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Unlocking Therapeutic Potential of Alkaloids Inhibiting Acetylcholine Esterase: A Comparative Molecular Docking and MD Simulation Analysis with Known Drugs of Galantamine and Physostigmine

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ABSTRACT

Alzheimer's disease is characterized by the degeneration of neurons in the central nervous system. Patients with Alzheimer's disease experience cognitive problems like memory loss and reasoning impairments, which are brought on by a decrease in neuronal activity and a drop in the levels of neurotransmitters in the intersynapse. The Fritillaria genus, which comprises a variety of culinary and medicinal plants from the Liliaceae family, is extensively cultivated and has a long history in Xinjiang, China. been used in Chinese traditional medicine. The primary component of this plant is alkaloids, of which there are over 40 known varieties. . Most of Alkaloids are the main important compounds used in treatment of different disease, so it will have an effective role in the treatment of Alzheimer's as well. *Insilico* approach including molecular docking, ADME, Toxicity, bioactivity check and Molecular Dynamic Simulation was applied for evaluation of their potential to treat Alzheimer's disease.Computationalfindings of the current study reveals thatHuperzine A (-9.6kcal/mol), Berberine (-10.6kcal/mol) andPiperine (-9.6kcal/mol) may act as a drug candidate as they follow all five guidelines of Lipinski,high binding affinities and having equal or less than 3Å of RMSF value in average, which indicates the stability of complexes.

Introduction

Alzheimer's disease is a chronic, progressive neurodegenerative illness characterized by increasing cholinergic neuron loss in the brain. Furthermore, AD coexists with central nervous system cholinergic impairment [1]. Patients with Alzheimer's disease experience cognitive problems like memory loss and thinking impairments due to a decrease in neuronal activity and a decrease in neurotransmitter concentrations in the intersynapse, which affects synaptic transmission negatively and leads to an imbalance of cholinergic neurotransmission in the brain [2]. Inflammation and oxidative damage are the initial stages of that type of illness [3].. Prior to the recent approval of the monoclonal antibody lecanemab, there were no drugs that could halt the progression of the disease (https://www.bmj.com/content/380/bmj.p73). Alzheimer's disease is currently treated with preventative therapy and symptomatic reduction, including medications based on natural products, as discussed in [2]. The development of extracellular Aβ-plaques and intracellular neurofibrillary tangles (NFTs) in various regions of Alzheimer disease patients are thought to be the two most important pathological features of the disease [4]. Several signaling pathways including oxidative [5], and calcium signaling pathways are activated by Aβ peptides' binding with cellular receptors [6]. In addition to increasing production of glutamate neurotransmitters in the synaptic region, they bind to synaptic plasticity related receptors [7]. Additionally, they interfere with transport across the axons [8], , increase tau hyper phosphorylation [7], contribute to memory impairment, and disrupt long term potentiation (LTP), lowering the strength of the connections between neurons [9]. Despite a great deal of research on the damaging processes associated with Aβ-peptides, the exact mechanism of their toxicity is still unknown. Further research is necessary because studies have not fully defined these receptors or the underlying signaling pathways associated with them, despite suggesting that receptor binding of Aβ aggregates may alter various important neuronal functions [6].

Negatively affecting cholinesterase enzymes, which were in charge of acetylcholine’s breakdown, is the major goal of treatment for Alzheimer's disease in order to raise acetylcholine levels in the synaptic gap.

Decreased amounts of acetylcholine in Alzheimer's patients generally linked to symptoms of poor memory, memory loss, and a steady decline in intellectual process [10]. It is still unknown which drug would be best for treating this condition [11]. Given that women experience Alzheimer's disease at a higher rate than males, more research is required to understand the pathophysiology of the disease and its fundamental underpinnings [12]. The homeostasis of living things is regulated by enzymes, which also catalyze critical physiological processes. In order to better the clinical state of a certain disease, it is feasible to employ the method of suppressing the activity of a particular enzyme in the treatment of diseases [3]. Acetylcholinesterase, a serine hydrolase enzyme, is primarily responsible for hydrolyzing acetylcholine and regulating the transmission of cholinergic impulses. The enzyme hydrolyzes the neurotransmitter acetylcholine into two inert compounds, choline and acetic acid [13]. Acetylcholinesterase is primarily responsible for the termination of nerve impulse transmission at cholinergic synapses by catalyzing the neurotransmitter acetylcholine and accelerating the buildup of β-amyloid peptides. The acute loss of memory problem is significantly reversed when acetylcholinesterase is blocked and the quantity of acetylcholine in the brain increases [14]. One of the most important therapeutic strategies for treating neurodegenerative diseases is to maximize the amount of the neurotransmitter acetylcholine at cholinergic synapses. Acetylcholinesterase inhibitors are used to stop the breakdown of acetylcholine in order to accomplish all of that [15]. Acetyl cholinesterase inhibitory activity is measured using the standard spectrophotometry method that Ellman suggested [16]. In contrast to the spectrophotometric approach, in silico research frequently employ molecular docking and quantitative structure activity relationship (QSAR) model analysis to assess acetyl cholinesterase inhibitory activity [17].

Magnificently nature contains a wide variety of bioactive compounds with potent acetyl cholinesterase inhibitory action. The creation of novel acetyl cholinesterase inhibitors with reduced toxicity and higher efficacy is required. The majority of research has been on how distinct kinds of alkaloids inhibit acetyl cholinesterase [11]. Alkaloids, whose activity involves inhibiting acetyl cholinesterase, are typically present as an active ingredient in the majority of medications used to treat neurodegenerative disorders [11].

