Current Trends in Pharmaceutical Research, 2024 Vol 11 Issue I
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2582-4783 (Online)

Research Article

IN SILICO INVESTIGATION OF *Zanthoxylum acanthopodium* DC. ESSENTIAL OIL COMPONENTS FOR ANTI-ALZHEIMER ACTIVITY

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Abstract

Background: *Alzheimer's disease (AD), is primarily associated with ageing populations and is characterised by neurodegeneration, synaptic damage, and neuronal loss. The existing medicines provide only symptomatic relief, they neither cure nor modify the disease condition, emphasising the need for novel therapeutic approaches.*

Objectives: *This study aims to assess the potential of Zanthoxylum acanthopodium DC. essential oil (ZA-EO) for AD through in-silico molecular docking analysis and ADMET study, targeting amyloid-beta (Aβ) and acetylcholinesterase (AChE).*

Material and Methods: *GC-MS was used to identify the components of ZA-EO. The structures of AChE and Aβ were obtained from the Protein Data Bank (PDB IDs: 4EY7 and 1AAP). Ligands preparation and optimization were carried out using the software ChemDraw and PyRx. Docking studies were carried out with PyRx, and interactions were visualized using BIOVIA Discovery Studio Visualizer. Further, ADMET properties were predicted using the tools SwissADME and admetSAR.*

Result and Discussion: *From the docking studies, binding energies were obtained ranging from -10.2 to -5.2 kcal/mol and -5.5 to -3.3 kcal/mol for AChE and Aβ respectively. Components SM9, SM12, and SM13 were found to have the most stable and potent interactions. ADMET analysis revealed excellent BBB permeability, intestinal absorption, and low oral toxicity without mutagenic effects and respiratory toxicity.*

Conclusion: *The study reveals that the selected bioactive components of ZA-EO possess significant anti-alzheimer activity and marked pharmacokinetic profiles. However, in vitro and in vivo investigations would be required to validate and develop potential lead compounds.*

Keywords: Alzheimer's disease; Neurodegeneration; Amyloid-beta; ADMET; Acetylcholinesterase.

Introduction

Alzheimer's disease (AD), poses a major global challenge, mostly among the ageing population. It is associated with neurodegeneration characterized initially by synaptic injury followed by neuronal loss. Currently, more than 46 million people globally are affected by AD, and projections estimate a surge to rise 131.5 million by 2050, highlighting the urgency for extensive research and effective interventions for combating this growing public health issue [1, 2]. Till now, the U.S. FDA has approved seven medications for the management of AD. They are- a partial NMDA receptor antagonist (memantine), cholinesterase inhibitors (donepezil, tacrine, galantamine and rivastigmine), and monoclonal antibodies (lecanemab and

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aducanumab). However, these drugs cannot fully cure or modify the disease but only provide symptomatic relief, and medicinal strength falls over time [3–5]. Therefore, it emphasizes the imperative need for efficient drug discovery and investigation to surmount these limitations. In the brain, inhibition of AChE emerges as a potential treatment approach for AD management [6, 7]. While other approaches are also been explored, attention to acetylcholinesterase (AChE) inhibitors has been paid making it a promising treatment option for the management of AD [8–10]. The ability of plant constituents and extracted compounds to target brain receptors implies that herbal treatments can play a remarkable role in the management of neurodegenerative disorders [11–13]. *Zanthoxylum acanthopodium* DC. (ZA), commonly known as prickly ash, toothache tree, lemon pepper tree, or sugarberry, is a shrub belonging to the Rutaceae family. The extracted essential oil of ZA fruits contains compounds such as eucalyptol, estragole, and β-caryophyllene, offering various pharmacological activities. In our previous study [14], the results of the GC-MS study of *Zanthoxylum acanthopodium* DC. essential oil (ZA-EO) was reported along with its potential Mosquito repellent [15], and anti-bacterial [16] activities. Further, the development of a controlled-release gel, herbal mosquito repellent ointment, a controlled-release gel, with the ZA-EO and evaluation such as Acute and Sub-chronic Dermal Toxicity Studies along with antimicrobial activity has been reported [14–16]. Studies show that *Zanthoxylum* plants possess a wide range of pharmacological activities in general, including larvicidal, analgesic, antioxidant, anti-inflammatory, antibiotic, cytotoxic, anthelmintic, antiviral, hepatoprotective, anticonvulsant, and antifungal properties [17–21]. In this paper, the results of the *in-silico* molecular docking analysis along with the ADMET study of components present in the ZA-EO for anti-alzheimer activity are reported. This research aimed to provide reliable evidence regarding the efficacy of *Zanthoxylum acanthopodium* DC. essential oil as a new, safe and potent candidate for AD that could be selected for further research. A part of the research work is reported here in this manuscript, however, the findings of the complete study will be reported in our subsequent manuscript(s).

