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Mechanistic Study of Novel Whitening Agents: Insights from Molecular Dynamics, Molecular Docking, and Network Pharmacology

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Abstract
In this study, we systematically investigated the mechanism of action of a novel skin-whitening active compound (Compound identifier: SCHEMBL14462430, hereafter referred to as Compound X) using molecular docking, molecular dynamics simulations, and network pharmacology approaches. Molecular docking results demonstrated that Compound X exhibits significant binding interactions with tyrosinase, a key target in skin whitening, with a binding free energy of -7.8 kcal/mol, indicating favorable binding affinity. Molecular dynamics simulations further validated the stability of the Compound X-TYR complex, revealing low flexibility and high structural stability throughout the simulation. The persistent presence of key hydrogen bonds suggested robust dynamic binding activity of Compound X. Additionally, integrated network pharmacology analysis and Western blot experiments revealed that Compound X likely regulates melanogenesis by inhibiting the phosphorylation of p38 protein in the Mitogen-Activated Protein Kinase signaling pathway. This study not only provides a promising candidate molecule for the development of skin-whitening agents but also establishes a theoretical foundation for further exploration of the mechanisms underlying skin-whitening compounds.

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Keywords: Artificial intelligence, Whitening activity, Molecular docking, Network pharmacology, Molecular dynamics simulations

1. Introduction

As the body's primary defense barrier against environmental factors, the skin serves as a crucial organ in preserving systemic homeostasis and overall health (Yang *et al*., 2024) [17]. The production and distribution of melanin are essential for protecting against ultraviolet radiation and photocarcinogenic effects, serving as a vital component of the skin's intrinsic defense mechanisms (Taghizadeh *et al*., 2024) [14]. However, excessive melanin synthesis and uneven distribution can lead to abnormal pigmentation, resulting in various skin issues such as chloasma, senile lentigo, and melasma (Karkoszka *et al*., 2024) [5]. These conditions can further cause skin aging, inflammatory infections, and impaired skin barrier function (Peltzer and Pengpid, 2017) [10]. In many Asian cultures, a preference for fair skin prevails, as it is often associated with purity, nobility, and elegance, symbolizing beauty and attractiveness (Shivakumar and Jafferany, 2020) [12]. Nevertheless, excessive pigmentation and the presence of blemishes can have adverse psychological effects, diminishing overall appearance and self-confidence (Karkoszka *et al*., 2024) [5]. Currently, treatment options for excessive skin pigmentation are limited to compounds like kojic acid, hydroquinone, arbutin, and azelaic acid (Ghani, 2022) [3]. However, long-term use of these products may pose health risks, such as the instability of natural arbutin, which can release hydroquinone, a substance with potential toxicity to bone marrow (Zhou *et al*., 2009) [18]. Additionally, hydroquinone has been reported to have potential mutagenic effects on mammalian cells, and prolonged use of kojic acid may compromise skin barrier function (Mota *et al*., 2025) [6].

Given the limitations of traditional whitening products in terms of ingredient selection and efficacy, the discovery of novel whitening compounds has become a research hotspot, aiming to provide safer and more effective solutions for skin whitening.

The traditional methods of drug discovery are both time-consuming and costly, imposing a significant economic burden on society and delaying the provision of effective treatments to patients (Jackson and Nahata, 2017) [4]. In the era of artificial intelligence (AI) and big data, the field of drug discovery is undergoing a revolutionary transformation. AI technologies, including machine learning and deep learning, have been widely applied across various stages of drug discovery, such as target identification, drug design, and ADMET property prediction (Pham *et al*., 2021) [11]. AI can extract subtle correlations between compound structures and activities from data, enabling highly accurate predictions of potential drug properties. This significantly shortens the drug discovery timeline, reduces costs, and enhances success rates (Nazarova *et al*., 2022) [7]. Utilizing advanced AI-driven methodologies, we successfully identified a promising depigmenting compound, denoted as Compound X, which exhibits substantial whitening activity. Despite its considerable potential, the precise mechanism of action underlying Compound X's efficacy remains to be elucidated through further in-depth investigations.

