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Short Communication

IN SILICO EXPLORATION OF ACETYLCHOLINESTERASE MODULATORY EFFECTS OF LIGNANS: A HYPOTHETICAL VIEW

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ABSTRACT

Acetylcholinesterase inhibition is desirable for the therapeutic management of certain disorders. In silico docking simulations were performed to predict the ability of several dietary lignans to interact with acetylcholinesterase (AChE), an enzyme involved in the regulation of neurotransmission. AutodockVina was used to simulate docking of various lignans such as arctigenin, hydroxymatairesinol, pinoresinol, secoisolariciresinol and sesamin employing chain A of human recombinant acetylcholinesterase (PDB: 4ey7). Conditions used for docking simulations were validated by evaluation of agreement between the predicted binding pose of the cognate ligand, donepezil, and its binding pose in the crystal data. Simulations and analysis of binding pocket revealed that selected lignans are likely to interact with the donepezil-site on AChE, and hence we opine that it is worth exploring AChE inhibitory potential of dietary lignans using biological models.

Keywords: Acetylcholinesterase, AutodockVina, Lignans

1. INTRODUCTION

Acetylcholinesterase (AChE, choline hydrolase, EC 3.1.1.7), is an enzyme that catalyses the hydrolysis of the neurotransmitter acetylcholine (ACh) [1]. Acetylcholine serves as a signalling molecule at neuron-neuron, neuro-muscular and neuro-glandular junctions. Biological activity of acetylcholine can be explained on the basis of activation of two different classes of receptors (muscarinic type and nicotinic type) [2, 3], leading to typical changes in post-synaptic or recipient cells. G-protein coupled receptors found in cardiac and smooth muscle cells convert acetylcholine signal into intracellular events by activating heterotrimeric G-proteins that control cellular events by modulating levels of secondary messengers such as cAMP, diacyl glycerol or Inositol triphosphate. Acetylcholine can also activate cationic ion channels in post synaptic cells such as neurons or skeletal muscle leading to excitatory activity. Acetylcholine activated ion channel (nicotinic ACh Receptor) is a transmembrane cationic channel made of 5 subunits. Binding of ACh on the extracellular domain of the receptor, leads to opening of cationic channel that permits movement into the cell of cations such as sodium ion. Membrane depolarization caused by influx of cations is responsible for the cellular events generated by ACh in postsynaptic cells that respond via nAChR. Acetylcholinesterase catalyzes hydrolysis of ACh into choline and acetate, thus terminating the ACh signal. Consequently, agents with propensity to modulate AChE activity will exert significant influence on processes governed by cholinergic systems.

Tolerable AChE inhibitors are desirable for management of Alzheimer's disease (AD), which is a serious neurodegenerative disease associated with memory loss. Pathology of AD is characterized by neuronal cell death and deficiency in cholinergic signalling has been deemed as a major causal mechanism associated with AD. Consequently, AChE inhibitors such as donepezil are employed for management of AD [4]. The concept of functional foods has emerged from knowledge of health promoting properties of many food-derived bioactives [5]. Many researchers have explored plant-derived molecules as AChE inhibitors for possible application as interventions for management of AD [6, 7]. It may be argued that molecules identified from plant sources that are widely consumed as a part of diet may be associated with better safety. Hence, we performed molecular docking simulations with common lignans to predict their propensity to interact with donepezil-site on AChE.

2. *IN SILICO* EXPLORATION- DOCKING SIMULATION

In silico docking simulations were performed to predict the propensity of selected lignans to interact with donepezil-binding site on the AChE. Crystal structure of acetylcholinesterase in complex with the inhibitor donepezil (PDB: 4ey7) was downloaded from the Protein Data Bank (https://www.rcsb.org/) as a pdb file and processed on a local computer to render the structure suitable for docking simulations. Initially, the structure was loaded on UCSF-Chimera and 'B' subunit was deleted. The non-covalent occupants were removed and the A chain was saved as a pdb file. The pdb file of A chain was then converted into the 'pdbqt' after adding polar hydrogens using MGL tools. The ligand files used in the study were downloaded from Pubchem database as 'sdf' files, which were first converted into 'pdb' format and then pdbqt format. AutodockVina was used to perform docking simulations [8] and output with best binding affinity values were saved as 'pdb' files for visualization and analysis of binding pocket. The docking simulations were performed with the grid centre of x, y, z=-6.5, -39.5, 27 and a grid box of 47x42x62 Å around the ligand site. Ligplot+ was used [9] for analyzing the binding pocket for hydrogen bonds and hydrophobic interactions between the ligand and the protein.

