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Integration of molecular docking and molecular dynamics simulations for studying potential tyrosinase inhibitors from *sargassum* genus

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Abstract. The copper-dependent enzyme tyrosinase is vital for the creation of melanin, the pigment responsible for coloration in skin, hair, and eyes. Because of the contribution of tyrosinase to unwanted skin darkening, the identification of secure and potent natural inhibitors is a major goal for scientists in the cosmetic and pharmaceutical industries. In this work, a dataset of 71 compounds originated from *Sargassum* genus has been investigated the ligand-binding affinity to tyrosinase via atomistic simulations. The compounds including difucodiphlorethol A and pseudotrifuhalol A were suggested that can inhibit GSK-3β via molecular docking and molecular dynamic simulations. The residues including His61, His259, Asn260, His263, Arg268, Met280, Gly281, Ser282 and Val283 play a crucial role in the ligand-binding process Furthermore, the toxicity prediction also indicates that these compounds would adopt less toxicity.

Keywords: molecular docking, molecular dynamics, *Sargassum*, tyrosinase inhibtors

Classification numbers: 1.2.1, 1.2.4

1. INTRODUCTION

Skin pigmentation disorders often cause significant aesthetic concerns, particularly among women. In Asia, consumers spend billions of US dollars annually on skin-lightening products

aimed at reducing sunspots, freckles, and melasma [1]. Melanin, a natural pigment in the human body, imparts color to the skin, hair, and eyes [2]. Melanocytes, specialized epidermal cells, produce melanin within organelles called melanosomes. Melanin synthesis occurs in melanosomes following the activation of tyrosinase, a crucial enzyme in this process [3]. Tyrosinase activity is stimulated by UV radiation, DNA damage (such as thymidine dinucleotides formed by UV exposure), melanocyte-stimulating hormone (MSH), and growth factors like bFGF and endothelin [4]. Therefore, melanin inhibition can be achieved by either suppressing tyrosinase activation or inhibiting its activity post-activation. Many skin-lightening and anti-melasma products currently utilize tyrosinase inhibitors as active ingredients. However, concerns regarding the safety and efficacy of common tyrosinase inhibitors like hydroquinone and arbutin have been raised [5, 6]. Consequently, the search for natural tyrosinase inhibitors remains a significant focus for the pharmaceutical and cosmeceutical industries.

The *Sargassum* genus has been recognized as a rich source of diverse compounds with significant bioactivities [7]. Numerous studies have reported the isolation of various bioactive metabolites from *Sargassum* species, demonstrating their potential in various applications such as anti-inflammatory, antioxidant, anticancer, v.v. [8-10]. Recent investigations have focused on exploring the skin-lightening and anti-melasma properties of these compounds, suggesting a promising avenue for the development of novel cosmeceutical products. The identification of tyrosinase inhibitors from *Sargassum* extracts holds great potential for addressing skin pigmentation disorders [11].

Computer aided drug design (CADD) offers a robust methodology for swiftly and precisely evaluating vast libraries of compounds for potential enzyme inhibitors. Its origins can be traced back to October 5, 1981, with the public ation of "Next Industrial Revolution: Designing Drugs by Computer at Merck" in Fortune magazine [12]. The impact of CADD continues to expand, driven by the significant reduction in time and costs associated with new drug development [13, 14]. CADD facilitates both the identification of novel inhibitors and the repurposing of existing drugs. CADD has played a role in the discovery of several marketed drugs, including dorzolamide, saquinavir, ritonavir, and indinavir [15, 16]. A core aspect of CADD involves utilizing computational techniques to identify potential inhibitors with strong binding affinity to a protein target. Therefore, the precise calculation of ligand-binding free energy is of utmost importance [17]. To address this challenge, researchers have developed various strategies, encompassing physics-based and knowledge-based approaches [18-20]. Integrating these methodologies can further enhance the efficacy of CADD.

In this study, we aim to use a combination of molecular docking and molecular dynamics simulation to search for potential tyrosinase inhibitors originated from *Sargassum* genus. In particular, a set of compounds isolated from *Sargassum* genus rapidly screened for ligand-binding affinity against tyrosinase. In the next stage, we performed atomistic simulations to refine the docking results and gain physical insights into the protein-ligand binding process. The findings of this study will provide a valuable foundation for directing future experimental investigations aimed at developing potential therapeutic agents for dermatological conditions.