In the field of drug discovery, molecular docking (Paggi *et al*., 2024) [8], molecular dynamics (MD) simulations (van der Westhuizen *et al*., 2022) [16], network pharmacology (Dong *et al*., 2021) [1], and extracellular experimental techniques (e.g., Western blot, WB) serve as a suite of complementary research tools, playing an indispensable role in drug design and development. Molecular docking technology predicts the binding modes and binding free energies of compounds with potential targets, providing critical initial insights for subsequent studies. Building on this, MD simulations further validate and refine these interactions by modeling the dynamic behavior of drug-target complexes, assessing their structural stability and binding persistence, thereby offering more reliable evidence for drug design. Concurrently, network pharmacology integrates multi-source data from chemistry, biology, and systems science to construct interaction networks between drugs and targets, systematically elucidating the complex mechanisms of drug action across multiple targets and pathways. Additionally, extracellular experimental methods such as WB can validate the predictions from molecular docking and MD simulations by detecting the effects of drugs on the expression or phosphorylation levels of specific proteins, thereby revealing drug mechanisms at the cellular level. In summary, by combining the predictive capabilities of molecular simulations and network pharmacology with the validation functions of extracellular experiments, researchers can establish a multi-level, comprehensive research framework. This integrated approach, spanning from atomic to cellular levels, not only significantly accelerates the drug discovery process but also greatly enhances the efficacy and precision of research, providing robust theoretical and technical support for the development of innovative therapeutics.

In this context, we employed a deep learning model to screen a large-scale compound library and identified a small-molecule compound with potential whitening activity and named it Compound X. Preliminary experimental results demonstrated that Compound X exhibits significant whitening effects in vitro; however, its precise mechanism of action remains elusive. To address this, the present study systematically investigates the whitening mechanism of Compound X by integrating molecular docking, MD simulations, and network pharmacology. This comprehensive approach aims to provide a theoretical foundation for the development of novel skin-whitening agents.

2. Method

The compound utilized in this study (Compound X) was identified through a deep learning-based skin-whitening activity prediction model, which screened a large-scale compound library using SMILES strings (Paul, 2025). The SMILES notation for Compound X is C1=CC=C(C(=C1)C2=CC(=O)C3=C(C(=C(C=C3O2)OC4C(C(C(C(O4)C(=O)O)O)O)O)O)O)O, with the compound identifier SCHEMBL14462430. Its molecular formula is $C_{21}H_{18}O_{12}$, and its molecular weight is 462.4 g/mol. Preliminary experimental data indicate that Compound X exhibits significant skin-whitening effects in vitro; however, its precise mechanism of action remains to be elucidated (Gafner *et al*., 2003) [2].

2.1 Molecular docking

The crystal structure of tyrosinase was retrieved from the RCSB Protein Data Bank (https://www.rcsb.org) and processed using PyMOL software to retain Chain A. The three-dimensional structures of selected compounds were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). Protein preparation, including dehydration and hydrogen addition, was performed using AutoDockTools (version 1.5.6), with the processed protein designated as the receptor. Concurrently, hydrogen atoms were added to the selected compounds, which were then designated as ligands. These optimized ligands were subsequently subjected to docking analysis. Molecular docking simulations were conducted using AutoDock Vina (version 1.1.2), with binding affinity scores reflecting intermolecular binding levels. The scoring values recorded by AutoDock Vina represent binding energy (kcal/mol); negative binding energy values between each ligand and receptor indicate spontaneous interactions, with decreasing values corresponding to enhanced binding affinity. Finally, molecular docking results were visualized using PyMOL software (http://www.pymol.org/).

2.2 Molecular dynamics simulation

MD simulations were performed for 100 ns using Gromacs 2022 (van der Westhuizen *et al*., 2022) [16]. The protein was modeled with the CHARMM36 force field, while the ligand topology was constructed using the GAFF2 force field parameters. The protein-ligand complex was placed in a cubic simulation box with periodic boundary conditions applied. The system was then solvated using the TIP3P water model, ensuring a minimum distance of 1.2 nm between the complex and the edges of the water box. Electrostatic interactions were treated using the Particle Mesh Ewald (PME) method, and the Verlet cutoff scheme was employed for non-bonded interactions. During the equilibration phase, the system underwent 100,000 steps of energy minimization, followed by equilibration in the NVT (constant number of particles, volume, and temperature) and NPT (constant number of particles, pressure, and temperature) ensembles.