Plants, particularly some blooming plants, are the main source of alkaloids, which are naturally occurring substances that typically contain carbon, hydrogen, nitrogen, and oxygen [18]. There are usually just a few varieties of alkaloids in a single plant species, even though several plant families, such as the Amaryllidaceae (amaryllis), Papaveraceae (poppies), Solanaceae (nightshades), and Ranunculaceae (buttercups), are particularly rich in a variety of alkaloids [19]. Many culinary and medicinal plants from the Liliaceae family, which is commonly grown in the Tian Shan Mountains and has long been used in traditional Chinese medicine, are found in the Fritillaria genus in Xinjiang, China. The primary component of this plant is alkaloids, of which over 40 varieties have been identified [20]. Alkaloids are categorized into several classes based on their pharmacokinetics, sources, and chemical structure [2]. The FDA has approved a number of medications to treat AD, including galantamine, memantine, tacrine, donepezil, and rivastigmine. According to studies, these medications can cause a variety of adverse effects, such as rhinitis, nausea, vomiting, anorexia, reversible hepatotoxicity, abdominal discomfort, and myasthenia. According to experimentally reported data, some alkaloids have drug-like qualities. For example, berberine can be used as a medication for various conditions because of its anti-inflammatory, vasorelaxation, and cardioprotective properties; it can also induce cancer cells to undergo apoptosis. Additionally, morphine has been used as an anticancer agent. The study is designed to evaluate potent compounds which may be non-toxic to use for AD treatment. Medicinal plants are natural source for the treatment of different disease which has less or no side effects. The study shows that our selected compounds are non-toxic and biologically active. The study was designed to evaluate potential alkaloids for treatment of Alzheimer disease by targeting Acetylcholine esterase (AchE).

Method And Substances

Retrieval of Structural Proteins

The PubChem database provided the 3D structure of alkaloid and reference medicinal compounds in standard data file (SDF) format [21]. The acetylcholinesterase protein's structure was obtained with a resolution of 2.50 Å from the Protein Data Bank (PDB ID 1EVE). The crystallographic database of proteins' and nucleic acids' three-dimensional structures is called the Protein Data Bank (PDB) (www.rcsb.org).

Preparation of Protein

Using the Discovery Studio 2021 client, the receptor protein's 3D structure was refined by eliminating ligands, water molecules, and hetatoms [22].

Ligand preparation and Molecular Docking

PyRx's default parameters were used for molecular docking [23]. To prepare for molecular docking, the ligand compounds were uploaded to PyRx (version 0.8), and the alkaloid compounds' 3D structures were modified using the protein data bank partial change and atom type (pdbqt) of SDF format [24]. The receptor protein was uploaded to PyRx and transformed into a macromolecule for docking. All ligand molecules' energies were reduced and transformed into pdbqt format [25].By docking the co-crystallized ligand, which has a binding affinity of -10.7 kcal/mol, docking was confirmed.

Protein Visualization

The docking findings were downloaded in CSV format (comma separated values) for additional screening. The compounds' protein-ligand interactions pass through the ADMET screening. were seen and examined using the Discovery Studio Visualizer v20.1.0 program.

Pharmacokinetics and Drug-likeness

Pharmacokinetic parameters, such as metabolism, excretion, absorption, and distribution, as well as Lipinski rules for drug-likeness, were examined using the SwissADME online server (http://www.swissadme.ch/index.php#).

Analysis of Toxicity

ProTox-ii web online server was used for the prediction of the toxicity of the compounds [26]. Further compounds hepatotoxicity, cytotoxicity and carcinogenicity were evaluated.

Molecular Dynamic Simulation

The MDS complexes were subjected to Eigenvalue and deformability evaluations using the iMODS programme. After the coarse-grained MDS, the goal of these studies was to find any residues that might still be deformed or unstable[27]. The bioactivities of proteins are influenced by their structural dynamics. However, protein flexibility is frequently too difficult to examine in wet laboratory settings, necessitating the employment of in-silico methods.Combining coarse-grained simulation models with the reconstruction of anticipated structures to all-atom representation is an efficient computational method for examining protein flexibility in a biological system. In this experiment, the CABSflex 2.0 server was used to conduct molecular dynamics (MD) simulations of the complex of several ligands, such as Huperzine A, Berberine, and Peprine with acetylcholine esterase.The "browse" option was used to upload the PDB file for the complexes to the server. CABS-flex uses a set of simulation parameters and distance constraints. The root-mean-square fluctuation (RMSF) of the protein structure was used to describe the outcomes of the MD simulations. Using Eq. (1), the root-mean-square-deviation time average, or RMSF, was calculated as follows:

RMSF = √ (\xi-\xi)1

where xi indicates the coordinate particle i and indicates the particle i's ensemble average position.

