International Journal of Botany Studies
www.botanyjournals.com
ISSN: 2455-541X
Received: 30-10-2021, Accepted: 16-11-2021, Published: 01-12-2021
Volume 6, Issue 6, 2021, Page No. 603-615

Molecular docking with different phytochemicals from the *Spatholobus genus* plant as medications against acetylcholinesterase enzyme that induces Alzheimer's disease in human

Diptendu Sarkar
Assistant Professor, Department of Microbiology, Ramakrishna Mission Vidyamandira, Belur Math, Howrah, West Bengal, India

Abstract
Alzheimer's disease is a catastrophic form of cognition that impairs a patient's capacity to think critically and hold a conversation. This is also termed as senile dementia, and is the most neurodegenerative disease. It mostly affects persons over the age of 65 year, however there have been found middle age people (age within 30-60 year) also experienced Alzheimer's complication. Medicinal herbs have been demonstrated to be important in improving the functionality of nervous system in a number of scientific studies. Phytochemicals from the *Spatholobus genus* plant were tested as folk remedies to the acetylcholinesterase enzyme (1ACJ) which triggers Alzheimer's disease in this study. We discovered that Medicarpin (interaction energy -9.9 Kcal/mol) is the best of the four molecules examined from *S. suberectus* for interacting with protein 1ACJ. We reported that Prestegane B has a higher binding potential to the target protein 1ACJ, i.e., -10.2 Kcal/mol with two hydrogen bonds in contact, than the other five molecules studied from *S. sinensis*. In this investigation, 12 phytocompounds from *S. suberectus* were examined. Maackiain had the strongest affinity with the target protein 1ACJ, with a -10.3 Kcal/mol. When compared to the experimental medications Donepezil and Tacrine, all of these compounds had a higher binding affinity. In furthermore, in silico drug likeness and ADMET analyses of the phytochemicals demonstrated significant therapeutic advantages. As a conclusion, the present investigation would serve as a springboard for much more exploration to assess the phytocompounds' effectiveness against Alzheimer's disease complications.

Keywords: Alzheimer's disease, senile dementia, medicinal herbs, acetylcholinesterase, drug likeness

Introduction

Alzheimer's disease is a fatal illness that also has a significant impact on a person's thoughts and behaviour. It is also referred as senile dementia which is perhaps the most typical kind of dementia. This disease is found to be a neurodevelopmental disorder that often begins gradually and cause complications [1]. The struggle to recall recent actions and discussions is just one of several markers of Alzheimer's disease. An individual with this disorder would experience serious memory problems as well as lack the power to carry out daily duties as when the disease advances [2]. The body's activities weaken over time, finally leading to fatality. There are no medications that can prevent the disease's advancement, while some can substantially alleviate symptoms. Aerobic exercises could be advantageous in terms of normal tasks but could maybe promote health [3]. Antipsychotics have been prescribed to treat behavioural difficulties or hallucinations caused by dementia, although they are not normally advised but they do provide little improvement but also raise the risk of premature mortality [4]. As per WHO report, globally, there were approximately 30 million people living with Alzheimer's disease in 2015, whereas with a projected 50 million people suffering from dementia by 2020. It mostly affects persons over the age of 65 year, however up to 10 percent of instances there have been found middle age people (age within 30-60 year) also experienced Alzheimer's complication [5]. Alzheimer's illness whose specific causes remain obscure. However, at a fundamental level, many brain proteins start malfunctioning, disrupting the functioning of central nervous system (neurons) thereby triggering a cascade of adverse outcomes. Neurons become injured, weaken their connectivity, and end up dying. Vascular dementia is thought to be caused by an interaction of genetic, behavioural, as well as environmental variables that affects the hippocampus over time across most people, according to researchers [1, 6]. Increased levels of amyloid beta, which forms amyloid plaques in the extracellular space, and tau proteins, which form neurofibrillary tangles in the periplasm, have been supposed to cause Alzheimer's disease by disrupting synaptic transmission and integration, potentially leading to degenerative disease [3, 7]. Acetylcholinesterase is a neurotransmitter-degrading enzyme, belongs to carboxylesterase family, catalyses the hydrolysis of acetylcholine and perhaps other choline esters. This is mostly located at a synapse between a motor neuron and a muscle fibre where its function helps to stop neurotransmission [8]. The use of specific substrates with selective antagonists, as well as kinetic performance, is being used to distinguish between distinct forms of cholinesterase. The vesicular acetylcholine importer, which would be found in the synaptic vesicle surface, synthesizes it in the cytosol of cholinergic neurons and transports it into presynaptic membrane [5, 8]. The depletion of cholinergic neurons as well as the resulting disturbance in dopaminergic signalling has also been proposed as one of the key reasons underpinning Alzheimer's disease related depressive episodes [6]. To treat the memory impairments associated with Alzheimer's disease, four acetylcholinesterase blockers named as tacrine, rivastigmine, galantamine, and donepezil

as well as memantine plus an NMDA receptor blocker, have been utilised. But, their use has only small advantages [9]. Although cholinesterase antagonists are ineffectual in many cases in delaying the progression of Alzheimer's disease [10], alternative drugs that target the cholinergic system may still be discovered.

Herbal remedies being native to India, and Ayurveda has produced different medication mixtures for numerous medical remedies [6]. Medicinal herbs have been demonstrated to be important in improving the functionality of nervous system in a number of scientific studies [11]. Phytochemical study showed the existence of different bioactive chemicals in herbal medicines, including tannins, lignans, polyphenols, flavonoids, sterols, triterpenes, and alkaloids. Many of these molecules have protection power to fight against amyloid formation, inflammation, block cholinesterase enzyme function, reduce cholesterol level in blood as well as antioxidant properties [12]. Because of their fewer side effects when compared to conventional pharmaceuticals and the necessity to meet the therapeutic demands of an ever-increasing population of the world, plant products have recently gained universal acceptance [13]. Spatholobus is a flower producing plant which belongs to legume family. In China, it is used widely for various medication purpose [14]. In the world, there are reported thirty-four species of *Spatholobus genus* [8]. The genus *Spatholobus* covers four species and they are *S. suberectus, S. parviflorus, S. sinensis,* and *S. dunn.* The publications of related to Alzheimer's disease by using biological activity of compounds from *Spatholobus genus* plants are still limited. The initial potential activity study of *Spatholobus genus* compounds is urgently required due to global demand to address senile dementia.

In medicinal chemistry and computer-aided drug creation, computer simulation is indeed a crucial technique [15]. Ligand-protein interaction aids in the prediction of a Ligand's as well as Protein's binding mechanism in specified 3D configurations. In silico approaches seem to be computer-based tools which have been commonly utilised in the domain of pharmacology to assist in the discovery of antagonists [16]. This approach investigates ligands having a high affinity for a protein receptor, as well as their drug-likeness characteristics including absorption, distribution, metabolism, excretion, and toxicity [9]. Blockers of the biological targets that are successful can be used to treat Alzheimer's disease. In this research, phytochemicals from the *Spatholobus genus* plant (total No 21) were screened as medications against the acetylcholinesterase enzyme (1ACJ) that causes Alzheimer's disease. The *in silico* docking approach have been used to accomplish this.

Materials and Methods

The in- silico study was carried out by using CB-Dock tool [17]. Protein preparation was carried out by Auto Dock Tools [18]. Ligand preparation was carried out by Auto Dock Vina. The Swiss ADME server used for drug likeness prediction of all compounds selected for study [13, 18]. Docking complex visualization was done by BIOVIA discovery studio.

Selection of target protein and Preparation of Protein Target Structure

The acetylcholinesterase structure with resolution 2.80 Å, whose PDB ID is 1ACJ and molecular weight is 60.99 kDa was downloaded in protein data bank format from the RCSC PDB and utilised for docking. It seems to have only one 537-amino-acid-residue protein chain (A) (Fig 1). X-RAY diffraction method have been used to determine this structure and maintained in PDB. The input files were prepared with Auto Dock Tools (ADT) 1.5.6. Molecules of water, HET atoms, as well as ions have all been completely removed. The polar hydrogen atoms have been given Kollman charges.

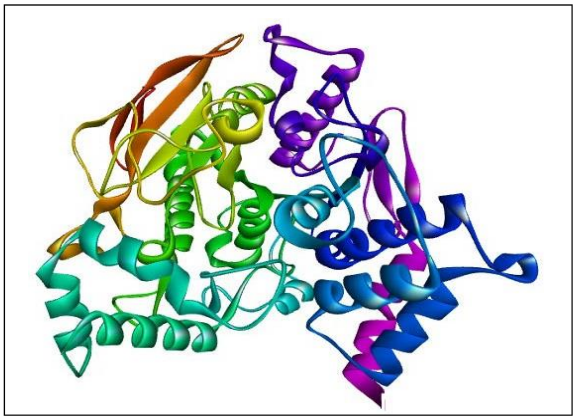


Fig 1: 3D picture of acetylcholinesterase targeting protein (PDB ID: 1ACJ)

Selection and Preparation of ligand molecules

Based on previous reports, 21 compounds of *Spatholobus genus* plant had been identified and used for docking study (Table 1). PubChem was used to determine the 3D structures of all the comounds. All Ligands being uploaded (mol2 format) in to the Auto Dock Tools, and the 'Ligand' option has been used to rectify the torsion tree, non-polar hydrogens, charges, and atom type. With all the structure further ADME prediction were carried out by using SWISS ADME to filter all bio active compounds based on Lipinski rule of five [19].

