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Comparative Molecular Docking Analysis of Phytoconstituents against Alzheimer's Disease Targets- An In-Silico Approach

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia and one of the leading causes of death. The Aim and objective of the present study is to perform *in-silico* docking analysis of the major active constituents identified in three Indian medicinal plants namely *Convolvulus pluricaulis*, *Coriandrum sativum* and *Panax ginseng* for its effectiveness against the targets of Alzheimer Disease. *In-silico* docking analysis was performed by Molegro Virtual Docker (MVD-2010, 4.2.0) and Schrodinger Mestro (V 11.8). In addition, Drug likeness property, pharmacokinetics (ADME) and safety profile prediction studies were performed to identify the best drug candidates using Qikpro and Toxicity Estimation Software Tool (T.E.S.T). The target for Alzheimer Disease is Acetylcholinesterase and Butyrylcholinesterase. The X-ray crystal coordinates of AChE (PDB ID: 4bdt) and BChE (PDB ID: 6eqq) obtained from the Protein Data Bank. The phytoconstituents of three medicinal plants were retrieved from PubChem compound database in mol format. The standard drugs Donepezil, Rivastigmine, Galantamine, Memantine was obtained from the drug bank in .mol format for comparison. It was analysed from the parameters of docking that the phytoconstituents from *Panax ginseng* showed better anti-Alzheimer activity compared to that of the standard drugs. Based on the research findings, further studies can be performed in *in-vitro* & *in-vivo* animal models of Alzheimer's disease to establish the efficacy of promising phytoconstituents.

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INTRODUCTION

Dr. Alzheimer, a neuropsychiatrist first described dementia as Alzheimer's disease (AD) or primary degenerative dementia of the Alzheimer's type (Huppert and Tym, 1986). The term Dementia characterizes the progressive decline in cognition that leads to impairment of activities involving social, normal and occupational. Cognition is the mind operation which aware us in all aspects which includes interpreting, memory, and Disturbances in the memory are the hallmark of AD (Geldmacher, 2004). AD is considered as a neurological disorder with progressive degeneration with symptoms that are treatable but has no known cure (Dorland, 1995).

The Etiology of Alzheimer's disease being unknown, but the effect of the disease process leads to neuronal injury. Evidence suggests that a chronic inflammatory process may contribute to neuron

pathogenesis. The major biochemical abnormality of AD occurs in the medial lobe (hippocampus) and cerebral cortex as a reduction of 40% to 90% of the enzyme choline acetyltransferase (Grant *et al.*, 2002). The deficiency of this enzyme causes decreased synthesis of Ach in the brain. The loss of acetyltransferase in the brain appears to begin before the onset of clinical symptoms. AD primarily affects the elderly and More than 100,000 people die of AD each year (Small *et al.*, 1997). The prevalence of dementia double every five years from the ages to 60 to 90. Patient with AD have been found to have cortical atrophy and significant loss of neuron.

Two hallmark histopathology features linked to AD are an increase in amyloid plaques and high density of neurofibrillary tangle (Yan *et al.*, 1994). Within neuronal cells are microtubules which are bundles of paired helical filamentous structure that are necessary for normal cell function. These microtubules are connected by tau protein and in patients with AD; tau protein is damaged and allows neurons to twist into filaments that destruct normal cell function. Amyloid plaques containing Aβ protein accumulate with normal ageing but occur in quantitative excess in AD. Aβ is the core of neuritic plaques and is a fragment from APP (Caputo and Salama, 1989). APP is a large transmembrane protein that is normally neuroprotective but in AD patient's cleavage results in excessive Aβ. Aβ forms the central core of amyloid plaques, which are dense insoluble deposits that form around neurons and disrupt cell function (Strittmatter *et al.*, 1993).

The disordered physiological process associated with Alzheimer's disease begins long before the understanding of the clinical symptoms. Risk factors include genetic predisposition and environmental conditions. AD collapses the person's ability to function in occupational or social situation. Several cognitive changes occur which includes: Progressive deterioration of short-term memory dysfunction (aphasia) and difficulty in recognizing dimensional figures (Chiti and Dobson, 2006). The diagnosis of Alzheimer's disease should include patient history and evaluating with the diagnostic standard such as in DSM-IV, laboratories and examining the physical and mental activities of the patient (Salloway and Correia, 2009). The key screening test in clinical setting is Clock Drawing Task. Cognitive impairment is indicated by the difficulty in drawing a clock with numbers in place and to place the bands at a specific time. An AD patient show cortical atrophy, a finding in many normal elderly, and is not diagnostic (McKhann *et al.*, 1984).

The AD's diagnosis requires postmodern examination or brain biopsy to identify characteristic neurofibrillary tangles and amyloid plaques for its conformation (Becker, 1994).

Historically, several medications have been proposed to treat AD, however, most early trials were undertaken without an understanding of the pathophysiology of the AD. In the last 10 years a number of medications have become available that are used to improve cognitive functioning though none have been able to prevent progression of this disease. In recent days, four AChE inhibitors are considered for the treatment.

MATERIALS AND METHODS

DruLiTo

The Eight natural phytoconstituents such as Chikusetsosaponin, Ginsenosides, Coriandrol, Betasitosterol, Convolamine, Scopoletin, Borneol, Gingerol and four standard currently used drugs in the treatment of Alzheimer's disease were selected as ligands for the study. The ligands' 2D structures were obtained from the PubChem online database. The ligands were saved in the Standard Database format (.sdf). Drulito software was used to screen all of the prepared ligands for drug likeliness properties.

Drulito's calculations were based on Lipinski's law, Veber's rule, BBB's rule, CMC-50, and other drug likeliness laws (Lipinski *et al.*, 1997). The compounds were subjected for drug likeliness properties.