2. MATERIALS AND METHODS

2.1. Protein and ligands preparation

The X-ray crystallographic model of tyrosinase enzyme was achieved from RCSB Protein Data Bank (PDB ID: 2Y9X) [21]. Its native inhibitor, tropolone, is selected as a reference ligand. A dataset of 71 compounds originated from *Sargassum* genus were collected from

previous literatures [22, 23]. Their structures are provided in Supporting information. The three-dimensional structures of studied compounds were prepared using MarvinSketch 19.27.0 and PyMOL 1.3.r1 [24]. Subsequently, geometry minimization and quantum chemical calculations were conducted at the B3LYP/6-31g(d,p) level using Gaussian 09 [25]. Proteins and ligands were prepared for docking using AutoDock Tools 1.5.6rc3 (ADT) [26]. The protein structures were prepared in order to obtain the correct ionization and tautomeric states of amino acid residues. To create a free receptor, water molecules were removed from the protein, then polar hydrogen atoms, default Kollman charges and solvation parameters were allocated to the protein atoms. ADT assigned the rigid roots to the ligand automatically, all other bonds were allowed to be rotatable. Since ligands are not peptides, Gasteiger charge was assigned and then nonpolar hydrogens were merged.

2.2. Molecular docking simulations

The molecular docking study utilized AutoDock 4.2.6 with Lamarckian genetic algorithm for searching the optimized dock pose together with a scoring function to calculate the binding affinity. The search space was restricted to a grid box size of 50 × 50 × 50 in x, y, and z dimensions, which was centered on the colchicine binding sites of protein with x, y, and z coordinates of -1.694, 28.955 and -41.782 Å, respectively. The spacing between grid points was 0.375Å. AutoDock was run by using parameters as follows: GA population size, 300; maximal number of energy evaluations, 25,000,000; and the number of generations, 27,000. A maximal number of 50 conformers were considered for each molecule, and the root-meansquare (RMS) cluster tolerance was set to 2.0 Å in each run. From the most favored cluster, the ligand conformation for further analysis was selected on the basis of lowest free binding energy.

2.3. Molecular dynamic simulations

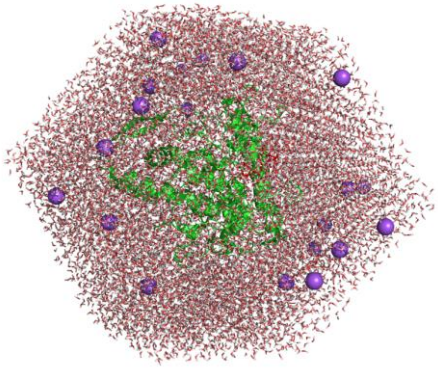

Figure 1. The MD conformations of tyrosinase + inhibitor systems in solution

The GROMACS package was utilized to simulate the behavior of the tyrosinase + inhibitors complex in solution [27]. In particular, tyrosinase/neutralized ions, water molecules, and inhibitors were parameterized via Amber99SB-iLDN [28], TIP3P water model [29], and general Amber force field [30], respectively. Among these, the information of marine compounds was obtained via quantum chemical calculations using the double hybrid functional B3LYP, basis set 6-31G(d,p), and implicit solvent (ε = 78.4). Additionally, the atomic charges of the ligands were calculated using the restrained electrostatic potential method [30]. The sEH complex was positioned in a dodecahedron box measuring 6.3 × 6.3 × 6.3 nm (Figure 1) and simulated under periodic boundary conditions [31]. The system comprises of ca. 28 000 atoms totally.

Furthermore, the solvated complex was minimized and equilibrated via the steepest descent method, NVT, and NPT simulations. In particular, the C_α atoms were positionally fixed via a small harmonic potential. The final conformation obtained from the NPT simulations was used as the starting structure for the MD simulations, which were run for a duration of 20 ns. During which, the C_α atoms of tyrosinase were also restrained via a small harmonic potential. The simulations were conducted three times to ensure thorough sampling during the simulation process.