Table 1: Ligand selected from *Spatholobus genus* plant and reference drugs for the study

Sl No	Compound Name	PubChem ID	Molecular Formula	Plant species
1	Medicarpin	336327	$C_{16}H_{14}O_4$	*S. parviflorus*
2	Biochanin A	5280373	$C_{16}H_{12}O_5$	
3	8-O-methylretusin	5319771	$C_{17}H_{14}O_5$	
4	Trans-4-Hydroxymellein	10262028	$C_{10}H_{10}O_4$	
5	Benzeneethanol	6054	$C_8H_{10}O$	*S. sinensis*
6	Liquiritigenin	114829	$C_{15}H_{12}O_4$	
7	Prestegane B	146425	$C_{20}H_{22}O_6$	
8	Medioresinol	181681	$C21_1H_{24}O_7$	
9	Vomifoliol	5280462	$C_{13}H_{20}O_3$	
10	Naringenin	932	$C_{15}H_{12}O_5$	*S. suberectus*
11	Protocatechuic acid ethyl ester	77547	$C_9H_{10}O_4$	

12	Maackiain	91510	$C_{16}H_{12}O_5$	
13	Medicarpin	336327	$C_{16}H_{14}O_4$	
14	Sativan	596401	$C_{17}H_{18}O_4$	
15	Isoliquiritigenin	638278	$C_{15}H_{12}O_4$	
16	Genistin	5281377	$C_{21}H_{20}O_{10}$	
17	Coumestrol	5281707	$C_{15}H_8O_5$	
18	Pseudobaptigenin	5281805	$C_{16}H_{10}O_5$	
19	Lupinalbin A	5324349	$C_{15}H_8O_6$	
20	Leonuriside A	14237625	$C_{14}H_{20}O_9$	
21	Trigraecum	14376438	$C_{16}H_{12}O_4$	
22	Donepezil	3152	$C_{24}H_{29}NO_3$	Drug molecule
23	Tacrine	1935	$C_{13}H_{14}N_2$	

Molecular Docking investigation

Molecular docking analysis performed with target like acetylcholinesterase enzyme by using CB-Dock tool [12]. Here first we uploaded prepared protein structure as macromolecule and then prepared ligand. Following uploading the relevant files, a perl script would help to process them. CB-Dock seems to be a protein-ligand docking approach that automatically detects binding sites, estimates centre as well as size, customises docking box size based on query ligands, and thereafter performs molecular docking utilizing Auto Dock Vina [13, 18]. It can speed up the docking process and enhance accuracy by anticipating target binding affinity locations utilizing a curvature-based cavity identification technique then query ligand binding poses employing Auto Dock Vina. Finally started blind docking after covering entire protein structure under grid box to screen best fitted bioactive compounds based on energy value. Each simulation was conducted roughly ten times, resulting in ten docked conformations. The bound poses typically reranked based on the docking score when the docking process is completed. The very first conformation would be the optimum binding pose, and indeed the matching location would be the query ligand's ideal binding site. Employing Discovery Studio software, the intra - molecular interactions such as hydrogen bonds, van der Waals, and hydrophobic interactions with that specific bioactive compounds have been clearly analysed.

Results and Discussion

Alzheimer's disease is an illness that affects cognitive impairment and other mental capabilities to drop substantially. Regardless of the fact that this disease is a major health concern, there is no proven therapy option for its treatment or prophylaxis [19]. The structural alterations in neurons caused by the various risk factors are thought to affect the cholinergic neurotransmitter network and, as a result, the perceptual functions that the prevalent neurotransmitter acetylcholine supports. As a result, current anti-medications Alzheimer's focus mainly on the cholinergic depletion [20]. In the present research, we employed a molecular docking approach to examine physiologically active compounds discovered from Spatholobus genus plant as medications against the acetylcholinesterase enzyme (1ACJ) that causes Alzheimer's disease. All total 21 phytocompounds were selected for screening and docking study. Table 1 listed the all 21 phytochemical compounds used during the *in-silico* study. Each of the substances was used to investigate the drugs' fundamental origins using the SWISS ADME once they were developed. Table 2 illustrate the fitness of the Lipinski 'Rule of Five of all 21 phytocompounds.

Table 2: Lipinski rule related information of selected phytocompounds studied along with reference drug molecule Donepezil and Tacrine. Given emphasis on molecular weight, number of hydrogen bond donor as well as acceptor, along with Log $P_{o/w}$ and Log S value of the phytocompounds.

Sl No	Compound Name	Molecular Weight (g/mol)	No. of H bond donor	No. of H bond acceptor	Log $P_{o/w}$	Log S	Lipinski Rule violation
1	Medicarpin	270.28	1	4	2.53	-3.64	0
2	Biochanin A	284.26	2	5	2.44	-3.92	0
3	8-O-methylretusin	298.29	1	5	2.67	-3.77	0
4	Trans-4-Hydroxymellein	194.18	2	4	1.08	-2.20	0
5	Benzeneethanol	122.16	1	1	1.64	-1.82	0
6	Liquiritigenin	256.25	2	4	2.07	-3.28	0
7	Prestegane B	358.39	2	6	2.77	-4.06	0
8	Medioresinol	388.41	2	7	2.33	-3.65	0
9	Vomifoliol	224.30	2	3	1.57	-1.45	0
10	Naringenin	272.25	3	5	1.84	-3.99	0
11	Protocatechuic acid ethyl ester	182.17	2	4	1.40	-2.27	0
12	Maackiain	284.26	1	5	2.36	-3.67	0
13	Medicarpin	270.28	1	4	2.53	-3.64	0
14	Sativan	286.32	1	4	2.99	-3.94	0
15	Isoliquiritigenin	256.25	3	4	2.37	-3.70	0
16	Genistin	432.38	6	10	0.42	-3.18	1
17	Coumestrol	268.22	2	5	2.46	-3.87	0
18	Pseudobaptigenin	282.25	1	5	2.51	-3.75	0
19	Lupinalbin A	284.22	3	6	2.20	-4.20	0
20	Leonuriside A	332.30	5	9	-0.79	-1.20	0
21	Trigraecum	268.26	1	4	2.87	-4.22	0

22	Donepezil	379.50	0	4	4.00	-4.81	0
23	Tacrine	198.26	1	1	2.59	-3.27	0

Molecular docking is a type of systems biology research wherein two substances combine to generate a stable compound. The docking experiment's output could be used to assess binding affinity, free energy, and complex stabilization [21]. The most popular and highly utilised methodologies for assessing the connection between ligand-protein structures at the atoms seem to be molecular docking with molecular dynamics modelling [13]. Breakthrough antagonists targeting disease-causing molecular targets can always be created utilising such strategies [18]. Because it is done before the laboratory component of any research, computer simulation can illustrate the viability of whatever catalytic process. We evaluated the 1ACJ protein antagonistic capability of 21 phytocompounds which have already been indicated to still have anti-cancerous function [9, 22]. by numerous studies in this paper. The compounds from S. *suberectus* are Medicarpin, Biochanin A, 8-O-methylretusin and Trans-4-Hydroxymellein used in this study (Table 1). Benzeneethanol, Liquiritigenin, Prestegane B, Medioresinol and Vomifoliol from *S. sinensis* are used here (Table 1). From *S. suberectus*, we used total 12 molecules and they are Naringenin, Protocatechuic acid, Ethyl ester, Maackiain, Medicarpin, Sativan, Isoliquiritigenin, Genistin, Coumestrol, Pseudobaptigenin, Lupinalbin A, Leonuriside A and Trigraecum (Table 1).

Among the four molecule tested from S. *suberectus*, we found that Medicarpin is the best one (Interaction energy -9.9 Kcal/mol) to interact with protein 1ACJ. It predicted during interaction 2 hydrogen bond with target protein (Table 3, Fig 2). In human leukaemia cell lines, Medicarpin enhance bone regeneration, osteoclastogenesis disease, as well as anti-cancer action [23]. The second highest interacting molecule was Biochanin A which is a isoflavone. This also has cancer preventive with neuroprotective function [24]. Its potential binding energy was found -8.7 Kcal/mol and during interaction exhibited 4 hydrogen bonds (Table 3, Fig 3). We found -8.5 Kcal/mol binding energy both for 8-O-methylretusin which is a flavonoid with antioxidant property [11] and volatile compound Trans-4-Hydroxymellein (Table 3, Fig 4 and 5). They also provided same number of hydrogen bond i.e., 3 during interaction with target protein 1ACJ. In comparison to reference two drugs used here i.e., Donepezil and Tacrine, all the four phytocompounds found to have better binding potential towards the target 1ACJ protein. Donepezil showed -8.4 Kcal/mol binding potential energy along with 3 hydrogen bonds during interaction (Table 6, Fig 23) whereas Tacrine produced – 9.4 Kcal/mol interaction energy along with 1 hydrogen bond during interaction with 1ACJ protein molecule (Table 3, Fig 24). Therefore, we can assume here tested all four molecules from S. *suberectus* could be used as one of the potent herbal drug components to treat the Alzheimer's disease.

Table 3: Phytochemical compounds from *S. suberectus* used for molecular docking

Sl No	Compound	Interaction energy (Kcal/mol)	Interacting residues	No of H Bonds in interaction	Fig No
1	Medicarpin	-9.9	Leu 146, Ser 145, Tyr 116, Tyr 130, Phe 448, Phe 197, Ile 444, Glu 199, Gln 225, Gly 198, Leu 143, Ile 115, Val 144, Val 113	2	2
2	Biochanin A	-8.7	Phe 330, Phe 339, Asp 392, Val 395, Ile 287, Leu 391, Ala 336, Leu 333, Gly 335, Phe 331, Ser 329, Tyr 334, Gly 328, Phe 330	4	3
3	8-O-methylretusin	-8.5	Asp 392, Asp 393, Val 395, Asn 99, Cys 402, Val 400, Asp 397, Ile 401, His 398, Glu 327, Gly 328, Ile 394	3	4
4	Trans-4-Hydroxymellein	-8.5	Phe 331, Phe 330, Gln 74, Asp 72, Trp 432, Ser 81, Phe 75, Leu 333, Ala 336, Leu 332	3	5

