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Molecular Docking Study of Alzheimer Disease Responsible Protein Inhibition Activity by Bioactive Ginkgolides

Ashish Kumar Swami[1], Sangita Sharma[2]
[1, 2]*Department of Chemistry, Hemchandracharya North Gujarat University, Patan-384265, Gujarat, India*

Structured Abstract: ***Terpenoids are major components present in herbal formulations of Ginkgo biloba which are considered to slow down progression of Alzheimer disease. Ginkgolide A, Ginkgolide B, Ginkgolide C, Ginkgolide M, Ginkgolide J, Ginkgolide K and Bilobalide are some of the terpenoids selected for computational theoretical calculations using DFT theory at B3LYP/6-311+G*(d,p) basic set level using Gaussian 16W. To study the interaction between selected terpenoids and selected proteins, molecular docking analysis is carried out using Argus Lab (4.0.1) and Auto Dock (4.2). Calculations are carried out on efficient shape-based search algorithm principle and a score base function to calculate the binding energies between them. ADMET analysis provide properties insight of terpenoids compounds. Results from calculated data reveal that there are possible interactions. This data can help in development of potent protein kinase inhibitor for the treatment of Alzheimer.***
Keywords: Alzheimer Disease; Terpenoid; DFT; Molecular Docking; Binding Energies; Inhibition; Drug Likeness

I. INTRODUCTION

Ginkgo biloba is a living fossil, it is the only survivor of one of the species originated 150 million years ago. Its components in modern science has been identified for the reasons of immutability.[1] Ginkgo biloba have been used as herbal medicine or dietary supplements for treatment of heart disease, eye ailments, tinnitus, cerebral and peripheral vascular insufficiency, injuries involving brain trauma, dementia, short-term memory improvement, cognitive disorders secondary to depression, vertigo, and various cognitive disorders.[2]

Leaves and root bark contain terpenoids, including the monomethyl-mononor diterpenes: Ginkgolide A, Ginkgolide B, Ginkgolide C but Ginkgolide M are found in the root bark; Ginkgolide J, pene Bilobalide in the leaves. Ginkgolides are reported to be antidepressant and antistress effects in different animal models, these appear to be mediated by antagonism of the GABA receptor and show elevating brain catechol amines and plasma corticosterone levels.[3],[4]

Alzheimer Disease marked by a gradual loss of cognitive functioning which can also incorporate losses of motor, emotional, and social functioning as well. It is a permanent and progressive disease that eventually renders people unable to care for themselves.[5]

Till time, there is no particular cure method available for AD, but the pathogenesis of the disease could be delayed by the use of natural antioxidants drugs.[6]

In most high-income country settings, where only around 50% of people living with Alzheimer's receive a diagnosis. In low and middle-income countries, less than 10% of cases are diagnosed. As populations age, due to increasing life expectancy, the number of people with AD is increasing.[7] It is estimate that there will be 50 million people worldwide living with Alzheimer's in 2015. Every year, nearly 10 million new cases are added, implying that 1 new case every 3 seconds and expected to rise to 82 million by 2030.[8-10]

In many articles, research papers and reports suggest that there is a direct physical interaction happen between proteins and antioxidant drug compound. Antioxidant drug compound binds to the protein which reduced neurological disorder activity and free radical generation.[11]

The structures of Ginkgolides A, B, C, J, and M only differ by the number and the position of hydroxyl groups on C1, C3, or C7 of the spirononane framework. In figure I and Table I show Ginkgolides how do defer its name on the basis of the position of hydroxyl groups position on R1, R2, and R3. Figure II is Bilobalide compound.[12-17]

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Table I Positioning of Group OH and H in Ginkgolides

Name	R_1	R_2	R_3
Ginkgolide A	OH	H	H
Ginkgolide B	OH	OH	H
Ginkgolide C	OH	OH	OH
Ginkgolide J	OH	H	OH
Ginkgolide M	H	OH	OH
Ginkgolide K	-	OH	H

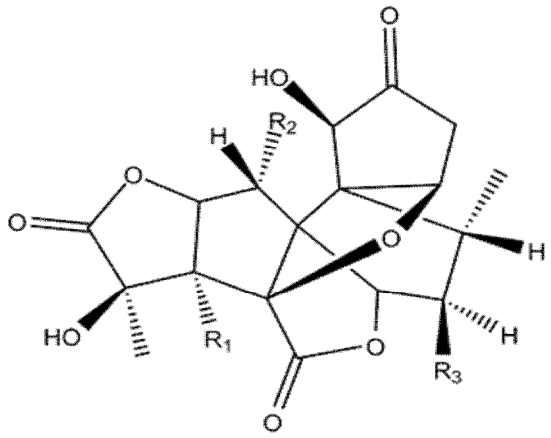


Figure I. Basic structure of ginkgolide with group position

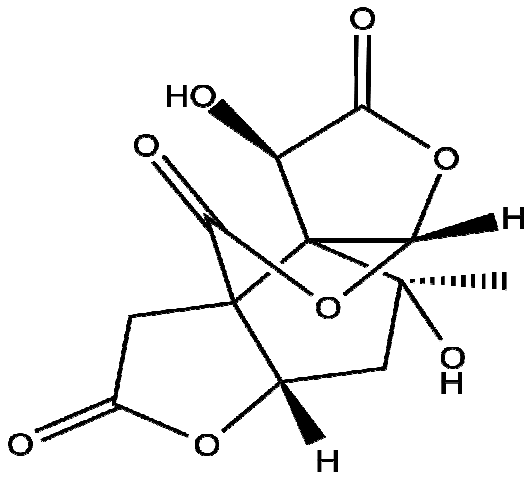


Figure II. Structure of bilobalide

II. MATERIAL AND METHODS

A. Software Used

Gaussian 16W package[18]
Gauss view 6.0[19]
Molecular graphics laboratory (MGL) tools Package (accessed March 14, 2020)
PMV- Python 2.7- language was downloaded from www.python.com(accessed March 17, 2020).[20]

