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MOLECULAR DOCKING OF POTENTIAL PHYTOCOMPOUNDS FOR SELECTIVE TARGETING OF AMYLOID BETA

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ABSTRACT

Objective: To explore the selected phytocompounds for their selective inhibitory activity with X-ray structure of amyloid beta peptide:antibody (Abeta1-40:12A11) complex using docking analysis.

Methods: The docking of the target protein (pdb id – 3IFN) with the phytochemical ligands was performed using the ArgusLab software. We have carried out flexible docking for nine structurally diverse phytocompounds (Niranthin, Phyllanthin, Hypophyllanthin, Beta-Glucogallin, Ginnalin C, Propyl gallate, Rubiadin, Emodin, Purpurin) for their selective amyloid beta peptide inhibitory activity.

Results: Nine molecular structures of phytocompounds targeting of amyloid beta (Abeta) peptide were optimized for the docking study. The molecular docking scores identify the ligands that bind with similar targeting of amyloid beta (Abeta) peptide. These compounds can be considered as having Alzheimer's disease-modifying potential.

Conclusions: These findings could be exploited in future for designing ligands in order to obtain novel molecules for selective targeting of amyloid beta.

Keywords: Phytocompounds, amyloid beta peptide

1. INTRODUCTION

Alzheimer's disease (AD) is one of the most common causes of dementia in the society **[1-2]**. Recent reports suggest that > 4.7 million people of ≥ 65 years of age are living with AD in the USA. AD is predicted to affect one in 85 people globally by 2050 **[1-2]**. The malfunctioning and gradual death of neurons in the disease results in loss of memory and cognitive functions **[3-4]**. The disease is characterized by accelerated accumulation of amyloid β (Aβ) plaque around neurons and hyperphosphorylated microtubule associated tau protein in the form of neurofibrillary tangles within the cells. **[3-4]**. In a published review by our research group, we have described and discussed the recent focus on therapeutic interventions targeting various Aβ-associated pathological mechanisms of AD and experimental strategies focusing on Aβ which aim to decrease the production of the protein, prevent its aggregation or increase the removal of it from the brain **[5].** It was noted that that Aβ represents a potent molecular target for pharmacological manipulation to perhaps prevent the onset and progression of Alzheimer's disease **[5].** In view of our previous biological and phytochemical studies employing bioassays relevant to the neuropharmacological screening of these three classes of compounds [Lignans, Tannins & Anthraquinones] has guided us to explore antialzzhemeir activity of the studied class of compounds **[6,7].** In order to assist in determining potential mechanisms of action of the selected various phytochemical compounds (Niranthin, Phyllanthin, Hypophyllanthin, Beta-Glucogallin, Ginnalin C, Propyl gallate, Rubiadin, Emodin, Purpurin) we have carried out flexible docking analysis for nine structurally diverse phytocompounds for their selective inhibitory activity with X-ray structure of Aβ peptide.

2. MATERIALS AND METHODS

Preparation of protein structure

Docking simulations was performed with the X-ray structure of Aβ peptide:antibody (Abeta1-40:12A11) complex (PDB: ID-3IFN) **[8-9].** The protein sequence was retrieved in the fasta format and the 3D structure was determined using CPH model server. All water molecules were removed and hydrogen atoms were added to the target protein molecule.

Preparation of the ligand structures

The ligand structures were generated using the tool CORINA. Three-dimensional optimizations of the ligand structures were done and saved as '.mol file'. Geometry optimizations of the ligands were performed according to the Hartree–Fock

(HF) calculation method using ArgusLab 4.0.1 (Mark A. Thompson, Planaria Software LLC, Seattle, WA, USA.) software **[10]**. The compounds included in the study are Niranthin, Phyllanthin, Hypophyllanthin, Beta-Glucogallin, Ginnalin C, Propyl gallate, Rubiadin, Emodin, Purpurin.

Protein-ligand docking using ArgusLab 4.0.1

ArgusLab is an electronic structure program that is based on the quantum mechanics. It predicts the potential energies, molecular structures; geometry optimization of structure, vibration frequencies of coordinates of atoms, bond length, and bond angle.

