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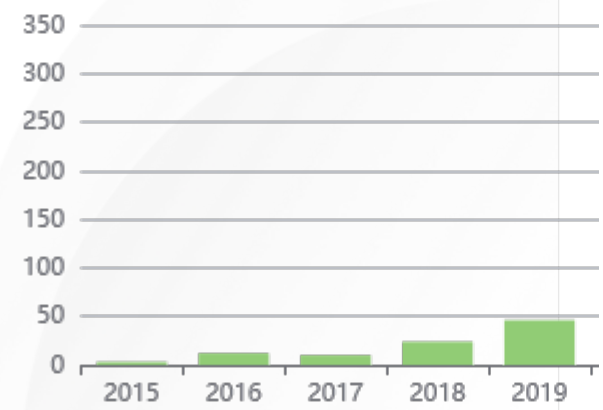

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Molecular Docking: Bioactive Compounds in Indramayu Mango (Mangifera indica L.) Peel Waste as NS5B Hepatitis C Virus (HCV) Inhibitor

Universitas Airlangga JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA Vol. 10 No. 1 (2023): JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA 1-10

2023 DOI: 10.20473/jfiki.v10i12023.1-10 Accred : Sinta 2

Anti-Inflammatory Effect of Red Dragon Fruit (Hylocereus polyrhizus) Peel on Male White Rat

Universitas Airlangga JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA Vol. 10 No. 1 (2023): JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA 22-29

2023 DOI: 10.20473/jfiki.v10i12023.22-29 Accred : Sinta 2

Molecular Docking of Bicycloproline Derivative Synthetic Compounds on Envelope Protein: Anti-SARS-CoV-2 Drug Discovery

Universitas Airlangga JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA Vol. 10 No. 1 (2023): JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA 11-21

2023 DOI: 10.20473/jfiki.v10i12023.11-21 Accred : Sinta 2

Characterization of Spanlastic System Loaded Green Tea Extract as Antioxidant for Skin

Universitas Airlangga JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA Vol. 10 No. 1 (2023): JURNAL FARMASI DAN ILMU KEFARMASIAN INDONESIA 30-37

2023 DOI: 10.20473/jfiki.v10i12023.30-37 Accred : Sinta 2

Study of Growth Curve of Lactobacillus plantarum FNCC 0026 and Its Antibacterial Activity

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Table of Content

Jurnal Farmasi dan Ilmu Kefarmasian Indonesia
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Analysis of Potential *Cinnamomum zeylanicum* Blume Essential Oil Against Alzheimer's Disease: A Molecular Docking Study

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Abstract

Background: *Alzheimer's Disease (AD) is a neurodegenerative disorder with progressive impairment of behavioural and cognitive functions and the most common cause of dementia. The pathophysiology of AD is associated with low acetylcholine, accumulation of amyloid beta plaque, and neurofibrillary tangles in the brain. Cinnamomum zeylanicum is known to have many medicinal properties, especially neuroprotective effects.* ***Objective:*** *This research was designed to determine the neuroprotective potential of the phytochemicals C. zeylanicum using an in silico study.* ***Methods:*** *There are 5 phytochemicals compounds of C. zeylanicum used in this study. It's qualified for Lipinski's rules of five and can cross blood brain barrier. The protein targets were AChE, BACE1, and GSK-3. Molecular docking and visualization were performed using Avogadro, AutoDock 4.2 PyMol and Biovia Discovery Studio 2019.* ***Results:*** *In silico results show that the main phytochemical compounds of C. zeylanicum Blume essential oil have great potency as an AD drug. The best interaction model of the compound was shown by trans-cinnamyl acetate and coumaric acid. Although the binding energy of the compounds is lower than AD drugs (donepezil, rivastigmine, galantamine), the binding energy is not much different from rivastigmine and galantamine.* ***Conclusion:*** *The phytochemical compounds of C. zeylanicum Blume essential oil have an effect as a neuroprotective agent for AD and should be investigated in future research.*

Keywords: *Alzheimer's Disease, Cinnamomum zeylanicum, Molecular Docking Study*

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INTRODUCTION

Alzheimer's Disease (AD) known as a neurodegenerative disorder that mostly attacks people over 65 years marked by insidious onset and progressive impairment of behavioral and cognitive functions including memory, comprehension, language, attention, reasoning, and judgment (Cassani *et al.*, 2018; Cortes-Canteli and Iadecola, 2020; Kumar *et al.*, 2022). AD is the supreme cause of dementia worldwide (60-80%) and also causes a decline in cognitive ability (Lucey, 2020; Litke *et al.*, 2021). In 2015, around 46.8 million people worldwide suffered from AD; it's predicted to be 82 million in 2030 and 152 million in 2050. About 10 million new cases of AD are reported yearly worldwide (Cassani *et al.*, 2018; Vinicius *et al.*, 2019). In the Asia-Pacific region, AD is estimated to increase from 23 million in 2015 to 71 million in 2050 (Alzheimer's Disease International and Alzheimer's Australia, 2014). In Indonesia, the prevalence of AD patients was about 1.2 million in 2013, and it was estimated to have a rapid increase to 1.9 million in 2030 and 3.9 million in 2050 (Ong *et al.*, 2021). The cause of this increase is due to increasing life expectancy worldwide. In 2015, life expectancy reached 72 years in Indonesia itself (Kumar *et al.*, 2022). This will have an impact on the health and socio-economic sectors (Ong *et al.*, 2021).

One of the pathophysiologies of AD is cholinergic neuron dysfunction caused by cholinergic toxicity. Overactivity of AChE will cause a significant decrease in ACh levels in the synaptic cleft in the cortex, hippocampus, and amygdala. It will disturb cholinergic neurons involved in brain functions such as learning, memory, attention, response, sleep, and the delivery of sensory information (Kumar *et al.*, 2022; Samanta, Ramesh and Govindaraju, 2022). Accumulation of Aβ plaques is also found in AD. This accumulation results in amyloid aggregation that promotes microglial activation and local inflammatory responses and leads to neurotoxicity. Amyloid deposition occurs around the meningeal and cerebral blood vessels and grey matter in AD (Dá Mesquita *et al.*, 2016; Tiwari *et al.*, 2019; Fan *et al.*, 2020; Kumar *et al.*, 2022). The presence of neurofibrillary tangles has been proven to have a relationship with AD. Hyperphosphorylation of the tau protein will form these tangles. The main function of tau protein is to stabilize axonal microtubules in the brain. Neurofibrillary tangles are stored in neurons and occur first in the hippocampus, then they are seen throughout the cerebral cortex (Long and Holtzman, 2019; Tiwari *et al.*, 2019; Kumar *et al.*, 2022). Some drugs that the FDAthe FDA approves approves for AD are donepezil, galantamine, and rivastigmine (Yiannopoulou and Papageorgiou, 2020). However, these drugs have side effects such as gastrointestinal disturbances, dyspepsia, nausea, vomiting, loss of appetite, diarrhea, muscle aches, loss of balance, headache, and hepatotoxicity (Kumar, Chowdhury and Kumar, 2017; Kallel *et al.*, 2019). In recent years, there is many studies to develop new anti-AD drugs with lesser side effects (Kareti and Pharm, 2020).

