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Insilico Bimolecular Interaction Studies of Natural Compounds for Treatment of Alzheimers Disease

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Abstract: ***To determine the natural composites that can be used as implicit medicines towards Alzheimer's complaint. Alzheimer's complaint is a nonstop progressive and multi-factored neurodegenerative complaint that's known to be the sixth leading cause of death and the most common cause of madness in old, aged people. Alzheimer's complaint is related to increased situations of the amyloid β peptide(Aβ) along with loss of neurons and synapses. The complaint process is largely associated with amyloid pillars, neurofibrillary befuddlements, and loss of neuronal connections in the brain. In our study, we will be exercising the structural and natural exertion information on specific ligands and compactly study the vital targets that are believed to be effective against Alzheimer's complaint. The early onset of the domestic Alzheimer's complaint is considered to do due to the mutations in one of three genes those garbling amyloid- beta precursor protein(APP) and Presenilins PSEN1 and PSEN2. utmost mutations in the APP and presenilin genes increase the product of the small proteins known as the amyloid beta(Aβ) 42 proteins, are the main element of the forming amyloid pillars. There are numerous selective targets for the event of anti-AD(Alzheimer's complaint) medicines, and thus the multi-factorial nature of this complaint involves multi-target-directed composites which may be salutary for announcement treatment. The complaint which is known to target the hippocampus that is associated with our memory, further this becomes responsible to instigate the first symptoms of memory impairment. As the complaint progresses so does the degree of memory impairment. The natural emulsion models were considered as multi-target leads using molecular docking ways and also completely analysed grounded on the list affinity values, RMSD values, stability and molecular interactivity studies for the determination of implicit medicine composites to make medicinals. Eventually, the foremost implicit multi-target natural composites against Alzheimer's complaint are determined and farther validated through the corresponding invitro studies.***

Keywords: Alzheimer's, Insilico, Medicines, Natural Composites, , Target protein, Molecular docking.

I. INTRODUCTION

Alzheimer's sickness could be a progressive neurological disorder that causes the brain to shrink (atrophy) and brain cells to die. Alzheimer's sickness is that the commonest reason for dementedness — never-ending decline in thinking, activity and social skills that affects a person's ability to perform severally. close to five.8 million individuals inside the North American nation age sixty five and older settle for Alzheimer's sickness. Of those, eightieth ar seventy five years recent and older. Out of the close to fifty million individuals worldwide with dementedness, between hour and seventieth ar calculable to own Alzheimer's sickness. the first signs of the sickness embody forgetting recent events or conversations. because the sickness progresses, an individual with Alzheimer's sickness can develop severe memory impairment and lose the flexibility to hold out everyday tasks. the event of the sickness takes place slowly bit by bit like phases.[49]

AD begins slowly. It first involves the parts of the brain that control thought, memory, and language. People with AD may have trouble remembering things that happened recently or names of individuals they know. A related problem, mild cognitive impairment (MCI), causes more memory problems than normal for people of an equivalent age. Many, but not all, people with MCI will develop AD. In AD, over time, symptoms worsen.

People might not recognize relations. they'll have trouble speaking, reading, or writing. they'll forget the way to brush their teeth or comb their hair. Later, they'll become anxious or aggressive, or stray from home. Eventually, they have total care. this will cause great stress for relations who must look after them. AD usually begins after age 60 and the danger goes up as you grow older. Our risk is additionally higher if a loved one has had the disease.

Most AD cases are sporadic and present considerable heterogeneity in terms of risk factor profiles and neuropathological features. First-degree relatives of Alzheimer patients have a higher lifetime risk of developing AD than the general population or relatives of nondemented individuals both genetic and shared environmental factors contribute to the phenomenon of familial aggregation.

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II. METHODOLOGIES

A. Protein Model Preparation For Docking Studies.

Relevant literature for Alzheimer's disease is collected from pubmed and PMC in the NCBI Database in order to identify the target protein for the disease, the pathways a compound may take to reduce the effects of the disease and accordingly determine the potential compounds. After sufficient literature collection and referencing, the main target protein was determined as "Secretase", **β**-Amyloid A4 protein and Glycogen Synthase Kinase 3(GSK3) along with other β-amyloid peptide pathways from Uniprot. The compounds along with their smile structures along with their isomeric smiles were then tabulated for further molecular docking studies using Pyrx software,wherein about 28 natural compounds as listed in Table 1 were taken for conduction of studies. The PDBE structural model of the target proteins of concern-Secretase,-Amyloid A4 protein and Glycogen Synthase Kinase 3(GSK3) in humans was first retrieved from the Swiss Model online server and the macromolecule structure was then loaded on Pyrx tool.

One must note that the water molecules are not involved in binding, and they must be eliminated before the conduction of any molecular docking and binding studies to make the computations easier and clear the binding pocket of possible water molecules that would distort the pose search. The water molecules and irrelevant chains must be eliminated, depending upon the area of study from the notepad sequence and only then the molecule must be loaded for efficient docking. The ligands of the 3D conformation ligands of the required natural compounds are downloaded from pubchem and then loaded into Pyrx software to carry out molecular docking with respect to Secretase,-Amyloid A4 protein and Glycogen Synthase Kinase 3(GSK3).The Binding affinities consisting of the ligands containing the lower and upper RMSD values as zero are prioritised as shown in Table2. The docked structures of the target protein and the chosen ligands are then saved in PDB format and analysed for their stability towards different conditions of temperature and pressure, reactivity, binding affinity to enable efficient action on the target site for the noted important proteins and minimize effects of Alzheimer's condition.

Several factors concerning Adsorption, Distribution, Metabolism, Excretion and Toxicity[ADMET] are also analysed utilising the pkcsm online web server. Ligands of natural compounds having a binding affinity of -7.0 and above are considered to have potential in targeting the required sites of the target proteins that have earlier been determined using the Cast-p online tool. The IGEMDOCK Software is utilized to obtain the 3D structures of the ligand-protein interactions and the results are now analysed depending upon the ligand binding capacity, hydrogen bonding and hence a crystal structure with reasonable resolution and binding affinity that have a slightly consensus profile in terms of binding residues (if possible) should be the top criteria. The binding residues (not the ligand functional group) biochemical and cellular activity is encoded by the interactions (allosteric/competitive or agonist/antagonist) from such domains/pocket and hence are key determining factors.

