Research Article

In silico analysis of the effect of vasicine and vasinone against human tyrosinase receptor in the management of hyperpigmentation of skin diseases

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Abstract

Objective: The aim of the study is to evaluate the effect of vasicine and vasinone against tyrosinase receptor in the management of hyperpigmentation of skin diseases by molecular docking approach. **Materials and Methods**: The computational analysis is carried out by autodock 4 tool. The standard used is kojic acid against the target Tyrosinase receptor with PCB code 5M8M and the target proteins were retrieved from the protein data bank. **Results and Conclusion**: The binding free energy of vasicine and vasinone with target tyrosinase receptor is -4.76 Kcal/ mol and -4.03 Kcal/mol, respectively. The inhibition constant of vasicine and vasinone against the target are 323.7μMand 1.12mM, respectively. The intermolecular energy between vasicine and the target is -5.06 Kcal/mol and that of vasinone against the same target of human tyrosinase receptor is -4.33Kcal/mol. Vasicine and vasinone have a maximum of five interactions with the target amino acid residues when compared to the standard kojic acid which also has a maximum of 5 interaction sites. Hence it can be concluded that vasicine and vasinone possess promising tyrosinase enzyme blocking activity.

Keywords: Vasicine, Vasinone, Anti tyrosinase activity, Docking, Siddha, Kuttam, *Adathoda vasica*

Introduction

Melanogenesis is a physiological process resulting in the synthesis of melanin pigments which are responsible for skin pigmentation and provide a beneficial effect in preventing skin damage under normal conditions (Bonaventure et al., 2013). Tyrosinase is the rate limiting enzyme involved in melanin synthesis. Hence inhibition of tyrosinase in melanin pathway has become increasingly important for medicinal and cosmetic products used as powerful skin whitening agents for treating skin disorders (Nico Smit et al., 2009).

Vasicine exhibited antimicrobial, antioxidant activity and hence can be effectively implemented in the treatment of skin diseases (Duraipandiyan et al., 2015). Siddha literatures refer to the implementation of *Adathodai vasica* leaves in treating Kuttam, which could be compared to the dermatological diseases including all spectrum of skin ailments, from hyperpigmentation to bullous eruptions. Leaves of *Adathoda vasica* has two principal alkaloids Vasicine and vasinone which are well known for their respiratory stimulatory effect (Lone et al., 2013). Elaborating the pharmacological activities of the alkaloid on basis of the evidence in siddha literatures, vasicine and vasinone are evaluated for their effect against human tyrosinase enzyme receptor in the management of hyperpigmentation of skin diseases (Kuttam).

Materials and methods

The auto dock methodology of docking study is applied to study the binding energy properties and intermolecular interactions of vasicine and vasinone against Human tyrosinase receptor.

Crystalline structure of the target protein Human tyrosinase (5M8M) was retrieved from the protein data bank and the

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protein clean-up process was done and the essential missing hydrogen atom were been added. Different orientation of the lead molecules with respect to the target protein was evaluated by Auto dock program and the best dock pose was selected based on the interaction study analysis. Docking calculations were carried out using Auto Dock 4 (Bikadi and Hazai, 2009; Halgren, 1998). Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. Docking calculations were carried out for test drug Vasicine, Vasinone and standard Kojic acid, against the target protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of Auto Dock tools (Morris et al., 1998). Affinity (grid) maps of ×× Å grid points and 0.375 Å spacing were generated using the Autogrid program (Morris et al., 1998). Auto Dock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (Solis and Wets, 1981). Initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied. The ligand properties of the compounds selected for docking is given in table 1.

Target details

The PDB code of the target Human tyrosinase enzyme is 5M8M and the 2D and3D structures of the lead compounds and the target are given in figure 1 and figure 2.