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Msms- MSMS library is used by the Pmv module msms Commands[21]
PCVolRen- The PCVolRen library is used in the PMV module[22]
ADT- AutoDock4.2.6. was downloaded from www.scripps.edu (accessed March 14, 2020)[23]
Isocontour- The isocontour library is used by the Pmv module[24]
Vision- Vision Software is a visual-programming environment[25]
Cygwin (a data storage) c:\program and Python 2.7 were simultaneously downloaded from www.cygwin.com(accessed March 14, 2020)[26]
Argus lab (4.0.1) was downloaded from http://www.arguslab.com/arguslab.com/ArgusLab.html(accessed March 7, 2020)[27]

B. Preparation and Optimization of Terpenoids

Chemical 3D structures of the selected terpenoids namely Ginkgolide A, Ginkgolide B, Ginkgolide C, Ginkgolide M, Ginkgolide J, Ginkgolide K and Bilobalide were retrieved from the Pub Chem database[28] and were optimized in Gaussian 16W software[18] using Density Functional Theory (DFT) by Becke gradient corrected exchange functional[29] and Lee-Yang-Parr correlation functional[30] with three parameters B3LYP method at 6-31+G* basis set level[31] Optimized structure of selected terpenoids were subjected to arrange energy minimization using Auto dock and Argus lab.

C. Preparation of Protein Structures

The solution structure of the β-amyloid protein Aβ-peptide chain (1–42) (PDB ID: 1IYT) and Binary complex structure of human tau protein kinase (PDB ID: 1J1C) was retrieved from the RCSB Protein Data Bank (PDB)[32] and necessary changes like removal of water molecules, extra chains and heteroatoms were done using 'Prepare Protein' module of Auto Dock 4.2.6.[23]and Argus Lab 4.0.1[27]

D. Pharmacokinetic Analyses of Ligands

The pharmacokinetic profile of the selected terpenoids was determined by optimizing their ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) clarification properties using swiss ADME[33] server online and toxicity calculated from PreADMET[34] server online data shown in Table II.

E. Drug Likeness Assessment

Insilco methods are computer-based methods widely used in the pharmacological field of science to help discover inhibitors with high binding capabilities with a protein target, drug-likeliness properties.[35] Other drug likeness rules like Lipinski's rule[36], Veber rule[37], MDDR-like rule[38], Ghose filter[39], BBB rule[40], CMC-50[41] and Quantitative Estimate of Drug-likeness (QED)[42] like rule are also applied. Drug-like properties of the selected terpenoids, were analyzed on the basis of physical properties, namely molecular weight (Mol.wt.), partition coefficient (AlogP), number of hydrogen bond acceptors (Num H acceptor) and number of hydrogen bond donors (Num H donor).[43]

F. Molecular Docking

The selected seven terpenoids with neuroprotective properties were subjected to molecular docking with both the targets, namely B-amyloid Aβ-peptide (1–42) and Tau protein kinase using Argus lab and Auto Dock 4.2.6. Best conformations were generated using the genetic algorithm for each compound in Auto dock and Argus lab software. Auto Dock 4.2.6 estimates binding energy and inhibitory constant of the ligands with respect to their targets on the basis of Lamarckian genetic algorithm.[44] The binding free energy was empirically calculated based on the energy terms and a set of coefficient factors. A three-dimensional grid of interaction energy was calculated using Auto Grid based on the macromolecular coordinates and the docking simulations were performed using Auto Dock 4.2.6. The binding energy and inhibition constant (Ki) are expressed as kcal/mol and micromolar (μm), respectively and was used to rank the docking positions of the terpenoids.[45] All analysis was done at 298.15 k temperature and proteins molecules were considered in rigid form and terpenoids in flexible form during docking. In this molecular docking analysis, there are some of the same residues take participated in both software. But we found binding energy level data are different.

1) *Argus Lab:* Docking with Argus software was that 1iyt protein kinase of β-amyloid protein as targeted at DEF binding site with selected residue of amino acid like 21ALA, 23ASP, 22GLU, 25GLY, 17LEU, 16LSY, 19PHE, 20PHE, 18VAL, 24VAL interacting with selected terpenoids and a new pose are garneted with specific values of energy. Binding site is selected with Site Box 30 x 30 x 30 angstroms dimensional and with 0.4 Grid resolution. For the AScore scoring function and ascore.prm parameter set was used to study this binding process. Docking engine generated energy data on the basis of Lamarckian Genetic Algorithm.