Materials and Methods

1. Components of ZA-EO

In our previous study [14], constituents of ZA-EO were separated and identified by gas chromatography-mass spectrometry (GC-MS). D-limonene (SM1) was the major compound having a percentage content of 24.0696% of the total content in the composition of ZA-EO. Other important essential constituents that were present (≥1% content) are Ocimene (SM2), Eucalyptol (SM3), 1-S-α-pinene (SM4), 1-R-α-pinene (SM5), α-pinene (SM6), 1,7,7-trimethyl-tricyclo-[2.2.1.0(2,6)] (SM7), 1-hepten-3-yne (SM8), Caryophyllene (SM9), Cis-beta terpineol (SM10), 2,3,5,8-tetramethyl-1,5,9-decatriene (SM11), 3,7,11,15-tetramethyl-(E,E,E)-2,6,10,14-hexa-decatetraenoic acid methyl ester (SM12), and 2,16-didehydro-20-hydroxy-19-oxo-curan-17-oic acid methyl ester (SM13). The composition of ZA-EO was found to be significantly different from other available literature data.

2. Protein preparation

The crystal structure of Aβ and AChE were derived from the Protein Data Bank (PDB) https://www.rcsb.org/. The PDB ID of the selected protein was 4EY7 (Fig 1) for AChE and 1AAP (Fig 2) for amyloid-beta (Aβ) [22, 23]. Prior to docking, polar hydrogen atoms were added to the proteins and charges were assigned. All the bound water molecules, other heteroatoms and co-crystallized ligands attached to the protein were removed. Subsequently, the protein's 3D structure was optimized by minimizing the energy using the CHARMm force field. 4EY7 consists of chains A, B, C, and D. Chain A

was kept and other chains were deleted for the docking study. The binding site of this protein was defined at (-13.930, -43.939, 29.559) around the co-crystallized ligand Donepezil's binding pocket. 1AAP consists of two identical chains A and B. Chain A was kept and chain B was deleted. The binding site of this protein was defined at (10.739, 20.239, 34.650).

3. Ligand preparation

The software ChemDraw Ultra 8.0 was used to draw the GC-MS detected compound structures (Fig 3). Finally, all the ligands were converted into three-dimensional (.mol) format. Before Docking the ligands were pre-processed through minimization, and conversion to AutoDock ligands (pdbqt) using the PyRx (Python Prescription Virtual Screening Tool).

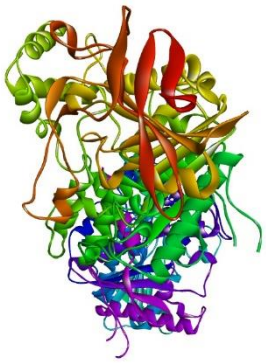


Fig. 1: 3D structure of 4EY7

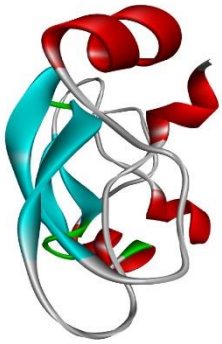


Fig. 2: 3D structure of 1AAP

4. Docking analysis

The receptors were imported in PyRx as macromolecules. Docking was carried out using the vina wizard of PyRx. Finally, binding interactions were observed using BIOVIA Discovery Studio Visualizer, obtained from https://discover.3ds.com/discovery-studio-visualizer-download.