Results and discussion

The results of the binding interactions between the lead compounds and the standard with that of the target human tyrosinase receptor are obtained by docking analysis and the docking pose of the standard kojic acid, vasicine and vasinone with the tyrosinase enzyme receptor are shown in figure 3a,4a,5a respectively. The interaction study with interaction analysis HB – plotting analysis (Hydrogen Bond formation) of kojic acid is shown in figure 3b, 3c, for vasicine it is shown in figure 4b,4c and for the alkaloid vasinone it is shown in figure 5b and 5c.The result of the receptor ligand complex for the standard kojic acid and the lead compounds vasicine and vasinone are shown in figure 3d, 4d and 5d respectively.

Table 1. Ligand properties of the compounds selected for docking

Compounds	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds	Log P
Vasicine	188.23 g/mol	$C_{11}H_{12}N_2O$	1	2	0	0.4
Vasinone	202.213 g/mol	$C_{11}H_{10}N_2O_2$	1	3	0	0.4
Kojic Acid	142.11 g/mol	$C_6H_6O_4$	2	4	1	-0.9

Table 2. Amino acid residue interaction of lead and standard against Tyrosinase enzyme (5M8M)

No of Interactions	Lead / Standard	Amino Acid Residue Binding						
5	Vasicine	196 VAL	198 LYS	212 ASP	293 LEU	391 THR	392 HIS	
5	Vasinone	196 VAL	198 LYS	212 ASP	216 GLU	293 LEU	391 THR	392 HIS
5	Kojic Acid	196 VAL	198 LYS	212 ASP	391 THR	392 HIS		

Table 3. Summary of the molecular docking studies of the lead compounds against Human Tyrosinase enzyme (5M8M) Receptor

Compounds	Binding Free energy Kcal/mol	Inhibition constant Ki µM (*mM)(**nM)	Electrostatic energy Kcal/mol	Intermolecular energy Kcal/mol	Total Interaction Surface	Frequency
Vasicine	-4.76	323.7	-0.64	-5.06	460.23	94%
Vasinone	-4.03	1.12*	-0.14	-4.33	462.59	52%
Kojic Acid	-3.55	2.49 *	-0.10	-3.39	374.94	98%

Amino acids such as196 VAL, 198 LYS, 212 ASP, 391 THR and 392 HIS are the core residue involved in mediating the Human Tyrosinase enzyme activity. Binding of the lead compounds with this core residue may inhibit the enzyme activity .Out of two compound's docked the compound Vasicine and Vasinone have 5 interactions with rank I when compared to that of the standard Kojic acid with the maximum of 5 interactions. Hence it can be concluded from the study that both the compounds vasicine and vasinone possess promising Tyrosinase enzyme blocking activity. The results of the amino acid residue interactions of vasicine, vasinone and kojic acid are given in table 2.

The results of the present study is summarised as follows and is listed in table 3. The Binding free energy of vasicine and vasinone against the human tyrosinase receptor is - 4.76 Kcal/mol and - 4.03 Kcal/mol and that of the standard kojic acid is -3.55 Kcal/mol. The Inhibitory constant Ki of the leads compounds vasicine and vasinone against the target is 323.7 µM and 1.12Mm and that of kojic acid is 2.49 nM. Both the lead compounds vasicine and vasinone rank I in interacting with the amino acid residues of the target with a maximum of 5 interactions. The standard kojic acid also has five interaction sites with the target in exhibiting its inhibitory effect on the human tyrosinase enzyme receptor.