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Similarly, 1j1c protein kinase of tau-protein was targeted at ADP binding site of chain-A amino acid. This amino acid has 83 ALA, 141 ARG, 64 ASN,186 ASN, 186 ASN, 133 ASP, 200 ASP, 185 GLN,65 GLY, 62 ILE, 132 LEU, 188 LEU, 85 LYS, 67 PHE, 66 SER, 134 TYR, 110 VAL, 135 VAL and 431 MG residue where interacted with seven terpenoid. All other selected parameter like scoring function, gird resolution, parameter set, binding site box dimensions and dock engine are same as used in case of β-amyloid protein.

2) *Auto Dock:* In auto dock software, the selected conditions are same as used in Argus lab software except site box size 110 x 110 x 110 angstroms and Grid resolution with volume of 1.0. When docked with selected terpenoids, 1iyt-kinase protein residues were not exactly same but are namely HIS 13, GLY 9, VAL 12, HIS 14, TYR 10, GLN 15, LYS 16, PHE 19, TYR 10, ASP 7, GLU3, GLU11, HIS 6, LEU 17, PHE 20, ALA 21, DEF 85, VAL 24, GLY 25, MET 35, LYS 28.

In case of tau protein 1j1c kinase residues again change as new residues are ADP 930, MG 931, GLN 685, PHE 360, ARG 383, THR 356, PRO 357, ARG 720, GLN 765, GLY 759, ASP 760, SER 761, ARG 220, ARG 723, TYR 716, GLY 762, GLN 265, GLY 262, ILE 228, TYR 517, LYS 594, PHE 523, VAL 626, LYS 591, PHE 67, VAL 69, LYS 86, GLY 68, TYR 127, LYS 771, GLN 599, LYS 594, LYS 591, TYR 617, LYS 123, GLU 125, LEU 88, GLN 795, ASP 90, LYS 91, and GLN 89 and that show interaction with terpenoids.

III. RESULTS AND DISCUSSION

β-amyloid protein Aβ-peptide (1–42) chain, a major component of amyloid plaques accumulates in neurons of AD brains.[46] Biochemical analysis of the amyloid peptides isolated from Alzheimer's disease brain indicates that β-amyloid protein Aβ-peptide (1–42) chain is the principal species associated with senile plaque amyloids, while β-amyloid (1-40) chain is more abundant in cerebrovascular amyloid deposit.[47] Tau proteins is member of microtubule associated with proteins this family. Microtubule-stabilizing protein abundant in neurons of the CNS. The tau abnormal function leads to neurodegenerative disorders. Tau is a phosphoprotein with 79 potential serine (Ser) and threonine (Thr) phosphorylation sites on the longest tau isoform. Phosphorylation has been reported on approximately 30 of these sites in normal tau proteins.[48] Understand computationally and biologically study of genetically programmed molecular mechanism that may help in the development of new therapeutic methods as well as in identification of antioxidant compound for finding a cure of AD.[49],[50] Therapeutic advancement approaches in AD study has provided better results of interaction with target molecules with its best physicochemical properties of selected drugs.[51] Proteins inhibitory activity leads antioxidant drug protease neurological disorders. This study checks the inhibition of proteins through computational theoretical analysis. Selected terpenoids compounds play vital role in finding of binding interface between the receptor and ligands.[52]

A. ADMET Analyses Rule

The ADMET descriptors used to describe these properties include aqueous solubility, blood–brain barrier penetration, CYP2D6 binding, human intestinal absorption, plasma protein binding (PPB) and hepatotoxicity and ADMET prediction for selected terpenoids are shown in Table II.

In this Table II calculated data are Presented in five parts (1) Physiochemical Properties (2) Lipophilicity (3) Water solubility (4) Pharmacokinetics (5) Druglikness.[53]

As for as Drug likeness rules are considered five different rules are applied to selected seven terpenoids. All the seven terpenoids fulfill all the conditions of Lipinski's rules except GC which does not follow second condition. In case of veber rules all terpenoids follow first condition but second condition followed by GA, GK and BB while other does not follow.

MDDR-like rule is followed by all terpenoids considering its all condition. In case of Ghose filtter rule GM and BB do not follow first condition but all other condition is followed by all the selected terpenoids. In case of BBB rule all terpenoids successfully fill to three condition of the rule.

CMC-50 rule is fully followed by all the selected compounds. QED rules is combination of eight characteristics condition which are already studied in above mention rules. All the terpenoids are drug like on the basis of in silico studies fulfill ADMET criteria and thus could subsequently be further experimentally screened using in vitro or in vivo strategies for new potential tool for further research study for AD.[54]

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Table II. Admet Properties Calculation [34],[35], [55], [56], [57],[87]

