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Research Article

In Silico Investigation of Piperine against Human Monoamine Oxidase-A (MAO-A) Enzyme – Vitiligo

M. Thenmozhi
Research Scholar , Department of Bioinformatics, School of Life Sciences, Bharathidasan University, Tiruchirappalli 620 024, Tamil Nadu, India

***Corresponding author**
M. Thenmozhi
Email: thenmozhimaruthadurai@email.com

Abstract: Vitiligo is a depigmentation disorder; Reactive Oxygen Species (ROS) plays a major role in the development of depigmentation. Monoamine oxidase-A(MAO-A) enzyme is one of the reasons in producing ROS by metabolizing norepinephrine which found to be high level in vitiligo patients. Inhibiting MAO-A enzyme prevents further depigmentation. Clinical studies proved that the isoquinoline alkaloids have inhibiting property against MAO-A enzyme. Piperine is a kind of quinoline alkaloid since it has been proved in treating vitiligo. In this work, computational analysis carried to study the inhibition efficacy of piperine against human MAO-A enzyme based on binding affinity and protein-ligand stability. From the results, we observed binding affinity based on the docking scores, protein-ligand stability based on the hydrogen as well as hydrophobic interactions. This computational analysis gives various insights about structural features of disease target, stability of complex formation through hydrogen bond and hydrophobic interactions.
Keywords: Vitiligo, Reactive oxygen species, Docking, Piperine

INTRODUCTION

Vitiligo is a dermatological disorder due to the loss of melanocytes from human epidermis results in depigmentation over skin. Autoimmunity and Oxidative stress are contributing to be the major sources for this disorder [1].

According to Oxidative stress, accumulation Reactive oxygen species (ROS) plays important role in oxidative stress[2]. There are various sources to produce reactive oxygen species. Mono amine oxidase-A level is also one of the sources for contributing reactive oxygen species production. In epidermis of patients with vitiligo was found to be increased MAO-A enzyme activity. MAO-A activity increases due to the norepinephrine synthesis instead of melanin synthesis. MAO-A metabolize the Norephinephrine which results in the production of ROS like Hydrogen peroxide and ammonia which are toxic to melanocytes [3]. Clinical studies proved that the isoquinoline alkaloids inhibition property against MAO-A enzyme [4].

Piperine is an alkaloid extracted from the herb *Piper nigerum* (Black pepper)[5]. Piperine has been proved to be an effective anti-vitiligo agent; various clinical studies have been done for melanocyte proliferation activity [6-7]. Apart from all here we performed computational analysis to study the inhibition efficacy of piperine against human MAO-A based on binding affinity as well as protein-ligand stability. Inhibition of human MAO-A enzyme in vitiligo prevent further melanocyte loss since MAO-A enzyme is one among the major sources of ROS production in vitiligo patients.

In this paper, computational study is carried out using Induced Fit Docking (IFD) module (Schrödinger software). From the results, binding affinity studied based on the docking score, protein-ligand stability studied based on hydrogen as well as hydrophobic interactions. It has been already reported that the binding affinity as well as protein-ligand stability directly relates to the drug efficacy[8-9].

MATERIALS AND METHODS

Protein preparation

Human Monoamine oxidase-A enzyme (MAO-A) ligand bound with 2.20 Å resolution X-ray crystallographic structure(2Z5X) was downloaded from the database protein data bank www.rcsb.org/pdb.The downloaded 3-D crystallographic structure of Human Monoamine Oxidase-A (Figure 1) was processed using protein preparation module of Schrödinger software with the preparation and refinement option before docking progress. During processing of the crystal structure [2Z5X], hydrogen atoms were added; formal charges along with bond orders were assigned and unwanted water molecules, HET atoms cofactors, ions

were deleted. Partial charges were assigned according to OPLS_2005 force field.