C. zeylanicum Blume is an aromatic plant from Sri Lanka and the Malabar coasts of India. It was usually us as seasoning in Asian traditional food and herbal medicine in different cultures and systems (Fahad *et al.*, 2018; Kallel *et al.*, 2019). It has many medicinal properties such as anti inflammatory, anti oxidant, analgesic,anti-cancer, anti-diabetic, anti-microbial, cardiovascular protective, cytoprotective, and neuroprotective (Momtaz *et al.*, 2017; Wang *et al.*, 2020). The herbal plants used to treat several diseases have developed rapidly in recent years (Kareti and Pharm, 2020). Plants are considered to be one of the sources of therapeutic active compounds, so this research was conducted to find new anti-AD drugs from herbal plants that might later have fewer side effects. *C. zeylanicum* Blume essential oil was chosen because it is believed to have a useful neuroprotective effect on AD. In previous studies, *C. zeylanicum* had anti-alzheimer's activity by inhibiting the nucleation process and the formation of tau filaments (Dhage *et al.*, 2021). Tepe and Ozaslan (2020) reported that *C. zeylanicum* had AChE inhibitory activity, which plays a role in the pathophysiology of AD. Frydman-Marom *et al*. (2011) also reported that *C. zeylanicum* can inhibit Aβ plaque accumulation in AD.

MATERIAL AND METHODS

System Configuration

This molecular docking study used operating Windows 10 OS 32 bit laptop with an Intel Core i3 processor and 2 GB RAM. Applications in silico research include Avogadro, AutoDock 4.2, Biovia Discovery Studio 2019, and PyMol.

Ligand and Protein Selection

C. zeylanicum Blume essential oil has the main phytochemical compounds namely cinnamaldehyde, *trans*-cinnamyl acetate, 1,4-benzene dicarboxylic acid, 1,8-cineole, α-pinene, coumaric acid, and 9-octadecenoic acid (Kallel *et al.*, 2019). The compound that is qualified for Lipinski's rule of five and can cross blood-brain barrier (BBB) is used in this molecular docking. The terms of Lipinski's rule of five can be checked through the website http://www.swissadme.ch/index.php. The qualified compounds will be compared with donepezil, galantamine, and rivastigmine, which are some of the FDA-approved drugs for AD (Yiannopoulou and Papageorgiou, 2020). The qualified compounds are cinnamaldehyde, *trans*-cinnamyl acetate, 1,8-cineole, α-pinene, and coumaric acid (Table 1). The 3D structure of the phytochemicals is downloaded from the website https://pubchem.ncbi.nlm.nih.gov and will be used as a ligand. The ligands were docked with the acetylcholinesterase/AChE receptor (PDB ID: 7E3H), β-site APP cleaving enzyme 1/BACE1 (GDP ID: 4DJU), and glycogen synthase kinase-3/GSK-3 (PDB ID: 1Q5K). These receptors play an important role in the pathophysiology of AD (Jagust, 2018). The protein structure was downloaded from the protein data bank (PDB) website http://www.rcsb.org.

Ligand Structure Optimization

The compounds downloaded in ".sdf" format are optimized using Avogadro software and saved in ".mol2" format. After that, the compounds in ".mol2"

format was converted to ".pdbqt" format using AutoDock 4.2 software.

Protein Structure Preparation

The macromolecular structure of the protein downloaded in ".pdb" format from Protein Data Bank (PDB) was searched for the active site using the BIOVIA Discovery Studio 2019 software. In AChE, BACE1, and GSK-3 proteins, there are two chains, Chain A and B. Then we choose chain A , which is used for docking using AutoDock 4.2 software. Proteins were optimized by adding polar hydrogens, merging non-polar, adding Kollman charges in proteins, and computing gasteiger in native ligands. After that, the receptor is separated from the native ligand and saved in ".pdbqt" format.

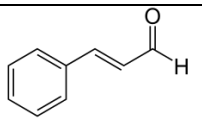
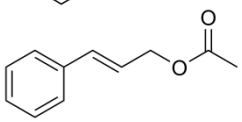
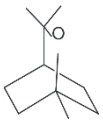
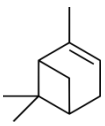
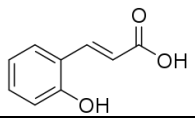
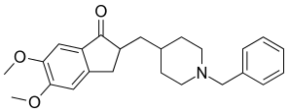
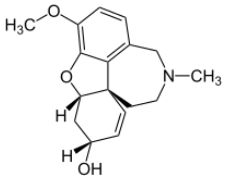
Grid Box Determination

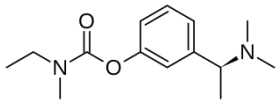
The size, centre coordinates, and spacing of the grid box are determined by the position of the native ligand using AutoDock 4.2 software. In AChE protein, the native ligand E20 grid was set in 40x40x40 (XYZ) point size, -43.74, 37.597, -30.039 centre coordinates, and 0.375 A spacing. In the BACE1 protein, the native ligand 0KK grid was set in 40x40x40 (XYZ) point size, 21,029, 10,689, 22,069 centre coordinates, and 0.375 A spacing. In the GSK-3 protein, the native ligand TMU grid was set in 40x40x40 (XYZ) point size, 23,148, 22.189, 8,978 centre coordinates, and 0.375 A spacing.

Molecular Docking

Proteins and ligands that have been prepared and grid boxes that have been determined are saved in ".gpf" format, and molecular docking is carried out with AutoDock 4.2 software. The ligand conformation output was analyzed using the Lamarckian Genetic Algorithm. Compounds that have the lowest bond energy (ΔG) show strong bonds and favourable conformations for ligand and protein interactions. After that, the results obtained in ".dlg" format are reopened using AutoDock 4.2 software to view the ligand bonds with amino acids and saved in ".pdb" format. The molecular docking results were visualized using the PyMol and BIOVIA Discover Studio 2019 software (Khaerunnisa, Suhartati and Awaluddin, 2020).

Table 1. Ligand Structure of Molecular Docking

Ligand	Molecular Formula	PubChem CID	Molecular Structure
C. zeylanicum blume essential oil			
Cinnamaldehyde	C_9H_8O	637511	
Trans-cinnamyl acetate	$C_{11}H_{12}O_2$	5282110	
1,8-cineole	$C_{10}H_{18}O$	2758	
α-pinene	$C_{10}H_{16}$	6654	
Coumaric acid	$C_9H_8O_3$	637542	
Alzheimer's disease drug			
Donepezil	$C_{24}H_{29}NO_3$	3152	
Galantamine	$C_{17}H_{21}NO_3$	9651	

Rivastigmine	$C_{14}H_{22}N_2O_2$	77991	

RESULTS AND DISCUSSION

C. zeylanicum Blume essential oil has 23 phytochemical compounds which represent at 99.39% of total essential oil. The main phytochemical compounds were cinnamaldehyde, *trans*-cinnamyl acetate, 1,4-benzene dicarboxylic acid, 1,8-cineole, α-pinene, coumaric acid, and 9-octadecenoic acid (Kallel *et al.*, 2019). Phytochemicals were screened before docking. Five phytochemical compounds were selected for molecular docking analysis. Due to Lipinski's rule of five, all of the ligands have zero violations, but 1,4-benzene dicarboxylic acid and 9-Octadecenoic acid can't cross the BBB, so the ligands are excluded (Table 2). Lipinski's rule of five terms consists of molecular weight <500 Da, log P <5, H-bond donor <5, and H-bond acceptor <10. Lipinski's rule of five can be used to classify the phytochemicals that may be effective in being used as drugs (Lipinski *et al.*, 2001). The compound must cross the BBB because the target receptor being inhibited is located in the brain (Pardridge, 2020).

