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UNPRECEDENTED IN SILICO MOLECULAR DOCKING INVESTIGATION OF *VIGNA VEXILLATA* AS A POTENTIAL THERAPEUTIC AGENT AGAINST ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease (AD) are neurodegenerative disorders that have emerged as among the serious health problems of the 21st century. The medications currently available to treat AD have limited efficacy and are associated with side effects. Natural products are one of the most vital and conservative sources of medicines for treating neurological problems. Phytochemicals of several medicinal plants has been reported for numerous health benefits. However, the effect of *Vigna vexillata* on AD has not yet been systematically investigated. To evaluate the neuroprotective effect of V. Vexillata phytochemicals, extensive in silico studies starting with molecular docking against 26 putative targets for AD were conducted. The findings were compared with three standard drugs using Auto dock vina software. Additionally, the physiochemical properties (Lipinski rule of five), (ADMET) profiles of *Vigna vexillata* were also studied. V. vexillate natural compounds comply with all five of Lipinski's drug-likeness rules with suitable ADMET profiles for therapeutic use. The docking scores (kcal/mol) showed comparatively higher potency against AD associated targets than currently used standard drugs. Overall, the potential binding affinity from molecular docking and other multiparametric drug-ability profiles suggest that V. vexillata compounds could be considered as a suitable therapeutic lead for AD treatment. Furthermore, the present results were strongly correlated with the earlier study on *Vigna vexillata* in a Parkinson's animal model. However, necessary in vivo studies must be required to use *Vigna vexillata* as a potential drug, where the in-silico results are more helpful to accelerate the drug development.

KEYWORDS: *Vigna vexillata*, Alzheimer's disease, Lipinski's rule, drug-likeness, ADMET, Acetylcholinesterase, Butyl cholinesterase.

1. INTRODUCTION

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases and is the most popular cause of dementia in adults. AD is marked by behavioural changes, cognitive impairments and imperfection in conducting routine life tasks, overall creating a major socio-economic strain on the health care system. It is reported that one new case of dementia is estimated to occur every three seconds in the world, where approximately 55 million individuals have dementia, affecting 60% in low- and middle-income countries. In fact, there are about 10 million new cases reported every year, and the overall number of dementia patients is estimated to hit 82 million in 2030 and 152 million in 2050. In Malaysia, the Alzheimer's Disease Foundation Malaysia estimates that there are currently around 50,000 individuals affected by the disease, and, by 2030, the figure is expected to be 100,000 and will continue to grow to 250,000 in 2050. Pathophysiologic changes of the disease include deficiency in the essential neurotransmitter acetylcholine (ACh), accumulation of amyloid plaques (Aβ), heavily phosphorylated tau proteins and imbalances in the glutamatergic system.[4]

To date, only five drugs are clinically approved, including the cholinesterase inhibitors tacrine, galantamine, donepezil, rivastigmine and the glutamatergic system modulator memantine. Nevertheless, these medications have limited effectiveness with many associated side effects. The availability of pre-clinical and clinical trials on mild to moderate AD dementia is timely for the development of more effective and safe natural alternatives.[4]

Despite the limited success of synthetic agents as potential multifunctional drugs against AD, the main limiting factors such as pharmacokinetics and safety issues remain challenging.[10]

Unfortunately, currently available medications provide only symptomatic relief and do not stop neurodegeneration, making novel drug discoveries important. Natural products can potentially offer effective and safe pharmacodynamic characteristics in challenging neurodegenerative diseases. Nevertheless, the number of biological pathways and proteins implicated in the diseases' pathogenesis, the complexity of the affected organs (especially the brain) and their aggressiveness remain the biggest obstacles toward drug development for AD. Plant-derived natural products, as well as their bioactive molecules, have been widely

researched in recent years for their therapeutic potential in a range of neurodegenerative diseases including AD. Among numerous molecules, flavonoids are slated to have an excellent neuroprotective profile based on the findings of several works of epidemiological research. *Vigna vexillata* (family: Fabaceae) is well known for its wide range of biological activities including antioxidant, anticancer, antidiabetic, anti-inflammatory and anti-ulcer. In addition, it has also been investigated in a behavioural study against Parkinson's, where the experimental animals demonstrated a progression of improved memory in PD-induced animals. Hence, V. vexillata is a promising agent in the management of neurodegenerative diseases including its prevention and treatment, contributed by its antioxidant effect. Apart from that, no studies have reported on the use of V. vexillate phytochemicals against neurodegenerative disorders, especially against AD. As it has shown effective result for PD so it could be effective against AD.

