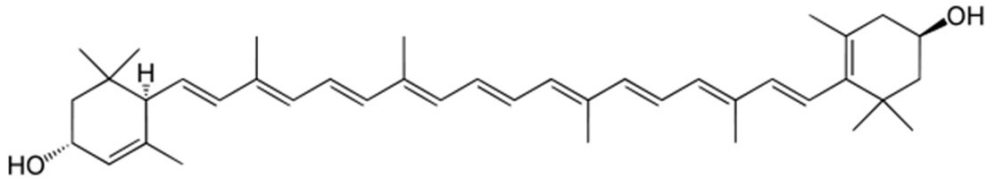

Figure 1. Two-dimensional structure of lutein

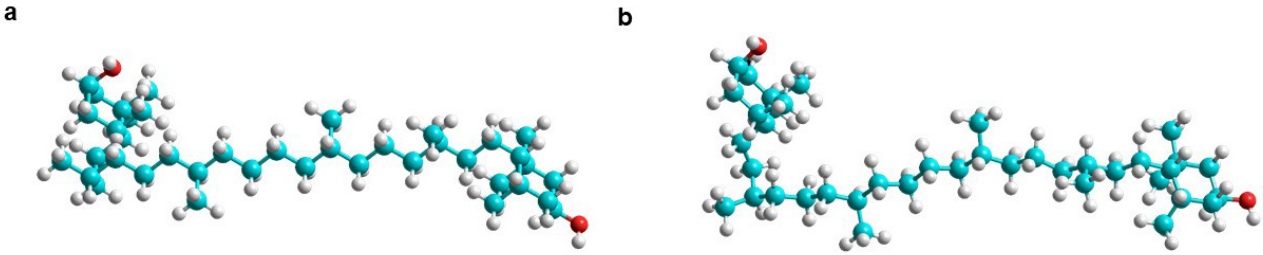

Figure 2. Three-dimensional structure of lutein. (a) single-point calculation of lutein structure, (b) geometry optimization of the lutein structure

MMP-1 from its native ligand N-hydroxy-2-[4-(4-phenoxy-benzenesulfonyl)-tetrahydro-pyran-4-yl]-acetamide (RS2) using Chimera 1.10.1 software [7].

Molecular docking validation

The validation of the molecular docking was carried out using the Autodock Tools application (Autodock 4.2 and Autogrid) by redocking the RS2 native ligand on the prepared MMP-1 protein. The grid box coordinates (x, y and z dimensions) had been set including the grid center at X = 9.166 Å, Y = -10.353 Å, Z = 38.398 Å, and grid size at at X = 62 Å, Y = 40 Å, Z = 40 Å. The validation parameter of molecular docking was based on the value of root mean square deviation (RMSD) with a value ≤ 3.0 Å [8].

Docking lutein to MMP-1 protein

The optimized lutein was then docked to the prepared MMP-1 protein using the Autodock 4.2 program with the same grid box size for validation. The results produced lutein with the lowest energy conformation [9].

Data analysis

The molecular docking process resulted in the binding energy and the hydrogen bonds between lutein and MMP-1 proteins. The stronger bond formed is indicated by the lower binding energy. The similarity of the amino acid residues involved in interaction indicated the similar pocket of RS2 native ligand of MMP-1 protein to lutein.

Results

Three-dimensional structure optimization of lutein

The optimization of the 3D structure of lutein was carried out using the AM-1 semi-empirical method using HyperChem 8 program (Figure 2). A single-point calculation and geometry optimization were performed in this process. Single point calculation determines the total molecular energy of the structure without optimizing the structure of the test compound. Geometry optimization minimizes the total energy of the test compound marked by a decrease in the structure's total energy. The total molecular energy of the single point calculation of lutein was -9541.96 kcal/mol and decreased to -11309.61 kcal/mol after geometric optimization indicated that the optimization was successful in obtaining a stable structure and lower energy.

MMP-1 protein preparation

The preparation of MMP-1 protein (PDB ID: 966C) was carried out by separating from RS2 native ligand using Chimera 1.10.1. The protein preparation obtained the pocket cavity for the docking process and the structure of the native ligand for validation process (Figure 3).

Molecular docking validation

The validation step was purposed to determine the conformational similarity between RS2 native ligand and MMP-1 protein by crystallography compared with experimental results. The validation process results