Table 2. ADME Analysis of *C. zeylanicum* Blume Essential Oil Compound

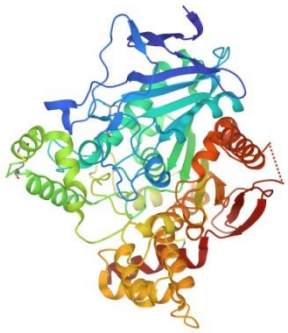
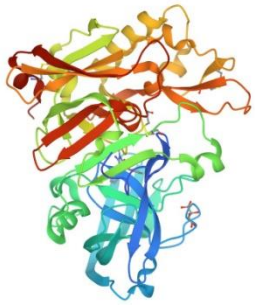
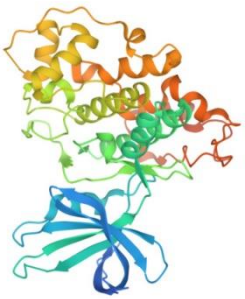
Phytochemical Compound	Lipinski's Rule of Five					BBB Permeant
	Molecular Weight	Log P	H-bond donor	H-bond acceptor	Violations	
Cinnamaldehyde	132,16	1,97	0	1	0	Yes
Trans-cinnamyl acetate	176,21	2,33	0	2	0	Yes
1,4-benzenedicarboxylic acid	166,13	1,13	2	4	0	No
1,8-cineole	154,25	2,67	0	1	0	Yes
α-pinene	136,23	3,44	0	0	0	Yes
Coumaric acid	164,16	1,26	2	3	0	Yes
9-Octadecenoic acid	282,46	5,71	1	2	0	No

AChE (PDB ID: 7E3H) is a cholinergic enzyme primarily found at postsynaptic neuromuscular junctions (NMJ). AChE immediately breaks down acetylcholine into acetic acid and choline in NMJ. AChE plays a critical role in AD (Trang and Khandhar, 2022). 7E3H has a total structure Weight of 120.37 kDa, an Atom Count of 8437, a Modeled Residue Count of 1054, a Deposited Residue Count of 1080, and one Unique protein chain. This receptor has a native ligand E20 that binds to 14 active site amino acids namely TYR072, ASP074, GLU202, TRP286, VAL294, PHE295, PHE338, TYR341, SER293, TRP086, GLY121, TYR124, TYR337, and HIS447. BACE1 (PDB ID: 4DJU) is a β-secretase involved in the β-amyloid peptide, a dominant component in AD (Gnanaraj *et al.*, 2022). 4DJU has a total structure Weight of 93.33 kDa, an Atom Count of 7068, a Modeled Residue Count of 779, a Deposited Residue Count of 828, and one Unique protein chain. This receptor has a native ligand 0KK that binds to 13 active site amino acids namely LEU091, ASP093, GLY095, SER096, VAL130, TYR132, TRP137, PHE169, TRP176, ILE179, ASP289, GLY291, and THR292 (Cumming *et al.*, 2012). GSK3 (PDB ID: 1Q5K) is a serine/threonine protein kinase that phosphorylates Tau protein, whose expression is associated with AD (Gnanaraj *et al.*, 2022). 1Q5K has a total structure Weight of 92.85 kDa, an Atom Count of 5930, a Modeled Residue Count of 689, a Deposited Residue Count of 828, and one Unique protein chain. This receptor has a native ligand TMU that binds to 12 active site amino acids, namely VAL061, ILE062, VAL070, ALA083, VAL135, PRO136, LEU132, LEU188, ASP133, TYR134, ARG141, and CYS199 (Bhat *et al.*, 2003). Table 3 also visualizes the 3D structure of each receptor at 2.45, 1.80, and 1.94 Å X-ray diffraction resolutions.

Based on the results of molecular docking, the phytochemical of *C. zeylanicum* Blume essential oil that has the strongest binding energy to the AChE receptor is *trans*-cinnamyl acetate (ΔG: -6.21 kcal/mol) with an inhibition constant of 27.84 μM. The other compounds, α-pinene, 1,8-cineole, coumaric acid, and cinnamaldehyde had binding energies of -5.96, -5.86, -5.76, and -5.50 kcal/mol with inhibition constants of 43.49, 50.56, 60.95, and 92.75 μM. In the AD drug, donepezil, galantamine, and rivastigmine had binding energies of -11.04, -8.05, and -7.29 kcal/mol with inhibition constants of 8.15 nM, 1.26 μM, and 4.52 μM. At the BACE1 receptor, the phytochemical of *C. zeylanicum* Blume essential oil with the strongest binding energy is *trans*-cinnamyl acetate (ΔG: -5.16 kcal/mol) with an inhibitory constant of 164.04 μM. The other compounds, cinnamaldehyde, coumaric acid, α-pinene, and 1,8-cineole have binding energies of -4.62, -4.51, -4.43, and -4.41 kcal/mol with inhibition constants of 408.29, 496.02, 567.62, and 583.24 μM. . Meanwhile, donepezil, galantamine, and rivastigmine had binding energies of -8.50, -6.08, and -5.89 kcal/mol with inhibition constants of 588.62 nM, 34.99 μM, and 47.78 μM. At the GSK-3 receptor, the phytochemical of *C. zeylanicum* Blume essential oil with the strongest

binding energy is coumaric acid (ΔG: -5.61 kcal/mol) with an inhibition constant of 77.41 µM. Other compounds, *trans*-cinnamyl acetate, 1,8-cineole, cinnamaldehyde, and α-pinene have binding energies of -5.47, -4.93, -4.92, and -4.83 kcal/mol with inhibition constants of 97.51, 245.32, 248.03, and 287.66 µM. Meanwhile, donepezil, galantamine, and rivastigmine had binding energies of -8.53, -6.29, and -6.22 kcal/mol with inhibition constants of 562.75 nM, 24.71 µM, and 27.74 µM (Table 4).