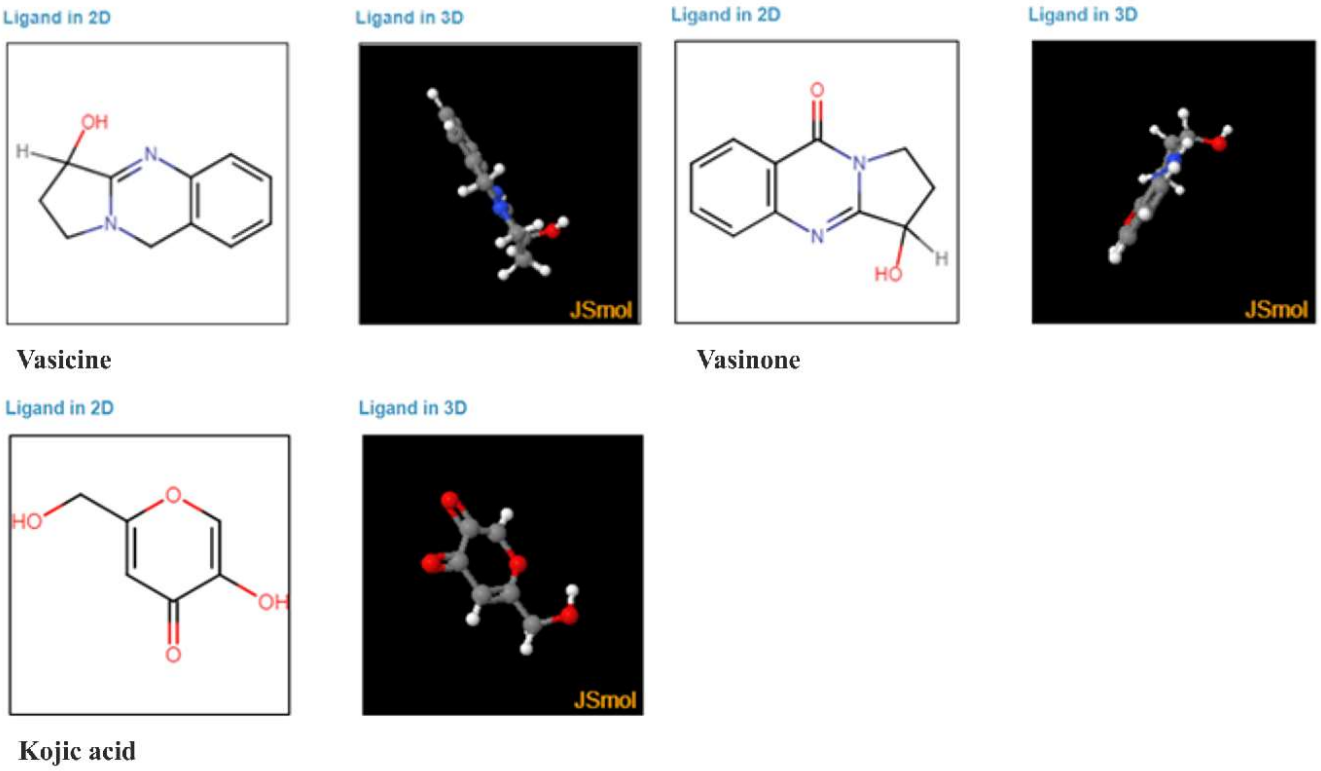


Figure 1. 2D and 3D Structure of the lead Compounds

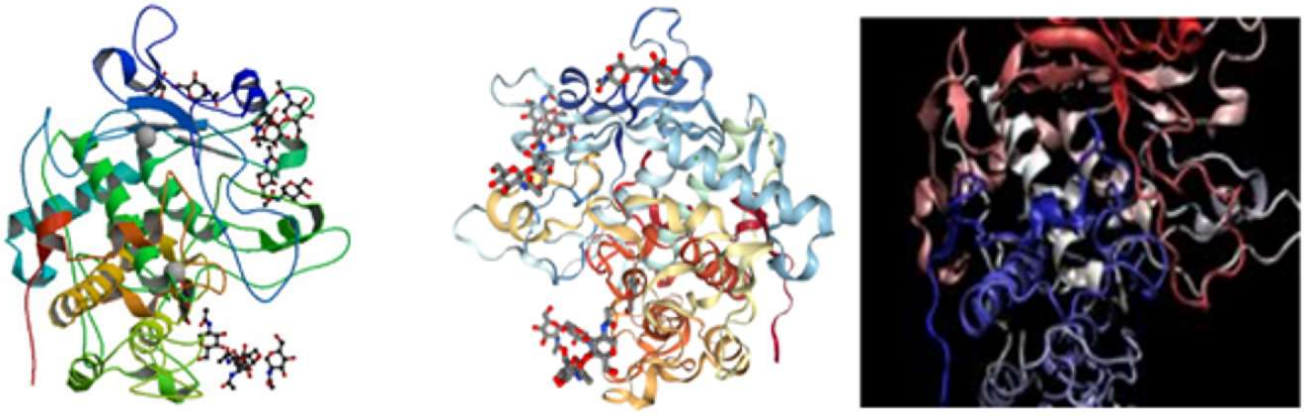


Figure 2. Human Tyrosinase - 5M8M Receptor Structure

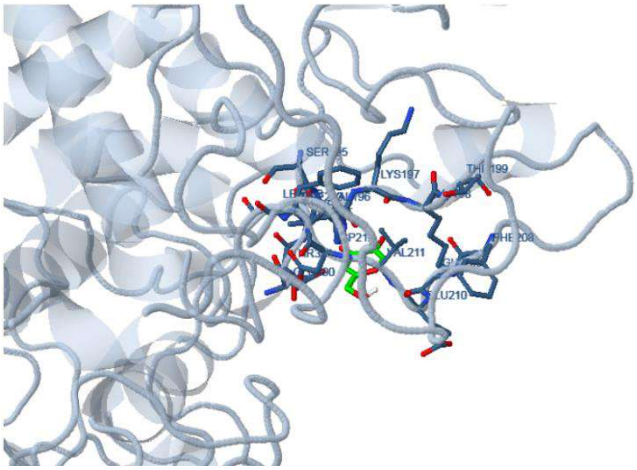
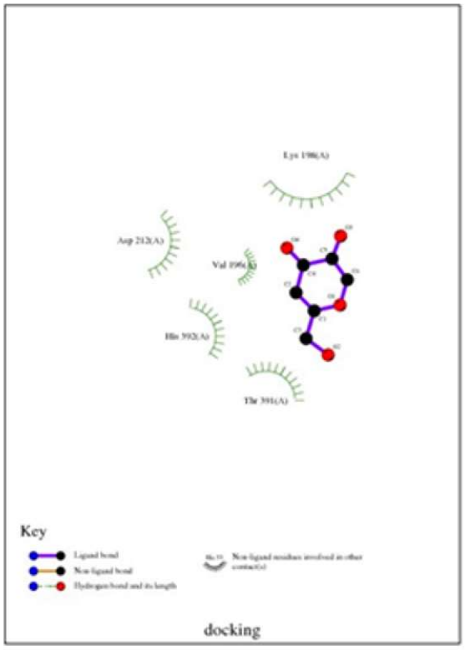


Figure 3a. Docking pose of Kojic acid with Tyrosinase enzyme (5M8M)