B. Protein Model Preparation For Docking Studies.

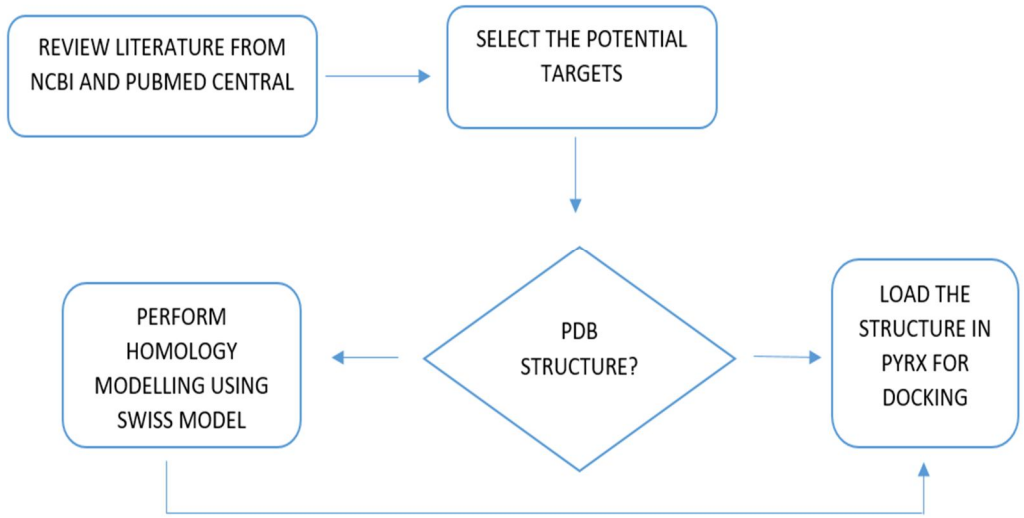


Figure 9: Protein preparation process

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C. Ligand Model Preparation For Docking Studies.

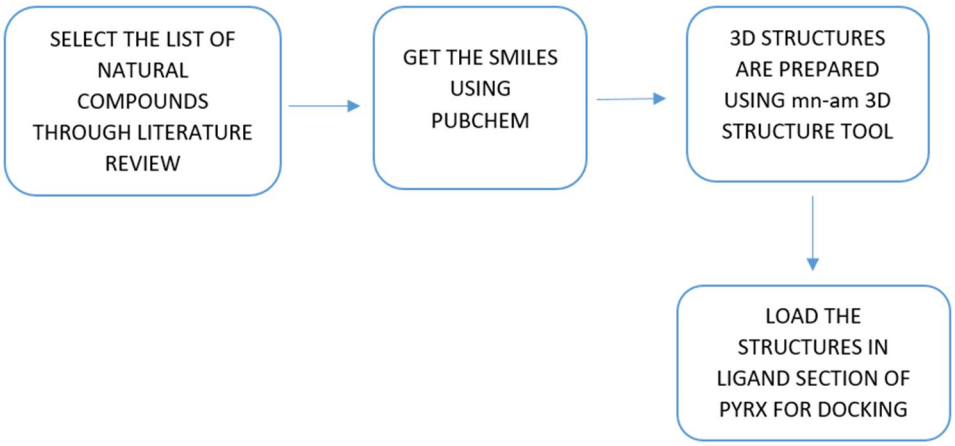


Figure 10: The flowchart represents an overview of methods that have been equipped in the project.

III.RESULTS AND DISCUSSION

A. Selection Of The Target Proteins And Natural Compounds.

1) *Target Proteins:* Target proteins play a very important role in the study of the disease and computational drug designs. Target proteins control the action and therefore the kinetic behaviour of medicine within the organism. The elucidation of structure, conformational signalling and catalytic properties of particular target proteins facilitates a rational design of medicine and biotechnological processes. The following table lets us look into the set of target proteins chosen for this project and studies.

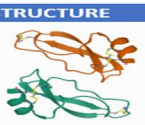
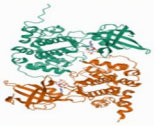
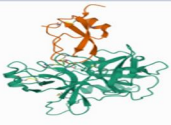
SL.NO	TARGET PROTEIN	PDB ID	3D STRUCTURE
1	α SECRETASE	1aap	
2	GLYGOGEN SYNTHASE KINASE 3	1j1b	
3	AMYLOID β PEPTIDE	1zjd	

Figure 12: The table represents the three target proteins chosen and the PDB ID and 3D structure for the same.

2) ***α*** *Secretase:* Ectodomain shedding of the amyloid precursor protein (APP) by the metalloprotease activity α-secretase may be a key regulatory event preventing the generation of the Alzheimer's disease (AD) amyloid β peptide. Proteases almost like α-secretase are essential for diverse physiological processes, like embryonic development, cell adhesion and neuronal guidance. Previously, several proteases were suggested as candidate α-secretases for APP, especially members of the ADAM family (a disintegrin and metalloprotease). Two recent studies analyzed primary neurons, which are the cell type affected in AD, and eventually demonstrated that the constitutively cleaving α-secretase activity is selectively mediated by ADAM10. An increase in α-secretase cleavage is taken into account a therapeutic approach for AD. However, the molecular mechanisms regulating α-secretase cleavage remain only partly understood. Signaling pathways activating protein kinase C and MAP kinase play a central role in stimulating α-secretase cleavage of APP. Additionally, several recent publications demonstrate that ADAM10 expression and α-secretase cleavage of APP are tightly controlled at the extent of transcription, e.g. by retinoic acid receptors and sirtuins, and at the extent of translation and protein trafficking. This review focuses on the recent progress made in unravelling the molecular identity, regulation and therapeutic potential of α-secretase in Alzheimer's disease. [52]