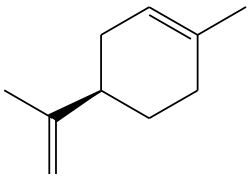
5. *In silico* ADMET analysis

In silico ADMET studies were carried out by the SwissADME and admetSAR for all the compounds. ADMET studies revealed the absorption, distribution, metabolism, excretion, intestinal absorption, carcinogenicity, mutagenicity, BBB permeation properties, acute oral toxicity, ames mutagenesis, and respiratory toxicity. These properties are significant for the prediction of novel compounds with improved pharmacokinetics and pharmacodynamic profiles [24]. Different molecular properties like LogP value (Octanol– water partition coefficient), TPSA (Total Polar Surface Area), molecular weight, nRB (Number of Rotatable Bond), HBD (Hydrogen Bond Donor) and HBA (Hydrogen Bond Acceptor) that are considered under Lipinski's rule of five were predicted using Swiss-ADME.

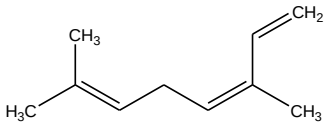
Results& Discussion

Several investigations have been conducted for the last three decades in drug development but nothing definitive was seen for AD treatment. These reasons have given rise to attention in the field of research for novel components with potential anti-alzheimer activity. Here, components present in ZA-EO identified by GC-MS were analysed for *in silico* molecular docking against two important target proteins of AD i.e.,

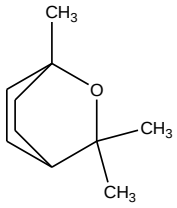
AChE and Aβ. All the components present in ZA-EO with a percentage content of (≥1%) were analysed against AD receptors (4EY7 and 1AAP).



SM1



SM2



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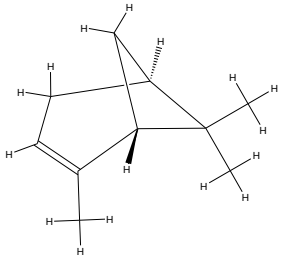

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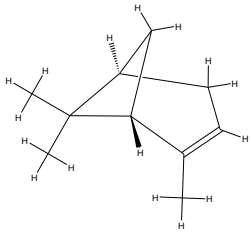

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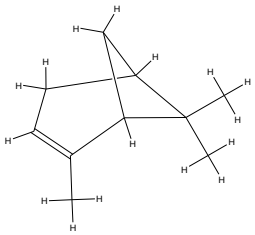
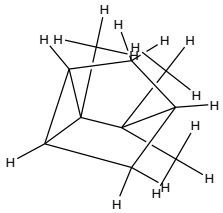
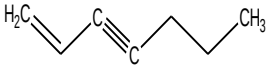


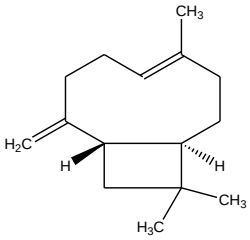
SM6



SM7



SM8



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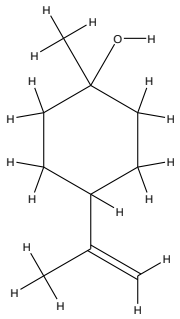
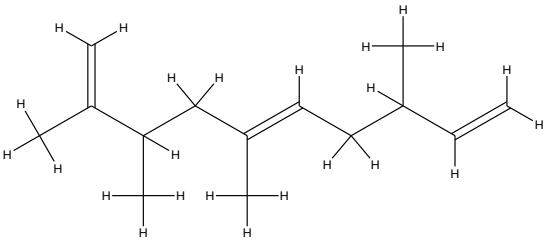
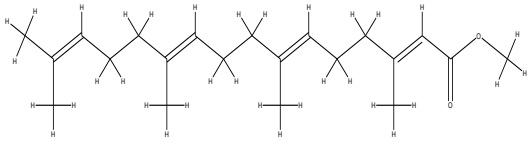


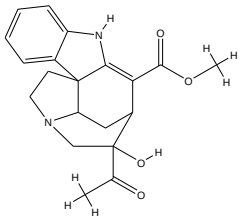
SM10



SM11



SM12



SM13

Fig. 3: Structures of the GC-MS detected components (≥1% content)

Molecular Docking Study

The docking results were analyzed based on the binding energy (*Table 1*) and the docked poses against AChE (4EY7) (*Fig. 4*) and Ab (1AAP) (*Fig. 5*). The amino acids involved in the binding interactions against AChE (4EY7) and Aβ (1AAP) are tabulated below (*Table 2*). The binding energies of the ligands ranged from –5.5 to −3.3 kcal/ mol for aβ (1AAP) and −10.2 to −5.2 kcal/ mol for AChE (4EY7).

