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

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ABSTRACT

Our aim of the study to performed molecular docking studies to identify potential binding affinities of the phytocompounds from *Solanum torvum* namely Methyl salicylate, Santalone, Solasonine, towards BACE1 for searching of lead molecule against alzheimer's disease. A wide range of docking score found during molecular docking by Schrodinger. Methyl salicylate, Santalone and Solasonine showed the docking score -3.821, -4.057 and 3.765 respectively. Among all the compounds Santalone showed best docking score towards BACE1. So, Santalone 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 *Solanum torvum*.

KEYWORDS: *Solanum torvum*, BACE1, Molecular docking, Santalone.

INTRODUCTION

Alzheimer's disease (AD) is a brain disorder named after German physician Aloes Alzheimer, who first described it in 1906. Alzheimer's disease is a progressive and neurodegenerative

disease that primarily affects the elderly population of over 65 years of age, and is estimated to account for 50 - 60% of the dementia cases.[1] The prevalence has been found to rise exponentially with age, ranging from 3.0% in patients aged 65 to 74 years to as much as 47.2% in those aged 85 years.[2,3] This condition is characterized by a progressive loss of memory, deterioration of virtually all intellectual functions, increased apathy, decreased speech function, disorientation, and gait irregularities. 60% - 70% of this disease leading to dementia.[4] 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.[6]

Among the potential new treatment options are certain naturally occurring phytochemicals. These compounds have been the subject of increasing interest on the part of consumers and manufacturers because numerous epidemiological studies have suggested an association between the consumption of polyphenolic phytochemical-rich foods or beverages and the prevention of certain neurological diseases, including 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 *Melissa officinalis*, *Commiphora whigitti*, *Galnthus nivalis*, *Panax ginseng*, *Bacoppa monneira*, *Angelica archangelica*, *Magnolia officinalis*, *Huperzia serrata*. 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]

Solanum torvum is a bushy, erect and spiny perennial plant used horticulturally as a rootstock for eggplant. Grafted plants are very vigorous and tolerate diseases affecting the root system, thus allowing the crop to continue for a second year. Solanum torvum is a small shrub commonly known as 'Turkey berry'. It is widely distributed in India, Pakistan, Malayan, China, Philippines, Thailand and tropical America.[9,10] Its edible fruits are used as

vegetable and are regarded as an essential in Thai cuisine. Its fruit and leaves which are rich in alkaloids can be used for Medicinal or ritual purposes. For many decades, different ethnic groups have used the dried stem and root of this plant for treatment of various ailments. Its Chinese medicinal name is Jinniukou. *Solanum torvum* was used in many Ayurvedic treatments; it has seeing diuretic and digestive properties. It used in the treatment for coughs, liver diseases. Solanum torvum used to reduce body heat and strengthening the body.[11]

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 *Solanum torvum* 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.[12] 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. Methyl salicylate, Santalone, solasonine. 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[13,14] 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.[15] 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.[16] To identify the potential anti Alzheimer's lead molecule, we have subjected the docking analysis of the active compounds of *S. torvum* Kuntze to the active site of BACE1. In order to study the interaction of the compounds Methyl salicylate, Santalone, Solasonine and 4IVT, we performed Glide docking analysis by Schrodinger suite v10.1, where among of these compounds Solasonine 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 Solasonine 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 Methyl salicylate, Santalone, Solasonine with BACE1 (PDB: 4IVT).

Compound Name	Docking Score	Glide emodel	Glide energy
Methyl salicylate	-3.821	-28.411	-22.798
Santalone	-4.057	-26.756	-21.387
Solasonine	-3.765	-29.13	-29.886

