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INSILCO IDENTIFICATION OF SUITABLE ACETUYLCHOLINESTERASE INHIBITORS FROM *MORINDA CITRIFOLIA LINN*. WITH REFERENCE TO ALZHEIMER'S DISEASE

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Keywords:

Alzheimer's disease (AD), Acetylcholinesterase, *Morinda Citrifolia Linn*, Docking studies, Huperizine-A as a drug molecule

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ABSTRACT: Alzheimer's disease, the most common form of dementia accounting for about 50-60% of the overall cases among persons over 65 years of age is characterized by the progressive decline in cognitive function, mediated through learning and memory. According to Cholinergic hypothesis, AD is caused by reduced synthesis of the neurotransmitter ACh, wherein the AChE levels were increased which causes damage to the cholinergic neurons finally leading to cognitive impairments. Hence, all therapies for AD are targeted at the cholinergic system. In this context, docking studies play key role in computer-aided drug design paradigms. As an attempt to identify such natural cholinomimetic and neuroprotective activities, a set of 25 drug molecules from the phytoconstituents of the plant, *Morinda citrifolia Linn.* Were collected from PubChem Database. These compounds were docked against human AChE (PDB ID: 1B41 and 1N5R) proteins retrieved from Protein Data Bank were performed by Pyrex Virtual Screening tool (Auto Dock Vina). After docking, among these 25 compounds, the drug molecule Huperizine A (854026) was found to have the highest binding energy with both target proteins viz.1B41 and 1N5R (-10.2- and -10.0 respectively) and it contains best binding affinity and interaction of amino acids on the active site of protein pocket binding region. Hence, Huperizine A was predicted as the best drug molecule with Anticholinesterase activity for AD.

INTRODUCTION: Alzheimer's disease (AD), is a slowly progressive disease of the brain that is characterized by impaired memory and disturbances in reasoning, planning, language, and perception. For a quarter of a century, the pathogenesis of Alzheimer's disease (AD) has been correlated with cholinergic system abnormalities and intellectual impairment [1]. Subsequently, the cholinergic hypotheses of AD gained considerable acceptance, stating that a serious loss of cholinergic function in the central nervous system contributed to cognitive symptoms [2].

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Over the years, both evidence for and challenges to the relationship between acetylcholine dysfunction and AD have been put forward [3]. The dramatic loss of synapses and degeneration of cholinergic cells results in the reduction of acetylcholine (ACh), which is believed to play a vital role in the cognitive impairment associated with AD. Recent study showed that Acetyl cholinesterase (AChE) plays a key role in accelerating Aβ plaques deposition. Thus, the cholinergic hypothesis has become the leading strategy for the development of anti-AD agents which are inhibitors of AChE [4]. At present, AChE inhibitors, Anti-amyloid vaccine and Vitamin E are recommended to treat AD but long-term exposure to these drugs causes side effects.

Hence our present search is focused on plant-derived natural products like *Morinda citrifolia L.*

commonly known as Indian Noni, one of the most significant sources of traditional medicine that may offer treatment for AD. The genus Morinda (Rubiaceae), includes around 80 species. Noni is the Hawaiian name for the fruit of *Morinda Citrifolia L*. Noni is native from Southeast Asia to Australia and is cultivated in Polynesia, India, the Caribbean, Central and northern South America [10]. The Polynesians have been using the Noni plant for food and medicinal purposes for more than 2000 years [11].

A wide variety of pharmacological activities have been attributed to the fruit, leaf and root extracts of noni such as antioxidant [12, 13] and hepatoprotective [14]. Nevertheless, there have been only a few reports on the use of noni for CNS disorders such as anxiolytic and antiepileptic [15], neuroprotective effect against stress-induced cognitive impairment [16] and some neuro pharmacological effects [17]. As the extracts and fruit juice of *M.citrifolia* have been shown to possess neuroprotective against Alzheimer's disease in some earlier studies [18, 19], in the present study a humble attempt has been made to design new lead molecules from *Morinda citrifolia L*., plant compounds with larger selectivity and AChE inhibitory activity for treating Alzheimer's disease.