The coupling constants for temperature and pressure were set to 0.1 ps, with a duration of 100 ps for each equilibration step. Both van der Waals and Coulombic interactions were calculated with a cutoff distance of 1.0 nm. Finally, the production MD simulation was conducted under constant temperature (310 K) and pressure (1 bar) conditions for a total duration of 100 ns.

2.3 Network pharmacology

The chemical structures of potential whitening-active compounds predicted by the model were acquired from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) or generated using ChemDraw software, subsequently saved in SDF or Mol format. The potential targets of these whitening-active compounds were predicted through PharmMapper (https://www.lilab-ecust.cn/pharmmapper/) and Swiss Target Prediction database (https://www.swisstargetprediction.ch/). Disease-related targets were systematically retrieved from GeneCards (https://www.genecards.org/), DisGeNET (https://www.disgenet.org/), and OMIM (https://www.omim.org/) databases using "whitening" and "melanin" as key search terms. Finally, the identified drug-disease target names were subjected to standardized normalization processing to ensure consistency across datasets.

The identified drug and disease targets were imported into the Venny 2.1 online tool (https://bioinfogp.cnb.csic.es/tools/venny/) to generate a Venn diagram, identifying overlapping targets between the active compounds and whitening-related targets. Subsequently, the overlapping targets were imported into the STRING database to construct a protein-protein interaction (PPI) network, which was then visualized using Cytoscape software.

The common drug-disease interaction targets were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses using the Metascape database. The results were then visualized using the bioinformatics online platform (http://www.bioinformatics.com.cn). This analysis aimed to elucidate the biological processes and signaling pathways potentially involved in the inhibition of melanin by the selected compounds with potential whitening activity.

2.4 Western blot

After drug treatment, B16F10 cells were lysed with pre-chilled cell lysis buffer on ice for 30 min (with vortex mixing every 10 min). The lysate was centrifuged at 12,000 rpm for 10 min at 4°C to collect the supernatant. Protein concentration was determined using the BCA method according to the kit instructions. Equal amounts of protein samples were separated by SDS-PAGE electrophoresis and transferred to an NC membrane. The membrane was blocked with shaking at 100 rpm at room temperature for 2 h, followed by overnight incubation with primary antibody at 4°C. The next day, the membrane was washed with TBST three times (5 min each), then incubated with secondary antibody at room temperature in the dark for 2 h. After thorough washing with TBST, ECL developing solution was evenly applied to the membrane surface. Images were captured using the Bio-Rad ChemiDoc MP imaging system (Bio-Rad Laboratories, Inc., United States), and band gray values were quantified with Image J 1.53 software.

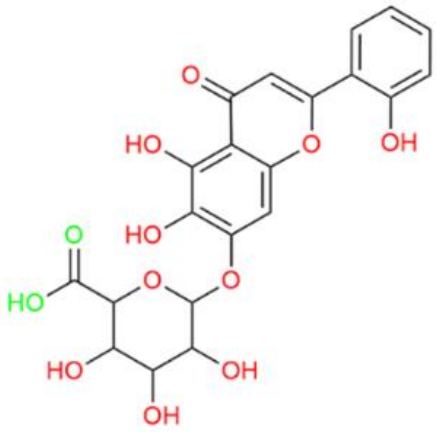
2.5 Statistical Analysis

Data analysis was conducted using GraphPad Prism 9.0 software. Results are presented as mean ± standard deviation (sd). To evaluate differences between groups, we employed one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Statistical significance was determined by a *p*-value less than 0.05.

3. Results and Discussion

Results

In preliminary experiments, we successfully developed a robust predictive model for skin-whitening activity based on the established Directed Message Passing Neural Network (D-MPNN) deep learning framework. Utilizing this model, we predicted and ranked over 30,000 compounds with unknown activity, among which the candidate compound Compound X (Figure 1) achieved a high prediction score of 0.99737. Following manual screening to exclude compounds with reported toxicity or inactivity, we experimentally validated this candidate. Literature indicates that Compound X is present in Scutellaria lateriflora, but its skin-whitening properties have not been previously reported. Subsequent cellular assays confirmed that this compound exhibits significant skin-whitening activity; however, its precise mechanism of action remains to be elucidated.



SCHEMBL14462430
Pridicted:0.99737
SMILES:
C1=CC=C(C(=C1)C2=CC(=O)C3=C(C(=C(C=C3O2)OC4C(C(C(C(O4)C(=O)O)O)O)O)O)O)O

Fig 1: Artificial intelligence driven discovery of a compound with potential whitening activity.