2.4. ADMET studies

Open bioactivity prediction online server Molinspiration and ProTox-II were utilized to evaluate the drug-like properties and the acute toxicity of all the research compounds. The admetSAR database was utilized to calculate the absorption, distribution, metabolism, elimination, and toxicity (ADMET) indexes of the studied compounds.

2.5. Analysis tools

The results from the AutoDock modeling studies were analyzed using PyMOL and Discovery Studio Visualizer. PyMOL was used to calculate the distances of hydrogen bonds as measured between the hydrogen and its assumed binding partner. A hydrogen bond (HB) is defined if the angle of an acceptor (A)–hydrogen (H)–donor (D) is larger than 135 with the distance from A to D is smaller than 0.35 nm. The ligand's protonation state was determined using the Chemicalize tools, a web application created by ChemAxon. The root-mean-square deviation (RMSD) of atomic positions was assessed using the "gmx rms" tool from GROMACS.

3. RESULTS AND DISCUSSION

3.1. Molecular docking results

Tyrosine enzyme is the rate-limiting enzyme involved in the synthesis of melanin. In the recent years, the tyrosinase inhibition in melanin synthetic pathway has attracted interests to the search for skin-whitening agents. In this study, the molecular docking simulation was conducted to investigate the potential inhibition activities of 71 compounds originated from *Sargassum* genus against tyrosinase enzyme (PDB ID: 2Y9X). Molecular docking is a useful tool to quickly find, for each protein interacting with the ligand, the optimal value of the score function. The objective of any docking calculation is to find the best pose, which corresponds to the lowest energy. AutoDock4 is among the most popular docking software with over 6,500 citations since 2010, thus, it is utilized in searching for potential inhibitors of tyrosinase enzyme. To validate the docking procedure, the co-crystallized ligand was redocked to ensure proper binding interactions with respect to those reported in the original state. The docking result is considered reliable when the RMSD value does not exceed 2.0 Å. Obtained results show that the docked pose of tropolone with the lowest binding free energy was compared with its native structure based on its RMSD value, which was 0.444 Å (Figure 2). This result suggests that the procedure and the set parameters were reproducible and appropriate for further docking simulation.

The inhibitory potential of studied compounds against tyrosinase enzyme was then investigated. According to the ranking criteria of AutoDock, the more negative docking energy suggests a higher binding affinity of the compound toward the targeted receptor [32]. Dock scores of studied ligands are presented in Table S1.

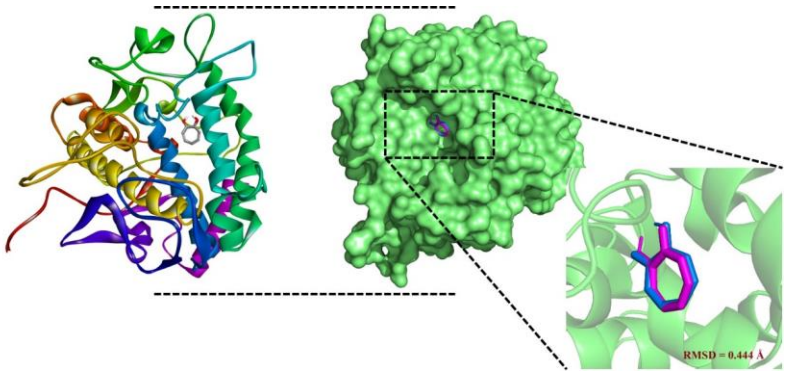

Figure 2. Dock pose of studied tropolone (blue) and native tropolone (magenta) in the active site of tyrosinase enzyme (PDB ID: 2Y9X)

Table 1. Binding-free energy and residue interactions of the potent compounds against tyrosinase enzyme

ID	Compound name	Binding free energies (kcal/mol)	H-bond interacting residues (preMD)	H-bond interacting residues (MD refined)
D11	difucodiphlorethol A	-13.62	Glu256, Gly281, Ser282	Arg268, Met280
D45	pseudotrifuhalol A	-13.99	Asn260, Arg268, Met280, Val283	Met280
	tropolone	-12.35	ND	ND

