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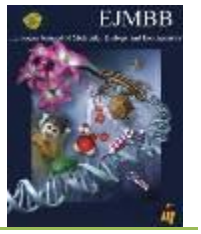

PHYTOCHEMICAL BASED INSILICO DRUG DESIGN OF POTENT INHIBITORS FOR PDE7B- A THERAPEUTIC TARGET FOR COGNITIVE ENHANCEMENT IN NEUROLOGICAL DISORDERS

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ABSTRACT
In the recent times, the role of Phosphodiesterase enzymes in neurological disorders has been of extensive focus in the field of research. Phytochemicals are explored as possible options to inhibit these enzymes. In the present study ought to focus the possible inhibition of PDE7B (i.e.phosphodiesterase-7B) using two phytochemical molecules namely Vasicine from *Adhatoda justiciae* and Forskolin from *Coleus forskohlii*plant respectively. These two molecules were docked against a modelled structure of PDE7B using 'autodock4'. The binding affinity estimated from *in-silico* docking for Vasicine was found to be stronger (-5.0kcal/mol) than Forskolin (-3.5-4.0kcal/mol). Based on this preliminary result, Vasicine would be selected as a prospective lead molecule for further development of inhibitors for PDE7B enzyme.

INTRODUCTION

Treating cognition impairment in neurological disorders has been a medical challenge till date. Recently, the role of Phosphodiesterase enzyme, PDE7B, (a cAMP specific enzyme) in neurological disorders, has been the centre focus in current research [1]. In this work, phytochemicals are explored as a possible option for designing effective inhibitors for PDE7B. A plethora of literature suggests that quinazoline compounds have better inhibitory activity against PDE7 enzyme. We surmise that vasicine, a quinazoline alkaloid from the plant *Adhatoda vasica*, can serve as a potential candidate for PDE7B inhibitor. In addition, forskolin, another phytochemical derived from Indian Forskolhii plant, *Coleus forskohlii*, which has shown increased cAMP levels in the brain, was also selected. We docked these two molecules against a modelled structure of PDE7B and found that both these molecules bind to two sites adjacent to each other [2]. Vasicine exhibited a phi-stacking with F377, encompassed by hydrophobic residues such as. I284, W337, V341, F345, L362, Y172. Whereas, Forskolin, bound to a shallow cavity present on the surface of PDE7B with many of its hydroxyl groups exposed to the solvents and its methyl groups interacting with F377, I284 [3].

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MATERIALS & METHODS

The 2D molecular structure of Vasicine and Forskolin were sketched using 'chempaint' and saved into Simplified Molecular Input Line Entry Specification format (SMILES). The 3D coordinates for PDE7B were generated through homology modelling using 'swisspdb', based on the x-ray crystal structure of PDE7A (3G3N) [4]. The energy was minimized for both the ligands and the structure was imported into 'ADT tools' for addition of hydrogen atoms. Similar to ligand, the structure of protein was imported into ADT tools and hydrogen atoms were added. Prior to docking, grid maps were generated for each ligand atom types using the program 'autogrid4'. The

docking was performed using 'autodock4' with genetic algorithm as the optimization protocol [5,6].

RESULTS & DISCUSSION

Blind docking of Vasicine and Forskolin onto PDE7B was performed using autodock4. The best docked conformation of the each of the ligands was identified through cluster analysis of 200 docked structures. The cluster with least binding energy and large number of conformations was chosen for the binding site analysis. A closer analysis of the binding site suggest that the 3-hydroxyl (OH) group of Vasicine makes a hydrogen bond (length 2.041 A), with carbonyl group (C=O) of Q374 . Further, the Quinazoline ring of Vasicine stacked neatly upon the aromatic ring of F377 (Phi-stacking). Additionally, the benzo- ring of Quinazoline was seen embedded within the hydrophobic environment of F345 and I284 (shown in Figures 1).

On the other-hand, the 6 hydroxyl group of Forskolin made a crucial hydrogen bond (2.015 A) with carbonyl group (C=O) of the backbone of Y380. Another hydrogen bond (salt bridge) was seen between the 5-carboxyl group (COOH) of Forskolin and backbone amide (NH) of N288.The 2-vinyl group of Forskolin was surrounded by hydrophobic residues such as F377, I381, L284, L362 (shown in Figures 2).

To consummate, both these ligands exhibit strong hydrophobic interactions and few critical hydrogen bonding but Vasicine showed a specific phi-stacking along with a hydrogen bond in a partially buried cavity far away from the surface. Whereas, Forskolin, interaction was dominated by two specific hydrogen bondings and hydrophobic interactions in a cavity present on the surface of the protein.

Figure 1. The docked structure of Vasicine and Forskolin onto PDE7B is shown in yellow. The binding site residues of PDE7B interacting with Vasicine & Forskolin is highlighted in red below.