Amyloid beta peptide was docked against nine bioactive compounds using ArgusLab Software. The interaction was carried out to find the favorable binding geometries of the ligand with the protein. Docking of the protein ligand complex was mainly targeted only to the predicted active site. Docking simulations were performed by selecting "ArgusDock" as the docking engine. The selected residues of the receptor were defined to be a part of the binding site. A spacing of 0.4 Å between the grid points was used and an exhaustive search was performed by enabling "High precision" option in Docking precision menu, "Dock" was chosen as the calculation type, "flexible" for the ligand, and the "AScore" was used as the scoring function. A maximum of 150 poses were allowed to be analyzed; binding site box size was set to 20 × 20 × 20 Å so as to encompass the entire active site. The A Score function, with the parameters read from the AScore.prm file, was used to calculate the binding energies of the resulting docked structures. All the compounds in the dataset were docked into the active site of protein, using the same protocol. The docking poses saved for each compound were ranked according to their dock score function. The pose having the highest dock score was selected for further analysis.

RESULTS

The details of molecular structures and properties of the nine compounds is summarized in **Table 1**. The structures of nine phytocompounds (ligands) were drawn in 2D and converted into 3D mol form. The ligands were first optimized for the docking analysis. The nine molecular structures of phytocompounds have affinity to the Amyloid Beta which was optimized for the final docking analysis.

Protein ligand interaction using ArgusLab 4.0.1

The molecular docking scores identify the ligands that bind with orientation as observed with Amyloid Beta. The 3-Dimensional presentation of interaction of

the ligand with Amyloid Beta is depicted in **Figure 1**. All of the phytocompounds (ligands) make good docking poses in comparison to the reference antibody.

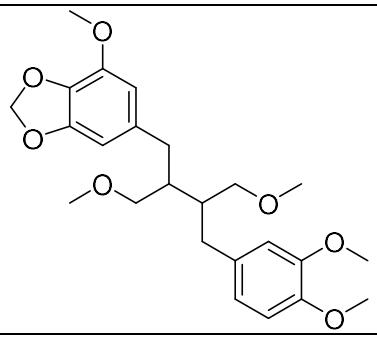
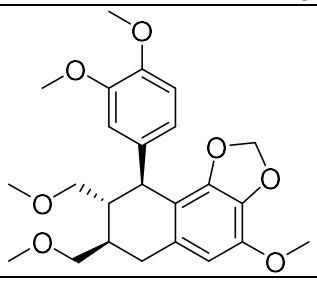
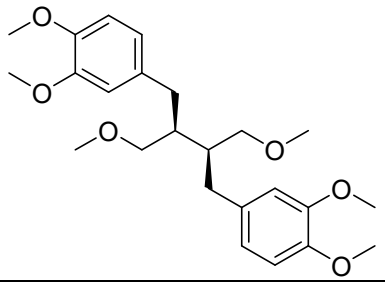
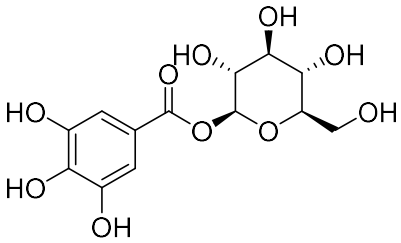
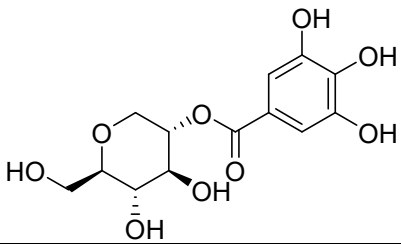
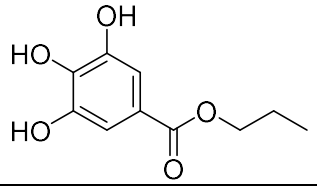
The protein-ligand interaction scores (total score values) obtained during docking, the docked poses obtained from visualization and the log values of the ligands are summarized in **Table 2**. The ligands docked with the target protein, and the best docking poses were identified. **Figure 1** shows the binding poses of the compounds (Niranthin, Phyllanthin, Hypophyllanthin, Beta-Glucogallin, Ginnalin C, Propyl gallate, Rubiadin, Emodin, Purpurin). This best docking poses shows how the ligand molecule fits into the binding region of the target protein. Intermolecular flexible docking simulations were performed and energy values were calculated from the docked conformations of the Amyloid beta complexes. Majority of the ligands had a greater binding affinity with the target protein. Inhibition was measured by the binding energy of the best ligand pose measured in kcal/mol. The binding pose and their energy are listed in **Table 2**.