Top dock score components interaction with 4EY7

The components that exhibited the highest docking scores and lowest binding energy include- SM13 (−10.2 kcal/mol), SM12 (−9.9 kcal/mol), SM9 (−8.7 kcal/mol), SM11 (−7.8 kcal/mol), SM6 (− 7.3 kcal/mol) and SM1 (−7.1 kcal/mol).

Top dock score components interaction with 1AAP

The components that exhibited the highest docking scores and lowest binding energy include-

SM13 (−5.5 kcal/mol), SM12 (−5.1 kcal/mol), SM9 (−4.7 kcal/mol), SM11 (−4.3 kcal/mol), SM4 (−4.3 kcal/mol), SM6 (−4.2 kcal/mol), SM3 (−4.1 kcal/mol).

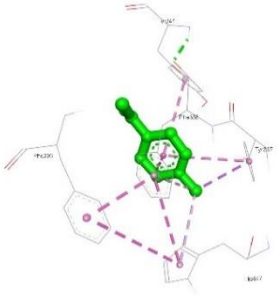
Table 1: Molecular docking results of designed ligands against AChE and Aβ

Sl no	Compound code	Binding Energy (-kcal/mol)	
		AChE (4EY7)	Aβ (1AAP)
1	SM1	7.1	3.9
2	SM2	6.2	3.7
3	SM3	6.9	4.1
4	SM4	6.9	4.3
5	SM5	6.6	4
6	SM6	7.3	4.2
7	SM7	6.6	4
8	SM8	5.2	3.3
9	SM9	8.7	4.7
10	SM10	6.7	4
11	SM11	7.8	4.3
12	SM12	9.9	5.1
13	SM13	10.2	5.5
14	DONEPEZIL	11.7	6.3

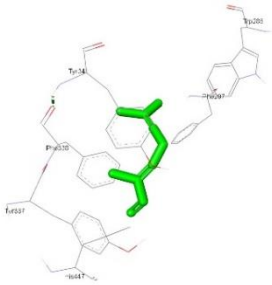
Table 2: Docking interactions (Contributing Binding Residues) of the compounds for proteins viz. AChE (4EY7) and Aβ (1AAP)

Compound code	Docking interactions	
	AChE (4EY7)	Aβ (1AAP)
SM1	PHE295, TYR337, PHE338, TYR341, HIS447	GLU7, GLN8, ALA9, TYR22, PHE23, ASP24, VAL25, THR26
SM2	TRP286, PHE297, TYR337, PHE338, TYR341	CYS5, SER6, GLU7, GLN8, ALA9, TYR22, PHE23, ASP24, VAL25, THR26, ASN43
SM3	ASP74, GLY121, TYR124, TYR337, PHE338, TYR341, HIS447	SER6, GLU7, GLN8, ALA9, TYR22, ASP24, VAL25, THR26
SM4	TYR72, TYR124, TRP286, VAL294, PHE295	GLU7, GLN8, ALA9, TYR22, PHE23, ASP24, VAL25, THR26
SM5	ASP74, TRP86, TYR124, TYR337, PHE338, TYR341	GLU7, GLN8, ALA9, TYR22, ASP24, VAL25, THR26
SM6	TYR337, PHE338, TYR341	CYS5, SER6, GLU7, GLN8, ALA9, TYR22, PHE23, ASP24, VAL25, ASN43
SM7	TYR124, TRP286, ARG296, PHE297, PHE338, TYR341	CYS5, SER6, GLU7, GLN8, ALA9, TYR22, PHE23, ASP24, VAL25
SM8	TYR124, TYR337, PHE338, TYR341, HIS447	SER6, GLU7, GLN8, ALA9, TYR22, PHE23, ASP24, VAL25, THR26
SM9	TRP86, TYR124, TYR337, PHE338, TYR341, HIS447	CYS5, SER6, GLU7, GLN8, ALA9, TYR22, PHE23, ASP24, VAL25, THR26, ASN43