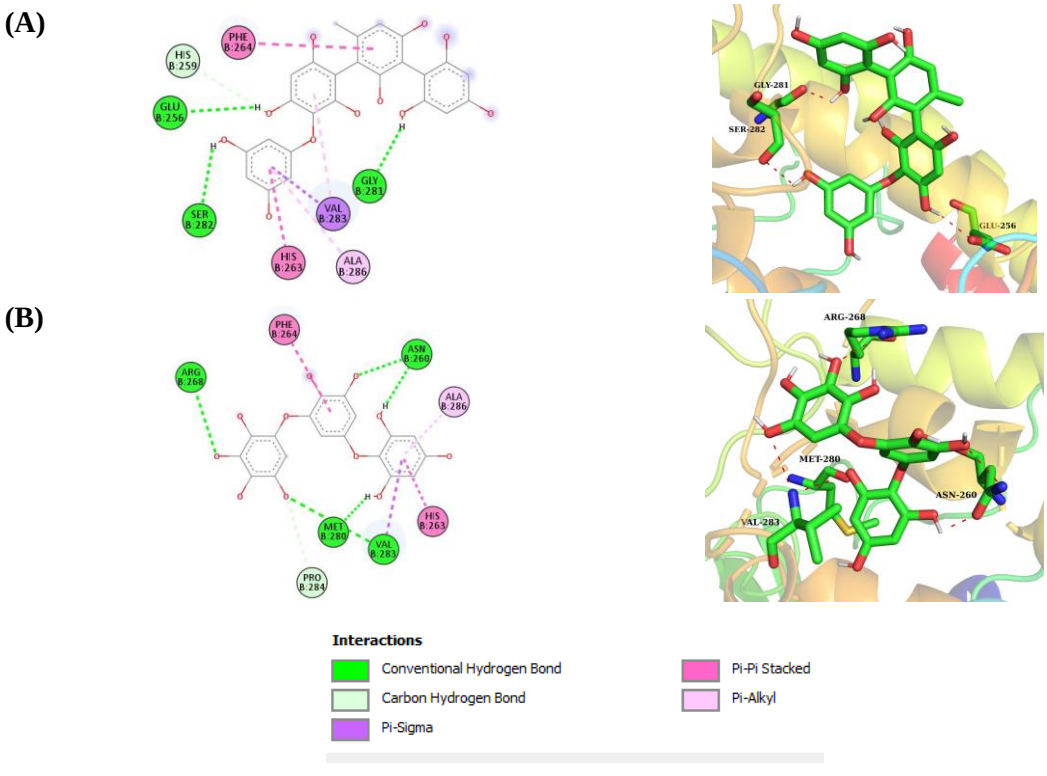

Figure 3. Interaction between the ligand difucodiphlorethol A (A) and pseudotrifuhalol A (B) in the complex with tyrosinase obtained via AutoDock4 docking package

Obtained results indicated that reference ligand tropoline docked to tyrosinase enzyme with a dock score of -12.35 kcal/mol, thus, any ligands with docking energy close to this threshold would be assumed to exhibit high binding affinity toward the targeted protein. It is indicated that, the docking energy ranged from -14.06 to -4.67 kcal/mol. Notably, compounds **D11** (difucodiphlorethol A), **D45** (pseudotrifuhalol A) are the top two potential ligands whose docking energies greatly exceeded those of reference compounds (-13.62; -13.99 kcal/mol, respectively). The binding-free energies, interaction type, and residues participating in interaction of two potent molecules are tabulated in Table 1.

The binding pose between top ligands to tyrosinase enzyme was estimated via PyMOL 1.3r1 and shown in Figure 3. Among these, the tyrosinase residues including Glu256, Gly281, Ser282 form 3 hydrogen bond (HB) contacts to difucodiphlorethol A. Compound pseudotrifuhalol A adopts 4 HB contacts to four residues of targeted enzyme involving Asn260, Arg268, Met280, Val283.