Table 3. Protein Target Associated with Alzheimer's Disease

Protein Target	PDB ID	Active Site	3D Structure
AChE (Acetylcholinesterase) Crystal structure of human acetylcholinesterase in complex with donepezil	7E3H	TYR072, ASP074, TRP086, GLY121, TYR124, GLU202, TRP286, SER293, VAL294, PHE295, TYR337, PHE338, TYR341, HIS447	
BACE1 (β-site APP Cleaving Enzyme 1) Structure of BACE bound to 2-imino-3-methyl-5,5-diphenylimidazolidin-4-one	4DJU	LEU091, ASP093, GLY095, SER096, VAL130, TYR132, TRP137, PHE169, TRP176, ILE179, ASP289, GLY291, THR292	
GSK-3 (Glycogen Synthase Kinase-3) crystal structure of glycogen synthase kinase 3 in complexed with inhibitor	1Q5K	VAL061, ILE062, VAL070, ALA083, LEU132, ASP133, TYR134, VAL135, PRO136, ARG141, LEU188, CYS199	

The molecular docking results are then visualized in Table 5. At the AChE receptor, the phytochemical of *C. zeylanicum* Blume essential oil, cinnamaldehyde binds to 9 amino acids with 7 van der Waals bonds, *trans*-cinnamyl acetate binds to 8 amino acids with 4 van der Waals bonds, 1,8-cineole binds to 8 amino acids with 2 van der Waals bonds, α-pinene binds to 8 amino acids with 4 van der Waals bonds, and coumaric acid binds to 12 amino acids with 9 van der Waals bonds. In the AD drug, donepezil binds to 14 amino acids with 6 van der Waals bonds, galantamine binds to 10 amino acids with 6 van der Waals bonds, and rivastigmine binds to 11 amino acids with 5 van der Waals bonds. At the BACE1 receptor, it was found that cinnamaldehyde binds to 11 amino acids with 5 van der Waals bonds, *trans*-cinnamyl acetate binds to 10 amino acids with 6 van der Waals bonds, 1,8-cineole binds to 7 amino acids with 2 van der Waals bonds, α-pinene binds to 7 amino acids with 3 van der Waals bonds, and coumaric acid binds to 10 amino acids with 7 van der Waals bonds. Meanwhile, donepezil binds to 17 amino acids with 11 van der Waals bonds, galantamine binds to 12 amino acids with 6 van der Waals bonds, and rivastigmine binds to 11 amino acids with 1 van der Waals bond. At the GSK-3 receptor, it was found that cinnamaldehyde binds to 12 amino acids with 8 van der Waals bonds, *trans*-cinnamyl acetate binds to 14 amino acids with 9 van der Waals bonds, 1,8-cineole binds to 9 amino acids with 3

van der Waals bonds, α-pinene binds to 11 amino acids with 4 van der Waals bonds, and coumaric acid binds to 11 amino acids with 5 van der Waals bonds. Meanwhile, donepezil binds to 12 amino acids with 6 van der Waals bonds, galantamine binds to 12 amino acids with 7 van der Waals bonds, and rivastigmine binds to 11 amino acids with 5 van der Waals bonds.

Table 4. Molecular Docking Results of Ligands with The Protein Target

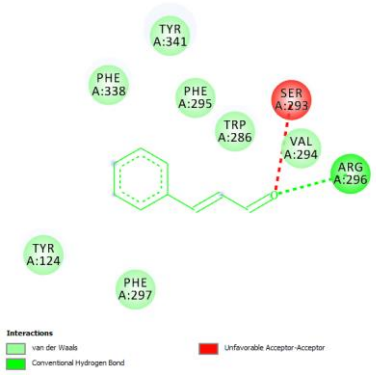
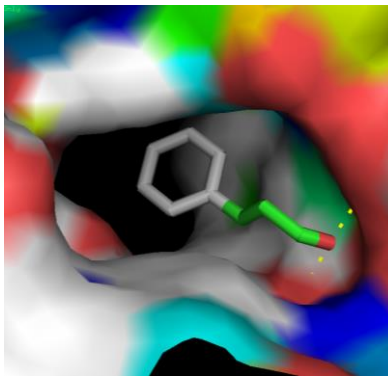
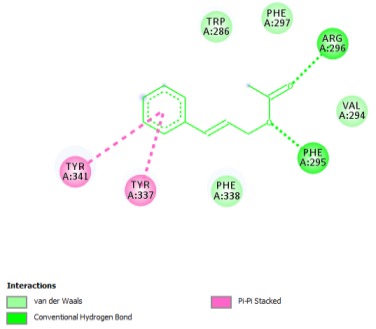
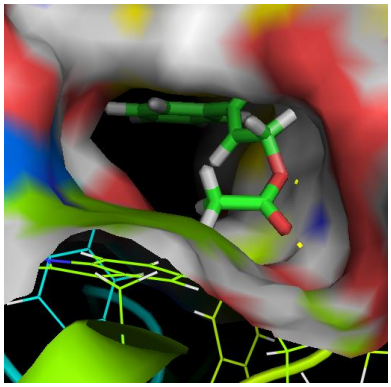
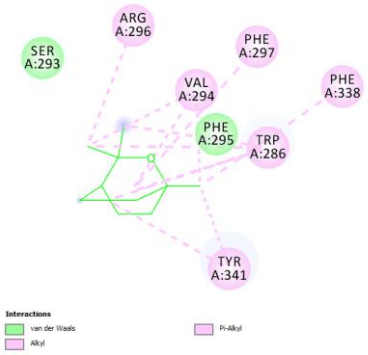
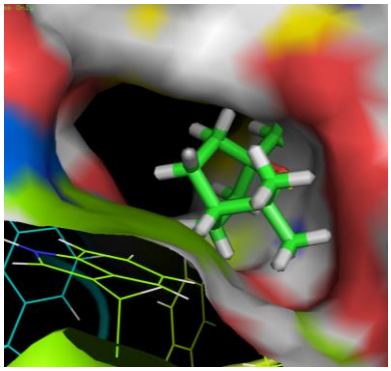
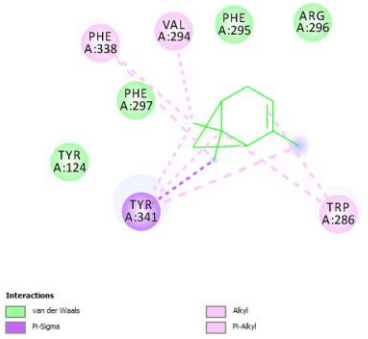
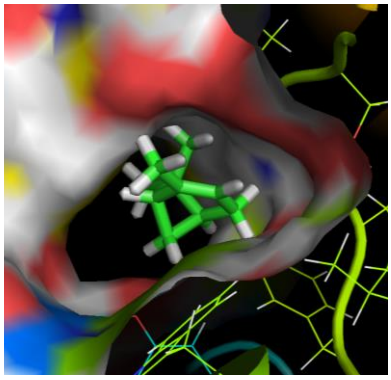
Ligand	Protein Targets Associated With Alzheimer's Disease					
	AChE		BACE1		GSK-3	
	ΔG (kcal/mol)	K_i	ΔG (kcal/mol)	K_i	ΔG (kal/mol)	K_i
C. zeylanicum blume essential oil						
Cinnamaldehyde	-5.50	92.75 µM	-4.62	408.29 µM	-4.92	248.03 µM
Trans-cinnamyl acetate	-6.21	27.84 µM	-5.16	164.04 µM	-5.47	97.51 µM
1,8-cineole	-5.86	50.56 µM	-4.41	583.24 µM	-4.93	245.32 µM
α-pinene	-5.96	43.49 µM	-4.43	567.62 µM	-4.83	287.66 µM
Coumaric acid	-5.76	60.95 µM	-4.51	496.02 µM	-5.61	77.41 µM
Alzheimer's disease drug						
Donepezil	-11.04	8.15 nM	-8.50	588.62 nM	-8.53	562.75 nM
Galantamine	-8.05	1.26 µM	-6.08	34.99 µM	-6.29	24.71 µM
Rivastigmine	-7.29	4.52 µM	-5.89	47.78 µM	-6.22	27.74 µM