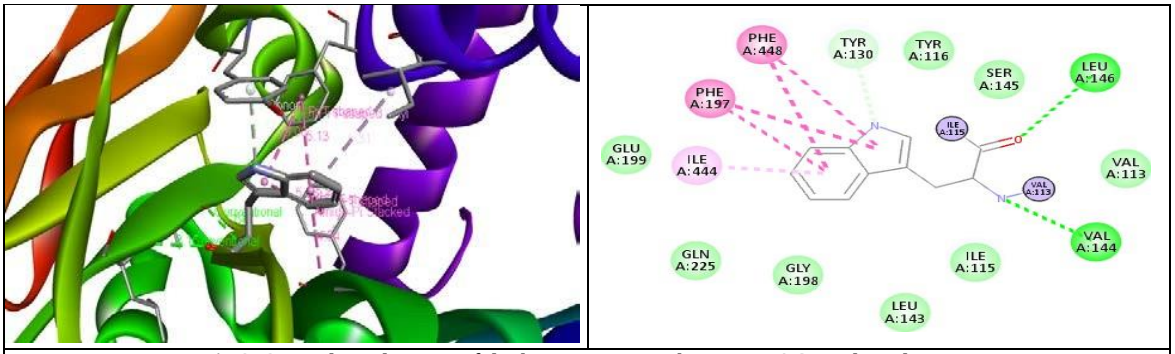


Fig 2: 3D and 2D diagram of docking interaction between 1ACJ and Medicarpin

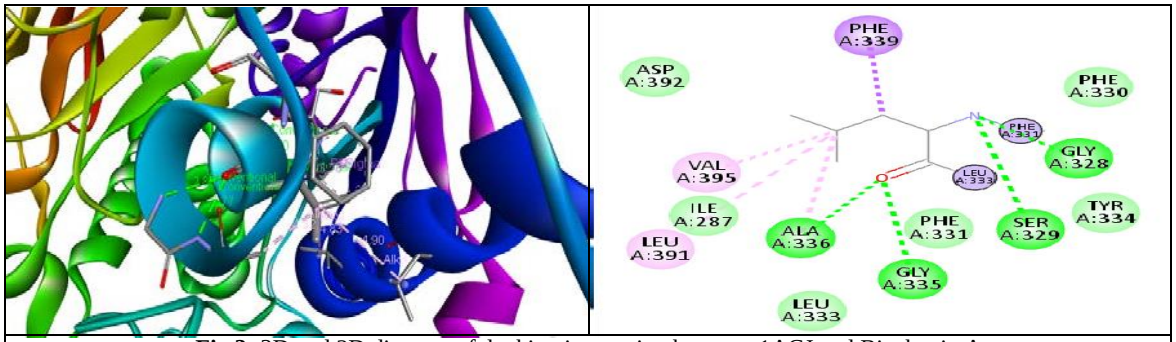


Fig 3: 3D and 2D diagram of docking interaction between 1ACJ and Biochanin A

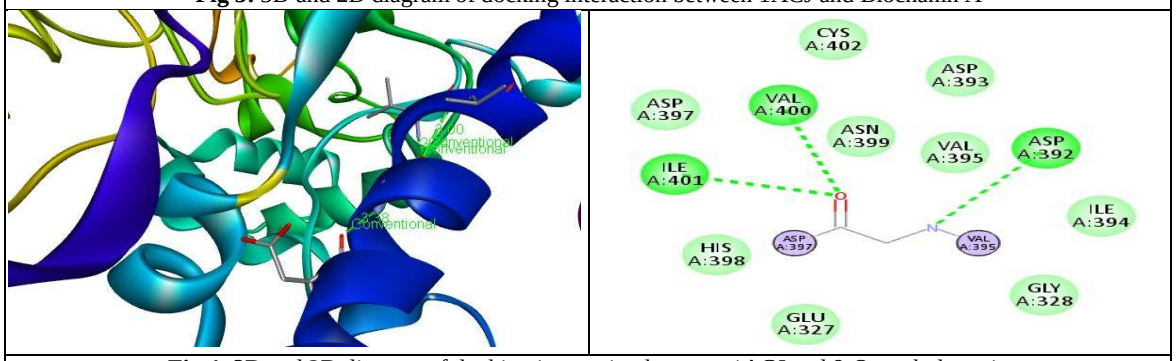


Fig 4: 3D and 2D diagram of docking interaction between 1ACJ and 8-O-methylretusin

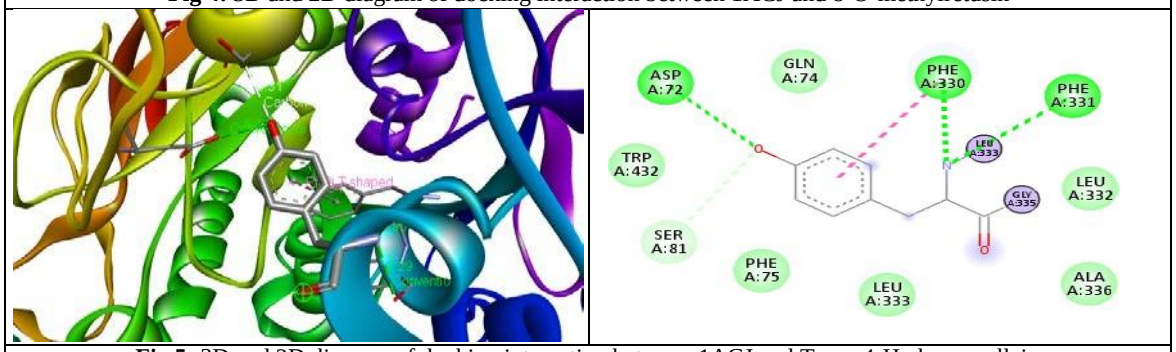


Fig 5: 3D and 2D diagram of docking interaction between 1ACJ and Trans-4-Hydroxymellein

Among the five molecule tested from *S. sinensis* we found that Prestegane B has greater binding potential toward target protein 1ACJ i.e., -10.2 Kcal/mol along with 2 hydrogen bond in interaction (Table 4, Fig 8). This Molecule also exhibited better binding energy in compares to both reference drugs - Donepezil (-8.4 Kcal/mol) (Table 6, Fig 23) and Tacrine (-9.4 Kcal/mol) (Table 6, Fig 24). Prestegane B found to have diuretic with natriuretic activity in mammalian system [20]. Also reported that this molecule has both antioxidant as well as anti-bacterial activities [25]. Other molecule named Liquiritigenin which is a flavonoid exhibited second highest binding potentiality (-9.4 Kcal/mol) with 1ACJ and showed only 1 hydrogen bond in this interaction (Table 4, Fig 7). This molecule used against menopausal hot flashes by some researcher and it has antioxidant potentiality [7, 19].

We found this phytomolecule has exact similar binding potential like Tacrine but lower than Donepezil. Rest of the molecules named as Benzeneethanol, Medioresinol and Vomifoliol from *S. sinensis* found to have -6.7 Kcal/mol (Table 4, Fig 6), -6.9 Kcal/ mol (Table4, Fig 9) and – 7.4 Kcal/ mol (Table 4, Fig 10) respectively. All these compounds found lesser binding affinity compare to tested drugs Donepezil as well as Tacrine. So, we can assume that among five phytomolecules tested from *S. sinensis*, Liquiritigenin and Prestegane B could be tested in vtrocally further to find more potency to address Alzheimer's disease complication in near future.

Table 4: Phytochemical compounds from *S. sinensis* used for molecular docking

Sl No	Compound	Interaction energy (Kcal/mol)	Interacting residues	No of H Bonds in interaction	Fig No
1	Benzeneethanol	-6.7	Phe 331, Phe 330, Gln 74, Asp 72, Trp 432, Ser 81, Phe 75, Leu 333, Ala 336, Leu 332	3	6
2	Liquiritigenin	-9.4	Phe 331, Phe 330, Phe 339, Trp 435, Lys 341, Ser 340, Phe 75, Trp 432, Tyr 334, Leu 332, Ala 336, Met 436, Gly 335, Ser 329	1	7
3	Prestegane B	-10.2	Trp 114, Ile 196, Ile 115, Phe 197, Val 180, Val 144, Leu 177, Leu 146, Thr 195, Val 194, Val 111	2	8
4	Medioresinol	-6.9	Phe 330, Phe 339, Asp 392, Val 395, Ile 287, Leu 391, Ala 336, Leu 333, Gly 335, Phe 331, Ser 329, Tyr 334, Gly 328	4	9