MATERIALS AND METHODS:

Noni (*Morinda citrifolia)*:

Scientific classification:

Kingdom : Plantae
(Unranked) : Angiosperms
(Unranked) : Eudicots
(Unranked) : Asterids
Order : Gentianales
Family : Rubiaceae
Genus : Morinda
Species : *M. citrifolia*

Tools and Softwares employed for Determination of the following parameters

S.No.	Name of the parameter	Tools/database employed
1	Collection of protein	NCBI, PDB and PubChem
2	Energy minimization	Argus lab
3	Active site prediction	CAST-p Server
4	Collection of Ligand molecules	PubChem
5	Protein Ligand docking	Auto Dock Vina (Pyrex)
6	Interaction and Visualization	Pymol
7	Prediction of ADME properties	Osiris, PASS Prediction and Mol inspiration

Preparation of Ligands for docking studies:

The 25 bioactive compounds of *M. citrifolia Linn*., were collected in 3D SDF format from PubChem database http://puBChEm.ncbi.nlm.nih.goc/). The compounds were added with hydrogen's and energy minimized with UFF force field using conjugate- gradient algorithm by Auto Dock and Pyrex [20]. Later, all lead molecules were converted in to Auto Dock Pdbqt format.

Preparation of Protein for docking studies:

The Acetylcholinesterase (PDB IDs: 1B41&1N5R) proteins were retrieved from Protein Data Bank. Then, these two proteins were opened with word document and removed hetero atoms then energy minimization will be performed by using Argus lab.

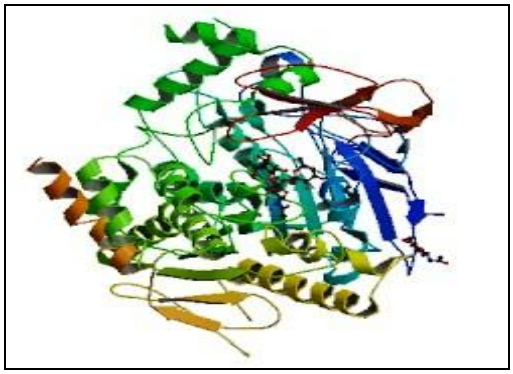
RESULTS:

Structural Details of Proteins:

Protein 1B41		Protein 1N5R	
Polymers	**2 (chain A & B)**	**Polymers**	**2 (chain A & B)**
PubMed id	11053835	PubMed id	12505979
Length	539 and 61	Length	543
Structural weight	66664.94	Structural weight	121351.43
Resolution	2.76A^0	Resolution	2.25A^0

PDB Structures of Both Human AChE Proteins:

PROTEIN 1B41 **PROTEIN 1N5R**



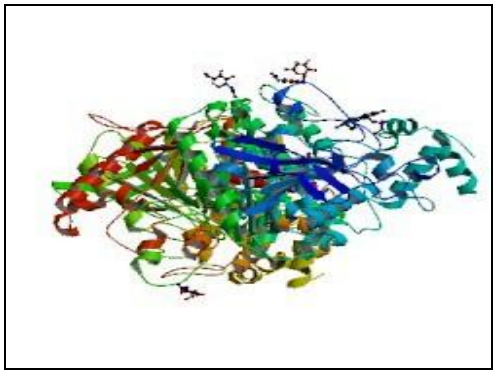
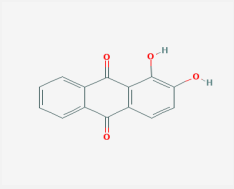
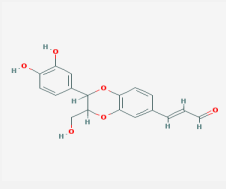
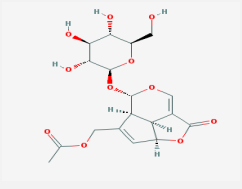
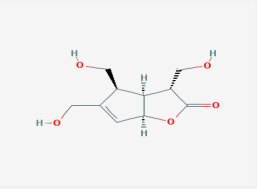