As depicted in Figure 2, the compound forms three hydrogen bonds with the His85 residue, with bond lengths of 2.3 Å, 2.8 Å, and 3.4 Å, and two hydrogen bonds with the Cys83 residue, with bond lengths of 2.2 Å and 3.5 Å. Additionally, it forms two hydrogen bonds with the Asn81 residue, with bond lengths of 2.9 Å and 3.0 Å. Furthermore, hydrophobic interactions were observed with the Val283 and Asn260 residues. Notably, His85 is a crucial amino acid residue surrounding the copper ion, and the interactions between Compound X and these residues result in its occupation of the active site of tyrosinase, leading to a decrease in tyrosinase activity. Experimental data indicate that the compound exhibits the lowest binding energy with tyrosinase (-7.8

kcal/mol), surpassing even the control (kojic acid, -7.11 kcal/mol (Talebi *et al*., 2022) [15], which further demonstrates the strength of their interaction. Our findings indicate that certain residues of tyrosinase, particularly Cys83, His85, and Val283, are involved in hydrogen bonding interactions with the compound, which contribute to the inhibition of tyrosinase catalysis. This suggests that the compound may be considered a promising tyrosinase inhibitor in melanogenesis.

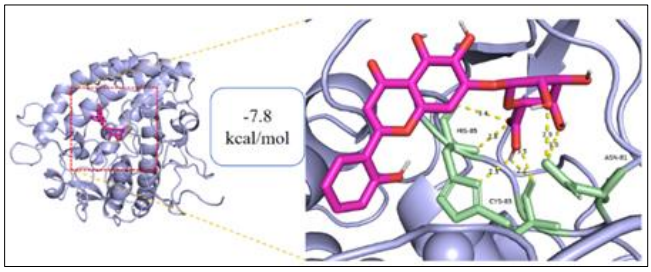


Fig 2: Molecular Docking of Compound X with TYR, Exhibiting a Lowest Binding Energy of -7.8 kcal/mol.

The root-mean-square deviation (RMSD) is a critical metric for evaluating the conformational stability of protein-ligand complexes, reflecting the deviation of atomic positions from their initial structure. Lower RMSD values indicate higher conformational stability of the complex. Analysis of the RMSD for the simulated system (Figure 3A) revealed that the complex reached equilibrium after 5 ns, with minor fluctuations around 1.6 Å, suggesting that the dynamic binding of Compound X to TYR exhibits high stability. Further analysis of the radius of gyration (Rg) and solvent-accessible surface area (SASA) (Figures 3B-C) demonstrated that both Rg and SASA remained stable with minor fluctuations throughout the simulation, indicating no significant structural contraction or expansion of the complex during the dynamic process. Additionally, hydrogen bonds play a crucial role in the dynamic binding between the ligand and protein. As shown in Figure 3D, the number of hydrogen bonds in the complex system consistently ranged between 0 and 6, with at least 3 hydrogen bonds present for the majority of the simulation time, indicating stable hydrogen bond interactions between Compound X and TYR. Finally, root-mean-square fluctuation (RMSF) analysis was performed to assess the flexibility of amino acid residues in the protein (Figure 3E). The results showed that the RMSF values of the complex system were generally low, with most residues exhibiting RMSF values below 2 Å, further confirming that Compound X exhibits low flexibility and high stability when bound to TYR. In summary, the molecular dynamics simulations demonstrate that the dynamic binding of Compound X to TYR exhibits excellent stability and binding activity.