3.2. Molecular dynamics studies

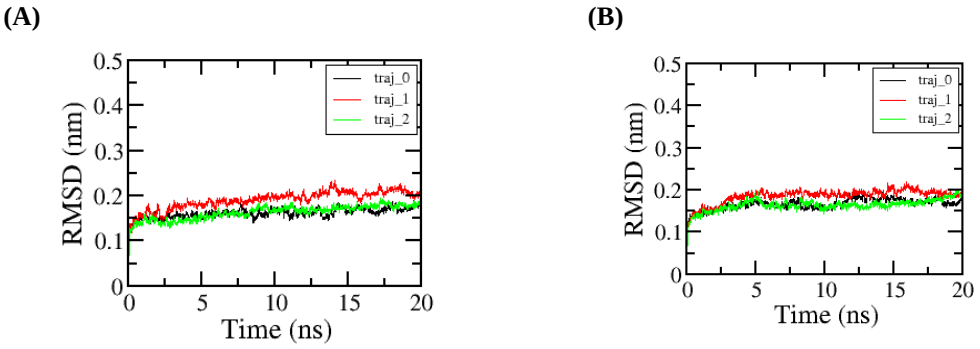

Figure 4. All-atoms RMSD of tyrosinase with difucodiphlorethol A (A) and pseudotrifuhalol A (B) over 3 independent MD simulations of 20ns

Although docking is rapid and frequently used for initial stage of virtual screening, however, docking results have limitations. In brief, the molecular docking approach typically applies several constraints to improve computational speed. Common limitations in molecular docking simulations include the absence of receptor dynamics, restricting the number of ligand trial positions, and using an implicit water model, among others. Molecular dynamic simulations were thus required to be performed to refine the results.

Each MD simulation with a length of 20ns was carried out to turn the tyrosinase + inhibitor complex into relaxed states, in which the docked conformations were employed as the initial structure of MD simulations. The outcomes, as displayed in Figure 4, illustrate that all examined systems reached equilibrium states shortly after 5 ns of MD simulations with RMSD variations around 0.2 nm.

This stability suggests minimal structural perturbations upon potential molecules binding, supporting the preservation of tyrosinase′s structural integrity within the timeframe of the simulations. The docking conformation between two potent ligands to tyrosinase enzyme are displayed Figure 5. It is observed that, difucodiphlorethol A forms 2 hydrogen bonds with Arg268, Met280 meanwhile pseudotrifuhalol A created one HB towards tyrosinase.

In addition, the equilibrated snapshots of tyrosinase and potential inhibitors were collected to probe the intermolecular SC (sidechain) and HB (hydrogen bond) contacts between ligands

and individual tyrosinase residues during MD simulations. The list of tyrosinase residues having SC/HB contacts to each potential inhibitor over equilibrated snapshots were reported in Table S2 of the Supporting Information. Besides, the residues forming both SC and HB to potential inhibitors were mentioned in Figure 6. It may argue that these residues including His61, His259, Asn260, His263, Arg268, Met280, Gly281, Ser282 and Val283 are crucial factors controlling the ligand binding process.

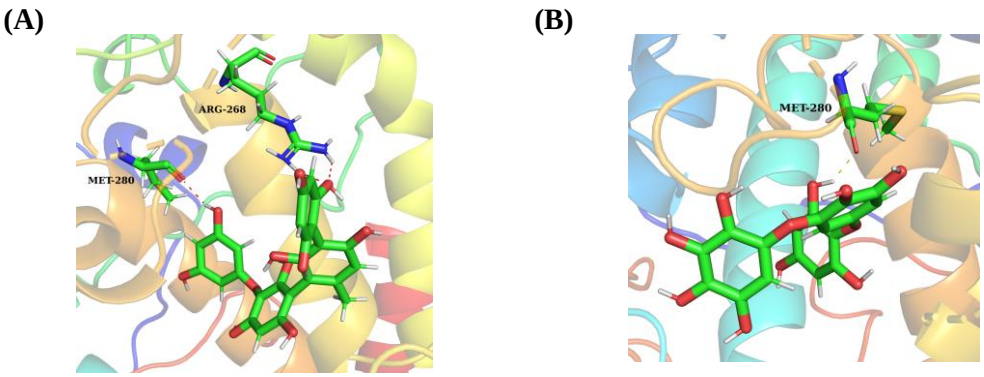

Figure 5. MD refined structure binding pose between difucodiphlorethol A (A) and pseudotrifuhalol A (B) to tyrosinase, which was obtained via clustering method over equilibrium snapshots of the complex with a cutoff of 0.2 nm