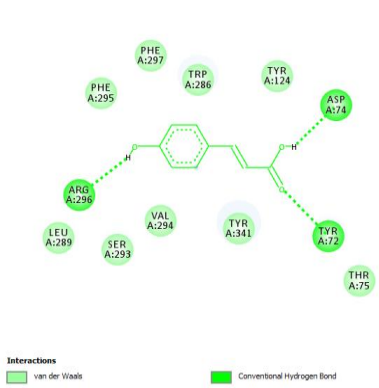
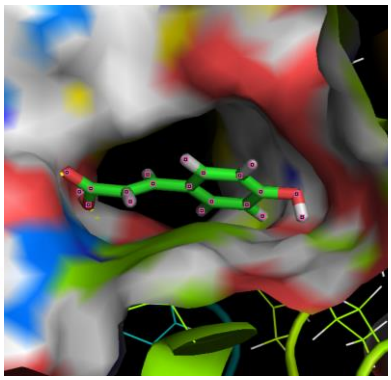
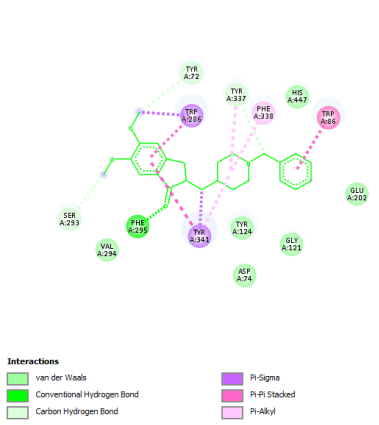
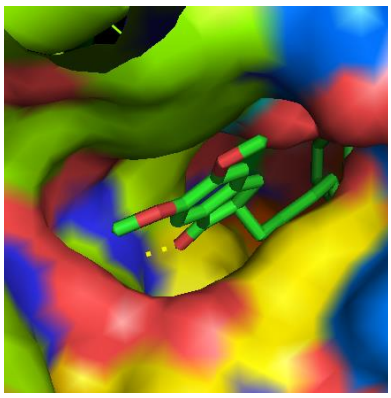
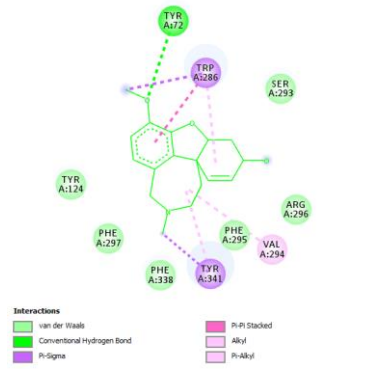
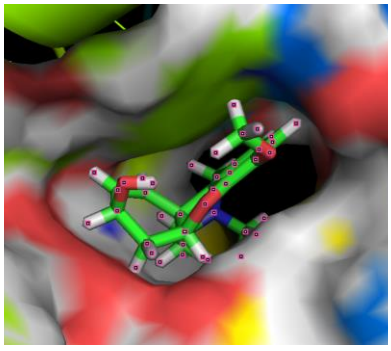
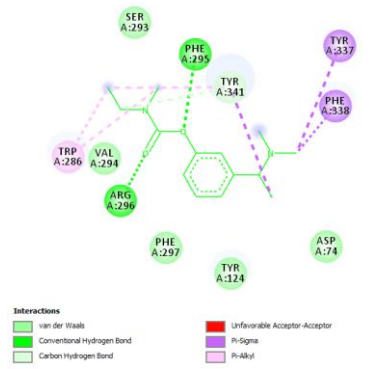
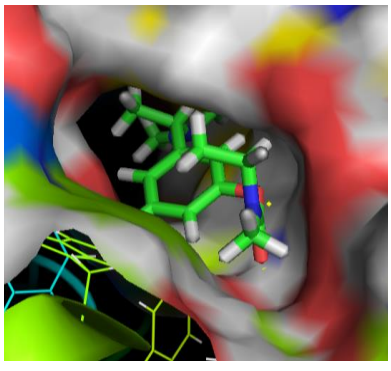
Cinnamaldehyde is a natural flavonoid and derivative compound of the volatile chemical aldehyde that gives cinnamon its flavour and aroma. Cinnamaldehyde is the main phytochemical compound of *C. zeylanicum* Blume essential oil (about 90%) (National Center for Biotechnology Information, 2022c). It has many pharmacological activities, including anti-inflammatory, antimicrobial, anti-cancer, anti-hyperglycemic, and neuroprotection (Zhang *et al.*, 2015). *Trans*-cinnamyl acetate is an acetate ester produced from the condensation of cinnamyl alcohol and acetic acid (National Center for Biotechnology Information, 2022b). Its pharmacological properties include anti-inflammatory, anticancer, antioxidant, antimicrobial, antidiabetic, anti-anxiety, antidepressant, and neuroprotection (Rao and Gan, 2014). Cinnamaldehyde and *trans*-cinnamyl acetate have neuroprotection functions that can be used for preventive and therapeutic nervous system diseases (Zhang *et al.*, 2015). 1,8-Cineole (eucalyptol) is an achiral aromatic component of many plants, including *C. Zeylanicum* (National Center for Biotechnology Information, 2022a). 1,8-Cineole has potential pharmacological properties such as anti-inflammatory, antioxidative, anti-cancer, and neuroprotection. 1,8-Cineole was used to treat nervous system disease (Cai *et al.*, 2020). α-pinene is an organic compound of the polyphenolic group terpene and a component of many aromatic, dietary plants, such as *C. Zeylanicum* (National Center for Biotechnology Information, 2022e). α-pinene has pharmacological properties such as antinociceptive and antioxidant. α-pinene has a strong anti-inflammatory effect in some pathological conditions. α-pinene also has neuroprotective effect, and it's capable of restoring BBB function and attenuating sensorimotor dysfunctions (Khoshnazar, Parvardeh and Bigdeli, 2020). Coumaric acid is derivative of cinnamic acid mono-hydroxylated at the phenyl group. It is the most abundant isoform and is found at significant levels in many plants, including *C. Zeylanicum* (National Center for Biotechnology Information, 2022d). Coumaric acid has many pharmacological activities, including anti-inflammatory, antidiabetes, antibacterial, hepatoprotective, nephronprotective, and neuroprotective. It has high free radical scavenging. Coumaric acid has potential preventive and therapeutic value for memory-impaired individuals, especially age-related memory-impaired in older people (Ferreira *et al.*, 2018).