3. RESULTS

Ligands used for the present study along with predicted affinities for AChE as well as nature of interactions involved in stabilizing the predicted model for each ligand are depicted in Table 1.

Table 1: *In silico* docking simulations, predicted affinity and nature of protein-ligand interactions

S. N.	Ligand	Predicted Affinity (kcal/mol)	Predicted interactions between protein and ligand
1	Donepezil	-11.8	**H-Bond**: Phe295 **Hydrophobic interactions**: His447, Gly448, Trp86, Tyr124, Tyr337, Tyr341, Trp286, Ser293, Tyr72, Phe338, Phe338, Val294
2	Sesamin	-11.5	H-bond: Ser293 **Hydrophobic interactions:**Phe295, Tyr124, His447, Ser203, Phe338, Tyr341, Trp286, Gly121 Val294 Leu289 Phe297
3	Hydroxymatairesinol	-10.2	H-bond: Asp74 Tyr341, Trp86 Hydrophobic interactions: Tyr72, Tyr124, Phe338 Ser293, Tyr337, Trp286, Phe295, Ser125, Asn87, Arg296 Val294, Gly121
4	Pinoresinol	-10.0	**H-bond**: Ser203 **Hydrophobic interactions:** Trp286, Tyr341, Tyr124, Trp86, Glu202, Gly448, Hist447, Phe338, Phe295, Tyr133, Gly120, Gly121, Phe297
5	Arctigenin	-9.9	**H-bond**; Phe295 , Tyr72 **Hydrophobic interactions**:Phe338, Tyr337, Trp86, Tyr124, Tyr341, Trp286, Val294, Asp74 Leu76 Phe297
6	Secoisolariciresinol	-9.2	**H-bonds**: Phe295, Ser203, Tyr124, Tyr72, Gly122 **Hydrophobic interactions:**Tyr341, Phe338, His447, Trp286, Val294, Phe297

Underlined interactions are common between predicted model and crystal data (disregarding the nature of interaction)

Before attempting docking simulations with selected lignans, an attempt was made to validate the docking parameters by analyzing the binding pose predicted by Vina for the cognate ligand, donepezil. As depicted in Fig 1A, predicted pose for predicted binding of donepezil (magenta) showed significant superimposition with its binding pose (yellow) in the crystal structure data. More importantly, docking simulation was able to accurately predict correctly most of the amino acids involved in stabilizing the protein-ligand complex. The nature of these interactions is depicted in Table 1 as well as Fig 2A. Agreement between the predicted model and crystal data for both binding pose as well as the interactions involved in binding pocket suggested that the parameters adopted

for performing docking simulations could be employed to hypothesize whether selected lignans have propensity to interact with the donepezil-site.

Compared to predicted binding affinity of the cognate ligand (donepezil, -11.8 Kcal/mol), the binding affinities of selected lignans was found to be in the order of Sesamin (-11.5 Kcal/mol)>Hydroxymatairesinol (-10,2 Kcal/mol)>pinoresinol (-10.0 Kcal/mol)>arctigenin (-9,9 Kcal/mol)>Secoisolariciresinol (-9.2kcal/mol). More importantly, all selected ligands were predicted to interact with the donepezil site on AChE (Fig 1B-F). The nature of interactions involved in stabilizing the predicted binding poses for each lignin is depicted in Table 1 and Fig. 2B-F.

