IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 6, May 2025
Impact Factor: 7.67

In Silico Studies on Neuroprotective Effects of Moringa Oleifera With Molecular Docking.

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Abstract: *Progressive loss and destruction to neurons is a hallmark of neurodegenerative diseases, which include Parkinson's and Alzheimer's. Historically, a variety of illnesses have been treated with Moringa oleifera, a plant with a wide range of therapeutic uses. Through the use of in silico techniques, this study sought to examine the possible therapeutic effects of Moringa oleifera components on neurological illnesses. In order to find possible lead drugs that target important proteins linked to neurodegenerative disorders, molecular docking and virtual screening were used. Our findings demonstrated that a number of Moringa oleifera compounds have positive interactions and high binding affinities with target proteins, indicating their potential as medicinal agents. The stability and binding free energy of these compounds were further confirmed by molecular dynamics modeling. This study shows that Moringa oleifera compounds have the potential to be effective treatments for neurological illnesses and sheds light on the molecular mechanisms behind their therapeutic benefits.*

Keywords: Moringa oleifera, neurodegenerative diseases, in silico studies, molecular docking, virtual screening, molecular dynamics simulation

I. INTRODUCTION

A group of diseases known as neurodegenerative diseases are defined by increasing harm to the brain, spinal cord, or peripheral nerves that impairs cognitive, motor, and functional abilities[1]. These illnesses have a major influence on patients, caregivers, and healthcare systems globally, and they are a major cause of morbidity and mortality[2]. Degenerative conditions such as Alzheimer's disease (AD) are caused by the degeneration of brain cells and culminate in dementia, which is characterized by a decline in cognitive function and a diminished capacity to carry out daily tasks[3]. There are a number of known risk factors, such as advanced age, genetic susceptibility, head trauma, vascular diseases, infections, and environmental variables[4]. It Is estimated that there are about 50 million AD patients worldwide, and This number is expected to rise quickly in the upcoming years, which raises questions about how it will affect families and the economy[5]. As of right now, the only pharmaceutical treatment for AD is the usage of cholinesterase inhibitors and N-methyl-d-aspartate antagonists, which are meant to alleviate symptoms rather than treat or prevent the illness[6]. Recent research has concentrated on employing multi-omics analyses to find naturally occurring substances and metabolites with neuroprotective qualities that can alter signaling pathways associated with neurovascular endothelial cells in the treatment of AD[7].

Plants have been the direct or indirect source of many medications[8]. To identify lead chemicals for potential medications for AD and associated conditions, massive chemical investigations on plants have been conducted worldwide in recent years[9]. Because of their effectiveness, safety, and affordability, herbal medications are becoming more and more popular worldwide[10]. Moringa olifera, often known as the drumstick tree or Suhanjana, is a member of the Moringaceae family[11]. It is found in many nations worldwide and is indigenous to subtropical areas. Because of its many therapeutic uses, it is regarded as a versatile medicinal plant[12]. According to certain research, it has neuroprotective properties and is thought to improve cognitive performance. It improves cholinergic function and reduces oxidative stress[13]. There have been numerous chemicals identified in the floral extract of M. olifera. Behenic acid, octadecenoic acid, heneicosanoic acid, flavonoids, glucosinolates, and phenolics are among them[14]. This plant

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yielded glycosidic flavonoids, such as quercetin 3-O-α-L rhamnosyl (1→ 6) β D-glucoside from M. olifera flower extract, kaempferol-7-O-β-D-alloside, and rhamnetin 3-O-(2``- galloyl)–β-D-galactopyranosyl-4`- β-D-xylopyranoside[15].

The Investigation and comprehension of complex systems are revolutionized by in silico research, a crucial component of contemporary scientific investigation[16]. Based on computational techniques, this novel methodology makes it possible to model, simulate, and forecast a wide range of events in disciplines like engineering, chemistry, biology, and materials science[17]. Originating from the Latin expression that means "in silicon," it represents the transition from analog to digital simulations in experiments. In order to find patterns, expedite research, and improve our comprehension of concepts, these computational studies make use of the enormous processing capacity of computers[18]. They are essential to more effective medicine, material, and technology design.This research examines the developments and uses of in silico research, highlighting its crucial influence on scientific inquiry in the twenty-first century. In order to better understand Alzheimer's disease, find new drugs, and create treatments, computational techniques in in silico studies are increasingly essential[19]. These investigations effectively manage large amounts of data, forecast results, and direct experimental research. However, even though these methods speed up research and provide insightful information, in vitro and in vivo studies are still necessary to validate results and develop successful Alzheimer's treatments[20].

Fig. Moringa Oleifera plant

II. METHOD AND MATERIALS

Materials

1.Moringa oleifera compound database: A database of bioactive compounds present in Moringa oleifera, such as PubChem or ChemSpider[21].

2.Protein structure databases: Databases of protein structures associated with neurodegenerative diseases, such as PDB or UniProt[22].

3.Computational software: Software for molecular docking, virtual screening, and molecular dynamics simulation, such as AutoDock Vina, GOLD, or GROMACS[23].

4.Bioinformatics tools: Tools for sequence analysis, structure prediction, and functional annotation, such as BLAST or InterProScan[24].

Methods

1. Compound selection: Selection of bioactive compounds from Moringa oleifera based on database search[25].

2. Protein target identification: Identification of protein targets associated with neurodegenerative diseases using database[26].

3. Molecular docking: Molecular docking simulations to predict the binding affinity and interactions between Moringa oleifera compounds and protein targets[27].