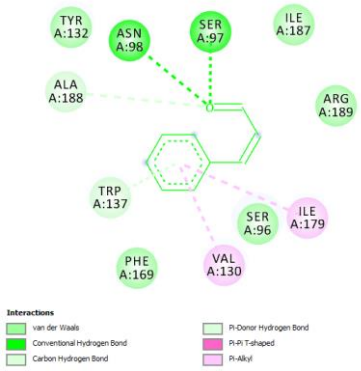
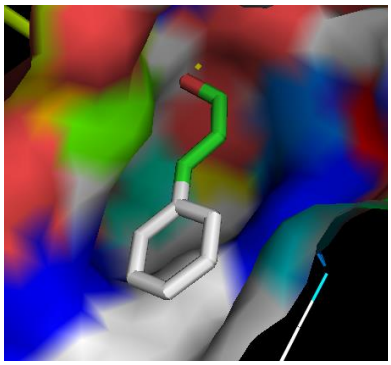
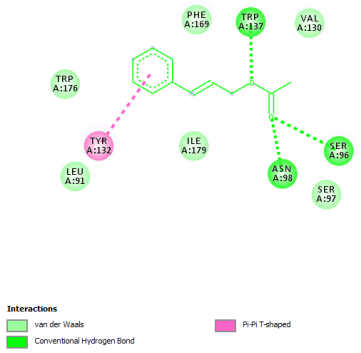
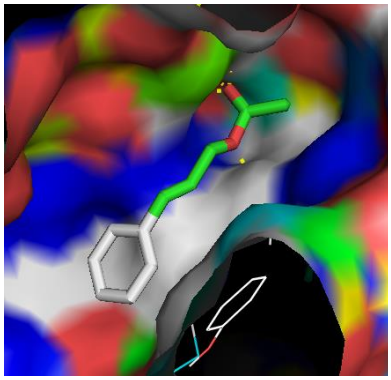
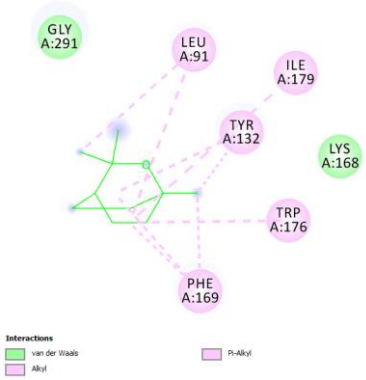
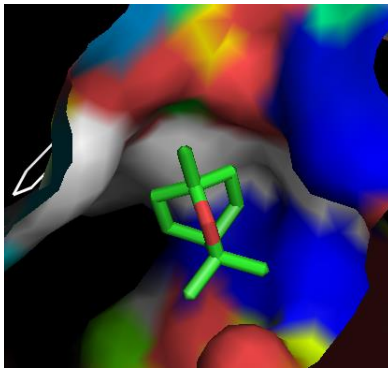
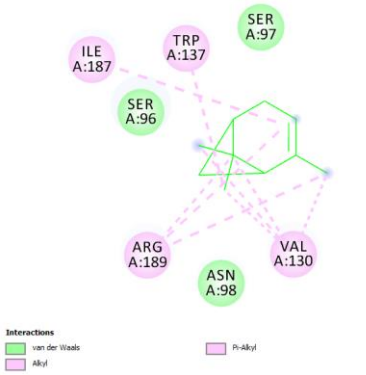
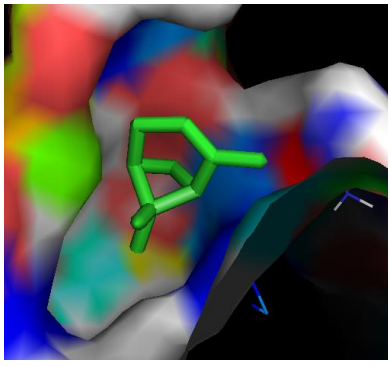
C. zeylanicum Blume essential oil, with its main phytochemical compound cinnamaldehyde, *trans*-cinnamyl acetate, 1,8-cineole, α-pinene, and coumaric acid, has a neuroprotective potential function. It was shown from molecular docking that it can inhibit the receptors AChE, BACE, and GSK-3. It prevents acetylcholinesterase from breaking down acetylcholine. The higher concentration of acetylcholine leads to better communication between nerve cells in the brain and may ease some symptoms of AD (Kumar *et al.*, 2022). *C. zeylanicum* Blume essential oil also prevents the accumulation and formation of Aβ plaques and neurofibrillary tangles in neurons from preventing neurotoxicity and worsening AD. It has an antioxidant, neurostimulator function, and prevents neuronal loss (Hamidpour *et al.*, 2015; Momtaz *et al.*, 2017; Hajinejad *et al.*, 2020).

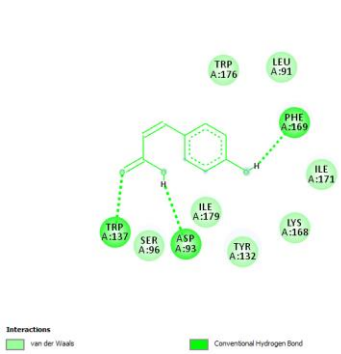
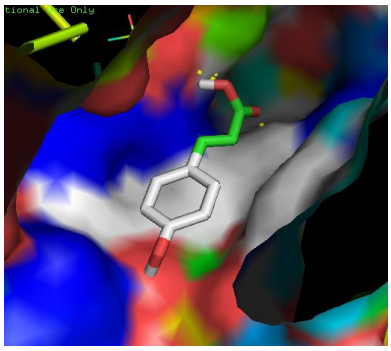
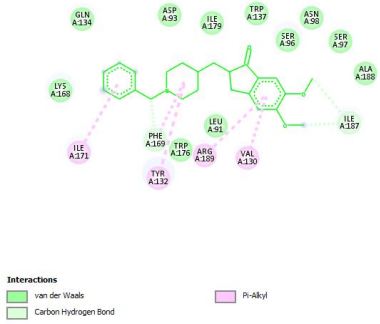
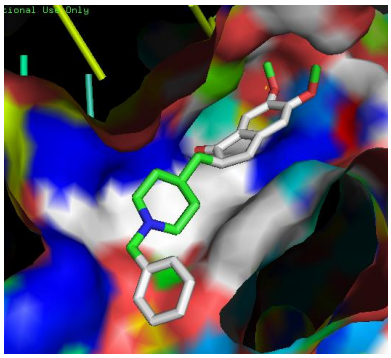
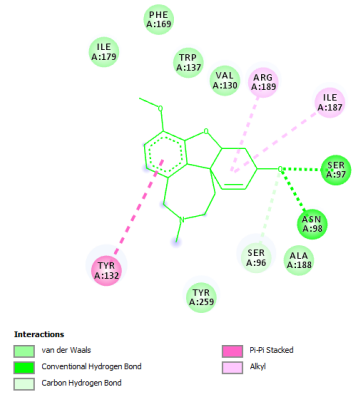
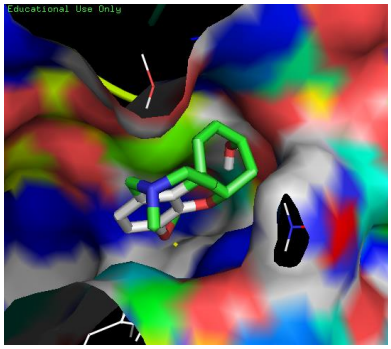
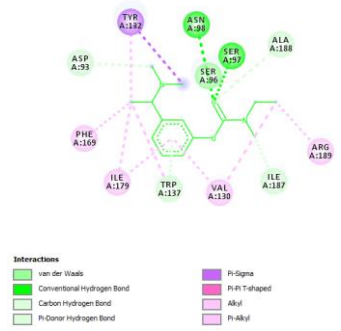
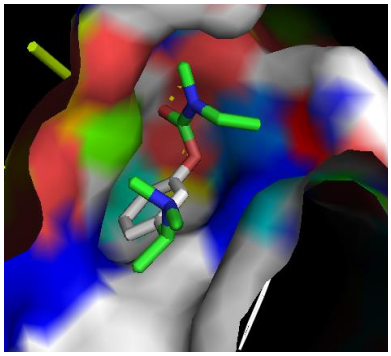
Table 5. Visualization of Ligands with The Protein Target