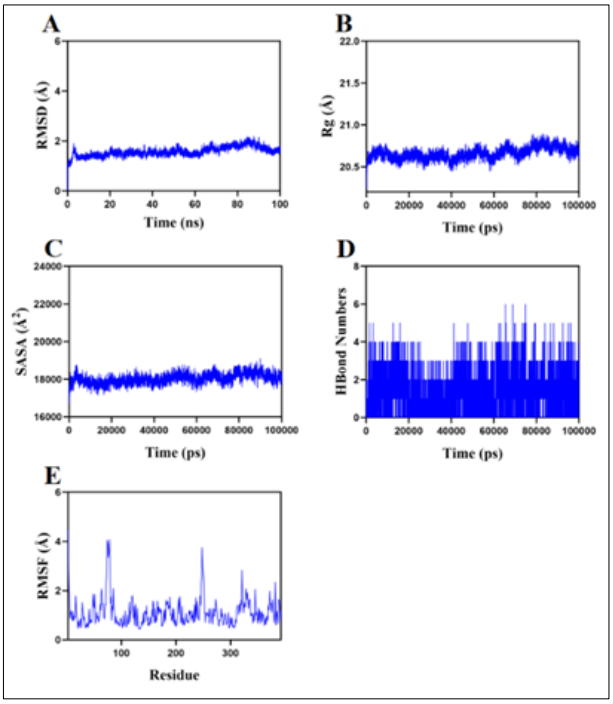


Fig 3: (A) RMSD. (B) Rg. (C) SASA. (D) Hydrogen bond number. (E) RMSF.

To further explore the molecular energy landscape and protein-ligand interactions, we employed free energy landscape (FEL) analysis to visualize the changes in free energy. In the FEL, energy minima correspond to stable states of the system, while energy maxima represent energy barriers associated with conformational changes. This approach not only predicts ligand binding affinity but also elucidates the mechanisms of molecular recognition. As shown in Figure 4, in the energy-minimized conformation of the complex, receptor residues MET-199, HIS-178, THR-197, LYS-180, PRO-175, and GLU-173 formed significant van der Waals interactions with the small molecule. Additionally, receptor residues GLN-44, GLN-41, and ASN-174 established stable conventional hydrogen bonds with Compound X. In summary, the FEL analysis indicates that the complex system exhibits stable binding, with Compound X demonstrating not only robust hydrogen bond interactions but also excellent dynamic binding properties with TYR.

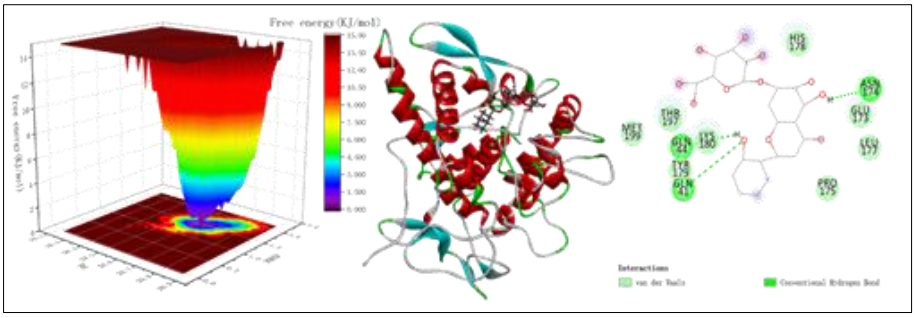


Fig 4: Visualizing free energy changes through FEL to explore molecular energy landscapes and protein ligand interactions.

Melanin production in the skin is a complex process, and to elucidate its mechanisms, this study employed network pharmacology to predict its signaling pathways. As shown in Figure 5A, Swiss Target Prediction identified 98 potential targets for Compound X, with 47 targets overlapping with those related to melanogenesis-related diseases. Using Cytoscape software, we visualized the core targets, and the results suggest that compound X may exert its skin-whitening effects by downregulating melanogenesis through the modulation of key targets, including the Epidermal Growth Factor Receptor (EGFR), Tumor Necrosis Factor (TNF), and Prostaglandin-Endoperoxide Synthase 2 (PTGS2), as illustrated in Figure 5B. Further analysis, as depicted in Figures 5C and 5D, involved GO and KEGG enrichment analyses using the Metascape database, revealing involvement in 167 biological processes (BP), 10 cellular components (CC), and 13 molecular functions (MF). KEGG pathway analysis indicated that the whitening effects of this compound are related to pathways such as Pathways in Cancer, MicroRNAs in cancer, the Mitogen-activated protein kinase (MAPK) signaling pathway, and chemical carcinogenesis-receptor activation. In the field of whitening, the MAPK pathway is considered to be the most fully supported and the most clearly defined research direction (Shon *et al*., 2023) [13]. Therefore, we chose MAPK pathway as the research focus to explore the mechanism of compound 10 in inhibiting melanin production in B16F10 cells.

