A DISSERTATION ON

EVALUATION OF AChE AND BChE INHIBITORS FROM PLANT DERIVED METABOLITES: AN *IN SILICO STUDY*

SUBMITTED TO THE

DEPARTMENT OF BIOSCIENCES

INTEGRAL UNIVERSITY, LUCKNOW

IN PARTIAL FULFILLMENT

FOR THE

DEGREE OF MASTER OF SCIENCE

IN MICROBIOLOGY

By

Shailendra Sagar Singh

M.Sc. Microbiology (IV Semester)

Department of Biosciences

Integral University

UNDER THE SUPERVISION OF

DR. MOHAMMAD HAYATUL ISLAM

Assistant Professor

Department of Biosciences

Integral University, Lucknow

DECLARATION

I hereby declare that the present work on "**Evaluation of AChE and BChE inhibitors From plant derived metabolites : An *In silico study***" is a record of original work done by me under guidance of (Supervisor) **Dr. Mohammad Hayatul Islam** Assistant Professor, Integral University**,** during Feb, 2022 to June , 2022, at Integral University, Lucknow. All the data which were provided in this thesis were through our own work.
I also declare not part of this thesis has previously been submitted to my Institution or any examining body for acquiring any diploma or degree.

Place: Integral University, Kursi road
Lucknow
Date: **Shailendra sagar Singh**

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Approved by University Grant Commission
Phone No.: +91(0522) 2890812, Fax No.: 0522-2890809
Kursi Road, Lucknow-226026 Uttar Pradesh (INDIA)

CERTIFICATE

TO WHOM IT MAY CONCERN

This is to certify that Mr. Shailendra Sagar Singh, a student of M.Sc. Microbiology (II Year, IV semester), Integral University has completed his Four months dissertation work entitled "**Evaluation of AChE and BChE inhibitors From plant derived metabolites: An *In silico study***" successfully. He has completed this work from Department of Biosciences, Integral University, under the guidance of **Dr. Mohammad Hayatul Islam,** Department of Biosciences, Integral University,Lucknow The dissertation was a compulsory part of his M.Sc Microbiology. I wish him good luck and bright future.

Dr. Mir Snober Shabnam
Head,
Department of Biosciences,
Integral University, Lucknow

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Kursi Road, Lucknow-226026 Uttar Pradesh (INDIA)

CERTIFICATE OF SUPERVISOR

This is to certify that Shailendra Sagar Singh completed his four months training from February – June , 2022 under my guidance and supervision. The results reported by his are genuine and script of the thesis has been written by candidate himself. The thesis entitled is "**Evaluation of AChE and BChE inhibitor From plant derivatives metabolites : An In *silico* study**" Therefore, being forwarded for the acceptance in partial fulfilment of the requirements for the award of the degree of Master of Science in M.sc Microbiology Department of Biosciences, Integral University, Lucknow (U.P.).

(Supervisor)
Dr. Mohammad Hayatul Islam
Assistant Professor
Department of Biosciences

ACKNOWLEDGEMENT

First of all, I bow in reverence to the Almighty for blessing me with strong will power, patience and confidence, which helped me in completing the present work.

I would like to express my special thanks to **Dr. Mir Snober Shabnam (Head, Department of Biosciences)** for given me an opportunity to join the department laboratory and providing all the necessary facilities ever since I started my work.

I would like to express my deep sense of gratitude to (Supervisor) **Dr. Hayatul Islam, Department of Biosciences** for his invaluable guidance throughout the course of my dissertation work and academic session. It would have been impossible to complete this work in so short a time without his constant guidance. I wish every trainee and research student were fortunate enough to have such an affectionate guide.

I am grateful to **Ms. Firdaus jahan**, who inspired and encouraged me during the course of my research. Despite her hectic schedule, she was always ready to answer my queries and clear up any confusion.

My thanks also go to all of my friends who were instrumental in my academic success.

My appreciation would be inadequate if I did not include my parents, with whose blessing I was able to successfully finish my aim. There are no words to convey how I feel about them. I discreetly express my gratitude to them.