Software used

1. Ligand preparation: Ligprep module from MVD-2010
2. Protein preparation: Protein Preparation wizard module from MVD-2010, Schrodinger maestro V 11.8 (Schrodinger 2018-4 package)
3. Molecular docking: Glide from MVD-2010, V 11.8 (Schrodinger 2018-4 package)
4. ADME calculation: Qikprop from MVD-2010, V11.8 (Schrodinger 2018-4 package)
5. Toxicity prediction: Toxicity Estimation Software Tool (TEST) 4.2.1

Molegro Virtual Docker

Preparation of Ligand

The 2D structures of the phytoconstituents and currently used naturally occurring drugs were retrieved from PubChem (Bolton *et al.*, 2008). As a total, 12

ligands were downloaded in the form of .sdf format (Standard database format) and ligand optimization was performed using default settings in

Molegro Virtual Docker (MVD-2010, 4.2.0). The structures (ligands) that were obtained were prepared for further research.

Preparation of Protein

The 3D structure of the target protein for Alzheimer's disease was retrieved from RCSB Protein Data Bank (Bernstein *et al.*, 1978). AChE (PDB ID: 4bdt) and BChE (PDB ID: 6eqq) X-ray crystal co-ordinates were obtained from the Protein Data Bank.These two PDBs were chosen for modelling studies because ChEs have a crystal structure that represents a pharmacological target for the creation of new drugs to treat AD. AChE comprises of a chain with a resolution of 3.104 Å BChE comprises of A chain with a resolution of 2.4 Å It is well known that PDB files often have poor or missing assignments of explicit hydrogens, and the PDB file format cannot accommodate bond order information. As a result, the MVD was used to assign acceptable bonds, bond orders, hybridization, and charges.The built-in cavity detection algorithm in MVD was used to measure the possible binding sites of both ChE receptors.

SCHRODINGER (GLIDE)

Molecular Docking

Molecular docking is computational study of protein-ligand interaction or their geometries. Besides these uses, docking is also useful to hit identification, lead optimization and bioremediation. There is enumerable software available to perform docking studies among which the GLIDE stands as the best due to its accuracy ad user-friendly options. Docking in glide involves various steps such as Ligand preparation, a protein preparation, site map and receptor grid generation, Docking and scoring.

Ligand preparation

The ligand preparation is done using the Ligprep tool in the software. The concept of ligand preparation involves taking the 2D or 3D structure and producing a corresponding low energy 3D structure and the options to expand the input structure by expanding the variations in ionization state, stereochemistry and ring conformations.

The ligands were imported in mol format and the force field OPLS3 were chosen. The pH of the target was set to 7.0 ± 2.0 and the molecule was desalted, additionally, tautomeric form was chosen to perform the keto-enol tautomerization.

The Epik option was chosen so that the best ligand is obtained from the state penalty score(kcal/mol) which represents highly favourable energy for docking. Finally, the Ligprep tool was processed with the ligand.

Protein preparation

The target protein used in this study is AChE (4bdt) and BChE (6eqq), were downloaded from the PDB website. Since they typically contain only heavy atoms and can include co-crystallized ligands, water molecules, metal ions, and co-factors, the standard structure from the PDB is not ideal for immediate use. Some structure is multimeric and need to be reduced to a single unit. The PDB compounds may miss some atom and continuity information which must be assigned with bond order and charges. This can be done by the protein preparation wizard (Sastry *et al.*, 2013). The bond order, hydrogens, zero-order bonds for metals, disulfide bonds, filling of missing side chains (using prime), and deletion of water beyond the proteins were performedand pre-processed using the wizard. The errors were reviewed, modified, minimized and prepared for docking.

Receptor Grid Generation

The grids represent the physical volume of the receptor specifically the active site where an attempt to dock the ligand is performed.

The grid volume was adjusted to the volume of the active site obtained from the site map generation and processed for docking.

Docking and Scoring

The docking wizard was used to start the process where the ligands, processed proteins and generated receptor grid were selected. The GLIDE SP method was adopted in this study and the process was run for 2 minutes. The docking and glide scores were calculated by the software and displayed once the process was complete. These scores were tabulated and the binding sites were analysed in the workspace. Once all the information were retrieved the project was saved in the maestro format.

ADMET

The 3D structure of the ligand molecule was imported in the workspace and processed for use. The normal mode was used in the qikprop tool to determine the ADMET properties. The results were obtained and analysed in the project table.

TEST (Toxicity estimation software tool)

The Fathead minnow dataset from the EPA ECOTOX database was used to train TEST.