Decomposed Interaction Energies in kcal/mol

hydrophobic	other
VAL196 (-0.0915)	LYS198 (-0.6994)
	ASP212 (-0.4215)
	THR391 (-0.3856)
	HIS392 (-0.3705)

Figure 3b. Interaction Study of Kojic acid with Tyrosinase enzyme (5M8M)

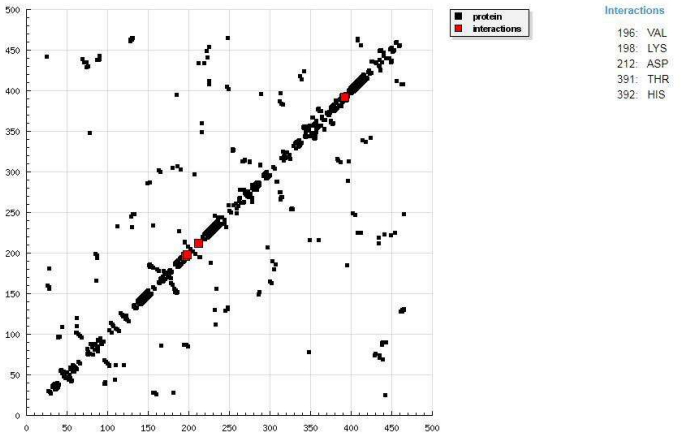


Figure 3c. Interaction Analysis HB - Plotting analysis (Hydrogen Bond formation)