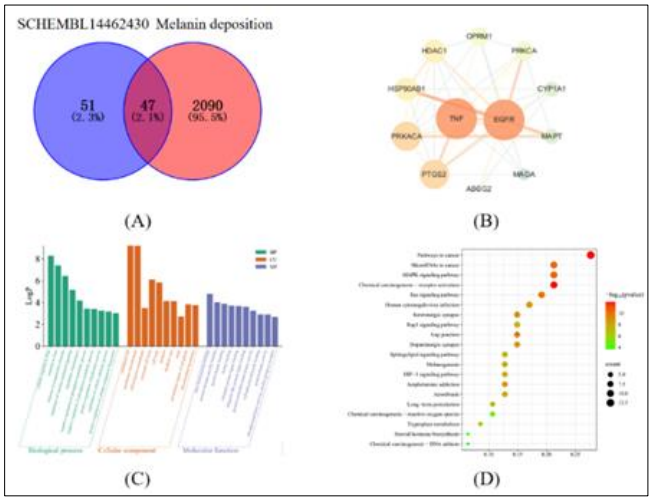


Fig 5: (A) Venn diagram. (B) PPI network. (C) GO enrichment analyses (D) KEGG enrichment analyses.

To investigate the regulatory effect of Compound X on melanin production in the MAPK signaling pathway, this study focused on analyzing the modulation of p38 protein by Compound X. The expression levels of p38 protein were detected and quantified in B16F10 cells using WB experiments to explore its impact on the signaling pathway. The experimental results, shown in Figure 6, indicate that different concentrations (25-100 μg/mL) of Compound X did not significantly affect the total expression level of p38 protein ($p > 0.05$); however, they exhibited a clear concentration-dependent effect on its phosphorylation state. Specifically, while the p-p38/p38 ratio in the 25 μg/mL treatment group did not reach statistical significance ($p > 0.05$), a decreasing trend was observed. In the 50 and 100 μg/mL treatment groups, the statistical differences in the p-p38/p38 ratio reached $p < 0.05$ and $p < 0.01$, respectively. This study suggests that Compound X may inhibit melanin production by blocking the phosphorylation process of p38 protein in the MAPK signaling pathway, thereby disrupting the MITF-TYR signal transduction.

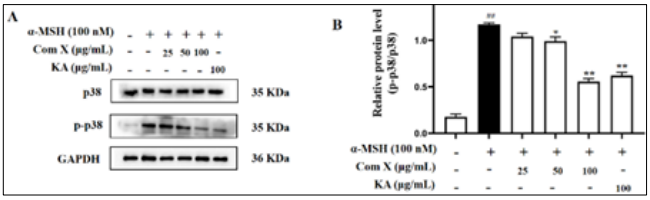


Fig 6: Effect of Compound X on p-p38/p38 protein expression. Data are presented as mean ± standard deviation (sd), n = 3. Compared to the control group, ##$p < 0.01$; compared to the model group, *$p < 0.05$ and **$p < 0.01$.

Discussion

In this study, we integrated AI technology with molecular docking, MD simulations, network pharmacology, and WB experiments to systematically elucidate the skin-whitening mechanism of Compound X. This multidisciplinary approach not only significantly accelerated the compound screening process but also provided a comprehensive analysis of the mechanism, spanning from atomic to systemic levels. However, certain limitations should be acknowledged. For instance, the relatively short time scale of the MD simulations may not fully capture the long-term binding behavior of compound X with the TYR target. Additionally, the WB experiments only validated that compound X reduces melanogenesis by inhibiting the phosphorylation of p38 in the MAPK signaling pathway, thereby blocking MITF-TYR signal transduction. Future studies should further investigate the regulatory effects of Compound X on other related proteins and validate it's in vivo whitening efficacy and safety through structural modifications and animal experiments, ultimately advancing its potential for clinical translation.

4. Conclusion

In this study, we successfully elucidated the mechanism of action of compound X, a skin-whitening agent identified through AI-driven screening. Molecular docking and MD simulations demonstrated that compound X exhibits high binding affinity and stability with key targets, such as TYR, and its dynamic binding behavior shows excellent conformational stability. Network pharmacology analysis further revealed that Compound X reduces melanogenesis by inhibiting the MAPK signaling pathway. WB experiments validated the inhibitory effect of Compound X on p38 phosphorylation, providing experimental support for the predicted results. These findings not only confirm the efficiency of AI technology in compound screening but also provide a new candidate molecule and a theoretical foundation for the development of skin-whitening agents.