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4. Virtual screening: Virtual screening to identify potential lead compounds with high binding affinity and favorable interactions[28].
5. Molecular dynamics simulation: Molecular dynamics simulation to study the dynamic behavior of protein-ligand complexes and predict binding free energy[29].
6. Pharmacokinetic and pharmacodynamic property prediction: Prediction of pharmacokinetic and pharmacodynamic properties, such as absorption, distribution, metabolism, and excretion, using in silico models[30].

2.1. Molecular Docking Calculation

Molecular docking calculations were performed to examine several features, including the binding energy of ligand-receptor complexes. The targeted protein is identified by ID 4EY7 in the PDB database[31]. Going forward, 25 bioactive chemicals that were extracted from Moringa oliefera were obtained from PubChem. To prepare the study's structure, Chimera 1.14 28 was used. This material preparation was done using the standard AMBER FF14SB and Gasteiger residues to give molecular compounds hydrogen and charge. A critical stage in redocking is technique validation, provided that all the molecules were produced[32]. Rivastigmine was used as a reference ligand for redocking. In order to get information on binding energy and amino acid residues, this medication was found on the receptor's active site. Because rivastigmine has a shorter half-life than other medications like donepezil and galantamine, it was selected as the reference ligand[33]. Additionally, the US Food and Drug Administration approved this medication as an anti-Alzheimer's medication. AutoDock Tools 1.5.6 was used to calculate molecular docking[34]. Molecular docking calculations were performed using 10 Lamarckian Genetic Algorithm runs 30 in a grid box measuring 68 × 72 × 68 with a spacing of 0.375 Å. Biovia Discovery Studio was used to view the complexes of molecular docking data in order to collect residue amino acids31 on the active site. Biovia Discovery Studio was used to view the complexes of molecular docking data in order to determine the amino acid residue on the active site[35].

2.2. Molecular Dynamic Simulation

The ligand-AChE complex, which came from molecular docking calculations, was subjected to the molecular dynamics simulation technique. Pterygospermine is the ligand, and its binding energies are lower than those of the control ligand. Following that, the outcomes of the molecular dynamics simulation were contrasted with the molecular dynamics computations of the control ligand, namely the rivastigmine-AChE complex[36]. The YASARA Structure Program, created by Bioscience GmBH, Vienna, Austria, was used to run a simulation. The first step was to use Option to enter each sample into the program. Following the selection of the Macro & Movie menus, the Set Target was chosen as the final action. The YASARA Structure software, created by Biosciences GmbH, was used to simulate molecular dynamics. The protein-ligand complex produced by molecular docking was used as an input file for the molecular dynamics simulation. With the target in the form of a protein complex and ligand pdb file of each compound, protein complexes (AChE) with ligands (Rivastugmine and Pterygospermine) are simulated using md_run.mcr after being submitted to the Yasara Structure Program through the Options menu and then choosing the Macro & Movie menu[37]. The simulation starts with a pH of 7.4, a temperature of roughly 310 K, and a potential energy minimization. To ensure that the simulations are similar to the physiological conditions of the human body, this condition is adjusted to match those conditions. Additionally, a prepared sample was used to execute molecular dynamic simulation using input macro. The following step involved setting a running time of 50,000 ps (50 ns) on macro md_run. The forcefield utilized in the Yasara Structure program is Amber14, with intramolecular forces computed every 1 fs and intermolecular forces calculated every 2 fs. Every 25 ps, trajectory data is collected, and data analysis is performed using the formula md_analyze.mcr to yield the radius of gyration, RMSD, number of hydrogen bonds in the solute, number of hydrogen bonds between the solute and solvent, and potential energy analysis. Additionally, a macro called md_analyzeres.mcr was used to perform the RMSF analysis, whereas MMPBSA was used to explore Molecular Mechanics, The md_analyzebindenergy.mcr macro was utilized. After 5 ns from the simulation time to the 50 ns simulation time, data creation is performed; the longer the simulation, the better the data analysis[38]. The RMSD analysis data is one of the parameters that determines the simulation time. The simulation time can be halted at a time

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range of 50 ns if there are no noticeable variations in the protein and ligand complexes. A macro md_analyze was used to analyze the potential energy, number of hydrogen bonds in the solute, number of hydrogen bonds between the solute and solvent, RMSD, and radius of gyration. The Radius of Gyration, RMSD, and RMSF measures were used to examine the data.

The stability of protein-ligand complexes under physiological conditions throughout time can be predicted using these three factors[39]. This stability cannot be further understood through molecular docking studies. The RG graph produced throughout the simulation period can also be used to ascertain the target protein's state, specifically whether it is folded or unfolded. The protein's folded state is indicated by the lowest value, while its unfolded structural state is shown by the highest value . While the Molecular Mechanics Poisson-Boltzmann Surface Area (MMPBSA) employed macro analyze bind energy, the RMSF analysis was conducted using macro md_analyzeres[40].