5	Vomifoliol	-7.4	Gly 355, Met 353, Pro 337, Glu 350, Asp 351, Lys 357, Val 356, Leu 358	4	10

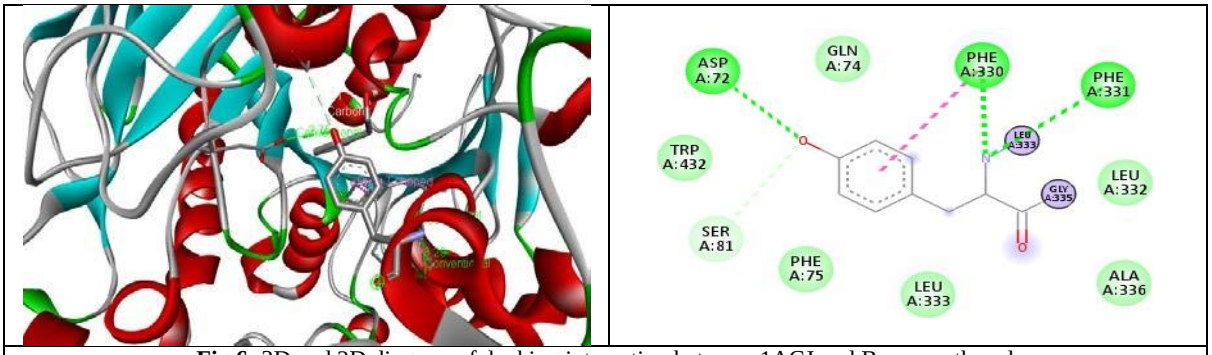


Fig 6: 3D and 2D diagram of docking interaction between 1ACJ and Benzeneethanol

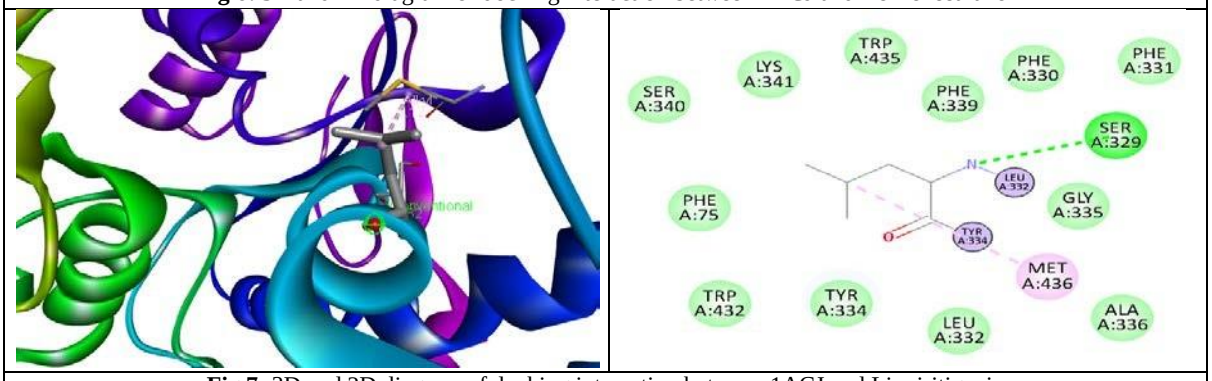


Fig 7: 3D and 2D diagram of docking interaction between 1ACJ and Liquiritigenin

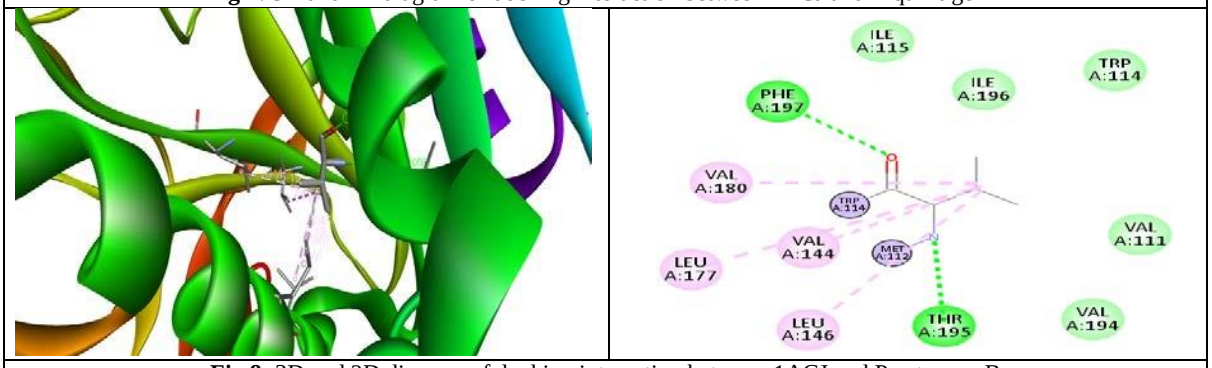


Fig 8: 3D and 2D diagram of docking interaction between 1ACJ and Prestegane B

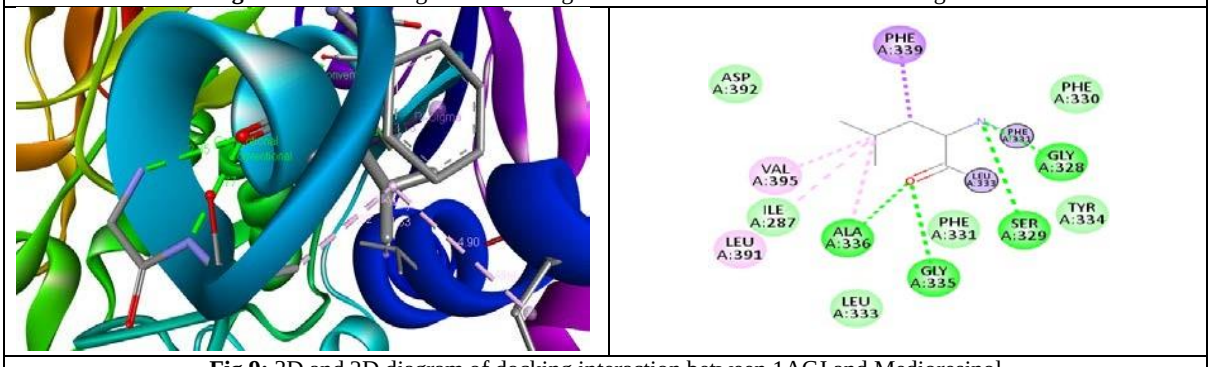


Fig 9: 3D and 2D diagram of docking interaction between 1ACJ and Medioresinol

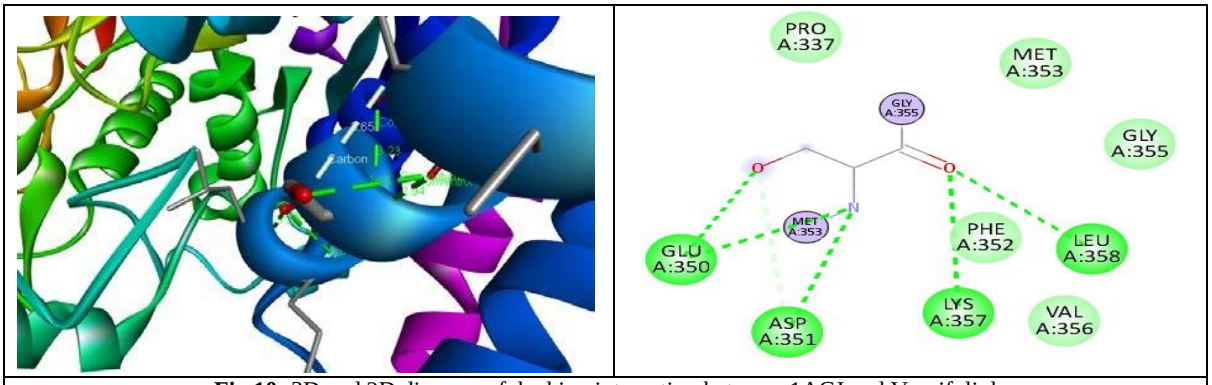


Fig 10: 3D and 2D diagram of docking interaction between 1ACJ and Vomifoliol

There are 12 phytocompounds were tested from *S. suberectus* in our study. Among these, Maackiain showed highest interaction with target protein 1ACJ i.e., -10.3 Kcal/mol (Table 5, Fig 13). This molecule also exhibited better interaction in compare to the reference drugs. Donepezil drug showed -8.4 Kcal/mol binding potential energy (Table 6, Fig 23) whereas Tacrine drug produced –9.4 Kcal/mol interaction energy (Table 3, Fig 24). Maackiain seems to be a revolutionary anti-inflammatory medication that inhibits histamine H1 receptor with interleukin-4 gene upregulation [26]. It also has antiallergic potentiality [19]. In near future this phytocompound can be tested for dementia related problem. Isoliquiritigenin (a chalcone) another compound, showed binding energy towards 1ACJ is -9.8 Kcal/mol (Table 5, Fig 16) which is also better than two tested drugs here. Antioxidant, anti-inflammatory, antimicrobial, hypoglycaemic, anti-epileptic, as well as anticancer properties are all present this chalcone [17]. This can also be used for dementia related problem [27]. Naringenin and Coumestrol two other compounds exhibited same binding energy i.e., -9.7 Kcal/mol (Table 5, Fig 11 and 18 respectively) and this was found again better than tested reference drugs here. Next compound Sativan also produced better binding energy than tested drugs and the energy value is -9.6 Kcal/mol (Table 5, Fig 15). As a psychedelic, analgesic, sedative, painkiller, and anti-inflammatory drug, sativan has been utilised [28]. Rest of the molecule from *S. suberectus* were utilised in this research found to have less interaction potential compare to the refence drugs used here (Table 5, Fig 11 to 22). Therefore, we can assume that Maackiain, Isoliquiritigenin, Naringenin, Coumestrol and Sativan to be tested further animal model to check their further potentiality towards the treatment of Alzheimer's disease.

Table 5: Phytochemical compounds from *S. suberectus* used for molecular docking

Sl No	Compound	Interaction energy (Kcal/mol)	Interacting residues	No of H Bonds in interaction	Fig No
1	Naringenin	-9.7	Ala 336, Gly 335, Pro 337, Asp 285, Pro 361, Ser 286, Lys 357, Ser 359, Ile 287, Val 360, Ser 354, Val 356, Gly 355	3	11
2	Protocatechuic acid ethyl ester	-6.8	Pro 337, Glu 350, Asp 351, Lys 357, Phe 352, Val 356, Leu 358, Gly 355, Met 353	4	12
3	Maackiain	-10.3	he 331, Phe 330, Gln74, Asp 72, Trp 432, Ser 81, Phe 75, Leu 333, Ala 336, Leu 332	3	13
4	Medicarpin	-7.1	eu 146, Phe 35, Val 180, Leu 177, Gln 178, Trp 179, Met 175, Asp 172, Leu 97, Arg 174, Gln 173, Leu 146	3	14
5	Sativan	-9.6	Asp 397, Arg 289, Phe 288, His 398, Cys 231, Pro 232, Trp 233, Pro 403, Val 395, Val 400, Gly 396	4	15
6	Isoliquiritigenin	-9.8	p 114, Ile 196, Ile 115, Phe 197, Val 180, Val 144, Leu 177, Leu 146, Thr 195, Val 194, Val 111	2	16
7	Genistin	-9.2	Leu 333, Ser 329, Gly 328, Phe 290, Phe 330, Glu 327, His 440, Phe 288, Val 395, Ile 287, Tyr 334, Ala 336, Leu 332, Gly 335,	3	17
8	Coumestrol	-9.7	Ala 336, Leu 358, Ile 287, Leu 332, Leu 333, Phe 331, Pro 337	2	18
9	Pseudobaptigenin	-7.5	Phe 331, Phe 330, Gln 74, Asp 72, Trp 432, Ser 81, Phe 75, Leu 333, Ala 336, Leu 332	3	19
10	Lupinalbin A	-6.7	Phe 330, Phe 339, Asp 392, Val 395, Ile 287, Leu 391, Ala 336, Leu 333, Gly 335, Ser 329, Tyr 334, Gly 328	4	20
11	Leonuriside A	-8.2	Phe 331, Phe 330, Gln 74, Asp 72, Trp 432, Ser 81, Phe 75, Leu 333, Ala 336, Leu 332	3	21
12	Trigraecum	-6.7	Arg 221, Lys 478, Thr 110, Thr 195, Val 111, Val 194, Pro 191, Asp 190, Lys 192, Arg 220, Ala 477	2	22

