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Comparative Anti–Alzheimer's Potential Evaluation of Curcumin and Curcumin Analogues obtained from ZINC Database: An *in-Silico* Validation

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Abstract

Curcumin and its eleven analogues obtained from the ZINC database were screened for its anti-Alzheimer's potential validated through in silico approach. Curcumin, eleven curcumin analogues from the ZINC database, and six standard anti-Alzheimer's drugs were obtained from SWISS ADME and Pub chem database. All obtained molecules were subjected to drug-likeness, molecular docking, and ADMET analysis. Curcumin and eleven curcumin analogues show no violations against five drug-likeness rules, whereas 2 standard drugs (CID_11269353, CID_46883536) out of 5 screened standard drug molecules shows violations in drug likeness property. Curcumin and curcumin analogues possess docking scores in the range of -7.5 to 9.9 Kcal/mol, whereas reference standard drugs docking score lies in the range of -6.4 to -11.0 Kcal/mol against all three Alzheimer's disease molecular targets. Finally, our present study has proven that curcumin analogues possess some novel anti-Alzheimer's properties over curcumin and standard reference drug. It needs to be validated and commercialized after in vivo preclinical trials.

Keywords: *Alzheimer's, Curcumin, Curcumin analogues, In silico, ZINC.*

Introduction

In the senescence phase of life, dementia is the most frequent problem. Dementia is the common term for loss of memory, language, problem-solving, and other thinking skills that are severe enough to impair daily life. Alzheimer's disease is the most important reason for dementia. Alzheimer's disease (AD) is a progressive neurological disorder that causes atrophy and death of brain cells. There are several factors that cause AD, but the most important factor is age. Approximately one in ten people over the age of 65 and close to 50% of people over 85 develop AD [1]. Early signs of this disease include forgetting recent events or conversations. As the disease progress, a person with AD will develop serious memory problems and lose the capacity to carry out their daily tasks. The pathological study of AD shows the deposition of amyloid-beta in the brain, neuritic plaque, neuro-fibrillary tangles, and rapid loss of synapses, and degeneration of basal cholinergic neurons [2].

The pathophysiology of this disease is quite complex and not completely understood. But in recent times, there are few hypotheses that tell the cause of this disease which includes cholinergic, amyloid, and Tau hypothesis. Considering the cholinergic and amyloid hypotheses for the cause of AD took three target enzymes, they are acetyl choliene esterase (AChE), butryl choline estraese (BuChE), and beta-secretase. Because, Acetylcholine (ACh), being the most important neurotransmitter found in CNS, is hydrolyzed by cholinesterases. Cognitive impairment is associated with the loss of Ach that are caused

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by reduced activity of choline acetyltransferase. From this perspective, we must focus on anticholinergenic drugs, which can inhibit both enzymes and up-regulate the level of Ach in CNS [3]. In Alzheimer's patients, we observe that the BuChE activity increases from 40%-90% and the AChE activity will neither remains the same nor gets decline [4]. Evidence has shown that AChE and BuChE both play an important role in accelerated pro-aggregation of β-Amyloid (Aβ) fibrils formation [5]. According to **beta amyloid hypotheses**, overproduction, and aggregation of Aβ peptide (**amyloid beta peptide)** leads to the formation of neuritic plaques in the CNS [6, 7]. Enzymes like beta-secretase cleavage enzyme (BACE 1) and gamma-secretase (γ secretase) are responsible for the formation of β amyloid peptides. So, in this case, β secretase is an important target for the development of the Anti-Alzheimer drug.

The treatment for AD is currently inadequate. Drugs approved by the FDA are limited to choline esterase inhibitors (such as tacrine, galantamine, dopepezil, rivastigamine) and an N-methyl-D-asperate (NMDA) antagonist (mematine) [8-10]. The above-approved agents are used for the treatment of symptoms, which can temporarily overcome memory and thinking problems. But research into specific drugs for this disease is still underway. The symptomatic drugs mentioned above causes side effects such as nausea, vomiting, anorexia, diarrhea, bradycardia, headache, insomnia, fatigue, auditory hallucination, and mild allergies [11-13].

In the present study, we are spotlighting on curcumin (a bright yellow chemical produced by plants of *Curcuma longa* species) and its ZINC analogues for treating AD. Because it has been used in various kinds of treatments like dementia and traumatic brain damage. Curcumin as an antioxidant, anti-inflammatory, and lipophilic action improves cognitive function in patients with AD. Due to various effects of curcumin, such as decreased Beta-amyloid plaques, delayed degradation of neurons, metal-chelation, anti-inflammatory, antioxidant, and decreased microglia formation, the overall memory in patients with AD has improved [14-17]. In the present study, a *silico*-based method was employed to identifying novel drug candidates from curcumin, and its ZINC database analogues useful in the treatment of AD was investigated.

Materials and Methods

Ligands Selection

Potential anti–Alzheimer's molecule curcumin and its closely related curcumin analogues (from the ZINC database) were chosen for the present study. To find out closely related curcumin analogues, curcumin (CID_969516) molecule SMILE notion obtained from PubChem database was pasted in the Swiss similarity tool of SWISS ADME online server to find the closely related curcumin analogue molecules from the ZINC database. Swiss similarity score cut off 0.8 was set as search criteria. 11 molecules of curcumin analogues possess swiss similarity score greater than 0.8 were selected and utilized for further *in silico* study.

Ligand Generation

The 2D SDF file formats of 11 curcumin analogues from the ZINC database were obtained from the SWISS ADME server. Curcumin (CID_969516), Six reference standard drugs Donepezil (CID_3152), Rivastigmine (CID_77991), Galantamine (CID_9651), Begacestat (CID_11269353), Avagacestat (CID_46883536), Semagacestat (CID_9843750) 2D SDF structures were obtained from Pubchem database server. The obtained 2D SDF files were submitted to an online SMILES converter and structure file generator and converted into 3D PDB file formats of ligands [18]. The obtained 3D PDB files were utilized for further study. Molecules selected for the present study is presented in Table 1.

