Quality and Durability of Agricultural and Food Staffs

e ISSN: 2783-3410

Journal Homepage: https://sanad.iau.ir/journal/qafj/

Research Paper

Ligand Engineering Based on Kojic Acid for Safe Tyrosinase Inhibition in Cosmetic and Agricultural Industries

Reza Farrokhi*, Dadkhoda Ghazanfari

Department of Chemistry, KeC., Islamic Azad University, Kerman, Iran

*Corresponding author Reza Farrokhi, Email: Rezafarrokhi53@gmail.com

Received: 04/07/2025, Accepted: 27/07/2025

Citation: Farrokhi R, Ghazanfari D, Ligand Engineering Based on Kojic Acid for Safe Tyrosinase Inhibition in Cosmetic and Agricultural Industries. *Quality and Durability of Agricultural Products and Food Stuffs*, 2025; 4(4). DOI: https://doi.org/10.71516/qafj.2025.1211065

Extended Abstract

Introduction Tyrosinase is a copper-containing enzyme that plays a pivotal role in melanogenesis, a biochemical pathway responsible for melanin biosynthesis in living organisms. Overproduction of melanin can lead to hyperpigmentation disorders such as melasma and even malignant melanoma. In agriculture, tyrosinase activity is also a major cause of enzymatic browning in postharvest fruits and vegetables, reducing their aesthetic and commercial value. Inhibiting tyrosinase is therefore critical not only in therapeutic and cosmetic applications but also in food preservation and crop enhancement. Although commonly used tyrosinase inhibitors like kojic acid, hydroquinone, arbutin, and rhododendrol have shown effectiveness, they come with significant clinical and safety limitations, including toxicity, allergenicity, and carcinogenic potential. Thus, there is a critical need for the development of safer and more effective tyrosinase inhibitors, especially those suitable for broad use across cosmetic, pharmaceutical, and agricultural domains. The objective of this study was to design and evaluate a novel ligand, derived structurally from kojic acid, that could inhibit tyrosinase with improved safety and efficacy. Using advanced in silico tools, molecular docking, and ADME-Tox evaluations, the study aimed to introduce a low-toxicity alternative suitable for real-world applications.

Methods This study employed a descriptive-analytical in silico approach involving several computational stages. The crystal structure of the tyrosinase enzyme (PDB ID: 5M8P) was obtained from the RCSB PDB database. Chain A, with the highest resolution, was selected as the target for docking simulations. Active binding sites were identified using Molegro Virtual Docker.Candidate ligands with high affinity for tyrosinase were selected from the ZINC database. Their 3D structures were extracted in SDF format from PubChem. A total of ten ligands were shortlisted based on binding affinities greater than 3000 nM.Using AutoDock

Vina via PyRx software, docking simulations assessed the binding energies and interaction potentials between ligands and the active sites of tyrosinase. All selected ligands were evaluated through FAF-Drugs4 for their absorption, distribution, metabolism, excretion, and toxicity profiles. Filters like PAINS and undesirable substructures were used to screen compounds for drug-likeness. Ligands were further analyzed for LD_{50} values, toxicity class, and potential carcinogenicity or mutagenicity using ProTox-II. Due to unsatisfactory safety profiles of most candidates, including kojic acid, ligand engineering was conducted using HyperChem software. A novel ligand with the formula $C_{14}H_{22}O_4$ was developed through structural optimization and iteration. The engineered ligand underwent the same docking and ADME-Tox procedures and was compared against kojic acid in terms of binding affinity, toxicity, and pharmacokinetic properties.

Results and Discussion The docking analysis showed that the engineered ligand $C_{14}H_{22}O_4$ exhibited a binding affinity of –6.5 kcal/mol, outperforming kojic acid (–6.0 kcal/mol). In ADME-Tox profiling, the new ligand passed all drug-likeness filters and was classified as "Accepted", whereas kojic acid was rejected due to unfavorable pharmacokinetics and low molecular weight. Toxicity assessment revealed a significant safety improvement: the engineered ligand had an LD_{50} of 4000 mg/kg and was categorized as Toxicity Class 5 (low toxicity), in contrast to kojic acid's LD_{50} of 550 mg/kg and classification in Toxicity Class 3. ProTox-II analysis confirmed that the engineered ligand showed no signs of hepatotoxicity, carcinogenicity, immunotoxicity, or mutagenicity. The compound's structural design improved its hydrophobic balance and molecular weight, making it more compatible for skin penetration and agricultural formulation without the associated risks of existing inhibitors. The results support the hypothesis that rational ligand engineering, based on natural compounds like kojic acid, can yield safer and more effective tyrosinase inhibitors. The study not only achieved a higher binding affinity but also ensured a significantly safer toxicological profile, making the new compound highly promising for industrial applications. In the cosmetic industry, the engineered ligand offers an effective alternative for skin-lightening products, especially in light of the banning or restriction of hydroquinone and rhododendrol in many countries. In agriculture, it provides a bio-safe method to delay enzymatic browning in perishable crops, potentially reducing postharvest losses and enhancing commercial shelf-life. Importantly, while some studies have explored the synthesis of novel inhibitors, they often lacked comprehensive safety profiling. This study fills that gap by integrating pharmacokinetic, toxicological, and molecular interaction analyses in a unified framework.

Conclusion This research successfully introduces a novel ligand ($C_{14}H_{22}O_4$) derived from kojic acid, engineered to safely and effectively inhibit tyrosinase. Its superior safety profile, stronger binding to the enzyme's active site, and favorable ADME characteristics make it a viable candidate for real-world applications in cosmetics, agriculture, and pharmaceuticals. Future directions include in vitro and in vivo validation of its biological efficacy, stability studies, and formulation development. The study demonstrates the power of in silico techniques in modern drug discovery and highlights a sustainable path toward the development of safer bioactive compounds for human and environmental health.

Keywords: Tyrosinase, Molecular docking, Low-toxicity inhibitor, Melanogenesis, Agriculture, Kojic acid.

Funding: There was no external funding in this study.
Authors' contribution: All authors contributed equally to the preparation of this manuscript.
Conflict of interest: The author declares that there is no conflict of interest.