The molecular docking study is a computational-based study used to investigate the potency of any derived candidate at a primary stage, targeting any disease-associated target. Currently, most researchers use advanced computational tools during 'hit' or 'lead' candidate selection. Indeed, natural products or phytochemicals tend to contain multi-potent biological activities. Therefore, evaluating individual potencies in a random experimental study is a complex and time-consuming procedure. In this situation, molecular docking is a more suitable approach to assess the strength of any desired natural products before conducting a randomized experimental study. In fact, to date, molecular docking is considered as an advanced and cost-effective technique to avoid the random practical or 'hit-and-trial' method of drug screening. However, molecular docking is an early guidance tool in contemporary drug discovery to minimize the time-resource and due to the fact that drug candidates for human use cannot be recommended in the absence of extensive experimental and pharmacological studies. Overall, molecular docking is user-friendly and is a good potential tool in drug development. Scientific evidence shows that the prediction results based on in silico studies are comparable with in vitro and in vivo results. In this study, a detailed in silico molecular docking investigation was conducted on V. vexillata with several protein targets in relation to AD for a new drug design and development. To clarify information on their thermodynamic and dynamic properties, as well as to confirm the docking results, molecular dynamics simulations were performed followed by the calculation of the binding free energy. Furthermore, to ensure V. vexillata safety and efficacy in the treatment of AD, its physicochemical, drug-likeness and ADMET profiles were also studied.

2. MATERIAL AND METHOD

i) Retrieval and Preparation of Protein: The target proteins were acetylcholinesterase, Butyl cholinesterase and β-secretase. The proteins were retrieved from PDB database. All the selected protein structure was validated using verify3D server and it has passed the server.

Sr.no:	PDB CODE	AchE Protein names
1	4M0E	Structure of human acetylcholinesterase in complex with dihydrotanshinone I
2	5HF5	Crystal structure of human acetylcholinesterase in complex with paraoxon in the unaged state (predominant acyl loop conformation)
3	5HF9	Crystal structure of human acetylcholinesterase in complex with paraoxon and HI6
4	5HFA	Crystal structure of human acetylcholinesterase in complex with paraoxon and 2-PAM
5	5HF6	Crystal structure of human acetylcholinesterase in complex with paraoxon in the aged state
6	4M0F	Structure of human acetylcholinesterase in complex with territrem B
7	5FPQ	Structure of Homo sapiens acetylcholinesterase phosphonylated by sarin
8	6NEA	Human Acetylcholinesterase in complex with reactivator, HLo7
9	7E3H	Crystal structure of human acetylcholinesterase in complex with donepezil
10	7E3D	Crystal structure of human acetylcholinesterase
11	5HQ3	Stable, high-expression variant of human acetylcholinesterase
12	6CQV	Crystal Structure of Recombinant Human Acetylcholinesterase in Complex with VX(+) and HI-6
13	5HF8	Crystal structure of human acetylcholinesterase in complex with paraoxon (alternative acyl loop conformation)
14	7E3I	Structure of human acetylcholinesterase in complex with tacrine
15	4PQE	Crystal Structure of Human Acetylcholinesterase
16	2X8B	Crystal structure of human acetylcholinesterase inhibited by aged tabun and complexed with fasciculin-II
Sr.no:	PDB CODE	BchE Protein names
1	1P0I	Crystal structure of human butyryl cholinesterase
2	4BDS	Human butyrylcholinesterase in complex with tacrine
3	6EQP	Human butyrylcholinesterase in complex with ethopropazine
4	6EQQ	Human butyrylcholinesterase in complex with huprine 19
5	7BO4	Human Butyrylcholinesterase in complex with 3-(2-(butyl(2-cycloheptylethyl)amino)ethyl)-1H-indol-6-ol
6	6F7Q	Human Butyrylcholinesterase complexed with N-Propargyliperidines
7	4BBZ	Structure of human butyrylcholinesterase inhibited by CBDP (2-min soak): Cresyl-phosphoserine addu
8	6ESY	Human butyrylcholinesterase in complex with thioflavine T
9	6ESJ	Human butyrylcholinesterase in complex with propidium
1	1SGZ	Beta-secretase