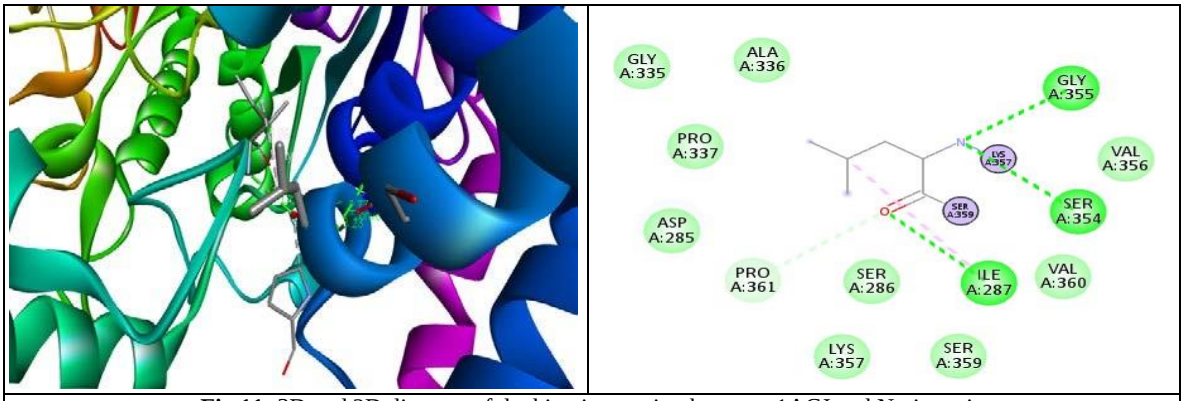


Fig 11: 3D and 2D diagram of docking interaction between 1ACJ and Naringenin

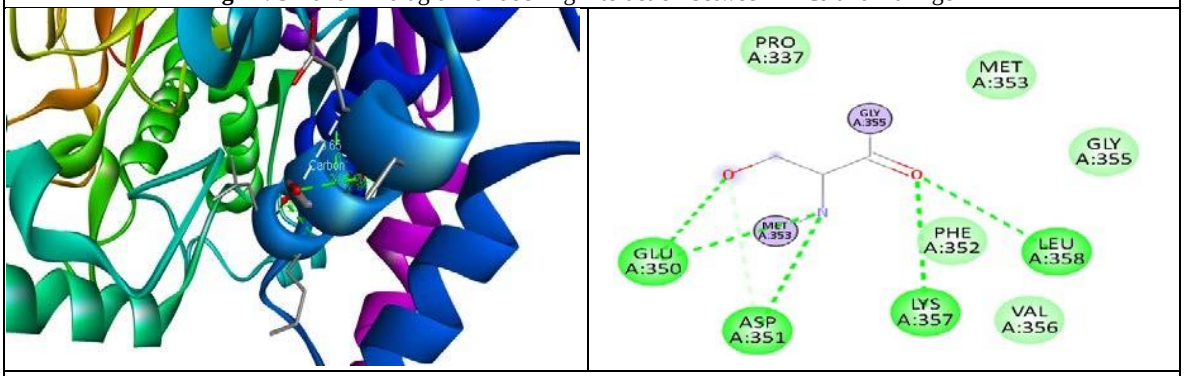


Fig 12: 3D and 2D diagram of docking interaction between 1ACJ and Protocatechuic acid ethyl ester

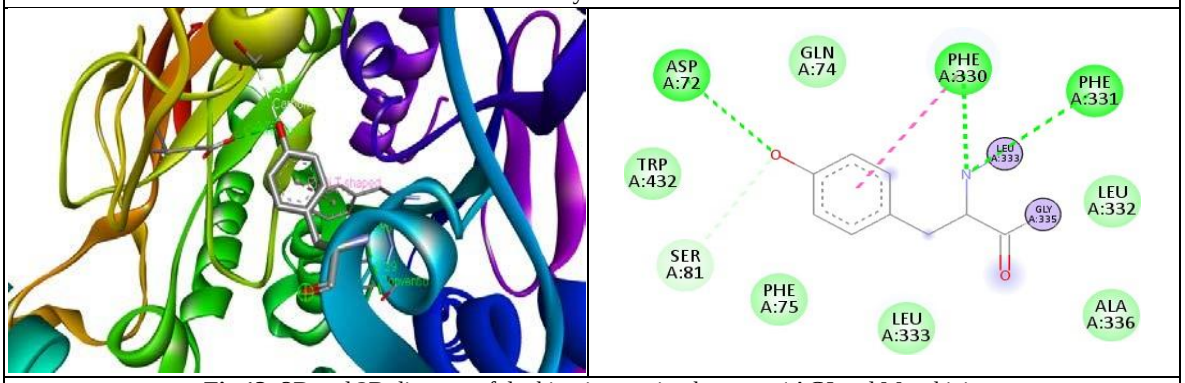


Fig 13: 3D and 2D diagram of docking interaction between 1ACJ and Maackiain

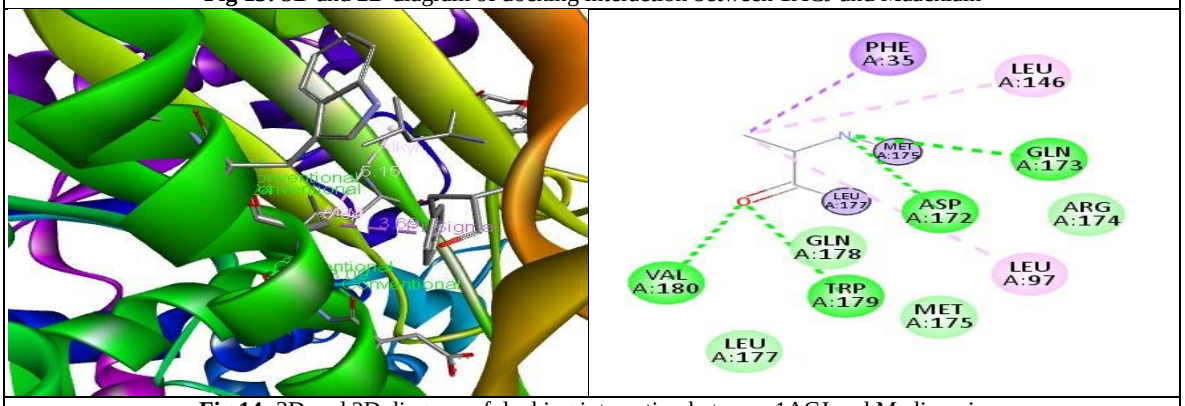


Fig 14: 3D and 2D diagram of docking interaction between 1ACJ and Medicarpin

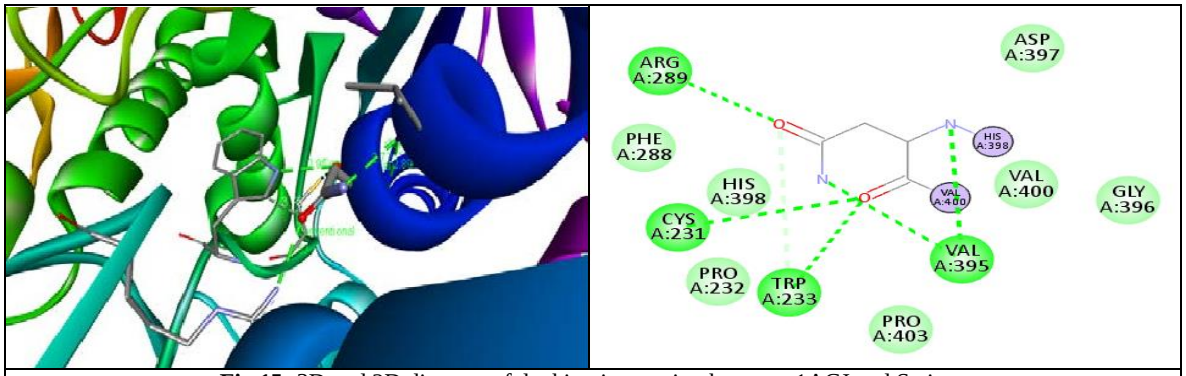


Fig 15: 3D and 2D diagram of docking interaction between 1ACJ and Sativan

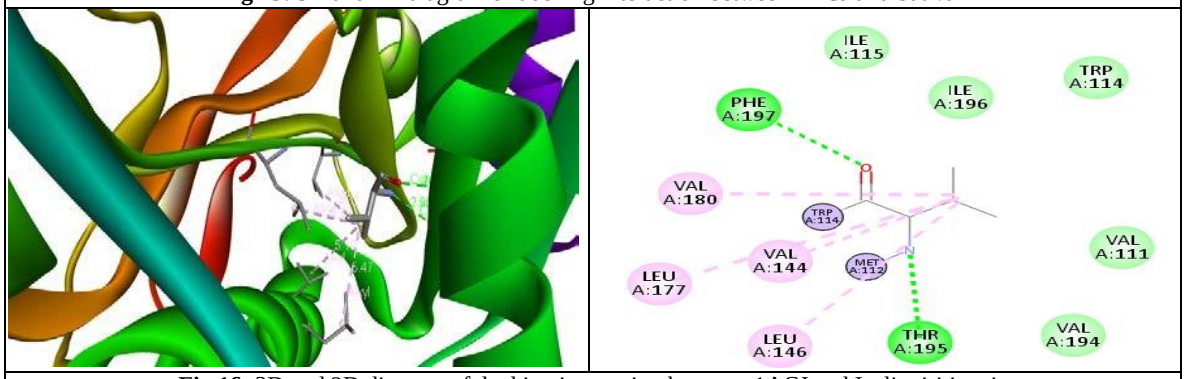


Fig 16: 3D and 2D diagram of docking interaction between 1ACJ and Isoliquiritigenin