TABLE 1: LIGANDS SELECTED FOR DOCKING STUDIES AGAINST AChE PROTEINS: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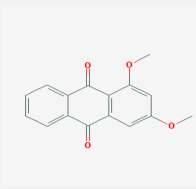	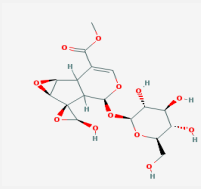	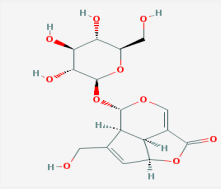	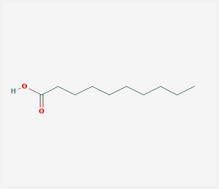	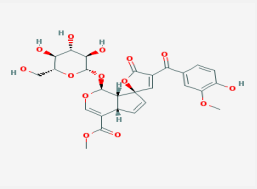
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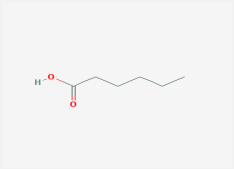	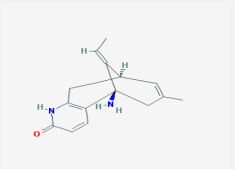	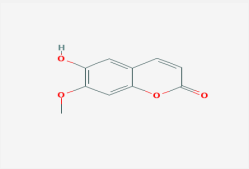	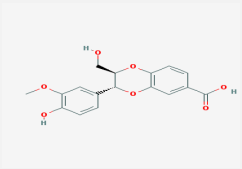	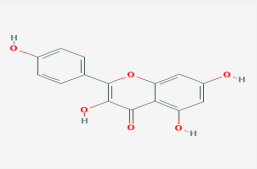
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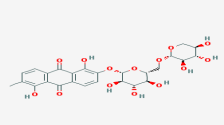	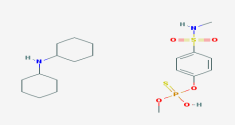	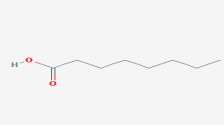	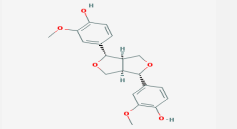	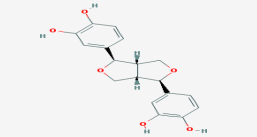
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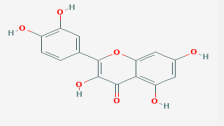	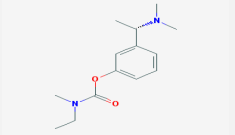	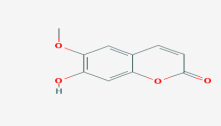	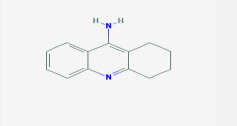	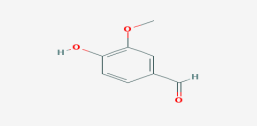
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Identification of Active site for AChE proteins:

The Pymol interaction of selected drug molecules on the binding pocket of AChE proteins active sites were predicted by using (CASTp) program (http://cast.engr.uic.edu) [21].

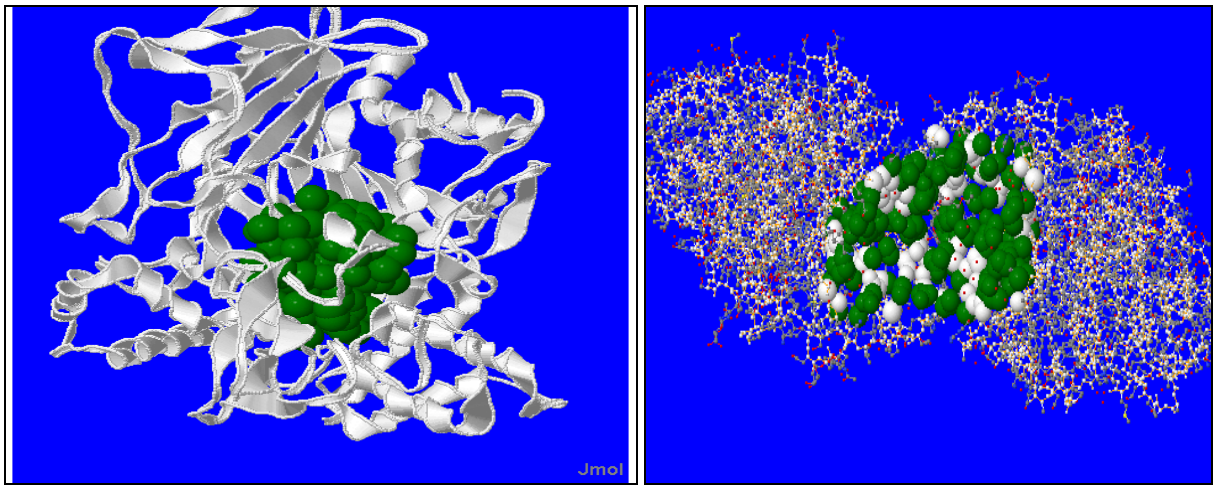
The predicted ligand binding pocket for AChE Proteins was shown in **Table 2** and **3**.