ii) Retrieval of Ligands: The databases PubChem were utilized to retrieve ligands. These ligands were selected for protein docking against the intended targets. Total 6 phytochemical were selected from the hydroalcoholic leaves extract detect using HPTLC method. These ligands' 3D structures were retrieved for docking and ADME research.

Pubchem ID	Phytochemical
5280343	Quercetin
370	Gallic acid
222284	Beta sitosterol
9064	Catechin
5280805	Rutin
6047	L-Dopa
ID	Drugs
3152	Donepezil
9651	Galantamine
77991	Rivastigmine

iii) ADME Analysis: In order to find the best pharmacokinetically relevant molecules, Swiss ADME was used to screen the ligands. The acronym ADME represents excretion, metabolism, distribution, and absorption. Lead similarity, blood-brain barrier permeability, and oral bioavailability are among the other variables that are taken into account. To examine how similar the selected ligands were to drugs, Lipinski's rule of five was applied. All the selected phytochemicals gave the good pharmacokinetic properties and showed to be promising compounds for further research.

iv) Virtual Screening and Visualization: PyRx was used to dock the ligands against the target protein.[1] A virtual screening program called PyRx can determine how well different ligands bind to a given target protein. PyRx is a rapid, user-friendly, and useful virtual screening tool. The Discovery Studio visualization tool was used to visualize the docked compounds.[2]

3. RESULTS AND DISCUSSION

3.1.Physicochemical, Drug-Likeness and ADMET Properties of V. vexillate phytochemicals

V. vexillata appears to follow all five of Lipinski’s drug-likeness criteria. According to the data acquired from Swiss software, it also passed Veber’s rule, the blood-brain barrier (BBB) likeness rule. All of the above findings indicate that it is a good potential drug-like molecule and a useful therapeutic agent against a variety of disorders including neurodegenerative disorders.

3.2. In Silico Results of V. vexillate against AD

Acetylcholinesterase and β-secretase are the two protein targets that the ligands were docked against. Acetylcholinesterase is an enzyme that hydrolyses acetylcholine to produce reusable derivatives. After the signal is transmitted, this enzyme's function is required to recycle the

acetylcholine under normal circumstances. On the other hand, plaques obstruct the neurons' synapses in Alzheimer's patients, delaying or eliminating signalling. By reducing the rate of acetylcholine's breakdown into the choline component, acetylcholinesterase inhibition might enhance signalling.

The individual ligands docking score against individual targets were recorded. As per the docking software, the docking score is always expressed in a negative value, where a higher negative value indicates a better potency. V. vexillate exhibited a docking score within −7 to −11 kcal/mol against the selected six AD-associated targets. Highly negative docking score indicates a better potency. Similarly, standard drugs exhibited docking scores within −5 to −11 kcal/mol against five AD-associated targets. List of highly negative scores.

Acetylcholinesterase:	
4moe	**Binding Affinity**
L-Dopa	-8.1
Beta sitosterol	-9.1
Quercetin	-9.4
Rutin	-8.8
Donepezil	-6.8
Galantamine	-7.1
Rivastigmine	-5.8
4mof1	**Binding Affinity**
L-Dopa	-10.1
Beta sitosterol	-11.3
Quercetin	-9.6
Rutin	-10.2
Catechin	-10.5
Donepezil	-8.9
Galantamine	-9.1
Rivastigmine	-8.7
5fpq1	**Binding Affinity**
L-Dopa	-9.5
Beta sitosterol	-9.1
Quercetin	-9.9
Rutin	-9.2
Catechin	-8.7
Donepezil	-6.8
Galantamine	-7.1