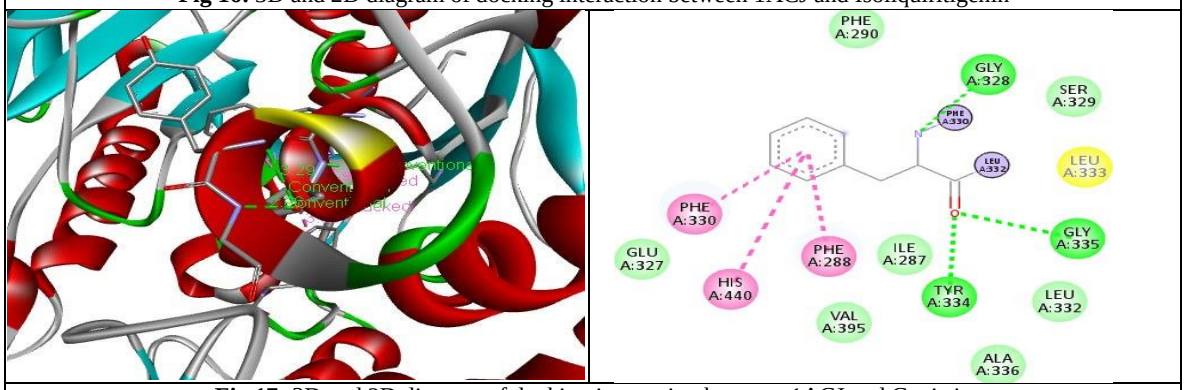


Fig 17: 3D and 2D diagram of docking interaction between 1ACJ and Genistin

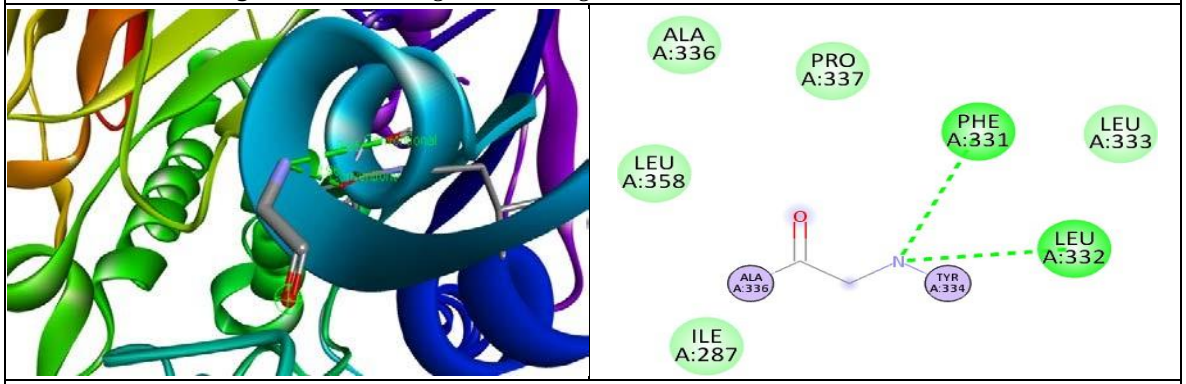
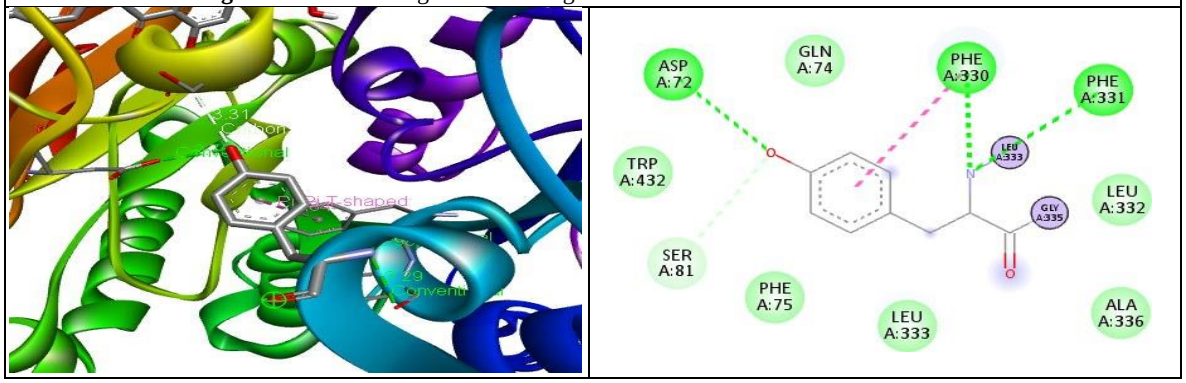


Fig 18: 3D and 2D diagram of docking interaction between 1ACJ and Coumestrol



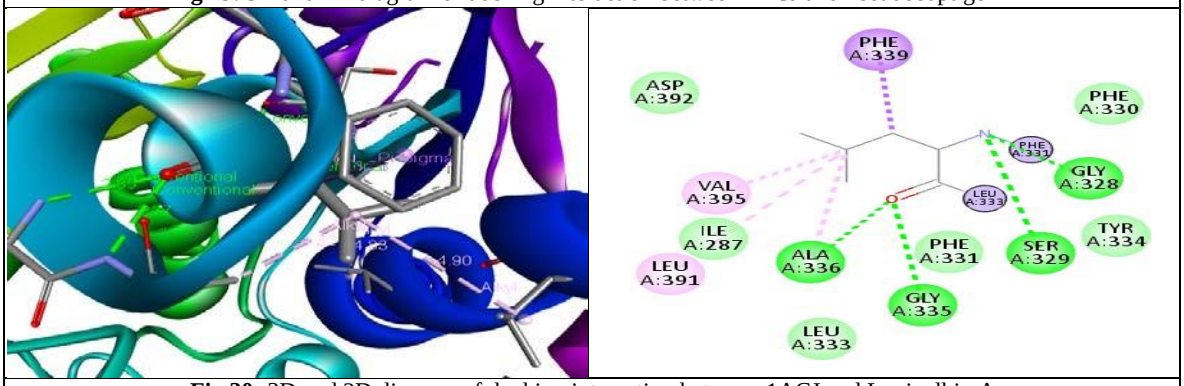


Fig 19: 3D and 2D diagram of docking interaction between 1ACJ and Pseudobaptigenin

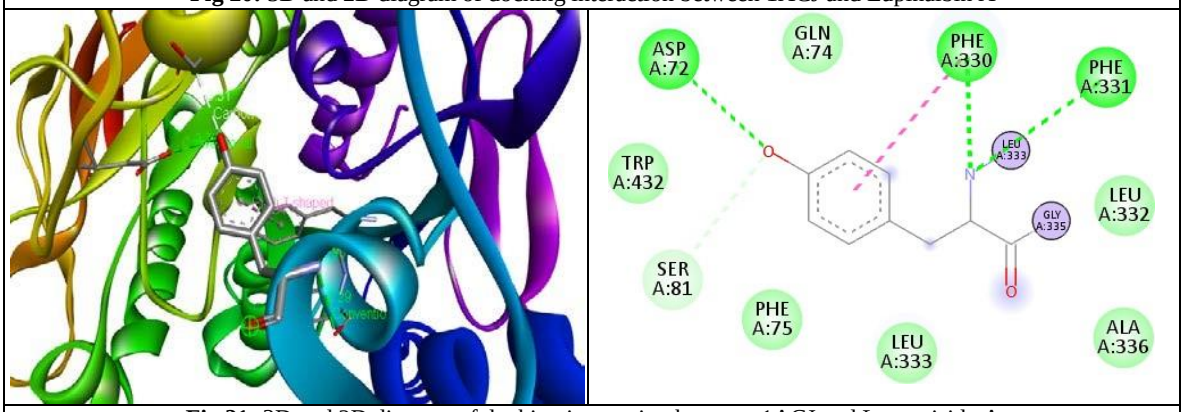


Fig 21: 3D and 2D diagram of docking interaction between 1ACJ and Leonuriside A

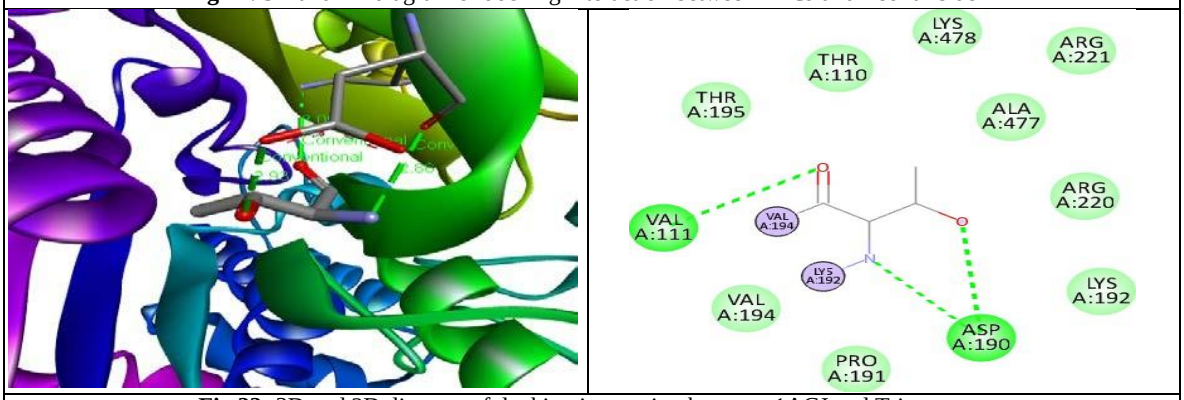


Fig 22: 3D and 2D diagram of docking interaction between 1ACJ and Trigraecum

Table 6: Common Alzheimer's disease treatment drug used for molecular docking

Sl No	Compound	Interaction energy (Kcal/mol)	Interacting residues	No of H Bonds in interaction	Fig No
1	Donepezil	-8.4	he 290, Ohe 330, Glu 327, His 440, Phe 288, Val 395, Tyr 334, Ala 336, Leu 332, Gly 335, Leu 333, Ser 329, Gly 328	3	23
2	Tacrine	-9.4	Ser 329, Phe 331, Phe 330, Phe 339, Trp 435, Lys 341, Ser 340, Phe 75, Trp 432, Tyr 334, Leu 332, Met 436, Ala 336, Gly 335	1	24