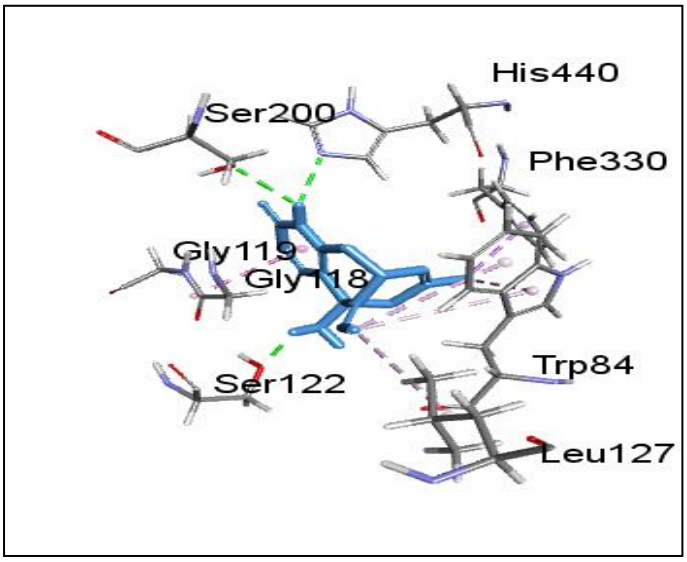
Results and Discussion

Molecular Docking

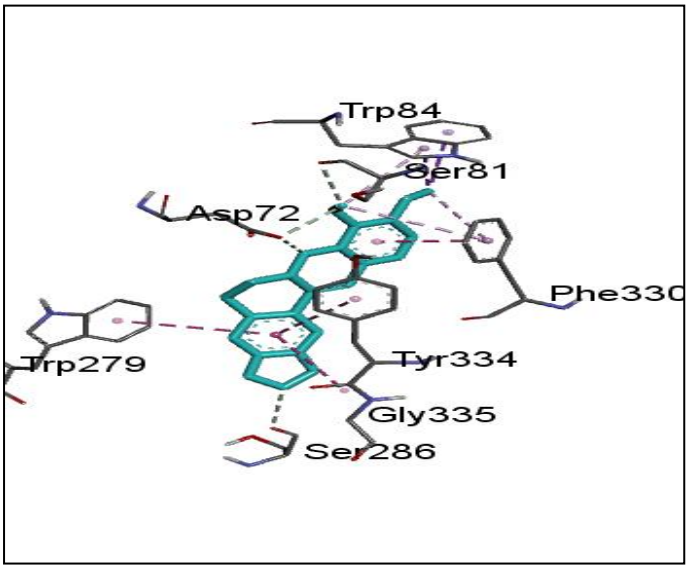
Table 1: PyRx molecular docking analysis of certain alkaloids.

S.No	Compounds	Binding Affinity(kcal/mol)	Bonding Type	Bond Category	Active amino acid residues
1	Berberine	-10.6	Hydrogen bond	Carbon hydrogen	SER A:81, A:286 ASP A:72,
			Hydrophobic	π- π bond	TYR A:334, TRP A:279, PHE A:330
2	caffeine	-6.7	Hydrogen bond	Conventional Hydrogen bond	SER A:12, LYS A:14
				Carbon H.B	GLY A:56
			Hydrophobic	π-Alkyl	PRO A:34

3	Geissospermine	-9.2	Hydrophobic	π-Alkyl	TRP A:233, PHE A:290,288, HIS A:440, TRP A:84
				π- π shaped	PHE A:331
4	Harmine	-8.3	Hydrogen	Conventional H.B	TYR A:121, GLU A:199
				Carbon H.B	TRP A:84,
			Hydrophobic	π- π shaped	PHE A:330
5	Hoperzine A	-9.6	Hydrophobic	π-Alkyl	TRP A:84, PHE A:330, HIS A:440
6	MORPHINE	-8.7	Hydrogen	Carbon H.B	GLU A:199
			Hydrophobic	π- π shaped	PHE A:330, TRP A:279,84
7	Nicotine	-6.9	Hydrogen	Conventional H.B	TYR A:458
			Hydrophobic	π-Alkyl	LEU A:456, 430, TYR A:442, VAL A:431, MET A:83
8	Piperine	-9.6	Hydrogen	Conventional H.B	ASN A:230
				Carbon H.B	CYS A:231
			Hydrophobic	π-Alkyl	PRO A:232,403, VAL A:236
9	salsoline	-7.6	Hydrogen	Conventional	TYR A:121
				Carbon	TYR A:130
			Hydrophobic	π-Alkyl	PHE A:330, TRP A:84
10	Glantamine	-9.3	Hydrogen Bond	Carbon H.B	PHE A:331
				Conventional H.B	TYR A:121, ASP A:72
11	Physostigmine	-8.5	Hydrogen	Carbon H.B	HIS A:440
			Hydrophobic	π- π shaped	TRP A:84 (2), PHE A:330 (2)
				Alkyl	TYR A:121, TRP A:84