Rivastigmine	-5.8
4pqe	**Binding Affinity**
L-Dopa	-8.4
Quercetin	-8.5
Donepezil	-6.8
Galantamine	-7.1
Rivastigmine	-5.8
5hf5	**Binding Affinity**
L-Dopa	-9
Quercetin	-9.3
Rutin	-8.5
Donepezil	-7.5
Galantamine	-7.9
Rivastigmine	-8.9
6nea	**Binding Affinity**
L-Dopa	-10.6
Quercetin	-9
Rutin	-9.6
Catechin	-10.7
Donepezil	-6.8
Galantamine	-7.1
Rivastigmine	-5.8
6o4w	**Binding Affinity**
L-Dopa	-10.1
Beta sitosterol	-10
Quercetin	-9.3
Rutin	-9.5

Catechin	-9.1
Donepezil	-8.5
Galantamine	-7.9
Rivastigmine	-8.9
7e3d	**Binding Affinity**
Quercetin	-9.4
Rutin	-8.8
Catechin	-9.2
Donepezil	-6.8
Galantamine	-7.1
Rivastigmine	-5.8
7e3h	**Binding Affinity**
L-Dopa	-9.9
Beta sitosterol	-10.2
Quercetin	-9.4
Rutin	-9.5
Catechin	-9.2
Donepezil	-6.8
Galantamine	-7.1
Rivastigmine	-5.8
7e3i	**Binding Affinity**
L-Dopa	-8.7
Beta sitosterol	-9.3
Quercetin	-9.1
Rutin	-8.9
Catechin	-8.9
Donepezil	-6.8

Galantamine	-7.1
Rivastigmine	-5.8
5HF9	**Binding Affinity**
Beta sitosterol	-9.1
Catechin	-9.2
Donepezil	-8.9
Galantamine	-8.5
Rivastigmine	-9.1
5HFA	**Binding Affinity**
Catechin	-9.2
Rutin	-7.5
L-Dopa	-7.1
Donepezil	-7.5
Galantamine	-7.8
Rivastigmine	-7.2
5HF6	**Binding Affinity**
Quercetin	-8.2
Gallic acid	-8.1
Beta	-7.9

sitosterol	
Catechin	-7.9
Rutin	-7.7
Donepezil	-6.8
Galantamine	-7.1
Rivastigmine	-5.8
5HQ3	**Binding Affinity**
Gallic acid	-7.9
Beta sitosterol	-7.8
Catechin	-7.8
Rutin	-7.7
L-Dopa	-7.6
Donepezil	-7.9
Galantamine	-7.5
Rivastigmine	-7.4
6CQV	**Binding Affinity**
Quercetin	-8.9
Gallic acid	-8.7
Beta sitosterol	-8.1

Catechin	-7.8
Donepezil	-8.1
Galantamine	-8.5
Rivastigmine	-7.8
5HF8	**Binding Affinity**
Beta sitosterol	-6.8
Catechin	-10.5
Rutin	-10.3
L-Dopa	-9.4
Donepezil	-11.5
Galantamine	-8.7
Rivastigmine	-7.1
2X8B	**Binding Affinity**
Quercetin	-7.3
Gallic acid	-7.2
Beta sitosterol	-7.1
Donepezil	-7.6
Galantamine	-7.7
Rivastigmine	-7.3

Butyl cholinesterase	
6eqq	**Binding Affinity**
Quercetin	-9
Gallic acid	-9.4
Rutin	-9.4
L-Dopa	-9.2
Donepezil	-9.7
Galantamine	-7.4
Rivastigmine	-6.8
6esj	**Binding Affinity**
Quercetin	-9.3
Gallic acid	-9.1
Beta sitosterol	-9.1
Catechin	-9.3
Donepezil	-9.9
Galantamine	-6.8
Rivastigmine	-7.5
6eqp	**Binding Affinity**
Beta	-8.6

sitosterol	
Catechin	-9.2
Rutin	-9.3
L-Dopa	-9.3
Donepezil	-9.7
Galantamine	-7.4
Rivastigmine	-6.8
6esy	**Binding Affinity**
Quercetin	-8.9
Gallic acid	-9
Beta sitosterol	-9.4
Catechin	-9.4
Donepezil	-9.9
Galantamine	-6.8
Rivastigmine	-7.5
6f7q	**Binding Affinity**
Gallic acid	-9.2
Beta sitosterol	-9.6
Rutin	-9.5