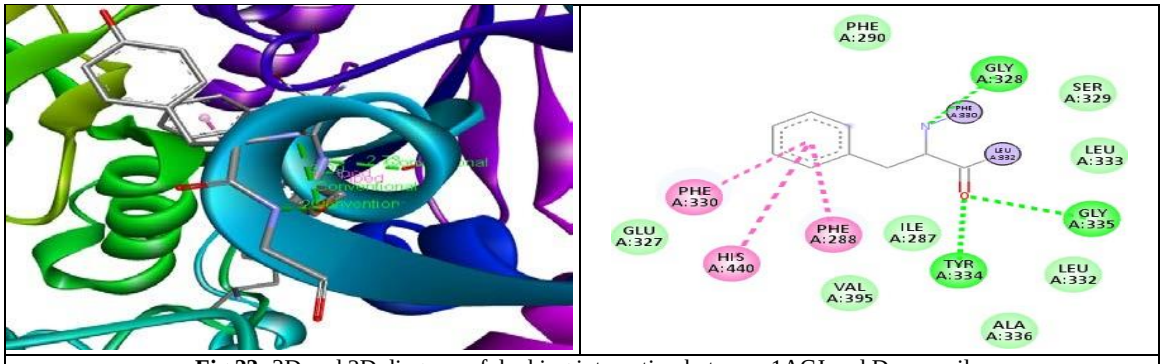


Fig 23: 3D and 2D diagram of docking interaction between 1ACJ and Donepezil

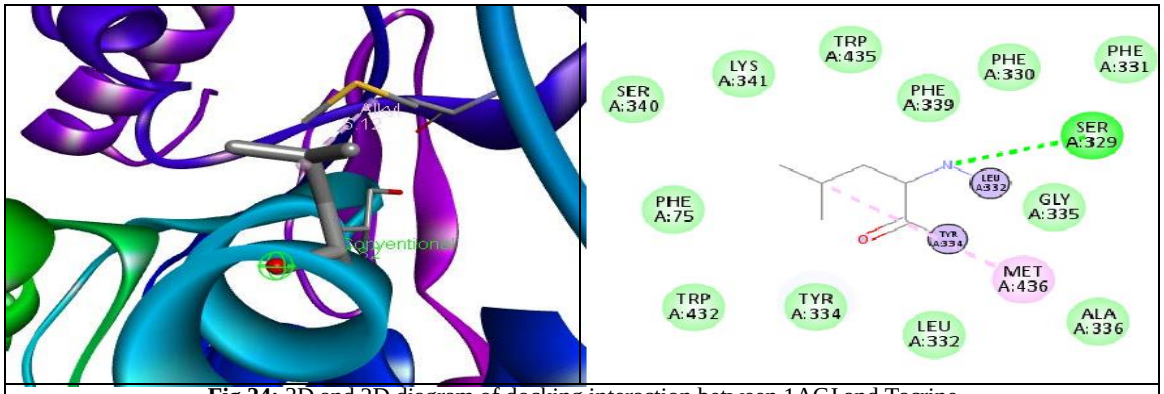


Fig 24: 3D and 2D diagram of docking interaction between 1ACJ and Tacrine

The much more difficult as well as critical challenge confronting global researchers right now is the search for drugs to combat the Alzheimer's disease. The current technique depends on an upsurge in acetylcholine synaptic accessibility to mitigate for the cholinergic shortfall caused by neuronal death [15]. The use of medicinal herbs in the treatment of Alzheimer's disease should have been assessed to the present therapeutic intervention. In East Asian countries, herbal therapy has traditionally been utilised to help address dementia illness and increase cognitive deficits [29]. According to a prospective study, incorporating Chinese herbal remedies to standard therapy produced considerable benefits in dementia sufferers, which became more obvious over time [30]. We evaluated 21 phytochemicals from *Spatholobus genus* plant that have been documented to have anti-protease properties as part of this drug discovery effort. Phytochemicals strive to allow the stable plant coordinate and defend itself, increasing its longevity. The alkaloids, terpenes, as well as phenolics are the three types of chemicals, with the order indicating their power from harmful to comparatively neutral [31]. Numerous phenolic as well as terpene compounds have also shown potency towards cholinergic decline and, much further than that, several of the variables that contribute to Alzheimer's disease, although conventional alkaloid-based treatments have not [32]. Furthermore, their comparatively harmless ecological duties suggest that they may be a prove to be beneficial of slowing neurobehavioral deterioration in Alzheimer's disease. Because cholinergic operation is essential for short-term memory, this was thought that the cholinergic shortfall in Alzheimer's disease would be to blame for almost all of the short-term memory problem [33]. Alzheimer's disease seems to be a neurological illness affecting people as they get older [6] Remembering and other critical cognitive capacity are gradually lost as brain cell interconnections as well as cells deteriorate and perish [34]. Although there is no remedy, drugs and managerial measures might help to alleviate sensations somewhat [35]. Regardless of the fact that Alzheimer's disease is indeed a significant public health concern, there seems to be no appropriate pharmaceutical option for its diagnosis and mitigation. The use of herbal remedies in the diagnosis and management of Alzheimer's disease patients should have been assessed to the present medical therapy. As a result, the goal of this research would have been to develop a lead molecule that could truly interact with a potential therapeutic target, thereby being beneficial in the management of Alzheimer's complications as well as senile dementia, and thus can help stop neurodegeneration and therefore can form an efficient therapeutic stimulant in the treatment of Alzheimer's disease by avoiding further neuron injury.

Conclusions

Alzheimer's disease is a fatal kind of cognition that has a significant impact on a patient's ability to analyze and communicate. Botanical therapies should have been compared to current conventional treatment in the diagnosis and management of Alzheimer's disease patients. Phytochemicals from the *Spatholobus genus* plant were tested as folk remedies to the acetylcholinesterase enzyme (1ACJ) which triggers Alzheimer's disease in this study. We discovered that Medicarpin (interaction energy -9.9 Kcal/mol) is the best of the four molecules examined from *S. suberectus* for interacting with protein 1ACJ. We reported that Prestegane B has a higher binding potential to the target protein 1ACJ, i.e., -10.2 Kcal/mol with two hydrogen bonds in contact, than the other five molecules studied from *S. sinensis.* In this investigation, 12 phytocompounds from *S. suberectus* were examined. Maackiain had the strongest affinity with the target protein 1ACJ, with a -10.3 Kcal/mol. When compared to the experimental medications Donepezil and Tacrine, all of these compounds had a higher binding affinity. In furthermore, in silico druglikeness and ADMET analyses of the phytochemicals demonstrated significant therapeutic advantages. As a conclusion, we can anticipate that all of these phytomolecules will be examined *in vitro* in the near future to see if they have higher potency in addressing Alzheimer's disease complications.

Acknowledgement

Sincerely acknowledging to Principal and Vice-Principal Maharaj of RKMV, Belur Math as well as to all faculty member of Microbiology department of RKMV.

Funding

This research did not receive any external funding.

Conflicts of Interest

The authors affirm that there is no conflict of interest in this study.

References

1. Sibanyoni MN, Chaudhary SK, Chen W, Adhami HR, Combrinck S, Maharaj V *et al*. Isolation, *in vitro* evaluation and molecular docking of acetylcholinesterase inhibitors from South African Amaryllidaceae. Fitoterapia,2020:146:104650. https://doi.org/10.1016/j.fitote, 2020, 104650.