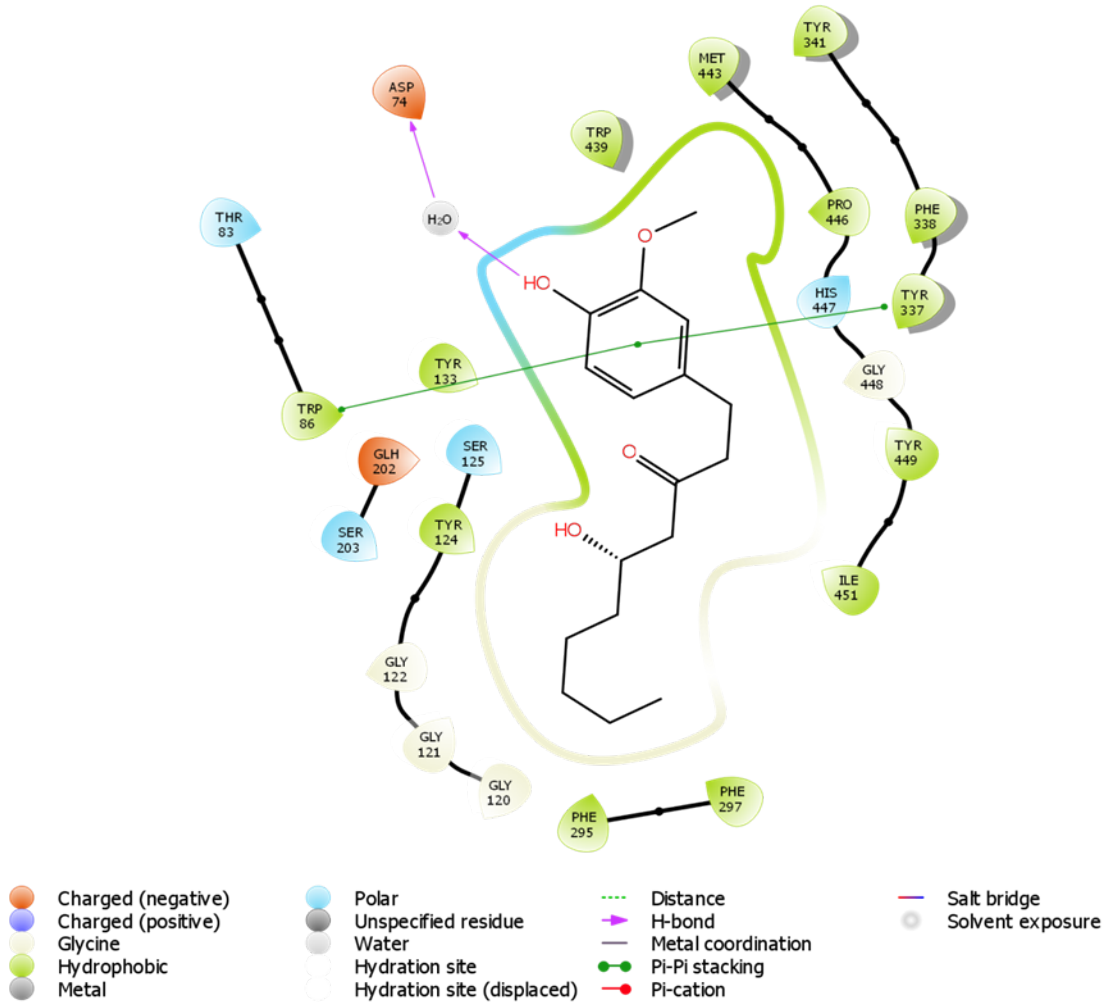

Figure 1: Ligand Interactions of AChE using Glide (Gingerol) using schrodinger docker

Table 1: Comparative analysis of drug likeness property using DruLito

S.No	Ligands	Lipinski					Veber		Blood Brain Barrier	
		nHD	nHA	Mol. Wt	LogP	nV	PSA	nRTB	nH	nACIDIC
1	Donepezil	0	4	359.21	2.633	0	31.8		4s	0
2	Memantine	0	4	379.21	2.13	0	38.77		4	0
3	Rivastigmine	0	4	250.17	1.363	0	32.78		4	0
4	Galantamine	1	4	287.15	1.197	0	41.93		5	0
5	Chikusetsosaponin	8	12	754.49	5.561	0	198.76		20	0
6	Gensenosides	10	14	800.49	3.873	0	239.20		24	0
7	Coriandrol	1	1	154.14	2.468	0			2	0
8	Beta-sitosterol	0	4	323.21	2.6	0	38.4		4	0
9	Convolamine	0	5	305.16	2.126	0	48		5	0
10	Scopoletin	1	4	192.04	0.97	0	55.76		5	0
11	Borneol	1	1	154.14	2.734	0	20.23		2	0
12	Gingerol	2	4	294.18	2.437	0	66.76		6	0