Shailendra Sagar Singh

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INTRODUCTION

Neurodegenerative disorders (NDD) constitute a set of pathological conditions originating from slow progressive and irreversible dysfunction and loss of neurons and synapses in selected areas of the nervous system which determine clinical presentation and course. The major basic mechanisms leading to neurodegeneration (ND) are considered multifactorial caused by genetic, environmental and endogenous factors related to aging, but their pathogenic role and their basic molecular mechanisms are not fully understood (Checkoway *et al*., 2011). NDDs currently are classified according to known genetic mechanisms and/or to the major compounds of their protein deposits. Based on critical conformational changes of proteins, these disorders are denoted as 'protein misfolding' diseases or proteinopathie (Golde and Miller *et al*., 2009; Uversky et al., 2009). Neurodegenerative diseases represent a major threat to human health. These age-dependent disorders are becoming increasingly prevalent, in part because the elderly population has increased in recent years (Heemels *et al*.,2016). Examples of neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia and the spinocerebellar ataxias. These diseases are diverse in their pathophysiology – with some causing memory and cognitive impairments and others affecting a person's ability to move, speak and breathe (Abeliovich and Gitler *et al*., 2016).

Alzheimer's disease

Alzheimer's disease Alzheimer disease (AD) is the most common neurodegenerative disease. It is insidious, progressive and degenerative disease.AD is the most common cause of the dementia. Dementia leads to the loss of cognitive functioning—like thinking, remembering, reasoning— behavioral abilities and it also can cause death. It is estimated that till 2050 around 11 million people will be influence of Alzheimer's disease (Alzheimer's, 2014, 2015).AD is named after Dr. Alois Alzheimer. In 1906, Dr. Alzheimer noticed some changes in the brain tissue of a woman who had died of an unknown and unusual mental illness. She have some symptoms like loss of memory, problem in communicating and unpredictable behavior. After her death Dr. Alzheimer examined her

brain and found many abnormal aggregated clumps and tangled fibers. These abnormal Clumbs which are now known as plaques and tangles in the brain tissues are considered some of the main features of Alzheimer's disease. Another feature of AD is the loss of connections between neuronal cells in the brain. Exact reason and pathophysiology of AD is still unclear and there is a no known cure of this disease (Mattson *et al*., 2004).

Symptoms

Alzheimer's disease is a progressive condition, meaning that the symptoms get worse over time. Memory loss is a key feature, and this tends to be one of the first symptoms to develop .The symptoms appear gradually, over months or years. If they develop over hours or days, a person may require medical attention, as this could indicate a stroke.

Symptoms of Alzheimer's disease include:

Memory loss: A person may have difficulty taking in new information and remembering information. This can lead to:

Repeating questions or conversations

Losing objects

Forgetting about events or appointments

Wandering or getting lost

Cognitive deficits: A person may experience difficulty with reasoning, complex tasks, and judgment. This can lead to:

A reduced understanding of safety and risks

Difficulty with money or paying bills

Difficulty making decisions

Difficulty completing tasks that have several stages, such as getting dressed

Problems with recognition: A person may become less able to recognize faces or objects or less able to use basic tools. These issues are not due to problems with eyesight.

Problems with spatial awareness: A person may have difficulty with their balance, trip over, or spill things more often, or they may have difficulty orienting clothing to their body when getting dressed.

Problems with speaking, reading, or writing: A person may develop difficulties with thinking of common words, or they may make more speech, spelling, or writing errors.

Personality or behavior changes: A person may experience changes in personality and behavior that include: Becoming upset, angry, or worried more often than before, A loss of interest in or motivation for activities they usually enjoy, A loss of empathy and compulsive, obsessive, or socially inappropriate behavior.

Treatment

There is no cure for Alzheimer's disease. Only symptomatic treatment is available. (Hussein W *et al*., 2018; Leblhuber F *et al*., 2018; Adlimoghaddam A *et al*., 2018)

Two categories of drugs are approved for the treatment of Alzheimer's disease: cholinesterase inhibitors and partial N-methyl D-aspartate (NMDA) antagonists.

Cholinesterase Inhibitors

Cholinesterase inhibitors act by increasing the level of acetylcholine; a chemical used by nerve cells to communicate with each other and is important for learning, memory and cognitive functions. Of this category, 3 drugs: donepezil, rivastigmine, and galantamine are FDA-approved for the treatment of Alzheimer's disease.

