A New Insight into Mushroom Tyrosinase Inhibitors: Docking, Pharmacophore-Based Virtual Screening and Molecular Modeling Studies

Kowsar Bagherzadeh1,2, Faezeh Shirgahi Talari1, Amirhossein Sharifi1, Mohammad Reza Gunjali2, Ali Akbar Saboury3, Massoud Amanlou1

1. Department of Medicinal Chemistry, Faculty of Pharmacy and Medicinal Plants Research Center, Tehran University of Medical Sciences, Tehran, Iran. 2. Center of Excellence in Electrochemistry, Faculty of Chemistry, University of Tehran, Tehran, Iran. 3. Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran.

Abstract

Tyrosinase, a widely spread enzyme in microorganisms, animals and plants, participates two rate limiting steps in melanin formation pathway which is responsible for skin protection against UV lights harm whose functional deficiency result in serious dermatological diseases. This enzyme seems to be responsible for neuromelanin formation in human brain as well. In this study, a well established set of computational methodologies were employed to extract a new set of compounds with high potency to inhibit enzyme mushroom tyrosinase.

Results and Discussions

Caving catalytic site tunnels: Possible pathways into the catalytic center and also the involved residues were identified employing CAVAE 3.0.1 software.

Dataset generation, and Pharmacophore model production

Virtual screening and Docking studies: Fourteen compounds (five groups) were chosen as the better ones according to their docking binding energy values, orientations in the catalytic pocket and modes of interactions.

Molecular Dynamic Simulations

Classical molecular dynamic simulation(s) was performed to ensure the stability of the obtained compounds in the binding pocket and also compare their modes of interactions and influence on the enzyme structure (speciality the route into the active site) in compare with that in complex with tyrosine.

Conclusion

1. The generated pharmacophore model provides a precise description of the features necessary for an appropriate binding of ligands with the studied protein.
2. Five new hits are introduced as potent inhibitors of mushroom tyrosinase.
3. Molecular dynamic simulation(s) proved the stability of the compounds in the pocket and their potential ability to inhibit mushroom tyrosinase function.
4. The copper bridging water molecule is of importance in stabilizing the substrate and/or ligands in the catalytic center.

References


For further information please contact: pmshari@ttu.ac.ir, kw_bagherzadeh@yahoo.com