Physiochemical Properties									References
Sr.No.	Terpenoids	BB[a]	GA[b]	GB[c]	GC[d]	GJ[e]	GM[f]	GK[g]	
1	Formula	$C_{15}H_{18}O_8$	$C_{20}H_{24}O_9$	$C_{20}H_{24}O_{10}$	$C_{20}H_{24}O_{11}$	$C_{20}H_{24}O_{10}$	$C_{20}H_{24}O_{10}$	$C_{20}H_{22}O_9$	
2	Molecular Weight	326.3	408.4	424.4	440.4	424.4	424.4	406.38	[58]
3	#Heavy atoms	23	29	30	31	30	30	29	[58]
4	#Aromatic heavy atoms	0	0	0	0	0	0	0	[58]
5	Fraction Csp3[h]	0.8	0.85	0.85	0.85	0.85	0.85	0.75	
6	#Rotatable bonds	1	1	1	1	1	1	1	[58]
7	#H-bond acceptors	8	9	10	11	10	10	9	[58]
8	#H-bond donors	2	2	3	4	3	3	2	[58]
9	MR[i]	71.2	92.13	93.29	94.45	93.29	93.25	91.62	[58]
10	TPSA[j]	119.36	128.59	148.82	169.05	148.82	148.82	128.59	[59]
11	Number of Electrons	172	216	224	232	224	224	216	
Lipophilicity									
12	iLOGP[k]	0.81	1.12	1.63	0.93	1.23	0.72	1.7	[60]
13	XLOGP3[l]	-0.27	0.59	-0.38	-1.36	-0.38	-0.3	0.1	[61]
14	WLOGP[m]	-0.74	-0.34	-1.37	-2.4	-1.37	-1.51	-0.42	[62]
15	MLOGP[n]	0.42	0.83	0.06	-0.7	0.06	0.06	0.74	[63],[64]
16	Silicos-IT Log P [o]	0.57	0.81	-0.07	-0.96	-0.07	-0.47	0.8	[65]
17	Consensus Log P[p]	0.16	0.6	-0.03	-0.9	-0.11	-0.3	0.58	[66]
Water solubility									
18	ESOL Log S[q]	-1.63	-2.68	-2.17	-1.65	-2.17	-2.22	-2.36	[67]
19	ESOL Solubility (mg/ml)	7.7	0.858	2.9	9.91	2.9	2.58	1.79	[67]
20	ESOL Solubility (mol/l)	0.0236	0.0021	0.00683	0.0225	0.00683	0.00608	0.0044	[67]
21	ESOL Class	Very soluble	Soluble	Soluble	Very soluble	Soluble	Soluble	Soluble	[67]
22	Ali Log S[r]	-1.78	-2.86	-2.28	-1.69	-2.28	-2.37	-2.36	[68]
23	Ali Solubility (mg/ml)	5.45	0.559	2.22	8.99	2.22	1.83	1.79	[68]
24	Ali Solubility (mol/l)	0.0167	0.00137	0.00522	0.0204	0.00522	0.00431	0.00441	[68]
25	Ali Class	Very soluble	Soluble	Soluble	Very soluble	Soluble	Soluble	Soluble	[68]
26	Silicos-IT LogSw	-1.12	-1.59	-0.77	0.06	-0.77	-0.32	-1.57	[65]
27	Silicos-IT Solubility (mg/ml)	24.8	10.6	72.7	500	72.7	205	11	[65]
28	Silicos-IT Solubility (mol/l)	0.0759	0.0259	0.171	1.14	0.171	0.483	0.027	[65]
29	Silicos-IT class	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	[65]
Pharmacokinetics									
30	GI absorption[s]	High	High	Low	Low	Low	Low	High	[69]
31	BBB permeant[t]	No	No	No	No	No	No	No	[36]
32	Pgp substrate[u]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[70]
33	CYP1A2 [v] inhibitor	No	No	No	No	No	No	No	[71],[76],[77]
34	CYP2C19 [w] inhibitor	No	No	No	No	No	No	No	[72],[76],[77]
35	CYP2C9 [x]	No	No	No	No	No	No	No	[73],[76],[77]

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	inhibitor								
36	CYP2D6 [y] inhibitor	No	No	No	No	No	No	No	[74],[76],[77]
37	CYP3A4 [z] inhibitor	No	No	No	No	No	No	No	[75],[76],[77]
38	log Kp (cm/s)[aa]	-8.48	-8.37	-9.16	-9.95	-9.16	-9.1	-8.71	[78]
	Druglikness								
39	Lipinski #violations	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	No; 1 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	[36]
40	Ghose #violations	No; 1 violation	Yes; 0 violation	No; 1 violation	No; 1 violation	No; 1 violation	No; 1 violation	No; 1 violation	[39]
41	Veber #violations	Yes; 0 violation	Yes; 0 violation	No; 1 violation	No; 1 violation	No; 1 violation	No; 1 violation	Yes; 0 violation	[37]
42	Egan #violations	Yes; 0 violation	Yes; 0 violation	No; 1 violation	No; 1 violation	No; 1 violation	No; 1 violation	Yes; 0 violation	[79]
43	Muegge #violations	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	No; 2 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	[80]
44	Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	[81]
45	PAINS #alerts	Zero alert	Zero alert	Zero alert	Zero alert	Zero alert	Zero alert	Zero alert	[82]
46	Brenk #alerts	1 alert	1 alert	1 alert	1 alert	1 alert	1 alert	1 alert	[41]
47	Leadlikeness #violations	Yes; 0 violation	No; 1 violation	No; 1 violation	No; 1 violation	No; 1 violation	No; 1 violation	No; 1 violation	[83]
48	Synthetic Accessibility(SA)	5.41	6.28	6.38	6.48	6.39	6.42	6.51	[84]
	Toxicity								
49	algae_at	0.177817	0.118374	0.157742	0.192339	0.166682	0.201843	0.124129	[85],[86]
50	Ames_test	non-mutagen	non-mutagen	non-mutagen	non-mutagen	non-mutagen	non-mutagen	non-mutagen	
51	Carcino_Mouse	negative	negative	negative	negative	negative	negative	negative	
52	Carcino_Rate	positive	positive	Positive	positive	positive	positive	positive	
53	daphnia_at	2.85214	3.077	2.00595	4.52813	3.06871	2.33042	0.789767	
54	hERG_inhibition	low_risk	low_risk	low_risk	ambiguous	low_risk	low_risk	low_risk	
55	medaka_at	9.75825	11.898	5.61048	27.5974	12.516	7.56479	0.930873	
56	minnow_at	6.79135	4.5476	7.31948	31.3197	8.25605	11.9864	1.36771	
57	TA100_10RLI	negative	negative	negative	negative	negative	negative	negative	
58	TA100_NA	negative	negative	negative	negative	negative	negative	Negative	
59	TA1535_10RLI	negative	negative	negative	negative	negative	negative	Negative	
60	TA1535_NA	negative	negative	negative	negative	negative	negative	Negative	