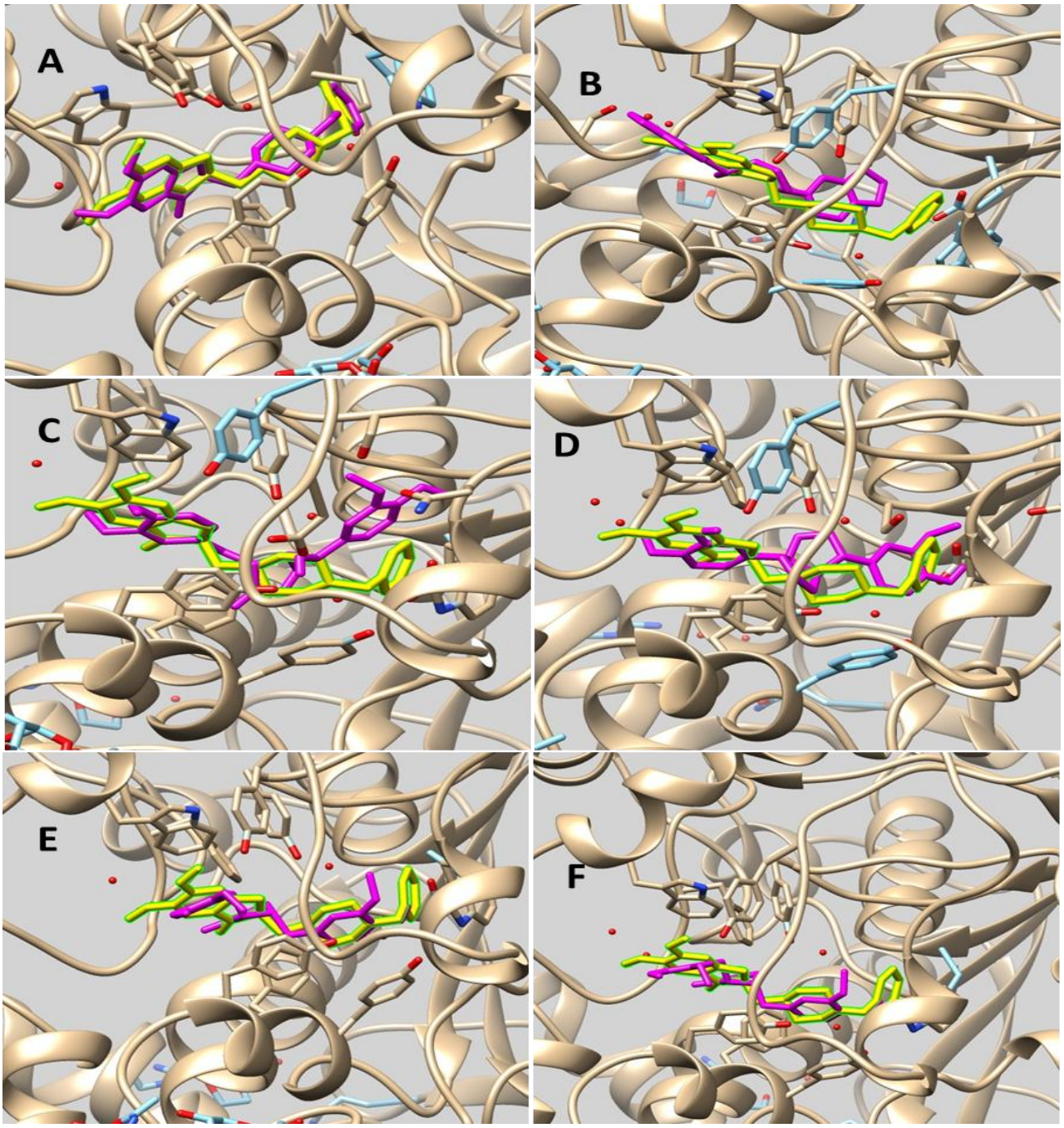

Fig.1: Predicted binding pose of donepezil and lignans (magenta) on acetylcholinesterasesuperimposed with binding pose of donepezil (Yellow). (A-Donepezil; B- Sesamin; C- Hydroxymatairesinol; D-Pinoresinol; E-Arctigenin; F- Secoisolariciresinol).