III. RESULT AND DISCUSSION

Seven chemicals from moringa leaves (Moringa oliefera)—beta carotene, lupeol acetate, sitogluside, tocopherol, chlorogenic acid, beta-sitosterol, and myricetin—violated Lipinski's Rule of Five (Table 1). Due to their molecular masses exceeding 500 Da, beta-carotene and sitogluside fail to distribute to the cell membrane when taken orally[41]. Conversely, the bioactive chemicals' adherence to Lipinski's Rule of Five facilitates drug penetration into cell membranes and streamlines distribution. In the meantime, MlogP has to do with a drug candidate's lipophilicity or hydrophobicity. A higher MlogP value indicates that the bioactive molecule is more likely to be hydrophobic. Because the medication diffuses widely and is long-retained in a lipid bilayer, it causes toxicity to the human body. Finally, an HBD violation of less than ≤5 results in problems with drug absorption in the human body[42]. All 18 of Moringa oliefera's bioactive components meet Lipinski's Rule of Five screening criteria. The purpose of ADMET study is to investigate the pharmacokinetics and toxicity of medication candidates made from oral moringa leaves. The main reasons why medication development fails are poor pharmacokinetics and toxicity. Research conducted in vitro can be completed more rapidly, but the outcomes must frequently be consistent with those obtained in vivo. Although in vivo research is expensive and time-consuming, it produces useful data[43]. As a result of its speed and low cost, the in silico approach is available to supplement these data . This metric forecasts how well a medicine will work in the human body to achieve its goal (Table 2). The Caco-2 and %HIA cells were used to test the drug absorption prediction. The %HIA number indicates how well a medication candidate is absorbed in the human gut. According to data in Table 2, the majority of ADMET tests fell between 70 and 100, suggesting that the human body absorbs them well. Additionally, Caco-2 cell modeling was used to forecast the oral route's capacity to absorb bioactive chemicals in vitro. The Blood-Brain Barrier (BBB) and Plasma Protein Binding (PPB) provide insight into how medications are distributed throughout the human body. Because the PBB parameter gauges a drug candidate's affinity for the central nervous system (CNS), it is essential in the development of anti-Alzheimer medications. Drugs must cross the BBB 8 and enter the central nervous system[44]. The BBB serves as a barrier between the central nervous system and the systemic circulation, protecting the brain. The active chemicals from moringa leaves in Table 2 generally have a BBB between 2.0 and 0.1, which indicates excellent absorption. Certain chemicals have poor absorption when their BBB is less than 0.1. Additionally, PPB is expressed as a percentage; a number greater than 90% signifies that the medication is chemically bound to blood plasma[45]. Additionally, the cytochrome P450 (CYP450) enzyme is involved in the drug metabolism factor, which increases the solubility of drugs in the human body. The medications taken may function as inducers, inhibitors, or substrates. CYP3A4 and CYP2D6 37 are the two CYP450 enzymes that are most important for drug metabolism[46]. The liver, kidney, lung, brain, endothelium, placenta, and lymphocytes are the main locations for CYP3A4, whereas the liver, brain, and heart are the main locations for CYP2D6. The majority of the chemicals derived from Moringa oleifera are anticipated to be non-inhibitory against CYP2D6, as shown in Table 2. The majority of Moringa oleifera compounds are inhibitors of CYP3A4[47]. The toxicity projections for two parameters—carcinogens and mutagens—are shown in Table 2. Finding microorganisms in compounds that cause DNA changes is the goal of the Ames test . All of the chemicals in Table 2 test positive for mutagens, suggesting that the drug may cause DNA mutation. Moreover, the majority of chemicals had no carcinogenic effects in mice[48]. The majority of the chemicals produced positive results, which is quite different from carcinogenic studies in rats. Using molecular

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docking calculations, 18 molecules should be determined based on Tables 1 and 2. The Lipinski Rule of Five is not broken by any of these substances[49]. This recommendation is founded on the commonalities among oral drugs. Compliance with Lipinski's rule is often linked to the drug's physicochemical qualities of water solubility and intestinal permeability[50].

No	Compounds	Lipinski's Rule of Five					
		Molecular Mass 500 (DA)	MlogP 5	Hydrogen Bond Acceptor (HBA) 10	Hydrogen Bond Donor (HBD) 5	Violation of Lipinsksi	Druglike
1	Rivastigmine			Control			
2	1,3 Dibenzil Urea	279	-0.41	6	3	0	Unviolate
3	1,4 Naftokuinon	158	1.621	2	0	0	Unviolate
4	Beta Carotene	536	12.605	0	0	2	Violate
5	Caffeic Acid	180	1.195	4	3	0	Unviolate
6	Chlorogenic Acid	354	-0.645	9	6	1	Violate
7	Ellagic Acid	302	1.241	8	4	0	Unviolate
8	Gamma Amino Butyric	103	-0.190	3	3	0	Unviolate
9	Kaempferol	286	2.305	6	4	0	Unviolate
10	Lupeol Asetat	468	8.595	2	0	1	Violate
11	Niazimin	399	0.874	8	2	0	Unviolate
12	Niazirin	279	-0.041	6	3	0	Unviolate
13	Pterygospermine	406	4.139	4	0	0	Unviolate
14	Quercetin	302	2.010	7	5	0	Unviolate
15	Sitogluside	576	5.849	6	4	2	Violate
16	Tocopherol	430	8.840	2	1	1	Violate
17	Beta Sitesterol	414	8.024	1	1	1	Violate
18	Vanilin	152	1.213	3	1	0	Unviolate
19	Glucocochlearin	375	-0.220	10	5	0	Unviolate
20	Myricetin	318	1.716	8	6	1	Violate
21	Genistein	270	2.415	5	5	0	Unviolate
22	Moringyne	312	-0,739	7	4	0	Unviolate
23	Rhamnetin	316	2.313	7	4	0	Unviolate
24	Apigenin	270	2.419	5	3	0	Unviolate
25	Daizein	254	2.713	4	2	0	Unviolate
26	Ferulic Acid	194	1.498	4	2	0	Unviolate