3) *Glycogen Synthase Kinase 3:* Glycogen synthase kinase (GSK)-3 has been proposed because the link between the 2 histopathological hallmarks of Alzheimer's disease , the extracellular senile plaques composed of beta-amyloid and therefore the intracellular neurofibrillary tangles formed from hyperphosphorylated tau. Thus, GSK-3 is one among the most tau kinases and it modifies several sites of the tau protein present in neurofibrillary tangles. Furthermore, GSK-3 is in a position to modulate the generation of amyloid-beta, also on answer this peptide. In several transgenic models, overexpression of GSK-3 has been related to neuronal death, tau hyperphosphorylation and a decline in cognitive performance. Lithium, a widely used drug for affective disorders, inhibits GSK-3 at therapeutically relevant concentrations and it's been demonstrated that this is often ready to prevent tau phosphorylation. In the present review, we summarize all these data and discuss the potential of GSK-3 inhibitors for Alzheimer's disease therapy, as well as some of their potential problems. [52]
4) *Amyloid β peptide*: The beta amyloid (A beta) protein may be a key molecule within the pathogenesis of Alzheimer's disease (AD). The tendency of the A beta peptide to aggregate, its reported neurotoxicity, and genetic linkage studies, have led to a hypothesis of AD pathogenesis that a lot of AD researchers term the amyloid cascade hypothesis. In this hypothesis, an increased production of A beta leads to neurodegeneration and ultimately dementia through a cascade of events. In the past 15 years, debate amongst AD researchers has arisen on whether A beta may be a cause or an impact of the pathogenic process. Recent in vitro and in vivo research has consolidated the idea that A beta is that the primary cause, initiating secondary events, culminating within the neuropathological hallmarks related to AD. This research has led to the event of therapeutic agents, currently in human clinical trials, which target A beta.

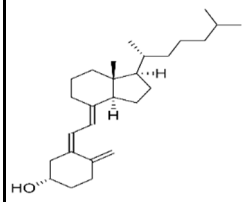
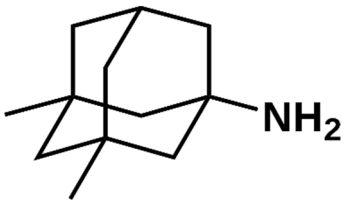
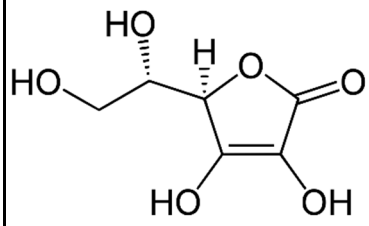
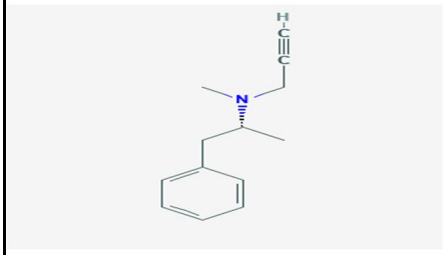
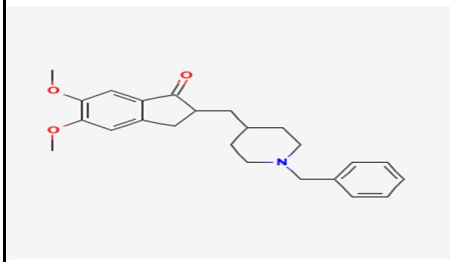
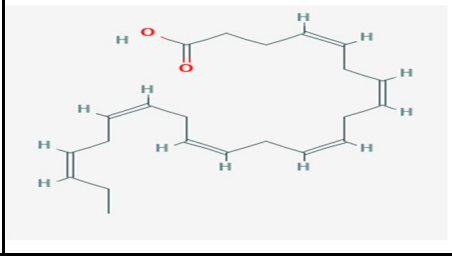
B. Natural Compounds

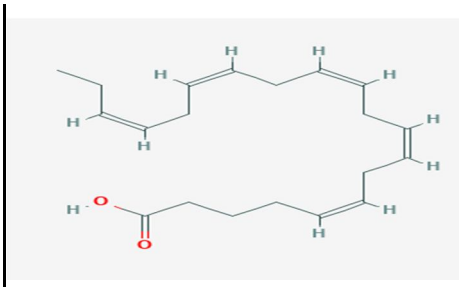
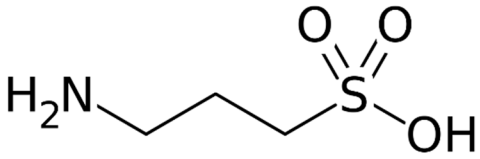
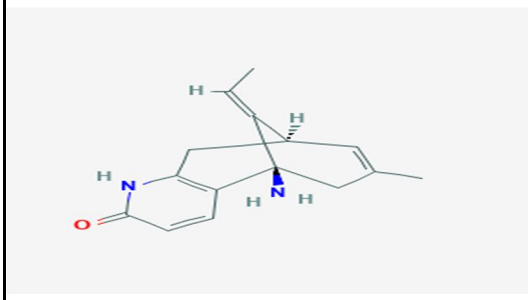
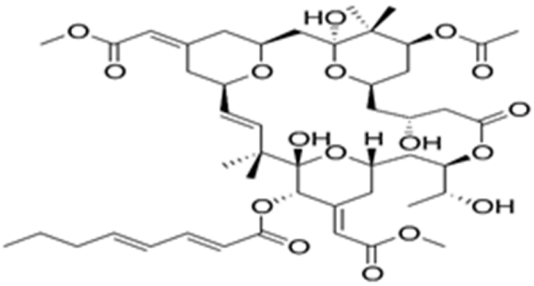
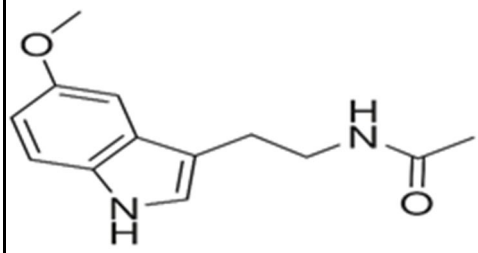
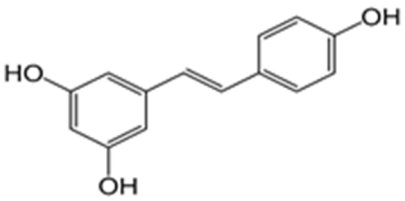
A natural product (NP) is usually defined as a compound or substance that's produced by living organisms. NPs are often classified by many criteria and characteristics, like source, biological function, biosynthetic pathway, physical and chemical properties, etc. Nowadays, NPs find a broad spectrum of applications associated with human life, including a crucial role in medicine. Notably, the utilization of natural products as medicines has been described throughout human history in terms of drugs associated with herbal medicines, potions, oils, remedies, and foods. Many of those substances are discovered by trial and error, and through the years they need become standard products in human lives. In the past few decades, natural products are a crucial source of potential drug hits and leads. However, development efforts in NP drug discovery have demonstrated a particular downturn in recent years. Despite this decline, the vast chemical space of natural products continues to supply abundant structural diversity for locating novel lead compounds with low relative molecular mass but 10% of the world's biodiversity has been explored to seek out potential biologically active compounds. Therefore, numerous lead NPs which will be used against a broad spectrum of diseases await discovery. Many drugs associated with diseases like malaria, tuberculosis, cancer, human immunodeficiency virus (HIV), inflammatory diseases, cardiac diseases, diabetes, etc. are derived from NPs. One area where natural compounds have also been found to possess great research potential and application is neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), schizophrenia, dementia, and neuropathic disorders.