Ligand preparation

Ligprep module of Schrödinger software was used to prepare ligand Piperine(Figure 2). Here it converts the format from Sd to Maestro format. . The addition of hydrogen bonds, partial charges was computed according to OPLS_2005 force field, using this module. Here prepared ligand chosen for further docking process according to their least potential energy.

Active Site Prediction

Active site residues predicted using web based server Qsite finder. PHE 108, ARG109,GLY110,ALA111, ILE180, ASN181, ILE207, PHE208, SER209, VAL210, THR211, GLY214, GLN215, HIS242, PRO243, VAL244, THR245, LEU259, ALA272, ILE273, PRO274, LEU277, THR278, LYS280, ILE281,HIS282, VAL303, LYS305, CYS323, ILE325, ILE335,THR336, LEU337,MET350, PHE352, TRP397. Predicted active sites are in the range of experimentally demonstrated active site residues[10].

Grid Generation

Grids were calculated for prepared proteins, it helps various ligand poses binds within the predicted binding pocket (predicted by Q-site finder). In Glide, grids were generated keeping the default parameters of Van der Waals scaling 1.00 and charge cut off 0.25 subjected to OPLS_2005 force field.

Induced Fit Docking

Induced fit docking protocol was adopted to perform docking calculations for the prepared ligand (Berberine) against Monoamine Oxidase- A enzyme. Initially glide docking was carried out. Side chains were trimmed based on the receptor and ligands Van de Waal's scaling of 0.70 and 0.50 respectively and the ligand poses set it to be 20poses. Then the prime side chain optimization and refine the residues within 5.0 Å with of top 20 ligand poses. Then the glide XP re-docking was carried out within 30 kcal/mol. Binding affinity of the each complex reflects as its glide score. The more negative Glide score refers more binding affinity of the complex [11].

RESULTS AND DISCUSSION

Based on the experimental study, piperine docked against human MAO-A enzyme and investigated piperine inhibition efficacy through *in silico* Induced Fit Docking (IFD) analysis which is a flexible docking approach.

The induced fit docking studies showed that the ligand piperine interacts with following interacting residues ALA68, TYR69. Glide score for the above said ligand piperine -11.5 kcal/mol. The interacting residues and its hydrogen bond length are measured, as well as glide score value is given in Table 1. For visual inspection, the interaction of piperine with active site of human MAO-A enzyme shown in Figure 3. Docked conformation of Human MAO-A enzyme with top ranked piperine ligand shown in Figure 4. Docked conformation of Human MAO-A enzyme with top ranked piperine ligand showing interaction with non-ligand residues involved in the hydrophobic interaction contacts in Red color Figure 5.

IFD analysis

The induced fit docking protocol adopted to perform computational docking studies, various parameters were analyzed from the docking results.

From the Glide scores, it shows that the ligand (piperine) bounds well in human MAO-A enzyme active site.

From the resulted top scoring poses were analyzed to observe the specific interactions to study the protein-ligand binding stability. Hydrogen and hydrophobic interactions were analyzed from the top scoring poses.

Analysis of Hydrogen bond analysis

According to the hydrogen bond interactions, ALA68, TYR69 these are the interacting residues found in top scoring docked pose of piperine. The hydrogen bond length between the piperine and the MAO-A enzyme lies below 2.5 Å. The bond length shows the interacting residues are nearer to the ligand which means it shows the stability of the bond. I began analyzing the active site interacting residues; interestingly TYR69 is one among the sixteen important interacting key residues found in MAO-A inhibitor Harmine. It strengthens our preliminary data analysis to ensure piperine may also have the inhibition property towards MAO-A enzyme.

Analysis of Hydrophobic interactions

According to hydrophobic interactions, there were 14 common interacting residues were observed from the top ranked docking poses which are as follows SER24, ILE23, ARG51, THR52, GLY67, GLN215, LYS305, PHE352, TYR407, THR435, GLY443, TYR444, MET445, ALA448.