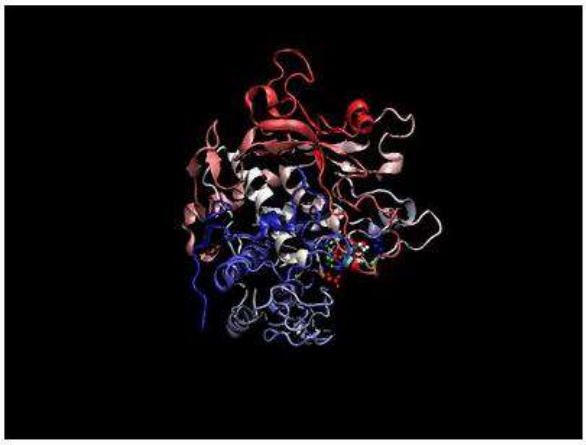


Figure 3d. Receptor ligand complex of Kojic acid with Tyrosinase enzyme (5M8M)

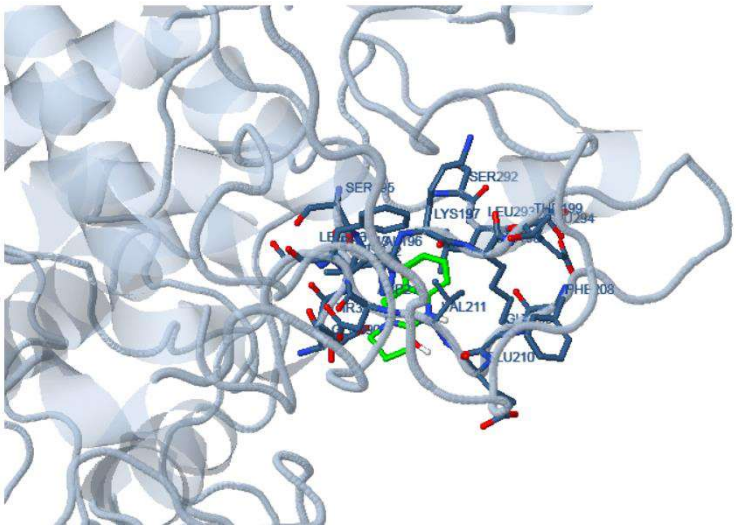
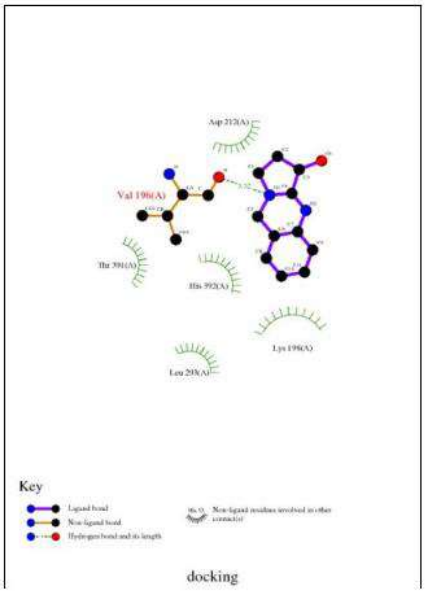


Figure 4a. Docking pose of Vasicine with Tyrosinase enzyme (5M8M)