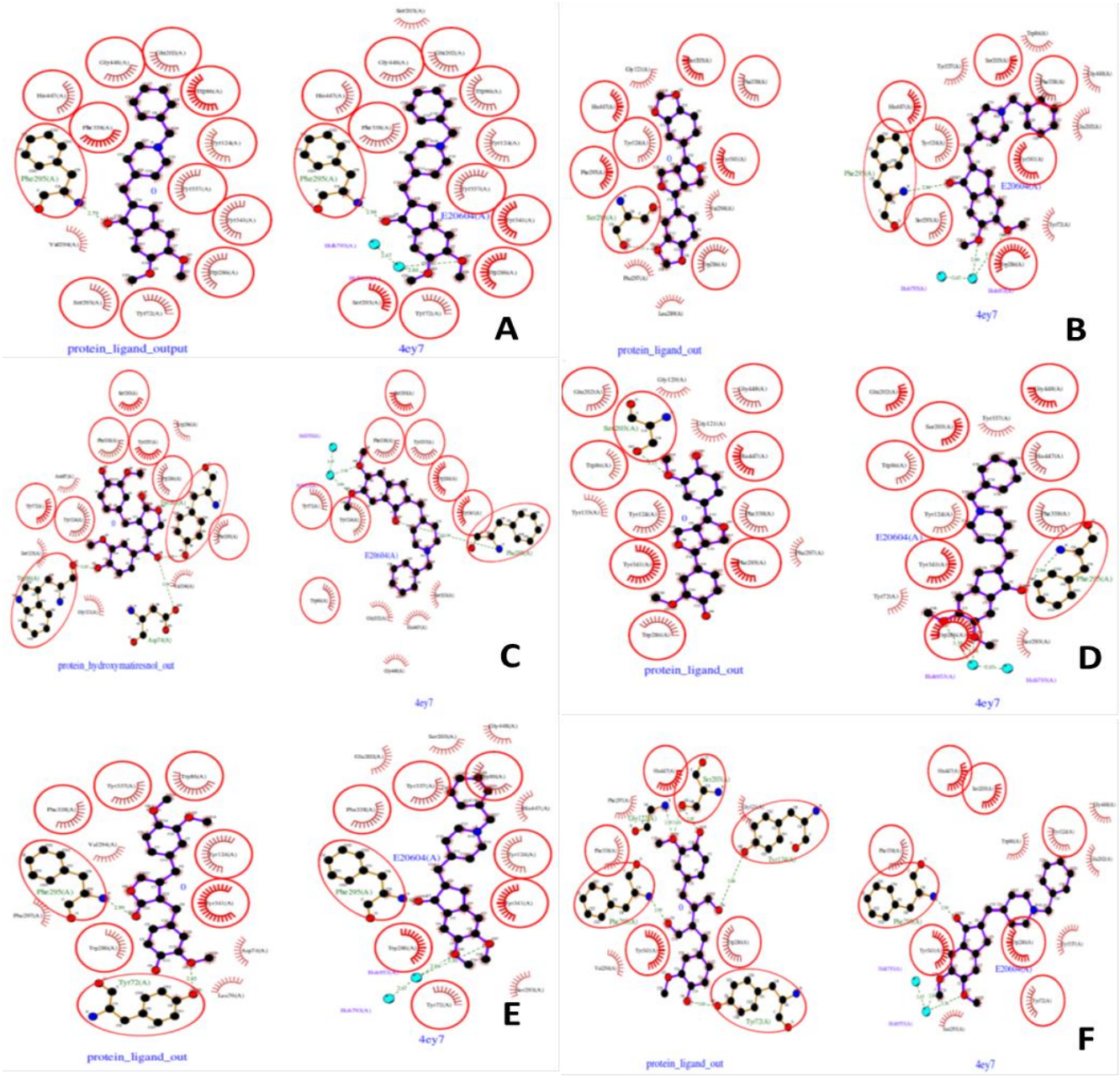

Fig. 2: Nature of predicted interaction between docked molecules and acetylcholinesterase. Circled interactions are conserved between the predicted model (left) and crystal data (right). (A-Donepezil; B- Sesamin; C- Hydroxymatairesinol; D- Pinoresinol; E-Arctigenin; F- Secoisolariciresinol)

4. CONCLUSION

Based on the predicted binding pose and analysis of binding pocket for each selected lignan, we opine that dietary lignans are good candidates for exploring their AChE inhibitory potential. This view is further strengthened by a report demonstrating the potential of secoisolarisiresinol to inhibit AChE in vitro [10]. Therefore, we conclude that dietary lignans are good candidates for studying anticholinesterase potential for exploitation as interventions for managing disorders where cholinergic hypothesis is applicable.

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6. REFERENCES

1. Sogorb MA, Vilanova E. *Toxicol Lett*., 2002;**128(1-3):**215-228.
2. Ishii M, Kurachi Y. Muscarinic *Curr Pharm Des*., 2006; **12:**3573-3581.
3. Albuquerque EX, Pereira EFR, Alkondon M, Rogers SW. *Physiol Rev*., 2009; **89(1):**73-120.
4. Mehta M, Adem A, Sabbagh M. *Int J Alzheimers Dis*., 2012; **2012:**1-8.
5. Bhaskarachary K, Vemula SR, Gavaravarapu SRM, Joshi AKR. *Proc Indian Natl Sci Acad*., 2016; **82:**1565-1577.
6. Mukherjee PK, Kumar V, Mal M, Houghton PJ. *Phytomedicine*, 2007; **14(4):**289-300.
7. Murray AP, Faraoni MB, Castro MJ, Alza NP, Cavallaro V. *Curr Neuropharmacol*., 2013; **11(4):**388-413.
8. Trott O, Olson AJ. *J Comput Chem*. 2010; **31(2):**455-461.
9. Wallace AC, Laskowski RA, Thornton JM. *Protein Eng*. 1995; **8(2):**127-134.
10. Köse,Leyla Polat; Gulcin I. *Rec Nat Prod*., 2017; **11(6):**558-561.