[a] BB- Bilobalide; [b]GA- Ginkgolide A; [c] GB- Ginkgolide B; [d] GC- Ginkgolide C; [e] GM- Ginkgolide M; [f] GJ- Ginkgolide J; [g] GK- Ginkgolide K; [h] Fraction Csp3-fraction of sp3 carbon; [i] MR- molecular refractivity; [j] TPSA-Topological Polar Surface Area; [k] iLOGP – implicit log P method; [l] XLOGP3- pure atom-additive model ; [m] WLOGP-Water Partition Coefficient; [n] MLOGP- Moriguchi method Partition Coefficient [o] Silicos-IT Log P- FILTER-IT (version 1.0.2) 2013, http://silicos-it.be.s3-website-eu-west-1.amazonaws.com/software/filter-it/1.0.2/filter-it.html [p] Consensus Log P- n-octanol/water partition coefficient [q] ESOL LogS -Estimated SOLubility Log S; [r] Ali Log S- Ali et al. linked log S with log Po/w [s] GI: Gastro Intestinal [t] BBB: Blood Brain Barrier [u] ; Pgp-P-glycoprotein; [v] CYP1A2: Cytochrome P450 family 1 subfamily A member 2 [w] CYP2C19- cytochrome P450 2C19 [x] CYP2C9-cytochrome P450 2C9 [y] CYP2D6: cytochrome P450 (CYP) 2D6 [z] CYP3A4- Cytochrome P450 3A4 [aa] Log Kp -Skin permeation coefficient.

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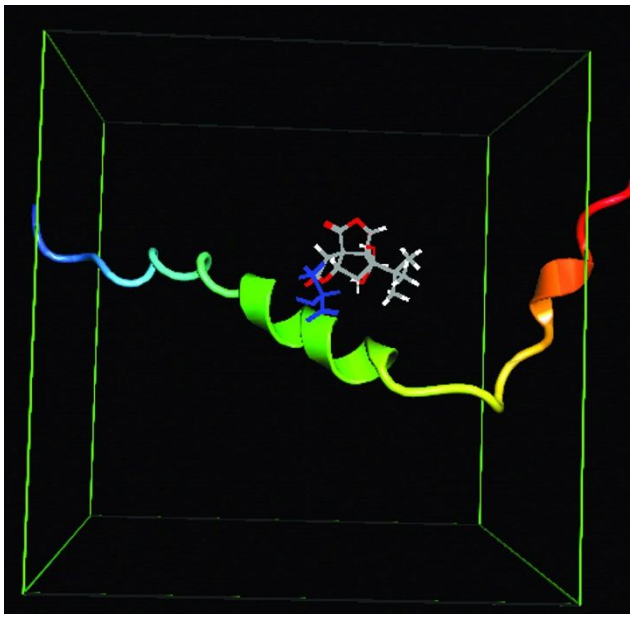


Figure III. Terpenoids docking interaction in Argus lab software with 1iyt protein kinase (GB interacted with 1iyt)

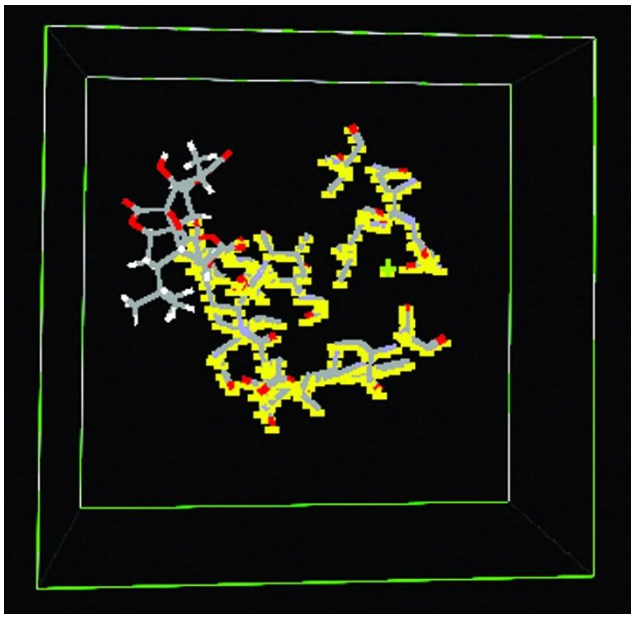


Figure iv. Terpenoids docking interaction in argus lab software with 1j1c protein kinase(GC interacted with 1iyt)