Decomposed Interaction Energies in kcal/mol

hydrogen bonds	hydrophobic	other
VAL196 (-0.2047)	HIS392 (-0.4251)	LYS198 (-0.6975)
	LEU293 (-0.3412)	ASP212 (-0.4193)
		THR391 (-0.3665)

Figure 4b. Interaction Study of Vasicine with Tyrosinase enzyme (5M8M)

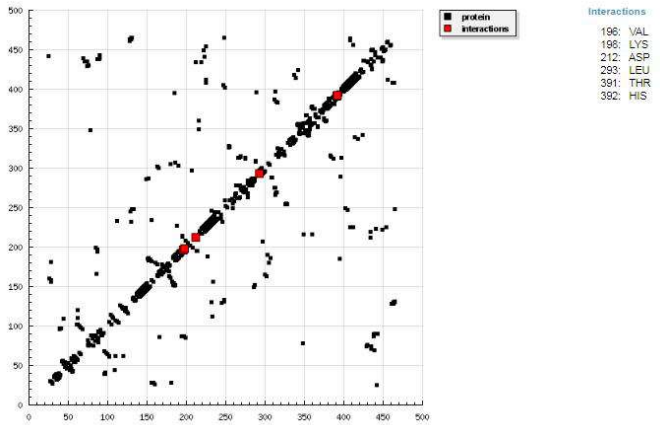


Figure 4c. Interaction Analysis HB - Plotting analysis (Hydrogen Bond formation)

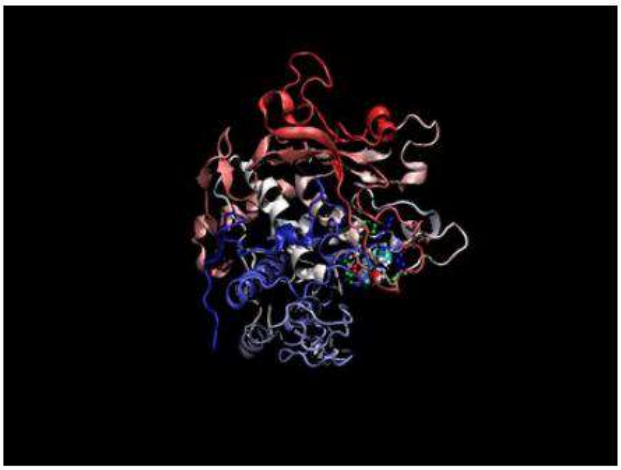


Figure 4d. Receptor ligand complex of Vasicine with Tyrosinase enzyme (5M8M)

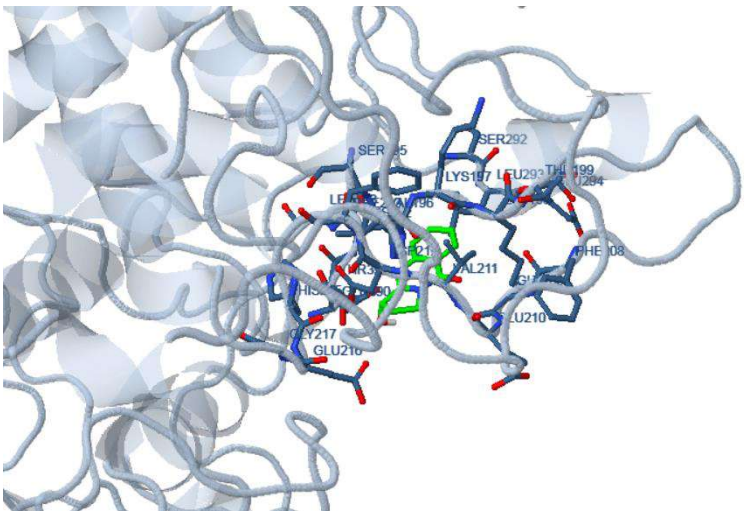
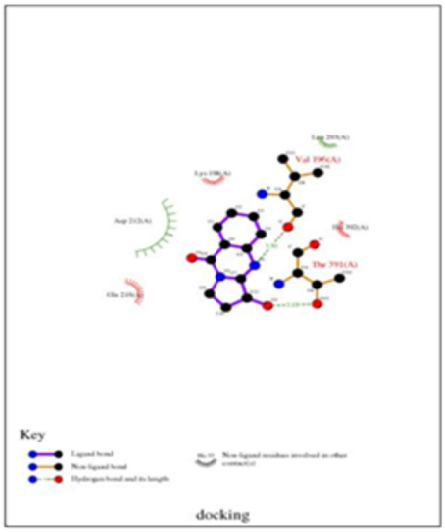