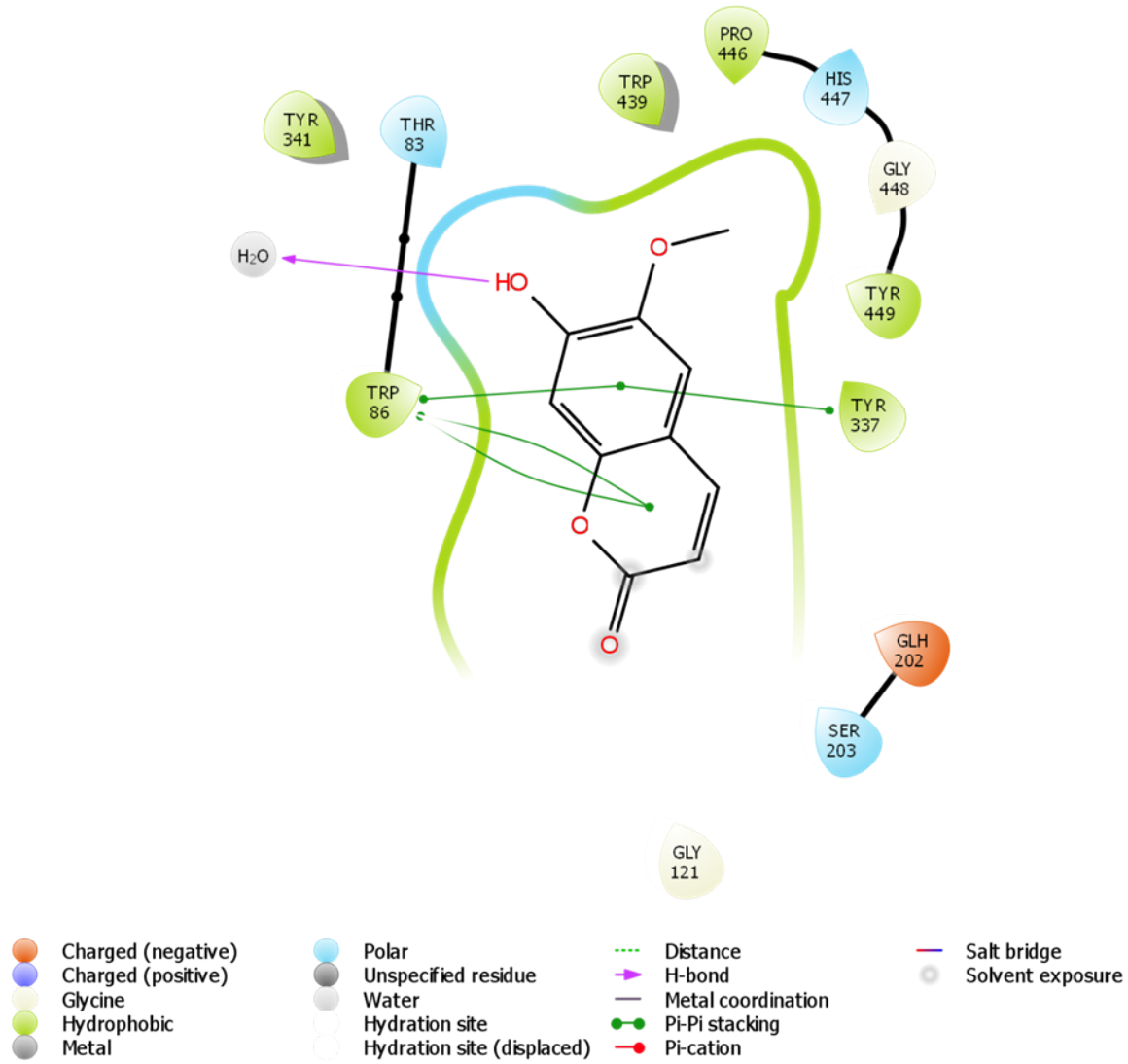

Figure 2: Ligand Interactions of AChE using Glide (Scopoletin) using schrodinger docker

Table 2: Predicted value for Oral rat LD_{50} - Log_{10} (mol/kg), Developmental toxicity, Ames Mutagenicity

Compound	Oral rat LD_{50} - Log_{10} (mol/kg)				Developmental toxicity				Ames Mutagenicity			
	HM	FM	NM	CM	HM	FM	NM	CM	HM	FM	NM	CM
Donepezil	2.77	3.35	2.84	2.99	0.70	0.97	0.67	0.79	0.13	0.37	0.33	0.28
Memantine	2.37	1.89	3.25	2.56	0.66	1.05	N/A	0.82	-0.29	0.05	0.67	0.11
Galantamine	2.75	2.82	2.79	2.79	0.91	1.37	1	1.05	0.59	0.34	0.33	0.42
Rivastigmine	2.50	3.20	3.11	2.94	0.85	1.74	N/A	1.15	0.65	0.66	0.67	0.66
Chikusetsosaponin	4.16	2.47	4.64	3.76	N/A	0.29	0.67	0.48	-0.07	0.22	0.00	0.05
Gensenosides	4.01	4	4.58	4.20	N/A	0.69	0.67	0.68	0.01	0.12	0.00	0.04
Coriandrol	1.89	1.80	2.09	1.93	1.03	0.63	1	0.81	-0.04	0.10	0.00	0.02
Beta-sitosterol	3.60	2.67	1.73	2.67	0.92	0.79	1	0.92	0.12	0.31	0.33	0.25
Convolamine	1.99	1.61	2.82	2.14	0.55	0.80	N/A	0.69	0.14	0.03	0.67	0.28
Scopoletin	1.90	2.56	2.39	2.28	0.83	0.91	0.33	0.70	0.21	0.38	0.00	0.20
Borneol	1.71	1.71	1.99	1.80	1.16	0.75	1	0.97	-0.16	-0.04	0.00	-0.07
Gingerol	2.65	2.77	3.61	3.01	0.57	0.64	0.33	0.55	0.02	0.01	0.33	0.12