CONCLUSION

We performed Induced Fit Docking (IFD) analysis for piperine against human MAO-A enzyme to study the inhibition efficacy based on binding affinity and protein-ligand stability. From the results, it ensures that the computationally predicted hydrogen bond forming aminoacid TYR69 is one among the sixteen key interacting residues found in harmine (Inhibitor of MAO-A). Based on this preliminary analysis helps to

understand piperine may also inhibit MAO-A enzyme like harmine(Inhibitor of MAO-A). In this paper i studied the relative contribution of the hydrogen bonds and the hydrophobic interactions of Piperine compound at the binding sites of Human MAO-A enzyme. The results are important in piperine based drug discovery process.

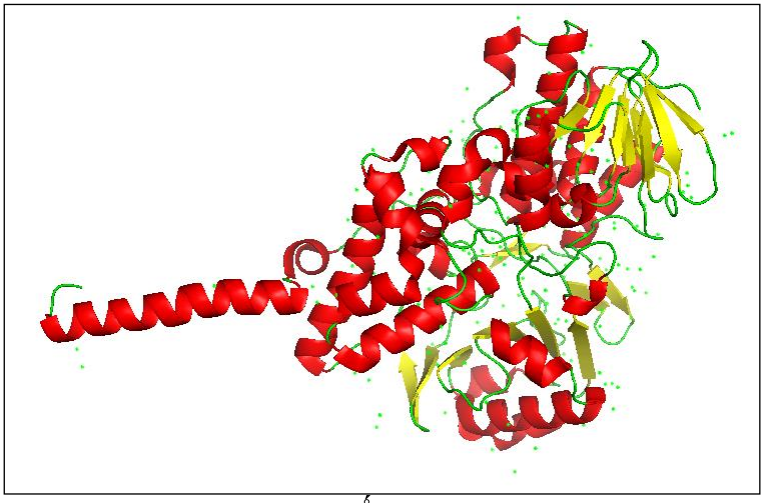

Fig-1: Structure of human MAO-A enzyme with 2.2Å resolution (2Z5X). The α-helix represents in red color, yellow color represents β-sheets, and green color represents loops

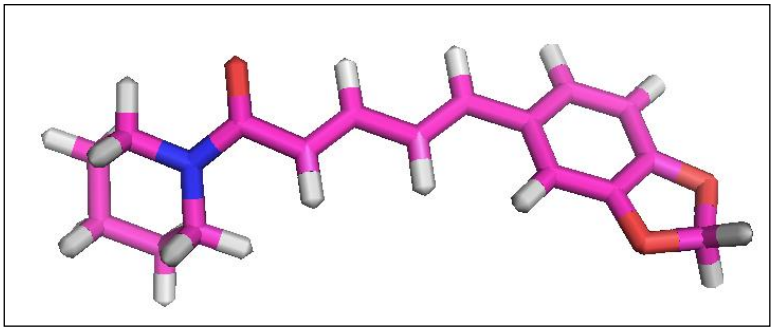

Fig-2: Figure 2 Piperine ligand structure

Table 1 Interaction energy, Molecular Hydrogen bond interactions of piperine with human Monoamine oxidase-A enzyme.

S.NO	Ligand Name	Hydrogen bond Interaction	Interacting Residues	Hydrogen bond Length Å	Docking score (kcal/mol)
1	PIPERINE	O…H O…H	ALA 68 TYR 69	1.9 Å 2.0 Å	-11.5