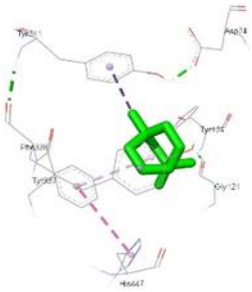
SM10	TRP86, GLY120, GLY121, GLY122, TYR133, GLU202, SER203, TYR337, TYR341, HIS447	SER6, GLU7, GLN8, ALA9, TYR22, PHE23, ASP24, VAL25
SM11	ASP74, TYR124, TRP286, PHE295, PHE297, TYR337, PHE338, TYR341, HIS447	GLU7, GLN8, ALA9, TYR22, ASP24, VAL25, THR26, PRO32, PHE33
SM12	TYR72, TRP86, GLY120, GLY121, GLY122, TYR124, TYR133, GLU202, SER203, TRP 286, VAL294, PHE295, PHE297, TYR337, PHE338, TYR341, HIS447, GLY448	GLU7, GLN8, ALA9, TYR22, PHE23, ASP24, VAL25, THR26, PHE33, PHE34
SM13	TRP86, GLY121, GLY122, TYR124, GLU202, SER203, ALA204, TRP 286, PHE295, PHE297, TYR337, PHE338, TYR341, HIS447	SER6, GLU7, GLN8, ALA9, TYR22, PHE23, ASP24, VAL25, THR26