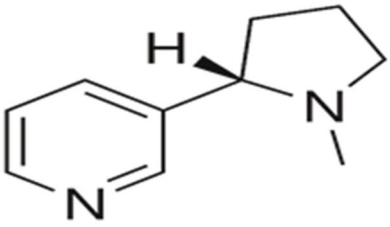
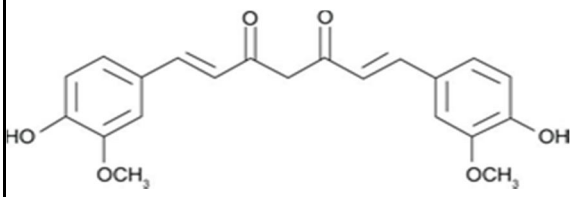
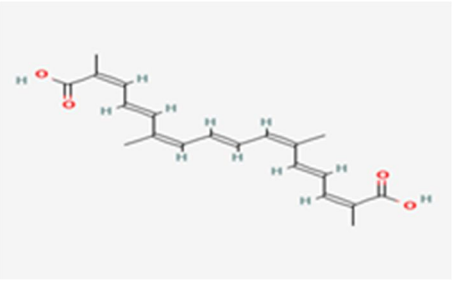
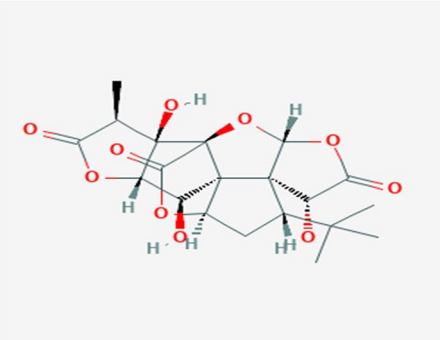
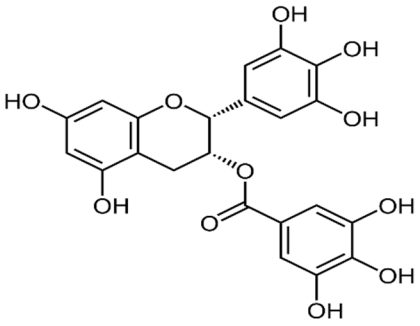
SL.NO	NATURAL COMPOUNDS	SL.NO	NATURAL COMPOUNDS
1	Cholecalciferol	15	Vitamin E
2	Memantine	16	Saffron
3	VITAMIN C	17	Ginkgolide-B
4	Selegiline	18	Epigallochatechin(Green Tea)
5	Donepezil	19	1,1-Dimethyl-3-phenylpropyl isobutyrate(Papaya)
6	Docosahexaenoic acid (DHA)	20	Sage217
7	Eicosapentaenoic acid	21	(2S)-2-Hydroxybutanedioic acid (Apple)
8	Homotaurine	22	20-Taraxasten-3beta-ol
9	Huperzine A	23	Lunasine
10	Bryostatin	24	Quercetins
11	Melatonin	25	Cianidanol
12	Resveratrol	26	Kaempferol
13	Nicotine	27	Berberine
14	Curcumin	28	Platycodin D

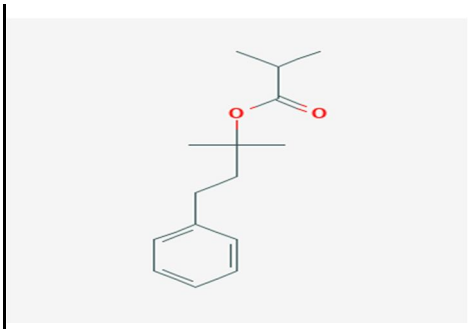
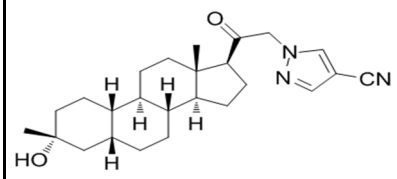
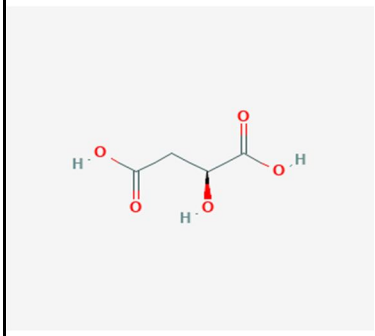
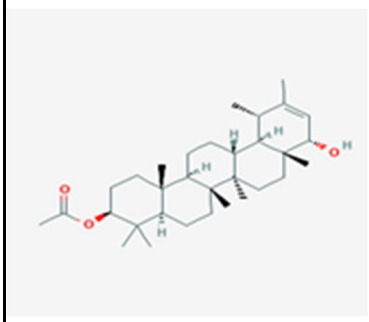
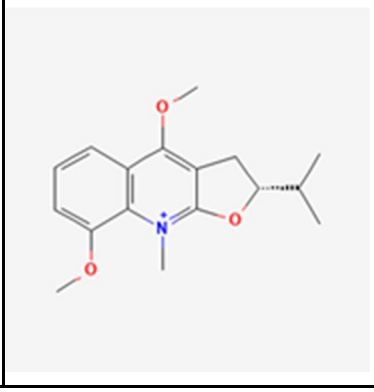
Table1: Selection Of 28 Natural Compounds