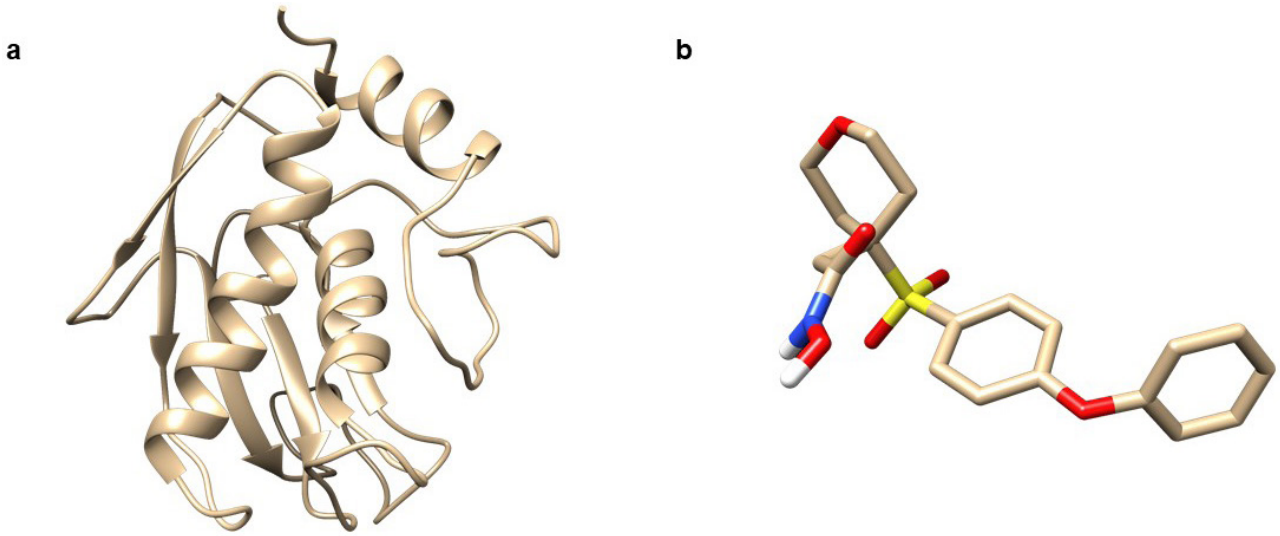

Figure 3. Three-dimensional structure of MMP-1. (a) MMP-1 without native ligand, (b) native ligand RS2 of MMP-1

Table 1. The result of molecular docking method validation

Protein	Ligand	Conformation	Binding energy (kcal/mol)	RMSD (Å)	Amino acid residues	Groups in hydrogen bonds
MMP-1	RS2	1*	-10.83	1.00	HIS 228 HIS 218 HIS 222	HE2-O31 HE2-O31 HE2-O31
		2	-8.60	2.20	LEU 181 ASN 180 ALA 182	HN-O26 HD21-O33 HN-O26
		3	-10.62	1.03	HIS 218 ALA 182 LEU 181 HI S228	HE2-O31 HN-O25 HN-O26 HE2-O31
		4	-8.91	2.2	ALA 182 HIS 218 HIS 228	HN-O25 HE2-O38 HE2-O38
		5	-9.15	1.39	LEU 181 HIS 218 HIS 228 ASN 180 HIS 222	HN-O25 HE2-O33 HE2-O33 HD21-O38 HE2-O33
		6	-8.98	2.66	ALA 182 TYR 240 LEU 181	HN-O25 HN-O33 HN-O26
		7	-10.68	1.06	HIS 218 HIS 228 ALA 182	HE2-O31 HE2-O31 HN-O25
		8	-9.09	2.7	TYR 240 LEU 181 ASN 180	HN-O38 HN-O26 HD21-O33
		9	-9.05	2.08	ALA 182	HN-O31
		10	-9.42	2.62	HIS 228 ALA 182 HIS 218	HE2-O38 HN-O25 HE2-O38