Table 1. Curcumin, Curcumin Analogues obtained from ZINC Database, Standard Drugs for Alzheimers Disease

S. No	Compound Category	Compound	Pubchem/Zinc Database ID
1	Curcumin	Curcumin	CID_969516
2	Curcumin Analogues	Curcumin Analogues Obtained from ZINC Database	ZINC00607794
3			ZINC00856144
4			ZINC04468855
5			ZINC04802476
6			ZINC07333416
7			ZINC13119472
8			ZINC13519235
9			ZINC17251958
10			ZINC18066836
11			ZINC31904839
12			ZINC33518298
13	Standard drugs for Alzheimer's Disease	Donepezil	CID_3152
14		Rivastigmine	CID_77991
15		Galantamine	CID_9651
16		Begacestat	CID_11269353
17		Avagacestat	CID_46883536
18		Semagacestat	CID_9843750

Drug-Likeness Property Calculation

Drug likeness nature of the curcumin, 11 curcumin analogues, and six reference standard drugs for Alzheimer's disease were analyzed using the SWISS ADME online server and examined based on the violations of drug-likeness rules such as Lipinski, Ghose, Veber, Egan, and Muegge. Compounds possessing zero violations were considered as good drug candidate molecules.

Compounds without violations and one, two, three violations are ranked descending order for *in silico* virtual screening of drug molecule for a given disease.

Receptors Preparation and Molecular Docking

To determine the anti-Alzheimer's activity of the curcumin and its analogues from the ZINC database, 3D crystal structure of three important Alzheimer's disease protein targets Acetyl Choline Esterase (PDB ID: 3LII), Butryl Choline Esterase (PDB ID: 6QAA), Beta Secretase (PDB ID: 4D8C) chosen and their three-dimensional structures were retrieved from Protein Database (PDB www.rcsb.org) [19]. AutoDockVina was used to explore the binding affinities between the receptors and ligands [20]. The grid map and grid size were calculated using auto grid to represent the protein binding size for docking. Optimal grid boxes are set for all three target proteins using autodock tools. Assessment of docking (~ 100 times), size of population (150), energy evaluation (maximum number 250,000) generations (maximum number 27,000), rate of mutations (0.02), rate of cross-over (0.8), the value of elitism (1) and other parameters set as default. The docking interactions were analyzed using receptor-ligand interaction options in Discovery Studio v2.5 visualizer tool.

Evaluation of ADMET Property

Novel drug candidates must possess good pharmacokinetic properties (i.e., ADMET). To

predict the various pharmacokinetic properties associated such as Adsorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) behavior of the shortlisted compounds based on high docking scores such as curcumin, three curcumin analogues (ZINC04468855, ZINC 07333416, ZINC 33518298) from ZINC database and two reference standard drugs Donepezil (CID_3152), Avagacestat (CID_46883536) was evaluated using pkCSM: predicting small-molecule pharmacokinetic properties online server.

Result

Drug-likeness Property

Results of drug-likeness property of curcumin, curcumin analogues, and standard drugs obtained from SWISS ADME server was tabulated in Table2. All screened curcumin and eleven curcumin analogues show no violations in all five drug-likeness rules viz. Lipinski, Ghose, Veber, Egan, and Muegge. Curcumin and eleven curcumin analogues show acceptable molecular weight in the range of 320.38 to 412.43. curcumin and elevan curcumin analogues show acceptable ranges of no of heavy atoms (HA), rotatable bond (RB), hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), molar refractivity (MR), topological polar surface area (TPSA), LogP values. Four reference standard drugs, namely Donepezil (CID_3152), Rivastigmine (CID_77991), Galantamine (CID_9651), and Semagacestat (CID_9843750) shown no violations for all five drug-likeness rules viz. Lipinski, Ghose, Veber, Egan, and Muegge. Whereas Begacestat (CID_11269353) shows single violations against Ghose drug-likeness rule, i.e., WLOGP value of 5.67, Avagacestat (CID_46883536) shown violations against Lipinski, Veber, Egan, and Muegge except for Veber rule.

Molecular Docking Study

Alzheimer's disease hypothesis and targets and their grid box size used for docking analysis presented in Table 3. Molecular docking analysis of Alzheimer's disease targets and ligand complexes and their molecular interactions result in detail were presented in Table 4 & 5. Curcumin and curcumin analogues possess docking scores in the range of -7.5 to 9.9 Kcal/mol against all three Alzheimer's disease targets. Whereas reference standard drugs possess docking scores in the range of -6.4 to -11.0 Kcal/mol against Alzheimer's disease, molecular target acetylcholine esterase (PDB ID 3LII) has a high binding affinity with reference standard drug Donepezil (CID_3152) with the docking score of -11.0 Kcal/mol. Curcumin and curcumin analogues (ZINC04468855) possess docking scores of -9.9 & -9.8 Kcal/mol against acetyl choline esterase enzyme target. Curcumin shown bonded and non-bonded interactions with Trp86, Tyr133, Glu202, Ser293, Tyr337 and Leu130, Trp286, Tyr341 residues of acetyl choline esterase enzyme, respectively. Similarly, Ser293, Phe295, and Tyr72, Trp86, Tyr124, Trp286, Phe338, Tyr341, His447 residues of acetyl choline esterase interactions with reference standard drug donepezil (CID_3152). 2D molecular interactions images of acetyl choline esterase (PDB ID 3LII) with curcumin, curcumin analogues and Alzheimer's standard drug shown in Figure 1 to 3.