B. Docking Analysis

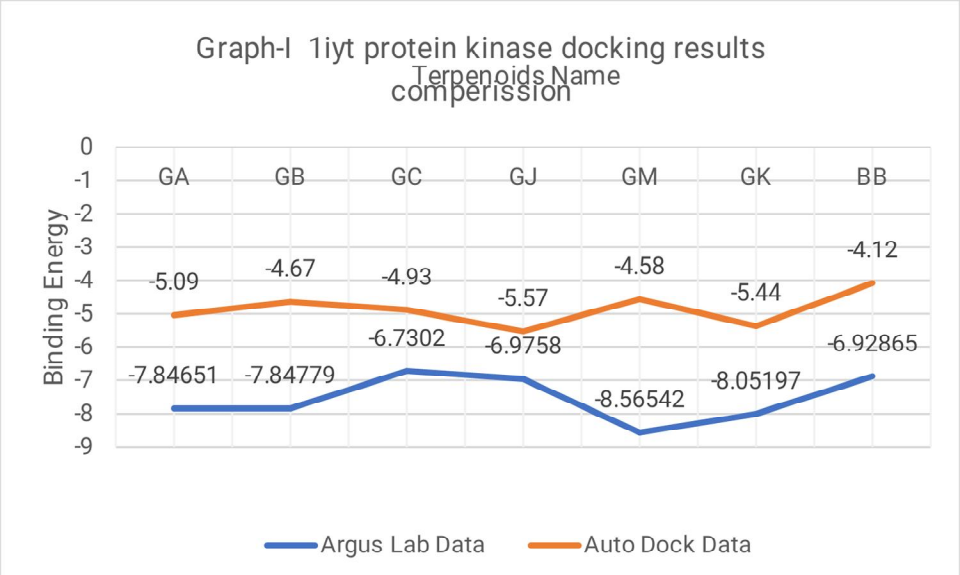
Results calculated from Argus lab 4.0.1 and Auto Dock 4.2.6 are compared in Table III. Figure III and Figure IV show interaction for β-amyloid protein and tau protein in Argus lab software respectively. Binding energy calculated for β-amyloid protein 1iyt kinase interaction level of energy with Argus Lab software between -6.7 to -8.5 kcal. $mole^{-1}$ and for tau protein 1j1c kinase interaction level of energy between -5.9 to -9.0 kcal. $mole^{-1}$. Similarly, the binding energy obtained by that two type of interactions with Auto Dock software are in range of -4.1 to -5.6 kcal. $mole^{-1}$ for 1iyt kinase of β-amyloid protein and -4.6 to -6.0 kcal. $mole^{-1}$ for 1j1c kinase Tau proteins. Here Ginkgolide-J gives highest docking interaction with β-amyloid protein 1iyt kinase is -5.57 kcal. $mole^{-1}$ and with Tau proteins 1j1c kinase is -5.95 kcal. $mole^{-1}$ in Auto Dock Software.

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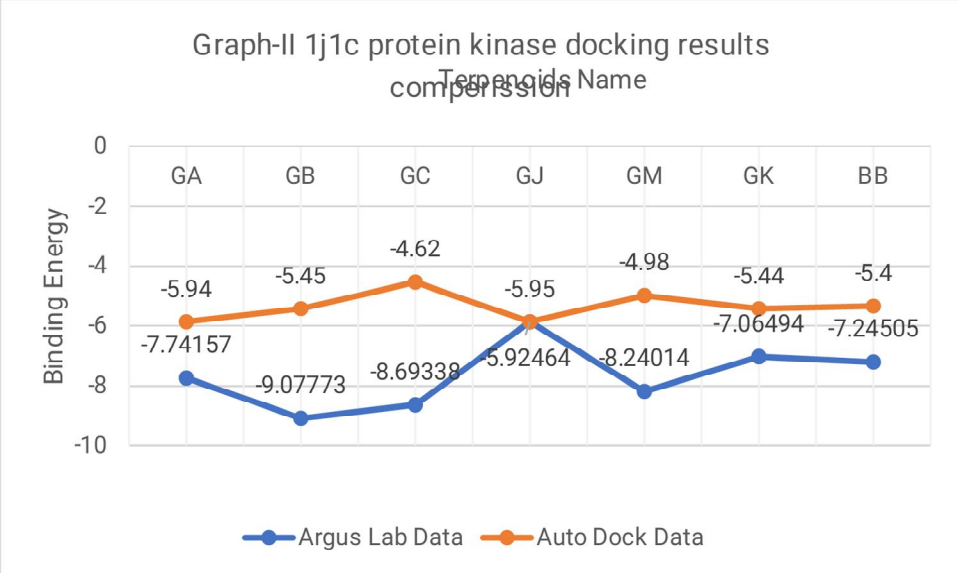
Table III. Docking analysis data of terpenoids with selected proteins.