Binding pockets of AChE protein active site:

1B41	Ser-203, Thr-83, Thr-238, Glu313, Gly-234, Arg-296, Tyr-337, Ser-125, Glu-202, Tyr-503, Gln-413, Asn-533, His-405, Trp-532
1N5R	Ser-203,Gln-202,Tyr-133,ly-120,Trp-86,Tyr-337,His-381,Asp-74,Tyr-124,Glu-202,Tyr-341,Tyr-133,Glu-71, Ser125.

Based on above pocket binding sites of both proteins it was evident that these drug molecules were able to bind to any one of the sub sites of selected target proteins and inhibit AChE activity.

Protein 1B41 **Protein 1N5R**



PICTURE1: SHOWING THE CAST-p POCKET BINDING SITES FOR AChE PROTEINS:

TABLE 2: INTERACTION STUDIES EMPLOYED BY 1B41 PROTEIN THROUGH PYMOL:

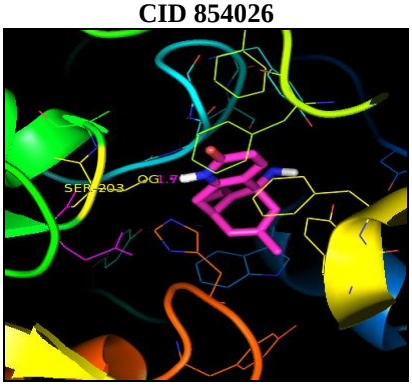
S.No.	Compound	Hydrogen bonding Protein and Ligand interaction	Amino acid	Distance	Binding Affinity
1	854026	OG----------HN	SER-203	1.7	- 10.2
2	1935	OH----------NH	THR-83	2.3	-8.1
		OG----------OH	THR-238	2.9	
		NC----------OH	GLU-313	3.1	
3	84298	NC----------OH	THR-238	3.1	-7.7
		OC----------HO	GLY-234	2.1	
		NH----------OC	ARG-296	3.0	
		NH----------OC	ARG-296	3.1	
		OH----------OH	TYR-337	2.9	
4	69894	OG----------OC	SER-125	3.1	-7.6
		OE----------OC	GLU-202	3.1	
		OH----------OH	TYR-503	2.8	
5	6293	NE----------OC	GLN-413	3.2	-7.6
		ND----------OC	ASN-533	3.4	
		OC----------HO	HIS-405	2.0	
6	5280343	OC----------HO	TRP-532	2.3	-7.5
		OC----------HO	GLY-234	2.2	
		OG----------OH	THR-238	3.1	

TABLE 3: INTERACTION STUDIES EMPLOYED BY 1N5R PROTEIN THROUGH PYMOL

S.No.	Compound	Hydrogen bonding Protein and Ligand Interaction	Amino acid	Distance	Binding Affinity
1	854026	OG---------- HN	Ser-203	1.9	**-10.0**
2	6293	OE----------HO	Glu-202	2.2	-9.7
		OH----------OC	Tyr-133	2.8	
		OH----------OH	Tyr-133	2.9	
		OC----------HO	Gly-120	2.3	
		OC----------OC	Trp-86	3.3	
		OH----------OC	Tyr-337	3.0	
3	361511	ND----------OC	His-381	3.1	-9.4
		ND----------OC	His-381	3.3	
4	5280863	OD----------HO	Asp-74	2.3	-9.2
		OH----------OH	Tyr-124	3.1	
		OH----------OC	Tyr-337	3.2	
		OE----------HO	Glu-202	1.9	
5	5459018	OC----------OC	Tyr-341	3.4	-8.7
		OH----------OH	Tyr-133	2.8	
		OH----------HO	Trp-86	2.2	
		OH----------OC	Tyr-337	3.3	
		OH----------OC	Tyr-337	2.9	
		OH----------OH	Tyr-341	3.2	
6	44593378	OD----------HO	Asp-74	2.8	-8.5
		NC----------OH	Asp-74	2.8	
		OH----------OH	Tyr-124	2.9	
		OH----------OC	Tyr-124	2.9	
		OH----------OH	Tyr-124	3.0	
		OE----------HO	Gln-71	2.3	
		OG----------OC	Ser-125	3.0	
		OG----------OC	Ser-125	3.0	
		OH----------OC	Tyr-337	3.1	
		OC----------H0	Trp-86	1.6	