Table 2. Drug Likeliness Calculation for Curcumin, Curcumin Analogues Obtained from ZINC Database and Standard Drugs for Alzheimer's Disease

S. No	Compound	MW	HA	RB	HBA	HBD	MR	TPSA	XLOGP3	WLOGP	MLOGP	Lipinski violation	Ghose violation	Veber violation	Egan violation	Muegge violation
1	CID_969516	368.38	27	8	6	2	102.8	93.06	3.2	3.15	1.47	0	0	0	0	0
2	ZINC00607794	366.41	27	4	5	2	105.3	75.99	4.29	4.12	2.19	0	0	0	0	0
3	ZINC00856144	394.46	29	6	5	0	114.23	53.99	4.95	4.72	2.61	0	0	0	0	0
4	ZINC04468855	366.41	27	4	5	2	105.3	75.99	4.29	4.12	2.19	0	0	0	0	0
5	ZINC04802476	352.38	26	4	5	2	100.49	75.99	4.29	3.73	2.19	0	0	0	0	0
6	ZINC07333416	320.38	24	3	3	1	96.78	46.53	4.29	4.4	2.19	0	0	0	0	0
7	ZINC13119472	352.38	26	4	5	2	100.49	75.99	3.75	3.73	1.97	0	0	0	0	0
8	ZINC13519235	366.41	27	4	5	2	105.3	75.99	4.29	4.12	2.19	0	0	0	0	0
9	ZINC17251958	380.43	28	4	5	2	110.1	75.99	4.55	4.36	2.4	0	0	0	0	0
10	ZINC18066836	352.38	26	4	5	2	100.49	75.99	3.75	3.73	1.97	0	0	0	0	0
11	ZINC31904839	412.43	30	6	7	2	113.47	94.45	3.7	3.74	1.33	0	0	0	0	0
12	ZINC33518298	380.43	28	4	5	2	110.1	75.99	4.55	4.36	2.4	0	0	0	0	0
13	CID_3152	379.49	28	6	4	0	115.31	38.77	4.28	3.83	3.06	0	0	0	0	0
14	CID_77991	250.34	18	6	3	0	73.12	32.78	2.29	2.44	2.34	0	0	0	0	0
15	CID_9651	287.35	21	1	4	1	84.05	41.93	1.84	1.32	1.74	0	0	0	0	0
16	CID_11269353	373.75	21	7	9	2	65.91	103.02	3.47	5.67	1.36	0	1	0	0	0
17	CID_46883536	520.88	34	10	11	1	112.31	127.77	3.98	6.53	2.66	1	2	0	1	1
18	CID_9843750	361.44	26	7	4	3	101.31	98.74	1.26	-0.33	0.28	0	0	0	0	0

MW – Molecular Weight, HA – Hydrogen Atoms, RB- Rotatable Bonds, HBA – Hydrogen Bond Acceptors, HBD - Hydrogen Bond Donars, MR-Molecular Refractivity, TPSA –Total Polar Surface Area

Table 3. Alzheimer's Disease Hypothesis and Targets and their Grid Box Size used for Docking Analysis

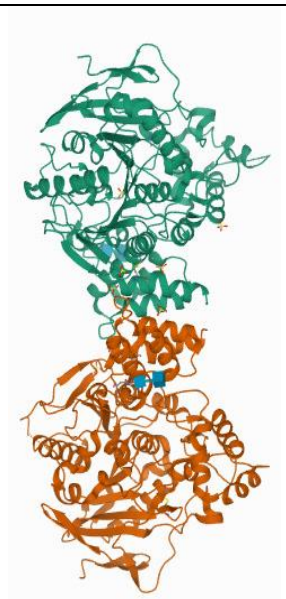
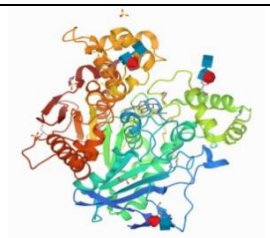
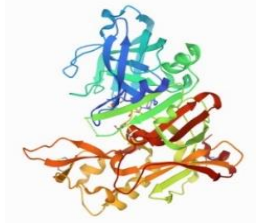
S.No.	Alzheimer's Disease Hypothesis	Target	PDB ID	Image	Grid Size (A°)
1	Cholinergic Hypothesis	Acetyl Choline Esterase	3LII		**X-63.70**
					Y- 63.05
					Z- 65.19
2		Butryl Choline Esterase	6QAA		**X -62.04**
					Y -57.07
					Z -73.04
3	Amyloid Hypothesis	Beta Secretase	4D8C		**X 64.98**
					Y 61.25
					Z 53.02

Table 4. Docking Score for Curcumin, Curcumin Analogues obtained from ZINC Database and Standard Drugs for Alzheimer's Disease against Target Proteins of Alzheimer Hypothesis

S. No	Compounds	Pubchem ID	3LII	6QAA	4D8C
1	Curcumin	CID_969516	-9.9	-8.3	-8.4
2	Curcumin Analogues obtained from ZINC Database	ZINC00607794	-9.5	-7.9	-8.6
3		ZINC00856144	-7.7	-7.7	-8.4
4		ZINC04468855	-9.8	-8	-8.1
5		ZINC04802476	-9.2	-8.1	-9.1
6		ZINC07333416	-9.5	-8.6	-8.9
7		ZINC13119472	-9.6	-7.7	-8.4
8		ZINC13519235	-7.8	-8.1	-8.2
9		ZINC17251958	-8.3	-8	-7.5
10		ZINC18066836	-9.7	-8	-7.8

11		ZINC31904839	-7.8	-7.6	-7.6
12		ZINC33518298	-8.3	-8.4	-8.4
13	Standard drugs for Alzheimer's Disease	CID_3152	-11.0	-8.0	-8.3
14		CID_77991	-7.1	-6.7	-6.4
15		CID_9651	-7.9	-7.6	-7.5
16		CID_11269353	-7.5	-7.0	-7.4
17		CID_46883536	-8.1	-8.6	-7.5
18		CID_9843750	-8.2	-7.7	-7.8

Table 5. Docking Interaction for Curcumin, Curcumin Analogues obtained from ZINC Database and Standard Drugs for Alzheimer's Disease against Target Proteins of Alzheimer Hypothesis