The natural compounds selected for the study are showcased in the table above. A detailed explanation of their chemical structures has been mentioned in the table below:

SL.NO	COMPOUND NAMES	STRUCTURES
1	Cholecalciferol	
2	Memantine	
3	VITAMIN C	
4	Selegiline	
5	Donepezil	
6	Docosahexaenoic acid (DHA)	

7	Eicosapentaenoic acid	
8	Homotaurine	
9	Huperzine A	
10	Bryostatin	
11	Melatonin	
12	Resveratrol	

13	Nicotine	
14	Curcumin	
15	Vitamin E	
16	Saffron	
17	Ginkgolide-B	
18	Epigallochatechin(Green Tea)	

19	1,1-Dimethyl-3-phenylpropyl isobutyrate(Papaya)	
20	Sage217	
21	(2S)-2-Hydroxybutanedioic acid (Apple)	
22	20-Taraxasten-3beta-ol	
23	Lunasine	

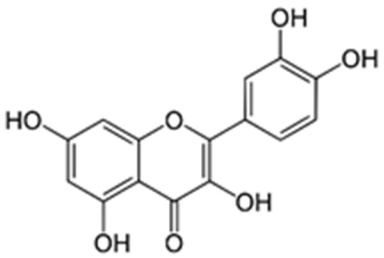
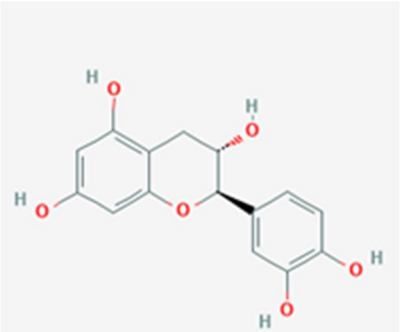
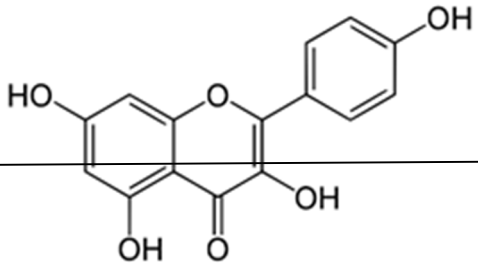
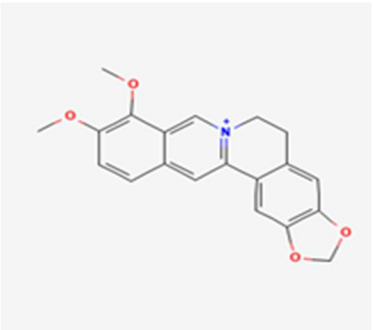
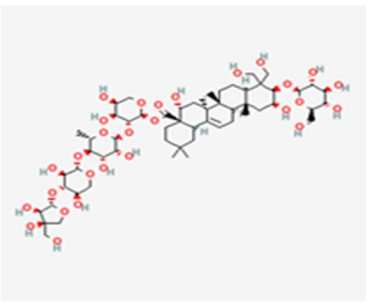
24	Quercetin	
25	Cianidanol	
26	Kaempferol	
27	Berberine	
28	Platycodin D	

Table 2: The Chemical Structures Of The Natural Compounds Were Obtained Using Pubchem.

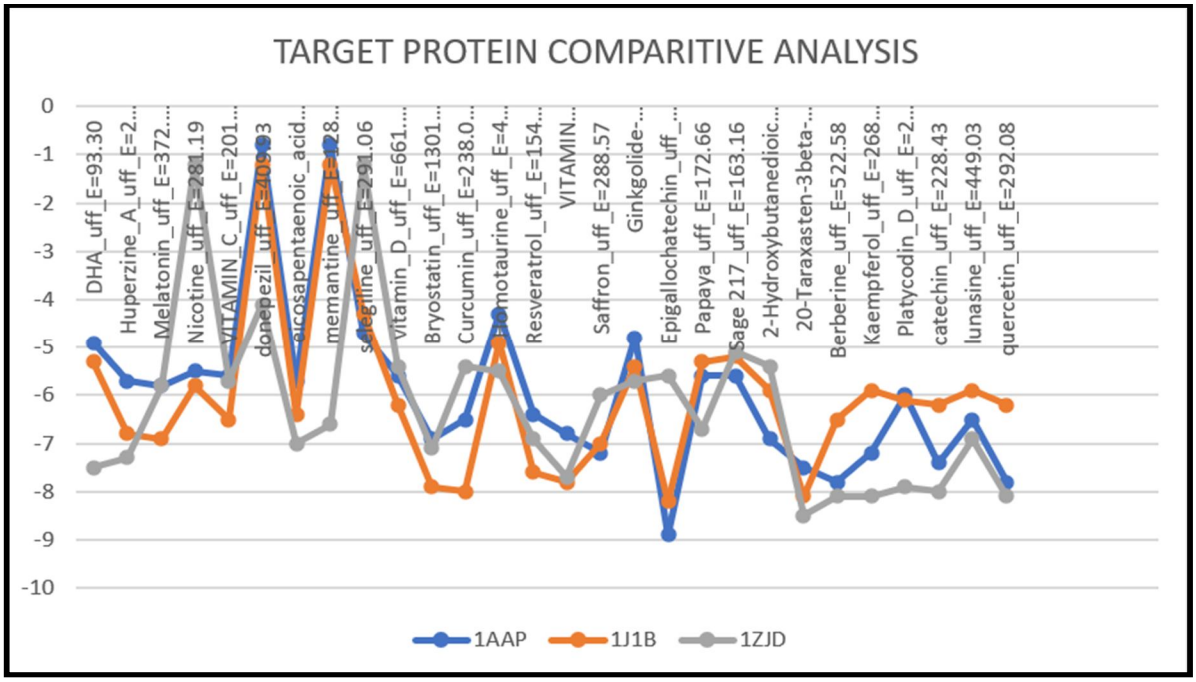
Table3: It represents the binding affinities of natural compounds against target proteins:-