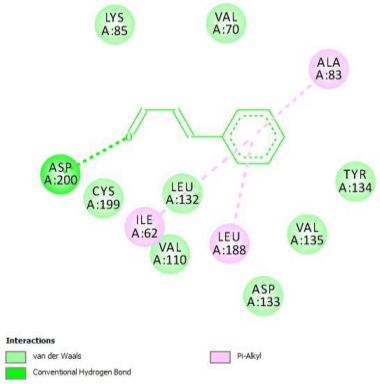
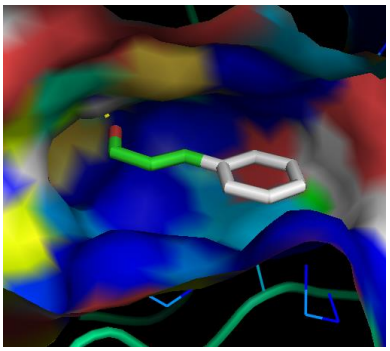
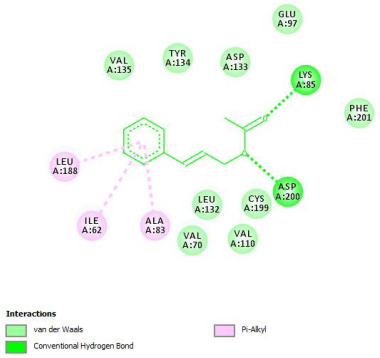
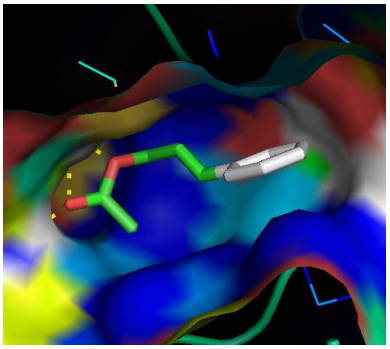
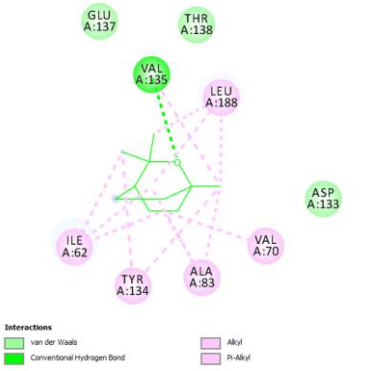
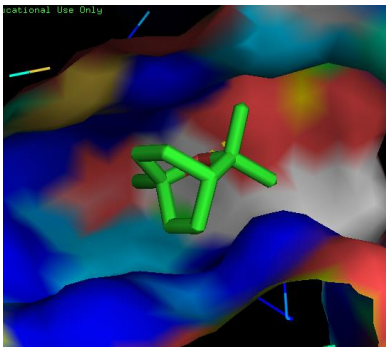
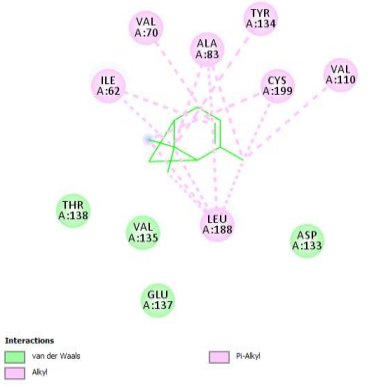
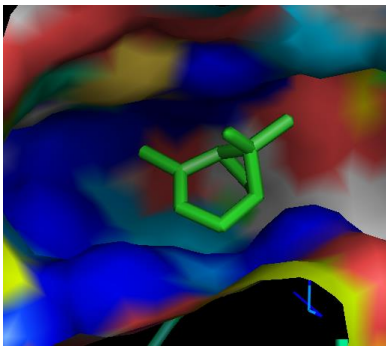
Protein	Ligand	Amino Acid Bond	2D Visualization	3D Visualization