S.No.	Docking Complex	Residues Involved in Bonded Interaction	Residues Involved in Non-Bonded Interaction	Docking Score
1	3LII- CID_969516	Trp86, Tyr133, Glu202, Ser293, Tyr337	Leu130, Trp286, Tyr341	-9.9
2	3LII- ZINC04468855	Val294	Tyr124, Trp286, Phe297, Phe338, Tyr341	-9.8
3	3LII- CID_3152	Ser293, Phe295	Tyr72, Trp86, Tyr124, Trp286, Phe338, Tyr341, His447	-11.0
4	6QAA- ZINC07333416	Thr253	Pro230, Cys400, Pro401, Trp522	-8.6
5	6QAA- ZINC33518298	Asp304, Tyr396, Lys408	Phe526, Pro527, Leu307	-8.4
6	6QAA- CID_46883536	Asn228, Phe526, Val529	Pro230, Pro303, Asp304, Asp395, Tyr396, Trp522, Pro527	-8.6
7	4D8C- ZINC04802476	Phe108, Gly219, Thr318	Tyr71, Val321	-9.1
8	4D8C- ZINC07333416	-	Tyr71, Tyr187	-8.9
9	4D8C-CID_3152	Gly34	Tyr71, Ile126	-8.3

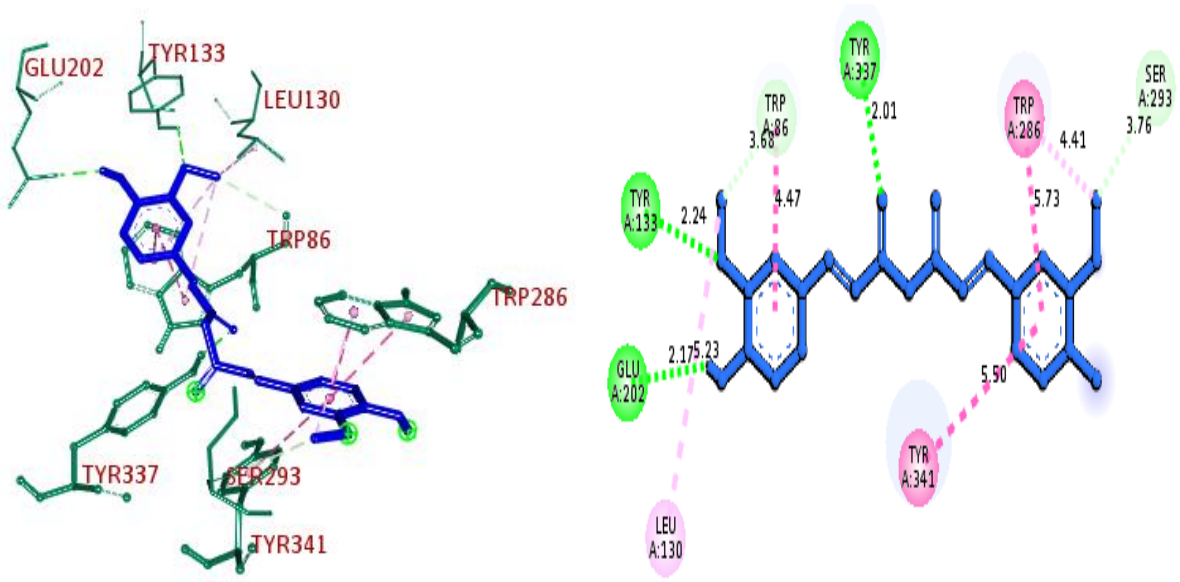


Figure 1. Docking 3D Pose and 2D Interaction Plot for 3LII-CID_969516 Complex (-9.9 Kcal/mol)

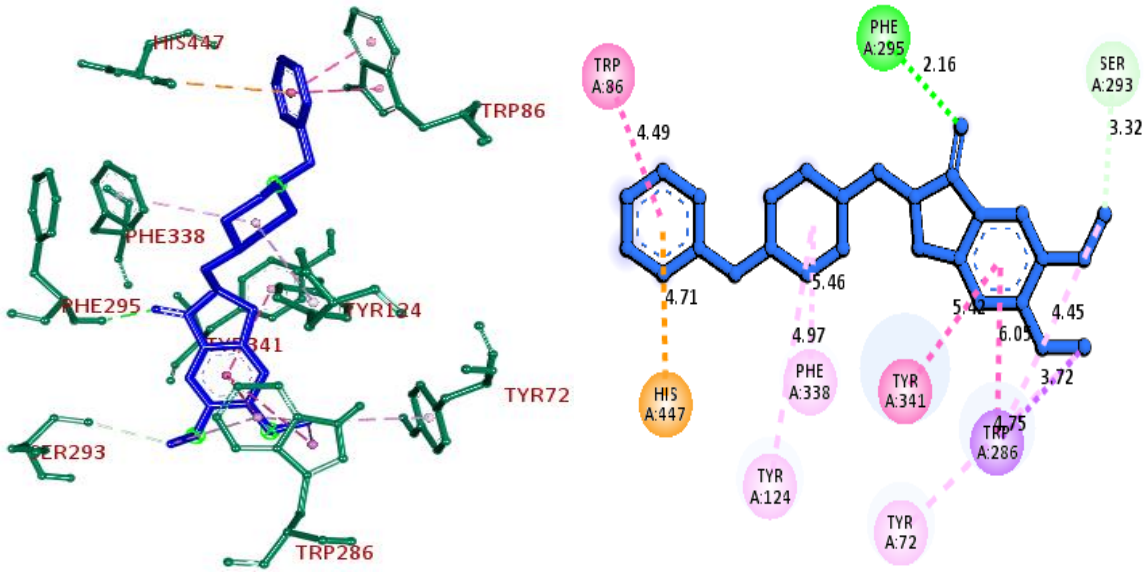


Figure 2. Docking 3D Pose and 2D Interaction Plot for 3LII-ZINC4468855 Complex (-9.8 Kcal/mol)