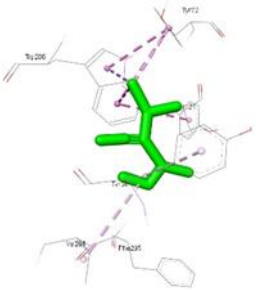
SM1



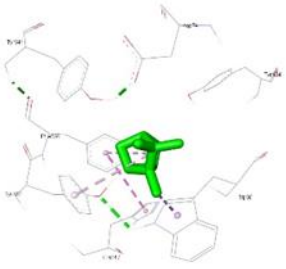
SM2



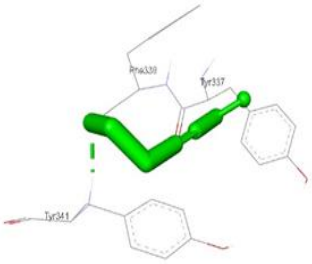
SM3



SM4



SM5



SM6

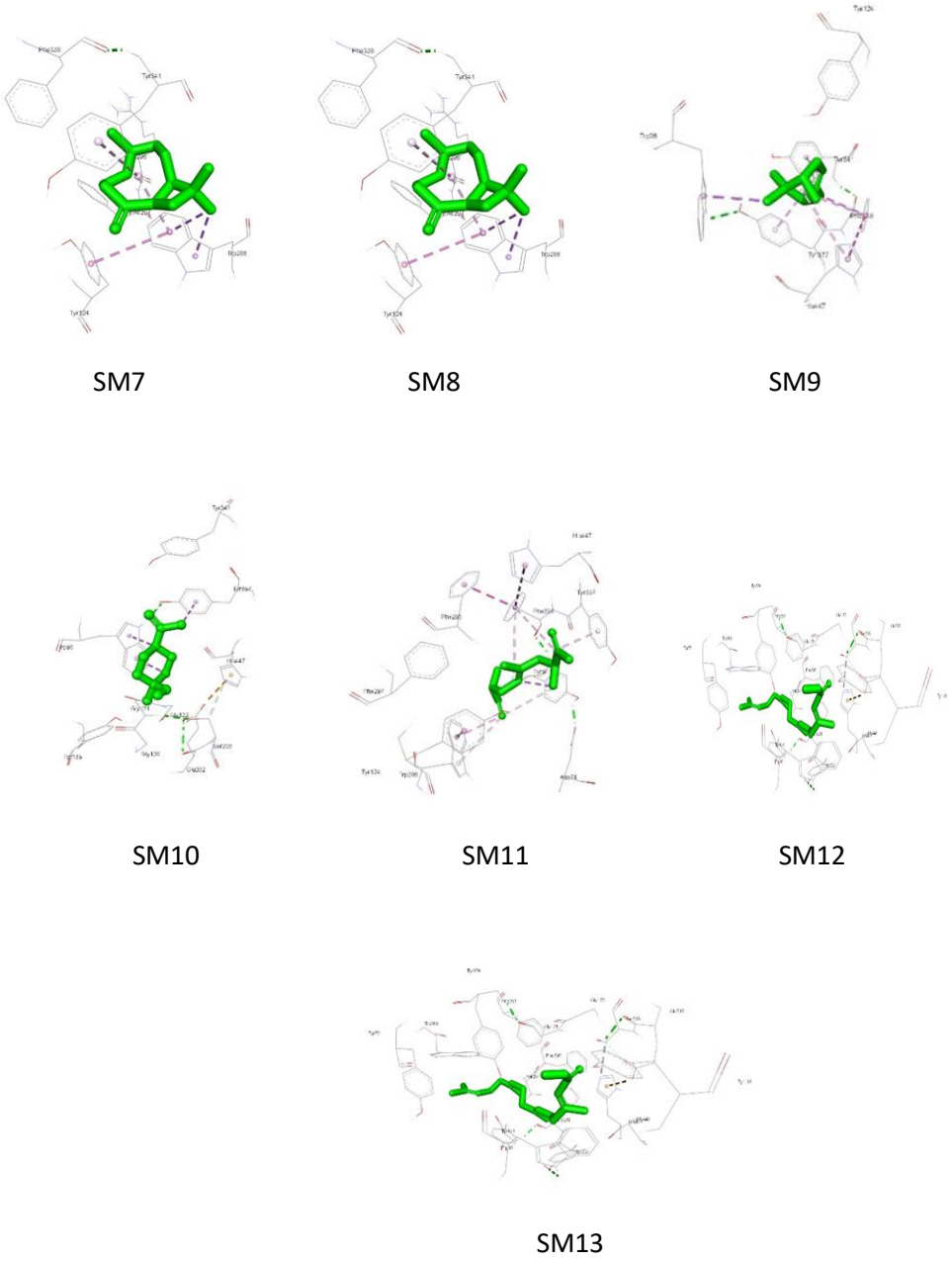
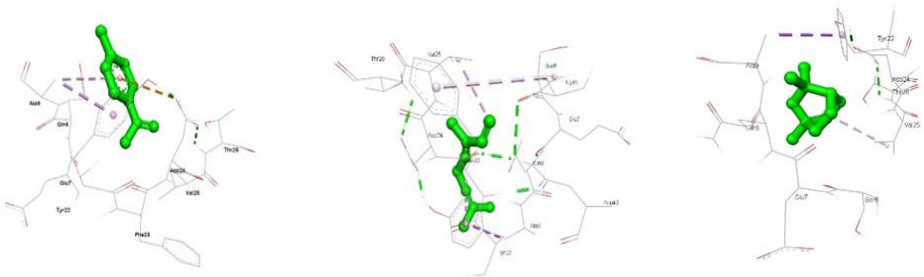


Fig. 4: Interaction of ligands against protein AChE (4EY7)