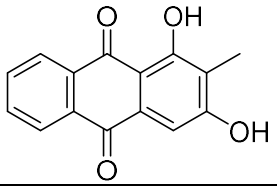
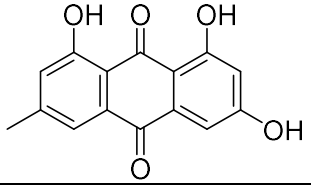
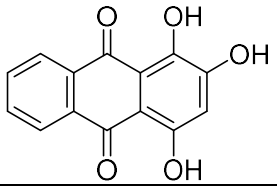
The obtained scores are in between -7.68 to -9.42. All the ligands docked deeply within the binding pocket region suggest their shape complementarily with Amyloid Beta. The molecular weights of the selected compounds range between 212.2- 432.21. The 3-Dimensional presentation of the docking studies of ligand molecules with Amyloid Beta are represented in **Figure 1.** Niranthin, Beta-glucogallin, and Rubiadin showed good docking scores and maximum number of docking poses. The results suggest these compounds are potent selective Amyloid Beta inhibitors. This study will be useful for the designing of novel Amyloid Beta inhibitors based on the docking analysis.

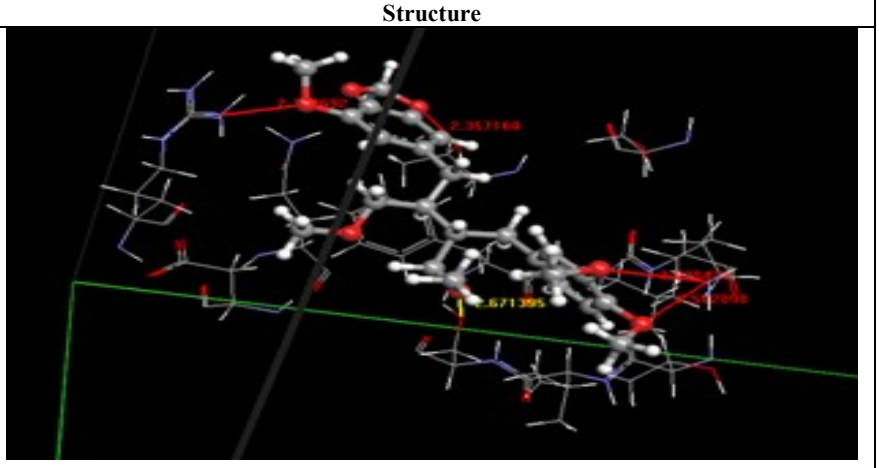
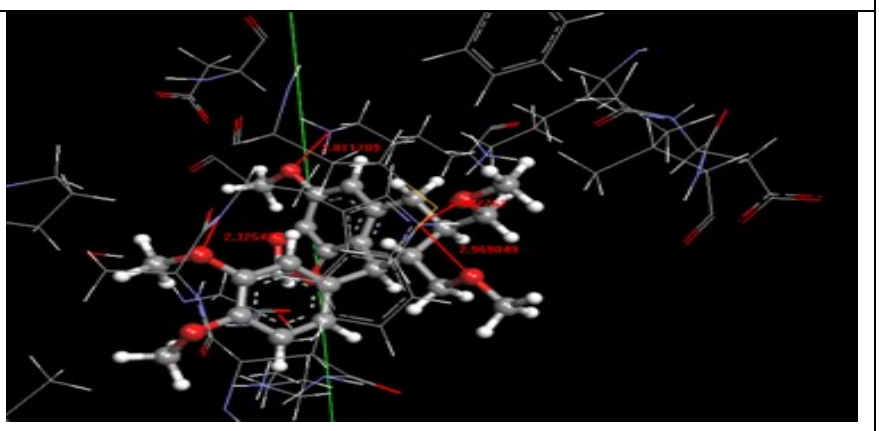
Table 1: List of Phytochemical classes and individual selected Phytoconstituents in the present study