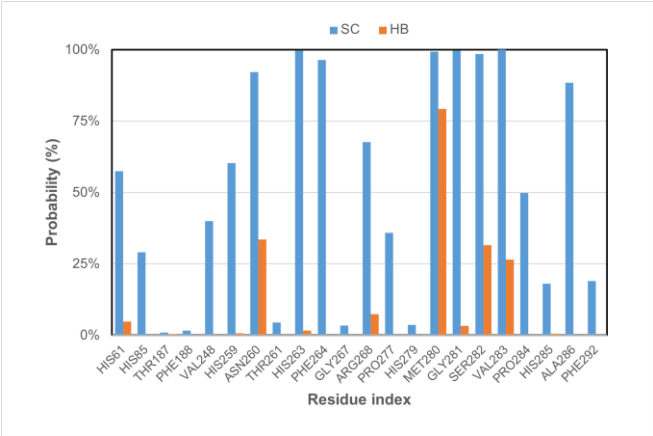

Figure 6. List of tyrosinase residues forming both SC and HB contacts to ligands. The obtained results were average over equilibrated snapshots of MD simulations.

3.3. ADMET evaluation

The potential inhibitors were further evaluated for pharmacokinetic properties and toxicity prediction using the Molinspiration and ProTox-II cheminformatic webservers. The obtained results are presented in Table2.

IDs	MW	HBD	HBA	LogP	MR[a] (cm^3/mol)	LD_{50} (mg/kg)	Toxicity prediction[b]	HIA
D11	496	10	11	4.17	125.21	600	4	0.9897
D45	406	9	11	2.19	94.24	550	4	0.8692

[a] Molar refractivity; [b] Toxicity ranking: 1 => 6 (High toxic to non-toxic)

The analysis of compounds difucodiphlorethol A and pseudotrifuhalol A revealed physicochemical properties conducive to oral drug development, as evidenced by adherence to Lipinski's rule of five, with fewer than three violations observed. Predicted pharmacokinetic parameters, toxicity profiles, and molecular docking simulations collectively suggest that both compounds exhibit promising tyrosinase inhibitory activity and drug-like characteristics, warranting further investigation. Toxicity assessments categorized compounds difucodiphlorethol A and pseudotrifuhalol A as possessing low toxicity (Class 4), demonstrating safety profiles comparable to the reference compound, tropolone. Furthermore, the predicted median lethal dose (LD_{50}) for both compounds exceeded that of the reference, indicating a potentially improved safety margin.

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) studies highlighted intestinal absorption as a critical factor for oral drug bioavailability. Human intestinal absorption (HIA) values for difucodiphlorethol A and pseudotrifuhalol A were determined to be 0.9897 and 0.8692, respectively. These values suggest high absorption potential across the intestinal epithelial barrier. Notably, difucodiphlorethol A exhibited a superior HIA value, implying a potentially higher bioavailability and thus, a greater developmental advantage compared to pseudotrifuhalol A. This disparity in HIA values, in conjunction with other favorable ADMET parameters, positions difucodiphlorethol A as a more promising candidate for further preclinical and clinical evaluations.

4. CONCLUSIONS

In this context, the binding free energy and pose between 71 compounds originated from *Sargassum* genus and tyrosinase was determined by using demanding computational methods. In particular, molecular docking and molecular dynamics simulations were employed to complete the task. Molecular docking simulations via AutoDock Vina was initial performed to preliminarily estimate the binding affinity and pose between ligands and tyrosinase. The outcome was then confirmed via molecular dynamics simulations. Two compounds including difucodiphlorethol A and pseudotrifuhalol A were indicated that can exhibit high ligand-binding affinity toward tyrosinase. Besides, the toxicity prediction also indicates that these compounds would adopt less toxicity. Therefore, it may argue that two compounds can play as potential inhibitors preventing tyrosinase. In addition, the residues including His61, His259, Asn260, His263, Arg268, Met280, Gly281, Ser282 and Val283 play a crucial role in the ligand-binding process. These findings might suggest valuable contribution for further wet lab experiments in drug development processes.

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Declaration of competing interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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