2. Ashrafian H, Zadeh EH, Khan RH. Review on Alzheimer's disease: Inhibition of amyloid beta and tau tangle formation. Int J Biol Macromol,2021:15:167:382-394. https://doi.org/10.1016/j.ijbiomac.2020.11.192
3. Khan J, Tousif MI, Saleem M, Nazir M, Touseef S, Saleem K *et al*. Insight into the phytochemical composition, biological activities and docking studies of Moringa oleifera Lam. to authenticate its use in biopharmaceutical industries. Industrial Crops and Products,2021:172:114042. https://doi.org/10.1016/j.indcrop.2021.114042.
4. Calfio C, Gonzalez A, Singh SK, Rojo LE, Maccioni RB. The Emerging Role of Nutraceuticals and Phytochemicals in the Prevention and Treatment of Alzheimer's Disease. J Alzheimers Dis,2020:77(1):33-51. https://doi.org/10.3233/jad-200443
5. Saleem H, Khurshid U, Sarfraz M, Tousif MI, Alamri A, Anwar S *et al*. A comprehensive phytochemical, biological, toxicological and molecular docking evaluation of Suaeda fruticosa (L.) Forssk.: An edible halophyte medicinal plant. Food and Chemical Toxicology, 2021**:**154:112348. https://doi.org/10.1016/j.fct.2021.112348.
6. Mohammadi MA, Farimani MM, Salehi P, Ebrahimi S.N, Sonboli A, Kelso C *et al*. Acetylcholinesterase-inhibitory activity of Iranian plants: Combined HPLC/bioassay-guided fractionation, molecular networking and docking strategies for the dereplication of active compounds. Journal of Pharmaceutical and Biomedical Analysis,2018:158:471-479. https://doi.org/10.1016/j.jpba.2018.06.026.
7. Karatoprak GS, Göger F, Çelik İ, Budak Ü, Akkol EK, Aschner M *et al*. Phytochemical profile, antioxidant, antiproliferative, and enzyme inhibition-docking analyses of Salvia ekimiana Celep & Doğan. South African Journal of Botany,2022:146:36-47.https://doi.org/10.1016/j.sajb.2021.09.033.
8. Bursal E, Yılmaz MA, Izol E, Türkan F, Atalar MN, Murahari M *et al*. Enzyme inhibitory function and phytochemical profile of Inula discoidea using *in vitro* and in silico methods. Biophysical Chemistry,2021:277:106629. https://doi.org/10.1016/j.bpc.2021.106629.
9. Song M, Min W, Wang J, Si X, Wang XJ, Liu YW *et al*. Design, synthesis and biological evaluation of new carbazole-coumarin hybrids as dual binding site inhibitors of acetylcholinesterase. Journal of Molecular Structure,2021:1229:129784. https://doi.org/10.1016/j.molstruc.2020.129784.
10. Swaraz AM, Sultana F, Bari MW, Ahmed KS, Hasan M, Islam MM *et al*. Phytochemical profiling of Blumea laciniata (Roxb.) DC. and its phytopharmaceutical potential against diabetic, obesity, and Alzheimer's. Biomedicine & Pharmacotherapy,2021:141:11185. https://doi.org/10.1016/j.biopha.2021.111859.
11. D'Onofrio G, Sancarlo D, Ruan Q, Yu Z, Panza F, Daniele A *et al*. Phytochemicals in the Treatment of Alzheimer's Disease: A Systematic Review. Curr Drug Targets,2017:18(13):1487-1498. https://doi.org/10.2174/1389450117666161102121553
12. Vaiserman A, Koliada A, Lushchak O. Neuroinflammation in pathogenesis of Alzheimer's disease: Phytochemicals as potential therapeutics. Mech Ageing Dev,2020:189:111259. https://doi.org/10.1016/j.mad.2020.111259
13. Khurshid Alam AHM. Phytochemicals, Antioxidants, and Cholinesterase Inhibitory Profiles of Elatostema Papillosum Leaves: an Alternative Approach for Management of Alzheimer's Disease. J Neurol Neuromed,2018:3(5):19-22. https://doi.org/10.29245/2572.942X/2018/5.1211
14. Rahman MA, Rahman MH, Biswas P, Hossain MS, Islam R, Hannan MA *et al*. Potential Therapeutic Role of Phytochemicals to Mitigate Mitochondrial Dysfunctions in Alzheimer's Disease. Antioxidants,2021:10:23. https://doi.org/10.3390/antiox10010023
15. Vaiserman A, Koliada A, Lushchak O. Neuroinflammation in pathogenesis of Alzheimer's disease: Phytochemicals as potential therapeutics. Mech. Ageing Dev, 2020, 189. https://doi.org/10.1016/j.mad.2020.111259
16. Martel J, Ojcius DM, Ko YF, Ke PY Wu CY, Peng H.H, Young JD *et al*. Hormetic Effects of Phytochemicals on Health and Longevity. Trends Endocrinol Metab,2019:30(6):335-346. https://doi.org/10.1016/j.tem.2019.04.001
17. Hannan A, Dash R, Haque N, Mohibbullah, Sohag A, Rahman A *et al*. Neuroprotective Potentials of Marine Algae and Their Bioactive Metabolites: Pharmacological Insights and Therapeutic Advances. Mar. Drugs,2020:10:20944. https://doi.org/10.3390/md18070347
18. Caruana M, Camilleri A, Farrugia MY, Ghio S, Jakubíčková M, Cauchi RJ *et al*. Extract from the Marine Seaweed Padina pavonica Protects Mitochondrial Biomembranes from Damage by Amyloidogenic Peptides. Molecules,2021:7:26(5):1444. https://doi.org/10.3390/molecules26051444
19. Ahman MH, Bajgai J, Fadriquela A, Sharma S, Trinh TT, Akter R *et al*. Therapeutic Potential of Natural Products in Treating Neurodegenerative Disorders and Their Future Prospects and Challenges. Molecules, 2021:2:26(17):5327. https://doi.org/10.3390/molecules26175327
20. Han HJ, Park SK, Kang JY, Kim JM, Yoo SK, Kim DO *et al*. Mixture of Phlorotannin and Fucoidan from Ecklonia cava Prevents the Aβ-Induced Cognitive Decline with Mitochondrial and Cholinergic Activation. Mar Drugs,2021:29:19(8):434. https://doi.org/10.3390/md19080434
21. Das A, Kuma S, Persoons L, Daelemans D, Schols D, Alici H *et al*. Synthesis, in silico ADME, molecular docking and *in vitro* cytotoxicity evaluation of stilbene linked 1,2,3-triazoles, *Heliyon*,2021:7(1):05893. https://doi.org/10.1016/j.heliyon.2020.e05893.
22. Govindarasu M, Ganeshan S, Ansari MA, Mohammad N, Alomary, Yahya SA, Alghamdi S *et al*. In silico modeling andmolecular docking insights of kaempferitrin for colon cancer-related molecular targets. *Journal of Saudi Chemical Society*,2021:25(9):101319. https://doi.org/10.1016/j.jscs.2021.101319.
23. Suryanarayana K, Robert AR, Kerru N, Pooventhiran T, Thomas R, Maddila S, Sreekantha B *et al*. Design, synthesis, anticancer activity and molecular docking

analysis of novel dinitrophenylpyrazole bearing 1,2,3-triazoles. *Journal of Molecular Structure*,2021:1243:130865. https://doi.org/10.1016/j.molstruc.2021.130865
24. Águila ID, Mendiola MA, Pradhan S, Sinha C, Torres EL. Synthesis, characterization, *in vitro* cytotoxic activity and molecular docking of dinuclear gold(I) complexes with terephthalaldehyde bis(thiosemicarbazones). *Polyhedron*,2021:210,115498. https://doi.org/10.1016/j.poly.2021.115498.
25. Águila ID, Mendiola MA, Pradhan S, Sinha C, Torres EL. Synthesis, characterization, *in vitro* cytotoxic activity and molecular docking of dinuclear gold(I) complexes with terephthalaldehyde bis(thiosemicarbazones). *Polyhedron*,2021:210:115498. https://doi.org/10.1016/j.poly.2021.115498.
26. Zhao L, Xiao S, Jiang S, Jin Y, Fang W, Wang Z *et al*. Detailed structural investigation of Crizotinib and the exploration of its antitumor potential by DFT calculations and molecular docking. *Journal of Molecular Structure*,2022:1248:131530. https://doi.org/10.1016/j.molstruc.2021.131530.
27. Oubella A, Mansouri AEE, Fawzi M, Bimoussa A, Laamari Y, Auhmani A *et al*. Thiazolidinone-linked1,2,3-triazoles with monoterpenic skeleton as new potential anticancer agents: Design, synthesis and molecular docking studies. *Bioorganic Chemistry*,2021:115:105184. https://doi.org/10.1016/j.bioorg.2021.105184.
28. Zilbeyaz K, Oztekin A, Kutluana EG. Design and synthesis of garlic-related unsymmetrical thiosulfonates as potential Alzheimer's disease therapeutics: *In vitro* and in silico study. *Bioorganic & Medicinal Chemistry*,2021:40:116194. https://doi.org/10.1016/j.bmc.2021.116194.
29. Das A, Kuma S, Persoons L, Daelemans D, Schols D, Alici H *et al*. Synthesis, in silico ADME, molecular docking and *in vitro* cytotoxicity evaluation of stilbene linked 1,2,3-triazoles, *Heliyon*,2021:7(1):05893. https://doi.org/10.1016/j.heliyon.2020.e05893.
30. Narayanan SE, Sekhar N, Rajamma RG, Marathakam A, Al Mamun A, Uddin MS *et al*. Exploring the Role of Aggregated Proteomes in the Pathogenesis of Alzheimer's Disease. Curr Protein Pept Sci,2020:21(12):1164-1173. https://doi.org/10.2174/1389203721666200921152246
31. Kim JM, Park SK, Kang JY, Park SB, Yoo SK, Han HJ *et al*. Ethyl Acetate Fraction from Persimmon (Diospyros kaki) Ameliorates Cerebral Neuronal Loss and Cognitive Deficit via the JNK/Akt Pathway in TMT-Induced Mice. Int J Mol Sci,2018:17:9(5):1499. https://doi.org/10.3390/ijms19051499
32. Rahman A, Rahman R, Zaman T, Uddin S, Islam R, Abdel-Daim MM *et al*. Emerging Potential of Naturally Occurring Autophagy Modulators Against Neurodegeneration. Curr. Pharm, Des,2020:26:772-779.https://doi.org/10.2174/1381612826666200107142541
33. Uddin M.S, Kabir M.T, Niaz K, Jeandet P, Clément C, Mathew B *et al*. Molecular Insight into the Therapeutic Promise of Flavonoids against Alzheimer's Disease. Molecules,2020:11:25(6):1267. https://doi.org/10.3390/molecules25061267
34. Zhao L, Xiao S, Jiang S, Jin Y, Fang W, Wang Z *et al*. Detailed structural investigation of Crizotinib and the exploration of its antitumor potential by DFT calculations and molecular docking. *Journal of Molecular Structure*,2022:1248:131530. https://doi.org/10.1016/j.molstruc.2021.131530.
35. Oubella A, Mansouri AEE, Fawzi M, Bimoussa A, Laamari Y, Auhmani A *et al*. Thiazolidinone-linked1,2,3-triazoles with monoterpenic skeleton as new potential anticancer agents: Design, synthesis and molecular docking studies. *Bioorganic Chemistry*,2021:115:105184. https://doi.org/10.1016/j.bioorg.2021.105184.
36. Ibrahim NA, Mansour YS, Sulieman AA. Antiemetic medications: Agents, current research, and future directions. International Journal of Pharmacy and Pharmaceutical Sciences. 2019:7-14.