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Table 2. ADMET test of bioactive compounds from moringa leaves (*Moringa oleifera*)

No.	Compounds	Adsorption		Distribution			Metabolisme, Excretion		Toxicity		
		%HIA	Caco-2 (nm sec^{-1})	MDCK	BBB	%PPB	CYP 3A4 Inhibition	CYP 2D6 Inhibition	Ames Test Mutagenicity	Mouse Carcinogenicity	Rat Carcinogenicity
1	Rivastigmine	97.95	55.51	0.87	0.08	79.83	Non	Inhibitor	Mutagen	Negative	Negative
2	1,3 Dibenzil Urea	92.80	21.31	41.99	2.95	99.73	Non	Inhibitor	Mutagen	Positive	Negative
3	1,4 Naftokuinon	99.52	20.90	60.05	1.78	68.54	Inhibitor	Non	Mutagen	Negative	Positive
4	Ascorbic Acid	33.15	2.48	0.88	0.11	5.30	Inhibitor	Non	Mutagen	Negative	Negative
5	Ellagic Acid	61.39	20.48	17.29	0.32	88.40	Inhibitor	Non	Mutagen	Negative	Positive
6	Gamma Amino Butyric	73.32	18.02	4.04	0.24	24.75	Inhibitor	Non	Mutagen	Positive	Negative
7	Kaempferol	79.43	9.57	79.43	0.28	89.60	Inhibitor	Non	Mutagen	Negative	Positive
8	Niazimin	73.16	19.71	2.25	0.02	56.23	Non	Non	Mutagen	Negative	Negative
9	Niazirin	75.22	0.84	37.24	0.03	48.12	Non	Non	Mutagen	Negative	Negative
10	Pterygospermine	97.82	5.4.49	0.08	0.05	94.06	Non	Inhibitor	Non-mutagen	Positive	Negative
11	Quercetin	63.48	3.41	13.35	0.17	93.23	Inhibitor	Non	Mutagen	Negative	Positive
12	Vanillin	93.05	19.59	122.18	0.56	63.14	Inhibitor	Non	Mutagen	Negative	Positive
13	Glucocochlearin	11.99	0.336	17.02	0.08	21.33	Inhibitor	Non	Mutagen	Negative	Positive
14	Genistein	88.12	5.74	39.43	0.17	89.73	Inhibitor	Non	Mutagen	Negative	Positive
15	Moringyne	62.99	13.59	62.99	0.10	46.04	Non	Non	Mutagen	Negative	Negative
16	Rhamnetin	66.11	16.11	21.92	0.05	87.98	Inhibitor	Non	Mutagen	Negative	Positive
17	Apigenin	87.31	10.52	44.30	0.59	100.0	Inhibitor	Non	Mutagen	Positive	Positive
18	Daizein	92.64	2.48	42.99	0.93	95.56	Inhibitor	Non	Mutagen	Negative	Positive
19	Ferulic Acid	90.60	21.11	228.55	0.75	50.41	Non	Non	Mutagen	Negative	Positive

3.1. MOLECULAR DOCKING CALCULATIONS

Redocking step two of the rivastigmineAChE receptor contact was used to begin the molecular docking calculation in this work. Rivastigmine is used as a control medication because it is FDA-approved in the United States and has a shorter half-life than donepezil. A safe synthetic substance called rivastigmine was created to increase the effectiveness of medications. One of the three anti-Alzheimer drugs in the world, this chemical is derived from the basic structure of physostigmine[51]. A cholinergic or parasympathomimetic drug, rivastigmine inhibits butylcholinesterase (BuChE)41 as well as AChE. In 4EY7, donepezil is a natural ligand of AChE. Rivastigmine binds to the AChE receptor via conventional hydrogen bonding to the amino acid residues PHE295 and TYR124, with a binding energy of -7.77 Kcal mol-1 (See Figure 2.B.). Furthermore, prior research indicates that the AChE active site is separated into three sections: the peripheral anionic site (TRP286, PHE295, TYR124, ASP74, and SER125), the long narrow aromatic gorge (TRP86, TYR133, ILE451, GLU202, and GLY448), and the catalytic active gorge (GLU334, SER203, and HIS447)[52]. It is known that PHE295 and TYR124 are part of the Peripheral anionic site active site based on the three active sites of AChE. The research findings in this study can also be compared to the three different kinds of AChE receptor active sites. Redocking the rivastigmine-AChE receptor complex yielded an RMSD value of 1.68 Å, demonstrating the method's high level of validation (Figure 1) . A suitable comparison position between the ligand before and after redocking is shown in Figure 1. The binding atom for the amino acid residue in the active site of the AChE receptor is the carbonyl oxygen atom, as seen in Figure 1. Both ligands have carbonyl oxygen atoms near one other, but the amine group is in the opposite position[53].

