WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 10, 1154-1161. Research Article ISSN 2277– 7105

MOLECULAR DOCKING FOR IDENTIFICATION OF NOVEL POTENTIAL BACE-1 INHIBITORS FOR ALZHEIMER'S DISEASE TREATMENT OF SOME ISOLATED COMPOUNDS FROM *MACARANGA DENTICULATA*

Mohammed Shoibe[1,2], Mohuya Majumder[3], Mohammad Shafiquer Rahman[1], Arafatul Mamur[1], Md. Sajjad Ul Hoque[1], Md. Mohaiminul Islam[3], Pooja Das[3], Hilton Banik[3], Abul Hasanat[1,2], Mohammad Shah Hafez Kabir[1,2*]

[1]Department of Pharmacy, International Islamic University Chittagong, Chittagong-4203, Bangladesh.

[2]GUSTO A Research Group, Chittagong-4000, Bangladesh.

[3]Department of Pharmacy, BGC Trust University Bangladesh, Chittagong-4000, Bangladesh.

Article Received on
20 Aug. 2016,

Revised on 09 Sept. 2016,
Accepted on 29 Sept. 2016

DOI: 10.20959/wjpr201610-7181

***Corresponding Author' Mohammad Shah Hafez Kabir**
Department of Pharmacy, International Islamic University Chittagong, Chittagong-4203, Bangladesh.

ABSTRACT

Our aim of the study to performed molecular docking studies to identify potential binding affinities of the phytocompounds from *Macaranga denticulata* namely 3-acetylaleuritolic acid, β-Sitosterol, macarangin, oleanolic acid, scopoletin, stigmasterol towards BACE1 for searching of lead molecule against alzheimer's disease. A wide range of docking score found during molecular docking by Schrodinger. 3-acetylaleuritolic acid, β-Sitosterol, macarangin, oleanolic acid, scopoletin, stigmasterol showed the docking score -2.707, -3.006, -5.788, -0.016, -5.35, -4.276 respectively. Among all the compounds macarangin showed best docking score towards BACE1. So, macarangin is the best compounds for selective BACE1 enzyme inhibition, as it possessed best value in Molecular docking. Further *in vivo* investigation need to identify BACE1enzyme inhibitory activity of isolated compounds from *Macaranga denticulata*.

KEYWORDS: *Macaranga denticulata*, BACE1, Molecular docking, macarangin.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder which is characterized by memory loss or loss of neurons and synapses in the cerebral cortex and certain subcortical regions among aged person.[1-5] 60 % - 70% of this disease leading to dementia.[6] The real cause of AD is poorly understood. Accordingly, WHO in 2015, approximately Worldwide, 47.5 million people have dementia and there are 7.7 million new cases every year. In a developing country, AD is a financially costly disease.

A possible therapeutic target for AD is β-amyloid cleavage enzyme (BACE-1) which represents the protease cleaved in the APP degradation process, leading to production of β-amyloid (βA). Thus, the BACE-1 enzyme is very important in drug discovery as a primary therapeutic target for AD.[5] This occurs as a result of, reduces the β-amyloid production, that become a promising target to control and progression of AD.[7]

Although there is no cure for AD, it can be managed with the available drugs, to some degree. A number of scientific researchers have been carried out on medicinal herbs. Herbs have anti-inflammatory and anti-oxidant activities that may be used in the treatment of AD. Some of the medicinal herbs used in this treatment are Salvia officinalis, *Rosmarinus officinalis*, *Curcuma longa*, *Matricaria recutita*, *Melissa officinalis*, *Commiphora whigitti*, *Galnthus nivalis*, *Panax ginseng*, *Bacoppa monneira*, *Angelica archangelica*, *Collinsonia Canadensis*, *Bertholettia excels*, *Tinospora cordifolia*, *Urticadioica*, *Magnolia officinalis*, *Huperzia serrata*, *Gingko biloba*, *Withania somnifera*. These herbs are responsible for slowing down the brain cell degeneration caused by alzheimer's. They enhance the brain's ability to function, and therefore, provide stability when used consistently.[8]

Macaranga denticulata Muell.-Arg. belongs to the family Euphorbiaceae. In Bangladesh, it is locally known as Burna, Burakochi, Ratabura, Mathura-ninia, Lepcha; Bura. It is a low evergreen tree, with a large spreading crown; young shoots, leaves and inflorescence rusty tomentose. Leaves large, peltate, denticulate or entire, base rounded. Flowers in axillary panicles. Fruit a capsule, about 6 mm diam.[9] The juice of the leaves and flowers is administered in cases of constipation, mucous stool and colic in Jointiapur of Sylhet in Bangladesh.[10]

Molecular docking is a key tool in computer-assisted drug design and development. Docking has been utilized to perform virtual screening on large libraries of compounds, and propose structural hypotheses of how the ligands bind with the target with lead optimization. Another potential application of docking is optimization stages of the drug-discovery cycle.