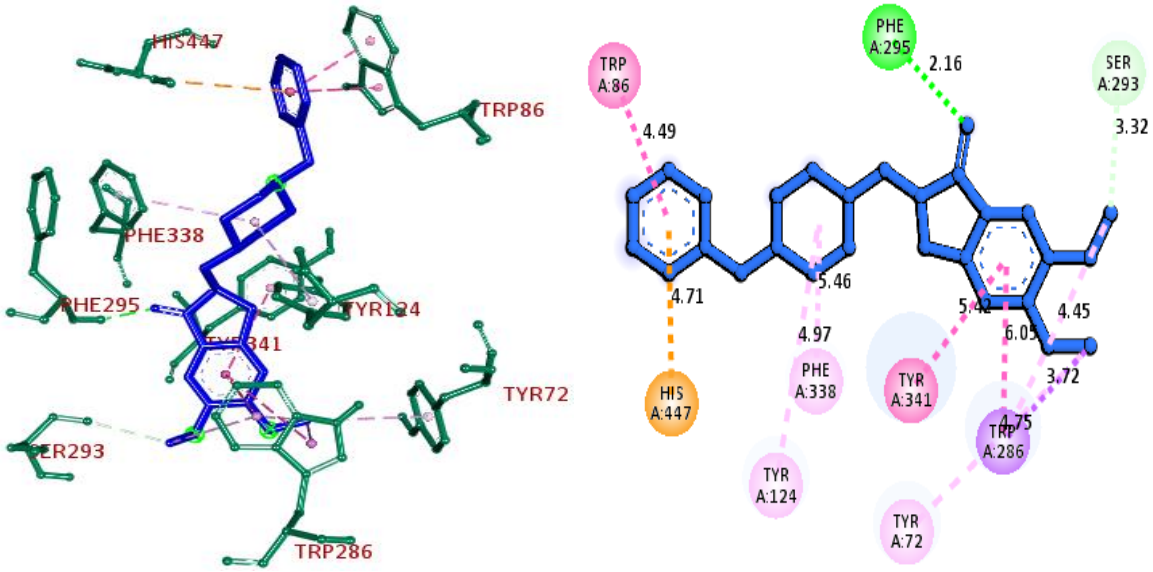


Figure 3. Docking 3D Pose and 2D Interaction Plot for 3LII-CID_3152 Complex (-11.0 Kcal/mol)

Similarly, butryl choline esterase possess the highest binding affinity with curcumin analogues (ZINC07333416) and reference standard drug Avagacestat (CID_46883536) with the docking score of -8.6 Kcal/mol. Another curcumin analogues (ZINC33518298) shows a binding affinity of -8.4Kcal/mol with butryl choline esterase enzyme. Thr253 and Pro230, Cys400, Pro401, Trp522 residues of butyl choline esterase interact with curcumin analogue ZINC07333416. Wherease avagacestat (CID_46883536) possess interactions with Asn228, Phe526, Val529 and Pro230, Pro303, Asp304, Asp395, Tyr396, Trp522, Pro527 residues of butryl choline esterase. 2D molecular interactions images of butryl choline esterase (PDB ID 6QAA) with curcumin analogues and Alzheimer's standard drug shown in Figure 4 to 6.

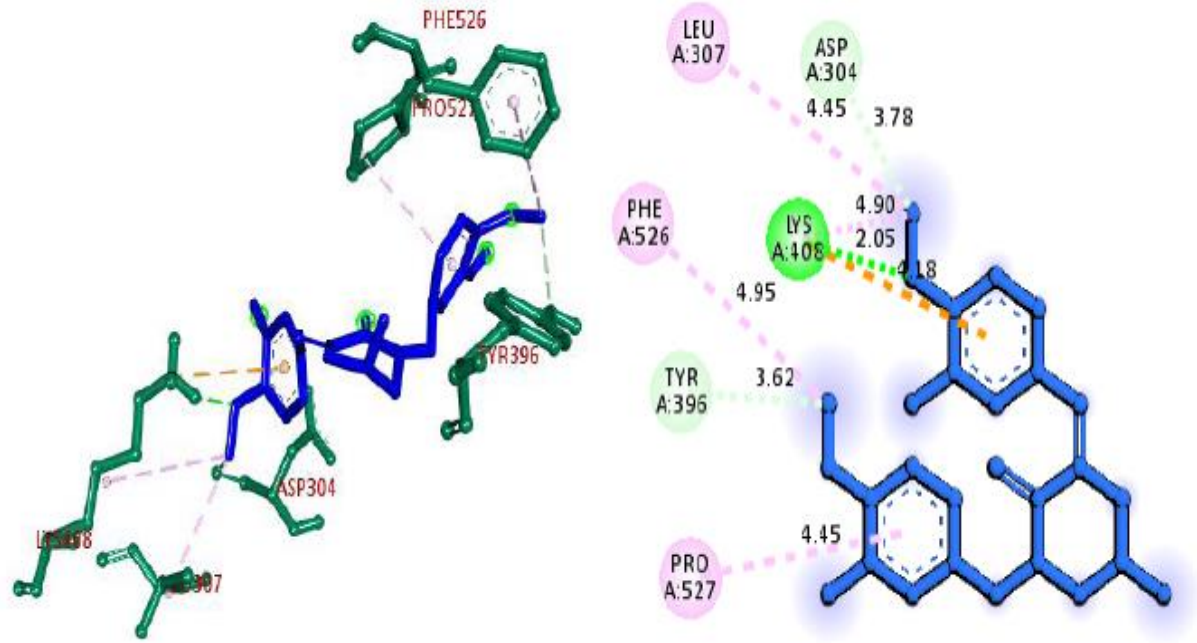


Figure 4. Docking 3D Pose and 2D Interaction Plot for 6QAA-ZINC7333416 complex (-8.6 Kcal/mol)