TABLE 4: PICTURE SHOWING THE INTERACTION BETWEEN 1B41 AND SELECTED LIGAND MOLECULE

CID 854026



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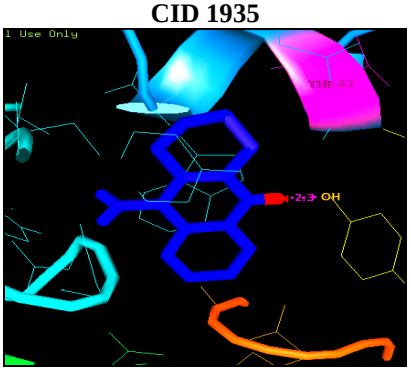

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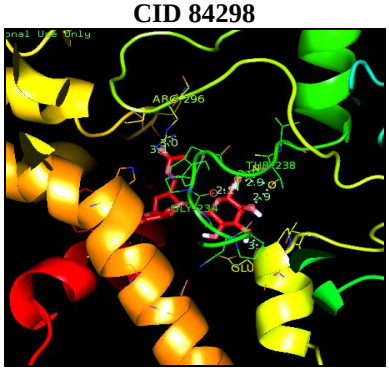

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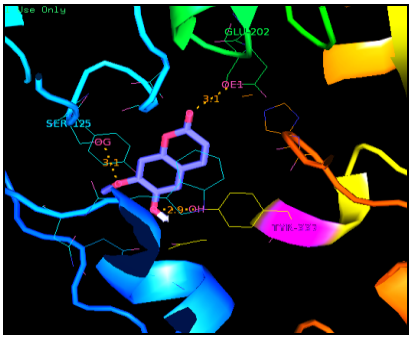

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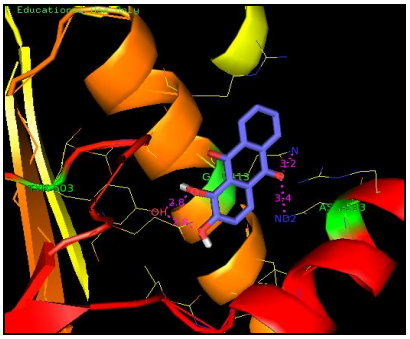

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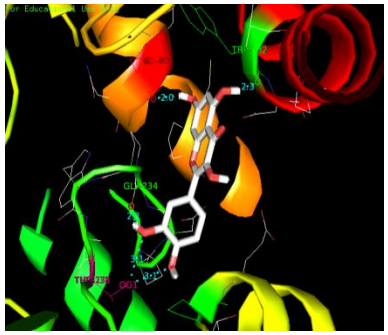