SL.NO.	COMPOUND NAMES	BINDING AFFINITY SCORES		
		1aap	1j1b	1zjd
1	DHA_uff_E=93.30	-4.9	-5.3	-7.5
2	Huperzine_A_uff_E=298.48	-5.7	-6.8	-7.3
3	Melatonin_uff_E=372.84	-5.8	-6.9	-5.8
4	Nicotine_uff_E=281.19	-5.5	-5.8	-1.2
5	VITAMIN_C_uff_E=201.51	-5.6	-6.5	-5.7
6	donepezil_uff_E=409.93	-0.8	-1.2	-4.1
7	eicosapentaenoic_acid_uff_E=83.96	-5.7	-6.4	-7
8	memantine_uff_E=128.88	-0.8	-1.2	-6.6
9	selegiline_uff_E=291.06	-4.7	-4.3	-1.2
10	vitamin_D_uff_E=661.57	-5.6	-6.2	-5.4
11	Bryostatin_uff_E=1301.24_uff_E=1264.88	-6.9	-7.9	-7.1
12	Curcumin_uff_E=238.06_uff_E=237.86	-6.5	-8	-5.4
13	Homotaurine_uff_E=476.94_uff_E=476.72	-4.3	-4.9	-5.5
14	Resveratrol_uff_E=154.09_uff_E=154.00	-6.4	-7.6	-6.9
15	VITAMIN E_uff_E=1135.21	-6.8	-7.8	-7.7
16	Saffron_uff_E=288.57	-7.2	-7	-6
17	Ginkgolide-B_uff_E=49.29	-4.8	-5.4	-5.7
18	Epigallochatechin_uff_E=837.62	-8.9	-8.2	-5.6
19	Papaya_uff_E=172.66	-5.6	-5.3	-6.7
20	Sage 217_uff_E=163.16	-5.6	-5.2	-5.1
21	2-Hydroxybutanedioic acid_uff_E=483.92	-6.9	-5.9	-5.4
22	20-Taraxasten-3beta-ol_uff_E=237.97	-7.5	-8.1	-8.5
23	Berberine_uff_E=522.58	-7.8	-6.5	-8.1
24	Kaempferol_uff_E=268.39	-7.2	-5.9	-8.1
25	Platycodin_D_uff_E=2042.98	-6	-6.1	-7.9
26	catechin_uff_E=228.43	-7.4	-6.2	-8
27	lunasine_uff_E=449.03	-6.5	-5.9	-6.9
28	quercetin_uff_E=292.08	-7.8	-6.2	-8.1

Table 3: Molecular Docking Analysis

The table 3 represents a detailed score review of binding affinities of twenty eight compounds, against three target proteins whose ID is pre-mentioned.

Highest binding affinities are highlighted for which further studies are explained in the discussion below.



Graph1: The graph above is composed using the binding affinities from table 2. It is to be noted here that higher the negative value, higher is the binding affinity.

Natural compounds having good binding scores are considered as potential ligands on which detailed studies were made.
The discussion of the same will be discussed further in the report.

C. Molecular Docking Images

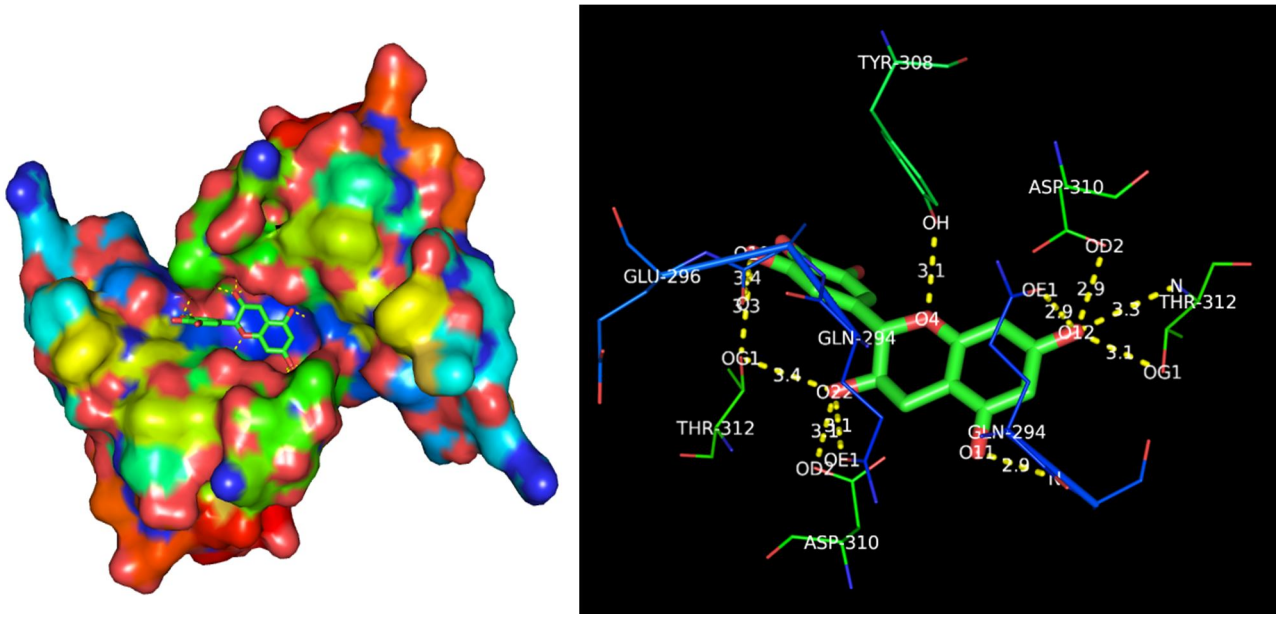


Figure 13: Docking Images Of Binding Pose In Secretase

The above image shows the molecular docking images of secretase as the target protein.
The image clearly shows the presence of 11 hydrogen bonds with good distance and the following amino acids:

- Tyrosine
- Aspartic Acid
- Threonine
- Glutamine
- Glutamic Acid

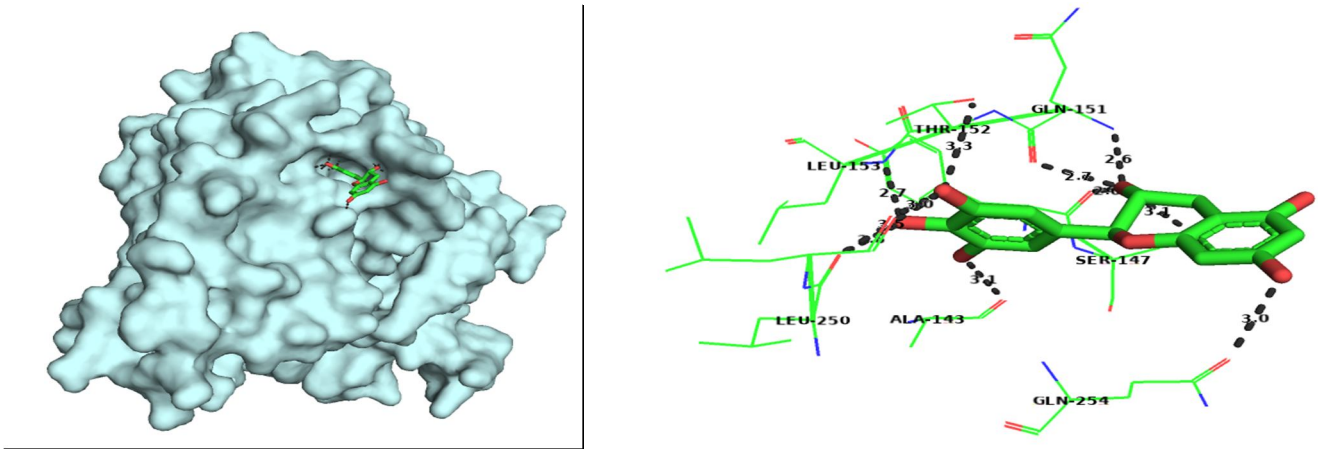


Figure 14: Docking Images Of Binding Pose In Gylcogen Synthase Kinase 3

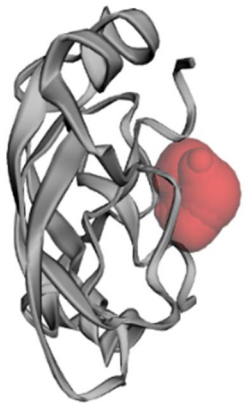
The above image shows the molecular docking images of secretase as the target protein.
The image clearly shows the presence of 11 hydrogen bonds with good distance and the following amino acids:

1) Glutamine
2) Serinine
3) Threonine
4) Alanine
5) Leucin

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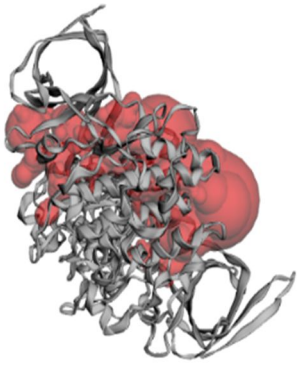
D. Active sites in the 3 target proteins upon castp analysis

1) 1AAP (Secretase)



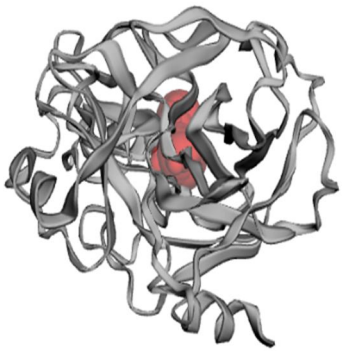
Area (SA)	Volume (SA)
71.420	61.741

2) 1J1B (Glycogen Synthase Kinase-3)



Area (SA)	Volume (SA)
3403.445	5656.284

3) 1ZJD (β-Amyloid A4)



Area (SA)	Volume (SA)
160.008	100.869

Figure 16: Castp Analysis

E. Admet Analysis For The Natural Compounds.

ADMET was performed on all 28 natural compounds to learn about how well they can be incorporated against Alzheimer's. Pkcsm was the online server employed in the ADMET analysis.