Sr. No.	Terpenoids	Docking Score with B-amyloid Kinase- 1iyt			Docking Score with Tau Protein Kinase-1j1c		
		Argus Lab kcal/mol	inhibition constant (Ki)uM (micromolar)	Auto Dock kcal/mol	Argus Lab kcal/mol	inhibition constant (Ki)uM (micromolar)	Auto Dock kcal/mol
1	Ginkgolide A	-7.84651	185.77	-5.09	-7.74157	43.96	-5.94
2	Ginkgolide B	-7.84779	377.73	-4.67	-9.07773	100.79	-5.45
3	Ginkgolide C	-6.73020	244.54	-4.93	-8.69338	407.98	-4.62
4	Ginkgolide J	-6.97580	82.45	-5.57	-5.92464	43.22	-5.95
5	Ginkgolide M	-8.56542	440.86	-4.58	-8.24014	225.33	-4.98
6	Ginkgolide K	-8.05197	102.59	-5.44	-7.06494	102.21	-5.44
7	Bilobalide	-6.92865	962.15	-4.12	-7.24505	110.31	-5.40

In Argus Software, Ginkgolide-M shows highest docking interaction with β-amyloid protein 1iyt kinase is -8.56542 kcal. mole-1 but with Tau proteins 1j1c kinase Ginkgolide-B shows highest docking interaction is -9.07773 kcal. mole-1. In this software study we found auto dock software result are valid as compared than Argus lab software because in every time in Argus lab software we found different value of interaction time, name of residues interaction and values of binding energy. May be this the limitation of Argus software as compare than auto dock software. Both software comparative result study data shown in Graph-I for and Graph-II.



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Negative values of binding energy suggest for that interactive behavior with these selected terpenoids and respective site. Generally, in binding process hydrogen bonding and Vander Waal, Covalent, Charge, Polar and Pi-interaction.[88] Many times, a cluster of interactions is also observed, which is seen in our study and shown in figure V and figure VI at the binding sites.

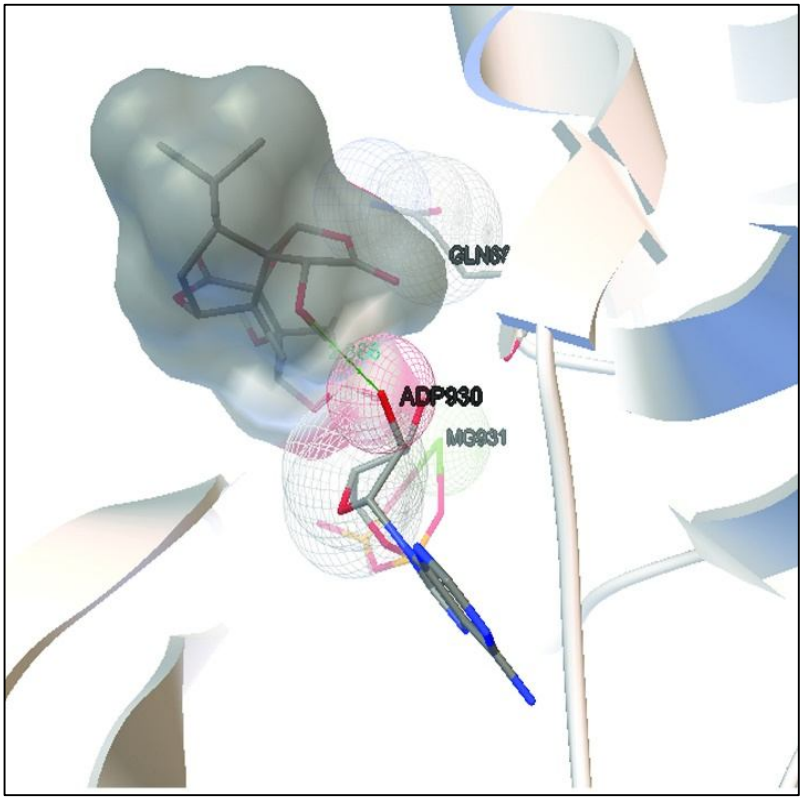


Figure V. Terpenoid docking interaction in autodock software with 1iyt protein kinase (GA interacted with 1iyt)

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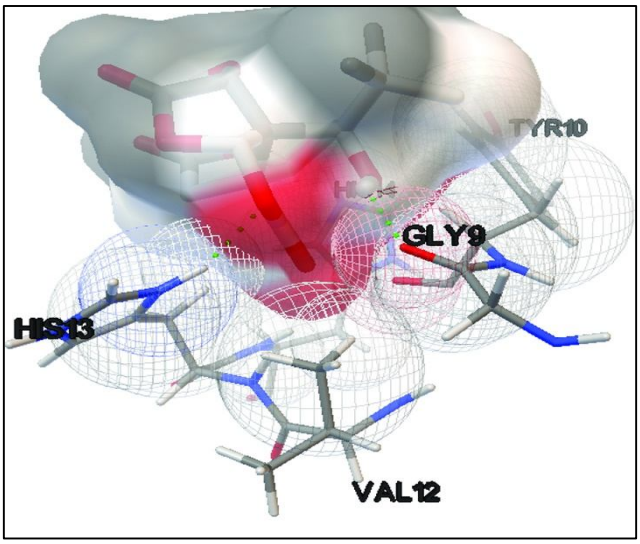


Figure VI. Terpenoids docking interaction in autodock software with 1j1c protein kinase (BB interacted with 1j1c)

IV. CONCLUSION

All the selected terpenoids show drug likeness character as predicted by ADMET and Drug likeness rule. All the selected terpenoids showed better alignment with active site of all amino acid residues. Binding energy values are negative for all the terpenoids indicating for interaction between β-amyloid and tau proteins kinases. Terpenoids namely Ginkgolide A, Ginkgolide B, Ginkgolide C, Ginkgolide M, Ginkgolide J, Ginkgolide K and Bilobalide may be responsible decreasing Alzheimer's in patients using Ginkgo biloba contents. Auto Dock gives better interaction sites visualization than Argus lab. Auto Dock software gives stability in result data of docking as compared to Argus Lab but these compounds necessary to investigate further research. we should be done clinical trials.