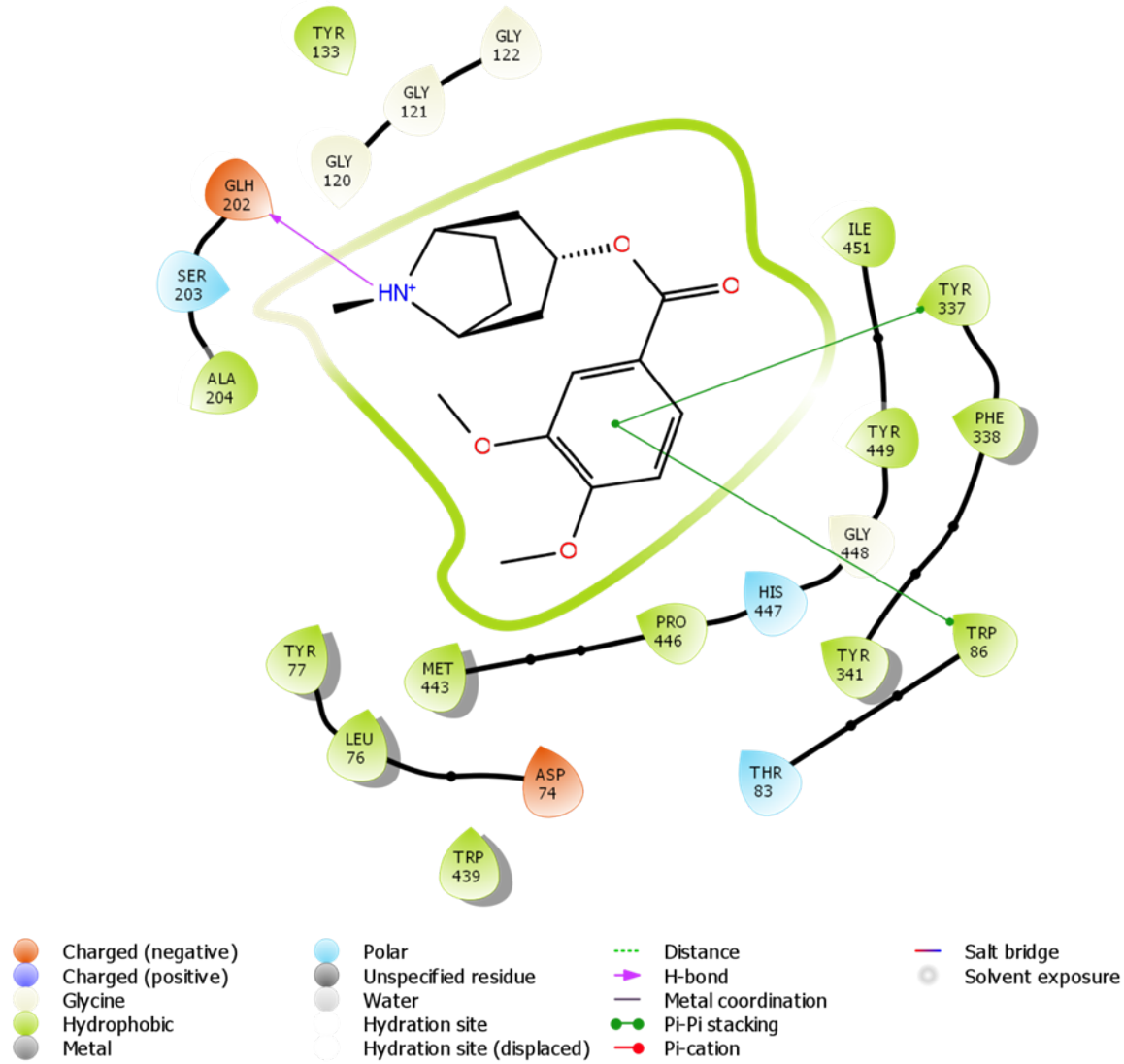

Figure 3: Ligand Interactions of AChE using Glide (Convolamine) using schrodinger docker

Table 3: Comparative docking analysis of ligands Using Molegro virtual Docker

Sl.No	Ligand	Moldock score of AChE		Moldock score of BuChE	
		MolDock score	Re rank score	MolDock score	Re rank score
1.	Donepezil	-90.64	-70.74	-124.46	-102.63
2.	Memantine	-96.51	-80.66	-124.72	-99.30
3.	Rivastigmine	-95.89	-76.75	-87.999	-66.89
4.	Galantamine	-84.05	-49.16	-105.64	-85.42
5.	Chikusetsosaponin	-119.47	-72.12	-108.55	-96.22
6.	Ginsenosides	-157.07	-118.2	-185.74	-110.0
7.	Coriandrol	-154.18	-110.4	-76.11	-63.88
8.	Beta-sitosterol	-91.54	-67.95	-124.19	-102.51
9.	Convolamine	-71.49	-64.26	-94.28	-72.85
10.	Scopoletin	-57.52	-50.3	-64.90	-59.01
11.	Borneol	-44.82	-32.41	-48.53	-45.97
12.	Gingerol	-81.65	-11.54	-111.44	-91.86

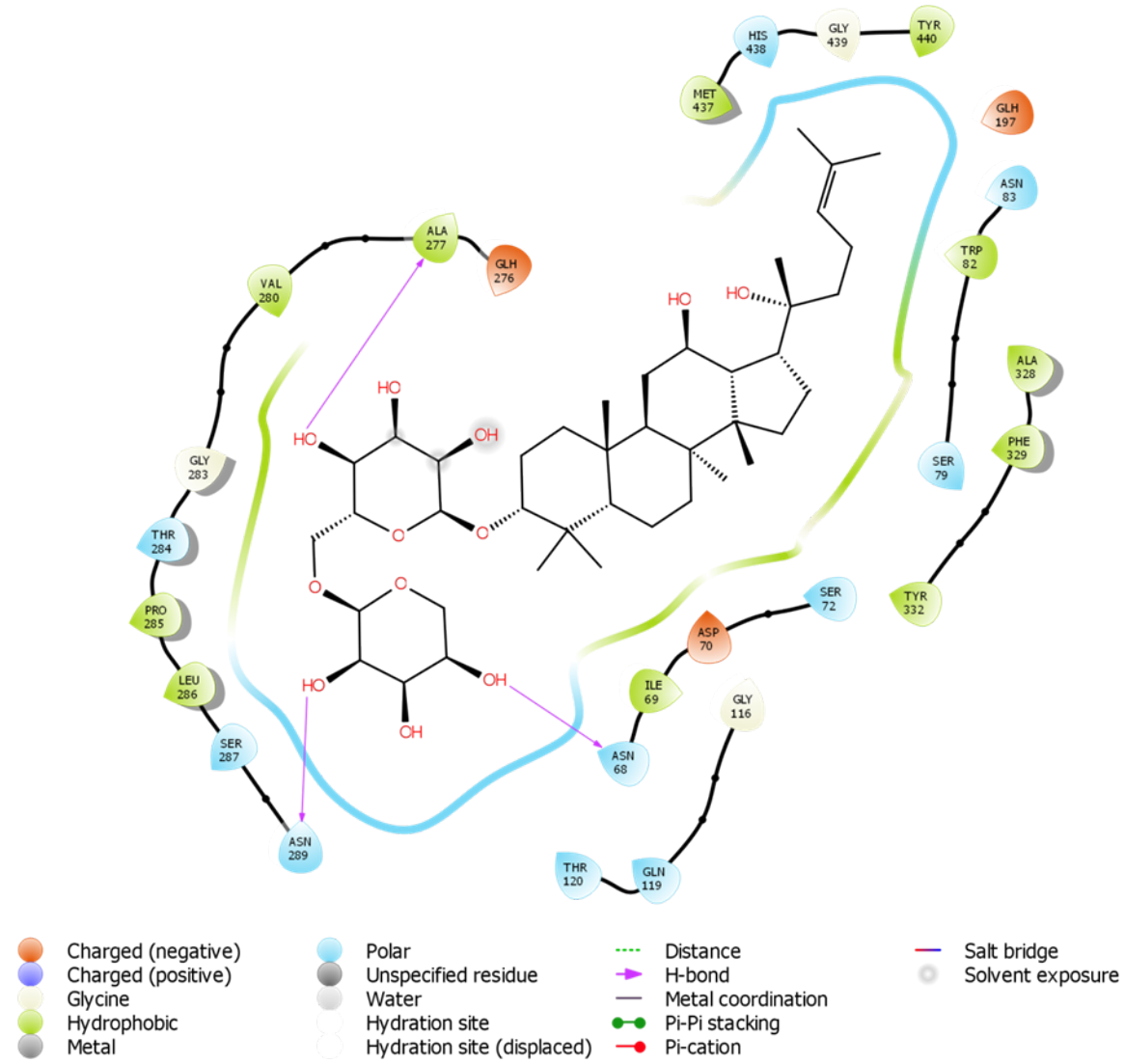

Figure 4: Ligand Interactions of BchE using Glide (Chikusetsosaponin) using schrodinger docker