In summary, the integration of AI technology with multidisciplinary methods demonstrates broad application prospects in drug discovery. This study offers novel insights for the development of skin-whitening drugs and highlights the potential of AI technology in innovative drug development for other therapeutic areas. With continuous technological advancements and deeper interdisciplinary collaboration, this research paradigm is expected to drive the discovery of more efficient and precise therapeutic solutions.

5. Reference

1. Dong Y, Zhao Q, Wang Y. Network pharmacology-based investigation of potential targets of Astragalus membranaceus–Angelica sinensis compound acting on diabetic nephropathy. Scientific Reports. 2021;11:19496.
2. Gafner S, Bergeron C, Batcha LL, *et al*. Analysis of Scutellaria lateriflora and its adulterants Teucrium canadense and Teucrium chamaedrys by LC–UV/MS, TLC, and digital photomicroscopy. Journal of AOAC International. 2003;86:453–60.
3. Ghani U. Azole inhibitors of mushroom and human tyrosinases: current advances and prospects of drug development for melanogenic dermatological disorders. European Journal of Medicinal Chemistry. 2022;239:114525.
4. Jackson K, Nahata MC. Rising cost of anticancer medications in the United States. Annals of Pharmacotherapy. 2017;51:706–10.
5. Karkoszka M, Rok J, Wrześniok D. Melanin biopolymers in pharmacology and medicine—skin pigmentation disorders, implications for drug action, adverse effects and therapy. Pharmaceuticals. 2024;17:521.
6. Mota S, Rego L, Sousa E, *et al*. Usage frequency and ecotoxicity of skin depigmenting agents. Pharmaceuticals. 2023;18:368.
7. Nazarova AL, Katritch V. It all clicks together: In silico drug discovery becoming mainstream. Clinical and Translational Medicine. 2022;12:e766.
8. Paggi JM, Pandit A, Dror RO. The art and science of molecular docking. Annual Review of Biochemistry. 2024;93.
9. Paul A. Dextrosinistral reading of SMILES notation: investigation into origin of non-sense code from string manipulations. Digital Chemical Engineering. 2022;15:100222.
10. Peltzer K, Pengpid S. Knowledge about, attitude toward, and practice of skin lightening products use and its social correlates among university students in five Association of Southeast Asian Nations (ASEAN) countries. International Journal of Dermatology. 2017;56:277–83.
11. Pham TH, Qiu Y, Zeng J, *et al*. A deep learning framework for high-throughput mechanism-driven phenotype compound screening and its application to COVID-19 drug repurposing. Nature Machine Intelligence. 2021;3:247–57.
12. Shivakumar S, Jafferany M. "The unfair drive to be fair": psychosocial aspects and implications of the use of skin lightening agents. Dermatologic Therapy. 2020;33:e14091.
13. Shon YJ, Kim WC, Lee SH, *et al*. Antimelanogenic potential of brewer's spent grain extract through modulation of the MAPK/MITF axis. Sustainable Materials and Technologies. 2023;38:e00721.
14. Taghizadeh B, Moradi R, Mirzavi F, *et al*. The protection role of human growth hormone on skin cells following ultraviolet B exposure. Journal of Photochemistry and Photobiology B: Biology. 2023;257:112961.
15. Talebi M, Majidi K, Bassam K, *et al*. Synthesis, biological evaluation, and molecular docking analysis of novel 1,3,4-thiadiazole-based kojic acid derivatives as tyrosinase inhibitors. Journal of Molecular Structure. 2023;1268:133707.
16. van der Westhuizen CJ, Stander A, Riley DL, *et al*. Discovery of novel acetylcholinesterase inhibitors by virtual screening, in vitro screening, and molecular dynamics simulations. Journal of Chemical Information and Modeling. 2022;62:1550–72.
17. Yang HL, Chen SJ, Yeh JT, *et al*. The anti-melanogenesis, anti-photoaging, and anti-inflammation of coenzyme Q0, a major quinone derivative from Antrodia camphorata, through antioxidant Nrf2 signaling pathways in UVA/B-irradiated keratinocytes. Journal of Functional Foods. 2024;116:106206.
18. Zhou H, Kepa JK, Siegel D, *et al*. Benzene metabolite hydroquinone up-regulates chondromodulin-I and inhibits tube formation in human bone marrow endothelial cells. Molecular Pharmacology. 2009;76:579–87.