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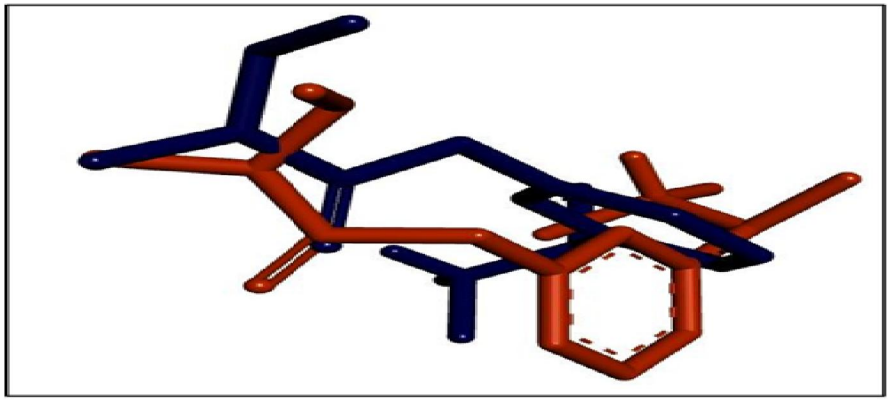

Figure 1. Comparison of rivastigmine in AChE (Dark blue before redocking and orange after redocking)

18 Moringa oleifera potential compounds that were chosen based on Lipinski's Rule of Five tests are listed in Table 3. Ten compounds—1,3 dibenzyl urea, ellagic acid, niazimin, niazirin, pterygospermine, glucocochlearin, rhamnetin, apigenin, and daizein—have lower binding energies than the control ligand, according to the findings. When researching ligand inhibitors' ability to prevent a disease, information on inhibition constants (μM) might also be very helpful. The computation's lower projected Ki value suggests that a modest dose is required to block a receptor[54]. The interactions in the rivastigmine+AChE receptor complex are explained in detail in Figure 2. Figure 2A shows the rivastigmine redocking against the AChE receptor in three dimensions. Inhibiting the AChE receptor entails binding to the drug-candidate ligand in the active region of the receptor. Traditional hydrogen bonds are the main interactions that could increase the amount of binding energy produced. At active site , support is another secondary interaction that strengthens the bond between the ligand and receptor. The control ligand links with five Van der Wals interactions against TYR337, VAL296, ASP74, GLY121, and SER125 and forms a conventional hydrogen bond with the amino acid residues TYR124 and PHE295. PHE338 and TYR341 amino acid residues also stacked via π-π interactions. The carbon-hydrogen bond with ARG296 and the π-sigma with TRP289 and PHE297, respectively, were observed (Figure 2B). One of the main interactions in molecular docking understanding using Autodock Tools is the conventional hydrogen bond[55]. Representative hydrogen bonds in the rivastigmine ligand region on the AChE receptor's active site are shown in Figure 2C. An acceptor is represented by the green area, and a donor by the light purple area. While TYR124 was bonded to the amine rivastigmine group at a bond distance of 1.66 Å, amino acid residue PHE295 was bonded to the carbonyl oxygen atom (2.17 Å) (Figure 2.D). PHE295's distance from the AChE receptor's active site showed a substantial interaction with TYR124. In order to gather important data, therapeutic candidates from Moringa oleifera were also computed using a similar technique for the AChE receptor (Table 3). As a possible anti-Alzeimer medication, Table 3 demonstrates that pterygospermine has the lowest binding energy of all the substances[56]. Of the 18 chemicals shown in Table 5, pterygospermine, a possible medication, has the lowest binding energy. Pterygospermine shows promise as a medication for an anti-Alzheimer alternative, according to molecular docking calculations. Figure 3 illustrates how pterygospermine interacts with the AChE receptor. Conventional hydrogen bond interactions were observed at amino acid residues TYR133 and GLU202 by the pterygospermine ligand[57]. Pterygospermine exhibited a distinct manner of interaction in contrast to the control ligand. Nonetheless, the AChE receptor's long narrow aromatic gorge active region contained both amino acid residues. In addition, Van der Wals interactions were seen in ILE451, GLY120, GLY121, ASP74, GLY126, SER125, VAL194, PHE295, PHE297, TYR124, GLY448, and TRP286[58]. The π-π stacking connection between pterygospermine and TYR341 and TRP86 was discovered. However, as carbon-hydrogen bond interactions, HIS447, TYR337, and PHE338 were connected to the ACHhE receptor's active site[59]. Generally speaking, the pterygospermine+AChE receptor complex's amino acid residue bond distance is greater than the rivastigmine+AChE receptor complex's hydrogen bond distance. The distance

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of TYR133 to the active site in the pterygospermine-AChE receptor complex was 2.53 Å. Meanwhile, GLU202 is farther away from the AChE receptor's active site (2.92 Å)[60].

Table 3. Molecular docking calculations of bioactive compounds from Moringa leaves against AChE receptors

No.	Compounds	ID PubChem	Binding Energy (kcal mol^{-1})	Ki constant (μM)	Conventional hydrogen bond
1	Rivastugmine	77991	-7.77	1.83	PHE295, TYR124
2	1,3 Dibenzil Urea	72889	-8.04	1.29	ASP74
3	1,4 Naftokuinon	8530	-6.31	23.88	PHE338
4	Caffeic Acid	689043	-4.83	287.87	SER203
5	Ellagic Acid	5281855	-7.84	1.82	GLU202, SER203, ASN87, ASP74
6	Gamma Amino Butyric	119	-3.4	1.62	GLY122, SER203, HIS447
7	Kaempferol	5280863	-7.62	1.63	HIS447, TYR341, TYR337, ASP74, TYR124
8	Niazimin	129556	-8.13	1.09	HIS447
9	Niazirin		-8.10	6.30	GLU202, HIS447, PHE 295
10	Pterygospermine	72201063	-10.28	0.22	TYR133, GLU202
11	Quercetin	5280343	-7.59	2.71	TRP86, GLN71, HIS 447
12	Vaniline		-5.38	113.91	
13	Glucocochlearin	5281135	-9.18	185.10	GLU202, SER203, GLY120, GLY121, ALA203, GLY122, HIS447, SER125
14	Genistein	5280961	-8.54	545.94	TYR124, ARG296
15	Moringyne	131751186	-7.73		ASP74, THR83, TYR124
16	Rhamnetin	5281691	-8.9	1.17	ASP74, GLN71
17	Apigenin	5280443	-8.00	91.37	GLU202, GLY120, TYR72
18	Daizein	5391140	-8.47	613.46	GLY122, ARG296, SEER203
19	Ferulic Acid	445858	-5.22	150.29	SER203

