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In-Silico studies of active constituents of A*calypha Indica* against Tyrosinase Kinase for Hyperpigmentation

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Abstract

The aim of the study is to evaluate the effect of caffeic acid and tri-o-methylellagic acid against tyrosinase receptor in the management of hyperpigmentation of skin diseases by molecular docking approach. The computational analysis is carried out by. Auto dock 4 tool. The standard used is kojic acid against the target Tyrosinase receptor with PDB code 5ZOD and the target proteins were retrieved from the protein data bank. caffeic acid and tri-o-methylellagic acid 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 caffeic acid and tri-o-methylellagic acid possess promising tyrosinase enzyme blocking activity.

Keywords: Caffeic acid, Tri-*o*-methylellagic acid, Tyrosinase, *Acalypha indica*..

Introduction

Melanins is the end-products of L-tyrosine complex multistep transformations which is widely distributed pigment found in bacteria, fungi, plants, and animals. Melanins are majorly insoluble and naturally consist of four types; allomelanin, eumelanin, neuromelanin, and pheomelanin[1].

Melanogenesis is the production of the melanin pigments; which is produced by cells called melanocytes. There are many proteins, hormones and enzymes are involved in melanogenesis process which may be regulating the melanin production directly or indirectly. Dermo-cosmetic applications of melanin and melanogenesis include mainly the modulation of the melanogenesis pathway to control skin colour like hyperpigmentation. Modulation of melanogenesis to alter the colour and its pattern is passion which has lot of demand and application in human medicine and cosmetics [2].

Melanogenesis control is the main approach for the treatment of abnormal skin pigmentation disorders. Tyrosinase is a key enzyme in the melanogenic pathway, responsible for catalysing two reactions in melanin biosynthesis. tyrosinase inhibitors are clinically useful for the treatment of dermatological disorders like senile lentigo, ephelides (freckles), solar lentigo (age spots), post inflammatory melanoderma and melasma, and also, they are important in the cosmetics industry for whitening and depigmentation after sunburn[3].

Acalypha indica a traditional *plant* has a wide variety nutrient such as carbohydrates, proteins, vitamins, and fat. The plant contains phenolic compounds like geraniin, corilagin, chebulagic acid and glucogallin. The plant also contains Ellagic acid, gallic acid which possess effective antioxidant property[4]. The plant is also said to possess antimicrobial[5], anti-venom property, anti-fertility activity, wound healing effect[6].

Materials and Methods

In silico analysis were carried out to study the binding properties and intermolecular interaction of caffeic acid and tri-*o*-methylellagic acid against Human tyrosinase receptor.

Crystalline structure of the target protein Human tyrosinase (5ZOD) was retrieved from the RCSB protein data bank and the target protein was refined using the discovery studio visualizer[7].

The Docking calculations were carried out using AutoDock4 for the constituents caffeic acid and tri-*o*-methylellagic acid. Kojic acid was chosen as the standard against the target protein model. Gasteiger partial charges were added to the ligand atoms.

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The Lipinski rule for the selected active constituents were compiled using molinspiration cheminformatic software. The ligands and the standard were compiled within the parameters for the Lipinski rule.

The results for the Lipinski rule are summarized in the Table-1.

The binding interaction of the ligand and standard with the human tyrosinase receptor was modulated using AutoDock4 and summarized in Table-2 and 3.

Results and Discussion

The results of the binding interactions between the lead compounds and the standard with that of the target humantyrosinase receptor are obtained by docking analysis and the docking pose of the standard kojic acid, caffeic acid and tri-*o*-methylellagic acid with the tyrosinase enzyme receptor are shown in Table-4.

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. It can be concluded from the study that both the compounds caffeic acid and tri-*o*-methylellagic acid possess promising Tyrosinase enzyme blocking activity.

Table-1: Ligand properties of the compounds selected for docking.

Compound	Molecular weight g/mol	Molecular formula	H bond donor	H bond acceptor	Rotatable bonds	Log p
Caffeic acid	180.16	$C_9H_8O_4$	3	4	2	0.94
Tri-*o*-methylellagic acid	344.27	$C_{17}H_{12}O_8$	8	1	3	1.83
Kojic acid	142.11	$C_6H_6O_4$	2	4	1	-0.9

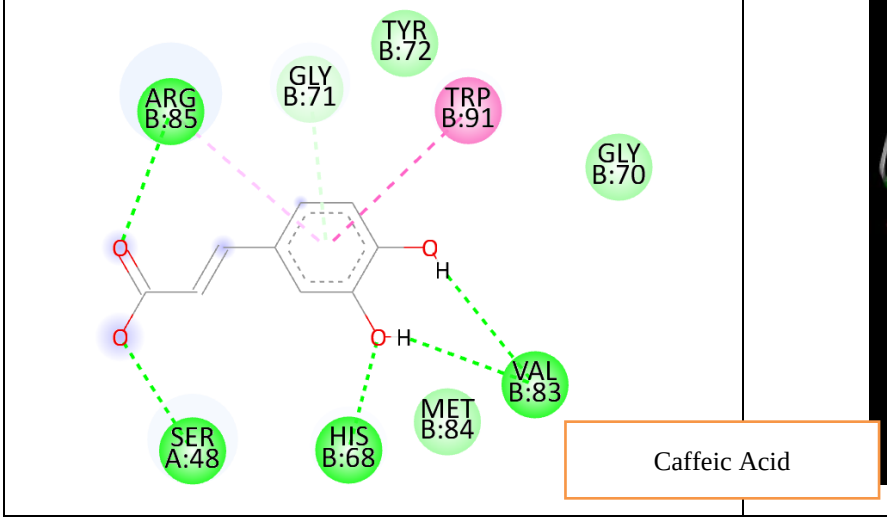
Table-2: Amino acid residue interaction of lead and standard against Tyrosinase enzyme (5ZOD).