L-Dopa	-10.2
Donepezil	-9.9
Galantamine	-6.8
Rivastigmine	-7.5
7bo4	**Binding Affinity**
Quercetin	-9.3
Gallic acid	-9.2
Beta sitosterol	-9.4
Catechin	-9.2
Donepezil	-9.9
Galantamine	-6.8
Rivastigmine	-7.5
4bds	**Binding Affinity**
Quercetin	-9
Rutin	-8.9
L-Dopa	-9.2
Gallic acid	-9.4
Donepezil	-9.7
Galantamine	-7.4
Rivastigmine	-6.8

4bbz	**Binding Affinity**
Quercetin	-9.2
Gallic acid	-9.1
Beta sitosterol	-9.6
Catechin	-10.1
Donepezil	-9.9

Galantamine	-6.8
Rivastigmine	-7.5
1p0i	**Binding Affinity**
Gallic acid	-9.1
Beta sitosterol	-9.4
Catechin	-9.3

Rutin	-10
Donepezil	-9.7
Galantamine	-7.4
Rivastigmine	-6.8

Beta-secretase	
1SGZ	**Binding Affinity**
Quercetin	-10.5
Gallic acid	-10.3
Beta sitosterol	-9.4

Catechin	-8.7
Rutin	-10.1
L-Dopa	-9.2
Donepezil	-9.9
Galantamine	-6.8
Rivastigmine	-7.5

The progression of AD involves the destruction of the cholinergic neurons in the brain, since most of the palliative treatments for AD involve the use of cholinesterase inhibitors (ChEIs) including donepezil, rivastigmine and galantamine that impede the action of acetylcholinesterase (AChE), which hydrolyzes acetylcholine (ACh). The main therapeutic approach in dealing with AD is via the enhancement of cholinergic neurotransmission by preventing one of the major neurotransmitters, ACh from being broken down by AChE, which in turn maintains the brain's ACh level to compensate for the loss of functioning brain cells. In AChE the investigated standard drugs exhibited docking scores between −7.3 to −11.0 kcal/mol, while V. vexillata showed a better docking score of −9.4 as compared with rivastigmine and galantamine. Overall, the results indicated that V. vexillata exhibited a comparatively similar and better potency to the standard drugs.

Here are the some highly negative dock poses.

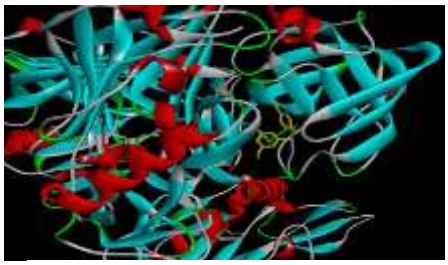

Fig1: L-Dopa with 4moe.

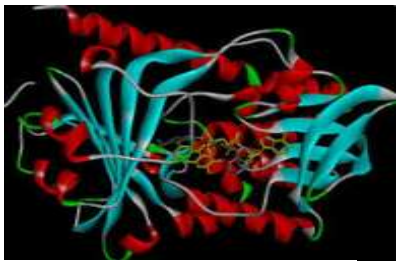

Fig2: Catechin with 4mof1.

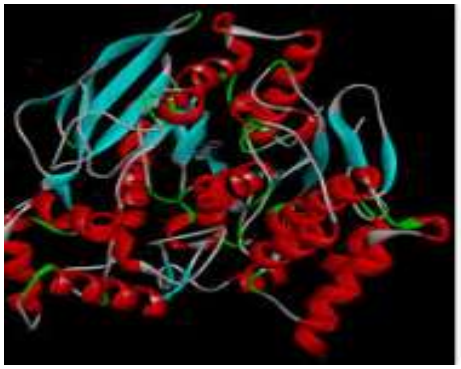

Fig3: Quercetin with 1SGZ.