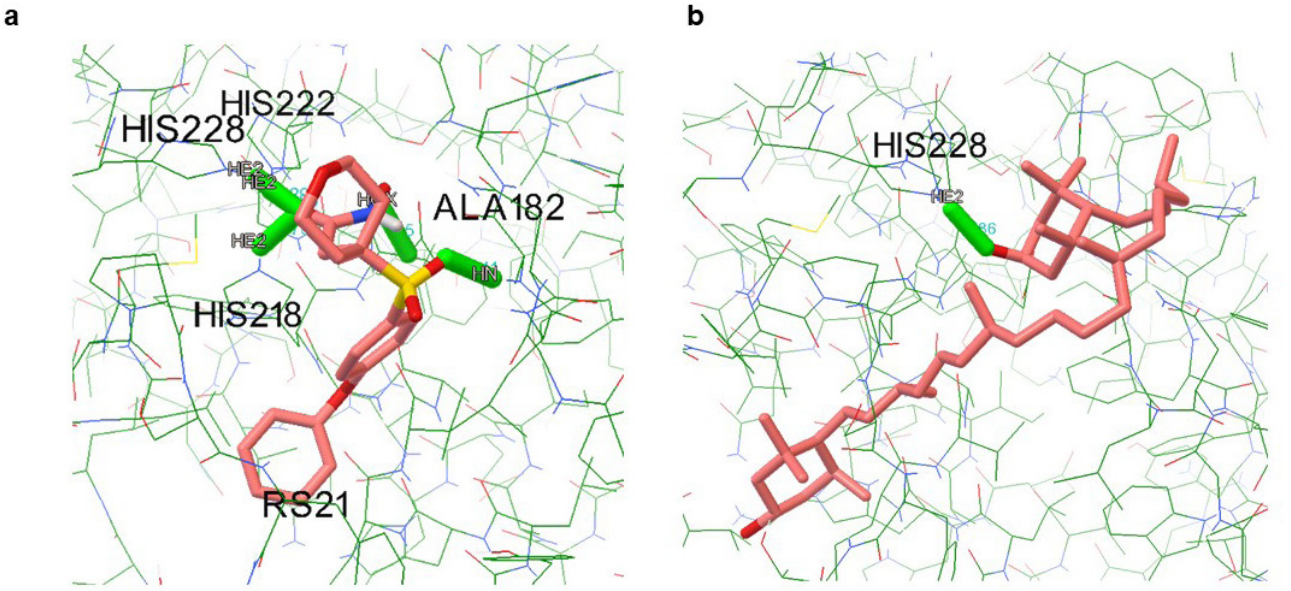

Figure 4. Visualization of the interaction. (a) visualization of RS2 native ligand interactions with MMP-1, (b) visualization of lutein interactions with MMP-1.

were ten conformations of RS2 native ligand to MMP-1 protein binding sites with different RMSD values and binding energies (Table 1). The selected conformation has the lowest RMSD value and meets the validation requirements (RMSD ≤ 3.0 Å). The RMSD parameter describes the changing of protein-ligand interaction in the crystal structure before and after docking [13]. The lower the RMSD value, the closer the conformation of the docked native ligand to the position of the target protein binding site [8]. The conformation 1 with an RMSD value of 1.0 Å suggested that the validation step was valid, and the binding energy of this conformation was -10.83 kcal/mol.

Docking lutein to MMP-1 protein

The optimized lutein was docked to the MMP-1 protein and produced ten conformations. The conformation with the lowest binding energy to the MMP-1 target protein showed the strongest and most stable bond. The binding energies of lutein to the MMP-1 protein are shown in Table 2**.** The lowest binding energy obtained in this study was conformation 2 with the binding energy of -12.28 kcal/mol. Lutein interacted with MMP-1 protein by hydrogen bonds through HIS 228 residue, similar to the hydrogen bonds formed by RS2 native ligand and MMP-1 protein (Figure 4).

Discussion

Lutein showed activity as an anti-photoaging agent with the mechanism of inhibition of the MMP-1 protein. Our results showed that lutein has an affinity for the MMP-1 with binding energy -12.28 kcal/mol, lower than RS2 native ligand of MMP-1 protein (-10.83 kcal/mol). In addition, lutein interacted with the MMP-1 protein by hydrogen bonding through HIS 228 residue. This interaction is similar to the hydrogen bonding formed by the RS2 native ligand and the MMP-1 protein.

The main mechanism of the lutein photoprotective effect is the presence of conjugated double bonds. This structure can absorb destructive light such as UV radiation [10]. The *in silico* study of astaxanthin derived from radio-resistant bacterium *Deinococcus* sp. strain WMA-LM9 showed that this carotenoid had a high binding affinity to MMP-1 protein with a binding energy of -10.5 kcal/mol [11]. Another *in vivo* study regarding 16-week supplementation with mixed carotenoids (beta-carotene and lycopene) and proanthocyanidins has been reported to reduce UV-dependent expression of MMP-1 [12].

The *in vitro* study conducted by Philips *et al.*, 2007 showed that lutein selectively inhibits MMP-1 expression, which has implications for strengthening ECM [13]. The expression of MMP-1 and NF-κB demonstrated the protective effect of carnosic acid and lutein on UV irradiation in HaCat keratinocyte

Table 2. The molecular docking result of lutein on target proteins MMP-1.

Protein	Ligand	Conformation	Binding energy (kcal/mol)	RMSD (Å)	Amino acid residues	Groups in hydrogen bonds
MMP-1	Lutein	1	-10,58	0.00	-	-
		2*	-12,28	0.00	HIS228	HE2-O
		3	-9,1	1.57	-	-
		4	-9,66	1.49	-	-
		5	-8,1	1.81	-	-
		6	-10,75	1.03	-	-
		7	-7,46	0.00	-	-
		8	-10,55	1.13	-	-
		9	-10,69	1.25	-	-
		10	-10,71	1.23	ALA184	HN-O

cell lines. UV irradiation induces MMP-1 expression through an inflammatory reaction via phosphorylation of NF-κB. As a result, carnosic acid and lutein significantly suppressed the expression levels of MMP-1 and NF-κB [14]. Overall, these studies support the evidence that lutein has anti-photoaging activity by inhibiting MMP-1, which could be useful in cosmetic and pharmaceutical preparations.

Conclusion

Lutein has an affinity for the target protein MMP-1 indicated by the binding energy of -12.28 kcal/mol. In addition, the hydrogen bonding interaction of MMP-1 protein with RS2 native ligand and lutein is similar through HIS 228 residue. Lutein has the potential as an anti-photoaging agent through the inhibition of the MMP-1.

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Declaration of interest

The authors declare no conflict of interests.

Author contributions

IGBK, PDF, NPLL conceptualized the study design, PDF and IAYPS investigated the data, IGBK and PDF wrote original draft, IGBK, PDF, IAYPS reviewed and edited final version, IGBK looked for the funding, NPLL supervised all experiments. All authors have read the final manuscript.

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