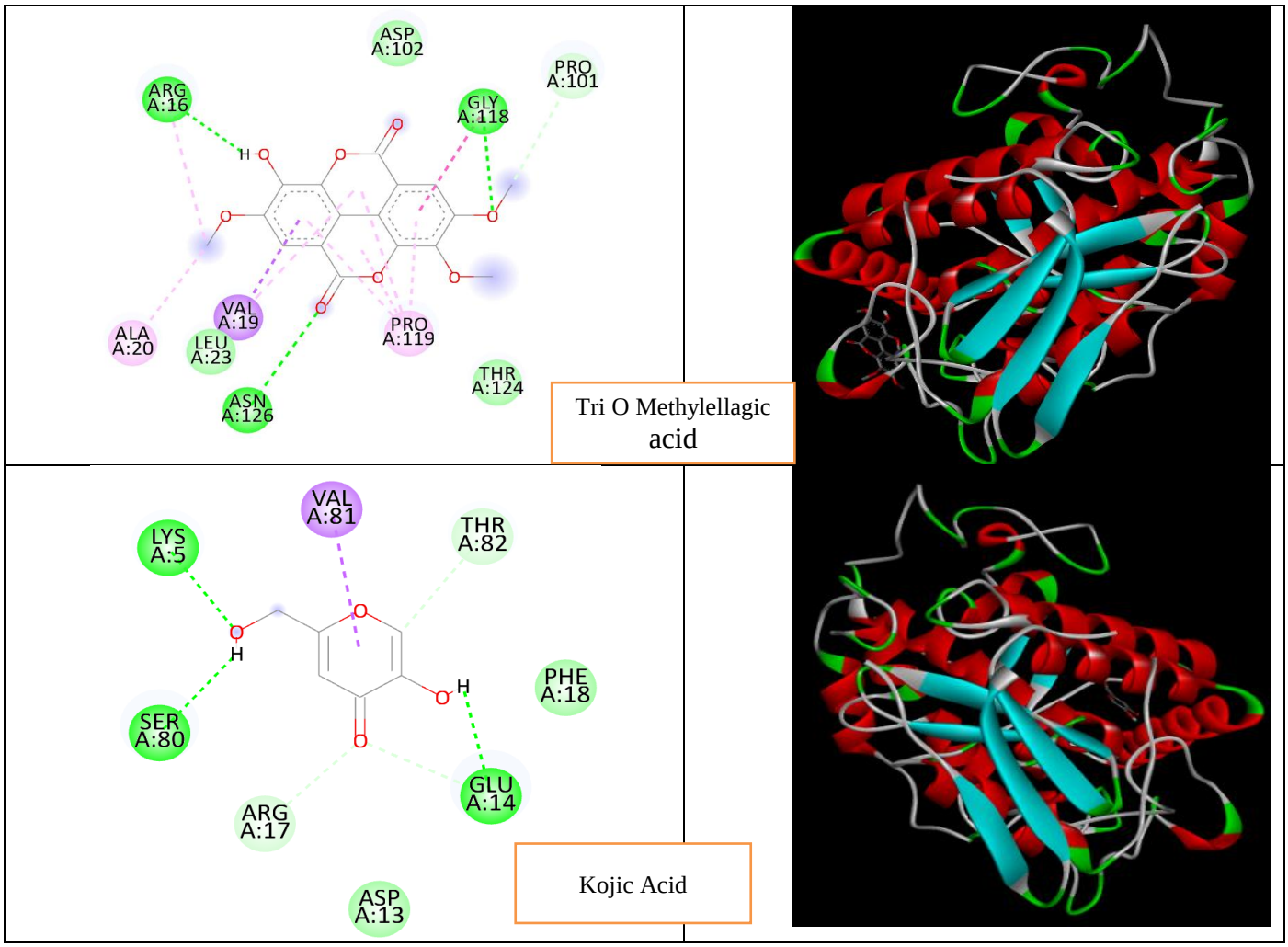
No of interaction	Lead/standard	Amino acid binding
6	Caffeic acid	TRP91, MET84, VAL83, HIS68, SER48, ARG85
8	Tri-*o*-methylellagic acid	ALA20, VAL19, LEU23, PRO119, GLY118, PRO101, ASP102, ARG16
6	Kojic acid	ARG17, GLU14, LYS5, SER80, THR82, VAL81

Table-3: Summary of the molecular docking studies of the lead compounds against Human Tyrosinase enzyme (5ZOD).

Compounds	Binding free Energy kcal/mol	Inhibition constant ki Mm	Electrostatic Energy kcal/mol
Caffeic acid	-4.1	991.17	-0.67
Tri-*o*-methylellagic acid	-5.07	193.31	-0.02
Kojic acid	-4.69	366.16	-0.34

Table-4: 2D and 3D binding interactions of ligands and standard against human tyrosinase receptor (5ZOD).

2D Interaction	3D Interaction
	



Conclusion

The present molecular docking study is focussed on the inhibitory effect of tyrosinase receptor for the management of hyperpigmentation using the constituents of *Acalypha indica*. From the results of the above study it can be concluded that caffeic acid and tri-*o*-methylellagic acid 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 hyperpigmentation skin diseases

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