Table 4: Comparative docking analysis of ligands Using Schrödinger software

Compound Name	Glide score	
	AChE	BuChE
Donepezil	-5.7	-6.5
Memantine	-5.7	6.5
Galantamine	-8.1	-5.2
Rivastigmine	-5.8	-5.2
Chikusetsosaponin	-	-8.7
Ginsenosides	-	-8.7
Coriandrol	-5.3	-4.4
Beta-sitosterol	-5.7	-6.5
Convolamine	-5.7	-4.1
Scopoletin	-7.5	-5.9
Borneol	-5.1	-5.1
Gingerol	-10.3	-7.4

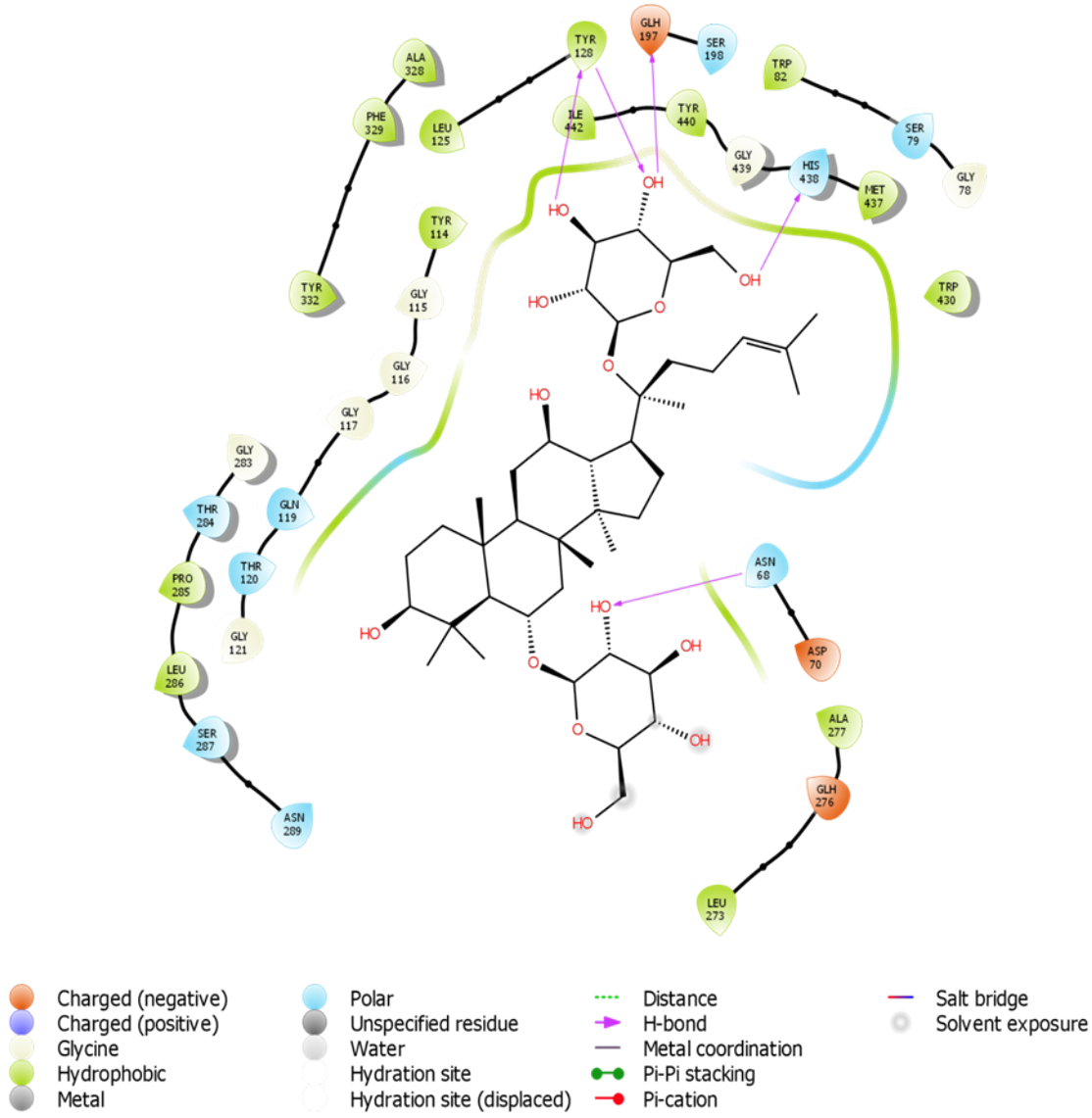

Figure 5: Ligand Interactions of BchE using Glide (Ginsenosides)

The twelve ligands were incorporated into the test tool using the smiles strings and CAS numbers to quickly assess chemical toxicity and can process multiple substances in a single run with batch mode.

Each read-across or regression model has specific applicability domain. The software calculates an approximate LC_{50} threshold based on each model's estimation, as well as a component model consensus average.

Using models like Fathead minnow, daphnia magna, T.pyriformis, Oral rat, Bioaccumulation factor, Developmental toxicity and mutagenicity various methods such as consensus method, Hierarchical clustering, single model, group contribution, FDA, and nearest neighbour, the ligands were accessed for their chemical toxicity and LC_{50} values.

RESULTS AND DISCUSSION

All the phytoconstituents are tested for Drug likeness Using Drulito Software werecomparatively evaluated in Table 1. The phytoconstituents' 'drug resemblance properties' were calculated using the 'The Lipinski law of five.' Drug likeness properties are present in all compounds except Chikusetsosaponin and Ginsenosides. Further studies can be carried to evaluate the *in-vitro* and *in-vivo* Anti-Alzheimer's activity of the selected medicinal plants and to find pharmacokinetic parameters.