Donepezil can be used in all stages of Alzheimer's disease. Galantamine and rivastigmine are approved for treatment in MCI and Dementia stage. Donepezil and galantamine are rapid, reversible inhibitors of acetylcholinesterase. Rivastigmine is a slow, reversible inhibitor of acetylcholinesterase and butyrylcholinesterase. Donepezil is

usually preferred of all because of once-daily dosing. Galantamine is available as a twice-daily tablet or as a once-daily extended-release capsule. It cannot be used in end-stage renal disease or severe liver dysfunction. Rivastigmine is available in an oral and transdermal formulation. The most common side effects of cholinesterase inhibitors are gastrointestinal-like nausea, vomiting, and diarrhea. Sleep disturbances are more common with donepezil. Due to increased vagal tone, bradycardia, cardiac conduction defects, and syncope can occur, and these medications are contraindicated in patients with severe cardiac conduction abnormalities.

Partial N-Methyl D-Aspartate (NMDA) Memantine

Partial N-Methyl D-aspartate (NMDA) antagonist Memantine blocks NMDA receptors and slows intracellular calcium accumulation. It is approved by the FDA for treating moderate to severe Alzheimer's disease. Dizziness, body aches, headache, and constipation are common side effects. It can be taken in combination with cholinesterase inhibitors (Khoury R et al., 2018).

It is also important to treat anxiety, depression, and psychosis, which is often found in the mid to late stages of Alzheimer's disease. Avoid tricyclic antidepressants, because of their anticholinergic activity. Antipsychotics are used for acute agitation, only if the patient or caregiver have been exhausted. However, their limited benefits should be weighed against the small risk of stroke and death.

Environmental and behavioral approaches are beneficial especially in managing behavioral problems. Simple approaches such as maintaining a familiar environment, monitoring personal comfort, providing security objects, redirecting attention, removing doorknobs and avoiding confrontation can be very helpful in managing behavioral issues. To minimize caregiver burden, mild sleep disturbances can be reduced by providing exposure to sunlight and providing daytime exercise. The expected benefits of the treatment are modest. Treatment should be stopped or modified if no significant benefits or if intolerable side effects. Regular aerobic exercise has been shown to slow the progression of Alzheimer's disease. It is well-known that two different cholinesterase (ChE) enzymes, acetylcholinesterase (AChE), and butyrylcholinesterase (BChE), are responsible for the hydrolysis of ACh within the brain.

AChE

Acetylcholinesterase (AChE) is a cholinergic enzyme primarily found at postsynaptic neuromuscular junctions, especially in muscles and nerves. It immediately breaks down or hydrolyzes acetylcholine (ACh), a naturally occurring neurotransmitter, into acetic acid and choline. (McHardy et al.,2015) The primary role of AChE is to terminate neuronal transmission and signaling between synapses to prevent ACh dispersal and activation of nearby receptors.

Acetylcholinesterase is involved in the termination of impulse transmission by rapid hydrolysis of the neurotransmitter acetylcholine in numerous cholinergic pathways in the central and peripheral nervous systems. The enzyme inactivation, induced by various inhibitors, leads to acetylcholine accumulation, hyperstimulation of nicotinic and muscarinic receptors, and disrupted neurotransmission. Hence, acetylcholinesterase inhibitors, interacting with the enzyme as their primary target, are applied as relevant drugs and toxins.

BChE

Acetylcholinesterase in nerve synapses terminates nerve impulse transmission by hydrolyzing the neurotransmitter acetylcholine. Butyrylcholinesterase acts as a backup for acetylcholinesterase, and as a scavenger for poisons that might inhibit acetylcholinesterase activity Butyrylcholinesterase is a nonspecific cholinesterase enzyme that hydrolyses many different choline-based esters.

Although the mechanism of catalysis is the same between both cholinesterases, the substrate reactivity between the two enzymes are quite different. In this respect, size matters. AChE hydrolyzes acetylcholine and small ester compounds, while BuChE hydrolyzes larger molecules such as butyrylcholine. This difference in substrate reactivity is apparent when considering the structural differences in the catalytic sites between the two enzymes.

The serine hydrolase butyrylcholinesterase (BChE), like the related enzyme acetylcholinesterase (AChE), co-regulates metabolism of the neurotransmitter acetylcholine. In the human brain BChE is mainly expressed in white matter and glia and in distinct populations of neurons in regions that are important in cognition and behavior, functions compromised in Alzheimer's disease (AD).