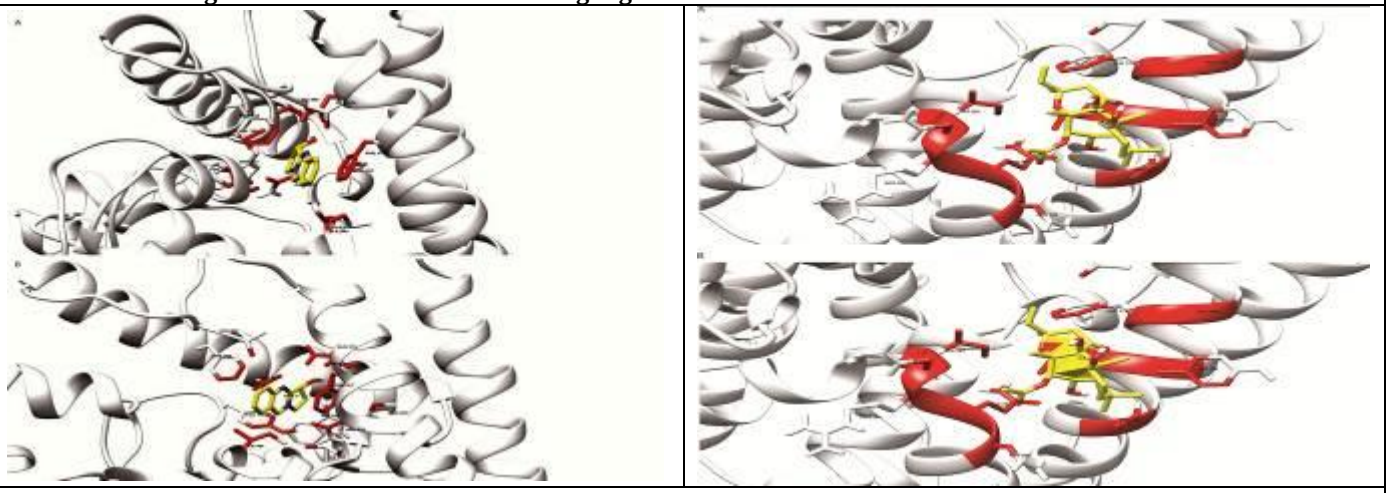

Figure 2. The docked structure of Vasicine and Forskolin onto PDE7B is shown in yellow. The binding site residues of PDE7B interacting with Vasicine & Forskolin is highlighted in red below.

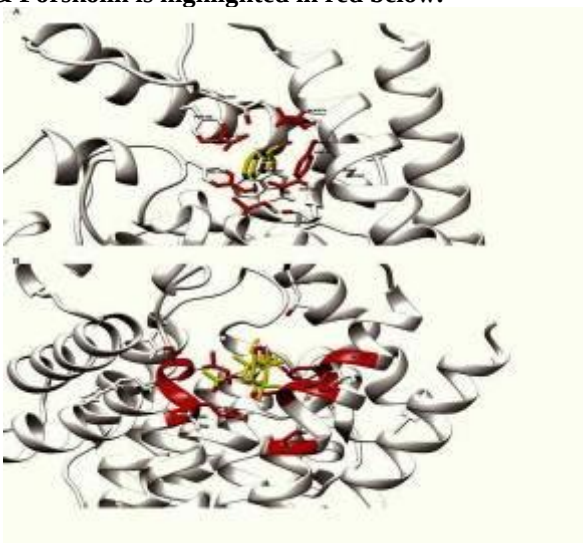

Table 1. ADME Properties of Forskolin and Vasicine (Software: Osiris data warrior)

Molecule	Forskolin	Vasicine
MMFF94_energy	161.337526	5.180197
Total_Molweight	410.505	188.229
cLogP	1.3206	0.2244
cLogS	-3.105	-1.531
H-Acceptors	7	3
H-Donors	3	1
Polar_Surface_Area	113.29	35.83
Druglikeness	-4.6773	3.3165
LE_from_Structure_No	0.42576	0.88192
LLE_from_Structure_No	7.6794	8.7756
LELP_from_Structure_No	3.1018	0.25444
Mutagenic	none	None
Tumorigenic	high	None
Reproductive_Effective	none	None
Irritant	low	None
Rings	3	3
Aromatic_Rings	0	1
sp3-Atoms	23	5

Comparatively, the binding affinity estimated from *in-silico* docking for Vasicine was found to be stronger (-5.0kcal/mol) than Forskolin (-3.5-4.0kcal/mol). Based on this preliminary result, we selected Vasicine as a prospective lead molecule for further development of inhibitors for PDE7B enzyme.

CONCLUSION

Vasicine showed strong binding affinity towards PDE7B enzyme, hence, it was selected as a potential lead compound for further development of inhibitors for PDE7B enzyme. In future, *in-vitro* and *in-vivo* studies will be performed on the lead molecule to validate whether the ligand shows adequate increase in cAMP levels in brain and improve cognition impairment caused by various neurological disorders.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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