The oral rat LD_{50}

The endpoint of the oral rodent LD_{50} is the measure of the compound (chemical mass per rodent body weight) that destroys half of the rodents when administered orally. The oral rodent LD_{50} was

directed in four methods for the selected compound and the discoveries were relatively assessed. All substances have been shown to have an acceptable toxicity limit for drug production and preclinical and clinical appraisal.

Developmental toxicity

Development toxicity leads to embryonic and fetal mortality, unsuccessful labour and other abnormalities like hepatotoxicity, lowered body weight, development and physical abnormalities (teratogenic effects). Developmental toxicity was performed in four approaches with all of the chosen compounds and the findings were comparatively analysed.Toxicity is indicated by a predicted value greater than 0.5.

Ames Mutagenicity

In Ames assay, frame-shift mutations or base-pair substitutions can be identified by exposure of histidine-dependent strains of Salmonella typhimurium to the test compound. When these strains are exposed to a mutagen, reversing mutations that restore the functional capacity of the bacteria to synthesise histidine will cause bacterial colony to develop on a medium histidine deficiency (revertants). A compound is labelled Ames positive if it greatly induces development of the reverting colony in at least one of the five strains. If a compound is positive for the Ames test, it could be a possible mutagen. Ames Mutagenicity was conducted in four methods for all of the chosen compounds and the findings were comparatively analysed in Table 2. Toxicity is indicated by a predicted value greater than 0.5. All the 8 phytoconstituents except convolamine are not mutagens based on the results on the Ames mutagenicity as predicted by TEST software.

Molegro virtual docker

The MolDock Score and Rerank scoring are utilized as the boundaries for dissecting the docking results. The phytoconstituents are positioned according to their MolDock Score.The MolDock Score is represented in Table 3.

The ligand having the most elevated mol dock and re rank score shows a strong affinity towards its target receptor.

In-silico docking analysis was performed for all 8 phytoconstituents such as Chikusetsosaponin, Ginsenosides, Coriandrol, Beta-sitosterol, Convolamine, Scopoletin, Borneol and Gingerol and Compared with Marketed drugs using Molegro virtual docker and Schrödinger software on Acetylcholinesterase (PDB ID: 4bdt)and Butylcholinesterase (PDB ID: 6eqq).

In Molegro software For AChE Moldock score of Gensenosides shows -157.07 followed by Coriandrol shows -154.18 and Chikusetsosaponin shows -119.47 which is higher than the score of marketed drugs. For BChE,Gensenosides shows Moldock Score of -185.74 that is higher than the marketed drug.

Schrodinger (GLIDE)

For AChE Moldock score of Gingerol shows Dock Score of -10.3 which is greater than the standard drugs. The Ligand Interactions of AChE with Gingerol,Scopoletin, Convolamineusing schrodinger docker were shown in Figures 1, 2 and 3 respectively.

For BuChE Moldock score of Chikusetsosaponin and Gensenosides shows -8.7 which is higher dock score than standard drugs were comparatively evaluated in Table 4. The ligand interactions of BChE with Chikusetsosaponin and Gensenosideswere shown in Figures 4 and 5.

The cholinergic deficit is one of the main neurochemical alterations in AD. The reason in the halt of neurotransmission is reduction in the levels of Ach due to anincrease in the levels of ChEs. The major neuro-pathological features of AD are neuritic plaques and neurofibrillarytangles associated with the remarkable increase in the levels of BChE and beta-amyloid aggregation (Ali *et al.*, 2016). Therefore ChE inhibitors are considered normal medications for the treatment of Alzheimer's disease. As a result, AChE and BChE inhibitors have become very common in the treatment of Alzheimer's disease. AChE inhibitors have demonstrated cognitive improvement, some stabilization of behaviours and mood, and may improve functioning during the course of the disease. NMDA receptor partial agonist is also accepted in moderate to serve AD treatment, in addition, some medications that may be protective against the development of Alzheimer's are being evaluated (Reekum *et al.*, 1997). The currently used drugs in the treatment of AD are Donepezil, Rivastigmine, Galantamine, Memantine.

In-silico medical research has the ability to accelerate the level of discovery while reducing the need for costly lab work and clinical trials. Computational tools offer the advantage of delivering new drug candidates more quickly and at a lower cost (Guedes *et al.*, 2014).

Panax ginseng extract improves AD symptoms in patients with AD, and the two main components of ginseng can help relieve symptoms. Ginsenosides have a number of neuroprotective properties that are linked to Alzheimer's disease. Dammarane gly-

cosides are a type of triterpenoid dammarane (Kim *et al.*, 2018).

Convolvulus pluricaulis (Shankhapushpi) is an herbal plant known for its medicinal properties. It is also known as morning glory. This herb is traditionally used as nerve tonic in India. This plant is widely used in Chinese and Indian herbal medicines to get relief from various diseases such as to cure Alzheimer, cough, epilepsy, anxiety, liver problems and to boost memory (Nazir, 2019). *Coriandrum sativum* Linné (Apiaceae; *C. sativum*) is a medicinal plant used as a traditional medicine in China, Iran, and India, among other countries., to treat indigestion, abdominal distention dspeptic complaints, loss of appetite, convulsions, insomnia, anxiety, rheumatoid arthritis, and other inflammatory diseases (Liu *et al.*, 2016).

In order to understand the affinity of binding of phytoconstituents to AChE and BChE in AD, marketed drugs Donepezil, Rivastigmine, Galantamine and Memantine were selected for *in silico* docking studies, which were carried out using Drulito, TEST Software, Molegro virtual docker and Schrodinger Glide software.