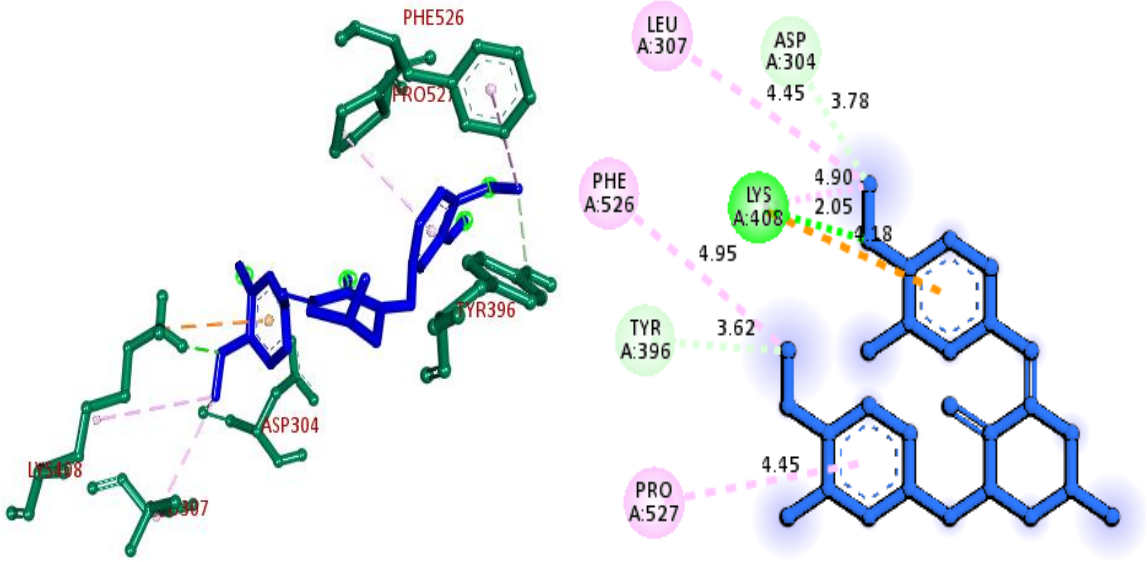


Figure 5. Docking 3D Pose and 2D interaction plot for 6QAA-ZINC33518298 complex (-8.4 Kcal/mol)

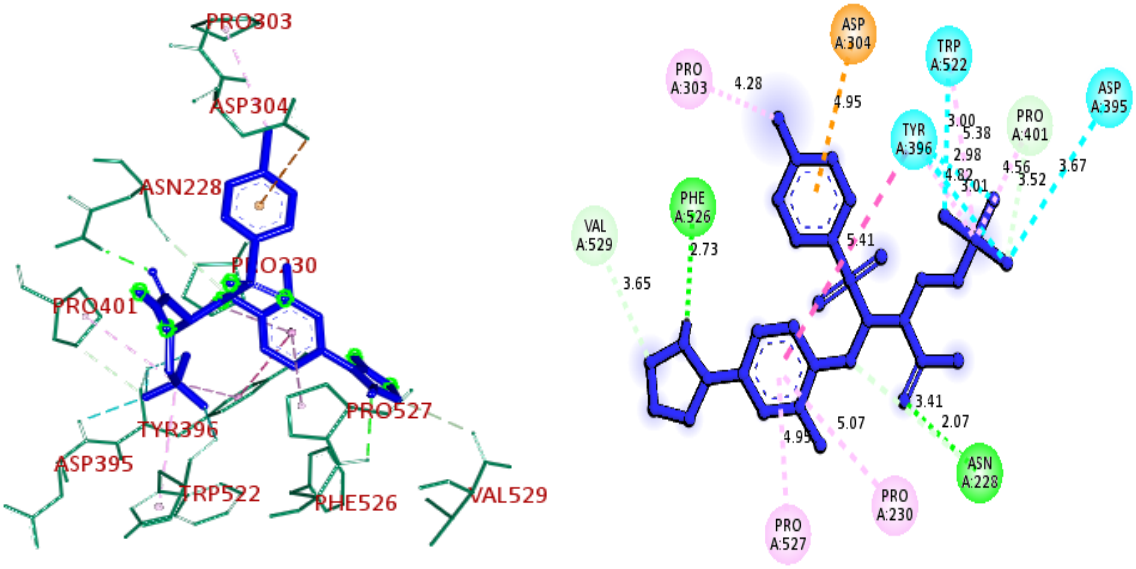


Figure 6. Docking 3D Pose and 2D interaction plot for 6QAA-CID_46883536 complex (-8.6 Kcal/mol)

Based on the amyloid hypothesis beta-secretase enzyme act as a promising target for Alzheimer's disease, and its molecular docking analysis results show that two curcumin analogues (ZINC04802476 & ZINC07333416) possess docking score of -9.1 and -8.9 Kcal/mol. Donepezil (CID_3152) possess a docking score of -8.3 Kcal/mol against the beta-secretase enzyme. Phe108, Gly219, Thr318, and Tyr71, Val321 residues of beta-secretase enzyme possess bonded and non-bonded interactions with curcumin analogues ZINC04802476. Gly34 and Tyr71, Ile126 residues of beta-secretase enzyme possess bonded and non-bonded interactions with reference standard drug donepezil (CID_3152). 2D molecular interactions images of beta-secretase (PDB ID 6QAA) with curcumin analogues and Alzheimer's standard drug are shown in Figures 7 to 9.