REVIEW OF LITERATURE

Prevalence of neurological disorders in India

India is going through a rapid phase of epidemiological transition with increase in Non-communicable diseases (NCDs), and neurological disorders form a significant proportion of NCDs (Lancet *et al*., 2017). There is a striking variation of various health parameters and magnitude of epidemiological transition between different states and regions in India (Gourie-Devi *et al*., 2017). In the developed countries, neuro epidemiological studies have been done for more than 50 years; however, in India as in other developing countries, confronted with grossly limited trained workforce in neurology and scant resources, this field did not develop till the late 1960s. (Gourie-Devi *et al*., 2014) The average crude prevalence rate of common neurological disorders in India is 2394 and ranged from 967 to 4070/100000 population with higher prevalence rate in rural compared to urban population.

INHIBITORS OF AChE

AChE inhibitors or anti-cholinesterases inhibit the cholinesterase enzyme from breaking down ACh, increasing both the level and duration of the neurotransmitter action. According to the mode of action, AChE inhibitors can be divided into two groups: irreversible and reversible**.** Reversible inhibitors, competitive or noncompetitive, mostly have therapeutic applications, while toxic effects are associated with irreversible AChE activity modulators.

Reversible Acetylcholinesterase Inhibitors in Alzheimer's Disease Treatment

AD is a progressive neurological disorder, the most common form of dementia, characterized by memory loss and other intellectual abilities serious enough to interfere with daily life (Thompson *et al*., 2012). The disease is associated with loss of cholinergic neurons in the brain and the decreased level of ACh (Lane *et al*., 2006). The major therapeutic target in the AD treatment strategies is the inhibition of brain AChE (Giacobini *et al*., 2004). There is no cure for AD, and reversible AChE inhibitors, employed in the therapy, treat symptoms related to memory, thinking, language, judgment and other thought processes. Actually, different physiological processes

related to AD damage or destroy cells that produce and use ACh, thereby reducing the amount available to deliver messages to other cells. Cholinesterase inhibitor drugs, inhibiting AChE activity, maintain ACh level by decreasing its breakdown rate. Therefore, they boost cholinergic neurotransmission in forebrain regions and compensate for the loss of functioning brain cells. No drug has an indication for delaying or halting the progression of the disease (Stahl *et al.,* 2000). Medications currently approved by regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to treat the cognitive manifestations of AD and improve life quality of the patients are: donepezil, rivastigmine and galantamine as reversible AChE inhibitors, and memantine as an NMDA receptor antagonist (Birks *et al*., 2006; Hyde *et al* ., 2013; Bond *et al* ., 2012). Tacrine was the first of the AChE inhibitors approved for the AD treatment in 1993, but its use has been abandoned because of a high incidence of side effects including hepatotoxicity (Birks *et al*., 2009; Watkins *et al*., 1994).

Inhibitors of BChE

In AD, BChE is found in association with pathology, such as β-amyloid (Aβ) plaques, particularly in the cerebral cortex where BChE is not normally found in quantity. Up to 30% of cognitively normal older adults have abundant Aβ deposition in the brain. Butyrylcholinesterase (BChE), also known as the “pseudo” or “non-neuronal” cholinesterase, is traditionally thought to have a restricted CNS distribution and to play little, if any, role in cholinergic transmission.

Butyrylcholinesterase is found in much lower concentrations, is traditionally known as the “pseudo” cholinesterase and is thought to have a much more restricted distribution in the brain (Mesulam *et al*., 2000). Although there is no convincing evidence that BChE plays a useful role in central cholinergic transmission, there is evidence that it modulates cholinergic transmission in smooth muscle (Norel *et al*., 1993).

In the human brain BChE is found mainly in white matter and glia and in distinct populations of neurons in regions, such as the amygdala, hippocampal formation (Darvesh *et al* ., 1998) and the thalamus (Darvesh *et al*., 2003), structures that are important in cognition and behavior. For example, in the thalamus, over 95% of the

neurons in the anteroventral and mediodorsal nuclei express BChE. The amygdala and hippocampal formation, that also have significant number of neurons expressing BChE, are among the first structures showing neurodegeneration in AD (Arnold *et al*., 1991).