Figure 5a. Docking pose of Vasinone with Tyrosinase enzyme (5M8M)



Decomposed Interaction Energies in kcal/mol

hydrogen bonds	hydrophobic	other
VAL196 (4.1666)	LEU293 (-0.262)	ASP212 (-43.016)
THR391 (4.8182)	HIS392 (0.33)	LYS198 (1.5435)
		GLU216 (7.1122)

Figure 5b. Interaction Study of Vasinone with Tyrosinase enzyme (5M8M)

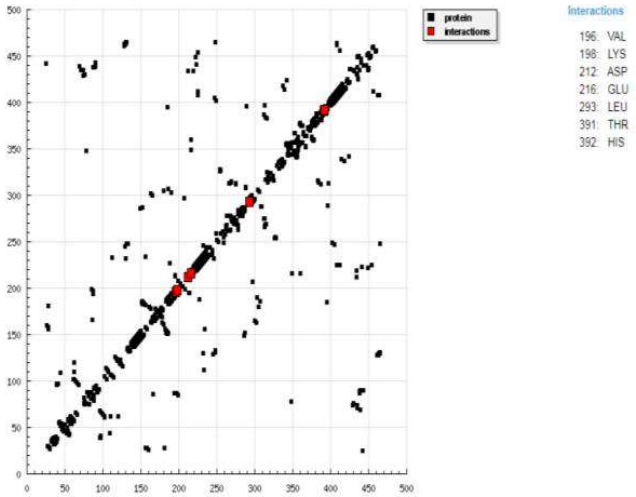


Figure 5c. Interaction Analysis HB - Plotting analysis (Hydrogen Bond formation)

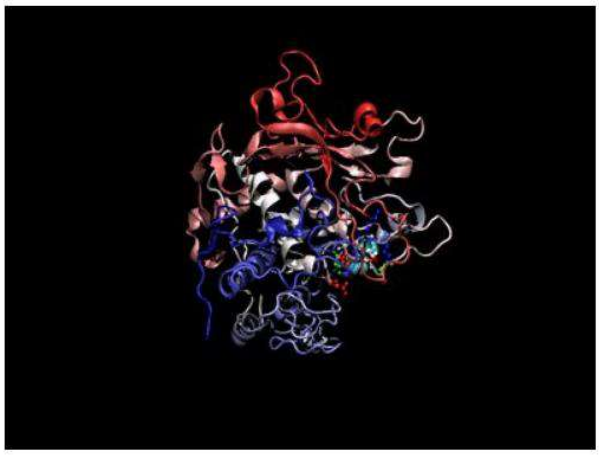


Figure 5d. Receptor ligand complex of Vasinone with Tyrosinase enzyme (5M8M)

Conclusion

The most active amino acid residues of the human tyrosinase enzyme receptor are 96 VAL, 198 LYS, 212 ASP, 391 THR and 392 HIS. From the results of the above study it can be concluded that vasicine and vasinone have tendency to bind with the active sites of tyrosinase enzyme receptor and that the bioactive alkaloids are effective in inhibiting the tyrosinase enzyme and can be implemented in the management of kuttam (hyperpigmentation skin diseases) as mentioned in siddha classical literatures.

Conflict of interest

The authors declare that there is no conflict of interest.

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