A



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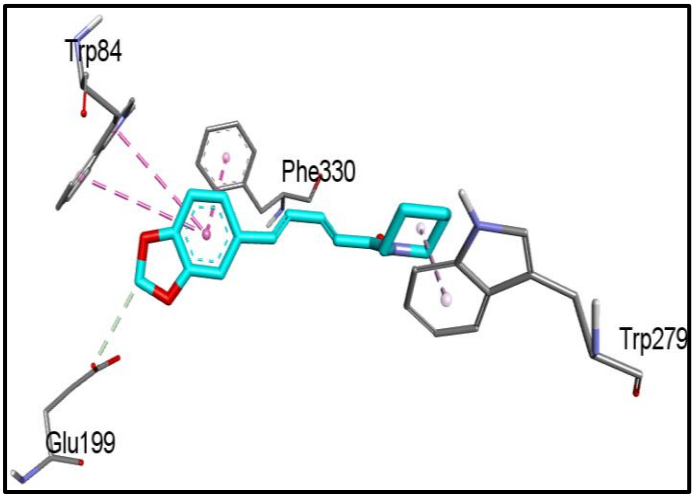
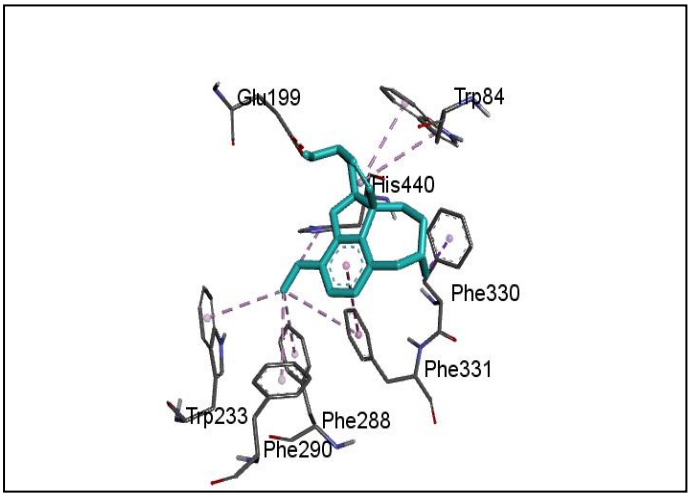


C



D

Figure 1. Protein-ligand interactions,Here**(A)**Huperzine A **(B)**Berberine**(C)**Peprine (**D**)shows interaction with receptor protein i.e., acetylcholine esterase

Human acetyl cholinesterase interacted with the geissoschizoline alkaloid molecule in binding locations, the active site and peripheral anionic site, through Tyr337, Phe295, Phe297, Phe338 and Tyr124, Trp286, Tyr341 amino acid residues respectively [28]. In the study that was presented, it was revealed that the geissospermine alkaloid molecule and acetyl cholinesterase interact through π-alkyl interactions with Trp233, Phe290, Phe288, His440, and Trp84 residues as well as π-π interactions with Phe331 residues. But there is any indication of hydrogen bonding residues. The presented study identified Ser81, Asp72 and Ser286 of berberine interacted with acetyl cholinesterase via hydrogen bonding (Figure1 B). Galantamine and acetyl cholinesterase's interaction resulted in the formation of the hydrogen bonding residues Ser203, Gly122, and Asp74 [17]. The interaction between galantamine and acetyl cholinesterase results in the formation of the hydrogen bonding residues Phe331, Tyr121, and Asp72, as shown in Figure1 D. As there are many π-π interactions between acetyl cholinesterase and the alkaloid compounds i.e.,berberine has Tyr334, Trp279, and Phe330 (Figure.1B), harmine has Phe330, morphine has Phe330, Trp279, and Trp84, and physostigmine has Trp84, Phe330 in existence. There are also found hydrogen bonding residues Tyr121, Glu199, Trp84 (harmine), Glu199 (morphine), His440 (physostigmine), Ser81, Asp72 and Ser286 (berberine) from the interaction among these compounds and acetyl cholinesterase. Ser125, Asp74, Tyr124 residues were found from the interaction among acetyl cholinesterase and indole alkaloid compounds 1 and 2 of Rauvolfiavomitoria through hydrogen bonding [29]. Indole alkaloid geissospermine interacted with acetyl cholinesterase through π-alkyl interaction with Trp233, Phe290, Phe288, His440 residues which shows in Figure 1.Isoquinoline alkaloid compound bind to acetyl cholinesterase through π-π interaction with Trp86, Tyr337, Trp439 and Tyr449 residues [30]. A π-π interactions between the isoquinoline alkaloid compounds berberine and morphine's Tyr334, Trp279, Phe330, and Phe330, Trp279, Trp84 residues with acetyl cholinesterase are shown in Figure 1. There are also found hydrogen boding residues Ser81, Asp72, Ser286, Tyr121, Tyr130 and Glu199 with berberine, salsoline and morphine of isoquinol alkaloid compounds and acetyl cholinesterase are shown in Figure 1. The interactions between caffeine and piperine, two alkaloid compounds, and acetyl cholinesterase were used to identify Ser12, Lys14, Gly56, and Cys231, Asn230 hydrogen bonding residues. These interactions are shown in Figure 1 and Table 1. The alkaloid compounds huperzine A, nicotine, physostigmine and piperine interacted with acetyl cholinesterase through π-alkyl interactions Trp84, Phe330, His440, Leu456,430, Tyr442, Val431, Met83, Tyr121, Trp84 and Pro232,403, Val236 respectively (Table 1). These compounds also revealed hydrogen bonding at Tyr458 (nicotine), His440 (physostigmine) and Cys231, Asn230 (piperine) with acetyl cholinesterase.

Drug-likeness and ADME Analysis

Table 2: list of specific ligands' pharmacokinetic and drug-like characteristics.