Plant metabolites as neuroprotecitve agents

Millions of people worldwide are currently affected by neurodegenerative diseases (NDDs) the most common being Alzheimer's disease (AD). NDDs are more common in countries with a high average life expectancy, and this has drawn the attention of researchers due to their social and economic impacts. NDDs, such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), are characterized by progressive loss of function and structure of the nerve cells. Although the actual cause of NDDs is still unknown, there are some common factors contributing to NDDs which include neuro-inflammation, β-amyloid (Aβ) aggregation, neurofibrillary tangle formation, oxidative stress, and impairment of mitochondrial function. However, ageing is considered as the greatest risk factor for NDDs (Ratheesh *et al*., 2017). Considering the fact that NDDs represent chronic and incurable conditions, bioactive compounds isolated from medicinal plants have become the best option to prevent and alleviate neurological disorders. Phytochemicals have become interesting therapeutic candidates due to their various biological properties including, but not limited to anti-oxidant, anti-inflammatory activities, neuroprotective effects and chemical characteristics such as direct uptake of free radicals, and modulation of enzymes associated with oxidative stress. (Perez-Hernandez *et al*., 2016). Nature remains to be a veritable source of medicines to mankind. Many important drugs such as vincristine, artemisinin, and gentamicin, which are still in use today, are obtained from natural sources or are designed on structural fingerprints of naturally occurring molecules (Alan *et al*., 2008). Furthermore, traditional medicine remains a vital alternative source of medicine all over the world today with some estimate suggesting to account to about 80% of the primary health care system in some developing countries (e.g., Nigeria, Ghana, China, and India [WHO 2004; Martins Ekor *et al*., 2014). The increasing incidence of resistance (especially to antibiotics and antimalarials), undesirable side

effects, high cost, and lack of efficacy after prolonged usage of the existing drugs in use has led to a renewed interest in the development of new drug candidates from natural sources (Goldfrank *et al*., 1982 ; Cowan *et al* ., 1999). For example, drugs such as amantadine, memantine, donepezil, selegiline, galantamine, and rivastigmine that are clinically available for the management of NDs are only able to provide symptomatic relief and slow the progression of the diseases (Waite et al ., 2015; Chen *et al*., 2014). These drugs, such as the synthetic donepezil, are also associated with side effects (Cacabelos *et al*., 2007). Hence, a great deal of research focus has been given in recent years to herbs and other natural products used in ethnomedicine around the world for age-related CNS diseases.

MATERIALS AND METHODS

Software required

Cygwin, a data storage c:\program was downloaded from www.cygwin.comb, MGL (Molecular Graphics Laboratory) tools AutoDock4.2 downloaded from www.scripps.edu, Discovery studio (DS) visualize 3.0 downloaded from www.accelerys.com, Accelrys draw download from www.accelrys.com and Python 2.5 downloaded simultaneously during cygwin download.

Ligand preparation

Plant derived bioactive compounds have been compiled (Table 1). The three-dimensional structures of these compounds are retrieved from the PUBCHEM open chemistry database.

Table 1: Compiled Compounds with their PubChem ID.

S.NO	Compound name	Pubchem id
1.	(E)-methylisoeugenol	637776
2.	Caryophyllene Oxide	1742210
3.	1-Decanol	8174
4.	1-octen-3-ol	18827
5.	alpha-Asarone	636822
6.	Sominone	44249449
7.	Furfuraldehyde	7362
8.	Myrcene	31253
9.	Donepezil*	3152
10.	Galantamine*	9651

Target preparation

The target proteins namely acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) retrieved from RCSB protein data bank database. The PDB-ID of our traget protein is 4M0E and 5DYW respectively.

Accelery Discover Studio tool is used to prepare the targets such a way that it has no ambiguities i.e. water molecules and small molecules along with the ligand/substrate and any HETATM attached are removed from the primary downloaded complex.

Table 2: Target protein with their RCSB-ID.

RCSB ID	Classification	Organism	Mutation
4MOE	Hydrolase	Homo sapiens	No
5DYW	Hydrolase	Homo sapiens	No

Standard drug preparation

Compound /drug which are commercially available or prescribed for AD treatment are Donepezil and Galantamine. These are considered as control for our study.