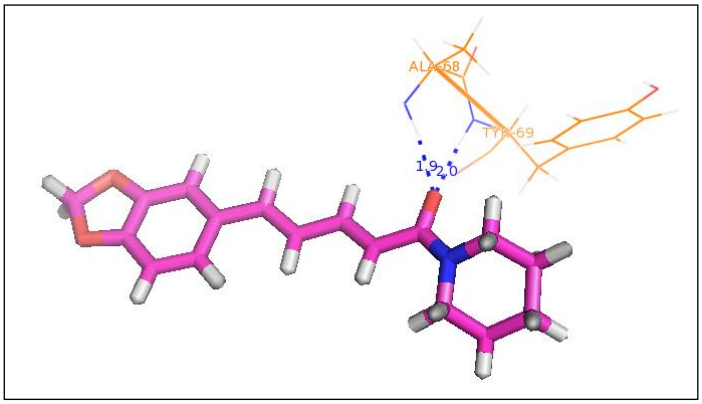

Fig-3: Interacted amino acid residues of human MAO-A enzyme with Piperine

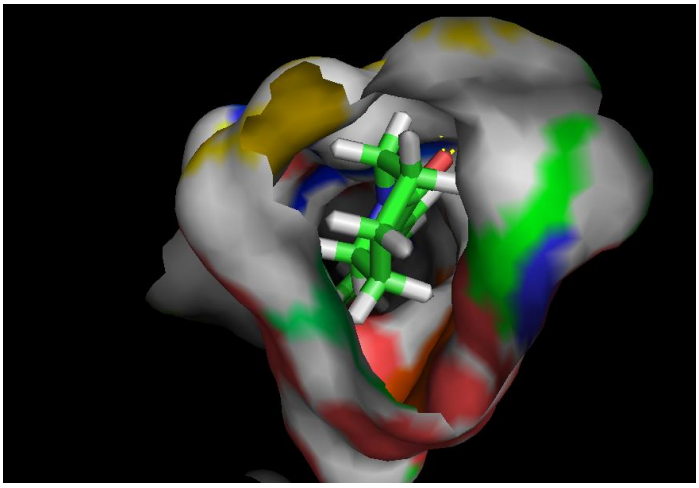

Fig- 4: Docked conformation of Human MAO-A enzyme with top ranked piperine ligand

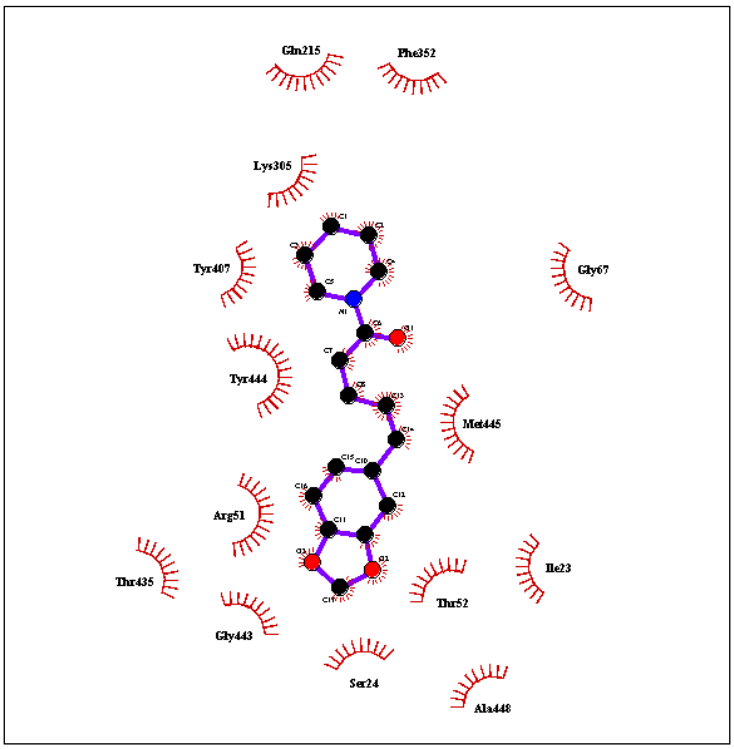

Fig-5: Docked conformation of Human MAO-A enzyme with top ranked piperine ligand showing interaction with non-ligand residues involved in the hydrophobic interaction contacts in Red color

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