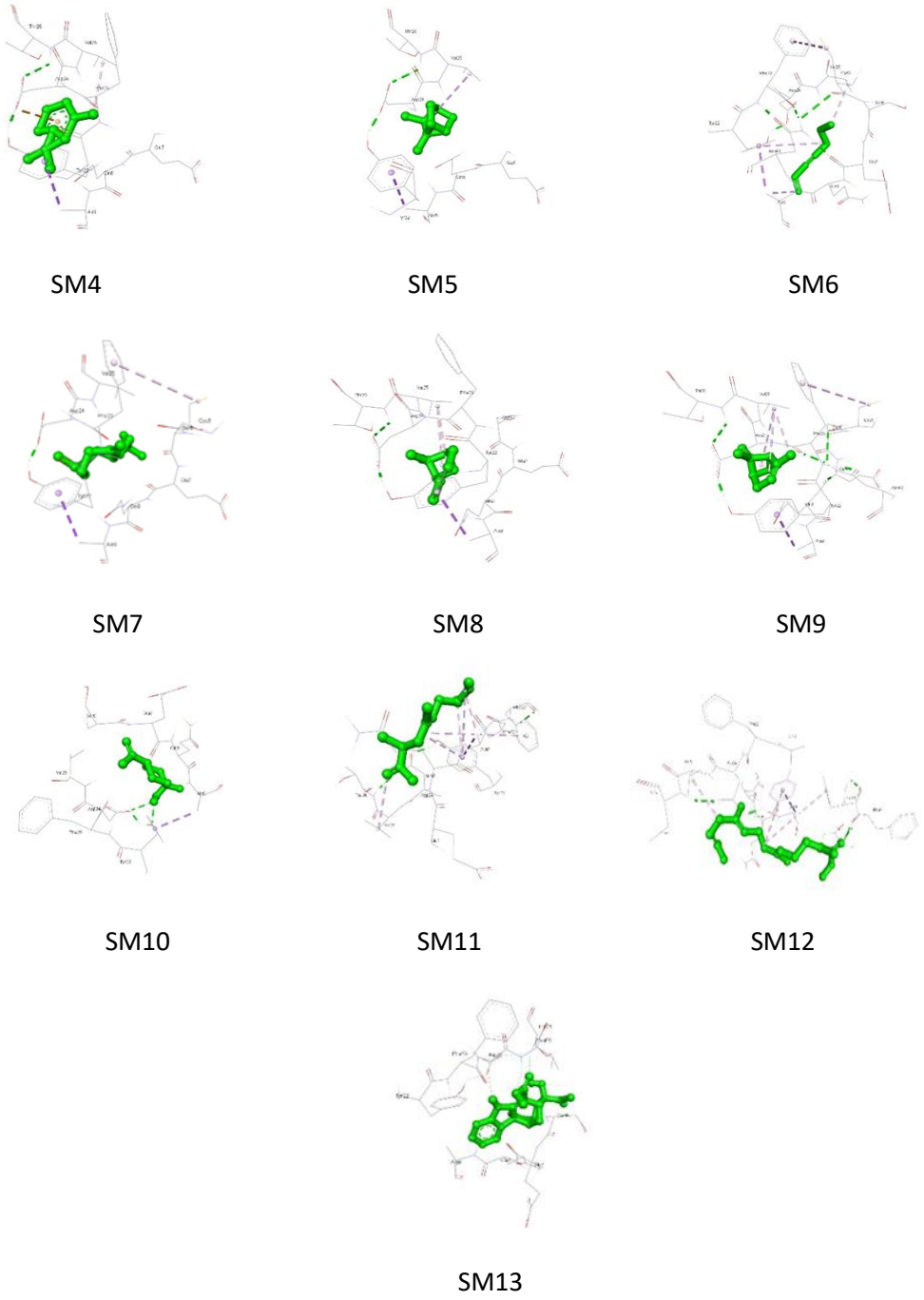


Fig. 5: Interaction of ligands against protein Ab (1AAP)

In silico ADMET analysis

Molecular property calculation

Among thirteen components, SM7 had shown one violation of Lipinski's rule whereas the remaining 6 compounds did not demonstrate any violations (*Table 3*).

ADMET prediction

Following Molecular docking, ADMET prediction was carried out for the compounds (*Table 4*). From the study, it was found that all the compounds had shown positive results for BBB penetration except SM13. No compounds had shown ames mutagenesis. Except for SM13, all the compounds had shown negative results for respiratory toxicity. For carcinogenicity, all except for 3 components had shown negative results (*Table 4*).

Table 3: Molecular properties of the compounds

Compound code	MW	nRB	nHBA	nHBD	TPSA	iLOGP	nViolations
SM1	136.23	1	0	0	0	2.72	0
SM2	136.23	3	0	0	0	2.91	0
SM3	154.25	0	1	0	9.23	2.58	0
SM4	136.23	0	0	0	0	2.63	1
SM5	136.23	0	0	0	0	2.63	1
SM6	136.23	0	0	0	0	2.63	1
SM7	136.23	0	0	0	0	2.53	1
SM8	94.15	1	0	0	0	2.41	0
SM9	204.35	0	0	0	0	3.25	1
SM10	154.25	1	1	1	20.23	2.41	0
SM11	192.34	6	0	0	0	3.65	1
SM12	318.49	11	2	0	26.3	3.65	1
SM13	354.4	3	5	2	78.87	2.5	0