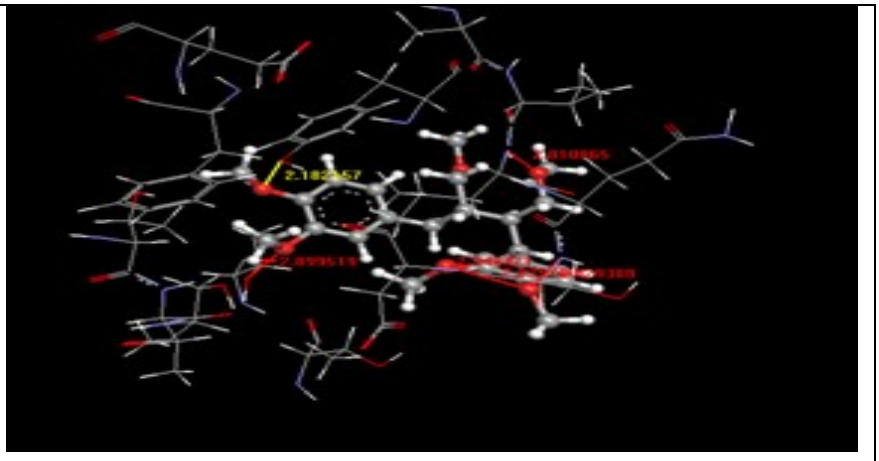
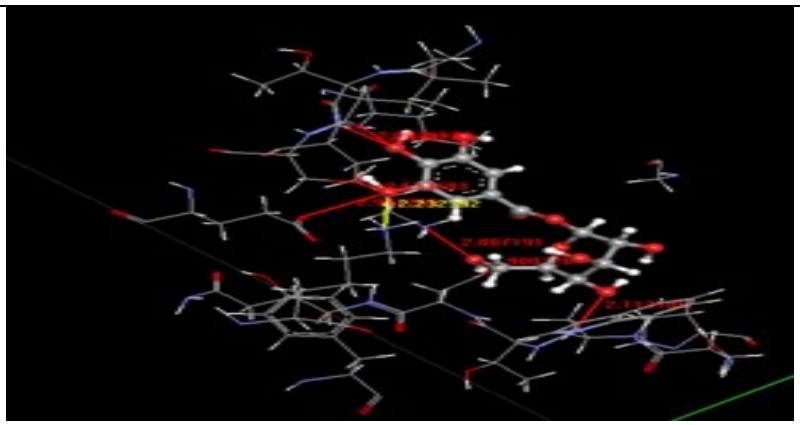
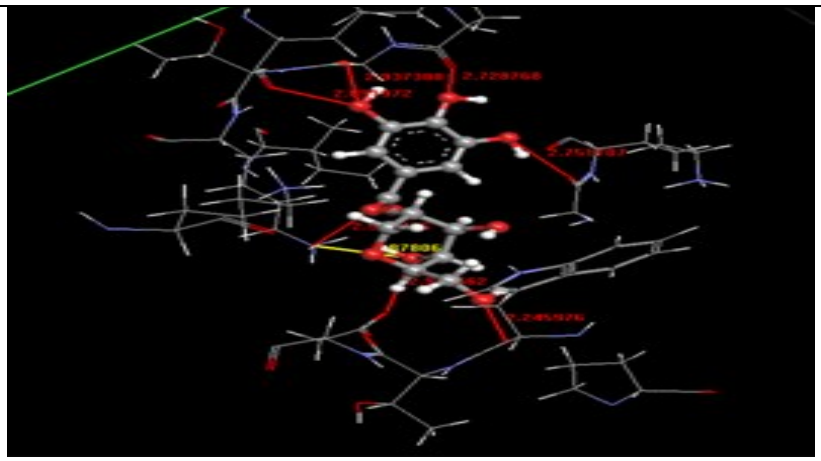
S. No.	Class compounds	Phytoconstituents	Molecular formula	Molecular weight
1	Lignans	Niranthin,	$C_{24}H_{32}O_7$	432.21
		Phyllanthin	$C_{24}H_{34}O_6$	418.5
		Hypophyllanthin	$C_{24}H_{30}O_7$	430.5
2	Tannins	Beta-Glucogallin,	$C_{13}H_{16}O_{10}$	332.26
		Ginnalin C,	$C_{13}H_{16}O_9$	316.26
		Propyl gallate	$C_{10}H_{12}O_5$	212.2
3	Anthraquinones	Rubiadin,	$C_{15}H_{10}O_4$	254.24
		Emodin,	$C_{15}H_{10}O5$	270.24
		Purpurin	$C_{14}H_8O_5$	256.21