3.2.MOLECULAR DYNAMICS SIMULATION

The ligand-protein complex's interaction dynamics can be investigated using molecular dynamic simulation using YASARA Structure at physiological pH 7.4 and 310K. The physiological salt's salinity of 0.9% was employed[61]. The two samples' viability can be preserved under this condition. Once macro md_analyze was performed, the potential energy analysis was received. The average potential energy increased significantly from 0 ns to 0.5 ns running duration, according to the analytical results from three samples (Figure 4)[62].

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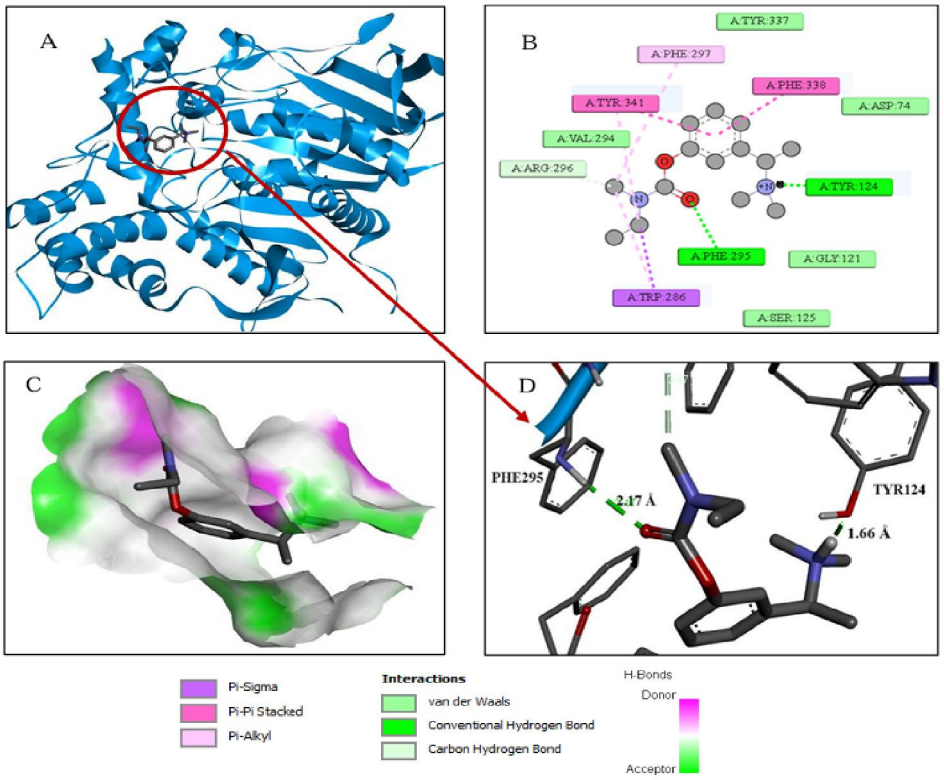
Volume 5, Issue 6, May 2025
Impact Factor: 7.67



Figue 2. 3D visualization of the rivastigmine+AChE receptor complex (A), 2D visualization of the rivastigmine+AChE receptor complex (B), representative hydrogen bonds (C), and atomic interactions between rivastigmine and atoms of the AChE receptor amino acids (D). Apart from that, there is a legend that can explain the interactions that occur

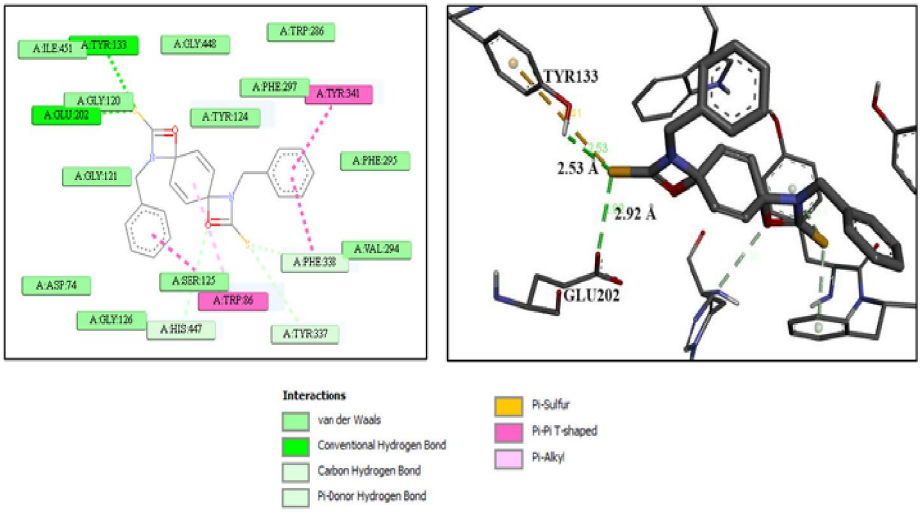


Figure 3. 2D visualization of the pterygospermine+AChE receptor complex (A) and the interaction of the pterygospermine ligand atoms with the amino acid residues of the AChE receptor (B)