A. Methyl salicylate
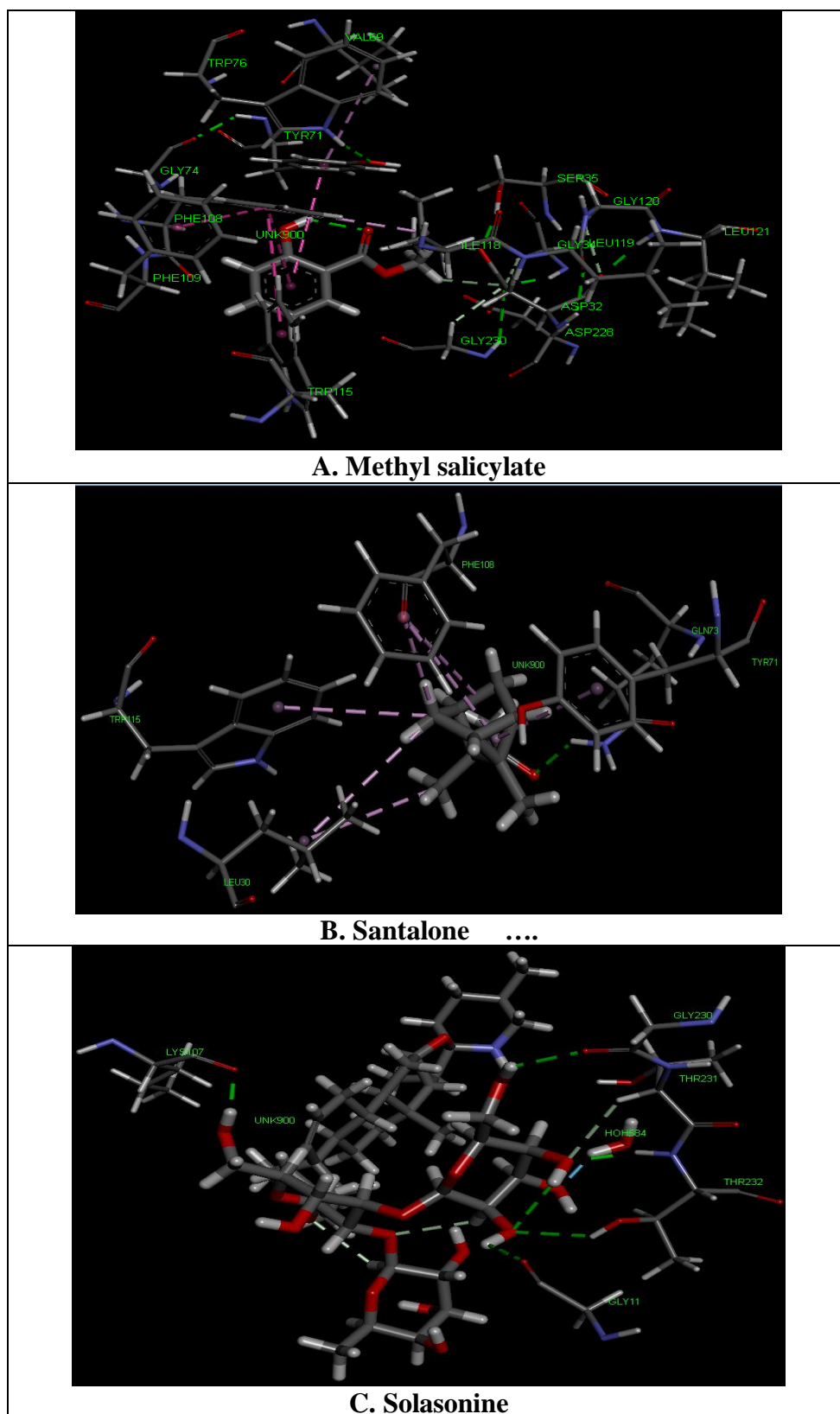

B. Santalone   ….

C. Solasonine

Figure 1: Docking results of A. Methyl salicylate, B. Santalone, C. Solasonine 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.[17] 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.[18] 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.

The anti-AD activities of the studied phytochemicals *in vitro* and *in vivo* have not documented, so it would be unwise to extrapolate these results to the human situation without proper clinical trials. So, we need to more focus on this research.

CONCLUSION

The present study revealed that among all the compounds Santalone showed best docking score. So, Santalone 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 *Solanum torvum*.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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