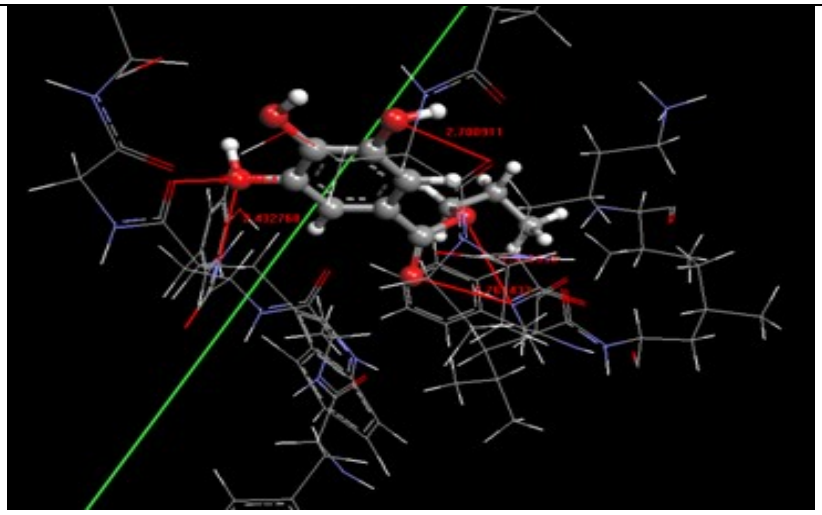
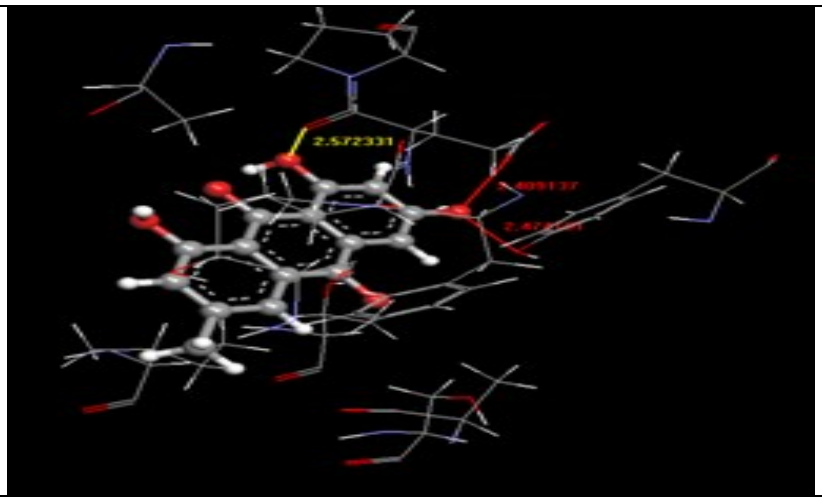
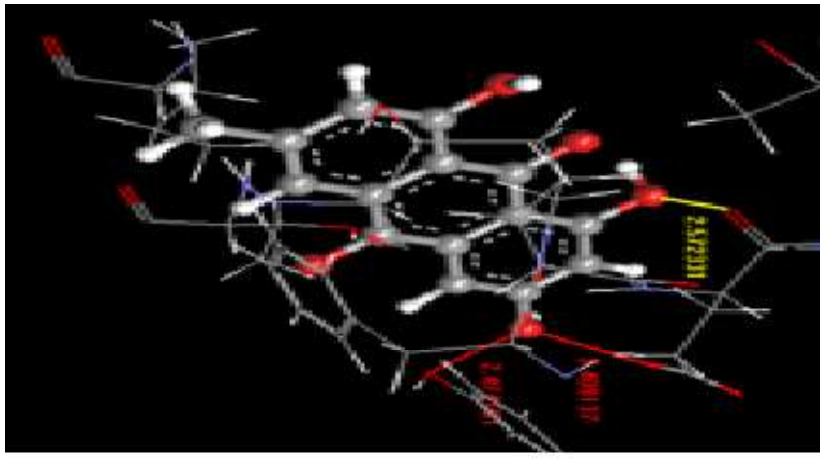
Table 2: Summary of docking analysis of Amyloid beta with selected phyto compounds