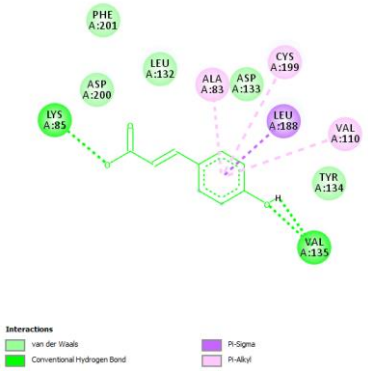
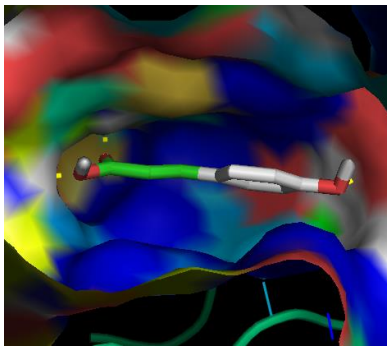
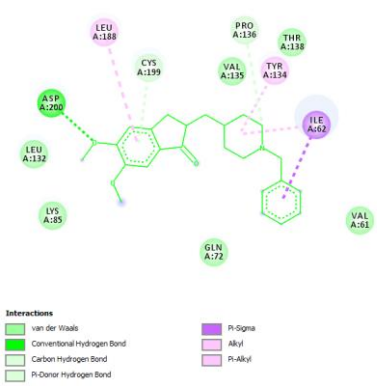
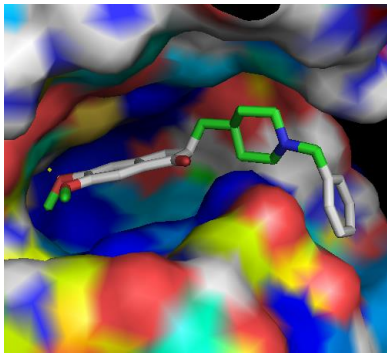
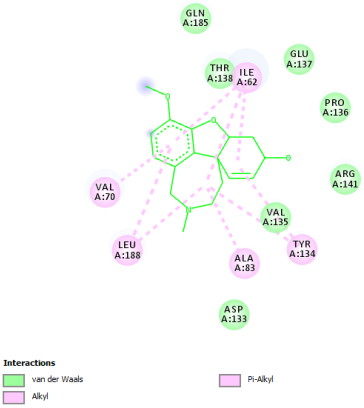
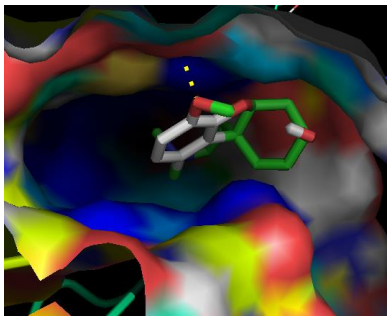
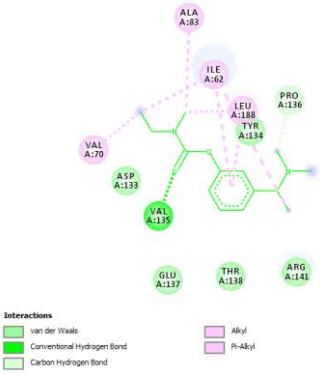
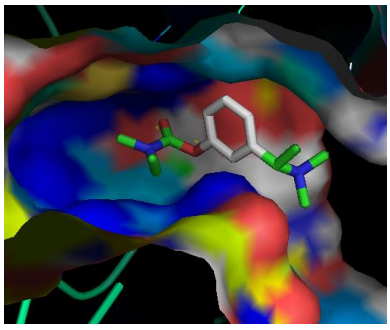
Protein	Ligand	Amino Acid Bone	2D Visualization	3D Visualization
AChE	Cinnamaldehyde	TYR124 TRP286 SER293 VAL294 PHE295 ARG296 PHE297 PHE338 TYR341		
	Trans-cinnamyl acetate	TRP286 VAL294 PHE295 PHE297 ARG296 TYR337 PHE338 TYR341		
	1,8-cineole	TRP286 SER293 VAL294 PHE295 ARG296 PHE297 PHE338 TYR341		
	α-pinene	TYR124 TRP286 VAL294 PHE295 ARG296 PHE297 PHE338 TYR341		

AChE	Coumaric acid	TYR072 ASP074 THR075 TYR124 TRP286 LEU289 SER293 VAL294 PHE295 ARG296 PHE297 TYR341		
	Donepezil	TYR072 ASP074 TRP086 GLY121 TYR124 GLU202 TRP286 SER293 VAL294 PHE295 TYR337 PHE338 TYR341 HIS447		
	Galantamine	TYR072 TYR124 TRP286 SER293 VAL294 PHE295 ARG296 PHE297 PHE338 TYR341		
	Rivastigmine	ASP075 TYR124 SER293 PHE295 TRP286 VAL294 ARG296 PHE297 TYR337 PHE338 TYR341		

BACE1	Cinnamaldehyde	SER096 SER097 ASN098 VAL130 TYR132 TRP137 PHE169 ILE179 ILE187 ALA188 ARG189		
	Trans-cinnamyl acetate	LEU091 SER096 SER097 ASN098 VAL130 TYR132 TRP137 PHE169 TRP176 ILE179		
	1,8-cineole	LEU091 TYR132 LYS168 PHE169 TRP176 ILE179 GLY291		
	α-pinene	SER096 SER097 ASN098 VAL130 TRP137 ILE187 ARG189		

Protein	Ligand	Amino Acid Bone	2D Visualization	3D Visualization
BACE1	Coumaric acid	LEU091 ASP093 SER096 TYR132 TRP137 LYS168 PHE169 ILE171 TRP176 ILE179		
	Donepezil	LEU091 ASP093 SER096 SER097 ASN098 VAL130 TYR132 GLN134 TRP137 LYS168 PHE169 ILE171 TRP176 ILE179 ILE187 ALA188 ARG189		
	Galantamine	ASP093 SER096 SER097 ASN098 VAL130 TYR132 TRP137 PHE169 ILE179 ILE187 ALA188 ARG189		
	Rivastigmine	ASP075 TYR124 SER293 PHE295 TRP286 VAL294 ARG296 PHE297 TYR337 PHE338 TYR341		

GSK-3	Cinnamaldehyde	ILE062 VAL070 ALA083 LYS085 VAL110 ASP133 LEU132 TYR134 VAL135 LEU188 CYS199 ASP200		
	Trans-cinnamyl acetate	ILE062 VAL070 ALA083 LYS085 GLU097 VAL110 LEU132 ASP133 TYR134 VAL135 LEU188 CYS199 ASP200 PHE201		
	1,8-cineole	ILE062 ALA083 VAL070 ASP133 TYR134 VAL135 GLU137 THR138 LEU188		
	α-pinene	ILE062 VAL070 ALA083 VAL110 ASP133 TYR134 VAL135 THR138 GLU137 LEU188 CYS199		

GSK-3	Coumaric acid	ALA083 LYS085 VAL110 LEU132 ASP133 TYR134 VAL135 LEU188 CYS199 ASP200 PHE201		
	Donepezil	VAL061 ILE062 GLN072 LYS085 LEU132 TYR134 VAL135 PRO136 THR138 LEU188 CYS199 ASP200		
	Galantamine	ILE062 VAL070 ALA083 ASP133 TYR134 VAL135 ARG141 PRO136 GLU137 THR138 GLN185 LEU188		
	Rivastigmine	ILE062 VAL070 ALA083 ASP133 TYR134 VAL135 PRO136 GLU137 THR138 ARG141 LEU188		

CONCLUSION

Molecular Docking of main phytochemical compounds of *C. zeylanicum* Blume essential oil has potency as Alzheimer's disease drug. These findings implicated that compounds could actively block the acetylcholinesterase, glycogen synthase kinase-3, and β site APP cleaving enzyme 1 activity. The best interaction model of the compound was shown by *trans*-cinnamyl acetate and coumaric acid. The binding energy of the compounds is lower than AD drugs (donepezil,

rivastigmine, galantamine), but it is not significantly different from AD drugs to inhibit the receptors. Our study can be used as the basis for conducting further research. In vitro studies, in vivo studies, pharmacokinetics and bioavailability of compounds, compound structures, and structure-activity relationships are needed to ensure the potency of *C. zeylanicum* Blume essential oil as an AD drug.

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CONFLICT OF INTEREST

There are no potential conflicts of interest to declare in this study.

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