	PROPERTIES							Lipophilicity	Water Solubility	Pharmacokinetics	Drug-likeness	BBP Permeable
COMPOUNDS	MW(g/mol)	H.B Donar	H.B Acceptor	MR	Ar.heavy atom	Rotatable Bond	TPSA	LogP(SILICOS-IT)	LogS(SILICOS-IT)	GI Absorption	Lipinski	Yes
Berberine	336.36	0	4	94.87	16	2	40.8	3.74	-5.92	High	0	No
Caffine	194.19	0	3	52.04	9	0	61.82	-0.5	-0.67	High	0	Yes
Geissosp	632.83	1	5	196	15	5	61.	4.96	-7.93	High	2	Yes

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Harmine	212.25	1	2	65.06	13	1	37.91	3.49	-5.11	High	0	Yes
Hoperzine A	242.32	2	2	72.87	6	0	58.88	3.05	-3.83	High	0	Yes
MORPHINE	285.34	2	4	82.27	6	0	52.93	1.34	-2.07	High	0	Yes
Nicotine	162.23	0	2	53.13	6	1	16.13	1.89	-2.62	High	0	Yes
Piperine	285.34	0	3	85.47	6	4	38.77	3.41	-3	High	0	Yes
Salsoline	193.24	2	3	59.11	6	1	41.49	1.94	-2.99	High	0	Yes
Physostigmine	275.35	1	3	84.93	6	3	44.81	0.93	-3.22	High	0	Yes
Galantmine	287.35	1	4	84.05	6	1	41.93	2.03	-2.96	High	0	Yes

H.B* Hydrogen Bond, MR* Molar Refractivity, AR* Aromatic, TPSA* Topological Polar Surface Area, GI* Gestrointestinal `

Since the majority of medications fail clinical trials, ADME (absorption, distribution, metabolism, and excretion) features should be taken into account while creating new medications. One of the greatest tools and a crucial step in the drug design process is ADME analysis [31]. The ADME characteristics and drug-likeness of certain alkaloids docked against Alzheimer disease are displayed in Table 2. MR ≤ (40-130), logP ≤5, number of hydrogen bond donors ≤ 5, and molecular weight ≤500 Dalton are all required per Lipinski requirements. According to veber's rule, TPSA should be ≤ 140Å for best oral drug bioavailability[32]. In our studied candidates only Geissospermine shows two violations i.e. molecular weight and which is 632.83 and molar refractivity which is 196.22. All the studied alkaloids show drug-likeness and follow all five rules of Lipinski. All selected alkaloids show high gastrointestinal absorption and blood-brain barrier penetration (BBP) except berberine whose absorption is high but cannot penetrate blood-brain barrier. The solubility logS show that Berberine and Harmine are moderately soluble; Geissospermine is poorly soluble while all others are soluble.

Toxicity

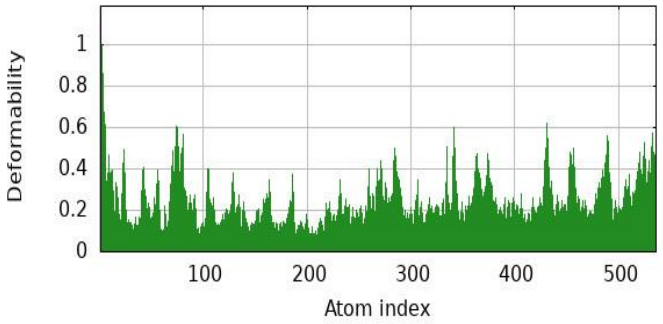
Table 3: All eleven chemicals' toxicity test results utilizing the ProTox-ii web server are listed.

Compounds	**Hepatotoxicity**	**Carcinogenicity**	**Cytotoxicity**
Berberine	Inactive	Active	Active
Caffine	Inactive	Inactive	Inactive
Geissospermine	Inactive	Inactive	Active
Harmine	Inactive	Inactive	Inactive
Huperzine A	Inactive	Inactive	Inactive
Morphine	Inactive	Inactive	Inactive
Nicotine	Inactive	Inactive	Inactive

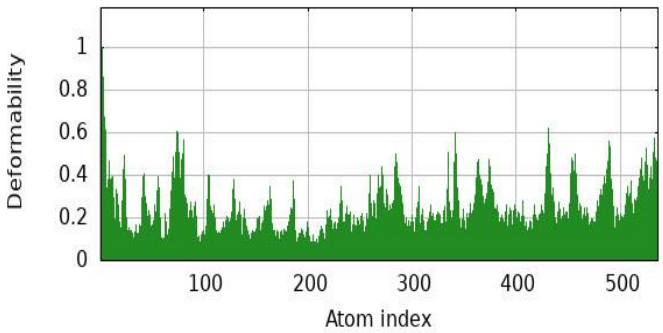
Piperine	Inactive	Active	Inactive
Salsoline	Inactive	Inactive	Inactive
Physostigmine	Inactive	Inactive	Inactive
Galantmine	Inactive	Inactive	Active

The results of toxicity (Table 3**)** shows that ligandscaffine, harmine, huperzine A, morphine, nicotine and salsoline and drug compound i.e. physostigmine are non-toxic while other compounds show some of the toxicity. The results show that berberine is carcinogenic and cytotoxic while Geissospermine and drug compound i.e. galantmineare cytotoxic and piperine is carcinogenic.