Table 3: Standard Compounds with their PubChem ID.

S.No.	Standard	PubChem ID
1.	**Donepezil**	3115
2.	**Galantamine**	9651

RESULTS AND DISCUSSION

Study of pharmacokinetic analyses and drug likeness

Pharmacokinetic analyses of over 100 plant derived compounds revealed that 10 compounds obeyed the all parameters of drug likeness (Table 3) and ADMET (Table 4). The molecular properties of these 10 compounds were then investigated using Molinspiration software to satisfy Lipinski's rule of five, which is essential for rational drug design and also to determine their bioactivity score (Molinspiration, 2016).

Table 4: The Lipinski's rule of five attributes of shortlisted compounds and control drugs.

S. No.	CompoundID	CompoundName	miLogP	TPSA	natoms	MW	nON	nOHNH	nviolations	nrotb	volume
1.	(E)-methylisoeugenol	637776	2.69	18.47	13	178.23	2	0	0	3	179.11
2.	Caryophyllene Oxide	1742210	4.14	12.53	16	220.3	1	0	0	0	234.01
3.	1-Decanol	8174	4.15	20.23	11	158.28	1	1	0	8	188.43
4.	1-octen-3-ol	18827	2.76	20.23	9	128.22	1	1	0	5	148.98
5.	alpha-Asarone	636822	2.49	27.70	15	208.26	3	0	0	4	204.66
6.	Sominone	44249449	4.63	86.99	33	458.64	5	3	0	3	450.37
7.	Furfuraldehyde	7362	0.98	30.21	7	96.08	2	0	0	1	84.59
8.	Myrcene	31253	3.99	0.00	10	136.24	0	0	0	4	162.24
9.	Donepezil	3152	4.10	38.78	28	379.50	4	0	0	6	367.89
10.	Galantamine	9651	1.54	41.93	21	287.36	4	1	0	1	268.19

Table 5: ADME/Tox properties of selected compounds and standard drugs.

		Toxicity			Absorption				Distribution		Metabolism
S.NO	**Compound**	**Mutagenicity (Ames Test)**	**Carcinogenicity**		**HIA**	**Caco 2**	**MDCK**	**Skin Permeability**	**PPB (Plasma Protein Binding)**	**BBB (Blood Brain Barrier)**	**CYP2D6 Inhibition**
			Mouse	**Rat**							
1.	(E)-methylisoeugenol	Mutagen	Positive	Positive	100.0	58.09	302.0	-1.426	92.84	1.108	Non
2.	Caryophyllene Oxide	Mutagen	Positive	Positive	100.0	56.34	218.8	-1.410	90.84	3.752	Non
3.	1-Decanol	Non-Mutagen	Positive	Negative	100.0	32.79	190.2	-1.066	100.0	2.379	Non
4.	1-octen-3-ol	Mutagen	Negative	Negative	100.0	43.31	60.53	-1.333	100.0	5.474	Non
5.	alpha-Asarone	Mutagen	Positive	Positive	100.0	58.09	324.9	-1.680	93.39	1.229	Non
6.	Sominone	Non-Mutagen	Positive	Negative	91.39	21.11	0.057	-3.713	100.0	1.352	Non
7.	Furfuraldehyde	Mutagen	Positive	Positive	99.28	26.38	57.30	-2.42	87.14	1.466	Non
8.	Myrcene	Mutagen	Negative	Positive	100.0	23.63	216.2	-0.632	100.0	9.101	Non
9.	Donepezil*	Mutagen	Negative	Negative	97.95	55.51	0.138	-3.041	84.61	0.187	Inhibitor
10.	Galantamine*	Mutagen	Negative	Negative	95.40	20.93	78.09	-4.176	25.77	0.578	Inhibitor

Molecular docking analysis

During the initial part of the study, we also docked the commercially available anti AD drugs donepezil and Galantamine with the identified binding sites to draw a comparison with the binding energy observed with the compounds. Donepezil and Galantamine were used as controls in the study. The ligand conformations of selected Eight compounds were then ranked according to their binding affinities with all key targets of AD.

Table 6: Molecular Docking results of AChE in terms of Binding energy and inhibition constant.