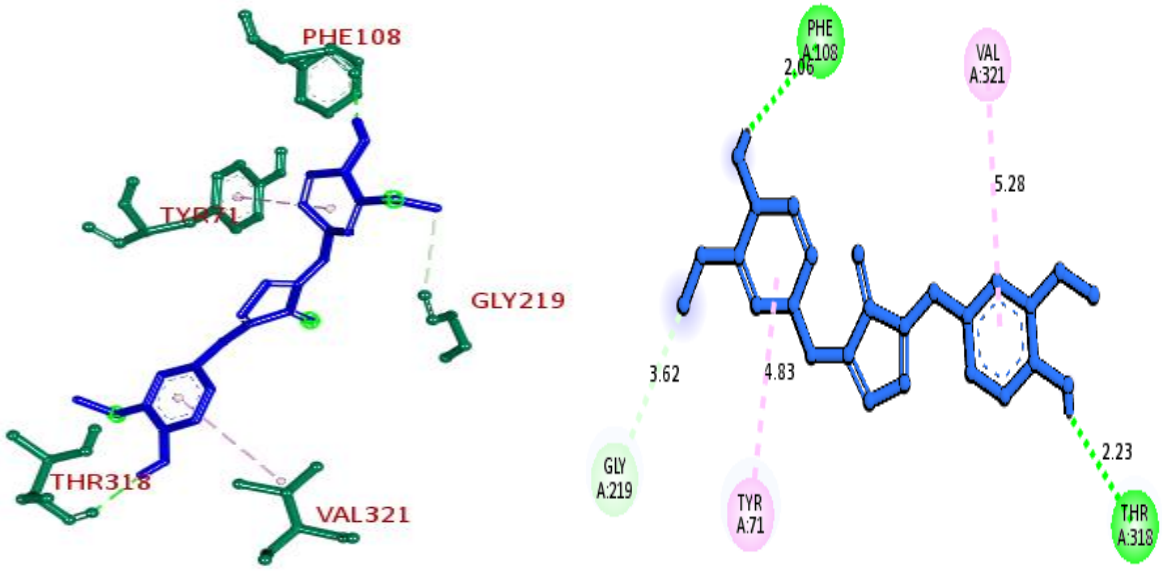


Figure 7. Docking 3D Pose and 2D interaction plot for 4D8C-ZINC4802476 complex (-9.1 Kcal/mol)

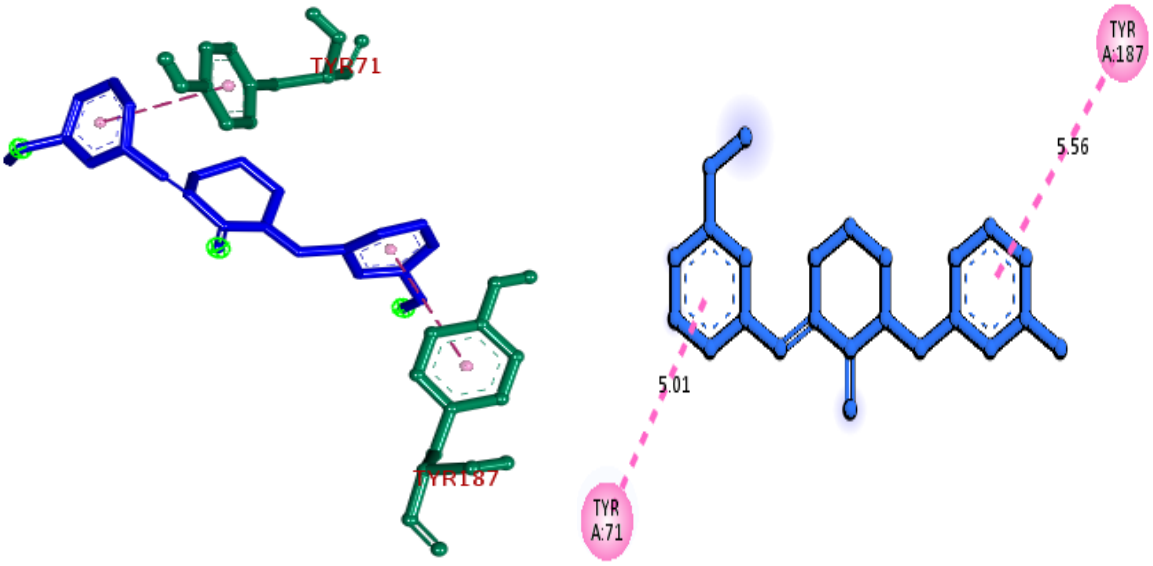


Figure 8. Docking 3D Pose and 2D interaction plot for 4D8C-ZINC7333416 complex (-8.9 Kcal/mol)

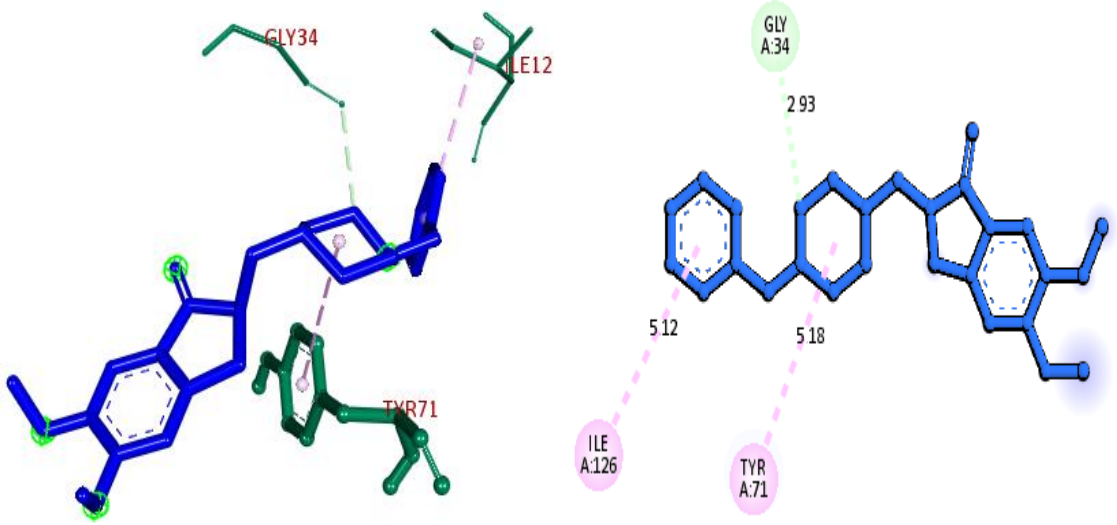


Figure 9. Docking 3D Pose and 2D interaction plot for 4D8C-CID_3152 complex (-8.3 Kcal/mol)