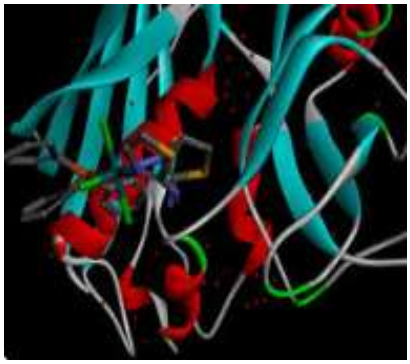

Fig4: Rutin with 1SGZ.

4. CONCLUSIONS

The current study demonstrates the phytochemicals found in Vigna vexillata have promise anti-Alzheimer properties. This is especially evident in their ability to inhibit two key enzymes involved in the pathophysiology of Alzheimer's disease, acetylcholinesterase, butyrylcholinesterase and β-secretase. The findings of the molecular docking study indicate that certain phytochemicals, such as gallic acid, quercetin, and catechin, have strong binding affinities that frequently outperform those of prescription medications like galantamine and rivastigmine. Furthermore, Vigna vexillata compounds' physicochemical characteristics and ADMET profiles follow Lipinski's rule, indicating their drug-likeness and potential for further development as therapeutic agents. Notably, these findings have not yet been reported in the literature, marking Vigna vexillata as a promising new candidate in the search for natural treatments for neurodegenerative diseases. These in silico results are promising, more in vitro and in vivo research is required to confirm Vigna vexillata safety and efficacy as a possible Alzheimer's disease treatment.

5. REFERENCES

1. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. *Methods in Molecular Biology*, 2015; 1263: 243–250. doi: 10.1007/978-1-4939-2269-7_19.
2. D Studio. (2008). Discovery studio life science modeling and simulations, Researchgate. Net, 1–8.
3. Kareti SR, Pharm SM. In silico molecular docking analysis of potential anti-Alzheimer's compounds present in chloroform extract of Carissa carandas leaf using gas chromatography MS/MS. *Current Therapeutic Research, Clinical and Experimental*, 2020; 93: 100615. doi: 10.1016/j.curtheres.2020.100615.

4. Basha FH, Waseem M, Srinivasan H. Cellular and molecular mechanism in neurodegeneration: Possible role of neuroprotectants. *Cell Biochemistry and Function,* 2021; 39(5): 613–622. doi: 10.1002/cbf.3630.
5. Dash R, Emran TB, Uddin MM, Islam A, Junaid M. Molecular docking of fisetin with AD associated AChE, ABAD and BACE1 proteins. Bioinformation, 2014; 10(9): 562–8.
6. Ghosh S, Nie A, An J, Huang Z. Structure-based virtual screening of chemical libraries for drug discovery. Curr Opin Chem Biol, 2006; 10(3): 194–202.
7. Ali M., Muhammad S., Shah M.R., Khan A., Rashid U., Farooq U., Ullah F., Sadiq A., Ayaz M., Ali M. Neurologically potent molecules from Crataegus oxyacantha; isolation, anticholinesterase inhibition, and molecular docking. *Front. Pharmacol,* 2017; 8: 327. doi:10.3389/fphar.2017.00327.
8. Patterson C. *The State of the Art of Dementia Research: New Frontiers.* Alzheimer's Disease International Edition; London, UK: 2018. World alzheimer report, 2018; 148.
9. Bui T.T., Nguyen T.H. Natural product for the treatment of Alzheimer's disease. *J. Basic Clin. Physiol. Pharmacol,* 2017; 28: 413–423. doi: 10.1515/jbcpp-2016-0147.
10. Ayaz M., Ullah F., Sadiq A., Kim M.O., Ali T. Natural products-based drugs: Potential therapeutics against Alzheimer's disease and other neurological disorders. *Front. Pharmacol,* 2019; 10: 1417. doi: 10.3389/fphar.2019.01417.