Our aim of the study to performed molecular docking studies to identify potential binding affinities of the selected phytocompounds from *Macaranga denticulata* towards BACE1 for searching of lead molecule against Alzheimer's disease.

MATERIALS AND METHODS

Protein Preparation

Three dimensional crystal structure of BACE1 (PDB id: 4IVT) was downloaded in pdb format from the protein data bank.[11] After that, structure was prepared and refined using the Protein Preparation Wizard of Schrödinger-Maestro v10.1. Charges and bond orders were assigned, hydrogens were added to the heavy atoms, selenomethionines were converted to methionines, and all waters were deleted. Using force field OPLS_2005, minimization was carried out setting maximum heavy atom RMSD (root-mean-square-deviation) to 0.30 Å.

Ligand Preparation

Compounds were retrieved from Pubchem databases, i.e. 3-acetylaleuritolic acid, β-Sitosterol, macarangin, oleanolic acid, scopoletin, stigmasterol. The 3D structures for these were built by using Ligprep2.5 in Schrödinger Suite 2015 with an OPLS_2005 force field. Their ionization states were generated at pH7.0±2.0 using Epik2.2 in Schrödinger Suite. Up to 32 possible stereoisomers per ligand were retained.

Receptor grid generation

Receptor grids were calculated for prepared proteins such that various ligand poses bind within the predicted active site during docking. In Glide, grids were generated keeping the default parameters of van der Waals scaling factor 1.00 and charge cutoff 0.25 subjected to OPLS 2005 force field. A cubic box of specific dimensions centred around the centroid of the active site residues (Reference ligand active site) was generated for receptor. The bounding box was set to 14 Å × 14 Å × 14 Å for docking experiments.

Glide Standard Precision (SP) ligand docking

SP flexible ligand docking was carried out in Glide of Schrödinger-Maestro v 10.1[12, 13] within which penalties were applied to non-cis/trans amide bonds. Van der Waals scaling factor and partial charge cutoff was selected to be 0.80 and 0.15, respectively for ligand atoms. Final scoring was performed on energy-minimized poses and displayed as Glide score. The best docked pose with lowest Glide score value was recorded for each ligand.

RESULTS

***In silico* Molecular Docking analysis**

Advances in computational techniques have enabled virtual screening to have a positive impact on the discovery process. Virtual screening utilizes docking and scoring of each compound from a dataset and the technique used is based on predicting the binding modes and binding affinities of each compound in the dataset by means of docking to an X-ray crystallographic structure.[14] Grid based docking study was used to analyze the binding modes of molecules with the amino acids present in the active pocket of the protein.[15] To identify the potential anti Alzheimer's lead molecule, we have subjected the docking analysis of the active compounds of *M. denticulata* Kuntze to the active site of BACE1. In order to study the interaction of the compounds 3-acetylaleuritolic acid, β-Sitosterol, macarangin, oleanolic acid, scopoletin, stigmasterol and 4IVT, we performed Glide docking analysis by Schrodinger suite v10.1, where among of these compounds macarangin shows highest docking score shown in Table 1. The negative and low value of free energy of binding demonstrates a strong favorable bond between BACE1 and macarangin in most favourable conformations. The results of docking analysis were described in Table 1 and the docking figure showed in Figure 1.

Table 1: Docking results of A. 3-acetylaleuritolic acid, B. β-Sitosterol, C. macarangin, D. oleanolic acid, E. scopoletin, F. stigmasterol with BACE1 (PDB: 4IVT).

Compound Name	Docking Score	Glide emodel	Glide energy
3-acetylaleuritolic acid	-2.707	-39.152	-31.118
β-Sitosterol	-3.006	-29.099	-26.037
macarangin	-5.788	-69.045	-53.865
oleanolic acid	-0.016	-38.234	-33.35
scopoletin	-5.35	-40.453	-30.341
stigmasterol	-4.276	-31.535	-31.098