ADMET Property

Pharmacokinetic results of curcumin, three ZINC database curcumin analogues (ZINC04468855, ZINC07333416, ZINC33518298) reference standard drug shown in Table 7. Human intestinal absorptions (HIA) of curcumin and three curcumin analogues values lie in the range of 79.13 to 83.79% in that drug donepezil (CID_3152) possess the highest HIA value 93.70%. Except ZINC 33518298 curcumin analogues and drug CID_46883536 all the screened molecules possess logBB value less than -1, so it has good BBB penetration capacity important for AD drug criteria. Curcumin analogues ZINC04468855 possess no inhibition against all five screened cytochrome enzymes, and other molecules show reasonable no of enzyme non-inhibition of drug metabolising enzymes. Curcumin analogues ZINC04468855, ZINC07333416, and donepezil (CID_3152) shows positive total clearance values and can be easily excreted. Except curcumin analogues ZINC33518298 all screened molecules shows no AMES toxicity. Except donepezil (CID_3152) all screened molecules show no hERG inhibition and hepatotoxicity. LD50 values lies in the range of 1.833 to 2.753.

Table 6. Pharmacokinetic Properties for Curcumin, Curcumin Analogues obtained from ZINC Database and Standard Drugs for Alzheimer's Disease

S.No	Pharmacokinetic Properties		Curcumin	Curcumin Analogues			Standard Drugs	
			CID_969516	ZINC 04468855	ZINC 07333416	ZINC 33518298	CID_3152	CID_46883536
1	**Absorption**	Human Intestinal Absorption (HIA %)	82.19	79.13	83.79	80.75	93.70	77.83
		Caco-2 Cell Permeability (cm/sec)	-0.093	1.317	1.445	1.485	1.273	0.601
		P-glycoprotein substrate	Yes	Yes	Yes	No	Yes	Yes
		Skin Permeability (log Kp, cm/hour)	-2.764	-2.282	-2.593	-2.735	-2.585	-2.754
		Pure Water Solubility (mol/L)	-4.01	-0.102	-3.412	-2.892	-4.648	-5.619
2	**Distribution**	CNS Permeability (log PS)	-2.99	-2.83	-2.83	-0.217	-1.464	-3.232
		Blood Brain Barrier Penetration (log BB)	-0.562	0.292	0.42	-1.393	0.157	-2.054
3	**Metabolism**	CYP_1A2 Inhibitor	Yes	No	Yes	Yes	No	No
		CYP_2C19_inhibitior	Yes	No	No	No	No	Yes
		CYP_2C9_inhibitior	Yes	No	No	No	No	Yes
		CYP_2D6_inhibitior	No	No	No	No	Yes	No
		CYP_3A4_inhibitior	Yes	No	No	No	Yes	Yes
4	**Excretion**	Total Clearance (log ml/min/kg)	-0.002	0.909	0.64	-56.833	0.987	-0.046
		Renal OCT substrate	No	No	No	No	Yes	No
5	**Toxicity**	AMES Toxicity	No	No	No	Yes	No	No
		HERG_inhibition	No	No	No	No	Yes	No
		Hepatotoxicity	No	No	No	No	Yes	Yes
		Oral Rat Chronic Toxicity (LOAEL)	2.228	4.567	-0.973	12.09	0.991	0.339
		Oral Rat Acute Toxicity (LD50)	1.833	2.482	2.482	2.482	2.753	2.611

Discussion

Drug-Likeness Property

SWISS ADME online platform is useful to screen the Physico-chemical property of drug molecules, and it validates any query molecules against five drug-likeness rules i.e., Lipinski, Ghose, Veber, Egan, Muegge. Drug likeness is used to assess whether query molecule has some important drug physico-chemical properties [21]. Our present study confirms that curcumin and eleven curcumin analogues possess drug-likeness property and no violations against five rules. All five-drug likeness rule is put together is a better tool to test its chemical and physical properties of query drug molecules [22, 23].

Molecular Docking Study

Similar *in silico* anti-Alzheimer's potential validation of 47 substances including two curcumins and 45 flavonoids with remarkable predicted pIC50 values against acetylcholine esterase and beta secretase ranging from 4.24–5.11 (AChE) and 4.52–10.27 (BACE-1) produces docking score in the range of −13.11 to −36.23KJ/mol [24].

Likewise, another study reveals that chloroform leaf extract of *C. carandas* was found to contain constituents that have affinities for the 2 targets f β-amyloid fibril and acetyl choline esterase. The best docking scores for curcumin possess –110.22 kcal/mol in iGEMdock scorer, and the compounds from chloroform leaf extract of *C.carandas* was found to possess higher scores than standard curcumin octacosane (– 152.58); hexacosane (–148.89); carbonic acid, eicosyl vinyl ester (–148.18); 1-heneicosanol (–135.38); N-nonadecanol-1 (–127.65); eicosane (–126.24); 3-eicosene, (E) (–125.79); 1-nonadecene (–120.26); tetratetracontane (–119.09); 9-octadecene, (E) (–114.18); squalene (–112.92); E-14-hexadecenal (–110.99); and hexadecanal (–110.67) score against β-amyloid fibril target of Alzheimer's disease. Similarly, our study curcumin analogues possess good binding affinity and docking scores against molecular targets of Alzheimers disease than standard reference drugs [25, 26].

ADMET Property

The blood-brain barrier membrane permeability (logBB) was considered as an important parameter for AD disease. BBB allows only small molecules and allows only the water and lipid-soluble and selective transport molecules such as plasma glycoprotein and glucose transporters into the central nervous system [23]. The lethal dose (LD50) is a standard measurement of acute toxicity used to evaluate the relative toxicity of phytocompounds [27].

Conclusion

The present study reveals that curcumin analogues obtained from the ZINC database possess some novel drug-likeness, ADMET, and binding affinity with molecular targets of Alzheimer's disease. These curcumin analogues from the ZINC database possess significant anti-Alzheimer's potentials when compared to that currently available Alzheimer's drugs. So, it needs further *in vitro*, and *in vivo* anti-Alzheimer's potential validation is needed to commercialize these ZINC curcumin analogue molecules for treating Alzheimer's disease.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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