S.No	Compound	Binding Energy (Kcal/mol)	Ki
1.	(E)-methylisoeugenol	-6.10	33.78 uM
2.	Caryophyllene Oxide	-7.83	1.83 uM
3.	1-Decanol	-5.20	154.59 uM
4.	1-octen-3-ol	-4.89	261.64 uM
5.	alpha-Asarone	-6.19	29.04 uM
6.	Furfuraldehyde	-4.96	229.93 uM
7.	Myrcene	-5.21	151.54 uM
8.	Sominone	-11.02	8.42 nM
9.	Donepezil*	-10.88	10.55 nM
10.	Galantamine*	-8.79	361.32 nM

Table 7: Molecular Docking results of BChE in terms of Binding energy and inhibition constant.

S.No	Compound	Binding Energy (Kcal/mol)	Ki
1.	(E)-methylisoeugenol	-5.54	87.18 uM
2.	Caryophyllene Oxide	-7.25	4.88 uM
3.	1-Decanol	-4.29	719.20 uM
4.	1-octen-3-ol	-4.83	287.10 uM
5.	alpha-Asarone	-5.22	148.64 uM
6.	Furfuraldehyde	-4.14	926.28 uM
7.	Myrcene	-4.69	362.29 uM
8.	Sominone	-10.82	11.75 nM
9.	Donepezil*	-8.92	291.14 nM
10.	Galantamine*	-7.52	3.10 uM

Binding energy results of target protein AchE with our screened compound and standard compound.

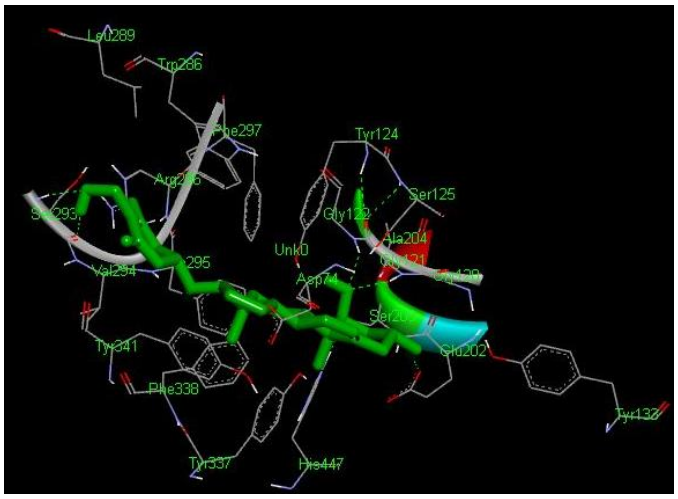

Figure 1 Sominone

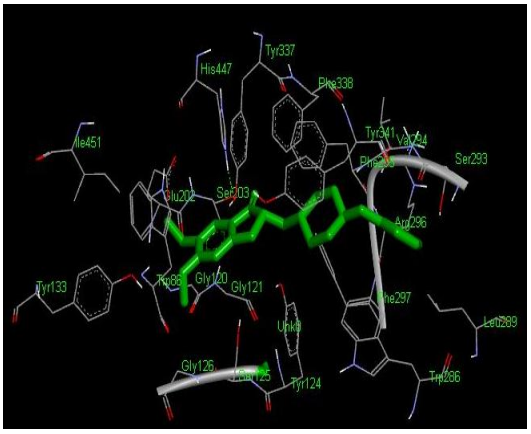

Figure 2 Donepezil

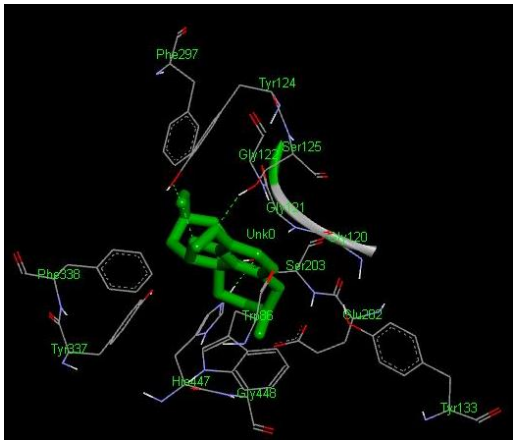

Figure 3 Galantamine

Binding energy results of target protein BchE with our selected compound and control drug.