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International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 6, May 2025
Impact Factor: 7.67

Furthermore, MMPBSA study from rivastigmine showed that the energy average of the implicity solute during running 50 ns is 6.850 kJ moland for pterygospermine is 37.377 kJ mol-1 , respectively (Table 4)[63]. Pandamarilactonine F N-oxide was the most promising and anticipated ligand as an anti-Alzheimer drug because increased binding energy also suggested a more compact association between ligand and protein. The gas phase energy, solvation-free energy, and the contribution from the solute's entropy configuration were added up to determine the Molecular Mechanics Poisson-Boltzmann Surface Area (MMPBSA) energy[64]. The more persistent and durable the binding energy in a complex, the closer the characteristic is to positive. Based on the configuration of solute entropy, free energy solvation, and gas phase energy, the MMPBA calculation was carried out. Eq. 1 is used to calculate the MMPBSA analysis. Table 4 displays each average energy over a 50 ns period[65].

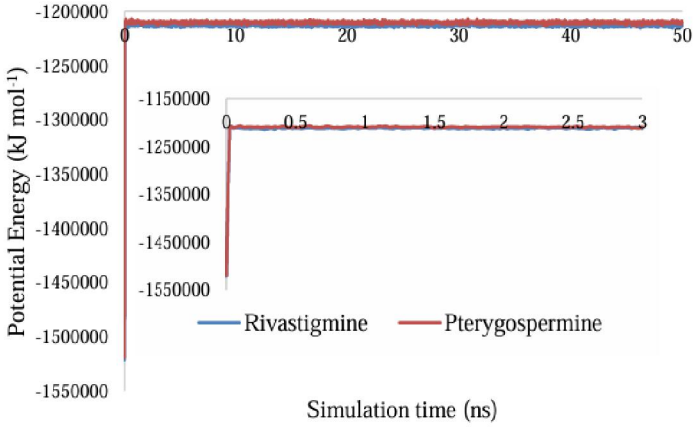

Figure 4. Potential energy of protein-ligand complex at 3 ns and 50 ns (blue line: rivastigmine and red line: pterygospermine)

Table 4. Components from MMPBSA equation

Energy	Rivastugmine Average	Pterygospermin Average
Epot Recept	-34265.211	-34255.981
Esolv Recept	-24426.497	-24565.717
Epot Ligand	32.802	-88.564
Esolv Ligand	-30.286	124.030
Epot Complex	-34265.220	-34255.983
Esolv Complex	-24430.822	-24567.627
Bind Energy [kJ mol^{-1}]	6.850	37.377

3.3.Total RMSD, RMSF, Ligand Configuration, and Radius of Gyration

An analytical score that shows conformational changes in macromolecules is called Root Mean Square Deviation (RMSD). The stability of the ligand-protein combination in this investigation is also predicted by this analysis. Following a contact with particular ligands, macromolecules function as receptors. The macro md_analyze is invoked to acquire the RMSD analysis[66]. As a deviation standard of conformation change, RMSD is also employed. For docking outcomes, the RMSD value is often less than 2Å. In simulated situations where the conformation change has negligible impact on dynamic stability, RMSD data shows sample stability. The absence of notable conformational changes—better known as the unfolding process—is what is meant by dynamic stability[67]. However, some of the receptors that came out of the simulation had an RMSD of 3 Å, which means that this receptor system undergoes a

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Volume 5, Issue 6, May 2025
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substantial conformational shift from its natural state. The RMSD values for both steady samples with some fluctuations are displayed in Figure 5A. Furthermore, the two samples' total RMSD showed an average value of 2 Å, indicating that there would not be a major change in the protein structure in either sample. For both samples, the C-alpha protein's RMSD was less than Figure 5B's overall RMSD value. However, the RMSD value of the Pterygospermine ligand did not differ significantly from that of the positive control, rivastigmine, suggesting that Pterygospermine may be an AChE inhibitor. The YASARA application can be used to view the RMSD of the ligand configuration in addition to the RMSD of the complete molecule. With a range of 2-2.5 Å, the ligand in the Rivastigmine complex is significantly more stable during the 50 ns simulation time, according to the RMSD ligand analysis[68]. In addition, the dynamics of the pterygospermine ligand were distinct from those of the rivastigmine ligand. The pterygospermine ligand's RMSD was smaller than the rivastigmine ligand's at the first simulation, which took place at 0-35 ns. Nonetheless, there were several notable modifications to the rivastigmine ligand system. The ligand's RMSD increased as a result of this substantial conformational shift, ranging from 3-3.5 Å (Figure 5C). Because of conformational changes in the pterygospermine ligand structure, pterygospermine has a higher positive energy value than rivastigmine, which is supported by the binding energy data[69]. The equilibrium conformation of the complete simulation system is described by the radius of gyration (RG) analysis. One method to forecast the simulation of sample solubility in a solution or liquid solvent is to use the RG value, which can also be defined as the radius of rotation of the dynamic movement of a protein-protein or protein-compound complex towards the solvent. The complexes' comparative results demonstrate that neither the protein folding during the simulation period nor the docking of the rivastigmine and pterygospermine ligands substantially altered the RG pattern (Figure 5D)[70].