Table 4: Prediction of ADMET properties of the ligands

Comp code	Intestinal absorption	BBB permeation	Carcinogenicity	Acute Oral Toxicity (Kg/mol)	Ames muta-genesis	Respiratory toxicity
SM1	+	+	−	1.551	−	−
SM2	+	+	+	1.597	−	−
SM3	+	+	−	1.537	−	−
SM4	+	+	−	0.789	−	−
SM5	+	+	−	0.789	−	−

SM6	+	+	−	0.980	−	−
SM7	+	+	−	1.159	−	−
SM8	+	+	+	2.536	−	−
SM9	+	+	−	1.524	−	−
SM10	+	+	−	1.214	−	−
SM11	+	+	+	1.074	−	−
SM12	+	+	−	2.076	−	−
SM13	+	−	−	2.439	−	+

According to X-ray crystallography, AChE has two binding sites- the PAS (peripheral anionic site) and the CAS (catalytic active site) which are connected by a gorge [25]. In human AChE, the CAS region contains SER203, TYR119, TYR124, TYR133, TRP86, GLU202, GLU 334, TRP439, TYR449, HIS447 and the Mid-George site contains ASP74, LEU76, PHE295, ARG296, PHE297 and PHE338. The PAS of AChE is present at the entry of the catalytic gorge which contains TYR 72, ASP 74, THR75, TYR 124, TRP 286, LEU289, SER 293, TYR341 and VAL 365 [25, 26]. Additionally, AChE interacts with Aβ via its PAS, and it was reported that AChE accelerates the deposition of Aβ into fibrils. Therefore, the inhibitors that preferentially interact with PAS residues are crucial for both AChE inhibition and Aβ aggregation prevention [25, 27–29]. The molecular docking study revealed that SM13, SM12 and SM9 were the most stable and potent compounds against AChE and Aβ through interaction with CAS and PAS pockets. Although results revealed that the ligands have higher binding energy than the reference Donepezil, the key interactions that have been observed with the active site justify the AChE inhibitory potential followed by the potential of inhibition Aβ of these compounds. Further, molecular properties calculation and ADMET prediction show that compounds have better intestinal absorption and BBB permeability and oral toxicity is less. None had shown ames-mutagenesis. Respiratory toxicity was shown by only one and they were non-carcinogenic except for 3 components. The present study supports the anti-alzheimer potential of the components present in ZA-EO. Thus, it is proven to be a potent lead with anti-alzheimer effect. To confirm these computational results, additional *in vitro* and *in vivo* studies are needed.

Conclusion

The current investigation revealed important bioactive components of ZA identified by GC-MS analysis that hold potential against the two important targets of AD A*β* and AChE. Aβ formation is a crucial step in AD, and it appears that the drugs intended to inhibit Aβ formation along with the potential of inhibition of AChE can promote multifunctional pharmacological activities. Thus, this computational analysis contributes to understanding the components with better binding interactions for the selected two proteins (AChE and Aβ) of AD. The molecular docking analysis of the ligands with 4EY7 and 1AAP showed compelling evidence that these components can be stable within the AChE active site. The compounds SM13, SM12 and SM9 were found to be more active and stable within the binding pocket. Most of the ligands interacted with CAS and PAS pockets of the enzyme and are capable of inactivating critical residue in the CAS and PAS domain of the enzyme active site. The present study exhibited potent compounds with

good binding energy to AD receptors (4EY7 and 1AAP) along with better pharmacokinetic properties. The ADMET analysis predicted no toxic effects of these compounds, showing them as possible alternatives for drug formulations. However, further *in vivo* and *in vitro* assessments of these components are required to confirm these results. Hence, they are proposed as possible drug candidates for AD treatment after further research.

Acknowledgement

The authors are thankful to the Botanical Survey of India (BSI), Eastern Region Circle, Shillong, Meghalaya, for authenticating the plant.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

No funding was received for conducting this study.

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How to cite this article:

Sahariah M, Sharma HK. *In Silico* Investigation of *Zanthoxylum acanthopodium* DC. Essential Oil Components for Anti-alzheimer Activity, *Curr Trends Pharm Res*, 2024; 11 (1): 1-14.