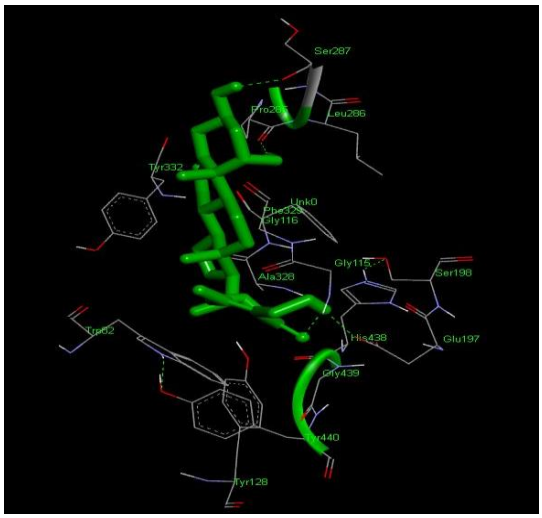

Figure 4:Sominone

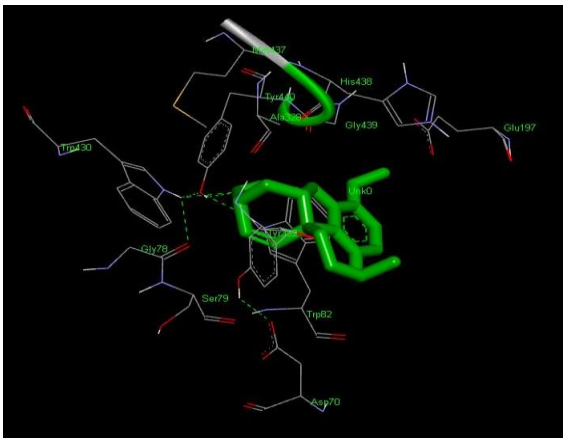

Figure 5: Donepezil

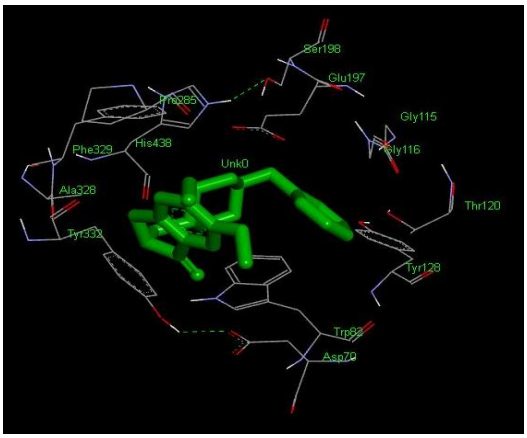

Figure 6: Galantamine

Molecular docking results are summarized in Table 6 and 7, all the selected compounds docked with the target AChE and BChE. Sominone showed the best binding affinity with both targets -11.02 and -10.82 kcal/mol respectively, as compare to other compounds and standard drug. Our control drugs Donepezil and Galantamine showed less binding affinity towards the protein target AChE and BchE. Donepezil and Galantamine with AchE showed the binding energy -10.88 kcal/mol and -8.79 kcal/mol while with BchE showed the binding energy -8.92 kcal/mol and -7.52 kcal/mol respectively. Hence, we can say that our compound sominone showed higher binding affinity as compared to our two control drugs.

Sominone belongs to the class of organic compounds known as triterpenoids. These are terpene molecules containing six isoprene units Glycyrrhetol is an extremely weak basic (essentially neutral) compound .Present study concluded that Sominone may be an inhibitor of Acetylcholinesterase and Butyrylcholinesterase to overcome from AD. Further In vitro and in vivo investigations are required.

Conclusion

Compounds that will inhibit the enzyme Acetylcholinesterase and Butyrylcholinesterase in AD brain are potential therapeutic agents. Among the all selected compounds on the basis of pharmacokinetic study Sominone was found to fulfill all the tested descriptors for both drugability and ADME/Tox. In addition molecular docking results suggested that Sominone bind significantly in the conserved sites of Acetylcholinesterase and Butyrylcholinesterase. Thus it is worth to carry further investigations at both *in vitro* and *in vivo* levels on them to be applied against AD.

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