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INDEX	SMILES	Absorption(Water solubility)	Absorption(CaCO2 permeability)	Distribution(VDss human)	Distribution(BBB permeability)	Metabolism(CYP1A2 inhibitor)	Excretion(Total clearance)	Toxicity(AMES toxicity)
1	Memantine	-2.663	1.338	0.943	0.586	No	0.914	No
2	Vitamin C	-1.556	-0.255	0.218	-0.985	No	0.631	No
3	Selegiline	-2.334	1.519	1.162	1.015	Yes	1.007	No
4	Donepezil	-5.133	1.27	1.242	0.153	No	1.235	No
5	Docosahexanoic acid (DHA)	-6.098	1.145	-0.709	-0.203	Yes	2.264	No
6	Eicosapentanoic acid	-5.976	1.588	-0.671	-0.145	Yes	2.155	No
7	Homotaurine	-0.179	0.686	-0.784	-0.333	No	0.601	No
8	Huperzine A	-2.496	1.211	0.974	0.105	Yes	0.64	No
9	Bryostatin	-3.716	0.202	0.073	-2.252	No	0.604	No
10	Melatonin	-2.472	1.218	0.082	-0.076	Yes	0.735	No
11	Resveratrol	-3.178	1.17	0.286	-0.048	Yes	0.076	Yes
12	Nicotine	-0.872	1.671	0.595	0.208	Yes	0.86	No
13	Curcumin	-4.01	-0.093	-0.215	-0.562	Yes	-0.002	No
14	Vitamin E	-6.901	1.345	0.709	0.876	No	0.794	No
15	Saffron	-3.281	0.514	-1.475	-0.166	No	1.197	No
16	Ginkgolide-B	-3.856	0.948	0.454	-0.575	No	0.308	No
17	Epigallochatchin (green Tea)	-2.969	-0.375	1.301	-1.377	No	0.328	No
18	1,1-Dimethyl3-phenyl propyl-isobutyrate (papaya)	-4.061	1.863	0.368	0.366	Yes	1.378	No
19	Sage 217	-5.343	0.672	0.218	-0.122	No	0.396	No
20	(2S) Hydroxybutandioic Acid	-1.381	-0.395	-0.998	-0.788	No	0.81	No
21	20-tara xasten-3beta-ol	-6.355	1.221	0.234	0.68	No	0.132	No
22	Lunasine	-2.34	1.846	0.85	0.305	Yes	0.722	No
23	Quercetin	-2.925	-0.228	1.559	-1.098	Yes	0.407	No
24	Cianidanol	-3.117	-0.283	1.027	-1.054	No	0.183	No
25	Kampherol	-3.04	0.032	1.274	-0.939	Yes	0.477	No
26	Berberine	-3.973	1.734	0.58	0.198	Yes	1.27	Yes
27	Platycodin-D	-2.885	-1.398	-0.4	-2.927	No	0.028	No
28	Vitamin D	-6.92	1.223	0.128	0.78	No	0.83	No

Table4: It Represents The Physio-Chemical Properties Of The 28 Selected Compounds

IV. CONCLUSION

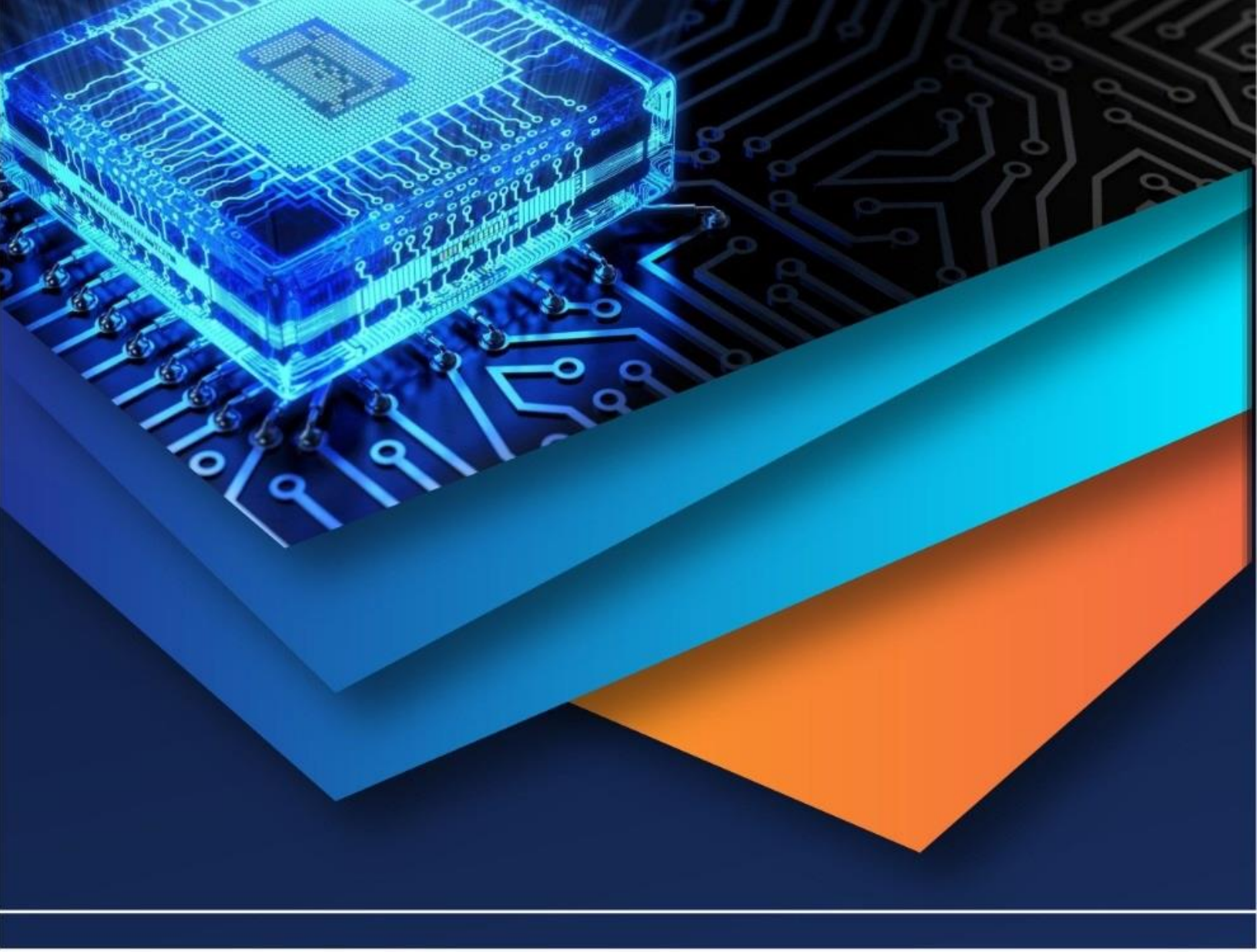
The 3D structure of the three target proteins was elucidated and the active sites of three target proteins was predicted. The 3D structures of the ligand molecules were analysed. Docking results showed that two natural compound Epigallochatechin (EGCC) and 20-taraxasten-3beta-ol are best potential ligands against 3 target proteins with the binding energy of -

Therefore these two are best lead molecules to reduce the effects of Alzheimer's disease after further clinical trials. Pharmacology dynamics through ADMET substantiates the conclusion drawn from our studies.

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