CONCLUSION

In our current research, we have chosen eight phytoconstituents namely Chikusetsosaponin, Ginsenosides, Coriandrol, Beta-sitosterol, Convolamine, Scopoletin, Borneol and Gingerol to test its affinity towards AchE and BuChE. Synthetic drugs produce side effects and toxicity, as well as various other therapeutic effects, have led to a rise in demand for plant-derived herbal medicines, which have been approved or are in various stages of clinical trials for a variety of diseases in recent decades. Despite the fact that synthetic chemistry dominates the current drug development and manufacturing field, the importance of plant-derived compounds in the treatment and prevention of various diseases cannot be neglected. In this study, eight ligands were investigated in order to find out the significant ligand against Alzheimer's disease. The ligand was selected based on its binding affinity against two targets of Alzheimer's disease [Acetylcholinesterase and Butyrylcholinesterase] and comparing their activity with the standard drugs available in the market. Findings of this experiment suggested that Gingerol can be administered if the treatment of AD focuses on inhibiting the AChE activity. Similarly, Chikusetsosaponin can be used to treat Alzheimer's disease by inhibiting BChE activity. Further studies can be performed in *in-vitro* & *in-vivo* experimental animal models of Alzheimer's disease to establish the efficacy of promising phytoconstituents.

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Conflict of Interest

The authors declare that they have no conflict of interest.

REFERENCES

Ali, B., Jamal, Q. M., Shams, S., Al-Wabel, N. A., Siddiqui, M. U., Alzohairy, M. A., Karaawi, M. A. A., Kesari, K. K., Mushtaq, G., Kamal, M. A. 2016. In Silico Analysis of Green Tea Polyphenols as Inhibitors of AChE and BChE Enzymes in Alzheimer's Disease Treatment. *CNS & Neurological Disorders - Drug Targets*, 15(5):624–628.

Becker, J. T. 1994. The Natural History of Alzheimer's Disease. *Archives of Neurology*, 51(6):585–585.

Bernstein, F. C., Koetzle, T. F., Williams, G. J., Meyer, E. F., Brice, M. D., Rodgers, J. R., Kennard, O., Shimanouchi, T., Tasumi, M. 1978. The protein data bank: A computer-based archival file for macromolecular structures. *Archives of Biochemistry and Biophysics*, 185(2):584–591.

Bolton, E. E., Wang, Y., Thiessen, P. A., Bryant, S. H. 2008. PubChem: Integrated Platform of Small Molecules and Biological Activities. *Annual Reports in Computational Chemistry*, pages 217–241.

Caputo, C. B., Salama, A. I. 1989. The amyloid proteins of Alzheimer's disease as potential targets for drug therapy. *Neurobiology of Aging*, 10(5):451–461.

Chiti, F., Dobson, C. M. 2006. Protein Misfolding, Functional Amyloid, and Human Disease. *Annual Review of Biochemistry*, 75(1):333–366.

Dorland, W. A. N. 1995. Dorland's illustrated medical dictionary. 28th ed. Philadelphia: W.B saunders, 1995 ISBN: 9780721628592.

Geldmacher, D. S. 2004. Differential diagnosis of dementia syndromes. *Clinics in Geriatric Medicine*, 20(1):27–43.

Grant, W. B., Campbell, A., Itzhaki, R. F., Savory, J. 2002. The significance of environmental factors in the etiology of Alzheimer's disease. *Journal of Alzheimer's Disease*, 4(3):179–189.

Guedes, I. A., de Magalhães, C. S., Dardenne, L. E. 2014. Receptor–ligand molecular docking. *Bio-*

physical Reviews, 6(1):75–87.

Huppert, F. A., Tym, E. 1986. Clinincal and neuropsychological assessment of dementia. *Br Med Bull*, 42:11–18.

Kim, H. J., Jung, S. W., Kim, S. Y., Cho, I. H., Kim, H. C., Rhim, H., Kim, M., Nah, S. Y. 2018. Panax ginseng as an adjuvant treatment for Alzheimer's disease. *Journal of Ginseng Research*, 42(4):401–411.

Lipinski, C. A., Lombardo, F., Dominy, B. W., Feeney, P. J. 1997. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, 23(1-3):3–25.

Liu, Q. F., Jeong, H., Lee, J. H., Hong, Y. K., Oh, Y., Kim, Y. M., Suh, Y. S., Bang, S., Yun, H. S., Lee, K., Cho, S. M., Lee, S. B., Jeon, S., Chin, Y. W., Koo, B. S., Cho, K. S. 2016. Coriandrum sativum Suppresses Aβ42-Induced ROS Increases, Glial Cell Proliferation, and ERK Activation. *The American Journal of Chinese Medicine*, 44(07):1325–1347.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., Stadlan, E. M. 1984. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, 34(7):939.

Nazir, R. 2019. Biotechnological Strategies for Production of Anti-Alzheimer compounds from Shankhapushpi. *Journal of the Gujarat Research Society*, 21(8):635–652.

Reekum, R. V., Black, S. E., Conn, D., Clarke, D. 1997. Cognition-enhancing drugs in dementia: a guide to the near future. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, 42(1):35–50.

Salloway, S., Correia, S. 2009. Alzheimer disease: Time to improve its diagnosis and treatment. *Cleveland Clinic Journal of Medicine*, 76(1):49–58.

Sastry, G. M., Adzhigirey, M., Day, T., Annabhimoju, R., Sherman, W. 2013. Protein and ligand preparation: parameters, protocols, and influence on virtual screening enrichments. *Journal of Computer-Aided Molecular Design*, 27(3):221–234.

Small, G. W., Rabins, P. V., Barry, P. P., Buckholtz, N. S., Dekosky, S. T., Ferris, S. H., Tune, L. E. 1997. Diagnosis and treatment of Alzheimer disease and related disorders: consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. *Jama*, 278(16):1363–1371.

Strittmatter, W. J., Saunders, A. M., Schmechel, D., Pericak-Vance, M., Enghild, J., Salvesen, G. S., Roses, A. D. 1993. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proceedings of the National Academy of Sciences*, 90(5):1977–1981.

Yan, S. D., Chen, X., Schmidt, A. M., Brett, J., Godman, G., Zou, Y. S., Scott, C. W., Caputo, C., Frappier, T., Smith, M. A. 1994. Glycated tau protein in Alzheimer disease: a mechanism for induction of oxidant stress. *Proceedings of the National Academy of Sciences*, 91(16):7787–7791.