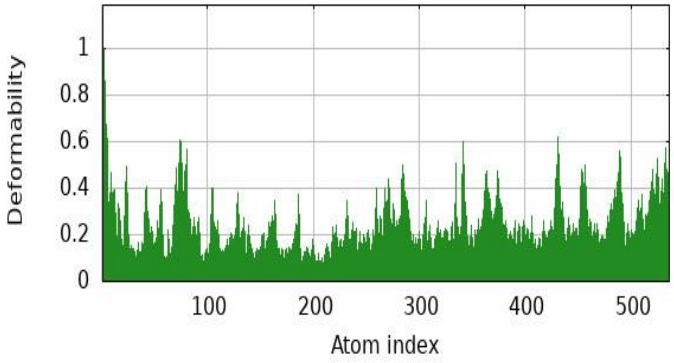
Molecular Dynamic Simulation



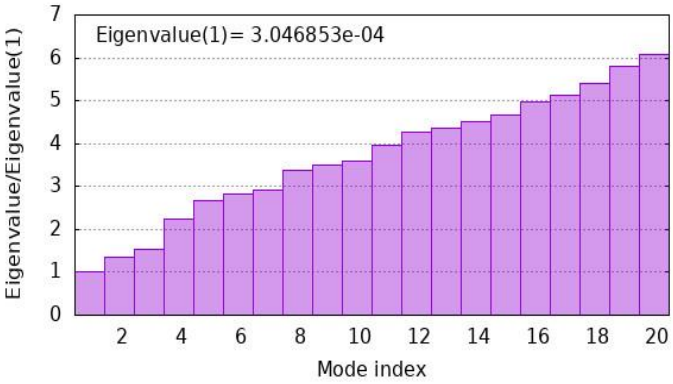
A Berberine



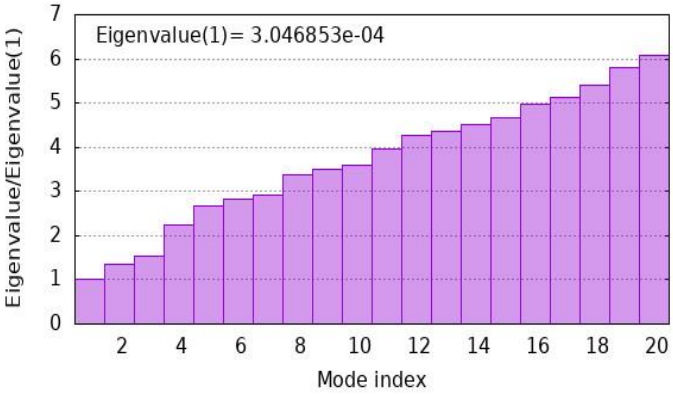
B Peprine



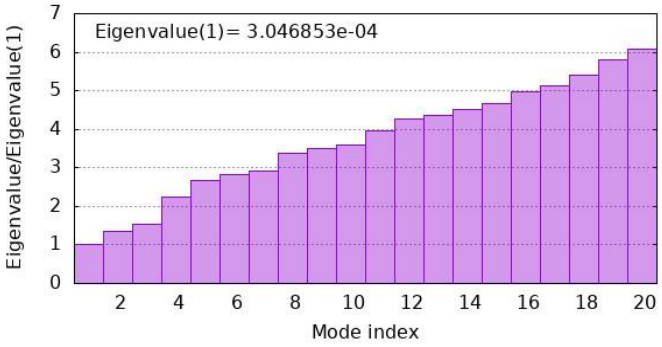
C Huperzine A



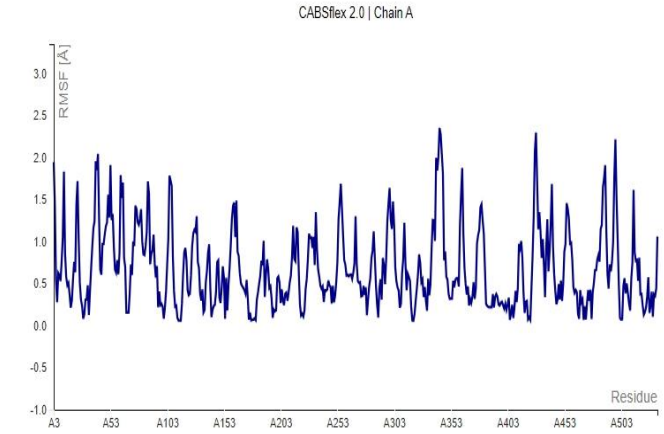
D Berberine



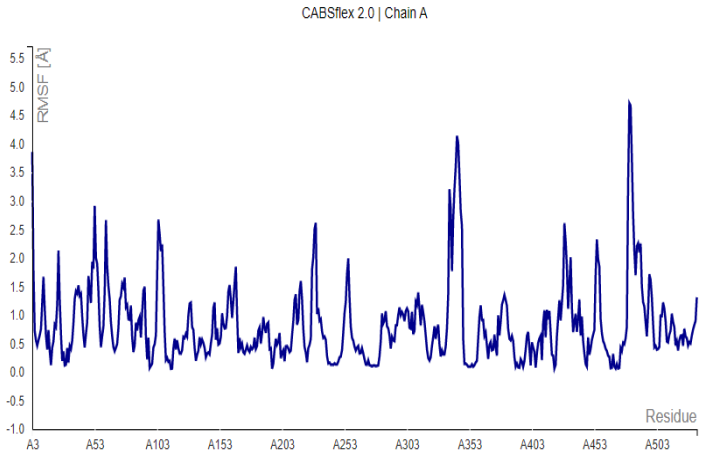
E Peprine



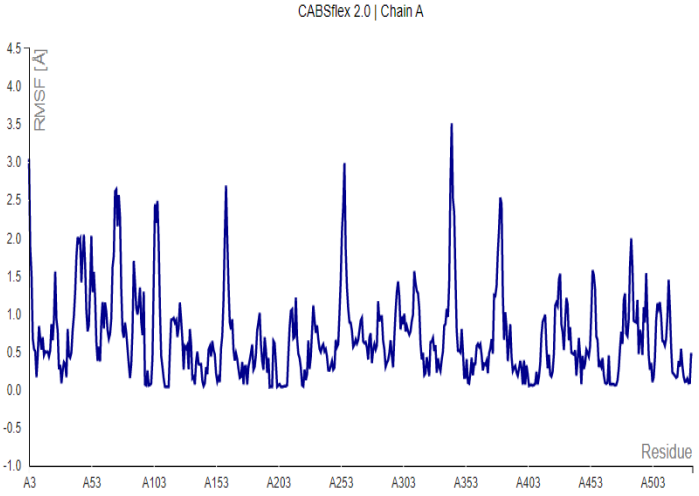
F Huperzine A



G Peprine



H Berberine



I Huperzine A

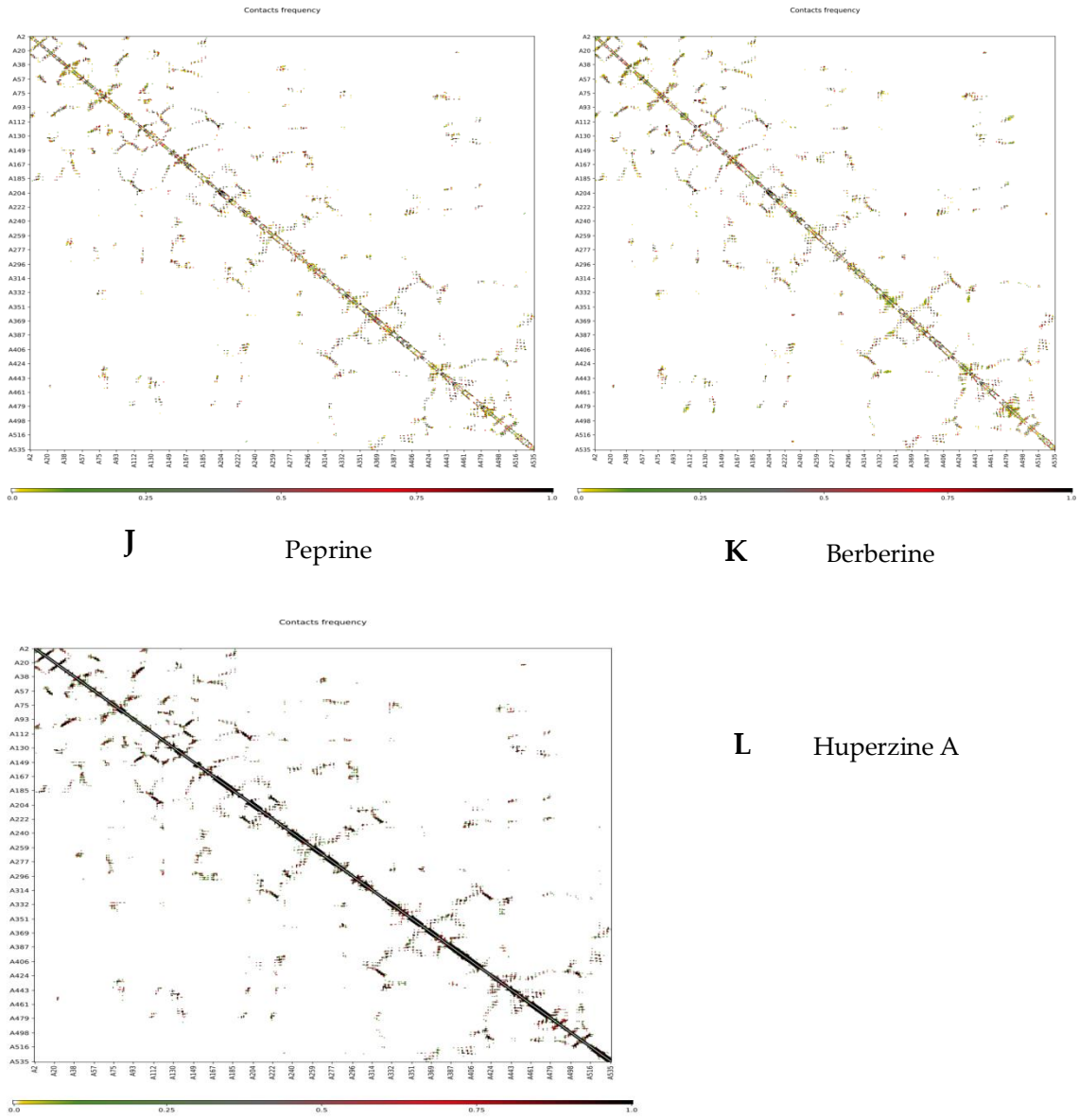


Figure 2: The MD simulation-modeled structural complex is displayed in (A–C). The deformability of the proteins with various natural substances that are used as a treatment for Acetyl Choline Esterase shows that residues interact with one another through deformation. The complexes' Eigenvalue (1) is represented as (D–F); in NMA, eigenvalues are linked to the energy of vibrational modes and deformation rather than a molecule's stiffness or hardness. The peptide-ligand complex's RMSF graph is shown by (G–I) (Peprine, Berberine, Huperzine A). The dot map, shown by (J–L), shows a significant residue-residue interaction between the target residues of acetylcholine esterase.

iMODs is a versatile toolkit for analyzing the atomic structures of peptides and natural compounds using Normal Mode Analysis (NMA) in internal coordinates (IC). The iMODs server is used to determine the type of contact and spacing between the interacting residues in (C). This makes vibrational analysis, motion animations, and simulations at different resolution levels easier, as seen in Fig. 2(A–F). Figure 2(G–I) shows the simulation's fluctuation plot (RMSF), and Figure 2(J–L) shows the residue contact map.