V. LIST OF ABBREVIATIONS

AD- Alzheimer disease
DFT- Density Functional Theory
B3LYP- Becke gradient corrected and Lee-Yang-Parr correlation functional
GABA-Gamma-AminoButyric Acid
MGL- Molecular Graphics Laboratory
3D- Three Dimensional
PDB- Protein Data Bank
ADMET- Absorption, Distribution, Metabolism, Excretion, and Toxicity
MDDR-Modern Drug Data Report
BBB- Blood brain barrier
CMC-50- Comprehensive Medicinal Chemistry drug-like index at 50%
QED- Quantitative Estimate of Drug-likeness
Mol.wt- Molecular Weight
ADP- Adenosine Diphosphate
CNS-Central Nervous System
GA- Ginkgolide A
GB- Ginkgolide B
GC- Ginkgolide C
GM- Ginkgolide M
GJ- Ginkgolide J
GK- Ginkgolide K
BB- Bilobalide

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VI. ACKNOWLEDGEMENTS

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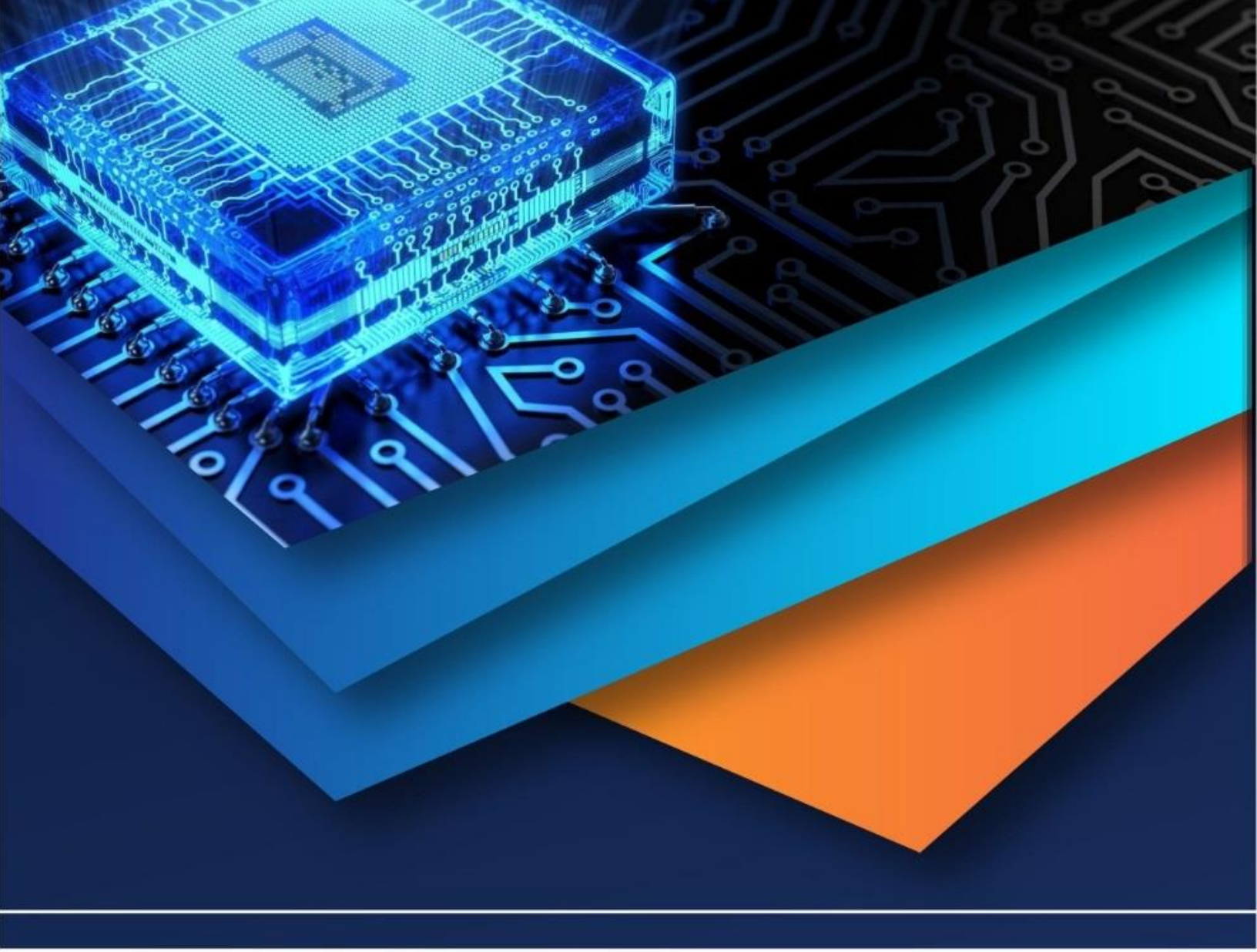
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