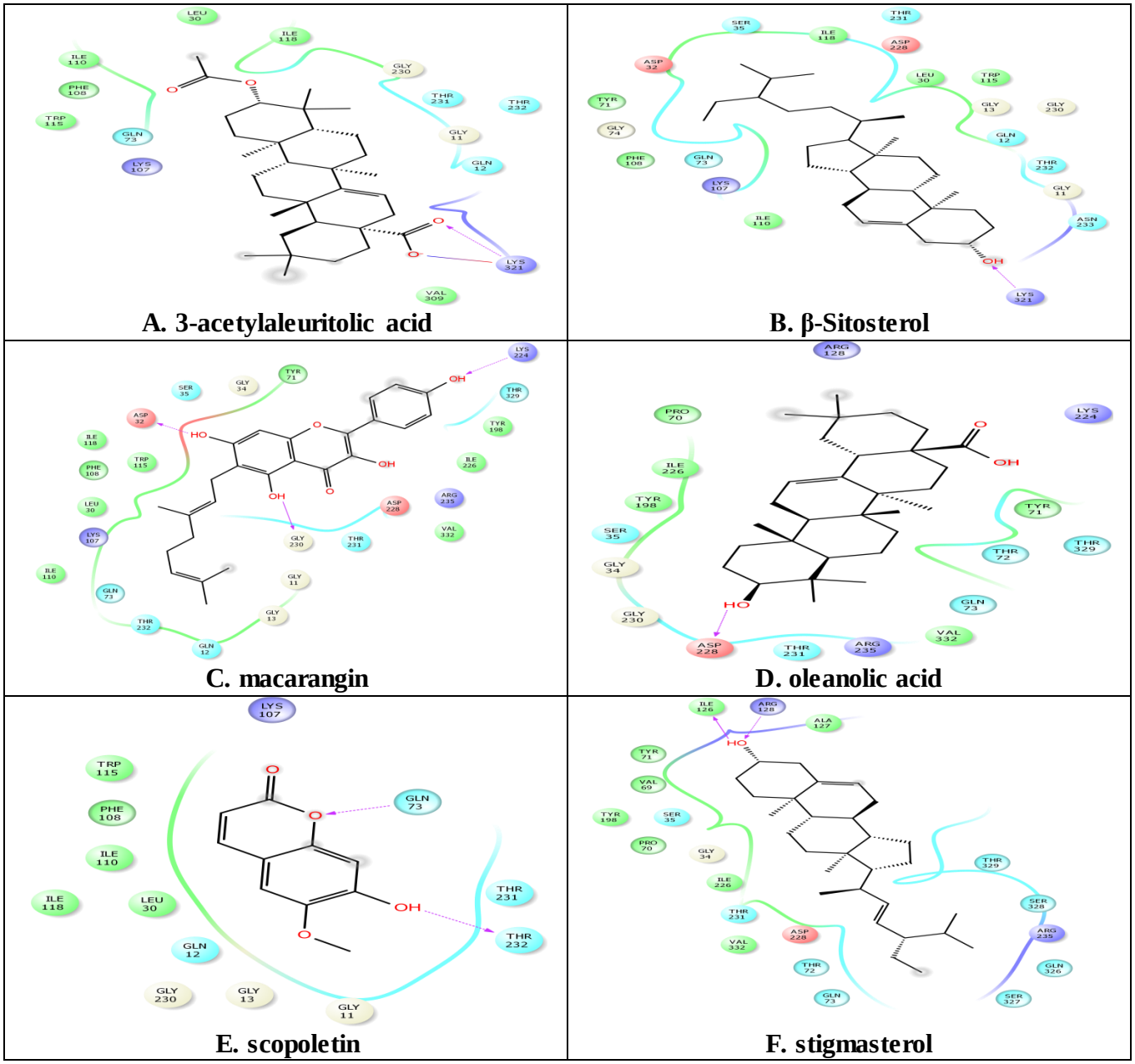

Figure 1: Docking results of A. 3-acetylaleuritolic acid, B. β-Sitosterol, C. macarangin, D. oleanolic acid, E. scopoletin, F. stigmasterol with BACE1 (PDB: 4IVT).

DISCUSSION

Phytochemicals are plant-derived chemical compounds that have potential health-promoting properties. A wide variety of phytochemicals has been shown to prevent certain chronic diseases, such as cancers and cardiovascular diseases, by mitigating or correcting cellular dysfunctions.[16] Polyphenolic phytochemicals are the most abundant dietary antioxidants; however, numerous studies performed in animal models or cell culture demonstrated that the antioxidant activity of these compounds is unlikely to be the sole explanation for their protective cellular effects. And phytochemicals also have ability to fix the AD problem. So

searching new drugs for AD from medicinal plants is not latest. But, it is very costly to discover the drugs in laboratory. *In silico* methods can help us to shorten the procedure of drug discovery by selecting the perfect drug for the diseases.

The aim of molecular docking is the accurate prediction of the structure of a ligand within the constraints of a receptor binding site and to correctly estimate the strength of binding. To explore effective drugs for the treatment of AD, different compounds against known and novel targets of AD could be designed and investigated using molecular docking. Dual or multiple inhibitors that inhibits two or more targets of AD may also be investigated. Currently there is no treatment to prevent or cure AD but several approved drugs can treat some of the symptoms and cause a modest and temporary improvement in memory. Targeting the direct cause of neuronal degeneration would constitute a rational strategy and hopefully offer better prospects for the treatment of AD. Several molecules for the above discussed targets have been withdrawn even from the clinical trials either due to their ineffectiveness in human trials or their nonspecificity for receptors. The brain, being the most complex organ, is difficult in terms of its structural accessibility and the presence of the blood–brain barrier and thus difficult for many *in vitro* molecules to be effective *in situ*. Therefore, special attention should be paid for the development of effective ligands against the potent targets of AD.[17] In a nut shell, molecular modeling and docking would be a promising aspect for novel drug design and would shorten the time span of drug discovery that could be further explored as possible therapeutic interventions for AD.