Using iMODserevr, an in silico study shows how three protein/compound complexes become stiff due to interactions between the ligand complex and the protein's highlight side chain residue. The hinges region in Figure 2a-c, which displays the deformability study of three compound-protein complexes, indicates that each complex has the same minimal distortion. Proteins with different natural compound therapies against acetylcholine esterase showed improved deformability in the chain of high hinge position areas. Additionally, a medium eigenvalue of 3.046853e-04 was ob-

served, indicating the complexes' stability and the energy needed to distort them.The more complex aspects of molecular stiffness, such the bond strength and structural characteristics seen in figure 2 D-F, are influenced by a variety of factors.

Plotting the MD research results against the Acetyl Choline Esterase protein residues revealed that most of the target macromolecule's active residues changed continuously at less than 3Å. This implies that the protein's structure is stable and doesn't substantially change from what it was before. The protein–ligand complex was subjected to MD simulation analysis utilizing a fluctuation plot (RMSF) in order to ascertain the stability of the interaction between the ligands Huperzine A, Piperine, and Berberine and the target protein Acetyl Choline Esterase.

The "contact map" in the image also provides a thorough perspective of the protein's residue-residue interaction pattern. Each dot on the map represents a pair of interacting residues, and the color of the map represents the frequency of these interactions. On a scale of 1.0, the presence of deep, dark colors signifies that the target residues of Acetyl Choline Esterase have many, strong residue interactions. Take a look at Figure 2 J-L.

Galantamine is a cholinesterase inhibitor that works in two different ways. By enhancing the intrinsic effects of acetylcholine on nicotinic receptors, this reversible acetylcholine esterase inhibitor raises cholinergic neurotransmission in the central nervous system (CNS) [33].As long as no new pharmaceutical treatments with comparable or superior clinical performance are developed, galantamine will remain one of the preferred first-line treatments for mild-to-moderate AD [34].

The trials suggest that long-term physostigmine treatment for Alzheimer's disease may be more advantageous than short-term treatment. This benefit may persist for up to a year in certain individuals [35].Morphine is essential in the treatment of AD because it binds to MOR in the central nervous system, which increases GABA levels in brain synapses and guards against oxidative stress-mediated neurotoxicity. Morphine protects against intracellular A (iAβ) venomousness in human and rat primary neuronal cells. It can reverse the electrophysiological alterations brought on by iAβ, including variations in capacitance and resting membrane potential. The injection of morphine reduced the Aβ-tempted neurotoxicity by activating MOR. According to a study, C57BL/6 mice whose spatial cognition had been adversely impacted by an intraperitoneal injection of scopolamine (1 mg/kg) may benefit greatly by taking harmine (20 mg/kg) orally for two weeks. Continuous administration of harmin (20 mg/kg) for 10 weeks also slightly improved the APP/PS1 mice's impaired memory. Furthermore, harmine may penetrate the blood-brain barrier, reach the brain parenchyma, and affect the expression of Egr-1, c-Jun, and c-Fos shortly after oral treatment [36] Harmine interacts to bind in the AChE active site, according to a molecular docking research. Thus, harmine is one of the finest alkaloids to inhibit AChE and fight Alzheimer's disease, according to a combined study that included both in vitro and in vivo testing. AChE and BuChE inhibitors have been shown to be useful in treating AD. Three species of salsola have been identified for the first time as AChE and BuChE inhibitors. Salsoline stands out for having a particular effect on BuChE, which is why it focuses on a novel approach to treating AD. Therefore, more work in this area is required [37].

In China, it has been widely used from ancient times to treat edoema, strains, contusions, and schizophrenia. Because HupA is selective, reversible, and well-tolerated, it inhibits AChE more effectively in vivo than galanthamine, donepezil, and rivastigmine. Accordingly, HupA was found to raise rat cortical acetylcholine levels more slowly than donepezil, rivastigmine, tacrine, and physostigmine. Additionally, it is being studied to treat age-related memory decline in clinical settings in the United States. Along with its well-established benefits for cholinergic function, the natural herb HuPA also has other neuroprotective qualities, such as regulating APP metabolism, lowering oxidative stress, apoptosis, and mitochondrial failure caused by Aβ, and preventing inflammation. Research on HupA may provide useful clues for developing more thorough and successful treatment strategies for AD and VaD[38].

Conclusion

The purpose of the study was to compare alkaloids' ability to inhibit acetylcholine esterase (AchE) to those of established medications used to treat Alzheimer's disease. Alkaloids are useful in the treatment of a variety of illnesses in-

cluding According to the current study's computational results, huperzine A, berberine, and piperine may function as therapeutic candidates because they meet all five of Lipinski's criteria, including having high binding affinities and an average RMSF value of 3Å or less, which denotes complex stability. Additional validation is sought through in vitro and in vivo investigations. Further results at preclinical settings are required to obtain more encouraging outcomes.

Conflicts of Interest

The authors declare no conflict of interest

Disclosure of Conflicting Interests

We have read and comprehended the declaration of interests policy, and we do not have any pertinent interests to disclose.

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