TABLE 5: PICTURE SHOWING THE INTERACTION BETWEEN 1N5R AND SELECTED LIGAND MOLECULES

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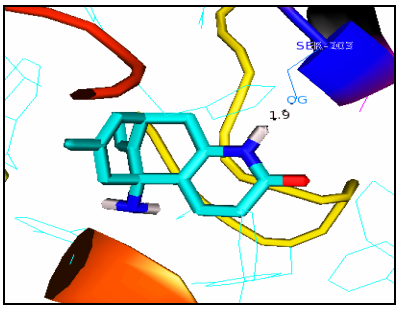
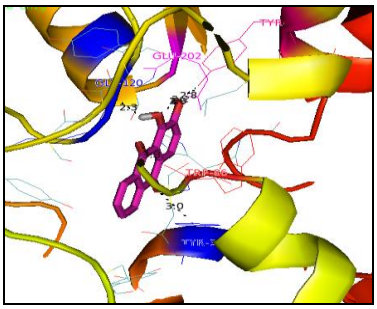
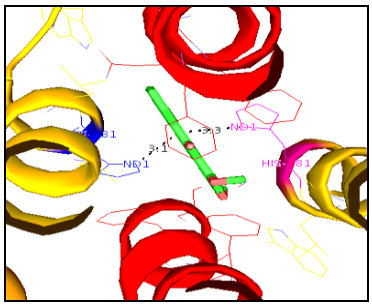
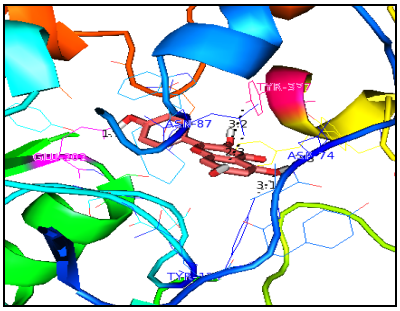
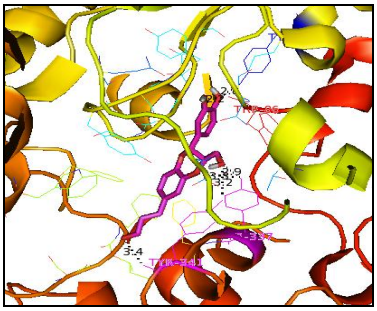
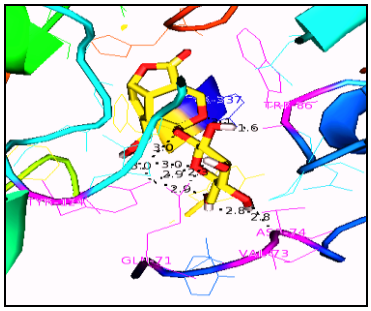
		
CID 5280863	**CID 5459018**	**CID 44593378**
		

Prediction of ADME Properties:

For the 25 drug molecules collected from *Morinda citrifolia Linn.*, plant, the biological activity properties like molecular weight, hydrogen bond donars, H-bond acceptors and Log P value were predicted according to Lipinski rule of five which describe their ADME properties important for a drug's pharmacokinetics in the human body. For this purpose, we used the tools like Osiris, Mol inspiration and PASS Prediction.

Osiris property prediction tool:

The OSIRIS Property Explorer is to draw chemical structures and calculate on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red, whereas green color indicates drug-conform behavior.

TABLE 6: ODATA SHOWING BIOLOGICAL ACTIVITY PROPERTIES FOR SELECTED LIGANDS OF 1B41

Compound	CLOG P	Solubility	Molecular weight	Drug Likeness	Drug score
854026	1.69	-2.47	242.0	0.27	0.58
1935	2.81	-3.51	198.0	-7.8	0.15
84298	0.03	-2.02	250.0	1.63	0.52
69894	1.55	-2.09	192.0	-3.44	0.149
6293	2.92	-4.14	240.0	-3.59	0.15
5280343	1.8	-2.49	302.0	1.6	0.32

TABLE7: DATA SHOWING BIOLOGICAL ACTIVITY PROPERTIES FOR SELECTED LIGANDS OF 1N5R

Compound	CLOG P	Solubility	Molecular weight	Drug Likeness	Drug score
854026	1.69	-2.47	242.0	0.27	0.58
6293	2.92	-4.14	240.0	-3.59	0.15
361511	3.31	-4.77	268.0	-3.05	0.36
5280863	2.1	-2.79	286.0	0.9	0.22
5459018	2.17	-2.79	328.0	-2.53	0.13
44593378	-0.56	-1.87	210.0	-1.85	0.33

Mol inspiration property prediction tool:

Mol inspiration supports internet chemistry community by offering freeon-line services for calculation of important molecular properties (logP, polar surface area, number of hydrogen bond donors and acceptors and others), as well as

prediction of bioactivity score for the most important drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, nuclear receptors etc.).