CONCLUSION

The present study revealed that among all the compounds macarangin showed best docking score. So, macarangin is the best compounds for selective BACE1 enzyme inhibition, as it possessed best value in Molecular docking. Further *in vivo* investigation need to identify BACE1 enzyme inhibitory activity of isolated compounds from *Macaranga denticulata*.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ACKNOWLEDGMENT

The authors thank GUSTO (A research group) for providing the software and the financial support.

REFERENCES

1. Goyal M, Dhanjal JK, Goyal S, Tyagi C, Hamid R, Grover A: Development of dual inhibitors against Alzheimer's disease using fragment-based QSAR and molecular docking. *BioMed research international.,* 2014; 2014.
2. Benzi G, Moretti A: Is there a rationale for the use of acetylcholinesterase inhibitors in the therapy of Alzheimer's disease? *European journal of pharmacology.,* 1998; 346(1): 1-13.
3. Belluti F, Bartolini M, Bottegoni G, Bisi A, Cavalli A, Andrisano V, Rampa A: Benzophenone-based derivatives: a novel series of potent and selective dual inhibitors of acetylcholinesterase and acetylcholinesterase-induced beta-amyloid aggregation. *European journal of medicinal chemistry.,* 2011; 46(5): 1682-1693.
4. Walsh DM, Selkoe DJ: Deciphering the molecular basis of memory failure in Alzheimer's disease. *Neuron.,* 2004; 44(1): 181-193.
5. AAP F: In silico Identification of Novel Potential BACE-1 Inhibitors for Alzheimer's Disease Treatment: Molecular Docking, Pharmacophore Modeling and Activity and Synthetic Accessibility Predictions.
6. Hu C, Ju R, Shen Y, Zhou P, Li Q: Clinical decision support for Alzheimer's disease based on deep learning and brain network. In: *2016 IEEE International Conference on Communications (ICC): 2016*: IEEE; 2016: 1-6.
7. Ghosh AK, Bilcer G, Hong L, Koelsch G, Tang J: Memapsin 2 (beta-secretase) inhibitor drug, between fantasy and reality. *Current Alzheimer Research.,* 2007; 4(4): 418-422.
8. Singhal AK, Naithani V, Bangar OP: Medicinal plants with a potential to treat Alzheimer and associated symptoms. *International Journal of Nutrition, Pharmacology, Neurological Diseases.,* 2012; 2(2): 84.
9. Uddin SB: Medicinal plants of Bangladesh. *Cell.,* 2014; 880: 1711065377.
10. Yusuf M, Chowdhury J, Wahab M, Begum J: Medicinal plants of Bangladesh. *Bangladesh Council of Scientific and Industrial Research, Dhaka, Bangladesh.,* 1994; 192.
11. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat T, Weissig H, Shindyalov IN, Bourne PE: The protein data bank. *Nucleic acids research.,* 2000; 28(1): 235-242.
12. Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, Repasky MP, Knoll EH, Shelley M, Perry JK: Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *Journal of medicinal chemistry.,* 2004; 47(7): 1739-1749.

13. Friesner RA, Murphy RB, Repasky MP, Frye LL, Greenwood JR, Halgren TA, Sanschagrin PC, Mainz DT: Extra precision glide: docking and scoring incorporating a model of hydrophobic enclosure for protein-ligand complexes. *Journal of medicinal chemistry.*, 2006; 49(21): 6177-6196.
14. Celmar Costa Franca T, Paula Guimaraes A, Augusto Cortopassi W, Alves Oliveira A, Castro Ramalho T: Applications of docking and molecular dynamic studies on the search for new drugs against the biological warfare agents Bacillus anthracis and Yersinia pestis. *Current computer-aided drug design.*, 2013; 9(4): 507-517.
15. Veeramachaneni GK, Raj KK, Chalasani LM, Annamraju SK, JS B, Talluri VR: Shape based virtual screening and molecular docking towards designing novel pancreatic lipase inhibitors. *Bioinformation.*, 2015; 11(12): 535.
16. Manach C, Mazur A, Scalbert A: Polyphenols and prevention of cardiovascular diseases. *Curr Opin Lipidol.*, 2005; 16(1): 77-84.
17. Kumar A, Nisha CM, Silakari C, Sharma I, Anusha K, Gupta N, Nair P, Tripathi T: Current and novel therapeutic molecules and targets in Alzheimer's disease. *J Formos Med Assoc.*, 2016; 115(1): 3-10.