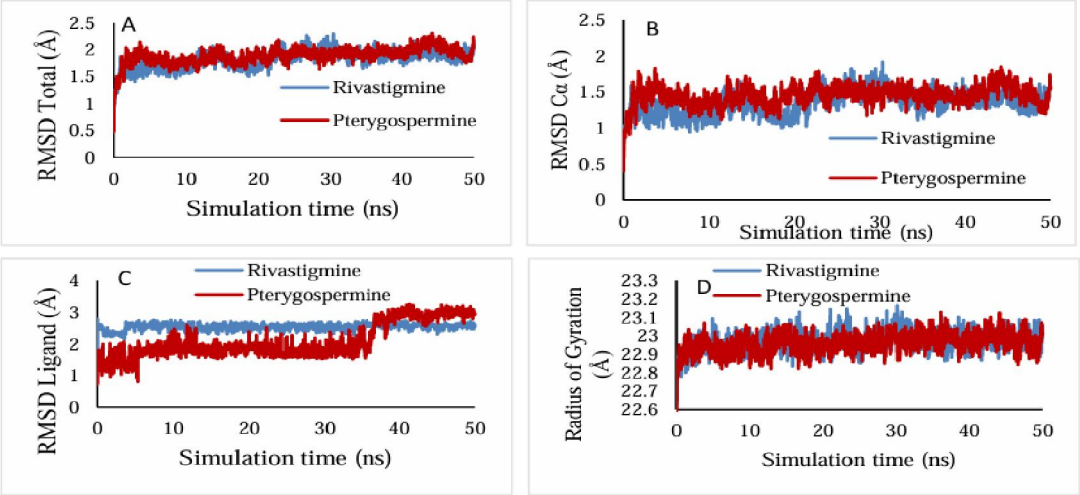

Figure 5. RMSD of rivastigmine and pterygospermine complexes to AChE (A), RMSD Cα of rivastugmine and pterygospermine complexes to AChE (B), RMSD of ligand configuration (C), dan Comparison of RG patterns between rivastigmine and pterygospermine complexes with AChE (D)

3.4.RMSF analysis of amino acid residue

Since Root Mean Square Fluctuation (RMSF) is associated with fluctuations at the level of the ligand's amino acid and nucleotide residues, it offers more precise information on conformational changes[71]. While high RMSF values caused deviations in the RMSD, RMSF measurements lower than 3Å suggested that ligand interactions with the enzyme were stable. The rivastigmine and pterygospermine complexes' amino acid residues of the AChE protein structure have an average RMSF value of about 2 Å[72]. Figure 6 illustrates that the RMSF values of multiple amino acid residues surpass 3 Å, Bond relaxation is therefore expected to have taken place in the target protein conformation, particularly for a number of residues with RMSF values greater than 4 Å[73]. Generally speaking, the RMSF of amino

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ISSN: 2581-9429
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acid residues is less than 3 Å, but the RMSF of residues that surpass 3 Å is negligible[74]. These residues of amino acids are ALA542, SER541, and GLU4. Analyses provided this information on amino acid residue[75].

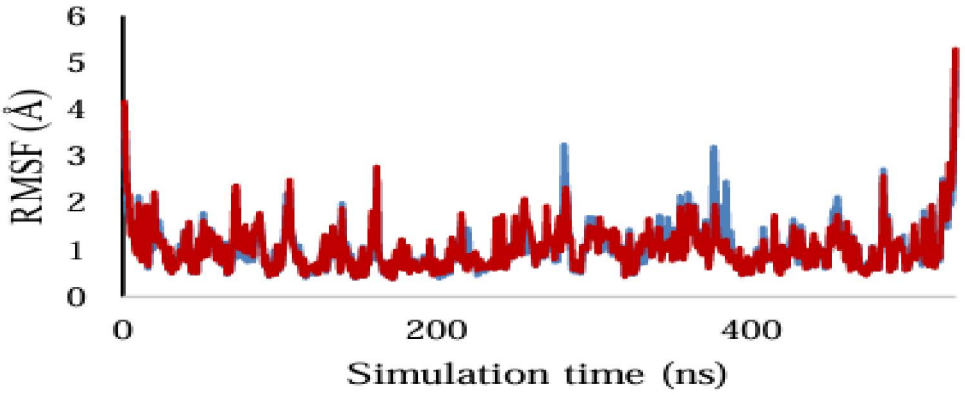

Figure 6. RMSF amino acid residues of AChE protein

IV. CONCLUSION

Molecular docking, molecular dynamics, and ADMET characteristics have been successfully used to study bioactive chemicals from Moringa oleifera to AChE[76]. For molecular docking calculations, the screening step yielded 18 bioactive molecules. With hydrogen bond interactions between amino acid residues TYR133 and GLU202 at the active AChE site, pterygospermine generates the lowest binding energy[77]. Using molecular dynamics, the pterygospermine+AChE and rivastigmine+AChE complexes were compared. The AChE complex's comparison with rivastigmine and pterygospermine reveals that, according to RMSD and RMSF data, the pterygospermine ligand interacts with AChE in a stable manner, just like the positive control (rivastigmine) does with AChE instead[78]. Adding ligands does not appear to have the ability to unfold the protein, according to the results of the Radius of Gyration research. Based on the findings, the pterygospermine ligand's conformation changed during the simulation period, resulting in rivastigmine having a better binding energy than pterygospermine[79]. The results of this work clearly demonstrate the role of the ligand-receptor interaction in AChE receptor inhibition; However, additional in vitro and in vivo research is necessary to develop new anti-Alzheimer's drugs[80].

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DOI: 10.48175/IJARSCT-26741

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