TABLE 8: DATA SHOWING BIOLOGICAL ACTIVITY PROPERTIES FOR SELECTED LIGANDS OF 1B41

Compound	GPCR Ligand	Ion channel Modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
854026	-0.06	0.16	-0.41	-0.32	-0.36	1.13
1935	-0.11	0.36	-0.37	-0.93.	-0.59	0.43
84298	0.23	0.18	-0.03	0.20	0.28	0.49
69894	-1.00	-0.65	-0.95	-0.81	-1.16	-0.24
6293	-0.26	-0.15	-0.01	-0.08	-0.38	0.28
5280343	-0.06	-0.19	0.28	0.36	-0.25	0.28

TABLE 9: 1 DATA SHOWING BIOLOGICAL ACTIVITY PROPERTIES FOR SELECTED LIGANDS OF1N5R

Compound	GPCR Ligand	Ion channel Modulator	Kinase inhibitor	Nuclear Receptor ligand	Protease inhibitor	Enzyme inhibitor
854026	-0.06	0.16	-0.41	-0.32	-0.36	1.13
6293	-0.26	-0.15	-0.01	-0.08	-0.38	0.28
361511	-0.18	-0.17	-0.04	-0.02	-0.23	0.12
5280863	-0.10	0.21	0.21	0.32	-0.27	0.26
5459018	0.21	0.02	0.10	0.37	0.25	0.36
44593378	0.34	0.11	0.09	0.21	0.27	0.57

Pass Prediction: It is possible with computer program to predict the Activity Spectra for Substances to predict the biological activity spectrum for a compound on the basis of its structural formula. PASS predicts 3678 pharmacological effects, mechanisms of action, Mutagenicity, Carcinogenicity, Teratogenicity and Embryotoxicity. All the best inhibitor compounds were analysed for their activity spectra using PASS.

TABLE 10: DATA GENERATED FOR SELECTED ANALOGUE, HUPERIZINE A FOR PREDICTION OF BIOLOGICAL ACTIVITY

S.No.	Pa	Pi	Biological Activity
1	0,781	0,004	Alzheimer's disease treatment
2	0,251	0,004	Butyrylcholinesterase inhibitor
3	0,261	0,243	Neurotransmitter antagonist
4	0,271	0,186	Dementia treatment
5	0,282	0,258	Platelet aggregation stimulant
6	0,343	0,116	Platelet derived growth factor receptor kinase
7	0,747	0,005	Cognition disorders treatment
8	0,800	0,005	Neurodegenerative diseases treatment
9	0,822	0,003	Antitoxic
10	0,859	0,003	Cholinergic

DISCUSSION: Our present study discusses about the prediction of the biological activity for the phytoconstituents of the plant, *M. citrifolia* plant compounds. Through application of the CAST-p tool which predict the pocket binding site of the selected protein Viz. , it was obvious that the following resedues were present in the active site of the proteins 1B41: Ser-203, Thr-83, Thr-238, Glu313,Gly-234, Arg-296, Tyr-337, Ser-125, Glu-202, Tyr-503, Gln-413, Asn-533, His-405, Trp-532 and in the protein 1N5R, the resedues were Ser-203,Gln-202,Tyr-133,Gly-120,Trp-86,Tyr-337, His-381, Asp-74,Tyr-124,Glu-202, Tyr 341,Tyr-133,Glu-71, Ser125. Based on these results it was inferred that the drug molecules will interact with the active sites of these two proteins and inhibit the activity of AChE levels in AD. Similarly, the results obtained through Osiris tool, it was understood that the drug molecule, Huperzine A has the highest drug score (0.58) and clog p, molecular weight, tpsa, druglikeness and solubility (**Table 6** and **7**). The molinspiration tool, one of the best activity predictor further supported that the drug molecule, Huperzine A with highest enzyme

activity (1.13) can inhibit the activity of AChE levels in AD. Then finally i predicted the PASS prediction ligand activity tool in these the drug molecule huperzine A shows Alzheimers disease treatment, dementia treatment and neurodegenerative disease treatment etc.,.

CONCLUSION: The results of the present study clearly demonstrated that the in silico molecular docking studies on selected phytoconstituents of the plant, *Morinda citrifolia Linn.*, exhibited best binding interactions with both proteins of the neurotransmitter AChE. Based on these results, it will be possible to develop suitable AChE inhibitors for treatment Alzheimer's disease.

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