S. No.	Name of Compound	Structure	Score kcal/mol	Amino acids with distance
1	Niranthin		-8.51	1298-N83LYS, 2.82A, 1298-N-83LYS, 2.56A, 315-O-21THR, 2.35A, 1189-N-77ARG, 2.78A, 1115-O-72SER, 2.67A
2	Hypophyllanthin		-8.16	4892-N-330LYS, 2.81A, 5794-N-383TRP, 2.96A, 5794-N-383TRP, 2.46A, 586-N-383TRP, 2.32A
3	Phyllanthin		-8.33	2625-N—180ASP, 2.82A, 2614-N-177LEU, 2.81A, 2578-N-177LEU, 2.81A, 1425-O-92THR, 2.89A, 2667-O-182 TYR, 2.18A
4	Beta-Glucogallin		-8.65	4932-O-332GLU, 2.93A, 3413-O-232SER, 2.53A, 4892-N330LYS, 2.80A, 5830-O-385ASP, 2.90A, 5457-N-362LYS, 2.23A, 3392-O-231 LEU, 2.44A
5	Ginnalin C		-8.70	--
6	Propyl gallate		-7.68	--

7	**Rubiadin**		**-9.42**	**4892N-330LYS, 2.99A**
8	**Emodin**		**-9.34**	**2667-O- 182TYR, 2.47A, 2274-O-155GLU, 2.40A, 2270-O-155GLU, 2.57A**
9	**Purpurin**		**-7.98**	**6174-O-408ARG, 2.98A, 6180N- 408ARG, 2.061A**

Name of Compound	**Structure**
Niranthin	
Hypophyllanthin	

Phyllanthin	
Beta-Glucogallin	
Ginnalin C	

Propyl gallate	
Rubiadin	
Emodin	

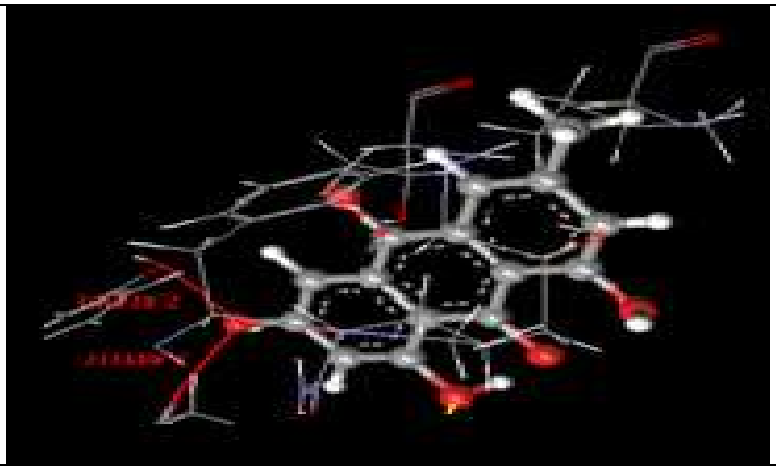
Purpurin	

Figure 1: Best Docking poses of selected compounds with Amyloid beta

DISCUSSION

The present study describes screening studies of the reported phytoconstituents (Niranthin, Phyllanthin, Hypophyllanthin, Beta-Glucogallin, Ginnalin C, Propyl gallate, Rubiadin, Emodin, Purpurin) by applying molecular docking technique for the first time. The nine molecular structures of phytocompounds have affinity to the Amyloid Beta system that have been docked and their obtained scores identify that these ligands bind with the similar orientation as observed with for Amyloid Beta-antibody.

Molecular Docking of reported molecules clearly reflected the binding of these molecules with Amyloid Beta- receptor model. These compounds showed better binding features in terms of energy scores in comparison to the different ligands **[11, 12]**. These compounds could be considered as good Amyloid Beta inhibitors. Thus, the significance of these plant derived medicinal compounds is highlighted by using docking analysis.

The current study dealt with the in silico investigation for alternative potent Amyloid Beta inhibitor with minimum side effects. The simulation reflects that the molecules are being more effectively interacting with Amyloid Beta, which is evident by the dock scores and also their size than the existing Amyloid Beta inhibitors **[9, 11, 12]**. The results indicate that the above mentioned molecules are predicted to be bioactive. Together, it can be predicted that the Amyloid Beta inhibitors might be responsible, at least in part, for their probable Alzheimer's disease modifying potential.

Although a comprehensive analysis of the available data would go far beyond the scope of the present work, the actual basic idea of the work coincides with the hypotheses which can summarize the potential of various phyto-compounds studied can act as a strategy for the

development of Alzheimer's disease modifying treatment regimen.

CONCLUSION

The phyto-compounds showed potent Amyloid Beta inhibitory activity. These findings could be exploited for future ligand design in order to obtain novel derivatives as selective Amyloid Beta inhibitor which will aid in the development of Alzheimer's disease modifying treatment regimen.

Conflict of interest statement

We declare that we have no conflict of interest.

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